Single Technology Appraisal

Cabotegravir for preventing HIV-1 in adults and young people [ID6255]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Cabotegravir for preventing HIV-1 in adults and young people [ID6255]

Contents:

The following documents are made available to stakeholders:

The **final scope** and **final stakeholder list** are available on the NICE website.

Pre-technical engagement documents

1. **Company submission summary** from ViiV Healthcare

2. **Company summary of information for patients (SIP)** from ViiV Healthcare

3. **Clarification questions and company responses**

4. **Community group, professional group and NHS organisation submissions** from:
   a. Terrence Higgins Trust
   b. UK Community Advisory Board
   c. British Association for Sexual Health and HIV
   d. British HIV Association
   e. English HIV and Sexual Health Commissioners' Group
   f. HIV Pharmacy Association
   g. NHS England

5. **External Assessment Report** prepared by Warwick Evidence

6. **External Assessment Report – factual accuracy check**

Post-technical engagement documents

7. **Technical engagement response from company:**
   a. Main response
   b. Cost-effectiveness results – to follow

8. **Technical engagement responses and statements from experts:**
   a. Greg Owen, PrEP Lead at Terrence Higgins Trust – community expert, nominated by Terrence Higgins Trust
   b. Rachael Jones, Consultant Physician – clinical expert, nominated by NHS England
   c. Michael Brady, Consultant in HIV and Sexual Health – clinical expert, nominated by ViiV Healthcare (company)

9. **Technical engagement responses from stakeholders:**
    a. National AIDS Trust
    b. British HIV Association
    c. English HIV and Sexual Health Commissioners' Group
    d. NHS England

10. **External Assessment Report critique of company response to technical engagement** prepared by Warwick Evidence**:**
    a. Main critique
    b. Post-technical engagement cost-effectiveness analyses

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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Document B

Company evidence submission

5th February 2024

File name	Version	Contains confidential information	Date
ID6255_Cabotegravir for PrEP_Document B_List_[noCON]	2	Yes	13th March 2024

Contents

Tables and figures

Abbreviations

Acronym	Definition
AE	Adverse event
AESI	Adverse event of special interest
AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
BASHH	British Association for Sexual Health and HIV
BHIVA	The British HIV Association
BMI	Body mass index
BNF	British National Formulary
CEAC	Cost-effectiveness acceptability curve
CEM	Cost-effectiveness model
CI	Confidence interval
DBS	Dried blood spot
DIC	Deviance information criterion
DNA	Deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
DXA	Dual-energy x-ray absorptiometry
eGFR	Estimated glomerular filtration rate
GBP	Great British Pounds
GI	Gastrointestinal
GP	General practitioner
HARS	HIV and AIDS reporting system
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HPTN	HIV Prevention Trials Network
HR	Hazard ratio
HRQoL	Health-related quality of life
HSE	Health Survey for England
HSUV	Health state utility value
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
INSTI	Integrase strand transfer inhibitor
ISR	Injection site reaction
ITC	Indirect treatment comparison
ITT	Intention-to-treat
LA	Long acting
mITT	Modified intention-to-treat
NG	NICE guideline
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OBSP	On blinded study product
OLE	Open-label extension
OWSA	One-way sensitivity analysis
PAS	Patient Access Scheme
PK	Pharmacokinetic
PrEP	Pre-exposure prophylaxis
PSA	Probabilistic sensitivity analysis
PY	Person years

Acronym	Definition
QALY	Quality-adjusted life year
QoL	Quality of life
RAM	Resistance-associated mutation
RCT	Randomised controlled trial
RNA	Ribonucleic acid
RR	Relative risk
SAE	Serious adverse event
SHS	Sexual health service
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard of care
SOC	System organ class
STI	Sexually transmitted infections
TAF/FTC	Tenofovir alafenamide with emtricitabine
TD/FTC	Tenofovir disoproxil with emtricitabine
TDF/FTC	Tenofovir disoproxil fumarate with emtricitabine
TFV	Tenofovir
TFV-DP	Tenofovir-diphosphate
U=U	Undetectable = un-transmittable
UKHSA	UK Health Security Agency
UN	United Nations
UNAIDS	The Joint United Nations Programme on HIV/AIDS
US	United States
WHO	World Health Organization
WHOQOL-HIV BREF	WHO Quality of Life-HIV Brief Version
WTP	Willingness to pay threshold

Glossary

Term	Definition
Cabotegravir	Cabotegravir long-acting injections, with or without oral cabotegravir
Cabotegravir LA	Cabotegravir long-acting injections (600 mg/3 mL)
Likely to be exposed to HIV	The terms ‘likely to be exposed to HIV’ and ‘at risk’ of HIV acquisition are used interchangeably; the former is the preferred term to align with person-first language, with ‘at risk’ used as a technical definition
Oral cabotegravir	Cabotegravir oral tablets (30 mg)
Oral pre-exposure prophylaxis (PrEP)	Refers to oral TD/FTC and TAF/FTC
Tenofovir disoproxil fumarate/emtricitabine (TDF/FTC)	Refers to tenofovir disoproxil in combination with the salt fumarate (TDF) with emtricitabine (i.e. Truvada or generic Truvada)
Tenofovir disoproxil/emtricitabine (TD/FTC)	Although PrEP trials have used TDF, salts other than fumarate may be used in generic formulations of tenofovir disoproxil;, therefore, tenofovir disoproxil (TD) with emtricitabine refers to any generic formulation where TD may be combined with fumarate, maleate, succinate or phosphate salts

Note, the language within this document has been aligned with recommended terminology from the People First Charter; the use of positive and inclusive language in the human immunodeficiency virus (HIV) field is vital, as people living with HIV or who are likely to be exposed to HIV experience stigma and discrimination, which is perpetuated by the use of inappropriate language (1).

B.1 Decision problem, description of the technology and clinical care pathway

Human immunodeficiency virus (HIV) is a retrovirus that infects and destroys immune cells that play a key role in fighting infections (2). HIV can be transmitted via the bodily fluids of a person living with HIV not on effective treatment during sexual contact.

The United Kingdom (UK) government's HIV Action Plan has committed to end HIV transmission in England by 2030 (3).

- Targets include zero new transmissions of HIV by 2030 (with an interim commitment to an 80% reduction in transmissions by 2025) (3).

Pre-exposure prophylaxis (PrEP) is an essential component of HIV prevention strategies (4), used to reduce the likelihood of acquiring HIV by preventing it from replicating in the body of people who are exposed (5).

- Generic tenofovir disoproxil with emtricitabine (TD/FTC) is the current UK standard of care (SoC) (6).
- Tenofovir alafenamide with emtricitabine (TAF/FTC) is available as a second line option for individuals who are intolerant of TD/FTC or for those who are contraindicated to TD/FTC (6). However, it is only licensed for at-risk men who have sex with men (7).

Some individuals in the UK are more likely to be exposed to HIV.

- The 2018 British HIV Association (BHIVA)/British Association for Sexual Health and HIV (BASHH) guidelines provide criteria for identifying individuals likely to be exposed to HIV who are eligible for PrEP (8), with National Institute for Health and Care Excellence (NICE) guideline 221 (NG221) (9) and the National Health Service (NHS) PrEP commissioning policy (6) offering PrEP using the criteria in the BHIVA/BASHH guidelines.
- Whilst underlying risk of HIV acquisition for an individual can be described via the criteria outlined in BHIVA/BASHH guidelines (8), including population- and clinical indicators, and factors related to sexual network and behaviours, it should be noted that it is not defined by individuals' biological or physiological characteristics.

Despite availability of oral PrEP, latest data show that the UK HIV Action plan targets will not be met by 2030, so further efforts/investments are required.

- A model-based analysis has shown if the current level of interventions are maintained, there is no chance of achieving the target of fewer than 50 new HIV acquisitions among gay, bisexual, and other men who have sex with men by 2030 (which equates to an incidence of less than 1 per 10,000 acquisitions per year) (10).

- In the UK in 2022, 4,040 people were newly diagnosed with HIV in the UK, a 19% rise from 2021 and a 21% rise from 2020 (11). In addition, only 71% of individuals with PrEP need initiated or continued PrEP (11), which is insufficient to achieve the HIV Action Plan's targets.

While oral PrEP is available in the UK, some individuals are underserved by current SoC, reflecting an unmet need where people do not or cannot access effective HIV prevention.

- The consequences of PrEP unmet need include suboptimal uptake, persistence, and adherence to oral PrEP. High adherence to oral PrEP is required for effective protection from HIV acquisition (8, 12-14), and published evidence has shown that individuals taking oral PrEP in real world settings have low adherence to oral PrEP (15).
- Drivers of unmet need affecting uptake, adherence, and persistence with oral PrEP include but are not limited to PrEP-related stigma (16), as well as an unacceptable dosing regimen, pill burden, and anxiety around missed doses (17-19).

Access to biomedical innovation such as cabotegravir for PrEP in the UK, to address unmet needs among people for whom oral PrEP is not appropriate, is key to meet the current UK objective of no new HIV transmissions by 2030 (3).

- Cabotegravir is the first and only long-acting injectable PrEP, and is administered less often than daily oral tablets, which provides an important option for people who are sub optimally adhering to daily oral PrEP and may increase uptake among people not taking or persisting with current options due to the pill burden.
- Cabotegravir provides a much-needed new option for people who need PrEP but are unable to take oral PrEP due to contraindications or medical intolerance, or because they have a limited ability to swallow pills.
- Having a long-acting injectable option provides people who experience PrEP-related stigma a more discreet protective option, for example by eliminating any need to conceal a medication bottle.

Improvements in PrEP uptake, adherence, and persistence with cabotegravir among people for whom oral PrEP is not appropriate will help towards addressing unmet need due to health-related challenges and social determinants of health. It will also help towards achieving the UK HIV Action Plan's aims and avoid the significant downstream individual and population-level clinical, humanistic, and economic burden associated with future HIV acquisitions.

B.1.1 Decision problem

Cabotegravir is anticipated to be indicated for [redacted] (Appendix C).

The submission focuses on people for whom oral PrEP is not appropriate and are therefore underserved by current standard of care (SoC; daily oral tenofovir disoproxil fumarate with emtricitabine [TDF/FTC]). High adherence to oral PrEP is required for effective protection from HIV acquisition (Section B.1.3.6.1.2) and adherence to oral PrEP is low in real-world settings (15). Some people are unable to adhere to daily oral PrEP due to health-related challenges (which may include physical, mental and cognitive symptoms and impairments, difficulties with day-to-day activities, challenges to social inclusion, and uncertainty or worry about future health (20)), and social determinants of health (defined as conditions with which people are born, grow, live, work, and age, that shape their level of power, income, and other determinants of life (21)). These determinants can play a crucial role in creating health inequities, which are avoidable differences in health status. In addition, some people cannot take oral PrEP despite their need, due to contraindications or medical intolerances, or due to limitations swallowing pills.

The appraisal population reflects individuals with an underlying risk of HIV acquisition, which may be influenced by several factors (Section B.1.3.4) and does not focus on subgroups presenting specific risk factors related to their biological or physiological characteristics. The proposed population reflects where there is currently the greatest unmet need for a new PrEP modality that can be addressed by the availability of cabotegravir.

The decision problem is presented in Table 1, which outlines any differences from the National Institute for Health and Care Excellence (NICE) final scope (22).

Table 1: The decision problem

	Final scope issued by NICE (22)	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People at risk of sexually acquired HIV-1 infection.	Adults and adolescents (weighing at least 35 kg) at risk of sexually acquired HIV for whom oral PrEP is not appropriate.	Current SoC meets the needs of the broad population of people likely to be exposed to HIV. However, there are still people who are likely to be exposed to HIV who are underserved by oral PrEP for the reasons described in Sections B.1.3.6. A new drug class, modalities, and or dosing frequencies, such as cabotegravir, will help to address the unmet needs for these individuals (Section B.1.3.7).
Intervention	Cabotegravir intramuscular injections with or without oral lead-in therapy.	As per the NICE scope.	N/A.
Comparator(s)	Established clinical management including tenofovir disoproxil or alafenamide in combination with emtricitabine or tenofovir alone.	• TDF/FTC (for individuals taking and sub-optimally adhering to oral PrEP). • No PrEP (for individuals who cannot take oral PrEP).	Single agent TD is not currently licensed as PrEP, but according to the BHIVA/BASHH guidelines can be considered as an alternative for heterosexual men and women (8); this population likely represents a small proportion of PrEP use in England and Wales. Furthermore, only tenofovir in combination with emtricitabine is commissioned by the NHS's specialised clinical commissioning policy for PrEP (6). The use of TAF/FTC (Descovy) is negligible in the UK among men who have sex with men and transgender women, and it is not approved for individuals assigned female sex at birth. • Over a 2-year period, only 0.185%‡ of PrEP users attending Dean Street, Chelsea (the largest sexual health clinic in Europe) and

	Final scope issued by NICE (22)	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			Westminster Hospital NHS Foundation Trust were prescribed TAF/FTC (23, 24). • Among a Scottish cohort of 1,744 PrEP users, only 0.4% had been initiated on TAF/FTC (25).
Outcomes	• Number of documented incident HIV infections. • Change in viral load. • Adverse effects of treatment. • HRQoL. • Renal function. • Liver function. • Bone mineral density. • Incidence of resistance mutations. • Adherence to treatment regimen.	• Number of documented incident HIV acquisitions[†]. • Adverse effects of treatment. • Renal function. • Liver function. • Bone mineral density. • Incidence of resistance mutations. • Acceptability scale assessments. • Adherence to study product. • Sexual risk factors (e.g. number of coital acts, sexual partners, condomless sex acts, condomless anal sex acts, frequency of reported transactional sex). • Incident STIs. • Weight, blood pressure, fasting glucose, and fasting lipids.	Aligned with draft scope, except change in viral load was not collected in the HPTN trials as the scope of the trials were to investigate cabotegravir for PrEP among individuals who are not living with HIV. In addition, no HRQoL data were collected. Note that acceptability scale assessments, sexual risk factors, incident STIs, weight, blood pressure, fasting glucose, and fasting lipids, as captured within the pivotal Phase 3 RCTs are also presented.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being	As per the NICE scope. The analysis will present cost-effectiveness results for the population at risk of HIV acquisition for whom oral PrEP options are not appropriate.	N/A.

	Final scope issued by NICE (22)	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	compared. Costs will be considered from an NHS and PSS perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products will be taken into account.		
Subgroups to be considered	If evidence exists, subgroups of people at risk of sexually acquired HIV-1 infection for whom the technology might be particularly clinically effective or value for money will be considered.	No subgroups are considered.	No subgroups are considered in this appraisal as the underlying risk of HIV acquisition should be the predominant consideration when initiating PrEP, irrespective of an individual's characteristics influencing their risk. The overall population considered in this appraisal reflects individuals with an underlying risk of HIV acquisition, in accordance with UK clinical guidelines(8), without focusing on subgroups presenting specific risk factors.
Special considerations including issues related to equity or equality	None specified.	PrEP is a key component of HIV prevention. While UK individuals have access to oral PrEP through the NHS, there are still some health inequities exacerbating unmet need for HIV prevention. which may be experienced by, but are not limited to, gender diverse populations and ethnic minorities (Section B.1.4).	–

†The term infections has been replaced with acquisitions throughout the dossier to align with the People First Charter (1); ‡TAF/FTC was recommended for 60 individuals, which was divided by the total number of patients eligible for PrEP (32,424).
Abbreviations: BHIVA/BASHH, British HIV Association/British Association for Sexual Health and HIV; HIV, human immunodeficiency virus; HPTN, HIV Prevention Trials Network; HRQoL, health-related quality of life; N/A, not applicable; NHS, National Health Service; NICE, National institute for Health and Care Excellence; PrEP, pre-exposure prophylaxis; PSS, Personal Social Services; QALY, quality-adjust life year; RCT, randomised controlled trial; SoC, standard of care; STI, sexually transmitted infection; TAF/FTC, tenofovir alafenamide/emtricitabine; TD, tenofovir disoproxil; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine; UK, United Kingdom.

B.1.2 Description of the technology being evaluated

A description of the technology being appraised (cabotegravir) is provided in Table 2. The summary of product characteristics (SmPC) and the United Kingdom (UK) public assessment report are provided in Appendix C.

Table 2: Technology being appraised

UK approved name and brand name	**Long-acting intramuscular injections:** Cabotegravir LA (Apretude). Cabotegravir LA can be used [redacted].
Mechanism of action	Cabotegravir is a second generation Integrase Strand Transfer Inhibitor (INSTI) that inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral DNA integration which is essential for the HIV replication cycle (26).
Marketing authorisation/CE mark status	Cabotegravir does not yet have marketing authorisation for the indication in this submission. A regulatory submission was made to the MHRA in [redacted], with approval anticipated in [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Cabotegravir LA is anticipated to be licensed by the MHRA [redacted] (Appendix C), [redacted] Cabotegravir oral tablets are anticipated to be licensed by the MHRA for [redacted] (Appendix C). Contraindications: • [redacted]
Method of administration and dosage	**Cabotegravir LA** Similar to other PrEP modalities, prior to starting cabotegravir, [redacted]

	[redacted] (Appendix C). [redacted] (Appendix C) [redacted] (Appendix C). **Cabotegravir oral** [redacted] (Appendix C). **Cabotegravir oral** [redacted] (Appendix C).
Additional tests or investigations	• [redacted] • [redacted] (Appendix C). • [redacted] (Appendix C). • [redacted] (Appendix C). • [redacted] (Appendix C).
List price and average cost of a course of treatment	**Cabotegravir LA** The list price of cabotegravir LA is [redacted] per single 600 mg/3 mL prolonged release suspension for injection vial (hospital only) The average cost of a course of cabotegravir LA injections (at list price) is [redacted] (based on a duration of treatment of [redacted] months estimated from the economic model). **Cabotegravir oral** [redacted].

	The list price of oral cabotegravir is [redacted] per pack of 30 x 30 mg tablets (hospital only).
Patient access scheme (if applicable)	[redacted]

Abbreviations: Cabotegravir LA, cabotegravir long-acting; DNA, deoxyribonucleic acid; HIV, human immunodeficiency virus; IM, intramuscular; MHRA, Medicines and Healthcare Products Regulatory Agency; NHSE, National Health Service England; PAS, Patient Access Scheme; PASLU, Patient Access Scheme Liaison Unit; PrEP, pre-exposure prophylaxis; SmPC, summary of product characteristics.

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 The value of prevention

Prevention refers to any action taken to decrease the chance of acquiring a disease or condition, and plays a central role in the UK government's health policies (27, 28). Effective prevention creates appropriate conditions for good health, reduces the burden of illness on individuals, releases capacity in health systems, improves national economic growth, and contributes to a healthier, more prosperous, and thriving society (28-31). Comprehensive HIV prevention, that uses a mix of biomedical, behavioural, and structural interventions, can have the greatest sustained impact on reducing new HIV acquisitions (10). Access to diagnosis, treatments and care mean that living with HIV has become a long-term condition (32). However, more progress must be made in HIV prevention for the UK government to meet its ambition of no new HIV transmissions by 2030 (3, 10).

B.1.3.1.1 *Effective prevention of HIV transmission is a key ambition of the UK government*

Equitable access and uptake of HIV prevention programmes through the availability of established and emerging biomedical interventions for HIV prevention is the first objective of the UK HIV Action Plan (3). Effective prevention reduces healthcare utilisation, leading to long-term expenditure savings (31). Investing in effective HIV prevention strategies can help to offset the high costs associated with HIV treatment (33), as well as the costs and resource utilisation resulting from the range of health-related challenges associated with living with HIV (Section B.1.3.8).

Broader societal benefits of HIV prevention (which are not captured in the economic model) include economic activity (34). Lost productivity due to preventable ill-health costs the UK economy an estimated £70 billion per year (31). Other benefits include

preventing the negative impacts living with HIV has on health-related quality of life (HRQoL) (Section B.1.3.8). Prevention also plays a key role in addressing social and structural determinants of health inequities; in the UK, much of the preventable risk factors for ill health are concentrated among groups of people who are socioeconomically disadvantaged (35). This is noticeable in the context of HIV where key and vulnerable populations such as gay, bisexual and other men who have sex with men, transgender individuals, sex workers, and migrant populations are disproportionately affected (Section B.1.4). Additionally, poverty and HIV outcomes are inextricably linked; according to the Positive Voices 2022 survey, 21.7% of people living with HIV were in receipt of means-tested benefit, which is nearly double that of the general adult population in 2021 (34). Thus, the prevention of HIV acquisition is key in addressing health inequalities among individuals living in the UK and supports a key aim of the National Health Service (NHS) (36).

B.1.3.1.2 *Further efforts are required to overcome current limitations and deliver ambitions set by prevention policies*

A shift from reactive treatment to prevention is required for the HIV Action Plan to succeed. Although combination prevention works in the UK(10), more action is needed due to unmet needs (Section B.1.3.6). Investments need to be sustained and built upon if the UK is to reach zero new transmissions by 2030(3), as there is no chance of achieving the UK HIV Action Plan's 2030 goal with current activities according to recent research(10). European modelling demonstrates that introducing cabotegravir would further accelerate ending HIV transmissions (37). Access to biomedical innovation for prevention is therefore key to meet the current UK objectives (Section B.1.3.7).

B.1.3.2 Disease overview

HIV is a retrovirus that infects and destroys immune cells that play a key role in fighting infections (2). HIV binds to the CD4 receptor and a co-receptor on the surface of these immune cells in order to gain entry to the host cell, where single strand HIV ribonucleic acid (RNA) is reverse transcribed into deoxyribonucleic acid (DNA) and inserted within the host genome (2). Once integrated, the virus uses the host cell machinery to multiply and spread (2). There are two main types of HIV; HIV-1 is considered more prevalent and more transmissible than HIV-2 (2). HIV is

transmitted via bodily fluids of an individual living with HIV who is not on effective treatment during sexual contact (blood, semen, and vaginal fluids; across mucosal surfaces), by vertical transmission (during pregnancy, birth, and breast feeding), and by sharing equipment used to inject drugs (32, 38). Untreated HIV progresses through three stages: primary/acute infection, through clinical latency (i.e. asymptomatic infection), to late-stage infection (also known as acquired immunodeficiency syndrome [AIDS]) (39).

Effective prevention of HIV at the population level requires adequate support for both people living with HIV, and individuals not living with HIV, to prevent onwards transmission (40, 41), as well as healthcare system readiness. Multiple behavioural and biomedical methods may be used to reduce the risk of HIV transmission, including using a male or female condom during sex, HIV/sexually transmitted infection (STI) testing (32), 'treatment as prevention' (people living with HIV on antiretroviral therapy [ART] achieve undetectable = untransmittable [U=U] status; viral load <200 copies mL prevents sexual transmission to partners) (42), and PrEP (Section B.1.3.2.1).

B.1.3.2.1 *Pre-exposure prophylaxis*

PrEP refers to using ART to prevent HIV among people likely to be exposed to HIV, and is an effective HIV prevention strategy (4, 40, 41, 43). PrEP enables people who are not living with HIV to have autonomy over their own HIV acquisition risk, without relying on a partner to know and disclose their HIV status, achieve an undetectable viral load through access and adherence to ART, or for their partner to implement other HIV prevention strategies alongside safer sex practices (41). Oral PrEP typically involves taking tablets orally daily or in some cases may be off-license event-based or on-demand oral PrEP (i.e. taking tablets before and after an episode of sexual activity) (6, 8, 9). Oral PrEP has been routinely commissioned by the NHS in England since July 2020, prescribed by specialist sexual health services (SHS) (6) (further details are provided in Section B.1.3.5).

The optimal utilisation of PrEP, as part of effective prevention programmes, across all populations likely to be exposed to HIV is critical for achieving the greatest individual- and population-level impact in reducing new HIV diagnoses. However, numerous steps in the PrEP continuum create barriers to optimal utilisation of oral

PrEP. The number of individuals actively using oral PrEP may be affected by barriers to initiation (uptake) and continued use for the prescribed duration (persistence), whereas barriers to adherence (i.e. the extent to which an individual's action matches the agreed recommendations of the prescriber) impact the effectiveness of oral PrEP among those who start it, and adherence to oral PrEP is low in real world settings (15) (further detail is provided in Section B.1.3.6).

B.1.3.3 Epidemiology of HIV and PrEP

HIV remains a major global public health issue (32). United Nations (UN) member states have committed to ending the HIV epidemic by 2030 (44, 45), which has been defined by the Joint United Nations Programme on HIV/AIDS (UNAIDS) as achieving less than 200,000 annual new HIV acquisitions globally (44). The UNAIDs 95-95-95 goals aim to ensure 95% of all people living with HIV know their HIV status, 95% receive sustained ART, and 95% of people receiving ART are virologically suppressed by 2025 (45). A fourth target has also been proposed, to ensure people living with HIV and virological suppression have good HRQoL (46). The HIV Action Plan for England, released in 2021, sets out the UK governments commitment to zero new transmissions of HIV in England by 2030, with an interim commitment to an 80% reduction in transmissions by 2025 (3). Prevention is a core strategy towards achieving these aims, and the HIV Action Plan includes PrEP-specific funding, goals to improve PrEP access in key populations, such as heterosexual and Black African individuals (11, 47), the establishment of a PrEP monitoring and evaluation framework, and the use of novel PrEP modalities (3, 48). The HIV Action Plan notes that PrEP is highly effective when taken as prescribed; however, taking a pill regularly may be challenging for some individuals, and that provision of a wider choice of PrEP methods, including injectables may improve uptake, acceptability, and adherence (3).

In the UK, the HIV treatment cascade continues to exceed the UNAIDS 95-95-95 goals (95%, 99%, 98%) (11, 47, 48); however, HRQoL among people living with HIV is worse than the general population (34). There also remains a significant number of new HIV diagnoses in the UK, with a rise in recent years. In 2022, 4,040 people were newly diagnosed with HIV, a 19% rise from 2021 and 21% rise from 2020 (11). In

total, 44% of diagnoses first made in England in 2022 were late diagnoses[a] (these were particularly high among individuals aged 50–64 years [61%], and individuals of Black African ethnicity [49%]) (11, 47). Individuals living with HIV who are diagnosed late are at greater risk of ill-health, disability, death, and onward transmission (11, 49, 50).

Related to the above, identification of the need for PrEP, initiation and continuation of prophylaxis remains suboptimal in England (Table 3). Furthermore, although 2022 saw improvements in the provision of PrEP, inequalities persist, particularly in relation to ethnicity and gender (11). Further improvements are needed, particularly for women and ethnic minority groups (11, 51). Indeed, Cambiano et al, 2023 has reported that without PrEP introduction, there would have been 2.16 times the number of acquisitions that actually occurred between 2012 and 2022, and if the current level of combination prevention, including PrEP, is maintained, there no chance of reaching the target of eliminating new HIV transmissions by 2030 (defined as fewer than 50 acquisitions among gay, bisexual, and other men who have sex with men), and that enhancing provision of PrEP (as well as HIV testing) can accelerate progress towards this goal (10).

Table 3: PrEP statistics in the UK (2022)

	2021†	2022
Proportion of individuals with PrEP need‡ accessing specialist SHSs	7.5% (88,216 of 1,183,155)	9.7% (121,547 of 1,249,511)
Gay, bisexual, and other men who have sex with men	65.0% (71,581 of 110,121)	68.6% (98,565 of 143,657)
Heterosexual men	1.4% (3,125 of 230,938)	1.8% (4,156 of 228,668)
Heterosexual and bisexual women	0.5% (3,041 of 628,886)	0.8% (4,602 of 595,303)
PrEP need identified¶	79.4% (70,081 of 88,216)	83.2% (101,124 of 121,547)
Initiation or continuation of PrEP among those with PrEP need	70% (61,510 of 88,216)	71% (86,324 of 121,547)
Gay, bisexual and other men who have sex with men	72% (51,689 of 71,581)	74% (72,457 of 98,565)
Heterosexual men	35% (1,080 of 3,125)	39% (1,599 of 4,156)
Heterosexual and bisexual women	24% (716 of 3,041)	36% (1,676 of 4,602)

Source: UKHSA 2023 (11, 47).
†First full year of data for routine NHS provision of oral PrEP; ‡Defined as 'at substantial risk of HIV acquisition

[a] CD4 count <350 cells/mm^3 of blood within 91 days of diagnosis, excluding those with evidence of recent infection (11)

and will benefit from receiving PrEP'; ¶Proportion of individuals not living with HIV with estimated PrEP need who had this need identified.
Abbreviations: HIV, human immunodeficiency virus; NHS, National Health Service; PrEP, pre-exposure prophylaxis; SHS, specialist sexual health services; UK, United Kingdom.

B.1.3.4 Identifying individuals who are likely to acquire HIV: recommendations from the British HIV Association (BHVIA)/ British Association for Sexual Health (BASHH) and HIV guidelines

In the UK, BHIVA/BASHH provides guidelines for identifying individuals who are more likely to acquire HIV who are eligible for PrEP (8):

Table 4: BHIVA/BASHH summary table of recommendations for PrEP

<table>
<tr><th colspan="2">Recommend PrEP</th></tr>
<tr><td colspan="2">• HIV-negative men who have sex with men and trans women who report condomless anal sex in the previous 6 months and on-going condomless anal sex.
• HIV-negative individuals having condomless sex with partners who are HIV positive, unless the partner has been on ART for at least 6 months and their plasma viral load is <200 copies/mL.</td></tr>
<tr><th colspan="2">Consider PrEP on a case-by-case basis</th></tr>
<tr><td>Population-level indicators, including
• Heterosexual Black African men and women
• Recent migrant to the UK
• Transgender women
• People who inject drugs
• People who report sex work of transactional sex</td><td>Clinical indicators:
• Rectal bacterial STI in the previous year
• Bacterial STI or HCV in the previous year
• PEPSE in the previous year; particularly where repeated courses have been used.</td></tr>
<tr><td rowspan="2">Sexual behaviour/sexual network indicators:
• High risk sexual behaviour: reporting condomless sex with partners of unknown HIV status, and particularly where this is condomless anal sex or with multiple partners
• Condomless sex with partners from a population group or country with high HIV prevalence
• Condomless sex with sexual partners who may fit the criteria of 'high risk of HIV'
• Engages in chemsex or group sex
• Reports anticipated future high-risk sexual behaviour
• Condomless vaginal sex should only considered high risk where other contextual factors or vulnerabilities are present</td><td>Drug use
• Sharing injecting equipment
• Injecting in unsafe setting
• No access to needle and syringe exchange programmes or opioid substitution therapy</td></tr>
<tr><td>Sexual Health Autonomy
Other factors that may affect sexual health autonomy
• Inability to negotiate and/or use condoms (or employ other HIV prevention methods) with sexual partners
• Coercive and/or violent power dynamics in relationships (e.g. intimate partner/domestic violence)
• Precarious housing or homelessness, and/or other factors that may affect material circumstances
• Risk of sexual exploitation and trafficking</td></tr>
</table>

Source: Brady 2019 (8).
Abbreviations: ART, antiretroviral therapy; BHIVA/BASHH, British HIV Association/British Association for Sexual Health and HIV; HCV, Hepatitis C virus; HIV, human immunodeficiency virus; PEPSE, post-exposure prophylaxis following sexual exposure; PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection; UK, United Kingdom.

B.1.3.5 Clinical pathway of care

Generic formulations of the combination ART tenofovir disoproxil with emtricitabine (TD/FTC; which may be combined with the salt fumarate [i.e. generic Truvada; TDF/FTC], while other generics may use different salts) is currently considered SoC for people who are not living with HIV but are likely to be exposed (6). In 2023, NHS England's commissioning policy was amended to include another formulation of tenofovir, oral tenofovir alafenamide/emtricitabine (TAF/FTC; Descovy®, Gilead), as a second line option for a limited population of individuals who are intolerant of or contraindicated to TD/FTC[b] (6). TAF/FTC is only licensed for a limited population of at-risk men who have sex with men, including adolescents (with body weight ≥35 kg) (7). Consequently, individuals assigned female sex at birth who are at risk of HIV acquisition from vaginal sex do not have a second-line option available if TD/FTC is not appropriate. Notably, tenofovir disoproxil monotherapy regimens are not licensed as PrEP but according to the BHIVA/BASHH guidelines can be considered only for heterosexual men and women (8); however, the NHS clinical commissioning policy only outlines the use of tenofovir in combination with emtricitabine (6).

Both the NHS clinical commissioning policy (6), and NICE guideline 221 (NG221) (9) consider PrEP eligibility according to the criteria in the BHIVA/BASHH 2018 guidelines (8). An overview of the BHIVA/BASHH guideline recommendations for identifying those who are more likely to acquire HIV is provided in Section B.1.3.4. The guideline's PrEP recommendations for different populations including men who have sex with men, heterosexual men and women, and transgender individuals are summarised in Appendix N, Section N.1.1. Note, PrEP recommendations for people who inject drugs (who are outside of the scope of the decision problem) are also provided by the guidelines (8).

[b] According to the commissioning policy, individuals meeting the PrEP criteria must also be confirmed as eligible for second-line treatment through a local multi-disciplinary team discussion, with shared decision-making regarding the risks and benefits of second-line PrEP, and cannot take usual first-line PrEP due to risk factors for TD/FTC use, including: reduction in estimated glomerular filtration (eGFR <60 mL/min) and clinical assessment suggests TAF/FTC would have a lower risk profile than TD/FTC; or proven renal toxicity with TD/FTC (acute or chronic); or osteoporosis with a high risk for fractures; or <18 years of age; or eGFR ≥60 mL/min in whom there is a progression reduction in glomerular filtration rate on TD/FTC and significant concurrent medical issues or monitoring/prescribing concerns which suggest TAF/FTC would have a lower risk profile than TD/FTC (6).

B.1.3.6 Unmet need

While oral PrEP is available in the UK, some individuals are underserved by current SoC, reflecting an unmet need where people do not or cannot access effective HIV prevention. Unmet needs for healthcare may lead to poor individual health outcomes, high health care costs, and productivity loss to individuals and society (52). A variety of different factors may drive unmet need for PrEP, including population-driven unmet need and system-driven unmet need (53); population-driven factors result in people not entering or accessing the healthcare system, such as age, gender-identity, ethnicity, socio-economic status, health status, knowledge and awareness, stigma, adherence and persistence; system-driven factors result in services not reaching target populations or they drop out of the system, such as policies, barriers to access, and workforce demands and capacity (51). The introduction of alternative PrEP options, such as cabotegravir, are therefore important to help to bolster nationwide prevention programmes, by addressing some of the population-driven factors such as stigma, adherence, and persistence, alongside meeting the individual unmet needs of people who would benefit from PrEP not currently served by the SoC (further details are provided in Sections B.1.3.6.1, B.1.3.6.2, and B.1.3.7).

B.1.3.6.1 *The scale and consequences of PrEP unmet need*

B.1.3.6.1.1 Issues with oral PrEP uptake

During the first full year of data for routine NHS provision of oral PrEP (2021), 70% (n=61,510) of people not living with HIV accessing specialist SHSs in England who were defined as having PrEP need initiated or continued oral PrEP. This number increased slightly to 71% (n=86,324) in 2022 (11), which is insufficient to achieve targets stated in the HIV Action Plan for England (3). Certain populations appear to be particularly unlikely to engage with PrEP in England, such as cisgender and transgender women (54), with clinical experts from large London SHSs at a UK advisory board confirming the majority of PrEP users are white men who have sex with men (55). According to the UK Health Security Agency (UKHSA), initiation or continuation of oral PrEP is low among heterosexual and bisexual women (24% in 2021; 36% in 2022), and heterosexual men (35% in 2021; 39% in 2022) (11). Overall, people of Black African ethnicity represented the lowest proportion of

individuals accessing a SHS defined as having a PrEP need who initiated or continued PrEP (47). Baseline characteristics of the PrEP Impact trial also show that 95.5% (20,403 of the 21,356) trial participants were cisgender men who have sex with men, of whom 76.2% were of White ethnicity, with less than 3% of all trial participants identifying as women, and 1.8% of all trial participants identifying as Black Africans (56).

B.1.3.6.1.2 Issues with oral PrEP adherence

Poor adherence to medications is a pervasive issue (57), and high adherence to oral PrEP is required for it to be effective (8, 12-14), and UK clinicians have stated that most new HIV diagnoses seen in their UK clinics are associated with inconsistent non-adherent dosing (55).

A systematic literature review (SLR) and meta-analysis of randomised controlled trials (RCT) investigating oral PrEP reported that across the identified studies, oral PrEP adherence ranged from 25% to 88%[c] as measured by plasma drug monitoring. Efficacy (as rate ratios) was strongly associated with adherence (measured by proportion with plasma drug detectable; $p<0.001$) (58). On average, a 10% reduction in adherence reduced efficacy by 13% (58). Furthermore, an SLR of studies reporting adherence to PrEP in real-world, non-interventional settings (n=54) found that the majority of individuals taking oral PrEP have low adherence to PrEP (15); only 20 out of 54 identified studies could be determined to have highly adherent participants (based on a definition of adherence of ≥80% representing high adherence as defined by Huic 2023 (59)). However, in 9 of these 20 studies, the high adherence was self-reported, and given that when people are self-reporting adherence, there is a tendency to over-report their adherence to PrEP, consequently 20 out of 54 studies reporting high adherence is likely an overstatement (15).

B.1.3.6.1.3 Issues with oral PrEP persistence

A substantial proportion of individuals on PrEP may discontinue use altogether. An SLR which included studies published up to December 2020 reported a pooled

[c] In this systematic literature review (SLR), adherence refers to the proportion of participants in the trials that adhered to the study drug; a study was defined as highly adherent if ≥80% of participants were adherent, and low adherence as <80% adherent ((58). The meta regression analysis investigating the relationship between efficacy and adherence only included studies that confirmed adherence through plasma drug detection rates

discontinuation rate for PrEP within 6 months of initiation of 41.0% (95% confidence interval [CI]: 18.8, 63.5) globally (16 studies) and 17.4% (95% CI: 13.0, 22.9) in Europe (6 studies) (60). Another United States (US)-based study reported a persistence to TDF/FTC of 70.2% and 57.4% at 6 and 12 months, respectively (61).

Individuals most vulnerable to HIV often use PrEP for shorter periods (62). While many individuals discontinue oral PrEP because of a change in circumstances, which means they are no longer likely to be exposed to HIV, a substantial proportion may be discontinuing for other reasons and remain likely to be exposed (62-64). Those who discontinue PrEP may not re-adjust their behaviour following discontinuation to account for their reduced protection against acquiring HIV, placing them at an ever-greater likelihood of being exposed compared with before they started using PrEP (65). Certain populations, for example women, may also be less likely to persist with oral PrEP (66).

An alternative PrEP option, such as a long acting injectable, for individuals who are unable to persist with daily oral PrEP, may help to improve persistence.

B.1.3.6.2 *Drivers of unmet need: limitations and barriers for use of oral PrEP*

B.1.3.6.2.1 PrEP-related stigma

Stigma is a significant barrier to oral PrEP uptake, adherence, and persistence (16). Stigma may be experienced by both current and prospective PrEP users, taking many forms across multiple levels, including structural stigma, where activities and policies create and maintain social inequalities for people with stigmatised identities, and individual-level stigma (67). Forms of PrEP stigma include enacted stigma (prejudice or discrimination towards a PrEP user as a result of their PrEP use), anticipated stigma (expected or future prejudice and discrimination by others towards PrEP users because of their PrEP use), and internalised stigma (PrEP prejudice and stereotyping towards oneself because of PrEP use) (16).

The use of PrEP can be stigmatised by its association with medications used to treat HIV (reflecting HIV-stigma) (16); this may result in stereotyping, discrimination, and status loss (68). People may also face negative stereotypes and prejudice related to their PrEP use such as being sexually irresponsible, promiscuous, or immoral; expressing resistance to condom use, infidelity, and face a lack of social support

from partners, family or friends (16). Some studies have reported that people may resort to hiding their medication and pill bottles in attempt to conceal that they are taking PrEP, and some people may experience extreme familial reactions, including separation from a spouse or partner (17, 69, 70). One UK study reported nearly one fifth of women reported they had not felt able to use an HIV prevention method despite wanting to (71). In addition, there are currently few feasibly prevention tools for women in violent relationships, as many traditional methods largely rely on a partners co-operation (72). Barriers to PrEP for these women may include potential partner interference (73).

A long-acting injectable PrEP option, such as cabotegravir, offers a more discreet form of protection by eliminating the need for daily dosing and may address the unmet need among individuals who experience stigma associated with PrEP eligibility.

B.1.3.6.2.2 Emotional/psychological challenges and side effects with oral PrEP

Individuals' may experience pill fatigue taking oral PrEP (18), and experience anxiety around the pill burden; a psychological factor among people switching from daily oral PrEP to a long-acting injectable PrEP included the desire to eliminate anxiety around missed dosing, and that an injection would be "less to think/worry about" (19). Furthermore, a real-world cross-sectional survey across five European countries, including the UK, reported the most common reason for individuals unlikely to receive PrEP in the future in the absence of alternative options was not wanting to take daily oral medication (74). People may also have concerns around side effects with oral PrEP (17). In studies across different European settings, one found PrEP users discontinued due to concerns around long-term side effects (24%), and not wanting to take a daily pill (23%) (63). Another reported during the 18 months of follow-up, 64/200 (32.0%) participants interrupted their PrEP regimen (daily or on-demand) temporarily, of whom 11/64 (17.2%) interrupted their regimen due to side effects (75). Overall, 128 participants (daily=96; on-demand=32) reported adverse events possibly, probably or definitely related to oral TDF/FTC as PrEP, with the majority of adverse events being gastrointestinal (GI) in nature (daily=76 [79.2%]; on-demand=23 [71.9%]). Another European real-world survey of PrEP use found the

most frequent physician-reported reasons for PrEP discontinuation included suboptimal adherence and issues around taking oral medications daily (74).

An injectable PrEP with a reduced dosing frequency which alleviates the pill burden associated with daily oral PrEP may address unmet need by improving both uptake, adherence, and persistence to PrEP among individuals for whom oral PrEP is not appropriate.

B.1.3.6.2.3 Other barriers to oral PrEP

An SLR of UK studies investigating modifiable barriers to PrEP delivery reported that in addition to societal stigma surrounding HIV and PrEP (as discussed in Section B.1.3.6.2.1), other barriers include lack of PrEP awareness and knowledge, willingness to use PrEP, access to PrEP provider, and self-perception of HIV risk (76). Another global SLR, investigating the reasons for non-adherence to PrEP reported that in addition to stigma, unacceptable dosing regimen, and concerns around side-effects, other reasons include low risk perception, low decision-making power, and the logistics of daily life (further details are provided in Appendix N, Figure 1) (17).

Importantly, specific populations, such as individuals from ethnic minority groups and heterosexual women, may also be particularly affected by certain barriers to the utilisation of oral PrEP (54, 77-79), which may be due to social and structural determinants of health that create barriers and limit engagement with sexual health services and uptake of PrEP (11). PrEP delivery in the UK is currently inequitable (54), and a study of UK cisgender and transgender women has noted that while HIV prevention efforts are reducing new diagnoses among men who have sex with men, this reduction is not occurring in women (54).

A long-acting injectable PrEP may help to encourage use among populations who face barriers limiting their PrEP utilisation. For example, one study has reported that social-structural factors specific to cisgender women often drove preferences for long-acting PrEP (80).

B.1.3.6.2.4 User Preference

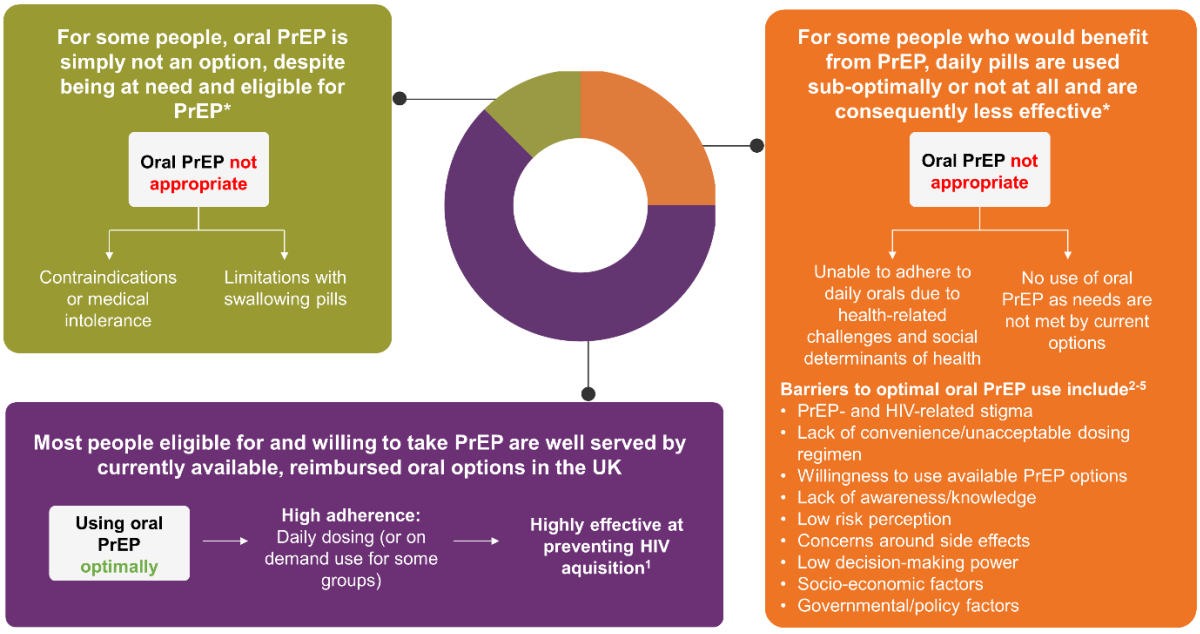
A facet of unmet need is orals being the only available PrEP modality. New modalities could meet the preferences of individuals to improve adherence and health outcomes. User preferences for PrEP, are important determinants of effective

utilisation of PrEP. An SLR of values, preferences, and perceptions of acceptability for injectable PrEP (n=62) reported that there is an overall interest, and often a preference for injectable PrEP, and that this modality may help to address issues with adherence to oral PrEP, and provide an option for individuals seeking privacy, discretion, or infrequent dosing (81). Importantly, people generally prefer to take medications less often, and are more adherent when their treatment regimen aligns with their preferences (57).

B.1.3.7 Position of cabotegravir in the clinical pathway of care

The proposed position of cabotegravir in the clinical pathway of care is as a PrEP option for individuals for whom oral PrEP is not appropriate (Figure 1). The proposed position of cabotegravir addresses some of the unmet needs among these individuals, which are described in Section B.1.3.6.

Figure 1: HIV PrEP unmet need and anticipated position of cabotegravir



***The green and orange boxes represent the anticipated positioning of cabotegravir.**
Sources: 1. Sullivan et al, 2023 (56); 2. Calabrese et al, 2020 (16); 3. Coukan et al, 2023 (76); 4. Sidebottom et al, 2018 (17); 5. National AIDS trust (51).
Abbreviations: HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis; UK, United Kingdom.

Specifically, cabotegravir is the first long-acting injectable PrEP, reducing the number of PrEP doses from 365 per year with daily oral PrEP to just six injections per year. An injectable that is administered less often than tablets, provides an important alternative PrEP method for individuals sub optimally adhering to daily oral PrEP who are therefore not achieving effective protection from HIV acquisition. It

may also increase uptake and persistence among individuals who need PrEP but are not using or continuing to use daily oral PrEP due to the pill burden. Additionally, as cabotegravir must be delivered by a healthcare professional, this provides them with the assurance of adhering to their PrEP regimen as prescribed.

Cabotegravir may help to improve PrEP uptake by providing a new option for people who need PrEP but cannot take current oral options, due to contraindications or medical intolerance. It also provides an alternative option for people who have a limited ability to swallow pills (taking oral cabotegravir prior to initiating injections is optional). In addition, if PrEP options are increased then uptake may be increased, with contraception as an example model (82).

Cabotegravir may also appeal to populations who are currently underrepresented among UK PrEP users but face a high burden of potential HIV diagnoses, such as individuals of Black African ethnicity, transgender women, and cisgender women (Section B.1.4). Additionally, having an injectable option may also provide people who experience PrEP-related stigma with a more discreet protective option as it eliminates the need to conceal a medication bottle; this is in line with the UK HIV Action Plan's objective to address HIV-related stigma (3).

A long-acting injectable PrEP option with superior efficacy versus daily oral PrEP robustly demonstrated through a large evidence base (Section B.2) has the potential to address issues and current unmet need in HIV prevention. In alignment with this goal, the World Health Organization (WHO) have recommended that cabotegravir should be delivered as an additional HIV prevention choice, as part of combination HIV prevention approaches, to support countries in achieving national targets of reducing new HIV acquisitions (83).

B.1.3.8 Burden of HIV

B.1.3.8.1 *Clinical and humanistic burden of HIV*

If preventative interventions are not available or are not effectively implemented, the consequences of HIV acquisition, which impacts on multiple areas of life including health, and functioning, multi-morbidity, HRQoL and psychological and emotional well-being, need to be considered.

Early diagnosis and sustained treatment is key to mitigate the impact of living with HIV on life expectancy, as the life-expectancy of people living with HIV with low CD4 cell counts remains up to 30 years lower than the general population (84). Late diagnoses are increasing in the UK, rising by 27% in 2022 versus 2020, with those diagnosed late in England in 2021 five times more likely to die within a year of their diagnosis compared with those diagnosed promptly (11); late diagnosis is also a risk factor for severe disability (50).

People living with HIV are more susceptible to opportunistic infections, and cancers, and are at a higher risk of developing comorbidities compared with HIV negative counterparts (85-87). Living with HIV also has a significant impact on HRQoL; factors affecting HRQoL include depression, HIV symptom burden, co-infections, HIV-related hospitalisations (88), drug and alcohol dependence, social isolation, difficulties disclosing HIV status, and discrimination (89). People living with HIV can also experience additional challenges of stigma, ageism, income insecurity, and lack of social support, which may impact or intersect with issues of living and ageing with HIV (90-93).

The Positive Voices 2022 survey (n=4,618 people living with diagnosed HIV) found that the population of people living with HIV is ageing with associated multi-morbidity, reporting an increase from 2017 in the prevalence of one or more additional long-term conditions (66.8% vs 60.9%, respectively) (34). A high prevalence of mental health conditions, particularly depression (31.7%) and anxiety (28.5%), was reported, with no reduction since the Positive Voices 2017 survey. Life satisfaction, and quality of life were also found to be worse than the general population, which also remained unchanged since 2017. Stigma also remains high, including feeling ashamed, low self-esteem, avoiding health services, and worry about being treated differently, along with high levels of discrimination, including experiencing physical and sexual violence. Unmet needs were widespread, including health, lifestyle, and social needs.

B.1.3.8.2 *Economic burden of HIV*

HIV is associated with a significant economic burden; therefore, the expansion of PrEP use has the potential to reduce healthcare system spending related to HIV management. The lifetime cost of managing HIV in the UK is estimated to be

~£400,000 (undiscounted) (33). The economic burden of HIV is largely attributable to treatment-associated costs. In 2016/17, the national spending on HIV specialised services in the UK was ~£540 million, with a total spend of £413.7 million on ART (33, 94).

In addition to direct costs, such as hospital costs and outpatient appointments (95), HIV is also associated with indirect costs, for example there is a disproportionate burden of unemployment among individuals living with HIV. The Positive Voices 2022 Survey reported high rates of unemployment among people living with HIV (10%) and one in five (21.7%) were claiming means-tested benefits. Unemployment was highest among people who identified as trans, non-binary or in another way (18.8%), women (14.3%), people of black African ethnicity (13.5%) and those of other minority ethnicities (12.7%) (34). These are key populations with an unmet need for HIV prevention who may experience health inequities (Section B.1.4) Economic inactivity is a risk factor for higher disability severity; it has been associated with significantly increased odds for “severe” and “moderate” disability among adults living with HIV in London (50). The Positive Voices 2022 survey population were also mostly physically inactive, with higher associated health service utilisation, whereby health service utilisation remained unchanged since 2017 (34).

As the economic burden associated with HIV in England is largely accounted for by healthcare costs associated with the management of HIV and AIDS, the impact on NHS resources of preventing further HIV acquisitions is likely to be substantial. Indeed, the costs associated with providing access to PrEP in the UK are likely to be offset by the benefits and savings resulting from preventing HIV and associated costs.

B.1.4 Equality considerations

PrEP is a key strategy for HIV prevention, as detailed in Sections B.1.3.1, B.1.3.2.1 and B.1.3.3. While UK individuals likely to be exposed to HIV currently have access to oral PrEP through the NHS, there are still some health inequities exacerbating unmet need for HIV prevention; these may be experienced by but are not limited to gender diverse populations and ethnic minorities, reflecting the importance of having a larger range of available PrEP modalities, such as a long-acting injectable, for people who would benefit from PrEP, regardless of the characteristics influencing

their risk. There are several key populations who are at risk for, and disproportionately affected by HIV, including groups protected under the Equality Act 2010 on the grounds of: gender identity, ethnicity and sexual orientation. Transgender individuals, women of Black African ethnicity, and gay, bisexual and other men who have sex with men, represent key populations at risk of HIV acquisition. These populations are also disproportionately affected by the wider social, economic, and environmental circumstances that impact on people's health, known as the social determinants of health, which influence health inequities (96, 97), and may experience higher unemployment rates (34).

- **Gender identity:** Globally, trans women and trans feminine individuals are 66 times more likely to acquire and live with HIV, and trans men and trans masculine individuals 6.8 times more likely versus other individuals aged over 15 years (98). In the Global North, including Europe, trans feminine individuals are 48.4 times more likely to acquire and live with HIV (98). Individual level risk factors significantly increase the risk of HIV acquisition, including condomless sex, coinfections with other STIs, transactional sex, and shared use of needles for hormone and/or silicon injections. Individual risk factors intersect with and result from other factors such as mental health challenges, substance use, and many forms of marginalisation and stigmatisation that limit, among other things, educational and work opportunities. Among people living with HIV, unemployment was highest among people who identified as trans, non-binary or in another way (18.8%) (34).
- **Ethnicity** (particularly people of Black African ethnicity and people coming to the UK from countries with a high HIV prevalence): In England in 2022, 36% (1,361) of new HIV diagnoses were in individuals previously diagnosed abroad, of which 44% (605 of 1,361) were people of Black African ethnicity (11, 47). In addition, people of Black African ethnicity constitute the second largest ethnic group of those first diagnosed with HIV in England (476 of 2,444 [19.5%]), and the largest in people exposed by sex between men and women (374 of 976 [38%]), increasing by 15% from 2021. In addition, Black African women represent the largest ethnic group of women first diagnosed in England (701 of 1,391). People of Black African ethnicity are also at higher risk of living with undiagnosed HIV in England (99). In addition, of all ethnic groups, people of

Black ethnicity had the highest diagnosis rate of new sexually transmitted infections in 2022, reflecting a need for HIV prevention (100). This trend is likely influenced by underlying socio-economic factors and the role they play in the structural determinants of health (100).

- **Sexual Orientation:** In England in 2022, men exposed through sex between men accounted for the largest proportion (30%) of new HIV diagnoses first made in England (724 of 2,444) (11). In England, gay, bisexual and other men who have sex with men represent the largest group of people living with undiagnosed HIV (99). Despite a reduction in new HIV diagnoses in England between 2014 and 2019 (3), an increasing trend in late diagnosis is observed among gay, bisexual and other men who have sex with men, from 30% in 2020, to 36% in 2021; this rise was sustained at 37% in 2022 (11), whereby late diagnosis is associated with greater risk of ill-health, disability, death, onward transmission and high healthcare costs (97). STIs continue to rise in incidence among gay, bisexual, and other men who have sex with men, and this population has been vulnerable to other infections such as the monkeypox outbreak and other less frequently reported STIs (100).

Inequities also exist in relation to differential uptake of PrEP. Knowledge/ awareness of PrEP is low among Black African men and cisgender women compared with gay, bisexual, and other men who have sex with men counterparts, and individuals may have misconceptions around what PrEP is, who it is for, and how it is accessed (101). UK surveys suggest cisgender and transgender women's engagement with PrEP services/uptake is low (51, 54). Barriers include poor awareness and acceptability, stigma (the impact of which is further discussed in Section B.1.3.6.2.1), ethnicity, restricted access to PrEP and exclusion from clinical trials (54). Clinical experts have confirmed in a UK advisory board that most of their PrEP users are White men who have sex with men, and that work is required to encourage PrEP uptake among women and other minority groups (55).

Oral PrEP is also not optimally meeting needs of all people who can benefit from PrEP. Currently, the only available method of administration for PrEP is oral tablets; there are individuals who could benefit from PrEP who are underserved by current options for a variety of reasons, including intolerance and medical contraindications,

fear of side effects, the requirement to take a pill regularly and a limitation to swallowing pills, the need to keep medication bottles hidden from other people due to stigma associated with PrEP eligibility, and concerns around side effects and perceived poor efficacy (17, 18, 62, 63, 102-113). PrEP stigma is a barrier to PrEP interest, uptake, and persistence, meaning individuals who would benefit from using PrEP are not able to experience that benefit due to fear or shame (16). HIV-related stigma is a commonly cited barrier to PrEP use. In a study of people of Black African heritage, 65% cited stigma as a major barrier to the uptake of PrEP (114). The reduction of PrEP stigma and its negative impact requires a shift in perspective, language, and programmes. Such a shift is necessary to ensure effective PrEP uptake and improve its utilisation by the individuals who need it most. Although PrEP stigma is often experienced at the community level (i.e., by potential and current users), it can be reinforced and even amplified by public health programmes, policy, and research. PrEP stigma disproportionately impacts disadvantaged groups and impedes scalability by influencing behaviour of both patients and healthcare professionals (115). The availability of a long-acting injectable PrEP may help to allay concerns around stigma and acceptability by removing the need for daily oral pills.

B.2 Clinical effectiveness

The efficacy and safety of cabotegravir for PrEP has been robustly demonstrated by two large randomised controlled trials (RCT), including:

- HPTN 083, a Phase 2b/3 RCT in adult (≥18 years) cisgender men and transgender women who have sex with men at risk of acquiring HIV (n=4,570).
- HPTN 084, a Phase 3 RCT in adults (aged 18–45 years) assigned female sex at birth at risk of acquiring HIV (n=3,224).
- Both trials included an up to 5-week oral lead-in phase, and a blinded injection phase, which was stopped early due to meeting pre-defined stopping criteria based on demonstrating superior efficacy versus daily oral PrEP. The trials are currently ongoing as open-label extensions, following an additional year of unblinded follow-up where participants received their randomly assigned study regimen without placebo while the study protocols were amended.

In both trials, cabotegravir demonstrated a statistically significant, superior reduction in incident HIV acquisitions compared with daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC).

- In the primary analysis of the blinded period (modified intention-to-treat [mITT]), cabotegravir demonstrated a 66% reduction versus TDF/FTC in the number of incident HIV acquisitions in HPTN 083 ($p<0.0001$) and an 88% reduction in HPTN 084 ($p<0.0001$).
- Post hoc-analyses, using extended retrospective virologic testing to better characterise the timing of HIV acquisitions revealed one case in the cabotegravir arm of each trial as a baseline infection, resulting in a revised reduction of 69% ($p=0.0003$) in HPTN 083 and 90% ($p<0.0001$) in HPTN 084.
- Superior efficacy was maintained during the additional year of unblinded follow-up; in an analysis of combined data from Steps 1 and 2 plus one year of unblinded follow-up, cabotegravir demonstrated a 66% reduction ($p<0.0001$) in HIV acquisitions versus TDF/FTC in HPTN 083, and an 89% reduction in HPTN 084.

Integrase strand transfer inhibitor (INSTI) resistance was very rare overall in the cabotegravir arm of HPTN 083, with no cases detected in HPTN 084. No participants who acquired HIV during the pharmacokinetic tail phase developed INSTI resistance.

- In HPTN 083, five cases of INSTI resistance were detected at the time of the post-hoc analysis of the blinded period; 10 cases detected from baseline until the end of one additional year of unblinded follow-up.
- In HPTN 083, from baseline to the end of unblinded follow-up, INSTI resistance was detected in all rare cases of breakthrough infections in the setting of on-time injections (n=6), in 2 individuals who initiated or re-initiated cabotegravir long acting (LA) with undiagnosed HIV, and in 2 during the oral lead-in.
- In HPTN 084, no INSTI resistance was observed in the cabotegravir arm.
- No participant in either trial who acquired HIV during the pharmacokinetic tail phase (i.e. the 16 cases of HIV acquisition that occurred >6 months since the last cabotegravir exposure) was found to have developed resistance to cabotegravir or other INSTIs.

Cabotegravir offers an adherence advantage by removing the need for daily oral pills.

- During the blinded phase in HPTN 083, 91.5% of person-years (PY) were considered to have been 'covered' by cabotegravir LA injections, while [redacted] participants had plasma tenofovir concentrations consistent with receipt of ≥4 TDF/FTC doses per week (≥4.2 ng/mL)[d].
- During the blinded phase in HPTN 084, 93% of PYs were considered to have been covered by cabotegravir LA injections, while 41.9% of plasma

samples yielded plasma TFV concentrations consistent with seven doses per week (≥40 ng/mL).

Suboptimal adherence in the TDF-FTC arm was observed in both trials. In both trials, cabotegravir was generally well-tolerated, with similar overall frequencies of adverse events (AEs), Grade 2–5 AEs, drug-related AEs, and AEs leading to discontinuation of study drug compared with the daily oral TDF/FTC arm, except for injection site reactions (ISRs).

- In HPTN 083, drug-related ISRs were reported in 81% of participants in the cabotegravir arm. However, ISRs were generally mild (Grade 1–2) and of short duration, with 2% (47 participants) in the cabotegravir arm discontinuing injections as a result of ISRs.
- In HPTN 084, drug related ISRs were reported in 38% of participants in the cabotegravir arm. However, ISRs were generally mild (Grade 1–2) and of short duration, with no study drug discontinuations due to ISRs.

In both trials, most participants transitioning into the open-label extension (OLE) phase chose cabotegravir over daily oral TDF/FTC.

- In HPTN 083, overall, 95.9% of US participants chose cabotegravir LA (96.9% in the cabotegravir arm; 94.8% in the TDF/FTC arm).
- In HPTN 084, 78% of participants chose cabotegravir LA (89% in the cabotegravir arm; 68% in the TDF/FTC arm).

The results of an indirect comparison demonstrate that cabotegravir is [redacted] in reducing the risk of HIV acquisition when compared with no PrEP.

- As HPTN 083 and HPTN 084 did not include a placebo arm, an indirect comparison of cabotegravir with no PrEP was conducted via a common comparator of TDF/FTC, including an adherence model. The relationship between TDF/FTC effectiveness and adherence was derived from a meta-regression.
- The results of the indirect comparison of cabotegravir versus no PrEP demonstrate that the effectiveness in reducing the risk of HIV acquisition is [redacted] across both trial populations with a relative HIV risk reduction of [redacted] in men who have sex with men and transgender women, and [redacted] in cisgender women.

Overall, the availability of an additional PrEP modality, which demonstrates superior efficacy to daily oral PrEP, can help to address unmet needs such as stigma, and suboptimal uptake, adherence, and persistence to oral PrEP.

[d] Pharmacological modelling suggests a minimum of six tablets per week are required to provide protection in vaginal tissue (116), while clinical studies among men who have sex with men indicate that adherence to four doses per week is required for effective protection from HIV acquisition (116-118).

B.2.1 Identification and selection of relevant studies

An SLR was conducted to identify relevant studies investigating the clinical efficacy of oral and long-acting PrEP in individuals at increased risk of HIV acquisition. The SLR identified 19 RCTs, previously described in an SLR by Huic 2023 (59). Appendix D contains the full details of the process and methods used in the clinical effectiveness SLR.

B.2.2 List of relevant clinical effectiveness evidence

The primary sources of evidence for the efficacy and safety of cabotegravir for PrEP considered by the submission are:

- **HPTN 083**[e]: A Phase 2b/3 RCT in adult (≥18 years) cisgender men and transgender women who have sex with men at risk of acquiring HIV (119) (Table 6).
- **HPTN 084**[f]**:** A Phase 3 RCT in adults (aged 18–45 years) assigned female sex at birth at risk of acquiring HIV (120) (Table 6).

Sources used for the data presented in this submission are summarised in Table 5. HPTN 083 and HPTN 084 are considered the primary sources of evidence from the clinical trial programme for decision making due to the outcomes reported.

Supportive evidence is provided by the Phase 2 trials, HPTN 083-01 and HPTN 084-01, evaluating the safety, tolerability, and acceptability of cabotegravir for adolescents (under the age of 18 years) assigned male or female at birth, respectively, as the license includes adolescents ≥35 kg (summarised in Appendix M). Other evidence, relevant to implementation considerations, is provided by the HPTN 083-02 sub-study exploring trial experiences, barriers to adherence, and other factors impacting study implementation or outcomes (Section B.2.6.1.4). Note, there are also published modelling analyses of the HPTN trials estimating the effectiveness of cabotegravir PrEP versus no PrEP (121, 122) (further details are provided in Section B.2.9).

[e] Sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), and jointly funded by NIAID and ViiV Healthcare
[f] Jointly funded by NIAID, and the National Institute of Mental Health (NIMH), the Bill & Melinda Gates Foundation and ViiV Healthcare
HPTN 083 and HPTN 084 are being conducted by the HPTN, with study product provided by ViiV Healthcare and Gilead Sciences

Table 5: Overview of the key clinical evidence sources informing the submission

Trial	Sections	Primary endpoint analyses summary	Key references
HPTN 083	B.2.3, B.2.6.1, B.2.7.1.1, B.2.10.1	• Primary analysis (mITT) • Post-hoc analysis using extended retrospective virologic testing to better characterise the timing of HIV acquisition (mITT, extended retrospective testing) • Updated analysis, incorporating data from one additional year of unblinded follow-up	HPTN 083 clinical study report (123), Landovitz et al, 2022 (119), Marzinke et al, 2022 (124), Marzinke et al, 2023 (125), and Landovitz et al, 2023 (126) and HPTN 083 clinical study report
HPTN 084	B.2.3, B.2.6.2, B.2.7.1.2, B.2.10.2		HPTN 084 clinical study report (127), and Delany-Moretlwe et al, 2022 (120)

Abbreviation: HIV, human immunodeficiency virus; HPTN, HIV Prevention Trials Network; mITT, modified intention-to-treat.

Table 6: Clinical effectiveness evidence

Study	HPTN 083 (NCT02720094) (119, 123)	HPTN 084 (NCT03164564) (120, 127)
Study design	Phase 2b/3, multicentre, randomised (1:1), double blind, double-dummy, active-controlled, non-inferiority trial	Phase 3, multicentre, randomised (1:1), double-blind, double-dummy, active-controlled, superiority trial
Population	Adult (≥18 years of age) cisgender men and transgender women who have sex with men at high risk† of acquiring HIV	Adults (aged 18–45 years) assigned female sex at birth at risk† of acquiring HIV
Intervention(s)	Active cabotegravir with TDF/FTC placebo	
Comparator(s)	Active TDF/FTC with cabotegravir placebo	
Indicate if study supports application for marketing authorisation	Yes	Yes
Indicate if study used in the economic model	Yes	Yes
Rationale if study not used in model	N/A	N/A
Reported outcomes specified in the decision problem	• **Number of documented incident HIV acquisitions‡** • **Adverse effects of treatment** • Changes in renal function • Changes in liver function • Changes in bone mineral density • Incidence of resistance mutations	• **Number of documented incident HIV acquisitions‡** • Adverse effects of treatment • Changes in renal function • Changes in liver function • Incidence of resistance mutations

Study	HPTN 083 (NCT02720094) (119, 123)	HPTN 084 (NCT03164564) (120, 127)
All other reported outcomes	• Adherence to study product • Acceptability scale assessments • Changes in weight, blood pressure, fasting glucose, and fasting lipids • Change in sexual risk behaviour • Incidence of STIs	• Adherence to study product • Survey of attitudes and willingness to use PrEP • Changes in weight • Change in sexual risk behaviour • Changes in weight, blood pressure, fasting glucose, and fasting lipids • Incidence of STIs • Pregnancy incidence, outcomes, and pregnancy-related AEs

Outcomes included in the economic model are in bold.
†For full details on definition of at high risk in HPTN 083 and at risk in HPTN 084 see Table 7; ‡The clinical trial documents, including the protocols and CSRs use 'infection'; however, acquisition is used in the submission to align with language recommended in the People First Charter (1).
Abbreviations: HIV, human immunodeficiency virus; HPTN, HIV Prevention Trials Network; N/A, not applicable; PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

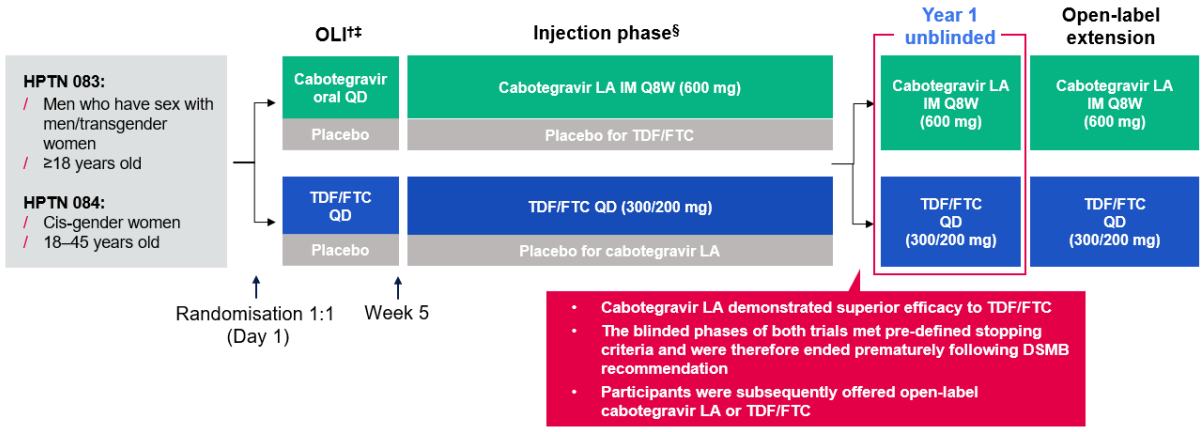
A summary of the methodology of HPTN 083 and HPTN 084 is provided in Table 7. The trials were originally designed to include three phases:

- **Step 1:** up to 5-week blinded oral tablet lead-in phase (to investigate cabotegravir tolerability, allowing for delays in return of Week 4 testing results; note, only participants with ≥50% adherence to oral tablets were permitted to proceed to Step 2, and participants who acquired HIV during this step permanently discontinued the study product, and were terminated from the study and referred for HIV-related care).
- **Step 2:** Blinded injection phase.
- **Step 3:** Open-label tail phase (to cover the pharmacokinetic [PK] tail of cabotegravir long acting [LA] injections), after which patients were to be transitioned to local HIV prevention services.

In both trials, data were reviewed every 6 months by an independent Data and Safety Monitoring Board (DSMB). On review of the results of the first pre-planned interim analysis in HPTN 083 (14th May 2020), and the second pre-planned interim analysis in HPTN 084 (5th November 2020), the blinded portion of the trials (Step 1 and 2) met the pre-defined stopping criteria and were stopped early. This was based

on recommendations from the independent DSMBs, which concluded that the pre-specified criteria for stopping the trials due to efficacy had been met (pre-specified HIV acquisition event numbers) (119, 120). After the trials were unblinded, instead of transitioning to the original protocol-defined Step 3 (detailed in Table 7), participants received their randomly assigned study regimen without placebo for 1 year, until the study protocols were amended. Study sites then transitioned to open label extension (OLE) studies (HPTN 083, April 2021; HPTN 084, November 2021), where participants had the option to continue their original randomised PrEP regimen or switch to the other regimen. Both OLEs are currently ongoing. A study design schematic is provided in Figure 2.

Figure 2: Schematic of HPTN 083 and HPTN 084 study design



†Oral tablets received QD for 5 weeks to verify safety of cabotegravir prior to injections. Active and PBO tablets and injections look alike to ensure blinding of staff and participants; ‡Active and PBO tablets and injections look alike to ensure blinding of staff and participants; §First two injections are 4 weeks apart, then Q8W thereafter. Abbreviations: DSMB, data safety monitoring board, HPTN: HIV Prevention Trials Network; IM, intramuscular; LA, long acting; OLE, open-label extension; Q8W, every 8 weeks; PBO, placebo; QD, once daily; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

Table 7: Summary of trial methodology for HPTN 083 and HPTN 084

Trial	HPTN 083 (119, 123, 128)	HPTN 084 (120, 127, 129)
Trial design	Ongoing, Phase 2b/3, multicentre, randomised (1:1[†]), double blind, double-dummy, active-controlled, non-inferiority trial	Ongoing, Phase 3, multicentre, randomised (1:1[†]), double-blind, double-dummy, active-controlled, superiority trial

Eligibility criteria for participants	**Key inclusion criteria**
	• Cisgender men and transgender women who have sex with men ≥18 years or older at the time of screening (male at birth)
	• At high risk for sexually acquiring HIV based on self-report of at least one of the following:
	  ○ Any condomless receptive anal intercourse in the 6 months prior to enrolment (condomless anal intercourse within a monogamous HIV seronegative concordant relationship does not meet this criterion)
	  ○ More than five partners in the 6 months prior to enrolment (regardless of condom use and HIV serostatus, as reported by the enrolee)
	  ○ Any stimulant drug use in the 6 months prior to enrolment
	  ○ Rectal or urethral gonorrhoea or chlamydia or incidence syphilis in the 6 months prior to enrolment
	  ○ SexPro score of ≤16 (US sites only)
	• In general good health as evidenced by clinical and laboratory assessments (from specimens obtained within 45 days prior to study enrolment)
	  ○ Non-reactive/negative HIV test results[¶]
	  ○ Haemoglobin >11 g/dL
	  ○ Absolute neutrophil count >750 cells/mm^3
	  ○ Platelet count ≥100,000/mm^3
		Key inclusion criteria
		• Born female
		• 18–45 years of age at the time of screening
		• Non-reactive HIV test results at screening and enrolment[¶]
		• Sexually active (i.e. vaginal intercourse on a minimum of 2 separate days in the 30 days prior to screening)
		• Score of ≥5 using a modified VOICE risk score (130)
		• Creatinine clearance ≥60 mL/min (using Cockcroft-Gault equation; using sex at birth for calculation)[§]
		• HBsAg negative and accepts vaccination
		• ALT <2x ULN and total bilirubin ≤2.5x ULN
		• HCV antibody negative
		• If of reproductive potential, must have a negative βHCG pregnancy test (sensitivity of ≤25 mIU/mL) performed (and results known) on the same day as and before initiating the protocol-specified study products at enrolment
		• Had documented evidence of surgical sterilisation or documented evidence of no uterus, or must agree to use a reliable form of long-acting contraception, during the trial and for 52 weeks after stopping the long-acting injectable, or 30 days after stopping the oral study product (including IUD, or IUS [meeting <1% failure rate as stated in the product label] or hormone-based contraceptive [implant or injectable; meeting <1% failure rate when used consistently and correctly as stated in the label]
		Key exclusion criteria
		• One or more reactive HIV test result at screening or enrolment, even if HIV acquisition is not confirmed
		• Pregnant or currently breastfeeding, or intends to become pregnant and/or breastfeed during the study

Trial	HPTN 083 (119, 123, 128)	HPTN 084 (120, 127, 129)
	○ Calculated creatinine clearance ≥60 mL/minute using the Cockcroft-Gault equation (use sex at birth for calculation)§ ○ ALT <2x ULN ○ Total bilirubin <2.5x ULN ○ HBsAg negative ○ HCV Ab negative ○ No Grade 3 or higher laboratory abnormalities on any laboratory tests **Key exclusion criteria** • One or more reactive HIV test result at screening or enrolment, even if HIV acquisition was not confirmed • Active or recent use of illicit IV drugs (within 90 days before enrolment) • Past/current participation in the active treatment group of an HIV vaccine trial (past participation in a monoclonal Ab study was not exclusionary) • Clinically significant CVD • Current or chronic history of liver disease or known hepatic or biliary abnormalities • Coagulopathy which wound contraindicate IM injection • Known or suspected allergy to any of the study product components • Buttock implants or fillers • History of seizure disorder • QTc interval (B or F) of >500 msec	• Current or past enrolment in an HIV vaccine or broadly neutralising antibody trial • Current or chronic history of liver disease or known hepatic or biliary abnormalities • History of seizure disorder • Clinically significant CVD • Coagulopathy which would contraindicate IM injection • Known or suspected allergy to any of the study product components • If potentially able to conceive, unwilling to adhere to long-acting contraception (IUD/IUS, injection, or implant) with a <1% failure rate when used consistently and correctly as stated in the product package insert/ manufacturer's guidelines
Settings and location where data were collected	43 sites in the US, Latin America, Asia, and Africa	20 sites in 7 countries in sub-Saharan Africa (Botswana, Eswatini, Kenya, Malawi, South Africa, Uganda, and Zimbabwe)

Trial	HPTN 083 (119, 123, 128)	HPTN 084 (120, 127, 129)
Concomitant medications	**Precautionary and prohibited medications** • Cabotegravir ○ Not to be administered concurrently: cytotoxic chemotherapy or radiation therapy, barbiturates, carbamazepine, oxcarbazepine, phenytoin, phenobarbital, rifabutin, rifampin, rifapentine, St John's wort ○ Prohibited within 7 days before and 7 days after injection: high dose aspirin (>325 mg per day), anagrelide, apixaban, argatroban, bivalirudin, clopidogrel, dabigatran, dalteparin, enoxaparin, fondaparinux, heparin, lepirudin, prasugrel, rivaroxaban, ticagrelor, ticlopidine, warfarin ○ Oral formation precautions: antacid products containing divalent cations must be taken at least 2 hours before or at least 4–6 hours after cabotegravir oral administration • TDF/FTC ○ Medications containing the following ingredients should not be administered concurrently: emtricitabine or tenofovir disoproxil fumarate, lamivudine, adefovir, tenofovir alafenamide, didanosine, atazanavir, ledipasvir/sofosbuvir, darunavir, lopinavir/ritonavir, orlistat	
Trial phases and drugs	Step 1 (oral tablet lead-in phase) to assess tolerability • Participants received blinded daily oral tablets for up to 5 weeks[††] ○ **Intervention:** Oral cabotegravir (one 30 mg tablet orally daily for up to 5 weeks, with or without food) and PBO for TDF/FTC (one tablet orally daily for 5 weeks with or without food) ○ **Comparator*:*** TDF/FTC 300 mg/200 mg fixed dose combination tablet (one tablet orally daily for 5 weeks, with or without food) and placebo for oral cabotegravir (one tablet orally daily for 5 weeks, with or without food) ▪ *Participants who took ≥50% of the oral tablets in Step 1 (as determined by pill count) and had acceptable laboratory results progressed to Step 2* ▪ *Participants who acquired HIV during Step 1 permanently discontinued the study product and were terminated from the study and referred to HIV-related care* Step 2 (injection phase) • Participants were to receive injections and daily oral tablets until Week 153 (~3 years from the date of the enrolment visit) in HPTN 083 or for up to 185 weeks in HPTN 084 ○ **Intervention:** cabotegravir LA 600 mg administered as one 3 mL IM injection in the gluteal muscle at two time points Q4W then Q8W thereafter and PBO for TDF/FTC tablet (one tablet orally daily, with or without food) ○ **Comparator:** TDF/FTC 300 mg/200 mg fixed dose combination tablet (one tablet orally daily with or without food) and PBO for cabotegravir LA (intralipid 20% fat emulsion infusion) administered as one 3 mL IM injection in the gluteal muscle at two time points Q4W then Q8W thereafter ▪ *In HPTN 083, participants who acquired HIV during Step 2 permanently discontinued the study product, were referred for immediate suppressive ART, and after 52 weeks were terminated from the study (and transitioned to continued HIV-related care) after quarterly monitoring of safety parameters, CD4 cell count and HIV viral*	

Trial	HPTN 083 (119, 123, 128)	HPTN 084 (120, 127, 129)
	load. Any participant who received at least one injection and discontinued injections prior to Week 153 was offered open-label TDF/FTC (Step 3 regimen) for 48 weeks, provided there were no clinical contraindications ▪ *In HPTN 084, any participant who acquired HIV during Step 2 permanently discontinued study product, was referred for care, and was followed at quarterly intervals for approximately 48 weeks. Participants who prematurely discontinued study product during Step 2 for any reason other than HIV acquisition were transitioned to open-label daily oral TDF/FTC for 48 weeks during Step 2 follow-up and then retained in annual testing for the duration of Steps 2 and 3* **Step 3 (tail phase)** • In both study arms, open-label daily oral TDF/FTC 300 mg/200 mg fixed dose combination tablet was to be offered at the end of Step 2, and was intended to be continued for 48 weeks (to cover the PK tail for patients receiving cabotegravir LA) • Upon early stopping of the blinded period of the trials, 19 individuals in HPTN 083, and no individuals in HPTN 084 had entered the protocol-defined Step 3 • After early stopping and unblinding, participants continued to receive their randomised study drug for 1 year while awaiting implementation of the OLE **OLE** • Participants were offered a choice of open-label daily oral TDF/FTC or cabotegravir LA, dependent on whether the participant wished to initiate or continue on cabotegravir LA, which group the participant was originally randomised to and whether the participant had completed the oral cabotegravir lead-in • For participants randomised to TDF/FTC wishing to initiate cabotegravir LA, there was an optional daily oral cabotegravir lead-in for ~4 weeks • Participants initiating cabotegravir LA for the first time (with or without oral lead-in) or participants who were eligible to re-start cabotegravir required a reloading dose of 2 injections, 4 weeks apart followed by cabotegravir LA injections Q8W In both trials, HIV testing, adherence, and risk-reduction counselling, and offer of condoms were provided at each study visit	
Primary outcomes (including scoring methods and timings of assessments)	**Primary efficacy outcome: The number of documented incident HIV acquisitions in Steps 1 and 2** • mITT analysis was used as the primary assessment (where participants determined to be HIV infected prior to randomisation were omitted from the analyses) • The HIV incidence rate was calculated as the total number of participants with confirmed incident HIV acquisition	**Primary efficacy outcome: The number of documented incident HIV acquisitions in Steps 1 and 2** • mITT analysis was used as the primary assessment (where participants determined to be HIV infected prior to randomisation were omitted from the analyses) • The HIV incidence rate was calculated as the total number of participants with confirmed incident HIV

Trial	HPTN 083 (119, 123, 128)	HPTN 084 (120, 127, 129)
	during study follow-up of Step 1, Step 2 (including time off randomised study product) up through 3 years from enrolment, divided by the PYs accumulated in each arm	acquisition during study follow-up of Step 1 and Step 2 (through the termination of the blinded portion of the trial) divided by the PYs accumulated in each arm
Other pre-specified outcomes used in the economic model/specified in the scope	• The number of documented incident HIV acquisitions in Step 2 • **Adverse effects of treatment** • Renal function as measured by change from baseline in creatinine and creatinine clearance levels • Liver function (as measured by changes from baseline in Grade 3 or 4 treatment-emergent liver enzyme abnormality observations) • Bone mineral density (as measured by changes in Z-score from baseline and DXA criteria for osteopenia and osteoporosis) • **Incidence of resistance mutations** (including but not limited to K65R, M184V/L, Q148R) among individuals who acquired HIV • **Adherence to study oral PrEP** (as measured by plasma and/or DBS levels of TDF in participants randomised to TDF/FTC)	• The number of documented incident HIV acquisitions in Step 2 • Adverse effects of treatment • Incidence of resistance mutations (including but not limited to K65R, M184V/L, Q148R)

Trial	HPTN 083 (119, 123, 128)	HPTN 084 (120, 127, 129)
Pre-planned subgroups	Incident HIV acquisitions in Steps 1 and 2 was analysed by important participant subgroup factors including: • Region • Age • Ethnic group • Gender identity • Baseline risk based on median number of sexual partners or median report of condomless receptive anal sex	Incident HIV acquisitions in Steps 1 and 2 was analysed by important participant subgroup factors including: • Age • BMI

Outcomes used in the economic model are in bold. †Stratified according to site; performed with the use of permuted blocks of 8, 10, or 12; ¶All HIV test results from the screening visit must be obtained and must all be negative/non-reactive. This includes testing for acute HIV infection, which must be performed within 14 days of enrolment. In addition, at least one HIV test result using blood drawn at the enrolment visit must be obtained prior to provision of study product and must be negative/non-reactive. Individuals who have one more reactive or positive HIV test result(s) were not enrolled, even if subsequent confirmatory testing indicated that they are not HIV infected; §Not protocol exclusionary, however sites should carefully consider the advisability of enrolling participants with calculated creatinine clearance 60–70 mL/min, as limited changes in creatinine clearance during study conduct could lead to protocol-mandated product holds and may alter the risk-benefit consideration of study participation; ††To allow for any delays in return of Week 4 testing results.

Abbreviations: Ab, antibody; ALT, alanine aminotransferase; ART, antiretroviral therapy; βCHG, beta-human chorionic gonadotrophin; BMI, body mass index; CVD, cardiovascular disease; DBS, dried blood spot; DXA, dual-energy x-ray absorptiometry; HBsAg, Hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HPTN, HIV Prevention Trials Network; IM, intramuscular; IUD, intrauterine device; IUS, intrauterine system; IV, intravenous; mITT, modified intention-to-treat; OLE, open-label extension; PBO, placebo; PK, pharmacokinetic; PY, person years; QTc, QT corrected for heart rate; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine; ULN, upper limit of normal; US, United States.

B.2.3.1 Baseline characteristics

B.2.3.1.1 *HPTN 083*

Key participant characteristics at baseline for HPTN 083 are presented in Table 8, and were generally well balanced between arms.

Table 8: HPTN 083: baseline participant characteristics (ITT)

Baseline characteristic	HPTN 083		
	Cabotegravir group (N=2,282)	Daily oral TDF/FTC group (N=2,284)	Overall (N=4,566)
Cohort, n (%)			
Cisgender men who have sex with men	2,013 (88.2)	1,979 (86.6)	3,992 (87.4)
Transgender women who have sex with men	266 (11.7)	304 (13.3)	570 (12.5)
Participants preferred not to answer	3 (0.1)	1 (<0.1)	4 (0.1)
Age category, n (%)			
18–29 years	1,572 (68.9)	1,508 (66.0)	3,080 (67.5)
30–39 years	498 (21.8)	550 (24.1)	1,048 (23.0)
40–49 years	145 (6.4)	170 (7.4)	315 (6.9)
50–59 years	60 (2.6)	50 (2.2)	110 (2.4)
≥60 years	7 (0.3)	6 (0.3)	13 (0.3)
Age, years			
Median (IQR)	26 (22–32)	26 (22–32)	26 (22–32)
Latinx or Hispanic ethnic group, according to geographic region, n/N (%)[†]			
US			
Yes	149/849 (17.6)	154/849 (18.1)	303/1,698 (17.8)
No	700/849 (82.4)	694/849 (81.7)	1,394/1,698 (82.1)
Missing	0	1/849 (0.1)	1/1,698 (<0.1)
Latin America			
Yes	894/980 (91.2)	912/984 (92.7)	1,806/1,964 (92.0)
No	86/980 (8.8)	72/984 (7.3)	158/1,964 (8.0)
SexPro score, according to geographic region, n/N (%)[‡]			
US			
≤16	729/849 (85.9)	718/849 (84.6)	1,447/1,698 (85.2)
>16	120/849 (14.1)	131/849 (15.4)	251/1,698 (14.8)
Latin America			
≤16	825/980 (84.2)	850/984 (86.4)	1,675/1,964 (85.3)
>16	155/980 (15.8)	134/984 (13.6)	289/1,964 (14.7)
Geographic region, n (%)			
US	849 (37.2)	849 (37.2)	1,698 (37.2)
Latin America			
Argentina	169 (7.4)	168 (7.4)	337 (7.4)
Brazil	395 (17.3)	401 (17.6)	796 (17.4)
Peru	416 (18.2)	415 (18.2)	831 (18.2)
Asia			
Thailand	275 (12.1)	278 (12.2)	553 (12.1)
Vietnam	100 (4.4)	99 (4.3)	199 (4.4)

Baseline characteristic	HPTN 083		
	Cabotegravir group (N=2,282)	Daily oral TDF/FTC group (N=2,284)	Overall (N=4,566)
Africa	78 (3.4)	74 (3.2)	152 (3.3)
Ethnicity, according to geographic region, n/N (%)†			
US			
Black	411/849 (48.4)	434/849 (51.1)	845/1,698 (49.8)
Non-black	437/849 (51.5)	414/849 (48.8)	851/1,698 (50.1)
Missing	1/849 (0.1)	1/849 (0.1)	2/1,698 (0.1)
Latin America			
Black or mixed	198/980 (20.2)	194/984 (19.7)	392/1,964 (20.0)
Indigenous	435/980 (44.4)	427/984 (43.4)	862/1,964 (43.9)
Asian	6/980 (0.6)	2/984 (0.2)	8/1,964 (0.4)
White	319/980 (32.6)	340/984 (34.6)	659/1,964 (33.6)
Other	22/980 (2.2)	21/984 (2.1)	43/1,964 (2.2)
Asia			
Asian	374/375 (99.7)	375/377 (99.5)	749/752 (99.6)
Other	1/375 (0.3)	2/377 (0.5)	3/752 (0.4)
Africa			
Black	62/78 (79.5)	57/74 (77.0)	119/152 (78.3)
Other	2/78 (2.6)	3/74 (4.1)	5/152 (3.3)
Mixed	14/78 (17.9)	14/74 (18.9)	28/152 (18.4)
Marital Status, n (%)			
Married, civil union or legal partnership	79 (3.5)	98 (4.3)	177 (3.9)
Living with primary or main partner	138 (6)	154 (6.7)	292 (6.4)
Have primary or main partner, not living together	171 (7.5)	164 (7.2)	335 (7.3)
Single, divorced or widowed	1,888 (82.7)	1,863 (81.6)	3,751 (82.2)
Other	6 (0.3)	5 (0.2)	11 (0.2)
Educational level, n (%)			
No schooling	2 (0.1)	6 (0.3)	8 (0.2)
Primary school	28 (1.2)	42 (1.8)	70 (1.5)
Secondary school	490 (21.5)	522 (22.9)	1,012 (22.2)
Technical training	187 (8.2)	188 (8.2)	375 (8.2)
College or university or higher	1,575 (69.0)	1,526 (66.8)	3,101 (67.9)

Source: Landovitz et al, 2021 (119).
†Reported by the participant; ‡SexPro is a Web-based tool which provides a sexual health promotion score. It is validated to predict the 6-month risk of HIV acquisition on the basis of sexual behaviours, sexual networks, substance use, history of sexually transmitted infections, race or ethnic group (US only), and age. Scores range from 1–20, with higher scores indicating a lower risk of acquiring HIV.
Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range; ITT, intention-to-treat; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine; US, United States.

B.2.3.1.2 *HPTN 084*

Key participant characteristics at baseline for HPTN 084 are presented in Table 9.

Participant characteristics were generally well balanced between study groups.

Table 9: HPTN 084: baseline participant characteristics (ITT)

Baseline characteristic	HPTN 084	
	Cabotegravir group (N=1,614)	Daily oral TDF/FTC group (N=1,610)
Self-reported gender identity†, n (%)		
Female	1,612 (99.9)	1,607 (99.8)
Male	0	3 (0.2)
Transgender male	2 (0.1)	0
Sexual activity in the past month‡, n/N (%)		
≥2 sex partners	878/1,609 (54.5)	877/1,600 (54.8)
Transactional sex	658/1,609 (40.9)	655/1,600 (40.9)
Partner living with HIV or unknown	542/1,609 (33.7)	558/1,600 (34.9)
Anal sex	90/1,609 (5.6)	95/1,600 (5.9)
Modified VOICE risk score¶		
Median (IQR)	6 (5–7)	6 (5–7)
BMI ≥30 kg/m^2		
n (%)	465 (28.8)	430 (26.8)
STI, n (%)		
Chlamydia trachomatis§	324/1,602 (20.2)	280/1,587 (17.6)
Neisseria gonorrhoeae§	112/1,602 (7.0)	98/1,587 (6.2)
Trichomonas vaginalis††	141/1,578 (8.9)	129/1,555 (8.3)
Positive syphilis serology‡‡	41/1,611 (2.5)	62/1,608 (3.9)
Country		
Botswana	46 (2.9)	45 (2.8)
Eswatini	80 (5.0)	80 (5)
Kenya	31 (1.9)	35 (2.2)
Malawi	113 (7)	111 (6.9
South Africa	653 (40.5)	655 (40.7)
Uganda	300 (18.6)	296 (18.4)
Zimbabwe	391 (24.2)	388 (24.1)
Age, years		
Median (IQR)	25 (22–30)	25 (22–20)
Aged <25 years, n (%)	814 (50.4)	816 (50.7)
Ethnic group (self-reported), n (%)		
Black African	1,569 (97.2)	1,554 (96.5)
Asian	2 (0.1)	3 (0.2)
Mixed race	2 (0.1)	8 (0.5)
White	0	1 (0.1)
Other	41 (2.5)	44 (2.7)
Marital status, n (%)		
Married, civil union, or legal partnership	169 (10.5)	174 (10.8)
Living with primary partner	106 (6.6)	118 (7.3)
Not living with primary partner	869 (53.8)	860 (53.4)

Baseline characteristic	HPTN 084	
	Cabotegravir group (N=1,614)	Daily oral TDF/FTC group (N=1,610)
Single, divorced, or widowed	465 (28.8)	454 (28.2)
Other	5 (0.3)	4 (0.2)
Education, n (%)		
No schooling	20 (1.2)	12 (0.7)
Primary school	251 (15.6)	255 (15.8)
Secondary school	1,154 (71.5)	1,182 (73.4)
Technical training	48 (3.0)	41 (2.5)
Tertiary education	141 (8.7)	120 (7.5)
Employed		
n (%)	451 (27.9)	427 (26.5)

Source: Delany-Moretlwe et al, 2022 (120).
†All participants were assigned female gender at birth; ‡15 missing (five in the cabotegravir group, and ten in the TDF/FTC group) computer assisted self-interview responses; ¶Modified risk score excludes variables for curable STIs and HSV-2 serostatus; §35 results not done or invalid (12 in the cabotegravir group and 23 in the TDF/FTC group; ††91 results invalid or not done (36 in the cabotegravir group and 55 in the TDF/FTC group); ‡‡Five results missing or not done (three in the cabotegravir group and two in the TDF/FTC group); defined positive if both non-treponemal and treponemal test were reactive.
Abbreviations: BMI, body mass index; HIV, human immunodeficiency virus; IQR, interquartile range; ITT, intention-to-treat; STI, sexually transmitted infection; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine; VOICE, Vaginal and Oral Interventions to Control the Epidemic.

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Analysis sets

A summary of the analysis sets relevant to data presented in the submission for HPTN 083 is provided in Table 10.

Table 10: Analysis sets relevant to data presented in the submission for HPTN 083 and HPTN 084

Analysis set	Definition	HPTN 083 (119, 123)			HPTN 084 (120, 129)		
		Cabotegravir N=2,283 n (%)	TDF/FTC N=2,287 n (%)	Total N=4,570 n (%)	Cabotegravir N=1,614 n (%)	TDF/FTC N=1,610 n (%)	Total N=3,224 n (%)
Randomised population	All participants who were randomised	2,283 (100.0)	2,287 (100.0)	4,570 (100.0)	1,614 (100.0)	1,610 (100)	3,224 (100.0)
ITT	All participants who were randomised, excluding those were inappropriately enrolled	2,282 (100.0)	2,284 (99.9)	4,566 (99.9)	1,614 (100.0)	1,610 (100.0)	3,224 (100.0)
mITT	The ITT population, excluding those who were found to be living with HIV at randomisation[†]	2,280 (99.9)	2,281 (99.7)	4,561 (99.8)	1,614 (100.0)	1,610 (100.0)	3,224 (100.0)
PP	Participants flagged for exclusion from Per Protocol population are based on the decisions made by the Protocol Deviations Adjudication Committee	[redacted]	[redacted]	[redacted]	1,598 (99.0)	1,600 (99.4)	3,198 (99.2)
Injection (Step 2 efficacy)	All mITT participants who received at least one injection, were not living with HIV at the time of the first injection and had at least one follow-up visit with non-missing HIV test results after the first injection	2,109 (92.4)	2,069 (90.5)	4,178 (91.4)	1,495 (92.6)	1,494 (92.8)	2,989 (92.7)
Safety population (primary analysis)	All ITT participants who received any oral or injectable product	2,281 (99.9)	2,285 (99.9)	4,566 (99.9)	1,614 (100.0)	1,610 (100.0)	3,224 (100.0)
Injection (Step 2 safety population)	All participants who progressed to Step 2 and received at least one injection	2,117 (92.7)	2,081 (91.0)	4,198 (91.9)	1,519 (94.1)	1,516 (94.2)	3,035 (94.1)

Analysis set	Definition	HPTN 083 (119, 123)			HPTN 084 (120, 129)		
		Cabotegravir N=2,283 n (%)	TDF/FTC N=2,287 n (%)	Total N=4,570 n (%)	Cabotegravir N=1,614 n (%)	TDF/FTC N=1,610 n (%)	Total N=3,224 n (%)
TDF/FTC adherence population	Cohort of participants randomly selected at baseline from the oral TDF/FTC group	–	[redacted]	[redacted]	–	[redacted]	[redacted]

Source: HPTN 083 clinical study report (123) and HPTN 084 (129) clinical study report and EMA apretude assessment report (12).
†HPTN 083 analysis period: primary analysis follow-up data included study time through completion of the blinded injection phase of the study follow-up (i.e.. Week 153 or the study-wide transition to Step 3, or the end of the blinded phase of the study, whichever occurred first).
Abbreviations: HPTN, HIV Prevention Trials Network; ITT, intention-to-treat; mITT, modified intention-to-treat; PP, per protocol; TDF/FTC, tenofovir disoproxil fumarate and emtricitabine.

B.2.4.2 Summary of the statistical analysis methods

A summary of the statistical analysis of HPTN 083 and HPTN 084 is provided in Table 11. As the trials met the pre-defined stopping criteria, only 19 participants had entered into the protocol defined Step 3 in HPTN 083 when the blinded portion of the trial was stopped early; therefore, efficacy analyses including Step 3 were no longer considered to be informative. No participants in HPTN 084 entered the protocol-defined step 3 after early stopping, consequently protocol-defined endpoints including Step 3 were not analysed in either study.

Table 11: Summary of statistical analysis methods

Trial name	HPTN 083 (123, 128, 131)	HPTN 084 (127, 129, 132)
Hypothesis objective	**Primary efficacy objective:** To compare HIV incidence among participants randomised to oral cabotegravir/cabotegravir LA (oral lead in and injections) versus oral TDF/FTC (Steps 1 and 2) **Primary safety objective:** To compare the safety of oral cabotegravir/cabotegravir LA versus oral TDF/FTC (Steps 1 and 2) using the primary safety endpoint of Grade 2 or higher clinical and laboratory AEs throughout the study	**Primary efficacy objective:** To evaluate the relative efficacy of oral cabotegravir/cabotegravir LA (oral lead-in and injections versus daily oral TDF/FTC for HIV prevention (Steps 1 and 2) **Primary safety objective:** To compare the relative safety of oral cabotegravir/cabotegravir LA (Steps 1 and 2) versus daily oral TDF/FTC for HIV prevention (Steps 1 and 2) using the primary safety endpoint of Grade 2 or higher clinical and laboratory AEs
Statistical analysis of primary endpoint	• HPTN 083 was designed as a non-inferiority study, with the ability to test for superiority using the O'Brien Fleming method. The non-inferiority margin was a HR of 1.23, which was chosen on the basis of previous placebo-controlled trials, with an alternative HR of 0.75 used as the pre-specified test for superiority. Superiority would be established if the HR point estimate is approximately 0.74 or less • The primary end point was evaluated in the mITT population, which excluded participants who were found to be living with HIV at enrolment. All incident acquisitions were included in the analysis, regardless of when the acquisition occurred and regardless of whether the participant received an injection • Cox regression, stratified according to geographic region and adjusted for early stopping, was used to estimate the HR for incident HIV acquisition in the cabotegravir group versus the TDF–FTC group; 95% CIs and p-values were based on the Wald statistic • The primary HR was adjusted for early stopping. A test for proportional hazards was performed with the use of Schoenfeld residuals, and a log-rank test, stratified	• HPTN 084 was designed as a superiority trial, with superiority established if the HR point estimate is within the bound of 0.54 for the HR • The primary endpoint was evaluated in the mITT population, in which any participant determined to be living with HIV prior to randomisation was omitted from the analysis • Cox regression, stratified according to site and including treatment arm as the only covariate, was used to estimate the HR and 95% CIs for incident HIV acquisition; if the number of events was small (<40) then the p-value was confirmed using a permutation test based on 100,000 random permutations of the treatment assignments; if there was a meaningful difference between the permutation and asymptotic procedures, the permutation p-value was used

Trial name	HPTN 083 (123, 128, 131)	HPTN 084 (127, 129, 132)
	according to geographic region, was performed as a sensitivity analysis • To support the non-inferiority hypothesis, a supportive analysis using OBSP censoring in the injection (Step 2) efficacy population, where study follow-up is censored when a participant does not receive blinded injection study product on time, was performed	
Statistical analysis of secondary endpoints	• Incidence of HIV acquisitions in Step 2: The same methods as detailed for the primary analysis were used for estimating effectiveness for these secondary objectives. For step 2 only, during the double-blind phase, persons who did not initiate Step 2, and acquisitions that occurred in Step 1 were omitted from the assessment of relative efficacy • To compare HIV incidence among the following subgroups: geographical region, age, ethnic group, and baseline risk, the same methods as details for the primary analysis were used for estimating effectiveness in each of the subgroups defined by the stated baseline characteristics. A test for significant interaction between intervention arm and subgroup was conducted as a test of effect modification • No formal statistical comparison was performed to evaluate and compare rates of HIV drug resistance among participants who acquire HIV during the study among participants receiving oral cabotegravir/cabotegravir LA versus oral TDF/FTC • For evaluating the acceptability of and preferences for cabotegravir LA versus oral TDF/FTC, descriptive statistics were used to summarise outcomes over the course of the study. Acceptability scores were compared using a linear mixed effects model with study arm as fixed effect	• Incidence of HIV acquisitions in Step 2: The HR comparing cabotegravir LA versus TDF/FTC and 95% CIs were estimated using a Cox proportional hazards model with treatment arm as the only covariate, stratified by site and using all HIV incidence data from Step 2 • To evaluate relative efficacy of oral cabotegravir/cabotegravir LA versus oral TDF/FTC in subgroups defined by the baseline factors of: age, HSV-2 serostatus, contraceptive method, and BMI, for each of the specified baseline factors, a cox proportional hazards model was fitted with treatment arm, baseline factor, and their interaction as covariates, stratified by site • To describe and model the relationship between HIV incidence and drug concentration levels, within each arm a Cox proportional hazards model with drug concentration as a continuous, time-dependent covariate was fit separately for each arm, with stratification by site. Martingale residual plots were used to guide selection of an appropriate functional form for drug concentration, starting with the assumption of a linear relationship between drug concentration and log hazard. Separate models were fit for different measures of drug levels (i.e. DBS, plasma). A model to predict drug concentrations in continuous time based on observed plasma and DBS drug levels was also investigated; the predicted values were then be used as a covariate in the analysis. Potential confounders (e.g. age, sexual risk behaviours) were included in the model. Once a

Trial name	HPTN 083 (123, 128, 131)	HPTN 084 (127, 129, 132)
		final model was selected, the (possibly adjusted) relationship between log relative risk (y-axis) and drug concentration (x-axis), with 95% CIs, were plotted for each arm • For evaluating the acceptability of and preferences for cabotegravir LA versus oral TDF/FTC, descriptive statistics were used to summarise outcomes
Statistical analysis of safety endpoints	• Local reactions were summarised descriptively, with Kruskal Wallis tests used to test for differences in severity between arms • AEs and laboratory values were summarised descriptively	• Local reactions were summarised descriptively, with Wilcoxon rank sum tests used to test for differences in severity between arms • AEs and laboratory values were summarised descriptively
Sample size and power calculation	• It was estimated that to achieve 90% power to detect an alternative HR of 0.75 and rule out the non-inferiority margin of 1.23 (at a one-sided type I error rate of 0.025), 172 incident HIV acquisitions (events) would need to occur. The power to detect superiority was 47% • Assuming an incidence of 1.75 events per 100 PY, the study aimed to enrol approximately 4,500 participants; a protocol amendment increased the target sample size from 4,500 to 5,000 • Formal interim analyses were planned for three time points during the trial, with analysis times corresponding to approximately when 25%, 50%, and 75% of the estimated total number of HIV acquisitions had been observed. The interim analyses were initially designed to monitor the trial for early stopping based on the interim monitoring boundary for superiority, or early evidence that cabotegravir LA is definitively more effective than daily oral TDF/FTC. However, due to concerns among study leadership about disruption to study execution resulting from COVID-19, the study protocol was amended, and these analyses instead monitored the trial for early stopping based on the non-inferiority boundary	• A total of 114 events were required to have 90% power to detect a HR of 0.54 for incident HIV acquisitions in the cabotegravir group compared with the TDF/FTC group with a one-sided significance level of 0.025, assuming five pre-planned (four interim and one final) analyses • Assuming an incidence of 2.07 cases per 100 PY in the TDF/FTC group, equal allocation to the groups, an average follow-up period of 2.6 years, and 5% loss to follow-up per year, a sample size of 3,200 participants was considered robust against uncertainties in adherence rates • Four interim and one final analysis of HPTN 084 were planned, with an O'Brien-Fleming spending function used to determine stopping boundaries. The trial was intended to continue until 114 events were reached or until a stopping boundary was crossed. Trial data from HPTN 084 were reviewed periodically by an independent data and safety monitoring board, and on November 5th 2020, at the planned second interim analysis it was concluded that predetermined criteria for stopping the blinded phase of the study due to established superior efficacy of cabotegravir LA had been met

Trial name	HPTN 083 (123, 128, 131)	HPTN 084 (127, 129, 132)
Data management and patient withdrawal	• In both trials, for the primary endpoints, HIV acquisition, safety events, and other biological endpoints, analyses were conducted assuming uninformative censoring. If loss to follow-up was low and similar between the arms additional sensitivity analyses were not conducted. However, if loss-to-follow-up was >20% or meaningfully different between arms (>5%-points), sensitivity of the results to assumptions about the missing data were investigated. Specifically, the inverse probability-of censoring weights to adjust for loss to follow-up (133) and compare the adjusted treatment effect to the unadjusted treatment effect was used. In addition in HPTN 083, a tipping-point analysis was performed whereby the difference from the observed treatment arm effect (either higher or lower than observed) that would have to exist in the missing data to meaningfully change interpretation of the results was determined. We also estimated the difference in treatment arm effect that would be observed if all participants who are lost-to-follow-up are assumed to have stopped taking PrEP • Behavioural and self-reported endpoints (e.g. acceptability) may also be subject to participant nonresponse. The analyses were based on a complete case approach. However, if non-response was high (>15%) or differential between arms (>5%-points) then sensitivity analyses using multiple imputation were performed. Baseline data were used to develop the imputation model and standard errors were adjusted using Rubin's method (134)	

Abbreviations: AE, adverse event; CI, confidence interval; DBS, dried blood spot; HIV, human immunodeficiency virus; HPTN, HIV Prevention Trials Network; HR, hazard ratio; HSV-2, herpes simplex virus-2; LA, long acting; mITT, modified intention-to-treat; OBSP, on blinded study product; PrEP, pre-exposure prophylaxis; PY, patient years; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

B.2.4.3 Participant flow

The participant flow for each trial is presented in Appendix D.

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

Appendix D contains quality assessment of each of the trials identified in the SLR.

B.2.6 Clinical effectiveness results of the relevant studies

B.2.6.1 HPTN 083

In HPTN 083, the blinded phase of the study was between December 2016 and May 2020, and the unblinded phase (Year 1) was between May 2020 and May 2021, with a combined analysis period between Dec 2016–May 2021 (the blinded and unblinded period). The analyses included:

- A pre-specified primary analysis of the blinded phase (modified intention-to-treat [mITT])
- Post-hoc analyses of the blinded phase including extended retrospective virologic testing, performed to better characterise the timing of HIV acquisition (mITT, extended retrospective testing)
- An updated analysis, evaluating new HIV acquisitions detected between May 2020 and November 2021 for which the first evidence of HIV acquisition was before May 15th 2021 (the first OLE visit); this allowed a 6-month window after the end of the first unblinded year for sites to detect acquisitions.

For the purposes of this dossier, the mITT population was chosen as a primary method of reporting as it excluded those who were found to be living with HIV at randomisation.

B.2.6.1.1 *Primary endpoint: Number of documented incident HIV acquisitions in Steps 1 and 2*

B.2.6.1.1.1 Primary analysis (mITT)

At blinded study termination, 52 participants who acquired HIV after enrolment were included in the pre-specified primary analysis. The primary efficacy analysis (mITT) demonstrated that cabotegravir was superior to daily oral TDF/FTC for preventing

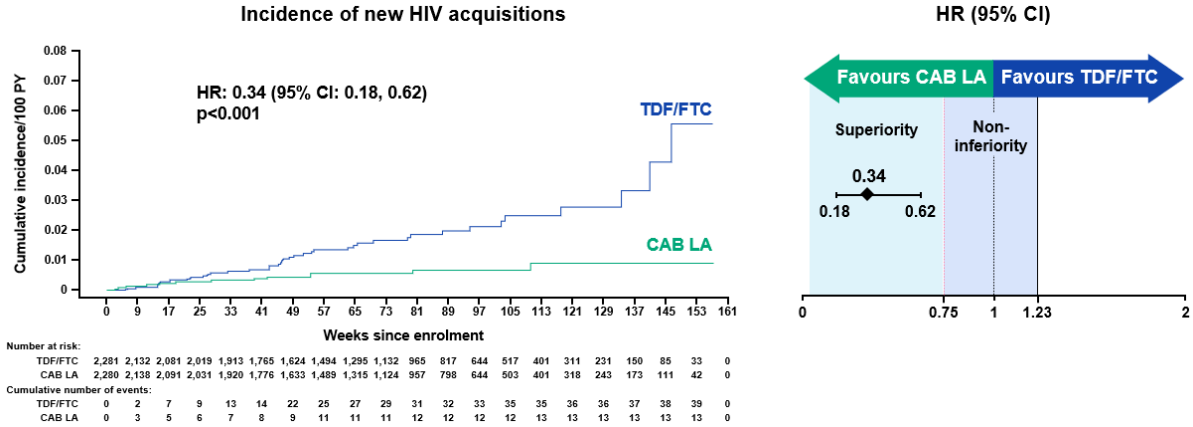
HIV acquisition, with a 66% reduction in the number of incident HIV acquisitions in Steps 1 and 2 (superiority [redacted]) (Table 12, Figure 3) (12, 123).

Table 12: HPTN 083: Primary endpoint – incident HIV acquisitions in Steps 1 and 2 (mITT)

	Cabotegravir N=2,280	Daily oral TDF/FTC N=2,281
Number of acquisitions	13	39
PY	3,211	3,193
Incidence rate/100 PY (95% CI)†	0.40 [redacted]	1.22 [redacted]
Unadjusted HR‡	–	[redacted]
Superiority p-value		[redacted]
Non-inferiority p-value		[redacted]
Bias-adjusted HR‡ (95% CI)	–	0.34 (0.18, 0.62)
Superiority p-value¶	–	[redacted]
Non-inferiority p-value¶	–	[redacted]

Source: HPTN 083 clinical study report (123) EMA Apretude assessment report (12).
The trial was stopped based on a breach of the first interim stopping bound (z=–4.00, p=0.000063), which was derived from an O'Brien-Fleming design with three planned interim analysis plus one final analysis. The p-values are two-sided. A HR<1 indicates a lower risk on cabotegravir versus TDF/FTC.
†The 95% CI for incidence rate is calculated using the exact Poisson method; ‡The unadjusted HR is based on a Cox proportional hazards model stratified by region; ¶Bias-adjusted to account for group-sequential trial time and early stopping.
Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; HPTN, the HIV Prevention Trials Network; HR, hazard ratio; mITT, modified intention-to-treat; PY, person-years; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

Figure 3: HPTN 083: Kaplan-Meier plot of incident HIV acquisitions in Steps 1 and 2 (mITT)



Source: Adapted from Landovitz et al, 2021 (119).
Abbreviations: CAB LA, cabotegravir long-acting; CI, confidence interval; HIV, human immunodeficiency virus; HPTN, the HIV Prevention Trials Network; HR, hazard ratio; mITT, modified intention-to-treat; PY, person-years; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

B.2.6.1.1.2 Planned supportive on-blinded study product analysis

Results of a planned supportive on-blinded study product (OBSP) analysis[g] were consistent with the primary efficacy analysis, with an 84% reduction in the incidence

[g] Analysis conducted using OBSP censoring of the Injection Step 2 Efficacy Population wherein study follow-up was censored at the first time during the Injection phase when the participant did not receive

of HIV acquisitions with cabotegravir versus daily oral TDF/FTC when participants remained on blinded injection study product (hazard ratio [HR]: 0.16; 95% CI: 0.06, 0.47) (12, 123).

B.2.6.1.1.3 Post-hoc analysis of the blinded study period (mITT, extended retrospective testing)

Post-hoc centralised testing of stored plasma samples, performed to better characterise the timing of HIV acquisition, determined that one of the incident HIV acquisitions in the cabotegravir group was a prevalent (baseline) infection (135). Therefore, a total of 12 incident acquisitions occurred in the cabotegravir group during the blinded period (no cases in the TDF/FTC arm were re-adjudicated as baseline infections). This post-hoc analysis of the blinded period (mITT, extended retrospective testing) yielded a 69% reduction in incident HIV acquisitions relative to daily oral TDF/FTC (HR: 0.31; 95% CI: 0.16, 0.58; p=0.0003) (135).

B.2.6.1.1.4 Updated analysis of primary endpoint (incorporating data from one additional year of unblinded follow-up)

In the analysis of incident HIV acquisitions during the first unblinded year, three incident HIV acquisitions were identified that occurred during the unblinded period but were not detected until after study unblinding (cabotegravir: 1; TDF/FTC: 2) (126). Data from these three acquisitions were combined with data from the mITT extended, retrospective testing analysis, resulting in a final total of 13 incident infections in the cabotegravir arm, and 41 in the TDF/FTC arm during the blinded period, with an updated HR of 0.31 (95% CI: 0.17, 0.58; p=0.0003) (126).

In total, 44 additional incident HIV acquisitions which occurred in the first unblinded year were included in the efficacy analyses of the unblinded year (12 in the cabotegravir group[h] and 32 in the TDF/FTC group) resulting in an HR of 0.35 (95% CI: 0.18, 0.69); p=0.0021 (126).

In the combined study period (Step 1 and 2, plus 1-year unblinded follow-up), a total of 25 incident acquisitions were observed with cabotegravir and 73 with TDF/FTC (HIV incidence rate of 0.54 per 100 PY, and 1.59 per 100 PY, respectively, HR: 0.34

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blinded injection study product according to the protocol schedule for any reason; this analysis only included participants who initiated injections (thus excludes incident HIV acquisitions that occurred during Step1 [blinded oral lead-in phase]).

[h] Five acquisitions were excluded from the efficacy analysis as they occurred >3 years after study initiation

[95% CI: 0.22, 0.53]; p<0.0001), representing a 66% reduction in HIV acquisitions with cabotegravir (126).

B.2.6.1.2 *Secondary endpoints*

B.2.6.1.2.1 Resistance mutations to study products among individuals acquiring HIV (including but not limited to K65R, M184V/L, Q148R)

HIV genotyping was performed during the first visit at which the HIV viral load was >500 copies/mL (123) and cases were divided into groups based on the relationship between cabotegravir exposure and the first visit with confirmed HIV acquisition (Table 13). At the time of the post-hoc analysis of the blinded period, of the 16 HIV cases detected, integrase strand transfer inhibitor (INSTI) resistance was detected in five participants (one with baseline infection and four with an incident HIV acquisition) (119).

To the end of the first year of unblinded follow-up, genotyping results were obtained for 33 of the 34 baseline and incident infections in the cabotegravir. Overall, major INSTI resistance-associated mutations (RAM) were observed in 10 cases. Development of INSTI resistance was commonly associated with the initiation of cabotegravir LA in participants with undiagnosed acute HIV infection (n=2 initiated or re-started cabotegravir with undiagnosed HIV), and with cases of breakthrough HIV acquisitions with on time injections (n=6). Importantly, no participant was found to have developed resistance to cabotegravir or other INSTIs during the pharmacokinetic ‘tail phase’. No INSTI resistance was detected among acquisitions that occurred in the setting of injection delays (DX cases; n=3), and acquisitions which occurred more than 6 months after the last cabotegravir exposure (B cases). Although the exact timing of the tail-phase cannot be determined, data from HPTN 077 suggests that cabotegravir concentrations were likely to be quantifiable in the time period leading to the first visit HIV acquisition was confirmed (includes cases DX3, B9–11, and B13–16) (126).

Table 13: HPTN 083: Summary of major INSTI RAMs (Steps 1 and 2, and one year on unblinded follow-up)

	HIV acquisitions			Major INSTI RAMs	
	Steps 1 and 2¶¶	1-year unblinded	Total	N (%)	INSTI
Baseline infections					
A: cabotegravir	4 (A1–A4)	–	4	1 (25)	E138E/K, Q148K/R
Incident					
B: No recent cabotegravir administration†	5 (B1–B5)††	11 (B6–B16)	16	0 (0)	N/A
C: cabotegravir OLI acquisition	3 (C1–C3)	–	3	2 (66)	E138E/A/K, G140G/S, Q148R
D: Adherent to cabotegravir LA injections	4 (D1–D4)‡‡	2 (D5§§–D6)	6	6 (100)	E138K, G140A, Q148R, N155H§, R263K
DX: Delayed cabotegravir injection‡	–	3 (DX1–DX3)	3	0 (0)	N/A
BR: cabotegravir restarted after acquisition¶	–	2 (BR1–BR2)	2	1 (50)	Q148R

Source: Marzinke at al, 2022 (124); Marzinke et al, 2023 (125).
†Participant had no cabotegravir LA injections or had their last injection ≥6 months prior to their first HIV acquisition was confirmed; ‡Infected <6 months after the last injection with ≥1 delayed injection (>70 days after the last injection); ¶No cabotegravir administration in the 6 months before the first visit with confirmed HIV acquisition; cabotegravir restarted at or after the first visit with confirmed HIV acquisition; §Determined with low viral load INSTI genotyping; all other cases of INSTI resistance were determined through GenoSure Prime (Monogram Biosciences) testing; ††No result for B4; ‡‡One case that was classified as a D case in the original analysis of Steps 1 and 2 had a single late injection (D1) (75 days after the previous injection); that case would have been classified as a DX case according to the updated classification system used in the updated analysis including the additional year of unblinded follow-up; ¶¶Extended retrospective virologic testing after the primary analysis was performed; this found one case, previously classified as an incident case, to have been living with HIV at enrolment (the case was initially designated B5 and was renamed as A3). A4 designates an additional baseline infection identified in the cabotegravir arm during extended retrospective testing; §§Backdated to blinded phase.
Abbreviations: HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; OLI, oral lead-in; RAM, resistance-associated mutation; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

In the TDF/FTC arm, genotyping was performed at the first visit HIV acquisition was confirmed for 40 of the 42 HIV cases in the TDF/FTC arm (two had no viraemic visit) (136). Seven cases had NNRTI resistance only, three had NNRTI and NRTI resistance, and one had NRTI resistance only. Genotyping was also performed for 27 of the 34 cases identified during the blinded period, with results obtained for 26 cases (one failed testing). Major RAMs were detected in 10 cases (125). Of these, six had the major NRTI RAM, M184I/V, at the first visit HIV acquisition was confirmed; one of those cases also had the K65R mutation. These mutations are associated with resistance to TDF/FTC. In addition, four of the six cases also had one or two major NNRTI RAMs; one of those four cases also had the protease

inhibitor RAM, M46L. The remaining four cases with a major RAM detected all had a single NNRTI mutation detected. No other major protease inhibitor RAMs were detected and no major INSTI RAMs were detected.

B.2.6.1.2.2 Acceptability scale assessments

Results for overall treatment satisfaction, study medication satisfaction questionnaire, and preference for oral or injectable product are provided in Appendix M.

B.2.6.1.3 *Other endpoints*

B.2.6.1.3.1 Adherence to study product

B.2.6.1.3.1.1 *Intervention adherence during Step 1*

Only participants with a pill count ≥50% and acceptable laboratory results progressed to Step 2. At Week 4, the adherence to oral study product was similar in both treatment arms; pill counts corresponding to 90–100% adherence were observed in 67% of participants in the cabotegravir arm and 66% of participants in the daily oral TFD/FTC arm (12, 123). The median total exposure to cabotegravir and to TDF/FTC during the oral phase was [redacted] days.

B.2.6.1.3.1.2 *Cabotegravir LA injection coverage during Step 2*

During the blinded injection phase, the median number of injection visits was [redacted] in both treatment groups, with [redacted] (123). [redacted] injection visits were within the allowable ±7-day window. Few (<1%) injection visits were missed in either treatment group prior to discontinuing randomised treatment (12, 123). In the updated primary blinded period, cabotegravir LA injection coverage was 91.5% (126), which declined to 79.9% during the additional year of unblinded follow up (126). Declining adherence over time was also observed in the TDF/FTC arm (Section B.2.6.1.3.3); however; coverage with cabotegravir remained higher than the levels of TDF/FTC adherence.

B.2.6.1.3.2 Plasma cabotegravir in individuals acquiring HIV (seroconversion population)

HIV cases in the cabotegravir arm were divided into groups and named (A–D, DX, or BR) based on factors related to exposure to the study drug (see Table 13 for detailed definitions). Of the 16 baseline and incident acquisitions detected to the end of the

blinded phase in the cabotegravir group (mITT, extended retrospective testing), four occurred before enrolment (i.e. were baseline infections; cases A1–A4), while five occurred with no recent exposure to cabotegravir (cases B1–B5; in two cases, open-label TDF/FTC was initiated after the participant had discontinued cabotegravir LA) (119) (Table 13). Three acquisitions occurred before cabotegravir injection (C1–C3; one case was non-adherent to oral cabotegravir) (Table 13). Four acquisitions occurred in individuals in the setting of on-time cabotegravir LA injections and expected plasma cabotegravir concentrations (D1–D4) (119) (Table 13). In the 18 additional cases reported in the cabotegravir arm during the unblinded year, five had recent cabotegravir administration (on time injections: two cases [D5-D6]; mostly in the setting of on-time cabotegravir LA injections, but with at least one injection with ≥8 week delay prior to HIV detection: three cases [DX1–DX3]), two cases had restarted cabotegravir after a ≥6 month interruption, and detection of HIV acquisition was delayed at the study site with participants receiving cabotegravir on or after HIV acquisition (BR1–BR2), and 11 cases had no recent cabotegravir administration (within 6-months), including two participants who never received cabotegravir (B6-B16) (125, 126) (Table 13). Although the exact timing of tail-phase acquisitions cannot be determined, based on data from HPTN 077 (137), it is likely that cabotegravir concentrations were quantifiable in the time period leading to the first visit HIV acquisition was confirmed in cases DX3, B9–11, and B13–B16 (126).

B.2.6.1.3.3 Plasma and/or DBS levels of TDF in participants randomised to TDF/FTC

Daily oral TDF/FTC adherence (measured using plasma tenofovir [TFV] and tenofovir-diphosphate [TFV-DP] concentrations in dried blood spots [DBS]) was assessed throughout Steps 1 and 2 of the study in a random subset of [redacted] participants enrolled into the daily oral TDF/FTC arm who provided at least one adherence result at baseline (TDF/FTC adherence population). Selection was stratified by geographical region and enrolment date.

During Steps 1 and 2, [redacted] of evaluated samples yielded plasma TFV concentrations consistent with ≥4 doses per week (i.e. ≥4.2 ng/mL); this adherence benchmark [redacted] at Week 4 to [redacted] at Week 81 (119, 123). In total, 73% of evaluated DBS samples yielded TFV-DP concentrations consistent with ≥4 doses per week (≥700 fmol/punch), decreasing from [redacted] at Week 4 to [redacted] at Week 81.

Overall, [redacted] of plasma TFV samples, and [redacted] of DBS TFV-DP samples were indicative of 7 doses per week ≥35.5 mg/mL or ≥1250 fmol/punch, respectively) (Table 14).

Table 14: HPTN 083: Summary of TDF/FTC adherence based on percentage of plasma TFV, and percentage of DBS TFV-DP concentrations within ranges by visit (TDF/FTC adherence population)

	N (%) within TFV concentration ranges (ng/mL) [target doses/week]					
Visit	**N**	**≥35.5 [7/wk]**	**≥4.2 to <35.5 [4 to <7/k]**	**≥2.5 to <4.2 [2 to <4/wk]**	**0.31– <2.5 [<2/wk]**	**NQ (<0.31)**
Wk 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wk 9						
Wk 17						
Wk 33						
Wk 57						
Wk 81						
Wk 105						
Wk 129						
Wk 153						
Step 3 (Day 0)						
Overall	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
N (%) within TFV-DP concentration ranges (fmol/punch) [target doses/week]						
Visit	**n**	**≥1250 [7/wk]**	**≥700 to <1250 [4 to <7/wk]**	**≥350 to <700 [2 to <4/wk]**	**<350 [<2/wk]**	**NQ (LLOQ)**
Wk 4	386	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wk 9	364					
Wk 17	351					
Wk 33	[redacted]					
Wk 57	254					
Wk 81	[redacted]					
Wk 105						
Wk 129						
Wk 153						
Step 3 (Day 0)						
Overall	[redacted]	[redacted] (34%)	[redacted] (39%)	[redacted] (10%)	[redacted] (9%)	[redacted] (9%)

Source: HPTN 083 clinical study report (123).
Abbreviations: DBS, dried blood spot; LLOQ, lower limit of quantification; NQ, not quantifiable; TDF/FTC, tenofovir disoproxil fumarate and emtricitabine; TFV, tenofovir; TFV-DP, intraerythrocytic tenofovir diphosphate; wk, week.

A graphical comparison of plasma TFV (Figure 4) and DBS TFV-DP (Figure 4) concentrations for the adherence and seroconversion populations [redacted] to TDF/FTC (123).

Figure 4. HPTN 083: Plasma TFV concentrations and DBS TFV-DP concentrations in the adherence population compared to the daily oral TDF/FTC seroconversion population

Source: HPTN 083 clinical study report (123).
Abbreviations: BLQ, below limit of quantification; DBS, dried blood spot; IQR, interquartile range; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine; TFV, tenofovir; TFV-DP, intraerythrocytic tenofovir diphosphate.

Notably, among the TDF/FTC adherence population, the proportion of DBS samples with TFV-DP concentrations consistent with ≥4 doses per week decreased during the additional year of unblinded follow-up to 59% from the 73% observed in the updated primary blinded period (126). Similar findings were observed when comparing plasma TFV concentrations during Step 2 to plasma TFV concentrations in the additional year of unblinded follow-up, with the proportion of samples with TFV concentrations consistent with ≥4 doses per week decreasing to 76% from the 86% observed during the updated primary blinded period (126).

In pre-specified subgroup analyses of ~400 daily oral TDF/FTC participants, adherence to daily oral TDF/FTC was lower among groups, as indicated by a lower proportion of Black versus non-Black (61.0% vs 78.1%, respectively) and transgender women versus men who have sex with men (60.5% vs 71.1%m respectively) achieving TFV-DP concentrations of ≥700 fmol/punch (consistent with ≥4 doses per week) during Steps 1 and 2 (138).

B.2.6.1.3.4 Number of sexual partners (primary and non-primary), numbers of coital acts, number of non-condom protected anal intercourse acts (insertive and receptive)

In the safety population, sexual risk factors, as captured by serial behaviour risk assessments, suggests a [redacted] of HIV risk in the cabotegravir and TDF/FTC groups, when evaluating for the number of sexual partners, coital acts, and number of condomless anal sex acts (123).

B.2.6.1.3.5 Sexually transmitted infections (rectal and urinary GC/CT, syphilis [adjudicated])

[redacted] in the incidence rates of STIs or hepatitis C virus (HCV) infections were observed between groups (Table 18), suggesting any changes in sexual-risk behaviour resulting from participation in the study were [redacted] between arms.

Table 15: HPTN 083: Summary of STIs and HCV (mITT)

	Cabotegravir (N=2,280) Incidence/100 PY			Daily oral TDF/FTC (N=2,281) Incidence/100 PY		
Syphilis		[redacted]			[redacted]	
Gonorrhoea (urine)		[redacted]			[redacted]	
Gonorrhoea (rectal)		[redacted]			[redacted]	
Chlamydia (urine)		[redacted]			[redacted]	
Chlamydia (rectal)		[redacted]			[redacted]	
Hepatitis C		[redacted]			[redacted]	

Source: HPTN 083 clinical study report (123).
Abbreviations: HCV, hepatitis C virus, HPTN, HIV Prevention Trials Network; mITT, modified intention-to-treat; PY, person years; STI, sexually transmitted infection; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

B.2.6.1.4 *Preference of participants transitioning into the open-label extension phase*

In HPTN 083, 95.9% of US participants transitioning into the OLE phase chose cabotegravir LA over daily oral TDF/FTC (96.9% of those initially randomised to cabotegravir, 94.8% of those initially randomised to the TDF/FTC arm) (139). The most common reasons for choosing cabotegravir injections was prefer injection and/or don't like pills (70.3%).

B.2.6.1.5 *Supportive evidence: HPTN 083-02 qualitative sub-study of factors influencing adherence to injectable PrEP and retention in an injectable PrEP research study*

B.2.6.1.5.1 Overview of HPTN 083-02 sub-study methodology

In HPTN 083, a subset of participants from HPTN 083 (from two US sites, and one international site) were purposively sampled for individual qualitative interviews (conducted November 2019–March 2020) to explore trial experiences, barriers to adherence, and other factors impacting study implementation or outcomes (140). Inclusion and exclusion criteria for this qualitative sub-study mirrored those of HPTN 083. Interviews were conducted prior to unblinding, with participants grouped based on adherence (measured by injection visit attendance):

- **Adherent (n=27)**: participants who received ≥2 consecutive injections within 10 weeks of their prior injection (the timeline of which began once injections were scheduled Q8W), at any point during the injection phase.
- **Non-adherent (n=12)**: participants who received any injection >10 weeks following their prior injection any point during the injection phase, but had not been lost to follow-up or prematurely left the trial.
- **Early discontinuers (n=1)**: Individuals not actively engaged in the study or engaged in a way other than described for the adherence and non-adherent groups.

As the study met the pre-defined stopping criteria and was unblinded early, recruitment goals across adherence categories were not met.

B.2.6.1.5.2 Overview of HPTN 083-02 sub-study results

Qualitative findings emerged across four domains (140). With regard to overall study experiences, participants viewed the study as a way to access a novel, convenient PrEP (injectable) at no cost and contribute to HIV prevention, with the study experience being superior to routine clinical practice. With regard to experiences with and perception of injectable PrEP, initial injection-related anxiety abated with experience, and discomfort was minimal and manageable. However, there were some concerns and misperceptions around injection efficacy and safety present. Facilitators of adherence to injectable PrEP included a desire to preserve health, with utilising medication for prevention viewed more favourably over medication for treatment. The clinical staff and environment, and social support around study participation were also factors for supporting adherence. Barriers to adherence to injectable PrEP were structural barriers to visit attendance (e.g. transportation, and financial challenges), unpredictable work schedules and time off work (see Section B.1.3.6 regarding unmet need).

B.2.6.2 HPTN 084

In HPTN 084, the blinded phase of the study was up to and including November 5th 2020. Analyses of the blinded period include the primary analysis (mITT), and a post-hoc analysis with further testing of stored plasma samples to better characterise the timing of HIV acquisitions during the blinded period (mITT, extended

retrospective virologic testing). An updated analysis is also available, incorporating data from an additional year of unblinded follow-up.

B.2.6.2.1 *Primary endpoint: Number of documented incident HIV acquisitions in Steps 1 and 2*

B.2.6.2.1.1 Primary analysis (mITT)

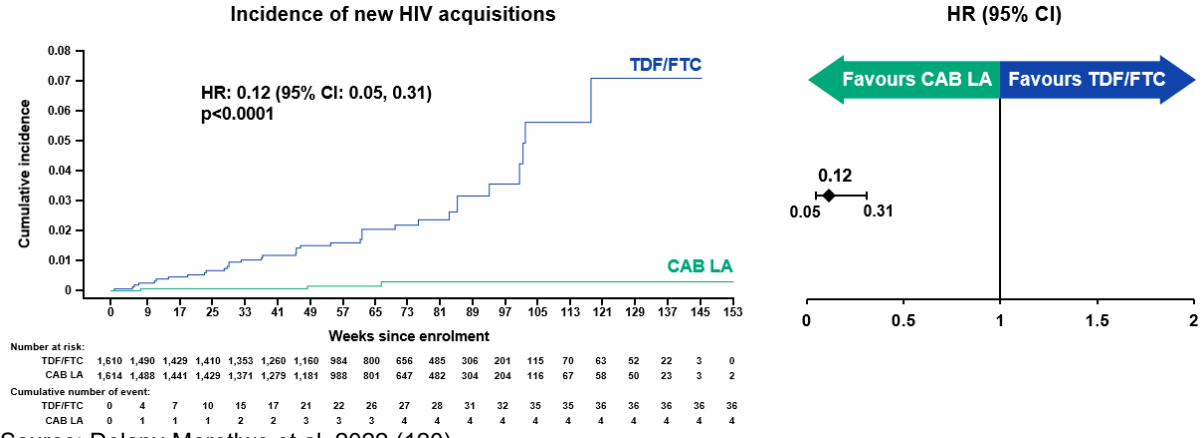
The primary efficacy analysis (mITT) demonstrated that cabotegravir was superior versus daily oral TDF/FTC for preventing HIV acquisition, with an 88% reduction in the number of incident HIV acquisitions in Steps 1 and 2 (superiority p<0.0001; Table 16, Figure 3) (12, 127).

Table 16: HPTN 084: Primary endpoint – incident HIV acquisitions in Steps 1 and 2 (mITT†)

	Cabotegravir N=1,614	Daily oral TDF/FTC N=1,610
Number of acquisitions	4	36
PY	[redacted]	[redacted]
Incidence rate/100 PY (95% CI)‡	0.20 [redacted]	1.85 [redacted]
Unadjusted HR‡; superiority p value	–	0.11 (0.04, 0.31); p<0.0001
Bias-adjusted HR¶ (95% CI); superiority p-value	–	0.12 (0.05, 0.31); p<0.0001

Source: HTPN 084 clinical study report (127) and EMA Apretude assessment report (12).
The p-values are two-sided. A HR<1 indicates a lower risk on cabotegravir versus TDF/FTC. The HR is based on a Cox proportional hazards model stratified by site.
†Efficacy analyses using the mITT population include data from Steps 1 and 2 as well as from participants who discontinued study product altogether and moved to annual follow-up in Step 1 or 2. ‡The 95% CI for incidence rate is calculated using the exact Poisson method; ¶The bias-adjusted HR, CI, and p-value account for the group sequential trial design and the decision to stop the trial at the second interim analysis.
Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; HPTN, the HIV Prevention Trials Network; HR, hazard ratio; mITT, modified intention-to-treat; PY, person-years; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

Figure 5: HPTN 084: Kaplan-Meier plot of incident HIV acquisitions in Steps 1 and 2 (mITT)



Source: Delany-Moretlwe et al, 2022 (120).
Abbreviations: HIV, human immunodeficiency virus; HPTN, the HIV Prevention Trials Network; mITT, modified intention-to-treat; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

B.2.6.2.1.2 Planned supportive on-blinded study product analysis

Results of a planned supportive OBSP[i] were consistent with the primary efficacy analysis, with a 95% reduction in the incidence of HIV acquisitions for the cabotegravir group compared with the oral TDF/FTC group when participants remained on blinded injection study product (HR: 0.05; 95% CI: 0.01, 0.37) (12, 127).

B.2.6.2.1.3 Planned supportive per-protocol analysis

Findings of a per-protocol analysis also supported the results of the primary analysis, demonstrating cabotegravir was superior versus daily oral TDF/FTC in the prevention of HIV acquisition (HR: 0.11; 95% CI: 0.04, 0.31; p<0.0001) (12, 127).

B.2.6.2.1.4 Post-hoc analysis of the blinded study period (mITT, extended retrospective testing)

Post-hoc testing of stored plasma samples, performed to better characterise the timing of HIV acquisitions, revealed one participant in the cabotegravir arm had a baseline HIV infection; thus, the final number of observed incident acquisitions during Steps 1 and 2 was 39 (3 in the cabotegravir arm and 36 in the daily oral TDF/FTC arm (120). Post-hoc analysis including this re-adjudication data resulted in a revised estimate of a 90% reduction in the risk of incident acquisition in the cabotegravir arm compared with the oral TDF/FTC arm (HR: 0.10; 95% CI 0.04, 0.27; p<0.0001) during the blinded period (135).

B.2.6.2.1.5 Updated analysis of primary endpoint (incorporating data from one additional year of unblinded follow-up)

In the 12-month unblinded period, 23 incident acquisitions (3 cabotegravir, 23 TDF/FTC) were detected, two of which were determined to have occurred during the blinded phase (1 cabotegravir; 1 TDF/FTC) (141, 142). Overall, in the combined study period (Step 1 and 2, plus 1-year unblinded follow-up), an HIV incidence rate of 0.18 per 100 PY in the cabotegravir arm (6 acquisitions) and 1.70 per 100 person-years (PY) in the daily oral TDF/FTC arm (56 acquisitions) was reported (HR: 0.11; 95% CI: 0.05, 0.24), representing an 89% reduction in the risk of HIV acquisition with cabotegravir.

[i] Analysis conducted using on blinded study product (OBSP) censoring of the Injection Step 2 Efficacy Population wherein study follow-up was censored at the first time during the Injection phase when the participant did not receive blinded injection study product according to the protocol schedule for any reason; this analysis only included participants who initiated injections.

B.2.6.2.2 *Secondary endpoints*

B.2.6.2.2.1 Plasma concentrations of cabotegravir in the individuals who acquired HIV (the cabotegravir seroconversion population)

Of the four incident HIV acquisitions detected in the primary analysis (mITT), one was found to have occurred at enrolment prior to cabotegravir administration during extended testing of stored plasma samples and was re-classified as a baseline infection (participant A1) (120, 143). Two acquisitions occurred in participants who had no evidence of recent cabotegravir exposure on history and did not receive any cabotegravir LA injections (B1 and B2). Case B1 [redacted] (127). For both individuals, cabotegravir concentrations were unquantifiable at the first visit with confirmed HIV acquisition (120). Another case of incident acquisition occurred during the injection phase of the study in a participant with delayed injection visits (case DX); the participant had cabotegravir concentrations <4 times the protein-adjusted concentration required for 90% viral inhibition at the first visit with confirmed HIV acquisition. Their last injection occurred 16.1 weeks prior to this visit.

During the unblinded year, in each of the two newly identified HIV acquisitions in the cabotegravir arm, neither had received an injection of cabotegravir LA (141, 144). The other case, which was determined to have occurred during the blinded phase, should have received the oral lead-in and did receive the first initiation injection of cabotegravir LA; however, during the oral lead-in phase the patient had no detectable concentrations of cabotegravir on four occasions. On retrospective testing it was found the patient was living with HIV at the time of the first initiation injection.

B.2.6.2.2.2 Plasma and DBS concentrations of TFV/TFV-DP in a subset of participants randomised to TDF/FTC

Daily oral TDF/FTC adherence was assessed throughout Steps 1 and 2, based on plasma TDF and DBS TFV-DP concentrations, in a random subset of [redacted] participants enrolled into the daily oral TDF/FTC arm (the adherence population) (127).

Overall, [redacted] of the adherence population plasma samples ([redacted]) yielded TFV concentrations consistent with seven doses per week (≥35.5 ng/mL)[j] and [redacted] ([redacted]) of evaluated samples yielded plasma TFV concentrations consistent with ≥4 doses per week. Adherence to seven doses per week [redacted] over time, decreasing from [redacted] at Week 4 ([redacted]) to [redacted] at Week 81 ([redacted]). Adherence to ≥4 doses per week [redacted] from [redacted] at Week 4 ([redacted]) to [redacted] at Week 81 ([redacted]).

Overall, only [redacted] of DBS samples ([redacted]) yielded TFV-DP concentrations consistent with seven doses per week, and [redacted]) of evaluated samples yielded TFV-DP concentrations consistent with ≥4 doses per week. Adherence of seven doses per week [redacted] from [redacted] at Week 4 ([redacted] to [redacted] at Week 81 ([redacted]), and adherence of ≥4 doses per week decreased from [redacted] at Week 4 ([redacted]) to [redacted] at Week 81 ([redacted]).

Table 17: HPTN 084: Summary of TDF/FTC adherence based on percentage of plasma TFV, and percentage of DBS TFV-DP concentrations within ranges by visit (TDF/FTC adherence population)

	N (%) within TFV concentration ranges (ng/mL) [target doses/week]					
Visit	**N**	**≥35.5 [7/wk]**	**≥4.2 to <35.5 [4 to <7/wk]**	**≥2.5 to <4.2 [2 to <4/wk]**	**NQ to <2.5 [<2/wk]**	**NQ (<0.31)**
All samples	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wk 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wk 9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wk 17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wk 33	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wk 57	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wk 81	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wk 105	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wk 129	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Step 3 (Day 0)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Individual average	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
N (%) within TFV-DP concentration ranges (fmol/punch) [target doses/week]						
Visit	**n**	**≥1250 [7/wk]**	**≥700 to <1250 [4 to <7/wk]**	**≥350 to <700 [2 to <4/wk]**	**<350 [<2/wk]**	**NQ (<31.25)**
All samples	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[j] Note, an alternative threshold of ≥40 ng/mL can be used to define daily use and was used in the cost-effectiveness analysis; 41.9% of participants had plasma TFV concentrations ≥40 ng/mL (120).

Wk 4		[redacted]			[redacted]			[redacted]			[redacted]			[redacted]	
Wk 33		[redacted]			[redacted]			[redacted]			[redacted]			[redacted]	
Wk 57		[redacted]			[redacted]			[redacted]			[redacted]			[redacted]	
Wk 81		[redacted]			[redacted]			[redacted]			[redacted]			[redacted]	
Wk 105		[redacted]			[redacted]			[redacted]			[redacted]			[redacted]	
Wk 129		[redacted]			[redacted]			[redacted]			[redacted]			[redacted]	
Individual average		[redacted]			[redacted]			[redacted]			[redacted]			[redacted]	

Source: HPTN 084 clinical study report (127).
Individual average is calculated as the average of the concentrations assessed at each displayed visit over the number of samples assessed for the participant during the study, applied to adherence categories.
Concentrations below the LLOQ (displayed as NQ) are imputed as the midpoint between zero and the LLOQ, then applied to the overall calculation prior to applying adherence category.
All samples includes all samples collected for each participant including unscheduled visits or multiple samples from the same visit. If there were two results from the same date and time, the value reported is the average
Abbreviations: DBS, dried blood spot; LLOQ, lower limit of quantification; NQ, not quantifiable; TDF/FTC, tenofovir disoproxil fumarate and emtricitabine; TFV, tenofovir; TFV-DP, intraerythrocytic tenofovir diphosphate; wk, week.

Graphical comparison of plasma TFV (Figure 6) and DBS TFV-DP concentrations (Figure 6) for the adherence and seroconversion populations demonstrates that seroconversion events in the daily oral TDF/FTC arm were [redacted], although a spectrum of adherence was observed in the population of individuals who acquired HIV (seroconversion population). Based on the aggregate plasma and DBS concentration results in the adherence population, [redacted].

Figure 6. HPTN 084: Plasma TFV and DBS TFV-DP concentrations in the adherence population compared with the daily oral TDF/FTC seroconversion population

[redacted]

Source: HPTN 084 clinical study report (127).
Abbreviations: BLQ, below limit of quantification; DBS, dried blood spot; EAC, Endpoint Adjudication Committee; FTC, emtricitabine; IQR, interquartile range; TDF, tenofovir disoproxil fumarate; TFV, tenofovir; TFV-DP, tenofovir diphosphate.

B.2.6.2.2.3 Survey of attitudes and willingness to use cabotegravir LA and TDF/FTC

Results for overall treatment satisfaction, acceptability of PrEP methods, preference, and self-reported adherence are provided in Appendix M.

B.2.6.2.3 *Other endpoints*

B.2.6.2.3.1 Resistance mutations to study products among individuals acquiring HIV

HIV genotyping was performed at the first visit where HIV viral load was >500 c/mL. Genotyping results were available for three of the four HIV cases in the cabotegravir arm identified during the blinded period. There were no major INSTI RAMs observed in the cabotegravir arm; one of the three participants with incident HIV acquisition had an INSTI polymorphism that was also detected in several participants in the daily oral TDF/FTC arm (120, 127, 143).

Genotyping results were available for 33 of the 36 participants with incident acquisitions during the blinded period in the TDF/FTC group (two failed testing, one with no viraemic sample) (143). In the TDF/FTC arm, one participant had an NRTI RAM (M184V), with poor adherence to TDF/FTC before HIV acquisition. Nine participants in the TDF/FTC group had NNRTI RAMS detected (mainly K103N), and INSTI mutations were detected in 10 samples (120, 143).

B.2.6.2.3.2 Adherence to study product

B.2.6.2.3.2.1 *Intervention adherence during Step 1*

Only participants with a pill count ≥50% and acceptable laboratory results progressed to Step 2. Adherence to oral study product at Week 4 was [redacted] treatment arms, with pill counts corresponding to 90–100% adherence observed in [redacted] of participants (127).

B.2.6.2.3.2.2 *Cabotegravir LA injection coverage during Step 2*

The median number of visits during Step 2 was [redacted] in both treatment arms and [redacted] of all participants completed ≥8 visits (127). Additionally, [redacted] injection visits were within a ±7-day window of the planned injection visit [redacted]. Few injection visits were missed in either treatment arm prior to discontinuing randomised treatment, cabotegravir: 8%; daily

oral TDF/FTC: 7%) (12). This translated into an injection coverage (defined as injections having been received with a delay of less than two weeks) of 93.0% in the cabotegravir (1,678 of 1,805 PY on study) and 93.1% in the daily oral TDF/FTC arm (1,671 of 1,794 PY on study) (120).

B.2.6.2.3.3 Sexual risk (number of partners, number of unprotected sex acts)

Sexual risk factors, captured by serial behaviour risk assessments evaluating the number of coital acts, number of condomless sex acts, and frequency of reported transactional sex, suggested a [redacted] level of HIV risk across the cabotegravir and daily oral TDF/FTC groups (127).

B.2.6.2.3.4 Incident STIs

There were [redacted] between the cabotegravir and daily oral TDF/FTC groups in the rates of incident STIs or HCV infections (127) (Table 18). Although STI analyses are not a direct assessment of behaviour, the [redacted] post-baseline incidence rates for STIs across the two groups [redacted] based on the [redacted] rates of incident STIs and HCV.

Table 18: HPTN 084: Summary of STIs and HCV (mITT)

	Cabotegravir (N=1,614) Incidence/100 PY	Daily oral TDF/FTC (N=1,610) Incidence/100 PY
Active syphilis	[redacted]	[redacted]
Gonorrhoea	[redacted]	[redacted]
Chlamydia	[redacted]	[redacted]
Trichomonas vaginalis	[redacted]	[redacted]
Hepatitis C	[redacted]	[redacted]

Source: HPTN 084 clinical study report (127).
Abbreviations: HCV, hepatitis C virus, HPTN, HIV Prevention Trials Network; mITT, modified intention-to-treat; STI, sexually transmitted infection; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

B.2.6.2.4 *Preference of participants transitioning into the open-label extension phase*

In HPTN 084, overall 78% of participants transitioning into the OLE phase chose cabotegravir LA over daily oral TDF/FTC (89% initially randomised to the cabotegravir arm; 68% initially randomised to the daily oral TDF/FTC arm) (145). Participants who chose CAB (n=1,931) preferred injections (77%), desired a convenient or discrete PrEP method (11%), valued CAB effectiveness (8%) or gave other/no reasons (4%).

B.2.7 Subgroup analysis

B.2.7.1 Incident HIV-1 acquisitions in Step 1 and 2 by subgroup

B.2.7.1.1 *HPTN 083*

Subgroup analyses in the mITT population showed that the direction and overall magnitude of effect with cabotegravir was consistent across the pre-specified subgroups and populations (age: <30, ≥30 years; cohort: men who have sex with men, transgender women; ethnic group: Black, Non-Black; region: US, Latin America, Asia, Africa), and with the overall mITT population (Appendix E). In the updated analysis including post-hoc extended retrospective testing, results for all subgroup analyses were also consistent with the overall protective effect.

B.2.7.1.2 *HPTN 084*

Subgroup analyses in the mITT population showed that the direction and overall magnitude of effect with cabotegravir was consistent across the pre-specified subgroups (age: <25, ≥25 years; body mass index [BMI]: <30 kg/m^2, ≥30 kg/m^2), and with the overall mITT population (Appendix E). In the updated analysis including post-hoc extended retrospective testing, results for all subgroup analyses were also consistent with the overall treatment effect.

B.2.8 Meta-analysis

Not applicable.

B.2.9 Indirect and mixed treatment comparisons

As the HPTN 083 and HPTN 084 trials did not include a placebo arm, no trial-based comparisons between cabotegravir and people not taking PrEP (no PrEP) are available. An indirect treatment comparison (ITC) was conducted to provide estimates of the effectiveness of cabotegravir compared with no PrEP, via a common comparator of TDF/FTC. A feasibility assessment of conducting an indirect comparison of the published PrEP evidence determined there is wide variation in effectiveness of oral TDF/FTC observed between populations, predominantly due to differences in adherence levels. Heterogeneity in adherence levels may confound estimates of effectiveness from the indirect comparison. To reduce the risk of confounding, the indirect comparison included a meta-regression, using aggregated

study data, to account for variation in TDF/FTC adherence between the studies included in the analysis.

Published estimates are available describing the relationship between adherence to and effectiveness of oral TDF/FTC, including a meta-regression (146), which was used to inform the methods of an indirect comparison estimating effectiveness of cabotegravir versus placebo (122). However, these analyses include limited reporting of source data, methods, and results, which are key limitations in the context of health technology assessment (HTA; see Appendix D for further details).

B.2.9.1 Objectives

The primary objective of this analysis was to provide an indirect estimate of the comparative effectiveness of cabotegravir compared with no PrEP via a common comparator of oral TDF/FTC. The secondary objective of this analysis was to describe the relationship between oral TDF/FTC effectiveness (compared with placebo) and adherence (measured using plasma levels) based on a meta-regression using aggregated study data to account for variation in adherence between the trials included in the indirect comparison (full details are provided in Appendix D).

The background incidence of HIV acquisition was also estimated for individuals not receiving PrEP in the HPTN 083 and HPTN 084 studies.

B.2.9.2 Methodology

B.2.9.2.1 *Identification and selection of studies*

The clinical SLR reported in Section B.2.1 and Appendix D identified all available evidence evaluating cabotegravir and TDF/FTC for individuals at increased risk of HIV acquisition. The following additional criteria were applied for inclusion in the indirect comparisons:

- **Interventions/comparators:** cabotegravir for PrEP, TDF/FTC, placebo or no PrEP.
- **Outcomes:** Treatment effect on risk of HIV acquisition expressed as a relative risk or hazard ratio (or sufficient statistics to allow these measures to be calculated).

- **Other:** Adherence to TDF/FTC (expressed as proportion of participants with measurable plasma levels).

B.2.9.2.2 *Methods*

Full details of the methods are provided in Appendix D. The indirect comparison, including the meta-regression used study level variables in absence of individual participant level data availability. The exposure variable was PrEP treatment (either cabotegravir or TDF/FTC) or no PrEP (placebo) as per the randomised treatment arms in the contributing trials. The outcome used in the analysis was the treatment effect on the risk of HIV acquisition (expressed as a relative risk or hazard ratio of event) as reported in the contributing trials. Adherence to TDF/FTC (expressed as proportion of participants with measurable plasma levels) as reported in the contributing trials was included as a potential confounding variable as a study level variable in a meta-regression. There is empirical evidence from Hanscom et al. 2019 (146) and O Murchu et al. 2022 (58) that there is significant variation in adherence to oral PrEP between trials and that it acts as a treatment effect modifier. It is expected that there will be less variation in the adherence (and effectiveness) in those opting to receive PrEP using cabotegravir due to its posology (intramuscular injections every two months, administered by a healthcare professional). Indeed, in HPTN 083 and HPTN 084, cabotegravir appeared to offer an adherence advantage versus TDF/FTC by removing the need for daily oral pills (Section B.2.12.1.3).

The indirect comparisons were implemented as Bayesian Hierarchical models and both fixed and random treatment effects analyses were conducted. The use of informative priors for the random treatment effect variance was considered if suitable published estimates were available. Sensitivity analyses were considered and conducted where feasible given available data.

B.2.9.3 Results

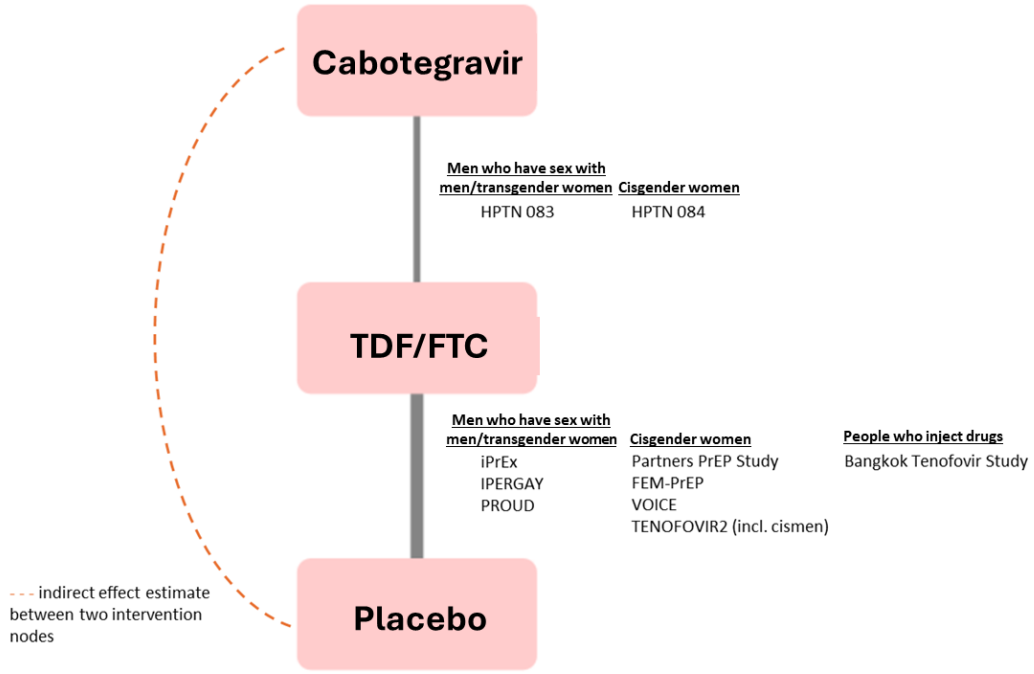
B.2.9.3.1.1 Overview of included studies

Of the 19 studies identified in the clinical SLR (Section B.2.1), ten were considered suitable for inclusion in the analysis given that they met the additional inclusion criteria of reporting TDF/FTC adherence based on plasma sampling (or pill count data for the relevant sensitivity analysis), listed in Table 19. It should be noted that

there is some heterogeneity with respect to the location and study population between the identified studies.

The available trials form a connected network; the network diagram is provided in Figure 7.

Figure 7: Network diagram of trials included in the analysis



Abbreviations: TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

Table 19: List of studies included in the ITC and their baseline characteristics

Study ID	Study location	Design	Treatment	N	Age (year) Mean (SD)/ Median [IQR]†	Gender cohort (%) Men who have sex with men	Transgender women	Heterosexual male	Heterosexual female	Prefer no answer
HPTN 083 (119)	Mixed	Double blind	Cabotegravir	2,282	26 [22–32]	88.2	11.7	–	–	0.1
			TDF/FTC	2,284	26 [22–32]	86.6	13.3	–	–	<0.1
iPrEx (117)	Mixed	Double blind	TDF/FTC	1,251	–‡	100	–	–	–	–
			Placebo	1,248	–‡	100	–	–	–	–
PROUD (147)	England	Open-label	TDF/FTC	273	35 [30–43]	100	–	–	–	–
			Deferred PrEP	267	35 [29–42]	100	–	–	–	–
IPERGAY (148)	Europe	Double blind	TDF/FTC event-driven	199	35 [29–43]	100	–	–	–	–
			Placebo	201	34 [29–42]	100	–	–	–	–
HPTN 084 (120)	Africa	Double blind	Cabotegravir	1,614	25 [22–30]	–	–	–	100	–
			TDF/FTC	1,610	25 [22–30]	–	–	–	100	–
FEM-PrEP (149)	Africa	Double blind	TDF/FTC	1,062	23 [range: 18–35]	–	–	–	100	–
			Placebo	1,058	23 [range: 18–35]	–	–	–	100	–
TENOFOVIR2 (150)	Africa	Double blind	TDF/FTC	611	–‡	–	–	54.2	45.8	–
			Placebo	608	–‡	–	–	54.4	45.6	–
Partners PrEP Study Continuation (151)	Africa	Double blind	TDF	2,215	33 [29–40]	–	–	62	–	–
			TDF/FTC	2,212	34 [28–40]	–	–	64	–	–
Bangkok Tenofovir Study (152)	Asia	–	TDF	1,204	–‡	–	–	80	–	–
			Placebo	1,209	–‡	–	–	80	–	–
VOICE (153)	Africa	–	TDF/FTC	1,003	25.2 (5.2)	–	–	–	100	–
			Placebo	1,009	25.3 (5.2)	–	–	–	100	–

†Mean age (SD) or median age [IQR] unless otherwise stated. Variance for mean ages is always in (), variance for median ages is always in []; ‡Age reported in age categories.

Abbreviations: IQR, interquartile range; ITC, indirect treatment comparison; SD, standard deviation; TDF, tenofovir diphosphate; TDF/FTC, tenofovir diphosphate/emtricitabine.

The study treatment effect estimates are provided in Table 20.

Table 20: Study Treatment Effect Estimates

Study	Treatment	Compar-ator	Population	RR of HIV acquisition	95% CI	TDF/FTC adherence (detectable in plasma)
Partners PrEP	TDF/FTC	Placebo	Male heterosexual	0.37	0.17, 0.8	0.81
Partners PrEP	TDF/FTC	Placebo	Female heterosexual	0.29	0.13, 0.63	0.81
Bangkok Tenofovir Study	TDF	Placebo	Male drug users	0.624	0.321, 0.822	0.66
Bangkok Tenofovir Study	TDF	Placebo	Female drug users	0.214	0.033, 0.832	0.66
iPrEx Trial	TDF/FTC	Placebo	Men who have sex with men	0.56	0.37, 0.85	0.50
VOICE	TDF/FTC	Placebo	Female heterosexual	1.04	0.73, 1.49	0.29
IperGay	TDF/FTC event-driven	Placebo	Men who have sex with men	0.14	0.02, 0.6	0.86
Tenefovir 2	TDF/FTC	Placebo	Female heterosexual	0.506	0.192, 1.215	0.77
Tenefovir 2	TDF/FTC	Placebo	Male heterosexual	0.199	0.031, 0.754	0.77
FEM-PrEP	TDF/FTC	Placebo	Female heterosexual	0.94	0.59, 1.52	0.36
PROUD	TDF/FTC	Deferred PrEP	Men who have sex with men	0.14	0.04, 0.36	0.88
HPTN 083	Cabotegravir	TDF/FTC	Men who have sex with men/ transgender women	0.34	0.18, 0.62	0.86
HPTN 084	Cabotegravir	TDF/FTC	Female heterosexual	0.12	0.05, 0.31	0.56

Abbreviations: CI, confidence interval; PrEP, pre-exposure prophylaxis; RR, relative risk; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

B.2.9.3.1.2 Relationship between adherence and effectiveness

There appears to be a strong relationship between adherence and effectiveness of TDF/FTC in reducing HIV acquisition, with no obvious deviation from the overall trend by study location or by population (Figure 8). There are insufficient studies to allow estimation of location or population specific slopes.

Figure 8: Relationship between adherence to TDF/FTC and effectiveness of TDF/FTC versus no PrEP in reducing HIV acquisition by study, population and location

The size of the bubbles on the plot is proportionate to the precision of the effectiveness estimate.
Abbreviations: HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

The results of the meta-regression component of the analysis are shown in Table 21. The model including sex as a covariable had a [redacted] Deviance Information Criteria (DIC) than the other two models (by approximately 2). This suggests that the inclusion of sex as a covariable [redacted] model fit (lower DIC indicates a better fitting model). This is aligned with the [redacted] of sex in Figure 8.

Table 21: Regression model results

Model	Intercept ($\propto$)†	Adherence co-efficient (β)†	Sex co-efficient (β)†	Model Fit (DIC)
Log relationship + Sex	[redacted]	[redacted]	[redacted]	[redacted]
Log relationship	[redacted]	[redacted]	–	[redacted]
Linear relationship	[redacted]	[redacted]	–	[redacted]
Log relationship (Excl. PROUD, IPERGAY & Bangkok)	[redacted]	[redacted]	–	[redacted]

†Mean and standard error of the posterior distribution.
Abbreviations : DIC, Deviance Information Criterion.

The DIC for the models with a linear and logarithmic relationship are [redacted], which is aligned with the [redacted] fit observed for these models in Figure 9. Visually, [redacted]. The

predicted relationship between adherence and effectiveness for each of the fitted models and the published regression models are shown in Appendix D.

Figure 9: Comparison of linear and logarithmic relationship between adherence to TDF/FTC and effectiveness of TDF/FTC versus no PrEP in reducing HIV acquisition by study population

The size of the bubbles on the plot is proportionate to the precision of the effectiveness estimate.
Abbreviations: HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

Based on these observations, the logarithmic model without the sex covariable was selected as the base-case model on the basis that there was no evidence that including the sex covariable [redacted] model fit and the use of a logarithmic functional form constrained the predicted relative risks to be positive (estimated % effectiveness to be less than 100%). Ideally, 'sex' would be included as an interaction effect; however, there are not enough data points to provide interpretable estimates. The log relationship was preferred primarily because it did not generate implausible negative values for relative risk (RR) (effectiveness greater than 100%) at high levels of adherence. The relationship estimated from this model is illustrated in Figure 10.

Figure 10: Relationship between effectiveness and adherence in the base case meta-regression model

Abbreviations: CAB-LA, cabotegravir long-acting; PrEP, pre-exposure prophylaxis; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

B.2.9.3.1.3 Results of the indirect comparison

The results of the indirect comparison are shown in Table 22. The predicted effectiveness of cabotegravir versus TDF/FTC is [redacted] for the cisgender women population (HPTN 084 trial) ([redacted]) versus the men who have sex with men and transgender women population (HPTN 083 trial) ([redacted]). This [redacted] with lower adherence to TDF/FTC observed in the HPTN 084 trial (56%), compared with the HPTN 083 trial (86%) (119, 120). When combining relative effectiveness of cabotegravir versus TDF/FTC and adherence level to TDF/FTC, the estimated effectiveness of cabotegravir versus no PrEP is [redacted] for the cisgender women population (HPTN 084 trial) and [redacted] for the men who have sex with men and transgender women population (HPTN 083 trial).

Table 22. Indirect comparison results (Log RRs) for the HPTN 083 and HPTN 084 trial populations

Parameter	Log RR		% Effectiveness		
	Mean	SD	Mean	2.5% CrI	97.5% CrI
Cabotegravir versus TDF/FTC (HPTN 083 population)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cabotegravir versus TDF/FTC (HPTN 084 population)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TDF/FTC versus no PrEP (HPTN 083 population)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TDF/FTC versus no PrEP (HPTN 084 population)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cabotegravir versus no PrEP (HPTN 083 population)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cabotegravir versus no PrEP (HPTN 084 population)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CrI, credible interval; HPTN, HIV Prevention Trials Network; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine; RR, relative risk; SD, standard deviation.

The estimated effectiveness of TDF/FTC versus no PrEP, cabotegravir versus no PrEP, and the no PrEP event rate arising from the various meta-regression models in men who have sex with men and transgender women (HPTN 083) and cisgender women (HPTN 084) populations are provided in Appendix D.

B.2.9.4 Uncertainties in the indirect and mixed treatment comparisons

There are several uncertainties that need to be taken into account when considering the results of the indirect comparison. The effectiveness of cabotegravir versus no PrEP was estimated using indirect comparison methods. The validity of the current analysis relies on the validity of the consistency assumption ($RR_{A\text{ vs. }C} = RR_{A\text{ vs. }B} \times RR_{B\text{ vs. }C}$) and the validity of the meta-regression used to predict the effectiveness of TDF/FTC versus no PrEP as a function of adherence to TDF/FTC, when used to estimate the effectiveness of TDF/FTC in the HPTN 083 and HPTN 084 trial populations. There are a number of limitations in assessing the validity of these assumptions, including:

- The HTPN 083 and HPTN 084 trials did not include no PrEP arms and there are no trials directly comparing cabotegravir versus no PrEP available to validate the predictions of effectiveness used within the analysis.
- The model used to predict the effectiveness of TDF/FTC versus no PrEP as a function of adherence to TDF/FTC was a meta-regression model. There were several identified characteristics that showed marked heterogeneity between

the trials. There were insufficient studies available to include other covariables in the meta-regression model alongside adherence.

- The model assumes that adherence to cabotegravir will be as observed within the HPTN 083 and HPTN 084 trials.

B.2.9.5 Conclusions of the indirect comparisons

Variation in adherence to TDF/FTC appears to be highly predictive of the effectiveness of TDF/FTC. It also appears that variation in adherence explains a large degree of the heterogeneity in TDF/FTC efficacy observed in study results. The indirect comparison of cabotegravir versus no PrEP suggests effectiveness in reducing the risk of HIV acquisition is [redacted] in men who have sex with men and transgender women (HPTN 083 population), and [redacted] in cisgender women (HPTN 084 population). [redacted] estimates of effectiveness for cabotegravir versus no PrEP were observed when using data from the HPTN 083 and HPTN 084 trials despite differences in population, setting and underlying rate of HIV acquisition. This supports the generalisability of results from the HPTN 083 and HPTN 084 trials to other populations. The results of the indirect comparison appear to be robust to the specification of the meta-regression component. The underlying rate of HIV acquisition for patients not receiving PrEP was estimated as [redacted] events per 100 PY in men who have sex with men and transgender women and [redacted] events per 100 PY in cisgender women. The indirect treatment comparison provides a robust estimate of the effectiveness of cabotegravir and TDF/FTC versus no PrEP which is used to inform clinical parameters in the base-case economic analysis.

B.2.10 Adverse reactions

Adverse reactions are reported for the safety population (all intention-to-treat [ITT] participants who received any oral or injectable product). An OBSP safety analysis was performed to assess the safety profile of cabotegravir and daily oral TDF/FTC during Steps 1 and 2.

B.2.10.1 HPTN 083

B.2.10.1.1 *Overall summary of adverse events*

Overall, similar proportions of participants in both study arms reported ≥1 adverse event (AE) during OBSP Steps 1 and 2 (Table 23) (12, 123). A higher proportion of participants in the cabotegravir group reported drug-related AEs versus the daily oral TDF/FTC group. Similar frequencies of Grade ≥2 AEs, and Grade ≥3 AEs were reported across both treatment arms, and the proportion of participants with serious adverse events (SAEs) and AEs leading to study drug discontinuation was low in both arms. In total, there were 10 fatal SAEs (four in the cabotegravir arm and six in the daily oral TDF/FTC arm).

Table 23. HPTN 083: Overall summary of OBSP AEs (Steps 1 and 2; Safety population)

	Cabotegravir (N=2,281) n (%)	Daily oral TDF/FTC (N=2,285) n (%)
Any AE	2,174 (95)	2,157 (94)
Drug-related AEs	1,874 (82)	1,355 (59)
Any AE, excluding ISR	2,143 (94)	2,151 (94)
Drug-related AE, excluding ISRs	1,075 (47)	1,134 (50)
ISR AE	1,740 (76)	726 (32)
Drug-related ISR AE‡	1,724 (81)	652 (31)
Any Grade ≥2 AEs	2,115 (93)	2,107 (92)
Drug-related Grade ≥2 AEs	1,391 (61)	951 (42)
Grade ≥2 AEs, excluding ISRs	2,092 (92)	2,103 (92)
Drug-related Grade ≥2 AEs, excluding ISRs	871 (38)	900 (39)
Grade ≥2 ISR AEs‡	1,022 (48)	139 (7)
Drug-related Grade ≥2 ISR AEs‡	1,009 (48)	121 (6)
Any Grade ≥3 AEs	745 (33)	754 (33)
Drug-related Grade ≥3 AEs	131 (6)	93 (4)
Grade ≥3 AEs, excluding ISRs	716 (31)	754 (33)
Drug-related Grade ≥3 AEs, excluding ISRs	84 (4)	93 (4)
Grade ≥3 ISR AEs‡	54 (3)	0
Drug-related Grade ≥3 ISR AEs‡	54 (3)	0
AEs leading to discontinuation of study drug	135 (6)	91 (4)
Drug-related AEs leading to discontinuation of study drug	67 (3)	24 (1)
ISRs leading to discontinuation of study drug	47 (2)	0

	Cabotegravir (N=2,281) n (%)	Daily oral TDF/FTC (N=2,285) n (%)
Any SAE	109 (5)	104 (5)
Drug-related SAE	4 (<1)	3 (<1)
Fatal SAEs†	4 (<1)	6 (<1)
Drug-related fatal SAEs	0	1 (<1)

Source: HPTN 083 clinical study report (123) and EMA Apretude assessment report (12).
†One additional death occurred during Step 3 (stab wound in the TDF/FTC arm); ‡N in this category is the number of participants who received at least one injection of study drug (Injection Safety Population) in Step 2 only.
Abbreviations: AE, adverse event; ISR, injection site reaction; OBSP, on blinded study product; SAE, serious adverse event; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

B.2.10.1.2 *Common adverse events*

The most common AEs (reported in >10% of participants) in the cabotegravir arm were injection site reactions (ISR; including injection site pain, injection site nodule, and injection site induration), creatinine renal clearance decreased and blood creatine phosphokinase increased (Table 24) (12, 123). As expected, ISRs were frequently reported during Step 2 (the injection phase) and were more common in the cabotegravir versus daily oral TDF/FTC arm.

Table 24. HPTN 083: Summary of common AEs (≥10% in either arm, Steps 1 and 2; Safety population)

Preferred Term	Cabotegravir (N=2,281) n (%)	Daily oral TDF/FTC (N=2,285) n (%)
Any AE	2,174 (95)	2,157 (94)
Injection site pain	1,713 (75)	688 (30)
Creatinine renal clearance decreased	1,576 (69)	1,661 (73)
Blood creatine phosphokinase increased	506 (22)	497 (22)
Blood creatinine increased	379 (17)	426 (19)
Nasopharyngitis	383 (17)	379 (17)
Headache	377 (17)	356 (16)
Diarrhoea	328 (14)	336 (15)
Anal chlamydia infection	264 (12)	297 (13)
Upper respiratory tract infection	264 (12)	271 (12)
Injection site nodule	263 (12)	13 (<1)
Lipase increased	255 (11)	272 (12)
Injection site induration	255 (11)	8 (<1)
Blood glucose increased	247 (11)	166 (7)
Pyrexia	232 (10)	112 (5)
Proctitis gonococcal	220 (10)	236 (10)
Aspartate aminotransferase increased	213 (9)	220 (10)
Alanine aminotransferase increased	186 (8)	220 (10)

Source: HPTN 083 clinical study report (123) and EMA Apretude assessment report (12).
Note: AEs occurring in ≥5 to <10% of participants are described in Appendix F.
Abbreviations: AE, adverse event; OBSP, on blinded study product; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

B.2.10.1.3 *Grade ≥2 AEs (primary safety endpoint) and Grade ≥3 AEs*

No marked difference in the overall frequency of Grade ≥2 AEs (the primary safety endpoint) was observed between the trial groups (Table 25).

Table 25: HPTN 083: Most frequent Grade ≥2 AEs (≥10% in either treatment group, Steps 1 and 2; safety population)

Preferred term	Cabotegravir (N=2,281) n (%)	Daily oral TDF/FTC (N=2,285) n (%)
Any Grade ≥2 AEs	2,115 (93)	2,107 (92)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Source: HPTN 083 clinical study report (123) and EMA Apretude assessment report (12).
Note, Grade ≥2 AEs occurring in ≥5 to <10% of participants are described in Appendix F.
Abbreviations: AE, adverse event; OBSP, on blinded study product; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

Grade ≥3 AEs occurred with similar frequency in both treatment groups, except for ISRs (injection site pain occurred in 50 [2%] of participants in the cabotegravir arm [all Grade 3] versus none in the TDF/FTC arm) (12, 123). The most common Grade ≥3 AEs excluding ISRs were blood creatine phosphokinase increased (cabotegravir: 323 [14%] participants; TDF/FTC: 308 [13%] participants) and creatinine clearance decreased (cabotegravir: 155 [7%] participants; TDF/FTC: 188 [8%] participants).

B.2.10.1.4 *Drug-related adverse events*

AEs which were considered drug-related by the investigator were more common with cabotegravir (1,874 [82%]) versus TDF/FTC (1,355 [59%]), with the difference mostly attributed to the increased rate of ISRs (12, 123). The most frequently reported drug-related AE was injection site pain for the cabotegravir arm (74%) and creatinine renal clearance decreased (32%) for the TDF/FTC arm (Table 26). Excluding ISRs, similar proportions of participants in both treatment arms experienced at least one drug-related Grade ≥2, or Grade ≥3 AE (Table 23).

Table 26. HPTN 083: Summary of drug-related AEs in ≥5% of participants (Steps 1 and 2; Safety population)

Preferred term	Cabotegravir (N=2,281) n (%)	Daily oral TDF/FTC (N=2,285) n (%)
Total drug-related AEs	1,874 (82)	1,355 (59)
Injection site pain	1,697 (74)	612 (27)
Creatinine renal clearance decreased	671 (29)	723 (32)
Injection site nodule	263 (12)	[redacted]
Injection site induration	255 (11)	[redacted]
Injection site swelling	204 (9)	[redacted]
Blood creatinine increased	166 (7)	169 (7)
Diarrhoea	[redacted]	115 (5)
Nausea	[redacted]	125 (5)

Source: HPTN 083 clinical study report (123) and EMA Apretude assessment report (12).
Note, drug-related AEs in ≥1% to <5% of participants is reported in Appendix F.
Abbreviations: AE, adverse event; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

B.2.10.1.5 *AEs leading to study drug discontinuation*

Overall, 135 (6%) participants in the cabotegravir arm and 91 (4%) participants in the TDF/FTC arm had AEs leading to discontinuation of the study drug (12, 123). The higher proportion in the cabotegravir arm was mainly driven by ISRs, with 48 (2%) participants experiencing AEs leading to study drug discontinuation in the general disorders and administration site conditions system organ class (SOC) versus none in the TDF/FTC arm.

B.2.10.1.6 *Serious adverse and other significant adverse events*

During Steps 1 and 2, 10 deaths were reported (four in the cabotegravir arm, six in the daily oral TDF/FTC arm). Only one death (cardiac disorder), which occurred in the TDF/FTC arm, was considered drug-related by the investigator (12, 123). The proportion of participants who experienced ≥1 SAE during Steps 1 and 2 was low overall, and similar between the treatment arms (5% of participants in both arms) (12, 123). The types and distribution of SAEs were similar across treatment arms. OBSP drug-related SAEs occurred in <1% of participants in either arm.

Pre-specified adverse events of special interest (AESI) for the cabotegravir arm included ISRs, hepatotoxicity, hypersensitivity reactions, rash, neuropsychiatric events, seizures, hyperglycaemia, weight gain, rhabdomyolysis, impact on creatinine and pancreatitis (Appendix F) (123). The overall frequency of non-ISR AESIs was similar in both treatment arms. There were [redacted]

[redacted]

A higher proportion of participants in the cabotegravir arm reported local ISR AEs versus the daily oral TDF/FTC arm; however, there were [redacted] In the cabotegravir arm, a total of [redacted] participants reported at least one drug-related ISR AE, most frequently injection site pain (81% of cabotegravir arm participants). In participants in the cabotegravir arm who experienced ≥1 ISR, the [redacted] developed a maximum ISR severity of Grade 1 [redacted] or Grade 2 [redacted] with [redacted] Grade 3 ISRs [redacted] and [redacted] ISRs with a severity Grade >3. Both the incidence and the intensity of reported ISRs [redacted] over time. Findings were similar for drug-related ISRs. Only 47 (2%) participants in the cabotegravir arm discontinued the study drug due to ISR AEs, all of which were reported as [redacted]. No participants discontinued the study drug due to ISR AEs in the daily oral TDF/FTC arm.

B.2.10.1.7 *Other safety evaluations and clinical laboratory evaluations*

Full details of other safety evaluations and clinical laboratory evaluations are provided in Appendix F. In brief, the proportion of participants with creatinine laboratory events, and creatinine clearance values were [redacted] between arms (123). The maximum intensity of Grade 3 or 4 treatment-emergent liver enzyme abnormality observations were also [redacted] between arms (123). In the dual-energy x-ray absorptiometry (DXA) subset, bone mineral density trajectories over 2 years were different between arms, with a gain in bone mineral density observed in the cabotegravir arm, and loss in the TDF/FTC arm (between arm difference of –2.3% (95%CI: –3.4, –1.1%); p< 0.01 at Week 105 (n=203) (154). Over 153 weeks (Step 1 and 2 OBSP), participants in both groups experienced weight gain, [redacted] (123).

Changes from baseline in blood pressure and pulse over time, and between treatment groups were [redacted], and blood glucose values were [redacted] between groups (123). Changes in lipid parameters and fasting glucose were similar between treatment groups (12, 123).

B.2.10.1.8 *Safety during the first year of open-label follow-up*

A summary of safety during the first year of unblinded follow-up is provided in Appendix F. Types, incidence rates, and differences between study groups of Grade ≥2 AEs were generally consistent with the blinded phase of the study (126).

B.2.10.2 HPTN 084

B.2.10.2.1 *Overall summary of adverse events*

Similar proportions of participants in both treatment arms reported ≥1 AE during OBSP Steps 1 and 2 (Table 27) (12, 127). A higher proportion of participants in the cabotegravir arm reported events that were considered by the investigator to be drug-related compared with participants in the daily oral TDF/FTC arm (68% vs 63%, respectively). Similar frequencies of Grade ≥2 non-ISR AEs were reported for both treatment arms, and the proportion of participants with SAEs and AEs leading to discontinuation of the study drug were low and similar between groups. No fatal SAEs were considered by the investigator to be related to the study drug.

Table 27: HPTN 084: Overall summary of all OBSP AEs (Steps 1 and 2; safety population)

	Cabotegravir (N=1,614) n (%)	Daily oral TDF/FTC (N=1,610) n (%)
Any AE	1,556 (96)	1,540 (96)
Drug-related AEs	1,098 (68)	1,014 (63)
Any AE, excluding ISRs	1,554 (96)	1,540 (96)
Drug-related AE, excluding ISRs	980 (61)	998 (62)
ISR AE†	578 (38)	166 (11)
Drug-related ISR AE†	575 (38)	163 (11)
Any Grade ≥2 AEs	1,489 (92)	1,480 (92)
Drug-related Grade ≥2 AEs	903 (56)	848 (53)
Grade ≥2 AEs, excluding ISRs	1,482 (92)	1,478 (92)
Drug-related Grade ≥2 AEs, excluding ISRs	833 (52)	841 (52)
Grade ≥2 ISR AEs†,‡	196 (13)	27 (2)
Drug-related Grade ≥2 ISR AEs†	192 (13)	25 (2)
Any Grade ≥3 AEs	265 (16)	274 (17)
Drug-related Grade ≥3 AEs	86 (5)	99 (6)
Grade ≥3 AEs, excluding ISRs	264 (16)	274 (17)
Drug-related Grade ≥3 AEs, excluding ISRs	85 (5)	99 (6)
Grade ≥3 ISR AEs†,‡	1 (<1)	1 (<1)
Drug-related Grade ≥3 ISR AEs†	1 (<1)	1 (<1)
AEs leading to discontinuation of study drug	17 (1)	22 (1)

	Cabotegravir (N=1,614) n (%)	Daily oral TDF/FTC (N=1,610) n (%)
Drug-related AEs leading to discontinuation of study drug	0	0
ISRs leading to discontinuation of study drug	0	0
Any SAE	25 (2)	33 (2)
Drug-related SAE	1 (<1)	3 (<1)
Fatal SAEs	2¶	0
Drug-related fatal SAE	0	0

Source: HPTN 084 clinical study report (127) and EMA Apretude assessment report (12).
†N is the number of participants who received at least one injection of study drug (Injection Step 2 Safety Population) in Step 2 only (cabotegravir: N=1,519, TDF/FTC: N=1,516); ‡No participant experience a Grade 4 or 5 ISR and 1 participants in each treatment group experienced one or more Grade 3 ISRs; ¶An additional AE (hypertensive heart disease) was reported during Step 2 non-OBSP.
Abbreviations: AE, adverse event; HPTN, HIV Prevention Trials Network; ISR, injection site reaction; OBSP, on blinded study product; SAE, serious adverse event; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

B.2.10.2.2 *Common adverse events*

The most frequently reported AEs (>30% of participants) in the cabotegravir arm were creatine renal clearance decreased, blood glucose increased, amylase increased, and injection site pain (Table 28) (12, 127). As expected with the method of administration, ISRs were reported during Step 2 (injection phase) and were more frequent in the cabotegravir group versus the daily oral TDF/FTC group.

Table 28: HPTN 084: Overall summary of common OBSP AEs (≥10% in either treatment group, Steps 1 and 2; safety population)

Preferred Term	Cabotegravir (N=1,614) n (%)	Daily oral TDF/FTC (N=1,610) n (%)
Number of participants with any AE	1,556 (96)	1,540 (96)
Creatinine renal clearance decreased	1,160 (72)	1,192 (74)
Blood glucose increased	584 (36)	451 (28)
Amylase increased	558 (35)	573 (36)
Injection site pain	522 (32)	147 (9)
Blood glucose decreased	425 (26)	439 (27)
Headache	377 (23)	373 (23)
Blood creatinine increased	363 (22)	347 (22)
Blood phosphorus decreased	278 (17)	322 (20)
Upper RTI	268 (17)	293 (18)
Blood creatine phosphokinase increased	237 (15)	263 (16)
ALT increased	232 (14)	228 (14)
Urinary tract infection	225 (14)	210 (13)
AST increased	212 (13)	181 (11)
Lipase increased	198 (12)	171 (11)
Dysfunctional uterine bleeding	161 (10)	161 (10)

Preferred Term	Cabotegravir (N=1,614) n (%)	Daily oral TDF/FTC (N=1,610) n (%)
Vulvovaginal candidiasis	139 (9)	162 (10)
Nausea	79 (5)	157 (10)

Source: HPTN 084 clinical study report (127) and EMA Apretude assessment report (12).
Note: AEs occurring in ≥5 to <10% of participants are described in Appendix F.
Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HPTN, HIV Prevention Trials Network; OBSP, on blinded study product; RTI, respiratory tract infection; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

B.2.10.2.3 *Grade ≥2 AEs (primary safety endpoint) and Grade ≥3 AEs*

Grade ≥2 AEs during Steps 1 and 2 (the primary safety endpoint) were observed in 92% of participants in both groups (Table 29) (12, 127).

Table 29: HPTN 084: Most frequent Grade ≥2 AEs (≥10% in either treatment group, Steps 1 and 2; safety population)

Preferred Term	Cabotegravir (N=1,614) n (%)	Daily oral TDF/FTC (N=1,610) n (%)
Number of participants with any AE Grade 2 or higher	1,489 (92)	1,480 (92)
[redacted]		

Source: HPTN 084 clinical study report (127) and EMA Apretude assessment report (12).
Note: Grade ≥2 AEs occurring in ≥5 to <10% of participants are described in Appendix F.
Abbreviations: AE, adverse event; HPTN, HIV Prevention Trials Network; OBSP, on blinded study product; RTI, respiratory tract infection; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine; UTI, urinary tract infection.

Grade ≥3 AEs occurred with similar frequency in both groups (cabotegravir: 16% vs daily oral TDF/FTC: 17%) (12, 127). AEs occurring in >1% of participants in the cabotegravir or daily oral TDF/FTC arms were creatinine renal clearance decreased (7% vs 8%, respectively), blood creatinine increased (4% vs 4%, respectively), blood creatine phosphokinase increased (3% vs 2%, respectively), and abnormal loss of weight (1% vs 2%, respectively).

B.2.10.2.4 *Drug-related adverse events*

In total, 68% of participants in the cabotegravir arm, and 63% of participants in the daily oral TDF/FTC arm experienced ≥1 drug-related AE (Table 27). [redacted]

[redacted]

Table 30: HPTN 084: Summary of common drug-related AEs (≥5% in either treatment group, Steps 1 and 2; safety population)

Preferred Term	Cabotegravir (N=1,614) n (%)	Daily oral TDF/FTC (N=1,610) n (%)
Number of participants with at least one AE considered related to study drug	1,098 (68)	1,014 (63)
Creatinine renal clearance decreased	692 (43)	[redacted]
Injection site pain	519 (32)	[redacted]
Amylase increased	252 (16)	[redacted]
Blood creatinine increased	213 (13)	[redacted]
Headache	190 (12)	[redacted]
Blood phosphorus decreased	169 (10)	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Source: HPTN 084 clinical study report (127) and EMA Apretude assessment report (12).
Note: Drug-related AEs occurring in ≥1% to <5% of participants is provided in Appendix F.
Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HPTN, HIV Prevention Trials Network; OBSP, on blinded study product; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

B.2.10.2.5 *AEs leading to study drug discontinuation*

Overall, 17 (1%) participants in the cabotegravir arm and 22 (1%) participants in the daily oral TDF/FTC arm had AEs leading to discontinuation of the study drug (12, 123). No participants in either arm had ISRs that led to discontinuation of the study drug. In the cabotegravir arm, 5 (<1%) participants had drug-related Grade ≥3 non-ISR AEs leading to discontinuation of study drug; none were SAEs. In the TDF/FTC group, 8 (<1%) participants had drug-related Grade ≥3 non-ISR AEs leading to discontinuation of study drug.

B.2.10.2.6 *Serious and other significant adverse events*

In total, three participants in the cabotegravir group died due to AEs (two during Step 2 OBSP [hypertensive heart disease, and headache]; one during Step 2 non-OBSP [cerebrovascular accident]) (12, 127). None of the deaths were considered to be

related to cabotegravir. No deaths were reported in the daily oral TDF/FTC arm up to the data cut-off for the blinded period). The proportion of participants who experienced ≥1 SAE during Steps 1 and 2 was similar between arms (2% in each group) (12, 127). The types and distribution of SAEs were similar across treatment arms, and all reported SAEs occurred in <1% of participants.

B.2.10.2.7 *Adverse events of special interest*

Pre-specified AESIs for the cabotegravir arm included ISRs, hepatotoxicity, hypersensitivity reactions, rash, neuropsychiatric events, seizures and seizure-like events, hyperglycaemia, weight gain, rhabdomyolysis, impact on creatinine and pancreatitis (127). Overall, cabotegravir injections were generally well tolerated, however a higher proportion of participants in the cabotegravir group (38%) reported local ISR AEs versus the daily oral TDF/FTC arm (11%) (12, 123) (Appendix D). There were [redacted] in either treatment group. The overall frequency of non-ISR AESIs was similar in both treatment arms. There were [redacted]

B.2.10.2.8 *Other safety evaluations*

Full details of other safety evaluations and clinical laboratory evaluations are provided in Appendix F. In brief, no notable trends in creatinine abnormalities were observed, and the maximum intensity of treatment-emergent liver laboratory parameters abnormality observations was [redacted] between groups. Over 153 weeks of Step 1 and Step 2 OBSP, there was an [redacted] in the median weight in [redacted] (127). Changes in vital signs (including blood pressure and pulse) from baseline over time and between treatment groups were [redacted] (127), and changes in lipid parameters and fasting glucose was similar between treatment groups (12).

In total, at the data cut-off date of 5th November 2020, there were 49 confirmed pregnancies (120). These participants were unblinded and received open-label TDF/FTC for the duration of pregnancy and breastfeeding; upon completion of

breastfeeding, participants could restart their original drug assignment). Further details on pregnancy incidence, and a summary of pregnancy-related outcomes and adverse events is provided in Appendix F.

B.2.11 Ongoing studies

Two Phase 4 implementation science trials, PILLAR (155) and EBONI (156), evaluating the integration of cabotegravir into standard of care across 40 clinics in the US, enrolling men who have sex with men and transgender men, and Black cisgender and transgender women, respectively are currently ongoing. So far, staff study participants have been surveyed, prior to participant enrolment and implementation of study activities. A high proportion of study staff participants in both studies felt extremely positive or positive about implementing cabotegravir (PILLAR: 85%; EBONI: 93%), and the majority perceived that implementation would be “very easy” or “somewhat easy” (PILLAR: 53%; EBONI: 73%) (157).

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Principal findings of the clinical evidence

B.2.12.1.1 *Cabotegravir provides substantial and statistically significant benefit in reducing the risk of HIV acquisition compared with daily oral TDF/FTC*

In both HPTN 083 and HPTN 084 trials, cabotegravir met the primary endpoint, demonstrating superior efficacy versus daily oral TDF/FTC in reducing the incidence of HIV acquisitions during Step 1 and Step 2 (primary efficacy analysis; 66% reduction [superiority p=0.0005] in HPTN 083, and 88% reduction [p<0.0001] in HPTN 084). Post-hoc analysis of the primary endpoint, using extended virologic testing to better characterise the timing of HIV acquisition, also demonstrated significantly fewer HIV acquisitions with cabotegravir. Supportive, and pre-specified subgroup analyses were consistent with the overall treatment effect (Section B.2.6.1.1, B.2.6.2.1, and B.2.7). The overall trial population in HPTN 084, and subgroups in HPTN 083 included key populations (such as cisgender women, men that have sex with men of Black African ethnicity, and transgender women) with unmet need and least likely to benefit from currently available PrEP options in

England. In addition, efficacy was maintained during an additional year of unblinded follow-up (Section B.2.6.1.1.4 and Section B.2.6.2.1.5).

B.2.12.1.2 *HIV acquisitions with resistance were rare and were observed for both cabotegravir and daily oral TDF/FTC*

In HPTN 083, resistance cases were rarely seen in both the cabotegravir and the TDF/FTC arms. During the combined study period (Step 1, 2, plus one-year of unblinded follow-up), INSTI resistance was detected in 10 (0.44%) cases among the 2,282 participants randomised to and eligible to receive cabotegravir (ITT population) (Section B.2.6.1.2.1). Although INSTI RAMs were detected in all of the rare cases of breakthrough acquisitions in individuals with on-time injections (n=6), all six participants were able to achieve virological suppression using NNRTI or boosted protease inhibitor-based ART (126). Importantly, no INSTI resistance was observed in the subset of cases where HIV was likely acquired during the cabotegravir tail phase (126). In HPTN 084, there were no cases of INSTI resistance detected in any cases in the cabotegravir arm during the blinded study period, with NRTI/NNRTI resistance detected in nine participants in the TDF/FTC arm (0.6% of study participants) (Section B.2.6.2.3.1).

B.2.12.1.3 *Cabotegravir offers an adherence advantage by removing the need for daily oral pills, which may help address unmet needs for individuals sub-optimally adhering to daily oral PrEP*

In HPTN 083, 91.5% of PYs were considered ‘covered’ by injectable cabotegravir LA or placebo across both arms during Step 1 and Step 2, while in the TDF/FTC adherence population, [redacted] of all plasma samples had TFV concentrations equating to adherence of ≥4 doses per week (the minimum protective dose (158); Section B.2.6.1.3.1.2, and B.2.6.1.3.3). This adherence advantage was maintained after 1 year of unblinded follow-up. In HPTN 084, during the blinded phase, 93% of PYs were covered by cabotegravir injections, while plasma TFV levels indicative of 7 doses per week were present in 41.9% of samples (Section B.2.6.2.2.2 and B.2.6.2.3.2.2). Given the strong correlation between adherence and PrEP efficacy, cabotegravir may provide substantial benefits in achieving sustained protection from HIV acquisition compared with daily oral TDF/FTC, which is particularly important among populations known to experience challenges with adherence. The adherence

advantage observed with cabotegravir in the HPTN 083 and HPTN 084 trials is expected to translate to a similar adherence advantage in real-world clinical practice. Importantly, optimising adherence to PrEP among key at-risk populations in the real-world will contribute towards meeting the UK HIV Action Plan's aims of zero new transmissions by 2030 (3).

B.2.12.1.4 *Cabotegravir is generally well tolerated, with comparable tolerability versus daily oral TDF/FTC, with the exception of injection site reactions*

The safety analyses demonstrated that the type and frequency of adverse events were similar between the cabotegravir and TDF/FTC groups, except for ISRs (Section B.2.10). Although ISRs were common among participants in the cabotegravir arm of HPTN 083 and HPTN 084, most ISRs were mild to moderate in severity, and few participants chose to discontinue injections due to ISRs across both trials. In each trial, similar proportions of participants in the cabotegravir and TDF/FTC groups experienced Grade ≥2 clinical or laboratory AEs (the primary safety endpoint). The rate of AEs leading to discontinuation of study drug, SAEs and deaths were low across both treatment groups. In general, AESIs were also reported in similar proportions of participants across treatment groups.

Importantly, there is currently no evidence to suggest that cabotegravir represents a risk for renal and bone health in the long-term. By contrast, the long-term use of oral TDF/FTC may be associated with concerns around renal and bone toxicity (13, 159-163). In addition, cabotegravir was associated with a [redacted] of GI AEs, and may provide an alternative PrEP option for individuals facing challenges with oral TDF/FTC side effects such as nausea or vomiting and diarrhoea.

B.2.12.1.5 *An indirect treatment comparison suggests that cabotegravir is highly effective in reducing the risk of HIV acquisition versus no PrEP*

The effectiveness in reducing the risk of HIV acquisition is [redacted] in both men who have sex with men and transgender women ([redacted]) and cisgender women ([redacted]). This suggests that usage of cabotegravir in individuals who are unable to take oral PrEP could substantially contribute to the UK achieving its aims of zero new HIV transmissions by 2030 (3).

Overall, availability of cabotegravir may appeal to a wide range of individuals at risk of HIV acquisition, meeting specific and individual needs of a diverse range of individuals wishing to use PrEP for whom oral PrEP is not appropriate.

B.2.12.2 Strengths and limitations of the clinical evidence base

B.2.12.2.1 *Strength of the clinical evidence base*

The efficacy and tolerability of cabotegravir for PrEP is supported by two large RCTs versus current UK SoC in populations at risk of HIV acquisition for diverse reasons. The efficacy of cabotegravir observed in the trials is generalisable to any UK individuals who have a similar level of underlying HIV risk to individuals included in the trial, regardless of any specific baseline characteristics or reasons for likely exposure to HIV. As the underlying risk of HIV does not depend on biological, physiological, or geographical factors, conclusions of the HPTN trials are relevant for the UK population at risk of HIV acquisition.

Both studies have a large sample size (mITT N=7,785 across both trials), across a broad range of geographic regions, representing various levels of HIV risk. Importantly, the evidence base includes data for cisgender women, who are typically underrepresented in HIV prevention clinical studies. Having data in populations where use of PrEP is currently underutilised, that reflects individuals seen in UK clinics such as cisgender women, was highlighted as a strength of trial data by clinicians at a UK advisory board (55). The baseline characteristics of trial participants were well balanced between study arms, and the outcome measures used are relevant to HIV prevention. As regimen adherence is a key factor influencing efficacy outcomes, a strength of the studies is that they adopted a double-blind, double-dummy design to prevent the potential for risk of bias in HIV risk exposure and ensured compliance to oral pills (and injections) would be similar across the treatment groups. In addition, sexual-risk behaviour, which contributes to an individual's likelihood of being exposed to HIV, has the potential to influence efficacy outcomes; however, rates of STIs (as a surrogate for sexual risk behaviour) in both studies showed participants maintained a level of sexual risk that was similar between treatment arms. This suggests the reduction in the number of incident HIV acquisitions in the cabotegravir group is due to the intervention rather than a difference in sexual risk behaviour between groups.

Consistent results were observed across the trials and pre-specified subgroups within trials, with the blinded portion of both trials stopped early due to the superior efficacy demonstrated by cabotegravir versus daily oral PrEP for preventing HIV acquisition (a pre-specified criteria based on HIV acquisition event numbers; Section B.2.6.1.1 and B.2.6.2.1). Both trials are ongoing as open-label extension studies to provide longer-term data on the efficacy and tolerability of cabotegravir.

B.2.12.2.2 *Limitations of the clinical evidence base*

A limitation of the HPTN 083 and HPTN 084 studies is that there are no UK participants or sites; however, the generalisability of the evidence base to UK clinical practice is discussed in Section B.2.12.3. In addition, due to ethical considerations, neither study included a placebo arm to act as a no PrEP comparator. The efficacy of cabotegravir versus no PrEP has been estimated using an indirect treatment comparison (Section B.2.9).

B.2.12.3 Generalisability of study results to UK clinical practice

Although no UK participants were included in the HPTN studies investigating cabotegravir for PrEP, the geographical scope of the studies is not unusual for HIV prevention clinical trials (58). The pivotal trials for cabotegravir recruited participants with diverse demographic characteristics, including Black African cisgender women (~97% of HPTN 084 participants were Black African women), transgender women (12% of HPTN 083 participants were transgender women), and ethnically diverse men who have sex with men (~50% of HPTN 083 participants in the US were Black) (Section B.2.3.1). The HPTN trial populations reflect individuals within the UK who have a reason to use PrEP due to an increased likelihood of being exposed to HIV. The trial populations are considered to reflect key populations with increased need for novel PrEP modalities in England, including populations who are disproportionately affected by HIV and/or poorly represented among PrEP users, including gay, bisexual, and men who have sex with men, transgender women, people of Black African ethnicity, and cisgender women. In the UK in 2022, people of White/White other, and people of Black African ethnicity represented the two largest ethnic groups first diagnosed in England (960 of 2,444 [28.2%], and 476 of 2,444 [19.5%], respectively) overall (47). Among gay, bisexual, and men who have sex with men, 58% of diagnoses first made in England were among people of White ethnicity

(11), meaning 42% were in people of other ethnicities, reflecting the ethnically diverse population of men who have sex with men enrolled in HPTN 083. Heterosexual women are also an important population affected by HIV in the UK. Women exposed by sex with men accounted for 23% of new HIV diagnoses first made in England in 2022 (11). HPTN 084 provides evidence for cisgender women, who are typically underrepresented in HIV prevention trials, and are associated with poor PrEP uptake in the UK (only 36% of heterosexual and bisexual women who have sex with men with PrEP need identified initiated or continued PrEP in 2022) (11). In a UK advisory board, clinicians confirmed that the trial populations can be considered reflective of UK clinical practice and populations with unmet need for PrEP, with the trials providing evidence in populations that have unmet need and are less well served in the current PrEP landscape (55). In addition, as described in Section B.2.9, the similar estimates of effectiveness for cabotegravir versus no PrEP seen in the HPTN 083 and 084 trials support the generalisability of the trials results to other populations.

The statistically significant superiority observed in both trials (Section B.2.6.1 and B.2.6.2), and the subgroup analyses of HPTN 083 demonstrating a similar direction and overall magnitude of risk reduction across pre-specified subgroups including age ≤30 vs >30 years, men who have sex with men versus transgender women, Black versus non-Black US participants, and region (US, Latin America, Asia, Africa) (Section B.2.7) demonstrate the efficacy of cabotegravir LA in reducing the risk of HIV across different populations.

Finally, the trial comparator (daily oral TDF/FTC) is consistent with the current UK SoC, and the concomitant services received during the trial (HIV testing, counselling, offer of condoms) are consistent with HIV prevention packages in current UK clinical practice (6, 8).

B.3 Cost effectiveness

The cost-effectiveness analysis demonstrates that cabotegravir is more effective and cost saving when compared with TDF/FTC and no PrEP in individuals at risk of HIV for whom oral PrEP is not appropriate.

- The population considered in the cost-effectiveness analysis reflects the populations from the clinical trials data used to inform the effectiveness in the economic model that is, men who have sex with men and transgender women (HPTN 083) and cisgender women (HPTN 084).

The generalisability of the HPTN trials (described in section B.2.12.3) demonstrates that the economic analysis is representative of the population described in this appraisal, that is, adults and adolescents (weighing at least 35 kg) at risk of acquiring HIV who are eligible for oral PrEP in accordance with BHIVA/BASHH guidelines (8), but for whom oral PrEP is not appropriate.

- The analysis compared cabotegravir to TDF/FTC and to no PrEP.
- The analysis utilises a Markov model developed in Excel to estimate the number of HIV acquisitions over a period of time during which individuals are at-risk, as a function of prophylaxis.
- The model considers a single time-period, of 5 years, in which a person is considered at elevated risk of HIV acquisition and is eligible for PrEP.
- The model considers an underlying risk of HIV acquisition of 4.9 events per 100 PYs for men who have sex with men and transgender women derived from GUMCAD data (8), and of [redacted] events per 100 PYs for cisgender women informed by the indirect treatment comparison.
- The model assumed that 1.38 secondary HIV infections are transmitted onward for every HIV acquisition event in men who have sex with men and transgender women and 0.8 secondary case in cisgender woman over a lifetime.
- The base-case analysis uses the relative risks of HIV acquisition with cabotegravir and TDF/FTC derived from the indirect treatment comparison at the adherence levels observed in the HPTN trials.
- Oral PrEP is included in the analysis at the NHS list price; cabotegravir was included at the list price.
- In the probabilistic base-case analysis, when compared with TDF/FTC cabotegravir resulted in a gain of [redacted] quality-adjusted life years (QALYs) and a minimal increase in costs of [redacted]. When compared against no PrEP, cabotegravir generated a gain of [redacted] QALYs and a cost saving of [redacted].
- Extensive one-way sensitivity analyses and scenario analyses were undertaken and cabotegravir remained cost-effective in nearly all scenarios.

B.3.1 Published cost-effectiveness studies

An economic SLR was conducted (initial SLR: May 2023, updated November 2023) to identify relevant economic evaluations, epidemiological models, cost and/or resource-use studies, and utility studies of PrEP from the published literature in individuals who are at an increased risk of acquiring HIV, including adult (≥18 years) men who have sex with men, transgender women, cisgender women and adolescents. A complete description of the search methodology, a PRISMA flow diagram, and detailed search results are presented in Appendix G. In total, 159 studies were included in the final review. Of the 66 economic evaluations identified, two were focused on the UK (Table 31). Additional details for the UK studies, and the European studies are provided in Appendix G.

Table 31: Summary list of published UK cost-effectiveness studies

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Cambiano et al, 2018 (164)	2018	Dynamic individual-based simulation model Cost year: 2013/14	Men who have sex with men (self-reporting condomless anal sex in the previous 3 months)	Event based tenofovir/ emtricitabine Discounted QALY gain: 40,000 (base case)	Mean cost per year of tenofovir/ emtricitabine (365 pills): £4,331	Dominant (base case)
Ong et al, 2017 (165)	2017	Static decision analytical model Cost year: 2014/2015	5,000 men who have sex with men with an initial 1-year high HIV risk period	Daily PrEP (tenofovir disoproxil fumarate/emtricitabine) at 86% effectiveness saved 361 discounted QALYs versus no PrEP Daily PrEP (tenofovir disoproxil fumarate/emtricitabine) at 64% effectiveness saved 247	Annual cost of PrEP: £4,331	£23,500 at 64% effectiveness

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
				discounted QALYs versus no PrEP		

Abbreviations: ICER, incremental cost-effectiveness ratio; PrEP, pre-exposure prophylaxis; QALYs, quality-adjusted life years; UK, United Kingdom.

B.3.2 Economic analysis

No existing economic evaluations of cabotegravir versus TDF/FTC and no PrEP in the UK were identified in the SLR of economic evaluation studies; it was therefore necessary to develop a de novo cost-effectiveness model (CEM) for the purpose of this appraisal, as described in the following sections.

B.3.2.1 Patient population

In line with the decision problem for this appraisal, the patient population comprises adults and adolescents (weighing at least 35 kg) considered to be at risk of acquiring HIV who are eligible for oral PrEP in accordance with BHIVA/BASHH guidelines (described in Section B.1.3.4 and B.1.3.5), but for whom oral PrEP is not appropriate. This represents the population with highest unmet need for PrEP in the UK as they are underserved by the existing SoC, namely oral PrEP, due to the reasons outlined in Section B.1.3.7.

The underlying risk of HIV acquisition is not defined by biological, physiological or geographical factors. The decision problem does not specifically divide PrEP-eligible individuals along gender or other lines. This approach is consistent with the protected nature of these underlying characteristics and the way PrEP is prescribed in clinical practice, namely on the basis of an individual's underlying reasons for HIV prevention (irrespective of who that individual is). The presented cost-effectiveness analysis uses pooled data from the two key clinical trials detailed above, HPTN 083, and HPTN 084. The proportion of cisgender women in the modelled population (3.14%) was estimated based on UKHSA data for people attending SHSs in England in 2022 with an identified PrEP need, with the remaining population consisting of transgender women and men who have sex with men (47). Data from UKHSA on

indicator (c) in 2022, reported 83,223 gay, bisexual and other men, and 2,695 heterosexual and bisexual women who have sex with men.[k]

B.3.2.2 Model structure

The published economic evaluations of oral PrEP use a variety of modelling approaches but can be broadly categorised as either static Markov- or dynamic transmission-models. The advantage of using a dynamic approach is the ability to readily capture onward (secondary) transmissions. The disadvantage, however, is the inherent complexity, resulting level of transparency, and potential difficulties of including features such as probabilistic sensitivity analysis (PSA) (166). The chosen design represents a compromise between these approaches: a static Markov model developed in Microsoft Excel, with the inclusion of the aggregate impact of secondary infections in terms of additional costs and quality-adjusted life year (QALY) losses linked to each primary infection (section B.3.3.6).

The model estimates the number of HIV acquisitions over a period of time during which individuals are at-risk, as a function of prophylaxis. The Markov model simulates the duration of prophylaxis and the resulting primary HIV acquisitions in a robust and transparent manner. The model compares PrEP with cabotegravir versus TDF/FTC and versus no PrEP. In the base case analysis, the use of TAF/FTC is assumed to be zero to reflect the negligible use of TAF/FTC in clinical practice (23-25).

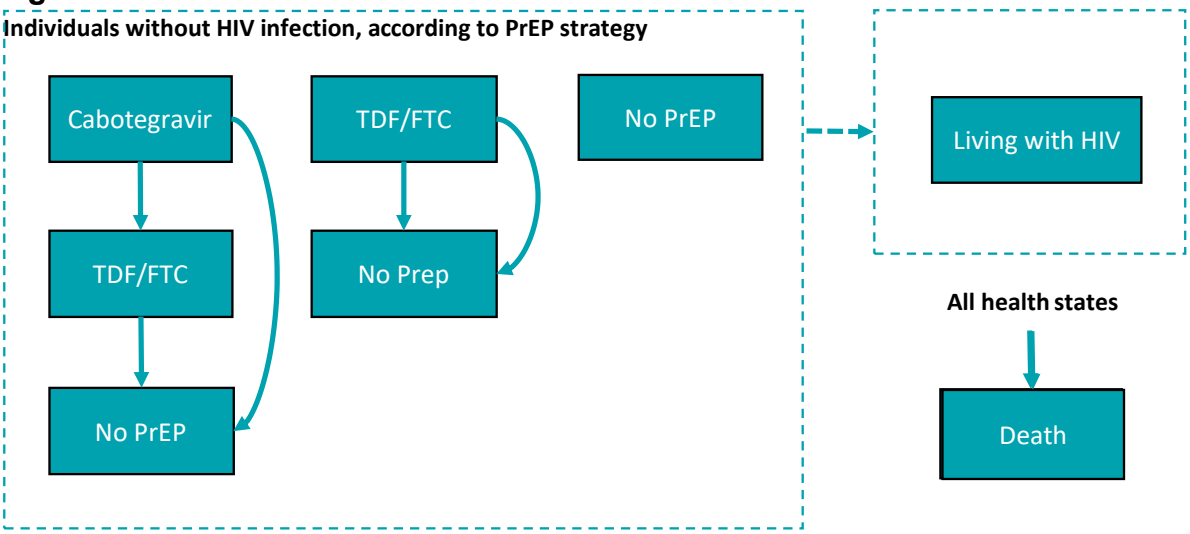
The structure of the model is shown in Figure 11. It consists of five health states. Two of these health states represent use of PrEP, with cabotegravir and TDF/FTC. The third represents people without PrEP who are likely to be exposed to HIV. The fourth state represents people who are living with HIV and the last health state represents death. The costs and health impact of secondary HIV infections are calculated separately and combined with the results from the Markov trace.

For the cabotegravir strategy, intervention is cabotegravir followed by either TDF/FTC or no PrEP after discontinuing cabotegravir, reflecting the

[k] In the UKHSA data, indicator (c) is defined as: 'The number of people who were HIV negative accessing specialist SHSs with PrEP need who had their need for PrEP identified at a clinical consultation. PrEP need identified is based on a combination of PrEP surveillance codes reported through GUMCAD within the previous 12 months of each consultation, including a PrEP eligibility code, being offered PrEP or being prescribed PrEP.'

recommendations in the product's SmPC. For the oral PrEP strategy, intervention is TDF/FTC followed by no PrEP after discontinuation. For the no PrEP strategy, the PrEP states are not populated and individuals enter the model in the no PrEP health state.

Figure 11: Model structure



Abbreviations: HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

B.3.2.2.1 *Model time horizon*

The model applies a lifetime horizon. The model considers a single time-period, of 5 years, in which a person is considered at elevated risk of HIV acquisition and is eligible for PrEP. The duration of the period of elevated risk was chosen to align with assumptions in the current NICE guidelines for reducing sexually transmitted infections (NG221) (9). The duration of the period of elevated risk is likely to be highly variable across individuals and the mean duration in the population is not known. The impact of alternative durations is examined in scenario analysis exploring 1-year and 10-year periods of elevated risk. At the end of the 5-year period of elevated risk, individuals are assumed to no longer be at risk of HIV acquisition and to cease any PrEP; there is no change in HIV status for the modelled cohorts after this point. The consequences of HIV acquisition are modelled over the lifetime of individuals.

B.3.2.2.2 *Model structure and assumptions*

The model assumes that while receiving PrEP, individuals have a lower risk of HIV acquisition than those not receiving PrEP, with protection levels dependent on their

selected PrEP option and their PrEP adherence (for TDF/FTC) and persistence. Individuals receiving PrEP also completed ongoing clinical consultations and testing, and those receiving cabotegravir LA could experience ISRs, which most likely arise at the beginning of the intervention period.

The model considers that individuals who acquired HIV discontinued use of any PrEP, then received HIV-related care including multiclass ARV treatment regimens, ongoing monitoring, and other related care, for the remainder of their lifetimes. The model also considers people who acquired HIV could subsequently transmit HIV (referred to as secondary infections), develop PrEP-related breakthrough resistance and were subject to HIV-specific mortality. Secondary infections (or onward transmission of HIV) were assumed to occur in the same cycle as primary infections, with onward transmission associated with recent HIV acquisition (167), and were subject to HIV-specific mortality from the first cycle of HIV acquisition (164).

B.3.2.2.3 *Model time cycle*

The model uses a time cycle of one month and a half cycle correction is not applied. Transitions are assumed to occur at the end of each time cycle. Hence the transitions reflect the proportion of the cohort acquiring HIV during the time cycle for whom their change in HIV status may not be immediately apparent.

B.3.2.2.4 *Costs and quality-adjusted life expectancy*

Modelled costs included PrEP-related costs (e.g., drug acquisition, administration, and monitoring costs) and the lifetime costs associated with living with HIV. Health outcomes included new primary and secondary HIV acquisitions and the associated losses in life expectancy and quality-adjusted life-years (QALYs). Quality-adjusted life expectancy for the index individual is modelled for the cohort as a function of HIV status. Individuals without HIV are assumed to have a HRQoL and mortality risk equivalent to general population norms.

B.3.2.2.5 *Key features of the analysis*

The key features of the economic analysis are summarised in Table 32. This is the first NICE technology appraisal of a regimen for HIV prevention and no previous submissions are available to inform the current evaluation. Parameter selection was consistent with the NICE Reference Case (9) and with clinical practice in the UK.

Table 32: Features of the economic analysis

	Previous evaluations	Current evaluation	
Factor	**NA**	**Chosen values**	**Justification**
Time horizon	NA	Lifetime (with an at-risk period of 5 years)	The lifetime horizon is consistent with the NICE guidelines for technology appraisal (168). An at-risk period of 5 years aligns with assumptions in the current NICE guidelines for reducing sexually transmitted infections (NG221) (9).
Source of efficacy data	NA	The relative risks of HIV acquisition with cabotegravir and TDF/FTC are calculated on the basis of observed HIV acquisition rates and adherence to TDF/FTC in HPTN 083 and HPTN 084. A meta-regression analysis is used to generate the relative risk of HIV acquisition as a function of adherence to TDF/FTC and this informs TDF/FTC effectiveness in the model.	The effectiveness of TDF/FTC is known to be strongly dependent on adherence. The meta-regression provides the best estimate of the relative risk of HIV acquisition for TDF/FTC at the adherence levels observed in HPTN 083 and HPTN 084.
Treatment waning effect	NA	No effectiveness was assumed for both TDF/FTC and cabotegravir, beyond the respective periods of persistence	The assumption for TDF/FTC reflects the pharmacokinetics of TDF/FTC (169). The assumption for cabotegravir is conservative given the data on pharmacokinetics, which indicate a half-life of 45 days after injection (137).
Source of mortality data	NA	Mortality for people with HIV was estimated by applying a rate ratio to the mortality of the general population of the same age and biological sex. The rate ratio was calibrated to generate a life expectancy shortfall matching reported values (84)	The rate ratio reflects the clinical evidence of increased mortality in people with HIV (170, 171)
Source of utilities	NA	Utility values for the general population as a function of age and sex are taken from data from	Data for the general population were selected to align with NICE guidelines for technology appraisal (168). Data on the

	Previous evaluations	Current evaluation	
		Hernández et al. 2022 (172). Utility values for people living with HIV were derived from general population values after application of an additive disutility derived from Miners 2014 (173)	impact of HIV status on HRQoL were selected on the basis of study size, relevance to the UK population and consistency with regard to the instrument used to measure HRQoL
Source of costs	NA	Costs of TDF/FTC were taken from the BNF with the lowest list price used for the base case analysis (174). Assumptions on resource use associated with monitoring patients on PrEP were based on guidelines from BHIVA/BASHH (8). Unit costs associated with patient monitoring were taken from the NIHR interactive costing tool (175). Costs associated with the treatment of HIV were taken from appropriate literature sources for the UK	Resource use data were aligned with guidance on the frequency and type of monitoring for the UK from the BHIVA/BASHH guidelines. Unit costs were selected from published literature considered most relevant to the UK setting

Abbreviations: BASHH, British Association for Sexual Health and HIV; BHIVA, British HIV Association; BNF, British National Formulary; HIV, human immunodeficiency virus; HRQoL, health-related quality of life; INSTI, integrase strand transfer inhibitor; LA, long acting; NA, not applicable ; NICE, National Institute for Health and Care Excellence; NIHR, National Institute for Health and Care Research; PK, pharmacokinetic ; PrEP, pre-exposure prophylaxis; TA, technology appraisal; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine; UK, United Kingdom.

B.3.2.3 Intervention technology and comparators

The posology of cabotegravir, the intervention, considered in the analysis is as per the licensed dosing regimen (see Section B.1.2). The licence states that [redacted] of cabotegravir LA. [redacted] (Appendix C).[redacted]

[redacted]

Individuals discontinuing cabotegravir LA are advised to initiate oral PrEP. The model assumes that [redacted] of individuals who discontinue cabotegravir receive TDF/FTC. Consulted clinical experts had uncertain views on whether the true value would be higher or lower in clinical practice. Scenario analyses are provided to explore the parameter further.

The active oral PrEP regimen considered in the analysis is TDF/FTC which represents the SoC for PrEP in the UK. The use of TD/FTC as oral PrEP was made widely available in the UK in 2020 (6) and NICE issued a recommendation that TD/FTC be made available to people at high risk of acquiring HIV in December 2021 (176). A number of different generic versions of TD/FTC are available, each of which consists of a single pill containing 200 mg of emtricitabine and 245 mg of tenofovir disoproxil fumarate. The SmPC for Truvada, the original branded formulation of TDF/FTC, specifies a once daily dosing schedule. The analysis considers the use of Truvada (TDF/FTC) according to its marketing authorisation. Effectiveness of TDF/FTC should be considered in connection with adherence as explained in the Section B.3.3.5.

The use of TAF/FTC as an oral PrEP regimen in the UK is recommended only for men who have sex with men who are intolerant or contraindicated to TDF/FTC (6). Recent evidence from the UK on the use of TAF/FTC suggests use is negligible in clinical practice (23-25). Hence the base case analysis does not consider the use of TAF/FTC.

The comparator no PrEP consists of no systemic prophylaxis. It is anticipated that health education and promotion of safer sex practices would be offered to individuals using cabotegravir, oral PrEP, as well as no PrEP. Such practices, however, are not quantified in the model.

B.3.3 Clinical parameters and variables

Clinical parameters used in the cost-effectiveness analysis included the risk of HIV acquisition, adherence to TDF/FTC, persistence, and the impact of HIV acquisition on mortality. Evidence on the risk of HIV acquisition was retrieved from GUMCAD data which presents the most relevant source for the UK and reflects the population

at risk of HIV acquisition (11). Data on onward transmission of HIV were taken from a recent UK modelling study (164). Evidence on persistence to PrEP was unavailable from HPTN 083 and HPTN 084 trials; therefore, persistence to TDF/FTC was taken from a US study in the absence of suitable data from the UK, validated with UK clinical experts. Data on life expectancy for people living with HIV were taken from a recent publication and the model was calibrated to ensure predicted life expectancy living with HIV matched the reported data (84).

B.3.3.1 Population characteristics

The model considers a cohort of 3.14% cisgender women, with the remainder being men who have sex with men and transgender women (see Section B.3.2.1). A single population is modelled to represent individuals likely to be exposed to HIV and in need of PrEP with weighted means for model parameters drawn from sources which differentiate cisgender women. The modelled population is aligned to the population in clinical trials and represents the population with the highest unmet need for PrEP in the UK, those who are currently underserved by existing SoC, i.e. oral PrEP due to the reasons outlined in Section B 1.3.7.

The median age of cisgender women in the HPTN 084 trial was 25 (120). The median age of men who have sex with men and transgender women in the HPTN 083 trial was 26 (177). A weighted mean age based on the population distribution of 25.98 years old was assumed for the population at model entry.

B.3.3.2 Underlying risk of HIV acquisition

People with an identified PrEP need are those with an elevated risk of exposure to HIV. As a consequence, people with an identified PrEP need will have a higher risk of HIV acquisition than the general population. There are a number of criteria outlined in the BHIVA/BASHH guidelines to identify persons with a PrEP need including criteria based on sexual behaviour such as condomless anal sex in the previous 6 months (8). The acquisition of a bacterial STI, especially a rectal bacterial STI, is strongly associated with condomless anal sex and is considered to be proxy for the risk of HIV acquisition. Hence the underlying rate of HIV acquisition for men who have sex with men and transgender women with an identified PrEP need was assumed to be 4.9 per 100 PYs, based on the value for men who have sex with men

and who had a rectal bacterial STI in the previous year (8) in GUMCAD data. No comparable UK data were available for cisgender women who are at elevated risk of HIV and have a PrEP need. The best estimate of the underlying risk of HIV acquisition in cisgender women was considered to be the underlying risk of [redacted] per 100 PYs estimated in the ITC (Section B.2.9) for the cisgender population (HPTN 084 population). This value is consistent with the threshold for PrEP eligibility recommended by the WHO that is, 3 per 100 PYs (178). The underlying risk of HIV acquisition for the modelled population was a weighted mean of the values for men who have sex with men and transgender women, and cisgender women ([redacted] per 100 person years).

HIV incidence was converted from an annual rate to a 1-monthly probability for use in the model.

B.3.3.3 Adherence to PrEP regimens

Data on adherence to TDF/FTC were taken from HPTN 083 and HPTN 084 for the respective populations (see Sections B.2.6.1.3.3 and B.2.6.2.2.2). The proportion of participants in HPTN 083 and HPTN 084 with detectable tenofovir (as measured by plasma TFV concentrations ≥ 0.31 ng/mL) was 86% and 56%, respectively. The proportion of participants in HPTN 083 with tenofovir consistent with adherence levels of four or more doses a week (as measured by plasma TFV concentrations ≥4.2 ng/mL) was [redacted]. The proportion of participants in HPTN 084 with tenofovir consistent with adherence levels of daily use (as measured by plasma TFV concentrations ≥ 40 ng/mL) was 41.9%. These data were used to estimate the effectiveness of TDF/FTC relative to no PrEP according to adherence observed in the trials (see Section B.3.3.4). They were also used to adjust the cost of TDF/FTC (see Section B.3.5.1.2).

Data on adherence to cabotegravir were available (see Sections B.2.6.1.3.2 and B.2.6.2.2.1). The effectiveness of cabotegravir was taken directly from the relevant trials which subsumed any impact of adherence. No adjustment was made to the cost of cabotegravir for adherence representing a conservative approach to costing.

B.3.3.4 Risk of HIV acquisition associated with cabotegravir for PrEP and TDF/FTC

The ITC (described in Section B.2.9) provides an estimate of the relationship between the effectiveness of TDF/ FTC versus no PrEP and the adherence to TDF/ FTC based on a meta-regression analysis. The outcome of this analysis was used to predict the adjusted effectiveness of TDF/ FTC versus no PrEP in the HPTN 083 and HPTN 084 studies at the levels of detectable adherence to TDF/ FTC observed in these studies (86% and 56%, respectively, as described in Section B.3.3.3). The measure of effectiveness was the reduction in risk of HIV acquisition. In addition, the ITC permitted an indirect estimate of the effectiveness of cabotegravir versus no PrEP for the populations of men who have sex with men and transgender women and cisgender women based on observed effectiveness of cabotegravir versus TDF/FTC in HPTN 083 and 084, respectively and predicted effectiveness of TDF/FTC versus No PrEP in both populations (Section B.2.9 and Appendix D).

To inform the indirect comparisons, the mITT primary analyses from the HPTN 083 and HPTN 084 studies were used. The indirect comparisons were made on the relative risk (RR) scale, and the analysis was implemented as a Hierarchical Bayesian model. The results of the indirect comparison were reported on the percentage (%) effectiveness scale, where: % effectiveness = (1-Relative Risk of HIV acquisition) x 100.

While previous analyses have assumed either a linear relationship between RR of HIV acquisition and adherence to TDF/FTC (179), or a linear relationship between the logarithm of RR of HIV acquisition and adherence to TDF/FTC (146), the current analysis considered both functional forms. The log relationship was preferred primarily because it did not generate implausible negative values for RR (effectiveness greater than 100%) at high levels of adherence. The inclusion of gender as a covariate did not improve model fit and hence the base case excluded gender. The final model for RR as a function of adherence to TDF/FTC was:

$$\text{Log } RR_{\text{TDF/FTC vs no PrEP}} = [redacted] - [redacted] * \text{adherence} \quad (1)$$

where adherence is expressed as the percentage of the population with any detectable tenofovir. The fitted function relating adherence to TDF/FTC and

effectiveness, along with the point estimates from the studies informing the analysis is provided in Section B.2.9.

Equation 1 and adherence data reported in HPTN 083 and HPTN 084 trials allows estimation of the relative risk of TDF/FTC compared with no PrEP in the populations of men who have sex with men and transgender women and cisgender women. The RR of cabotegravir compared with no PrEP is calculated as the product of the RR of cabotegravir compared with TDF/FTC and the relative risk of TDF/FTC compared with no PrEP (Table 33). The risk of HIV acquisition with each PrEP option can then be calculated from the risk with no PrEP. The calculations are shown in Table 34. The key model inputs are the rates of HIV acquisition as a function of PrEP. The model applies a weighted mean of the values for men who have sex with men and transgender women, and cisgender women for each type of PrEP.

Table 33: Calculation of effectiveness of cabotegravir and TDF/FTC compared with no PrEP

Population	Detectable adherence to TDF/FTC	RR (TDF/FTC) calculated*	Effectiveness of TDF/FTC versus no PrEP*	RR cabotegravir versus no PrEP	Effectiveness of cabotegravir versus no PrEP
Men who have sex with men and transgender women	86%	[redacted]	[redacted]	[redacted]	[redacted]
Cisgender women	56%	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HPTN, HIV Prevention Trials Network; PrEP, pre-exposure prophylaxis; RR, relative risk; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

Note that values used in the CEM for TDF/FTC effectiveness differ slightly from the reported headline results for the ITC. In the CEM, TDF/FTC effectiveness is calculated from alpha and beta coefficients using regression equation using the mean of the posterior of the coefficients. This gives a slightly different value to the mean of the posterior distribution for TDF/FTC effectiveness, due to non-linearity.

Table 34: Calculation of HIV acquisition rate with no PrEP

Population	Effectiveness of TDF/FTC versus no PrEP	Effectiveness of cabotegravir versus no PrEP	Rate of HIV acquis. with no PrEP (per 100 PY)	HIV acquis. in the TDF/FTC arm (per 100 PY)	Rate of HIV acquis. with cabotegravir (per 100 PY)
Men who have sex with men and transgender women	[redacted]	[redacted]	4.9	[redacted]	[redacted]
Cisgender women	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weighted mean	–	–	[redacted]	[redacted]	[redacted]

Abbreviations: acquis, acquisition; HIV, human immunodeficiency virus; HPTN, HIV Prevention Trials Network; PrEP, pre-exposure prophylaxis; RR, relative risk; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

B.3.3.5 Risk of HIV acquisition after discontinuation of prophylaxis

The risk of HIV acquisition in individuals discontinuing TDF/FTC was assumed to immediately rise to the risk for no PrEP. Individuals discontinuing cabotegravir and commencing TDF/FTC were assumed to experience an immediate rise in risk of HIV, to the risk level of TDF/FTC. Likewise, individuals discontinuing cabotegravir without commencing TDF/FTC were assumed to experience an immediate rise in risk of HIV to the risk level associated with no PrEP. In practice, cabotegravir LA persists in the body for up to one year or more after discontinuation (180). There is limited data to accurately quantify the residual efficacy of cabotegravir LA in the PK tail, hence it was conservatively assumed that there is no additional reduction in risk of HIV acquisition attributable to cabotegravir LA in the PK tail.

B.3.3.6 Onward transmission of HIV

The number of secondary transmissions of HIV was informed by a published cost-effectiveness analysis of TDF/FTC which utilised the HIV synthesis model, a dynamic, individual-based stochastic model of HIV transmission (164). Over a time horizon of 80 years the model estimated that the introduction of TDF/FTC would lead to a reduction of 44,300 HIV acquisitions of which 42% were directly averted by prophylaxis and 58% were averted as the result of prevention of onward

transmission. Hence it was assumed that for each HIV acquisition prevented by prophylaxis, a further 58/42=1.38 onward transmissions were prevented.

B.3.3.7 Risk of PrEP-related breakthrough resistance-associated mutations

Individuals who acquired HIV while receiving PrEP could develop PrEP-related breakthrough RAMs and require different ARV treatment regimens than individuals without resistance mutations (181). Data on the incidence of treatment resistant acquisitions were available from the HPTN 083 trial (see Section B.2.6.1.2.1 and Table 35); there were no breakthrough resistant acquisitions in the HPTN 084 trial. The likelihood of acquiring a RAM was included in the model. The RAM was assumed to be INSTI resistance for cabotegravir and NRTI resistance for TDF/FTC, reflecting the mode of action of each drug. The proportion of all HIV acquisitions with RAMS was calculated for each arm of the HPTN 083 trial ([redacted] INSTI resistant HIV infections in the cabotegravir arm [N=[redacted]] and [redacted] NRTI-resistant HIV infections in the TDF/FTC arm [N=[redacted]]) and applied to all HIV acquisitions in the model occurring whilst individuals were using the respective PrEP.

Table 35: Total HIV acquisitions and PrEP-Related Breakthrough Resistance Incidence (Events/Person-year)

Trial arm (active PrEP)	HIV acquisitions total	INSTI resistant acquisitions total	NRTI resistance acquisitions total
Cabotegravir	[redacted]	[redacted]	[redacted]
TDF/FTC	[redacted]	[redacted]	[redacted]

Abbreviations: HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PrEP, pre-exposure prophylaxis; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

B.3.3.8 Risk of resistant HIV infection following discontinuation of PrEP

The base-case analysis assumed that the risk of acquiring treatment resistant HIV reverted to the risk associated with the alternative PrEP regimen at the point where a person changed their PrEP modality. This is consistent with assumptions on the risk of HIV acquisition after discontinuation of PrEP (Section B.3.3.5).

The relative risk of acquiring INSTI resistant HIV compared with non-resistant HIV following discontinuation of cabotegravir in the period in which the drug remains in vivo (the ‘PK tail’) is unknown.

B.3.3.9 Persistence to PrEP

Available data on persistence to TDF/FTC in a UK setting were limited to a poster publication presenting data from a small sample of PrEP users from a sexual health clinic in South-East London (182). Consequently, data on persistence were taken from a US study which reported persistence over 12 months for 24,232 people commencing TDF/FTC. (61) Persistence at 6 and 12 months was 70.2% and 57.4%, respectively. These values are supported by a recent SLR which reported a pooled discontinuation rate for PrEP within 6 months of initiation of 41.0% (95% CI: 18.8, 63.5) globally (16 studies) and 17.4% (95% CI: 13.0, 22.9) in Europe (6 studies) (60). Persistence at 6 months was used to calculate a monthly discontinuation probability of 5.73% over the first six months assuming a constant rate of discontinuation. Data from 6 to 12 months were used to calculate a monthly discontinuation probability of 3.3% assuming a constant rate of discontinuation. The discontinuation probability of 3.3% was applied to each month beyond 6 months.

Cabotegravir persistence was not directly assessed in the HPTN 083 and HPTN 084 clinical trials. Persistence with cabotegravir is anticipated to be higher than that for TDF/FTC for three key reasons. Firstly, the convenience of a bimonthly injection of cabotegravir compared with the requirement to take TDF/FTC daily is likely to improve persistence, corroborated by UK clinicians who indicated that a 50% improved persistence could be observed with cabotegravir versus oral PrEP. Secondly, as cabotegravir provides an additional modality that addresses barriers common to both adherence and persistence (17, 183), it may improve continuation of PrEP over time. This trend would be consistent with the experience in contraception, where matching women’s preferred modality increased persistence (82). Finally, in the PK tail, residual concentrations of cabotegravir may remain in systemic circulation for prolonged periods of time (up to 12 months or longer). There is no data available providing an accurate quantification of the residual efficacy of cabotegravir in the PK tail. The assumption that individuals' risk of HIV acquisition immediately changes following discontinuation of cabotegravir LA is simplistic and may not capture individuals who are still within the 2-month period of cabotegravir effectiveness in the approved dosing interval from their last injection. This was too complex to capture in the model structure, but was nonetheless reflected in the assumptions on persistence to cabotegravir. In the base case it was assumed that

persistence at both 6 and 12 months was 20% higher for cabotegravir compared with TDF/FTC which is consistent with published US cost-effectiveness analysis of cabotegravir (184). This generated a monthly discontinuation of 2.82% in the first six months and 3.30% after six months. Hence the assumption of higher persistence translated into a lower monthly discontinuation probability for cabotegravir over the first six months compared with TDF/FTC and equal monthly discontinuation probabilities for cabotegravir and TDF/FTC after 6 months. An assumption of a 35% increase in persistence for cabotegravir compared with TDF/FTC was tested in scenario analysis, reflecting clinical opinion of the likely impact of the greater convenience of cabotegravir compared with TDF/FTC.

Individuals discontinuing cabotegravir are recommended to commence oral PrEP if they are still likely to be exposed to HIV. The proportion of individuals discontinuing cabotegravir who would commence TDF/FTC was assumed to be [redacted] in the absence of data. Likewise, no data were available to estimate the discontinuation rate for TDF/FTC following cabotegravir. Consequently, a discontinuation probability of [redacted] per month was assumed. This is much higher than discontinuation rates assumed for TDF/FTC, and hence is a conservative assumption.

B.3.3.10 Transition to TAF/FTC

The base case analysis assumed individuals taking oral PrEP were on TDF/FTC as it represents SoC in England (6). To reflect the small proportion of individuals who may transition to TAF/FTC in practice, a scenario analysis is presented using data from PrEP users in England attending Dean Street (the largest sexual health clinic in Europe) Chelsea and Westminster Hospital NHS Foundation Trust, who were prescribed TAF/FTC (0.185% individuals received TAF/FTC over a 2-year period) (23, 24).

B.3.3.11 Incidence of adverse events

Data on the incidence of adverse events associated with cabotegravir were taken from the HPTN 083 and 084 trials for the respective groups of men who have sex with men and transgender women, and cisgender women, respectively. Data on the incidence of ISRs were included in the model. Data were classified according to severity. The data were weighted by the proportion of cisgender women in the

population to estimate a population incidence for mild, moderate and severe ISRs (Table 36). The cost of treating ISRs was included as a one-off cost at commencement of cabotegravir LA. No AEs were considered for either the TDF/FTC or no PrEP strategies.

Table 36: Injection site reactions observed in HPTN 083 and HPTN 084, and incorporated in the model

Reaction severity	HPTN 083	HPTN 084	Modelled value
Mild (Grade 1)	33.8%	[redacted]	[redacted]
Moderate (Grade 2)	45.1%	[redacted]	[redacted]
Severe (Grade 3)	2.6%	[redacted]	[redacted]

Source: Landovitz et al, 2021 and ViiV Healthcare data on file (185).
Abbreviations: HPTN, HIV Prevention Trials Network.

B.3.3.12 Mortality before and after HIV acquisition

Data on mortality for people without HIV were taken from general population data for England and Wales for the period 2018–2020 (186). Individuals who acquired HIV were modelled to experience losses in life expectancy. Data on mortality for people living with HIV was also based on the general population data for England and Wales after application of standardised mortality ratios (SMRs). The SMRs were calculated using life expectancy data from a recent study of European and North American cohorts and the UK Collaborative HIV Cohort (84). The study considered mortality data for 206,891 people living with HIV and reported life expectancy estimates from the age of 40 for men and women (according to sex assigned at birth) who commenced ART either before or after 2015. Life expectancy was longer in people commencing ART after 2015. For men commencing ART after 2015, life expectancies were 37.0 (95% CI: 36.5, 37.6) compared with a general population value of 40.7 years. For women commencing ART after 2015, life expectancies were 39.0 (95% CI: 38.5, 39.5) compared with a general population value of 45.8 years. The data indicate a reduction in life expectancy of 3.7 and 6.8 years for men and women living with HIV, respectively. The model assumes that the impact of living with HIV on mortality is similar for men who have sex with men and transgender women since no data can be identified reporting the SMR for transgender women. This assumption is likely to be conservative since evidence suggests that transgender women have lower life expectancy (187-189).

Application of SMRs of 1.50 and 2.18 to general population mortality data for England and Wales for the period 2018–2020 from the age of 40 years generated a

reduction in life expectancy of 3.7 and 6.8 years for men and women, respectively. These SMRs were applied to the mortality rate for people acquiring HIV in the model.

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

No HRQoL data were collected in the clinical trials. HRQoL data used in the modelling were sourced from published literature (Section B.3.4.3).

B.3.4.2 Mapping

Mapping was not undertaken as no HRQoL measures suitable for mapping were collected in either HPTN 083 or HPTN 84.

B.3.4.3 Health-related quality-of-life studies

The HRQoL SLR, described in Section B.3.1, identified four utility studies, one of which focused on the UK (Miners et al, 2014) (173). Full details of the process and methods to identify and select relevant HRQoL evidence is provided in Appendix H. Miners et al, used data from two UK cross-sectional surveys the Antiretrovirals, Sexual Transmission Risk and Attitudes (ASTRA) study, and the Health Survey for England (HSE) 2011 to compare HRQoL in people living with HIV and the general population. The population analysed comprised 3,151 participants in ASTRA and 7,424 participants in HSE 2011 who had complete EQ-5D-3L data. The study reported that the EQ-5D-3L utility score was lower for individuals with HIV compared with the general population (marginal effect in utility score adjusted for differences in age and sex/sexuality: –0.11; 95% CI: –0.13, –0.10; $p<0.0001$).

B.3.4.4 Adverse reactions

No disutility is applied for the AEs modelled. AEs noted in the trials were predominantly mild and transient and were not considered to have a meaningful impact on overall HRQoL. The profile of adverse events was similar across arms in both trials (see Sections B.2.10.1.1. and B.2.10.2.1). In addition, it was assumed that individuals choosing to receive PrEP view the choice positively, as benefits like decreased anxiety about acquiring HIV infection may outweigh potential negative feelings on issues such as ISRs.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

Individuals without HIV were assumed to have the same HRQoL as the general population of the same age. A health state utility value (HSUV) was calculated as a function of age and the proportion of cisgender women in the modelled population using values from Hernandez Alava et al. 2022 (172). The HRQoL impact associated with HIV acquisition was captured by applying the disutility value from the Miners et al, study (173) (described in B.3.4.3 and summarised in Table 37) to the utility for the general population. The value was applied in an additive manner to the baseline HSUV as this best reflected the underlying assumptions of the linear regression model which estimated the disutility after controlling for age.

Table 37: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Individuals without HIV	Age and sex specific	–	Section B.3.4.5	NICE-recommended values
HIV infection disutility	–0.011	–0.14, –0.10	Section B.3.4.3	Large UK study which measured HRQoL using EQ-5D-3L instrument

Abbreviations: HIV, human immunodeficiency virus; HRQoL, health-related quality of life; NICE, National Institute for Health and Care Excellence; UK, United Kingdom.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

The economic SLR searches, described in Section B.3.1, included cost and healthcare resource use studies. Details of the SLR and the relevant cost and healthcare resource use studies identified are presented in Appendix I.

Where applicable, costs were inflated to 2022/23 values prior to utilisation in the model – the Hospital and Community Health Services Index was applied for the years 2012/13 to 2014/15, and the NHS Cost Inflation Index was applied for the years 2015/16 to 2021/22, both as reported in Unit Costs of Health and Social Care 2022 (190). The pay indices were applied to wages and the prices indices to other

costs. The increases for pay and prices from 2021/22 to 2022/23 were estimated as the average respective values for the previous three years.

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 *Drug acquisition costs for cabotegravir*

The cost of a single injection dose 600 mg of cabotegravir LA is [redacted] at the list price. The second dose is administered one month after the first dose with two-monthly intervals after the second dose (Appendix C). Hence seven doses are administered in the first year and six doses in subsequent years. The annual cost in the first and subsequent years were divided by 12 and applied as a monthly cost to people persisting with cabotegravir LA. The resulting monthly costs were [redacted] and [redacted] in the first year and subsequent years, respectively.

An [redacted]. The model assumed that [redacted] of people commencing cabotegravir would be prescribed an oral lead-in. The cost for 30 tablets containing 30 mg of oral cabotegravir (Apretude) is [redacted] at the list price. The cost per day was [redacted]. A cost of 4 weeks supply was calculated as [redacted] * 28 = [redacted], which was included in the model once at cabotegravir initiation.

Costs of both oral cabotegravir and cabotegravir LA are summarised in Table 38.

B.3.5.1.2 *Drug acquisition costs for TDF/FTC*

The cost of TDF/FTC was taken from the BNF. The lowest cost for a generic formulation of £34.20 for 30 tablets was selected. The model conservatively assumes that the drug acquisition costs for TDF/FTC reflect the number of pills corresponding to the level of adherence to TDF/FTC modelled. In some instances, TDF/FTC may be delivered as per dosing schedule and a scenario analysis accounting for wastage was considered to assess the impact of capturing the costs of the full pack of TDF/FTC on the model results.

Costs for TDF/FTC were adjusted for adherence. Data on adherence to TDF/FTC were taken from the HPTN 083 and HPTN 084 trials and applied to the corresponding population in the model. In HPTN 083, the proportion of men who have sex with men and transgender women taking four or more pills a week was

reported to be [redacted] on the basis of plasma TFV concentrations (see Section B.2.6.1.3.3 and section B.3.3.3) (123). The mean number of pills per week in those taking four or more pills was estimated as 5.5 pills (assuming the midpoint of the range from four to seven pills). The proportion of men who have sex with men and transgender women taking zero pills per week was estimated as 14% on the basis of data from HPTN 083 indicating detectable tenofovir in 86% of individuals in the control arm (119). The remaining [redacted] of individuals were assumed to be taking two pills per week representing the midpoint of the category of one to three pills. Overall, the weighted average number of pills per week among men who have sex with men and transgender women is calculated as [redacted]. In HPTN 084, the proportion of cisgender women using TDF/FTC daily (threshold used to define high adherence for cisgender women) was reported to be 41.9% based on plasma TFV concentrations (120). The proportion of cisgender women estimated to be taking zero pills per week was 44.1%. The remaining 14.0% of cisgender women were assumed to be taking 3.5 pills a week based on the midpoint of the range from one to six pills. Consequently, the weighted average number of pills consumed per week for the cisgender women population was calculated as 3.42. A weighted average of the figures for men who have sex with men and transgender women, and cisgender women of [redacted] pills per week, equating to [redacted] pills per month was applied in the model. The calculations are shown in Table 39.

Table 38: Calculation of monthly costs of cabotegravir (List price)

Drug	Formu-lation	Pack size	Cost	Dose	Cost per dose	Cost in first year	Cost in subseq-uent years
Cabotegravir oral	Oral 30 mg tablet	30	[redacted]	Once daily (for 4 weeks)	[redacted]	[redacted]	–
Cabotegravir LA	Vial 600 mg solution	1	[redacted]	Monthly for first 2 months and then every 2 months	[redacted]	[redacted]	[redacted]

Abbreviations: cabotegravir LA, cabotegravir long-acting.

Table 39: Calculation of pill consumption for TDF/ FTC

Parameter	No adherence (0 pills per week)	Low adherence	High adherence	Weighted average weekly pills
Calibrated distribution for HPTN 083	14.0%	[redacted]	[redacted]	–
Assumed mean pill count per week	0	2	5.5	[redacted]
Calibrated distribution for HPTN 084	44.1%	[redacted]	41.9%	–
Assumed mean pill count per week	0	3.5	7	[redacted]
Weighted population mean	–	–	–	[redacted]

Abbreviations: HPTN, HIV Prevention Trials Network; PrEP, pre-exposure prophylaxis.

Table 40: Costs of TDF/FTC

Drug	Pack size	Cost	Dosing schedule	Cost per dose	Doses per month	Cost per month
TDF/FTC	30 tablets	£34.20	Once per day	£1.14	[redacted]	[redacted]

Abbreviations: PrEP, pre-exposure prophylaxis; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

B.3.5.1.3 *Administration costs for cabotegravir LA*

Administration of cabotegravir LA was assumed to be undertaken during regular monitoring visits and to require 15 minutes of time from a band 5 nurse. The unit cost for one hour of a time for a band 5 nurse of £46 was taken from the Unit costs of health and social care 2022 (190). The cost was inflated from 2021/22 to 2022/23 GBP and divided by 4 to generate an administration cost of £11.85. The inflation rate from 2021/22 to 2022/23 was taken as the mean of the rate for the preceding three years (190). The annual cost for the first year and subsequent years was divided by 12 and applied as a monthly cost in the model.

No administration costs were assumed for TDF/FTC as an orally administered intervention.

B.3.5.1.4 *Monitoring costs*

Oral PrEP is provided by specialist sexual health clinics in England and Wales. Attendance is every 2–3 months and people are tested for HIV along with tests for other STIs. The monitoring tests undertaken at each clinic visit were informed by the recommendations in the BHIVA/BASHH guidelines (8). The unit cost of each test with the exception of syphilis and eGFR was obtained from the National Institute for Health Research (NIHR) interactive costing tool (175). The unit costs of a test for syphilis and eGFR were taken from NHS Cost Collection data (191). Unit costs were inflated to 2022/23 values and are listed in Table 41.

The frequency of testing in the first and subsequent years for men who have sex with men and transgender women, and for cisgender women, were informed by the BHIVA/BASHH guidelines (8). Tests of kidney function (eGFR, urinalysis, serum creatinine) were assumed to occur only at the initial assessment. Testing for hepatitis B was assumed to occur once annually. Testing for hepatitis C was assumed to occur once annually in men who have sex with men and transgender women only. A pregnancy test was assumed to be undertaken in cisgender women only. Testing frequency in the first and subsequent years for both cabotegravir and TDF/FTC, and the resulting costs are shown in Table 42. Annual test costs for men who have sex with men and transgender women, and for cisgender women, were weighted according to the proportion of cisgender women in the population. Annual costs were divided by 12 and applied as a monthly cost in the model.

Table 41: Unit costs of monitoring tests

Test	Unit cost from source	Unit cost inflated to 2022/23 GBP	Source
HIV antigen/ antibody test	£12	£12.44	NIHR (87806)
Hepatitis B test	£11	£11.40	NIHR (86704)
Chlamydia test	£11	£11.40	NIHR (87810)
Gonorrhoea test	£46	£47.67	NIHR (87850)
Syphilis test	£8.53	£8.65	NSNC (DAPS07)
Hepatitis C antibody test	£27	£27.98	NIHR (86803)
Serum creatinine	£12	£12.44	NIHR (82575)
eGFR test	£191.42	£194.19	NSNC (IMAGOP RN27A)
Urinalysis	£19	£19.69	NIHR (81000)
Urine pregnancy test	£9	£9.33	NIHR (84703)

Abbreviations: eGFR, estimated glomerular filtration rate; GBP, Pounds Sterling; HIV, human immunodeficiency virus; NIHR, National Institute of Health Research interactive costing tool; NSNC, National Schedule of NHS Costs year 2021/22.

Table 42: Frequency of testing and resulting monitoring costs

Test	Number of tests in first year (men who have sex with men and transgender women)	Number of tests in first year (cisgender women)	Number of tests in subsequent years (men who have sex with men and transgender women)	Number of tests in subsequent years (cisgender women)	Unit cost of test	Total cost in first year (men who have sex with men and transgender women)	Total cost in first year (cisgender women)	Total cost in subsequent years (men who have sex with men and transgender women)	Total cost in subsequent years (cisgender women)
HIV antigen/ antibody test	6	6	4	4	£12.44	£74.61	£74.61	£49.74	£49.74
Hepatitis B test	1	1	0	0	£11.40	£11.40	£11.40	£0.00	£0.00
Chlamydia test	5	5	4	4	£11.40	£57.00	£57.00	£45.60	£45.60
Gonorrhoea test	5	5	4	4	£47.67	£238.34	£238.34	£190.68	£190.68
Syphilis test	5	5	4	4	£8.65	£43.27	£43.27	£34.61	£34.61
Hepatitis C antibody test	5	0	4	0	£27.98	£139.90	£0.00	£111.92	£0.00
Serum creatinine	1	1	0	0	£12.44	£12.44	£12.44	£0.00	£0.00
eGFR test	1	1	0	0	£194.19	£194.19	£194.19	£0.00	£0.00
Urinalysis	1	1	0	0	£19.69	£19.69	£19.69	£0.00	£0.00
Urine pregnancy test	0	6	0	4	£9.33	£0.00	£55.96	£0.00	£37.31
Overall test costs						£790.83	£706.89	£432.54	£357.93
Weighted population test costs							£788.19		£430.20

Abbreviations: eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus.

Attendance frequency at a sexual health clinic for TDF/FTC was assumed to be aligned with monitoring, consistent with guidance from BHIVA/BASHH (8). An additional visit at commencement of treatment and one month later was assumed such that visits in the first year would occur at months 0, 1, 3, 6, 9, and 12 for a total of six visits. People receiving cabotegravir LA were assumed to attend a sexual health clinic for each administration (seven in the first year and six in subsequent years). Data on the cost of sexual health services in the UK is limited. Each attendance at a sexual health clinic was assumed to last for 30 minutes. The cost of attendance was calculated by applying half an hour of a medical consultant's time. A cost per hour for a consultant of £113 was derived from the unit costs of health and social care 2022 and inflated to 2022/23 values to generate a visit cost of £58.20. Annual costs for consultation time were £407 and £349 for cabotegravir in the first and subsequent years, respectively. The analogous costs for consultation time for TDF/FTC were £349 and £233, respectively.

Annual test costs in the first year and subsequent years were divided by 12 and applied in each relevant monthly cycle. Likewise, annual consultation costs were divided by 12 and applied in each relevant monthly cycle.

Table 43 reports the total monthly costs associated with each of the active PrEP options. No costs were assumed for the no PrEP option on an assumption that this option was associated with a complete withdrawal from sexual health services.

Table 43: Monthly costs associated with provision of cabotegravir or TDF/FTC

Item	Cabotegravir one-off cost	Cabotegravir in first year	Cabotegravir in subs years	TDF/FTC in first year	TDF/FTC in subs years
Oral lead-in	[redacted]	–	–	–	–
PrEP	–	[redacted]	[redacted]	£22.90	£22.90
Administration	–	£6.91	£5.92	–	–
Monitoring visits	–	£33.95	£29.10	£29.10	£19.40
Monitoring tests	–	£65.68	£35.85	£65.68	£35.85
Total	[redacted]	[redacted]	[redacted]	£117.68	£78.15

Abbreviations: PrEP, pre-exposure prophylaxis; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

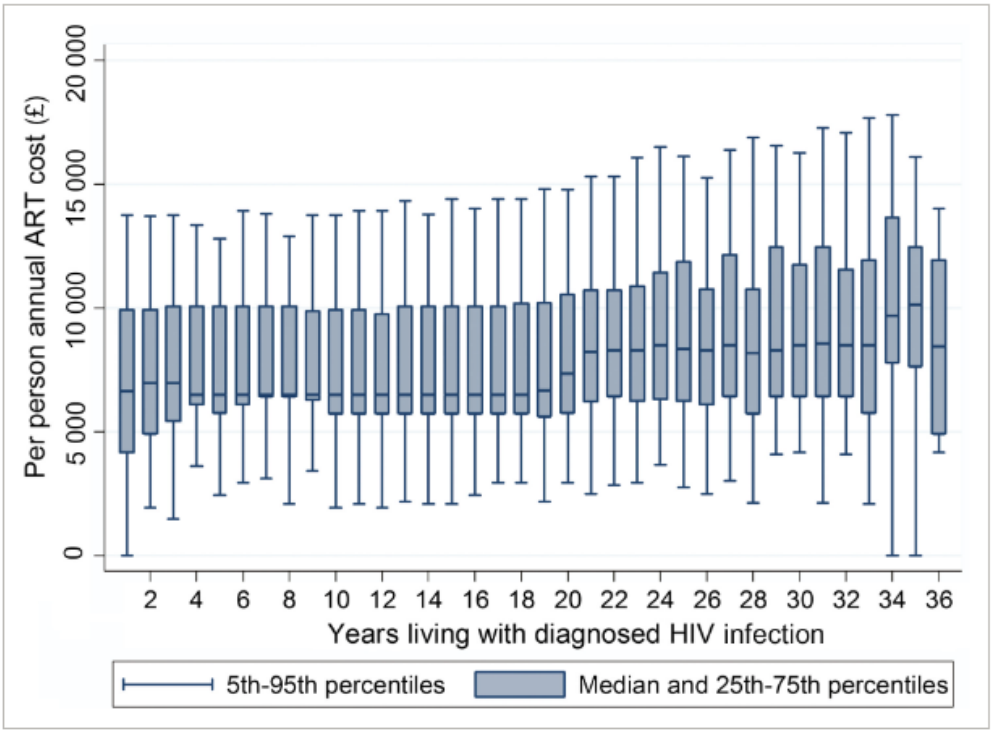
B.3.5.2 Health-state unit costs and resource use

B.3.5.2.1 *HIV management costs*

Individuals who acquired non-resistant HIV infection in the model incurred costs associated with HIV-related care on a monthly basis, including the cost of ART and costs associated with visits and monitoring. Individuals who acquired HIV with PrEP-related breakthrough resistance were assumed to incur higher costs than individuals without resistance for a period of time.

Data on the cost of ART were taken from a UK publication on the cost of ART for HIV (33). In this study, data on 68,801 patients in the HIV and AIDS reporting system (HARS) were combined with cost data from the BNF to estimate the cost of ART over time since diagnosis with HIV. Costs were similar over the first 18 years and were higher after that point (Figure 12). The reason for the elevated costs after 18 years was not discussed, but may reflect increasing levels of age related health challenges and resistant HIV strains. The cost of ARTs for non-resistant HIV was taken as the mean of the median ART costs reported in Ong et al, 2019 over the first 20 years. The mean annual cost of £6,687 (2016/17 Great British Pounds [GBP]) was inflated to a 2022/23 value of £7,294. The cost of ARTs for resistant HIV was taken as the mean of the median ART costs reported in Ong et al, 2019 over the years 21 to 36. The mean annual cost of £8,646 (2016/17 GBP) was inflated to a 2022/23 value of £9,430.

Figure 12: Costs of ART as a function of time since diagnosis



Abbreviations: ART, anti-retroviral therapy.

Additional costs of healthcare associated with HIV acquisition were taken from a recent UK analysis of secondary care costs (95). The study utilised data from the HIV patient record system from North Middlesex University Hospital NHS Trust on 1,763 people with HIV with a 6-year median duration of follow-up and a mean age 37.3 years, 59% of which were Black African heterosexual women or men. The study reported unadjusted mean costs of £439 (2018/19 GBP) per quarter. The 3-monthly cost reported included hospital appointments/visits, day-case visits, inpatient episodes, CD4 tests, viral load tests, and resistance tests. The costs were divided by three and inflated to 2022/23 values to generate a cost of £154.98 per month for secondary inpatient and outpatient care. These costs were added to the monthly cost for ART to generate a monthly cost for the treatment of non-resistant HIV and resistant HIV of £762.80 and £940.84. The monthly cost of treating non-resistant HIV was applied to all people who acquired HIV without a RAM in the model. For people acquiring either NRTI or INSTI resistant HIV, the monthly costs of treating resistant HIV were assumed. The average duration of first-line treatment was conservatively estimated to be 16.2 years (discounted), based on a 2011 study (192). After the end of first-line treatment, costs for non-resistant HIV were assumed to be the same as for resistant HIV. To facilitate implementation in the model without additional health

states, the discounted additional cost of treating resistant HIV was calculated over the duration of first-line treatment (16.2 years after discounting) and applied as a one-off cost. The one-off additional cost for INSTI or NRTI resistance was £34,611.

B.3.5.3 Adverse reaction unit costs and resource use

Management costs for ISRs were estimated by severity and were applied as a one-off cost. Mild ISRs were assumed to require no medical management. Treatment of moderate ISRs was assumed to consist of the use of 800 mg of ibuprofen three times daily for three days. Treatment of severe injection site reactions was assumed to include a physician visit in addition to the cost of ibuprofen. A cost of £4.90 for 60 tablets of 400 mg strength was taken from the BNF generating a cost per event of £4.90/ 60 *18 = £1.47. The cost was further multiplied by seven on the assumption that moderate or severe injection site reactions occurred at each injection in the first year. Hence a cost for ibuprofen of £10.29 was assumed for both moderate and severe injection site reactions.

A further cost of a single consultation with a General practitioner (GP) was assumed for people experiencing severe ISRs. The duration of the consultation was assumed to be 24.5 minutes. A cost per minute for a GP of £4.51 (2012/22 GBP) was obtained from the Unit Costs of Health and Social Care and inflated to 2022/23 values to generate a cost of £4.65. Hence the consultation cost was calculated to be £113.83. The total cost for a severe ISR including ibuprofen was £124.12.

The costs of £10.29 and £124.12 for moderate and severe ISRs were combined with a weighted mean of the incidence of ISRs for men who have sex with men and transgender women and for cisgender women (Table 36). A resulting one-off cost of £8.31 was applied to people receiving cabotegravir (Table 44).

Table 44: Costs of adverse events associated with cabotegravir and included in the model

Adverse event	Frequency	Medication cost	Clinician time	Total cost
Mild ISR	[redacted]	–	–	0
Moderate ISR	[redacted]	£10.29	–	£4.53
Severe ISR	[redacted]	£10.29	£113.83	£3.13
Total	–	–	–	£7.66

Abbreviations: cabotegravir LA, cabotegravir long-acting; ISR, injection site reaction.

B.3.5.4 Miscellaneous unit costs and resource use

No additional costs were included in the CEM.

B.3.6 Severity

The impact of living with well controlled HIV on life expectancy does not justify the application of a severity modifier.

B.3.7 Uncertainty

The model has been constructed in line with NICE's reference case and key parameters are derived from high quality studies. They include:

- The relative risk of HIV acquisition with cabotegravir and TDF/FTC based on observed rates from HPTN 083 and HPTN 084 (see Section B.2.3).
- The use of indirect treatment comparison methods to estimate the effectiveness of cabotegravir and TDF/FTC versus no-PrEP, using TDF/FTC as a common comparator (see Section B.2.9.3.1.3).
- A systematic review and meta-regression to assess the relationship between HIV acquisition and adherence to oral PrEP (see Section B.2.9).
- National surveillance data (GUMCAD) to estimate the risk of HIV (see Section B.3.3.2).
- Large UK studies to quantify the disutility and non-ART health care costs of HIV (see Sections B.3.4.5 and B.3.5.2.1).

Model validation has been undertaken both internally and by an external team of health economists (Section B.3.14). Uncertainty in the economic model was evaluated by undertaking probabilistic and deterministic sensitivity analysis (B.3.11). Scenario analyses were also run (Section B.3.11.3).

B.3.8 Managed access proposal

Cabotegravir is not considered as a candidate for a managed access scheme.

B.3.9 Summary of base-case analysis inputs and assumptions

B.3.9.1 Summary of base-case analysis inputs

A summary of variables applied in the economic model is provided in Table 45.

Table 45: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Population characteristics			
Age of men who have sex with men and transgender women	26 years	25.78 to 26.22 (Normal)	Patient characteristics, Section B.3.3.1
Age of cisgender women	25 years	24.82 to 25.18 (Normal)	Patient characteristics, Section B.3.3.1
Proportion of cisgender women	3.14%	3.0% to 3.2% (Beta)	Patient characteristics, Section B.3.3.1
Clinical parameters – HIV acquisition			
Underlying risk of HIV acquisition in men who have sex with men and transgender women	4.9 events per 100 person years	4.4 to 5.4 (Normal)	Risk of HIV acquisition, Section B.3.3.2
Underlying risk of HIV acquisition in cisgender women	[redacted] events per 100 person years	[redacted] (sampled values from the posterior distribution)	Risk of HIV acquisition, Section B.3.3.2
Relative reduction in risk of HIV incidence with TDF/FTC (men who have sex with men and transgender women)	[redacted]	[redacted] (Beta)	Risk of HIV acquisition, Section B.3.3.2
Relative reduction in risk of HIV incidence with TDF/FTC (cisgender women)	[redacted]	[redacted] (Beta)	Risk of HIV acquisition, Section B.3.3.2
Relative reduction in risk of HIV acquisition with cabotegravir (men who have sex with men and transgender women)	[redacted]	[redacted] (sampled values from the posterior distribution)	Risk of HIV acquisition, Section B.3.3.2
Relative reduction in risk of HIV acquisition with cabotegravir in cisgender women	[redacted]	[redacted] (sampled values from the posterior distribution)	Risk of HIV acquisition, Section B.3.3.2
Secondary HIV acquisitions per primary acquisition (men who have sex with men and transgender women)	1.38	1.11 to 1.65 (Normal)	Onward transmission of HIV, Section B.3.3.6
Secondary HIV acquisitions per primary acquisition (cisgender women)	0.8	0.65 to 0.96 (Normal)	Onward transmission of

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
			HIV, Section B.3.3.6
Proportion of HIV acquisitions acquired with cabotegravir which are INSTI resistant	41.7%	13.5% to 85.3% (Beta)	Risk of resistant HIV, Section B.3.3.7
Proportion of HIV acquisitions acquired with TDF/FTC which are NRTI resistant	15.4%	5.7% to 29.9% (Beta)	Risk of resistant HIV, Section B.3.3.7
Clinical characteristics – adherence and persistence			
Percentage of men who have sex with men and transgender women with high adherence to TDF/FTC	[redacted]	Not varied	Risk of HIV acquisition, Section B.3.3.2
Percentage of men who have sex with men and transgender women with detectable tenofovir	86.0%	82.4% to 89.3% (Beta)	Risk of HIV acquisition, Section B.3.3.2
Percentage of cisgender women with high adherence to TDF/FTC	41.9%	Not varied	Risk of HIV acquisition, Section B.3.3.2
Percentage of cisgender women with detectable tenofovir	55.9%	53.7% to 58.1% (Beta)	Risk of HIV acquisition, Section B.3.3.2
Persistence with TDF/FTC at 6 months	84.2%	83.3% to 85.2% (Beta)	Persistence to PrEP, Section B.3.3.9
Persistence with TDF/FTC at 12 months	70.2%	69.4% to 71.0% (Beta)	Persistence to PrEP, Section B.3.3.9
Increase in persistence for cabotegravir compared with TDF/FTC	20%	10% to 30% (Normal)	Persistence to PrEP, Section B.3.3.9
Clinical parameters – use of second line PrEP			
Proportion of people commencing TDF/FTC after discontinuing cabotegravir	[redacted]	[redacted] (Beta)	Persistence to PrEP, Section B.3.3.9
Monthly discontinuation rate for TDF/FTC after cabotegravir	[redacted]	[redacted] (Beta)	Persistence to PrEP, Section B.3.3.9
Monthly probability of transition from TDF/FTC to TAF/FTC	0.0%	0.7% examined in one-way sensitivity analysis (61)	Transition to TAF/FTC, Section B.3.3.10

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Clinical parameters – adverse events			
Proportion of men who have sex with men and transgender women experiencing mild ISRs with cabotegravir	33.8%	31.8% to 35.8% (Beta)	Incidence of adverse events, Section B.3.3.11
Proportion of men who have sex with men and transgender women experiencing moderate ISRs with cabotegravir	45.1%	43.0% to 47.2% (Beta)	Incidence of adverse events, Section B.3.3.11
Proportion of men who have sex with men and transgender women experiencing severe ISRs with cabotegravir	2.6%	2.0% to 3.3% (Beta)	Incidence of adverse events, Section B.3.3.11
Proportion of cisgender women experiencing mild ISRs with cabotegravir	[redacted]	23.5% to 27.9% (Beta)	Incidence of adverse events, Section B.3.3.11
Proportion of cisgender women experiencing moderate ISRs with cabotegravir	[redacted]	10.4% to 13.7% (Beta)	Incidence of adverse events, Section B.3.3.11
Proportion of cisgender women experiencing severe ISRs with cabotegravir	[redacted]	0.0% to 0.24% (Beta)	Incidence of adverse events, Section B.3.3.11
Parameters relating to mortality and HRQoL			
Rate ratio for mortality following HIV acquisition in men who have sex with men and transgender women	1.50	1.20 to 1.79 (Normal)	Mortality after HIV acquisition, Section B.3.3.12
Rate ratio for mortality following HIV acquisition in cisgender women	2.18	1.75 to 2.61 (Normal)	Mortality after HIV acquisition, Section B.3.3.12
Disutility associated with HIV acquisition	0.11	0.10 to 0.13	HRQoL date used in the CEA, Section B.3.4.5
Cost parameters – cost of PrEP regimens			
Cost of oral cabotegravir, 30 x 30 mg tablets	[redacted]	Not varied	Acquisition costs for cabotegravir, Section B.3.5.1.1
Proportion of people prescribed oral lead-in prior to cabotegravir injection	[redacted]	[redacted] (Normal)	Acquisition costs for cabotegravir, Section B.3.5.1.1

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Cost of single 600mg cabotegravir injection dose	[redacted]	Not varied	Acquisition costs for cabotegravir, Section B.3.5.1.1
Cost of TDF/FTC, 30 x 200 mg/ 245 mg tablets	£34.20	Not varied	Acquisition costs for TDF/FTC, Section B.3.5.1.2
Cost of TAF/FTC, 30 x 200 mg/ 245 mg tablets	£355.73	Not varied	Acquisition costs for TDF/FTC, Section B.3.5.1.2
Annual administration costs for cabotegravir in first year	£82.93	£67.47 to £99.95 (Gamma)	Administration costs for cabotegravir and TDF/FTC, Section B.3.5.1.3
Annual administration costs for cabotegravir in subsequent years	£71.08	£57.83 to £85.67 (Gamma)	Administration costs for cabotegravir and TDF/FTC, Section B.3.5.1.3
Cost parameters – clinical consultations			
Annual sexual health clinic visit costs, first year, cabotegravir	£407.43	£331.50 to £491.07 (Gamma)	Monitoring costs, Section B.3.5.1.4
Annual sexual health clinic visit costs, subsequent years, cabotegravir	£349.23	£284.14 to £420.92 (Gamma)	Monitoring costs, Section B.3.5.1.4
Annual sexual health clinic visit costs, first year, TDF/FTC	£349.23	£284.14 to £420.92 (Gamma)	Monitoring costs, Section B.3.5.1.4
Annual sexual health clinic visit costs, subsequent years, TDF/FTC	£232.82	£189.43 to £280.61 (Gamma)	Monitoring costs, Section B.3.5.1.4
Cost parameters – monitoring costs			
Annual test costs, first year, men who have sex with men and transgender women, cabotegravir	£790.83	£643.45 to £953.17 (Gamma)	Monitoring costs, Section B.3.5.1.4
Annual test costs, first year, cisgender women, cabotegravir	£706.89	£575.15 to £852.00 (Gamma)	Monitoring costs, Section B.3.5.1.4
Annual test costs, first year, men who have sex with men and transgender women, TDF/FTC	£790.83	£643.45 to £953.17 (Gamma)	Monitoring costs, Section B.3.5.1.4

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Annual test costs, first year, cisgender women, TDF/FTC	£706.89	£575.15 to £852.00 (Gamma)	Monitoring costs, Section B.3.5.1.4
Annual test costs, subsequent years, men who have sex with men and transgender women, cabotegravir	£432.54	£351.94 to £521.34 (Gamma)	Monitoring costs, Section B.3.5.1.4
Annual test costs, subsequent years, cisgender women, cabotegravir	£357.93	£291.23 to £431.41 (Gamma)	Monitoring costs, Section B.3.5.1.4
Annual test costs, subsequent years, men who have sex with men and transgender women, TDF/FTC	£432.54	£351.94 to £521.34 (Gamma)	Monitoring costs, Section B.3.5.1.4
Annual test costs, subsequent years, cisgender women, TDF/FTC	£357.93	£291.23 to £431.41 (Gamma)	Monitoring costs, Section B.3.5.1.4
Cost parameters – adverse event costs and HIV treatment costs			
Cost associated with moderate injection site reactions	£10.29	£8.37 to £12.40 (Gamma)	Adverse reaction unit costs and resource use, Section B.3.5.3
Cost associated with severe injection site reactions	£124.12	£100.99 to £149.60 (Gamma)	Adverse reaction unit costs and resource use, Section B.3.5.3
Monthly cost of ART for non-resistant HIV	£607.82	£494.55 to £732.60 (Gamma)	Health state unit costs, Section B.3.5.2.1
Monthly cost of healthcare for HIV	£154.98	£126.10 to 186.80 (Gamma)	Health state unit costs, Section B.3.5.2.1
Annual cost of ART for resistant HIV	£9430.36	Not varied	Health state unit costs, Section
Monthly secondary care costs associated with HIV	£154.98	£126.10 to £186.80 (Gamma)	Health state unit costs, Section B.3.5.2.1
Mean time to development of resistant HIV (after discounting)	16.2 years	15.00 to 17.40 (Gamma)	Health state unit costs, Section B.3.5.2.1

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; HRQoL, health-related quality of life; PrEP, pre-exposure prophylaxis; TAF/FTC, tenofovir alafenamide/emtricitabine; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

B.3.9.2 Assumptions

A summary of model assumptions if provided in Table 46.

Table 46: Model assumptions

Category	Assumption	Justification
Model settings (Section B.3.2.2)	Individuals are at increased risk of HIV for a period of 5 years which may not capture the heterogeneity in the duration of the periods where individuals may be at-risk of HIV	A single at-risk period is modelled for parsimony. The duration aligns the risk of HIV acquisition in the TDF/FTC arm with UK data on lifetime risk. In reality, individuals may have multiple periods of time in which they are at risk of HIV acquisition. Consideration of this in the model would have greatly increased the model complexity, but would have had little impact on the fundamental comparison of costs and rate of HIV acquisition during periods of risk of HIV acquisition. Alternative at-risk period duration of 1 and 10 years are explored in scenario analyses.
	No half cycle correction applied	The one-month cycle length was assumed to be sufficiently short to capture model transitions.
Population and comparators (Section B.3.3.1)	The model while populated with data representative of the HPTN trials populations, generate results that can be generalisable to the population considered in the appraisal (individuals at risk of HIV in the UK).	The model uses efficacy data from the HPTN trials which represents populations of men who have sex with men and transgender women (HPTN 083) and cisgender women (HTPN 084), and weighted model results are presented in the base case analysis. The HIV underlying risks selected in the model (4.9 and [redacted] per 100 PY) are reflective of the baseline HIV incidence for any individuals at risk of HIV regardless of their gender or sexual orientation. Thus, the economic model results are generalisable to the population considered in this appraisal, that is individuals at risk of HIV for whom oral PrEP is not appropriate.
	The proportion of cisgender women eligible for PrEP in the CEM is informed by data that reflect both cisgender and transgender women	GUMCAD data report numbers of women who have sex with men (heterosexual and bisexual) eligible for PrEP and does not report data specifically for cisgender and transgender women. The proportion of cisgender women in the CEM may be overestimated and the proportion of men who have sex with men and transgender women may be underestimated. Scenario analyses are included presenting the results of both populations separately.
	TAF/FTC is not considered explicitly as a comparator	The use of TAF/FTC in the UK is negligeable according to UK evidence and this approach is conservative since TAF/FTC has similar efficacy as TDF/FTC but is more costly. A 0.185% monthly rate of individuals transitioning to TAF/FTC while receiving TDF/FTC is examined in a scenario analysis. This value is based on UK evidence from Dean Street data (23, 24).
Clinical effectiveness (Section B.3.3.4)	The underlying risk of HIV for cisgender women is assumed to be [redacted] per 100 PY	In absence of UK data reporting the underlying risk of cisgender women at risk of HIV, the analysis has applied the underlying HIV incidence rate estimated in the ITC for the HPTN 084 trial population. The value also accords with

Category	Assumption	Justification
	according to the HIV incidence with no PrEP estimated in the ITC for this population	the WHO threshold incidence of 3 HIV infections per 100 PY considered as the basis for recommending PrEP (178).
	The risk of HIV acquisition on TDF/FTC is a function of adherence	The economic analysis models the efficacy of TDF/FTC as a function of adherence assuming that no other confounding affects the efficacy of TDF/FTC. This is supported by the findings of an SLR of adherence studies and by the results of the meta-regression. Clinical experts consulted validated this assumption noting that a very small number of cases of biological failures have been reported worldwide (note: clinical virological failures) and rarely, some people may take longer to achieve optimal doses or require dose adjustment.
	Persistence with cabotegravir is higher than that observed for TDF/FTC	The increased convenience of cabotegravir and the addition of a new PrEP modality is considered likely to increase persistence. This is consistent with the experience in contraception (82). The assumption also reflects the duration of partial protection from HIV acquisition for a period of time following discontinuation of cabotegravir. In absence of data available to inform cabotegravir persistence, an assumption of 20% improved persistence was made. This assumption is likely conservative considering clinical expert opinion indicated that improved persistence of 50% could be anticipated for cabotegravir when compared with TDF/FTC and hence, an alternative assumption of 35% improved persistence is presented in scenario analyses.
Cost and resource use inputs (Section B.3.5)	There is no wastage of TDF/FTC	The base-case analysis assumed that any oral PrEP which was not taken as directed would be saved and used for another day. In reality, wastage of unused TDF/FTC is likely meaning that the analysis has underestimated the true cost of TDF/FTC. A scenario analysis accounting for wastage of TDF/FTC is presented.
	The costs associated with HIV disease progression and resistance acquired over time is not modelled	The development of HIV resistance over time was not explicitly captured in the model as this would have greatly increased model complexity. Additional costs associated with PreP-related breakthrough resistance were captured in the model as a one-off cost.
	Costs of treating non-resistant and resistant HIV are the same after 16.2 discounted years	In reality, durations of first line ARV may now be shorter because of the availability of additional ARV options and the possibility of regimen optimization in the setting of viral suppression. A conservative assumption of increased costs for the treatment of resistant HIV compared with non-resistant HIV for 16.2 discounted years was applied.

Abbreviations: ARV, anti-retroviral; CEM, cost-effectiveness model; HIV, human immunodeficiency virus; HPTN, HIV Prevention Trials Network; PrEP, pre-exposure prophylaxis; PY, person year; QALY, quality adjusted life year; TAF/FTC, tenofovir alafenamide/emtricitabine; TAF/FTC, tenofovir alafenamide with emtricitabine; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine; WHO, World Health Organisation.

B.3.10 Base-case results

B.3.10.1 Base-case incremental cost-effectiveness analysis results

The deterministic base case results are provided in Table 47 and Table 48. For all results, the list price of cabotegravir has been compared to the list price of TDF/FTC. Cabotegravir generates a QALY gain of [redacted] versus TDF/FTC and [redacted] versus no PrEP. Cabotegravir is cost-effective versus TDF/FTC at a WTP threshold of £20,000 per QALY, generating a small increase in costs of [redacted]. Cabotegravir dominates no PrEP with a cost saving of [redacted]. At willingness-to-pay (WTP) threshold values of £20,000 and £30,000 per QALY, the incremental net health benefit (NHB) of cabotegravir compared with TDF/FTC was 0.15 and 0.17, respectively. At WTP threshold values of £20,000 and £30,000 per QALY, the incremental NHB of cabotegravir compared with no PrEP was 1.99 and 1.54, respectively.

Table 47: Base-case deterministic results cabotegravir versus TDF/FTC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental NHB at £20,000 per QALY	Incremental NHB at £30,000 per QALY
TDF/FTC	[redacted]	[redacted]	[redacted]	–	–	–	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£5,580	0.15	0.17

Cabotegravir is included at the list price. TDF/FTC is included at the lowest available price on the BNF.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years; TDF/FTC, Tenofovir disoproxil fumarate with emtricitabine.

Table 48: Base-case deterministic results cabotegravir versus no PrEP

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental NHB at £20,000 per QALY	Incremental NHB £30,000 per QALY
No PrEP	[redacted]	[redacted]	[redacted]	–	–	–	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant (–£44,509; South-East quadrant)	1.99	1.54

Cabotegravir is included at the list price.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life year; TDF/FTC, Tenofovir disoproxil fumarate with emtricitabine.

B.3.11 Exploring uncertainty

B.3.11.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was conducted in order to assess the impact of parameter uncertainty on the results. The analysis involved varying the inputs by randomly assigning a parameter value from predefined uncertainty distributions for each parameter in the model. Costs and outcomes were then recorded for 10,000 evaluations of the model with random sampling of parameters in each evaluation.[l]

Table 49 presents the outputs of the PSA comparison for cabotegravir versus TDF/FTC; the corresponding scatterplot and cost-effectiveness acceptability curve (CEAC) are presented in Figure 13 and Figure 14, respectively.

The results show an incremental gain of [redacted] QALYs and incremental costs of [redacted] if cabotegravir is used instead of TDF/FTC. The incremental NHB for cabotegravir compared with TDF/FTC at a WTP threshold of £20,000 and £30,000 per QALY is 0.15 and 0.17. The CEAC shows that there is an [redacted] probability cabotegravir is the most cost-effective option at a WTP threshold of £30,000 per additional QALY.

Table 49: PSA base case cost-effectiveness results for cabotegravir versus TDF/FTC

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus baseline (£/QALY)	Incr. NHB at £20,000 per QALY	Incr. NHB at £30,000 per QALY
TDF/FTC	[redacted]	[redacted]	–	–	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	£4,409	0.15	0.17

Cabotegravir is included at the list price. TDF/FTC is included at the lowest available price on the BNF.

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TDF/FTC, Tenofovir disoproxil fumarate with emtricitabine.

[l] Examination of the convergence plot indicated that 1,000 iterations were ample to allow stabilisation of the mean ICER across iterations.

Figure 13: Cost-effectiveness scatterplot of cabotegravir versus TDF/FTC

Abbreviations: PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life year; TDF/FTC, Tenofovir disoproxil fumarate with emtricitabine.

Figure 14:Cost-effectiveness acceptability curve of cabotegravir versus TDF/FTC

Abbreviations: PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life year; TDF/FTC, Tenofovir disoproxil fumarate with emtricitabine.

Table 50 presents the outputs of the PSA comparison for cabotegravir versus no PrEP; the corresponding scatterplot and cost-effectiveness acceptability curve (CEAC) are presented in Figure 15 and Figure 16, respectively.

The results show an incremental gain of [redacted] QALYs and an incremental cost saving of over [redacted] if cabotegravir is used instead of no PrEP. Cabotegravir dominates no PrEP and generates incremental NHB of 1.95 and 1.49 at WTP thresholds of £20,000 and £30,000 per QALY, respectively. The CEAC shows that there is a [redacted] probability cabotegravir is cost saving. [redacted] (Figure 15).

Table 50: PSA base case cost-effectiveness results for cabotegravir versus no PrEP

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus baseline (£/QALY)	Incr. NHB at £20,000 per QALY	Incr. NHB at £30,000 per QALY
No PrEP	[redacted]	[redacted]	–	–	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	Dominant (–£48,991; South-East quadrant)	1.95	1.49

Cabotegravir is included at the list price.
Abbreviations: ICER, incremental cost-effectiveness ratio; PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life year; TDF/FTC, Tenofovir disoproxil fumarate with emtricitabine.

Figure 15: Cost-effectiveness scatterplot of cabotegravir versus no PrEP

Abbreviations: PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life year.

Figure 16: Cost-effectiveness acceptability curve of cabotegravir versus no PrEP

Abbreviations: PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life year.

B.3.11.2 Deterministic sensitivity analysis

A deterministic OWSA was conducted to explore the effect of uncertainty associated with varying individual model inputs. By adjusting each parameter individually, the sensitivity of the model results to that parameter can be assessed. The OWSA involved varying one parameter at a time to upper and lower confidence intervals (CI; the low value is the lower bound of the 95% CI, the high value is the upper bound of the 95% CI). In the absence of data, the CI was estimated by assuming a SE of 10% of the mean and applying an appropriate distribution (see Section B.3.9.1).

Figure 17 presents the results of the OWSA comparing cabotegravir with TDF/FTC. The two most influential parameters are the beta and alpha coefficients for the regression model of the log of RR of HIV acquisition with TDF/FTC as a function of adherence (see Section B.2.9.3.1.3). The beta and alpha parameters of the regression model and the RR of HIV incidence with cabotegravir in the men who have sex with men and transgender women population were the only parameters which generated an ICER above £30,000 per QALY when varied, and no parameter generated an ICER above £52,000 per QALY. The sensitivity of the ICER to

uncertainty in the alpha and beta parameters of the regression model is likely to have been overestimated because the OWSA ignores correlation across the two parameters.

Figure 18 presents the results of the OWSA comparing cabotegravir with no PrEP. The three most influential parameters for the comparison of cabotegravir with no PrEP are the monthly cost of ART regimens, the disutility associated with HIV acquisition, and the underlying rate of HIV acquisition with no PrEP. No parameter generated an ICER above £30,000 per QALY across the range of values considered, indicating that the inference that cabotegravir is cost-effective is robust to OWSA across all of the parameters.

Figure 17: Tornado diagram with cabotegravir versus TDF/FTC

Abbreviations: ARV, antiretroviral; cabotegravir LA, cabotegravir long-acting; CI, confidence interval; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; MSM, men who have sex with men; NRTI, nucleoside reverse transcriptase inhibitor; PK, pharmacokinetic; PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life year; SMR, standardised mortality ratio; TDF/FTC, Tenofovir disoproxil fumarate with emtricitabine.

Figure 18: Tornado diagram with cabotegravir versus no PrEP

Abbreviations: ARV, antiretroviral; CI, confidence interval; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; MSM, men who have sex with men; PK, pharmacokinetic; PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life year; SMR, standardised mortality ratio; TDF/FTC, Tenofovir disoproxil fumarate with emtricitabine.

B.3.11.3 Scenario analysis

A range of probabilistic scenario analyses were conducted to test the robustness of the model to alternative model inputs and assumptions. In the base case, the population considered is men who have sex with men, transgender women and cisgender women. In scenario analysis, the men who have sex with men and transgender women population and the cisgender women population were considered separately. The base-case analysis assumes that persistence is 20% higher in individuals on cabotegravir compared with individuals on TDF/FTC. In scenario analysis, this percentage was varied to 35%. In the base case, [redacted] of individuals who receive cabotegravir are assumed to require oral lead-in. Scenario analyses were run in which 5% individuals required oral lead-in and 95% individuals required oral lead-in. A scenario analysis was run in which it was assumed that TDF/FTC doses not taken were wasted. The base-case analysis assumed individuals were at risk of acquiring HIV for five years. In scenario analysis, this was varied to one and ten years. A scenario analysis was run in which a discount rate of 1.5% was applied for costs and outcomes reflecting NICE guidance for discounting of public health interventions (193). For the population of men who have sex with men and transgender women only, a scenario analysis was run in which 0.185% of individuals receiving TDF/FTC transitioned to TAF/FTC each month reflecting the small proportion of patients receiving TAF/FTC observed in data from PrEP users in England attending Dean Street (the largest sexual health clinic in Europe) Chelsea and Westminster Hospital NHS Foundation Trust (23, 24).

In all the scenarios examined, cabotegravir remained cost-effective at a WTP threshold of £30,000 per additional QALY.

Table 51: Probabilistic scenario analysis for cabotegravir compared with TDF/FTC and cabotegravir compared with no PrEP

Scenario	Base case parameter	Value in scenario analysis	Rationale	ICER versus TDF/FTC	ICER versus no PrEP
Base case				£4,409	Dominant (–£48,991; SE quadrant)
Cisgender women population	3.14% of the population	100% of the population	Clarify cost-effectiveness in this part of the population	£7,013	Dominant (–£19,973; SE quadrant)
Men who have sex with men and transgender women population	96.86% of the population	100% of the population		£6,056	Dominant (–£49,491; SE quadrant)
Men who have sex with men and transgender women on TDF/FTC receive TAF/FTC each month	0%	0.185%	In real-world, a small proportion of men who have sex with men and transgender women may receive TAF/FTC	£3,154	–
Persistence for cabotegravir compared with TDF/FTC	Increased persistence of 20%	Increased persistence of 35%	Increased convenience of cabotegravir is likely to improve persistence but the extent is unknown	Dominant (–£4,555; SE quadrant)	Dominant (–£48,510; SE quadrant)
Percentage of individuals requiring oral lead in	[redacted]	5%	[redacted]	£2,236	Dominant (–£44,991; SE quadrant)
	[redacted]	95%		£4,829	Dominant (–£47,821; SE quadrant)
Drug wastage for TDF/FTC	No wastage	Missed TDF/FTC doses are wasted	Wastage is unknown but likely	£2,825	Dominant (–£49,090; SE quadrant)
At-risk period	At-risk period of 5 year	At-risk period of 1 year	The duration of the at-risk period is unknown	£25,149	Dominant (–£45,548; SE quadrant)
	At-risk period of 5 years	At-risk period of 10 years		£16,370	Dominant (–£42,410; SE quadrant)

Scenario	Base case parameter	Value in scenario analysis	Rationale	ICER versus TDF/FTC	ICER versus no PrEP
Discount rate for costs and outcomes	3.5%	1.5%	A value of 1.5% has been advocated for use in public health interventions (193)	Dominant (–£27,438; SE quadrant)	Dominant (–£57,789; SE quadrant)

Abbreviations: PrEP, pre-exposure prophylaxis; SE, South-East; TDF/FTC, Tenofovir disoproxil fumarate with emtricitabine.

B.3.12 Subgroup analysis

Not applicable as there are no subgroups considered.

B.3.13 Benefits not captured in the QALY calculation

In absence of data to inform the utility for the PrEP and no PrEP health states, the model applies general population HRQoL and does not reflect utility decrement that may be associated with being at risk of HIV acquisition whether a person is receiving PrEP or not. The benefits of receiving PrEP for individuals at risk of HIV, while hard-to-quantify, may include reducing the fear of HIV, sexual quality of life improvements (194), and addressing stigma which can limit engagement, opportunity, wellbeing, and social acceptance for individuals with certain social identities, often resulting in discrimination (67, 195, 196), posing barriers to HIV prevention and PrEP uptake, adherence and persistence (67, 197-199). Individuals who are receiving oral PrEP but have challenges or have a suboptimal adherence to TDF/FTC may have a utility decrement compared with those for whom TDF/FTC is appropriate. As described in Section B.1.3.7, by improving adherence, and reducing stigma, cabotegravir is likely to improve the HRQoL of individuals at risk of HIV who are underserved by current SoC; however, this is not reflected in the QALY.

The impact of HIV on HRQoL is likely underestimated. HRQoL and mental well-being are adversely affected, for example by stigma, when living with HIV (67). PrEP stigma may drive disparities, with stigma experienced by potential and current users often reinforced or amplified by public health programmes, policies and research, and PrEP stigma disproportionately impacts disadvantaged groups (115). Strong evidence shows that HRQoL and mental well-being are adversely affected by stigma when living with HIV (200, 201). Although this analysis accounts for the impact that living with HIV has on affected people's health-related quality of life (HRQoL), using EQ-5D-3L data from a large UK study (173), the EQ-5D instrument may have limitations in discriminating different health states when living with HIV, and ceiling effects (202, 203). Consequently, the benefit of cabotegravir of maintaining HRQoL by reducing HIV acquisitions and associated utility decrement may be underestimated in the economic model.

The model perspective while in line with the NICE reference guide may not fully capture the benefits of cabotegravir on a societal or public health level described in Section B.1.3.1. Indeed, the economic model doesn't reflect the consequences of unemployment (Section B.1.3.8.2) or the impact on people with carer responsibilities which may underestimate cabotegravir's benefits.

B.3.14 Validation

B.3.14.1 Validation of cost-effectiveness analysis

Key modelling issues, including the CEM structure, clinical- and economic-evidence, were discussed at a European advisory board with independent health economists (204). A UK advisory board was also conducted with health economists and clinical experts to ensure the model structure, assumptions, and key parameters, were all appropriate for a UK context (55). Feedback from both meetings was incorporated into the final model design.

In alignment with good practice, the CEM coding has been extensively validated throughout the development process. Validation has been performed internally and by two external agencies, in each instance using team members who were not involved in the original model development. These procedures included verification of all input data with original sources and programming validation. Programming validation included checks of the model results, calculations, data references, model interface and Visual Basic for Applications coding. Additionally, a US version of the model has recently been published in a peer-reviewed journal (184) which was validated using the Assessment of the Validation Status of Health-Economic decision models (AdViSHE) tool (205).

B.3.15 Interpretation and conclusions of economic evidence

B.3.15.1 Summary of cost-effectiveness analysis

When using the net price of cabotegravir, the base-case cost-effectiveness analysis demonstrates that cabotegravir provides [redacted] additional QALYs at a minimal additional cost of [redacted] per person compared with TDF/FTC in individuals at risk of HIV acquisition and for whom TDF/FTC use is suboptimal, thus it is cost-effective at WTP of £30,000 per QALY with an ICER of £5,580. When compared with no PrEP,

cabotegravir is dominant as the reduction in HIV acquisitions translate into [redacted] additional QALYs and cost savings of [redacted] per person.

The PSA results show that cabotegravir is [redacted] and [redacted] likely to be cost-effective at a willingness to pay per additional QALY of £30,000 when compared with TDF/FTC use and no PrEP respectively. The deterministic sensitivity- and scenario-analyses indicate that these findings are robust to alternative assumptions.

B.3.15.1.1 *Limitations*

No RCT was identified comparing cabotegravir with no PrEP. An ITC was undertaken based on the results from an SLR. The ITC results showed that the effectiveness of cabotegravir in reducing the risk of HIV acquisition is [redacted] in both men who have sex with men and transgender women ([redacted] in the HPTN 083 population) and cisgender women ([redacted] in the HPTN 084 population).

The single HIV health state within the model aims to reflect the costs and health outcomes associated with living with HIV, a complex and chronic condition, requiring simplifying assumptions. For example, a single one-off cost was estimated to represent the additional cost burden of acquiring INSTI- or NRTI- resistant HIV.

As cabotegravir is a novel intervention, there is limited evidence that can inform certain parameters; for example, persistence to cabotegravir, cannot be verified against other long-acting injectables for PrEP as no others exist. Nonetheless, alternative sources from the literature were considered to estimate this parameter along with clinical experts' opinion.

B.3.15.1.2 *Strengths*

The model design has been carefully considered to accurately capture the number of HIV acquisitions whilst individuals are at risk, depending on the modality of PrEP in a transparent approach. Importantly, the modelling approach is consistent with published economic models in evaluating PrEP options (described in Section B.3.1) and a thorough internal and external validation of the model was performed.

A key strength of the modelling approach relates to the high quality of the evidence used to inform the effectiveness of cabotegravir and TDF/FTC. Indeed, the analysis has benefitted from two high quality trials, the HPTN 083 and HPTN 084, which offer head-to-head comparisons of cabotegravir against the UK SoC for PrEP, TDF/FTC.

Both trials demonstrated a significant reduction in HIV acquisition with cabotegravir compared to TDF/FTC.

Performing the ITC allowed for an estimate of the relative risk of HIV acquisition of cabotegravir and TDF/FTC versus no PrEP and had the added benefit of allowing the efficacy of TDF/FTC as a function of adherence to be modelled. It is a well-established predictor of TDF/FTC effectiveness and adds to the model's ability to reflect real-world outcomes.

In summary, the clinical evidence used in the economic analysis provides a robust estimate of the comparative effectiveness of cabotegravir versus no PrEP and TDF/FTC vs no PrEP at the level of adherence observed in the HPTN trials. The results can also be considered robust and reflective of individual experience; inevitable evidence limitations have been addressed by sensitivity analyses and external validation with clinical experts.

B.3.15.2 Conclusions

The lack or limited availability of suitable PrEP options for individuals underserved by the current SoC for PrEP in England remains a significant challenge, resulting in unmet need where people do not or cannot utilise, adhere and persist with effective HIV prevention. As recent data show the UK HIV Action Plans targets will not be met by 2030 (10), further efforts and investments are required.

Two robust clinical trials demonstrate superior efficacy of cabotegravir versus daily oral PrEP and show that it offers an adherence advantage by removing the need for daily oral pills. An indirect treatment comparison suggests that cabotegravir is [redacted] in reducing the risk of HIV acquisition versus no PrEP. This has been demonstrated in wide diversity of people who would benefit from PrEP and is representative of people with an unmet PrEP need in the UK.

In the cost-effectiveness analysis cabotegravir is associated with additional QALYs ([redacted] versus oral PrEP and [redacted] versus no PrEP), generating minimal additional costs of [redacted] versus oral PrEP and cost savings of [redacted] versus no PrEP. The resulting ICER versus oral PrEP is £5,580, while cabotegravir is dominant versus no PrEP.

Overall, cabotegravir is a novel PrEP modality providing people who need HIV prevention with an innovation that is clinically superior, cost-effective and that can reduce future health service utilisation associated with HIV acquisition. This provides a vital intervention for those with unmet need, to support individuals, populations, and the UK government to meet the HIV Action Plan to end HIV transmissions by 2030.

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B.5 Appendices

The following appendices are included with the submission as separate documents:

Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Price details of treatments included in the submission

Appendix L: Checklist of confidential information

Appendix M: Clinical effectiveness evidence

Appendix N: Supplementary information for Section B1

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Cabotegravir for preventing HIV-1 in adults and young people [ID6255]

Summary of Information for Patients (SIP)

February 2024

File name	Version	Contains confidential information	Date
ID6255_Cabotegravir for PrEP_Summary of information for patients	2	No	14th February 2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for community organisations and community experts participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

Please note for this appraisal NICE will be using "community organisations" and "community experts" in place of patient organisations/experts and will be referring to "people at risk of sexually acquired HIV-1 infection" in place of "patients".

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Cabotegravir (Apretude)

1b) Population this treatment will be used by. Please outline the main population that is being appraised by NICE:

Adults and adolescents (at least 35 kg) at risk of human immunodeficiency virus (HIV) for whom oral pre-exposure prophylaxis (PrEP) is not appropriate. The population describes people who are underserved by the current UK standard of care, which involves taking a daily pill orally to prevent HIV acquisition (1). Taking oral PrEP as prescribed is required for full protection from HIV acquisition (2, 3). The people likely to use cabotegravir includes those who cannot take daily oral PrEP as prescribed due to health-related challenges (which may include physical, mental, and cognitive symptoms, difficulties with day-to-day activities, challenges to social inclusion, and uncertainty or worry about future health (4)) as well as social determinants of health (the conditions with which people are born, grow, live, work, and age that shape the level of power, income, and other determinants of life (5)). Cabotegravir may also be used by people who need PrEP but whose health conditions mean they cannot take oral PrEP because it may be harmful for them, or who have a limited ability to swallow pills.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

A marketing authorisation application is pending for cabotegravir for PrEP. The anticipated dates for approval are provided in Table 2 in Document B of the Company submission.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and community groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

ViiV Healthcare has provided charitable unrestricted grants to support people living with HIV to the following stakeholder community organisations: George House Trust; GMFA – The Gay Men's Health Charity; HIV i-Base; NAM; National AIDS trust; NAZ; Positively UK; Sophia Forum; UK-CAB.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of people at risk of sexually acquired HIV-1 infection and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Human immunodeficiency virus and the impact of living with the condition

HIV attacks a type of white blood cell that plays a key role in fighting infections. It is transmitted via the bodily fluids of people who are living with HIV who are not on effective treatment, for example during condomless sex (6). Without effective treatment, the immune system of a person living with HIV becomes weakened, leaving them vulnerable to infections and diseases. Progression to late-stage infection, where the immune system is severely compromised, can lead to life-threatening illnesses such as severe infections and some types of cancer (6). The life expectancy of individuals with a weakened immune system due to uncontrolled HIV remains up to 30 years lower than the general population (7). Living with HIV has a significant impact on people's health-related quality of life because of factors such as HIV symptoms burden, co-infections, HIV-related hospitalisations, depression (8), drug and alcohol dependence, social isolation, and difficulties discussing HIV status (9). People living with HIV can also experience unemployment, unmet health and lifestyle needs, and HIV-related stigma including inequity in healthcare settings, negative attitudes towards men that have sex with men and African and Afro-Caribbean people, negative self-image, feelings of shame, fear of discussing HIV, isolation, and anticipating discrimination (10-12). In addition to the challenges of living with HIV, quality of life may also be affected among people who may benefit from PrEP, such as people likely to be exposed to HIV, for example many gay and bisexual men experience uncertainty and anxiety about HIV, particularly related to condomless and anal sex (13).

How many people live with the condition?

In 2020, an estimated 106,890 people in the UK were living with HIV, the majority of whom (97,740) were in England (14). In 2022, 4,040 people were newly diagnosed with HIV in the UK, representing a 19% rise from 2021 and 21% rise from 2020 (15). Of these, 3,805 were in England. The UK government's HIV Action Plan for England (2022 to 2025) aims to achieve zero new HIV transmissions by 2030, and reduce HIV- and acquired immunodeficiency syndrome (AIDS)-related deaths, and HIV-related stigma (16). HIV prevention is one of the four core themes for achieving the UK HIV action plan's aims.

Preventing HIV acquisition: pre-exposure prophylaxis

PrEP refers to the use of antiretroviral therapies to prevent HIV among people who are likely to be exposed to HIV. Multiple studies have reported that the use of PrEP reduces HIV-related anxiety among people who are likely to be exposed (13, 17-20). In 2022, there were 121,547 people accessing sexual health services in England with a need for HIV prevention and PrEP (15), however

there remains unmet need for PrEP (21). Effective prevention of future HIV acquisitions will contribute to ending the HIV epidemic, and will limit the significant clinical, humanistic, and economic burden living with HIV has on both individuals, and healthcare systems.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts people at risk of sexually acquired HIV-1 infection. Are there any additional diagnostic tests required with the new treatment?

As cabotegravir will be used for HIV prevention, the criteria used to identify individuals who are eligible to receive PrEP in the UK, rather than describing how HIV is diagnosed, are detailed below. The UK National Health Service's (NHS) PrEP policy (1), and guidelines from the National Institute for Health and Care Excellence (NICE) (22) consider a person's eligibility for PrEP as per criteria defined by the British HIV Association (BHIVA)/British Association for HIV and Sexual Health (BASHH) 2018 guidelines (3). According to these, people who are likely to be exposed to HIV include:

- HIV-negative men who have sex with men and transgender women who report condomless anal sex in the previous 6 months and ongoing condomless anal sex.
- HIV-negative people having condomless sex with partners who are HIV-positive, unless their partner has been on antiretroviral therapy for more than 6 months and they cannot pass on the virus sexually (as measured by their plasma viral load being less than 200 copies per/mL).
- People at increased risk of HIV acquisition through a combination of factors (case-by-case basis) that may include population level indicators, clinical indicators, sexual behaviour/sexual network indicators, drug use, or sexual health autonomy (for example, inability to negotiate and/or use condoms [or employ other HIV prevention methods] with sexual partners).

Clinical care related to PrEP delivery in the UK includes supporting people who are taking PrEP to get regular HIV tests and screening for other sexually transmitted infections (every 3 months) (22). Cabotegravir users, like oral PrEP users, also require regular HIV testing alongside comprehensive HIV prevention strategies including safer sex practices, in order to comply with guidelines.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for populations of people at risk of sexually acquired HIV-1 infection? If so, please explain what these are.

Currently, the only available PrEP options in the UK are oral tablets, which are prescribed via specialist sexual health services in England for individuals who are considered likely to be exposed to HIV as defined in the BHIVA/BASHH guidelines (see Section 2b) (1, 3). Non-brand-name forms

of the combination antiretroviral therapy tenofovir disoproxil with emtricitabine (TD/FTC)[a] is considered standard of care for people who are not living with HIV but are likely to be exposed (1). In addition, tenofovir alafenamide with emtricitabine (TAF/FTC) is available within a limited population of people who cannot take TD/FTC due to health conditions which mean it may be harmful for them, for example reduced kidney function or kidney toxicity with TD/FTC and people with high risk of bone fractures (broken bones) or osteoporosis (a disease characterised by low bone mass and bone deterioration) (1, 23). However, TAF/FTC is only licensed in the UK for men who have sex with men, including adolescents (with body weight ≥35 kg) (23), therefore individuals assigned female sex at birth who are likely to be exposed to HIV from vaginal sex do not have another option available if they are unable to take TD/FTC. Oral PrEP needs to be taken daily so that optimum protective effect can be achieved for people who may be exposed to HIV.

The proposed use of cabotegravir in the UK is among people for whom oral PrEP is not appropriate; these people as well as key reasons are described in detail in Section 1b.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when people at risk of sexually acquired HIV-1 infection input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to people at risk of sexually acquired HIV-1 infection and carers and where their greatest needs are. Such research can inform the selection of endpoints relevant to people at risk of sexually acquired HIV-1 infection in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **needs of people at risk of sexually acquired HIV-1 infection and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Being likely to be exposed to HIV has a significant impact on people's daily lives, for example many gay and bisexual men experience HIV anxiety, particularly around condomless and anal sex (13). Studies have shown that using PrEP reduces HIV-related anxiety and fear among people who are likely to be exposed (13, 17-20).

Some people may prefer an injectable PrEP option over oral PrEP, and people's preference may have an impact on whether they decide to take the currently available oral options, and how well they take them. The HPTN 077 study in men and women (including transgender men and women) likely to be exposed to HIV, investigated how acceptable participants found injectable PrEP, their prevention preferences, and their future interest in injectable PrEP. In the study, the preference for injectable PrEP was higher than daily oral TDF/FTC, and this increased over time: 61% of participants at the beginning of the study and 78% of participants at the final injection preferred injectable PrEP administered every 8 or 12 weeks versus other PrEP options (daily oral pill, vaginal ring [for people assigned female at birth], or rectal gel [for people assigned male at birth]) (24).

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to people at risk of sexually acquired HIV-1 infection relating to the mechanism of action and how the medicine interacts with the body

[a] Note, non-brand name drugs can use different tenofovir disoproxil salts; TD/FTC is an inclusive term of all formulations of tenofovir disoproxil with emtricitabine. TDF/FTC may be used in some places in this document and the Company submission, for example when referring to the clinical trials investigating cabotegravir for PrEP, as this specifically refers to tenofovir disoproxil/emtricitabine where tenofovir disoproxil is combined with the salt fumarate.

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to people at risk of sexually acquired HIV-1 infection and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

How cabotegravir works

Cabotegravir is an integrase strand transfer (INSTI) inhibitor. In an individual who is exposed to HIV, cabotegravir prevents HIV DNA from integrating with human DNA by blocking the action of the HIV enzyme integrase; this stops HIV from replicating (making new copies of itself in the body) and spreading from the site of infection.

What is new about this prevention?

Cabotegravir long-acting is an extended-release injectable suspension, and therefore eliminates the need for daily dosing, offering a more discreet form of protection from HIV. This is particularly important for individuals who may experience stigma associated with PrEP eligibility.

The draft UK summary of product characteristics is provided in Document B, Appendix C.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to people at risk of sexually acquired HIV-1 infection why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

No.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect people at risk of sexually acquired HIV-1 infection and caregivers? How does this differ to existing treatments?

Cabotegravir long-acting for PrEP is administered as a single 600 mg (3 mL) injection into the buttock muscle, given 1 month apart for the first 2 months, after which injections are then given once every 2 months (Document B, Appendix C). Optional cabotegravir daily oral tablets may be prescribed for approximately 1 month before the first injection, to assess the tolerability of the medicine. Oral cabotegravir also provides an option to cover a planned missed injection visit. Cabotegravir injections should be administered by a healthcare professional.

Importantly, cabotegravir long-acting injections provide individuals at risk of HIV acquisition a new PrEP option that does not require daily oral tablets; having an injection every 2 months reduces the number of PrEP doses per year from 365 with daily oral PrEP to just six injections per year.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

The primary evidence for the efficacy (how effective a drug is) and safety of cabotegravir comes from two large randomised controlled trials:

- **HPTN 083** (NCT02720094) in 4,570 men who have sex with men (87%) and transgender women who have sex with men (12%) at risk of sexually acquiring HIV.
- **HPTN 084** (NCT03164564) in 3,224 cisgender women at risk of sexually acquiring HIV.

In these studies, participants were randomly allocated to receive cabotegravir injections every 2 months (after receiving daily oral cabotegravir tablets for up to 5 weeks) or daily oral TDF/FTC, allowing researchers to compare these PrEP options.

The trials were designed so that the participants and the researchers were not able to distinguish which PrEP method was being received during the double-blinded stage of the trials. This blinded stage was stopped early in both trials due to cabotegravir showing higher efficacy than daily oral TDF/FTC (as recommended by independent Data and Safety Monitoring Boards which reviewed the trial data). Participants then continued on their randomised study product for 1 year of un-blinded follow-up (their allocated PrEP regimen was no longer unknown), while the study protocols were updated to include an open-label extension study where participants had the option to continue receiving their original randomised PrEP regimen or switch to the other regimen. The open-label extensions are currently ongoing.

An overview of the study locations, and the key criteria for selecting trial participants for HPTN 083 and HPTN 084 is provided in Table 1.

Table 1: HPTN 083 and HPTN 084: overview of study design

	HPTN 083 (25, 26)	HPTN 084 (27)
Settings and locations where data were collected	43 sites in the United States, Latin America, Asia, and Africa	20 sites in 7 countries in sub-Saharan Africa (Botswana, Eswatini, Kenya, Malawi, South Africa, Uganda, and Zimbabwe)
Criteria for people to be included in the study	• Cisgender men and transgender women who have sex with men ≥18 years of age • Not living with HIV at screening and enrolment • At high risk for sexually acquiring HIV • In general good health as evidenced by clinical and laboratory assessments	• Cisgender women, 18–45 years of age • Not living with HIV at screening at enrolment • At high risk of sexually acquiring HIV • Negative pregnancy test • Use of long-acting contraception
Criteria for people to be excluded from the study	• One or more reactive HIV test result at screening or enrolment, even if HIV acquisition was not confirmed • Active or recent use of illicit intravenous drugs (within 90 days before enrolment) • Current or chronic history of liver disease	• One or more reactive HIV test result at screening or enrolment, even if HIV acquisition is not confirmed • History of liver disease • Pregnant or currently breastfeeding, or intends to become pregnant and/or breastfeed during the study

Supportive evidence for the submission is provided by:

- The Phase 2 trials HPTN 083-01 and HPTN 084-01, evaluating the safety, tolerability, and acceptability of cabotegravir for adolescents (under the age of 18 years) assigned male or female at birth, respectively. Preliminary results among cisgender female adolescents (HPTN 084-01) demonstrate safety and efficacy, with high adherence to injections (>90%) and preferred choice (>90%) of cabotegravir injections compared to daily oral TDF/FTC (28, 29).
- HPTN 083-02, a sub-study of HPTN 083 exploring trial experiences, barriers to taking PrEP as prescribed, and other factors impacting study implementation or outcomes (Document B, Section B.2.6.1.4) which showed people viewed the study as a way to access a novel,

convenient PrEP (injectable) at no cost, and that initial injection-related anxiety abated with experience, and discomfort was minimal and manageable (30).

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to people at risk of sexually acquired HIV-1 infection than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

HPTN 083 and HPTN 084: Prevention of HIV acquisition

HPTN 083 and HPTN 084 were designed to test whether cabotegravir is superior to (i.e. better than) daily oral TDF/FTC for preventing HIV acquisition. Results from both HPTN 083 and HPTN 084 demonstrate that cabotegravir can successfully reduce HIV acquisitions compared with daily oral TDF/FTC.

During the blinded portion of the trials, pre-defined analyses of study data found that cabotegravir demonstrated a 66% reduction in new HIV acquisitions in HPTN 083 (25), and an 88% reduction in HPTN 084 (27). The results of both trials met the statistical criteria for superiority of cabotegravir versus daily oral TDF/FTC. Another analysis of the blinded phase was also carried out which was defined after the study data were collected. In this extended analysis, the number of new HIV acquisitions during the blinded phase was re-evaluated after more extensive testing of participants stored blood plasma samples was carried out, which more accurately identified the time at which any HIV acquisitions occurred. The efficacy of cabotegravir was unchanged in this analysis, with revised estimates indicating cabotegravir provided a 69% reduction in new HIV acquisitions in HPTN 083, and 90% reduction in HPTN 084 versus TDF/FTC (31).

Importantly, the protective benefits of cabotegravir have been demonstrated in individuals with unmet need who are least likely to benefit from currently available PrEP options in England, including cisgender women (studied in HPTN 084), and across subgroups in HPTN 083 which included key populations such as men who have sex with men of Black African ethnicity, and transgender women (Document B, Appendix E). In addition, the efficacy of cabotegravir was maintained during an additional year of un-blinded follow-up (26, 32).

HPTN 083 and HPTN 084: The development of resistance mutations

Drug resistance is when HIV can continue to replicate despite use of the drug as a result of a mutation (a change in its genetic material). The development of resistance to therapies used for PrEP may compromise future treatment options if an individual acquires HIV. In HPTN 083, resistance mutations were very rarely seen in both the cabotegravir and the TDF/FTC arms. In the blinded trial phase plus an additional year of unblinded follow-up, resistance to cabotegravir (INSTI resistance) was detected in only 10 (0.44%) cases among the 2,282 participants who were allocated to and eligible to receive cabotegravir (26). Among the very rare cases where HIV acquisition occurred while receiving on time cabotegravir LA injections, INSTI resistance-associated mutations were detected in all (n=6), but all six people were able to achieve an undetectable level of the virus when treated with other types of anti-retroviral therapy (26). Importantly, no resistance to cabotegravir was observed in cases where HIV was likely to have been acquired when patients had delayed or no recent cabotegravir injections but cabotegravir was probably still present in the body (26). In HPTN 084, there were no cases of INSTI resistance detected in any cases of HIV acquisition in the cabotegravir arm during the blinded study period (27).

HPTN 083 and HPTN 084: Adherence to PrEP

Effective protection from HIV acquisition requires adherence to oral PrEP, meaning a person takes it as prescribed, both in terms of how much of the medicine is taken and how often (2, 3). Importantly, HPTN 083 and HPTN 084 have shown that cabotegravir injections offer an adherence advantage over daily oral TDF/FTC by removing the need for daily oral pills. During the blinded period in HPTN 083, 92% of observed person time[b] was protected by cabotegravir injections (25, 26), while drug concentration measurements in people on TDF/FTC showed the proportion of people taking the minimum effective dose of four or more tablets per week was 72.3% according to blood samples (25). In HPTN 084, 93% of person time was protected by cabotegravir injections, while 41.9% of people had TDF/FTC plasma concentrations consistent with daily use (≥40 ng/mL) and 18% of people had blood levels indicating they were taking four or more doses of TDF/FTC per week (27).

Indirect treatment comparison

A limitation of the HPTN 083 and HPTN 084 studies is that while they were designed to make reliable statistical comparisons of cabotegravir with daily oral TDF/FTC, no comparison is available versus no PrEP in these research trials, because not providing PrEP to people who need it would not be appropriate. To investigate this, an indirect treatment comparison was performed; this method of analysis compares cabotegravir versus the no PrEP arm of other clinical trials which have a common comparator of TDF/FTC. The analyses also accounted for any differences among the included trials in the extent to which individuals took PrEP as prescribed, as this has been shown to affect PrEP efficacy. Overall outcomes of this analysis were directionally consistent with the trial results.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of people at risk of sexually acquired HIV-1 infection and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

No quality-of-life measures were used to assess the impact of using cabotegravir versus daily oral TDF/FTC in either HPTN 083 or HPTN 084. However, participants did report their acceptability of and preferences for cabotegravir versus daily oral TDF/FTC. Direct comparisons of the oral versus injectable method of administration was not possible due to the study design, however patients in both studies reported a high level of overall satisfaction for a long-acting injectable, with factors such as convenience, flexibility, ease of use, and discretion being important factors (33, 34). In HPTN 083, satisfaction with study medication was self-assessed via two questionnaires; in both treatment arms, the overall satisfaction with injectable and oral study medication was high and consistent for the duration of the study with similar overall scores.

A published global systematic literature review, which included 62 unique references, reported that there is an overall preference for injectable PrEP, with much interest in this method, including cabotegravir (35).

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as

[b] A measure accounting for the number of people in the study, and their amount of time in the study

opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Like all drugs, cabotegravir can cause side effects, although not everybody gets them. Safety results from HPTN 083 and HPTN 084 demonstrated that cabotegravir is generally well tolerated; the type and number of adverse events were similar between the cabotegravir and TDF/FTC groups, except for injection site reactions, which were more common with cabotegravir (as expected with the method of administration). However, most injection site reactions were only mild to moderate severity, and few people chose to discontinue injections due to injection site reactions across both trials. Apart from injection site reactions, the most common side effects with cabotegravir (which may affect more than 1 in 10 people) include headache, diarrhoea, feeling hot (pyrexia) and changes in liver function (an increase in the liver enzyme transaminase) (31). Common side effects, which may affect up to (1 in 10 people) include depression, anxiety, abnormal dreams, difficult sleeping (insomnia), dizziness, feeling sick (nausea), vomiting, stomach pain (abdominal pain), wind (flatulence), rash, muscle pain (myalgia), lack of energy (fatigue), and generally feeling unwell (malaise) (31).

3h) Summary of key benefits of treatment for people at risk of sexually acquired HIV-1 infection

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for people at risk of sexually acquired HIV-1 infection, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

HIV prevention is critical to achieve the UK HIV Action Plan's aims of zero new transmissions of HIV, AIDS, and no HIV-related deaths by 2030 (16). However, not all people who are likely to be exposed to HIV are currently achieving sufficient protection from HIV acquisition using available oral PrEP options. This is concerning not just on an individual level, but because it can also limit the population-level impact of PrEP in preventing new HIV transmissions for the UK as a whole. Key areas of unmet need relate to:

- Not all people who need PrEP are taking current oral PrEP options (only 71% of people at need for PrEP initiated or continued PrEP in 2022 (15))
- Some people may not be taking PrEP as prescribed (not adherent), and
- Some people may not continue using PrEP for the full duration they are likely to be exposed to HIV (not persistent).

Having additional effective and tolerable PrEP options with different methods of administration and a reduced dosing frequency may help to address some of these areas of unmet need in those people for whom these additional options are appropriate.

Effectiveness and safety of cabotegravir

As described in Section 3e, cabotegravir is the first long-acting injection for PrEP that has demonstrated a clinically meaningful and statistically significant reduction in HIV acquisitions versus daily oral TDF/FTC in two large, robust randomised controlled trials (25-27). It is generally well tolerated, with side effects that are broadly similar to TDF/FTC, except for injection site reactions, as expected with the method of administration.

Method and frequency of administration of cabotegravir

An injectable that is administered less often than tablets provide an important alternative PrEP option for individuals who are not taking daily oral PrEP as prescribed and are therefore not

achieving optimal protection from HIV acquisition. Importantly, the clinical trials demonstrated that cabotegravir offers an adherence advantage versus daily oral PrEP by removing the need for daily oral pills. Additionally, as cabotegravir must be delivered by a healthcare professional, this also provides assurance that people are taking their PrEP as prescribed.

Cabotegravir may also help to improve PrEP uptake and further the population-level impact of PrEP, as it provides a new option for people who need PrEP but cannot take current oral options. For example, some people cannot take oral TD/FTC because their health conditions mean it may be harmful to them, or they are intolerant to TD/FTC due to symptoms like diarrhoea or feeling sick. Although TAF/FTC is available for a subset of individuals who cannot take TD/FTC, this option is not licensed for individuals assigned female sex at birth (23), therefore cabotegravir also provides these underserved individuals an alternative to TD/FTC. Additionally, there is no evidence to suggest that cabotegravir represents a risk for kidney and bone health in the long-term, while the long-term use of oral TD/FTC may be associated with concerns around kidney and bone toxicity (36-41) .

Cabotegravir may also appeal to populations who are currently underrepresented among UK PrEP users but face a high burden of potential HIV diagnoses, such as individuals of Black African ethnicity, transgender women, and cisgender women (see Section 3l for further details). Having an injectable option may also provide people who experience PrEP-related stigma with a more discreet protective option as it eliminates the need to conceal a medication bottle; this is in line with the UK HIV Action Plan's objective to address HIV-related stigma (16). Finally, an injectable method of administration provides an alternative option for people who have a limited ability to swallow pills (note, taking oral cabotegravir prior to initiating injections is optional).

Summary
Taken together, the introduction of another, effective, generally well tolerated PrEP regimen, with a different method of administration that is longer-acting and therefore requires dosing less often could meet the need of individuals underserved by currently available oral PrEP options, which will help to bolster nationwide HIV prevention programs, and contribute towards achieving the UK HIV Action Plan's aims of zero new transmission of HIV by 2030.

3i) Summary of key disadvantages of treatment for people at risk of sexually acquired HIV-1 infection

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for people at risk of sexually acquired HIV-1 infection, caregivers and their communities when compared with current treatments. Which disadvantages are most important to people at risk of sexually acquired HIV-1 infection and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

In the absence of regular HIV testing, use of oral or long-acting injectable PrEP can result in a person who acquires HIV remaining undiagnosed for a long period of time, inducing resistance to anti-retroviral therapy. Therefore, there is a potential risk of developing resistance to cabotegravir if an individual acquires HIV either before or while taking cabotegravir for PrEP or after discontinuing cabotegravir for PrEP. The development of resistance mutations may limit future therapeutic options. Although resistance to cabotegravir (INSTI resistance) was extremely rare overall in the cabotegravir arm of HPTN 083, with no cases detected in HPTN 084, regular HIV testing and taking cabotegravir long-acting as prescribed is essential to minimise the risk of developing resistance.

3j) Value and economic considerations

Introduction for people at risk of sexually acquired HIV-1 infection:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating people at risk of sexually acquired HIV-1 infection and how the health of people at risk of sexually acquired HIV-1 infection will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by people at risk of sexually acquired HIV-1 infection; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for people at risk of sexually acquired HIV-1 infection or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

How the model reflects the condition

The economic analysis estimates the number of new HIV acquisitions over a period of time when people are more likely to be exposed to HIV, based on the PrEP option they are receiving. The model includes six health states that a person can be in: taking cabotegravir for PrEP, taking TDF/FTC as PrEP, taking TAF/FTC as PrEP, taking no PrEP, living with HIV, and death.

Modelling how much a treatment extends life

The impact of HIV on life expectancy was estimated using the death rate (mortality) of the UK general population (of the same age and sex) and adjusting it using available evidence. The relative chance of HIV acquisition with cabotegravir and oral PrEP are calculated based on the HIV acquisition rates in the HPTN 083 and HPTN 084 trials. The model also includes an adjustment for the likelihood of HIV acquisition according to levels of adherence to oral PrEP, based on a separate analysis of relevant trials.

Modelling how much a treatment improves quality of life

People without HIV are assumed to have a quality of life and risk of death that is equivalent to the general population. Acquiring HIV is assumed to increase the risk of death and reduce quality of life. Utility is a word used to describe quality of life; utilities are measured on a scale of zero to one, where zero indicates death and one indicates full health. Utility values for the general population (based on a person's age and sex) are taken from Hernández et al. 2022 (42). Utility values for people living with HIV were derived from general population values after including a decrease in utility for HIV reported by Miners 2014 (43). The decrease in utility score for people living with HIV was assessed using the EQ-5D-3L questionnaire, which is the preferred utility measurement instrument by NICE.

Modelling how the costs of treatment differ with the new treatment

Compared with oral PrEP, cabotegravir leads to an increase in expected health care costs. However, it is estimated to be less costly compared with no PrEP when HIV treatment costs are included. The monthly administration and monitoring costs were assumed to be higher for cabotegravir than oral PrEP, as an injection by a health care professional every 2 months is required. The predicted costs of HIV care were lower with cabotegravir than oral PrEP or no PrEP because of fewer HIV acquisitions.

Uncertainty
The population addressed by the Company submission is people at risk of HIV acquisition for whom oral PrEP options are not appropriate, including people who are not taking oral PrEP as prescribed (known at not adherent). The extent to which not taking PrEP as prescribed affects a person's level of protection from HIV has been estimated by an analysis of published studies. While this analysis used the best available data and robust methods, and the results are in alignment with similar previously published analyses, there remains uncertainty around the effectiveness of oral PrEP in people who are not taking it as prescribed (not adherent). This uncertainty impacts the estimate of the likelihood of acquiring HIV with both oral PrEP and cabotegravir.

The cost-effectiveness estimate is most influenced by the relationship between the extent to which PrEP is taken as prescribed (adherent) and the rate of HIV acquisition. The next most important parameters are the rate of HIV acquisition with no PrEP and the relative rate of HIV acquisition with cabotegravir. The parameters used in the cost-effectiveness model have been taken from relevant studies performed in England whenever possible. This includes for example, the costs of HIV care, utility values and number of secondary infections.

Cost-effectiveness results
The cost-effectiveness analysis demonstrates the value of cabotegravir as an alternative to oral PrEP in individuals for whom oral PrEP is not appropriate and when compared with no PrEP.

Additional factors
Application of a severity modifier is not considered to be applicable.

As prevention of HIV is very complex with many health-related factors, there are benefits with cabotegravir that are hard to measure; this includes any impact of cabotegravir on PrEP- or HIV-stigma, which is discussed further in Section 3k.

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Method of administration, dosing frequency and drug-drug interactions
Cabotegravir is the first and only long-acting injectable for Prep, expected to provide people with a new method of HIV prevention when currently not served by the daily oral standard of care. This new alternative injection option provides people who would benefit from PrEP with a different method of administration. When injected, the time it takes for the concentration of cabotegravir to be reduced by one-half in the body is approximately 40 days (44), which is substantially longer than that of oral TDF/FTC (45). Both laboratory and clinical data also suggest that cabotegravir has a low likelihood of causing or being subject to significant interactions with other drugs (44). Cabotegravir also reduces the number of yearly doses required from 365 with daily oral TDF/FTC to just six injections, is a preferred modality for HIV prevention (35), and has been shown to be superior to daily oral TDF/FTC for preventing HIV acquisition across a broad range of people who are more likely to be exposed to HIV (25, 27).

HIV-and PrEP-related stigma
There are benefits with cabotegravir that are hard to quantify and may not have been captured in the economic model, which need to be considered. Stigma is a social process known to limit

engagement, opportunity, wellbeing, and social acceptance for individuals with certain social identities, often resulting in discrimination (46-48) and posing barriers to HIV prevention and PrEP use (46, 49-51). Different types of stigma, related to living with HIV, create these major barriers, such stigma towards oneself, intrapersonal and interpersonal stigma (including public perceptions and related social responses towards stereotypes and negative attitudes), and structural stigma (including organisational activities and policies that create and maintain social inequalities) (46). PrEP stigma may also drive disparities, with PrEP stigma experienced by potential and current PrEP users often reinforced or amplified by public health programmes, policies and research, and PrEP stigma disproportionately impacting disadvantaged groups (52). Societal and political prejudice also results in unacceptable delays and limitations to accessing highly effective interventions that prevent transmissions of HIV (53). There is also strong evidence to show that people's quality-of-life and mental well-being are adversely affected by stigma when living with HIV (12, 54, 55). Although the analysis takes into account the impact that living with HIV has on people's health-related quality-of life using data from a large UK study (43), the method used to collect data (EQ-5D-3L) has limitations in the ability to discriminate different health states when living with HIV, and ceiling effects (i.e. the aspects explored in the EQ-5D-3L may not reflect what matters to people living with HIV (56, 57); therefore, the full impact of living with HIV, particularly associated with HIV-related stigma, are likely not captured. For example, benefits may include improvements in sexual quality of life, including reducing the fear of HIV (58).

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

There are potential equity issues that should be taken into account when considering cabotegravir for PrEP, and the provision of an alternative PrEP option could promote health equity by addressing unmet needs among people who are likely to be exposed to HIV, as well as providing another option that can meet the unmet needs for different PrEP options, peoples preferences, optimise discretion, and alleviate stigma associated with taking PrEP. .

As such, while oral PrEP is available in the UK via the NHS, there are still health inequities that may be experienced by but are not limited to gender diverse populations and ethnic minorities. Several key populations are more likely to be exposed to HIV and are disproportionately affected by it, including groups of people that are protected under the Equality Act 2010 based on their:

- Gender identity – globally, trans women and trans feminine individuals are 66 times more likely to acquire and live with HIV, and trans men and trans masculine individuals 6.8 times more likely than other individuals aged over 15 years (59).
- Ethnicity – particularly people of Black African ethnicity and people coming to the UK from countries where there are a large number of people living with HIV; in 2022, 36% of new HIV diagnoses were among people who were diagnosed abroad, 44% of which were people of Black African ethnicity (15, 60). In addition, people of Black African ethnicity represent the second largest ethnic group first diagnosed with HIV in England (19.5%).
- Sexual orientation – men exposed through sex between men accounted for the largest proportion (30%) of new HIV diagnoses first made in England in 2022. In addition, the

proportion of gay, bisexual, and other men who have sex with men in England diagnosed late increased from 30% in 2020 to 37% in 2022 (15); late diagnosis is associated with poor outcomes, increased risk of ongoing HIV transmission and high healthcare costs (61).

Inequalities also exist in relation to the degree that PrEP is used among different groups of people, with low knowledge/awareness of PrEP among certain populations, as well as misperceptions around PrEP eligibility. There is a particular unmet need in the UK among women and certain ethnic minorities. UK surveys suggest that cisgender and transgender women's engagement with PrEP services/PrEP uptake is poor (21, 62). Clinical experts have confirmed in discussions with ViiV Healthcare that most of their PrEP users are White men who have sex with men, and that work is required to encourage PrEP uptake among women and other minority groups (63).

Another important issue is the harmful consequences of stigma (64), which disproportionately impacts minority and disadvantaged groups and hinders the scale of PrEP use by influencing behaviour of both people who would benefit from PrEP and healthcare professionals (52). PrEP stigma is a barrier to people's interest in and access to PrEP, actually taking PrEP, and to continuing to take it. It means that individuals who would benefit from using PrEP are not able to experience the HIV prevention benefits due to fear or shame. More specifically, PrEP use has been linked to a range of negative judgments and social concerns, including fear that others will misperceive PrEP use as HIV treatment and assume that the "PrEP user" is a person living with HIV (reflecting HIV stigma) (65). One study has reported that 65% of people of Black African heritage name stigma as a major barrier for PrEP use (66). The reduction of PrEP stigma and its negative impact requires a shift in perspective, language, and programmes. The availability of additional PrEP methods, such as long-acting injectables, may help to alleviate concerns around stigma by helping to optimise discretion and reduce the fear of inadvertent disclosure from the requirement to take daily oral pills and keep medication bottles hidden.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that people at risk of sexually acquired HIV-1 infection would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that the community and people at risk of sexually acquired HIV-1 infection can access.

- The HIV Prevention Trials Network Website
- HPTN 083 key study publications: Landovitz et al, 2021; Landovitz et al, 2023
- HPTN 084 key study publication: Delany-Moretlwe et al, 2022
- NICE guideline 221 – Reducing sexually transmitted infections
- BHIVA/BASHH 2018 clinical guidelines
- The UK HIV Action Plan
- Not PrEPared report

Further information on NICE and the role of people at risk of sexually acquired HIV-1 infection and the community**:**

- Public Involvement at NICE
- NICE's guides and templates for patient involvement in HTAs
- EUPATI guidance on patient involvement in NICE
- EFPIA – Working together with patient groups
- National Health Council Value Initiative

- INAHTA
- European Observatory on Health Systems and Policies. Health technology assessment – an introduction to objectives, role of evidence, and structure in Europe

4b) Glossary of terms

Acceptability: The ability and willingness for a person to use or administer PrEP as intended

Adherence: How consistently and appropriately people use PrEP while the intention or opportunity for its use is still there (i.e. the extent to which a person takes their PrEP as prescribed, in terms of how much and how often they take it)

Blinded phase: Blinding is the concealment of group allocation from one or more individuals involved in a clinical research study. Double-blinding means that doctors and their patients do not know which treatment patients are receiving

Cabotegravir: Refers to cabotegravir injections with or without cabotegravir oral

Cabotegravir long-acting: Specifically refers to cabotegravir injections

Cabotegravir oral: Specifically refers to cabotegravir oral tablets

Clinical trial/clinical study: A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease

Efficacy: The measurement of a medicine's desired effect under ideal conditions, such as in a clinical trial

Randomised controlled trial: A trial where patients are randomly assigned to groups to test a specific drug, treatment or intervention

Statistically significant: A statistically significant result means the findings are unlikely to be a result of chance, and show a 'real' difference

Superior: The intervention is clinically better than the comparator

Tolerability: The degree to which a drugs adverse effects can be tolerated

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Cabotegravir for preventing HIV-1 in adults and young people ID6255

Company response to the EAG clarification questions

March 2024

File name	Version	Contains confidential information	Date
ID6255_cabotegravir for PrEP EAG clarification questions response_[Redacted]	1	No	13th March 2024

Section A: Clarification on clinical effectiveness data

A1. Please clarify how many reviewers undertook the risk of bias assessment?

Two reviewers undertook the risk of bias assessment.

A2. PRIORITY. Appendix D, section D.1.3, table 6: Were the SLR eligibility criteria presented in Appendix Table 6 applied to the 19 studies identified in the Huic 2023 review?

Yes, the 19 studies identified in Huic 2023 were confirmed for inclusion with the eligibility criteria in Appendix D, Table 6.

A3. Appendix D, section D.1.1. Please provide a Table comparing studies included in each of the four systematic reviews identified, noting which studies were included in the ITC.

A comparison of studies included in each of the four identified systematic literature reviews (SLR) is provided in Table 1.

Table 1: RCTs included in published SLRs

Study	Intervention	Comparator	Population	High risk?	O' Murchu 2022 (1)	Lazarus 2021 (2)	Fonner 2023 (3)	Huic 2023 (4)	Included in ITC?
Hosek 2013 (Project PrEPare) (5)	TDF/FTC	Daily PrEP versus placebo or 'no pill'	Men who have sex with men	Yes	x			x	No
Grohskopf 2013 (CDC Safety Study) (6)	TDF	Immediate or delayed PrEP versus immediate or delayed placebo	Men who have sex with men	Yes	x			x	No
Grant 2010 (iPrEx [NCT00458393]) (7)	**TDF/FTC**	**Daily PrEP versus placebo**	**Men who have sex with men**	**Yes**	**x**			**x**	**Yes**
McCormack 2016 (PROUD [NCT02065986]) (8)	**TDF/FTC**	**Immediate PrEP versus delayed PrEP**	**Men who have sex with men**	**Yes**	**x**			**x**	**Yes**
Molina 2015 (IPERGAY [NCT01473472]) (9)	**TDF/FTC**	**Intermittent ('on-demand'‡) PrEP versus placebo**	**Men who have sex with men**	**Yes**	**x**			**x**	**Yes**
Mutua 2012 (IAVI Kenya Study [NCT00971230]) (10)	TDF/FTC	Daily or intermittent PrEP versus daily or intermittent placebo	Men who have sex with men/ female sex workers	Yes	x			x	No
Kwan 2021 [CUHK_CCRB00606] (11)	TDF/FTC	Daily vs on-demand PrEP	Men who have sex with men	Yes				x	No

Study	Intervention	Comparator	Population	High risk?	O' Murchu 2022 (1)	Lazarus 2021 (2)	Fonner 2023 (3)	Huic 2023 (4)	Included in ITC?
Mayer 2020 (DISCOVER [NCT02842086]) (12)	TAF/FTC	Daily PrEP TAF/FTC vs TDF/FTC	Men who have sex with men/ transgender Women	Yes				x	No
Landovitz 2021 (HPTN 083 [NCT02720094]) (13)	**Cabotegravir LA**	**TDF/FTC**	**Men who have sex with men/ transgender women**	**Yes**			**x**	**x**	**Yes**
Kibengo 2013 (IAVI Uganda Study [NCT00931346]) (14)	TDF/FTC	Daily or intermittent PrEP versus daily or intermittent placebo	Sero-different heterosexual couples	Yes	x			x	No
Baeten 2012 (Partners PrEP Study [NCT00557245]) (15)	**TDF/FTC and TDF only**	**Daily PrEP versus placebo**	**Sero-different heterosexual couples**	**Yes**	**x**			**x**	**Yes, connected to Partners PrEP Study Continuation .**
Baeten 2016 (Partners PrEP Study Continuation) (16)	**TDF/FTC and TDF only**	**TDF/FTC versus TDF**	**Sero-different heterosexual couples**	**Yes**	**x**			**x**	**Yes, connected to Partners PrEP Study**
Bekker 2018 (ADAPT Cape Town [NCT01327651]) (17)	TDF/FTC	Daily, time and event-driven PrEP	Female heterosexual	Yes	x			x	No
Marrazzo 2015 (VOICE [NCT00705679]) (18)	**5 arms: TDF/FTC, TDF only, 1%**	**Daily PrEP versus placebo**	**Female**	**Yes**	**x**			**x**	**Yes**

Study	Intervention	Comparator	Population	High risk?	O' Murchu 2022 (1)	Lazarus 2021 (2)	Fonner 2023 (3)	Huic 2023 (4)	Included in ITC?
	TDF vaginal gel, oral placebo and placebo vaginal gel								
Peterson 2007 (NCT00122486) (19)	TDF	Daily PrEP versus placebo	Female	Yes	x			x	No
Thigpen 2012 (TENOFOVIR2 [NCT00448669]) (20)	**TDF/FTC**	**Daily PrEP versus placebo**	**Male/ female heterosexual**	**Yes**	**x**			**x**	**Yes**
Van Damme 2012 (FEM-PrEP [NCT00625404]) (21)	**TDF/FTC**	**Daily PrEP versus placebo**	**Female**	**Yes**	**x**			**x**	**Yes**
Delany-Moretlwe 2022 (HPTN 084 [NCT03164564]) (22)	**Cabotegravir LA**	**TDF/FTC**	**Female**	**Yes**			**x**	**x**	**Yes**
Choopanya 2013 (Bangkok Tenofovir Study [NCT00119106]) (23)	**TDF**	**Daily PrEP versus placebo**	**People who inject drugs**	**Yes**	**x**			**x**	**Yes**
Landovitz 2018 (Cabotegravir LA HPTN 077 [NCT02178800]) (24)	Cabotegravir LA IM 600 mg Q8W	Placebo	Male/ female/ transgender women/ transgender men	No		x	x		No
Markowitz 2017 (ÉCLAIR [NCT02076178]) (25)	Cabotegravir LA IM 800 mg Q12W	Placebo	Male	No		x	x		No
Spreen 2014 (NCT01756131) (26)	Cabotegravir LA IM 100,	Placebo	Male/ female	No		x			No

Study	Intervention	Comparator	Population	High risk?	O' Murchu 2022 (1)	Lazarus 2021 (2)	Fonner 2023 (3)	Huic 2023 (4)	Included in ITC?
	200, 200 × 2, 400, 400 × 2 mg single dose Cabotegravir LA SC 100, 200, 400 mg single-dose								
Spreen 2014 (NCT01593046) (27)	Cabotegravir LA IM 800/SC 200 × 3 mg Q4W Cabotegravir LA IM 800/IM 200 × 3 Q4W + RPV-LA IM 1200/900 mg Cabotegravir LA IM 800/IM 400 × 3 Q4W + RPVLA IM 1200/900 mg Cabotegravir LA IM 800 mg Q12W		Male/ female	No		x			No
Bekker 2020 (Rilpivirine LA HPTN 076 [NCT02165202]) (28)	RPV-LA IM 1200 mg Q8W		Female	No		x			No
Verloes 2015 (NCT01031589) (29)	RPV-LA IM 1200/600/600 mg Q4W	Placebo	Male/ female	No		x			No

Study	Intervention	Comparator	Population	High risk?	O' Murchu 2022 (1)	Lazarus 2021 (2)	Fonner 2023 (3)	Huic 2023 (4)	Included in ITC?
Jackson 2014 (NCT01275443) (30)	RPV-LA IM 300, 600, 1,200 mg		Male/ female	No		x			No

Note: A systematic review was conducted to identify studies of cabotegravir LA for PrEP and TDF/FTC as PrEP. From those studies identified in this review, the bolded studies were identified as eligible for the current analysis in that they met the additional inclusion criteria of reporting TDF/FTC as PrEP adherence based on plasma sampling (or pill count data for the relevant sensitivity analysis).

Abbreviations: cabotegravir LA, cabotegravir long-acting; IM, intramuscular; ITC, indirect treatment comparison; PrEP, pre-exposure prophylaxis; QXW, every X weeks; RCT, randomised controlled trial; RPV-LA, rilpivirine long-acting; SC, subcutaneous; SLR, systematic literature review; TAF/FTC, tenofovir alafenamide/emtricitabine; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

A4. PRIORITY. Document B: Please clarify how many participants in each arm (for HPTN 083 and HPTN 084 trials) were excluded at the end of step 1 due to <50% adherence.

In both HPTN 083 and HPTN 084, Step 1 comprised the oral tablet lead in phase to assess tolerability to cabotegravir (31, 32). Participants were randomised 1:1 to Arm A and Arm B:

- Arm A: Daily oral cabotegravir (30 mg tablets) and daily oral placebo for tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) for 5 weeks
- Arm B: Daily oral TDF/FTC and daily oral placebo for cabotegravir for 5 weeks.

Any participant who acquired human immunodeficiency virus (HIV) during Step 1 did not proceed to Step 2 (the injection phase) and were terminated from the study and referred for HIV-related care. Participants with pill counts resulting in less than 50% adherence as assessed by pill count at the Week 4 visit did not transition to Step 2. Participants in Step 1 of the study who were unable to transition to Step 2 for any reason other than HIV acquisition were asked to attend annual visits until 3 years from the date of enrolment. These participants remained blinded to their original randomised assignment until all participants completed Step 2 of the study.

In HPTN 083, in the randomised population (cabotegravir N=2,283; TDF/FTC N=2,287), [redacted] participants in the cabotegravir arm, and [redacted] participants in the TDF/FTC arm discontinued the investigational product during Step 1 due to low oral adherence according to the protocol (33). Discontinuation of the investigational product could result in entering annual follow-up or study termination. In total, [redacted] participants in the cabotegravir arm and [redacted] participants in the TDF/FTC arm discontinued the investigational product without termination during Step 1, while [redacted] in each arm discontinued with termination. In the safety population (cabotegravir N=2,281, TDF/FTC N=2,285), [redacted] of participants in the cabotegravir arm and [redacted] of participants in the TDF/FTC arm demonstrated <50% adherence at Week 4.

In HPTN 084, in the randomised population (cabotegravir N=1,614; TDF/FTC N=1,610), [redacted] participants in the cabotegravir arm, and [redacted] participants in the TDF/FTC arm discontinued the investigational product during Step 1 due to low oral adherence without termination (34). In the safety population (cabotegravir N=1,614; TDF/FTC N=1,610), [redacted] participants in the cabotegravir arm and [redacted] participants in the TDF/FTC arm had adherence <50% at Week 4.

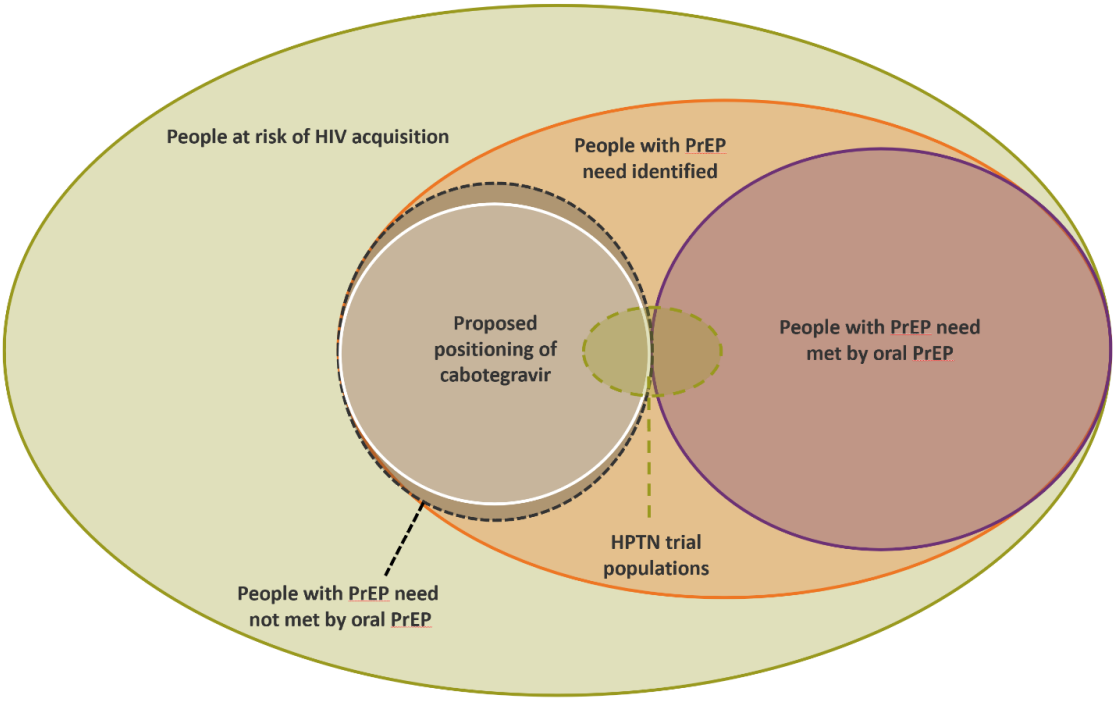
A5. PRIORITY. Document B, Figure 1, page 30: Please clarify how the populations in studies HPTN 083 and HPTN 084 are aligned with the proposed positioning of cabotegravir in the clinical pathway described.

The HPTN clinical trials recruited men who have sex with men and transgender women (083) and cis-gendered women (084) at risk of HIV acquisition. Assessment of sexual behaviour including partners and sexually transmitted infection (STI), was included in the trials serving as a proxy for the risk of HIV acquisition. In the clinical care pathway of HIV prophylaxis, several population categories are defined, such as: individuals at risk of HIV, individuals with pre-exposure prophylaxis (PrEP) need identified and individuals initiating or continuing PrEP.

Cabotegravir is being positioned as an alternative to oral PrEP in the United Kingdom (UK) for people whose needs are not currently met by the existing options. Figure 1 illustrates how the populations in the HPTN trials are nested within the broader categorisations of groups considered for PrEP. Eligibility for PrEP in the UK is currently determined on the basis of recent sexual behaviour (as per the British HIV Association/British Association for Sexual Health and HIV [BHIVA/BASHH] guidelines) (35, 36). The specificity of the criteria means that people eligible for PrEP in the UK are nested within the broader licensed population. Among these eligible individuals are those whose needs are met by existing oral options (people who access and engage with services, are able to take oral PrEP and optimally adhere to it), and those with remaining unmet need (people who cannot consider oral dosing, or who for many complex reasons including individual health-related challenges or the social and structural determinants of health, do not find it possible or easy to adhere optimally). To an extent, both of these populations are present in the HPTN trials; however, there are ethical issues that may have arisen, had the HPTN trials

deliberately attempted to recruit people with known significant issues adhering to one of the trial arms (37).

Figure 1: Proposed positioning of cabotegravir



Abbreviations: HPTN, HIV Prevention Trials Network; PrEP, pre-exposure prophylaxis.

Individuals enrolled in the trials likely reflect people who have a need for PrEP in the UK (note, full details on the generalisability of study results to UK clinical practice are provided in Document B, Section B.2.12.3), as noted by clinical experts at a UK advisory board (38). The experts also highlighted that HPTN 084 is a valuable source of evidence due to the paucity of data in cisgender women (38). Thus, there is sufficient rationale to extrapolate data from across the trial populations to people who would benefit from PrEP in clinical practice settings (38). Notably, this already has precedent, whereby the clinical need for alternatives to TDF/FTC resulted in the National Health Service (NHS) clinical commissioning policy and resultant prescribing of tenofovir alafenamide/emtricitabine (TAF/FTC), extrapolating from the available evidence (12, 36). In addition, the NHS has previously recommended oral PrEP based on evidence mostly conducted in populations beyond the UK (7, 9, 15, 20).

Uptake of cabotegravir for PrEP should be based on the shared decision-making discussions between people who would benefit from PrEP and their healthcare professional about the most suitable HIV prevention modality for their individual circumstances; a person-centred model increases biomedical covered time during periods of increased risk of HIV acquisition and significantly reduces HIV incidence (39).

A6. PRIORITY. Can you clarify the characteristics of the population ineligible for oral PrEP? Are patients ineligible to take oral tablets due to medical reasons with ingesting substances equally at risk of HIV infection as those of the study population?

Note, during the clarification call, it was confirmed with members of the Evidence Assessment Group (EAG) that the request for ineligible population referred to both the population ineligible to take oral PrEP within the clinical trials, and the population for whom oral PrEP is not appropriate within the clinical pathway.

The population "ineligible" for oral PrEP in the clinical pathway

The population for whom oral PrEP is not appropriate includes individuals who cannot take oral PrEP due to medical reasons such as contraindication or intolerance to oral PrEP. Oral TDF/FTC as PrEP is very commonly (≥1 in 10) associated with gastrointestinal events such as diarrhoea, vomiting and nausea, as well as dizziness, headache, rash, weakness, and hypophosphatemia (40). Whilst these adverse events (AE) are typically mild and self-limiting, a small proportion of individuals who experience them may choose to discontinue oral TDF/FTC as PrEP (35, 41). In studies across different European settings, AEs are commonly reported as a reason for discontinuation (42-45). Additionally, some individuals who are at high risk of HIV acquisition may not be able to initiate oral TDF/FTC as PrEP because they are contraindicated or have pre-existing medical conditions, including renal or bone comorbidities (40). Other individuals may include those with health issues such as central nervous system (CNS) disorders, cognitive impairment or mental health conditions who may not be able to self-sufficiently take oral PrEP (46-48). This would limit the effectiveness of their regimen whilst still being at risk of acquiring HIV. Individuals with health issues such as swallowing difficulty and malabsorption may not be able to achieve adequate drug levels via the oral route,

also limiting effectiveness. Psychological reasons may include pill phobia, non-adherence to oral PrEP as a result of a psychiatric diagnosis, and significant stress and anxiety from hiding medications as a result of fear of disclosure, violence, external stigma and/or confidentiality loss.

In addition to medical intolerance or contraindications, oral PrEP may not be appropriate for individuals with suboptimal adherence and/ or persistence. This may include individuals who have demonstrated previous non-adherence or non-persistence. For example, a 2022 SLR reported the proportion of PrEP users exhibiting suboptimal adherence of daily oral TDF/FTC within 6 months of PrEP initiation was 37.7% (95% confidence interval [CI]: 8.4–66.9) globally (four studies), and a pooled discontinuation rate for PrEP within 6 months of initiation of 41.0% (95% CI: 18.8–63.5) globally (16 studies) (49). Other populations which may sub-optimally adhere to PrEP include adolescent populations; a meta-analysis of 41 samples from 29 studies (N=8,679) found that only 64% of adolescents and young people demonstrated adequate PrEP adherence (50). Other individuals who may be sub-optimally adhering to, not initiating, or discontinuing daily oral PrEP include those experiencing pill fatigue (42, 51), or sub-optimally adhering due to an inconvenient daily dosing schedule (52), or who have concerns around medication adherence (53, 54). Individuals may also experience fear of disclosure or have confidentiality concerns (55), and there is intensified stigma surrounding PrEP/HIV in specific cultures and subpopulations (53, 55, 56).

Individuals ineligible to take oral PrEP in HPTN 083 and HPTN 084

In HPTN 083, there were 1,879 screen failures; reasons included “unwilling to adhere to study procedures ([redacted]), opinion of the study investigator ([redacted]), and abnormal liver of kidney function tests ([redacted]).

In HPTN 084, there were 1,551 participants who were screened but not enrolled; reasons included not willing and able to undergo all required study procedures [redacted] and medical condition that, in the opinion of the investigator of record would interfere with the conduct of the study [redacted]

The exclusion of participants with contraindications to oral PrEP from the trial programme is not expected to impact the applicability of the relative treatment effect from the trials to the UK clinical setting. In brief, pharmacokinetic data for

cabotegravir long-acting (LA) have shown no clinically important pharmacokinetic differences between subjects with severe renal impairment (creatinine clearance [CrCl] <30 mL/min and not on dialysis) and matching healthy subjects. In addition, similar safety and pharmacokinetic data have also been observed between adults living with HIV and paediatrics receiving cabotegravir + rilpivirine LA for the treatment of HIV, while subgroup data by age from HPTN 083 and HPTN 084 did not show any evidence of treatment effect modification.
Furthermore, there is no evidence to suggest the treatment effect of cabotegravir LA will differ in patients intolerant or sub-optimally adhering to oral PrEP, where discontinuation of oral PrEP is necessitated. The protocol defined discontinuation of individuals with poor adherence during the oral lead-in phase in the studies of cabotegravir LA was primarily instituted to minimise the potential for bias in favour of cabotegravir LA, given the known confounding of adherence on oral PrEP effectiveness. The underlying risk of HIV acquisition of individuals for whom oral PrEP is not appropriate is independent of their physiological or biological characteristics that explain oral PrEP ineligibility. However, oral PrEP can reduce the risk of HIV; therefore, it is only in the total absence of it that there is an elevated risk of HIV.

HIV incidence for people not receiving PrEP was informed using UK data from the BHIVA/BASHH guidelines (35) for men who have sex with men/transgender women and from the HPTN 083 trial for cisgender women, as estimated by the indirect treatment comparison (ITC).

While the BHIVA/BASHH guidelines provide eligibility criteria for PrEP (35), it is anticipated that these criteria will change in the near future (57). Reasons for HIV prevention based on individuals' risk factors are indiscriminatory to the reasons for ineligibility to oral PrEP. An alternative PrEP modality such as injectable cabotegravir, provides a new HIV prevention option for people for whom oral PrEP is not appropriate.

A7. Appendix D, Figures 4 and 5: Please explain the N's in the 3rd box from the bottom for each arm: Figure 4 (2121, 1701 etc.) and Figure 5 (1442, 1002, etc).

HPTN 083 and HPTN 084 trials have reported this data within the participant flow diagrams, which represents the proportion of participants who were retained and attended follow-up visits at designated time intervals (e.g.: 6/12/18 months). The trials continued recruiting up to study close, meaning participants had a wide diversity in follow-up duration and explains the reducing participant numbers over time within the "retained" data box. The retained data therefore represents the proportion of participants retained at a specific time interval, and the proportion who attended that follow-up visit at that time interval.

A8. Appendix D, Figure 5: there is a footnote missing for the asterisk against '1119 not eligible (1119 not eligible' stated in the second box from the top). Why does the number not eligible add up to 1156 not 1119?

The footnote should state that "One person could have had more than one reason for exclusion".

A9. PRIORITY. Why did HPTN 084 include only up to age 45 years?

HPTN 084 recruited participants who met eligibility inclusion criteria, including being aged 18–45 years at the time of screening. The study was targeted towards the most at-risk populations of women in each geographic setting (i.e., those with highest HIV incidence) in Sub Saharan African (SSA), including sexually active women evidenced with a score of >5 using an empiric HIV risk scoring tool called the modified VOICE risk score (58), which is a risk assessment tool to predict HIV acquisition and is validated among African women aged 18–45 years.

A10. PRIORITY. Document B, section B.2.6.1.1.4: the first paragraph of this section states that there were 1 CAB, 2 TDF/FTC HIV infections in the first unblinded year. Then it states there was a total of 44 additional

infections (12 CAB, 32 TDF/FTC). What is correct number of total incident infections in the first year unblinded?

This is a typographical error; the statement should read that “In the analysis of incident HIV acquisitions during the first unblinded year, three incident HIV acquisitions were identified that occurred during the **blinded** period but were not detected until after study unblinding (cabotegravir: 1; TDF/FTC: 2) (see Table 3) (59). These three acquisitions were retrospectively backdated and combined with data from the original blinded analysis to obtain updated incidence rates in each group during the primary blinded analysis period (59). These data were excluded from the analysis of the first unblinded year; therefore, a total of 44 incident HIV acquisitions (12 in the cabotegravir arm, 32 in the daily oral TDF/FTC arm) were included in the efficacy analysis of the first unblinded year.

A11. Document B, page 61: Footnote [h] states: “Five acquisitions were excluded from the efficacy analysis as they occurred >3 years after study initiation”. Are these five part of the 12 incident infections in the CAB group during the 1-year unblinded period?

For participants with incident HIV acquisition, the acquisition date was calculated as the midpoint between the first HIV-positive date and the last HIV-negative date. Acquisitions occurring greater than 3 years after enrolment are described but were prespecified to be excluded from efficacy analyses. Therefore, in total there were 17 incident cases during the blinded year, with 12 included in the analysis as five occurred >3 years after study initiation (Table 2).

Table 2: Summary of the timing of HIV acquisitions and the number of cases included in the assessment of HIV incidence

	Total no. cases	No. incident cases	# cases included in the HIV incidence assessment†
Blinded phase (updated)			
Cabotegravir	17	13‡	13‡
TDF/FTC	44	41	41
First unblinded year			
Cabotegravir	17	17	12¶
TDF/FTC arm	32	32	32
Total (updated analysis)			
Cabotegravir	34	30	25¶
TDF/FTC arm	73	73	73

Source: Landovitz et al, 2023 supplementary information (59).
†This group is limited to incident acquisitions that occurred <3 years after study initiation; ‡One prevalent (baseline) infection in the cabotegravir arm was initially characterised as an incident infection and was included in the HIV incidence assessment in the primary mITT analysis; this case is not included here; ¶Excludes five acquisitions that occurred >3 years after study initiation.
Abbreviations: HIV, human immunodeficiency virus; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

A12. Document B, section B.2.6. We are unable to correctly follow the number of HIV infections (incident/prevalent) that feeds into the primary and secondary analysis of HPTN 083 trial. Please provide the number of HIV infections that were included in the following analysis for HPTN 083 trial using the following format:

In the primary analysis (modified intention-to-treat [mITT]), HIV acquisition was identified in 57 participants, including 5 participants (cabotegravir: 2; daily oral TDF/FTC: 3) with undetected HIV at enrolment (prevalent infections); therefore, 52 participants who acquired HIV after enrolment were included in the pre-specified primary analysis of incident HIV acquisitions (mITT) (13 in the cabotegravir arm, 39 in the TDF/FTC arm) (33). Post-hoc centralised testing of stored plasma samples, performed to better characterise the timing of HIV acquisition, determined that one of the incident HIV acquisitions in the cabotegravir group was a prevalent (baseline) infection (60), therefore this analysis determined a total of 12 incident acquisitions occurred in the cabotegravir group during the blinded period. During the updated analysis of the primary endpoint, which incorporated an additional year of unblinded follow-up, there were three HIV acquisitions detected which occurred during the blinded period, however, were not detected until after study unblinding (cabotegravir: 1; TDF/FTC: 2); this yielded a final total of 13 incident HIV acquisitions in the cabotegravir arm and 41 in the TDF/FTC arm during the blinded period. A further 17

incident acquisitions in the cabotegravir arm (of which 12 were included in the efficacy analysis as per pre-specified criteria [they occurred <3 years after study initiation]) and 32 in the TDF/FTC arm occurred during the first year of unblinded follow-up.

Table 3: Summary of prevalent and incident HIV acquisitions

Analysis	Cabotegravir N=2,280 N (IR/100 PY)	Daily oral TDF/FTC N=2,281 (IR/100 PY)
Pre-specified primary analysis (mITT) of the blinded period; B.2.6.1.1.1		
Baseline (prevalent) infections	2 (NR)	3 (NR)
Incident acquisitions	13 [redacted]	39 [redacted]
Post-hoc analysis of the blinded period (mITT extended retrospective testing); B.2.6.1.1.3		
Baseline (prevalent infections)	3 (NR)†	3 (NR)
Incident acquisitions	12 (0.37)	39 (1.22)
Updated analysis of primary endpoint incorporating data from one additional year of unblinded follow-up; B.2.6.1.1.4		
Updated analysis of the blinded study period	13 (0.41)‡	41 (1.29)‡
First unblinded year analysis	12 (0.82)	32 (2.27)
Combined period	25 (0.54)	73 (1.59)

Source: HPTN 083 clinical study report (33) ; EMA Apretude Assessment report (60); Landovitz et al, 2023 (59).
†One incident acquisition identified as a prevalent (baseline) infection in extended virologic testing; ‡During the updated analysis of the unblinded period, one acquisition in the cabotegravir arm and two in the TDF/FTC arm which were detected during the unblinded year were backdated to the blinded period.
Abbreviations: HIV, human immunodeficiency virus; mITT, modified intention-to-treat; NR, not reported; PY, person years; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

A13. Why was HPTN 083 a non-inferiority trial and HPTN 084 superiority?

HPTN 083 was a non-inferiority study, assessing whether a hazard ratio (HR) of ≥1.23 for cabotegravir LA versus daily oral TDF/FTC for the rate of acquiring HIV could be ruled out (13). This trial was designed as a non-inferiority study because large, high quality clinical trials have previously established that TDF/FTC can be a highly effective HIV PrEP agent when adherence to the drug is high (Partners-PrEP, IPERGAY, and PROUD) (8, 9, 15). Therefore, rather than comparing cabotegravir LA for PrEP to placebo, a non-inferiority trial was proposed to evaluate whether cabotegravir LA for PrEP is non-inferior to the active comparator TDF/FTC (13, 61). The trial included a pre-specified option to test for superiority of cabotegravir LA for PrEP over daily oral TDF/FTC as PrEP, based on crossing the O'Brien-Fleming boundary, in the event that cabotegravir LA for PrEP was substantially more effective than daily oral TDF/FTC as PrEP (62). The interpretation of the HPTN 083 results was prepared by the Protocol Statisticians and Chair of the Study Monitoring Committee of the HIV Prevention Trials Network (HPTN), an independent

collaborative network of academic researchers committed to conducting trials to the quality standards. Trial data were reviewed approximately every 6 months by an independent Data Safety Monitoring Board (DSMB) (13). On 14th May 2020, the DSMB determined that the O'Brien-Fleming boundary had been crossed and recommended that the blinded portion of the trial should be terminated (62). The superiority of cabotegravir LA for PrEP in the HPTN 083 trial has also been accepted by the Food and Drug Administration (FDA), European Medicines Agency (EMA), with others pending (63).

For HPTN 084, due to the disparate results of TDF/FTC as PrEP in cisgender women in previous studies, a non-inferiority margin could not be established (18, 21). It was thus mandated by the FDA that HPTN 084 be designed as a superiority study.

A14. Is oral cabotegravir a longer-term option for prevention of HIV-1? Please provide any trials of oral cabotegravir for the prevention of HIV-1

Oral cabotegravir cannot be used as a longer-term option for prevention of HIV-1. The drug has a half-life of approximately 40 hours after an oral dose, which enables once-daily dosing (64). The efficacy associated with the long-term use of oral cabotegravir for HIV-1 prevention has not been studied. Therefore, there is no data to support the use of oral cabotegravir for PrEP [redacted].

Oral cabotegravir is anticipated to be licensed for [redacted]

A15. Document B, page 61: *"In the combined study period (Step 1 and 2, plus 1-year unblinded follow-up), a total of 25 incident acquisitions were observed with cabotegravir and 73 with TDF/FTC (HIV incidence rate of 0.54 per 100 PY, and 1.59 per 100 PY, respectively, HR: 0.34 [95% CI: 0.22, 0.53]; p<0.0001), representing a 66% reduction in HIV acquisitions with cabotegravir (126)."* There were 39 incident infections in step 1 and 2 (mTT population) and

32 additional infections in 1-year unbended period), please clarify how you arrived to the number 73?

As previously described in Table 3 above, during the updated analysis incorporating data from the first unblinded year, two additional HIV acquisitions were detected in the TDF/FTC arm that were found to have occurred during the blinded period, which were combined with the 39 cases identified during the previous analyses of the blinded period. Therefore, a final total of 41 acquisitions were determined to have occurred in the TDF/FTC arm during the blinded period. A further 32 acquisitions were found to have occurred during the first unblinded year in the TDF/FTC, making the combined total for the blinded period and the first unblinded year 73 incident acquisitions.

A16. PRIORITY. Please provide individual-level data on adherence to CAB among patients in the CAB arm of the HPTN083 trial that were diagnosed with HIV during the trial. Please complete the table below for each incident/prevalent HIV infection in the CAB arm of HPTN083.

Please provide individual-level data on adherence to CAB in the HPTN04 trial following the table format below.

Please note, the HPTN trials are independent from ViiV Healthcare, who provided the study product; therefore, ViiV Healthcare do not own the data and do not have access to unpublished individual patient data.

The IC_{90} of a drug is the drug concentration that will inhibit replication of 90% of HIV virus. The HPTN trials report data on three plasma cabotegravir concentration thresholds (8x PA-IC_{90} [1.35 g/mL]; 4x PA-IC_{90} [0.664 g/mL]; 1x PA-IC_{90} [0.166 g/mL]). In HPTN 077 8x PA-IC_{90} (1.35 g/mL) was tentatively set as the target protection concentration (65), because the 4x PA-IC_{90} (0.664µg/mL), as determined to be relevant for protection in non-human primate (NHP) simian human immunodeficiency virus (SHIV) challenge studies, was achieved in only one-third of ECLAIR participants (25).

HPTN 083

In HPTN 083, acquisitions in the cabotegravir arm were classified into six groups (A, B, C, D, DX, and BR), based on the relationship between the administration of cabotegravir and the first HIV-positive visit (66) (see Document B, Section B.2.6.1.2.1, Table 13; Document B Section B.2.6.1.3.2). These cases are summarised in Table 4, alongside the number of injections, number of late injections, and cabotegravir concentration at the first positive visit.

Table 4: HPTN 083: Classification of HIV acquisitions in the cabotegravir arm

	Study phase	HIV acquisitions			
		Participant	Number of injections	Number of late injections	Plasma cabotegravir concentration at the first positive visit (µg/mL)[†††]
A: Cabotegravir (prevalent infections)	Steps 1 and 2[¶¶]:4 (A1–A4)	A1	0	0	BLQ
		A2	1	0	BLQ
		A3	2	0	BLQ
		A4	2	0	BLQ
Incident acquisitions					
B: No recent cabotegravir administration[†]	Steps 1 and 2: 5 (B1–B5)[††]	B1	2	1	0.065
		B2	0	0	BLQ
		B3	4	0	0.100
		B4	NR	NR	NR
		B5	0	0	BLQ
	1-year unblinded: 11 (B6–B16)	B6	0	0	BLQ
		B7	0	0	BLQ
		B8	3	0	BLQ
		B9	6	0	BLQ
		B10	9	1	0.067
		B11	5	2	BLQ
		B12	NR	NR	NR
		B13	6	2	BLQ
		B14	19	0	BLQ
		B15	19	0	0.110
		B16	19	1	BLQ
C: cabotegravir OLI acquisition	Steps 1 and 2: 3 (C1–C3)	C1	2	0	6,301
		C2	0	0	BLQ
		C3	1	0	10.690
		D1	10	1	1.613

	Study phase	HIV acquisitions			
		Participant	Number of injections	Number of late injections	Plasma cabotegravir concentration at the first positive visit (µg/mL)†††
D: Adherent to cabotegravir LA injections	Steps 1 and 2: 4 (D1–D4)‡‡	D2	6	0	1.405
		D3	5	0	1.504
		D4	4	0	2.017
	1-year unblinded: 2 (D5§§–D6)	D5	5	0	1.906
		D6	15	0	1.824
DX: Delayed cabotegravir injection‡	1-year unblinded: 3 (DX1–DX3)	DX1	7	3	0.495
		DX2	10	1	BLQ
		DX3	6	1	0.041
BR: cabotegravir restarted after acquisition¶	1-year unblinded: 2 (BR1–BR2)	BR1	9	1	BLQ
		BR2	20	1	BLQ
Total cases	–	34			

Source: Marzinke at al, 2022 (67); Marzinke et al, 2023 (66).
†Participant had no cabotegravir LA injections or had their last injection ≥6 months prior to their first HIV acquisition was confirmed; ‡Infected <6 months after the last injection with ≥1 delayed injection (>70 days after the last injection); ¶No cabotegravir administration in the 6 months before the first visit with confirmed HIV acquisition; cabotegravir restarted at or after the first visit with confirmed HIV acquisition; ††No result for B4; ‡‡One case that was classified as a D case in the original analysis of Steps 1 and 2 had a single late injection (D1) (75 days after the previous injection); that case would have been classified as a DX case according to the updated classification system used in the updated analysis including the additional year of unblinded follow-up; ¶¶Extended retrospective virologic testing after the primary analysis was performed; this found one case, previously classified as an incident case, to have been living with HIV at enrolment (the case was initially designated B5 and was renamed as A3). A4 designates an additional baseline infection identified in the cabotegravir arm during extended retrospective testing; §§Backdated to blinded phase; †††The cabotegravir LA regimen used in this study was targeted to achieve concentrations of >=4xPA-IC90 in 80% of individuals and >=8xPA-IC90 in 50% of individuals.
Abbreviations: BLQ, below the limit of quantification; HIV, human immunodeficiency virus; OLI, oral lead-in.

A full summary of the D cases, where cabotegravir acquisitions occurred despite on-time injections is provided below:

- **D1–D4:** These four participants acquired HIV despite mostly on-time cabotegravir LA injections. The first HIV positive visit was Week 57 for case D1, Week 27 for case D2, Week 17 for case D3, and Week 19 for case D4 (68). These participants had 2–7 injections before the first HIV-positive visit; the median cabotegravir concentration at that visit was 1.56 µg/mL (interquartile range: 1.48–1.71). In these four cases, cabotegravir concentrations were ≥8× PA-IC_{90} at 83% of the evaluable visits before the first HIV-positive visit and were ≥4× PA-IC_{90} at 95% of those visits (69) (further

information is provided in the Supplementary information of Marzinke et al, 2021 (69)).

- **D5:** HIV acquisition occurred during the blinded period; the participant received five on-time cabotegravir injections prior to the first HIV-positive visit (21 days after the last administration). At this visit, the viral load was 59 copies/mL and the site detected the acquisition 42 days later. The cabotegravir concentration was 1.906 µg/mL at the first HIV-positive visit. The cabotegravir concentration-time profile indicates consistent on-time dosing with rapidly declining concentrations of cabotegravir after typical peak concentrations. Low cabotegravir trough concentrations were observed (all <4x PA-IC_{90}), likely attributed to high cabotegravir LA absorption rate constant (66).

- **D6:** The participant had 14 on-time cabotegravir injections prior to the first HIV-positive visit and received an additional injection at the first HIV-positive visit. The cabotegravir concentration at the first HIV-positive visit was 1.824 µg/mL, and the viral load was 2,020 copies/mL. In 97%, and 83% of previous study visits, the concentrations of cabotegravir were ≥4× PA-IC_{90} and ≥8× PA-IC90, respectively. However, five out of six trough cabotegravir concentrations immediately preceding the first HIV-positive visit were <8× PA-IC_{90}, including one cabotegravir concentration that was <2× PA-IC_{90} (66).

Importantly, all six of the breakthrough acquisitions, among the 2,282 participants randomised to the cabotegravir arm, went on to achieve virological suppression (59).

Note, while only the ‘D cases’ are discussed in detail in this response, further details on the key events and laboratory results for all participants in the cabotegravir arm of HPTN 083 who acquired HIV and were classified into other groups (A, B, C, DX, BR) is provided in Marzinke et al, 2021 (68), and Marzinke et al, 2023 (66).

HPTN 084

In HPTN 084, acquisitions in the cabotegravir arm were also classified based on the relationship between the administration of cabotegravir and the first visit at which HIV acquisition was detected (70). A summary of acquisitions detected to the end of

the blinded period is provided in Table 4, alongside the number of injections and plasma cabotegravir concentration at the first site-positive visit.

Table 5: HPTN 084: Classification of HIV acquisitions in the cabotegravir arm

Acquisition type and classification group	HIV acquisitions in the cabotegravir arm	Number of injections prior to first HIV-positive site visit	Plasma cabotegravir concentration at the first site-positive visit (mcg/mL)
Living with HIV at study enrolment	A1	5	2.58
No recent cabotegravir exposure	B1	0	BLQ
	B2	0	NR
Acquired during the cabotegravir injection phase	DX	9	0.416
Total	4	–	–

Source: Adapted from Eshleman et al, 2022 (70).
Abbreviations: BLQ, below the limit of quantification; HIV, Human immunodeficiency virus; NR, not reported.

Note, while this response only provides a detailed discussion of the 'D cases' for HPTN 083, as no participants acquired HIV in the context of on-time injections in HPTN 084, and acquisitions were very rare, a summary of the four HIV acquisitions which were classified into other groups is provided below:

- **A1**: this participant was living with HIV at study enrolment. The site first detected evidence of HIV acquisition 32.3 weeks later. This participant received oral cabotegravir and five cabotegravir injections prior to the first site-positive visit. According to cabotegravir concentrations, this individual was not taking cabotegravir consistently during the oral lead in, while during the injection phase, the concentrations of cabotegravir did not exceed 8× PA-IC_{90} until after the second injection, remaining above this level through the first site-positive visit, where the cabotegravir concentration was 2.58 mcg/mL (70).

- **B1:** HIV acquisition was detected 10.9 weeks after study enrolment. No cabotegravir injections were received and cabotegravir concentrations were below the limit of quantification at all visits (70).

- **B2:** due to pregnancy, oral cabotegravir was discontinued 5.1 weeks after enrolment. The concentrations of cabotegravir were <4× PA-IC90 during the oral lead-in phase. The first HIV-positive visit occurred 1 year after oral cabotegravir was stopped, and 3.1 weeks after TDF/FTC provision was interrupted because the participant was not able to refill the medication, and 17.3 weeks after delivery of a healthy infant (70).

- **DX:** HIV was acquired while receiving cabotegravir injections. In the oral phase, cabotegravir concentrations were all below the limit of quantification, suggesting non-adherence. Nine cabotegravir injections were received, with the ninth administered at the first site-positive visit. In total, three injections occurred outside of the protocol-specified allowable windows (including the eighth and ninth which occurred 16.1 weeks apart). After cabotegravir injection initiation, the cabotegravir concentration was ≥8× PA-IC_{90} in all plasma samples collected before the first HIV-positive visit but <4× PA-IC_{90} (0.416 mcg/mL) at the first HIV-positive visit. The cabotegravir concentration at the time of the eighth injection could not be determined due to a sample processing error (70).

Further details are provided in Eshleman et al, 2022 (70) and the clinical study report (34).

A17. Can the company provide information on people who had a breakthrough infection while being fully adherent to the intervention as defined in the study: i.e. number of breakthrough infections/total number of patients fully adherent to the intervention for both cabotegravir and TDF/FTC. Can the company calculate a relative risk for this group of patients?

In the trials, assessment of adherence to oral PrEP was done on a randomly selected group of patients (TDF/FTC adherence population in HPTN 083 [redacted]; HPTN 084 [redacted]) (32, 33) therefore, the request of calculating the relative risk is not feasible. In addition, the number of HIV acquisitions in the trials is very small (for example there were 6 breakthrough HIV acquisitions in the cabotegravir arm in the setting of on-time injections in HPTN 083 (59, 66) and none in HPTN 084 (22, 70))

compared with the large overall trial sample size (randomised population: HPTN 083 N=4,570; HPTN 084 N=3,224) (32, 33).

A18. Priority: Please provide the WinBUGS files along with the data used to conduct the indirect comparison analyses and meta-regressions as reported in Appendix D.

The WinBUGS code is provided in Appendix A at the end of this document.

A19. How generalizable are the clinical effectiveness and adherence data from the trial populations to UK settings, considering potential differences in adherence barriers and education levels between the trial populations and the UK population?

Whilst the HPTN trials were conducted in geographic locations other than the UK, this is not uncommon in research, including in the areas of HIV prevention and treatment.

A systematic review of the literature demonstrated that the variation in adherence to TDF/FTC as PrEP appears to be highly predictive of the effectiveness of TDF/FTC as PrEP vs no PrEP and explains a large degree of the heterogeneity observed in PrEP study results. Through a meta-regression, there is no obvious deviation from the overall trend seen by consideration of location of the studies or patient population (Document B, Section B.2.9.3 and Appendix D). There are of course nuanced variations in adherence barriers across geographies, including cultural, social, economic, and structural factors that could impact medicine adherence. Educational levels and health literacy may also differ between the general population in some of those locations and the UK population. However, as per the response to Question A5, there is sufficient rationale to extrapolate the clinical efficacy and relative adherence data from across the trial populations to that of the submission's decision problem population. As response to Question A5 details, precedents exist when such data was used to inform reimbursement decisions in the UK (36).

The key data from HPTN 083 and HPTN 084 which is used in the ITC informing the cost-effectiveness analysis are the relative effectiveness of cabotegravir compared with oral PrEP. The underlying risk of HIV acquisition in the model is aligned with UK

data (35). The indirect treatment comparison provides a robust estimation of the effectiveness of oral PrEP as a function of adherence; the analysis updates previous published analyses but the findings are in alignment. Adherence to oral PrEP in the HPTN 083 study was moderate/high (86% detectable tenofovir [TFV] in plasma), and from this perspective, likely representative of a broad group of oral PrEP users than those whose needs are not being met by oral PrEP (Figure 1). This can be explored in the model, but the main impact of this is that the effectiveness of oral PrEP in UK clinical practice for the proposed population, whose needs are not met by oral PrEP, is likely to have been overestimated by the trial data. The effectiveness of cabotegravir is not impacted, as it is reflective of the adherence to injection appointments observed in the trial, and real-world data demonstrates adherence to injection appointments remains high in practice (71, 72). The ITC also estimates the relative HIV risk reduction of cabotegravir vs no PrEP, which is used to inform the cabotegravir effectiveness in individuals who are not eligible for oral PrEP (these individuals are not represented in the HPTN trials, as for ethical reasons it was not appropriate to include a placebo arm (73).

A20. Adherence for cis-gender females was obtained from the HPTN 084 study conducted in sub-Saharan Africa, where there may be challenges related to women's rights. For instance, adherence to daily oral contraceptive pills in these settings is often lower compared to adherence observed in high-income settings among individuals using daily contraceptive pills. Could you please clarify why such low adherence rates would be relevant to both cisgender females and transgender males in the UK population?

The HPTN study populations included cisgender and transgender women. There is limited data on PrEP among women in Europe; however, SLR data is available that identifies cisgender and transgender women experience many barriers to PrEP that can negatively impact on adherence to oral PrEP (74). A pooled analysis of 6,296 participants from post approval studies of PrEP in cisgender women across diverse geographies (Kenya, South Africa, India, Uganda, Botswana, and the United States [US]) has reported that less than 40% of participants achieved the highly protective benchmark of consistently taking at least 4 doses per week, and that participants showed dramatic declines in adherence by 96 weeks (75, 76). The low adherence

observed calls for adherence support measures that are tailored to the unique needs of women, and the development and implementation of new PrEP methods, such as long-acting PrEP (76).

Currently in the UK, 4 out of every 5 women living with diagnosed HIV are migrants, and 3 in 4 are from minority ethnic communities (77). With currently available PrEP methods, according to the UK Health Security Agency (UKHSA), only 41.9% of women at need for PrEP initiated or continued PrEP in 2022, reducing to 29.8% among women of Black African ethnicity (78). Importantly, Black African women represent the largest ethnic group of women diagnosed with HIV in England (701 of 1,391) as well as those first diagnosed in England (287 of 766). Furthermore, the incidence of STIs may be considered as a proxy for the risk of HIV acquisition, and STIs are also rising among young women and people of Black ethnicity in England (79).

Importantly, there are similarities observed in women's barriers to PrEP (although transgender women have some specific barriers related to gender affirming hormone therapy), that negatively impact uptake, adherence, and persistence across different health systems and geopolitical landscapes in Europe, Africa, and the Americas (55, 74, 80-84). For example, barriers can be related to the social and structural determinants of health. Furthermore, barriers to PrEP can be individual, interpersonal, community and structural; therefore, can transgress geographical borders.

Importantly, using contraception as a model, it has been shown that the use of contraception increases with the introduction of new methods, and that a wider choice of methods is better able to meet the individual needs of women and couples (85), which has been mirrored during person-centred models of HIV prevention offering choice between cabotegravir LA, oral PrEP and post-exposure prophylaxis (PEP), whereby people who are offered choices results in increased coverage and reduced HIV incidence (39).

A21. Please repeat the ITC with the exclusion of studies with populations (e.g. drug users) and interventions (e.g. gel) that are not aligned with the NICE scope.

The interventions considered in the clinical SLR PICOS criteria informing the ITC were long-acting injectable PrEP (e.g. cabotegravir), oral PrEP (e.g. TDF-FTC, TAF-FTC) and placebo or no PrEP.

The adherence meta-regression was conducted excluding the following studies:

- The PROUD study, as it did not report adherence based on plasma levels for a random sample of subjects (McCormack 2016 (8)). It was also an open label study.
- The Bangkok study as it recruited male and female intravenous drug users (23).
- The IPERGAY study as the intervention was on-demand TDF/FTC as PrEP (86).

The results, excluding these studies, are presented in Table 6.

Table 6: Results of the adherence meta-regression excluding studies with populations and interventions that are not aligned with the NICE scope

Model	Parameter	% Effectiveness	2.5 % CrI	97.5 % CrI
Log relationship (Excl PROUD, Bangkok, IPERGAY)	% Effect TDF/FTC vs No PrEP (HPTN 083)	[redacted]	[redacted]	[redacted]
Log relationship (Excl PROUD, Bangkok, IPERGAY)	% Effect TDF/FTC vs No PrEP (HPTN 084)	[redacted]	[redacted]	[redacted]

Abbreviations: CrI, credible interval; ITC, indirect treatment comparison; NICE, National Institute for Health and Care Excellence; PrEP, pre-exposure prophylaxis; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

A22. For the ITC: is the treatment in the 'No PReP' arms similar across studies? Please provide a table with details and a discussion of similarity of the trials.

A table detailing the PrEP definitions across trials with 'No PrEP' arms is provided in Table 7. Six studies included the same definition (placebo matches to TDF/FTC

schedule), while the other two studies had different definitions as described in Table 7.

Table 7: No PrEP definitions across studies included in the ITC

StudyID	No PrEP definition	Comment
HPTN 083	NA	NA
iPrEx	Placebo matched TDF/FTC schedule	–
PROUD	Deferred PrEP; PrEP was deferred for a period of 1 year	Results are reported from the first year, therefore comparison is with no PrEP
IPERGAY	Placebo matched on-demand TDF/FTC schedule	Sensitivity analysis conducted excluding this trial
HPTN 084	NA	NA
FEM-PrEP	Placebo matched TDF/FTC schedule	–
TENOFOVIR2	Placebo matched TDF/FTC schedule	–
Partners PrEP Study Continuation	Placebo matched TDF/FTC schedule	–
Bangkok Tenofovir Study	Placebo matched TDF/FTC schedule	–
VOICE	Placebo matched TDF/FTC schedule	–

Abbreviations: ITC, indirect treatment comparison; NA, not applicable; PrEP, pre-exposure prophylaxis; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

Section B: Clarification on cost-effectiveness data

B1. Document B, page 108, Model structure: The model includes a 'no PrEP' state, but guidelines recommend switching to another effective PrEP regimen rather than no PrEP if someone discontinues a PrEP regimen. Can you please clarify why patients who discontinue TDF/FTC are not allowed to subsequently receive cabotegravir while patients on cabotegravir who discontinue LAI go on to receive daily oral tablets? In HPTN 083 and HPTN 084, patients randomised to receive daily oral pills opted to receive the LAI.

The individuals considered in the appraisal are those whose needs cannot be optimally met in the current PrEP landscape; including but not limited to those who

are sub-optimally adhering to oral PrEP, those who cannot take oral PrEP due to medical contraindication or intolerance, or who have limitations with swallowing pills. This is not equivalent to the post oral PrEP use in broad population or in the individuals who discontinue by choice, hence use of cabotegravir post oral PrEP is not modelled (see Document B, Section B.1.1).

The clinical decision is at the point of PrEP initiation as to whether an individual should take an oral PrEP or long-acting PrEP option in case oral PrEP is not suitable as detailed in Question A5. Thus, the cost-effectiveness model reflects the decision problem. Note, individuals discontinuing from cabotegravir LA in the model and initiating TDF/ FTC for 12 months is reflective of the summary of product characteristics (Appendix C).

B2. PRIORITY. Can you please clarify the justification for a 5-year at-risk period time horizon with a model starting age of 26 given that among those first diagnosed in England in 2022, 9%(232) were aged 15-24, 31% (750) were aged 25-34, 37% (904) were aged 35 to 49, 19% (467) were aged 50 to 64 and 4% (91%)were aged over 65. The time horizon chosen by the model does not fully account for the ages. Given periods of elevated risk may reoccur over the long term and clinical guidelines recommend need-based ongoing PrEP.

Can the company also clarify why the starting age for PREP was chosen to be 26 and not 18 years old.

The cost-effectiveness model structure considers a single at-risk period to ensure simplicity and tractability. The at-risk period of 5 years used in the model reflects assumptions in the economic analysis informing the National Institute for Health and Care Excellence (NICE) guidelines for reducing STIs (NG221) (87), and is not age-specific. Scenario analyses were conducted, where the at-risk period was extended to 10 years (Document B, Section B.3.11.3); cabotegravir remained cost-effective at a willingness to pay (WTP) threshold of £30,000/quality-adjusted life years (QALY). The time-horizon of the cost-effectiveness model is a life-time time horizon.

The median age used in the cost-effectiveness model was informed by the HPTN 083 and HPTN 084 trials, which is consistent with the source of the efficacy/adherence data used in the ITC and subsequently the cost-effectiveness analysis. The risk period discussed covers 26–31 years of age under the 5-year scenario and 26–36 years of age under the 10-year scenario. This is consistent with the average age of individuals on PrEP in the UK, as confirmed by UKHSA data and described by clinicians (38, 78). Not every individual will be at risk from 18 years of age and the period of heightened risk will occur at different ages for different individuals, and may change over time, depending on an individual's sexual and affectional relationships and other external factors in their lives. Using the median age from the clinical trials, rather than a younger starting age better represents the overall distribution of PrEP users and balances the representation of period of risk with the remaining lifetime HIV-related costs and health impacts if an individual acquires HIV. Whilst diagnosis data provides a useful indication of the age distribution of people living with HIV entering care in the UK, it is not necessarily directly analogous to the age of acquisition of HIV. Indeed, a recent report by the UKHSA highlights the proportion of diagnoses (44% of people diagnosed with HIV in 2022 in England) that were classified as 'late' (88), suggesting that HIV acquisition may occur prior to when these individuals present for HIV testing and care.

B3. Can you please clarify the distinction between persistence and adherence as applied in the economic model? Given that persistence was unavailable in the economic model [*sic: should read 'clinical trials'*], is it unreasonable to assume that patients with a very low blood concentration of TDF/FTC may have stopped taking daily pills (rather than being non-adherent) given that plasma concentration of these tablets may persist for long periods of time?

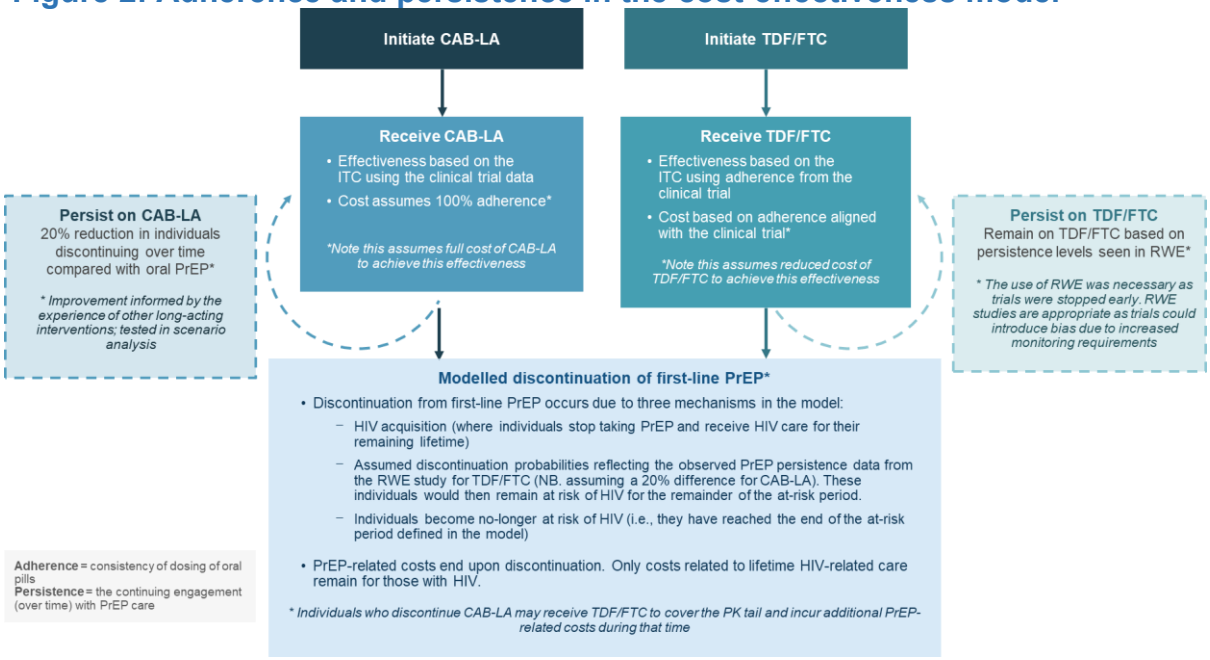
Note, during the clarification call, the EAG confirmed that the following sentence "Given that persistence was unavailable in the economic model […]" should be replaced with "Given that persistence was unavailable in the clinical trials".

Adherence is defined as taking the optimal PrEP dose to reach protective drug concentrations, according to reported risk of HIV acquisition (49), with oral PrEP efficacy highly dependent on adherence (89). Persistence is defined as the duration of time a person continues with PrEP without interruption (90) and may be

considered as the ability to remain on PrEP after initiation, with persistence a critical implementation issue (49, 91). Both adherence and persistence are considered distinct elements in conceptual frameworks of PrEP care (with retention in care reflecting persistence) (92), and are reported as distinct outcomes in real-world studies of PrEP (49, 93, 94). Furthermore, in clinical trial settings, adherence and persistence are assessed via different methodologies; for example, adherence can be measured using drug concentrations in blood, plasma, or urine assays, whereas persistence can be measured by recorded interruptions in PrEP refill prescriptions (31, 32, 91, 93, 95, 96). Collectively, PrEP adherence and persistence are distinctly measurable processes that can lead to improved outcomes and reduced HIV incidence (97).

A schematic illustrating how both adherence and persistence are represented in the cost-effectiveness model is presented in Figure 2.

Figure 2: Adherence and persistence in the cost-effectiveness model



Abbreviations: CAB-LA, cabotegravir long-acting; HIV, human immunodeficiency virus; ITC, indirect treatment comparison; PrEP, pre-exposure prophylaxis; RWE, real-world evidence; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

In the cost-effectiveness model, the adherence measures informing the clinical effectiveness of oral PrEP are based on the measured detectable plasma TFV from across visits from adherence subpopulations in the HPTN 083 (390 individuals) and HPTN 084 trials (405 individuals) (13, 22). These are the appropriate adherence

measures, as these reflect a summary of adherence in the population over the time-period of evaluation in the trials and will determine the observed effectiveness. Furthermore, this adherence measure is reliable (e.g. compared to self-report) (96) and comparable to that reported in the other TDF/FTC studies identified for use in the ITC, and that this is essential to integrating evidence across studies in the ITC. Due to the short half-life of TDF (following a single oral dose of TDF, the plasma terminal elimination half-life of tenofovir is approximately 17 hours) these measures could reflect relatively short-term changes in dosing, and therefore capture adherence (98). The incorporation of adherence into the model is represented in the second column of the schematic 'Initiate TDF/FTC', with effectiveness based on the ITC (utilising the meta-regression specifying the relationship between adherence and effectiveness), using the observed adherence measures discussed above from the clinical trials.

Persistence in the model determines whether individuals stay in PrEP care or discontinue their PrEP (as represented in the schematic). It reflects continued engagement with PrEP programmes and care over time. Persistence on oral PrEP in the model is based on data from a large real-world evidence (RWE) database study in the US (where non-persistence was defined as a >90-day gap from last day of supply and suggests permanent discontinuation or a treatment break) (95). Furthermore, costs of PrEP are adjusted to reflect adherence whilst retained in the PrEP programme, whereas following discontinuation individuals will no longer incur PrEP costs.

In this way, the model considers adherence and persistence to be distinct inputs. The summary measure used to represent adherence in the model (measured detectable plasma TFV) considers visits over the course of the study, and so does not assess whether individuals who present with undetectable levels of TDF/FTC do so on repeated visits. However, the percentage of individuals receiving their planned injections remained high throughout the blinded period of the trial in both arms suggesting continued engagement (most injection visits were within the allowable ±7-day window [HPTN 083: cabotegravir: [redacted], TDF/FTC: [redacted]; HPTN 084: cabotegravir: [redacted], TDF/FTC: [redacted]. By contrast, it is unlikely that individuals who have stopped taking their PrEP would continue to attend regular visits in practice.

Furthermore, clinical trial participants may be more likely to persist on PrEP than individuals in a real-world setting. Finally, both HPTN trials were stopped early and follow-up of the individuals in the trial was censored. This means that, even if trial data had been available, RWE is more appropriate to inform persistence in the economic model, hence the Oglesby 2021 study was selected (95). Oglesby et al, also concluded that the persistence observed in real-world setting was lower than reported in clinical trials, which corroborates the risk of bias associated with assessing persistence in a clinical trial setting.

The distinction between adherence and persistence is commonly captured in economic models describing the impact of PrEP care. Examples include the study conducted by O'Murchu et al, evaluating the cost-effectiveness of an oral PrEP programme in Ireland, where clinical effectiveness of PrEP was derived from a meta-analysis of 6 trials (75% effectiveness) (99), and retention rates based on a study from a prospective cohort study from Australia (a 76% one-year retention rate) (100). Other modelling studies have explicitly explored the impact of interventions targeting PrEP initiation, adherence, and persistence; with adherence (categorised as 'low', 'medium' and 'high' reflecting different levels of clinical effectiveness) and persistence (defined in the study as average days until PrEP discontinuation) specified independently (101). In a modelling study exploring the PrEP continuum of care in adolescent sexual minority males in the US, empirical estimates of uptake, adherence and retention (defined as continued participation in the PrEP program, regardless of adherence) from the EPIC and ATN113 studies were inputted into the model, with adherence based on tenofovir-diphosphate (TFV-DP) levels and attendance across the weeks of the study used to inform retention (persistence) in the model (102). Finally, modelling studies have also reflected persistence through assumptions about median duration of PrEP use (e.g. 5 years) (103) and discontinuation may be modified based on changing eligibility over time (re-assessment at defined intervals) (104). Thus, we are confident that it is important to account for both persistence and adherence explicitly in this cost-effectiveness model, and that we have avoided any potential for double counting between the two constructs by leveraging the data which we have.

B4. Can you please clarify why persistence was not subsumed in the clinical effectiveness results? The effectiveness of TDF/FTC would normally include persistence (and adherence) to the drug.

As described above, in answering Question B3, the data reported from the HPTN clinical trials are limited in the extent to which they could be used to inform real-world persistence in the model. As the trials were stopped early, follow up of the individuals in the trial was censored and it is not possible to use this data to inform persistence.

In the model, persistence parameters were informed by RWE to reflect the likely discontinuation patterns observed in practice. We utilise data from a large US database study to represent time engaged and using PrEP (and therefore receive PrEP effectiveness and incurring PrEP costs in the model) (95). Whilst on treatment, the model reflects the adherence levels and effectiveness observed in the key trials HPTN083 and HPTN084. These data are further used to adjust down the cost of oral PrEP assuming no wastage. As discussed, similar approaches have been used in other modelling studies, including that by O'Murchu et al, (99), to determine the cost-effectiveness of oral PrEP in Ireland with PrEP effectiveness and persistence considered distinct and from separate data sources.

B5. Can you clarify if 50% of participants of oral lead in tablets for cabotegravir are subject to the same adherence rates as those used for the TDF/FTC comparator? If this is not the case, can you please clarify why this was not done?

The model assumed full adherence for participants receiving oral lead-in tablets for cabotegravir, which reflected the clinical trial evidence. At the end of the trial Step 1 (oral lead-in), in HPTN 083, only [redacted] of participants in the cabotegravir arm, and [redacted] in the TDF/FTC arm had discontinued the investigational product due to low oral adherence according to the protocol (33). In HPTN 084, less than [redacted] of participants in either arm discontinued the investigational product during Step 1 due to low oral adherence (34). This assumption in the economic model implies the full cost of lead-in tablets will be incurred in the cabotegravir LA arm of the model. Furthermore, the effectiveness of the oral cabotegravir component of the cabotegravir oral regimen in the model was not assessed separately from the cabotegravir LA component, so effectiveness could not be adjusted.

Finally, a scenario analysis exploring a situation where 0% of individuals receive an oral lead-in was presented and confirmed that cabotegravir is cost-effective versus TDF/FTC and cost-saving versus no PrEP.

B6. Can you please clarify if 50% of participants of oral lead in tablets for cabotegravir are subject to the same adherence rates as those used for the TDF/FTC comparator? If this is not the case, can the company clarify why this was not done?

The EAG confirmed this query is a duplication of B5. Please see the response above.

Section C: Textual clarification and additional points

C1. Appendix D, Table 33. Can you please provide the reference pack for the studies. We can't seem to find a number of them (such as Brown 2022, Bunge 2023, Herrera 2023, Mahomed 2023, Mathews 2023, McGowan 2022, Moodley 2023)

The references listed in Appendix D, Table 33 have now been provided in the folder labelled 'ID6255_Clarification question C1'.

C2. Appendix D, excluded studies: the reasons for exclusion are not clearly listed. For instance, HPTN 069/ACTG A5305 study, randomised to (i) maraviroc; (ii) maraviroc + emtricitabine; (iii) maraviroc + tenofovir disoproxil fumarate; or (iv) tenofovir disoproxil fumarate + emtricitabine.

In section D.2.3, Table 33 publications excluded at the full-text screening stage reports the reason for excluding studies from the SLR. For instance, HPTN 069/ACTG A5305 study was excluded based on the population that did not align with the SLR search criteria.

In section D.3.1, the studies identified in the SLR but excluded from the ITC are presented. The scope of the SLR was broader than the ITC which included an additional criteria of reporting TDF/FTC adherence, based on plasma sampling (or pill count data for the relevant sensitivity analysis) leading to exclusion of ten studies.

C3. Can you clarify the rational that suggests injections are preferable/less stigmatised to pills?

In Document B, Section B.1.3.6.2.1, the submission describes PrEP-related stigma, including social stigma. Several studies have reported that participants experience PrEP-related stigma in diverse ways, including stereotyping, rejection, and discrimination (including transphobia, and homophobia) (105). Importantly, injectable PrEP could avoid some of the key challenges that are associated with social stigma (106). For example, there are individuals who do not initiate oral PrEP due to fear of discovery of their PrEP use as a result of their family, partners, or peers finding their pills. This may reveal their elevated HIV-risk, and inadvertently disclose them as a member of the LGBTQ+ community or someone who uses drugs, for example (105). While eliminating the need to have PrEP medication in a person's possession will not eradicate stigma associated with PrEP use, it may help to decrease the contribution of stigma to PrEP non-uptake and non-adherence by making the use of PrEP easier to conceal (107).

Consequently, barriers to oral PrEP, such as stigma, means injectable PrEP might be more appealing for some individuals, and may result in higher overall uptake of PrEP (108, 109).

The majority of participants in HPTN 077 preferred injectable PrEP (110), and as discussed in Document B, Section B.2.6.1.4, and B.2.6.2.4, during the open label extension of HPTN 083 and HPTN 084, the majority of participants chose cabotegravir LA as a preferred option compared to TDF/FTC; 95.9% of participants (111, 112).

PrEP-related stigma mirrors experiences of HIV-related stigma. In alignment with the accepted advantages of a long-acting injectable for addressing HIV-related stigma (113), it is anticipated that long-acting injectable PrEP will also address PrEP-related stigma.

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Appendix A: WinBUGS code

Logarithmic model

```
model{

	#vague priors for regression co-efficients

	#co-efficient for TDF vs.no PrEP effect
	d_TDF_FTC~dnorm(0,1.0E-4)

	#intercept
	alpha~dnorm(0,1.0E-4)

	#co-efficients for adherence (change in log RR per unit change in proportion adherent)
	betaAdher~dnorm(0,1.0E-4)

	#read data from TDF/FTC trials
	for(ii in 1:nObs){

		#convert reported SE for log RR to precision to match JAGS parameterisation of normal likelihood
		tau[ii] <- 1/(pow(se[ii],2))

		#regression equation predicting RR for TDF/FTC trials
		x[ii] <- alpha+betaAdher*adherProp[ii]

		#normal likelihood including observed log RR
		mn[ii] ~ dnorm(x[ii], tau[ii])

		resdev[ii] <- (mn[ii]-x[ii])*(mn[ii]-x[ii])*tau[ii]

	}
```

```
totresdev <- sum(resdev[])


#read data from CAB-LA trials
for(jj in 1:nObsCab ){

    #vague priors for CAB vs. TDF effect co-efficients
    cabTdfLRR[jj] ~ dnorm(0,1.0E-4)

    #prior for no PrEP log event rate for each trial
    compLogRate[jj] ~ dnorm(0.0,1.0E-2)

    #poisson likelihood for no PrEP event rate data.  Note inclusion of log
person-years of exposure as offset
    compR[jj] ~ dpois(exp(compLogRate[jj]+log(compYears[jj])))

    #convert rate to 100 patient-years denominator
    compRate[jj] <- exp(compLogRate[jj])*100

    #convert reported SE for log RR to precision to match JAGS
parameterisation of normal likelihood
    tauCab[jj] <- 1/(pow(seCab[jj],2))

    #normal likelihood including observed log RR
    cabTdfLRR[jj] ~ dnorm(mnCab[jj],tauCab[jj])

    #convert to RR
    cabTdfRR[jj] <- exp(cabTdfLRR[jj])

    #convert to Percentage effectiveness
    cabTdfPercEffect[jj] <- (1-cabTdfRR[jj])*100

    #estimate effectiveness of TDF/FTC vs no PrEP at the level of
TDF/FTC adherence seen in the CAB-LA trial based on betaAdher
```

```
            adjTdfNoPrepLRR[jj] <- alpha+betaAdher*adherPropCab[jj]

            #convert to RR
            adjTdfNoPrepRR[jj] <-  exp(adjTdfNoPrepLRR[jj])

            #convert to Percentage effectiveness
            adjTdfNoPrepPercEffect[jj] <- (1-adjTdfNoPrepRR[jj])*100

            #estimate effectiveness of CAB-LA vs no PrEP (ITC) based on
predicted effectiveness of TDF/FTC vs. No PrEP
            indirectCabNoPrepLRR[jj] <- cabTdfLRR[jj] + adjTdfNoPrepLRR[jj]

            #convert to RR
            indirectCabNoPrepRR[jj] <- exp(indirectCabNoPrepLRR[jj])

            #convert to Percentage effectiveness
            indirectCabNoPrepPercEffect[jj] <- (1-indirectCabNoPrepRR[jj])*100

            #convert to event rate in no PrEP arm by applying inverse estimated
treatment effect for TDF/FTC vs no PrEP
            baseRate[jj] <- compRate[jj]/adjTdfNoPrepRR[jj]

        }
}
```

Logarithmic model with sex covariable

```
model{

        #vague priors for regression co-efficients


        #co-efficient for TDF vs.no PrEP effect
        d_TDF_FTC~dnorm(0,1.0E-4)
```

```
        #intercept
        alpha~dnorm(0,1.0E-4)

        #co-efficients for sex main effect
        betaSex~dnorm(0,1.0E-4)

        #co-efficients for adherence (change in log RR per unit change in proportion
adherent)
        betaAdher~dnorm(0,1.0E-4)

        #read data from TDF/FTC trials
        for(ii in 1:nObs){

                #convert reported SE for log RR to precision to match JAGS
parameterisation of normal likelihood
                tau[ii] <- 1/(pow(se[ii],2))

                #regression equation predicting RR for TDF/FTC trials
                x[ii] <- alpha+betaSex*sex[ii]+betaAdher*adherProp[ii]

                #normal likelihood including observed log RR
                mn[ii] ~ dnorm(x[ii], tau[ii])

                #resdev[ii] <- (mn[ii]-x[ii])*(mn[ii]-x[ii])*tau[ii]

        }

        #totresdev <- sum(resdev[])


        #read data from CAB-LA trials
        for(jj in 1:nObsCab ){
```

```
                #vague priors for CAB vs. TDF effect co-efficients
                cabTdfLRR[jj] ~ dnorm(0,1.0E-4)

#prior for no PrEP log event rate for each trial
                compLogRate[jj] ~ dnorm(0.0,1.0E-2)

                #poisson likelihood for no PrEP event rate data.  Note inclusion of log
person-years of exposure as offset
                compR[jj] ~ dpois(exp(compLogRate[jj]+log(compYears[jj])))

                #convert rate to 100 patient-years denominator
                compRate[jj] <- exp(compLogRate[jj])*100

                #convert reported SE for log RR to precision to match JAGS
parameterisation of normal likelihood
                tauCab[jj] <- 1/(pow(seCab[jj],2))

                #normal likelihood including observed log RR
                mnCab[jj] ~ dnorm(cabTdfLRR[jj],tauCab[jj])

                #convert to RR
                cabTdfRR[jj] <- exp(cabTdfLRR[jj])

                #convert to Percentage effectiveness
                cabTdfPercEffect[jj] <- (1-cabTdfRR[jj])*100

                #estimate effectiveness of TDF/FTC vs no PrEP at the level of
TDF/FTC adherence seen in the CAB-LA trial based on betaAdher
                adjTdfNoPrepLRR[jj] <-
alpha+betaSex*cabSex[jj]+betaAdher*adherPropCab[jj]

                #convert to RR
                adjTdfNoPrepRR[jj] <-  exp(adjTdfNoPrepLRR[jj])
```

```
            #convert to Percentage effectiveness
            adjTdfNoPrepPercEffect[jj] <- (1-adjTdfNoPrepRR[jj])*100

            #estimate effectiveness of CAB-LA vs no PrEP (ITC) based on
predicted effectiveness of TDF/FTC vs. No PrEP
            indirectCabNoPrepLRR[jj] <- cabTdfLRR[jj] + adjTdfNoPrepLRR[jj]

            #convert to RR
            indirectCabNoPrepRR[jj] <- exp(indirectCabNoPrepLRR[jj])

            #convert to Percentage effectiveness
            indirectCabNoPrepPercEffect[jj] <- (1-indirectCabNoPrepRR[jj])*100

            #convert to event rate in no PrEP arm by applying inverse estimated
treatment effect for TDF/FTC vs no PrEP
            baseRate[jj] <- compRate[jj]/adjTdfNoPrepRR[jj]

        }
}
```

Linear model

```
model{

        #vague priors for regression co-efficients

        #co-efficient for TDF vs.no PrEP effect
        d_TDF_FTC~dnorm(0,1.0E-4)

        #intercept
        alpha~dnorm(0,1.0E-4)

        #co-efficients for adherence (change in log RR per unit change in proportion
adherent)
```

```
betaAdher~dnorm(0,1.0E-4)

#read data from TDF/FTC trials
for(ii in 1:nObs){

        #convert reported SE for log RR to precision to match JAGS
parameterisation of normal likelihood
        tau[ii] <- 1/(pow(se[ii],2))

        #regression equation predicting RR for TDF/FTC trials
        y[ii] <- max(0.001,alpha+betaAdher*adherProp[ii])

        #convert to log RR to match trial estimator
        x[ii] <- log(y[ii])

        #normal likelihood including observed log RR
        mn[ii] ~ dnorm(x[ii], tau[ii])

        resdev[ii] <- (mn[ii]-x[ii])*(mn[ii]-x[ii])*tau[ii]

}

totresdev <- sum(resdev[])


#read data from CAB-LA trials
for(jj in 1:nObsCab ){

        #vague priors for CAB vs. TDF effect co-efficients
        cabTdfLRR[jj] ~ dnorm(0,1.0E-4)

        #prior for no PrEP log event rate for each trial
        compLogRate[jj] ~ dnorm(0.0,1.0E-2)
```

```
#poisson likelihood for no PrEP event rate data.  Note inclusion of log person-years of exposure as offset
compR[jj] ~ dpois(exp(compLogRate[jj]+log(compYears[jj])))

#convert rate to 100 patient-years denominator
compRate[jj] <- exp(compLogRate[jj])*100

#convert reported SE for log RR to precision to match JAGS parameterisation of normal likelihood
tauCab[jj] <- 1/(pow(seCab[jj],2))

#normal likelihood including observed log RR
mnCab[jj] ~ dnorm(cabTdfLRR[jj],tauCab[jj])

#convert to RR
cabTdfRR[jj] <- exp(cabTdfLRR[jj])

#convert to Percentage effectiveness
cabTdfPercEffect[jj] <- (1-cabTdfRR[jj])*100

#estimate effectiveness of TDF/FTC vs no PrEP at the level of TDF/FTC adherence seen in the CAB-LA trial based on betaAdher
adjTdfNoPrepRR[jj] <- alpha+betaAdher*adherPropCab[jj]

#convert to RR
adjTdfNoPrepLRR[jj] <-  log(adjTdfNoPrepRR[jj])

#convert to Percentage effectiveness
adjTdfNoPrepPercEffect[jj] <- (1-adjTdfNoPrepRR[jj])*100

#estimate effectiveness of CAB-LA vs no PrEP (ITC) based on predicted effectiveness of TDF/FTC vs. No PrEP
indirectCabNoPrepLRR[jj] <- cabTdfLRR[jj] + adjTdfNoPrepLRR[jj]
```

```
            #convert to RR
            indirectCabNoPrepRR[jj] <- exp(indirectCabNoPrepLRR[jj])

            #convert to Percentage effectiveness
            indirectCabNoPrepPercEffect[jj] <- (1-indirectCabNoPrepRR[jj])*100

            #convert to event rate in no PrEP arm by applying inverse estimated
treatment effect for TDF/FTC vs no PrEP
            baseRate[jj] <- compRate[jj]/adjTdfNoPrepRR[jj]

        }
}
```

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Cabotegravir injections for preventing HIV-1 in adults and young people [ID6255]

Community Organisation Submission

About you

1.Your name	[redacted]
2. Name of organisation	Terrence Higgins Trust
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Terrence Higgins Trust is the UK's leading HIV and sexual health charity and employs around 235 staff nationally. Terrence Higgins Trust provides support for those affected by HIV and leads on HIV policy work. It also delivers a range of Integrated Sexual and Reproductive Health Services across England in partnership with NHS and other organisations. These are funded by Public Health. Other services are funded by Department of Health and UK Health Security Agency.
4b. Has the organisation received any funding from the company (ViiV) bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? **If so, please state the name of the company, amount, and purpose of funding.**	Yes • £60,000 from GSK for the Barclays Gala sponsorship, unrestricted funding – unrelated to the technology, one-off funding. • £5,235 from ViiV for the Tackle HIV challenge, unrestricted funding – unrelated to the technology, one-off funding.

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of people at risk of sexually acquiring HIV-1 and carers (if applicable) to include in your submission?	**1/ Annual PrEP user surveys** I Want PrEP Now (IWPN) (a website which is owned by Terrence Higgins Trust), in collaboration with Public Health England and PrEPster conducted three annual PrEP user surveys (2017, 2018, 2019) and a follow-up final PrEP user survey in 2021.[1] Participants were recruited via social media promotion, LGBT+ media, geo-positioning 'hook-up' apps (Grindr/Scruff/Hornet) used by gay, bisexual and other men who have sex with men (GBMSM), through existing networks and those of the wider HIV and sexual health sector, and through the IWPN mailing list. The survey asked participants for basic demographic information and captured data on: • Type of sex and sexual partners • PrEP access (NHS and self-sourcing) • Access issues and barriers • PrEP use • Condom use • Substance use • PrEP users experience of discussing their PrEP use with partners, friends, family, and healthcare professionals • Stigma and self-stigma • The effects of PrEP use (or lack of access to PrEP) on the mental health and sex lives/ experiences of sexual pleasure of participants. 2/ **Not PrEPared report** The Not PrEPared report [2] by Terrence Higgins Trust, National AIDS Trust, PrEPster, Sophia Forum, and the One Voice Network collected data from local authority sexual health commissioners, clinic staff, PrEP users

	who had experienced issues accessing PrEP and those who sought to access PrEP but were unsuccessful. The report provided the results of three surveys: 1. PrEP service users and those seeking to use PrEP. 2. Clinicians involved in providing PrEP. 3. Sexual health service commissioners and providers across the UK. **Local Authority/providers survey** The Local Authority survey ran from 5 April 2022, with responses received until 16 June 2022. The questionnaire was sent as a Freedom of Information (FOI) request to all local authorities across England. The vast majority of local authorities in England responded to the FOI requests (134 out of 151), either directly, or via their service providers. **Clinical staff and community surveys** The community and clinical staff surveys were both hosted on SNAP and were available online from 8 June to 17 July 2022 and collected data from PrEP service users and PrEP service providers respectively. Eligibility criteria for the community survey included individuals having tried either successfully or unsuccessfully to access PrEP and also having experienced difficulties in doing so. These experiences had to be recent (October 2021 up until the close of the survey in July 2022). The clinical staff survey was open to all staff working in services that provided PrEP. The survey focused on providing a snapshot of PrEP services asking about practice, PrEP prescribing and supply issues. Terrence Higgins Trust, National AIDS Trust, PrEPster, Sophia Forum and One Voice Network promoted the clinical staff and community surveys through Twitter, Instagram, newsletters, online news outlets and reaching out to their contacts and enhanced promotion through paid advertisement in an attempt to increase awareness of the survey among women, Black communities, and people living outside London and North West England. Targeted online advertisements ran from 27 June to 12 July 2022. 79 clinicians responded to the Healthcare Provider survey and 1,120 service users responded to the community survey.

	Case studies Survey responses from PrEP users were supplemented by case studies. These were individuals who had responded to the community survey and opted-in for further contact. The research team contacted 12 individuals, from a wide geographical area, wide demographics, and who reported different narratives of difficulty accessing PrEP. Everyone who responded was given a telephone interview to share more about their experiences. **3/ HIV Prevention England (HPE)** HPE is the national HIV prevention programme for England. It is part of Terrence Higgins Trust and funded by the Department of Health and Social Care. HPE delivers a programme of HIV prevention work for those most affected by HIV in England, mainly gay and bisexual men, Black African people, and other populations in whom evidence demonstrates higher or emerging burden of HIV prevalence. Since 2016, HPE and Terrence Higgins Trust have collected PrEP focused insights from individuals and groups from key-populations including Black African people, trans and non-binary people, gay, bisexual and other men who have sex with men, and healthcare professionals. The numerous projects explored general HIV awareness and literacy, awareness of risk and proximity to risk, awareness and use of post exposure prophylaxis (PEP), awareness and use of PrEP, PrEP access issues, and HIV and PrEP stigma. This information was gathered using surveys, focus groups, and in-depth interviews. HPE conducts annual insights work on PrEP knowledge and use as part of the evaluation process for each year's national campaign. Each year, on average, there are approximately 1,000 responses from GBMSM and 250-300 from Black African people on these PrEP-specific questions.

[1] Aidsmap (2021). Available at: https://www.aidsmap.com/news/feb-2021/better-access-prep-uk-especially-through-nhs-services
[2] National AIDS Trust et al (2022) Not PrEPared. Available at: https://www.nat.org.uk/sites/default/files/publications/Not%20PrEPared.pdf

Living with the condition

6. How does being at risk of sexually acquiring HIV-1 affect people?	There is a dynamic relationship between HIV and the people it affects. Often, those most at risk of HIV have one or more minority identity or are marginalised in some way. People living through other adverse life experiences such as precarious housing or intimate partner violence are also more at risk of HIV. An HIV diagnosis might exacerbate these issues or create them in the first place. Living under the burden of known HIV risk, as is the case with GBMSM, can lead to poorer outcomes in many aspects of life and wellbeing. Living under an unknown burden of HIV risk, as is more often the case in heterosexual populations, can also have life-changing health impacts. These populations experience higher rates of late diagnosis and death within 12 months of diagnosis.

Current treatment of the condition in the NHS

7. What do people at risk of sexually acquired HIV-1 infection or carers (if applicable) think of current treatments and care available on the NHS?	The treatment and care delivered in most clinics is high quality but can be exceedingly difficult to access because these services are massively underfunded. This is often challenging for the clinician and the patient. However, there is a lack of diversity and choice in PrEP drugs and service delivery models. PrEP is still only available from level 3 sexual health clinics.
8. Is there an unmet need for people at risk of sexually acquired HIV-1 infection?	Yes. There is huge unmet need in most at-risk groups outside of GBMSM. There has been a concerted effort to redress this but with very modest results. According to data from UKHSA [3], in 2022 HIV diagnoses first made in England (diagnoses which were not previously made abroad, and which were instead first made in the UK or England) among GBMSM in England decreased by 8% from 784 in 2021 to 724 in 2022. UKHSA proposes that the fall in diagnoses in this population, together with high and sustained numbers in testing for HIV, suggest incidence i.e. 'HIV transmission' continues to decline. In contrast, the number of diagnoses first diagnosed in England among people exposed through sex between men and women increased by 12% from 870 in 2021 to 976 in 2022. Between 2021 and 2022, the number of new HIV diagnoses first made in England in women exposed through sex with men rose by 26% from 447 to 564 but fell by 3% (423 to 411) among men exposed through sex with women. UKHSA states that the lower HIV testing rates within this group suggests HIV transmission continues within England as well as abroad. In short, the assumption is that actual new infections in GBMSM has slowed significantly while new infections in heterosexuals from key populations (particularly Black African women) is rising. Robust mathematical modelling is required to gain a clearer picture. People who are unable to be in possession of daily antiretroviral medication or who need a discreet HIV prevention option, currently have their needs unmet. These people might include GBMSM who are not 'out' to their household. People experiencing sexual or physical abuse or coercive control. People in care or part of a prison population.
9. Where would people prefer to go to receive prophylactic treatment? (hospital / GP surgery /pharmacy / other)	It very much depends on the type of person and what other services they are already accessing or consider to be acceptable. A large proportion of gay, bisexual and other men who have sex with men find accessing sexual health services from sexual health clinics to be highly acceptable. There is evidence to support offering PrEP for trans people from gender identity services. Similarly, there is evidence to suggest integrating a PrEP offer into sexual and reproductive health services is more appealing for women.

[3] UKHSA (2023). Available at: https://www.gov.uk/government/statistics/hiv-annual-data-tables/hiv-testing-prep-new-hiv-diagnoses-and-care-outcomes-for-people-accessing-hiv-services-2023-report#acknowledgements

Advantages of the technology

10. What do people at risk of sexually acquired HIV-1 infection or carers (if applicable) think are the advantages of the technology? • How would having a prophylactic treatment available impact the lives of people at risk of sexually acquired HIV-1 (for example, how would it change the activities people do, or how they feel?) • How would the effectiveness of treatment impact this?	CAB-LA is the first and only PrEP modality that has proved highly effective in women, in all PrEP studies to date. It would be prudent to acknowledge that the biological, behavioural, and social barriers to PrEP effectiveness for those who are currently under-represented and/or underserved in HIV prevention services can only be mitigated by increasing the choices available to those individuals and communities. We have plenty of evidence of the ways that PrEP use has improved the lives and sex lives of gay and bisexual men. They report better mental health and wellbeing with less anxiety. Many experience more autonomy and control, healthier sex and relationship choices, and an increase in intimacy and pleasure. Anecdotally, trans people have reported a 'clearing of head space' to allow them to focus on their gender needs without the added stress of HIV risk. There is very little record of the experience of heterosexual men and women in these studies. While we can't expect these benefits to be felt as intensely, on a population level, in cis-heterosexuals (because of much lower HIV prevalence), it is logical to expect that anyone (regardless of identity) who has identified they are at risk of contracting HIV would also benefit from the improvements listed above by using PrEP. Provided people can attend their bi-monthly injection visits, this is the most effect HIV prevention tool we have ever had, with no need to be burdened with pill adherence.

Disadvantages of the technology

11. What do people at risk of sexually acquired HIV-1 infection or carers (if applicable) think are the disadvantages of the technology?	The 'concerns' rather than 'disadvantages' are that people miss appointments, or struggle with adherence in the oral pill lead-in, or don't complete the oral pill cessation regimen. As with any medication, there is a risk of adverse side effects and this drug has a very long tail but the oral lead in mitigates this concern somewhat. This medication in delivered as an injection, therefore injection site reactions might be considered a disadvantage.

Population of people at risk of sexually acquired HIV-1 infection

12. Are there any groups of people at risk of sexually acquired HIV-1 infection who might benefit more or less from the technology than others? If so, please describe them and explain why.	Not all people at risk of HIV-1 will need CAB-LA. The majority of oral PrEP users i.e. GBMSM, take generic TD/FTC. It is well tolerated with high levels of acceptability. Adherence is generally good or adequate in the majority of these users. A small number of these people might require support with adherence or access to a long-acting injectable. A small number of GBMSM will have clinical indicators for TAF/FTC eligibility, due to reduction in renal function. A small number of these might benefit from access to a long-acting injectable. TAF/FTC might also be indicated for a small number of young adults and adolescents, due to bone mineral density. Some of these individuals might benefit from CAB-LA. Some people belonging to one or more of these HIV risk indicator groups might be more likely to find CAB-LA a better choice, or the only PrEP option suitable and effective for them: • Female sex workers • Black African heterosexuals • People under 25 • People experiencing homelessness • People with substance misuse • People from minority ethnic groups • People experiencing domestic abuse/intimate partner violence • People accessing reproductive health and unplanned pregnancy services • Recent migrants.

Equality

13. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	From an equity and equalities perspective, in regards to HIV PrEP options, CAB-LA appears to be both effective and have high acceptability in women. Access to CAB-LA could potentially address the inequalities caused by disparities in effectiveness of oral PrEP in women compared with men who have sex with men. • CAB-LA has the potential to be revolutionary for adolescent girls and young women in sub-Saharan Africa who are disproportionately affected by HIV, and for women in other parts of the world including high income countries with low PrEP uptake in women. • CAB-LA could also address huge disparities in PrEP uptake across populations and subpopulations including female sex workers, Black African heterosexuals, people under 25, people experiencing homelessness, people with substance misuse, people from minority ethnic groups, people experiencing domestic abuse/intimate partner violence, people accessing reproductive healthcare and unplanned pregnancy services, and recent migrants. • CAB-LA could remove barriers to access for women and subpopulations who don't visit sexual health clinics with the same frequency as GBMSM. For example, women who prefer to get their sexual and reproductive health through their GP/family doctor, which makes current PrEP services inaccessible. • CAB-LA can address equity and barriers to access by challenging the current provision model/technology.

Other issues

14. Are there any other issues that you would like the committee to consider?	We would just like to reiterate how much this technology will benefit women at risk of acquiring HIV. A group which is often over-looked with little to no inclusion in new HIV medication trials. The results from HPTN084 (in women and people assigned female at birth) were ground-breaking.

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission.	• CAB-LA PrEP has the potential to be a game changer for HIV prevention in women and other people (non-GBMSM). • Making CAB-LA PrEP available and easily accessible for those who need it is vital for equity in HIV prevention offerings. • The most underserved individuals and key populations stand to benefit most from commissioning CAB-LA PrEP. • CAB-LA PrEP needs to be offered in settings outside of specialist sexual health services and integrated into other services. However, lack of precedent/existing pathways should not prohibit NICE from recommending this technology.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Cabotegravir injections for preventing HIV-1 in adults and young people [ID6255]

Community Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for community submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	UK-CAB (UK Community Advisory Board)
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The UK Community Advisory Board (UK-CAB) is a network for community HIV treatment advocates across the UK, it has approximately 800 members. Most of the membership are people living with HIV, or are connected to the HIV sector (e.g. work for HIV and sexual health VCSE organisations) to cover both HIV treatment and prevention services. It has three main aims: • To develop and strengthen this network. We use an online forum and at meetings. • To provide training on treatment issues, and sharing resources across the network. • To support community representation when this affects our care. This includes on guideline panels, research studies and national commissioning groups. Reps are elected by our members. UK-CAB projects have been funded by various Trusts and grant providers. Some costs for UK-CAB meetings are covered by support from pharmaceutical companies (see details below), these companies have no influence on the content of our meetings or work, and employees of pharmaceutical companies cannot be members of UK-CAB.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company,**	£16,008 from ViiV Healthcare (Awarded May 2023). This funding enabled UK-CAB to carry out work in line with the aims of the network as stated above, including a full day meeting for our membership to discuss the latest technical advances in HIV medicine, and up-to-date guidance around our treatment and care within NHS HIV services. The content of all our meetings, and the focus of our strategy is solely decided by members who provide input to our Steering Group.

amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of people at risk of sexually acquiring HIV-1 and carers (if applicable) to include in your submission?	Our extensive experience working within the HIV and sexual health sector. Our membership is rooted in the communities and populations most affected by HIV. Capturing feedback and thoughts at our meetings, we have followed this technology as it has progressed through various clinical trials for a considerable time, enabling us to discuss concerns and benefits of the technology with people affected by HIV, and members who work closely with the affected populations (especially sector colleagues working in outreach and health promotion roles directly within communities). We have spoken closely with other organisations including Africa Advocacy Foundation, HIV i-Base, National AIDS Trust, Positively UK, Terrence Higgins Trust and Sophia Forum to ensure we are able to provide feedback from the communities affected by HIV, in all their diversity. We have also highlighted a recent report from UKHSA, Positive Voices 2022. This is the largest survey of people living with HIV in the UK, representing 1 in 20 people living with the virus. The report provides some insights into the lives and impact HIV has on people living with the virus. Whilst it does not look at the experiences of people at risk of HIV, it provides some context of potential issues people will avoid facing due to staying 'HIV free', and also some of the experiences beyond life with the virus that those at risk of HIV may also face (due to living in the same circumstances and communities as their HIV negative peers). This report can be accessed here: https://www.gov.uk/government/publications/hiv-positive-voices-survey/positive-voices-2022-survey-report.

Living with the condition

6. How does being at risk of sexually acquiring HIV-1 affect people?	**Impact of being 'at risk' of HIV** One of the complex issues in responding to this question is that not all groups and populations understand that they may be affected by HIV. The majority of people with HIV are from marginalised or underserved communities within the general population. There is a history of groups and populations who carry the heaviest 'burden' of HIV being stigmatised and blamed for the ongoing HIV epidemic. HIV-negative people may fear these experiences, and being ostracised from their communities as much as they fear the health concerns of HIV itself. Historically, within the sexual networks of gay and bisexual men there was an understandable fear surrounding sex and HIV before the introduction of pill-based PrEP (as well as the knowledge of the benefits of Treatment as Prevention for people living with the virus e.g. 'U=U'). Oral PrEP has enabled people who are happy and able to take a daily pill (or via event-based dosing) to remove much of that fear. The lack of fear helps people enjoy sex and have closer and more intimate relationships overall. Other populations who are affected by HIV often have a more complex relationship in recognising their risk. Whilst there is a history of the sexual networks of gay and bisexual men understanding some level of risk, the same cannot fully be said for other populations. Heterosexual Black African men and women for example can feel as though blame or judgement is being appropriated to them in relation to HIV-risk, rather than the fact that it is understood there are disproportionate numbers of people with undiagnosed HIV in the sexual networks of their population. Experiences of talking about HIV-related risk can feel like prejudice towards a person's ethnic background, heritage, or migration status. The conversations about sexual health can be difficult and complex. Knowledge of HIV and HIV prevention strategies tends to be much lower amongst heterosexual populations of all ethnicities, largely due to ongoing misconceptions that HIV is something that only affects gay men. **The potential benefits of being protected from acquiring HIV, and experiences likely to be shared by people with HIV and their at risk HIV negative peers in their communities (Results from Positive Voices 2022 survey)** We believe some of the results from UKHSA's Positive Voices 2022 are pertinent to this appraisal.

	Improving accessing to PrEP via the new technology could potentially avoid some of the issues and experiences that people who are diagnosed with HIV have to live with, in particular with regards to their mental health and wellbeing: • 48% of people with HIV experienced depression and anxiety (compared to 33% in the general population) • 64% of people with HIV reported having ever been diagnosed with one or more long-term conditions, which they have to manage alongside their HIV diagnosis – this can lead to complications and complex decision making around drug-drug interactions, polypharmacy etc. • 45% of people with HIV felt ashamed of their HIV status • 32% reported low self-esteem due to their HIV status • 1 in 25 reported having been verbally harassed because of their HIV status in the last year Furthermore, the results highlight populations impacted by abuse, and unmet needs around their sexual wellbeing. Injectable (rather than pill-based) PrEP, and improved PrEP access has the potential to enable HIV negative people at risk of HIV to access PrEP safely, and privately without potential abusers being aware. Positive Voices 2022 found that: • 1 in 4 people had experienced physical violence • 1 in 7 reported ever being sexually assaulted • High levels of unmet need regarding relationship advice, and help and advice around their sex lives.

Current treatment of the condition in the NHS

7. What do people at risk of sexually acquired HIV-1 infection or carers (if applicable) think of current treatments and care available on the NHS?	Since the introduction of pill-based PrEP, conversations about sex and the prevention of HIV and sexually transmitted infections (STIs) have generally been easier to have with gay men (and to a degree some bisexual men, although they are often put together as a homogenous group of people in research and public health statistics). Some gay and bisexual men will even refuse to engage in sexual activity with someone who is either not on PrEP, or who isn't living with HIV and taking effective treatment (because once on effective HIV treatment they can't pass it on). With such low uptake of pill-based PrEP in other populations, primarily Black African heterosexual men and women, and other groups affected by HIV, conversations conducted during outreach and health promotion activities are often focused on describing the fact that PrEP even exists. This is often met with surprise at how far we have come in the medical advancements of HIV, but the personal benefits to the individuals engaged are often missed, this is especially true of older adults, who often respond with comments such as "young people must know about this", despite the fact that HIV impacts people of all ages, and unlike STIs like chlamydia, does not disproportionately impact adolescents.
8. Is there an unmet need for people at risk of sexually acquired HIV-1 infection?	Yes. Currently pill-based PrEP is not accessible to everyone. It requires either daily adherence to a medication, which does not suit everyone. Some potential users are concerned about other people seeing or finding their pills. As with contraception, it is likely that offering a range of HIV prevention options, including long-acting methods, will increase the total number of people using effective HIV prevention. We strongly believe this new technology should be approved to ensure everyone at risk of HIV can access an effective prevention method.
9. Where would people prefer to go to receive prophylactic treatment? (hospital / GP surgery /pharmacy / other)	Pill-based PrEP is currently only accessible via sexual health services. The majority of gay and bisexual men who take PrEP access it from these services, and are usually (or become) regular attendees of the services, and engaged in their sexual health and wellbeing. We believe that access to both existing PrEP and to the new technology would be improved if it was available in other settings, in particular in GP surgeries and/or community pharmacies, especially for people who wish to stay protected from HIV but remain discreet in doing so, and fear repercussions or even violence if they were found to be using sexual health clinics in a hospital setting. The associated stigma of attending sexual health services cannot be underestimated, many can feel judged for using them (even by staff), impacting on their ability to access testing and look after their sexual health.

Advantages of the technology

10. What do people at risk of sexually acquired HIV-1 infection or carers (if applicable) think are the advantages of the technology? • How would having a prophylactic treatment available impact the lives of people at risk of sexually acquired HIV-1 (for example, how would it change the activities people do, or how they feel?) • How would the effectiveness of treatment impact this?	The principal benefits of the technology are: • Removing the burden of taking a pill every day (or for an extended period of time), especially important for people who experience conditions such as dysphagia, or who already have a high pill burden of other medications • Adherence to regular clinic visits is more feasible for some people than adherence to daily pill-taking • A discreet means of receiving protection from HIV e.g. not needing to worry about pills being found by other people (partners, family, others in shared accommodation) • Providing public health benefit by providing an additional prophylactic option which is accessible to a wider demographic of people than met by current pill-based options. • More people would benefit from healthy sex lives, regular HIV testing (and therefore STI screening etc.), empowered to have sex without fear. • People in relationships where they know their partner is having additional sexual relationships can remove the added fear of acquiring HIV, as can those in abusive relationships People would need to be reassured of the effectiveness of PrEP. As discussed, this is complex, and many people at risk of HIV do not necessarily understand they are. This new technology has to the potential to open up educational conversations to ensure people at risk of HIV know what choices are available to them.

Disadvantages of the technology

11. What do people at risk of sexually acquired HIV-1 infection or carers (if applicable) think are the disadvantages of the technology?	If the technology was made available, people at risk of HIV would have two different methods of accessing PrEP (i.e. a pill-based regimen [currently two different combinations] or an injectable prophylactic). This choice would alleviate most concerns – e.g. if they're worried about side effects of one method, they can explore using the alternative; if they struggle to swallow pills, the injectable offers a solution; if they have a needle phobia, then the existing pill-based option would still provide them with access to protection against HIV.

Population of people at risk of sexually acquired HIV-1 infection

12. Are there any groups of people at risk of sexually acquired HIV-1 infection who might benefit more or less from the technology than others? If so, please describe them and explain why.	We don't believe any group would benefit less than others if this technology was made available, with an existing pill-based option we believe the vast majority of people who could benefit from PrEP would have an accessible choice if the technology was approved.
	
	Rather than specific population groups, there will be individuals with specific circumstances who might benefit more from an injectable intervention, as opposed to pill-based PrEP. These may include people at risk of sexually acquired HIV and:
	• Experience dysphagia
	• People who do not want pill-based medication to be found on their person/where they live
	  ○ People living in shared accommodation, who might want to keep treatment they are taking private
	  ○ People having sexual relationships outside of a perceived committed relationship, who want to protect themselves and their partner from HIV (and the reverse)
	  ○ Sex workers who want to keep their PrEP use private from clients or people around them who might question why they are at risk of HIV
	  ○ People who experience domestic violence and/or sexual abuse
	  ○ Young people/young adults who still live with their parents or family
	• Who already have a high burden of pill-based treatments (due to older age, living with a number of long-term conditions etc.)

Equality

13. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Many of the points raised in our submission can be applied to anyone at risk of HIV. However, we know some groups are disproportionately impacted by some concerns more than others. For example, women, trans and gender diverse people are more likely to experience abuse and violence from partners.

Other issues

14. Are there any other issues that you would like the committee to consider?	No. We would just like to reiterate our strong opinion that the technology is made available due to the points we have raised in this submission.

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission.	• PrEP is an effective HIV prevention strategy, and cabotegravir is a clinically proven preventative treatment • Currently access to PrEP is not possible for some of the most marginalised people at risk of HIV, those who find themselves living in vulnerable circumstances, and people at risk of HIV who experience conditions such as dysphagia • Improving access to PrEP means more people can be protected from HIV, and so can their sexual partners. There is both a personal and public health benefit to the intervention • We believe the new technology will have an additional benefit of making more people aware of HIV, engaging at risk people in wider conversations about their sexual health and wellbeing • Providing a choice of HIV prevention interventions, including this new technology is the strongest tool we have to protect all people at risk of HIV from acquiring the virus. We strongly hope this new technology will be approved

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Cabotegravir injections for preventing HIV-1 in adults and young people [ID6255]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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- Your response should not be longer than 13 pages.

NICE National Institute for Health and Care Excellence

About you

1. Your name	[redacted]
2. Name of organisation	BASHH -British Association of Sexual Health and HIV
3. Job title or position	
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	British Association of Sexual Health and HIV, is a national specialty body and a registered charity. We are funded entirely by membership fees.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	We receive no funding from ViiV to deliver our organisation, however ViiV do occasionally provide industry sponsorship of educational events, for example this year, ViiV have sponsored an industry stand at the national BASHH conference and this will include them delivering an industry symposium. This meets all the guidance form GMC and ABPI. This sponsorship is approximately £20,000.
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	This intervention prevents acquisition of HIV in those receiving Injectable cabotegravir according the MHRA licence
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Prevent of HIV acquisition whilst on Cabotegravir PrEP
8. In your view, is there an unmet need for people at risk of sexually acquired HIV-1 and healthcare professionals in this condition?	There is an unmet need. Evidence describes LA Cabotegravir PrEP as a superior PrEP intervention compared to standard oral PrEP. In addition, there are specific groups who have health conditions that contraindicate use of standard PrEP or who unable to adhere to oral therapies. There have been significant unmet needs described in groups at risk of HIV acquisition. Black women and some Heterosexual identifying GBMSM had additional barriers to taking oral prep including unintended disclosure. Ethnic minority GBMSM also experience unmet need. LA Cabotegravir PrEP offers the opportunity to access HIV Prevention for people who cannot take oral PrEP and for whom tablets at home would be unsafe or lead to disclosure.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Pharmacological HIV PrEP currently is offered as oral daily or event based treatment, standard therapy tenofovir disoproxil and emtricitabine in a single table, or in specific clinical scenarios, alternative oral PreP tenofovir Alafenamide/emtricitabine single tablet formulation.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	BASHH guidelines from 2018 currently guide practice. A full review of current evidence is complete and an updated BASHH guideline is due to be released in summer 2024. https://www.bashh.org/resources/5/hiv_preexposure_prophylaxis_2018
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	In England, in keeping with BASHH/BHIVA guideline and NICE practice, all PrEP is delivered in specialist (Level 3) sexual health services. Anyone attending sexual health clinics will be assessed for eligibility for PrEP and begin the PrEP care pathway via their local service. This is current practice across all our devolved nations in the UK.
9c. What impact would the technology have on the current pathway of care?	There will be additional costs to deliver this care. It will continue to be delivered via specialist sexual health services across the UK. To access this intervention, people will still need to access sexual health services and will require GUM Physicians within these services to manage the pathway.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	LA Cabotegravir will be used in populations already identified as have PrEP need who have identified challenges to engage with standard PrEP. People with new PrEP need will also be considered for PrEP and if required receive injectable PrEP. Injectable PrEP will increase access to HIV prevention for groups currently unable to access or use standard methods. Additional monitoring and management will be required for injectable PrEP and will be delivered in keeping with BASHH clinical guidance. Additional HIV antibody/antigen screening and HIV RNA viral load testing will be used.
10a. How does healthcare resource use differ between the technology and current care?	Cabotegravir is a new PrEP therapy, the drug is licenced for PrEP use (licence held by ViiV healthcare). Direct drug costs will be described by other submissions. NHSE have developed a comprehensive costing model for delivery costs in services. People using injectable PrEP will currently need to access this from specialist sexual health services and require regular review by

	experienced nursing and medical staff. The pathway described will include initiation, follow up and review according to patient needs. Standard oral prep is currently managed by sexual health services but can be delivered online or remotely, and face-to-face by a range of staff once stable on PrEP. Screening tests can be delivered remotely with a requirement to be reviewed in face-to-face services at least once a year for the least complex patients. The recurrence of review increases if complications are identified and where additional renal monitoring is required.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Only specialist sexual health services
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No new equipment is required. The additional costs will be in staff time and additional HIV Ab/Ag and HIV RNA testing. Additional clinical time for initiation appointments will be necessary. There will be some training required for initial delivery for nursing staff regarding the injection specifics. This is likely to be short lived and limited.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	There will be significant benefit to new and current PrEP users. There will be a new cohort of PrEP users who cannot currently use oral therapies. Some current PrEP users may benefit from injectable therapy due to improved adherence to Prep.
11a. Do you expect the technology to increase length of life more than current care?	The technology aims to reduce HIV acquisition in the UK. It has been demonstrated that Injectable Cabotegravir PrEP is superior to oral standard PrEP in reducing new HIV transmissions. Cabotegravir PrEP will be a key tool in meeting the HIV action plan goal of no new HIV infections in England by 2030 (https://www.gov.uk/government/publications/towards-zero-the-hiv-action-plan-for-england-2022-to-2025)
11b. Do you expect the technology to increase health-related quality of life more than current care?	There is a significant role for injectable PrEP. Groups at risk of HIV infection acquisition in the UK may have a number of obstacles to standard and oral PrEP. This includes people in relationships where they are unable to assert the use of condoms, relationships where HIV status is a cause of potential of partner violence, people who cannot tolerate oral treatments, have contraindications to the use of standard oral Prep or alternative oral PrEP therapies. In these groups, person centred ownership of HIV prevention will significantly reduce risk of acquiring HIV and improve mental health for those currently unable to manage their own prevention opportunities.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Injectable PrEP will be more effective in people where injectable LA therapy is more tolerable than oral therapies, in particular women and trans men, women of black African origin and people with direct side effects of oral standard PrEP. This may include renal dysfunction, deteriorating bone health, early age at commencing PrEP (where bone health is more susceptible to tenofovir disoproxil reducing bone mass density), people for whom adherence to oral therapies are a significant challenge for a variety of identifiable reasons and those unable to disclose the use of PrEP to intimate partners. Injectable therapy must be delivered in a face-to-face setting and within a window period of no more than seven days around the due date of injection delivery. Injection must be delivered every 2 months. If attendance to specialist services are challenging, injectable PrEP may not be effective and alternatives must be recommended. This logistical requirement must be discussed with users prior to commencement of injectable PrEP.

The use of the technology

13. Will the technology be easier or more difficult to use for people at risk of sexually acquired HIV-1 or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting acceptability to people at risk of sexually acquired HIV-1 or ease of use or additional tests or monitoring needed.)	For PrEP users- they must attend face-to face services every 2 months to receive this therapy and have HIV RNA testing at each attendance. This is results in 6 attendances compared to a minimum of one two attendance for standard oral PrEP. There will be 6 extra blood tests for HIV RNA and 4 additional HIV Ab/Ag testing compared to standard PrEP. Injectable PrEP users will not require regular renal monitoring that is required with standard oral PrEP. The injections can cause discomfort and can result in injection site reactions. Less than 4% of these reactions are considered grade 3/4 or result in discontinuation. Acceptability will be driven by PrEP users current needs and challenges in accepting standard PrEP. Injectable PrEP will be more acceptable to some users. Studies have identified high rates of acceptability but none of these have been conducted in the UK. It is not envisaged LA Cabotegravir PrEP will be more acceptable that standard PrEP for most current users. For services, the initiation process is more complex than for standard PrEP and, for most services and senior nurse and consultant will be required for initiation. For continuation band 6 nurses will be required to deliver the injections and a medical prescriber will be required to prescribe ongoing care in the vast majority or services. GUM physicians will be required to review the results of screening tests and

	manage any equivocal or abnormal HIV RNA tests. This will be a higher cost delivery to services than standard oral PrEP. Liver function testing will also be required at baseline.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Eligibility for injectable therapy will be based on HIV negative testing, ongoing risk of exposure to HIV infection, absence of contraindications to cabotegravir injectable therapy and acceptability of delivery mechanism to patient. All those commencing PrEP injectable therapy will be advised of the requirement for in service delivery, some users may decide to use oral Cabotegravir prior commencing injectable therapy to test tolerability. Stopping injectable therapy will be planned and users will be required to be followed up for a year after stopping PrEP. If users stop Injectable PrEP and have ongoing risk of exposure to HIV they will need to switch to alternative PrEP if clinically appropriate. Users will need to repeat HIV Ab/Ag testing for 12 months after stopping injectable PrEP
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the	Current unmet need for PrEP is identified in heterosexual women and some gay and bisexual men, in particular ethnic minority groups. In these groups, injectable PrEP could have a significant impact, reducing the rate of acquisition of HIV in these groups.

way that current need is met?	PrEP need may not be met for a number of reasons (1). Cabotegravir Injectable PrEP may not address all unmet need in all those with PrEP need. Cabotegravir PrEp is superior for prevention in women(2). *(1) Coukan F, Sullivan A, Mitchell H, et al Impact of national commissioning of pre-exposure prophylaxis (PrEP) on equity of access in England: a PrEP-to-need ratio investigation.Sexually Transmitted Infections 2024;**100:**166-172.* *(2) doi.org/10.1016/S0140-6736(22)00538-4*
16a. Is the technology a 'step-change' in the management of the condition?	Long-acting PrEP to prevent HIV is likely to bring a huge change in how PrEP is taken and delivered, without the need for daily or regular tablets. Lenacapavir subcutaneous injectable PrEP, a twice yearly injectable, may also be available in the next two years. Though real-world data on the demand and impact of injectables for PrEP is limited, it is likely many will still choose daily or event based oral PrEP.
16b. Does the use of the technology address any particular unmet need of the population of people living with HIV-?	A TA for Cabotegravir , in conjunction with injectable Rilpivirine, for treatment of people living with HIV is already approved. This has no impact on that approval.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the quality of life of people at risk of sexually acquired HIV-1?	Side effects include Local injection site reactions- up to 80% of people will experience local injection site reactions of any severity. This may result in increased face-to-face appointments to review and manage these, the

	numbers expected to cease treatment due to injection site reactions represent less than 5% of those included in HPTN 083 and HPTN 084. Abnormalities in liver Function tests were identified in people taking cabotegravir PrEP though not more frequently than the placebo groups. Baseline LFTs and exclusion of viral and other cause hepatitis should be performed. Low severity (Grade 1 and 2), frequent side effects may impact on tolerability. Discontinuation of injectable PrEP in HPTN 083 and 084, due to side effects was 3.8%. However, low level side effects in real world cohorts may impact on clinic demand, tolerability and discontinuation.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Both HPTN 083 and 084 were conducted outside of the UK setting. HPTN 083 participants were GBMSM in united states setting and HPTN 084 participants were black women enrolled in a number of sub-Sharan African countries. There are clear differences in these populations however some of the obstacles to standard care are generalisable. HPTN 084 identifies people with poor access to healthcare settings and lack of ownership of HIV prevention interventions. This relates well to women of African descent or origin living in the UK. The clinical practice of these trials is similar to those that will be implemented in the UK.

18a. If not, how could the results be extrapolated to the UK setting?	See above
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Overall reduction in HIV acquisition. In women, significant reductions in new HIV diagnoses compared with standard care, reduced new HIV diagnoses in GBMSM with adherence issues.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Rates of new HIV diagnoses are the target outcome, these are significantly improved in the Injectable Cabotegravir arm of both trials. Long term tolerability and adherence to injectables are not describes past 153 weeks in GBMSM (HPTN 083) and 48 weeks in Cis Gender Women(HPTN 084)
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not yet identified
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	Real world data are limited.

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Inequity of access to PrEP in the UK is identified and is significant increased for Cis gender women, especially black women, older age and people living outside London. It is imperative that this policy should be implemented in a way that enables access to injectable PrEP across all regions in England with a focus on older people and black women. There are system barriers that may be overcome with focussed use of this technology.
21b. Consider whether these issues are different from issues with current care and why.	The obstacle to care are complex, it is clear that method of delivery is important for some groups and may overcome barriers to PrEP access.

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• Injectable PrEP presents an opportunity to further reduce new HIV acquisitions and should be available to groups who can benefit from this intervention. • Additional monitoring and care may be needed in the first 12-24 months of this implementation, further clinical evidence based on real world data may amend these clinical practices. • Specialist sexual health services and GUM physicians must be part of this implementation to ensure safety for patients • Implementation of Injectable cabotegravir will be more costly initially than standard of care, this must be balanced against individual and system benefits achieved by reducing new HIV acquisitions. • Those eligible and in need of alternative PrEP are often groups who already experience obstacles to care, socioeconomic challenges and structural disadvantage. NICE should seek to contribute to overcome these barriers by enabling these groups to access the best interventions to prevent HIV including injectable PrEP.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Cabotegravir injections for preventing HIV-1 in adults and young people [ID6255]

Professional organisation submission

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- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	British HIV Association
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	BHIVA is the leading UK association representing professionals in HIV care. Since 1995, the association has been committed to providing excellent care for people living with and affected by HIV. BHIVA is funded from a number of different sources: 1) membership subscriptions, 2) pharmaceutical companies, 3) revenue from the journal, "HIV medicine"
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	Yes: Unrestricted funding for charitable activities. 1) ViiV Healthcare – manufacturer of Cabotegravir a. Major sponsorship of BHIVA (annual fee): £37,000 b. Conference sponsorship and company representative registration fees: £80,062.50 c. Registration fees for healthcare professionals to attend conference 2023: £10,710 2) Gilead Sciences – manufacturer of Descovy (Tenofovir alafenamide/ emtricitabine) a. Gilead's Research Scholars Program in HIV: Building the Future Together (fee for email): £500 b. Registration fees for healthcare professionals to attend conference 2023: £20,000 c. Major sponsorship of BHIVA (annual fee): £37,000 d. Conference sponsorship and company representative registration fees: £95,295.84

5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The prevention of the acquisition of HIV.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	This is not a technology that produces a treatment response *per se*. Current oral formulations of PrEP can reduce the incidence of HIV acquisition in populations at risk by greater than 90% in comparison to placebo. As placebo-controlled trials in this area are no longer ethical, statistical non-inferiority or superiority to comparator agents used as PrEP in the relevant population would be clinically significant.
8. In your view, is there an unmet need for people at risk of sexually acquired HIV-1 and healthcare professionals in this condition?	Yes.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Oral formulations of PrEP are available as generic tenofovir-df/emtricitabine (TDF/FTC) 245/200mg and proprietary tenofovir-af/emtricitabine (TAF/FTC) 25/200mg. Oral TDF/FTC has been widely implemented through specialist sexual health clinics, although there are reported problems in access and calls to broaden provision of PrEP outside specialist clinics. The majority of uptake has been seen in gay, bisexual and other men who have sex with men (GBMSM). Oral TAF/FTC is available in specific circumstances, e.g. renal dysfunction, subject to MDT approval. There are reported difficulties in implementation across England.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	The BHIVA/BASHH guidelines https://www.bashhguidelines.org/media/1189/prep-2018.pdf
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care within specialist sexual health clinics is well defined.
9c. What impact would the technology have on the current pathway of care?	This technology would likely require some differences from the current pathway. Initiation and follow-up would be undertaken in specialist services, with some assessment for benefit and suitability of users of the technology. Recommended initiation would be with oral medication initially, followed by a visit for the first injection. There would then be a higher frequency of visits – every 2 months vs every 3-6 months. There would likely be less monitoring for toxicity. Testing for sexually transmitted infections would occur at the same frequency. There would likely need to be particular arrangements for follow-up of missed visits, owing to the long PK tail of cabotegravir.
10. Will the technology be used (or is it already used) in the same way as current	It is likely that this technology will serve the same purpose but may be offered for particular groups who are more vulnerable and less able to adhere to daily oral medication, e.g. young people, marginalised people.

care in NHS clinical practice?	
10a. How does healthcare resource use differ between the technology and current care?	See above re differences with current pathway. A trained clinician would be required to administer the injection in a clinical setting every 8 weeks. There may need to be some flexibility around the visit, so that injections can be administered within a "window". Additional time may be required to administer the injection. There will likely need to be additional resource for follow-up and recall of non-attendance for scheduled visits. Discontinuation of injectable PrEP would require additional monitoring, owing to the long PK tail.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist sexual health clinics.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Investment in training of clinicians, although IM injection is a common technique. Possible investment in HIV testing technology – see below.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	In select groups it is indeed likely to provide meaningful benefits. The HPTN083 study demonstrated superiority of this technology over oral TDF/FTC in GBMSM and transgender women. Within this study - as in other studies of PrEP - adherence is a key determinant of success. There is evidence that more marginalised groups (specifically African American GBMSM) benefited the most from the injectable formulation. The HPTN084 study demonstrated notably superior efficacy in women, in comparison to oral PrEP. Previous studies of (oral) PrEP in women have generally produced more mixed results with respect to efficacy in comparison to studies in GBMSM. The benefits of this technology then lie in the advantages with respect to adherence, in particular those for whom adherence to daily oral medication is challenging owing to their vulnerabilities or other life difficulties. This would include vulnerable young people, people with substance use problems, people from marginalised communities. A further smaller group that would derive benefits are those with an identified need for PrEP, but who have advanced kidney dysfunction, meaning that TAF/FTC is unsafe.

11a. Do you expect the technology to increase length of life more than current care?	While HIV is now a long-term condition with excellent treatment and prognosis, people may not access testing and late diagnosis is still a problem in the UK and a chief determinant of prognosis. Therefore, preventing HIV transmission at a population level and for the individual has a number of benefits including increasing length of life.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes. Prevention of HIV will of course mean prevention of a long-term, stigmatising condition. Oral PrEP-users report that it can reduce HIV-related anxiety and therefore improves their enjoyment of sex. Engagement in PrEP services offers opportunities for delivery of sexual health promotion as well as delivery of other interventions such as referral to drug and alcohol services, smoking cessation etc…
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	There are particular populations at higher risk for HIV in the UK, as can be assessed in healthcare settings.

The use of the technology

13. Will the technology be easier or more difficult to use for people at risk of sexually acquired HIV-1 or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting acceptability to people at risk of sexually acquired HIV-1 or ease of	There are some difficulties and practical implications as indicated above in terms of the model of care delivery, capacity within sexual health services, and follow-up after discontinuation. Evidence suggests that this method of PrEP delivery is highly acceptable to people with PrEP need and removes the need for daily adherence. There is a question over the best testing technology for ascertaining HIV acquisition in people using cabotegravir. The number of HIV acquisitions in clinical trials have been small, but a proportion of those found to have acquired HIV have done so, while apparently attending for regular injections, and in this context antigen/antibody detection has been delayed. In the same cases there have also been prolonged periods where the HIV viral load is undetectable on quantitative RNA testing.

use or additional tests or monitoring needed.)	The FDA have recommended confirmation of negative antigen/antibody testing with RNA testing. A qualitative RNA test is available, though not in wide clinical use. The benefits of this stringent approach compared to the cost in ordinary clinical use is uncertain, with cost likely to be prohibitive.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	N/A
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. This is the first long-acting PrEP formulation. There is an analogy to be made with long-acting contraception, e.g. Depo-provera vs oral contraceptive pills. This technology provides additional choice for those with PrEP need and is an enhancement of the current offer that may have particular benefits for more disadvantaged individuals, as discussed above.
16a. Is the technology a 'step-change' in the	Yes

management of the condition?	
16b. Does the use of the technology address any particular unmet need of the population of people living with HIV-?	No
17. How do any side effects or adverse effects of the technology affect the management of the condition and the quality of life of people at risk of sexually acquired HIV-1?	The principal side effect is pain at the site of injection. Injection site reactions are possible. These are generally mild, short-lived and manageable.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	HIV incidence, adverse events, adherence. Pharmacokinetics Drug resistance in those who acquire HIV.

	These were measured.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	There are demonstration projects that have been conducted in e.g. Sub-saharan Africa and a large implementation study is about to start in Brazil. There have been no surprises so far with many participants expressing preference for the injection over oral formulation.

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	People with certain protected characteristics are among the most likely to benefit from this technology.
21b. Consider whether these issues are different from issues with current care and why.	

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• Long acting cabotegravir as PrEP is a striking innovation in biomedical prevention of HIV. • Cabotegravir as PrEP has demonstrated statistical superiority over oral TDF/FTC PrEP, although the latter also has high efficacy. • Certain sub-populations who face challenges and other vulnerabilities are likely to benefit the most from this technology. • There are resource considerations for sexual health services, and some uncertainties around the best way to implement the technology in routine clinical care. •

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Single Technology Appraisal

Cabotegravir injections for preventing HIV-1 in adults and young people [ID6255]

NHS organisation submission (ICBs and NHS England)

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 10 pages.

About you

1. Your name	[redacted], [redacted], [redacted], [redacted], [redacted]
2. Name of organisation	English HIV and Sexual Health Commissioners Group (EHSHCG) on behalf of ADPH
3. Job title or position	Executive members of EHSHCG / Local Authority Sexual Health Commissioners

4. Are you (please select Yes or No):	Commissioning services for an ICB or NHS England in general? No Commissioning services for an ICB or NHS England for the condition for which NICE is considering this technology? No Responsible for quality of service delivery in an ICB (for example, medical director, public health director, director of nursing)? No An expert in treating the condition for which NICE is considering this technology? No An expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? No Other (please specify): Commissioning sexual health services for a Local Authority
5a. Brief description of the organisation (including who funds it).	The English HIV and Sexual Health Commissioners Group (EHSHCG) is a peer network run by commissioners for commissioners for improved population and patient level outcomes in sexual health and HIV in England. The EHSHCG is supported by funding from the Local Authorities and secretarial support from the Association of Directors of Public Health (ADPH).
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

Current treatment of the condition in the NHS

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	HIV testing: increasing uptake among people who may have undiagnosed HIV (2016) NICE guideline 60. BHIVA/BASHH guidelines on the use of HIV pre-exposure prophylaxis (PrEP) 2018 Commissioning guidance and national documents that are used for the commissioning of sexual health services, in which PrEP is routinely delivered include: • Integrated Sexual Health Services Specification • Making It Work: a guide to whole systems commissioning of sexual and reproductive health and HIV • Routine commissioning of HIV preexposure prophylaxis (PrEP) in England. Monitoring and evaluation framework. • Towards Zero: The HIV action plan for England 2022-2025 • HIV Pre-Exposure Prophylaxis (PrEP) suggested service specification
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There is currently a defined pathway of care for PrEP as it currently is required to be delivered within specialist sexual health services. However, there is a difference of opinion between professionals in different organisations which has the potential to result in increased variation in approaches over time (e.g. provision in different settings). Not all commissioned sexual health services are delivered by NHS providers. There are some current issues with provision of TAF/Descovy PrEP from non-NHS sexual health providers. The guidance from NHS-E is limiting: The current process is to prescribe via Blueteq forms (not available to those in non-acute setting) and via an HIV MDT (usually run by a different organisation). If cabotegravir injections are approved for use in sexual health services, there would need to be a clear process that enables all providers of sexual health care to prescribe and administer equitably.

8. What impact would the technology have on the current pathway of care?	It is the responsibility of NHS England to meet the costs of PrEP medication, including injectables if approved, which do cost more that the oral tablets (although potentially more cost effective) Injectable PrEP may be more beneficial for people from some 'higher risk' groups for whom adherence to a daily medication may be difficult (e.g. those with complex needs such as street sex workers or people who inject drugs). The provision of injectable PrEP therefore offers a new opportunity to improve uptake of PrEP in under-represented groups. A different pathway could be considered in this instance to optimise uptake and adherence. There are capacity implications of injectable PrEP as 6 annual clinic attendances would be required compared to 4 clinic attendances for oral PrEP, plus additional HIV testing. Impact of this on service capacity should be considered particularly as sexual health services are experiencing funding and capacity issues (https://www.local.gov.uk/publications/breaking-point-securing-future-sexual-health-services). There may be some added benefits of seeing people in clinic more regularly who may be more vulnerable to STIs and reinfection and this additional contact could prove beneficial to the service user and the wider community in terms of potential onward re-infections if not tested regularly.

The use of the technology

9. To what extent and in which population(s) is the technology being used in your local health economy?	PrEP is now routinely commissioned across all specialist sexual health services. According to the Public Health Outcomes Framework, of all those attending sexual health services 9.7% are at a substantial HIV risk, and therefore could benefit from receiving PrEP. Of those who are identified as having a PrEP need, 71% of them are initiated on to PrEP or continue PrEP. On a population level this is largely benefiting Gay and Bisexual Men who have Sex with Men (GBMSM) who have good knowledge of PrEP. There is less uptake from other populations who are at higher risk of acquiring HIV and would benefit including people from Black African communities, people from migrant communities, sex workers, trans women, and injecting drug users. Factors for this include stigma of HIV and STIs and unwillingness to access sexual health services, and difficulty adhering to a daily medication.

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The assessment of need within sexual health services is likely to remain the same. However, administration will vary due to the different clinical requirements of administering oral medication and injectable medication.
10a. How does healthcare resource use differ between the technology and current care?	The assessment process will remain the same, however there will be additional resource required in terms of additional capacity to meet the additional appointments and undertake additional testing. There will also be some additional resource considerations in terms of storage and disposal of injections and clinical equipment.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Ensure that both prescribing and administering responsibilities are clear and funded. Delivery of PrEP in Primary Care (pharmacy, GPs) would be beneficial especially for those who may be less likely to access via sexual health services (due to stigma, access)Specialist sexual health services to include outreach and partnership working with drug and alcohol services in primary care settings could be considered.

Table 3. Estimated total costs of PrEP per person

Estimated Annual PrEP Costs		**Year 2+**	**Notes**
Acquisition cost of TDF-FTC PrEP medication	£816.72	£816.72	NHS Indicative Price
PrEP Initiation Attendance	£77.20*	-	Assumes 1 PrEP initiation attendance
PrEP Continue Attendance	£142.02*	£189.36*	Assumes 3 PrEP continuation visits

Total cost per person - [redacted], excluding STI/HIV testing – so a little more, £1,600 area

Estimated annual cabotegravir costs		**Notes year 2+**	
Acquisition cost of cabotegravir medication	£9,124.28	£7,182.12	Based on 7 injections and oral lead in during Year 1 and 6 injections during Year 2
Administration cost of injection	£82.95	£71.10	Assume 7 injections in Year 1 and 6 injections in Year 2
PrEP initiation attendance	£77.20	-	Assumes 1 PrEP initiation attendance

	PrEP continuation attendance	£284.04	£284.05	Assumes 6 PrEP continuation visits in Year 1 and 6 in Year 2
	HIV Test	£352.11	£352.11	Assumes 6 HIV tests per year
	Total cost per person - [redacted] per person			
	Source: advance product notice on injectable PrEP			

10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Additional investment will be required within the system wherever the technology is being provided to meet additional costs of drugs, prescribing and administration. This may be pharmacy, primary care or sexual health services. Investment in a central reporting system/database may be required.
10d. If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	PrEP is currently only formally delivered within specialist sexual health services and additional testing is STI/HIV /kidney function tests are required as part of this assessment/ongoing treatment. No other settings to our knowledge are currently providing PrEP. Potentially oral PrEP is still available online privately for those who choose to pay for it.
11. What is the outcome of any evaluations or audits of the use of the technology?	The safety, tolerability and efficacy of cabotegravir was evaluated in two randomised, double-blind, double-dummy, trials - HPTN 083 and HPTN 084.17,18 The trials demonstrated superiority of cabotegravir compared to

	daily oral TDF-FTC, for PrEP in HIV-uninfected cis-gendered GBSMSM, transgender women, and cis-gendered women.17,18 HPTN 083 enrolled 4,566 participants (cis-gendered GBMSM and transgender women) in the United States and Latin America, and HPTN 084 enrolled 3,224 cis-gendered women 18 to 45 years old in sub-Saharan Africa.17,18 Efficacy • Cabotegravir provides a statistically significant benefit in reducing the risk of HIV acquisition compared with daily oral PrEP TDF-FTC, across diverse populations at-risk of HIV acquisition.17,18 • Cabotegravir demonstrated a 66% reduction (HR 0.34; 95% CI 0.18, 0.62; p-value<0.0001]) in cis-gendered GBMSM and transgender women and an 88% reduction (HR 0.12; 95% CI 0.05, 0.31; p-value<0.0001), in cis-gendered women at the risk of acquiring HIV compared to daily oral TDF-FTC.17,18 Due to the mode and frequency of administration, cabotegravir will require several changes to the current patient pathway: • Mode of Administration – compared to the oral PrEP options, which are self-administered, cabotegravir LA is a injection administered by an HCP, with nurses likely to be the main provider of care19 (Figure 2). • Frequency of Administration - administration for cabotegravir LA will be every 2 months after initiation. • HIV testing (and potentially different type of test) - prior to receiving PrEP, individuals must have a recently documented negative HIV test. For oral PrEP, testing is recommended to take place every 3 months. Cabotegravir may require testing every 2 months. HPTN 083 - Efficacy and safety of long-acting cabotegravir compared with daily oral tenofovir disoproxil fumarate plus emtricitabine to prevent HIV infection in cisgender men and transgender women who have sex with men 1 year after study unblinding: a secondary analysis of the phase 2b and 3 HPTN 083 randomised controlled trial - The Lancet HIV HPTN 084 – Cabotegravir for the prevention of HIV-1 in women: results from HPTN 084, a phase 3, randomised clinical trial

Equality

12a. Are there any potential equality issues that should be taken into account when considering this treatment?	Stigma of HIV – certain groups are disproportionately impacted and promotion of PrEP needs to be tailored to the needs of populations and settings. That PrEP is currently only available via specialist sexual health services is an equality issue for some groups who are unwilling to access sexual health services for cultural reasons and stigma of HIV. Provision via primary care settings offer an opportunity to overcome this barrier. Where there are contraindications due to health issues (e.g. kidney function), it is vital to ensure access to all PrEP options. There is limited info in the equality impact re if/who the trial has benefited and a lack of info re certain high risk groups.
12b. Consider whether these issues are different from issues with current care and why.	Possible cultural perception of injections/vaccines and whether suitable in some faiths (ingredients). Vaccine hesitancy and distrust of medical professionals/government which may impact decision making.

Thank you for your time.

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Single Technology Appraisal

Cabotegravir injections for preventing HIV-1 in adults and young people [ID6255]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

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About you

NICE National Institute for Health and Care Excellence

1. Your name	[redacted]
2. Name of organisation	HIV Pharmacy Association
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):

5a. Brief description of the organisation (including who funds it).	The HIV Pharmacy Association (HIVPA) was established in the UK in 1991 with the aim of promoting excellence in the pharmaceutical care of people living with HIV. HIVPA delivers high quality education, support and networking opportunities to pharmacists and pharmacy technicians, facilitating professional and personal development for the benefit of people living with HIV. HIVPA is the primary source of professional expertise in HIV pharmacy; working with the British HIV Association (BHIVA), the RPS, NHS and third sector organisations. HIVPA's involvement at a national level includes:- • Representation on the NHS England HIV Clinical Reference Group and HIV Drugs Sub-group • Representation on relevant British HIV Association (BHIVA) working groups, e.g. national treatment guidelines and national standards of care • Delivering education and training to a wide range of pharmacy colleagues and other healthcare professional colleagues at other national conferences such as the Clinical Pharmacy Congress • Peer review of patient information produced by national HIV charities HIVPA is funded by membership fees and unrestricted educational grants for pharmaceutical industry sponsors.

5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	Yes. £13,000 unrestricted educational grant from ViiV healthcare, utilised to partially fund the annual conferences and face to face educational events.
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To prevent transmission of HIV to those at risk of acquiring it.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduction in HIV acquisition risk equal or greater than that observed with tenofovir/emtricitabine based oral pre-exposure prophylaxis.
8. In your view, is there an unmet need for people at risk of sexually acquired HIV-1 and healthcare professionals in this condition?	Yes. Not all people at risk of acquiring HIV are able to take oral medication, including those who may where these is a risk of compromised confidentiality, those experience domestic abuse or modern slavery, or those who may struggle with adherence. Whilst tenofovir alafenamide based PrEP is available for those with renal impairment, it is only licensed for those with an estimated glomerular function of 30ml/minute or greater, so cabotegravir presents a licensed option for those with renal function below this threshold. A very small number of individuals may have a reported allergy to either tenofovir or emtricitabine and cabotegravir could be used A very small number of individuals or may have undergone abdominal surgery or have a condition affecting absorption of oral medicines from the stomach. The parenteral administration of cabotegravir would be an alternative option.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	First line prevention consists of emtricitabine/tenofovir disoproxil based oral tablets and second line prevention consists of emtricitabine/tenofovir alafenamide for those who have a contraindication to first line prevention.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	BHIVA/BASHH guidelines on the use of HIV pre-exposure prophylaxis (PrEP) 2018. Update pending.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	PrEP is currently supplied for service users via Level 3 Sexual Health clinics. The current pathway of care stipulates that the service delivery cost for PrEP is the commissioning responsibility of the Local Authority and NHS England is responsible for the funding of PrEP drugs. Emtricitabine/tenofovir disoproxil over-labelled stock is obtained by level 3 clinics on a free-of-charge basis via wholesaler, and NHSE reimburse the wholesaler directly. Sexual health clinics are not directly reimbursed by NHSE. The commissioning policy 'Reimbursement for the use of generic and second line drugs for Pre Exposure Prophylaxis (PrEP) for the prevention of HIV (2112)' was updated in April 2023 to include a second line PrEP treatment option of tenofovir alafenamide (TAF) and emtricitabine (FTC) for people who are intolerant of, or have contraindications to, the first line treatment tenofovir disoproxil (TD) and FTC. The current pathway in accordance with policy is that when an individual is identified as needing TAF PrEP in a Level 3 Sexual Health clinic, they are discussed in regional/local PrEP multidisciplinary meeting set up and presided over by level 3 GUM Physicians with (Certificate of Completion of Specialty Training) CCST in Genitourinary Medicine and the multidisciplinary team. The second line PrEP is approved in accordance with clinical guidance where appropriate. Due to contractual arrangement there is currently inequity of access to second line PrEP treatment because patients cannot access it in the same way as first line from the same sexual health provider. As this is a high cost drug it cannot be pre-paid for by NHS England and sexual health clinics without on-site pharmacists, an HIV service or that are not part of an acute trust cannot procure the drug. Not all Level 3 sexual health clinics currently have links with commissioned HIV providers for the purpose of forming

	MDTs and accessing TAF PrEP through existing procurement contracts and arrangements for reimbursement of drug costs. The same inequity will apply for injectable cabotegravir. In Wales, the service delivery cost and funding for PrEP drugs is the commissioning responsibility of the Local Health Board. There is no reimbursement from Welsh Government so expenditure lies with each LHB. Descovy has not been approved for use for PrEP in Wales, and can only be obtained via a local Individual Patient Funding Request (IPFR). Therefore funding lies with each LHB.
9c. What impact would the technology have on the current pathway of care?	If the drug is approved for anyone who meets the marketing authorisation requirements, a significant amount of resource will need to be invested into sexual health services in order to make this deliverable.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	No, there is currently no injectable formulation of PrEP and the prescribing and administration of this will require design of new pathways.
10a. How does healthcare resource use differ between the technology and current care?	Need for more frequent and longer appointments for administration of drug and also viral load testing requiring a venous sample at each appointment, which is currently not a requirement for available PrEP, the cost of viral testing will significantly increase the cost of care provided.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	As a third line option for PrEP, for those who cannot take TFD/FTC or TAF/FTC based PrEP.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Training, although there is some experience of using this drug in the context of HIV treatment, not all sexual health clinics are associated with an HIV service, so further training will be required to roll this out nationally, Cabotegravir injection can't be self-administered, and requires skilled administration by trained staff to ensure correct positioning, needle choice and to minimise bruising.
11. Do you expect the technology to provide clinically meaningful	In a small number of people, yes.

benefits compared with current care?	
11a. Do you expect the technology to increase length of life more than current care?	In a small number of people, yes.
11b. Do you expect the technology to increase health-related quality of life more than current care?	In a small number of people, yes.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	More effective in those who have suboptimal adherence to oral PrEP or those with contraindications to currently available PrEP.

The use of the technology

13. Will the technology be easier or more difficult to use for people at risk of sexually acquired HIV-1 or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting acceptability to people at risk of sexually	There will be an increased frequency of clinic visits (6 times per year) for drug administration and HIV RNA testing which may be challenging for some service users and will also present a financial burden to some. This will also significantly affect clinic capacity and access to appointments.

acquired HIV-1 or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Viral load testing as above.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes
16a. Is the technology a 'step-change' in the management of the condition?	Yes
16b. Does the use of the technology address any particular unmet need of	n/a

the population of people living with HIV-?	
17. How do any side effects or adverse effects of the technology affect the management of the condition and the quality of life of people at risk of sexually acquired HIV-1?	Minimal side effects have been reported mostly related to injection site reactions. From clinical trial and current experience in treating HIV, individuals very rarely need to stop treatment due to side effects.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	No, these are conducted in the setting of a service that is appropriately reimbursed for activity.
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Incidence of HIV transmission – this was primary end point in the HPTN trial in the intention to treat population Adverse effects/tolerability – particular focus in the ÉCLAIR study (primary end point of safety and tolerability after first and last injection)
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	

18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	As described above regarding access to this drug which will require a contract with NHS England to access which not all sexual health clinics have.
21b. Consider whether these issues are different from issues with current care and why.	

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• Exact place in therapy to be defined • Delivery pathway options to be defined • Skill and expertise required for administration Significant resource required for implementation • •

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About you

1. Your name	[redacted]
2. Name of organisation	NHS England Specialised Commissioning
3. Job title or position	[redacted]

4. Are you (please select Yes or No):	Commissioning services for an ICB or NHS England in general? Yes Commissioning services for an ICB or NHS England for the condition for which NICE is considering this technology? Yes Responsible for quality of service delivery in an ICB (for example, medical director, public health director, director of nursing)? No An expert in treating the condition for which NICE is considering this technology? No An expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? Yes or No Other (please specify):
5a. Brief description of the organisation (including who funds it).	NHS England
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

Current treatment of the condition in the NHS

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	BHIVA/BASHH Guidelines on the use of HIV PrEP https://www.bhiva.org/PrEP-guidelines NHS England Commissioning policy: Reimbursement for the use of generic and second line drugs for pre exposure prophylaxis (PrEP) for the prevention of HIV https://www.england.nhs.uk/publication/reimbursement-for-the-use-of-generic-drugs-for-pre-exposure-prophylaxis-prep-for-the-prevention-of-hiv/
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	PrEP services are provided by Local Authority commissioned Level 3 sexual health services, in line with British HIV Association (BHIVA) and British Association for Sexual Health and HIV (BASHH) PrEP guidelines. https://www.bhiva.org/PrEP-guidelines NHS England funds the medicines. First line PrEP therapy consists of tenofovir disoproxil and emtricitabine (TD/FTC). Second line PrEP therapy consists of tenofovir alafenamide with emtricitabine (TAF/FTC) for individuals who are intolerant of, or have contraindications to, TD/FTC. This is also an oral treatment. There is a population of individuals in whom an alternative, non-oral option is required.

8. What impact would the technology have on the current pathway of care?	Cabotegravir would be an alternative PrEP option. Current PrEP therapies are oral treatments, cabotegravir would be the first parenteral preparation. Cabotegravir is an intramuscular injectable, long-acting form of PrEP, with the first two injections administered four weeks apart, followed thereafter by an injection every eight weeks. Cabotegravir was shown to be safe and highly effective among cisgender women, cisgender men who have sex with men, and transgender women who have sex with men in two randomized controlled trials, HPTN 083 and HPTN 084. These studies found that use of cabotegravir resulted in a 79% relative reduction in HIV risk compared with oral PrEP, where adherence to daily oral medication may have been suboptimal. Long-acting injectable products have also been found to be acceptable and sometimes preferred in studies examining community PrEP preferences. Significant resource would be required to implement this therapy in sexual health clinics. It is estimated that a visit / appointment would take approximately 60 minutes, which without additional staffing resource, will displace other activity e.g. 3-4 sexual health users within a one-hour period. It is likely that an HIV viral load blood test will be required at each visit. For services funded via the integrated tariff structure, there is no tariff to reimburse cabotegravir use, only a tariff for non-complex, oral PrEP provision. For services funded via a block contract, injectable PrEP may exert further financial and administrative pressures on the system. Individuals using cabotegravir PrEP will need to be placed on reliable recall systems in order to prevent loss to follow-up. Due to the fact that cabotegravir remains in the system for up to a year (the tail), should a person cease cabotegravir PrEP, and remain at risk of HIV acquisition, they will require an alternative 'bridging' PrEP solution. Unless linked with an NHS Trust in provision of HIV services, some PrEP providers may have challenges in delivering cabotegravir PrEP and may need to develop pathways to ensure access.

The use of the technology

9. To what extent and in which population(s) is the technology being used in your local health economy?	This technology is currently being used by a small number of providers through compassionate access use schemes directly with the manufacturer.

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	There are currently no injectable PrEP therapies available. Implementation of cabotegravir PrEP will require significant investment in resource as detailed above.
10a. How does healthcare resource use differ between the technology and current care?	Current care: People receiving oral PrEP are reviewed by clinical teams 2-4 times a year, in 20-minute appointments, via a mixture of in-person and virtual care. An HIV antibody/antigen (Ab/Ag) test is carried out every three months (users may opt for online testing twice in a year) and tests to assess renal function are performed annually in uncomplicated individuals. Oral PrEP medicines can be collected from clinic or delivered to a person's home. Cabotegravir PrEP: People receiving cabotegravir PrEP would require review by a senior clinician at every administration visit (clinical nurse specialist, pharmacist, or doctor) and will require 20 minutes observation post drug administration. Tests for HIV viral load will be required at every visit, HIV Ab/Ag testing every 3 months and sexual health screening four times a year. In services reimbursed with a tariff, the cost of sexual health screening and non-complex PrEP provision falls within the current tariff, whilst an HIV viral load would represent a significant additional cost. It is likely the decision to use parenteral cabotegravir will require multi-disciplinary discussion and approval. A prior approval form will be required for the use of parenteral cabotegravir as PrEP. Not all level 3 specialist sexual health services are linked to an acute commissioned HIV provider, and have challenges with putting pathways in place, thus there may be logistical issues around cabotegravir PrEP provision/access. There will also be an oral formulation of cabotegravir available for an oral lead-in phase for individuals who may need to be trialled for tolerability, or those who may need bridging therapy they are unable to attend for an injection within the designated window.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This technology will be used in specialist sexual health clinics commissioned to deliver PrEP services.

10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Services will require dedicated training on the use of cabotegravir PrEP. Teams who are unfamiliar with the intramuscular administration of cabotegravir may need dedicated training on injectable delivery and management of injection site reactions. Injectable cabotegravir does not require refrigeration but services should also have supplies of oral cabotegravir to use as a bridging/induction therapy where required. Providers of cabotegravir PrEP will require access to HIV viral load testing (this is not necessarily the case for all sexual health providers in England). Systems will need reliable recall systems to prevent loss to follow-up. Expanding capacity to avoid displacement of other activity.
10d. If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	<u>Before starting:</u> Documented negative HIV Ag/Ab test result within one week before initial cabotegravir injection No signs/symptoms of acute HIV infection No contraindicated medications or condition <u>At start:</u> Initial dose 600 mg cabotegravir administered as one 3 ml intramuscular injection in the gluteal muscle Second dose four weeks after first dose (month 1 follow-up visit) Every eight weeks thereafter (month 3,5,7, follow-up visits etc) <u>At follow-up visit one month after first injection:</u> HIV Ag/Ab test and HIV viral load <u>At follow-up visits every two months (beginning with the third injection – month 3):</u> HIV Ag/Ab test and HIV viral load <u>At follow-up visits every three months (beginning with the third injection- month 3):</u> sexual health screening

	At follow-up visits when discontinuing cabotegravir injections: Re-educate patients about the “tail” and the risks during declining cabotegravir levels Assess ongoing HIV risk and prevention plans If PrEP is indicated, prescribe daily oral F/TDF or F/TAF beginning within eight weeks after last injection Continue follow-up visits with HIV testing quarterly for 12 months
11. What is the outcome of any evaluations or audits of the use of the technology?	HIV Prevention Trials Network. HPTN 084 Study Demonstrates superiority of CAB LA to oral FTC/TDF for the prevention of HIV. 2020 Landovitz RJ, Donnell D, Clement ME, et al. Cabotegravir for HIV prevention in cisgender men and transgender women. N Engl J Med. 2021;;385(7):595-608 Tolley EE, Zangeneh SZ, Chau G, et al. Acceptability of Long-Acting Injectable Cabotegravir (CAB LA) in HIV-Uninfected Individuals: HPTN 077. AIDS Behav 2020:1-12. Landovitz RJ, Li S, Eron Jr JJ, et al. Tail-phase safety, tolerability, and pharmacokinetics of long-acting injectable cabotegravir in HIV-uninfected adults: a secondary analysis of the HPTN 077 trial. The Lancet HIV. 2020;

Equality

12a. Are there any potential equality issues that should be taken into account when considering this treatment?	Access to cabotegravir PrEP will provide a treatment option for a cohort of people in whom the current PrEP options are unsuitable, therefore this will reduce health inequalities. There are no studies with PrEP TAF/FTC which include women, and so it is important to highlight the large number of women in the studies for whom cabotegravir is a great treatment option. There are currently challenges with accessing the second line PrEP therapy TAF/FTC in certain areas of the country because not all Level 3 Sexual Health providers have / are able to establish links with commissioned HIV services. There is ongoing work to identify potential solutions, with the aim to resolve challenges before cabotegravir PrEP is recommended, if it receives a positive recommendation.
12b. Consider whether these issues are different from issues with current care and why.	As above

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External Assessment Group's report

Title: *Cabotegravir for preventing HIV-1 in adults and young people [ID6255]*

Produced by	*Warwick Evidence*
Authors	Henry Nwankwo, Assistant Professor, Warwick Evidence, University of Warwick Jill Colquitt, Senior Reviewer, Effective Evidence LLP Felix Achana, Honorary Senior Research Fellow, Warwick Evidence, University of Warwick Naila Dracup, Information Specialist, Warwick Evidence, University of Warwick Pranshu Mundada, Research Associate, Warwick Evidence, University of Warwick Priyanka Chaudhuri, Research Associate, Warwick Evidence, University of Warwick Angela Mwape, Research Fellow, Warwick Evidence, University of Warwick. Emma Loveman, Senior Reviewer, Effective Evidence LLP Lena Al-Khudairy, Associate Professor, Warwick Evidence, University of Warwick
Correspondence to	*Lena Al-Khudairy* *Lena.al-khudairy@warwick.ac.uk*
Date completed	*16.04.2024*

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Declared competing interests of the authors

None.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

If an EAG duplicates a table, figure, or reasonable amount of text from the company submission in the EAG report: sources is listed under all table and figures in the report where applicable.

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Contributions of authors

HN: led the cost-effectiveness section.

JC: senior clinical reviewer and led the clinical section.

FA: led the ITC and supported the cost-effectiveness section.

ND: Information Specialist, conducted the searches and referencing.

PM: supported cost-effectiveness section .

PC: supported clinical section.

AM: supported clinical section.

EL: supported the clinical section, write-up and review of this report.

LAK: supported clinical section and led this appraisal.

Please note that: Sections highlighted in blue and underlined are 'confidential' (CON). Figures that are CON have been bordered with blue. Depersonalised Data (DPD) is highlighted in pink."

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1 Executive summary

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to **Error! Reference source not found.** explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 *Overview of the EAG's key issues*

Table 1. Summary of key issues		
ID	**Summary of issue**	**Report sections**
Issue 1	**The population is narrower than the decision problem.**	2.3
Issue 2	**Generalisability of the HPTN population**	3.5.1.1
Issue 3	**Inclusion of studies in the ITC that were conducted in populations different from the population of interest as specified in the scope**	3.4.1
Issue 4	**Inclusion of studies in CS ITC that does not meet the specified population of interest as described in the NICE scope**	3.5
Issue 5	**CS ITC analyses did not account for measurement error in adherence levels in the meta-regression of treatment effect on adherence to CAB-LA.**	3.4.1
Issue 6	**Restricting treatment costs to period of heightened risk (assumed 5-years in the CS base-case) over a life-time risk capping the treatment costs which could favour CAB-LA in cost-effectiveness.**	4.3
Issue 7	**Inappropriateness of the no PrEP as a Comparator in the model**	4.4, 4.5
Issue 8	**Inappropriateness of Baseline risk of HIV acquisition**	4.7.1.1
Issue 9	**Transition to TDF/FTC following discontinuation from cabotegravir**	4.7.1.2
Issue 10	**Adherence to TDF/FTC**	4.7.1.5
Issue 11	**Improved persistence to cabotegravir**	4.7.1.3
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Issue 13	**Starting age of Participants**	4.7.1.4.1
Issue 14	**Duration of assumed aggregate risk period to reflect lifetime risk of sexually acquired HIV acquisition**	4.7.1.4.2

Table 1. Summary of key issues		
ID	**Summary of issue**	**Report sections**
Issue 15	**Cabotegravir injection administrative costs**	4.9.2, 4.9.2.1
Issue 16	**Drug acquisition and administration**	4.9.1, 4.9.1.1

1.2 *Overview of key model outcomes*

Overall, the technology is modelled to affect QALYs by:

- Baseline HIV incidence rate
- Assumption of improved persistence to cabotegravir
- Transition to TDF/FTC following discontinuation from cabotegravir.
- Duration of assumed aggregate risk period
- Adherence to PrEP regimens
- Overall, the technology is modelled to affect costs by:
- Drug acquisition and administration costs
- Cabotegravir administration frequency
- Adverse events costs
- HIV management costs

The modelling assumptions that have the greatest effect on the ICER are:

- Baseline HIV incidence
- Assumed improved persistence to cabotegravir
- Transition to TDF/FTC following discontinuation from cabotegravir.
- Duration of assumed aggregate risk period.
- Frequency of administration of cabotegravir

Increased cabotegravir acquisition costs due to implications of restarting cabotegravir over the lifetime of the cohort.

1.3 *The decision problem: summary of the EAG's key issues*

Issue 17: The population is narrower than the decision problem	
Report section	2.3Table 3
Description of issue and why the EAG has identified it as important	The population of the NICE scope includes people at risk of sexually acquired HIV-1 infection. However, the main evidence submitted by the company for the comparison of CAB-LA with TDF/FTC is limited to adults aged ≥18 years in specific populations, i.e. men who have sex with men/transgender women, or cisgender women <45 years**.** "*PrEP is not appropriate*" is not aligned with the NICE scope or [redacted] Additionally, the clinical evidence submitted by the company comprised of people taking oral PrEP/placebo for oral PrEP, therefore not aligned with those 'for whom oral PrEP is not appropriate'
What alternative approach has the EAG suggested?	None.
What is the expected effect on the cost-effectiveness estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	None.

1.4 *The clinical effectiveness evidence: summary of the EAG's key issues*

Issue 18: Generalisability of the HPTN population	
Report section	3.5.1.1
Description of issue and why the EAG has identified it as important	The clinical evidence (HPTN trials) did not include UK patients. The EAG examined the PrEP Impact Trial in England population in comparison to the HPTN trials. The population in England had a different ethnic distribution, and was older in age. This can impact the generalisability of the clinical evidence to UK settings in relation to risk of HIV acquisition, uptake, and adherence.
What alternative approach has the EAG suggested?	Compare clinical evidence to UK populations and identify issues of uncertainty and how this can affect clinical practice.
What is the expected effect on the cost-effectiveness estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	Compare clinical evidence to UK populations and identify issues of uncertainty and how this can affect clinical practice.

Issue 19: Inclusion of studies in the ITC that were conducted in populations different from the population of interest as specified in the scope	
Report section	3.4.1
Description of issue and why the EAG has identified it as important	The disparity between the intended and actual populations modelled is notable. The decision problem outlined in the CS identifies the target population as individuals at risk of sexually acquired HIV-1 for whom oral PrEP is not appropriate and are therefore underserved by current standard of care. However, this description does not align with NICE's scope, which defines the population as "People at risk of sexually acquired HIV-1 infection." Upon closer examination of the economic model's structure and accompanying Excel workbook, it becomes evident that the modelled population is much broader than intended by the CS. In fact, it appears to better correspond with the population described in NICE's scope. For instance, the model structure includes a provision for individuals receiving CAB-LA to transition to oral PrEP, indicating that the model could not have been applied solely to a population ineligible for oral PrEP based on this criterion alone. Additionally, other factors contribute to the broadening of the model's scope, such as the incorporation of treatment effect estimates from the HPTN trials and other trials included in the ITC. These trials recruited individuals who were eligible to take oral PrEP, further expanding the population encompassed by the model. Overall, the discrepancy between the intended and actual populations modelled raises concerns about

	the alignment of the economic model with the original decision problem. This divergence may have implications for the generalisability and applicability of the model's findings to the target population specified by the CS.
What alternative approach has the EAG suggested?	None. The EAG aims solely to clarify that the ICERs generated for CAB-LA versus TDF/FTC, based on the population modelled in the economic model, are appropriate for decision-making. This population is much broader than the one the CS intended to model, which would have been narrower and potentially unsuitable for the decision problem under consideration.
What is the expected effect on the cost-effectiveness estimates?	The EAG considers that only the ICER for CAB-LA versus TDF/FTC is relevant. The other ICER generated for CAB-LA versus "no PrEP" is deemed irrelevant because "no PrEP" is not a specified comparator within NICE's scope.
What additional evidence or analyses might help to resolve this key issue?	None

Issue 20: Inclusion of studies in CS ITC that does not meet the specified population of interest as described in the NICE scope	
Report section	3.5, Table 24
Description of issue and why the EAG has identified it as important	The company's ITC included data from one trial (Bangkok Tenofovir study) that was conducted among drug users and the IperGay study, which compared event-driven TDF versus placebo in the ITC meta-regression analyses. The population in the Bangkok study differs from individuals at high risk of sexually

	transmitted HIV-1 infection and assesses TDF alone, whilst iperGay study should not have been included in the ITC on grounds of intervention.
What alternative approach has the EAG suggested?	The EAG re-run the ITC analysis excluding the Bangkok Tenofovir and IperGay studies.
What is the expected effect on the cost-effectiveness estimates?	The updated analyses, which excluded studies considered unsuitable for inclusion in the ITC due to population or intervention incompatibility, generated similar estimates of the treatment effect for CAB-LA versus TDF/FTC and CAB-LA versus the "no PrEP" intervention. The expected impact on cost-effectiveness is anticipated to be minimal.
What additional evidence or analyses might help to resolve this key issue?	None

Issue 21: CS ITC analyses did not account for measurement error in adherence levels in the meta-regression of treatment effect on adherence to CAB-LA	
Report section	3.4.1
Description of issue and why the EAG has identified it as important	The CS meta-regression analysis does not address the issue of measurement error in adherence. Measurement error refers to the discrepancy between the observed value of a variable (in this case, adherence to TDF/FTC) and its true unobserved value.[1, 2] As adherence is a measured covariate, its true value is uncertain and can only be inferred from the data. Failure to account for measurement error may lead to biased estimates of the relationship

	between efficacy and adherence resulting from regression attenuation bias /regression to the mean.
What alternative approach has the EAG suggested?	The EAG's analyses addressed this issue by formulating a binomial distribution for the number of people adherent to oral PrEP in the TDF/FTC arm of each trial, simultaneously handling measurement error and inclusion of studies not reporting adherence. In this updated analysis, the treatment effect is regressed on the unobserved but true value of adherence instead of the observed measure which is prone to error. Accounting for measurement error, the EAG's approach aimed to provide more accurate estimates of the relationship between TDF/FTC effectiveness and adherence, mitigating the risk of bias.
What is the expected effect on the cost-effectiveness estimates?	The impact on parameter estimates was minimal as similar estimates were obtained for from the EAG models compared with the company's model.
What additional evidence or analyses might help to resolve this key issue?	None

Issue 22: Restricting treatment costs to period of heightened risk (assumed 5-years in the CS base-case) over a life-time risk capping the treatment costs which could favour CAB-LA in cost-effectiveness.	
Report section	4.3
Description of issue and why the EAG has identified it as important	The CS model structure allows a variable at-risk period of one to ten years which is the duration when individuals face an elevated risk of infection and thus require "PrEP" medication. However, the 5-year

	maximum risk period in the CS base-case, in the opinion of the EAG, is not substantiated by sufficient evidence. The EAG is concerned that this effectively caps the treatment costs to five years, potentially leading to an underestimation of CAB-LA treatment costs since the injections are administered during periods of heightened risk. If the injections were to be used for longer than five years, this would effectively cap the cost of CAB-LA treatment to five years. Considering that the injections entail higher acquisition and administration costs compared to oral PrEP via TDF/FTC (which involves no administration costs), limiting treatment to five years could bias the ICER in favour of CAB-LA. Our clinical advisor confirmed that while a 5-year risk period is commonly used, people at the highest risk of HIV acquisition are likely to stay on cabotegravir longer than the average PrEP-eligible individual.
What alternative approach has the EAG suggested?	The EAG opted for a longer at-risk period of 10 years, which was included in the economic model workbook as its base-case. Ideally, the preference would have been for the model to be constructed so that the at-risk period could be varied as desired, but this was not the case. The company's model allowed the at-risk period to vary from one to a maximum of ten years.
What is the expected effect on the cost-effectiveness estimates?	The expected impact would be an increase in the treatment costs associated with CAB-LA, thereby making CAB-LA less cost-effective relative to TDF/FTC.
What additional evidence or analyses	The EAG recommends that the company modify the model structure and implementation to allow for

might help to resolve this key issue?	variation in the at-risk period across a much broader range of values.

1.5 *The cost-effectiveness evidence: summary of the EAG's key*

Issue 23: inappropriateness of the no PrEP as a comparator	
Report section	4.4, 4.5
Description of issue and why the EAG has identified it as important	The company compared cabotegravir to no PrEP. The use of no PrEP as a comparator is beyond the scope of the decision problem issued by NICE. The population for whom oral PrEP is inappropriate is poorly defined in the decision problem. The model relies on data from the HPTN trials, and trials included in the ITC where suitability for oral PrEP was not determined. . Furthermore, in the company's base case [redacted] of patients who stop taking cabotegravir transition into daily oral PrEP undermining arguments on the use of cabotegravir in patients whom oral PrEP is inappropriate and the comparison to no PrEP.
What alternative approach has the EAG suggested?	The EAG has recommended removing no PrEP as a comparator. Cabotegravir vs TDF/FTC is the most appropriate comparison for this appraisal. The EAG clinical advisor conformed that there are no studies with placebo or no PrEP as this is unethical.
What is the expected effect on the cost-effectiveness estimates?	There is no effect on the comparison between cabotegravir and oral TDF/FTC. Cabotegravir dominates no PrEP in the company base case.
What additional evidence or analyses might help to resolve this key issue?	For a no PrEP population to be considered, the characteristics of this population need to be clearly and explicitly outlined. Furthermore, this population needs to be sufficiently distinct from the population currently on oral PrEP in the UK.

Issue 24: Baseline risk of HIV acquisition	
Report section	4.7.1.1
Description of issue and why the EAG has identified it as important	Baseline risk of HIV acquisition for the men who have sex with men population was assumed to be equivalent to HIV incidence in men who have sex with men with recent rectal STI (4.9 per 100 person-years). The incidence value includes individuals with unknown HIV status. The estimate may be biased by previously undiagnosed HIV.
What alternative approach has the EAG suggested?	The EAG has recommended restricting the population used to calculate HIV incidence to individuals with known HIV status. i.e. individuals with HIV testing in the previous year. Baseline incidence of HIV in men who have sex with men population who were tested in the previous year and had recent rectal bacterial STI was 3.9 per 100 person-years. We explored a scenario using the incidence of HIV in men who have sex with men population HIV test done in the previous year.
What is the expected effect on the cost-effectiveness estimates?	Reducing the HIV incidence rate significantly increases the ICER as shown in Table 34.
What additional evidence or analyses might help to resolve this key issue?	Baseline incidence is a subject of considerable uncertainty. The company need to address the implicit bias in the selected baseline incidence given the availability of HIV incidence rate in men who have sex with men with recent rectal bacterial STI and were tested for HIV in the previous year (i.e. known HIV status). The EAG explores a scenario assuming the HIV incidence in men who have sex with men population with a HIV test in the previous year (1.9 per 100 person-years).

Issue 25: Transition to TDF/FTC following discontinuation from cabotegravir	
Report section	4.7.1.2
Description of issue and why the EAG has identified it as important	The company assumes that [redacted] of people in the cabotegravir arm who discontinue cabotegravir administration subsequently go on to receive oral PrEP. The justification for this assumption is unclear given arguments on the positioning of cabotegravir in individuals for whom oral PrEP is inappropriate. While patients who discontinue cabotegravir may go on to receive daily oral TDF/FTC in clinical practice, patients who discontinue oral TDF/FTC could also go on to receive cabotegravir.
What alternative approach has the EAG suggested?	The EAG has argued that an equivalent assumption be made for people receiving oral PrEP. Due to the limitations in the structure of the economic model, the EAG was not able to implement an equivalent transition from TDF/FTC to cabotegravir. Hence, we conservatively assumed that patients who discontinue cabotegravir do not subsequently transition to oral TDF/FTC.
What is the expected effect on the cost-effectiveness estimates?	Removing transition from cabotegravir to daily oral TDF/FTC significantly increases the ICER as shown in 175
What additional evidence or analyses might help to resolve this key issue?	The company should change the economic model to allow for an equivalent transition from TDF/FTC to cabotegravir. Evidence from the HPTN 083 and HPTN 084 trials do show that individuals on TDF/FTC subsequently received cabotegravir.

Issue 26: Adherence to TDF/FTC	
Report section	4.7.1.5
Description of issue and why the EAG has identified it as important	Adherence is a key driver for relative effectiveness of oral TDF/FTC in the model. Adherence information was derived from the HPTN 083 and HPTN 084 trials and used to reflect adherence in men who have sex with men and cisgender women respectively. Cisgender women were assumed to have a much lower adherence (56%) compared with transgender women and men who have sex with men (86%). The HPTN 084 trial was conducted exclusively in sub-Saharan Africa countries where there are differences to UK settings.
What alternative approach has the EAG suggested?	In the absence of reliable data on adherence to oral PrEP in the UK population. The EAG argues for an equivalent adherence in the men who have sex with men and cisgender women population.
What is the expected effect on the cost-effectiveness estimates?	Assuming equivalent adherence in the trial population slightly increases the ICER as shown in 6
What additional evidence or analyses might help to resolve this key issue?	Evidence on adherence to oral PrEP in the cisgender women population in a UK setting or settings with similar health and social structures can help resolve uncertainties around cisgender women adherence to TDF/FTC

Issue 27: Improved persistence to cabotegravir	
Report section	4.7.1.3
Description of issue and why the EAG has identified it as important	The company assumes a 20% increase in persistence to cabotegravir relative to TDF/FTC. There is no evidence that underpins the assumed 20% increased persistence. Indeed, persistence in a real-world setting is likely to be lower than those observed under trial conditions. Given the significant burden on both individuals and health care systems in ensuring on-time injections and the additional inconvenience of ISR to patients, persistence to cabotegravir is likely to be lower than persistence to oral PrEP in clinical practice.
What alternative approach has the EAG suggested?	The EAG has assumed equivalence in persistence between both trial arms. We explored a scenario assuming 10% lower persistence in cabotegravir compared to TDF/FTC given significant burden in drug administration and risk of moderate to severe injection site reactions.
What is the expected effect on the cost-effectiveness estimates?	Assuming equivalent persistence in the trial population significantly increases the ICER.
What additional evidence or analyses might help to resolve this key issue?	The company need to provide evidence of improved persistence to cabotegravir relative to oral TDF/FTC in a real-world setting.

Issue 28: Disutility for HIV	
Report section	4.8.1.1
Description of issue and why the EAG has identified it as important	The company applies a disutility of –0.11 for HIV. This estimate was derived from a study conducted between 2011 and 2012. Following the British HIV Association (BHIVA) treatment guidelines update in 2016, recent HIV regimens have led to decreased pill burden and reduced side-effects which should impact health-related quality of life. Our clinical advisor confirmed that there has been significant reduction in pill burden and side effects from HIV regimens following the updated guidelines in 2016
What alternative approach has the EAG suggested?	The Positive Voices Survey in 2022 reported a utility of 0.77 in people living with HIV, lower than the score of 0.82 in among the general population indicating a disutility of –0.05.
What is the expected effect on the cost-effectiveness estimates?	Applying a disutility of -0.05 for HIV increases the ICER as seen in 6.1.1.
What additional evidence or analyses might help to resolve this key issue?	None

Issue 29: Starting age of Participants	
Report section	4.7.1.4.1
Description of issue and why the EAG has identified it as important	The company assumes a starting age of 26 in the model cohort to align with the weighted median age of the HPTN 083 and HPTN 084 trial population.
What alternative approach has the EAG suggested?	The EAG argues that the starting age of the model is set to 33 years to reflect the median age of PrEP users in the UK
What is the expected effect on the cost-effectiveness estimates?	Increasing the model starting age slightly increases the ICER as shown in Table 34
What additional evidence or analyses might help to resolve this key issue?	The starting age of the cohort should reflect the median starting age of PrEP users in the UK rather than the median age of participants in non-UK trials.

Issue 30: Duration of risk period	
Report section	4.7.1.4.2
Description of issue and why the EAG has identified it as important	The model uses a single 5-year risk period to represent the lifetime risk duration for individuals eligible for PrEP. A single five-year risk period could underestimate CAB-LA treatment costs.
What alternative approach has the EAG suggested?	The EAG has suggested changing the duration of the on-risk period from 5 years to 10 years to account for uncertainties associated with a single risk period. Our clinical advisor confirmed that while a 5-year risk period is commonly used, people at the highest risk of HIV acquisition are likely to stay on cabotegravir longer than the average PrEP-eligible individual.
What is the expected effect on the cost-effectiveness estimates?	The impact of varying this individual parameter increases the ICER as shown in table 34.
What additional evidence or analyses might help to resolve this key issue?	Exploring a longer risk period duration beyond the 10-year period currently allowed in the model could provide more information on the impact of risk duration on the cost-effectiveness.

Issue 31: Cabotegravir injection administrative costs

Report section	4.9.2, 4.9.2.1
Description of issue and why the EAG has identified it as important	The company assumption of 15-minute administration time for cabotegravir LA injections by a band 5 nurse, resulting in a per-visit cost of £11.85, may not accurately reflect resource requirements. Evidence submitted to NICE from NHS England suggests administration of cabotegravir takes about 60 mins. Furthermore, clinical advisor consulted by the EAG suggested that an hour of clinical activity is expected for the first injection visit. Subsequent injection visits are expected to take about 40 mins of clinical activity.
What alternative approach has the EAG suggested?	Administration costs for cabotegravir costs was changed from 15-minute band 5 nurse to an hour of activity in the clinic (i.e. 20 mins band 5 nurse for observation, 40 mins clinical activity representing the weighted average a pharmacist, consultant, and clinical nurse specialist wage. Additionally, patients receiving cabotegravir are required to take a HIV test at every visit. Hence, no reduction in HIV tests from year 2 in people receiving cabotegravir.
What is the expected effect on the cost-effectiveness estimates?	The impact of varying this individual parameter increases the ICER as shown in table 34.

What additional evidence or analyses might help to resolve this key issue?	Further expert clinical opinion would provide clarity on the administrative burden of cabotegravir injection. Gathering real-world data from current cabotegravir LA injection sites could provide more clarity on resource utilisation.

Issue 32: Drug acquisition and administration

Report section	4.9.1, 4.9.1.1
Description of issue and why the EAG has identified it as important	The SmPC recommends doses every two months after the initial two doses one month apart, while NHS England suggests doses every 8 weeks following the initial doses 28 days apart. This discrepancy leads to an underestimation of drug acquisition costs by 6.5%% and 7.4%% over 5- and 10-year risk periods respectively. This is significant given the considerable cost per injection (£[redacted]). Our clinical advisor confirmed that cabotegravir is given every 8 weeks after the initial two doses and in multiple global trials they are involved in, cabotegravir is given every 8 weeks. Also, there was no consideration of the impact of aggregating lifetime risks of HIV acquisition into a single risk period. The model overlooks the potential need for multiple treatment cycles due to varying risk patterns over an individual's lifetime, which could further impact drug acquisition and administration costs. The model has not accounted for the reliable recall systems needed for the injection treatment regime, which could affect the overall cost-effectiveness assessment. Our clinical advisor also confirmed that re-starting cabotegravir would incur an extra injection dose and additional costs

What alternative approach has the EAG suggested?	Drug acquisition and administration costs for cabotegravir increased by 5% to account for potential increases in lifetime costs of cabotegravir due to discrepancy in frequency of administration and changing risk patterns over the lifetime of the cohort. The EAG clinical advisor support the EAG approach to follow NHS England submission.
What is the expected effect on the cost-effectiveness estimates?	The ICER was increased as shown in table 34.
What additional evidence or analyses might help to resolve this key issue?	Clarity on the resource implications and expert clinical opinion regarding the appropriate dosing frequency for cabotegravir injections is crucial. Furthermore, clarity on the impact of aggregating dynamic risk patterns into a single risk period on cabotegravir acquisition/use can help reduce uncertainty.

1.6 *Summary of EAG's preferred assumptions and resulting ICER*

Table 2: Summary of EAG's preferred assumptions and ICER

Scenario	Incremental cost	Incremental QALYs	ICER (change from company base case)
Company's base case	[redacted]	[redacted]	£5,580
EAG preferred base case assumptions			
Baseline risk of HIV acquisition for no PrEP cohort changed from 4.9 per 100 person-years to 3.9 per 100 person-years	[redacted]	[redacted]	£22,999 (£17,419)
Patients who stop cabotegravir PrEP do not transition to receive oral PrEP	[redacted]	[redacted]	£21,848 (£16,268)
Adherence to TDF/FTC for cisgender women set equal to men who have sex with men / transgender women population	[redacted]	[redacted]	£6,932 (£1,352)
No relative improvement in persistence to cabotegravir	[redacted]	[redacted]	£31,653 (£26,073)
Per cycle application of ISR costs and disutility	[redacted]	[redacted]	£5,583 (£3)
Aggregate risk period increased from 5 years to 10 years	[redacted]	[redacted]	£17,815 (£12,235)
Adjust cabotegravir admin costs to reflect increased administrative costs	[redacted]	[redacted]	£8,520 (£2,940)
Adjust dosing schedule to reflect Q8W schedule rather than 2 months.	[redacted]	[redacted]	£9,701 (£4,121)

Scenario	Incremental cost	Incremental QALYs	ICER (change from company base case)
Increase drug acquisition, visit and administration costs by 5% to account for re-starting cabotegravir due to dynamic risk of HIV acquisition over cohort lifetime.	[redacted]	[redacted]	£9,525 (£15,781)
Increase starting age of the model from 26 to 33 years.	[redacted]	[redacted]	£8,647 (£3,067)
Disutility of -0.05 applied for HIV in place of a disutility of -0.11 used by the company.	[redacted]	[redacted]	£11,209
EAG's preferred base case ICER	[redacted]	[redacted]	£334,635 (£329,055)

External Assessment Group Report

2 INTRODUCTION AND BACKGROUND

2.1 *Introduction*

Remit of the appraisal

The company submission (CS) appraise the clinical and cost effectiveness of cabotegravir (CAB-LA) for preventing sexually acquired HIV-1 infection in at-risk individuals weighing at least 35 kg in those for whom oral PrEP is not appropriate.

Condition and symptoms

HIV is an infection that attacks and weakens the body's immune system by targeting and destroying CD4 positive T cells (CD4+T), crucial for fighting infections.[3] It achieves this by binding to the CD4 receptor and co-receptor on the host cell surface, allowing entry and replication. Some HIV viral components are recognized and eliminated by the immune system, while others are reverse-transcribed into HIV DNA and integrated into the host cell. This integration leads to a latent phase where viral gene expression is inhibited.[4]

The latent phase can begin early in an infection, during which individuals may experience a short flu-like illness or remain asymptomatic.[5] However, HIV remains active, progressively weakening the immune system over several years. Severe immune damage leads to symptoms such as weight loss, chronic diarrhoea, night sweats, skin problems, recurrent infections, and life-threatening illnesses.[6]

HIV is transmitted through bodily fluids of infected individuals with detectable virus load (less than 200 viral load copies per ml), including blood, breast milk, semen, and vaginal fluids. Other modes of transmission include perinatally acquired HIV and sharing drug injection equipment.[3, 7]

HIV is considered a chronic and episodic health condition. It is categorised into two subtypes: HIV-1 and HIV-2. HIV-1 is more prevalent worldwide whereas HIV-2 is mostly concentrated in Western Africa and has a slower progression.[8] This technology appraisal focuses on HIV-1, referred to as HIV unless otherwise stated.

Prevention strategies

In the UK, a combination of HIV prevention strategies exists to meet the different prevention needs of any given population.[9] These strategies employ a mix of biomedical`, behavioural and structural interventions subdivided into four units namely: primary prevention`, HIV testing`, secondary prevention`, and empowerment and wellbeing.[10] Figure 1 shows these strategies, with primary prevention including the use of condoms, and biomedical interventions, the focus of this appraisal.

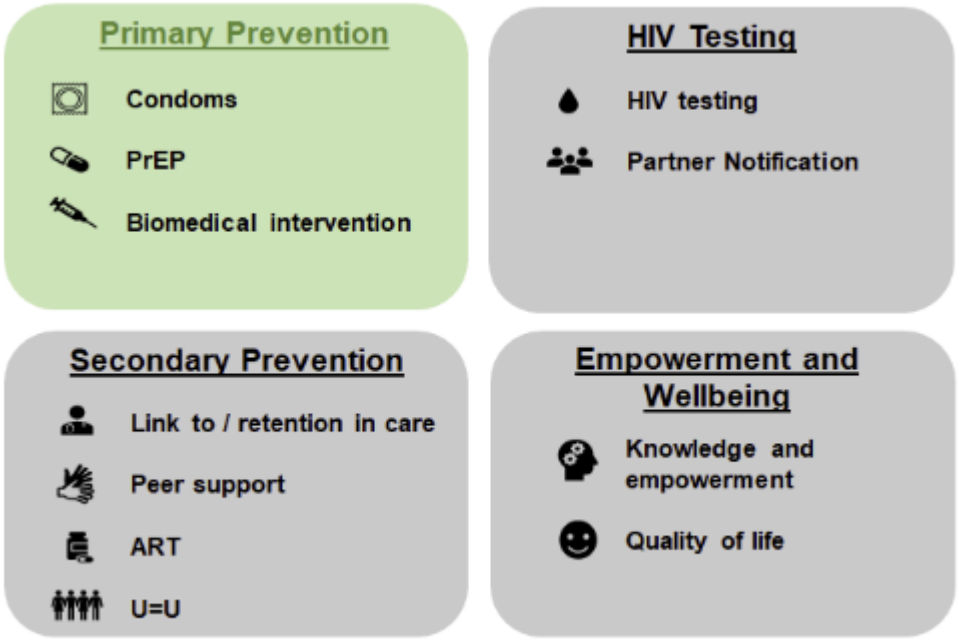


Figure 1. HIV prevention strategies adopted in the UK (Gov UK 2021)[10]

In primary prevention, condoms are effective in preventing HIV, other sexually transmitted infections (STIs), and unwanted pregnancies. While it is recognised that no single method alone can completely prevent HIV transmission or suit every individual's needs,[9] HIV PrEP demonstrates high effectiveness in preventing HIV transmission. It is now routinely offered through specialist sexual health services (SHS) in the UK.[9] However, a variation in the awareness, accessibility, availability, and uptake of primary prevention initiatives among different demographic groups exists which warrants further investigation to ensure effective prevention efforts.[10]

Pre-exposure prophylaxis

PrEP is an antiretroviral therapy (ART) used to prevent HIV among HIV-negative individuals.[10] The PrEP Impact Trial showed that the use of HIV PrEP intake over

several years reduced the chances of HIV acquisition by 86%.[11] When taken consistently as prescribed, various studies report that PrEP reduces the risk of acquiring HIV by at least 74% to 84%.[11, 12]PrEP is indicated for use in sexually active individuals that are at high risk of developing HIV.[13]

HIV epidemiology

HIV is a global health concern affecting more than 1.5 million people per year.[9] In England, a rise in HIV diagnoses has been reported from 3,118 cases in 2021 to 3,805 cases in 2022.[14] However, most of these infections are attributable to people previously diagnosed abroad (69% increase from 805 cases in 2021 to 1,361 cases in 2022). Therefore, this is not reflective of a rise in HIV transmissions in England.[14] The number of HIV diagnoses first made in England rose by 6% from 2,313 cases in 2021 to 2,444 cases in 2022, with variations among population groups. Among gay, bisexual, and other men who have sex with men (GBMSM), diagnoses fell by 8%, particularly outside London, while diagnoses among heterosexual individuals increased by 14% in London and 11% outside London. The rising rate of diagnoses despite lower testing rates suggest transmission within this group.

According to a report by UK HSA (2023), the proportion of individuals with an identified PrEP need accessing specialist sexual health services in England rose from 7.5% in 2021 to 9.7% in 2022.[14] Among those needing PrEP, the percentage identified increased from 79% to 83% in 2022, with the largest rise seen in heterosexual and bisexual women, followed by heterosexual men and GBMSM. Additionally, the proportion on PrEP increased slightly from 70% to 71% in 2022, with the largest increase observed in heterosexual and bisexual women, followed by heterosexual men and GBMSM. Therefore, these rises are likely due to a combination of an increase in PrEP service delivery as well as improvements in the coding and reporting of PrEP activity at SHSs.[14, 15]

2.2 *Background*

CAB-LA is a long-acting injection option (extended-release injectable suspension) to reduce the risk of sexually acquired HIV-1.[16]

Mechanism of action

CAB-LA, an integrase strand transfer inhibitor (INSTI), inhibits HIV replication.[16] It achieves this by preventing the viral DNA from integrating into the CD4+ T cells, a crucial step in the HIV replication cycle. This integration process is essential for the virus to establish chronic infection. CAB-LA is administered by healthcare professionals. The treatment begins with two monthly injections of 600 mg (3-ml) each, followed by a maintenance dose (600 mg (3-ml)) of one injection every two months. Before starting the injections, patients may take CAB oral tablets for about a month to ensure tolerability.

Treatment overview

In the US, three HIV medications have been approved by the Food and Drug Administration (FDA) for use as PrEP, which include oral tenofovir disoproxil fumarate/ emtricitabine (TDF/FTC), oral tenofovir alafenamide/ emtricitabine (TAF/FTC), and CAB-LA.[17] The choice of medication depends on an individual's needs. Inconsistent adherence to PrEP may lead to insufficient medication levels in the bloodstream, reducing its effectiveness against the virus.[17]

In the UK, the use of oral PrEP was approved in 2020.[18] Currently, TDF/FTC is the standard of care (SoC), TAF/FTC is a second line option for people whom TDF/FTC may not be appropriate, TAF/FTC is only licensed for at-risk men who have sex with men including adolescents (with a body weight of at least 35 kg)[19] However, a variation in PrEP uptake by men who have sex with men in the UK has been reported due to a number of demographic factors, including age and ethnicity.[11]

Position of the technology in the pathway

The company states that CAB-LA is anticipated to be indicated for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired human immunodeficiency virus (HIV)-1 infection in at-risk individuals weighing at least 35 kg. The proposed position of CAB-LA in the clinical pathway is as a PrEP option for individuals for whom oral PrEP is not appropriate and are therefore underserved by current SoC; The EAG clinical advisor states that individuals whom oral PrEP is not appropriate are likely to be people who cannot tolerate oral PrEP or people where the tablets represent a risk. However, the EAG clinical advisor stated that PrEP should be offered to people regardless of their gender or sexual orientation, who would benefit from a reduction in

HIV risk, such as HIV-negative gay, bisexual, and other men engaging in condomless sex with HIV-positive partners (viral load not <200 copies/ml), as well as heterosexual men and women, trans women, trans men, nonbinary individuals, and those likely to engage in condomless sex with high-risk partners.

According to the NHS England submission to this appraisal the proposed implementation of the technology will require significant investment in the NHS as there are currently no injectable PrEP therapies available. For instance, additional resource for people receiving CAB-LA will require a senior clinician at every administration visit, observation for 20 minutes post administration, HIV viral load tests at every visit, HIV Ab/Ag testing every 3 months, and sexual health screening four times a year[1].

2.3 *Critique of company's definition of decision problem*

The EAG's critique of the company's definition of the decision problem is presented in Table 3.

[1] The NHS England submission for this STA (Cabotegravir injections for preventing HIV-1 in adults and young people [ID6255]: NHS organisation submission (ICBs and NHS England)

Table 3: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	People at risk of sexually acquired HIV-1 infection.	Adults and adolescents (weighing at least 35 kg) at risk of sexually acquired HIV for whom oral PrEP is not appropriate.	Current SoC meets the needs of the broad population of people likely to be exposed to HIV. However, there are still people who are likely to be exposed to HIV who are underserved by oral PrEP for the reasons described in Sections B.1.3.6. A new drug class, modalities, and or dosing frequencies, such as cabotegravir, will help to address the unmet needs for these individuals (Section B.1.3.7).	The EAG considers that *'Adults and adolescents (weighing at least 35 kg) at risk of sexually acquired HIV'* is in line with the NICE scope and matches the anticipated Marketing Authorisation. However, the main clinical evidence submitted by the company for the comparison of CAB-LA with TDF/FTC is limited to adults aged ≥18 years in specific populations, i.e. men who have sex with men/transgender women, or cisgender women <45 years. The statement *'…for whom oral PrEP is not appropriate'* is not aligned with the NICE scope

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
				or [redacted] However, the clinical evidence submitted by the company comprised of people taking oral PrEP/placebo for oral PrEP, therefore not aligned with those 'for whom oral PrEP is not appropriate'. The EAG has concerns regarding the generalisability of the submitted clinical evidence to the relevant population in England and Wales eligible for treatment.
Intervention	Cabotegravir intramuscular injections with or	As per the NICE scope.	N/A.	The EAG agrees that the intervention is broadly in line with the NICE scope. However, the intervention used in the submitted evidence involved an oral lead-in stage in all cases. The EAG

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	without oral lead-in therapy.			clinical advisor considered that in UK clinical practice the oral lead-in would be an option for people worried about side-effects.
Comparator(s)	Established clinical management including tenofovir disoproxil or alafenamide in combination with emtricitabine (TDF/FTC or TAF/FTC) or tenofovir alone.	• TDF/FTC (for individuals taking and sub-optimally adhering to oral PrEP). No PrEP (for individuals who cannot take oral PrEP).	Single agent TD is not currently licensed as PrEP, but according to the BHIVA/BASHH guidelines can be considered as an alternative for heterosexual men and women);[20] this population likely represents a small proportion of PrEP use in England and Wales. Furthermore, only tenofovir in combination with	As stated above, the EAG considers that the submitted clinical evidence includes only those who are able to tolerate PrEP. The EAG considers that TDF/FTC is an appropriate comparator for the submitted populations. TD alone can be offered only to heterosexual men and women where FTC is contraindicated.[20] TAF/FTC is licensed in the UK for men who have

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			emtricitabine is commissioned by the NHS's specialised clinical commissioning policy for PrEP.[19] The use of TAF/FTC (Descovy) is negligible in the UK among men who have sex with men and transgender women, and it is not approved for individuals assigned female sex at birth. • Over a 2-year period, only 0.185%[b] of PrEP users attending Dean Street, Chelsea (the largest sexual health clinic in Europe) and	sex with men (≥35kg) only and is commissioned for individuals meeting certain criteria who are intolerant of, or have contraindications to TDF/FTC.[19] The EAG agrees that numbers eligible for TD alone and TAF/FTC are likely to be low, but considers these cannot be excluded as comparators. In addition, the EAG believes that the company's calculation of the proportion with TAF/FTC at Dean Street, Chelsea (0.185%) uses an inappropriate combination of numerator and denominator.[b]

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			Westminster Hospital NHS Foundation Trust were prescribed TAF/FTC.[21] • Among a Scottish cohort of 1,744 PrEP users, only 0.4% had been initiated on TAF/FTC.[22]	No PrEP is not an appropriate comparator in this appraisal, and all provided evidence included participants who were eligible for PrEP.
Outcomes	• Number of documented incident HIV . • Change in viral load. • Adverse effects of treatment. • HRQoL.	• Number of documented incident HIV acquisitions[a]. • Adverse effects of treatment. • Renal function. • Liver function.	Aligned with draft scope, except change in viral load was not collected in the HPTN trials as the scope of the trials were to investigate cabotegravir for PrEP among individuals who are not living with HIV. In	The EAG acknowledges that data on viral load and HRQoL were not collected in the HPTN trials. The focus of the submission is otherwise focused on appropriate outcomes.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	• Renal function. • Liver function. • Bone mineral density. • Incidence of resistance mutations. Adherence to treatment regimen	• Bone mineral density. • Incidence of resistance mutations. • Acceptability scale assessments. • Adherence to study product. • Sexual risk factors (e.g. number of coital acts, sexual partners, condomless sex acts, condomless anal sex acts, frequency of	addition, no HRQoL data were collected. Note that acceptability scale assessments, sexual risk factors, incident STIs, weight, blood pressure, fasting glucose, and fasting lipids, as captured within the pivotal Phase 3 RCTs are also presented.	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
		reported transactional sex). • Incident STIs. Weight, blood pressure, fasting glucose, and fasting lipids.		
Economic analysis				
Subgroups	If evidence exists, subgroups of people at risk of sexually acquired HIV-1 infection for whom the technology might be particularly clinically effective or value for money will be considered	No subgroups are considered.	No subgroups are considered in this appraisal as the underlying risk of HIV acquisition should be the predominant consideration when initiating PrEP, irrespective of an individual's characteristics influencing their risk. The overall population considered in this	The EAG notes that incident HIV acquisitions in the HPTN trials were analysed by 'important subgroup factors' (CS Tables 7 and 11), including region, age, ethnic group, gender identity and baseline risk (HPTN 083), and age, HSV-2 serostatus, contraceptive method, and BMI (HPTN 084).

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			appraisal reflects individuals with an underlying risk of HIV acquisition, in accordance with UK clinical guidelines,[20] without focusing on subgroups presenting specific risk factors.	Therefore it would have been possible for the company to assess subgroups for whom the technology might be particularly clinically effective or value for money.
Special considerations including issues related to equity or equality	None specified.	PrEP is a key component of HIV prevention. While UK individuals have access to oral PrEP through the NHS, there are still some health inequities exacerbating unmet need for HIV prevention. which may	-	No comment.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
		be experienced by, but are not limited to, gender diverse populations and ethnic minorities (Section B.1.4).		

[a]The term infections was replaced with acquisitions throughout the CS.[b] The denominator is 32,424 patients accessing PrEP at 56 Dean Street (Chelsea Westminster Trust) during a 2 year period, from January 2020 to December 2021. The numerator is 60 patients prescribed TAF/FTC out of 125 patients referred to the multidisciplinary team at the same clinic from other UK clinics (a complex clinical PrEP referral service) between June 2021 to April 2023.

3 CLINICAL EFFECTIVENESS

3.1 *Critique of the methods of review(s)*

A summary of the EAG critique for each methodological step of the SLR and cross-references to the relevant section in the CS where more detail can be found is presented in Table 4.

An overview of the key points of interest from the critique of the SLR follows, and the full EAG assessment using the modified ROBIS can be found in Appendix 1. Overall, the EAG considered the risk of bias of the company SLR to be of high concern, with only one aspect of the methodology considered to be low concern.

Table 4.Summary of the EAG's critique of the company SLR

Method step	Section(s) of CS of relevance	EAG overall assessment
Eligibility criteria	CS Appendix D Table 6	Unclear concern
Searches and selection of studies	CS Appendix D.1.1 to D.1.4	Unclear concern
Data extraction and risk of bias assessment	CS Appendix D.1.5 and D.1.6	Low concern
Evidence synthesis	CS Appendix D.2 and D.3	High concern

3.1.1 Searches

The company carried out a targeted search for systematic literature reviews (CS Appendix D.1.2.1) on the single database Embase via Embase.com (CS Appendix D.1.2.1 Targeted Search for SLRs). The date that the search was ran was not provided. The search includes broad and appropriate search terms for human immunodeficiency virus (HIV) and pre-exposure prophylaxis (PrEP) and systematic reviews, incorporating database-specific indexing terms and free-text terms.

The targeted systematic review search identified a recently published systematic review of randomised controlled trials and systematic reviews published in 2023.[23] The company updated the search strategy carried out by Huic et al (2023), which

was undertaken in November 2022. The section Data Sources (CS Appendix D 1.1) reports that the systematic review by Huic et al 2023 had updated two systematic reviews.[23-25] The search strategies carried out by the company, Huic et al (2023), O'Murchu (2022) and Fonner (2023) are all reasonably sensitive and search across a range of appropriate sources including databases and grey literature, including ongoing trials via clinical trials registries and HTA bodies and databases. However, each review reports different search strategies and approaches, including search terms, limits used, and sources searched, thus varying in sensitivity. Therefore the 'top up' searches carried out by the company are not a true update of the 2023 searches carried out by Huic et al.[23]

The company carried out a 'top up' search to identify randomised controlled trials published since the search was carried out by Huic et al (2023) in November 2022. (CS Appendix D.1.1) The company limited their searches to studies published from January 2022 and didn't limit by day or month, which is good practice and takes into consideration inconsistencies in the indexing of publication dates across databases.[26]

Reasonably comprehensive searches were carried out in appropriate databases, including Medline, Medline-In-Process, Embase, and the Cochrane Library on the 1st November 2023. The EAG would recommend searching international databases, for example Global Health, African Index Medicus (AIM), INDMedor LILACS (Latin American and Caribbean Center on Health Sciences Information), due to the global prevalence of HIV (CS Appendix D.1.1.2).

The search strategies for each database, Medline, Medline-in-Process, Embase (Embase.com) and the Cochrane Library (Wiley) and numbers for each line are provided (CS Appendix D.1.2.2 Table 2, D.1.2.3, Table 3). The databases Medline, Medline-In-Process and Embase are searched concurrently via Embase.com (CS Appendix D.1.1.2 Table 2). The EAG would recommend searching databases separately, as each database contains distinct thesauri. Searching across multiple databases simultaneously can make it less easy to spot errors, as the search results are less likely to produce low or zero results. Medline indexing terms are not included, including 'HIV' or the narrower terms 'HIV-1 or HIV-2' and 'HIV infections'. The search strand for PrEP does not include specific names of types of PrEP such as Tenofovir or Cabotegravir, as per the search carried out by Huic et al (2023).[23]

The EAG would recommend searching for keywords in addition to the title and abstract fields in the free-text searches to increase the sensitivity of the searches. The free text terms are phrase searches for the condition or intervention. Searching for adjacency or the Boolean AND operator would increase the sensitivity, for example, ((human immun*) AND (deficiency virus*)). The validated rct filter by Ganville (2019) was used to restrict the results to randomised controlled trials.[27] The search was combined correctly using the appropriate Boolean operators.

The Cochrane Central Register of Controlled Trials (CENTRAL) search via the Cochrane Library contains major issues in the application of search limits (CS Appendix D.1.2 CS Table 3). The indexing and free text terms for HIV and PrEP are all applied correctly and effectively translated. The search lines #7 and #8 are to limit the search to randomised controlled trials by combining the search with the single free-text search line 'random*:ti,ab'. The CENTRAL database only contains randomised controlled trials or quasi-rcts; therefore, lines #7 and #8 are likely to have removed potentially relevant randomised controlled trials.[28] Line #9 tells the database to limit the results from line #8 'with Publication Year from 2022 to 2023', 'in Trials' (CENTRAL). The Cochrane Library contains in-built filters to restrict search results for a single year, or the user can enter a range (for all content). There are in-built limits on the right-hand side of the search terms box to limit by original publication year (CENTRAL Trials only) or date published on the Cochrane Library. The EAG have tested running searches using this command and believe that the search terms in line #9 are only searching for records with the terms 'with' and 'publication' and 'year' and '2022' and '2023'. The EAG re-ran this search and used the database inbuilt limits for the specific years 2022 and 2023 and the search results were 280 compared to 18 retrieved in the company's search (CS Appendix D.1.2.2 Table 3).

Conference abstracts were searched via the conference websites for the word 'random' and via Embase.com. The search strategy for the search carried out on Embase.com is reported in CS Table 4 (CS Appendix D.1.2.2). The search contains relevant indexing and free text terms for HIV and PrEP and relevant specific conferences using the issue and journal name and full names or acronym terms for the conference in fields ip (Issue) and jt (Journal title) or nc (Conference name). The EAG notes that this approach may not be as comprehensive as directly

handsearching all relevant conference abstracts directly via conference websites.[29] The clinical trials registries WHO ICTRP and ClinicalTrials.gov were searched to identify ongoing clinical trials using a broad range of terms; however, the numbers of search results or results selected are not reported. Hand searching specific journals, reference list checking and contacting experts was not carried out. The EAG would also recommend searching for health technology assessments via databases such as the International HTA Database (INAHTA) and individual HTA bodies. The search terms and concepts are combined correctly and appropriately using Boolean operators. An appropriate and reasonably comprehensive search filter from a recognised source (SIGN) was applied to identify systematic reviews.[30] This was also combined using the Boolean operator AND with the Cochrane EMBASE highly sensitive search filter for randomised controlled trials. The EAG assumes that this was applied to identify systematic reviews of randomised controlled trials (this is not outlined in the methods). The EAG note that the inclusion of search terms for randomised controlled trials and systematic reviews is not standard practice when applying systematic review search filters, and the EAG note that this could potentially exclude systematic reviews that have either not been indexed with terms related to randomised controlled trials or do not mention randomised controlled trials in the title or abstract fields. Despite this being a targeted search, the EAG would recommend searching additional sources including Medline, the Cochrane Database of Systematic Reviews, and supplementary searches of the repository of systematic reviews Epistemonikos, Google or Google Scholar. The EAG recommend searching Medline and Embase as, although Embase contains the same journals that are indexed on Medline; each database contains distinct indexing terms, namely MeSH (Medical Subject Headings in Medline and EMTREE in Embase) and the same search strategy can produce different search results.[31]

3.1.2 SLR methods

The company SLR identified four published SLRs which were used as a source of studies. The company's eligibility criteria were applied to each of the included studies from these existing SLRs and 19 studies were considered eligible. The EAG checked these studies and considered that two studies were not appropriate to the NICE scope: the Bangkok Tenofovir Study[32] does not meet the NICE scope as it was in injecting drug users; and the IperGay study used event-driven (not daily) treatment

with TDF/FTC (Appendix 2).[33] The CS then applied additional criteria for the inclusion of studies in the ITC (Section B.2.9.2.1), including a requirement for treatment adherence to have been expressed as the proportion of participants with measurable plasma levels. It is unclear if these additional criteria were defined *a priori* or whether the adherence outcome measure requirement was appropriate, this is discussed more in 3.3 Ten studies were included in the company ITC (including Bangkok Tenofovir Study[32] and IperGay study[33] noted above). The EAG notes that the Partners PreP Continuation study[34]) is listed in CS Table 19 as an included study, however the company (correctly) did not include this in their ITC. The company did, however, include the Partners Prep Study[34] which is not listed in CS Table 19 (the EAG agrees with this inclusion but notes the wrong data were used in the ITC, see 3.3). Of the nine studies included in the SLR but excluded from the ITC, the EAG agreed with the exclusion of eight studies. The EAG considered that the IAVI Uganda Study[35] should have been included in the ITC (see 3.3). The EAG assessment of studies included and excluded from the ITC is summarised in Appendix 2.

The company's SLR did not identify any other relevant studies from their own searches. Nine studies were identified but all were excluded (CS Appendix D Table 33). The EAG checked these studies and although the EAG differed from the company's reason for exclusion for some, it was agreed that none of these studies were relevant to the company ITC (Appendix 2).

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Overview of key trials

The primary sources of evidence for the assessment of clinical effectiveness of CAB-LA for preventing HIV-1 infection comes from two RCTs:

- HPTN 083 (NCT02720094): Phase 2b/3 RCT in adult (≥18 years) cisgender men and transgender women who have sex with men at risk of acquiring HIV[36] and main publication.[37]

- HPTN 084 (NCT03164564): Phase 3 RCT in adults (aged 18–45 years) assigned female sex at birth at risk of acquiring HIV[36] and main publication Delany-Moretlwe 2022[38]

The two trials were multi-centre, randomised, double-blind, active-controlled trials, whereby each arm received both an IM injection (either cabotegravir or placebo) and oral tablets (either TDF/FTC or placebo). The trials were originally planned with three phases, but the blinded portions of the trials (Steps 1 and 2, see below) were stopped early when they met pre-defined stopping criteria for efficacy at the first pre-planned (for HPTN 083) or second pre-planned (for HPTN 084) interim analyses. The open label extension study for each trial is currently ongoing.

Trial phases for HPTN 083 and HPTN 084:

- Step 1: up to 5-week blinded oral tablet lead-in phase to investigate cabotegravir tolerability;
    - only participants with ≥50% adherence to oral tablets were permitted to proceed to Step 2 [redacted] of participants across arms in each trial discontinued due to low adherence, Clarification A4),
    - participants who acquired HIV during this step permanently discontinued the study product and were terminated from the study.
- Step 2: Blinded injection phase until Week 153 (HPTN 083) or Week 185 (HPTN 084).
- Step 3: Planned open-label tail phase (to cover the pharmacokinetic tail of cabotegravir long-acting injections) with oral TDF/FTC. But, after trials were stopped early and unblinded, participants received their randomly assigned study regimen without placebo for 1 year, then transitioned to open label extension studies where participants had the option to continue their original randomised PrEP regimen or switch to the other regimen.

A summary of the trial methodology with cross-reference in the relevant sections in the CS where more detail can be found is presented in Table 5.

Table 5. Summary of HPTN 083 and HPTN 084 methodology

Method step	Summary details	Section(s) of CS of relevance or other source
Method of randomisation	Randomisation 1: 1 ratio, stratified according to site; performed with the use of permuted blocks of 8, 10, or 12, assigned electronically at enrolment. The randomisation scheme was generated, operationalised and maintained by the HPTN Statistical and Data Management Center.	CS Table 7 Landovitz 2021[37] Delany-Moretlwe, 2022[38] Trial protocols[39, 40]
Eligibility criteria	*HPTN 083* • Cisgender men and transgender women who have sex with men • Age ≥18 years • At high risk for sexually acquiring HIV • In general good health as evidenced by clinical and laboratory assessments • Non-reactive/negative HIV test results *HPTN 084* • Born female • Age 18-45 years • Sexually active • Score of ≥5 using a modified VOICE risk score • Non-reactive HIV test results • Negative pregnancy test • Evidence of surgical sterilisation, no uterus, or reliable long-acting contraception	CS Table 7
Trial drugs by period of study	Step 1: Oral cabotegravir or placebo and oral placebo or TDF/FTC Step 2: Cabotegravir or placebo IM injections AND placebo or TDF/FTC oral tablets	CS Table 7

	Step 3: Oral TDF/FTC (083: n=19, 084: n=0 as trial stopped early); remaining patients received randomised study dug OLE: Choice of oral TDF/FTC or cabotegravir injection with optional oral cabotegravir lead-in.	
Primary and key secondary endpoints of relevance to the decision problem	Primary endpoint: Incident HIV acquisition in Steps 1 and 2 Key secondary endpoints: *HPTN 083* Changes in renal function Changes in liver function Bone mineral density Incidence of resistance mutations Adherence to study product (tertiary endpoint) *HPTN 084* Changes in renal function [a] Changes in liver function [a] Incidence of resistance mutations[a]	CS Table 7
Statistical analysis	*HPTN 083* Non-inferiority trial, with the ability to test for superiority using the O'Brien Fleming method. Non-inferiority margin was a HR of 1.23, with an alternative HR of 0.75 used as the pre-specified test for superiority. Superiority would be established if the HR point estimate is approximately 0.74 or less. Cox regression, stratified according to geographic region and adjusted for early stopping, was used to	CS Table 5, CS Table 6, B.2.4.1, CS Table 11

	estimate the HR for incident HIV acquisition, 95% CIs and p-values were based on the Wald statistic. The primary HR ratio was adjusted for early stopping. Schoenfeld residuals was used as a test for proportional hazards, and sensitivity analysis was performed using the log-rank test by stratification according to geographic region. *HPTN 084:* Superiority trial, with superiority established if the HR point estimate is within the bound of 0.54 for the HR. Clarification A13 explained that due to the disparate results of TDF/FTC as PrEP in cisgender women in previous studies, a non-inferiority margin could not be established. Cox regression, stratified according to site and including treatment arm as the only covariate, was used to estimate the HR and 95% CIs for incident HIV acquisition; if the number of events was small (<40) then the p-value was confirmed using a permutation test based on 100,000 random permutations of the treatment assignments; if there was a meaningful difference between the permutation and asymptotic procedures, the permutation p-value was used *Both trials* mITT analysis set (excluding those inappropriately enrolled and those who were found to be living with HIV at randomisation) Post-hoc analysis using extended retrospective virologic testing to better characterise the timing of	

	HIV acquisition (mITT, extended retrospective testing) Updated analysis, incorporating data from one additional year of unblinded follow-up	

[a] These are stated in CS Table 6, but not listed in HPTN 084 protocol or NCT record (resistance testing was undertaken but not specified as an outcome). mITT: modified ITT; OLE: open label extension.

3.2.2 Populations

3.2.2.1 HPTN 083

HPTN 083 was conducted in 43 sites in US, Latin America, Asia and Africa [37%, 43%, 16% and 3% of enrolled participants, respectively (NCT02720094)]. The trial included adult (age 18 years and over) cisgender men and transgender women who have sex with men (male at birth) who were at high risk for sexually acquiring HIV based on self-report of at least one of the following:

- Any condomless receptive anal intercourse in the 6 months prior to enrolment (except within a monogamous HIV seronegative concordant relationship)
- More than five partners in the 6 months prior to enrolment
- Any stimulant drug use in the 6 months prior to enrolment
- Rectal or urethral gonorrhoea or chlamydia or incidence syphilis in the 6 months prior to enrolment
- SexPro score of ≤16 (US sites only; web-based tool for estimating personalized HIV risk score, scores range from 1 (highest risk) to 20 (lowest risk), with a score of ≤16 indicating high risk of HIV). The EAG notes that 85% of those tested (69% of all randomised participants) had a score of ≤16, and that this eligibility criterion was a protocol amendment.

Participants were required to be in general good health according to clinical and laboratory assessments, including HIV non-reactive HIV test results. Further eligibility criteria are listed in CS Table 7.

3.2.2.2 HPTN 084

HPTN 084 was conducted in 20 sites in 7 countries in sub-Saharan Africa (Botswana, Eswatini, Kenya, Malawi, South Africa, Uganda, and Zimbabwe). The

trial included participants aged 18 to 45 years, born female, and sexually active with a modified VOICE risk score of at least 5 (indicating high risk of HIV). Participants were also required to have a non-reactive HIV test, a negative pregnancy test and have evidence of surgical sterilisation, no uterus, or use of a reliable long-acting contraception. Further eligibility criteria are listed in CS Table 7. The EAG asked why females aged over 45 years were excluded (Clarification A9); the company stated in response that 'the study was targeted towards the most at-risk populations of women in each geographic setting (i.e., those with highest HIV incidence) in Sub Saharan African (SSA), including sexually active women evidenced with a score of >5 using an empiric HIV risk scoring tool called the modified VOICE risk score Balkus, 2016[41] which is a risk assessment tool to predict HIV acquisition and is validated among African women aged 18–45 years.' It is not clear what the company means by 'in each geographic setting'.

As both trials limited inclusion to adults aged 18 years and over, they excluded at-risk adolescents (age 13 to 17 years), who are a relevant group in this appraisal (the anticipated marketing authorisation specifies 'sexually acquired HIV-1 infection in at-risk individuals weighing at least 35 kg', so eligibility for the drug is defined by a weight cut-off rather than an age.) The EAG clinical expert advised that numbers of 13- to 17-year-olds in the UK would be very small, but would include young men who have sex with men and potentially vulnerable adolescents such as those within the care system. The company provided supporting evidence from two single arm Phase 2 studies for adolescent males aged <18 years and adolescent females aged <18 years.

The EAG clinical expert suggested that other subgroups relevant to this appraisal who may not be represented by the trials include:

- HIV-negative individuals having condomless sex with people living with HIV partners whose plasma viral load is not <200 copies/ml
- Heterosexual men and women at greater risk of HIV acquisition (including women aged over 45 years)
- Trans men and nonbinary people at greater risk of HIV acquisition

- People who, regardless of gender or sexual orientation, are likely to have condomless sex with people at risk of HIV

The EAG has additional concerns regarding the generalisability of the population of the trials to that of the relevant population in the UK (see section 3.5.1.1)

3.2.3 Interventions

In step 1, participants in the intervention group received oral cabotegravir 30 mg one daily for up to 5 weeks, and placebo for TDF/FTC (one tablet daily for 5 weeks). According to the provisional marketing authorisation, cabotegravir tablets may be used as an oral lead in prior to the initiation of cabotegravir injection to assess tolerability to cabotegravir, or following discussion with the individual, the physician may proceed directly to cabotegravir injection. The EAG clinical expert stated that in UK clinical practice, it is likely that an oral lead-in would be an option for people worried about side-effects. Participants in the comparator group received TDF/FTC 300 mg/200 mg fixed dose combination tablet (one tablet orally daily for 5 weeks) and placebo for oral cabotegravir (one tablet daily for 5 weeks).

In step 2, the intervention group received CAB-LA 600 mg administered as one 3 mL IM injection in the gluteal muscle at two time points 4 weeks apart and every 8 weeks thereafter, and placebo for TDF/FTC (one tablet orally daily, with or without food). The comparator group received TDF/FTC 300 mg/200 mg fixed dose combination tablet (one tablet orally daily) and PBO for CAB-LA (intralipid 20% fat emulsion infusion) administered as one 3 mL IM injection in the gluteal muscle at two time points 4 weeks apart and every 8 weeks thereafter.

Step 3: due to early stopping of the blinded periods of the trial, 19 participants from HPTN 083 and none from HPTN 084 entered Step 3, where both arms received open-label daily oral TDF/FTC 300 mg/200 mg fixed dose combination tablet.

OLE: Participants were offered a choice of open-label daily oral TDF/FTC or CAB-LA. Participants randomised to TDF/FTC wishing to initiate CAB-LA could have an optional daily oral cabotegravir lead-in for about 4 weeks. Those initiating CAB-LA for the first time (with or without oral lead-in) or participants who were eligible to re-start cabotegravir required a reloading dose of 2 injections, 4 weeks apart followed by CAB-LA injections every 8 weeks.

At each study visit, HIV testing and risk reduction counselling were provided, and condoms were offered. Participants also received adherence counselling and monitoring: the protocol for HPTN 083 states to this was in a manualised/standardised fashion with an individualised intervention for participants who have self-reported or evidenced challenges with adherence; and in HPTN 083 the protocol describes education around the importance of daily pill adherence and supporting strategies that link pill taking to the participant's daily routine, and counselling focused on the importance of returning for injection visits on or as close to the scheduled date as practical[39, 40]

As each arm in the trials received both an IM injection and oral tablets, the trials do not provide a comparison of adherence between IM injection and oral tablets. However, it does provide a measure of adherence between the two-arms. Receiving both an IM injection and oral tablets is not reflective of clinical practice, although the EAG acknowledges the necessity of implementing the double-blind stage of the trial design to minimise various biases, including selection, allocation, and outcome/performance bias, in estimating treatment effects.

3.2.4 Risk of bias in HPTN 083 and HPTN 084

The company assessed the risk of bias of the HPTN 083 and HPTN 084 (along with other studies identified by the SLR) using the minimum criteria recommended by NICE. A tabulation of the assessment is presented in CS Appendix D Tables 39 to 41, but a narrative description is not provided. The company's assessment identified no sources of biases in the trials. The EAG completed an independent assessment of HPTN 083 and HPTN 084 using Cochrane RoB version 2 (see 6.2). Overall, the EAG judged the trials to raise some concerns in two domains, but not to be at high risk of bias for any domain. There were some concerns regarding the potential for unblinding of care providers due to a possible slight difference in appearance between CAB-LA IM injection and placebo IM injection, and it was unclear whether deviations from the intended intervention arose because of the trial context. However, the modified ITT analysis, which excluded participants with HIV at baseline, was appropriate. The EAG had identified some concerns regarding potential for bias due to missing outcome data. The proportions pf participants retained and attending follow-up reduced from around 91% at 6 months to 75% at 24 months in HPTN 083 and from around 94% to 77% (CAB-LA arm) respectively in

HPTN 084. In addition, the observed number of HIV incidences in the CAB-LA arm was lower (HPTN 083: n =13 and HPTN 084: n = 4) than the number of participants who had no HIV test results (HPTN 083: n = 37 and HPTN 084: n=22). Reasons for missing follow-up visits or not undergoing HIV testing were not provided, and there is no evidence that the results was not biased by missing outcome data.

3.2.5 Baseline characteristics in HPTN 083 and HPTN 084

In the HPTN083 trial, 6333 participants (Appendix D, CS) were assessed for eligibility (*n* = 1763 were not enrolled/excluded). Participants underwent randomisation where they were allocated to CAB-LA (*n* = 2283, 1 was inappropriately enrolled) or oral PrEP. (*n* = 2287, 3 were inappropriately enrolled). Baseline characteristics (Table 6) included 2282 in the CAB-LA arm and 2284 in the oral PrEP arm.

In the HPTN084 trial, 4878 participants were assessed for eligibility (*n* = 1654 were not enrolled/excluded). Participants underwent randomisation where they were allocated to CAB-LA (*n* = 1614) or oral PrEP (*n* = 1610) where baseline characteristics were presented (Table 7).

Participant characteristics were generally well balanced within study groups (CAB-LA vs oral PrEP), Table 6, and Table 7. However, there were several imbalances across trials. A key difference was the racial and ethnic breakdown. In HPTN 083, there was a wider spread of racial groups and proportions of each group. Whereas, in HPTN 084, the majority of participants were from Black ethnicity. This is likely due to the recruitment countries of each trial: HPTN 083 spans the US, Latin America, Asia, and Africa, whilst HPTN 084 only includes participants from sub-Saharan African countries. There was also an imbalance in marital status. HPTN 083 participants were mainly single, divorced or widowed, whereas the majority of HPTN 084 reported ‘Not living with primary partner’.

Educational status was not balanced across trials. HPTN 083 had a higher percentage of participants who have had tertiary education (college, university, or higher), whilst the majority of HPTN 084 had a secondary education.

Table 6. HPTN 083 - summary of key baseline participant characteristics (ITT)[37]

Baseline characteristic	HPTN 083	
	CAB-LA	Oral PrEP
N	2282	2284
Cohort, %		
Cisgender men who have sex with men	88.2	86.6
Transgender women who have sex with men	11.7	13.3
Prefer not to say	0.1	<0.1
Age groups, %		
18–29 years	68.9	66.0
30–39 years	21.8	24.1
40–49 years	6.4	7.4
50–59 years	2.6	2.2
≥60 years	0.3	0.3
Age, years		
Mean (SD)[1]	[redacted]	[redacted]
Median (IQR)	26 (22-32)	26 (22-32)
Race, %[1]		
White	[redacted]	[redacted]
American Indian or Alaska Native	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]
Asian	[redacted]	[redacted]
Mixed race	[redacted]	[redacted]
Native Hawaiian or Other Pacific Islander	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Ethnicity, %		
Hispanic/Latino	46	47
Not Hispanic/Latino	54	53
Not reported	0	<1
Geographic region, %		

US	37.2	37.2
Argentina	7.4	7.4
Brazil	17.3	17.6
Peru	18.2	18.2
Thailand	12.1	12.2
Vietnam	4.4	4.3
Africa	3.4	3.2
Marital status, %		
Married, civil union or legal partnership	3.5	4.3
Living with primary or main partner	6	6.7
Have primary or main partner, not living together	7.5	7.2
Single, divorced or widowed	82.7	81.6
Other	0.3	0.2
Education, %		
No schooling	0.1	0.3
Primary school	1.2	1.8
Secondary school	21.5	22.9
Technical training	8.2	8.2
College or university or higher	69.0	66.8

Source: Landovitz et al, 2021 (119)
[1] Source: HPTN 083 Clinical Study Report

Table 7. HPTN 084 - summary of key baseline participant characteristics (ITT)[38]

Baseline characteristic	HPTN 084	
	CAB-LA	Oral PrEP
N	1614	1610
Sex assigned at birth, %		
Male	0	0
Female	100	100
Gender identity, %		

Male	0	<1
Female	99.9	99.8
Transgender male	<1	0
Age groups, %[i]		
18-25 years	[redacted]	[redacted]
26-35 years	[redacted]	[redacted]
36 to 45 years	[redacted]	[redacted]
Age, years		
Mean (SD)[i]	[redacted]	[redacted]
Median (IQR)	25 (22–30)	25 (22–20)
Race		
White	0	<2
Black or African American	>99	>99
Asian	<1	<1
Ethnicity, %		
Hispanic/Latino	0	0
Not Hispanic/Latino	100	100
Country, %		
Botswana	2.9	2.8
Eswatini	5.0	5
Kenya	1.9	2.2
Malawi	7	6.9
South Africa	40.5	40.7
Uganda	18.6	18.4
Zimbabwe	24.2	24.1
Marital status, %		
Married, civil union or legal partnership	10.5	10.8
Living with primary partner	6.6	7.3
Not living with primary partner	53.8	53.4

Single, divorced or widowed	28.8	28.2
Other	0.3	0.2
Education, %		
No schooling	1.2	0.7
Primary school	15.6	15.8
Secondary school	71.5	73.4
Technical training	3.0	2.5
College or university or higher	8.7	7.5

Source: Delany-Moretlwe et al, 2022 (120).
[l] Source: HPTN 084 Clinical Study Report

3.2.6 Overview of results from HPTN 083 and HPTN 084

3.2.6.1 HIV acquisition

The primary outcome of incident HIV acquisitions from HPTN 083 and HPTN 084 can be seen in Table 8. In the mITT analysis of incident HIV acquisitions in Steps 1 and 2 of both HPTN 083 and HPTN 084 CAB-LA appears to be effective at reducing HIV acquisitions compared with daily oral TDF/FTC PrEP.

In HPTN 083, in men who have sex with men and transgender women, the CAB-LA group had 13 acquisitions compared with 39 in the TDF/FTC group, demonstrating a 66% reduction of incidence during Steps 1 and 2 in the bias-adjusted HR, which accounted for the group sequential trial design and the decision to stop the trial at the second interim analysis. The HPTN study group also conducted on-blinded study product (OBSP) analysis, which censored the injection Step 2 efficacy population follow-up at the first time during the injection phase when the trial participant did not receive the allocated product schedule for any reason, therefore it excludes incident HIV acquisitions occurring during Step 1. At Step 2, the OBSP analysis shows a large preventative effect with CAB-LA, with [redacted] acquisitions in this group compared to [redacted] in the TDF/FTC group, resulting in an 84% reduction (see Table 8).

HPTN 084, in those assigned female at birth, also saw a larger effect of CAB-LA than TDF/FTC on HIV acquisition. At Steps 1 and 2, 4 participants acquired HIV in

the CAB-LA group, compared to 36 participants on daily oral TDF/FTC PrEP, indicating an 88% reduction of incident acquisitions in the bias-adjusted HR. Similarly, in the Step 2 OBSP analysis, there was a 95% reduction in HIV acquisitions on CAB-LA versus TDF/FTC, see Table 8.

Table 8. Incident HIV acquisitions in Steps 1 and 2 of HPTN 083 and HPTN 084

	HPTN 083		**HPTN 084**	
	CAB-LA	**Daily oral TDF/FTC**	**CAB-LA**	**Daily oral TDF/FTC**
Primary Efficacy Endpoint – incident HIV acquisitions in Steps 1 and 2 (mITT)				
N	2280	2281	1614	1610
Number of acquisitions	13	39	4	36
Person Years	3,211	3,193	[redacted]	[redacted]
Incidence rate/100 Person Years (95% CI)	0.40 [redacted]	1.22 [redacted]	0.20 [redacted]	1.85 [redacted]
Unadjusted HR (95% CI)	–	[redacted]	–	0.11 (0.04, .31)
Superiority p-value	-	[redacted]	–	p<0.0001
Non-inferiority p-value	-	[redacted]	NA	NA
Bias-adjusted HR (95% CI)	-	0.34 (0.18, 0.62)	-	0.12 (0.05, .31)
Superiority p-value	-	[redacted]	-	p<0.0001
Non-inferiority p-value	-	[redacted]	NA	NA
Supportive Analysis: Incident HIV-1 Infections While On Blinded Study Product (OBSP; Injection Step 2 Efficacy Population)				
N	[redacted]	[redacted]	[redacted]	[redacted]

Number of acquisitions	[redacted]	[redacted]	[redacted]	[redacted]
PY	[redacted]	[redacted]	[redacted]	[redacted]
Incidence rate/100 PY (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)		0.16 (0.06, 0.47)		0.05 (0.01, 0.37)
Superiority p-value		[redacted]		[redacted]

Abbreviations: HR: Hazard Ratio; NA: not applicable; TDF/FTC: tenofovir disoproxil fumarate/emtricitabine.

Source: adapted from CSs Table 12 and 16 and CSRs.

Both trials conducted post-hoc testing of stored plasma samples to better characterise the timing of HIV acquisition during the blinded phases of Steps 1 and 2 and these were presented in CS Sections B.2.6.1.1.3 and B.2.6.2.1.4 respectively. As post hoc analyses are prone to bias these have not been reproduced by the EAG.

3.2.6.2 Updated Analyses

The CS reports updated analysis of HIV acquisitions in Sections B.2.6.1.1.4 and B.2.6.2.1.5 for the two trials respectively, these analyses incorporated data from year one of the unblinded follow-up.

During the blinded phase of the HPTN 083 trial, there were three additional incident HIV acquisitions (CAB-LA n=1; TDF/FTC n=2) which were detected only after study unblinding. In an updated analysis of the blinded phase there were therefore 13 acquisitions in the CAB-LA arm, and 41 in the TDF/FTC arm, with an updated HR of 0.31 (95% CI: 0.17-0.58; *p*=0.0003). In the first unblinded year analysis, there were a total of 44 acquisitions (CAB-LA: 12; TDF/FTC: 32), with an HR of 0.35 (95% CI: 0.18, 0.69; *p*=0.0021). This analysis excluded 5 acquisitions in the CAB-LA arm which were excluded from the analysis as they occurred >3 years after study initiation (which was a prespecified exclusion, clarification A11). Finally, in the combined period, consisting of Step 1 and 2, plus 1-year unblinded follow-up, a total

of 98 HIV acquisitions occurred, with 25 in the CAB-LA arm, and 73 in the TDF/FTC arm. The HR of the combined period is 0.34 (95% CI: 0.22-0.53; *p* <0·0001).

In trial HPTN 084, in the updated analysis, there were 23 acquisitions that had occurred during the first unblinded year [CAB-LA: 3; TDF/FTC: 20 (B.2.6.2.1.5 incorrectly states this as 23)]. Of these, two additional HIV acquisitions were determined to have occurred during the blinded phase, with one in the CAB-LA arm, and one in the TDF/FTC arm. The combined period (Step 1 and 2, plus 1-year unblinded follow-up) had an HR of 0.11 (95% CI: 0.05, 0.24), with 6 acquisitions in the CAB-LA arm and 56 in the TDF/FTC arm.

Secondary analyses were conducted to evaluate incident HIV acquisitions that occurred during Step 2 only, using the Injection Step 2 Efficacy Population, these were reported in the CSRs but have not been reproduced by the EAG.

3.2.6.3 Adherence

The EAG noted some discrepancies between adherence by plasma drug detection in CS Table 20 (which were used in the ITC) and in CS Appendix D Tables 22 and 26. The EAG also had concerns regarding the extraction and calculation of these data from the original publications of some studies. For example, the calculation of adherence in Partners PrEP,[42] iPrEx Trial[43] and FEM-PrEP[44] excluded participants aho had acquired HIV and had low adherence. The 88% adherence rate reported for PROUD[42] appears to be from the following statement in the publication: 'sufficient study drug was prescribed for 88% of the total follow-up time', and not from plasma detection as implied by the CS. Plasma drug detection in 52 sampled participants *who reported they were taking PrEP was* 100%.[42] Completion rates of self-reported adherence measures were low in PROUD and data were not reported.

Table 9. Adherence by drug detectable in plasma presented in the CS Tables and original trial publications

Study	CS Table 20	**1.** CS App D Table 22 - Summary **2.** CS App D Table 26 – by Plasma	Original trial publication and EAG comments
Partners PrEP	0.81	1. High: 82% by plasma drug detection	TDF was detected in 3 of 12 (25%) participants who acquired HIV and in 374 of 464 samples (80.6%, which aligns with CS value of 81%)

Study	CS Table 20	**1.** CS App D Table 22 - Summary **2.** CS App D Table 26 – by Plasma	Original trial publication and EAG comments
Baeton 2012[42]		2. NR in App D Table 26	(note that this is 464 samples, participants n=100 in TDF/FTC arm) from those who did not acquire HIV. The EAG considers that this estimate of adherence is biased as it excludes those who acquired HIV (and who had low adherence). Estimate by apply the percentage of samples to n=100 without HIV, gives TDF detected in 81. Total 84/112 = 75%
Bangkok Tenofovir Study Choopanya 2013[32]	0.66	1. Low: 67% by plasma drug detection 2. TDF arm 66%	66%, aligned with value in ITC
iPrEx Trial Grant 2010[43]	0.50	1. Low: 51% by plasma drug detection 2. NR in App D Table 26	Study drug detected in: Seronegative: 22/43 (51%) Seropositive: 3/34 (8.8%) The EAG considers that this estimate of adherence is biased as it excludes those who acquired HIV (and who had low adherence). Total 25/77 = 32.5%
VOICE Marrazo 2015[45]	0.29	1. Low: 29% by plasma drug detection 2. TDF/FTC arm: 29%	29%, aligned with value in ITC
IperGay Molina 2015[33]	0.86	1. High: 86% by plasma drug detection 2. Event driven 82%-100% across months 1 to 10	86%, aligned with value in ITC
Tenefovir 2 Thigpen 2012[46]	0.77	1. High: 84.1% by pill count	2 of 4 (50%) infected with HIV had TDF detected, 55 of 69 (79.7%, aligns with 80% in CS Appendix)

Study	CS Table 20	**1.** CS App D Table 22 - Summary **2.** CS App D Table 26 – by Plasma	Original trial publication and EAG comments
		2: TDF 80%, FTC 81%	without HIV matched by sample date had TDF detected. Overall total across infected and uninfected: 57/73 = 78%. Unable to find company's value of 77%, but minor difference, and inclusion of HIV and non-HIV infected participants appropriate.
FEM-PrEP Van Damme 2012[44]	0.36	1. Low: 24% by plasma drug detection 2. Beginning of infection window: 35% End of infection window 37%	Target plasma level of tenofovir Women with seroconversion: 7 of 27 (26%) at the beginning of the infection window (excluding 6 women for whom the window started at enrollment), 7 of 33 (21%) at the end of the window, 4 of 27 (15%) at both visits Uninfected control participants 27 of 78 (35%) at the beginning of the infection window 35 of 95 (37%) at the end of the window, 19 of 78 (24%) at both visits. It is unclear whether the number at 'both visits' was in addition to, or already counted in, the numbers at the beginning and end of infection window. The 36% used in the ITC appears to be based on only uninfected participants, the EAG considers that this estimate of adherence is biased as it excludes those who acquired HIV (and who had low adherence). Total 99/338 = 29%
PROUD McCormack 2016[42]	0.88	1. High: 88% by self-report and plasma drug detection 2. 100%	Plasma drug detection in 52 sampled *participants who reported taking PrEP:* 100%. Unclear if they had HIV or not. States sufficient study drug was prescribed for 88% of the total follow-up time. The 88% used in

Study	CS Table 20	**1.** CS App D Table 22 - Summary **2.** CS App D Table 26 – by Plasma	Original trial publication and EAG comments
			the ITC appears to be based on this, and is not based on plasma drug detection as implied by the CS.
HPTN 083	0.86	1. Plasma drug detection not reported 2. 86% (TDF ≥0.31 ng/mL); 74.2% (TDF ≥40 ng/mL)	86% (concentrations above the lower limit), aligned with value in the ITC [redacted] in CS Section B.2.6.1.3.3 using a threshold of ≥4.2 ng/mL for plasma TFV]
HPTN 084	0.56	1. Plasma drug detection not reported 2. 55.9% (TDF ≥0.31 ng/mL); 41.9% (TDF ≥40 ng/mL)	55.9% (concentrations above the lower limit), aligned with value in the ITC [redacted] in CS Section B.2.6.2.2.2 using a threshold of ≥4.2 ng/mL for plasma TFV]

3.2.6.3.1 Adherence during Step 1

Adherence to Step 1 of each trial was measured through pill count in both CAB-LA and TDF/FTC arms. In HPTN 083, at Week 4, 67% of participants taking oral cabotegravir and 66% in daily TDF/FTC demonstrated 90-100% adherence to the study product. In HPTN 084, 90-100% adherence at Week 4 was seen in [redacted] of participants in both groups.

Participants with pill counts resulting in ≥50% adherence progressed to the injection phase (Step 2). This appears to be the case in both trials, although this was not clearly stated in protocol of HPTN 084, which only states that participants progressed if adequate safety was achieved.

3.2.6.3.2 Adherence to injections (CAB-LA or placebo)

Adherence to injections in Step 2 of the trials was measured by the number of injection visits. The CS states that [redacted]' injection visits in both trials occurred within the allowable ±7-day window. No definition for '[redacted]' was reported but the EAG agrees the proportions of injection visits within the ± 7 day window were

approximately [redacted] and [redacted], CAB-LA and TDF/FTC respectively in HPTN 083, and [redacted] CAB-LA and TDF/FTC respectively in HPTN 084. Less than one per cent of each arm of HPTN 083 and 7%-8% of HPTN 084 missed injections (Table 10). The CS reports that for CAB-LA the injection coverage (defined as injections having been received with a delay of less than two weeks) was 91.5% for trial HPTN 083 and 93.0% for HPTN 084.

Data regarding changes in adherence over time is only available for HPTN 083, where CAB-LA injection coverage declined from 91.5% during the updated primary blinded period, to 79.9% during the first unblinded year.[47]

Table 10. Summary of Adherence to CAB-LA Injection Dosing Schedule (Injection Step 2 Safety Population)

	HPTN 083		HPTN 084	
Timeliness of Injections Relative to Date of Projected Dosing Visits	**CAB-LA (n=2117)**	**TDF/FTC (n=2081)**	**CAB-LA (n=1519)**	**TDF/FTC (n=1516)**
No. of injection visits	[redacted]	[redacted]	[redacted]	[redacted]
Approximate % of injections out of the total injection visits at various time windows				
-7 days to -1 day	[redacted]	[redacted]	[redacted]	[redacted]
0 days	[redacted]	[redacted]	[redacted]	[redacted]
1 day to 7 days	[redacted]	[redacted]	[redacted]	[redacted]
Missed injection	[redacted]	[redacted]	[redacted]	[redacted]
Early out of window injections (more than 7 days early relative to projected visit date) number of days relative to the projected visit date				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Late out of window injections (more than 7 days late relative to projected visit date) number of days relative to the projected visit date				
n	[redacted]	[redacted]	[redacted]	[redacted]

Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

Source: adapted from HPTN 083 CSR, Table 8, p. 66 and HPTN 084 CSR, Table 12, p. 81.

3.2.6.3.3 Adherence to TDF/FTC

Adherence to TDF/FTC was assessed in small subsets of both trials, evaluated based on plasma tenofovir (TFV) concentrations, and intraerythrocytic tenofovir-diphosphate (TFV-DP) concentrations collected as dried blood samples (DBS). The benchmark for adherence were concentrations estimated to be consistent with ≥4 doses per week (≥4.2 ng/mL; ≥700 fmol/punch), the dosage at which TDF/FTC is an effective PrEP agent.[43] Overall, in HPTN 083 approximately [redacted] (TFV) and 73% (TFV-DP) of samples were consistent with this benchmark (Table 11). In the trial publication[47] they report the threshold for plasma TFV concentrations in those with at least 40 ng/mL (≥7 doses/week) to be reached in 74.2% and TFV-DP equivalent to at least 4 doses to be 72.3%. In HPTN 084, an overall ~[redacted] of plasma samples yielded TFV results consistent with ≥4 doses/week, and ~[redacted] were consistent with ≥4 doses/week in TFV-DP. Further detailed breakdown can be seen in CS Table 14 and 17.

HPTN 083 appears to have a relatively higher adherence to TDF/FTC compared to HPTN 084. There was also a [redacted]

This difference in adherence between trials is possibly due to gender-based differences. Studies identified by a systematic literature review on adherence performed by the company found several studies reported low adherence in cisgender women in Africa. For example, the DREAMs PrEP study showed that 84% of its population of Kenyan cisgender women self-reported taking ≥4 doses in the past week; however, the equivalent DBS indicated that only 4.6% met the ≥700 fmol/punch mark.[48] Similarly, pill count data from cisgender women in Mozambique showed that 90% of women displayed 90-100% adherence to pill, yet DBS measures indicated that adherence was only 44%.[49]Landovitz 2023[47] reports proportions of TFV-DP concentrations in DBS and plasma TFV concentrations for the first

unblinded year for HPTN 083, in Figure 2. The proportion of samples that are consistent with ≥4 doses/week is higher during the blinded period compared to the unblinded year. There are no data from the unblinded period for 084 regarding adherence.

The EAG notes there was no assessment of adherence to oral placebo in the CAB-LA arm in both trials. Adherence measures in the trials were therefore not reflective of real-world practice as participants have both injections and oral. In addition, the EAG comment that comparisons of rates of adherence to CAB-LA and adherence to TDF/FTC are not appropriate.

Table 11. Summary of TDF/FTC adherence based on percentage of plasma TFV, and percentage of DBS TFV-DP concentrations within ranges by visit (TDF/FTC adherence population)

	HPTN 083			HPTN 084		
	% within TFV concentration ranges consistent with target doses/week					
Visit	**N Samples**	**7/wk**	**4 to <7/wk**	**N**	**7/wk**	**4 to <7/wk**
Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wk 129	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wk 153	[redacted]	[redacted]	[redacted]	-	-	-
Overall	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit	**% within TFV-DP concentration ranges consistent with target doses/week**					
Wk 4	386	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wk 129	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wk 153	[redacted]	[redacted]	[redacted]	-	-	-
Overall	[redacted]	34	39	[redacted]	[redacted]	[redacted]

Source: adapted from CS Table 14 and 17.

3.2.7 Plasma CAB-LA in HIV-acquired participants

Plasma CAB-LA was assessed in those acquiring HIV during the study and summary results were presented in CS Section B.2.6.1.3.2 and B.2.6.2.2.1. There is little consistency in the findings as there were generally individual reasons per participant reported. The EAG has summarised the key information only and has verified this with the trial publication and CSR.

In HTPN 083, 16 participants acquired HIV during Steps 1 and 2. The CS reports that of the 12 HIV cases occurring in step 2, five occurred with no recent exposure to CAB-LA; three occurred before CAB-LA injection and four occurred during on-time CAB-LA when the plasma CAB-LA concentration was as expected. Three participants acquired HIV during the oral lead-in. Following extended virological testing after the primary analysis, one case was deemed to be a baseline acquisition, but had previously been classified as an incident acquisition. During the unblinded year there were 18 additional cases and the CS reports that two had on time injections and three were in the setting of on-time injections but had at least one injection with ≥8-week delay prior to HIV detection. Two cases had restarted CAB-LA after a ≥6-month interruption and detection of HIV was delayed at the study site, and 11 cases had no CAB-LA within 6-months.

In HPTN 084, 4 HIV acquisitions were identified: two had not received any CAB-LA injections and two occurred during active injections. Of the participants whose acquisitions were during the injection phase, one (Case DX) had experienced delays to injections outside of the allowable window, and one (Case A1) was reported to have demonstrated inconsistent adherence to CAB OLI and was subsequently re-classified as a baseline infection.[50]

3.2.8 Secondary outcomes

Secondary outcomes reported in the CS included:

- Renal function.
- Liver function.
- Bone mineral density.

- Incidence of HIV drug resistance mutations among participants who acquire HIV

The CS states that change in viral load and HRQoL data were not collected in the trials. The CS also reports that acceptability scale assessments, sexual risk factors, incident STIs, weight, blood pressure, fasting glucose, and fasting lipids were outcomes in the two trials (presented in CS Appendix F) but as these were not scoped outcomes the EAG has not reproduced these here.

3.2.8.1 Renal function

Renal function was measured by change from baseline in creatinine and creatinine clearance levels and reported in the CS with the adverse events.

In the safety population of trial HPTN 083 blood creatinine increased in 17% in the CAB-LA arm and in 19% in the TDF/FTC arm, Table 12 Creatinine renal clearance decreased in 69% of the participants in the safety population in the CAB-LA arm and 73% in the TDF/FTC arm. Although no statistical analyses were undertaken to compare these rates it would appear that rates were similar between groups.

Grade ≥2 creatinine AEs were reported in CS Table 25 where there was [redacted] Grade ≥3 blood creatinine increases were reported to be [redacted] in the CSR. Grade ≥3 creatinine clearance decreased in 7% in the CAB-LA arm and 8% in the TDF/FTC arm.

Creatinine events considered to be drug-related were reported in 29% and 32% for the CAB-LA and TDF/FTC arms respectively for creatinine renal clearance decreased and in 7% in each arm for blood creatinine increased, Table 12. There were [redacted] The CS reports that adverse events of special interest [redacted]

An OBSP safety analysis was also undertaken and summary results for creatinine reported in CS Appendix F. In steps 1 and 2 the maximum post-baseline creatinine changes occurred in [redacted] of participants in the CAB-LA arm and [redacted] of participants in

the TDF/FTC arm. In both groups, [redacted] of participants had Grade ≥3 blood creatinine elevations. The maximum post-baseline creatinine clearance changes occurred in [redacted] of participants in the CAB-LA arm and [redacted] of participants in the TDF/FTC arm. In the CAB arm, [redacted] had creatinine clearance changes of Grade ≥3 compared to [redacted] in the TDF/FTC arm.

In the trial HPTN 084 safety population, blood creatinine increased in 22% in both the CAB LA arm and the TDF/FTC arm, Table 12. Creatinine renal clearance decreased in 72% of the participants in the CAB-LA arm and 74% in the TDF/FTC arm. These rates were comparable across arms.

Grade ≥2 creatinine AEs were reported in CS Table 29 where rates [redacted] Grade ≥3 creatinine renal clearance decreased in 7% in the CAB-LA arm and 8% in the TDF/FTC arm. Grade ≥3 blood creatinine increased in 4% in both arms respectively.

Creatinine renal clearance decrease that was considered to be drug-related were reported in 43% in the CAB-LA arm and [redacted] in the TDF/FTC arm, and for blood creatinine increased the rates were 13% and [redacted] for the two arms respectively, Table 12.

The CS reports that adverse events of special interest [redacted]

In the OBSP analysis (CS Appendix F) the maximum post-baseline graded creatinine changes in blood creatinine occurred in [redacted] in the CAB-LA arm and [redacted] in the TDF/FTC arm. Grade 3 blood creatinine changes occurred in [redacted] in the CAB LA arm and [redacted] in the TDF/FTC arm. Grade 4 creatinine elevations occurred in [redacted] in the CAB LA arm and [redacted] in the TDF/FTC arm. The maximum post-baseline graded creatinine clearance changes occurred in [redacted] of participants in the CAB LA arm and [redacted] of participants in the TDF/FTC arm. Grade 3 creatinine clearance changes were seen in [redacted] in the CAB LA arm and [redacted] in the TDF/FTC arm. Grade 4 events were [redacted] in either arm.

Table 12. Creatinine events in HPTN 083 and HPTN 084, steps 1 and 2, Safety population

n (%)	HPTN 083		HPTN 0 84	
	CAB-LA n=2,281	**TDF/FTC, n=2,285**	**CAB-LA n=1,614**	**TDF/FTC, n=1,610**
Creatinine renal clearance decreased	1,576 (69)	1,661 (73)	1,160 (72)	1,192 (74)
Blood creatinine increased	379 (17)	426 (19)	363 (22)	347 (22)
Considered drug related				
Creatinine renal clearance decreased	671 (29)	723 (32)	692 (43)	[redacted]
Blood creatinine increased	166 (7)	169 (7)	213 (13)	[redacted]

Reproduced from CS Tables 24-26 and 28-29.

3.2.8.2 Liver function

Liver function was measured by changes from baseline in Grade 3 or 4 treatment-emergent liver enzyme abnormality observations. The CS reports that for both HPTN 083 and HPTN 084 trials the maximum intensity of Grade 3 or 4 treatment-emergent liver enzyme abnormality observations were [redacted] between arms Table 12. Summary Grade 3 and Grade 4 events in the safety population, taken from the CSR, can be seen in and the EAG concurs that the rates were similar between arms in both trials. Rates of any grade liver enzyme AEs in the safety populations were [redacted] Similarly, [redacted]. ALT ≥3xULN and total bilirubin ≥2xULN required expedited reporting in both trials. During Steps 1 and 2 in trial HPTN 083, [redacted] met this criteria. In trial HPTN 084 [redacted] met these criteria.

Table 13. Grade 3 and Grade 4 Liver enzyme observations in HPTN 083 and HPTN 084 (Safety population)

n (%)	HPTN 083		HPTN 0 84	
	CAB-LA n=2,281	**TDF/FTC, n=2,285**	**CAB-LA n=1,614**	**TDF/FTC, n=1,610**

Alanine Aminotransferase Grade 3 Grade 4	[redacted]	[redacted]	[redacted]	[redacted]
Aspartate Aminotransferase Grade 3 Grade 4	[redacted]	[redacted]	[redacted]	[redacted]
Bilirubin Grade 3 Grade 4	[redacted]	[redacted]	[redacted]	[redacted]
Alkaline Phosphatase Grade 3 Grade 4	[redacted]	[redacted]	[redacted]	[redacted]

Reproduced from HPTN 083 CSR table 48 and HPTN CSR table 64

3.2.8.3 Bone mineral density

Bone mineral density was measured by changes in Z-score from baseline and dual-energy x-ray absorptiometry (DXA) for osteopenia and osteoporosis in HPTN 083, in a subset of participants from study sites that had the DXA scanning facilities (CS Appendix F). Examinations at week 57 and week 105 were undertaken in 254 participants (132 CAB-LA; 122 TDF/FTC). The CS Appendix F reports that at the lumbar spine, the median percentage change in BMD increased with CAB-LA (0.82%) and decreased with TDF/FTC (–0.82%), with a between arm difference of –1.6% (95% CI: –2.4, –0.87); p< 0.01 at 57 weeks (n=248), citing a conference abstract by Brown et al.[51] The CS Appendix F also states that the difference persisted to Week 105, where the between arm difference was –2.3% (95%CI: –3.4, –1.1%); p< 0.01 (n=203) and that the CS also reports that similar results were observed at both the femoral neck and total hip. The EAG has not been able to fully verify any of these data from the conference abstract provided although note that the figure presented in the abstracts does show an increase in BMD for CAB-LA and a decline for TDF/FTC. The CSR for trial 083 states that the [redacted] As a subgroup analysis the reliability of these data is not clear.

3.2.8.4 Incidence of resistance mutations

Both studies evaluated rates of HIV drug resistance among participants who acquire HIV during the study (as secondary outcomes in HPTN 083 and tertiary outcomes in HPTN 084). CS sections B.2.6.1.2.1 and B.2.6.2.3.1 report resistance mutations to study products among those who acquired HIV in the two trials respectively. The resistance mutations included K65R, M184V/L and Q148R, and HIV genotyping was performed at the first visit when the HIV viral load was greater than 500 copies/mL. Post hoc analyses for the study periods steps 1 and 2 and 1-year of unblinding in HPTN 083 were undertaken by grouping participants by the CAB-LA exposure status at the time of HIV acquisition. Results are presented in CS Table 13 but these have not been reproduced by the EAG. In HPTN 083, over the periods of steps 1 and 2 and 1-year of unblinding, major integrase strand transfer inhibitor (INSTI) resistance-associated mutations (RAM) were observed in 10 cases in the CAB-LA arm, and none were observed in the TDF/FTC arm. In the TDF/FTC arm, at genotyping performed at the first visit HIV acquisition was confirmed, there were 7 cases with NNRTI only resistance, three with both NNRTI and NRTI resistance and one with NRTI only resistance. Ten cases of major RAMs were detected during the blinded period (6 major NRTI, 4 of which also had one or two major NNRTI, and 4 single NNRTI). In HPTN 084 there were no major INSTI RAMS observed in the CAB-LA arm or the TDF/FTC arm. In the TDF/FTC arm there was one NRTI RAM, NNRTI RAMS in 9 participants and INSTI mutations in 10 samples.

3.2.9 Adverse events from HPTN 083 and HPTN 084

Adverse events were reported for the Safety Populations in HPTN 083 and HPTN 084, defined as all ITT participants (all randomised participants, excluding those inappropriately enrolled) who received any oral or injectable product.

On blinded study product (OBSP) safety analysis during Step 1 and Step 2 was presented in the CS (section B.2.10). This is not defined in the CS, but the CSR states [redacted] The EAG considers that there is the potential for AEs

to be missed that occurred after censoring in the OBSP analysis, but notes that there is a footnote in CS Table 27 (reproduced in Table Table 14 below) listing an AE occurring during the non-OBSP of HPTN 084. It is unclear whether there were any non-OBSP AEs in HPTN 083.

Safety analysis which included AEs occurring until the first injection date or 120 days post randomization, whichever occurred first (for Step 1) and through to 48 weeks after the last injection, was also planned but not reported in the CS.

3.2.9.1 Overview of adverse events

An overview of adverse events is presented in Table 14. In HPTN 083, drug-related AEs were more common in the CAB-LA group compared with the TDF/FTC group (82% vs 59%), whereas the difference between arms was less in HPTN 084 (68% vs 63%), see Table 15 for details. Drug-related AEs excluding injection site reactions (ISRs) were similar between the arms of each trial, but slightly higher in HPTN 084 than HPTN 083. ISRs and drug-related ISRs were higher in the CAB-LA arms than the TDF/FTC arms of each trial, but those in the CAB-LA arm of HPTN 083 (cabotegravir: ISR 76%, drug-related ISR 81%) were higher than those in the CAB-LA arms of HPTN 084 (CAB-LA: ISR 38%, drug-related ISR 38%). A similar pattern was observed for Grade ≥2 ISR and drug-related ISR adverse events. The frequency of Grade ≥3 adverse events were similar across arms of each trial; Grade ≥3 AEs excluding ISRs were higher in HPTN 083 than 084 (see Table 16 for details).

SAEs and adverse events leading to study drug discontinuation were low and similar between arms of each trial (Table 14). In HPTN 083 there were 10 fatal SAEs (four in the CAB-LA arm and six in the TDF/FTC arm). In HPTN 084 there were 3 fatal SAEs, both in the CAB-LA arm (one occurred during non-OBSP). Only one of the fatal SAEs (in TDF/TTC arm of HPTN 083) was considered to be related to the study drug.

Table 14. Overview of adverse events in HPTN 083 and HPTN 084 during Steps 1 and 2

	HPTN 083		HPTN 084	
n (%)	**CAB-LA (N=2,281)**	**TDF/FTC (N=2,285)**	**CAB-LA (N=1,614)**	**TDF/FTC (N=1,610)**
Any AE	2,174 (95)	2,157 (94)	1,556 (96)	1,540 (96)
Drug-related AEs	1,874 (82)	1,355 (59)	1,098 (68)	1,014 (63)
Any AE, excluding ISR	2,143 (94)	2,151 (94)	1,554 (96)	1,540 (96)
Drug-related AE, excluding ISRs	1,075 (47)	1,134 (50)	980 (61)	998 (62)
ISR AE[a]	1,740 (76)	726 (32)	578/1519 (38)	166/1516 (11)
Drug-related ISR AE[a]	1,724/2117 (81)	652/2081 (31)	575/1519 (38)	163/1516 (11)
Any Grade ≥2 AEs	2,115 (93)	2,107 (92)	1,489 (92)	1,480 (92)
Drug-related Grade ≥2 AEs	1,391 (61)	951 (42)	903 (56)	848 (53)
Grade ≥2 AEs, excluding ISRs	2,092 (92)	2,103 (92)	1,482 (92)	1,478 (92)
Drug-related Grade ≥2 AEs, excluding ISRs	871 (38)	900 (39)	833 (52)	841 (52)
Grade ≥2 ISR AEs[a,b]	1,022/2117 (48)	139/2081 (7)	196/1519 (13)	27/1516 (2)
Drug-related Grade ≥2 ISR AEs[a]	1,009/2117 (48)	121/2081 (6)	192/1519 (13)	25/1516 (2)
Any Grade ≥3 AEs	745 (33)	754 (33)	265 (16)	274 (17)
Drug-related Grade ≥3 AEs	131 (6)	93 (4)	86 (5)	99 (6)
Grade ≥3 AEs, excluding ISRs	716 (31)	754 (33)	264 (16)	274 (17)

	HPTN 083		HPTN 084	
n (%)	**CAB-LA (N=2,281)**	**TDF/FTC (N=2,285)**	**CAB-LA (N=1,614)**	**TDF/FTC (N=1,610)**
Drug-related Grade ≥3 AEs, excluding ISRs	84 (4)	93 (4)	85 (5)	99 (6)
Grade ≥3 ISR AEs[a,b]	54/2117 (3)	0/2081	1/1519 (<1)	1/1516 (<1)
Drug-related Grade ≥3 ISR AEs[a]	54/2117 (3)	0/2081	1/1519 (<1)	1/1516 (<1)
AEs leading to discontinuation of study drug	135 (6)	91 (4)	17 (1)	22 (1)
Drug-related AEs leading to discontinuation of study drug	67 (3)	24 (1)	0	0
ISRs leading to discontinuation of study drug	47[e] (2)	0	0	0
Any SAE	109 (5)	104 (5)	25 (2)	33 (2)
Drug-related SAE	4 (<1)	3 (<1)	1 (<1)	3 (<1)
Fatal SAEs	4 (<1)	6[c] (<1)	2[d]	0
Drug-related fatal SAEs	0	1 (<1)	0	0

Source: CS Tables 23 and 27. AE, adverse event; ISR, injection site reaction; OBSP, on blinded study product; SAE, serious adverse event; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

[a] N in this category is the number of participants who received at least one injection of study drug (Injection Safety Population) in Step 2 only (see CS Table 10 for analysis sets), apart from ISR AE in HPTN 083, which uses the Safety Population – the CS and CSR do not specify a reason for this discrepancy.

[b] For HPTN 084: no participant experienced a Grade 4 or 5 ISR and 1 participant in each treatment group experienced one or more Grade 3 ISRs

[c] One additional death occurred during Step 3 (stab wound in the TDF/FTC arm).

[d] An additional AE (hypertensive heart disease) was reported during Step 2 non-OBSP.

[e] 48 (2%) participants experienced AEs leading to study drug discontinuation in the general disorders and administration site conditions system organ class (CS B.2.10.1.5).

3.2.9.2 Drug-related adverse events

[redacted]. Other drug-related AEs were similar between arms (Table B). Injection site pain was more common in HPTN 083 than HPTN 084, whereas [redacted], see below for details on renal function.

Table 15. Drug-related AEs in ≥5% of participants in either trial (Steps 1 and 2; Safety population)

	HPTN 083		HPTN 084	
Preferred term n (%)	**CAB-LA (N=2,281)**	**TDF/FTC (N=2,285)**	**CAB-LA (N=1,614)**	**TDF/FTC (N=1,610)**
Total drug-related AEs	1,874 (82)	1,355 (59)	1,098 (68)	1,014 (63)
Injection site pain	1,697 (74)	612 (27)	519 (32)	[redacted]
Creatinine renal clearance decreased	671 (29)	723 (32)	692 (43)	[redacted]
Amylase increased	[redacted]	[redacted]	252 (16)	[redacted]
Headache	[redacted]	[redacted]	190 (12)	[redacted]
Blood phosphorus decreased	[redacted]	[redacted]	169 (10)	[redacted]

	HPTN 083		HPTN 084	
Preferred term n (%)	**CAB-LA (N=2,281)**	**TDF/FTC (N=2,285)**	**CAB-LA (N=1,614)**	**TDF/FTC (N=1,610)**
Injection site nodule	263 (12)	[redacted]	[redacted]	[redacted]
Injection site induration	255 (11)	[redacted]		
Injection site swelling	204 (9)	[redacted]	[redacted]	[redacted]
Blood creatinine increased	166 (7)	169 (7)	213 (13)	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			[redacted]	[redacted]
[redacted]			[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	115 (5)		
Nausea	[redacted]	125 (5)	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: CS Tables 26 and 30, CSRs

Abbreviations: AE, adverse event; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

3.2.9.3 Adverse events Grade ≥2 and Grade ≥3

The overall frequency of Grade ≥2 AEs was the primary safety endpoint in both trials (Table C). The most common AEs in CAB-LA arm of HPTN 083 were

[redacted], [redacted] In HPTN 084 these were [redacted] Grade ≥3 AEs were generally balanced between arms of each trial, [redacted] See Renal Function section.

Table 16. Most frequent Grade ≥2 (≥10% in either trial) and Grade ≥3 A Es (≥1% in either trial), Steps 1 and 2; safety population)

	HPTN 083		HPTN 084	
Preferred term n (%)	**CAB-LA (N=2,281)**	**TDF/FTC (N=2,285)**	**CAB-LA (N=1,614)**	**TDF/FTC (N=1,610)**
Any Grade ≥2 AEs	2,115 (93)	2,107 (92)	1,489 (92)	1,480 (92)
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
Any Grade ≥3 AEs				

	HPTN 083		HPTN 084	
Preferred term n (%)	**CAB-LA (N=2,281)**	**TDF/FTC (N=2,285)**	**CAB-LA (N=1,614)**	**TDF/FTC (N=1,610)**
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				

Source: adapted from CS Tables 25 and 29 and CSRs

Abbreviations: AE, adverse event; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

3.2.9.4 Common adverse events

The most common adverse events are summarised in Table D. In HPTN 083, the most common AEs in the CAB-LA arm were ISRs (including injection site pain, injection site nodule, and injection site induration), creatinine renal clearance decreased and blood creatinine phosphokinase increased (see **Renal function** section). In HPTN 084, the most common AEs in the CAB-LA arm creatinine renal clearance decreased, blood glucose increased, amylase increased, and injection site pain. There were differences between the trials in some adverse events, for example amylase increased, blood glucose increased and blood phosphorus decreased were

more common in HPTN 084; and ISRs, nasopharyngitis and diarrhoea were more common in HPTN 083 (Table 17).

Table 17. Summary of common AEs (≥10% in either trial, Steps 1 and 2; Safety population) in HPTN 083 and HPTN 084

	HPTN 083		HPTN 084	
Preferred Term n (%)	**CAB-LA (N=2,281)**	**TDF/FTC (N=2,285)**	**CAB-LA (N=1,614)**	**TDF/FTC (N=1,610)**
Any AE	2,174 (95)	2,157 (94)	1,556 (96)	1,540 (96)
Injection site pain	1,713 (75)	688 (30)	522 (32)	147 (9)
Creatinine renal clearance decreased	1,576 (69)	1,661 (73)	1,160 (72)	1,192 (74)
Amylase increased	[redacted]	[redacted]	558 (35)	573 (36)
Blood glucose decreased	[redacted]	[redacted]	425 (26)	439 (27)
Blood creatine phosphokinase increased	506 (22)	497 (22)	237 (15)	263 (16)
Blood creatinine increased	379 (17)	426 (19)	363 (22)	347 (22)
Nasopharyngitis	383 (17)	379 (17)	[redacted]	[redacted]
Headache	377 (17)	356 (16)	377 (23)	373 (23)
Blood phosphorus decreased	[redacted]	[redacted]	278 (17)	322 (20)
Diarrhoea	328 (14)	336 (15)	[redacted]	[redacted]
Anal chlamydia infection	264 (12)	297 (13)		
Chlamydia infection			[redacted]	[redacted]
Upper respiratory tract infection	264 (12)	271 (12)	268 (17)	293 (18)

	HPTN 083		HPTN 084	
Preferred Term n (%)	**CAB-LA (N=2,281)**	**TDF/FTC (N=2,285)**	**CAB-LA (N=1,614)**	**TDF/FTC (N=1,610)**
Injection site nodule	263 (12)	13 (<1)	[redacted]	[redacted]
Lipase increased	255 (11)	272 (12)	198 (12)	171 (11)
Injection site induration	255 (11)	8 (<1)		
Blood glucose increased	247 (11)	166 (7)	584 (36)	451 (28)
Pyrexia	232 (10)	112 (5)		
Proctitis gonococcal	220 (10)	236 (10)		
Aspartate aminotransferase increased	213 (9)	220 (10)	212 (13)	181 (11)
Alanine aminotransferase increased	186 (8)	220 (10)	232 (14)	228 (14)
Urinary tract infection			225 (14)	210 (13)
Dysfunctional uterine bleeding			161 (10)	161 (10)
Vulvovaginal candidiasis			139 (9)	162 (10)
Nausea	[redacted]	[redacted]	79 (5)	157 (10)

Source: Adapted from CS Tables 24 and 28, CSRs

Note: AEs occurring in ≥5 to <10% of participants are described in **Error! Reference source not found.**.

Abbreviations: AE, adverse event; OBSP, on blinded study product; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

3.2.9.5 Adverse events of special interest (AESI)

Pre-specified AESI are presented Table 18. Apart from ISRs, the frequency of AESI were similar between arms.

Table 18. Summary of AESIs

Preferred term, n (%)	HPTN 083		HPTN 084	
	CAB-LA (N=2,281)	TDF/FTC (N=2,285)	CAB-LA (N=1,614)	TDF/FTC (N=1,610)
ISR	1,740/2117 (82)[a]	726(32) [a b]	578 (38) [c]	166 (11) [c]
Hypersensitivity reactions	[redacted](2)	[redacted] (2)	[redacted](<1)	[redacted] (<1)
Hepatotoxicity	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted] (4)	[redacted] (4)	[redacted] (4)	[redacted](4)
Neuropsychiatric Events (in ≥4% of participants)				
Sleep Disorders	217 (10)	248 (11)	81 (5)	76 (5)
Depression	115 (5)	108 (5)	7 (<1)	12 (<1)
Anxiety	99 (4)	97 (4)	16 (<1)	11 (<1)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: CS Appendix F Tables 4 and 9.

[a] Number of participants with ≥1 ISR AE. [b] Reported in CS Appendix F Table 4 as [redacted] but this appears to be an error. [c] N=1,159 for cabotegravir arm and N=1,516 for TDF/FTC arm. Abbreviations: AESI, adverse event of special interest; ISR, injection site reaction; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

3.2.9.6 Adverse events during pregnancy

Pregnancy-related adverse events and outcomes in HPTN 084 are presented in CS Appendix F.1.2.5.3.5. Outcomes for the [redacted] confirmed pregnancies, and outcomes for pregnancies ending before confirmation/pending confirmation [redacted].

3.2.9.7 Safety during open-label follow-up

Incidence rates/100 person years of Grade≥2 adverse events during the first year of open label follow-up are reported in CS Appendix F Table 5 for HPTN 083 (data not reported for HPTN 084). Incidence rates of pyrexia were statistically significantly higher with CAB-LA compared with TDF/FTC, while incidence rates of decreased creatinine clearance were statistically significantly higher with TDF/FTC. In addition, the newly observed events of increased blood pressure, malaise, increased total and LDL cholesterol, and proctitis occurred at a significantly increased rate with CAB-LA during the first unblinded year. ISRs were not reported CS Appendix F, Table 5, but it is stated that ISRs 'reduced over time, reported at approximately half of the rate than that observed during the blinded phase, and did not lead to any discontinuations of CAB-LA during the first unblinded year'.

3.2.10 Subgroup analysis

No subgroup analyses were considered in the company decision problem; however, pre-specified subgroup analyses were undertaken in HPTN 083 and HPTN 084 and reported in CS Appendix E.

In HPTN 083 pre-specified subgroups were age (< 30: ≥30 years), gender (transgender women; men who have sex with men), race (Black/African American: Non-black, ethnicity (Hispanic: non-Hispanic), region (US: Latin America: Asia: Africa), sex partner (≤ median: > median) and condomless anal sex (≤ median: >median) and incident HIV acquisitions across these subgroups can be seen in CS Appendix E Figure 1

In HPTN 084 pre-specified subgroups were age (< 25: ≥25 years), BMI (< 30: ≥30) and can be seen in CS Appendix E Figure 2.

CS Section B.2.7.1 states that these pre-specified subgroups in both trials across Steps 1 and 2 show results consistent with the overall treatment effect of CAB over TDF/FTC.

3.2.11 Phase 2 CAB-LA studies

The company provided supportive evidence from two single-arm Phase 2 studies (CS Appendix M), which aimed to evaluate the safety, tolerability and acceptability of cabotegravir in healthy, HIV-negative individuals:

- Male adolescents age <18 years (HPTN 083-01)
- Cisgender female adolescents age < 18 years (HPTN 084-01)

The key methods of the studies are summarised in Table 19.

Table 19. Key methods of Phase 2 studies

	HPTN 083-01 **Males <18 years**	**HPTN 084-01** **Females <18 years**
Location	4 sites in the US	Uganda, Zimbabwe, and South Africa
Status	Ongoing	Complete
Duration of study/study steps	Step 1: oral cabotegravir 30 mg daily for up to 5 weeks Step 2: cabotegravir LA 600 mg at Weeks 5, 9, 17, 25, and 33 (8-week intervals) after a 4-week loading dose. Step 3: option to continue cabotegravir LA or receive TDF/FTC for 48 weeks	Step 1: oral cabotegravir 30 mg daily for up to 5 weeks Step 2: cabotegravir LA 600 mg at 8-week intervals after a 4-week loading dose for 29 weeks Step 3: option of TDF/FTC for 48 weeks or enrolment in cabotegravir LA OLE study, continuing cabotegravir LA or 48 weeks
Key inclusion criteria	Assigned male sex at birth (includes men who have sex with men, transgender women, and gender non-conforming people) Below 18 years of age Body weight ≥35 kg Sexually active In generally good health	Assigned female sex at birth Below 18 years of age Body weight ≥35 kg Self-reported sexual activity with a male (oral, anal, vaginal) in the past 12 months Negative pregnancy test, not breastfeeding, and willing to use a reliable form of long-acting contraception In generally good health

	HPTN 083-01 Males <18 years	HPTN 084-01 Females <18 years
Number of participants	Planned 50 participants to ensure ≥35 participants progressed to injection phase 12 participants screened, 9 enrolled and received cabotegravir	69 screened, 55 enrolled and entered Step 1. 53 entered Step 2 52 entered Step 3

3.2.11.1 Baseline characteristics of Phase 2 cabotegravir studies

Baseline characteristics are summarised in Table 20. The mean [redacted] In HPTN 083-01, [redacted] of participants were white and [redacted] were Black or African American. Sixty-seven percent were men who have sex with men and [redacted] were transgender women. In HPTN 084-01, 100% were Black African, 27% weighed 35 to <50 kg, 25% had more than one sex partner living with HIV, and 22% had had transactional sex in the last month.

Table 20. Baseline characteristics of Phase 2 cabotegravir studies

Characteristic	HPTN 083-01 Males <18 years (N=9)	HPTN 084-01 Females <18 years (N=55)
Mean age, yrs (range)	[redacted]	16 (12-17)
Black or African American, n (%)	[redacted]	100
White, n (%)	[redacted]	
Mixed race, n (%)	[redacted]	
Men who have sex with men, n (%)	[redacted]	
Transgender women	[redacted]	
Other†, n (%)	[redacted]	
Weight kg		
Mean (SD)	[redacted]	
35 to <50 kg, (%)	[redacted]	27

Characteristic	HPTN 083-01 Males <18 years (N=9)	HPTN 084-01 Females <18 years (N=55)
≥50 kg, (%)	[redacted]	73
BMI, mean (SD)	[redacted]	
Gonorrhoea (%)		7
Chlamydia (%)		31
>1 one sex partner living with HIV (%)		25
Median episodes of vaginal sex in past month		2
Anal sex past month (yes) (%)		5
Transactional sex past month (%)		22
Significant depressive symptoms, (%)		36

†The participant answered “working on it”.

Source: CS Appendix Tables 3 and 4, CSRs.

3.2.11.2 Key results of Phase 2 cabotegravir studies

3.2.11.2.1 HPTN 083-01, male adolescents

- Challenges to recruitment such as sexual and gender minority adolescent populations and the COVID-19 pandemic meant that only 9 participants (of 50 planned) were enrolled. Results should therefore be viewed with caution.
- [redacted] significant new safety findings were identified. Of Grade ≥2 AEs, [redacted] had at least one event, [redacted] had creatinine renal clearance decreased, and [redacted] had injection site pain.
- [redacted]
- [redacted] discontinued the injection treatment prematurely due to intolerability of injection or burden of study procedures.

- Cabotegravir pharmacokinetics suggested [redacted] adherence during the oral phase.
- Adherence: [redacted] of injection visits occurred within ±3 days of the projected dosing visit.
- [redacted] HIV incident infections were identified at time of analysis.

3.2.11.2.2 HPTN 084-01, female adolescents

- No new safety concerns were identified. AEs and clinical laboratory findings ≥Grade 2 were [redacted] with HPTN 084.
- Grade ≥2 AEs were experienced by [redacted] of participants; [redacted] had creatinine renal clearance decreased, [redacted] had amylase increased, and [redacted] had blood creatinine increased. Abnormal uterine bleeding, blood glucose decreased, and urinary tract infection were each experienced by [redacted] of participants.
- ISRs were experienced by [redacted] they were [redacted], and [redacted] result in study drug discontinuations.
- SAEs were experienced by [redacted], none were drug-related.
- Three participants neuropsychiatric events (an AESI), these were Grades 1, 2 and 4.
- Cabotegravir pharmacokinetics suggested [redacted] adherence during the oral phase.
- Adherence: [redacted] of injection visits occurred within ±3 days of the projected dosing visit.
- There were no incident HIV acquisitions.
- Of the 52 participants who entered Step 3 (follow-up phase), 7% chose TDF/FTC, and 92% chose cabotegravir LA.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The EAG's judgement on trials included and excluded from the company's ITC is discussed in section 3.1.2 (SLR Methods) and in further detail in section 3.4.2 below, and summarised in Appendix 2.

A summary of comparator studies included in the company's ITC and/or EAG ITC is available in Appendix 4.

Characteristics of studies included in the ITC

Nine comparator studies were included in the ITC by either the company or EAG. iPrEX,[43] IPERGAY,[33] and PROUD[42] predominantly enrolled men who have sex with men and transgender women; FEM-PrEP[44] and VOICE[45] focused on cisgender women; Tenofovir 2[46] included both cisgender men and women; the Partners PrEP[34] and IAVI Uganda[35] studies involved serodifferent partners where one partner was living with HIV (seropositive) and the other was HIV negative (seronegative) and the Bangkok Tenofovir study[32] included male and female drug users in Thailand.

Most studies were conducted as double-blind trials, except for PROUD McCormack,[42] which was open-label. There was variability in follow-up duration across studies, ranging from 4 months to 4 years.[32, 35] The studies were conducted across various regions: South America the USA, South Africa and Thailand for iPrEX;[43] Canada and France for IPERGAY;[33] Thailand for the Bangkok Tenofovir study;[32] Kenya, South Africa, and Tanzania for FEM-PrEP;[44] South Africa, Uganda, and Zimbabwe for VOICE;[45] Botswana for Tenofovir 2;[46] Kenya and Uganda for Partners PrEP;[34] Uganda for IAVI Uganda; [35] with only one study being undertaken in England (PROUD[42]). Participants' ages varied across studies. Most studies recruited from 18 years while some studies focused on specific age groups such as 18 to 39 (Tenofovir 2).[46] Although there was inconsistency in methods for reporting the age of participants across the included studies, it can be seen in CS Appendix D, Table 10, that in most studies the majority of participants were aged in the region of 18 to 40 years.

CS Appendix D also reports details of other participant characteristics in these studies such as the level of education, sexual risk factors and drug use in Tables 13 to 18.

The level of risk from HIV and methods of risk assessment varied among studies. The most commonly used factor for risk was the number of recent sexual partners (iPrEx;[43] IPERGAY;[33] FEM-PrEP;[44] Tenofovir2;[46] VOICE;[45] Partners PrEP;[34] IAVI Uganda;[35] Bangkok Tenofovir study[32]), sex with a partner living with HIV (iPrEx; [43]

Tenofovir2; [46] IAVI Uganda[35]) and anal sex (iPrEx; [43] FEM-PrEP;[44] VOICE[45]). Full details can be seen in CS Appendix D Tables 14 to 17.

The company applied the minimum criteria recommended by NICE to assess the risk of bias of the comparator studies, presenting these by study in CS Appendix D.5, Tables 39-41. No overall statement of risk of bias was presented and the ROB assessments were not explicitly incorporated into the SLR or ITC. On examination of Appendix D Table 40, it became apparent that the company had confused allocation concealment with blinding of assigned interventions during the trial.

The EAG re-assessed randomisation, allocation concealment and blinding in all comparator studies included in the ITC (either by the company or EAG), focusing only on the eligible interventions in trials with more than two arms. The EAG considers that all studies except PROUD[42] have a low risk of bias based on these criteria. PROUD[42] was an open label study without a placebo control therefore is at risk of bias due to deviations from the intended interventions and bias from knowledge of the intervention. Due to time constraints, the EAG has not independently verified the CS assessments for the other risk of bias criteria for these comparator studies.

Overview of results of comparator studies included in the ITC.

In studies of men who have sex with men and transgender women the iPrEx[43] study and IPERGAY[33] showed significant reductions in HIV acquisition with TDF/FTC compared with placebo (HR 0.53 [95% CI 0.36, 0.78] and RRR 82 [95% CI 36, 97] for the two trials respectively), Appendix 4, PROUD[42] demonstrated efficacy with immediate TDF/FTC compared with deferred TDF/FTC (RRR 86 [90% CI 64, 96). However, in participants of cisgender women FEM-PrEP,[44] found no significant difference between TDF/FTC and placebo (HR 0.94 [95% CI 0.59, 1.52]). VOICE[45] examined various interventions among African women, with TDF/FTC versus placebo where there was also no significant benefit from TDF/FTC (HR 1.04 [95% CI 0.73, 1.49]). Tenofovir2[46] showed efficacy of TDF/FTC among heterosexual men and women (RR 61.7 [95% CI 15.9, 82.6]), while Partners PrEP[34] demonstrated effectiveness among serodifferent heterosexual partners (HR 0.25 [95% CI 0.13, 0.45]). The Bangkok Tenofovir Study targeted drug users and reported efficacy with

TDF (RR 0.49 [95% CI 9.6, 72.2]). The IAVI Uganda study[35] focused on serodifferent partners but no HIV acquisitions were detected.

Adherence measures reported by these comparator studies can be seen in Table 9.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

3.4.1 Summary of the CS ITC and Meta-regression Analyses

The company conducted an indirect treatment comparison (ITC) of cabotegravir long-acting (CAB-LA) plus placebo versus tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) and placebo. Detailed description of the indirect treatment comparison (ITC) and meta-regression analyses are provided in section B.2.9 of the CS document B, with technical specifics outlined in Appendix D.
The company's rationale for conducting these analyses, as outlined in sections B.1.1 and B.1.1.1 of the CS, revolves around addressing the absence of a placebo arm in the HPTN 083 and HPTN 084 trials. These trials lacked a comparator group of individuals not taking PrEP, thereby making direct comparisons between CAB-LA and individuals not on PrEP unfeasible.

Given this constraint, the company opted for an ITC approach to provide estimates of CAB-LA's effectiveness compared to no PrEP, utilising TDF/FTC as a common comparator. It is noteworthy that the company's definition of the Decision Problem (CS document B, Section B.1.1) states that "Cabortegravir is anticipated to be indicated for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired human immunodeficiency virus (HIV)-1 infection in at-risk individuals" and that "the submission focuses on people for whom oral PrEP is not appropriate and are therefore underserved by current standard of care". This necessitate the comparison of CAB-LA to a "no PrEP" comparator because of the CS focus on people for whom oral PrEP is not appropriate who would be underserved by TDF/FTC, the current UK standard of care in HIV prophylaxis.

A second rationale for the ITC/meta-regression emanates from evidence suggesting that effectiveness of TDF/FTC can vary significantly across populations due to

differences in adherence levels[24, 52] which may confound the results of the ITC. To address this potential confounding factor, the company undertook a meta-regression using aggregated study data to accommodate the variation in TDF/FTC adherence observed among the included trials. This approach enabled a more accurate estimation of CAB-LA's comparative effectiveness against no PrEP, while simultaneously mitigating biases associated with adherence-related confounders.

In the data used to inform the ITC/meta-regression generated from the CS's SLR, adherence to TDF/FTC was measured heterogeneously across and within trials using different methods (CS Appendix D, Section D.2.2.5.3) examples of which include dry blood spot (DBS) drug detection, pill counts, self-reporting, plasma drug detection and medication event monitoring. Despite the presence of several methods measuring adherence, the CS chose to use adherence measured by detectable plasma levels in its meta-regressions (sensitivity analyses used adherence as measured by pill count data (CS Appendix D Section D.3.1).

The CS rationale for choosing detectable plasma levels as the primary measure of adherence is based on its assessment that the other methods such as pill counts and self-reports were too unreliable and associated with biased assessment of adherence to oral PrEP.O'Murchu, [24] As a consequence, of the 19 studies that the CS SLR found to be eligible for inclusion in the ITC, only 10 studies met the additional inclusion criteria based on adherence measured by plasma sampling. The remaining 9 studies were excluded despite having other measures of adherence that could have been used when detectable plasma levels of TDF/FTC is unavailable (CS Appendix D, Section D.3.1). The EAG acknowledges that, the inclusion of studies with other adherence measures may introduce significant uncertainty into the analysis, it is still preferable than the whole sale exclusion of studies that do not report the desired adherence which in itself also introduces bias in the parameter estimates.

The company reported implementing Bayesian Hierarchical models for the ITC, conducting both fixed and random treatment effects analyses. While the ITC WinBUGS code was provided upon request (A18), only the fixed effects code was available. The CS stated that consideration was given to the use of informative priors

for random treatment effect variance if suitable published estimates were accessible (CS document B, Section B.2.9.2.2) however, the corresponding estimates of treatment effect variances or references to the published literature were not provided in the CS.

Outcomes eligible for inclusion in the ITC were 1) treatment effect on risk of HIV acquisition, expressed as a relative risk or hazard ratio; and 2) adherence to TDF/FTC, expressed as the proportion of participants with detectable plasma levels. Sensitivity analyses considered pill counts as an alternative measure of adherence (Appendix D, Section D.3.1), however the results of these analysis were not presented in the CS and accompanying appendices. Some of the included studies reported hazard ratios (HRs) as effect measure whilst others reported the relative risk ratio (RRs). Regardless of what effect measure was reported, HRs and RRs were assumed to provide the same magnitude of treatment effect in HIV prophylaxis, hence were used interchangeably in the ITC. Combining different effect measures in a single meta-analysis may introduce bias, with its impact on overall benefit estimates unknown. However, the assumption that effect measures approximate each other may be appropriate if the outcome event is rare (i.e. less than 5% event rate). Thus, combining effect measures this way may not be of great concern given that HIV incident infection is a rare event in the UK (i.e. the baseline incidence is < 5%).

Out of 19 identified studies, 10 met inclusion criteria for the ITC, with 9 excluded due to inadequate adherence measurement. Notably, three studies (Bangkok Tenofovir Study, Partners PrEP, and Tenofovir 2) were split by sex/population, increasing the number of studies in the meta-regression from 10 to 13. In studies that were divided by sex, the overall estimate of adherence in the TDF/FTC arm was applied to both male and female cohorts, implying assumptions of equal adherence between men and women. However, in reality, adherence is likely to differ by sex. The meta-regression conducted by the CS could not account for this discrepancy, which may have biased the results of the ITC meta-regression.

The company fitted linear and logarithmic models of the relationship between TDF/FTC adherence and effectiveness in reducing HIV acquisition. Logarithmic models were preferred as they do not generate implausible negative values for relative risk (RR) (effectiveness greater than 100%) at high levels of adherence

which can happen with the linear parametrization (last paragraph of CS document B, Section B.2.9.3.1.2).

Results of the company's ITC and meta-regression analyses revealed a robust relationship between TDF/FTC effectiveness and adherence (Table 21, Figure 2), with higher adherence correlating with greater effectiveness. However, a number of limitations and uncertainties must be addressed to interpret these findings accurately.

Table 21. Company's ITC results

Model	Intercept ($\propto$)[a]	Adherence co-efficient (β) [a]	Sex co-efficient (β) [a]	Model Fit (DIC)
Log relationship + Sex	[redacted]	[redacted]	[redacted]	[redacted]
Log relationship	[redacted]	[redacted]	–	[redacted]
Linear relationship	[redacted]	[redacted]	–	[redacted]
Log relationship (Excl. PROUD, IPERGAY & Bangkok)	[redacted]	[redacted]	–	[redacted]

[a] Mean and standard error of the posterior distribution. DIC, Deviance Information Criterion.

Source: reproduced from CS Table 21

Figure 2. Relationship between effectiveness and adherence in the base case meta-regression model
Abbreviations: CAB-LA, cabotegravir long-acting; PrEP, pre-exposure prophylaxis; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

Source: reproduced from CS Figure 10.

3.4.2 EAG Critique

The EAG acknowledges that while the no PrEP intervention is not directly relevant to the decision problem or the economic model scope, the ITC remains pertinent as it enables the modelling of baseline HIV incidence in the economic model. This parameter, estimated for UK PrEP-naïve men who have sex with men at 4.9 per 100 person-years and slightly lower for PrEP-naïve heterosexual/cisgender women at [redacted] per 100 person-years from the company's ITC analyses, serves as the incident rate in the no PrEP comparator arm of the ITC (CS document B, section B.3.3.2). In

the model, the ITC results were applied to these baseline incident figures to derive HIV incidence under TDF/FTC and CAB-LA comparators. Without the ITC, the results of the CAB-LA trials could not have been mapped to the data on baseline incidence of HIV, given the absence of a placebo control in these trials.

While the evidence presented in the indirect treatment comparison provides valuable insights into the comparative effectiveness of CAB-LA and TDF/FTC, the analysis is not without its limitations. These include the study selection process, methodology, and assumptions underlying the meta-regression approach. Additionally, EAG found that incorrect estimates of adherence were applied in the company's ITC for 4 trials (Partners PrEP [53], iPrEx[43], FEM-PrEP[44] and PROUD[42]) and corrected them in the EAG re-analyses of the ITC data (See Table 22).

Table 22. Comparison of adherence values used in the company's and EAG's ITC analyses

Study	Adherence used in company's ITC	Adherence used in EAG ITC	Reason for EAG's corrections
Partners PrEP study, Male	**0.81**	**0.75**	We applied the percentage of samples to n=100 without HIV, we have TDF in 81 of 100. n with TDF: 81+3 = 84 N with and without HIV: 12 + 100 = 112 84/112 = 75%
Partners PrEP study, Female	**0.81**	**0.75**	
iPrEx Trial	**0.5**	**0.325**	The overall adherence value is much lower if seropositive patients are included: Study drug detected in Seronegative: 22/43 (51%) Seropositive: 3/34 (8.8) Total 25/77 = 32.5%
VOICE	0.29	0.29	
Tenefovir 2, Female	**0.77**	**0.78**	Reported value from Thigpen 2012 is 0.78

Tenefovir 2, Female	**0.77**	**0.78**	Reported value from Thigpen 2012 is 0.78
FEM-PrEP	**0.36**	**0.29**	The calculation 99/128 (77%) is incorrect. The proportions in uninfected control patients were 35%, 37%, 24%, and in patients living with HIV were 26%, 21%, 15%. The company used 36%, which is the middle of the first two values. If the calculation is 99/338, the proportion would be 29.2%, which looks like a more realistic value.
HPTN 083	0.86	0.86	
HPTN 084	0.56	0.56	
PROUD	**0.88**		The EAG was unable to determine the most appropriate adherence measure to use from McCormack 2016 study. In total there were 99 cases (if we assume those at both visits are not double counted). For the denominator there were 33 infected cases and 95 uninfected matched controls (total 128), but N at the beginning of the infection window is lower. 99/128 = 77% but I am not certain that is correct?
Bangkok Tenofovir Study	0.66	0.66	
Bangkok Tenofovir Study	0.66	0.66	
IperGay	0.86	0.86	
IAVI Uganda study	Excluded	0.98	

The absence of direct CAB-LA versus no PrEP comparisons introduces potential biases, and reliance on aggregated study data rather than individual participant data may limit the precision of estimates. Assumptions regarding CAB-LA adherence and the generalisability of findings across different populations and settings also warrant careful consideration. These issues are discussed in the EAG commentary below:

Overall, the ITC/meta-regression analyses were conducted appropriately, providing robust estimates of the relationship between CAB-LA and the no PrEP interventions while incorporating oral PrEP adherence. By employing a meta-regression analysis based on aggregated study data, the ITC addressed variations in TDF/FTC adherence levels and derived estimates of CAB-LA effectiveness compared to no PrEP.

Issue 1: Generalisability: The HPTN trials were conducted in different countries and did not include UK patients, raising questions about their generalisability to the UK population (3.5.1.1). At the clarification stage, the EAG raised concerns about the trial evidence and the ITC's applicability to the UK population, the company maintained that the trial data would be applicable to the UK population (**A19 in the c**ompany response to EAG Clarification Letter).

Issue 2: Inclusion of diverse populations and heterogeneous interventions: The ITC included the Bangkok Tenofovir Study, which recruited heterosexual drug users, a population different from the intended population of interest. The EAG was able to re-run the analyses excluding these studies based on population criteria. Additionally, the EAG recommends excluding the IperGay study due to differences in intervention. This study compared event-driven TDF/FTC versus placebo, which the EAG believes is not directly comparable to daily TDF/FTC.

Issue 3: Exclusion of studies based on lack of adherence by plasma estimate: The exclusion of nine studies from the ITC based solely on the absence of measuring adherence by plasma levels is contentious. However, of the nine studies excluded by the company due to lack of plasma adherence data, the EAG considered that eight should be excluded for other reasons. The included studies with plasma adherence data measured this in only a sub-sample of the trial population in the TDF/FTC arms. This implies that trials with adherence measures in the ITC meta-regression do not fully account for TDF/FTC adherence in the whole TDF/FTC-arm population (as only a sub-sample of the TDF/FTC population reported this measure). Alternative measures of adherence include medication event monitoring systems, pill counts and self-report. While acknowledging the limitations of these measures,

the EAG suggests that including studies with alternative adherence measures in the meta-regression would be preferable.

Issue 4: Measurement Error in Adherence: The CS meta-regression analysis does not address the issue of measurement error in adherence. Measurement error refers to the discrepancy between the observed value of a variable (in this case, adherence to TDF/FTC) and its true value.[1, 2, 54]

As adherence is a measured covariate, its true value is uncertain and can only be inferred from the data. Failure to account for measurement error may lead to biased estimates of the relationship between efficacy and adherence. One potential consequence of ignoring measurement error is regression to the mean.

Regression to the mean occurs when extreme values of a variable measured with error tend to move closer to the mean upon subsequent measurement.[55] In the context of the meta-regression, failure to correct for measurement error could result in biased estimates of the relationship between TDF/FTC effectiveness and adherence. This bias arises because trials with extreme adherence values are likely to exhibit less extreme values upon subsequent measurement, leading to an underestimation of the true relationship between adherence and effectiveness. The EAG's analyses addressed this issue by formulating a binomial distribution for the number of people adherent to oral PrEP in the TDF/FTC arm of each trial, simultaneously handling measurement error and inclusion of studies not reporting adherence. In this updated analysis, the treatment effect is regressed on the unobserved but true value of adherence instead of the observed measure which is prone to error. Accounting for measurement error, the EAG's approach aimed to provide more accurate estimates of the relationship between TDF/FTC effectiveness and adherence, mitigating the risk of biased conclusions due to regression to the mean.

3.5 *Additional work on clinical effectiveness undertaken by the EAG*

Additional evidence

Ongoing studies reported in the CS Appendix D, Table 31 were checked, and no recently published studies were identified. An ongoing alert for new studies was set-up throughout this assessment. Thirteen potentially relevant publications were identified. Potentially relevant studies were assessed against the scope and no eligible studies were identified.

EAG ITC analyses

Table 23 below provides a comparison of data included in the company's and the EAG ITC analyses. Two studies (Bangkok Tenofovir Study[32] and IperGay[33]) were excluded from the EAG analyses on grounds of study population and intervention respectively. PROUD[42] was included in the company's original analysis but excluded from the updated analysis presented at clarification (Company's response letter, A21) on grounds that it did not report adherence based on plasma levels for a random sample of subjects and open label study. However, the EAG disagrees with this assessment and as the PROUD study did report adherence and 'open-label' is not an exclusion criteria. Additionally, the EAG assessed that the IAVI Uganda study[35] meets the inclusion criteria but zero incident HIV events was observed in both arms on account of which the this study was excluded. The EAG determined that it is preferable to include IAVI by adding a continuity correction (0.5 added to numerator and denominator in both arms) as reported elsewhere.[56, 57] Overall the EAG ITC included a total of 9 studies reporting 11 data points on account of two studies (Partners PrEP study[34] and Tenefovir 2[46]) reporting separate effectiveness separately for men and women.

Table 23. Data included in the company's and EAG ITC analyses

												TDF/FTC arm statistics			
ID	**Study**	**Company's original ITC**	**Company's Clarification A21**	**EAG ITC**	Treatment	Comparator	population	RR	LCI	UCL	Adherence	nTDF	% male	n	r
1	Partners PrEP study, Baeten 2012[a]	ü	ü	ü	TDF/FTC	Placebo	Male heterosexual	0.37	0.17	0.8	**0.75**	2215	0.64	1009	756
1	Partners PrEP study, Baeten 2012[a]	ü	ü	ü	TDF/FTC	Placebo	Female heterosexual	0.29	0.13	0.63	**0.75**	2215	0.64	567	426
2	iPrEx Trial, Grant 2010	ü	ü	ü	TDF/FTC	Placebo	Men who have sex with men	0.56	0.37	0.85	**0.325**	1251	1	1251	407

3	VOICE, Marrazo 2015	ü	ü	ü	TDF/FTC	Placebo	Female heterosexual	1.04	0.73	1.49	0.29	1003	1	1003	291
4	Tenefovir 2, Thigpen 2021	ü	ü	ü	TDF/FTC	Placebo	Female heterosexual	0.51	0.19	1.22	**0.78**	611	0.54	280	218
4	Tenefovir 2, Thigpen 2021	ü	ü	ü	TDF/FTC	Placebo	Male heterosexual	0.2	0.03	0.75	**0.78**	611	0.54	331	258
5	FEM-PrEP, Van Damme 2012	ü	ü	ü	TDF/FTC	Placebo	Female heterosexual	0.94	0.59	1.52	**0.29**	1062	1	1062	308
6	HPTN 083, Landovitz 2021	ü	ü	ü	Cabotegravir	TDF/FTC	Men who have sex with men/ transgen	0.34	0.18	0.62	0.86	2284	1	2284	1964

							der women								
7	HPTN 084, Delany-Moretlwe 2022	ü	ü	ü	Cabotegravir	TDF/FTC	Female heterosexual	0.12	0.05	0.31	0.56	1610	1	1610	902
8	**PROUD, McCormack 2016**	**ü**	**X**	**ü**	TDF/FTC	Deferred PrEP	Men who have sex with men	0.14	0.04	0.36		273	1	273	NA
9	**Bangkok Tenofovir Study, Choopanya 2013**	**ü**	**X**	**x**	TDF	Placebo	Male drug users	0.62	0.32	0.82	0.66	1204	0.8	963	636
9	**Bangkok Tenofovir Study, Choopanya 2013**	**ü**	**X**	**x**	TDF	Placebo	Female drug users	0.21	0.03	0.83	0.66	1204	0.8	241	159

10	**IperGay, Molina 2015**	**ü**	**X**	**x**	TDF/FTC event-driven	Placebo	Men who have sex with men	0.14	0.02	0.6	0.86	199	1	199	171
11	**IAVI Uganda study, Kibengo 2013****	**x**	**X**	**ü**	TDF/FTC	TDF/FTC intermittent		1	0.02	48.5	0.98			24	23.5
12	Partners PrEP Continuation, Beaton 2014[a]	x	X	x											
13	DISCOVER, Mayer 202	x	x	x											
14	IAVI Kenya Study,	x	x	x											

	Mutua 2012													
15	Project PrEPare, Hosek 2013	x	x	x										
16	Kwan 2021	x	x	x										
17	CDC Safety Study, Grohskopf 2013	x	x	x										
18	ADAPT Cape Town, Bekker 2018	x	x	x										
19	Peterson 2007	x	x	x										

[a] The CS appears to have switched the references for Beaton 2012 and Beaton 2014. Bold font indicate differences in inclusion.

[b]Percentage female as RR/HR is estimated separately for male and females.

****IAVI Uganda study, Kibengo 2013 reported zero events in both arms. The EAG applied a continuity correction by adding 0.5 to the numerator and denomator of both arms to enable this study to be included in the ITC.**

The EAG fitted both fixed and random effects meta-regression models, with a uniform (0,100) prior specified for the between-study standard deviation parameter in the random effects analyses. Random effects models were preferred because they produced the lowest Deviance Information Criterion (DIC) values compared to fixed effects models.

The results of the EAG analyses (random effects model) are presented in Table 24 alongside the results from both the company's original and updated analyses, as presented in Clarification A21. While the EAG analysis yielded identical results to the company's original analysis, there were minor differences in the results when excluding data from the PROUD, IPERGAY, and Bangkok studies. The EAG acknowledges that the differences observed between its ITC analyses and the company's analyses, when applied to the economic model, are unlikely to substantially alter the magnitude of cost-effectiveness of CAB-LA compared with TDF/FTC produced from the company's base case.

In the economic model, the alpha and beta parameters are of particular interest as they serve as inputs for model parameterization (CS document B Section B.3.3.4). The estimates of alpha and beta, denoted as mean with corresponding standard error presented within brackets, were derived from the EAG's Indirect Treatment Comparison (ITC) log-linear meta-regression model. This model included the PROUD study but excluded data from the IPERGAY, Bangkok, and IAVI Uganda studies. The estimated values for alpha and beta were found to be [redacted] and [redacted], respectively, compared to the company's log-linear model estimate of [redacted] and [redacted] for alpha and beta. The EAG estimated values were used to inform the EAG's base case analysis.
When applied in the economic model, the generated mean relative risk reductions for TDF/FTC versus no PrEP amounted to 77%. This was determined through the formula Log(RR_TDF/FTC vs no PrEP) [redacted], where 0.86 represents the adherence proportion observed in the HPTN083 trial. Applying this formula across all models fitted by the EAG analyses (Table 24), the effectiveness of Cab-LA versus no PrEP of [redacted] in the men who have sex with men population (HPTN083) and [redacted] in the cisgender women population (HPTN084). For TDF/FTC,

effectiveness percentages varied from [redacted] to [redacted] for HPTN03 and from [redacted] to [redacted] at levels of adherence observed in the HPTN084.

Table 24: EAG ITC meta-regression results

			Cab-LA vs. No PrEP		TDF/FTC vs. No PrEP	
Model	Intercept (∝)†	Adherence co-efficient (β)†	HPTN083	HPTN084	HPTN083	HPTN084
Company's analyses						
Log relationship	[redacted]	[redacted]	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Log relationship (Excl. PROUD, IPERGAY & Bangkok)	[redacted]	[redacted]	[redacted]	[redacted]%	[redacted]%	[redacted]%
EAG Analyses						
Log relationship	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log relationship (Excl. PROUD, IPERGAY & Bangkok)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG analysis: Log relationship (Excl. IPERGAY & Bangkok)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG analysis: Log relationship (Excl. IPERGAY & Bangkok) includes IAVI Uganda study	0.5189 (0.4479)	-2.2413 (0.7395)	90.9%	93.5%	74.6%	51.4%

Source: Adapted from CS Table 21 and EAG ITC and meta-regression analyse

3.5.1.1 Generalisability of HPTN 083 and HPTN 034 trials

The HPTN trials were conducted in different countries and did not include UK patients. HPTN 083 was conducted in 43 sites in US, Latin America, Asia and Africa. HPTN 084 was conducted in 20 sites in 7 countries in sub-Saharan Africa (Botswana, Eswatini, Kenya, Malawi, South Africa, Uganda, and Zimbabwe). Therefore, generalisability to the UK population is of concern. The EAG looked at the PrEP Impact Trial in England[11], a multicentre trial conducted at 157 Sexual Health Services across England. The population consisted of (*n* = 21,356) participants, majority of whom where cisgender men who have sex with men (95.5%) of White ethnicity and born in the UK. Representation from Black groups (African at 1.8%, Caribbean 1.6%, Other 0.6%) was the lowest in frequency in contrast to the HPTN trials Table 6 and Table 7. The mean age of participants was 35.3 (10.9) years which is older than the HPTN trials.

As both HPTN trials limited inclusion to adults aged 18 years and over, they excluded at-risk adolescents (age 13 to 17 years), who are a relevant group in this appraisal (the anticipated marketing authorisation specifies 'sexually acquired HIV-1 infection in at-risk individuals weighing at least 35 kg', so eligibility for the drug is defined by a weight cut-off rather than an age.) The EAG clinical expert advised that numbers of 13- to 17-year-olds in the UK would be very small (2.4% aged 16-19 years in the PrEP Impact Trial), but would include young men who have sex with men and potentially vulnerable adolescents such as those within the care system. The PrEP Impact Trial had 2.3% of cisgender men who have sex with men aged 16-19 years.

The selection criteria used in Step 1 of the HPTN trials, which required participants to demonstrate at least 50% adherence to oral PrEP during the lead-in phase, may have implications for the generalisability of trial results to routine clinical practice and real-world settings.

1. Participant Selection: Excluding participants with low adherence to oral PrEP during the lead-in phase may have inadvertently introduced selection bias. This is because, individuals who are highly motivated and adherent to treatment may not represent the broader population of individuals who could benefit from PrEP in real-

world settings. The EAG asked for clarification on how many participants were excluded at the end of Step 1 due to <50% adherence. Clarification response A4 reported that in HPTN 083 [redacted] participants in the CAB-LA arm, and [redacted] participants in the TDF/FTC arm discontinued the investigational product during Step 1 due to low adherence. In HPTN 084, in the randomised population [redacted] participants in the CAB-LA arm and [redacted] participants in the TDF/FTC arm discontinued during Step 1 due to low adherence. Despite the low numbers being excluded on the <50% adherence criteria, the EAG is concerned that this bias may limit the applicability of trial findings to populations with varying levels of adherence and motivation to adhere to preventive measures.

2. Underrepresentation of Non-Adherent Populations*:* populations eligible for PrEP may include individuals with varying levels of adherence and motivation, including those who struggle with consistent medication adherence. Excluding individuals with low adherence during the lead-in phase may result in the underrepresentation of these populations in the trial, leading to potential discrepancies between trial outcomes and real-world effectiveness.

3. External Validity: The stringent adherence criteria used in the trial may compromise the external validity of the findings, as they may not accurately reflect the challenges and complexities encountered in routine clinical practice. Real-world PrEP programs often aim to reach individuals who face barriers to adherence, such as stigma, access issues, or competing priorities, which may not be fully captured in trial settings.

4. ***Generalisability of Effectiveness***: The effectiveness of CAB-LA observed in trial participants who demonstrated ≥50% adherence to oral PrEP may not necessarily translate to real-world populations with lower adherence levels. The trial results may overestimate the effectiveness of CAB-LA when implemented in settings where adherence is suboptimal, leading to unrealistic expectations and potential disappointment among clinicians and patients.

5. ***Implications for Implementation Strategies:*** Trial results influenced by highly adherent participants may not adequately inform implementation strategies for PrEP programs in real-world settings. Strategies tailored to support individuals with varying

levels of adherence and motivation are therefore essential for optimising the effectiveness of PrEP at the population level

Table 25. Characteristics of PrEP Impact Trial[11]

	All participants n=21,356	Cisgender men who have sex with men n=20,403	Cisgender heterosexual men n=137	Cisgender heterosexual women n=309	Transgender women n=319	Transgender men n=141	Non-binary individuals n=43
Age, years							
Mean (SD) age, years	35.3 (10.9)	35.3 (10.9)	41.1 (12.4)	34.8 (10.6)	34.5 (11.7)	31.5 (10.2)	29.2 (9.9)
Median (IQR) age, years	33 (27 - 42)	33 (27 - 42)	39 (31-51)	33 (27-42)	31 (26-41)	28 (24-38)	27 (23-32)
Age range, years	16 - 86	16 - 86	21 -76	17-65	17-68	18-78	19-71
Age group							
16-19 years	2.4%	2.3%	0.0%	3.2%	3.8%	1.4%	2.3%
20-24 years	12.3%	12.1%	5.1%	14.2%	16.0%	27.0%	34.9%
25-29 years	21.4%	21.5%	17.5%	18.1%	21.6%	27.0%	30.2%
30-34 years	19.0%	19.1%	15.3%	23.0%	17.9%	12.8%	11.6%
35-39 years	14.7%	14.8%	14.6%	9.7%	13.5%	9.9%	7.0%
40-44 years	9.9%	9.9%	10.2%	11.0%	10.3%	9.2%	7.0%

45-49 years	8.4%	8.4%	9.5%	9.1%	4.7%	8.5%	2.3%
50-54 years	5.9%	5.9%	8.0%	7.1%	4.4%	2.8%	2.3%
55-59 years	3.3%	3.3%	11.7%	2.9%	2.5%	0.0%	0.0%
≥60 years	2.9%	2.8%	8.0%	1.6%	5.3%	1.4%	2.3%
Ethnic Group							
White	75.4%	76.2%	48.9%	58.9%	59.6%	70.2%	58.1%
Black African	1.8%	1.5%	19.0%	10.7%	0.9%	0.7%	2.3%
Black Caribbean	1.6%	1.6%	6.6%	2.6%	0.3%	1.4%	0.0%
Black Other	0.6%	0.6%	0.7%	1.3%	0.6%	1.4%	0.0%
Asian/Asian British	5.1%	5.0%	7.3%	3.9%	10.7%	7.1%	11.6%
Mixed	4.3%	4.2%	4.4%	6.8%	9.4%	7.1%	11.6%
Other	3.8%	3.8%	2.2%	7.2%	7.2%	5.0%	4.7%
Unknown	7.2%	7.1%	11.0%	11.3%	11.3%	7.1%	11.6%
Region of Birth							
UK	61.0%	61.3%	52.6%	53.4%	47.3%	65.3%	62.8%
Europe (excl. UK)	15.1%	15.3%	3.7%	12.6%	8.2%	10.6%	18.6%
Caribbean	0.5%	0.5%	1.5%	0.0%	0.3%	0.0%	0.0%
Sub-Saharan Africa	2.8%	2.6%	20.4%	10.7%	0.9%	0.7%	2.3%
South Asia	1.3%	1.3%	2.2%	1.0%	0.9%	2.1%	0.0%
Central America	0.3%	0.3%	0.0%	0.0%	1.3%	0.0%	0.0%
North America	1.7%	1.8%	0.7%	0.3%	0.6%	5.7%	0.0%

South America	3.5%	3.2%	0.7%	7.1%	17.2%	4.3%	2.3%
Other	6.3%	6.3%	2.9%	3.2%	12.2%	5.0%	4.7%
Unknown	7.7%	7.6%	15.3%	11.7%	11.0%	6.4%	9.3%
Region of residence							
London	52.9%	53.1%	35.8%	46.0%	59.3%	52.5%	41.9%
Midlands and East	12.3%	12.2%	15.3%	18.1%	11.9%	9.9%	11.6%
North	15.8%	15.9%	16.8%	14.9%	12.2%	10.6%	18.6%
South	17.4%	17.3%	27.7%	16.5%	13.8%	25.5%	25.6%
UK other	0.4%	0.4%	0.7%	0.7%	0.6%	0	0
Abroad	0.1%	0.1%	0	0	0	0	0
Unknown	1.1%	1.0%	3.7%	3.9%	2.2%	1.4%	2.3%
Index of Multiple Deprivation							
1 (most deprived)	20.8%	20.6%	19.7%	30.7%	21.0%	24.1%	23.3%
2	32.3%	32.5%	28.5%	25.6%	28.2%	29.1%	39.5%
3	21.5%	21.5%	27.0%	17.8%	22.9%	25.5%	16.3%
4	14.3%	14.4%	11.7%	12.9%	14.4%	14.2%	14.0%
5 (least deprived)	9.6%	9.6%	8.8%	8.4%	10.7%	5.7%	4.7%
Unknown	1.6%	1.5%	4.4%	4.5%	2.8%	1.4%	2.3%

3.6 *Conclusions of the clinical effectiveness section*

The CS appraise the clinical and cost effectiveness of CAB-LA for preventing sexually acquired HIV-1 infection in at-risk individuals weighing at least 35 kg. The population of the NICE scope includes people at risk of sexually acquired HIV-1 infection. However, the main evidence submitted by the company for the comparison of CAB-LA with TDF/FTC is limited to adults aged ≥18 years in specific populations. The statement '…for whom oral PrEP is not appropriate' is not aligned with the NICE scope or the anticipated Marketing Authorisation. However, the clinical evidence submitted by the company comprised of people taking oral PrEP/placebo for oral PrEP, therefore not aligned with those 'for whom oral PrEP is not appropriate.

The primary sources of evidence for the assessment of clinical evidence of cabotegravir for preventing HIV-1 infection comes from two RCTs: HPTN 083 (adult (≥18 years) and HPTN 084 (aged 18–45 years). The primary outcome of incident HIV acquisitions from HPTN 083 and HPTN 084. In the mITT analysis of incident HIV acquisitions in Steps 1 and 2 of both 083 and 084 trial CAB-LA for PrEP was superior at reducing HIV acquisitions compared to daily oral TDF/FTC PrEP (SoC).

The HPTN trials were conducted in different countries and did not include UK patients. As both HPTN trials limited inclusion to adults aged 18 years and over, they excluded at-risk adolescents (age 13 to 17 years), who are a relevant group in this appraisal (the anticipated marketing authorisation specifies 'sexually acquired HIV-1 infection in at-risk individuals weighing at least 35 kg', so eligibility for the drug is defined by a weight cut-off rather than an age.) The EAG clinical expert advised that numbers of 13- to 17-year-olds in the UK would be very small (2.4% aged 16-19 years in the PrEP Impact Trial), but would include young men who have sex with men and potentially vulnerable adolescents such as those within the care system. The PrEP Impact Trial had 2.3% of cisgender men who have sex with men aged 16-19 years.

The company conducted an ITC of CAB-LA plus placebo versus TDF/FTC and placebo. The company's ITC included data from one trial (Bangkok Tenofovir study) that was conducted among drug users and the the IperGay study, which compared

event-driven TDF/FTC versus placebo in the ITC meta-regression analyses. The population in the Bangkok study differs from individuals at high risk of sexually transmitted HIV-1 infection and assesses TDF alone, whilst iperGay study should not have been included in the ITC on grounds of intervention. The EAG replicated the ITC correcting for various errors and adjustments. Overall, the EAG ITC included a total of 9 studies reporting 11 data points on account of two studies (Partners PrEP study and Tenefovir 2) reporting separate effectiveness separately for men and women. The ITC results were mainly driven by the HPTN trials. The EAG analysis yielded identical results to the company's original analysis, there were minor differences in the results when excluding data from the PROUD, IPERGAY, and Bangkok studies. The EAG acknowledges that the differences observed between its ITC analyses and the company's analyses, when applied to the economic model, are unlikely to substantially alter the magnitude of cost-effectiveness of CAB-LA compared with TDF/FTC produced from the company's base case.

The CS meta-regression analysis does not address the issue of measurement error in adherence. Measurement error refers to the discrepancy between the observed value of a variable (in this case, adherence to TDF/FTC) and its true unobserved value. As adherence is a measured covariate, its true value is uncertain and can only be inferred from the data. Failure to account for measurement error may lead to biased estimates of the relationship between efficacy and adherence resulting from regression attenuation bias /regression to the mean. The EAG's analyses addressed this issue by formulating a binomial distribution for the number of people adherent to oral PrEP in the TDF/FTC arm of each trial, simultaneously handling measurement error and inclusion of studies not reporting adherence. In this updated analysis, the treatment effect is regressed on the unobserved but true value of adherence instead of the observed measure which is prone to error. Accounting for measurement error, the EAG's approach aimed to provide more accurate estimates of the relationship between TDF/FTC effectiveness and adherence, mitigating the risk of bias.

4 COST EFFECTIVENSS

4.1 *EAG comment on company's review of cost-effectiveness*

Economic systematic literature reviews (SLR) comprising of economic evaluations (CS Appendix G), epidemiological models, cost and/or resource-use studies (CS Appendix I), and utility studies (CS Appendix H) for individuals eligible for human immunodeficiency virus (HIV) pre-exposure prophylaxis (PrEP) was conducted. An update of the SLR was conducted in November 2023.

4.1.1 Search strategies for cost-effectiveness section

A wide and appropriate range of sources were searched to identify economic and health-related quality of life (HRQoL) studies, which included medical databases and specific databases including the School of Health and Related Research Health Utilities Database (ScHARRHUD), Cost-Effectiveness Analysis (CEA) and the EQ-5D Publications Database. Grey literature searching of relevant conference abstracts, HTA bodies and clinical trials registries was also carried out. CS Appendix G.1.1.2 states that 'Bibliographies of up to 10 of the most relevant robust economic analyses, systematic reviews, and HTAs were searched for further studies of interest'. The company clarified in their factual accuracy comments that these were reported in Appendix G.2.1.3. Table 23 'Hand searches

For the original SLR, bibliographic lists of five relevant systematic reviews and meta-analyses were searched for relevant articles that were not identified in the electronic searches.'

The company carried out initial searches for studies relating to HIV and PrEP and economic models, utilities or resource use and costs on the 26th May 2023. The company did not carry out separate searches for economic models, utilities or resource use. The searches were run on Embase via Embase.com, PubMed, EconLit (EBSCO), the Cochrane Library (Wiley), ScHARRHUD, the CEA Registry, and the EQ-5D Publications database (CS Appendix G.1.1.2 Table 1 to Table 6). The company carried out a 'protocol amendment after level 2 screening of the original search had been completed', whereby the search strategy was amended to broaden the search terms for the population, whereby the search terms for HIV were

not combined with terms for prevention or PrEP, as per the initial search. The EAG note that the initial search strategy (CS Appendix G.1.2.2.1.1 Tables 1-6) was not sufficiently sensitive, as the population search terms were combined using the Boolean operator AND with the search terms for the intervention, that is, prevention or PrEP (CS Appendix G.1.2.2.1.1). These terms were also combined with specific named interventions for PrEP using the Boolean operator AND. This may have resulted in some broader, relevant evaluations being missed. The initial searches were restricted to studies published after 2013, comments, letters, editorials, or case reports were removed and limited to conference abstracts.

The EAG believe that the amended 'additional' search, carried out on the 24th July 2023 alleviated the issues from the original search (CS Appendix G.1.2.2.1.2 Tables 7-12). The EAG notes reporting both searches maximises the transparency of the search process. The amended search includes a broad range of database-specific indexing and free text terms for the population: people with HIV combined with free text and database specific indexing terms for the intervention, which includes broader terms such as 'primary prevention' as well as specific drug, trade and chemical names for specific named forms of PrEP. The searches were combined with an extensive range of indexing and free text terms for economic models, utilities and resource use and costs. The searches were limited to studies published between 01st January 2013-the 24th July 2023, as studies published after this date were 'expected to be out of date… as the first PrEP option, TDF/FTC was approved in 2012; therefore, any studies before 2012 would not be appropriate for this SLR.' The EAG believe that it was reasonable to limit the search for this reason but to ensure thoroughness, it would have been optimal to have limited the search to studies published from 2012. Additional limits were applied to remove the publication types editorials, comments, letters, case reports or studies. Animal studies were also removed, and no language restrictions were applied. The Embase search included both articles and conference abstracts (Appendix G.1.2.2.1.2 Table 7).

There are major issues with the Cochrane Library searches, as limits have been applied incorrectly (CS Appendix G.1.2.2.1 Table 3, CS Appendix G.1.2.2.1.2 Table 9 and CS Appendix G.1.2.2.1.3 Table 15).[28] Line #25 of the initial search (CS Appendix G.1.2.2.1 Table 3) is an attempt to apply a date limit by inputting: 'with Cochrane Library publication date from Jan 2023 to present'. The Cochrane Library

has in-built limiters which allows the user to restrict by specific years. Line #25 tells the database to limit the results from line # 'with Publication Year from 2022 to 2023', 'in Trials' (CENTRAL). The Cochrane Library contains in-built filters to restrict search results for a single year, or the user can enter a range (for all content). There are also limits on the right-hand side of the search terms box to limit by original publication year (CENTRAL Trials only) or date published on the Cochrane Library. The EAG have tested running searches using this command and note that the search terms in line #25 only searches for records with the terms 'with' and 'publication' and 'year' and '2022' and '2023'; therefore, significantly reducing the search results and removing potentially relevant results.

To increase the sensitivity of the searches, the EAG would recommend searching for keyword headings using the text field .kf in Medline rather than .hw, which searches in the Subject heading word (CS Appendix G.1.2.2.1.2 Table 8, CS Appendix G.1.2.2.1.3 Table 14.

Conference abstracts were searched in Embase via Embase.com, by running the original Embase search and the application of in-built limits to restrict the results to conference abstracts. Internet and grey literature searches were carried out and the search terms and numbers of results are provided. (CS Appendix G.1.2.2.2 Table 19)

Two studies that the company used to inform the model would not have been retrieved from the literature searches that they carried out, as they are not related to PrEP[58],[59]. The company should report any additional targeted searches carried out to identify studies relating to specific parameters.

4.2 *Summary and critique of the company's submitted economic evaluation by the EAG*

4.2.1 NICE REFERENCE CASE CHECKLIST

Table 26. NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Most direct health effects were included in the economic model. Disutility for adverse events such as ISR have not been considered.

Perspective on costs	NHS and PSS	The model considered costs from an NHS and PSS perspective but did not fully account for the resource implications of administering cabotegravir in clinics. Furthermore, the model does not consider cost implications of stopping and re-starting cabotegravir during periods of changing risks. Limiting the maximum at-risk period to five years could potentially result in an underestimation of CAB-LA treatment costs since the injections are discontinued after this period of heightened risk. If the injections were to be used for longer than five years in practice, this would cap the cost of CAB-LA treatment at five years. Given that the injections incur higher acquisition and administration costs compared to oral PrEP via TDF/FTC (which requires fewer resources for administration), capping treatment to five years would

Element of health technology assessment	**Reference case**	**EAG comment on company's submission**
		favour CAB-LA in terms of cost-effectiveness.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on health effects	Based on systematic review	Yes
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Health-related quality of life data was not collected in the HPTN 083 and HPTN 084 trials. Disutility for infection was gotten from a study by Miners *et al*[60]
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	No comment

Element of health technology assessment	Reference case	EAG comment on company's submission
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, a standardised instrument for use as a measure of health outcome.		

4.3 *Model structure*

The company used a static Markov model, including the aggregate impacts of secondary HIV following primary HIV. The model has a cycle length of 1 month and a lifetime horizon. The model assumes an aggregate risk period of 5 years within which individuals are at risk of HIV. Afterwards, individuals are assumed to be no longer at risk of HIV.

The model consists of 5 health states:

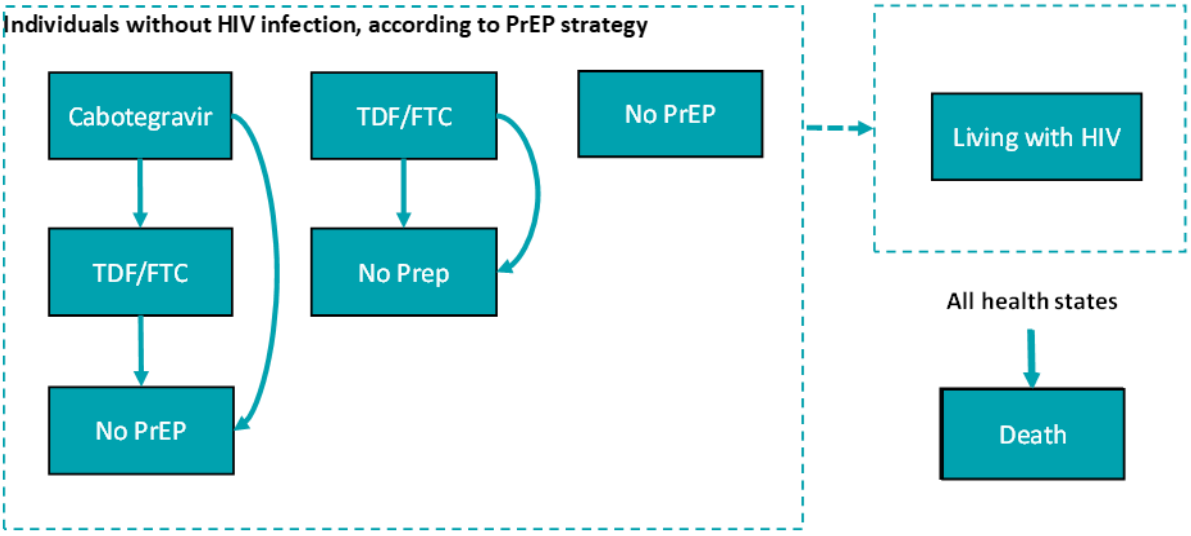
1. Cabotegravir(PrEP)
2. TDF/FTC (PrEP)
3. No PrEP,
4. Living with HIV, and
5. Death

The cohort begins from the PrEP health states (Cabotegravir and TDF-FTC) with transitions to either another PrEP health state or a no prep health state, Living with HIV and death. [redacted] of the cohort in cabotegravir PrEP state who discontinue cabotegravir, transition to a TDF/FTC PrEP state while the rest transition to a no prep health state. All individuals who discontinue TDF/FTC transition to a no prep health state. The number of HIV is a function of prophylaxis for patients at risk of infection. During the 5-year HIV acquisition risk period, those in the no prep health state have a baseline risk of HIV acquisition (4.9 per 100 person-years for men who have sex with men and transgender women and [redacted] per 100 person-years for cisgender women). An ITC incorporating a meta-regression model using the data from the pivotal trials (HPTN 083 and HPTN 084) and from studies from a systematic literature review, was used to estimate the relative reduction in HIV acquisition for patients on cabotegravir and TDF/FTC. These estimates were used to adjust the baseline risk of HIV transmission to reflect the reduction in risk of HIV transmission for individuals on PrEP for the duration of the risk period and to estimate the relationship between the effectiveness of TDF/ FTC versus no PrEP and the adherence to TDF/ FTC based on a meta-regression analysis.

Infected cohort transition to the Living with HIV state and a lifetime transmission rate was applied to new primary infections to account for secondary seroconversions. All health states can transition to the death state. The proportion of the cohort in the living with HIV state have increased mortality risk while general population mortality is applied to other health states.

After the 5-year risk period elapses, individuals are assumed to no longer be at risk of HIV acquisition and transmission. Consequently, all PrEP medications (both oral PrEP and the injections) are discontinued and the PrEP treatment costs are no longer applied beyond the 5-year heightened risk period assumed in the base case.

The model compares cabotegravir to oral PrEP (TDF-FTC) and no PrEP. A



schematic of the described Markov model can be is shown Figure 3.

Figure 3. Model structure
Abbreviations: HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

Reproduced from CS Document B, Section B.3.2.2, Figure 11

The key features of the model and justifications are shown in the Table 27 below.

Table 27. Features of the economic analysis

	Previous evaluations	**Current evaluation**	
Factor	**NA**	**Chosen values**	**Justification**
Time horizon	NA	Lifetime (with an at-risk period of 5 years)	The lifetime horizon is consistent with the NICE guidelines for technology appraisal.[61]. An at-risk period of 5 years aligns with assumptions in the current NICE guidelines for reducing sexually transmitted infections (NG221).[62]

Source of efficacy data	NA	The relative risks of HIV acquisition with cabotegravir and TDF/FTC are calculated based on the estimated HIV acquisition rates from the ITC and adherence to TDF/FTC in HPTN 083 and HPTN 084. A meta-regression analysis is used to generate the relative risk of HIV acquisition as a function of adherence to TDF/FTC and this informs TDF/FTC effectiveness in the model.	The effectiveness of TDF/FTC is known to be strongly dependent on adherence. The meta-regression provides the best estimate of the relative risk of HIV acquisition for TDF/FTC at the adherence levels observed in HPTN 083 and HPTN 084.
Treatment waning effect	NA	No effectiveness was assumed for both TDF/FTC and cabotegravir, beyond the respective periods of persistence	The assumption for TDF/FTC reflects the pharmacokinetics of TDF/FTC.[63] The assumption for cabotegravir is conservative given the data on pharmacokinetics, which indicate a half-life of 45 days after injection.[64]
Source of mortality data	NA	Mortality for people with HIV was estimated by applying a rate ratio to the mortality of the general population of the same age and	The rate ratio reflects the clinical evidence of increased mortality in people with HIV.[65, 66]

		biological sex. The rate ratio was calibrated to generate a life expectancy shortfall matching reported values.[58]	
Source of utilities	NA	Utility values for the general population as a function of age and sex are taken from data from Hernández et al. 2022.[67] Utility values for people living with HIV were derived from general population values after application of an additive disutility derived from Miners 2014.[60]	Data for the general population were selected to align with NICE guidelines for technology appraisal.[61]Data on the impact of HIV status on HRQoL were selected on the basis of study size, relevance to the UK population and consistency with regard to the instrument used to measure HRQoL.
Source of costs	NA	Costs of TDF/FTC were taken from the BNF with the lowest list price used for the base case analysis.[68] Assumptions on resource use associated with monitoring patients on PrEP were based on guidelines from BHIVA/BASHH.[20] Unit costs associated with patient monitoring were	Resource use data were aligned with guidance on the frequency and type of monitoring for the UK from the BHIVA/BASHH guidelines. Unit costs were selected from published literature considered most relevant to the UK setting.

		taken from the NIHR interactive costing tool.[69] Costs associated with the treatment of HIV were taken from appropriate literature sources for the UK.	

Abbreviations: BASHH, British Association for Sexual Health and HIV; BHIVA, British HIV Association; BNF, British National Formulary; HIV, human immunodeficiency virus; HRQoL, health-related quality of life; INSTI, integrase strand transfer inhibitor; LA, long acting; NA, not applicable ; NICE, National Institute for Health and Care Excellence; NIHR, National Institute for Health and Care Research; PK, pharmacokinetic ; PrEP, pre-exposure prophylaxis; TA, technology appraisal; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine; UK, United Kingdom.

Reproduced from CS Document B, Section B.3.2.2.5, Table 32

4.3.1 EAG comment

- The Markov states in the model appropriately captures all clinically relevant health states.
- The model uses a single 5-year risk period to represent the lifetime risk duration for individuals eligible for PrEP. Patients begin PrEP at 26 years and are risk free at 30 years. However, among those first diagnosed in England in 2022, 9%(232) were aged 15-24, 31% (750) were aged 25-34, 37% (904) were aged 35 to 49, 19% (467) were aged 50 to 64 and 4% (91) were aged over 65.[70]In their clarification response (company's response letter to EAG clarification question B2), the company argued periods of heightened risk will occur at different ages for different individuals and will change over time depending on an individual's sexual and affectional relationship. Hence a 5-year single-risk period was used to reflect aggregated lifetime riskto ensure simplicity. The EAG agrees that risk of HIV acquisition is dynamic, and individuals may choose a

PrEP prophylaxis based on an assessment of their own risk. However, the implicit assumptions in the way risk were modelled are unaccounted for in the way the acquisition and administration of cabotegravir were modelled. For example, while an individual may resume taking daily oral pills (TDF/FTC) when they transition from low-risk to high-risk sexual behaviour, the company submission states: *"participants initiating cabotegravir LA for the first time (with or without oral lead-in) or participants who were eligible to re-start cabotegravir required a reloading dose of 2 injections, 4 weeks apart followed by cabotegravir LA injections Q8W".* This suggests re-starting cabotegravir incurs an extra cabotegravir LA injection dose.

Additionally, limiting the maximum at-risk period to five years could underestimate cabotegravir treatment costs if aggregate lifetime risks exceed 5 years.

The 5-year risk period used by the company was derived from a modelling study by Cambiano et al which estimated a mean time of 4.5 years spent on PrEP among men who have sex with men initiating PrEP.[71] In their model, a baseline incidence of 2 per 100 person years was assumed and the PrEP programme were stopped if HIV incidence in the men who have sex with men population fell below 1 in 1000. The estimated mean time of 4.5 years on PrEP relied on these assumptions. The population considered in the company's submission are individuals at high risk of HIV characterised by a much higher incidence rate (4.9 per 100 person years) reflecting HIV incidence in men who have sex with men with recent rectal bacterial STI. Thus, the population modelled by the company is narrower and likely to stay on PrEP longer than the broader men who have sex with men population modelled by Cambiano et al. Given that cabotegravir injections incur higher acquisition and administration costs compared to oral PrEP which incurs no administration costs, capping treatment to five years biases the ICER in favour cabotegravir.[71] The EAG clinical advisor states that there is no real-world data to show how long individuals stay on oral PrEP.

4.4 *Population*

HPTN 083 was a Phase 2b/3 RCT conducted in cisgender adult (≥18 years) men who have sex with men, and transgender women who have sex with men (n=4,570) and HPTN 084 was a Phase 3 RCT in cisgender women (aged 18-45 years) at risk of HIV (n=3224). HPTN 083 trial recruited participants from 43 sites in the US, Latin America,

Asia and to a lesser extent, Africa. HPTN 084 trials recruited participants from 7 countries in sub-Saharan Africa (Botswana, Eswatini, Kenya, Malawi, South Africa, Uganda, and Zimbabwe).

The proportion of cisgender women in the modelled population (3.14%) was estimated based on UKHSA data for people attending SHSs in England in 2022 with an identified PrEP need, with the remaining population (96.9%) consisting of transgender women and men who have sex with men.[20]

The mean age of the population at model entry was assumed to be 26 years old, reflecting the weighted mean age of the HPTN 083 and HPTN 084 trial population.

4.4.1 EAG comment

- The CS stated that "the population comprises of adults at risk of HIV acquisition for whom oral PrEP is inappropriate". However, the model relies on data (effectiveness and adherence) from the HTPN trials and trials included in the ITC, where the patients recruited were individuals for whom oral PrEP was deemed appropriate; otherwise, they could not be randomised to the TDF/FTC arms. Thus, the trial population modelled was broader and more aligned with the decision problem statement than claimed in the CS, which specifically intended to model a population for whom oral PrEP is not appropriate.
- The population described in the decision problem (section B.1.1, CS document B): "adults and adolescents at risk of sexually acquired HIV for whom oral PrEP is not appropriate" does not align with the final scope as stated by NICE, which is people at risk of sexually acquired HIV. It is unclear to what extent the population in both the HPTN 083 and HPTN 084 trials meet the criteria outlined in the decision problem (i.e. people for whom oral PrEP is inappropriate), neither trial included eligibility criteria based on ability/inability to take oral PrEP. However, as mentioned earlier, the actual population modelled in the CS economic model does rely on data from the HPTN trials and trials in the ITC, where suitability for oral PrEP was not determined. The patients recruited were individuals for whom oral PrEP appeared to be appropriate. Thus, the EAG believes the modelled population was broader than as claimed in CS section B.1.1.1 (Document B) and more aligned with the decision problem statement which specifically intended to model a population for whom oral PrEP is not

appropriate. Therefore, ERG considers that only the ICERs generated from cabotegravir vs TDF/FTC base-case are appropriate for decision making.

- Unfortunately, both HPTN 083 and HPTN 084 trials did not recruit participants in the UK or Europe. Hence, the extent to which findings are generalisable to the UK population is uncertain. Given the strong relationship between adherence and effectiveness (for the TDF/FTC comparison), questions on the generalisability of the trial population to the UK population is explored in more detail when issues around adherence is discussed in subsequent sections.

4.5 *3.2.4 Intervention and Comparators*

Cabotegravir is compared with oral PrEP(TDF/FTC) and no PrEP.

4.5.1 EAG comment

- Oral PrEP is an appropriate comparator and fits within the scope of decision problem guidance issued by NICE. However, no PrEP is not an appropriate comparator and does not align with the final scope issued by NICE.
- The population for whom oral PrEP is inappropriate as described in the company's decision problem is unclear. In their clarification response, the company principally argues that (i) sub-optimal adherence to oral PrEP regimens, (ii) drug-related adverse events and (iii) unspecified medical conditions can make people ineligible for oral PrEP. The EAG addresses these three main reasons below.
    - There is no evidence to suggest that a bi-monthly cabotegravir intramuscular injection would be more appropriate for people who cannot optimally adhere to oral PrEP. Given the significant administrative burden on both PrEP users and NHS clinics to ensure on-time injections, it is unclear the extent to which cabotegravir can improve adherence above TDF/FTC adherence levels in the UK.
    - In HPTN 083, 82% of participants receiving cabotegravir had drug related AEs compared to 59% of participants who received daily oral TDF/FTC. Indeed, 6% of participants on cabotegravir had more adverse events leading to discontinuation of the study drug compared to 4% in the daily oral TDF/FTC arm (Table 23, Company Submission Document B).

For these reasons, the EAG considers no PrEP an inappropriate comparator and argues for its exclusion as a comparator in this appraisal. Th EAG clinical advisor agree with the EAG rational as there are no studies with a placebo or no PrEP because it is unethical.

4.6 *Perspective, time horizon and discounting*

The analysis is performed from a National Health Service (NHS) and Personal Social Services (PSS) perspective, in line with NICE reference case. A lifetime horizon is used but the base case only considers a 5-year period where an individual is at risk of sexually acquired HIV and therefore eligible for PrEP. After the 5-year risk period, they are assumed to no longer be at risk of HIV and can neither get infected nor transmit HIV. Costs and benefits, i.e. life years and QALYs gained, are discounted at a per annum 3.5% discount rates in line with the NICE reference case.[72]

4.7 *Treatment effectiveness and extrapolation*

The effectiveness of oral TDF/FTC and cabotegravir is derived from an indirect treatment comparison using information from the HPTN 083 and HPTN 084 clincal trials, and a SLR and meta-analysis of RCTs investigating oral PrEP. Meta-regression models were used to estimate the relative reduction in risk of HIV acquisition of TDF/FTC as a function of adherence to PrEP in TDF/FTC vs no PrEP and CAB-LA vs no PrEP comparisons. For the cabotegravir vs no PrEP comparison, as there were no studies directly comparing cabotegravir to no PrEP, an ITC was used to estimate the relative reduction in risk of HIV acquisition, underpinned by the consistency assumption ($RR_{A\ vs.\ C} = RR_{A\ vs.\ B} \times RR_{B\ vs.\ C}$) and the validity of the meta-regression used to estimate the effectiveness of TDF/FTC vs no PrEP. Adherence to cabotegravir was assumed to be subsumed in the relative effectiveness of cabotegravir vs TDF/FTC in the HPTN 083 and HPTN 084 trials. The relative reduction in risk of HIV transmission estimated from the ITC and meta-regression models was used to adjust the baseline incidence of HIV in individuals on no PrEP.

The baseline incidence of HIV was derived from a PrEP naive population and assumed to be incidence observed in the economic model cohort allocated to no PrEP intervention. The baseline HIV incidence (4.9 per 100 person years) for men who have

sex with men was assumed to be equivalent to HIV incidence in the men who have sex with men and transgender women population with a recent rectal bacterial STI. A baseline incidence of [redacted] per 100 person-years for cisgender women was used.[20]
Relative risk reductions estimated at the adherence levels observed in the HPTN trials was then applied to the baseline incidence rate to derive incident infections in the economic model cohorts allocated to CAB-LA and TDF/FTC interventions.

The model also considered treatment persistence which was used to model discontinuation of PrEP regimens and was estimated to be 70.2% between 0-6 months and 57.4% at 12 months.[73]Persistence to cabotegravir was assumed to be 20% higher than persistence to TDF/FTC. In the cabotegravir arm, [redacted] of patients who discontinue the drug are assumed to receive TDF/FTC while the rest receive no PrEP. In the TDF/FTC arm, all patients who discontinue the drug are assumed to receive no other PrEP option. When patients transition to no PrEP, they are assumed to be at baseline risk of HIV acquisition (4.9 per 100 person years for men who have sex with men and [redacted] person years for cisgender women) for the duration of the risk period.
A lifetime secondary transmission of HIV was assumed to be 1.38 for every HIV acquisition in men who have sex with men and 0.80 in cisgender women. A weighted average of both transmission rates (1.36) was applied to primary infections in each arm. The difference in secondary seroconversions between the cabotegravir and TDF/FTC cohort was captured in the model. After the risk period of 5 years in the model base case, individuals can no longer acquire HIV. Patients who acquire HIV were assumed to have a reduced life expectancy relative to the general population of 3.7 and 6.8 years in men and women, respectively. Patients who acquire HIV are assumed to have a lifetime disutility of 0.11.

4.7.1 EAG comment

4.7.1.1 Baseline risk of HIV acquisition

The company assumed the baseline risk of HIV acquisition in the men who have sex with men population was equivalent to HIV incidence in a subset of the men who have sex with men population with recent rectal bacterial STI.[20] The incidence value used for the company base case includes individuals with unknown HIV status who may already have HIV which could lead to bias. However, Brady *et al* also reported the HIV

incidence rate for men who have sex with men with recent rectal bacterial STI and who had been tested for HIV in the previous year (defined as 42 to 365 days prior)). The EAG argues that the incidence rate of 3.9 per 100 person-years is a more reliable estimate than the estimate used by the company because it considers knowledge of HIV status.

4.7.1.2 Transition from cabotegravir to oral PrEP for patients in the cabotegravir arm

The model assumes that [redacted] of people who discontinue cabotegravir transition to oral PrEP but does not make an equivalent assumption in the oral TDF/FTC arm. In their clarification response, the company argued that the distinction between the population considered in this appraisal (i.e. individuals whose needs could not be met by oral PrEP) and oral PrEP use in the broad population (i.e. individuals who discontinue by choice) underpinned their decision to assume non-equivalent use of cabotegravir in the post-oral PrEP population. The justification for assuming [redacted] of people receiving cabotegravir, transition to receive oral PrEP after discontinuation is unclear given the positioning of cabotegravir (i.e. people for whom oral PrEP is inappropriate).

The EAG argues that an equivalent assumption be made for people receiving oral PrEP, i.e., individuals who discontinue TDF/FTC are allowed to transition to a cabotegravir PrEP state before transitioning to a no PrEP state. Indeed, after the end of the first year of unblinded-follow-up, in both HPTN 083 and 084 trials, participants who transitioned to the OLE in both the cabotegravir and TDF/FTC arms had the option to opt for the alternative PrEP option from originally assigned PrEP. Due to the limitations in the structure of economic model, the EAG was not able to implement an equivalent transition from oral TDF/FTC to cabotegravir. Hence, we conservatively assumed that patients who discontinue cabotegravir do not subsequently transition to oral TDF/FTC.

4.7.1.3 Relative improvements in persistence in cabotegravir compared to oral PrEP

The company assumed a 20% increase in persistence to cabotegravir relative to TDF/FTC. The company argues that an intramuscular injection of every two months with cabotegravir would improve the convenience of cabotegravir in addition to providing an additional modality that addresses barriers to both adherence and

persistence. The EAG argues that persistence in a real-world setting is likely to be lower than those observed in trial conditions. Submission received from NHS England Specialised Commissioning {#ref 58} suggested that each injection visit from a patient is likely to take around 60 mins and a reliable recall system will be required to prevent loss to follow-up. Furthermore, drug-related ISR occurred in 81% of people and 2% of people discontinued cabotegravir due to ISR in HPTN 083.

Given the significant burden on both individuals and health care systems in ensuring on-time injections and the additional inconvenience of ISR to patients, persistence to cabotegravir is likely to be lower than persistence to oral PrEP.

The EAG argues that persistence to cabotegravir should be set equal to oral TDF/FTC.

The requirement of trained health care professionals to administer injections, the administrative burden on sexual health clinics in establishing reliable recall systems to ensure on-time injections, the burden on PrEP users to commute to sexual health clinics to receive on-time injections (and the time spent at clinics at each visit) and the potential effects of injection site reactions may lead to lower persistence to cabotegravir compared to oral PrEP users who are unlikely to face any of these issues. Due to these issues, scenarios were also explored to estimate the impact of reduced persistence to cabotegravir relative to oral PrEP on the ICER.

4.7.1.4 Risk period for HIV transmission

4.7.1.4.1 Inception of risk

The model assumes a five-year period where the cohort is at risk of HIV acquisition. In their clarification response, the company argues that the five-year risk period is a non-age specific assumption of the lifetime risk of the cohort. However, the single-risk period does not consider the impact of risk inception on cohort outcomes. A five-year risk period beginning at a latter age (e.g. 35 or 45) is likely to lead to higher ICERs than the period chosen in the model. In the company base case, the cohort begins at 26 years while the median age of PrEP users in the UK is about 33 years (reference: PrEP use and unmet PrEP-need among men who have sex with men in London prior to the implementation of a national PrEP programme, a cross-sectional study from June to August 2019). The EAG considers that the starting age of the model is increased to 33 years to match the median age of PrEP users in the UK.

4.7.1.4.2 Duration of risk

Among those first diagnosed in England in 2022, 9%(232) were aged 15-24, 31% (750) were aged 25-34, 37% (904) were aged 35 to 49, 19% (467) were aged 50 to 64 and 4% (91) were aged over 65.[70]

The EAG argues that the use of a single five-year risk period is inadequate to model the lifetime risk of HIV acquisition in people at risk of infection. A higher risk period should more accurately reflect the long-term costs and consequences of implementing cabotegravir in the broader population.

The application of the risk period in the economic model makes it difficult to vary beyond 10 years to assess its impact on costs and benefits associated with comparators. The EAG would have preferred a model that allows for longer risk periods to explore the effects of longer risk duration on the cost-effectiveness.

4.7.1.5 Adherence to PrEP regimens

Adherence to daily oral PrEP is a key driver of the relative effectiveness of oral TDF/FTC compared to both CAB-LA and no PrEP in the model cohort. The company assumed that adherence to cabotegravir is subsumed within the effectiveness of cabotegravir to TDF/FTC. However, the clinical trials (HPTN 083 and HPTN 084) used a modified ITT analysis excluding participants who were non-adherent to cabotegravir oral lead-in tablets prior to intramuscular injections. Hence, the effectiveness of cabotegravir does not consider the impact of non-adherence to cabotegravir lead-in tablets.

In the economic model, [redacted] of participants were assumed to take cabotegravir oral lead-in tablets prior to commencing cabotegravir injections and there is an implicit assumption of full adherence to a daily oral cabotegravir tablet. It is unclear why participants are assumed to fully adhere to daily oral cabotegravir lead-in tablets given the explicit assumptions on adherence to daily oral TDF/FTC in the economic model.

Adherence of participants in the HPTN 083 and HPTN 084 trials was assumed to reflect adherence to the men who have sex with men / transgender women and cisgender women population respectively, in the UK . Both trials were conducted in non-UK settings, raising questions about the generalisability of adherence to oral PrEP from the respective populations to a UK population. Indeed, cisgender women were assumed to have a much lower adherence (56%) compared to transgender women

and men who have sex with men (86%). The HPTN 084 trial was conducted in sub-Saharan Africa countries with different sociocultural norms and health systems to the UK. In their clarification response, the company argued that Black African Women represent the largest ethnic group of women diagnosed with HIV in England, and those first diagnosed with HIV in England. Hence, social and structural barriers to health access in sub-Saharan Africa can transgress geographical borders and are likely to persist in England.

However, HIV first diagnosed in England does not necessarily mean that infection was acquired in England. Indeed, women of black African origin first diagnosed in England living with HIV, 77% were born abroad and 31% also arrived in England the same year as their diagnosis suggesting that new previously undiagnosed infections were likely acquired abroad.[70] Furthermore, it is unclear the extent to which social and structural determinants of health in countries with weaker health systems would persists in the UK.

The EAG considers that the gender-based differences in adherence observed between the HPTN 083 and HPTN 084 populations is unlikely to reflect adherence levels in the UK population. Despite uncertainties in the applicability of the adherence data in men who have sex with men / transgender women from the HPTN 083 trial to the PrEP UK population, the EAG assumes equivalent adherence in the absence of more reliable and suitable data.

4.7.1.6 Adverse effects

The company only included injection site reaction AEs in their base-case. The ISR data were incorporated into a model, classified according to severity as mild, moderate, and severe. To estimate the overall population incidence, the ISR data were weighted based on the proportion of cisgender women. The modelled incidence rates are mentioned in below Table 28. The cost of treating ISRs was included as a one-off cost at the commencement of cabotegravir treatment. No adverse events were considered for the comparator tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) or no PrEP strategies.

Table 28. Injection site reactions observed in HPTN 083 and HPTN 084, and incorporated in the model

Reaction severity	HPTN 083	HPTN 084	Modelled value
Mild (Grade 1)	33.8%	[redacted]	[redacted]
Moderate (Grade 2)	45.1%	[redacted]	[redacted]
Severe (Grade 3)	2.6%	[redacted]	[redacted]

Source: Landovitz et al, 2021[37] and ViiV Healthcare data on file[36]

Abbreviations: HPTN, HIV Prevention Trials Network.

Reproduced from CS Document B, Section B.3.3.11, Table 36

4.8 *Health-related quality of life*

No HRQoL data were collected in the HPTN 083 and HPTN 084 clinical trials that evaluated cabotegravir for PrEP. Mapping of clinical outcomes to utilities was not undertaken because no HRQoL measure suitable for mapping were used in the trials. A systematic literature review (SLR) was conducted to identify utility studies, described in Section B.3.1 and Appendix H. Four studies were identified and a disutility value of –0.11 from Miners et al. was applied to all HIV positive health state.[60] Those without HIV had general population utilities. No disutility were applied for adverse events (AEs). This was based on the company's assumption that AEs noted in the trials were mostly mild with no meaningful HRQoL impact. They also assumed that individuals choosing PrEP view it positively, so benefits may outweigh potential negative impacts like injection site reactions.

4.8.1 EAG comment

4.8.1.1 Disutility for HIV

Health-related quality of life was derived from the study by Miners et al using the EQ-5D-3L insturment in respondents attending outpatient clinics between 2011 and 2012.[60] Following the British HIV Association (BHIVA) treatment guidelines update in 2016, recent HIV regimens have led to decreased pill burden and reduced side-effects.[20, 74] A wider range of treatment options and reduced side effects from new treatment options might improve health related quality of life in individuals living with HIV.[74]Indeed, a more recent evaulation of the health-related quality of life in individuals living with HIV using the EQ-5D-5L reports a utility of 0.77, lower than a utility score of 0.82 in the general population indicating a disutility of –0.05.[74] A HIV disutility of –0.05

was assumed in the EAG base case. For the sensitivity analysis, we assumed a variation of 10%.

4.8.1.2 Disutility for AEs

The EAG disagrees with the company's rationale for not applying disutility for adverse events. Indeed, 2% of individuals discontinued cabotegravir due to ISR. Given the higher proportion of AEs leading to the study discontinuation in the cabotegravir relative to oral TDF/FTC (6% vs 4%), the decision not to apply a disutility for AEs goes against NICE recommendations that all direct health effects be considered (reference NICE guide to methods for technology appraisals) and biases the ICER in favour of cabotegravir.[72]

The EAG could not find disutility for ISR in injectable HIV PrEP as cabotegravir is the only approved injectable HIV PrEP and health related quality of life information was not available from the HPTN 083 and HPTN 084 trials. Following a review of the literature, we identified a disutility of -0.01 in a study on users of injectable treatment for type 2 diabetes with mild ISR and a disutility of –0.247 in a study of older adults taking a first dose of recombinant zoster vaccine with severe ISR. The EAG could not find a disutility estimate for moderate ISR so we conservatively assumed equivalence between disutility for mild and moderate ISR. The EAG applied a disutility of -0.01 for mild ISR[75] and a disutility of -0.247 for severe ISR.[76] A weighted disutility of -0.015 was applied per cycle to reflect the population distribution of mild, moderate and severe ISR as seen in Table 28 above.

4.9 *Resources and Cost*

The model considers costs made up of the following categories: drug acquisition costs, NHS visit costs, health state unit costs (living with HIV), and adverse event costs. [redacted]

4.9.1 Cabotegravir acquisition costs

The analysis considers drug acquisition costs for CAB- LA injections [redacted] with 7 doses in year 1 and 6 doses annually thereafter, as well as optional oral cabotegravir lead-in [redacted]). For TDF/FTC, a

generic monthly cost of £34.20 was used, adjusted for differential adherence levels from clinical trials [redacted] pills/week for men/transgender women and [redacted] pills/week for cisgender women. The model conservatively assumes that the drug acquisition costs for TDF/FTC reflect the number of pills corresponding to the level of adherence to TDF/FTC modelled. The calculation for pill consumption is described below in Table 29 Table 30**Error! Reference source not found.** describes the summary of drug acquisition costs for cabotegravir and TDF/FTC.

Table 29. Calculation of pill consumption for TDF/ FTC

Parameter	No adherence (0 pills per week)	Low adherence	High adherence	Weighted average weekly pills
Calibrated distribution for HPTN 083	14.0%	[redacted]	[redacted]	–
Assumed mean pill count per week	0	2	5.5	[redacted]
Calibrated distribution for HPTN 084	44.1%	[redacted]	41.9%	–
Assumed mean pill count per week	0	3.5	7	[redacted]
Weighted population mean	–	–	–	[redacted]

Abbreviations: HPTN, HIV Prevention Trials Network; PrEP, pre-exposure prophylaxis.

Table 30. Calculation of monthly costs of cabotegravir (List price)

Drug	Formu-lation	Pack size	Cost	Dose	Cost per dose	Cost in first year	Cost in subseq-uent years	Doses per month	Cost per month
CAB-oral	Oral 30	30	[redacted]	Once daily	[redacted]	[redacted]	–		–

	mg tablet			(for 4 weeks)					
CAB-LA	Vial 600 mg solution	1	[redacted]	Monthly for first 2 months and then every 2 months	[redacted]	[redacted]	[redacted]		–
TDF/FTC		30 tablets	£34.20	Once per day	£1.14	–	–	[redacted]	[redacted]

Abbreviations: cabotegravir LA, cabotegravir long-acting. PrEP, pre-exposure prophylaxis; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

4.9.1.1 EAG comment

There is a discrepancy in the frequency of visits for cabotegravir injections between the Summary of Product Characteristics (Appendix C) and evidence submitted through NHS England by clinicians using cabotegravir in the NHS. The SmPC recommends doses [redacted] (one month apart), while evidence submitted by NHS England suggests doses every 8 weeks (after first two initial doses 28 days apart). The CS also suggested an eight-weekly administration time in the description of the trial interventions “cabotegravir LA 600 mg administered as one 3 mL IM injection in the gluteal muscle at two time points Q4W then Q8W thereafter” (CS Document B Table 7)

An eight-weekly visit would lead to 7 visits in the first year and 6.5 visits in the subsequent years rather 6 visits in the subsequent years in the company base case. Over a 5-year and 10-year risk period, this accrues to about 2 and 4.5 injection visits respectively; or an underestimation of drug acquisition costs by 6.45% and 7.37% over a 5 and 10-year risk period, respectively. The discrepancy between the SmPC report

in the CS Document B, and both the trial methodology in CS Document B and evidence submitted by NHS England Specialised Commissioning[77] significantly affects the ICER given the significant drug acquisition costs ([redacted] per injection). The EAG assumes an 8-weekly administration schedule and adjusts cabotegravir acquisition and administration costs accordingly. The EAG clinical advisor agree with the use of the NHS England Specialised commissioning.

Drug acquisition costs does not consider the impact of aggregating risks of HIV acquisition over a lifetime on individual. For example, the assumption of an aggregate five-year risk period to reflect lifetime risk of HIV acquisition implicitly assumes individuals stop and re-start cabotegravir over their lifetimes. However, stopping, and re-starting cabotegravir incurs additional costs. The company submission states that "participants who were eligible to re-start cabotegravir required a reloading dose of 2 injections, 4 weeks apart followed by cabotegravir LA injections Q8W" (CS Document B. Table 7). If cabotegravir were stopped and restarted just once over the lifetime of an individual on PrEP, the drug acquisition cost increases by 8.3% in the second year and 1.5% over the lifetime of the cohort (assuming a total risk period of 5 years with 7 injection visits in the first year and 6.5 visits in subsequent years). In a real-world setting, individuals at risk of HIV acquisition are likely to re-start PrEP multiple times over their lifetime. Hence, the EAG conservatively assumes a 5% increase in cabotegravir acquisition and administration costs. The EAG clinical advisor agree with the EAG approach of stopping and restarting.

4.9.2 Cabotegravir administration costs

The analysis accounts for the administration cost of CAB-LA injections, assuming 15 minutes of a band 5 nurse's time per administration at a cost of £11.85 per injection visit. No administration cost was included for oral TDF/FTC as it is an orally administered intervention.

4.9.2.1 EAG comment

The estimated administration costs for cabotegravir (£11.85, i.e., 15 minutes wage costs of a Band 5 nurse), appears to significantly underestimate the actual resource implications of using cabotegravir in sexual health clinics. According to evidence

submitted by [redacted][77][redacted]), a visit/appointment for cabotegravir administration is estimated to take approximately 60 minutes and a review by a senior clinician is required at every administration visit (clinical nurse specialist, pharmacist, or doctor). Individuals given the injection will also require 20 minutes observation post drug administration. The estimated drug administration costs used by the company does not account for the additional time and higher staff costs associated with senior clinician reviews and post-administration observation.

Indeed, NHS England submission[77] [redacted]) suggests that the significant burden of administering cabotegravir could lead to the displacement of about 3-4 sexual health activities for each cabotegravir visit.

In the EAG base case, the cost per injection has been calculated using the weighted mean average hourly wage for a senior clinician, such as a clinical nurse specialist, pharmacist, or doctor, for a period of 40 minutes, 20 mins band 5 nurse for observation. This reflects 40 mins clinical activity and 20 mins of observation. This approach accurately reflects the resource implications and associated costs of administering cabotegravir injections in sexual health clinics, as it accounts for the involvement of higher-skilled healthcare professionals and the longer time required for each injection visit. Our approach conservatively estimates administration costs as it neither accounts for the opportunity cost of displaced sexual health activities in clinics nor the costs of implementing reliable recall systems to prevent loss of follow-up.

4.9.3 Monitoring costs

The monitoring costs undertaken at each clinical visit were informed by the recommendations in the BHIVA/BASHH guidelines. Testing frequency in the first and subsequent years for men who have sex with men, transgender women, and cisgender women followed the BHIVA/BASHH guidelines. Kidney function tests (eGFR, urinalysis, serum creatinine) were only assumed during the initial assessment. Hepatitis B testing occurred annually, while hepatitis C testing occurred annually for men who have sex with men and transgender women only. Pregnancy testing was conducted for cisgender women exclusively. Test frequencies for cabotegravir and TDF/FTC, along with costs, are detailed in Table 31. Annual test

costs were averaged based on the proportion of cisgender women in the population and converted to monthly costs. The costs are summarized in Table 31 below.

Table 31. Unit costs of monitoring tests

Test	Unit cost from source	Unit cost inflated to 2022/23 GBP	Source
HIV antigen/ antibody test	£12	£12.44	NIHR (87806)
Hepatitis B test	£11	£11.40	NIHR (86704)
Chlamydia test	£11	£11.40	NIHR (87810)
Gonorrhoea test	£46	£47.67	NIHR (87850)
Syphilis test	£8.53	£8.65	NSNC (DAPS07)
Hepatitis C antibody test	£27	£27.98	NIHR (86803)
Serum creatinine	£12	£12.44	NIHR (82575)
eGFR test	£191.42	£194.19	NSNC (IMAGOP RN27A)
Urinalysis	£19	£19.69	NIHR (81000)
Urine pregnancy test	£9	£9.33	NIHR (84703)

Abbreviations: eGFR, estimated glomerular filtration rate; GBP, Pounds Sterling; HIV, human immunodeficiency virus; NIHR, National Institute of Health Research interactive costing tool; NSNC, National Schedule of NHS Costs year 2021/22.

Attendance frequency at a sexual health clinic for TDF/FTC followed BHIVA/BASHH guidance (8), with an extra visit at treatment initiation and one month later, totalling six visits in the first year (months 0, 1, 3, 6, 9, and 12). Cabotegravir LA recipients attended the clinic for each administration, seven times in the first year and six times thereafter. Costs were based on limited UK sexual health service data, assuming each clinic visit lasted 30 minutes, costing £58.20 per visit. Annual consultation costs were £407 and £349 for cabotegravir in the first and subsequent years, respectively, and £349 and £233 for TDF/FTC. Both test and consultation costs were divided by 12 and applied monthly. See Table 32 below which reports the total monthly costs

associated with each of the active PrEP options. Costs were not considered for the no PrEP option, assuming this choice entailed a complete disengagement from sexual health services.

Table 32. Monthly costs associated with provision of cabotegravir or TDF/FTC

Item	CAB one-off cost	CAB in first year	CAB in subs years	TDF/FTC in first year	TDF/FTC in subs years
Oral lead-in	[redacted]	–	–	–	–
PrEP	–	[redacted]	[redacted]	[redacted]	[redacted]
Administration	–	£6.91	£5.92	–	–
Monitoring visits	–	£33.95	£29.10	£29.10	£19.40
Monitoring tests	–	£65.68	£35.85	£65.68	£35.85
Total	[redacted]	[redacted]	[redacted]	£117.68	£78.15

Abbreviations: PrEP, pre-exposure prophylaxis; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

4.9.3.1 EAG comment

The company assumed equivalence in number of monitoring tests between cabotegravir and oral TDF/FTC. Evidence from NHS England Specialised Commissioning [77] suggests that for HIV antigen test will be required at every visit for individuals on cabotegravir PrEP rather than every three months after the first year on PrEP currently assumed by the company.

4.9.4 HIV management costs

Individuals who contracted non-resistant HIV in the model faced monthly costs for HIV-related care, covering ART expenses and associated visits and monitoring. Those acquiring HIV with PrEP-related breakthrough resistance were anticipated to experience higher costs for a period.

ART cost data were sourced from a UK study analyzing 68,801 patients in the HIV and AIDS reporting system (HARS), combined with data from the British National Formulary (BNF). Costs remained stable for the initial 18 years, then increased, possibly due to age-related health challenges and resistant HIV strains. Mean annual ART costs for non-resistant HIV were £7,294 (2022/23 GBP) over the first 20 years, while resistant HIV costs averaged £9,430 annually over years 21 to 36.
Healthcare costs related to HIV acquisition were derived from a UK analysis of secondary care costs, indicating £154.98 per month for inpatient and outpatient care. These costs were added to the monthly ART expense, resulting in monthly treatment costs of £762.80 for non-resistant HIV and £940.84 for resistant HIV. For individuals acquiring NRTI or INSTI-resistant HIV, the latter cost was applied. The average duration of first-line treatment was estimated at 16.2 years, with costs post-first-line treatment assumed to mirror those for resistant HIV. To simplify implementation, the discounted additional cost of treating resistant HIV during first-line treatment was calculated and applied as a one-time expense, amounting to £34,611 for INSTI or NRTI resistance.

4.9.5 Adverse reaction unit costs and resource use

Management costs for injection site reactions (ISRs) were estimated based on severity and applied as a one-time expense. Mild ISRs were assumed to require no medical intervention. Treatment for moderate ISRs involved using 800 mg of ibuprofen three times daily for three days. Severe ISRs necessitated a physician visit along with ibuprofen. Using a cost of £4.90 for 60 tablets of 400 mg strength from the BNF, the cost per event of ibuprofen was calculated as £1.47. Assuming moderate or severe ISRs occurred at each injection in the first year, the total cost for ibuprofen was £10.29. Additionally, a single consultation with a General Practitioner (GP) for severe ISRs, lasting 24.5 minutes, incurred a cost of £113.83. Thus, the total cost for severe ISR management, including ibuprofen, was £124.12. These costs were combined with the weighted mean incidence of ISRs for different populations, resulting in a one-time cost of £7.66 for individuals receiving cabotegravir. See Table 33 for details.

Table 33. Costs of adverse events associated with cabotegravir and included in the model

Adverse event	Frequency	Medication cost	Clinician time	Total cost
Mild ISR	[redacted]	–	–	0
Moderate ISR	[redacted]	£10.29	–	£4.53
Severe ISR	[redacted]	£10.29	£113.83	£3.13
Total	–	–	–	£7.66

Abbreviations: cabotegravir LA, cabotegravir long-acting; ISR, injection site reaction.

4.9.5.1 EAG comment

The EAG disagrees with the application of a one-off cost for injection site reactions. Adverse event costs, i.e., costs for managing ISR, should be applied at each cycle. The EAG base case applies ISR costs at each cycle rather than as a one-off cost.

4.10 *Severity*

The company states that the impact of living with well-controlled HIV on life expectancy does not justify the application of a severity modifier. Hence, no severity modifiers were used in the model.

5 COST-EFFECTIVENESS RESULTS

5.1 *Company's cost-effectiveness results*

A summary of the variables used in the model are shown below in Table 34. Table 34

Table 34. Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission

Population characteristics			
Age of men who have sex with men and transgender women	26 years	25.78 to 26.22 (Normal)	Patient characteristics, Section B.3.3.1
Age of cisgender women	25 years	24.82 to 25.18 (Normal)	Patient characteristics, Section B.3.3.1
Proportion of cisgender women	3.14%	3.0% to 3.2% (Beta)	Patient characteristics, Section B.3.3.1
Clinical parameters – HIV acquisition			
Underlying risk of HIV acquisition in men who have sex with men and transgender women	4.9 events per 100 person years	4.4 to 5.4 (Normal)	Risk of HIV acquisition, Section B.3.3.2
Underlying risk of HIV acquisition in cisgender women	[redacted] events per 100 person years	[redacted] (sampled values from the posterior distribution)	Risk of HIV acquisition, Section B.3.3.2
Relative reduction in risk of HIV incidence with TDF/FTC (men who have sex with men and transgender women)	[redacted]	[redacted] (Beta)	Risk of HIV acquisition, Section B.3.3.2
Relative reduction in risk of HIV incidence with TDF/FTC (cisgender women)	[redacted]	[redacted] (Beta)	Risk of HIV acquisition, Section B.3.3.2
Relative reduction in risk of HIV acquisition with cabotegravir (men who	[redacted]	[redacted] (sampled values from the	Risk of HIV acquisition, Section B.3.3.2

have sex with men and transgender women)		posterior distribution)	
Relative reduction in risk of HIV acquisition with cabotegravir in cisgender women	[redacted]	[redacted] (sampled values from the posterior distribution)	Risk of HIV acquisition, Section B.3.3.2
Secondary HIV acquisitions per primary acquisition (men who have sex with men and transgender women)	1.38	1.11 to 1.65 (Normal)	Onward transmission of HIV, Section B.3.3.6
Secondary HIV acquisitions per primary acquisition (cisgender women)	0.8	0.65 to 0.96 (Normal)	Onward transmission of HIV, Section B.3.3.6
Proportion of HIV acquisitions acquired with cabotegravir which are INSTI resistant	41.7%	13.5% to 85.3% (Beta)	Risk of resistant HIV, Section B.3.3.7
Proportion of HIV acquisitions acquired with TDF/FTC which are NRTI resistant	15.4%	5.7% to 29.9% (Beta)	Risk of resistant HIV, Section B.3.3.7
Clinical characteristics – adherence and persistence			
Percentage of men who have sex with men and transgender women with high adherence to TDF/FTC	[redacted]	Not varied	Risk of HIV acquisition, Section B.3.3.2
Percentage of men who have sex with men and	86.0%	82.4% to 89.3% (Beta)	Risk of HIV acquisition, Section B.3.3.2

transgender women with detectable tenofovir			
Percentage of cisgender women with high adherence to TDF/FTC	41.9%	Not varied	Risk of HIV acquisition, Section B.3.3.2
Percentage of cisgender women with detectable tenofovir	55.9%	53.7% to 58.1% (Beta)	Risk of HIV acquisition, Section B.3.3.2
Persistence with TDF/FTC at 6 months	84.2%	83.3% to 85.2% (Beta)	Persistence to PrEP, Section B.3.3.9
Persistence with TDF/FTC at 12 months	70.2%	69.4% to 71.0% (Beta)	Persistence to PrEP, Section B.3.3.9
Increase in persistence for cabotegravir compared with TDF/FTC	20%	10% to 30% (Normal)	Persistence to PrEP, Section B.3.3.9
Clinical parameters – use of second line PrEP			
Proportion of people commencing TDF/FTC after discontinuing cabotegravir	[redacted]	[redacted] (Beta)	Persistence to PrEP, Section B.3.3.9
Monthly discontinuation rate for TDF/FTC after cabotegravir	[redacted]	[redacted] (Beta)	Persistence to PrEP, Section B.3.3.9
Monthly probability of transition from TDF/FTC to TAF/FTC	0.0%	0.7% examined in one-way sensitivity analysis.[73]	Transition to TAF/FTC, Section B.3.3.10
Clinical parameters – adverse events			
Proportion of men who have sex with men and transgender women	33.8%	31.8% to 35.8% (Beta)	Incidence of adverse events,

experiencing mild ISRs with cabotegravir			Section B.3.3.11
Proportion of men who have sex with men and transgender women experiencing moderate ISRs with cabotegravir	45.1%	43.0% to 47.2% (Beta)	Incidence of adverse events, Section B.3.3.11
Proportion of men who have sex with men and transgender women experiencing severe ISRs with cabotegravir	2.6%	2.0% to 3.3% (Beta)	Incidence of adverse events, Section B.3.3.11
Proportion of cisgender women experiencing mild ISRs with cabotegravir	[redacted]	23.5% to 27.9% (Beta)	Incidence of adverse events, Section B.3.3.11
Proportion of cisgender women experiencing moderate ISRs with cabotegravir	[redacted]	10.4% to 13.7% (Beta)	Incidence of adverse events, Section B.3.3.11
Proportion of cisgender women experiencing severe ISRs with cabotegravir	[redacted]	0.0% to 0.24% (Beta)	Incidence of adverse events, Section B.3.3.11
Parameters relating to mortality and HRQoL			
Rate ratio for mortality following HIV acquisition in men who have sex with men and transgender women	1.50	1.20 to 1.79 (Normal)	Mortality after HIV acquisition, Section B.3.3.12
Rate ratio for mortality following HIV acquisition in cisgender women	2.18	1.75 to 2.61 (Normal)	Mortality after HIV acquisition,

			Section B.3.3.12
Disutility associated with HIV acquisition	0.11	0.10 to 0.13	HRQoL date used in the CEA, Section B.3.4.5
Cost parameters – cost of PrEP regimens			
Cost of oral cabotegravir, 30 x 30 mg tablets	[redacted]	Not varied	Acquisition costs for cabotegravir, Section B.3.5.1.1
Proportion of people prescribed oral lead-in prior to cabotegravir injection	[redacted]	[redacted] (Normal)	Acquisition costs for cabotegravir, Section B.3.5.1.1
Cost of single 600mg cabotegravir injection dose	[redacted]	Not varied	Acquisition costs for cabotegravir, Section B.3.5.1.1
Cost of TDF/FTC, 30 x 200 mg/ 245 mg tablets	£34.20	Not varied	Acquisition costs for TDF/FTC, Section B.3.5.1.2
Cost of TAF/FTC, 30 x 200 mg/ 245 mg tablets	£355.73	Not varied	Acquisition costs for TDF/FTC, Section B.3.5.1.2

Annual administration costs for cabotegravir in first year	£82.93	£67.47 to £99.95 (Gamma)	Administration costs for cabotegravir and TDF/FTC, Section B.3.5.1.3
Annual administration costs for cabotegravir in subsequent years	£71.08	£57.83 to £85.67 (Gamma)	Administration costs for cabotegravir and TDF/FTC, Section B.3.5.1.3
Cost parameters – clinical consultations			
Annual sexual health clinic visit costs, first year, cabotegravir	£407.43	£331.50 to £491.07 (Gamma)	Monitoring costs, Section B.3.5.1.4
Annual sexual health clinic visit costs, subsequent years, cabotegravir	£349.23	£284.14 to £420.92 (Gamma)	Monitoring costs, Section B.3.5.1.4
Annual sexual health clinic visit costs, first year, TDF/FTC	£349.23	£284.14 to £420.92 (Gamma)	Monitoring costs, Section B.3.5.1.4
Annual sexual health clinic visit costs, subsequent years, TDF/FTC	£232.82	£189.43 to £280.61 (Gamma)	Monitoring costs, Section B.3.5.1.4
Cost parameters – monitoring costs			
Annual test costs, first year, men who have sex with men and transgender women, cabotegravir	£790.83	£643.45 to £953.17 (Gamma)	Monitoring costs, Section B.3.5.1.4
Annual test costs, first year, cisgender women, cabotegravir	£706.89	£575.15 to £852.00 (Gamma)	Monitoring costs, Section B.3.5.1.4

Annual test costs, first year, men who have sex with men and transgender women, TDF/FTC	£790.83	£643.45 to £953.17 (Gamma)	Monitoring costs, Section B.3.5.1.4
Annual test costs, first year, cisgender women, TDF/FTC	£706.89	£575.15 to £852.00 (Gamma)	Monitoring costs, Section B.3.5.1.4
Annual test costs, subsequent years, men who have sex with men and transgender women, cabotegravir	£432.54	£351.94 to £521.34 (Gamma)	Monitoring costs, Section B.3.5.1.4
Annual test costs, subsequent years, cisgender women, cabotegravir	£357.93	£291.23 to £431.41 (Gamma)	Monitoring costs, Section B.3.5.1.4
Annual test costs, subsequent years, men who have sex with men and transgender women, TDF/FTC	£432.54	£351.94 to £521.34 (Gamma)	Monitoring costs, Section B.3.5.1.4
Annual test costs, subsequent years, cisgender women, TDF/FTC	£357.93	£291.23 to £431.41 (Gamma)	Monitoring costs, Section B.3.5.1.4
Cost parameters – adverse event costs and HIV treatment costs			
Cost associated with moderate injection site reactions	£10.29	£8.37 to £12.40 (Gamma)	Adverse reaction unit costs and resource use, Section B.3.5.3

Cost associated with severe injection site reactions	£124.12	£100.99 to £149.60 (Gamma)	Adverse reaction unit costs and resource use, Section B.3.5.3
Monthly cost of ART for non-resistant HIV	£607.82	£494.55 to £732.60 (Gamma)	Health state unit costs, Section B.3.5.2.1
Monthly cost of healthcare for HIV	£154.98	£126.10 to 186.80 (Gamma)	Health state unit costs, Section B.3.5.2.1
Annual cost of ART for resistant HIV	£9430.36	Not varied	Health state unit costs, Section
Monthly secondary care costs associated with HIV	£154.98	£126.10 to £186.80 (Gamma)	Health state unit costs, Section B.3.5.2.1
Mean time to development of resistant HIV (after discounting)	16.2 years	15.00 to 17.40 (Gamma)	Health state unit costs, Section B.3.5.2.1

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; HRQoL, health-related quality of life; PrEP, pre-exposure prophylaxis; TAF/FTC, tenofovir alafenamide/emtricitabine; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

Cabotegravir versus TDF/FTC had an incremental cost of [redacted] and QALYs of [redacted]. The ICER for the base case is £5,580/QALY. Cabotegravir was dominant against no PrEP with cost savings of [redacted] and QALYs of [redacted]. The results for the company's base case cost-effectiveness analysis are presented in Table 35 and below Table 36.

Table 35. Base-case deterministic results cabotegravir versus TDF/FTC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental NHB at £20,000 per QALY	Incremental NHB at £30,000 per QALY
TDF/FTC	[redacted]	[redacted]	[redacted]	–	–	–	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£5,580	0.15	0.17

Cabotegravir is included at list price. TDF/FTC is included at the lowest available price on the BNF.

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years; TDF/FTC, tenofovir disoproxil fumarate with emtricitabine.

Table 36. Base-case deterministic results cabotegravir versus no PrEP

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental NHB at £20,000 per QALY	Incremental NHB £30,000 per QALY

No PrEP	[redacted]	[redacted]	[redacted]	–	–	–	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant (–£44,509; South-East quadrant)	1.99	1.54

Cabotegravir is included at list PAS price.

5.2 *Company's sensitivity analysis*

The company conducted a range of sensitivity analyses on the base case to assess the impact of parameter uncertainty. the company conducted probabilistic and deterministic sensitivity analyses. The results for the company probabilistic analysis are shown in Table 37, Table 38below.

Table 37. Base-case probabilistic results cabotegravir versus TDF/FTC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental NHB at £20,000 per QALY	Incremental NHB at £30,000 per QALY
TDF/FTC	[redacted]	[redacted]	–	–	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	£4,409	0.15	0.17

Cabotegravir is included at list price. TDF/FTC is included at the lowest available price on the BNF.

Abbreviations: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALYs, quality-adjusted life years; TDF/FTC, tenofovir disoproxil fumarate with emtricitabine.

Table 38. Base-case probabilistic results cabotegravir versus no PrEP

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental NHB at £20,000 per QALY	Incremental NHB £30,000 per QALY
No PrEP	[redacted]	[redacted]	–	–	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	Dominant (–£48,991; South-East quadrant)	1.95	1.49

Cabotegravir is included at list price.

Abbreviations: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life year.

The CEACs and ICER plane for the cabotegravir vs TDF/FTC and cabotegravir vs no PrEP is shown below in Figures below.

[redacted] 4 [redacted] Abbreviations: QALY, quality-adjusted life year; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

[redacted] 5 [redacted]

[redacted] Abbreviations: QALY, quality-adjusted life year; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

Abbreviations: PrEP,

6 pre-exposure prophylaxis; QALY, quality-adjusted life year.

7

Abbreviations: PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life year.

The company conducted a set of one-way deterministic sensitivity analyese to explore the impact of key model parameter on the ICER. A tornado diagram showing the impact of varying cabotegravir versus TDF/FTC and no PrEP is shown below.

8 Abbreviations: ARV, antiretroviral; CABOTEGRAVIR, cabotegravir long-acting; CGW, cisgender women; CI, confidence interval; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; MSM, men who have sex with men; NRTI, nucleoside reverse transcriptase inhibitor; PK, pharmacokinetic; PrEP, pre-exposure prophylaxis; TDF/FTC, tenofovir disoproxil fumarate with emtricitabine; TGW, transgender women.

9 Abbreviations: ARV, antiretroviral; CABOTEGRAVIR, cabotegravir long-acting; CGW, cisgender women; CI, confidence interval; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; MSM, men who have sex with men; PK, pharmacokinetic; PrEP, pre-exposure prophylaxis; SMR, standardised mortality ratio; TGW, transgender women.

The company also conducted a range of scenario analyses to explore the impact of various scenarios on the ICER. These are shown in Table 39.

Table 39. Scenario analysis for cabotegravir compared with TDF/FTC and cabotegravir compared with no PrEP (probabilistic)

Scenario	Base case parameter	Value in scenario analysis	Rationale	ICER versus TDF/FTC	ICER versus no PrEP
Base case	–	–	–	£5,580	Dominant (–£44,509; SE quadrant)
Cisgender women population	3.14% of the population	100% of the population	Clarify cost-effectiveness in this part of the population	£7,013	Dominant (–£19,973; SE quadrant)
Men who have sex with men and transgender women population	96.86% of the population	100% of the population		£6,056	Dominant (–£49,491; SE quadrant)
Some individuals (men who have sex with men and transgender women) on TDF/FTC receive	0%	0.185%	In real-world, a small proportion of the population of men who have sex with men and transgender women may	£3,154	Dominant (–£50,748; SE quadrant)

TAF/FTC each month			receive TAF/FTC		
Persistence for cabotegravir compared to TDF/FTC	Increased persistence of 20%	Increased persistence of 35%	Increased convenience of cabotegravir is likely to improve persistence but the extent is unknown	Dominant (–£4,555; SE quadrant)	Dominant (–£48,510; SE quadrant)
Percentage of individuals requiring oral lead in	[redacted]	5%	[redacted]	£2,236	Dominant (–£44,991; SE quadrant)
	[redacted]	95%		£4,829	Dominant (–£47,821; SE quadrant)
Drug wastage for TDF/FTC	No wastage	Missed TDF/FTC doses are wasted	Wastage is unknown but likely	£2,825	Dominant (–£49,090; SE quadrant)

5.3 *Model validation and face validity check*

The company undertook several validity checks, including internal and external validity. These validation checks involved verification of all input data and programming validation. A US version of the model is published in a peer-reviewed journal[78] which was validated using the Assessment of the Validation Status of Health-Economic decision models (AdViSHE) tool.[79]

6 EXTERNAL ASSESSMENT GROUP ADDITIONAL ANALYSES

6.1 *Based on the EAG critique of the company's preferred assumptions and analysis*

6.1.1 EAG revised base case

The changes made to the company model are described below.

EAG 01: No PrEP is an inappropriate comparator and should not be considered in the cost-effectiveness analyses.

Based on the reasons outlined in Section 3.2.3, comparisons between cabotegravir and no PrEP is not presented in the EAG analyses.

EAG 02: Baseline risk of HIV acquisition

Due to the uncertainty around the estimate used for the baseline risk of HIV acquisition, the EAG prefers a baseline risk of 3.9 per 100 person-years. This incidence rate reflects the HIV incidence of individuals with recent HIV test and rectal bacterial STI infection.

EAG 03: Patients who stop cabotegravir PrEP do not transition to receive oral PrEP

The company argues that the population considered for cabotegravir PrEP are those for whom oral PrEP is inappropriate while simultaneously assuming that [redacted] of patients on stop cabotegravir PrEP subsequently go on to receive oral PrEP. A similar assumption is not made in the oral TDF/FTC group which biases the ICER in favour of cabotegravir. The EAG prefers no transitioning from cabotegravir to oral PrEP.

EAG 04: **Adherence to TDF/FTC**

Due to the lack of evidence showing gender-based differences in adherence to oral PrEP in the UK, and the unreliability of adherence data from the HPTN 084 study which was conducted in participants from sub-Saharan Africa, the EAG prefers to set adherence for cisgender women equal to transgender women and men who have sex with men.

EAG 05: Persistence to cabotegravir

Due to the lack of evidence on the company's base case assumption of improved persistence of cabotegravir compared to oral PrEP, the EAG considers no relative improvement in persistence to cabotegravir compared to oral PrEP.

EAG 06: Per cycle application of ISR costs and disutility

Costs of treating ISR was also applied per cycle rather than as a one-off cost. A disutility value of –0.015 was assumed for ISR and applied per cycle.

EAG 07: Duration of risk period

Duration of on-risk period changed from 5 years to 10 years to account for uncertainties associated with a shorter risk period.

EAG 08: Cabotegravir administration costs

Administration costs for cabotegravir costs changed from 15-minute band 5 nurse to an hour of activity in the clinic (i.e. 20 mins band 5 nurse for observation, 40 mins clinical activity representing the weighted average a pharmacist, consultant, and clinical nurse specialist wage.

EAG 09: Cabotegravir dosing schedule

Cabotegravir was assumed to be administered every 8 weeks rather than 2 months in the company base case. EAG preferred frequency of visit was applied to cabotegravir administration costs and cabotegravir HIV antigen tests cost.

EAG 10: Cabotegravir acquisition costs

Drug acquisition and administration costs for cabotegravir increased by 5% to account for potential increases in lifetime costs of cabotegravir administration during to changing risk patterns over the lifetime of the cohort.

EAG 11: Starting age of model

The starting age of the model cohort was increased from 26 years to 33 years to match the median age of PrEP users in the UK

EAG 12: Disutility for HIV

Disutility for HIV changed from –0.11 to -0.05 based on reasons outlined in Section 4.8.1.1

Table 40 Impact of individual EAG preferred model assumptions on ICER

Preferred assumption	ICER
Company base case	[redacted]
EAG02	[redacted]
EAG03:	[redacted]
EAG04:	[redacted]

EAG05:	[redacted]
EAG06:	[redacted]
EAG07:	[redacted]
EAG08:	[redacted]
EAG09:	[redacted]
EAG10:	[redacted]
EAG 11:	[redacted]

6.1.2 EAG deterministic base case results

The cumulative effect of the EAG changes on the company deterministic base case is shown in Table 41 below. Cabotegravir had incremental costs of [redacted] and QALYs of [redacted] The ICER for the base case is £334,635.

Table 41 Base-case deterministic results cabotegravir versus TDF/FTC

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
TDF/FTC	[redacted]	[redacted]	[redacted]	–	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£334,635

Cabotegravir is included at list price. TDF/FTC is included at the lowest available price on the BNF.

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years; TDF/FTC, tenofovir disoproxil fumarate with emtricitabine.

6.1.3 EAG Sensitivity analyses

The EAG conducted probabilistic sensitivity analyses on the base case to assess the impact of parameter uncertainty. The results for the company probabilistic analysis are shown in Table 42 below.

Table 42: Base-case probabilistic results cabotegravir versus TDF/FTC

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
TDF/FTC	[redacted]	[redacted]	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	£339,509

The CEAC and ICER plane for the EAG Base case is shown in the figures below.

[redacted].

[redacted]

6.1.4 EAG scenario analysis

Given the sensitivity of the base case assumptions to parameters in the model, the EAG explored the following scenarios. All EAG base case assumptions were maintained.

Scenario 1: Alternative alpha and beta parameters were estimated to reflect the EAG concerns with uncertainties around the ITC conducted by the company.

Scenario 2: Given the significant logistical challenges of implementing reliable recall systems in clinics administering cabotegravir, the potential impact of severe injection site reaction and the potential challenges to patients in meeting on-time injections, persistence to cabotegravir was assumed to be 10% lower than oral TDF/FTC.

The impact of both scenario analysis is shown in Table 43 below

Scenario 3: Alternative baseline HIV incidence rate was assumed using estimates from the men who have sex with men population with recent HIV tests and bacterial STI infection. A baseline HIV incidence rate of 3.3 per 100 person years was assumed.

Scenario 4: Alternative baseline incidence rate of 1.9 per 100 person years was assumed to reflect HIV incidence in the men who have sex with men population with HIV test done in the previous year.

Table 43 Impact of EAG scenarios on EAG base case

	Incremental costs	Incremental QALYs	ICER £/QALY
Scenario 1	[redacted]	[redacted]	[redacted]
Scenario 2	[redacted]	[redacted]	[redacted]
Scenario 3	[redacted]	[redacted]	[redacted]
Scenario 4	[redacted]	[redacted]	[redacted]

6.2 *Conclusion of the cost-effectiveness section*

The model structure used by the company appears to appropriately capture the decision problem. The EAG has the following concerns about the cost-effectiveness analysis presented by the company detailed in **Error! Reference source not found.** and Section **Error! Reference source not found.**.

The key drivers of the cost-effectiveness analysis are the assumption of increased persistence to cabotegravir, post-oral PrEP use in the cabotegravir cohort, baseline HIV incidence rate for no PrEP cohort at risk of sexually acquired HIV, duration of risk period, cabotegravir acquisition and administration costs, and frequency of cabotegravir administration. The impact of aggregating lifetime risk of HIV acquisition into a single continuous period IS unexplored in the company base case and could significantly affect the ICER estimates presented in the EAG preferred base case assumptions.

Other important factors that had an impact on the ICER includes, starting age of the model, adherence to PrEP regiments and per cycle application of costs and disutility for ISR associated with cabotegravir injection.

APPENDICES

6.0 *Appendix 1*

Table 44. EAG assessment of risks of bias of the CS systematic review in relation to the scope of the appraisal (modified ROBIS)

ROBIS domain, and signalling questions	EAG's rating	Reasoning
1: Study eligibility criteria		
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	**No**	The objectives of the review were not clearly defined. Eligibility criteria are reported in CS Appendix D (Table 6). These criteria were pre-defined and based on the decision problem and the criteria in the published Huic 2023 SR[23] but this was wider than the NICE scope. Additional criteria were applied to assess studies for inclusion the ITC and it is unclear if these criteria were pre-defined.
1.2 Were the eligibility criteria appropriate for the review question?	**Probably no**	The eligibility criteria were wider than the NICE scoped question. Two included studies met the CS criteria but would not have met the NICE scope. An additional set of criteria were used to select studies for the ITC (CS Section B.2.9.2.1) and the EAG has some concerns about the appropriateness of these.

1.3 Were eligibility criteria unambiguous?	**Probably no**	Eligibility criteria were generally clear, however, there are ambiguities about what interventions/comparators were eligible
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate?	**Yes**	Restrictions on study design, RCTs, were appropriate
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate?	**Probably yes**	English Language only publications were included which is likely appropriate. SLR suggests only studies published since 2022 were eligible but this only relates to the update search post the published SR by Huic 2023[23]
Concerns regarding specification of study eligibility criteria	**Unclear concern**	Not all eligibility criteria were specified *a priori* and the EAG has some concerns about the relevance of some included studies
2: Identification and selection of studies		
2.1 Did the search include an appropriate range of databases/ electronic sources for published and unpublished reports?	**Probably yes**	Targeted searches were undertaken and then update searches of existing SRs were performed using a reasonable and appropriate range of databases including grey literature and ongoing trials.

2.2 Were methods additional to database searching used to identify relevant reports?	**Probably no**	Existing SRs were used to identify relevant studies and the CS SLR applied their eligibility criteria to the studies in these SRs (clarification A2). Hand searching specific journals, reference list checking and contacting experts was not carried out.
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	**Probably no**	The search structure and use of filters may have limited the number of studies identified. The EAG re-ran some searches with different limits and identified more hits, but no additional relevant studies were identified.
2.4 Were restrictions based on date, publication format, or language appropriate?	**Probably No**	Studies not in English Language were excluded therefore there is a potential for publication bias
2.5 Were efforts made to minimise errors in selection of studies?	**Yes**	Screening of abstracts and full papers was by two independent reviewers with consensus or a third reviewer for any discrepancy.
Concerns regarding methods used to identify and/or select studies	**Unclear concern**	Some potential for studies to have been missed from the SLR
3: Data collection and study appraisal		
3.1 Were efforts made to minimise error in data collection?	**Yes**	Data were extracted by a single reviewer and checked by a second reviewer.

3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	**Yes**	The primary studies, HPTN 083 and HPTN 084 were summarised in the CS and sufficient study characteristics for all studies included in the SLR were reported both narratively and in Tables 9 – 20 in CS Appendix D.
3.3 Were all relevant study results collected for use in the synthesis?	**Yes**	Relevant study results were reported in the narrative synthesis.
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	**Yes**	ROB using the Centre for Reviews and Dissemination questions was applied to included RCTs.
3.5 Were efforts made to minimise error in risk of bias assessment?	**Yes**	Two reviewers undertook the risk of bias assessment (clarification response A1)
Concerns regarding methods used to collect data and appraise studies	**Low concern**	Data collection methods and processes appear appropriate.
4: Synthesis and findings		
4.1 Did the synthesis include all studies that it should?	**Probably no**	One study was excluded which the EAG considered met the inclusion criteria (IAVI Uganda Study [35])
4.2 Were all predefined analyses followed or departures explained?	**No information**	No discussion of predefined analyses reported

4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	**Probably no**	The ITC/meta-regression analyses were conducted appropriately but there are limitations in the study selection process, methodology, and assumptions underlying the meta-regression approach and a potential impact of unmeasured confounders on treatment effect estimates.
4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis?	**Probably no**	Bayesian Hierarchical models were used, and fixed and random treatment effects analyses were conducted. However, there was heterogeneity in study populations and treatments used in the 'No PReP' comparator arms was not the same across all of the studies included in the ITC (clarification A22) and the meta-regression does not address measurement error in adherence outcomes.
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	**Probably yes**	Sensitivity analyses were reported to be undertaken (CS Appendix D.3.3.6), however, limited results were presented.
4.6 Were biases in primary studies minimal or addressed in the synthesis?	**No**	Bias was not explicitly incorporated into the findings/ conclusions of the SLR

Concerns regarding the synthesis and findings	**High concern**	More than one question has no or probably no response
Risk of bias	**High concern**	Only one aspect of risk of bias considered to be low concern

6.1 *Appendix 2 EAG assessment of eligibility of studies*

The company included 19 studies in their SLR, all identified from existing systematic reviews. Of these 19 studies, ten were included in the ITC and nine were excluded from the ITC. The EAG assessment of the eligibility of these studies is presented in Table 45, and Table 46 respectively.

The company's own searches identified nine additional studies; all were excluded. The EAG assessment of these studies is presented in Table 45.

Table 45. EAG assessment of ten studies included in the company ITC

Included study	EAG comment
Partners PrEP Continuation Beaton 2014[53]	P: Heterosexual men and women. serodifferent couples (seropositive partners not on ART). The placebo arm of the original PrEP trial (see excluded studies), were re-randomised to TDF/FTC or TDF. I: TDF/FTC C: TDF O: Adherence by plasma in cases with HIV and cases randomly selected from both arms. **EAG decision: Exclude (comparator)** ***CS Table 19 lists this as an included study but it was not included in their ITC.***
Bangkok Tenofovir Study Choopanya 2013[32]	P: Male and female dug users in Thailand (background states 'in some countries in eastern Europe and central Asia, more than 80% of all HIV are related to drug use'). Only 22% >1 partner in last 12 weeks, 38% sex with casual partner, 5% men who have sex with men. I: TDF C: Placebo

Included study	EAG comment
	O: Adherence by plasma in cases with HIV and in cases without HIV in 4 of 17 clinics. **EAG decision: Exclude (population and intervention)**
iPrEx Trial Grant 2010[43]	P: Men who have sex with men /transgender women (aligns with HPTN 083) I: TDF/FTC C: Placebo O: Adherence by plasma level in HIV positive and subgroup of 43 seronegative **EAG decision: Include**
VOICE Marrazo 2015[45]	P: Heterosexual women in Africa age 18-45, recent vaginal intercourse but no other requirement for risk (otherwise aligns with HPTN 084) I: TDF/FTC I: TDF I: TDF gel C: Placebo (oral arm and gel arm) O: Adherence by plasma in case-cohort design – random subcohort selected from active groups and enriched with HIV acquisition. **EAG decision: Include (TDF/FTC arm and oral placebo arm only)**
IperGay Molina 2015[33]	P: Men who have sex with men (aligns with HPTN 083) I: TDF/FTC event-driven (before and after sexual activity) C: Placebo O: Adherence by plasma on first 113 participants. **EAG decision: Exclude (intervention)**
Tenefovir 2 Thigpen 2021[46]	P: Heterosexual men and women aged 18-39 years in Botswana. Sexually active (≥1 partner in last 3 months) but no other requirement for risk. Men not aligned with HPTN 083. Women may be aligned with HPTN 084 – some indications of risk level in Characteristics table.

Included study	EAG comment
	I: TDF/FTC C: Placebo O: Adherence by plasma in HIV positive and 69 negative samples matched by data. **EAG decision: Include**
FEM-PrEP Van Damme 2012[44]	P: Heterosexual women in Africa age 18-35 'at increased risk for HIV ' (defined although different from HPTN 084; population aligns with HPTN 084) I: TDF/FTC C: Placebo O: Adherence by plasma in HIV positive and matched negative controls (three controls per positive case), matched on study site and duration of participation in study. **EAG decision: Include**
PROUD McCormack 2016[42]	P: Men who have sex with men (UK study) I: TDF/FTC C: Deferred TDF/FTC after 1 year (no placebo) O: Adherence by plasma only in 52 participants who reported taking PrEP (therefore not appropriate). Also by questionnaire and diary but low completion rates (and results not reported). **EAG decision: Include (but no usable adherence data)**
HPTN 083 Landovitz 2021[37]	P: Men who have sex with men / transgender men I: TDF/FTC C: Placebo **EAG decision: Include**
HPTN 084 Delany-Moretlwe 2022[38]	P: Cisgender women I: TDF/FTC C: Placebo **EAG decision: Include**

Table 46. EAG assessment of nine studies excluded from the company ITC

Excluded study	EAG comment
DISCOVER Mayer 2020[80]	P: Men who have sex with men I: TDF/FTC C: TAF/FTC O: Adherence: (pill counts and DBS). Incidence rate ratio HIV **EAG decision: Exclude (comparator)**
IAVI Kenya Study Mutua 2012[81]	P: Men who have sex with men and female sex workers I: TDF/FTC C: Placebo O: Adherence [medication event monitoring system (MEMs - opening of the pill bottle recorded electronically) and self-report]. HIV acquisition not assessed (CS App D Table 21 has 1 event in placebo arm, this was reported as an adverse event. Study not designed to assess HIV acquisition). **EAG decision: Exclude (outcomes)**
Project PrEPare Hosek 2013[82]	P: Men who have sex with men I: Behaviour + TDF/FTC C: Behaviour + Placebo C: Behaviour alone O: Adherence (various self-reported). HIV acquisition not assessed: exclude. (CS App D Table 21 has zero events, assume this was based on the sentence 'there were no HIV seroconversions…during the study'). **EAG decision: Exclude (outcomes)**
Kwan 2021[83]	P: Men who have sex with men I: TDF/FTC daily C: TDF/FTC on-demand

	O: Adherence (questionnaires at visits). HIV anigen/antibody tested at each visit,but results not reported. (CS App D Table 21 has 1 event but unable to identify this in publication) **EAG decision: Exclude (outcomes, comparator)**
CDC Safety Study Grohskopf 2013 [84]	P: Men who have sex with men I: TDF daily I: TDF after 9 month delay C: Placebo daily / delayed O: Adherence (pill count, MEMS, self-report). HIV acquisition **EAG decision: Exclude (intervention)**
ADAPT Cape Town Bekker 2018[85]	P: African women I: TDF/FTC daily I: TDF/FTC twice a day + post-sex I: TDF/FTC event driven (one tablet both before and after sex) O: Adherence (plasma). HIV acquisition. **EAG decision: Exclude (comparator)**
Peterson 2007[86]	P: Women at high risk of HIV I: TDF C: Placebo O: HIV acquisition RR. (No measure of adherence). **EAG decision: Exclude (intervention)**
Partners PrEP study Baeten 2012[34]	P: Heterosexual men and women. Serodiscordant couples (seronegative partners randomised. Seropositive partners not on ART) I: TDF/FTC I: TDF C: Placebo O: Adherence (pill counts, plasma but only at seroconversion visit). HIV acquisition.

	EAG decision: Include ***CS Table 19 does not list this as an included study, but it was included in their ITC.***
IAVI Uganda study Kibengo 2013[35]	P: HIV-uninfected heterosexual adults cohabiting and had unprotected vaginal sex in last 3 months with infected partner not on ART. I: TDF/FTC (daily arm / intermittent arm) C: Placebo (daily arm / intermittent arm) O: Adherence (MEMS, self-report), HIV acquisition **EAG decision: Include (daily intervention and placebo arms only)**

Table xx EAG assessment of nine studies identified by company's searches and excluded from SLR

Title	CS reason for exclusion	EAG reason for exclusion	EAG comments
Brown, T. T. 2022 Bone changes with candidate PrEP regimens containing tenofovir disoproxil fumarate and/or maraviroc and/or emtricitabine in US men and women: HPTN 069/ACTG A5305 Journal of Antimicrobial Chemotherapy	Population	Comparato r	Relevant to SLR according to CS Table 6 criteria. Agree exclude from ITC as no placebo arm.
Bunge, K 2023 DELIVER: A Safety Study of a Dapivirine Vaginal Ring and Oral PrEP for the Prevention of HIV During Pregnancy Journal of	Population	Interventio n and outcomes	Pregnant women not an explicit exclusion criterion (but likely appropriate). Outcomes not

Title	CS reason for exclusion	EAG reason for exclusion	EAG comments
acquired immune deficiency syndromes (1999)			relevant and intervention not eligible
Delany-Moretlwe, S. 2022 Cabotegravir for the prevention of HIV-1 in women: results from HPTN 084, a phase 3, randomised clinical trial The Lancet	Duplicate	Duplicate	Duplicate of an included study
Eshleman, S. H 2022Characterization of Human Immunodeficiency Virus (HIV) Infections in Women Who Received Injectable Cabotegravir or Tenofovir Disoproxil Fumarate/Emtricitabine for HIV Prevention: HPTN 084 Journal of Infectious Diseases	Duplicate	Linked publication (not an exclude)	This is an additional publication of HPTN 084 but not a duplicate publication.
Herrera, C 2023 Dose finding study for on-demand HIV pre-exposure prophylaxis for insertive sex in sub-Saharan Africa: results from the CHAPS open label randomised controlled trial eBioMedicine	Population	Population, outcomes	Agree population inappropriate (ex-vivo HIV challenge).
Mahomed, S. 2023 Safety and pharmacokinetics of escalating doses of neutralising monoclonal antibody CAP256V2LS administered with and without VRC07-523LS in HIV-negative women in South Africa (CAPRISA	Population	Interventio n, population unclear	Unclear population, exclude on intervention.

Title	CS reason for exclusion	EAG reason for exclusion	EAG comments
012B): a phase 1, dose-escalation, randomised controlled trial The Lancet HIV			
Matthews, R. P 2023 A Randomized, Double-Blind, Placebo-Controlled, Phase 1 Trial of Radiopaque Islatravir-Eluting Subdermal Implants for Pre-exposure Prophylaxis Against HIV-1 Infection Journal of acquired immune deficiency syndromes (1999)	Population	Population, intervention	Agree population inappropriate (low risk HIV), also intervention.
McGowan, I. M 2022 An Open-Label Pharmacokinetic and Pharmacodynamic Assessment of Tenofovir Gel and Oral Emtricitabine/Tenofovir Disoproxil Fumarate AIDS Research and Human Retroviruses	Population	Comparator	Tenofovir gel vs oral emtricitabine/tenofovir disoproxil fumarate. No placebo so not relevant to ITC.
Moodley, D 2023 Pregnancy and neonatal safety outcomes of timing of initiation of daily oral tenofovir disoproxil fumarate and emtricitabine pre-exposure prophylaxis for HIV prevention (CAP016): an open-label, randomised, non-inferiority trial The Lancet HIV	Population	Outcomes	Not an explicit exclusion criteria to exclude pregnant women (but likely appropriate) but excluded on outcomes.

6.2 *Appendix 3 Risk of bias HPTN 083 and HPTN 084*

Risk of bias was assessed by the EAG separately for each trial, however as the methodology and responses were similar, they have been combined in the Table below for ease of reference.

Table 47. Risk of bias HPTN 083 and HPTN 084

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	Randomisation 1: 1 ratio, stratified according to site; performed with the use of permuted blocks of 8, 10, or 12, assigned electronically at enrolment. The randomization scheme was generated, operationalized and maintained by the HPTN Statistical and Data Management Center.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	Groups were well balanced
	Risk of bias judgement	**Low**	
Bias due to deviations from intended	2.1.Were participants aware of their assigned intervention during the trial?	PN	Participants and study site staff were blinded until the trial was stopped early. Oral placebo tablets were

interventions	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY	designed to visually match, however the study protocol does not make a statement regarding visual matching of the injection placebo, Intralipid 20% fat emulsion infusion. The EAG notes that the colour of this is milky white, whereas IM cabotegravir is a white to slightly pink coloured suspension. The protocol also notes potential side effects of Intralipid when used as an intramuscular injection. If these side effects and injection site reactions differ from those of IM cabotegravir there is the potential for unblinding.
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NI	Not clear, information not provided
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations	NA	

	from intended intervention balanced between groups?		
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	Modified ITT excluding participants with HIV at baseline.
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Some concerns**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	N	Proportions retained and attending follow-up reduced from around 91% at 6 months to 75% at 24 months in HPTN 083 and from around 94% to 77% (CAB-LA arm) respectively in HPTN 084. In addition, the observed number of HIV incidences in the CAB-LA arm was lower (HPTN 083: n =13 and HPTN 084: n = 4) than the number of participants who had no HIV

			test results (HPTN 083: n = 37 and HPTN 084: n=22).
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	N	No evidence the result was not biased by missing outcome data.
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	PY	It is possible that reasons for participants not attending follow-up could be linked to their health status. Reasons for missing data were not provided, however, the proportions with follow-up were similar between groups. In HPTN 084, there appears to be an imbalance between the numbers 'retained' at 30 months (cab 76.9%, TDF/FTC 90.9%, but the N was small (11 and 13, respectively). It is unclear whether it is likely that missingness in the outcome depended on its true value.
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	PN	
	Risk of bias judgement	**Some concerns**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	Limited details provided but likely to be appropriate
	4.2 Could measurement or ascertainment of the	N	

	outcome have differed between intervention groups?		
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	All reactive/positive HIV test results were reviewed by an independent HIV Endpoint Adjudication Committee whose responsibility is to determine whether the test results meet the primary endpoint of the study of HIV
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data	Y	Statistical analysis plan provided. Trial stopped early and unblinded according to prespecified plan.

	were available for analysis?		
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple eligible analyses of the data?	N	Although some of the analyses were post hoc, all planned analyses were reported.
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

6.3 *Appendix 4 comparator studies included in the company's ITC and/or EAG ITC*

Summary table of comparator studies included in the company's ITC and/or EAG ITC

Study details	Summary PICO (see CS Appendix Tables 9-20 for more details)	Key results for eligible arms (see CS Appendix Tables 21-27 for more details)
Men who have sex with men and transgender women		
iPrEx Trial Grant, 2010[43] Blinding: Double-blind Country: Brazil, Ecuador, Peru, South Africa, Thailand, and USA	P: Men or Transgender women who have sex with men I: TDF/FTC C: Placebo (adherence): plasma drug detection level in HIV positive and subgroup of 43 seronegative; self-report	HIV acquisitions TDF/FTC: 38/1251 Placebo: 72/1248 HR (95% CI): 0.53 (0.36, 0.78) p<0.001 ITT TDF/FTC: 36/1251 Placebo: 64/1248 HR (95% CI) (TDF/FTC): 0.56 (0.37, 0.85) p=0.005 mITT Adherence:

Study details	Summary PICO (see CS Appendix Tables 9-20 for more details)	Key results for eligible arms (see CS Appendix Tables 21-27 for more details)
Follow-up: Median, maximum range: 1.2 years, 2.8 years	Mean/median age: reported in age categories	Plasma drug detection (FTC) and Tenofovir (TFV): Seronegative participants: 22/43 (51%) Seropositive participants: 3/34 (8.8%) Rate of pill use on ≥50% of days (by pill count, self-report, and dispensation records) TDF/FTC: Beyond 8 weeks: mean 95%. Placebo: Beyond 8 weeks: mean 95%
IPERGAY Molina, 2015[33] Blinding: Double-blind Country: Canada, France Follow-up: Median, IQR range: 9.3 months, (4.9 – 20.6) ***Excluded from EAG ITC (intervention not eligible: event-driven)***	P: Men or Transgender women who have sex with men I: TDF/FTC event-driven (before and after sexual activity) C: Placebo (adherence): plasma drug detection on first 113 participants; self-report Age, median (IQR range): TDF/FTC: 35 (29 – 43) Placebo: 34 (29 – 42)	HIV acquisitions TDF/FTC: 2/199 Incidence/100 person years (95% CI): 0.91 (not reported) p= not reported RRR (95% CI): 0.86 (0.40, 0.98) P = 0.002 mITT RRR (95% CI): 82 (36, 97) P = 0.002 ITT Placebo: 14/201 Incidence/100 person years (95% CI): 6.60 (not reported) p= not reported mITT Adherence: Plasma drug detection (tenofovir): 86% Self-report reported according to correct use based on events (not extracted as intervention not relevant)
PROUD McCormack, 2016[42] Blinding: Open label Country: England	P: Gay and other men who have sex with men I: TDF/FTC C: Deferred TDF/FTC after 1 year (no placebo) (adherence): plasma drug detection in 52 sampled participants	HIV acquisitions TDF/FTC immediate group: 3/268 Incidence/100 person years (95% CI): 1.2 (0.4, 2.9) p= 0.0001 TDF/FTC deferred group: 20/255 Incidence/100 person years (95% CI): 9.0 (6.1, 12.8) p = 0.0001 RRR (90% CI): 86 (64, 96)

Study details	Summary PICO (see CS Appendix Tables 9-20 for more details)	Key results for eligible arms (see CS Appendix Tables 21-27 for more details)
Follow-up: Median: 2 years	who reported taking PrEP (n=273); self-report Age, median (IQR range): TDF/FTC (immediate group): 35 (30 – 43) TDF/FTC (deferred group): 35(29 – 42)	Rate difference : 7.8 per 100 person-years (90% CI: 4.3 – 11.3) Adherence: Plasma drug detection (Tenofovir) in those who reported taking PrEP: 100% Self report: low completion rates, data not reported. States sufficient study drug was prescribed for 88% of the total follow-up time
Cisgender women		
FEM-PrEP Van Damme, 2012[44] Blinding: Double-blind Country: Kenya, South Africa, and Tanzania Follow-up: Median: Up to 60 weeks	P: Heterosexual women in Africa age 18-35 'at increased risk for HIV' I: TDF/FTC C: Placebo (adherence): plasma drug detection in HIV positive and matched negative controls (three controls per positive case), matched on study site and duration of participation in study; pill count; self-report. Age: Mean/median (IQR range): TDF/FTC: 23 (range: 18 – 35) Placebo: 23 (range: 18 – 35)	HIV acquisitions TDF/FTC: 33/1024 Incidence/100 person years (95% CI): 4.7 (not reported) p = not reported HR (95% CI): 0.94 (0.59, 1.52) p= 0.81 Placebo: 35/1032 Incidence/100 person years (95% CI): 5 (not reported) p= not reported Adherence Plasma drug detection: Women with seroconversion 7/27 (26%) at the beginning of the infection window (excluding 6 women for whom the window started at enrollment), 7/ 33 (21%) at the end of the window /27 (15%) at both visits Uninfected control participants 27/78 (35%) at the beginning of the infection window 35/95 (37%) at the end of the window 19 of 78 (24%) at both visits Self-report, pill count (95%)

Study details	Summary PICO (see CS Appendix Tables 9-20 for more details)	Key results for eligible arms (see CS Appendix Tables 21-27 for more details)
VOICE Marrazo, 2015[45] Blinding: Blinding of oral intervention vs placebo, and gel intervention vs placebo Country: South Africa, Uganda, and Zimbabwe Follow-up: (Not reported)	P: Heterosexual women in Africa age 18-45, recent vaginal intercourse but no other requirement for risk I: TDF/FTC I: TDF I: TFV gel C: Placebo (oral arm and gel arm) - Adherence: plasma in case-cohort design, random subcohort selected from active groups and enriched with HIV acquisition; pill count; self-report Age: Mean/median: TDF/FTC: 25.2(5.2) Placebo: 25.3 (5.2)	HIV acquisitions TDF/FTC: 61/1003 Incidence/100 person years (95% CI): 4.7 (3.6, 6.1) p= not reported HR (95% CI): 1.04 (0.73, 1.49), p=0.81 Placebo (Oral): 60/1009 Incidence/100 person years (95% CI): 4.6 (3.5, 5.9) Adherence Plasma drug detection TDF/FTC (TFV): 29% Self-reporting (90%), Pill count (86%)
Cisgender men and women		
Tenefovir 2 Thigpen, 2012[46] Blinding: Double-blind Country: Botswana Follow-up: Median, max 1.1 years, 3.7 years	P: Heterosexual men and women aged 18-39 years in Botswana. Sexually active (≥1 partner in last 3 months) but no other requirement for risk. I: TDF/FTC C: Placebo (adherence): plasma drug detection in HIV positive and 69 negative samples matched by data; pill count; self-report Age: Mean/median: reported in age categories	HIV acquisitions TDF/FTC: 10/611 Placebo: 26/608 RR (95% CI): 61.7 (15.9, 82.6) p=0.03 ITT TDF/FTC: 9/610 Incidence/100 person years (95% CI): 1.2 (not reported) p= (not reported) Efficacy (95% CI): 62.2 (21.5, 83.4) p=0.03 mITT Placebo: 24/599 Incidence/100 person years (95% CI): 3.1 (not reported) p= (not reported) ITT Placebo: 24/606 Incidence/100 person years (95% CI): 3.1 (not reported) p= not reported mITT Plasma drug detection (TDF):

Study details	Summary PICO (see CS Appendix Tables 9-20 for more details)	Key results for eligible arms (see CS Appendix Tables 21-27 for more details)
		2/4 (50%) participants who were infected with HIV 55/69 (79.7%) matched controls Self-reported: 94.4% Pill count: 84.1% (For the preceding 3 days)
Serodifferent		
Partners PrEP Baeten, 2012[34] Blinding: Double-blind Country: Kenya, Uganda Follow-up: Median: Up to 36 months	P: Serodifferent heterosexual men and women I: TDF I: TDF/FTC C: Placebo (adherence): plasma drug detection Age: Mean/median: reported in age categories	HIV acquisitions TDF/FTC: 13/1579 HR (95% CI): 0.25 (0.13, 0.45 p< 0.001 RR (95% CI): 0.75 (0.55, 0.87) p<0.001 mITT Placebo: 52/1584 mITT TDF/FTC: 16/1579 HR (95% CI): 0.27 (0.16, 0.48) p= 0.001 ITT Placebo: 58/1584 ITT TDF/FTC: 9/566 HR (95% CI): 0.34 (0.16, 0.72) RR (95% CI): 0.66 (not reported) p=0.005 women Placebo: 28/619 women TDF/FTC: 4/1010 HR (95% CI): 0.16 (0.06, 0.46) p= 0.001 RR (95% CI): 0.84 (not reported) p=0.001 men Placebo: 24/959 men Adherence data Plasma drug detection (Tenofovir in TDF/FTC arm): 3/12 (25%) participants who acquired HIV and in 374/464 (80.6%) samples (n=100 participants) who did not acquire HIV

Study details	Summary PICO (see CS Appendix Tables 9-20 for more details)	Key results for eligible arms (see CS Appendix Tables 21-27 for more details)
		Pill count and Study bottles: 92.1%.
People who inject drugs		
Bangkok Tenofovir Study Choopanya, 2013[32] Blinding: Double-blind Country: Thailand Follow-up: Mean, SD: 4.0 years, 2.1 ***Excluded from EAG ITC (population and intervention not eligible)***	P: Male and female drug users in Thailand. I: TDF C: Placebo (adherence): plasma drug detection: HIV positive cases and in HIV negative cases in 4 of 17 clinics. Age: Mean/median: reported in age categories	HIV acquisitions TDF: 17/1204 Incidence/100 person years (95% CI): 0.35 (0.21, 0.56), p=0.01 Placebo: 33/1209 Incidence/100-person years (95% CI): 0.68 (0.47, 0.96), reference RR (95% CI): 0.49 (9.6, 72.2); p=0.01 Adherence: Plasm drug detection: 66%
Included in the EAG ITC (but not the company ITC)		
IAVI Uganda study Kibengo, 2013[35] Blinding: Blinding of daily intervention vs placebo, and intermittent dosing vs placebo Country: Uganda Follow-up: Median: 4 months	P: Serodifferent heterosexual partners I: TDF/FTC (daily dosing) I: TDF/FTC (Intermittent dosing) C: Placebo (adherence): medication event monitoring system (MEMS) Age: Mean/ range: TDF/FTC: 26 (20-26) Placebo: 27 (20 – 38) Age: Mean (range): TDF/FTC: 33 (20-47) Placebo: 33 (26 – 47)	HIV acquisitions No acquisitions detected Adherence by MEMS: 98%, Self-report

Study details	Summary PICO (see CS Appendix Tables 9-20 for more details)	Key results for eligible arms (see CS Appendix Tables 21-27 for more details)
Not included in company's ITC		

P: population; I: intervention; C: comparator(s); O: outcome (adherence measure). CI, confidence interval; HR, hazard ratio; RRR, relative risk reduction; TAF/FTC, tenofovir alafenamide/emtricitabine; TDF, tenofovir disoproxil fumarate; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine. See Table 9 for discrepancies between reporting of adherence in CS document B Table 20, CS Appendix D Table 22, and the original trial publications.

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Single Technology Appraisal

Cabotegravir for preventing HIV-1 in adults and young people [ID6255]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Thursday 25 April** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

Contents

Issue 1 High priority: Misrepresentation of the company's decision problem population

Description of problem	Description of proposed amendment	Justification for amendment	EAG
Page 14, the EAG state: *"The disparity between the intended and actual populations modelled is notable. The decision problem outlined in the CS identifies the target population as individuals at risk of sexually acquired HIV-1 infection, who are ineligible for oral PrEP and thus not adequately served by current standard care. However, this description does not align with NICE's scope, which defines the population as "People at risk of sexually acquired HIV-1 infection."* This uses incorrect language and misrepresents the CS, which does not identify the population who are ineligible for oral PrEP.	Please remove "*ineligible for oral PrEP and thus*", and amend to the following: "*The disparity between the intended and actual populations modelled is notable. The decision problem outlined in the CS identifies the target population as individuals at risk of sexually acquired HIV-1, not adequately served by current standard care. However, this description does not align with NICE's scope, which defines the population as "People at risk of sexually acquired HIV-1 infection".*	The proposed wording aligns with the company description of the population in the decision problem, which is people for whom oral PrEP is not appropriate and are therefore underserved by current SoC (daily oral TDF/FTC). This population encompasses individuals with health-related challenges or social determinants of health that may result in oral PrEP not being appropriate. The EAG's current description may suggest a more restricted population than that considered in the CS.	Amended to align with the text in section B.1.1 of the CS.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
Page 14, the EAG state: *"Upon closer examination of the economic model's structure and accompanying Excel workbook, it becomes evident that the modelled population is much broader than intended by the CS. In fact, it appears to better correspond with the population described in NICE's scope."* This is a misleading description of the modelled population and how it relates to population described in the company's decision problem.	Please remove this paragraph.	The population in the decision problem consists of individuals at risk of acquiring HIV for whom oral PrEP is not appropriate. The company does not use the word "ineligible for oral PrEP" in its description of the population. The population considered in the economic model also represents individuals for whom oral is not appropriate including those who cannot take oral PrEP (comparison vs no PrEP) and those who can take oral PrEP but have challenges with adherence (comparison vs TDF/FTC). It is factually incorrect to state that the modelled population is broader than that of the decision problem.	Not a factual error, hence no change.
Page 14, the EAG state: *"These trials recruited individuals who were eligible*	Please amend the sentence to *"People in the trials were taking oral PrEP or oral placebo..."*	In the ITC, no trials included eligibility criteria that specified	Not a factual error, no change.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
to take oral PrEP, further expanding the population encompassed by the model." This wording does not align with the wording used to describe the population recruited by the trials included in the ITC.		either the ability or inability to take oral PrEP.	
Page 19, the EAG state: *"The population ineligible for PrEP is poorly defined in the decision problem. The model relies on data from the HPTN trials10 and trials included in the ITC where participants recruited were eligible for oral PrEP."* This uses incorrect language and misrepresents the CS, and does not reflect the trial eligibility criteria.	Please remove the statement.	The EAG's description of individuals ineligible for oral PrEP does not align with the Company's decision problem population and may suggest a more restricted population than that considered in the company submission. In addition, in the ITC trials did not include eligibility criteria that specified either the ability or inability to take oral PrEP.	Not a factual error, The statement has been slightly amended to: "*The population for whom oral PrEP is inappropriate is poorly defined in the decision problem. The model relies on data from the HPTN trials, and trials included in the ITC where suitability for oral PrEP was not determined.*"
Page 105, the EAG states:	Please remove this part of the statement.	This statement is not accurate since it reflects a misunderstanding of the	Not a factual error, no change.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
"The EAG acknowledges that while the no PrEP intervention is not directly relevant to the decision problem or the economic model scope…" This is incorrect representation of the CS decision problem population.		population in the company submission decision problem. A comparison with no PrEP is relevant to the decision problem since there is currently no alternative PrEP options for people unable to take oral PrEP which may be a result of the inappropriateness of oral PrEP.	
Page 125, the EAG states: *"However, the clinical evidence submitted by the company comprised of people taking oral PrEP/placebo for oral PrEP, therefore not aligned with those 'for whom oral PrEP is not appropriate'."* People in the TDF/FTC arms of the trials included those for whom oral PrEP is not appropriate, evidenced by sub-optimal adherence to	Please amend to the following: *"However, the clinical evidence submitted by the company comprised of people taking oral PrEP/placebo for oral PrEP, which included some people sub-optimally adhering to oral PrEP'."*	The proposed amendment accurately reflects the population enrolled in the trials.	Not a factual error, no change.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
oral PrEP during Step 2 of the HPTN trials.			
Page 139, the EAG states: *"It is unclear to what extent the population in both the HPTN 083 and HPTN 084 trials meet the criteria outlined in the decision problem (i.e. people ineligible for oral PREP), as eligibility for oral PrEP was not determined in either trial."* Incorrect representation of the CS decision problem population and inaccurate representation of the trial eligibility criteria.	Please amend to the following: *"It is unclear to what extent the population in both the HPTN 083 and HPTN 084 trials meet the criteria outlined in the decision problem (i.e. people for whom oral PrEP is not appropriate), as neither trial included eligibility criteria based on ability/inability to take oral PrEP."*	The proposed amendment accurately describes the terms and language used in the CS, which is critical to avoid misinterpretation of the Company's approach, and accurately reflects the trials' eligibility criteria.	Amended.
Page 139, the EAG states: *"However, as mentioned earlier, the actual population modelled in the CS economic model does relies on data from the HPTN trials, where the patients recruited were*	Please amend to the following: "*However, as mentioned earlier, the actual population modelled in the CS economic model does rely on data from the HPTN trials, which did not include or exclude participants based*	The proposed amendment accurately reflects the trial eligibility criteria.	Not a factual error. The section has been slightly amended to: *"However, as mentioned earlier, the actual population modelled in the CS*

Description of problem	Description of proposed amendment	Justification for amendment	EAG
individuals for whom oral PrEP was deemed appropriate." Misrepresentation of the trial eligibility criteria.	*on their ability or inability to take oral PrEP."*		*economic model does rely on data from the HPTN trials and trials in the ITC, where suitability for oral PrEP was not determined"*
Page 140, the EAG states: *"The population ineligible for oral PrEP as described in the company's decision problem is unclear."* This is a misrepresentation of the CS decision problem population.	Please amend to the following: *"The population for whom oral PrEP is not appropriate as described in the company's decision problem is unclear."*	The population in the decision problem consists of individuals at risk of acquiring HIV for whom oral PrEP is not appropriate. The company does not use the word "ineligible for oral PrEP" in its description of population. The EAG's current description may suggest a more restricted population than that considered in the CS.	Amended.
Page 143, the EAG states: *"transition to receive oral PrEP after discontinuation is unclear given the positioning of cabotegravir (i.e. people ineligible for oral PrEP)."*	Please amend to the following: *"transition to receive oral PrEP after discontinuation is unclear given the positioning of cabotegravir (i.e. people for whom oral PrEP is not appropriate)."*	The population in the decision problem consists of individuals at risk of acquiring HIV for whom oral PrEP is not appropriate. The company does not use the word "ineligible for oral PrEP" in its	Amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
Incorrect representation of the CS decision problem population.		description of the population. Furthermore, suggested transition to oral PrEP reflects the SmPC. The EAG's current description may suggest a more restricted population than that considered in the CS.	
Page 173, the EAG states: *"*The company argues that the population considered for cabotegravir PrEP are ineligible for oral PrEP" Incorrect representation of the CS decision problem population.	Please amend to the following: *"The company argues that the population considered for cabotegravir PrEP are those for whom oral PrEP is not appropriate".*	The population in the decision problem consists of individuals at risk of acquiring HIV for whom oral PrEP is not appropriate. The company does not use the word "ineligible for oral PrEP" in its description of the population. The EAG's current description may suggest a more restricted population than that considered in the CS.	Amended.

Issue 2 High priority: Misleading reporting of trial dosing and schedule and SmPC dosing schedule

Description of problem	Description of proposed amendment	Justification for amendment	EAG
On page 31, the EAG state: *"The SmPC recommends doses every two months after the initial two doses, while NHS England suggests doses every 8 weeks following the initial doses 28 days apart."* Use administration every 8 weeks does not reflect	Please remove mentions of the dosing schedule that may suggest departure from dosing schedule described in the draft SmPC. Alternatively, if the EAG prefers considering an off-label dosing schedule proposed by NHSE this must be thoroughly justified and referenced to avoid any potential suggestion of off-label use.	Any analyses considering dosing schedules that may impact resource use and costs should reflect the draft SmPC. The draft SmPC states: [redacted]	This refers to a brief summary of the smPC dosing schedule within the Summary of the EAG's key issues table. The submission by Anna Kafkalias of NHSE Specialised Commissioning is referenced within the main text and should be accessible by the company. This is a key issue for discussion by the committee and the committee clinical expaert as we sought clarity from our clinical adviser but that was not resolved. There is a discrepancy between the dosing schedule stated in the smPC and the dosing schedule described in the HPTN 083, HPTN 084 trials and submission from NHS

Description of problem	Description of proposed amendment	Justification for amendment	EAG
the SmPC and the dosing schedule modelled by the CS.			England Specialised Commissioning. Failure to account for all direct costs and health effects goes against NICE reference case. No changes have been made.
Page 138, the EAG states: *"For example, while an individual may resume taking daily oral pills (TDF/FTC) when they transition from low-risk to high-risk sexual behaviour, restarting*	Please amend to the following: *"For example, while an individual may resume taking daily oral pills (TDF/FTC) when they transition from low-risk to high-risk sexual behaviour, restarting cabotegravir requires* [redacted] *"*	It is important to align the initiation/re-initiation of cabotegravir for PrEP to the dosing schedule described in the draft SmPC, which outlines an optional one-month lead-in of cabotegravir tablets.	This has been changed to: "*For example, while an individual may resume taking daily oral pills (TDF/FTC) when they transition from low-risk to high-risk sexual behaviour, the company submission states: "participants initiating cabotegravir LA for the first time (with or without oral lead-in) or participants who were eligible to re-start cabotegravir required a reloading dose of 2 injections, 4 weeks apart followed by cabotegravir LA injections Q8W". This suggests re-starting cabotegravir incurs an extra*

Description of problem	Description of proposed amendment	Justification for amendment	EAG
cabotegravir requires either a month-long oral lead-in tablets or an injection of cabotegravir .” Misrepresentation of the SmPC. Oral lead in is used to assess tolerability and is optional.			*cabotegravir LA injection dose.”*
Page 138, the EAG states: *“Afterwards, a second administration of*	Please amend to the following: “*Afterwards a second administration of cabotegravir is required before the recommended schedule of an*	It is important that the EAG assessment of the CS aligns with the draft SmPC dosing schedule to avoid any suggestion of off-label use and following NICE reference case for technology appraisal.	Please see above response.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
cabotegravir is required before the recommended 8-weekly treatment schedule can resume." This is unreferenced and a misleading description of the cabotegravir dosing schedule in the draft SmPC.	*injection every two months can resume".*		
Page 150, the EAG states that: *"The CS also*	Please remove.	In Document B Table 7 the company has provided a summary of the clinical trial methodology in which cabotegravir was administered as described by the EAG.	Not a factual error.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
suggested an eight-weekly administration time in the description of the trial interventions" This is a misrepresentation of the CS.		The company has considered the draft SmPC dosing schedule in the economic analysis as per NICE reference case.	
Page 150, the EAG states that: *"The company submission states that "participants who were eligible to re-start*	Please remove.		Not a factual error.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
cabotegravir required a reloading dose of 2 injections, 4 weeks apart followed by cabotegravir LA injections Q8W" (CS Document B. Table 7)." This is a misrepresentation of the CS.			
Page 174, the EAG states that: "*Cabotegravir was assumed to be administere*	Please remove mentions of the dosing schedule that may suggest departure from dosing schedule described in the draft SmPC. Alternatively, if the EAG prefers considering an alternative dosing schedule	Any analyses involving dosing schedules that may impact resource use and costs should reflect the draft SmPC. The draft SmPC states: [redacted]	Not a factual error.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
d every 8 weeks rather than 2 months in the company base case." Use of administration every 8 weeks does not reflect the draft SmPC and the dosing schedule modelled by the CS.	proposed by NHSE this must be thoroughly justified and referenced to avoid any potential suggestion of off-label use.	[redacted]	

Issue 3 High priority: Omission of the description of the approach to modelling cisgender women for underlying risk

Description of problem	Description of proposed amendment	Justification for amendment	EAG
Page 134, the EAG states:	Please amend to the following:		Amended.

"During the 5-year HIV acquisition risk period, those in the no prep health state have a baseline risk of HIV acquisition (4.9 per 100 person-years)." This is a misrepresentation of the CS' base-case.	*"During the 5-year HIV acquisition risk period, those in the no prep health state have a baseline risk of HIV acquisition (4.9 per 100 person-years for men who have sex with men and transgender women and [redacted] per 100 person-years for cisgender women)."*	Omission of the cisgender women cohort within the economic analysis does not fully represent the CS.	
Page 141, the EAG states: *"The baseline HIV incidence (4.9 per 100 person years) was assumed to be equivalent to HIV incidence in the MSM population with a recent rectal bacterial STI."* This is a misrepresentation of the Company's base-case.	Please amend to the following: "The baseline HIV incidence (4.9 per 100 person years) for men who have sex with men was assumed to be equivalent to HIV incidence in the men who have sex with men and transgender women population with a recent rectal bacterial STI. A baseline incidence of [redacted] per 100 person-years for cisgender women was used."		Amended.

Issue 4 High priority: Misleading description of the company assumption for the duration of the elevated risk period

Description of problem	Description of proposed amendment	Justification for amendment	EAG
Page 17, the EAG state: *"The CS model structure limits the maximum at-risk period to five years…"* This statement is misleading as the model allows a range of values up to 10 years.	Please amend to the following: *"The CS model structure allows a variable at-risk period of one to ten years."*	The proposed amendment avoids any confusion regarding how the at-risk period is implemented in the model.	The section has been changed to: *"However, the 5-year maximum risk period in the CS base-case is not substantiated by sufficient evidence"* We have also added the following statement to Section 4.3.1 "*The 5-year risk period was derived from a modelling study by Cambiano et al which estimated a mean time of 4.5 years spent on PrEP among MSM initiating PrEP. In their model, a baseline incidence of 2 per 100 person years was assumed and the PrEP programme were stopped if HIV incidence in the MSM population fell below 1 in 1000. The estimated mean time of 4.5 years on*

Description of problem	Description of proposed amendment	Justification for amendment	EAG
			PrEP relied on these assumptions. *The population considered in the company's submission are individuals at high risk of HIV infection charactersied by a much higher incidence rate (4.9 per 100 person years) reflecting HIV incidence in MSM with recent rectal bacterial STI. Thus, the population modelled by the company is narrower and likely to stay on PrEP longer than the broader MSM population*
Page 17, the EAG state: "*However, the 5-year maximum risk period in the CS base-case lacks evidence support."*	Please amend to the following: "However, the 5-year risk period in the CS base-case*, in the opinion of the EAG, is not substantiated by sufficient evidence*"	The duration of the period of elevated risk of HIV acquisition in the CS aligns with the assumptions in the current NICE guidelines for	Amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
This is factually inaccurate, as evidence is provided in the Company's submission to justify the use of this at-risk period.		reducing sexually transmitted infections (NG221) (1).	
Page 18, the EAG state: *"Only 5-year and 10-year periods were allowed."* The statement is incorrect. The duration of elevated risk in the CEM can be varied with any number between 1 and 10 years, and this has been tested in sensitivity analyses.	Please amend to the following: *"The company's model allowed the at-risk period to vary from one to ten years."*	The EAG's statement is a misrepresentation of the company's economic model.	Amended.
Page 138, the EAG states: *"the company argued periods of heightened risk will occur at different ages for different individuals and will change over time depending on an individual's sexual and affectional relationship"*	Please amend to the following: *"the company argued periods of heightened risk will occur at different ages for different individuals and will change over time depending on an individual's sexual and affectional relationship and that the 5-year period used in the model reflects assumptions in the economic analysis*	Fully reporting the company response to clarification questions is key to providing an accurate overview of company's approach.	Not a factual error.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
There is missing information and this misrepresents the company's response to clarification questions.	*informing the National Institute for Health and Care Excellence (NICE) guidelines for reducing STIs (NG221)."*		
Page 142, the EAG states: *"After the risk period of 5 years in the model base case, individuals can no longer acquire or transmit HIV."* This is a misrepresentation of the Company's model.	Please amend to the following: Remove "*or transmit HIV"* from the sentence.	The estimate of onward secondary transmissions used in the model refers to the lifetime of the individual not just the 5-year period at risk.	Amended.

Issue 5 High priority: Discrepancy between deterministic and probabilistic results in the cost-effectiveness analyses results section

Description of problem	Description of proposed amendment	Justification for amendment	EAG
Table 42, page 176, the EAG reports a probabilistic ICER versus baseline (£/QALY) for cabotegravir	The Company believe the results of deterministic and probabilistic sensitivity analysis should be broadly	The probabilistic analysis appears to have been incorrectly reported.	Amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
versus TDF/FTC of "*£552,763"* and in table 41, page 175 the EAG reports a deterministic ICER of *"£212,232".* There is misalignment between deterministic and probabilistic results. Comparable results for the probabilistic analysis could not be produced with the EAG economic model suggesting a potential error in the probabilistic ICER.	aligned and would encourage a QC of these figures. The company has run probabilistic analysis using the EAG amended model and has generated ICERs broadly aligned with the deterministic ICER for the EAG preferred base case.		

Issue 6 Improved persistence to cabotegravir

Description of problem	Description of proposed amendment	Justification for amendment	EAG
Page 143, the EAG states: *"The company argues that a bi-monthly intramuscular injection cabotegravir would*	Please amend to the following: *"The company argues that an intramuscular injection every two months with cabotegravir would improve the convenience of*	It is important to fully reflect the company's approach and rationale behind assumptions described in the submission.	Amended to *"The company argues that an intramuscular injection of cabotegravir every two months would be more*

Description of problem	Description of proposed amendment	Justification for amendment	EAG
be more convenient than daily oral pills." This is a partial description of the company rationale for improved persistence, which may be misleading.	*cabotegravir in addition to providing an additional modality that addresses barriers to both adherence and persistence".*		*convenient than daily oral pills."*
Page 144, the EAG states: *"Scenarios were also explored to estimate the impact of reduced persistence to cabotegravir relative to oral PrEP on the ICER."* This is a misleading scenario analysis based on the absence of a description of the rationale for the assumptions in the scenario analysis.	Please add a clear description of the evidence supporting a scenario of reduced persistence with cabotegravir vs. TDF/FTC or consider removing the sentence and scenario analysis, if unjustified.	Scenarios without a clear and transparent rationale may be perceived as unjustifiably biased against cabotegravir.	This scenario was explored in relation to the reasons outlined in Issue 11 of the EAG summary of key issues and the reasons outlined in section 4.7.1.3. We have added the following statement to Section 4.3.1.7 *"The requirement of trained health care professionals to administer injections, the administrative burden on sexual health clinics in establishing reliable recall systems to ensure on-time injections, the burden on PrEP users to commute to sexual health clinics to receive on-time injections (and the time spent at*

Description of problem	Description of proposed amendment	Justification for amendment	EAG
			clinics at each visit) and the potential effects of injection site reactions may lead to lower persistence to cabotegravir compared to oral PrEP users who are unlikely to face any of these issues. Due to these issues, scenarios were also explored to estimate the impact of reduced persistence to cabotegravir relative to oral PrEP on the ICER"

Issue 7 Disutility of HIV acquisition

Description of problem	Description of proposed amendment	Justification for amendment	EAG
Page 132, the EAG states *"No"* regarding whether the source of preference data for valuation of changes in health-related quality of life	Please amend to *"No comment".*	The CEM in the CS used data from a UK population (Miners et al. 2014 (2)) that was directly reported by people living with HIV. Hence an assessment that this	Amened.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
are a representative sample of the UK population. This is inaccurate, as the disutility measurement is obtained from an English study.		criterion is unmet is not correct.	
Page 147, the EAG states: *"While it is appropriate to apply a disutility for HIV acquisition, the EAG argues that a lifetime disutility for HIV acquisition is not evidence-based."* This statement is incorrect.	Please remove the statement suggesting that lifetime disutility application is not evidence based.	In section B.1.3.8.1 of the CS, the Company provided evidence demonstrating that living with HIV can have a lifetime effect on reducing HRQoL. It is incorrect to state that lifetime disutility is not evidence based. The Positive Voices 2 survey demonstrates that the impact of living with HIV on quality of life occurs across the life-course (3). The results of the Positive Voices survey were conducted among: "The median age of participants was 52 years (age range: 20 to 90 years), with half aged between 43 and 60 years. Participants had been	We accept the company's argument, and the statement is removed and replaced with the following: "Health-related quality of life was derived from the study by Miners et al using the EQ-5D-3L instrument in respondents attending outpatient clinics between 2011 and 2012. Following the British HIV Association (BHIVA) treatment guidelines update in 2016, recent HIV regimens have led to decreased pill burden

Description of problem	Description of proposed amendment	Justification for amendment	EAG
		diagnosed with HIV between 1982 and 2021, with a median of 15 years since diagnosis, and half were diagnosed between 10 and 21 years ago. 1 in 10 participants (10.46%, 473 of 4,540) were diagnosed in 1995 or earlier, before the introduction of highly active antiretroviral therapy (HAART)."	and reduced side-effects. A wider range of treatment options and reduced side effects from new treatment options might improve health related quality of life in HIV positive individuals (reference Positive Voices 2022). Indeed, a more recent evaulation of the health-related quality of life in HIV positive individuals using the EQ-5D-5L reports a utility of 0.77, lower than a utility score of 0.82 in the general population indicating a disutility of –0.05 (Positive Voices 2022). A HIV infection disutility of –0.05 was assumed in the EAG base case. For the sensitivity analysis, we assumed a

Description of problem	Description of proposed amendment	Justification for amendment	EAG
			variation of 10% from the mean estimate.”
Page 147, the EAG states: *“Indeed, studies that suggests that well controlled HIV infection tend to have comparable quality of life to the general population.[55]”* The referenced study is not sufficient to make the assertation that people living with HIV have a comparable QoL to the general population. The study is from Indonesia and has a sample of 129 people living with HIV. The study does not compare QoL scores to the general population and the objective of the study is to "investigate the synergistic and independent effects of adherence to ART and viral load on QoL among people with HIV/AIDS ".	Please remove this scenario from the analysis or provide references with evidence supporting this statement.	The referenced study does not provide any basis for the claim that people living with HIV have comparable QoL to the general population. The CS references two large studies carried out in the UK (Miners et al 2014 (2), Positive Voices 2022 (3)) which show the impact that HIV has on QoL for people in the UK. There is no justification to say on a population level that people living with HIV' QoL converges to that of the general population after a period of time.	We accept the company’s argument, and the statement is removed and replaced with the statement above.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
Page 178, the EAG states: "*Disutility for HIV infection was set equal to risk period. Afterwards, utility levels were assumed to converge to general population levels."* There is no evidence to suggest that people living with HIV have equal HRQoL vs the general population. The assumption to limit HIV disutility to a period equal to the period of elevated risk of HIV acquisition is unjustified.	This assumption should be converted back to the programming suggested by the company or further justified by the EAG with robust supporting evidence.	The lifetime impact of HIV on QoL is evidenced by numerous studies (2-4). The study cited by the EAG to suggest impact of HIV on QoL is limited in time is actually a cross-sectional study comparing QoL and adherence to ART. The study neither shows an improvement over time, nor makes a comparison with a similar population of people without HIV. It does suggest people with good ART adherence can enjoy a high quality of life. It does not demonstrate any evidence of convergence with general population values over time.	The EAG accepts the company's argument and removes the scenario.

Issue 8 Drug acquisition and administration

Description of problem	Description of proposed amendment	Justification for amendment	
Page 33, the EAG report states: *"Increase drug acquisition costs by 20% to account for re-starting cabotegravir due to dynamic risk of HIV acquisition over cohort lifetime."* The statement is incomplete; this also increases administration and visits costs.	Please amend to: "*Increase drug acquisition costs, visit and administration costs*…"	The proposed wording accurately reflects implementation in the model.	Amended
Page 150, the EAG states that: *"If cabotegravir were stopped and restarted just once over the lifetime of an individual on PrEP, the drug acquisition cost increases by 13.5%."* The calculation and interpretation of the 13.5% is	The comments should be removed as the calculation is unclear and the statement is misleading.	The EAG's justification is misleading. If cabotegravir was stopped and restarted over the period currently modelled, the effective discontinuation rate would be higher than the RWE used to inform the model. The model incorporates a relatively high rate of discontinuation of	The statement has been clarified. The EAG has also re-calculated the number of visits based on an Q8W administration schedule. The statement has been replaced with the following: *"If cabotegravir were stopped and restarted just once over the lifetime of an individual on PrEP, the drug*

Description of problem	Description of proposed amendment	Justification for amendment	
unclear and needs contextualization.		PrEP and higher initial cost of cabotegravir. Whilst restarting cabotegravir would increase costs, it would also reduce HIV acquisition compared with either oral PrEP or no PrEP. The model already captures the appropriate cost of PrEP and the impact on HIV acquisition over a period of persistence to PrEP, aligning with published evidence.	*acquisition cost increases by 8.3% in the second year and 1.5% over the lifetime of the cohort (assuming a total risk period of 5 years with 7 injection visits in the first year and 6.5 visits in subsequent years)"*
Page 28, the EAG states that: *"Evidence submitted to NICE from NHS England suggests administration of cabotegravir takes about 60 mins."* and Page 151, the EAG states that: *"a visit/appointment for cabotegravir administration is*	Further justification is required to support this statement. Evidence exists demonstrating shorter administration time for long-acting cabotegravir, including the time for observation at every visit.	Further justification is needed to help substantiate the EAG's assumption and avoid risk of bias.	This statement was extracted from the submission by Anna Kafkalias of NHS England Specialised Commissioning (NICE clinical expert). We were not able to resolve this with the clinical advisor and we welcome the committee's input.

Description of problem	Description of proposed amendment	Justification for amendment	
estimated to take approximately 60 minutes“ Insufficient justification is provided to support this assumption.			

Issue 9 Evidence synthesis/indirect treatment comparison

Description of problem	Description of proposed amendment	Justification for amendment	EAG
Page 51, the EAG report states that the evidence synthesis is of *“High concern”.* The company consider this to be an unfounded conclusion.	Please amend: “*high concern*” to “*low concern”*	The sensitivity analyses provided by the company have confirmed the robustness of the evidence synthesis results. The results are also corroborated the HPTN statistics group published analyses (5, 6). The EAG report also states that “*Overall, the ITC/meta-regression analyses were conducted appropriately, providing robust estimates of the relationship between CAB-LA and the no PrEP*	Not a factual error. Details of how this conclusion was reached using the modified ROBIS tool are provided in ERG report Appendix 1.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
		interventions while incorporating oral PrEP adherence." suggesting the absence of concerns with the evidence synthesis.	
Page 51, the EAG report states: *"The company carried out a targeted search for systematic literature reviews (CS Appendix D.1.2.1) on the single database Embase via Embase.com (CS Appendix D.1.2.1 Targeted Search for SLRs)."* The search in Embase.com captures Medline and Embase.	Please amend to: *"The company carried out a targeted search for systematic literature reviews (CS Appendix D.1.2.1) on Medline and Embase via Embase.com (CS Appendix D.1.2.1 Targeted Search for SLRs)."*	The proposed amendment corrects the factual inaccuracy.	Not a factual error. The company submission CS Appendix D.1.2.1 Targeted Search for SLRs reports that the search strategy was carried out on Embase.com and does not report which databases were searched.
Page 99, the EAG report states: *"Two studies included in the ITC that should be excluded on a population or intervention*	Please remove *"drug users"* from the bracket or alternatively, reword as follows:	It is important that the report accurately describes the studies included in the ITC.	Amended and additional text added for clarity: The company applied the minimum criteria recommended by NICE to assess the risk of bias of

Description of problem	Description of proposed amendment	Justification for amendment	EAG
basis (drug users: Bangkok Tenofovir Study, IperGay).” The text is misleading, as it suggests that the population in both studies, consists of drug users.	*"(drug users: Bangkok Tenofovir Study; on-demand TDF/FTC as PrEP: IperGay)*”		the comparator studies, presenting these by study in CS Appendix D.5, Tables 39-41. No overall statement of risk of bias was presented and the ROB assessments were not explicitly incorporated into the SLR or ITC. On examination of Appendix D Table 40, it became apparent that the company had confused allocation concealment with blinding of assigned interventions during the trial. The EAG re-assessed randomisation, allocation concealment and blinding in all comparator studies included in the ITC (either by the company or EAG), focusing only on the eligible interventions in trials with more than two arms. The EAG considers that all studies except PROUD (McCormack 2016) have a low risk of

Description of problem	Description of proposed amendment	Justification for amendment	EAG
			bias based on these criteria. PROUD (McCormack 2016) was an open label study without a placebo control therefore is at risk of bias due to deviations from the intended interventions and bias from knowledge of the intervention. Due to time constraints, the EAG has not independently verified the CS assessments for the other risk of bias criteria for these comparator studies.
Page 102, the EAG states: *"The remaining 9 studies were excluded despite having other measures of adherence that could have been used when detectable plasma levels of TDF/FAC is unavailable "* This is a misrepresentation of the quality of the analysis presented by the CS.	Please clarify by adding the following: "*…The inclusion of studies with other adherence measures would introduce significant uncertainty into the analysis*".	It is important to fully reflect methods and rationale for including or excluding studies. The approach taken by the company is consistent with previously published literature (6).	Amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
Page 104, the EAG states: *"However, several limitations and uncertainties must be addressed to interpret these findings accurately".* This is an overstatement of the numbers of limitations in the analysis.	Please amend "*several*" to language that is more reflective of the actual number of limitations highlighted, for example by specifying the number of limitations.	The company has addressed several inaccuracies in the limitations laid out in the EAG report and considers this conclusion inaccurate.	Amended.
Page 109, the EAG states: *"Additionally, EAG found that incorrect estimates of adherence were applied in the company's ITC for 4 trials (Partners PrEP , iPrEx, FEM-PrEP and PROUD)"*	Please amend table 22 to align with the values used in the company submission.	Preferential sampling for participants living with HIV were not accounted for in the adherence trials. The 'corrected' values do not account for this and hence are biased.	The EAG considered the company's original estimates to be biased in cases where they excluded participants who had acquired HIV. The EAG performed a simple computation to include these participants. For PROUD, the study only reported adherence data by plasma levels for people who reported they were taking PrEP – this value was 100%, not 88% as stated by

Description of problem	Description of proposed amendment	Justification for amendment	EAG
			the company, and is not representative of all participants in the intervention arm. Whilst acknowledging that preferential sampling was not undertaken, the EAG considers their estimates to be less biased than those proposed by the company.
Page 125, the EAG states: *"the IperGay study, which compared event-driven TDF versus placebo in the ITC meta-regression analyses".* This study investigated event driven TDF/FTC, not TDF alone.	*Please amend to the following:* "*the IperGay study, which compared event-driven TDF/FTC versus placebo in the ITC meta-regression analyses"*	The proposed amendment accurately reflects the intervention included in IperGay.	Amended.
Page 134, the EAG states: *"An ITC using the data from the pivotal trial (HPTN 083 and HPTN 084) and a meta-*	Please replace with the following: *"An ITC incorporating a meta-regression model using the data from the pivotal trials (HPTN 083 and HPTN*	The current wording is misleading and could be interpreted as the ITC being based on the pivotal trials only and the meta-	Amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
regression analysis including studies from a systematic literature review, was used to estimate the relative reduction in HIV acquisition for patients on cabotegravir and TDF/FTC." This is a misleading description of the ITC and meta-regression model.	*084) and from studies from a systematic literature review, was used to estimate the relative reduction in HIV acquisition for patients on cabotegravir and TDF/FTC".*	regression being a separate analysis using studies identified in the SLR.	
Page 134, the EAG states: *"These estimates were used to adjust the baseline risk of HIV transmission to reflect the reduction in risk of HIV transmission for individuals on PrEP for the duration of the risk period."* This is a misrepresentation of the ITC approach described in the CS.	Please amend to the following: "*These estimates were used to adjust the baseline risk of HIV transmission to reflect the reduction in risk of HIV transmission for individuals on PrEP for the duration of the risk period and to estimate the relationship between the effectiveness of TDF/ FTC versus no PrEP and the adherence to TDF/ FTC based on a meta-regression analysis*"	It is important that the ITC and how it is implemented in the economic model is clearly described.	Ameded. "*These estimates were used to adjust the baseline risk of HIV transmission to reflect the reduction in risk of HIV transmission for individuals on PrEP for the duration of the risk period and to estimate the relationship between the effectiveness of TDF/ FTC versus no PrEP and the adherence to TDF/…*

Description of problem	Description of proposed amendment	Justification for amendment	EAG
Page 141, the EAG states: "*Meta-regression models were used to estimate the relative reduction in risk of HIV acquisition as a function of adherence to PrEP in TDF/FTC vs no PrEP and CAB-LA vs no PrEP comparisons*." This is a misleading description of the ITC methods.	Please amend to the following: *"Meta-regression models were used to estimate the relative reduction in risk of HIV acquisition of TDF/FTC as a function of adherence to TDF/FTC".*	The current wording could be interpreted as the meta-regression established the relationship between relative risk reduction (RRR) and adherence for both TDF/FTC and cabotegravir versus no PrEP when it only applies to the RRR for TDF/FTC versus no PrEP.	Amended: *"Meta-regression models were used to estimate the relative reduction in risk of HIV acquisition of TDF/FTC as a function of adherence to TDF/FTC".*
Page 178, the EAG states: *"Alternative alpha and beta parameters were estimated given uncertainties around the ITC conducted by the company."* The ITC has been demonstrated to be robust in the CS. It should be clearer that concerns related to	Please amend to the following: *"Alternative alpha and beta parameters were estimated to reflect the EAG concerns with uncertainties around the ITC conducted by the company."*	The sensitivity analyses provided by the company demonstrated the robustness of the ITC. It is important that the description of uncertainty clearly reflects that it is the EAG's opinion. In addition, the company notes that the EAG's analysis produced results that also corroborated with the original analysis and that the results are robust to	Amended: *"Alternative alpha and beta parameters were estimated to reflect the EAG concerns with uncertainties around the ITC conducted by the company."*

Description of problem	Description of proposed amendment	Justification for amendment	EAG
uncertainty in the ITC reflect the EAG's opinion.		either the inclusion or exclusion of the PROUD, IPERGAY and Bangkok studies.	

Issue 10 Clinical effectiveness evidence

Description of problem	Description of proposed amendment	Justification for amendment	EAG
Page 65, the EAG states: "*Mean SD age, years and race, % appear to have been reported using data from the CSR by EAG. The baseline characteristics are reported in the randomised population in the CSR, while the other values in this table are reported for the ITT population, as per the table heading (Source: Landovitz 2021).*" Mean age and race have a footnote symbol "[1]" however the footnote is missing.	Please either remove these data as they are reported for a different population to that specified by the table heading, or clarify using a footnote that the population is the randomised population for these data.	Accuracy of the data.	Sources added for clarity and highlighted accordingly.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
And Page 67: "*Age groups, %, mean (SD) age, and ethnicity appear to have been reported using data from the CSR by EAG. The baseline characteristics are reported in the randomised population in the CSR, while the other values in this table are reported for the ITT population, as per the table heading (Source: Delany-Moretlwe 2022).*" The table contains a footnote symbol "[i]", however the footnote is missing.			
Page 68, the EAG states: *"In the mITT analysis of incident HIV acquisitions in Steps 1 and 2 of both HPTN 083 and HPTN 084 CAB-LA appears to be effective at reducing HIV acquisitions*	Please replace: "*CAB-LA appears to be effective*" with "*cabotegravir LA for PrEP was superior".*	The statistical superiority was confirmed in both trials and should be adequately described.	Not a factual error.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
compared with daily oral TDF/FTC PrEP." The EAG have stated cabotegravir appears to be effective; however, cabotegravir met superiority thresholds in both the HPTN 083 and HPTN 084 studies.			
Page 68 the EAG states: The value for cohort, % – prefer not to say for the TDF/FTC arm is incorrect.	Please amend *"0.1"* to *"<0.1"*	Accurate reporting of the data as per the CS and Landovitz 2021 (7).	Added.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
Page 68, the EAG states: "*The company also conducted on-blinded study product (OBSP) analysis"* This is incorrect, as the HPTN study group are independent from the company and the company was not the study owner or sponsor.	Please replace: *"the Company"* with *"the HPTN study group"*	Accuracy of the study owner and sponsor is important to understand the impartiality of the study teams from the company submission.	Amended.
Page 78, the EAG state: *"Plasma CAB-LA was assessed in those acquiring HIV during the study and summary results were presented in CS Section B.2.6.1.3.2."* Plasma cabotegravir LA was also reported in Section B.2.6.2.2.1	Please amend to the following: *"Plasma cabotegravir LA was assessed in those acquiring HIV during the study and summary results were presented in CS Section B.2.6.1.3.2 and B.2.6.2.2.1."*	Accurate cross referencing to the company submission.	Amended.
Page 81, the EAG states: *"The CS reports that for both HPTN 083 and HPTN 084*	Please remove the statement that no data were presented in the CS or appendix.	Appendix F, Section F.1.1.5.2 and F.1.2.5.2 reports Grade 3 or 4 treatment-emergent liver	Amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
trials the maximum intensity of Grade 3 or 4 treatment-emergent liver enzyme abnormality observations were [redacted] *between arms Table 12. No data were presented in the CS or CS Appendix."* Incorrect statement.		enzyme abnormality observations.	
Page 83, the EAG states: *"…major integrase strand transfer inhibitor (INSTI) resistance-associated mutations (RAM) were observed in 10 cases in the CAB-LA arm, and none were observed in the TDF/FTC arm."* The statement may be misleading; there were 76 participants who acquired HIV in the TDF/FTC arm (for the same study period [post-hoc analysis] describing the 10 INSTI resistance in the CAB	Please amend to the following: *"major integrase strand transfer inhibitor (INSTI) resistance-associated mutations (RAM) were observed in 10 cases in the CAB-LA arm, and 25 had major NRTI and/or NNRTI RAMs in the TDF/FTC arm".*	This section is on incidence of resistance mutations; it would be factually accurate to report all RAMs from both arms, including INSTI, NRTI and NNRTI RAMs.	Unclear how the '25' is deduced. Details as stated in the CS added after 'and none were observed in the TDF/FTC arm': In the TDF/FTC arm, at genotyping performed at the first visit HIV acquisition was confirmed, there were 7 cases with NNRTI only resistance, three with both NNRTI and NRTI resistance and one with NRTI only

Description of problem	Description of proposed amendment	Justification for amendment	EAG
arm) and 25 had major NRTI and/or NNRTI RAMs.			resistance. Ten cases of major RAMs were detected during the blinded period (6 major NRTI, 4 of which also had one or two major NNRTI, and 4 single NNRTI).
Page 82, the EAG report states: "*In HPTN 084 there were no major INSTI RAMS observed in the CAB-LA arm or the TDF/FTC arm."* This is potentially misleading as it is not inclusive of NRTI and/or NNRTI RAMs. In HPTN 084, there were 36 participants who acquired HIV in the TDF/FTC arm and one had a major NRTI RAM.	Please amend to the following: *"In HPTN 084 there were no major INSTI RAMS observed in the CAB-LA arm or the TDF/FTC arm, with one major NRTI RAM observed in the TDF/FTC arm"*	This section is on incidence of resistance mutations; it would be factually accurate to report all RAMs from both arms, including INSTI, NRTI and NNRTI RAMs.	Details as stated in the CS added after 'or the TDF/FTC arm': In the TDF/FTC arm there was one NRTI RAM, NNRTI RAMS in 9 participants and INSTI mutations in 10 samples.
Page 84, the EAG states: *"ISRs and drug-related ISRs were higher in the CAB-LA*	Please amend to the following: *"ISRs and drug-related ISRs were higher in the CAB-LA arms than the*	The proposed amendment clarifies the data. The original wording may imply Grade ≥2	Amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
arms than the TDF/FTC arms of each trial, but those in the CAB-LA arm of HPTN 083 (cabotegravir: ISR 76%, drug-related ISR 81%) were higher than those in the CAB-LA arms of HPTN 084 (CAB-LA: ISR 38%, drug-related ISR 38%). A similar pattern was observed for Grade ≥2 adverse events". Misleading statement.	*TDF/FTC arms of each trial, but those in the CAB-LA arm of HPTN 083 (cabotegravir: ISR 76%, drug-related ISR 81%) were higher than those in the CAB-LA arms of HPTN 084 (CAB-LA: ISR 38%, drug-related ISR 38%). A similar pattern was observed for Grade ≥2 ISR and drug-related ISR adverse events".*	adverse events were higher, which is incorrect.	
Page 87: Footnote e states that the company reported *"[e] 48" ISRs leading to discontinuation of the study drug in "CS B.2.10.1.5."* Incorrect representation of the CS.	Please remove.	The CS wording is "' 48 (2%) participants experiencing AEs leading to study drug discontinuation in the general disorders and administration site conditions system organ class (SOC)"; therefore, the reported data point does not refer to injection site reactions leading to study drug discontinuation.	The full sentence in the CS states: 'The higher proportion in the cabotegravir arm was mainly driven by ISRs, with 48 (2%) participants experiencing AEs leading to study drug discontinuation in the general disorders and administration site conditions system organ class (SOC) versus

Description of problem	Description of proposed amendment	Justification for amendment	EAG
			none in the TDF/FTC arm.' Footnote changed to: '48 (2%) participants experienced AEs leading to study drug discontinuation in the general disorders and administration site conditions system organ class (CS B.2.10.1.5).
Page 87: The EAG report amylase increased in the cabotegravir LA as "[redacted]" and "[redacted]" in the TDF/FTC arm of HPTN 083. Incorrect data point.	Please update to "[redacted]" for the cabotegravir arm and "[redacted]" for the TDF/FTC arm.	Accurate reporting of trial data as per the CSR and company submission.	Amended.
Please 87: The EAG report blood phosphorous decreased in	Please update to "[redacted]".	Accurate reporting of trial data as per the CSR and company submission.	Amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
the TDF/FTC arm as "[redacted]in HPTN 083. Incorrect data point.			
Page 88: The EAG report AST increased to be "[redacted]" in the cabotegravir arm, and "[redacted]" in the TDF/FTC arm of HPTN 084. Incorrect data point.	Please amend to: [redacted]" for cabotegravir and "[redacted]" for TDF/FTC	Accurate reporting of trial data as per the CSR and company submission.	Amended.
Page 90: The EAG report blood creatinine increased in the cabotegravir arm to be "[redacted]" in HPTN 083. Incorrect data point.	Please amend to: "[redacted]"	Accurate reporting of trial data as per the CSR and company submission.	Amended.
Page 92: The EAG report a value of *"<5%"* in both arms for pyrexia in HPTN 084.	Please provide the reference or remove these data.	Accurate reporting of trial data as per the CSR and company submission.	Amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
The Company cannot locate these values in either of the referenced sources.			
Page 94, the EAG states: *"Incidence rates of decreased creatinine clearance… were statistically significantly higher with CAB-LA compared with TDF/FTC."* Incorrect statement.	Please remove decreased creatinine clearance from the statement and clarify that the rate was statistically significantly higher with TDF/FTC for decreased creatinine clearance versus cabotegravir.	The incidence rates were 61.67 per 100 PY with cabotegravir, and 68.43 per 100 PY with TDF/FTC (p=0.02) (8).	Amended.
Page 93, the EAG states: *"[b] Reported in CS Appendix F Table 4 as* [redacted] *but this appears to be an error."* Thank you for identifying the error with number and proportion of ISR AEs in the TDF/FTC arm. The company accept this change, however note that the data in Table 18 reports AEs for steps 1 and 2 safety population (OBSP), with the expectation of ISR in	Please amend to the following: ISR cabotegravir LA arm: *n=*[redacted]	The reporting aligns with Table 18 in the CSR and EMA EPAR reporting analyses in the Step 1 and 2 on blinded study product (OBSP) safety populations.	No change, Table 18 presents CS Appendix F Tables 4 and 9, as stated in the footnote.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
the HPTN 083 cabotegravir LA arm, which is reporting the Step 2 safety population only. To align with the HPTN 083 CSR (table 14, page 78) and EMA EPAR (section 2.5.8.1, table 17, page 109), we would request that this cell aligns with reporting step 1 and 2 OBSP safety population			
Page 94, the EAG states: *"although this is based on observation of the data only as no statistical analyses were reported."* This is inaccurate, as the figures presented in the CS include HR's and p-values.	Please remove.	There are statistical analyses reported for the subgroups.	The EAG was not referring to the HRs and p-values presented for the subgroups themselves, but to the comparison of the subgroups with the overall treatment effect. The EAG acknowledges that this could be misinterpreted, therefore the sentence has been removed.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
Page 95: Missing dosing regimen for oral cabotegravir in the key methods of the Phase 2 studies table.	*Please amend to the following for both trials:* *"Step 1: oral cabotegravir 30 mg daily for up to 5 weeks"*	Accurate reporting of the trial methodology/dosing regimen.	Amended.
Page 120, the EAG states: *"2. Underrepresentation of Non-Adherent Populations: Real-world populations eligible for PrEP may include individuals with varying levels of adherence and motivation…"* The clinical trials are not designed as real-world evidence.	Please amend the wording to the following: *"2. Underrepresentation of Non-Adherent Populations: populations eligible for PrEP may include individuals with varying levels of adherence and motivation…"*	The clinical trials are not designed as real-world evidence.	Amended.
Page 125, the EAG states: *"CAB-LA appears to be effective at reducing HIV acquisitions compared to daily oral TDF/FTC PrEP (SoC)."* The EAG have defined cabotegravir LA as being	Please replace: *"CAB-LA appears to be effective…"* with *"cabotegravir LA for PrEP was superior…".*	The statistical superiority was confirmed in both trials and should be adequately described.	Amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
effective; however cabotegravir LA met superiority thresholds in both HTPN 083 and HPTN 084 studies.			
Page 143, the EAG states: *"Indeed, after the end of the blinded period of both HPTN 083 and 084 trials, PrEP users in both cabotegravir and TDF/FTC opted for the alternative PrEP option from originally assigned PrEP."* Incorrect description of the trial design.	Please amend to the following: *"Indeed, after the end of the first year of unblinded-follow-up, in both HPTN 083 and 084 trials, participants who transitioned to the OLE in both the cabotegravir and TDF/FTC arms had the option to opt for the alternative PrEP option from originally assigned PrEP."*	Choice was introduced at the beginning of the open-label extension (OLE) after the first unblinded year, not at the end of the blinded period.	Amended.
Page 144, the EAG states: *"Furthermore, ISR occurred in 81% of people and 2% of people discontinued cabotegravir due to ISR".* Incomplete statement.	Please amend to the following: *"Furthermore, drug-related ISR occurred in 81% of people and 2% of people discontinued cabotegravir due to ISR in HPTN 083"*	Accurate reporting of trial data and clarification of the data source.	Amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
Page 145, the EAG states: "However, the clinical trials (HPTN 083 and HPTN 084) used a modified ITT analysis excluding participants who were non-adherent to cabotegravir oral lead-in tablets prior to intramuscular injections." Misleading statement.	Please amend to: *However, the clinical trials (HPTN 083 and HPTN 084) used a modified ITT analysis excluding those who were found to be living with HIV at randomisation."*	Incorrect definition of the mITT population.	Not a factual error. No changes made.
Page 173, the EAG states: *"the unreliability of adherence data from the HPTN 084 study which was conducted in participants from sub-Saharan Africa..."* The statement made by the EAG that this is unreliable is unfounded.	Please remove reference to the data being *"unreliable".*	The trial is based on a large sample size (N=3,224).	Not a factual error. We argued within our report that our concerns with the adherence used in the model stem from the settings the studies were conducted in rather than the sample size. No changes made.

Issue 11 Other features of the economic analysis

Description of problem	Description of proposed amendment	Justification for amendment	EAG
Page 19 the EAG states: *"Furthermore, in the company's base case, 50% of patients who stop taking cabotegravir transition into daily oral PrEP undermining arguments on the use of cabotegravir in patients whom oral PrEP is inappropriate and the comparison to oral PrEP.* " The CS model is in line with the SmPC, therefore this claim is unfounded.	Please remove this sentence.	The population in the decision problem consists of individuals at high-risk of acquiring HIV for whom oral PrEP is not appropriate. The company does not use the word "ineligible for oral PrEP" in its description of the population. Furthermore, suggested transition to oral PrEP reflects the SmPC.	This section has been changed to: "Furthermore, in the company's base case, 50% of patients who stop taking cabotegravir transition into daily oral PrEP undermining arguments on the use of cabotegravir in patients whom oral PrEP is inappropriate and the comparison to no PrEP"
Page 22, the EAG states: *"CGW were assumed to have a much lower adherence (46%) compared to TGW and MSM (86%)."* Incorrect data point.	Please amend to the following: *"Cisgender women were assumed to have a much lower adherence (56%) compared with transgender women and men who have sex with men (86%)."*	The correct data should be reported.	Value amended.
Page 135, the EAG states:	Please amend to the following:	The relative risk reduction for cabotegravir and TDF/FTC	Amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
"The relative risks of HIV acquisition with cabotegravir and TDF/FTC are calculated based on observed HIV acquisition rates and adherence to TDF/FTC in HPTN 083 and HPTN 084". This is a misrepresentation of the relative risk reduction used in the CEM.	*"The relative risks of HIV acquisition with cabotegravir and TDF/FTC are calculated based on the estimated HIV acquisition rates from the ITC and adherence to TDF/FTC in HPTN 083 and HPTN 084."*	are estimated from an ITC that includes but is not limited to the HPTN trials.	
Page 139, the EAG states: *"However, the model relies on data (effectiveness and adherence) from the HTPN trials and trials included in the ITC, where the patients recruited were individuals for whom oral PrEP was deemed appropriate".* This is a misrepresentation of the trial's eligibility criteria.	Please remove the statement.	The appropriateness of oral PrEP is not an eligibility criterion in the HPTN clinical trials. To avoid any confusion, it is important to distinguish being eligible for a regimen and that regimen being appropriate for the individual. Reduced adherence is a marker of where oral PrEP is not appropriate. Furthermore, in both trials there was oral non-adherence observed, and therefore oral PrEP was not appropriate for those during Steps 1 and 2.	Not a factual error, no amendment.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
Page 140, the EAG states: *"Cabotegravir intramuscular injections is compared…"* This is a misleading description of the intervention.	Please remove *"intramuscular injections".*	In the economic model, some individuals may have an oral lead-in that is reflected in the cost-effectiveness analysis. It is incorrect to restrict the intervention to cabotegravir intramuscular injections when describing the modelled intervention.	Amended.
Page 154, the EAG states: *"The company assumed equivalence between cabotegravir and oral TDF/FTC."* Incomplete sentence.	Please revise the sentence to clarify what Company assumption the EAG is referring to: *"The company assumed equivalence in XXX between cabotegravir and oral TDF/FTC"*	To ensure a clear understanding of EAG comment, it would be helpful to describe what assumption the EAG is referring to in this sentence.	The statement has been changed to the following: "The company assumed equivalence in number of monitoring tests between cabotegravir and oral TDF/FTC"

Issue 12 Use of inappropriate language

Description of problem	Description of proposed amendment	Justification for amendment	EAG
Throughout report. The company consider the EAG's use of wording	Please amend these words or phrases to the following throughout: • "*HIV positive"* to *"living with HIV"*	The language within the company submission has been aligned with	Terminology is now amended when referring to individuals.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
throughout the report to be inconsistent with the People First Charter (9).	• *"mother-to-baby transmission"* to either *"vertical transmission"* or *"perinatally acquired HIV"* • *"Infected cohort"* to *"cohort living with HIV"* • "*HIV infection"* to *"HIV"* • "*Serodiscordant"* to *"serodifferent"*	recommended terminology from the People First Charter; the use of positive and inclusive language in the human immunodeficiency virus (HIV) field is vital, as people living with HIV or who are likely to be exposed to HIV experience stigma and discrimination, which is perpetuated by the use of inappropriate language (9).	
Throughout report. CAB and CAB-LA are not approved abbreviations in the language lexicon of this intervention.	Please amend: • "CAB" to "cabotegravir" • "CAB-LA" to "cabotegravir long-acting"	The CS uses the terminology cabotegravir, oral cabotegravir, and cabotegravir LA for clarity. The proposed amendment reflects the wording used in the CS. Consistency in language lexicon is critical to avoid any risk of misunderstanding.	Not a factual error. The report spells out abbreviations beforehand.
Throughout report.	Please amend:	Abbreviations are considered dehumanising, and should be written out in full (9, 10)	Amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
The CS spells out populations in full	• "MSM" to "men who have sex with men" • "CGW" to "cisgender women" • "TGW" to "transgender women"		
Page 138, the EAG states: *"Capping treatment to five years biases the ICER in favour cabotegravir"* Misleading language.	Please amend to the following: *"Matching prophylaxis to five years…"* *Modelling a shorter at risk period generates a lower ICER for cabotegravir,*	The propose wording accurately reflects the CS. The word capping suggests that treatment costs were curtailed whilst the impacts of other parameters, including HIV acquisition, were modelled. Prophylaxis costs are assumed to stop because people are no longer at elevated risk of HIV.	Not a factual error.
Page 142, the EAG states: *"relative to the general population of 3.7 and 6.8 years in men and women, respectively"* Inconsistent language and misrepresentation of the CS.	Please amend to the following: *"3.7 years in men who have sex with men and transgender women and 6.8 years in cisgender women"*	It is important to use consistent wording to accurately reflect the CS.	The CS states: The data indicate a reduction in life expectancy of 3.7 and 6.8 years for men and women living with HIV, respectively.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
Page 142, the EAG states: *"The company assumed the baseline risk of HIV acquisition in the MSM population was equivalent to HIV incidence in a subset of the MSM population with recent rectal bacterial STI".* Inconsistent language.	Please amend: *"MSM"* To *"men who have sex with men and transgender women".*	It is important to use consistent wording to accurately reflect the CS.	Amended.
Page 147, the EAG states: *"Four studies were identified and a disutility value of –0.11 from Miners et al. was applied to all HIV positive health state (reference Miners et al)."* Misleading description of disutility application in the CEM.	Please amend to the following: "*Four studies were identified and a disutility value of –0.11 from Miners et al. was applied to all individuals in the living with HIV health state*".	The proposed amendment clarifies application of disutility in the economic model.	Not a factual error. This is referring to the health state.

Issue 13 Other issues

Description of problem	Description of proposed amendment	Justification for amendment	EAG
Page 15, the EAG states: *"The other ICER generated for CAB-LA versus "no PrEP" is deemed irrelevant because "no PrEP" is not a specified comparator within NICE's scope."* Incorrect statement.	Please remove.	The NICE scope states "including" TDF/FTC, which implies that other comparators are not excluded (11). In addition, the comments on the NICE draft scope also states "The company can make a case for which comparators are appropriate in their submission" (12). A sizeable proportion of the population assessed as at elevated risk of acquiring HIV and in need of PrEP are not currently receiving PrEP. This population is described in detail in the CS in section B1.3.6. This population is over-represented by marginalised groups. It would be inequitable to exclude consideration of this population.	Not factual error, not amendment.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
Page 37, Figure 1 states: *"PrEP"* and *"Biomedical intervention"* as separate. PrEP is a biomedical intervention.	Please amend the primary prevention box to state: *"Biomedical interventions (PrEP, PEP)".*	Accurate reporting of biomedical intervention for primary prevention of HIV is required.	Amended.
Page 38, the EAG report states: *"When taken consistently as prescribed, various studies report that PrEP reduces the risk of acquiring HIV by at least 74% (xx) to 84%."* The date is not included.	Please include the date.	The date is required for accurate reporting.	The (xx) deleted.
Page 39, the EAG states: *"TAF/FTC is a second line option for people whom TDF/FTC may not be appropriate, including adolescents (with a body weight of at least 35 kg).[17]"* The current wording in unclear, and implies that	Please amend to: *TAF/FTC is a second line option for people whom TDF/FTC may not be appropriate; TAF/FTC is only licensed for* at-risk men who have sex with men *including adolescents (with a body weight of at least 35 kg) (REF: MHRA SmPC).*	The proposed amendment avoids misinterpretation.	Added.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
TDF/FTC is not licensed for adolescents.			
Page 132–133, in Table 26 the EAG uses "*Yes*" where the EAG appears to agree the company's approach aligns with the NICE reference case. The response does not match the purpose of the cell.	Where the EAG agrees that the company's approach is aligned with NICE reference case, using "*no comment"* would be a clearer indication of EAG's views.	The proposed amendment aims to facilitate interpretation of EAG review of company submission against the NICE reference case.	Not a factual error.
Page 132, in Table 26 the EAG uses "*No*" where the EAG appears to disagree the company's approach aligns with the NICE reference case. The response does not match the purpose of the cell.	Where the EAG disagrees that the company's approach is aligned with NICE reference case, a detailed description of the reasons for misalignment would be a clearer depiction of EAG's view.		Not a factual error.
Page 133, the EAG states: *"About [redacted] of the cohort in cabotegravir PrEP state who discontinue cabotegravir…"*	Please remove *"about".*	The proposed amendment accurately reflects the CS; "about" suggests that the value is approximate, which is incorrect.	Amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
The current wording is misleading.			
Page 140, the EAG states: *"Given the significant administrative burden on both PrEP users and NHS clinics to ensure on-time injections, it is unclear the extent to which cabotegravir can improve adherence above TDF/FTC adherence levels in the UK."* The implication that regular visitation with cabotegravir could present a significant burden on both the NHS and users, which might not translate to improved adherence is inaccurate.	Please remove.	The level of adherence to cabotegravir in the HPTN trials is higher compared with oral PrEP users. In addition, several publications, report that the additional visitations, conducted along with dose administration, play a crucial role in providing ongoing support and guidance. It has been established that regular check-ins with their healthcare professional improve retention in care, hence adherence and persistence. It is crucial to consider that frequent consultations for cabotegravir users serve as an opportunity to discuss the user's PrEP journey, address any concerns or questions, and ensure adherence to the medication. The regular visits create an open line of	Not a factual error. No changes made.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
		communication through which healthcare professionals can empower cabotegravir for PrEP users to effectively manage their regimen and stay protected against HIV (13, 14).	
Page 140, the EAG states: *"It is also unclear the extent to which people with serious medical conditions preventing them from taking oral PrEP regimens are equally at risk of sexually acquired HIV infection."* Unreferenced statement.	Please remove or add clear and referenced justification for this statement.	The company would like to request clarification on the definition of a serious health condition and any evidence of its association with likelihood of HIV acquisition. The company has interpreted this comment as an association between a person's ability to function in day-to-day life and risk of HIV acquisition. Systematic review- and meta-analysis data demonstrate that a decrement in functioning (known as disability) does not reduce the risk of HIV acquisition (15). Consequently, we intend to mitigate any interpretation of	The justification for amendment is misleading. During clarification response, the EAG asked the company to clarify the population ineligible for oral PrEP and justify the comparison to 'no PrEP'. The company argued that individuals considered in the appraisal are "*those who cannot take oral PrEP due to medical contraindication or intolerance, or who have limitations with swallowing pills*". The referenced statement is a critique of the company's response to our questions, made clear within the text. We have removed the statement but our

Description of problem	Description of proposed amendment	Justification for amendment	EAG
		unintentional ableism in this statement.	concerns about the population “ineligible” or for whom oral PrEP is inappropriate remain.
Page 144, the EAG states: *“Submission received from NHS England”* No reference provided.	Please add the appropriate reference.	Clarification of the source used for the assumption.	Reference added.
Page 147, the EAG states: *" The EAG applied a disutility of -0.01 for mild ISR [56] and a disutility of -0.247 for severe ISR.[57]"* Description of sources and justification for assumption is missing.	Please add description of the references and justify the assumptions supporting the selection of ISR disutilities.	Providing a clear description of the source for disutilities values is important for contextualisation. Notably, these references are not studies in HIV PrEP and therefore a description of the assumptions made is needed to assess the validity.	The EAG argued that it is inappropriate not to apply disutility for ISR given the frequency of moderate and severe ISR. Cabotegravir is the only approved injectable PrEP and the company did not estimate disutility from cabotegravir injections in the HPTN trials. Disutility for ISR was not included and justified on the assumption that choosing to receive

Description of problem	Description of proposed amendment	Justification for amendment	EAG
			PrEP outweighs negative feelings on issues such as ISR. The EAG disagrees with this rationale and argues that ISR serious conditions that should be considered in the appraisal. Failure to do so goes against NICE's recommendations that all direct health effects be considered in an economic appraisal. Despite the very minimal impact on the ICER (£3 in the company base case), it is important disutility for adverse events be considered. We have added the following text: "Given the higher proportion of AEs leading to the study discontinuation in the

Description of problem	Description of proposed amendment	Justification for amendment	EAG
			cabotegravir relative to oral TDF/FTC (6% vs 4%), the decision not to apply a disutility for AEs goes against NICE recommendations that all direct health effects be considered (reference NICE guide to methods for technology appraisals) and biases the ICER in favour of cabotegravir. The EAG could not find disutility for ISR in injectable HIV PrEP as cabotegravir is the only approved injectable HIV PrEP and health related quality of life information was not available from the HPTN 083 and HPTN 084 trials. Following a review of the literature, we identified a disutility of -0.01 in a study on users

Description of problem	Description of proposed amendment	Justification for amendment	EAG
			of injectable treatment for type 2 diabetes with mild ISR and a disutility of –0.247 in a study of older adults taking a first dose of recombinant zoster vaccine with severe ISR”
Page 171, the EAG states: *“A US version of the model is published in a peer-reviewed journal (reference pack184)”* Incorrect reference.	Please add the correct reference.	The correct reference is important to access the source, if required.	Reference added

Description of problem	Description of proposed amendment	Justification for amendment	EAG
Page 127, the EAG states: *"To increase the sensitivity of the searches, the EAG would recommend searching for keyword headings using the text field .kf in Medline rather than .hw, which searches in the Subject heading word (CS Appendix G.1.2.2.1.2 Table 8, CS Appendix G.1.2.2.1.3 Table 14 "*	Please remove.	The.hw. field has been used to have the most accurate possible translation from Embase.com to Ovid Medline. In Embase, we have searched in title (ti), abstract (ab) and index terms (de). The most accurate translation for Ovid Medline would be .ti,ab,hw. (or .tw,hw. as used in our search).	This is not a factual error. It is the EAG opinion and recommendation.
Page 170, the EAG report the base-case probabilistic ICER as "£5,580". This is incorrect reporting of the deterministic ICER.	Please amend to: "£4,409"	Accurate reporting of model results.	Amended.
Page 126, the EAG states: *"There are major issues with the Cochrane Library searches, as limits have been applied incorrectly (CS Appendix G.1.2.2.1 Table 3, CS Appendix G.1.2.2.1.2*	Please amend to reflect that conference abstracts are captured within the Cochrane Library searches.	The Cochrane Library does include conference abstracts. Chapter 4 of the Cochrane Handbook includes this section: *"Many of the records in CENTRAL have been identified through systematic*	Amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
Table 9 and CS Appendix G.1.2.2.1.3 Table 15). Lines #22, #23 and #24 of the initial, additional and update searches are an attempt to remove conference abstracts; however, the Cochrane Library does not contain conference abstracts.25 The EAG believe that applying this line would remove any studies that mention 'conference abstracts', which is likely to remove potentially relevant results."		*searches of MEDLINE, Embase, CINAHL Plus, the Australasian Medical Index, KoreaMed, ClinicalTrials.gov and the trial records available through the WHO International Clinical Trials Registry Portal (see online Technical Supplement). CENTRAL, however, also includes citations to reports of randomized trials that are not included in MEDLINE, Embase or other bibliographic databases; citations published in many languages; and citations that are available only in conference proceedings or other sources that are difficult to access. It also includes records from trials registers and trials results registers beyond ClinicalTrials.gov and the WHO portal."* (Chapter 4: Searching for and selecting studies | Cochrane Training).	

Description of problem	Description of proposed amendment	Justification for amendment	EAG
		The term “conference abstract” used to be utilised in the Cochrane Library to identify that publication type, but an update changed that term to “conference proceeding”. We do search for the term in all text, and all instances are captured. Thus, there is no risk of potentially relevant results being excluded.	
Page 126 the EAG states: *“The Embase search was limited to conference abstracts (Appendix G.1.2.2.1.2 Table 7). The EAG believes that this Embase search should not have been limited to conference abstracts, as this could potentially exclude relevant published studies that are not conference abstracts and a search for conference abstracts via*	Please amend to reflect that the Embase search included both articles and conference abstracts.	The Embase searches included both articles and conference abstracts. As presented in Table 1, Table 7, and Table 13 of the HIV PrEP Health Economic Support Economic Systematic Literature Review Update: Final Report dated 24 January 2024 the searches included search strings for both articles (#17) and conference abstracts (#18), with #19 combining both of these search strings.	Text amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
Embase should have been carried out separately. "			
Page 125, the EAG states: *"Reference lists of 'up to 10 of the most relevant robust economic analyses, systematic reviews and, HTAs' were also searched to supplement the main searches; however, the company did not report which studies these were carried out for. (CS Appendix G.1.1.2). "*	Please amend to reflect that the CS did provide the list of studies of which the references lists were searched.	The publications for which reference lists were searched are presented in Table 23 of Appendix G.	Text amended.

Issue 14 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG
Page 15, 17, 18 (several locations), 102, 103, 106, 108 (several locations), 109 (several locations), 117 (several locations), 118 (several locations), 126, 131	Please amend: *"… TDF/FAC…"* to *"… TDF/FTC…"*	Drug name amended for accuracy.	Amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
Incorrect drug name			
Page 21 Incorrect drug name	Please amend: *"… TCF/FTC…"* to *"… TDF/FTC…"*	Drug name amended for accuracy.	Amended.
Page 125 Typographical error.	Please amend: *"The primary sources of evidence for the assessment of clinical evidence of cabotegravir for preventing HIV-1 infection comes from two RCTs"* to *"The primary sources of evidence for the assessment of clinical effectiveness of cabotegravir for preventing HIV-1 infection comes from two RCTs".*	Typographical error.	Amended.
Page 143 Incorrect drug name	Please amend: *"… TBF/FTC…"* to *"… TDF/FTC…"*	Drug name amended for accuracy.	Amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
Page 145 Incorrect drug name	Please amend: *"… TBD/FTC…"* to *"… TDF/FTC…"*	Drug name amended for accuracy.	Amended.
Throughout report	Please re-format incorrectly formatted references throughout, for example "This integration leads to a latent phase where viral gene expression is inhibited.Chen, 2022 #481}" on page 36	Formatting suggestion	We re-ran the refence check. In text referencing has been updated along the bibliography.
Page 24, the EAG states: *"Afterwards, participants are no have a disutility for HIV infection but are still subject to greater mortality compared to the general population"* Typographical error – sentence needs to be amendment	Please amend to: *"Afterwards, participants have no disutility for HIV infection but are still subject to greater mortality compared to the general population"*	Appropriate sentence structure	Amended.
Page 36, the EAG states:	Please amend to:	It is important to provide accurate data on what	Amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
"HIV is transmitted through bodily fluids of infected individuals with detectable virus load (less than 200 viral load copies per ml)…" A viral load of <200 copies is considered undetectable, and therefore untransmittable.	*"HIV is transmitted through bodily fluids of infected individuals with detectable virus load (i.e. is not less than 200 viral load copies per ml) (CITE: Broyles LN, Luo R, Boeras D, Vojnov L. The risk of sexual transmission of HIV in individuals with low-level HIV viraemia: a systematic review. Lancet. 2023;402(10400):464-71.)"*	constitutes a viral load that can be transmitted.	
Page 39" *"CAB-LAHIVinfo"*	Please amend: *"CAB-LAHIVinfo"* *to* *"cabotegravir"*	Typographical error and incorrect abbreviation	Amended.
Page 40, the EAG states: *"…sex with HIV-positive partners (viral load <200 copies/ml)…"* Viral load <200 copies/ml is considered undetectable, therefore untransmittable.	Please amend to: "*…sex with HIV-positive partners (whose viral load is not <200 copies/ml)…"*	It is important to provide accurate data on what constitutes a viral load that can be transmitted.	Amended.
Page 56, the EAG states: *"Planned open-label tail phase (to cover the*	Please amend to:	The proposed amendment reflects the wording used in the CS. Consistency in language	Amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
pharmacokinetic tail of CAB-LA long-acting injections) with oral TDF/FTC." This is inconsistent with the language lexicon, and repeats long-acting.	*"Planned open-label tail phase (to cover the pharmacokinetic tail of cabotegravir long-acting injections) with oral TDF/FTC."*	lexicon is critical to avoid any risk of misunderstanding.	
Page 100 *"Table XX. PROUD[38]"* Missing table number.	Please add the table number.	Formatting/typographical error.	Appendix included.
Page 101 *"Carbotegravir"* Incorrect drug name	Please amend: *"Carbotegravir"* to *"Cabotegravir"*	Typographical error	Corrected.
Page 108: *"Section XX"* Incomplete cross reference.	Please add the correct cross reference.	Formatting error.	Removed.
Page 118 "HPTN04" Incorrect trial name.	Please amend: *"HPTN04"* to	Typographical error	Corrected.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
	"HPTN 084"		
Page 118 "PReP" Incorrect formatting of abbreviation.	Please amend: *"PReP"* to *"PrEP"*	Formatting error.	Amended.
Page 133 "prep" Incorrect formatting of abbreviation.	Please amend: *"prep"* to *"PrEP"*	Formatting error.	Amended.
Page 134 Incorrect positioning of figure, title, and abbreviations	Please move the table to after the end of the sentence.	Improve report structure and improve readability.	Not a factual error.
Page 138, the EAG states: *"4% (91%) were aged over 65"*	Please amend to the following: *"and 4% (91) were aged over 65"*	This accurately reflects the data source and avoids confusion.	Amended.
Page 141, the EAG report states:	Please amend to the following: ($RR_{A \text{ vs. } C} = RR_{A \text{ vs. } B}$ X $RR_{B \text{ vs. } C}$)	Typographical error.	Added.

Description of problem	Description of proposed amendment	Justification for amendment	EAG
"($RR_{A\ vs.\ C} = RR_{A\ vs.\ B}$ ´ $RR_{B\ vs.\ C}$)"			
Page 144, the EAG states: *"4% (91%) were aged over 65"* The figure 91 is an absolute number, not a proportion.	Please amend to the following: *"and 4% (91) were aged over 65"*	This accurately reflects the data source and avoids confusion.	Amended.
Page 138 "The EAG agress" Typographical error.	Please amend to *"agrees"*	Typographical error.	Amended.
Page 154, the EAG states: "Suggests that test for HIV antigen test". Repetition of the word test.	Please amend to *"suggests that for HIV antigen test"*	Typographical error.	Amended.
Page 173, the EAG states: *'The assumptions made to the company model are described below.'*	Please amend to "The changes made to the company model are described below."	Typographical error.	Amened.

Incorrect marking

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG
EAG report, throughout	The confidential information is highlighted blue but is not underlined	Please underline, as per the approach to marking confidential information as specified by NICE	Please see below
EAG report, page 19 **EAG report, page 21** **EAG report, page 142** **EAG report, page 143**	Incorrect confidentiality marking of the proportion of people in the cabotegravir arm who discontinue cabotegravir administration and subsequently go on to receive oral PrEP	Please mark as CON: [redacted]"	Amended.
EAG report, page 31	The draft SmPC is not currently in the public domain.	Please mark as CON: The SmPC recommends doses [redacted]	Amended.
EAG report, page 31	Incorrect confidentiality marking of the list price, which is not publicly available and therefore is commercially sensitive information	Please amend to: "This is significant given the considerable cost per injection ([redacted])."	Amended.
EAG report, page 56	Incorrect confidentiality marking of the proportion of participants	Please mark as CON:	Amended.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG
	discontinuing due to low adherence	"proceed to Step 2 [redacted] of participants across…"	
EAG report, page 60	Confidentiality marking not required	Please unmark: The EAG notes that 85% of those tested (69% of all randomised participants)	Removed.
EAG report, page 65	The mean (SD) age, and race % appear to have been reported from the CSRs; this is unpublished data from the HPTN 083 trial	Please mark all data points for mean (SD) age, and race (%) as CON.	Amended.
EAG report, page 67	The age groups, mean (SD) age, and ethnicity, % appear to have been reported from the CSRs; this is unpublished data from the HPTN 084 trial	Please mark all data points for age groups, mean (SD) age, and ethnicity (%) as CON	Amended
EAG report, page 75	Confidentiality marking not required	Please unmark as follows: Less than one per cent of each arm of HPTN 083 and 7%-8% of HPTN 084 missed injections	Removed.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG
EAG report, page 76	Confidentiality marking not required	Please unmark as follows: and 73% (TFV-DP) of samples were consistent with this benchmark	This data is from the CSR however marking removed.
EAG report, page 105	Incorrect confidentiality marking of the baseline HIV incidence for the cisgender women population, which is derived from unpublished ITC results.	Please mark as CON: This parameter, estimated for UK PrEP-naïve MSM at 4.9 per 100 person-years and slightly lower for PrEP-naïve heterosexual/cisgender women at [redacted] per 100 person-years from the company's ITC analyses	Marked.
EAG report, page 133	Incorrect confidentiality marking of the proportion of people in the cabotegravir arm who discontinue cabotegravir administration and subsequently go on to receive oral PrEP	Please mark as CON: About [redacted] of the cohort in cabotegravir PrEP state who discontinue cabotegravir, transition to a TDF/FTC PrEP	Marked.
EAG report, page 142	Incorrect confidentiality marking of the incidence for the cisgender women population, which is derived from unpublished ITC results	Please amend to: "4.9 per 100 person years for MSM and [redacted] per 100 person years for CGW"	Amended.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG
EAG report, page 148	Incorrect confidentiality marking of the adherence levels	Please mark as CON: "adjusted for differential adherence levels from clinical trials [redacted] pills/week for men/transgender women and [redacted] pills/week for cisgender women."	Amended.
EAG report Table 32, page 153	Incorrect confidentiality marking of adjusted cost of oral PrEP base on adherence pill count distribution.	[redacted]"	Amended.
EAG report, page 164	Incorrect marking up of model results, which could result in back calculation of the confidential cabotegravir list price	Please mark as CON: Cabotegravir versus TDF/FTC had an incremental cost of [redacted] and QALYs of [redacted]. The ICER for the base case is £5,580/QALY. Cabotegravir was dominant against no PrEP with cost savings of [redacted] and QALYs of [redacted].	Amended.
EAG report, Page 173	Incorrect confidentiality marking of the proportion of people in the cabotegravir arm who discontinue cabotegravir administration and subsequently go on to receive oral PrEP	Please mark as CON: "simultaneously assuming that [redacted] of patients on stop cabotegravir PrEP subsequently go on to receive oral PrEP."	Amended.

References

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7. Landovitz RJ, Donnell D, Clement ME, Hanscom B, Cottle L, Coelho L, et al. Cabotegravir for HIV prevention in cisgender men and transgender women. N Engl J Med. 2021;385(7):595-608.
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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Cabotegravir for preventing HIV-1 in adults and young people [ID6255]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for comments is **5pm** on **Monday 10 June**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Table 1: About you

Your name	[redacted], [redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	ViiV Healthcare

Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Not applicable
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	None

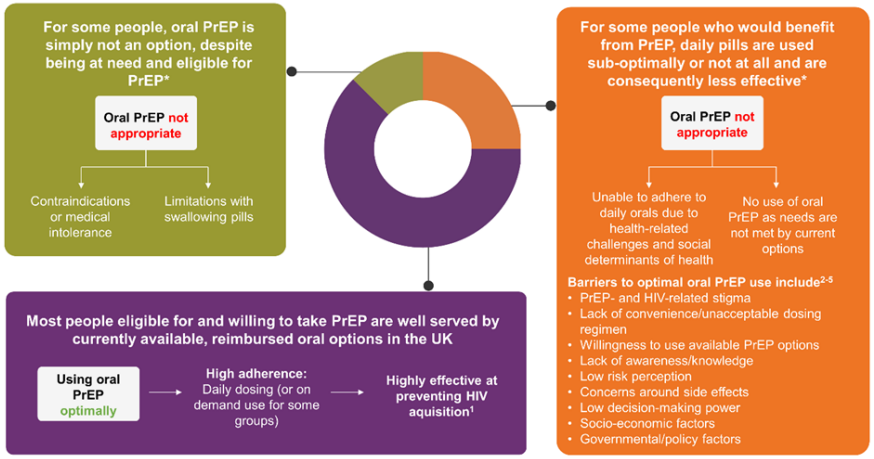
Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2: Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: The population is narrower than the decision problem (section 2.3 of EAR)	No	***The company believe that the EAG have misinterpreted the description of the decision problem population in the CS. For some individuals with a PrEP need identified, oral PrEP options are not appropriate either because they cannot take oral PrEP or because they are unable to optimally adhere to an oral PrEP regimen.*** **Distinction between being eligible for oral PrEP and oral PrEP not being appropriate** The decision problem population (i.e., individuals for whom oral PrEP is not appropriate), while narrower, is aligned with the NICE scope (1) and the marketing authorisation for cabotegravir for PrEP (2). In several key issues, the EAG have misinterpreted the description of the population in the decision problem, instead referring to "ineligibility" for oral PrEP. It is essential to understand that the population in the decision problem consists of individuals at high risk of acquiring HIV-1 for whom oral PrEP is not appropriate, which does not use the word "ineligible". PrEP eligibility, as described within the BHIVA/BASHH guidelines (3), is based on population level indicators, clinical indicators, sexual behaviour and sexual network indicators, drug use, sexual health autonomy or other factors that may affect sexual health autonomy. Individuals can meet these criteria and be eligible for oral PrEP, but that does not mean oral PrEP will be an appropriate option to meet their HIV prevention needs.

		The Company's decision problem population considers individuals who have a PrEP need identified (and are eligible for PrEP) but whose HIV prevention need is not met by current options, either because they cannot take oral PrEP or because they are unable to optimally adhere to it. **Population represented in the cost-effectiveness analysis** The population considered in the economic model represents individuals at high-risk of HIV acquisition who are eligible for oral PrEP in accordance with BHIVA/BASHH guidelines (3), for whom oral PrEP is not appropriate, including those who: 1) Cannot take oral PrEP (comparison vs no PrEP) 2) Can and are taking oral PrEP but have challenges resulting in sub-optimal adherence to it (comparison vs TDF/FTC), which may be for a variety of health, social or structural reasons. **Clinical efficacy data used in the economic analysis** The EAG expressed concerns with the population within both the HPTN trials not meeting the criteria outlined in the decision problem (i.e., people for whom oral PrEP is not appropriate), indicating that neither trial included eligibility criteria based on the ability/inability to take oral PrEP. Whilst the ability / inability to take oral PrEP was not a trial inclusion criterion, TDF/FTC adherence levels reported in the HPTN 083 and HPTN 084 trials demonstrate that oral PrEP was not used optimally by all participants. Irrespective of potential motivation for research participation, it is common to observe suboptimal adherence in oral PrEP studies as demonstrated in a systematic review and meta-analysis (4). The proportion of participants in HPTN 083 and HPTN 084 with undetectable TDF/FTC, as measured by plasma TFV concentrations <0.31 ng/mL, was 14% and 44%, respectively. These data indicate that the trials represent a broad group of oral PrEP users, including some participants exhibiting sub-optimal adherence to daily TDF/FTC; therefore, within the trials it was observed that oral PrEP was not appropriate to meet some of the participants' HIV prevention needs. Because oral PrEP adherence is required for oral PrEP to be effective, this aligns with the population within the decision problem of people for whom oral PrEP is not appropriate. The EAG also comment that the main evidence submitted by the company for the comparison of cabotegravir with TDF/FTC is limited to adults aged ≥18 years in specific populations, i.e., men who

		have sex with men / transgender women, or cisgender women <45 years. These populations are representative of the majority of individuals who are expected to receive cabotegravir in the UK. **Unmet need** While the proposed reimbursement population of "individuals at high risk of HIV-1 acquisition for whom oral PrEP is not appropriate" is narrower than the marketing authorisation for "individuals at high risk of HIV-1 acquisition", this is suitable for NHS clinical and commissioning pathways for PrEP. This is because oral PrEP meets the HIV prevention needs of many people who have a PrEP need identified (purple box in Figure 1). However, there remains a quantifiable unmet need in England (green and orange boxes in Figure 1), which is driven by suboptimal uptake, adherence, and persistence to oral PrEP; therefore, new innovations are required to meet the needs of people at high risk of HIV-acquisition who are underserved by current oral options, and to reach the UK HIV Action Plan's target of zero new transmissions by 2030 (5). **Figure 1: HIV PrEP unmet need**  ***The green and orange boxes represent the anticipated positioning of cabotegravir.** Sources: 1. Sullivan et al, 2023 (6); 2. Calabrese et al, 2020 (7); 3. Coukan et al, 2023 (8); 4. Sidebottom et al, 2018 (9); 5. National AIDS trust (10). Abbreviations: HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis; UK, United Kingdom.

<table>
<tr>
<td>Issue 2: Generalisability of the HPTN population (section 3.5.1.1 of EAR)</td>
<td>No</td>
<td>
There are no UK patients in the HPTN trials; this issue is acknowledged but not considered a significant limitation given that the effectiveness of cabotegravir will be consistent across settings as demonstrated in the ITC. The effectiveness of TDF/FTC is driven by adherence and the economic model considers suboptimal adherence to TDF/FTC, in line with the population in the decision problem.

Extrapolation of HIV prevention trial data to other settings is frequent according to UK clinical experts

Although the HPTN studies did not include UK sites, this is not uncommon in NICE appraisals. HCPs have confirmed that within the fields of HIV prevention and treatment, they are comfortable with extrapolating data from different settings, and do this often (11). They also noted that evidence of PrEP efficacy in cisgender women is limited and the data from HPTN 084 is highly valuable (11). In addition, the reasons for engaging with oral PrEP for HIV prevention will be transferable regardless of the setting, as evidenced by high proportions of post-migration HIV acquisition in Western Europe (12).

The definition of HIV acquisition risk in the HPTN trials is consistent with UK clinical guidelines

While the Company acknowledge that some differences between the trial populations and individuals potentially receiving PrEP in the UK may exist, these differences (such as sites, location, ethnicity, and socioeconomic factors) are not unique to these trials and are present in the majority of HIV prevention and treatment studies. However, when considering the definition of PrEP eligibility there is a significant degree of overlap between the trials and UK clinical practice.

The BHIVA/BASHH guidelines criteria for PrEP eligibility and the trial inclusion criteria are consistent, describing people at high risk of HIV acquisition (Table 3).

Table 3: HPTN 083, HPTN 084 inclusion criteria and BHIVA/BASHH criteria for PrEP eligibility
<table>
<tr><th>HPTN 083</th><th>HPTN 084</th><th>BHIVA/BASHH</th></tr>
<tr><td>• Any condomless receptive anal intercourse in the 6 months prior to enrolment (condomless anal intercourse within monogamous HIV</td><td>• Born female
• 18–45 years at the time of screening
• Willing and able to provide informed consent</td><td>• HIV-negative men who have sex with men and transgender women who report condomless anal sex in the previous 6 months and</td></tr>
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seronegative concordant relationship does not meet this criterion) • More than 5 partners in the 6 months prior to enrolment (regardless of condom use and HIV serostatus, as reported by the enrolee) • Any stimulant drug use in the 6 months prior to enrolment • Rectal or urethral gonorrhoea or chlamydia or incident syphilis in the 6 months prior to enrolment • In the US, a SexPro score of ≤16 was also applied, which essentially summarises the above criteria	• Willing and able to undergo all required study procedures • Non-reactive HIV test results at Screening and Enrolment • Sexually active (i.e., vaginal intercourse on a minimum of two separate days in the 30 days prior to Screening) • Score of >5 using a modified VOICE risk score • No plans to re-locate or travel away from the site for >8 consecutive weeks during study participation • CrCl ≥60 mL/min • HBsAg negative and accepts vaccination	on-going condomless anal sex • HIV-negative individuals having condomless sex with partners who are HIV positive, unless the partner has been on ART for at least 6 months and their plasma viral load is <200 copies/mL

Abbreviations: ART, antiretroviral therapy; BHIVA/BASHH, British HIV Association/British Association for Sexual Health and HIV; CrCl, creatinine clearance; HBsAg, Hepatitis B surface antigen; HIV, human immunodeficiency virus; US, United States.

Conclusions from the indirect treatment comparison support that geographical location is not a treatment effect modifier

The ITC reported [redacted] estimates of effectiveness for cabotegravir versus no PrEP in the analyses in men who have sex with men and transgender women (the HPTN 083 study population) and cisgender women (the HPTN 084 study population) despite the differences in setting ([redacted] and [redacted], respectively). These observations support the generalisability of the results of the HPTN trials to other populations. Furthermore, the meta-regression establishing the relationship between adherence and effectiveness of TDF/FTC confirms that adherence is the true determinant of TDF/FTC effectiveness estimates. The level of adherence to TDF/FTC considered in the economic analysis, and therefore the resulting effectiveness of TDF/FTC, reflects those observed in the HPTN 083 and HPTN 084 clinical trials. Effectiveness is determined by the level of adherence observed in the population, regardless of the geographical location.

		Comparing the populations of the HPTN trials with the IMPACT trial population is not appropriate and could lead to bias Although the EAG suggest comparing the HPTN population with the PrEP IMPACT population, this would likely cause bias. There are substantial PrEP IMPACT trial inequities that widened post-commissioning of oral PrEP in England (13), across gender, ethnicity, and region of residence, especially those of older age, women of Black ethnicity and those outside of London (14), with Black women being underserved with the largest PrEP equity gap (15) and 278-fold post-commissioning difference in PrEP to need ratio for Black African women (0.3) compared with White men (96.0) (13, 14). Additionally, the demographics of the PrEP IMPACT study (6) reflect people who are most activated and engaged in HIV prevention, with the majority of study participants being white men who have sex with men, born in the UK, and not experiencing deprivation. Therefore, the PrEP IMPACT study evaluating implementation does not fully reflect the wider HIV prevention needs of people across the UK, particularly where there are disparities in opportunities to prevent HIV acquisitions (16), and among those who are more likely to acquire HIV and have unmet PrEP needs (17). However, the HPTN trials intentionally recruited ethnically diverse men who have sex with men and transgender women, and Black cisgender women who have sex with men, reflecting populations with unmet PrEP need in the UK.
Issue 3: Inclusion of studies in the ITC that were conducted in populations different from the population of interest as specified in the scope (section 3.4.1 of EAR)	No	***The studies included in the ITC and the population considered in the appraisal comprise individuals who are eligible for PrEP; not all individuals eligible for PrEP take oral PrEP or use it optimally, as evidenced by the inclusion of placebo arms and trials reporting suboptimal oral PrEP adherence. The relationship between adherence and oral PrEP effectiveness is informed by the meta-regression, and the ITC is used to estimate the relative effectiveness of cabotegravir or TDF/FTC versus no PrEP. The HPTN trials were well conducted multi-national trials and there is no reason to believe that the effectiveness of cabotegravir is not transferable to settings not directly represented within the trials.*** **Alignment of studies included in the ITC and the Company's decision problem population** The EAG are concerned about disparities between the intended and actual populations modelled, and the inclusion of trials recruiting individuals eligible for oral PrEP in the ITC. As described in response to key issue 1, there is a misunderstanding of the Company's decision problem population (people for whom oral PrEP is not appropriate) and the definition of PrEP eligibility. The trials

included in the ITC correspond to the clinical SLR PICOS criteria described in Table 4 that also specifically reported adherence on the basis of plasma samples.

Table 4: Clinical efficacy SLR eligibility criteria

Population	• Cisgender women, men who have sex with men, and transgender women aged 18 years and older who are at an increased risk of acquiring HIV-1 • Adolescents who are at an increased risk of acquiring HIV-1
Intervention/ comparators	• Long-acting injectable PrEP (including e.g. cabotegravir for PrEP) • Oral PrEP (including e.g. TDF/FTC, TAF/FTC) • Placebo or no PrEP
Outcomes	Incidence of HIV acquisition; cases of HIV averted; adherence to PrEP; AEs; incidence of other STIs; behavioural changes (including condom use); drug resistance
Study design	RCTs
Other	English Language only

Abbreviations: AE, adverse event; HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis; RCT, randomised controlled trial; SLR, systematic literature review; STI, sexually transmitted infection; TAF/FTC, tenofovir alafenamide/emtricitabine; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

The trials included in the ITC and the population considered in the appraisal consist of individuals eligible for PrEP; this does not mean that all individuals eligible for PrEP are taking oral PrEP or are using oral PrEP optimally, resulting in oral PrEP not being appropriate for their HIV prevention needs. Indeed, this is evidenced by trials including placebo arms and trials reporting suboptimal levels of TDF/FTC adherence (as described in Table 19 and Table 20, section B.2.9.3 of the CS Document B).

The meta-regression is used to inform the relationship between adherence and effectiveness of oral PrEP and the ITC is used to estimate the relative effectiveness of cabotegravir or TDF/FTC versus no PrEP

As described in CS document B section 2.9, it is well established that adherence will be the primary determinant of effectiveness of TDF/FTC, and that differences observed between populations would

		primarily be mediated by differences in adherence. In the economic analysis versus TDF/FTC, the TDF/FTC adherence levels reported in the HPTN trials (86% of individuals sampled had detectable TDF in plasma in HPTN 083 and 56% in HPTN 084]) are used to inform TDF/FTC adherence and effectiveness in the economic model. Reflecting the observed adherence and effectiveness levels from the HPTN 083 trial in the Company's base-case analysis is conservative ([redacted] have TDF/FTC concentration corresponding to high adherence) (4). Populations who are underserved by current SoC may have lower levels of adherence to TDF/FTC than observed in clinical trials, which can be explored using the meta-regression relationship specified. Indeed, with lower adherence, effectiveness of TDF/FTC would be lower, leading to a greater differential in effectiveness between TDF/FTC and cabotegravir and greater cost-effectiveness of cabotegravir than presented in the base case for underserved populations. The ITC included trials with placebo arms that are used to inform the efficacy of interventions compared with 'no PrEP'. The efficacy of the 'no PrEP' comparator in the economic model is informed with UK data corresponding to the underlying risk of HIV acquisition for individuals who are eligible for PrEP (have a PrEP need identified) but are not taking oral PrEP (3). **Extraction and calculation of adherence data** While the EAG noted in Section 3.2.6.3 of their report that there were concerns regarding the extraction and calculation of adherence data from the original publications of some studies in the ITC, the estimated adherence rates accounted for adherence in the sampled participants for both those who acquired HIV and those who did not. The Company estimated the weighted average according to the proportion of trial participants who acquired HIV. As the proportions of patients who acquired HIV in these trials were low, the weighted average was close to the adherence in the sample of patients who did not acquire HIV.
Issue 4: Inclusion of studies in CS ITC that does not meet the specified population of interest as described in the	No	***Studies conducted outside of the NICE scope were included in the ITC base-case analysis; however, this is not necessarily a material issue given the results of the ITC are robust to the inclusion or exclusion of certain studies.*** The Company's ITC included data from the Bangkok Tenofovir study and the IPERGAY study, which were excluded by the EAG in their analyses. The results of the ITC are robust to the inclusion or exclusion of the PROUD, IPERGAY, and Bangkok studies as demonstrated in the Company's sensitivity analyses, and with the EAG analysis yielding similar results to the Company's ITC. The

NICE scope (section 3.5 of EAR)		EAG also acknowledged that the differences observed between the ITC analyses and the Company's analyses, when applied to the economic model, are unlikely to substantially alter the magnitude of cost-effectiveness of cabotegravir compared with TDF/FTC produced from the Company's base case. It is therefore important to consider this key issue in the context of the EAG's conclusion that the analysis generated similar results to the Company's ITC. Although the Bangkok study was conducted in a different population, it is informative in an analysis examining the relationship between adherence and effectiveness. The Company note there may be other differences between this study and the other study populations; therefore, it was excluded in a sensitivity analysis. PROUD and IPERGAY were also excluded in sensitivity analyses due to differences between these and the remaining studies in terms of assessment of adherence and mode of PrEP administration. As stated above, the results of the ITC were robust in these sensitivity analyses.
Issue 5: CS ITC analyses did not account for measurement error in adherence levels in the meta-regression of treatment effect on adherence to CAB-LA (section 3.4.1 of EAR)	No	***The Company agree with the EAG's approach to account for measurement error in adherence levels in the meta-regression of treatment effect and are reassured that the modification causes minimal changes, confirming the robustness of the ITC results.*** The robustness of the analysis is demonstrated by the fact that the EAG's analysis yielded similar results to the Company's. The Company treated the observed adherence as a fixed value as per the previous published meta-regressions (18-20). Adherence measured by detectable plasma levels was chosen, as self-report was felt not to be reliable (self-reported measures are subject to multiple biases including social desirability and recall bias) (21, 22), and pill count data were infrequently available. This approach also aligns with the other published studies (18-20). The Company agree that the EAG's approach, formulating a binomial distribution for the number of people adherent to oral PrEP in the TDF/FTC arm of each trial, represents an incremental improvement in the analysis and are reassured that the modification causes a minimal change in results. This analysis, and the conclusions further corroborate the overall conclusion that the ITC is robust and suitable for decision making. As part of the critique of the Company's approach to adherence measurement, the EAG state in Section 3.4.2, Page 106 of their report that "incorrect estimates of adherence were applied in the Company's ITC for four trials (Partners PrEP (9), iPrEx (10), FEM-PrEP (11), and PROUD (12)) and

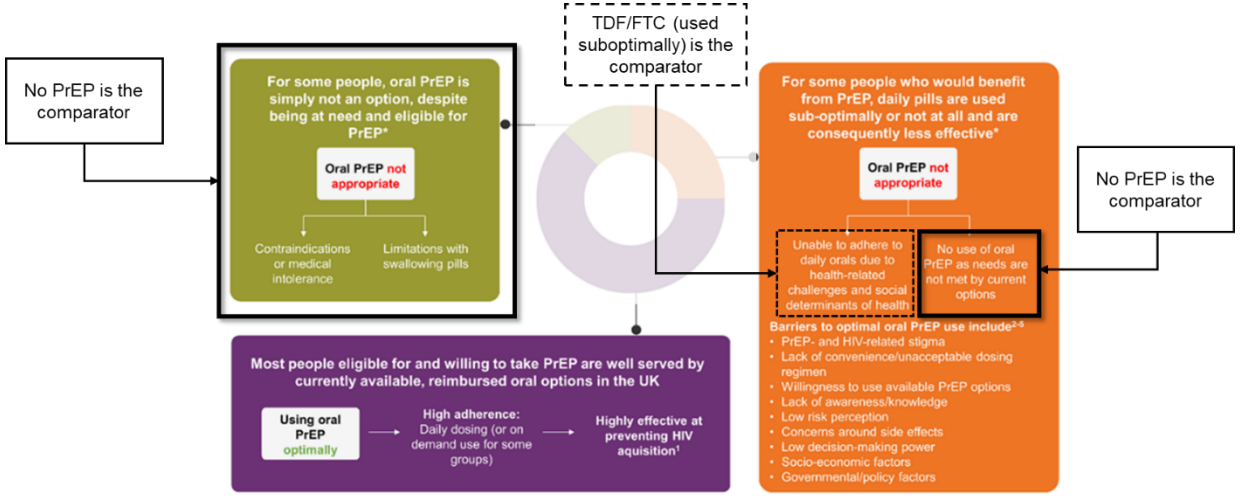
		corrected them in the EAG re-analyses of the ITC data." However, the EAG did not account for the preferential sampling of individuals who acquired HIV in the adherence studies. The EAG's 'corrected' values do not account for this and hence are biased. The CS used weighted averages to account for this and therefore the Company consider the ITC analysis used in their base case cost-effectiveness to be appropriate.
Issue 6: Restricting treatment costs to period of heightened risk (assumed 5-years in the CS base-case) over a life-time risk capping the treatment costs which could favour CAB-LA in cost-effectiveness (section 4.3 of EAR)	No	***Based on real-world data on PrEP persistence and UK clinical expert opinion, an assumed at-risk period of no longer than 5 years is deemed reasonable and appropriate for decision making where the purpose of the modelling analysis is to compare use of PrEP modalities.*** **Real-world evidence demonstrates a high rate of discontinuation** The EAG indicate a preference for a model allowing the at-risk period to be varied across a much broader range of values, while the Company's model allowed the at-risk period to vary from one to a maximum of 10 years; treatment costs are applied in both arms for all who remain on prophylactic care during the defined at-risk period. The real-world evidence used to inform persistence to oral PrEP in the economic model demonstrates a high rate of discontinuation (over 40% of people at 12 months) (23). Extrapolation of the real-world persistence data in the economic model leads to a decreasing proportion of individuals on PrEP and an increasing proportion of individuals on no PrEP over time so that in both the TDF/FTC and cabotegravir arms, the proportion of individuals who remain on PrEP after 5 years is 15% or lower. Single periods over which people are at-risk beyond 5 years, in combination with the available data on discontinuation, imply high levels of disengagement with PrEP provision, which are not consistent with data in the UK indicating that the majority of people with an assessed need for PrEP are accessing PrEP. In addition, UK clinical experts indicated that PrEP is mostly used for short-term periods ranging from 6 months to 2 years, while only a small percentage use it for longer durations, corroborating that a 5-year period of elevated risk may be considered as an upper limit and hence conservative. In summary, there are no data to support modelling an extended period of time beyond 5 years of elevated risk and as such receiving associated prophylactic care.

Issue 7: Inappropriateness of "no PrEP" as a Comparator in the model (sections 4.4 and 4.5 of EAR)	No	***The Company consider no PrEP to be an appropriate comparator, as there is no established clinical management, or alternative biomedical HIV prevention for individuals who cannot take oral PrEP but are otherwise eligible for PrEP. This population is quantifiable from UKHSA GUMCAD data (i.e., those with a PrEP need identified who do not initiate or continue PrEP).*** **No PrEP is a valid comparator in this appraisal** The Company consider no PrEP to be an appropriate comparator, and do not believe that it is "beyond the scope of the decision problem" as suggested by the EAG. The NICE final scope states that comparators are "established clinical management including tenofovir disoproxil or alafenamide in combination with emtricitabine or tenofovir alone" and does not explicitly exclude no PrEP as a comparator. For individuals who cannot have oral PrEP, there is no 'established clinical management' or alternative biomedical HIV prevention and as such 'no PrEP' is an appropriate comparator for these individuals. The EAG also state that the population "ineligible for oral PrEP" is poorly defined in the decision problem and "for a no PrEP population to be considered, the characteristics of the population need to be clearly and explicitly outlined" and "sufficiently distinct from the population currently on oral PrEP". However, as discussed in response to key issue 1, the Company's decision problem population is defined as individuals for whom oral PrEP is not appropriate, which includes those who are otherwise eligible for but do not or cannot take oral PrEP for a variety of reasons. These individuals are distinct from individuals who are currently on oral PrEP in the UK. In England, 15% of people who have a PrEP need identified, do not initiate or continue oral PrEP (24). This reflects both an unmet need, and a population of people with a need for HIV prevention that are not accessing or using oral PrEP. This quantifiable "no PrEP" population in the UKHSA GUMCAD data (i.e. those with a PrEP need identified who do not initiate or continue PrEP) alongside continued new HIV acquisitions in England, with 3,805 new HIV diagnoses in England in 2022, demonstrates there are people in England who require HIV prevention who would fall into the category of "no PrEP" (17). Figure 2 describes the population groups considered in the decision problem and the relevant comparators.

Oral PrEP may not be appropriate for all individuals who are eligible for PrEP; this population is captured in the clinical trials, reflected by some participants sub-optimally adhering to oral PrEP

The clinical trials include people who are eligible for PrEP but are not limited to people for whom oral PrEP is appropriate; this is reflected by the adherence levels in the trial, which demonstrated that oral PrEP was not appropriate for every individual (see response to key issue 3 for further details).

Figure 2: Cabotegravir comparators



***The green and orange boxes represent the anticipated positioning of cabotegravir.**
Sources: 1. Sullivan et al, 2023 (6); 2. Calabrese et al, 2020 (7); 3. Coukan et al, 2023 (8); 4. Sidebottom et al, 2018 (9); 5. National AIDS trust (10).
Abbreviations: HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine; UK, United Kingdom.

The Company's updated cost-effectiveness analysis removes the assumption of [redacted] transition onto TDF/FTC for individuals who cannot take oral PrEP (comparison vs no PrEP)

The EAG state that the "[redacted] of patients who stop taking cabotegravir transition to daily oral PrEP undermines arguments on the use of cabotegravir in patients whom oral PrEP is inappropriate and

		the comparison to oral PrEP." As described in response to key issue 9, the modelling of this transition reflects the SmPC recommendation following discontinuation of cabotegravir and the Company has removed this transition in the comparison versus no PrEP, reflecting people who cannot take oral PrEP, in its updated cost-effectiveness analysis.
Issue 8: Inappropriateness of Baseline risk of HIV acquisition (section 4.7.1.1 of EAR)	No	***The Company maintain an HIV incidence of 4.9 HIV acquisitions per 100 person years (PY) to be the most appropriate value; this limits the risk of bias resulting from not capturing those with limited current utilisation of sexual health services (SHS) and is aligned with evidence reporting HIV incidence in a population of individuals at high-risk of HIV acquisition. This value is supported by the results of the ITC.*** The baseline risk of HIV acquisition considered in the Company's economic model reflects the HIV incidence in England and Wales for individuals at high risk of HIV acquisition who are not receiving PrEP. In the BHIVA/BASHH guidelines (3), incidence is reported of 4.9 HIV acquisitions per 100 PY for men who have sex with men who had a rectal bacterial STI in the previous 12 months, and 3.9 HIV acquisitions per 100 PY for men who have sex with men who had a rectal bacterial STI and an HIV test in the previous 12 months. The EAG argue that the latter estimate of 3.9 per 100 PY is more appropriate because the HIV test in the previous year ensures that the HIV acquisition is recent. It is important to recognise that in practice, whilst a negative HIV test at PrEP initiation is required, clinical experts consulted confirmed an additional negative test in the year prior to initiation is not a PrEP eligibility criterion. To avoid creating bias through not capturing those with limited current utilisation of SHS, the Company consider an incidence of 4.9 per 100 PY to be representative of the decision problem population. The estimated background risk of HIV acquisition derived from the ITC for the HPTN 083 population is within a range of [redacted] HIV acquisitions per 100 PY in men who have sex with men). The ITC results support the Company's preferred value to inform the HIV incidence for individuals on no PrEP in the economic model. HIV incidence should also be considered in the context of rising new HIV and STI diagnoses in England. Despite reductions in new HIV acquisitions in previous years, new HIV diagnoses in England are rising alongside large increases in STIs, which may reflect sexual behaviour with increased risk for HIV acquisition. New HIV diagnosis increased by 3% from 3,026 in 2020 to 3,118 in 2021, and by 22% from 3,118 in 2021 to 3,805 in 2022 (17). Additionally, the number of HIV diagnoses first made in England are rising in certain groups including heterosexual men and women

		living in London (14% rise from 284 in 2021 to 325 in 2022) and outside London (11% rise from 586 to 651), gay and bisexual men who have sex with men of Asian (17% from 75 to 88) and mixed or other ethnicity (25% from 71 to 89), and a rise that is particularly steep in women living outside London who were exposed through sex with men (31% from 300 in 2021 to 393 in 2022). This rising trend is mirrored by rising incidence of STIs (25), which may be considered as a proxy for the risk of HIV acquisition (indicator for condomless sex). The diagnosis of new STIs increased among people in England by 23.8% between 2021 and 2022 (392,453 new diagnoses in 2022 compared to 317,022 new diagnoses in 2021) (25). In 2022 there were large increases in the number of new diagnoses of gonorrhoea (50.3%, from 54,961 to 82,592), chlamydia (24.3%, from 160,279 to 199,233) and infectious syphilis (primary, secondary, and early latent stages; 15.2%, from 7,543 to 8,692) compared with 2021. The number of gonorrhoea diagnoses in 2022 is the largest annual number reported since records began, and the number of syphilis diagnoses the largest annual number reported since 1948 (25, 26). The UK government has acknowledged that the UKHSA data on STIs in 2022 is deeply concerning and identified that despite access to PrEP being highly effective in some groups, the focus on men had created inequality with a 26% increase in HIV diagnoses among heterosexual women (27). Finally, the Company does not consider the EAG's scenario testing (using 1.9 per 100 PY) to be appropriate for the decision problem (individuals with a high risk of HIV acquisition). This incidence rate does not represent the population under consideration as they do not have the marker of high risk (recent STI as a proxy for condomless anal sex in the previous 6 months). It is vital to follow the guidelines definition to ensure that the underlying risk is reflective of the population considered in the appraisal.
Issue 9: Transition to TDF/FTC following discontinuation from cabotegravir (section 4.7.1.2 of EAR)	Yes	***The transition from cabotegravir to TDF/FTC in the comparison versus TDF/FTC intends to model the PK tail following discontinuation of cabotegravir as recommended in the SmPC. The Company agree that in comparison versus no PrEP, for individuals who cannot take oral PrEP, 0% of individuals should transition to TDF/FTC after discontinuing cabotegravir. This is reflected in the Company's updated base-case analysis of cabotegravir versus no PrEP.*** In the economic model, the transition from cabotegravir to TDF/FTC represents the use of an alternative PrEP modality (not long-acting) in the PK tail as recommended in the SmPC, "Residual concentrations of cabotegravir may remain in the systemic circulation of individuals for prolonged periods (up to 12 months or longer); therefore, the prolonged release characteristics of Apretude

		injection should be taken into consideration when the medicinal product is discontinued and alternative not long-acting forms of PrEP are taken, as long as or at any time the risk of acquiring HIV is present in the months after discontinuation of Apretude" (2). It is important to distinguish this approach from modelling sequences where alternative longer-term PrEP modalities are considered upon discontinuation of cabotegravir or TDF/FTC. Furthermore, the comparator arm in the economic model should not include cabotegravir as a follow-on medicine if the model is to address this decision problem, which is specifically to assess the cost-effectiveness of the introduction of cabotegravir. Hence, a transition from oral PrEP to cabotegravir would not be appropriate in the oral PrEP comparator arm. In the population of individuals who are sub-optimally adherent to oral PrEP, the model considers that only [redacted] of individuals will receive TDF/FTC in the PK tail and applies a high rate of discontinuation of [redacted] monthly so that only a small proportion of individuals are still on TDF/FTC after 1 year. The Company maintains its original approach, which is in line with the SmPC recommendation of alternative not long-acting forms of PrEP to be taken in the months following discontinuation of cabotegravir. In the population of individuals who cannot take oral PrEP, the company accepts and agrees with the EAG that individuals would not receive TDF/FTC in the PK tail and has provided an updated cost-effectiveness comparison of cabotegravir versus no PrEP.
Issue 10: Adherence to TDF/FTC (section 4.7.1.5 of EAR)	No	***The company has provided evidence that disagrees with the EAG's assumption of equivalent adherence in men who have sex with men and transgender women, and cisgender women populations.*** While the EAG argue for equivalent adherence in men who have sex with men and transgender women, and cisgender women populations, clinical expert opinion and published evidence support that adherence for cisgender women is lower than in men who have sex with men and transgender women (9, 28-30). For example, as noted by Sidebottom et al, both the FEM-PrEP and VOICE trials failed in young African women, and these trials are associated with poor adherence to oral PrEP (24% and 29% of non-seroconvertors, respectively, had detectable TDF) (9, 31, 32). In a global systematic review, the pooled estimate of suboptimal adherence among cisgender women and girls who continued PrEP was 56.1% (95% CI: 44.0, 67.5) (4), and in a pooled analysis of 11 studies

		including 6,296 cisgender women less than 40% achieved high protection through consistently taking at least 4 doses per week with dramatic declines in adherence by Week 96 (28). In addition, cis-gender women have less PrEP options compared with men who have sex with men and transgender women, as they are not able to use TAF/FTC or event-based dosing (3, 33). The EAG's assumption of equal adherence in these populations is not substantiated by any evidence. The company accepts that there is a lack of evidence on adherence to oral PrEP amongst cisgender women in England and Wales. The company would argue that the data from HPTN 084 on adherence in cisgender women outside the UK is a better estimate of adherence of cisgender women in England and Wales than data from a population of men who have sex with men and transgender women in HPTN 083. The Company note that 38% of HIV acquisitions in England in 2022 in cisgender women occurred in women of Black African ethnicity (17). It is also worth noting that 36% of people newly diagnosed with HIV in England in 2022 were previously diagnosed abroad and that in 49% of cases, the region of origin was Africa. Consequently, there are cultural similarities between many cisgender women eligible for PrEP in the UK and the trial population in HPTN 084.
Issue 11: Improved persistence to cabotegravir (section 4.7.1.3 of EAR)	No	***Recently published real-world evidence has been provided that demonstrates a high persistence to cabotegravir, further supporting the assumption of 20% improved persistence versus oral PrEP applied in the economic model.*** **Real-world evidence supports the assumption of improved persistence with cabotegravir** There is real-world evidence demonstrating the high persistence to cabotegravir: • In one study, 93% persistence (7% discontinuation; defined as ≥128 days without a cabotegravir LA injection) was observed over a median of 7 months follow-up (IQR: 4.7 to 9.5) in the OPERA cohort of routine clinical care in the US (34) • In another, 94% persistence (aka: continuation) and no missed injections was reported in the 12-month TRIO cohort of routine clinical care in the US. Among 43 individuals with ≥3 injections, 27 (63%) had all injections after their second on time injection (35). In addition, UK clinical experts we consulted indicated that a 20% persistence advantage over oral PrEP was a reasonable assumption, and further commented that they would expect up to 50% improvement in persistence.

		The EAG's assumption of reduced persistence to cabotegravir versus oral PrEP is misaligned with recently published real-world evidence Recently published evidence (described above) confirms that real-life persistence with cabotegravir is high. Therefore, the Company considers the EAG's scenario of reduced persistence versus oral PrEP to be implausible and not justified. The EAG's rationale for assuming persistence to be lower with cabotegravir than oral PrEP is based on the "significant burden on both individuals and healthcare systems in ensuring on-time injections and the additional inconvenience of injection site reactions (ISRs) to patients." The population considered in the decision problem is individuals for whom oral PrEP is not appropriate. It is implausible to state that people who are receiving a more suitable PrEP modality are less likely to persist than individuals who are receiving a PrEP option that is not meeting their needs. Indeed, recently published evidence demonstrates that providing PrEP modalities that meet peoples' needs improves outcomes, including increased biomedical covered time and reduced HIV incidence (36). The implementation of cabotegravir persistence in the model is likely conservative. It is important to note that in the CS, a 20% increase in persistence was applied to the proportion of people persisting with cabotegravir treatment at six and 12 months. The resulting monthly discontinuation rates are reduced in the first 6 months for cabotegravir compared with oral PrEP, but thereafter are equal across the two arms. Hence, the assumption of increased persistence does not impact the discontinuation rate beyond 6 months. Whilst real-world implementation data for cabotegravir for PrEP is only available for a limited time-period, recently published real-world evidence (described above) demonstrates that persistence to cabotegravir is high and is supportive of a lower probability of discontinuation over this time relative to oral PrEP. It is likely that persistence improvements will be maintained beyond the 6 months post-initiation and so the Company's approach to modelling persistence can be considered conservative. As described in section B.3.3.9 (CS document B), long-acting interventions are commonly associated with improvements in persistence. This is observed with long-acting contraceptives, where matching women's preferred modality increased persistence (82). Clinical experts consulted confirmed they would expect comparable improvement in persistence with long-acting contraceptives and HIV prevention modality.

<table>
<tr>
<td>Issue 12: Disutility associated with living with HIV (section 4.8.1.1 of EAR)</td>
<td>No</td>
<td>
Clinical and methodological arguments presented by the Company strongly disagree with the EAG's decision to inform the HIV disutility with EQ-5D-5L data. The disutility value used by the Company is estimated with EQ-5D-3L in line with the NICE reference case (37).

The EAG have assumed a disutility associated with living with HIV of –0.05 from the 2022 Positive Voice survey results (38). The disutility preferred by the EAG uses the EQ-5D-5L instrument and applies the 5L tariff estimated by Devlin et al, which NICE does not currently recommend (37). Conversely, Miners et al, 2014 (38) preferred by the Company, uses the EQ-5D-3L version of the questionnaire and the NICE recommended UK 3L valuation set.

A study published by Popping et al. (39, 40) analysing the Positive Voices 2017 survey results allows us to compare the distributions per domain between the EQ-5D-5L of the Positive Voice survey and the EQ-5D-3L in Miners et al. (38). The importance of choosing either the EQ-5D-5L or EQ-5D-3L to estimate a disutility can be demonstrated by comparing the absolute differences between the proportion of responses by people living with HIV and the general populations on each of the domains, for each study (Table 5).

For example, in Popping et al., 81% and 72% of the general population and people living with HIV respectively reported no problems with mobility, leading to an absolute difference of 9%. In Miners 2014, the corresponding proportions are 80% and 73%, leading to a difference of 7%. With the exception of the anxiety and depression domain, the absolute differences in domain responses are very similar across the studies. Overall, this suggests that it is the choice of 5L or 3L tariff that is driving the difference in disutility score, not that newer treatments have improved HRQoL.

Table 5: Comparison of disutility values in Popping 2021 and Miners et al, 2014
<table>
<tr><th></th><th colspan="2">No problems (absolute % difference)</th><th colspan="2">Most severe level (absolute % difference)</th></tr>
<tr><th></th><th>Popping</th><th>Miners</th><th>Popping</th><th>Miners</th></tr>
<tr><td>Mobility</td><td>9</td><td>7</td><td>–1</td><td>0</td></tr>
<tr><td>Self-care</td><td>8</td><td>8</td><td>1</td><td>0</td></tr>
<tr><td>Usual act.</td><td>11</td><td>12</td><td>0</td><td>1</td></tr>
<tr><td>Pain</td><td>2</td><td>2</td><td>0</td><td>2</td></tr>
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</table>

		<table><tr><td>Anxiety/dep.</td><td>19</td><td>23</td><td>2</td><td>7</td></tr></table> Note: the values for Popping relate to the 40–60-year age group, which is the closest age match to Miners, 2014. Abbreviations: Dep., depression; act, activities. The two Positive Voices surveys indicate that HRQoL in people living with HIV is lower than the general population and this has not improved between 2017 and 2022; there has been little change in the proportion of people reporting problems across all EQ-5D-5L domains since the original 2017 survey, except for pain and discomfort, which has increased (39). HRQoL scores for people living with HIV in England are largely driven by lower scores in the anxiety/depression domain of the EQ-5D-5L (39, 41, 42), and HIV prevalence in people in contact with mental health services is 2.5 times higher compared with the general population (43). Stigma is associated with higher rates of depression (44).
Issue 13: Starting age of Participants (section 4.7.1.4.1 of EAR)	Yes	***The Company agree with using UK data to inform the median age in the economic model. Using the latest UKSHA data available, the Company consider a revised median age of 31 for men who have sex with men and transgender women, and 29 years for cisgender women in the updated base case analysis.*** The EAG have stated that "the starting age of the cohort should reflect the median starting age of PrEP users in the UK rather than the median age of participants in non-UK trials". The Company agree that UK data may be more appropriate to inform age in the economic analysis and that the UKHSA is the appropriate source. Data from the UKHSA indicate that the median age of those accessing oral PrEP for both men who have sex with men and transgender women, and cisgender women falls within the groups aged 25–34. Assuming a uniform distribution of ages within this age group, the company estimates the median age for men who have sex with men and transgender women is 33.8 years. The corresponding figure for cisgender women is 31.1 years. The Company suggest that the midpoint of this range should align with the cohort age at the midpoint of the 5-year period of elevated risk modelled. Hence, the Company argue that the starting age for cohorts in the model should be 2.5 years less than the median age estimated from the UKHSA data. The Company's base case cost-effectiveness analysis has been updated to reflect a period of elevated risk commencing at age 31 for a cohort of men who have sex with men and transgender women, and 29 for cisgender women.

Issue 14: Duration of assumed aggregate risk period to reflect lifetime risk of sexually acquired HIV acquisition (section 4.7.1.4.2 of EAR)	No	***The Company consider the simplified model structure to be appropriate for decision-making; the model in the CS captures the relevant costs of PrEP and the downstream impacts of HIV acquisition during a period over which people would be eligible for PrEP.*** As discussed in response to key issue 6, extending the risk period to 10 years is not appropriate based on real-world evidence of persistence. Indeed, the model's persistence factor implies that most people who are not living with HIV and could still benefit from PrEP would have already discontinued PrEP and returned to their baseline risk after approximately 3.5 years. This also represents poor coverage of the PrEP programme, with significant periods of high risk over the lifetime not covered by a PrEP intervention. The Company's model captures the relevant costs of PrEP and the downstream impacts of HIV acquisition during a period over which people would be eligible for PrEP. This duration will vary between individuals and no data on the mean duration could be found. The Company remain aligned with the assumptions on the mean duration presented in their original submission. Whilst no direct evidence on the duration is available, the real-world evidence on the rate of discontinuation and the proportion of people with an assessed need for oral PrEP who are accessing oral PrEP would indicate that the mean duration may be shorter than 5 years and is highly unlikely to be longer, which is consistent with clinical expert opinion (as reported in response to key issue 6).
Issue 15: Cabotegravir injection administrative costs (sections 4.9.2 and 4.9.2.1 of EAR)	Yes	***The Company's updated base case analysis considers administration of cabotegravir requires two 30-minute initiation injection appointments, with 20-minute appointments for subsequent injections.*** The EAG's assumption overestimates the cabotegravir long-acting (LA) administration time. In a previous HTA of cabotegravir as treatment for HIV (cabotegravir + rilpivirine), NICE previously considered the assumption of a 15-minute administration time to be acceptable (45), However, real-world evidence from clinical practice is now available to support the administration timings used in the updated model: A UK multi-centre service evaluation of cabotegravir and rilpivirine pathways (SHARE LAI-net) demonstrates appointment length was between 30 to 60 minutes, with an appointment length of ≤40 minutes in 78% (n=7/9) of NHS HIV clinics (note: cabotegravir + rilpivirine requires two injections with rilpivirine requiring cold chain storage) (46).

		[redacted] A lead nurse from a large urban sexual health clinic has advised that for compassionate use of cabotegravir for PrEP a 30-minute appointment would be appropriate; suggesting the injection itself is quick to draw up and administer and considered very similar to giving a treatment for gonorrhoea, which requires a slow plunge of the syringe for around 5-10 seconds. In UK SHS, penicillin antibiotic syphilis injections are intramuscular injections, similar to cabotegravir. The UK syphilis guidelines (BASHH 2015) state that "*all patients should be kept on clinic premises for 15 minutes after receiving the first injection to observe for immediate adverse reactions*" (47). Given all the above information, the Company believe that assuming two initial 30-minute appointments and then subsequent 20-minute appointments for the administration of cabotegravir LA is reasonable.
Issue 16: Drug acquisition and administration (sections 4.9.1 and 4.9.1.1 of EAR)	No	***In line with NICE reference case and final scope (1, 48), the Company consider it is appropriate to model the cabotegravir dosing schedule in line with its marketing authorisation.*** **Cabotegravir dosing schedule** The Company modelled costs associated with cabotegravir acquisition, visits and administration following the dosing schedule as described in the SmPC, in line with the NICE reference case (48), which states "*When we recommend medicines we expect that healthcare professionals will prescribe or advise their use within the terms of their UK marketing authorisations, as described in manufacturers' SmPCs.*" (48). In addition, the NICE final scope states 'Guidance will only be issued in accordance with the marketing authorisation' hence cabotegravir has been modelled this way" (1). The EAG consider an alternative dosing schedule informed by an NHSE submission. At the technical engagement call, the EAG clarified that consulted clinical experts had been using cabotegravir following the clinical trials schedule. The Company acknowledge that in practice, there

		may be some variability in administration date (the SmPC indicates that individuals may be given injections up to 7 days before or after the date of the target injection date (2)); however, best practice is to administer cabotegravir in line with the SmPC recommendation that is, continuation injections administered every 2 months following initiation injections. ***The EAG's approach to model incremental costs that could incur if restarting cabotegravir during the modelled risk-period without considering effects on health outcomes is inappropriate and misaligned with the model structure.*** **Multiple treatment cycles due to discontinuation and restarting over an individual's lifetime** The EAG have noted that the model does not explicitly represent discontinuation and restarting of PrEP over an individual's lifetime, and that this could further impact drug acquisition and administration costs. The EAG propose to illustrate this in the economic model by applying a 5% incremental cost to cabotegravir. Considering the model structure, modelling costs associated with people resuming PrEP is not appropriate without considering effect on health outcomes. The model captures the costs associated with cabotegravir initiation within the first 2 months. In practice, it is plausible that individuals may have several periods of elevated risk throughout a lifetime but there is no evidence reporting the average frequency of these periods throughout individuals' lifetimes. Furthermore, attempting to model multiple risk periods (which may be highly variable amongst individuals) would require a complex modelling approach without improving the clinical validity of the model structure to the decision problem. The model captures the increased initial costs of cabotegravir within the first 2 months and then utilises real-world evidence of persistence to inform the rate of discontinuation of PrEP. Thus, the model captures the full cost and benefits of cabotegravir use over a period of elevated risk. If individuals subsequently restart PrEP, this would be considered as a separate period of risk. The company would argue that the modelled single time period is representative of each period of elevated risk an individual may experience during their lifetime. The company argues that explicit modelling of increased costs and benefits of cabotegravir throughout multiple single time periods is unlikely to be materially different from the cost-effectiveness of cabotegravir than what is presented. As individuals must be HIV negative to be eligible for PrEP, prior periods of risk would not influence the characteristics of the individuals entering the modelled population/decision problem. There is no reason to believe that the costs and benefits do not scale proportionally leaving the ICER essentially

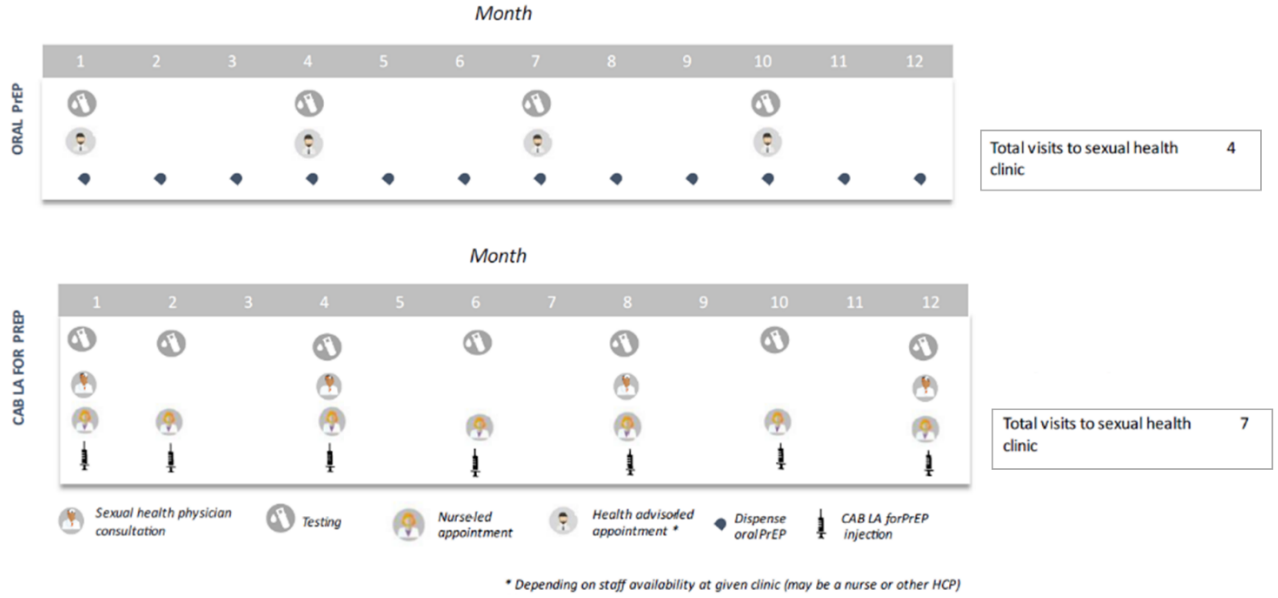
		the same. Indeed, the age distribution of current PrEP users does in fact represent a cross-sectional snapshot of periods of elevated risk across the lifetime of those engaged in the PrEP programme, and we reflect this distribution though using the median age in the model. The EAG's approach to inflating costs associated with cabotegravir acquisition, administration and visits, effectively assumes that patients are stopping and restarting PrEP during the period of persistence indicated by the real-world evidence. This would indicate true discontinuation rates much higher than those used in the model, which are informed by real-world data. The Company consider this approach to be overly simplistic, poorly aligned with the available real-world evidence and not appropriate to evaluate the cost-effectiveness of multiple cycles of cabotegravir use with varying risk patterns over an individual's lifetime.
Other issue identified by NICE technical team: **Implementation of cabotegravir injections** In what clinical settings could/would cabotegravir injections be administered compared to where oral PrEP is currently administered?	No	***Injectable PrEP will be administered in SHS, which have experience in administering intragluteal injections for infectious diseases.*** **Administration setting** We anticipate commissioning policy and service specifications to state that cabotegravir for PrEP (Apretude) injections will be administered in Level 3 SHS in England, which is where oral PrEP is currently administered (49). • Level 3 (specialist) SHS in England provide risk assessment, initiation and clinical follow up and monitoring of HIV PrEP (50). • SHSs providing specialist services in England, including HIV prevention, are commissioned by local authorities (51). **Injectables competency** Level 3 SHSs have extensive experience of administering intramuscular injections, for example injectable antibiotics for syphilis and gonorrhoea (52). In addition, several HCPs have reported similarities with the administration of injectable contraceptives, including both injection administration and setup of regular appointments for the recipient and the clinic (12-weekly appointments for injectable contraception), **Administration process and resource capacity**

Cabotegravir LA is to be administered as a single 3mL intramuscular gluteal injection, with the first two injections administered 1 month apart and subsequent injections administered every 2 months. An optional 1-month oral lead-in and bridging during which cabotegravir 30 mg tablets can be taken orally once daily is also available to assess tolerability (2).

Differences in patient pathway between oral PrEP and cabotegravir

Comparison to the current oral PrEP treatment environment is described in Figure 3.

Figure 3: Current oral PrEP environment



Source: EMA 2009 (53); EMC 2024 (2, 54).
Abbreviations: PrEP, pre-exposure prophylaxis.

Due to the mode and frequency of administration, cabotegravir will require certain changes to the current patient pathway:

		• **Mode of Administration** – compared to oral PrEP options, which are self-administered, cabotegravir LA is an injection administered by an HCP, with nurses likely to be the main staff group administering intramuscular injections. • **Frequency of Administration** – administration for cabotegravir LA will be every 2 months after initiation (2). • **HIV testing (and potentially different type of test)** – prior to receiving PrEP, individuals must have a recently documented negative HIV test. For oral PrEP, HIV testing is recommended using combined HIV antigen/antibody test (plus point of care test if same day initiation is preferable) before initiation and monitoring tests performed every 3 months (3). For cabotegravir LA, individuals must be tested for HIV-1 prior to initiating cabotegravir and at each subsequent injection of cabotegravir. A combined antigen/antibody test as well as an HIV-RNA-based test should both be negative. Prescribers are advised to perform both tests, even if the result of the HIV-RNA-based test will become available after cabotegravir injection (2).

Abbreviations: BHIVA/BASHH, British HIV Association/British Association for Sexual Health and HIV; CI, confidence interval; CS, company submission; EAG, evidence assessment group; GUMCAD, Genitourinary Medicine Clinical Activity Dataset; HCP, healthcare professional; HIV, human immunodeficiency virus; HPTN, HIV Prevention Trials Network; HRQoL, health-related quality of life; HTA, health technology assessment; ICER, incremental cost-effectiveness ratio; IQR, interquartile range; ISR, injection site reaction; ITC, indirect treatment comparison; LA, long acting; NHS, National Health Service; NHSE, National Health Service England; NICE, National Institute for Health and Care Excellence; PICOS, population, intervention, comparison, outcomes, study design; PK, pharmacokinetic; PrEP pre-exposure prophylaxis; PY, person-years; RNA, ribonucleic acid; SHS, sexual health services; SLR, systematic literature review; SmPC, summary of product characteristics; SoC, standard of care; STI, sexually transmitted infection; TDF/FTC, tenofovir disoproxil fumarate with emtricitabine; TFV, tenofovir; UK, United Kingdom; UKHSA, United Kingdom Health Security Agency; US, United States.

Additional issues

Not applicable.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 6: Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Issue 15: Cabotegravir injection administrative costs (sections 4.9.2 and 4.9.2.1 of EAR)	No RNA testing included	Cost of RNA testing included for patients on cabotegravir: 7 tests in Year 1, followed by 6 tests in Year 2+	• ICER vs oral PrEP: £8,844 ○ Change of +58% • ICER vs no PrEP: Dominant (–£43,407; South-East quadrant) ○ Change of +2%
Other issue identified by NICE technical team: **Implementation of cabotegravir injections**	Antigen/antibody HIV testing included 6 tests in Year 1, followed by 4 tests in Year 2+ for patients on cabotegravir	Antigen/antibody HIV testing included at every injection administration for patients on cabotegravir: 7 tests in Year 1, followed by 6 tests in Year 2+	• ICER vs oral PrEP: £5,783 ○ Change of +4% • ICER vs no PrEP: Dominant (–£44,440; South-East Quadrant) ○ Change of 0%
Issue 13: Starting age of Participants (section 4.7.1.4.1 of EAR)	Starting age of 26 for men who have sex with men and transgender women, starting age of 25 for cisgender women	Starting age of 31 for men who have sex with men and transgender women, starting age of 29 for cisgender women	• ICER vs oral PrEP: £7,778 ○ Change of +39% • ICER vs no PrEP: Dominant (–£42,966; South-East quadrant) ○ Change of +3%

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Issue 15: Cabotegravir injection administrative costs (sections 4.9.2 and 4.9.2.1 of EAR)	Administration time of 15 minutes for all administrations of cabotegravir LA	Administration time of 30 minutes for first two administrations of cabotegravir LA, followed by administration time of 20 minutes for all subsequent administrations of cabotegravir LA	• ICER vs oral PrEP: £5,902 ○ Change of +6% • ICER vs no PrEP: Dominant (–£44,400; South-East quadrant) ○ Change of 0%
Issue 9: Transition to TDF/FTC following discontinuation from cabotegravir (section 4.7.1.2 of EAR)	[redacted] of individuals transition to TDF/FTC after discontinuing cabotegravir in the comparison with no PrEP	0% of individuals transition to TDF/FTC after discontinuing cabotegravir in the comparison with no PrEP	• ICER vs oral PrEP: £5,580 ○ Change of 0% • ICER vs no PrEP: Dominant (–£42,872; South-East quadrant) ○ Change of +4%
Company's revised base case following technical engagement	Incremental QALYs vs oral PrEP: [redacted] Incremental QALYs vs no PrEP: [redacted]	Incremental costs vs oral PrEP: [redacted] Incremental costs vs no PrEP: [redacted]	• ICER vs oral PrEP: £11,616 ○ Change of +108% • ICER vs no PrEP: Dominant (–£39,932; South-East quadrant) ○ Change of +10%

Abbreviations: ICER, incremental cost-effectiveness ratio; HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life year; RNA, ribonucleic acid; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

Sensitivity analyses around revised base case

Probabilistic sensitivity analysis

Table 7: PSA base case cost-effectiveness results for cabotegravir versus TDF/FTC

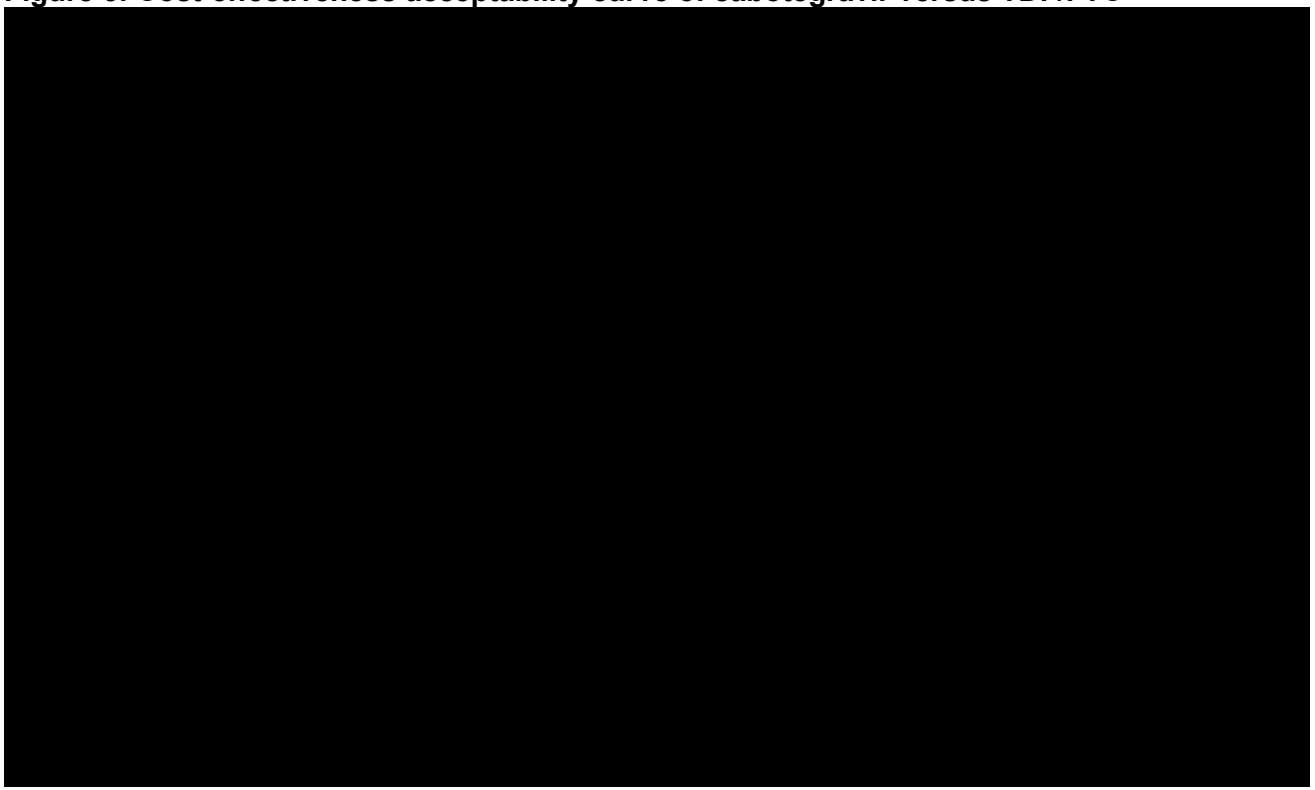
Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus baseline (£/QALY)	Incr. NHB at £20,000 per QALY	Incr. NHB at £30,000 per QALY
TDF/FTC	[redacted]	[redacted]	–	–	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	£10,924	0.09	0.12

Abbreviations: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

Figure 4: Cost-effectiveness scatterplot of cabotegravir versus TDF/FTC

Abbreviations: QALY, quality-adjusted life year; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

Figure 5: Cost-effectiveness acceptability curve of cabotegravir versus TDF/FTC



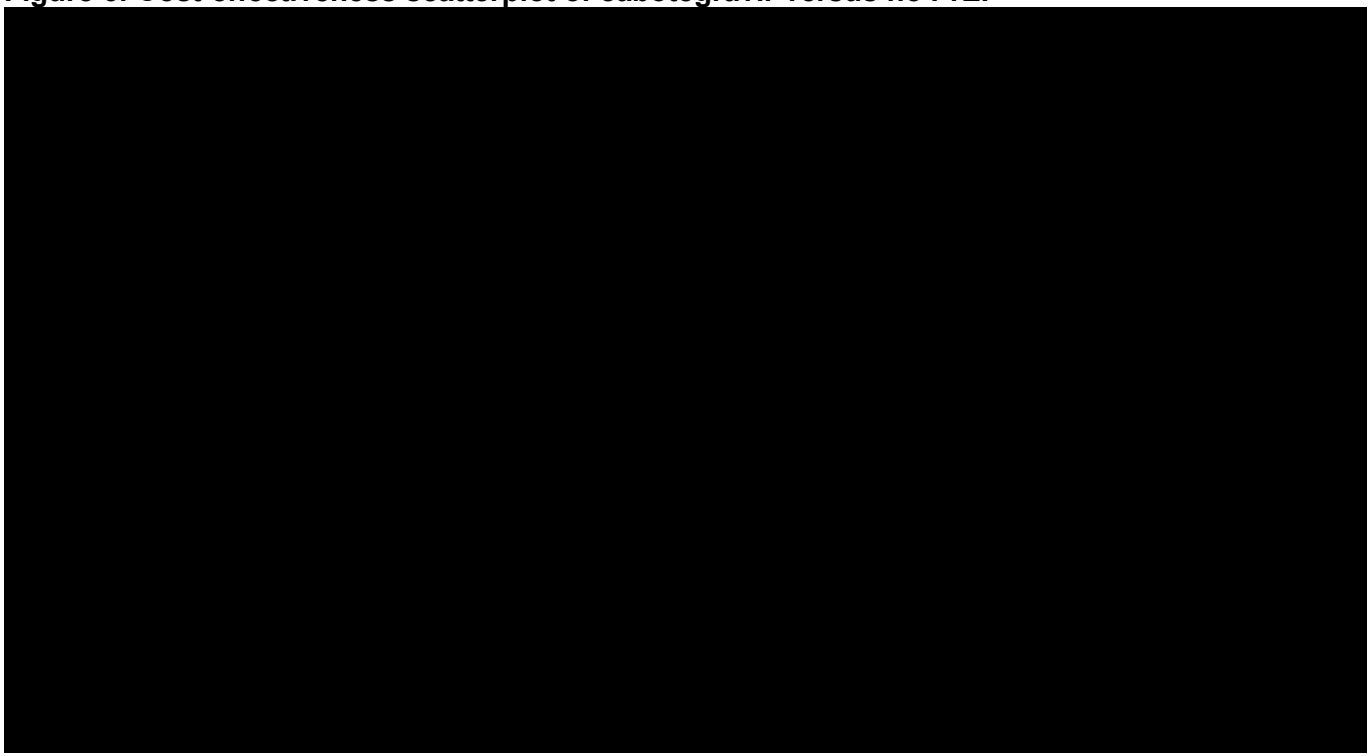
Abbreviations: QALY, quality-adjusted life year; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

Table 8: PSA base case cost-effectiveness results for cabotegravir versus no PrEP

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus baseline (£/QALY)	Incr. NHB at £20,000 per QALY	Incr. NHB at £30,000 per QALY
No PrEP	[redacted]	[redacted]	–	–	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	–£43,616	1.66	1.28

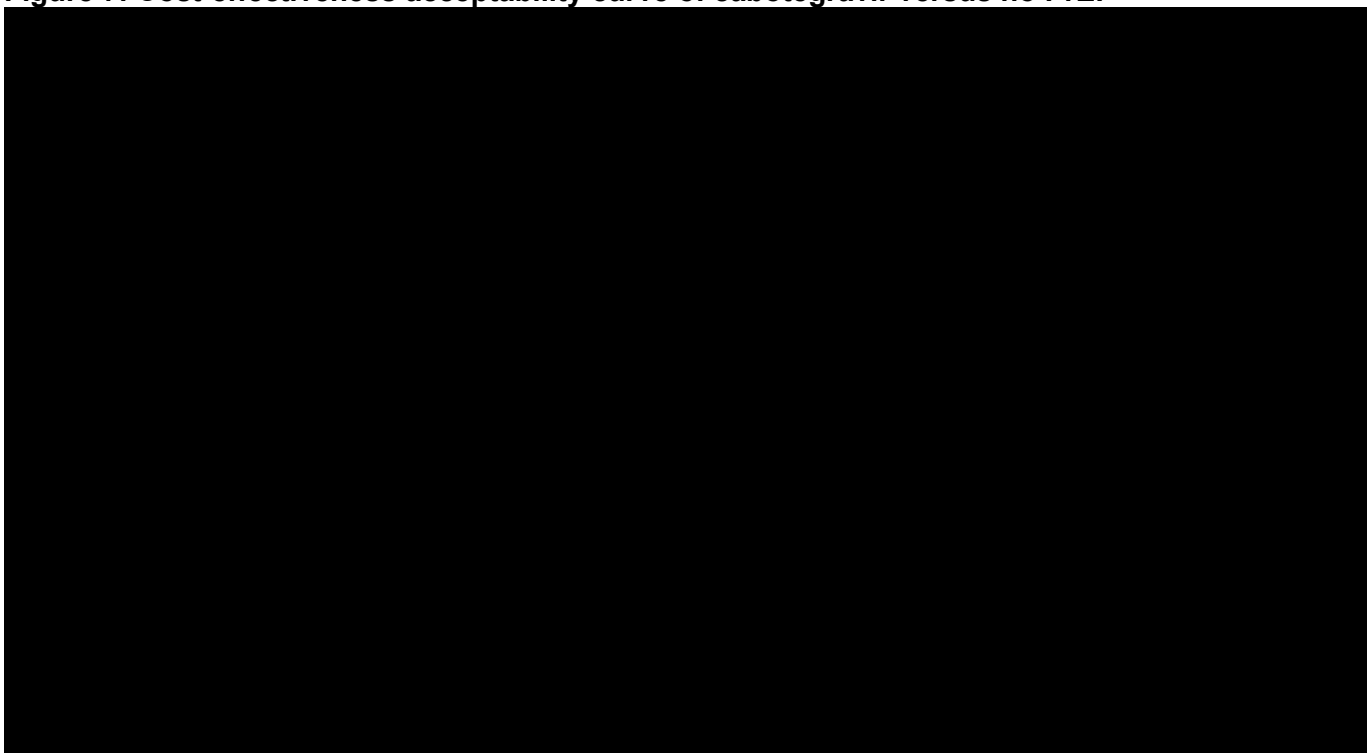
Abbreviations: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; PrEP, pre-exposure prophylaxis; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

Figure 6: Cost-effectiveness scatterplot of cabotegravir versus no PrEP



Abbreviations: PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life year.

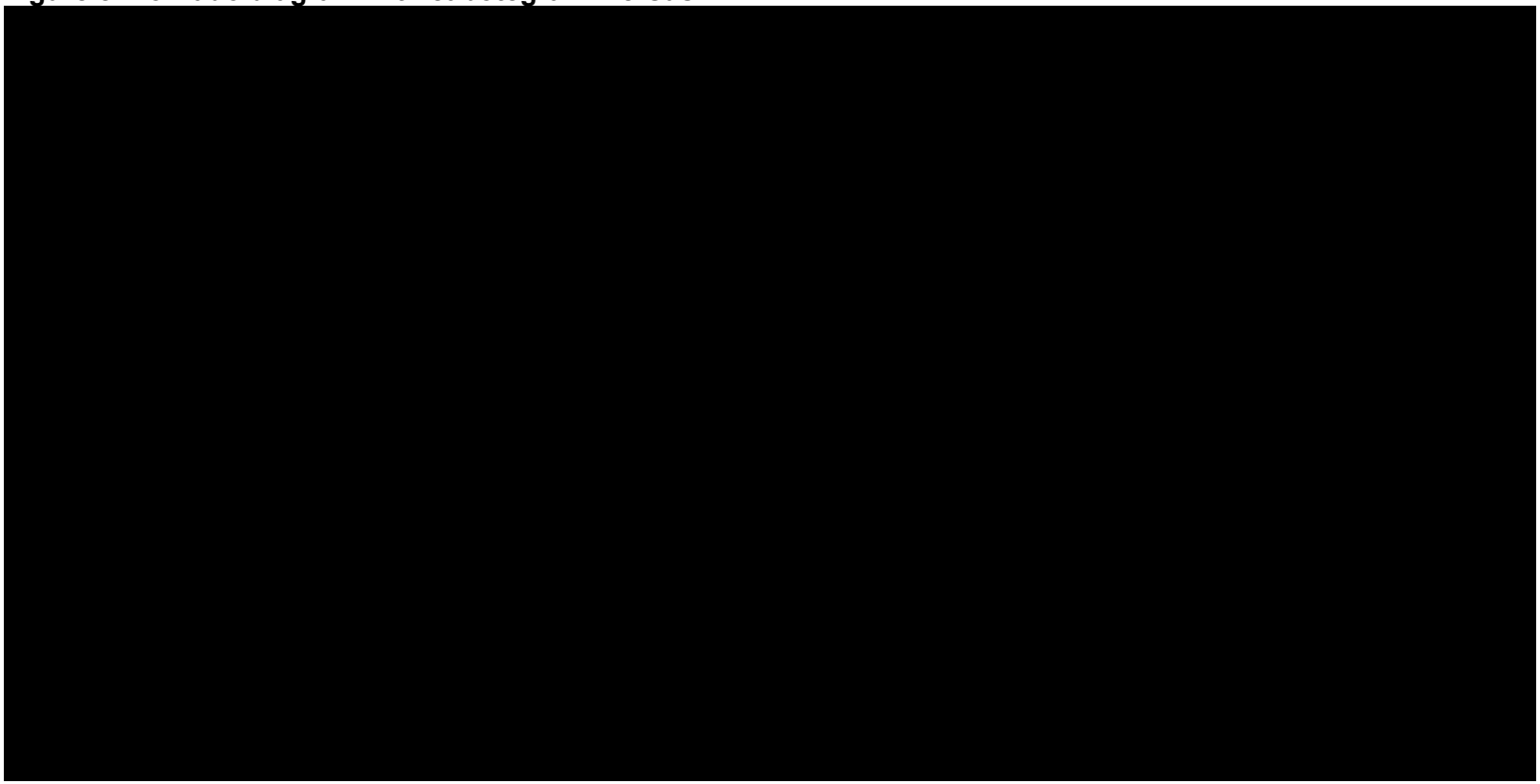
Figure 7: Cost-effectiveness acceptability curve of cabotegravir versus no PrEP



Abbreviations: PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life year.

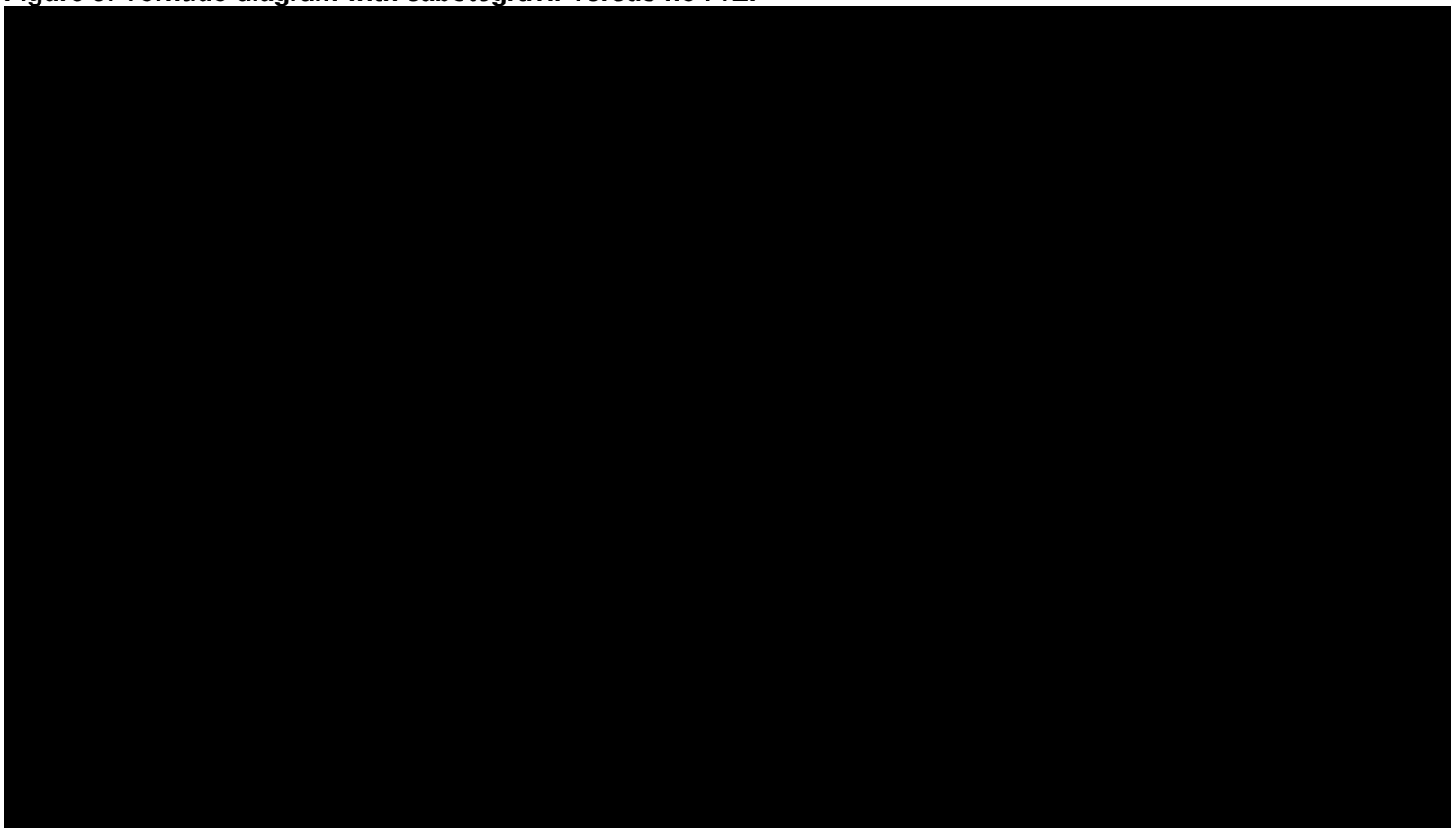
Deterministic sensitivity analysis

Figure 8: Tornado diagram with cabotegravir versus TDF/FTC



Abbreviations: ARV, antiretroviral; cabotegravir LA, cabotegravir long-acting; CI, confidence interval; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; MSM, men who have sex with men; NRTI, nucleoside reverse transcriptase inhibitor; PK, pharmacokinetic; PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life year; SMR, standardised mortality ratio; TDF/FTC, Tenofovir disoproxil fumarate with emtricitabine.

Figure 9: Tornado diagram with cabotegravir versus no PrEP



Abbreviations: ARV, antiretroviral; CI, confidence interval; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; MSM, men who have sex with men; PK, pharmacokinetic; PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life year; SMR, standardised mortality ratio; TDF/FTC, Tenofovir disoproxil fumarate with emtricitabine.

Scenario analysis

Table 9: Probabilistic scenario analysis for cabotegravir compared with TDF/FTC and cabotegravir compared with no PrEP

Scenario	Base case parameter	Value in scenario analysis	Rationale	ICER versus TDF/FTC	ICER versus no PrEP
Base case	–	–	–	£10,924	Dominant (–£43,616; SE quadrant)
Cisgender women population	3.14% of the population	100% of the population	Clarify cost-effectiveness in this part of the population	£14,098	Dominant (–£14,744; SE quadrant)
Men who have sex with men and transgender women population	96.86% of the population	100% of the population		£12,366	Dominant (–£44,560; SE quadrant)
Men who have sex with men and transgender women on TDF/FTC receive TAF/FTC each month	0%	0.0077%	In real-world, a small proportion of men who have sex with men and transgender women may receive TAF/FTC	£11,138	–
Persistence for cabotegravir compared with TDF/FTC	Increased persistence of 20%	Increased persistence of 35%	Increased convenience of cabotegravir is likely to improve persistence but the extent is unknown	Dominant (–£32; SE quadrant)	Dominant (–£43,890; SE quadrant)
Percentage of individuals requiring oral lead in	[redacted]	5%	An oral lead-in is recommended in the SmPC but may not be implemented	£10,103	Dominant (–£44,301; SE quadrant)
	[redacted]	95%		£13,418	Dominant (–£42,802; SE quadrant)

Scenario	Base case parameter	Value in scenario analysis	Rationale	ICER versus TDF/FTC	ICER versus no PrEP
Drug wastage for TDF/FTC	No wastage	Missed TDF/FTC doses are wasted	Wastage is unknown but likely	£10,491	Dominant (–£43,640; SE quadrant)
Discount rate for costs and outcomes	3.5%	1.5%	A value of 1.5% has been advocated for use in public health interventions (55)	Dominant (–£20,646; SE quadrant)	Dominant (–£54,065; SE quadrant)

Abbreviations: PrEP, pre-exposure prophylaxis; SE, South-East; TAF/FTC, tenofovir alafenamide/emtricitabine; TDF/FTC, Tenofovir disoproxil fumarate with emtricitabine; SmPC, summary of product characteristics.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Cabotegravir for preventing HIV-1 in adults and young people [ID6255]

Community expert statement and technical engagement response form

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (EAR) and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about being at risk of, or living with HIV or caring for a person at risk of, or living with HIV. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

A community perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

Community expert statement

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for community experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to the community that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Community expert statement

The deadline for your response is **5pm** on **Monday 10 June.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: At risk of, or living with HIV or caring for a person at risk of, or living with HIV

Table 1 About you, HIV, current treatments and equality

1. Your name	Greg Owen
2. Are you (please tick all that apply)	☒ A person at risk of, or with HIV? ☐ A person with experience of the treatment being evaluated? ☐ A carer of a person at risk of or with HIV? ☒ A community organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Terrence Higgins Trust
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a community expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: **I am the PrEP and HIV Prevention Lead for Terrence Higgins Trust** ☐ I have completed part 2 of the statement **after attending** the expert

	engagement teleconference ☒ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of being at risk of, or living with HIV? **If you are a carer (for someone at risk of, or living with HIV) please share your experience of caring for them**	I am a 44-year-old gay man and therefore had a community risk indicator for HIV acquisition. I was born in July 1980, just one year before the first cases of AIDS (then just a mysterious unknown illness) were reported in the United States. I became aware of a deadly virus that killed gay men at the exact same time that I started to realise that I might be gay and so I have felt hunted since I was about eight years old. As a young teenager, I observed (in the media) people dying of AIDS related illnesses. I started having sex with other men in 1996, when I was 16, just before highly active antiretroviral treatment (HAART) became available. Every sexual encounter was terrifying if I dug deep enough, and was always followed with bouts of fear, panic, guilt, shame, and regret. In 2013, I came out of a seven-year relationship and for the following two years my life was quite chaotic and unstable. I was engaging in activities which put me at an elevated risk of acquiring HIV. These activities included sex work and survival sex/sex for shelter, as I was also homeless. I was heavily involved in sexualised drug use or 'chemsex' and at times was an injecting drug user (crystal meth or methamphetamine and mephedrone, also known as 4-methylmethcathinone, 4-MMC, and 4-methylephedrone). My condom use, at the time, was at best 'patchy' and at worse non-existent. I became aware of Truvada PrEP in 2013. Initially, I was very sceptical of the effectiveness of the drug, the potential adverse side effects of the drug, and I was heavily and negatively influenced by the stigma and slut-shaming levied at gay and bisexual men who used the drug. Further to that, I didn't believe that PrEP was legitimate or worked because I presumed that if a drug existed which stopped

	people getting HIV at almost 100% biological effectiveness, then we would all know about it. That it would have made mainstream media headlines and that it would have been championed by government, charities, and community. In August 2015, I eventually managed to get hold of some Truvada from a HIV positive friend who had changed his medication. I was excited to begin taking PrEP. When I attended a sexual health clinic in London for an HIV test to confirm that I was still HIV negative (I had tested HIV negative earlier in that year), my test result was reactive, and it was then confirmed as an HIV positive diagnosis. I have been lucky. I have navigated my diagnosis and the reality of living with HIV relatively well. But I have quite a lot of privilege. I'm a white, cis man, with a supportive family, and I belong to a community that is no stranger to this condition. I don't belong to a religion or have a job that would penalise or persecute me for being HIV positive. That said, it has not been without its challenges and emotional taxes. One of the first things that hit me on the day of my diagnosis, was that I would never be able to have biological children of my own. I was diagnosed before the U=U (undetectable = untransmittable) message was conceived. The Partner 1 study (the study of serodiscordant couples, which proved that a person living with HIV who has an undetectable viral load cannot transmit the virus to their sexual partners) had only released some preliminary data at that point and would not publish results until 2016. As I was living in London at the time and my family was back home in Belfast, it was heartbreaking for me, and one of the most difficult things I have had to do, to call one of my younger brothers (who is also gay) and to ask him to go visit my mum and dad and to tell them I was HIV positive. I didn't want them to find out through word of mouth or social media.

	In those first few weeks and months I was terrified if I cut myself and started bleeding. I was working in a bar in Soho at the time and would often nick or scratch my fingers, it happens in that line of work. I felt like a biological hazard to the people around me. None of whom knew about my diagnosis. I deliberately do not share my HIV status with dentists because I have heard some horror stories of how people have been treated by dentists and GPs who are not aware of the current evidence around what being undetectable means. My barber in London knows that I am HIV positive as he follows my work on PrEP on social media, and when I get cut during a wet shave it has the potential to send me into a panic and leave me with a lingering anxiety and paranoia for the rest of the day, even though I know there is no risk of me transmitting HIV this way. There are certain parts of the world that I cannot travel to because my HIV medication is not permitted there. There are parts of the world where being HIV positive can mean being incarcerated. I sometimes struggle with my mental health but not because of my HIV status. I generally struggle with anxiety, occasional low mood, and burnout. When these experiences become severe and I cannot manage them, my adherence to my daily medication is impacted and I have missed doses of medication. Sometimes a couple of days. Sometimes a week. But thankfully, not often. I know friends who struggle with this more than me. I have recently relocated to Belfast in Northern Ireland, and I don't feel comfortable or able to share my HIV status here. There is still some animosity towards the LGBT+ community from certain parts of the general public here. The Democratic Unionist Party (DUP) still actively campaign against our rights. I would only leave myself more vulnerable by being open my HIV positive status. I have friends in

	Belfast who live openly with HIV, and they have received terrible abuse and even death threats. I also worry about what will happen when I get older and potentially need additional support with activities of daily living or if I need care. I worry how I'll be treated and what my care will look like.
7a. What do you think of the current prevention methods, treatments and care available for HIV on the NHS? **7b. How do your views on these current prevention methods and treatments compare to those of other people that you may be aware of?**	I think the current provision of standard oral PrEP (generic Truvada or TD/FTC) works well for the majority of people who use it i.e. gay, bisexual, and other men who have sex with men (GBMSM). The concern is that not everyone who could benefit from taking PrEP can access it. Anecdotally, I get reports of people who cannot get a PrEP appointment at a sexual health clinic – for PrEP initiation and also for continuation ie prescription refills. Many people are still self-sourcing PrEP online from overseas because of this. Some people who were using NHS PrEP have reverted to self-sourcing and subsequently self-managing their ongoing monitoring. It was encouraging to see the newer Descovy PrEP (emtricitabine, tenofovir alafenamide fumarate or TAF PrEP), licenced in spring 2023. However, systems issues and barriers with reimbursement and over-labelling meant the drug did not reach those who needed it until spring 2024. It must be stated explicitly that the vast majority of PrEP users are gay, bisexual and other men who have sex with men. Cis women who have sex with men are not currently using PrEP in significant numbers. Studies of oral PrEP in women have returned results which show that daily oral PrEP is not appealing to women and that adherence is low. PrEP is only available from level 3 sexual health clinics, and this is undoubtably a barrier for certain group of people and individuals. So, explicitly, I must state that PrEP options and provision for women and other people who are not

	men who have sex with men, is extremely lacking. Currently, we are not giving these people what they want, the way they want it, and so they are not using it. In my own experience, I cannot fault the HIV care I have received but I was fortunate to be able to attend 56 Dean Street, in London, which is one of Europe's busiest and best sexual health and HIV clinics. I value the standard of care that I receive there so much that I have not transferred my HIV care to the local GUM clinic in Belfast. Instead, I travel to London every six months for my HIV appointments and to collect my HIV treatment. Unfortunately, HIV care, as with HIV prevention/PrEP is not the same quality in every part of the UK. Those in more rural areas often experience poorer service and fewer options. The views I have expressed are shared by my colleagues in the HIV sector, people living with HIV, and PrEP users. There is a consensus that this is an accurate account of HIV treatment and HIV prevention in the UK in 2024.
8. If there are disadvantages for people of current NHS prevention methods and treatments for HIV (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Adherence/pill burden Access to appointments Users face demands on time and money – for some this is prohibitive People with renal issues People with bone mineral density issues People who cannot swallow pills People who cannot be in possession of drug People who are experiencing coercive control or unable to negotiate their boundaries PrEP users who experience stomach upset while taking oral PrEP
9a. If there are advantages of cabotegravir over current prevention methods and treatments on the NHS please describe these. For example, the effect on	Daily pill burden eliminated as evidenced in CAB-LA for HIV treatment. Will have benefits for adherence and for mental health - for prevention will have benefits for adherence and discretion

your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does cabotegravir help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	It's difficult to differentiate these benefits on an oral PrEP vs CAB-LA basis. The crux is that both technologies, when used correctly, offer the same end point benefits i.e. the user does not acquire HIV and remains HIV negative. It's more a case of how do we get there and which route is best – for who, and why, and how do we facilitate that. For example a cis gay man who is satisfied with taking daily oral PrEP (or on-demand PrEP when he needs it), who doesn't struggle with adherence, who isn't stigmatised for taking oral PrEP, who is able to navigate this option well and without issue, will obtain the same benefits as pertains to quality of life, ability to continue work, education, self-care, and care for others as a cis woman at parity of risk, who prefers or will only consider using a long-acting injectable PrEP. I acknowledge this is a rather simplified example. I also acknowledge that the evidence does not yet exist to support acceptability of CAB-LA PrEP in key populations in the UK. However, we do have evidence that women and other people outside of the GBMSM population are underserved, currently and historically.
10. If there are disadvantages of cabotegravir over current prevention methods and treatments on the NHS please describe these. For example, are there any risks with cabotegravir? If you are concerned about any potential side effects you have heard about, please describe them and explain why	The tail on CAB-LA could be considered a disadvantage for some users. The requirement to continue on oral PrEP for 12 months upon cessation of CAB-LA will be challenging for some people. Current guidelines for TD/FTC require a maximum of only 7 days of daily dosing and as few as 2 days of daily dosing for GBMSM and other people assigned male at birth. The soon to be published (for public consultation) updated BASHH BHIVA PrEP guidelines will advise the same dosing for TAF/FTC. Incorrect injection technique by healthcare professionals, leading to subtherapeutic drug levels is a slight concern. The requirement to visit clinic every two months will be a disadvantage for some users. Currently, PrEP users (in many places in the UK) only need to visit clinic

	every six months and can use self-sampling for their STI and HIV testing on alternate quarters. Self-sampling is not currently provided for renal blood tests.
11. Are there any groups of people who might benefit more from cabotegravir or any who may benefit less? If so, please describe them and explain why Consider, for example, if people also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	I have nothing further to add, beyond what I have already submitted on behalf of Terrence Higgins Trust.
12. Are there any potential equality issues that should be taken into account when considering HIV and cabotegravir? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	I have nothing further to add, beyond what I have already submitted on behalf of Terrence Higgins Trust.
13. Are there any other issues that you would like the committee to consider?	

Part 2: Technical engagement questions for community experts

Issues arising from technical engagement

The issues raised in the EAR are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a community perspective would be most relevant and valuable. If you think an issue that is important to the community has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the community organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR, the community organisation responses will also be considered by the committee.

Table 2 Issues arising from technical engagement

The population is narrower than the decision problem (section 2.3 of EAR)	Nothing to add
Generalisability of the HPTN population (section 3.5.1.1 of EAR)	Nothing to add
Inclusion of studies in the ITC that were conducted in populations different from the population of interest as specified	Nothing to add

Community expert statement

in the scope (section 3.4.1 of EAR)	
Inclusion of studies in CS ITC that does not meet the specified population of interest as described in the NICE scope (section 3.5 of EAR)	Nothing to add
CS ITC analyses did not account for measurement error in adherence levels in the meta-regression of treatment effect on adherence to CAB-LA. (section 3.4.1 of EAR)	Nothing to add
Restricting treatment costs to period of heightened risk (assumed 5-years in the CS base-case) over a life-time risk capping the treatment costs which could favour CAB-LA in cost-effectiveness (section 4.3 of EAR)	Nothing to add
Inappropriateness of the no PrEP as a Comparator in the	Nothing to add

Community expert statement

model (sections 4.4 and 4.5 of EAR)	
Inappropriateness of Baseline risk of HIV acquisition (section 4.7.1.1 of EAR)	Nothing to add
Transition to TDF/FTC following discontinuation from cabotegravir (section 4.7.1.2 of EAR)	Nothing to add
Adherence to TDF/FTC (section 4.7.1.5 of EAR)	Nothing to add
Improved persistence to cabotegravir (section 4.7.1.3 of EAR) We consider community perspectives may particularly help to address this issue Would you expect there to be higher or lower persistence for individuals taking cabotegravir injections compared to oral PrEP?	In the absence of evidence, I'm not sure what more I can add to this. It is impossible to offer much context here. My only thought (for women and other people who can become pregnant) is to draw comparisons and potential for service integration with long-acting injectable hormonal contraception, which lasts 8 to 13 weeks. What does persistence look like with this technology? How often do ISRs lead to cessation of treatment? Can we draw comparisons with CAB-LA? For GBMSM, I think I would be inclined to agree that a 60-minute appointment every two months is much less appealing than a 20–30-minute clinic visit every 6 months which might lead to lower persistence or reverting back to oral PrEP but I can't offer a confident opinion. I would expect this question will become more pertinent when a 6-monthly injectable PrEP is licenced.

	But for women and other people at risk of HIV who do not 'want' to take daily oral PrEP, CAB-LA every 2 months might be acceptable.
Disutility for HIV infection (section 4.8.1.1 of EAR) We consider community perspectives may particularly help to address this issue What is your experience of the quality of life of people living with HIV?	This point is complex and deeply nuanced. As mentioned in question 6 above 'I have been lucky that I have navigated my diagnosis and the reality of living with HIV relatively well. But I have quite a lot of privilege. I am a white, cis man, with a supportive family, and I belong to a community that is no stranger to this condition. I don't belong to a religion or have a job that would penalise or persecute me for being HIV positive.' But for other people, an HIV positive diagnosis can be devastating and have catastrophic effects on their life, relationships, and general wellbeing. I have friends who have not fared so well. An close friend of mine developed serious health issues shortly after acquiring HIV and almost lost his life on 2 occasions. In 2014, a friend and former colleague died by suicide shortly after receiving a HIV positive diagnosis. There is still stigma attached to living with HIV, even for GBMSM. Those of us from that community who are HIV positive are a minority within a minority, but, within a minority that has comparatively high levels of HIV awareness and literacy. Alongside a legacy of visible activism and leadership. This is not the same for everyone. Some cisgender women living with HIV who I speak with report a very different experience, where they find being minoritised and marginalised due to their HIV status to be extremely taxing – emotionally and mentally. They also express feelings of loneliness and being overlooked or 'forgotten about'. I'm aware that the appraisal has already received data from the Positive Voices surveys, so I won't duplicate information. The communities most affected by and vulnerable to HIV are communities which are already minoritised. At-risk individuals are often marginalised, disadvantaged, or discriminated against because of parts of their identity or behaviours. Subsequently acquiring HIV can further compound these issues further.

	People living with HIV are more likely to experience poor mental health, substance misuse, unemployment, homelessness, and loneliness.
Starting age of Participants (section 4.7.1.4.1 of EAR)	Nothing to add
Duration of assumed aggregate risk period to reflect lifetime risk of sexually acquired HIV acquisition (section 4.7.1.4.2 of EAR)	Nothing to add
Cabotegravir injection administrative costs (sections 4.9.2 and 4.9.2.1 of EAR)	Nothing to add
Drug acquisition and administration (sections 4.9.1 and 4.9.1.1 of EAR)	Nothing to add
Other issue identified by NICE technical team: **Implementation of cabotegravir injections** In what clinical settings could/would	As mentioned in the community organisation submission that I drafted on behalf of Terrence Higgins Trust, I would expect CAB-LA to be made available in level 3 sexual health clinics (as current oral PrEP is). However, I would stress that limiting CAB-LA to that setting alone would be incredibly counterproductive. If we wish to diversify the type of people who use PrEP, it is imperative that we diversify access points i.e. other clinical settings and integration with other services.

cabotegravir injections be administered compared to where oral PrEP is currently administered?	
Are there any important issues that have been missed in EAR?	Not that I have noticed

Abbreviations: CAB-LA, cabotegravir injections; CS, company submission; HIV, human immunodeficiency virus; ITC, indirect treatment comparison; PrEP pre-exposure prophylaxis; TDF/FTC, tenofovir disoproxil fumarate with emtricitabine (oral PrEP)

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- CAB-LA will be a niche intervention
- I would not recommend broad access as most current PrEP users find oral PrEP highly acceptable
- This technology has the potential to increase the diversity of PrEP users
- People who are not from the LGBT community can often face more difficult experiences living with HIV
- CAB-LA might be the only PrEP option which appeals to women and other people (who are not GBMSM)

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Cabotegravir for preventing HIV-1 in adults and young people [ID6255]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **Monday 10 June.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Preventing/treating HIV and current prevention/treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Rachael Jones
2. Name of organisation	NHSE HIV CRG Clinical Member and Consultant Physician at Chelsea and Westminster NHS Foundation Trust
3. Job title or position	Consultant Physician
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the prevention/treatment of people with HIV? ☐ A specialist in the clinical evidence base for HIV or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have	☐ Yes

anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil
8. What is the main aim of treatment for HIV? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The main aim of treatment for HIV is to control viral replication and prevent HIV morbidity and mortality. HIV prevention therapies are designed to protect the user from HIV acquisition.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease	Non-inferiority or superior efficacy in reducing HIV transmission/acquisition in well executed, randomised controlled studies demonstrate a significant treatment/intervention response to me. Ideally, HIV Pre-exposure prophylaxis therapies would be suitably efficacious to protect fully against HIV acquisition in diverse populations. Cabotegravir was shown to be safe and highly effective among cisgender women, cisgender men who have sex with men, and transgender women who have sex with men in two randomized controlled trials, HPTN 083 and HPTN 084. These studies found that use of cabotegravir resulted in a 66% (083) and 88% (084) relative reduction in HIV risk compared with oral PrEP, where adherence to daily oral medication may have been suboptimal. Subsequent real world data (RWD) have also highlighted cabotegravir's success in preventing HIV acquisition outside of the trial setting. Furthermore, studies have shown a marked reduction in stigma and PrEP anxiety in individuals using injectable PrEP

activity by a certain amount)	therapy with the vast majority of participants in the HPTN studies opting to continue, or switch to injectable therapy on trial cessation. Pregnancy data are also reassuring in that dosing levels do not need to be altered and there is no increase in negative outcomes. Adverse events occurred at a low level in the studies, the main issue being reported relating to injection site reactions (ISR), however, the majority of cabotegravir users have reported injectable therapy to be acceptable and feasible, fitting in to their everyday life. Reports from clinicians state that concerns regarding cabotegravir delivery were abated within four months.
10. In your view, is there an unmet need for patients and healthcare professionals in people at risk of, or with HIV?	In my view, there is a major issue in the UK regarding PrEP awareness. Key populations at greatest risk of HIV acquisition have little or no knowledge of PrEP or its availability. The recent UKHSA data (2022) detailing PrEP using populations vs those newly diagnosed with HIV imply that we are not doing enough to target those most at risk, even when allowing for the proportion of individuals who may have acquired HIV abroad. UKHSA figures show that in 2022, there were 86k PrEP users of whom 68% identified as white, 1.8% black African, 84% gay or bisexual men who have sex with men (GBMSM), 4% heterosexual. In contrast, of the 4040 individuals newly diagnosed with HIV, 34% identified as white, 28% black African. Only 29% were GBMSM and 28% heterosexual women. As with contraception, it is well evidenced that a plethora of options leads to greater uptake of prevention strategies. As detailed in other responses within this submission, multiple studies have demonstrated that England's standard of care PrEP therapy (emtricitabine and tenofovir disoproxil or F/TDF) is suitable for the majority of PrEP users. However, it is estimated that approximately 1-2% of individuals will require an alternative to F/TDF for reasons such as renal or bone complications, co-morbidities or intolerance. A proportion of these individuals will be able to use second-line therapy (emtricitabine and tenofovir alafenamide or F/TAF-as per the NHSE HIV PrEP policy). F/TAF has not been studied in cis-women, and while future guidelines may support its use in this population, data are lacking. Both F/TDF and F/TAF are oral medications and hence for individuals who struggle with tenofovir toxicity, swallowing, stigma, or for those where there may be confidentiality issues e.g. those living in hostels, prisons or shared accommodation, a long-acting, injectable preparation is required. In general, oral PrEP requires a high level of adherence to be effective and real-world evidence suggests this level of adherence is achieved by only a fraction of PrEP users. [redacted]

	[redacted]. A non-oral, long-acting solution would be ideal for those struggling with adherence or PrEP persistence.
11. How is HIV currently prevented/treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	HIV is treated using combination antiretroviral therapy. HIV acquisition is prevented via a variety of health prevention strategies including barrier methods, treatment as prevention, HIV pre and post-exposure prophylaxis. The main guidelines used by England's clinicians are: BHIVA/BASHH Guidelines on the use of HIV PrEP https://www.bhiva.org/PrEP-guidelines • Please note that these have been updated and are currently under review NHS England Commissioning policy: Reimbursement for the use of generic and second line drugs for pre exposure prophylaxis (PrEP) for the prevention of HIV https://www.england.nhs.uk/publication/reimbursement-for-the-use-of-generic-drugs-for-pre-exposure-prophylaxisprep-for-the-prevention-of-hiv/ The pathway of care is well-defined and there are little differences in opinion across providers with regard to treatment decisions. PrEP services are provided by Local Authority commissioned Level 3 sexual health services in line with BHIVA/BASHH guidelines. The drug costs are reimbursed via NHSE. A service user will be identified as being at risk of HIV acquisition and PrEP recommended at which point a shared decision making process will be undertaken. As detailed above, first line therapy is oral F/TDF which can be taken daily or as an event-based strategy. For those in whom F/TDF is not appropriate, following discussion in a dedicated multi-disciplinary meeting, the second line therapy of oral F/TAF may be recommended. Given this is a high cost drug, the Blueteq system is used.

[redacted]

Cabotegravir is the first available parenteral PrEP option. As detailed in the evidence sections, this agent has been well studied in key populations at high risk of HIV acquisition.

Given its high cost, it is likely that CAB-LA would require 'sign-off' from a dedicated MDT. Level 3 Providers have already formed networks in order to deliver these MDTs to support F/TAF PrEP access.

Currently, individuals prescribed oral PrEP undergo routine screening and are provided with a 3-6 month oral PrEP supply, often under a patient group directive (PGD). At three monthly intervals, PrEP users are asked to undergo sexual health screening, adherence and general health review and HIV antibody/antigen testing to ensure HIV has not been acquired. If a person acquires HIV while taking PrEP, they are at risk of driving resistance in the virus. In most centres, the standard PrEP user would not be added to a recall system, they would be asked to rebook (at their convenience) within 3-6 months.

The cabotegravir pathway is different.

If deemed eligible for cabotegravir PrEP, following appropriate baseline screening, the service user would be offered an cabotegravir tablet oral lead in (OLI) for one month or the option to commence CAB-LA injectables immediately.

Cabotegravir is administered as an intramuscular injectable, with the first two injections administered four weeks apart, followed thereafter by an injection every eight weeks or two months*. Staff will need to be competent in giving the injection. CAB-LA users will need to remain in clinic for monitoring post-injection. Many sexual health providers will be unfamiliar with cabotegravir administration and hence senior clinical involvement will be required.

*it should be noted that in the HPTN studies, doses were given every eight weeks and guidelines will likely reflect this, however, the manufacturers are clear that dosing can be every two months for simplicity.

	Furthermore, there may be issues with CAB-LA access for providers who are not linked to NHS acute Trusts/HIV centres e.g. CLCH. As is the case with F/TAF, shared care agreements and Blueteq access may be required. Blueteq is not currently available within non-NHS centres. Some services will not have an on-site pharmacy and/or may need to access CAB-LA from NHS Trusts via a shared care agreement leading to potential delays in commencing CAB-LA. At each CAB-LA injection, an HIV antigen/antibody test should be taken, along with an HIV RNA viral load. Level 3 sexual health providers do not routinely request HIV RNA viral load tests other than in exceptional circumstances, hence, this represents a change to the pathway which has significant financial impact. Some providers will need to design a viral load testing process. This is also a relatively expensive test (not covered within the existing PrEP tariff or block contracts) and hence adds a financial burden to CAB delivery. Despite rumours, there is no dedicated local authority PrEP grant which might be used to support enhanced PrEP delivery. There is a seven day window period on either side of the follow-up CAB-LA injection date. Clinics will need to set up a reliable recall system in order to ensure future attendance with a mechanism for flagging if a PrEP user has been lost-to-follow-up. This will represent a further financial burden to clinics at a time when workforce challenges are common place and services are already stretched. It is imperative that injections are given on time as CAB-LA has a long half-life and for one year after CAB-LA cessation, the CAB-LA user must be followed with three monthly HIV RNA viral load testing/HIV Ag/Ab screening and an alternative protection against HIV acquisition must be employed. Should a person acquire HIV with low level CAB-LA in their system, there is a risk of HIV drug resistance which may limit future HIV therapy options.
12. Will the technology be used (or is it already used) in the same	Please see the response to qn 11 for more detail. CAB-LA PrEP will have a significant impact on healthcare resource. The user will need to be reviewed, undergo blood tests and a sexual health screen and have the injection administered. If this takes 45 minutes, this means that one PrEP user will have been seen rather than three users on standard of care PrEP.

way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Given the complexity, CAB-LA PrEP should be delivered via level 3 sexual health providers who are well skilled to discuss PrEP options, undertake and interpret the relevant tests, address other sexual health needs, provide the injection and instigate recall procedures. As detailed above, major investment is required. I would suggest: - A complex PrEP tariff for those services reimbursed via tariff - A PrEP support grant for those services under block contract - Training of staff re injectable CAB-LA data - Training of staff to administer the injection - Funding for the equipment and cost of HIV viral load testing - Funding for adequate recall systems I would also suggest discussion with the submitting company re: possible financial support for the HIV RNA viral load screening test and dedicated staff training packages.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	I do expect CAB-LA to provide clinically meaningful benefits compared with current care given the findings from the studies and RWD. Using the contraception analogy, CAB-LA availability would increase PrEP uptake in key populations reducing HIV rates. We know that most PrEP failure is linked with poor adherence, injectable therapy (with good recall systems) should thus reduce this risk.

• Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Simplistically, given the superiority of CAB-LA with respect to preventing HIV acquisition, CAB-LA should increase length of life more than the current care given the unacceptable high rates of late HIV diagnosis which we continue to observe in the UK. Multiple studies and modelling data imply that CAB-LA use results in fewer QALYs lost than oral PrEP.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	As per the UKHSA data from 2022, there are specific populations at greater risk of HIV acquisition. Although future guidelines may support its use, F/TAF PrEP has not been approved in non-GBMSM/trans women populations and hence CAB-LA may be improve options for these key populations in whom data are lacking. Given its long-acting nature it is likely to be more beneficial in individuals with adherence, stigma, swallowing, absorption, confidentiality challenges. Furthermore, there are a small proportion of individuals in whom tenofovir products are contra-indicated where an alternative PrEP agent is necessary. It may be less effective in truly needlephobic people or those who struggle with routine appointments. It should be avoided in those co-prescribed certain anticonvulsants and antimycobacterial agents due to drug interactions. As with all intramuscular preparations, there may be some necessary some challenges in individuals on anticoagulant therapy.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical	Please see question 11 which outlines the challenges in CAB delivery compared with current care.

implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Given the likely cost of drug, it is likely that a multidisciplinary review meeting will be required for sign off. The Blueteq process is used for F/TAF, presumably this will be similar for CAB-LA. Please see the response to question 11 for more detail re starting and stopping CAB-LA and the extra tests required, particularly on cessation. People who acquire HIV while prescribed CAB-LA will need to be reviewed and managed on an individualised basis depending on the outcome of results.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes, studies have shown reduction in stigma and anxiety on switching to CAB which is unlikely to be captured in QALY calculations. Pregnancy related data are also not captured in the QALY work. The QALYs do not demonstrate acceptability or feasibility of CAB among service users or clinicians.

• Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in	Given the knowledge that most PrEP failures are driven by poor adherence to oral agents, CAB-LA does represent a step-change in the management of HIV prevention. A second injectable PrEP option is also showing great success in clinical studies and these modalities are likely to represent the future of PrEP delivery. As detailed above, CAB-LA addresses underserved populations having been trialled in a wide demographic. There are data in pregnancy, it will support individuals struggling with adherence to or absorption of oral meds, stigma, anxiety, confidentiality and swallowing issues. In individual in whom tenofovir based PrEP is not appropriate, there are a dearth of PrEP options currently.

the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	As detailed in the studies, the main CAB-LA related adverse events are injection site reactions, however, these do not appear to fuel non-adherence and on cessation of the studies, the majority of trial participants opted to remain on, or switch to, CAB-LA. Other side-effects were reported at low levels and not at greater rates than standard of care PrEP. The need to monitor CAB_LA users for up to one year post-cessation may prove challenging in the real world setting.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they	None of the clinical studies were performed in the UK but the key populations within the studies reflect the cohorts most at risk of HIV acquisition in northern Europe. It is more difficult to extrapolate the RWD from the USA/southern Africa settings given our differing healthcare structures. The most important outcomes for me are: -superiority over standard of care PrEP in reducing HIV acquisitions seen in the large clinical trials but also supported by subsequent RWD in diverse populations -low risk of discontinuation due to ISR (2.4% in 083, 0% in 084) -low risk of adverse events in all populations as per studies and RWD -acceptability and feasibility for service users and clinicians CAB-LA was trialled against standard of care oral PrEP options in trials, there has not been a 'no PrEP' comparison.

measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	There have not been adverse effects that were not apparent in clinical trials of which I am aware however, we have used CAB-LA as PrEP in a very small number of individuals. In contrast, we have greater experience of injectable CAB in PLWH. No unexpected AEs have been observed to my knowledge.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No-a systematic review should be sufficient. The drug company may have further data which are not in the public domain and some small cohort studies/reports may not be captured e.g. BASHH 2024 had an oral presentation on some of the individuals in whom CAB-LA had been prescribed in the UK via the compassionate access programme.
22. How do data on real-world experience compare with the trial data?	The RWD reflects the trial data and provides added reassurance.

23. In clinical practice, is cabotegravir for the prevention of HIV likely to be scheduled for administration every 8 weeks or every 2 months? Although the difference between these two time periods is small, it has a large impact on the cost-effectiveness estimates.	Cabotegravir is administered as an intramuscular injectable, with the first two injections administered four weeks apart, followed thereafter by an injection every eight weeks or two months*. Staff will need to be competent in giving the injection. CAB-LA users will need to remain in clinic for monitoring post-injection. Many sexual health providers will be unfamiliar with cabotegravir administration and hence senior clinical involvement will be required. *it should be noted that in the HPTN studies, doses were given every eight weeks and guidelines will likely reflect this, however, the manufacturers are clear that dosing can be every two months for simplicity. Extrapolating from HIV treatment experience, service users prefer two monthly dates vs eight weeks for ease of planning. For clinics, two months is important as many will not have weekend access.
24. In clinical practice, how is it decided if a person taking oral PrEP is non-adherent and/or intolerant to the treatment? Is there a clear set of criteria or can it be a subjective decision?	This is a subjective decision, the clinician can only use the information with which they are provided from the PrEP user. This is the same for stigma/confidentiality issues. In clinical practice, other than in exceptional circumstances, we do not routinely do objective measures of adherence e.g. drug levels from plasma/hair for example or formal pill counts-these are resources employed within the trial setting. One might infer that adherence is lessened if an individual has an excess of unexpected pill supply, however, this is also unreliable given they may have switched to event-based dosing or stopped PrEP during episodes of lower risk. Some intolerances are more apparent e.g. those with objective signs such as rash, renal function decline, neurology but others e.g. nausea, head-ache, abdominal pain are again, subjective.

23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people	There remains little data on the use of CAB-LA in trans-men, non-binary individuals, PWID and young people under 18 (there is a sub-study which included approx. 50 female adolescents). We know that one of the key populations most at risk of HIV acquisition include those who may be reticent to engage in healthcare systems. Given that current commissioning supports PrEP delivery via Level 3 providers, this may exacerbate health inequity. Overall, I think that if this evaluation serves to embed CAB-LA in routine clinical practice, it will improve health inequality by improving PrEP options for minoritised communities.

with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from	

issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

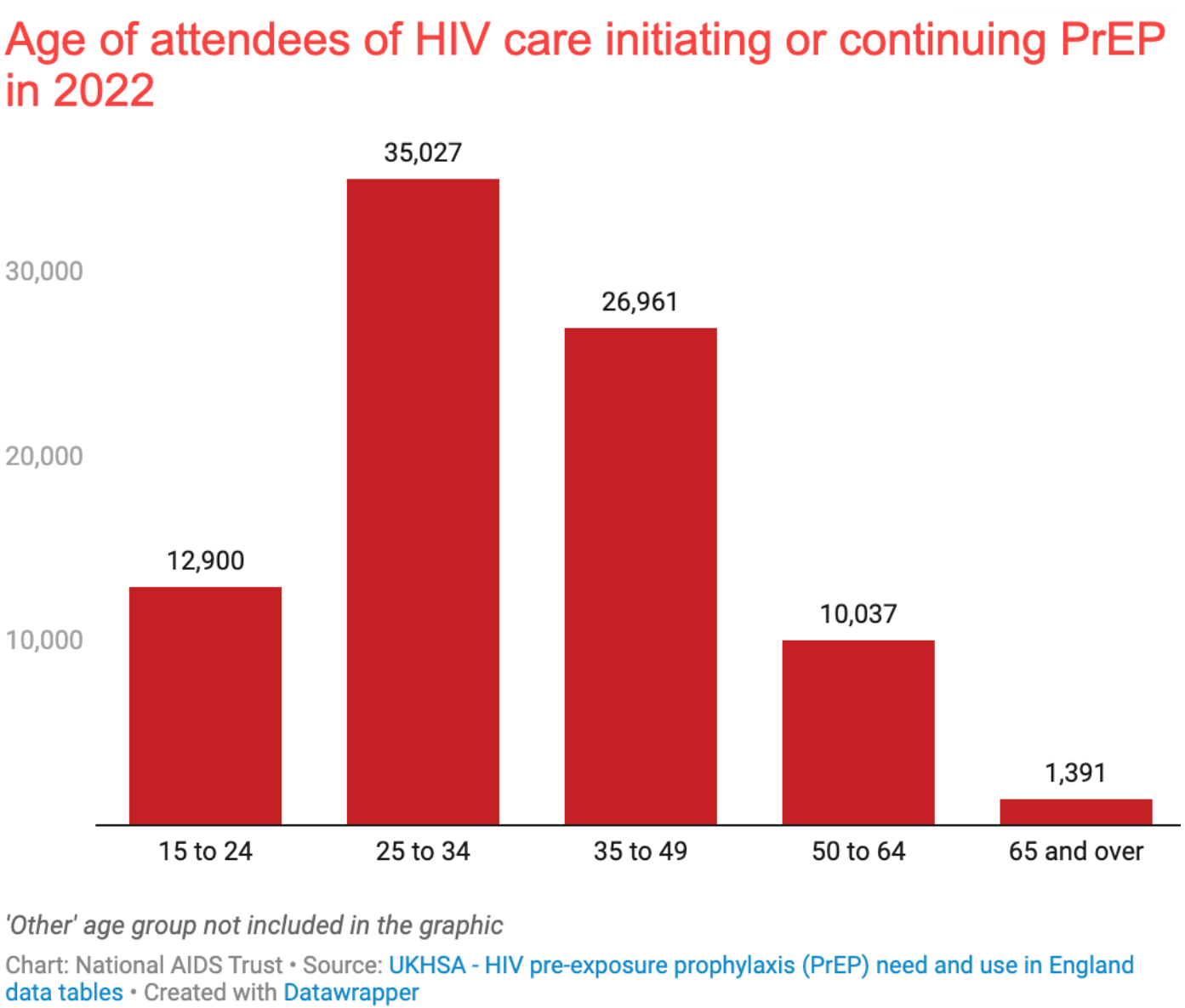
The population is narrower than the decision problem (section 2.3 of EAR) Can you comment on the appropriateness of the proposed positioning of cabotegravir? How would the population of people for whom oral PrEP is not appropriate be	The CS outlines the CAB-LA suitable population as people for whom oral PrEP is not appropriate and are underserved by current standard of care PrEP. The population encompasses those with health or social determinants of health challenges that may mean that oral PrEP is not an appropriate option. There is a challenge in extrapolating data from 083 and 084 where CAB-LA was trialled in individuals who had not necessarily identified as having pre-determined or pre-detected issues with oral medication and indeed, all had an oral lead in phase. This is not to say that some of those enrolled in the HPTN studies would not have struggled with oral medication. The NICE population scope would encompass all people at risk of HIV-infection and given that this agent in superior in clinical studies, depending on true economic feasibility (which stretches beyond drug costs given the impact on services) it may be appropriate not to restrict access to this agent. Individuals in whom oral PrEP is not appropriate may be identified from the clinical history when detailing age, co-morbidities e.g. renal/bone issues, adherence, swallowing, absorption, tolerance issues or

identified in clinical practice?	adverse events. Baseline and on-going screening e.g decline in renal function or proteinuria may demonstrate potential toxicity, demonstrating a need to switch.
Generalisability of the HPTN population (section 3.5.1.1 of EAR) Are the populations in the HPTN clinical trials generalisable to UK clinical practice?	The HPTN studies investigated CAB-LA use in a diverse population reflective of the UK population at risk of HIV acquisition. 084 is particularly useful in providing data on cis-women where there is a paucity of evidence for other agents e.g. F/TAF. Some groups were under-represented in HPTN e.g. those that identify as non-binary, under 18s (small sub-study), trans-men, PWID.
Inclusion of studies in the ITC that were conducted in populations different from the population of interest as specified in the scope (section 3.4.1 of EAR)	The population of interest is deemed to be those at risk of HIV acquisition in whom oral PrEP is unsuitable and who are thus underserved by current oral PrEP options. The ITC includes studies which enrolled ALL individuals deemed to be at risk of HIV acquisition i.e. much broader than the suggested target population. The ITC was required given there was not a 'no PrEP' arm in the HPTN studies. As a substitute, initially the company used various TDF/FTC studies which may have had a 'no PrEP' arm as a comparison testing the validity of consistency assumptions and the validity of a meta-regression. Most TDF/FTC failures were ascribed to adherence issues, however, there was no consistent measurement of adherence within the studies used. Ipergay was also included, when this examined the use of event-based oral therapy. Furthermore, the populations studied varied largely, with the Bangkok Tenofovir study including PWID. This demonstrates the challenges of cross-comparing studies, however, I'm not sure how this issue could be addressed fully in an RCT given a 'no PrEP' arm would be unethical. The ITC is probably the best interpretation we have given there is no dedicated study of individuals in whom oral options are not appropriate vs a no-PrEP population.

Inclusion of studies in CS ITC that does not meet the specified population of interest as described in the NICE scope (section 3.5 of EAR)	See response above
CS ITC analyses did not account for measurement error in adherence levels in the meta-regression of treatment effect on adherence to CAB-LA. (section 3.4.1 of EAR)	See above-this is an issue with cross-comparison of studies.
Restricting treatment costs to period of heightened risk (assumed 5-years in the CS base-case) over a life-time risk capping the treatment costs which could favour CAB-LA in cost-effectiveness (section 4.3 of EAR)	When first developed PrEP was not thought to be a long-term intervention. The company will have opted for five years as this is likely to represent the period of greatest HIV acquisition risk. They reference using five years as this reflects the assumptions in the economic analysis informing the NICE guidelines for reducing STIs. There are limited data on PrEP 'persistence' and where this is available, it tends to be in relation to oral PrEP. I do not think that 5-10 year data is unreasonable, however, it would be good to see longer-term modelling data re: the cost benefit of prolonged CAB-LA. It will be incredibly difficult in practice, should CAB-LA be permitted for a shorter periods only.
Inappropriateness of the no PrEP as a	See response above. A 'no-PrEP' arm would be unethical.

Comparator in the model (sections 4.4 and 4.5 of EAR)	
Inappropriateness of Baseline risk of HIV acquisition (section 4.7.1.1 of EAR)	I note that the company use the baseline risk of HIV acquisition in MSM to be equivalent to HIV incidence in a subset of this population with recent rectal bacterial STI, however, there may be individuals within this population who are already (potentially unknowingly) living with HIV. Other studies may have a more reliable estimate and I would support the EAG's comment around using the incident rate of 3.9 per 100 person-years.
Transition to TDF/FTC following discontinuation from cabotegravir (section 4.7.1.2 of EAR)	As detailed throughout the submission, the population of interest is deemed to be those at risk of HIV acquisition in whom oral PrEP is unsuitable and who are thus underserved by current oral PrEP options. Transition to TDF/FTC on cessation of CAB-LA is unlikely to be possible in the majority of this population.
Adherence to TDF/FTC (section 4.7.1.5 of EAR)	I note the comment re adherence to TDF/FTC driving relative effectiveness in the EAR and concerns re the HPTN ITT analysis excluding individuals who were non-adherent to oral CAB-LA. I think this may be less of an issue in clinical practice as individuals with adherence issues would not start with an oral CAB-LA lead-in, they would commence injections. As per the multiple TDF studies included within this review, it is clear that poor adherence to TDF/FTC does drive effectiveness, this is also observed in clinical practice anecdotally.
Improved persistence to cabotegravir (section 4.7.1.3 of EAR) Would you expect there to be higher or lower persistence for	Personally, I would expect there to be a higher persistence for individuals taking CAB-LA injections compared to oral PrEP. If we use the company population, these would be individuals who are motivated to use PrEP but have issues with oral therapies. Even if this population is expanded to include all individuals for whom PrEP would be appropriate, it is likely that people starting CAB-LA will be placed on dedicated recall systems in

individuals taking cabotegravir injections compared to oral PrEP? Please outline reasons.	order to ensure on-going review. Given concerns re the CAB 'tail' service providers will be keen to ensure that anyone who has received a CAB injection are actively recalled where required. The open-label follow-up in the HPTN studies demonstrated that the majority of participants opted to continue an injectable PrEP option on study cessation, implying high levels of motivation to use CAB-LA. I note the EAG response which comments that CAB-LA users may face barriers which are not observed in those using oral PrEP. This is not the case, as those using oral PrEP are required to attend sexual health services and undergo testing e.g. renal and HIV/hepatitis bloods and STI screening and on-going prescription of oral PrEP at three month intervals within most UK services.
Disutility for HIV infection (section 4.8.1.1 of EAR) What is the impact on quality of life when HIV infection occurs?	It is better to use more recent data, translatable to a UK population when reviewing QoL in PLWH given the improvements in antiretroviral options over the last decade. A recent article from the French ANRS group** demonstrated that of the 965 PLWH included, 98.4% were on antiretroviral therapy, 94.7% were virally-suppressed, 63.5% reported good/very good QoL. Median scores (0–100) were highest for physical (69;Q1, Q3: 56, 81) and environmental (69; 56, 75) QoL and lowest for social (56; 44, 69) and psychological (56; 44, 69) QoL. PLWH with ≥ 3 comorbidities, HIV-related stigma, or income of < 1500€/month had poorer median adjusted physical, psychological, social, and environmental QoL scores compared to reference groups. While more than half of PLWH reported good/very good QoL, they had not achieved good QoL in 90% of PLWH. Multi-morbidity, HIV-related stigma, and social determinants were consistently and independently associated with poorer QoL. They highlighted that addressing structural factors in addition to those indirectly related to HIV is required to attain good QoL in all PLWH. **Barger, D., Hessamfar, M., Neau, D. *et al.* Factors associated with poorer quality of life in people living with HIV in southwestern France in 2018–2020 (ANRS CO3 AQUIVIH-NA cohort: QuAliV study). *Sci Rep* **13**, 16535 (2023). https://doi.org/10.1038/s41598-023-43434-x

Starting age of Participants (section 4.7.1.4.1 of EAR) At what age do individuals usually start taking PrEP in UK clinical practice?	

Duration of assumed aggregate risk period to reflect lifetime risk of sexually acquired HIV acquisition (section 4.7.1.4.2 of EAR)	As detailed above, PrEP was designed to be a temporary intervention. Studies detailing PrEP persistence are rare and often flawed as individuals may move to alternative care providers and hence may not have ceased PrEP use. I would have preferred to see a longer term CAB-LA model.
Cabotegravir injection administrative costs (sections 4.9.2 and 4.9.2.1 of EAR) Who would administer cabotegravir injections in practice and how long would administration take?	Administration of CAB-LA injections will be performed by various members of the MDT depending on competence. In centres with a degree of CAB experience e.g. in the HIV setting, it is likely that band 5/6 nurses will administer the agent. In other settings, it is likely to be a senior medic. Administration may only take minutes, however, some centres may require the individual to remain in clinic after the injection for monitoring. The PrEP user will also need to have an HIV RNA viral load and HIV Ag/Ab tests, plus a sexual health screen at this juncture. It is important to note that there will be extra time which must be factored in at each appointment. The PrEP user will need to be reviewed, they may have questions e.g. regarding potential side-effects or the ability to attend for future injections. It is likely that senior medical intervention will be required for the first few visits. The drug will also need to be prescribed and obtained from pharmacy. Note that this may be a laborious process for some services without an on-site pharmacy requiring intensive pre-planning. The service user will then need to be placed on recall for their next injection. These ‘hidden’ costs must be factored in to any pathway.
Drug acquisition and administration (sections 4.9.1 and 4.9.1.1 of EAR)	Drug acquisition costs for TDF/FTC will vary depending on the generic preparation used. Costs are also lower for PrEP cohorts using event-based dosing as fewer pills are used. I note the discrepancy in whether CAB-LA should be given eight weekly or two monthly. The drug company is clear that two-monthly is sufficient. The guidelines will likely say eight weekly as they use the schedule from within the clinical studies. Most clinicians will be confident following the two monthly

	schedule. I suspect that the majority of users will not opt for the oral lead in so more modelling may be required around this.
Other issue identified by NICE technical team: **Implementation of cabotegravir injections** In what clinical settings could/would cabotegravir injections be administered compared to where oral PrEP is currently administered?	Given this is an IM injection, CAB-LA will need to be delivered within a healthcare setting by a qualified healthcare professional (HCP). Oral PrEP is currently commissioned via Level 3 sexual health providers, however, it may be given within the outreach setting by HCPs. It should be noted that stocks of F/TDF are frequently from an 'overlabelled' supply and hence readily available within the sexual health setting. Access to CAB-LA from services without an on-site NHS linked pharmacy may prove more challenging. We are keen for PrEP delivery to move beyond sexual health clinics in time in order to improve access.
Are there any important issues that have been missed in EAR?	There is little focus on the associated, non-drug costs of CAB-LA administration. Sexual health services are already under immense pressure and grossly underfunded. While most Providers are passionate about improving PrEP access and choices in order to meet the needs of underserved populations, CAB-LA will represent more pressure on the workforce and finances of providers. There is also a concern that given the intricacies of CAB-LA prescribing and administration, routine activity may be further 'pushed out' and access issues may be further exacerbated.

Abbreviations: CAB-LA, cabotegravir injections; CS, company submission; HIV, human immunodeficiency virus; ITC, indirect treatment comparison; PrEP pre-exposure prohylaxis; TDF/FTC, tenofovir disoproxil fumarate with emtricitabine (oral PrEP). CS, company submission

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

PrEP is an excellent HIV prevention tool, however, we are failing to reach those at greatest risk of HIV acquisition and there is a need for alternative PrEP options in the UK to support uptake, reduce health inequality and meet the HIV Action Plan.
CAB-LA PrEP is safe, well-tolerated and superior to oral PrEP, significantly reducing rates of HIV acquisition.
CAB-LA has been trialled in key populations most at risk of HIV acquisition with good outcomes and few adverse events.
CAB-LA is needed for people experiencing stigma, adherence, swallowing or absorption challenges, or tenofovir intolerance.
While efficacy, QALY and cost-effectiveness data are clear, services may require extra funding to deliver CAB-LA.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Cabotegravir for preventing HIV-1 in adults and young people [ID6255]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **Monday 10 June.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

NICE National Institute for Health and Care Excellence

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Preventing/treating HIV and current prevention/treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Michael Brady
2. Name of organisation	Kings College Hospital NHS Foundation Trust
3. Job title or position	Consultant in HIV and Sexual Health Medicine
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the prevention/treatment of people with HIV? ☐ A specialist in the clinical evidence base for HIV or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	I have none
8. What is the main aim of treatment for HIV? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	There are two main aims of treatment for HIV – both of which rely on sustained suppression of HIV replication (as measured by an undetectable HIV viral load): Firstly – by suppressing the virus, preventing further damage to the immune system and allowing immune function to recover, HIV therapy prevents disease

	progression, prevents HIV associated illness and morbidity and prevents the development of advanced disease and AIDS-defining illnesses. The second aim is to prevent onward transmission. Effective HIV therapy with a suppressed HIV viral load (< 200 rna copies/ml) gives a zero risk of HIV transmission to sexual partners and significantly reduces risk of HIV transmission through other routes (e.g. breastfeeding or through injecting drug use).
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	A *clinically* significant treatment response would be measured over years or decades. It is one where HIV-related disease is prevented or reversed. For someone who is diagnosed early who is asymptomatic and well and before significant immune damage has occurred it would be the prevention of *ever* having an HIV related condition. For someone who is diagnosed at a later stage who has already developed an HIV-related condition it would be supporting resolution of that infection / disease and the prevention of recurrence of that or any other HIV related disease. Reduction of disease activity is measured by a reduction (to undetectable) of HIV viral load and an improvement of immune function as measured by the CD4 count. A clinically significant *prevention* response would be PrEP that is a highly effective and safe intervention at preventing HIV acquisition in a range of populations at risk of HIV. Cabotegravir demonstrated this in both the HPTN083 and HPTN084 studies.
10. In your view, is there an unmet need for patients and healthcare professionals in people at risk of, or with HIV?	For patients there is certainly unmet need in the provision of HIV prevention (PrEP), with data from the UKHSA showing that heterosexual men and women (and particularly black African women) are much less likely to get their PrEP need met when attending sexual health clinics. https://www.gov.uk/government/statistics/hiv-annual-data-tables/hiv-testing-prep-new-hiv-diagnoses-and-care-outcomes-for-people-accessing-hiv-services-2023-report Similarly other groups such as younger GBMSM, GBMSM from ethnic minority communities and trans and non-binary people are less likely to know about and

	access PrEP. There are also infrastructural challenges in the system, significant proportion of people struggling to access PrEP through sexual health services as evidenced by the 'Not PrEPared' report which demonstrates that everyone can struggle to access PrEP, but inequities in access and uptake are more pronounced for those in already marginalised and underserved communities: https://www.nat.org.uk/sites/default/files/publications/Not%20PrEPared.pdf Although existing oral PrEP options meets the needs of the majority of people who currently access PrEP (mostly GBMSM) there is a proportion of people for whom current models of service delivery are not acceptable or accessible and for whom oral PrEP is not an option – either due to medical complications or co-morbidities (renal / bone), stigma or situations where confidentiality is essential, and an injectable option is needed. In terms of those living with HIV we see unmet need in terms of those living with undiagnosed HIV in terms of HIV testing (53.1% of Black African people are diagnosed late which has been consistently higher than white, Asian or people from other ethnic groups). This reflects challenges in HIV testing strategies and provision. Those diagnosed late have greater morbidity and mortality compared to people diagnosed at an earlier stage and have a greater risk of transmitting the virus to others. https://www.ethnicity-facts-figures.service.gov.uk/health/physical-health/hiv-infection-with-late-diagnosis/latest/ There is also unmet need for those living with diagnosed HIV, who are aware of their infection but, for whatever reason, are not accessing HIV clinical care or who are accessing care but do not have a fully suppressed HIV viral load. Data from UKHSA (2022) estimates that of the 11,985 people (lower level estimate) with transmissible levels of virus, an estimated 4,400 (37%) remained undiagnosed while 7,585 were living with diagnosed HIV, of which: 147 (1.2%) were diagnosed but not linked to care, 4,444 (37%) were not retained in care,

	1,195 (10%) attended care but were not receiving treatment, and 1,799 (15%) were on treatment but were not virally suppressed. https://www.gov.uk/government/publications/hiv-monitoring-and-evaluation-framework/hiv-action-plan-monitoring-and-evaluation-framework#theme-3-reduce-the-number-of-people-with-transmissible-levels-of-virus-1 Heterosexual people, those from ethnic minorities (particularly black African women) are most likely to dis-engage from care. Strategies to improve retention and re-engagement in care are essential to address this. There is an educational unmet need for non-HIV healthcare professionals regarding both HIV prevention and treatment, with surveys demonstrating some lack of knowledge about PrEP, advances in HIV treatment and care and U=U (Undetectable equals Untransmittable – the fact that people living with HIV with an undetectable viral load cannot pass the virus on to their sexual partners). This risks people not being tested for HIV or people receiving inaccurate, outdated and stigmatising information and limits the opportunities for healthcare professionals to recommend PrEP and signpost people to sexual health services who provide PrEP
11. How is HIV currently prevented/treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	HIV in the NHS is treated in specialist HIV services. There are clinical guidelines used in the treatment of HIV published by the British HIV Association (BHIVA): https://www.bhiva.org/HIV-1-treatment-guidelines The pathway of care is well defined in that people diagnosed with HIV (whether in sexual health services, primary care, A+E departments or through HIV self-sampling or self-testing services) are referred (or self-refer) into specialist HIV services. These arrangements and pathways are well established and, in my view, there isn't any variation or differences of opinion between professionals across the NHS about this. The technology wouldn't have any impact on the current pathway of care for HIV treatment in the NHS. HIV is prevented (in its broadest sense) through a combination of approaches including health promotion messaging, condom use, increasing HIV testing, PrEP, early diagnosis of those living with HIV and rapid access to HIV treatment

	to ensure people achieve and undetectable viral load and therefore cannot transmit the virus to their sexual partners. Relevant to this technology is the provision of PrEP. PrEP is currently only available in sexual health services. There are national clinical guidelines for the use of PrEP: https://www.bhiva.org/PrEP-guidelines There is also a policy for commissioning of PrEP in England: https://www.england.nhs.uk/publication/reimbursement- for-the-use-of-generic-drugs-for-pre-exposure-prophylaxisprep-for-the- prevention-of-hiv/ The pathway of care is well defined although there are differences in views as to whether PrEP should *only* be available in sexual health services with many professionals in the sector believing that, to address inequalities in access and uptake of PrEP, it should also be available in other settings e.g. primary care, including community pharmacy and through online services. This will be reflected in the updated UK PrEP guidelines (2024). Whilst the technology probably wouldn't have much impact on the *pathway* of care as it would be commissioned for delivery in specialist sexual health services it would have an impact on the *delivery* of PrEP care within these services as they would need to be able to provide the injectable service (and be funded for the extra work, tests etc that would entail). Services will also have to ensure they have reliable 'call and re-call' processes in place to ensure people attend for their injections and are re-called if they do not attend. This represents a further pressure on capacity and funding for injectable PrEP provision. The provision of Cabotegravir within clinical services would differ from that of oral PrEP (where often people attend just twice a year and access STI and HIV testing online). Staff would need training in administration of the injection and capacity needed to accommodate the regular injection schedule. There is also the additional requirement for more frequent HIV testing and HIV viral load

	monitoring. Sexual Health services do not typically or regularly request HIV viral load testing and there is therefore a financial impact of this extra testing. Whilst many sexual health services are integrated with specialist HIV services (who already have capacity to deliver injectable therapy to people living with HIV) there are sexual health services that are not integrated with HIV services and are provided by independent organisations (commissioned by local authorities). These services have struggled to provide TAF/FTC PrEP and will have similar problems providing injectable PrEP.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The technology should be used in the same clinical setting as current provision of PrEP on the NHS i.e. in specialist sexual health settings. There is an existing PrEP pathway and model of care in these settings and, for many services, there will be existing expertise on the provision of cabotegravir injections to people living with HIV. The healthcare resource required would differ from current standard of care as this is an injectable form of PrEP with an even greater need to ensure adherence than with oral PrEP. This obviously means that all appointments will need to be face-to-face and every 2 months (whereas with oral PrEP appointments can be virtual – telephone or online) and face to face appointments can be as infrequent as every 6 or 12 months (with online STI testing and 6-month prescriptions of oral PrEP) As well as the increased frequency of visits and the associated costs of staff time, consumables and overheads there would need to be capacity and resource to support people to attend every 2 months e.g. appointment reminders and follow-up for those who don't attend their appointments. There is also the cost of extra HIV Ab/Ag and HIV viral load testing that cabotegravir injections required compared to current care with oral PrEP.

	There would need to staff training when the technology is introduced for those staff working in sexual health services who will be providing injectable PrEP but have no experience of providing the injections to people living with HIV.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	In view of the impressive trial data and the likely benefits of adding an injectable PrEP option to our current care (oral PrEP) in terms of acceptability, adherence and uptake of PrEP for those not currently accessing PrEP, I would expect an increase in health-related quality of life and increase in length of life when compared to current care. The introduction of injectable PrEP will give an alternative option of effective HIV prevention for those who can't (or won't) take oral PrEP and provides an alternative for people at risk of HIV of who are not currently accessing PrEP. This should increase the number of people at risk of HIV who are protected from HIV acquisition, further drive down HIV infections and reduce the number of people with recently acquired HIV. Preventing HIV in a greater number of people will prevent HIV-related morbidity and mortality and prevent the negative effect that HIV acquisition and living with HIV can have on an individual's quality of life and potential reductions of life expectancy that HIV can bring.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The efficacy of all PrEP options is driven by people's ability to adhere to the medication. The superior efficacy of Cabotegravir PrEP over oral TDF/FTC seen in HPTN083 and HPTN084 is driven by greater acceptability and adherence. It is likely therefore that the technology will be more effective in those who struggle to adhere to PrEP and those for whom oral PrEP is not acceptable (for whatever reason). In my opinion these groups are more likely to be heterosexual people from ethnic minorities, but there will be people from all communities who would benefit from PrEP who would find injectable PrEP more acceptable and easier to adhere to and therefore more effective. For similar reasons, Cabotegravir injectable PrEP will be more effective for those individuals who cannot tolerate oral PrEP or who have side-effects or toxicities from oral PrEP – who could be from any group who would benefit from PrEP

15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	For the reasons given above, for some patients the technology will be easier to use than oral PrEP, the current standard of care as they will have been selected (or self-selected) because it is something that they find more acceptable and easier to adhere to. There will be practical implications for healthcare professionals and service provision of delivering injectable PrEP: • Staff will need to be trained to provide injectable PrEP. • Services will need capacity (both staff and space) to be able to accommodate more frequent (2-monthly) appointments. • There is a cost to more frequent HIV testing and HIV viral load testing required – which could continue for a year after and individual stops injectable PrEP. • Services will need the capacity and resource to have more robust appointment reminders and follow-up procedures to ensure people attend for their injections and are actively and quickly recalled if they do not attend. These are not routinely used in the care pathway for people on oral PrEP
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	There will be 'rules' based on an assessment of risk for HIV acquisition (in the same way there are for oral PrEP) and 'rules' based on an individual's eligibility for injectable PrEP based on, for example, contraindications to or intolerance of oral PrEP or other barriers to oral PrEP. These would be based on both commissioning guidance and clinical guidelines. It will be necessary for the individual to have an HIV test at (and perhaps repeated soon after) starting injectable PrEP to ensure they are not already HIV positive. This is the same as for oral PrEP and is therefore not *additional* testing. The decision to stop Cabotegravir injectable PrEP would be based on either the fact that an individual no longer needs PrEP as their risk of HIV acquisition has

	reduced or due to an intolerance to injectable PrEP e.g. due to injection site reactions.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	People who are at greater risk of HIV acquisition are more likely to suffer from poor mental health partly, but not only, because of worry about HIV. It can also be related to other stressors in their lives. There is evidence that PrEP improves mental health – with the most marked improvements being to anxiety (specifically anxieties about HIV acquisition). There is less evidence demonstrating improvement to other mental health conditions such as depression. There is evidence that PrEP improves the quality of people's sex lives and can address HIV related stigma. The improvements to adherence and reducing HIV-related stigma would also be expected to contribute to improved quality of life during the time that individuals are using injectable PrEP. As far as I can see, none of these aspects of improved quality of life are included in the QALY calculation.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	I think the technology is innovative and makes both significant and substantial impact on health-related benefits. It brings a 'step-change' in HIV prevention in that it is the first injectable option adding choice for people at risk of HIV acquisition and an option other than oral PrEP. This has been supported by the results of the HPTN083 and HPTN084 studies which both demonstrated superiority to oral PrEP in different populations at high risk of HIV acquisition i.e. cisgender men who have sex with men (MSM) and transgender women) and heterosexual women in sub-Saharan Africa. The technology addresses a number of unmet needs for the populations at risk of HIV acquisition. These include providing, for the first time, an injectable alternative to oral PrEP which addresses issues for those who cannot tolerate oral PrEP and for those for whom oral PrEP is not acceptable for whatever reason. It supports those who struggle to adhere to oral PrEP regimens and

	those who do not want to keep oral PrEP tablets at home. Studies have demonstrated that a significant proportion of 'at risk' populations would both find injectable PrEP acceptable as well as prefer this option to oral PrEP. The technology also has the considerable benefit of not affecting renal function (unlike oral PrEP) which gives us an effective HIV prevention strategy that can be used in people with, or at risk of, renal dysfunction and a 'switch strategy' for those who experience reductions in renal function whilst on oral PrEP.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The main side-effect demonstrated in HPTN083 and HPTN084 was injection site reactions (mostly pain). These can be well explained and managed and I don't consider them to be a significant barrier to injectable PrEP. In both studies most injection site reactions were mild or moderate in severity, were reported at the first injection and diminished over time In HPTN083 2.4% discontinued the injections due to injection site reactions and there were no discontinuations due to injection site reactions in HPTN084. I think the benefits of injectable PrEP (in terms of both reductions in HIV acquisition risk and improvements in quality of life) outweigh this specific adverse effect.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The clinical trials reflect current UK clinical practice in terms of how HIV acquisition risk is identified and in terms of the larger 'key populations' who would benefit for PrEP – which is reassuring despite the fact that the trials were not carried out in the UK. I think the significance of the biomedical impact of injectable Cabotegravir demonstrated in the trials suggest that these results can be extrapolated to the UK setting. I think that we would see similar impacts in the UK populations of GBMSM, transgender women, heterosexual women and other groups at risk of HIV acquisition. I think the key important outcomes are efficacy, adherence, adverse events and acceptability – all of which were addressed in the trials. Both HPTN083 and HPTN084 demonstrated superior efficacy when compared to oral PrEP, mild and manageable adverse events (injection site reactions) which decreased over time

	with few (if any) discontinuations as a result and good levels of acceptability and adherence. These all predict excellent long-term clinical outcomes in terms of preventing HIV acquisition. I am not aware of any adverse effects that have come to light subsequent to the clinical trials from 'real world' experience. Having said that experience of injectable Cabotegravir PrEP in the UK is limited to just a few individuals – but we have more experience of injectable Cabotegravir in the *treatment* of HIV and I'm not aware of any previously unknown adverse events in this population.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	The real-world experience compares very favourably with the trial data and supports their findings. This is similar to what we have seen when real world data / experience of oral PrEP is compared to data from RCTs.
23. In clinical practice, is cabotegravir for the prevention of HIV likely to be scheduled for administration every 8 weeks or every 2 months? Although the difference between these two time periods is small, it has a large impact on the cost-effectiveness estimates.	I think that in clinical practice cabotegravir would be scheduled for every 2 months rather than every 8 weeks. This is easier for patients and clinics to schedule. As the clinical trials used 8-weekly dosing it is likely that national clinical guidelines will reflect this in their recommendations.
24. In clinical practice, how is it decided if a person taking oral PrEP is non-adherent and/or intolerant to the treatment? Is there a clear set of criteria or can it be a subjective decision?	There are no objective measures of non-adherence or intolerance to oral PrEP, and we assess both of these through the history we take and rely on patient self-reporting. We do not routinely use objective measures (as used in the trials) of drug adherence.

25. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	I don't think there are any specific *negative* equalities issues that would exclude people protected by equalities legislation or have a different or adverse impact on them. If anything, I think there are *positive* equalities impact. The HPTN083 and HPTN084 studies provide data on effective PrEP in transgender women and cisgender women from sub-Saharan Africa which is currently lacking. Also – as discussed above – there are populations with protected characteristics under equality law who would potentially benefit from injectable PrEP and therefore this approach could go some way to address existing inequalities in terms of access, uptake and impact of PrEP for marginalised and underserved populations. Increasing access and choice in terms of PrEP options should have a positive impact in terms of equalities for people with a range of protected characteristics included, and probably not limited to, gender reassignment, race, sex and sexual orientation.

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

The population is narrower than the decision problem (section 2.3 of EAR) Can you comment on the appropriateness of the proposed positioning of cabotegravir? How would the population of people for whom oral PrEP is not appropriate be	I think the proposed positioning of cabotegravir is sensible. Currently available oral PrEP (with either TDF-FTC or TAF-FTC) is highly acceptable, well tolerated and well adhered to by the vast majority of people taking PrEP. However, there are a small proportion of people currently taking PrEP for whom oral options are either not tolerated or not acceptable. There is also a recognised (but hard to quantify) number of people who are at risk of HIV acquisition but for whom current clinical delivery service models or current PrEP options are not acceptable and, therefore, they do not access the benefits of PrEP. There are people who have medical contraindications (the majority of which will be related to renal or bone function) but also, potentially, those who struggle to swallow tablets for whom the proposed positioning of cabotegravir is appropriate. There are also people for whom there are a range of stigma or socio-economic related factors (as detailed in the documentation) that either impacts on their ability to adhere to oral PrEP or prevents them from accessing PrEP in the first place. The proposed positioning of cabotegravir could potentially meet the needs of these individuals.

identified in clinical practice?	As current (and cheaper) oral options for PrEP will (and should) remain the mainstay of PrEP provision for the majority, a detailed framework for targeting this more expensive injectable PrEP option at those underserved or not served at all by current oral PrEP options will be important and I think the proposed positioning is a reasonable approach to this. The population for whom oral PREP is not appropriate would be identified as part of standard (and current) clinical care models. We are already able to identify people who would benefit from injectable Cabotegravir PrEP through detailed discussions with people eligible for PrEP or currently taking PrEP that covers medical history, co-morbidities and drug history, adherence, tolerability and side-effects. Testing at baseline and on-going monitoring of renal and bone function that is already current practice would identify those who might benefit from injectable PrEP to reduce or prevent toxicities. These approaches are relevant for those who access PrEP. Injectable PrEP gives us the opportunity to increase access to those who don't see PrEP as relevant or acceptable to them and who are not currently accessing PrEP, so assessment for eligibility for injectable PrEP in clinical settings should be supported by raising awareness of this option in communities who currently don't access PrEP.
Generalisability of the HPTN population (section 3.5.1.1 of EAR) Are the populations in the HPTN clinical trials generalisable to UK clinical practice?	I think the populations in HPTN clinical trials are generalisable to UK clinical practice. The vast majority of people taking oral PrEP in the UK are GBMSM as studied in HPTN083. Black African women at risk of HIV acquisition are underserved and under-represented in cohorts of people taking PrEP in the UK and therefore the data in cisgender African women in HPTN084 is particularly helpful. Transgender women have been under-represented in trials of oral PrEP (despite being included in eligibility criteria for some studies) and therefore the fact that 12.5% of participants in HPTN083 were transgender women makes this data useful and generalisable to the UK. There remain a number of groups wo are not represented in PrEP trials (and are either under-represented or not included in the HPTN studies) which is a challenge for these smaller and underserved groups e.g. young people, people who inject drugs, trans men and non-binary people. This has been the case in all PrEP trials and, whilst the data are lacking for these groups, should not impact on our ability and efforts to ensure those from these groups who are at risk of HIV acquisition have access to all available PrEP options.

	PrEP provision in the UK has always been informed and underpinned by generalisability from clinical trials in other settings. The only major PrEP trials that included UK participants were in GBMSM (PROUD and RCT. Whilst I think this has contributed to inequalities in access to PrEP from other groups it has not precluded wider provision and, when other groups at high risk of HIV acquisition, are informed about PrEP and supported to access it we see similar benefits to those studied in clinical trials.
Inclusion of studies in the ITC that were conducted in populations different from the population of interest as specified in the scope (section 3.4.1 of EAR)	I think undertaking this analysis is challenging, but a reasonable attempt and approach has been made. As detailed above, I think the 'population of interest' for injectable cabotegravir PrEP is those for whom oral PrEP is not tolerated, not medically suitable or not acceptable due to stigma, psychological or socio-economic factors. These individuals are, by definition, very hard to identify and include in clinical trials in a way that supports meaningful and robust evaluation. The ITC includes people at risk of HIV acquisition, which is not the same (but will include some) of the people described above. I think this reflects the data available rather than the approach of the ITC. Since the early clinical trials of PrEP that demonstrated efficacy that was mostly related to adherence – it has not been ethical to have a comparison arm that does not take PrEP, which has also informed the approach in the ITC. When we consider the population in the UK and, specifically, the population of interest, there really are no studies that are directly relevant. Of note – the ITC includes studies in different settings, different 'at risk' populations (GBMSM, heterosexual individuals and couples and people who inject drugs) and different dosing schedules (both daily and event-based dosing). With the limited number (and design) of existing studies, meta-analysis, comparing between studies and 'generalisability' of studies is difficult and very limited. However, I think the approach taken in the ITC is probably as good as it can be with all that in mind.

Inclusion of studies in CS ITC that does not meet the specified population of interest as described in the NICE scope (section 3.5 of EAR)	I don't have anything else to add to the above
CS ITC analyses did not account for measurement error in adherence levels in the meta-regression of treatment effect on adherence to CAB-LA. (section 3.4.1 of EAR)	I don't have anything else to add to the above
Restricting treatment costs to period of heightened risk (assumed 5-years in the CS base-case) over a life-time risk capping the treatment costs which could favour CAB-LA in cost-effectiveness (section 4.3 of EAR)	There are many challenges in defining the period of heightened risk for HIV acquisition. An individual's risk of HIV acquisition will change over time and 'come and go' as sexual behaviour and sexual partner change varies. Whilst we can usually identify risk at a specific point in time (based on current sexual practice, recent STI acquisition or PEP provision for example), it is difficult to determine how long that risk continues and how it varies over time. Some people will have a relatively short period of heightened HIV risk, for some it will persist for many years and some people will move in and out of periods of heightened risk. I note that the decision to use '5 years' as a time period is based on analysis informing NICE guidance for reducing STIs, but I'm not sure how 'transferrable' this is. Whilst risk of STIs and risk of HIV can be similar

	– they are not always the same and will be different for different populations (e.g. GBMSM compared to heterosexual cisgender African women). I also note that the 5 years estimate refers to the economic modelling of Cambiano *et al* which estimated a mean time of 4.5 years on PrEP for MSM – but this is relatively 'old' data and only applies to GBMSM. I think the assumed 5 years of heightened risk is a reasonable estimate and will cover most people at risk of HIV acquisition, although their risk may not be consistent throughout that time and, for some, risk will be for less time than that and, for some it will extend beyond 5 years.
Inappropriateness of the no PrEP as a Comparator in the model (sections 4.4 and 4.5 of EAR)	A 'no-PrEP' arm is inappropriate and unethical and has been so for well more than a decade since the early trials demonstrated the effectiveness of PrEP at preventing HIV transmission.
Inappropriateness of Baseline risk of HIV acquisition (section 4.7.1.1 of EAR)	Assessments of baseline risk of HIV acquisition are difficult, but there are indicators of significant risk in GBMSM such as recent bacterial STI or recent rectal bacterial STI. Estimates of risk are 'easier' in GBMSM than in heterosexual people or other populations as we have better and more detailed data from UKHSA to estimate risk. It should be noted that the data referred to in section 4.7.1.1 is from 2014 – but gives us a reasonable estimate – if not a recent one. There is potential bias involved in included people living with undiagnosed HIV contributing to the figures – but I would certainly not be able to estimate the degree to which that impacts on the data. I think it would impact much less on data from 2024, compared to data from 2014 as rates of undiagnosed HIV are much lower in men who have sex with men now compared to a decade ago. Having said that – based on these data – when only looking at those with a negative HIV test in the last year an incident rate of 3.9 per 100 person-years seems reasonable (with the caveats mentioned above).

Transition to TDF/FTC following discontinuation from cabotegravir (section 4.7.1.2 of EAR)	Some of the population of interest (it's hard to define the proportion) would not necessarily transition to TDF-FTC following discontinuation of cabotegravir because, by definition, oral PrEP was not suitable for them in the first place. This would be the people for whom there is a medical contraindication. However – there are some people for whom cabotegravir injectable PrEP is a more suitable option (e.g. related to stigma or socio-economic issues) where, if cabotegravir where not appropriate but was not medical contraindicated, they could be supported to continue PrEP with an oral formulation. These currently underserved populations would be engaged in services to support their approach to HIV prevention and therefore in a setting that could address the 'non-medical' reasons that make oral PrEP unsuitable for them. If their risk of HIV acquisition remained high and cabotegravir injection became not an option for them, I think some would move onto oral PrEP to prevent HIV and an estimate of 50% is not unreasonable.
Adherence to TDF/FTC (section 4.7.1.5 of EAR)	I think adherence is complex and not a 'static' consideration – it changes over time and a number of factors impact on it. I don't think it is unreasonable to assume good adherence to the oral cabotegravir lead in prior to starting injections as there is a real incentive to adhere at this early stage as it is a 'means to the end' of injectable PrEP. I think we see similar good adherence to HIV treatment in the early stages for similar benefit incentives – and then, for many reasons and different times, people can struggle with adherence later on. I don't think it is a concern that poor adherence to TDF-FTC means poor adherence to cabotegravir tablets. It is not essential that everyone has the oral lead-in before starting cabotegravir injectable PrEP and if there were real concerns about adherence to tablets, individuals would not start with oral cabotegravir and start injections straight away.

	As a general comment – poor adherence to TDF-FTC (and all PrEP options) does drive PrEP efficacy – this has been demonstrated both in clinical trials and in real world experience.
Improved persistence to cabotegravir (section 4.7.1.3 of EAR) Would you expect there to be higher or lower persistence for individuals taking cabotegravir injections compared to oral PrEP? Please outline reasons.	I would expect there to be higher persistence for individuals taking cabotegravir injectable PrEP compared to oral PrEP. I think this would be partly because we would identify individuals who would 'do well' on injectable PrEP and who are motivated to take it. Also – it will be necessary for clinical services to adapt to provide more support for people on injectable PrEP than we currently provide for people on oral PrEP and for that support to be more holistic in terms of addressing stigma, psychological or socio-economic issues. In some way I think this will start to reflect the MDT approach in HIV services. The model of service delivery will also need to support greater persistence as it will be necessary to ensure that people have appointments booked, appointment reminders and robust processes for 'call and re-call' in place so people can keep their appointments and people who DNA are quickly followed up.
Disutility for HIV infection (section 4.8.1.1 of EAR) What is the impact on quality of life when HIV infection occurs?	Whilst it is true that quality of life for people living with HIV has improved considerably over recent decades, we must not underestimate the negative impact on quality of life that an HIV diagnosis can bring – even for those who are diagnosed early, are well and appear to be coping with their diagnosis. Treatment options have improved considerably with reduced pill burden and reduced toxicities / side-effects and people are less likely to get ill or require medical intervention or hospital admission than in previous years. However – these are just a few, relatively simplistic, components of quality of life.

	Stigma, shame, discrimination and guilt are common and the impact on mental health and relationships is still significant. Reliance solely on data that looks at the proportion of people living with HIV who are accessing care, taking treatment and have an undetectable viral loads masks complex issues related to quality of life. For example, the most recent Positive Voices survey (2022) demonstrated that there has been little change in quality of life and life satisfaction since 2017. Compared to the general population, people living with HIV continued to fare worse across both these measures. The largest difference was among people reporting anxiety or depression (48.1% of people living with HIV compared to 33% of the general English population). Of note, and relevant to equality considerations for underserved communities, life satisfaction, health-related quality of life, and resilience outcomes for people who identified as trans, non-binary, or in another way were worse than for other people living with HIV.
Starting age of Participants (section 4.7.1.4.1 of EAR) At what age do individuals usually start taking PrEP in UK clinical practice?	The largest group who access PrEP in England are those aged 25 – 34 followed by the 35 – 49 age group and then those aged 15 – 24 https://www.gov.uk/government/statistics/hiv-annual-data-tables
Duration of assumed aggregate risk period to reflect lifetime risk of sexually acquired HIV acquisition (section 4.7.1.4.2 of EAR)	As detailed above – the estimates of the period of time that people are at risk of HIV acquisition is complex and variable. I note that the EAG would have preferred a model that allows for longer risk periods, but I think this would introduce greater variability and uncertainty over a longer time period. I think that a 5-year assumption is reasonable, acknowledging that there is variation over this time and more data is needed to confirm the

	assumptions. We would be able to easily provide this data through reporting to UKHSA (both for currently available oral PrEP and for injectable PrEP in the future).
Cabotegravir injection administrative costs (sections 4.9.2 and 4.9.2.1 of EAR) Who would administer cabotegravir injections in practice and how long would administration take?	Cabotegravir would be administered in Sexual Health services and who would do that would depend on the skill mix and staffing of the service. I think it would mostly be delivered be registered nurses (Bands 5, 6 or 7) and, in some settings, by doctors. There will be some degree of senior medical capacity required to provide training, advice and support, management and clinical governance for what will be a novel process in Sexual Health services. As detailed above there are other capacity and funding considerations e.g. the appointment times, consumables and administrative support required to book appointments, remind people of appointments and to recall people who DNA appointments. There are also the costs of more frequent HIV testing and additional HIV viral load testing not needed for those on oral PrEP.
Drug acquisition and administration (sections 4.9.1 and 4.9.1.1 of EAR)	Certainly drug acquisition and administration costs for generic TDF-FTC are low - especially for those taking event-based dosing - and would be greater (as described) for cabotegravir injectable PrEP In my opinion, most people won't require or request the optionally oral lead in dosing of cabotegravir. As above – I think that injectable cabotegravir PrEP should be given every 2 months rather than every 8 weeks. This would be easier for patients to schedule and also easier for clinics who will not be open on weekends. Clinicians (and patients) will be confident about this as it reflects current practice for injectable therapy for people living with HIV. It should be noted that clinical guidelines are likely to recommend 8-weekly dosing as they will reflect the protocols of the clinical trials – but they can be edited to acknowledge the 2-monthly dosing recommendations (albeit, perhaps, as a good practice suggestion rather than a graded recommendation).

Other issue identified by NICE technical team: **Implementation of cabotegravir injections** In what clinical settings could/would cabotegravir injections be administered compared to where oral PrEP is currently administered?	Cabotegravir injections will need to be administered in a healthcare setting by an appropriate healthcare professional. In view of the current model of NHS commissioned PrEP this is likely to be in a Sexual Health service. This reflects how oral PrEP currently commissioned and delivered, although there are developments underway to deliver oral PrEP through online services or in other settings e.g. primary care. I think it is important to address issues of PrEP equity and access that all PrEP options are delivered in a range of clinical settings, so anything that limits the setting for provision should be avoided
Are there any important issues that have been missed in EAR?	Nothing else from me

Abbreviations: CAB-LA, cabotegravir injections; CS, company submission; HIV, human immunodeficiency virus; ITC, indirect treatment comparison; PrEP pre-exposure prohylaxis; TDF/FTC, tenofovir disoproxil fumarate with emtricitabine (oral PrEP). CS, company submission

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Cabotegravir injectable PrEP is highly effective, acceptable, safe and well-tolerated, offering a superior option to oral PrEP.
Cabotegravir injectable PrEP has been studied in a number of key populations at risk of HIV acquisition (GBMSM, transgender women and women from sub-Saharan Africa) with results that are generalisable to the UK population.
Increasing the choice of PrEP options through availability of cabotegravir injectable PrEP would be a significant step-change to our approach to HIV prevention and, I think, essential to our goal of ending HIV transmissions by 2030.
Cabotegravir injectable PrEP gives us a real opportunity to address existing inequities in PrEP provision and to better meet the HIV prevention needs of underserved (or not served) communities.
Our existing model of care for PrEP provision would be able to adapt to deliver cabotegravir injectable PrEP quite easily (and there is commitment to do that) but there are capacity and funding issues for services that would need to be addressed.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

Single Technology Appraisal

Cabotegravir for preventing HIV-1 in adults and young people [ID6255]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for comments is **5pm** on **Monday 10 June**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	National AIDS Trust
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: ● the name of the company ● the amount ● the purpose of funding including whether it related to a product mentioned in the stakeholder list ● whether it is ongoing or has ceased.	Funding received from ViiV Healthcare (since June 2023) 30 June 2023 - £69,663 HIV Prevention 1 September 2023 - £49,000 HIV Outcomes 29 April 2024 - £20,000 core funding
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	

Table 1 About you

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
The population is narrower than the decision problem (section 2.3 of EAR)	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Generalisability of the HPTN population (section 3.5.1.1 of EAR)	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Inclusion of studies in the ITC that were conducted in populations different from the population of interest as specified in the scope (section 3.4.1 of EAR)	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Inclusion of studies in CS ITC that does not meet the specified population of interest as described in the NICE scope (section 3.5 of EAR)	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
CS ITC analyses did not account for measurement error in adherence levels in the meta-regression of treatment effect on adherence to CAB-LA (section 3.4.1 of EAR)	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses

Restricting treatment costs to period of heightened risk (assumed 5-years in the CS base-case) over a life-time risk capping the treatment costs which could favour CAB-LA in cost-effectiveness (section 4.3 of EAR)	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Inappropriateness of “no PrEP” as a Comparator in the model (sections 4.4 and 4.5 of EAR)	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Inappropriateness of Baseline risk of HIV acquisition (section 4.7.1.1 of EAR)	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Transition to TDF/FTC following discontinuation from cabotegravir (section 4.7.1.2 of EAR)	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Adherence to TDF/FTC (section 4.7.1.5 of EAR)	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Improved persistence to cabotegravir (section 4.7.1.3 of EAR)	Yes	A long-acting injectable has the potential to improve persistence and address barriers that some communities have in their access to oral PrEP. For example, access to a CAB-LA would address challenges that people may face with pill burden which undermines adherence. Access to CAB-LA would also mitigate concerns that someone may have from taking oral PrEP if it is misinterpreted to be HIV treatment. This is because of concerns related to stigma, discrimination and intimate partner violence. Given that women at higher risk of acquiring HIV may experience intimate partner violence and not be in a position to negotiate safe sex, CAB-LA

		would also give women more control and safety in their sex lives and relationships. Despite the EAR noting the burden which on-time injections could have on individuals and health care systems, through the option of an injectable addressing some of the above challenges which mean that some people are unable to persist with daily oral PrEP, persistence to an injectable option could be improved. A study among US men who have sex with men found that most respondents would choose long-acting PrEP regardless of cost, clinic time, side effects or protection level.[1] Whilst this is a US study, despite the system and individual burdens which the EAR highlights, it does suggest that they could be addressed through the willingness and preference to use injectable PrEP over other modalities. In the field of contraception, the expanded availability of options, including combined injectable birth control, along with informed decision-making, has led to improved uptake and continued use of these methods. By similarly expanding the range of PrEP methods and focusing on individuals who encounter barriers to accessing oral PrEP, we can anticipate similar improvements in uptake and persistence. In addition, the challenges noted in the EAR around the requirement of trained healthcare professionals to administer injection, and the administrative burden on sexual health clinics, could be mitigated through improved efficiencies in the delivery of oral PrEP. Guided by the UK Government's PrEP Roadmap, the UK should ensure that oral PrEP can be accessed beyond sexual health services. This could include GPs and community pharmacies, plus termination of pregnancy and gender services. Through doing this, it would free up service capacity within sexual

[1] Cole et al (2024) Willingness and preferences for long-acting injectable PrEP among US men who have sex with men: a discrete choice experiment. Available at: https://bmjopen.bmj.com/content/14/4/e083837

		health clinics for the administration and effective provision of CAB-LA injections.
Disutility for HIV infection (section 4.8.1.1 of EAR)	Yes	People living with HIV continue to face structural and health barriers that hinder their health-related quality of life (HRQoL). It is welcome that the EAR notes the findings from the Positive Voices 2022 report which found that people living with HIV report a utility of 0.77, lower than a utility score of 0.82 in the general population. Beyond the EQ-5D-5L model, the Positive Voices 2022 report also found that people living with HIV have higher levels of unmet needs in several key domains compared to the general population. For example, the Positive Voices report finds that more than half of people living with HIV do not routinely have enough money to easily cover their basic needs. HIV is also a stigmatised condition and this stigma impacts on the HRQoL of people living with HIV. Research shows that HIV-related stigma is correlated with higher rates of depression, emotional distress and anxiety, poorer physical health, lower levels of adherence to antiretroviral medications and access to and usage of health and social services, all of which affect someone's HRQoL. [2] [3] Whilst the Positive Voices 2022 report is a useful tool to consider the disutility for HIV, a key limitation is that the survey doesn't include data for people disengaged from HIV care. Hospitals in urban areas in England are reporting that people previously diagnosed with HIV but not accessing care are now the leading driver of hospital admissions related to HIV. Disengagement from HIV care is the result of many factors, including experiencing complex medical and mental health needs, poverty, discrimination and fear of stigma. Given that there could be approximately 14,000 people in the UK with diagnosed HIV but not linked to care, their HRQoL is likely to be significantly worse than the overall data which the Positive Voices 2022 report puts forward.

[2] National AIDS Trust (2016) Tackling HIV stigma - what works. Available at https://www.nat.org.uk/sites/default/files/publications/Jun_16_Tackling_HIV_Stigma.pdf

[3] UK Health Security Agency (2024) Positive Voices 2022: survey report. Available at: https://www.gov.uk/government/publications/hiv-positive-voices-survey/positive-voices-2022-survey-report

		Therefore in considering disutility for HIV, in addition to recent research and advances in HIV care noted in the EAR, it would be important to consider the experiences of people disengaged from HIV care and the wider socio-economic and stigma challenges associated with living with HIV.
Starting age of Participants (section 4.7.1.4.1 of EAR)	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Duration of assumed aggregate risk period to reflect lifetime risk of sexually acquired HIV acquisition (section 4.7.1.4.2 of EAR)	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Cabotegravir injection administrative costs (sections 4.9.2 and 4.9.2.1 of EAR)	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Drug acquisition and administration (sections 4.9.1 and 4.9.1.1 of EAR)	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Other issue identified by NICE technical team: **Implementation of cabotegravir injections** In what clinical settings could/would cabotegravir injections be administered compared to where oral PrEP is currently administered?	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses

Abbreviations: CAB-LA, cabotegravir injections; CS, company submission; HIV, human immunodeficiency virus; ITC, indirect treatment comparison; PrEP pre-exposure prohylaxis; TDF/FTC, tenofovir disoproxil fumarate with emtricitabine (oral PrEP)

Additional issues

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Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

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Insert key issue number and title as described in the EAR	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the EAR	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.

Insert key issue number and title as described in the EAR	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case

PLEASE DESCRIBE HERE

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Cabotegravir for preventing HIV-1 in adults and young people [ID6255]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

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Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for comments is **5pm** on **Monday 10 June**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	[redacted] on behalf of BHIVA – British HIV Association
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	**ViiV** **Unrestricted funding is received from ViiV as well as other pharmaceutical companies to support the charitable activities of BHIVA. Restricted funding is received from ViiV to support research grant awards made by BHIVA to applicants conducting implementation research.**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**Not applicable**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
The population is narrower than the decision problem (section 2.3 of EAR)	Yes	While superiority of CAB LA as PrEP was demonstrated in the trials HPTN 083 and 084, the intention is to utilise long-acting PrEP who are most likely to benefit. A planned sub-analysis of HPTN 083 demonstrated higher HIV incidence among US Black men who have sex with men (MSM) and transgender women (TGW) than their non-White counterparts (Hyman Scott et al, CROI 2023). This resulted in a hazard ratio of 0.28 vs 0.86 for the same comparison. The increased incidence in this group was associated with lower adherence to TDF/FTC as determined by drug levels in dried blood spot. Thus, in people with determinants of lower adherence to oral PrEP, Cabotegravir would be likely more cost-effective.
Generalisability of the HPTN population (section 3.5.1.1 of EAR)	No	It is true that IMPACT recruited largely white MSM. PrEP initiation in heterosexual people has been low in the UK and the UK heterosexual population is very different from the population recruited in HPYN 084. As noted in the EAR, excluding people with lower adherence may underestimate the efficacy of cabotegravir. I am not aware of data from IMPACT that analyses the

		demographics of clinic attendees who did not take part in the trial, or those that did not attend further follow-up (another visit within a year of starting the trial). UKHSA surveillance data indicates that white cisgender MSM have seen the steepest decline in HIV diagnoses. While numbers are small, MSM from other ethnic groups (Black or Asian) have seen either a levelling off or an increase in HIV diagnoses, which suggests that there may be populations in the UK with higher need and poorer access to sexual health services and HIV prevention technologies. These groups may be more analogous to those who benefited most in HPTN 083.
Inclusion of studies in the ITC that were conducted in populations different from the population of interest as specified in the scope (section 3.4.1 of EAR)	No	It is true that the socio-economic conditions, healthcare systems and background HIV incidence in some of the included studies are different from the UK population. However, I think that the key point in this analysis is that adherence to oral PrEP is the key driver of efficacy and this is applicable to the UK population.
Inclusion of studies in CS ITC that does not meet the specified population of interest as described in the NICE scope (section 3.5 of EAR)	No	No comment
CS ITC analyses did not account for measurement error in adherence levels in the meta-regression of treatment effect on adherence to CAB-LA (section 3.4.1 of EAR)	No	No comment
Restricting treatment costs to period of heightened risk (assumed 5-years in the CS base-case) over a life-time risk capping the treatment costs which could favour	No	There is uncertainty about how this issue would play out in clinical practice. In reality, an individual's risk for HIV acquisition varies over time, with some people "tailoring" their use of PrEP to periods of higher risk (e.g. when sexually active with more than one partner).

CAB-LA in cost-effectiveness (section 4.3 of EAR)		
Inappropriateness of “no PrEP” as a Comparator in the model (sections 4.4 and 4.5 of EAR)	No	It is true that there is uncertainty about whether people who have difficulty maintaining appropriate adherence to oral PrEP, might also have difficulty attending regularly for cabotegravir injections. If people with higher levels of need are specifically targeted for injectable PrEP, then there may be a resource demand for clinical services in recalling and retaining individuals using this intervention. For individuals at risk of HIV acquisition, a long-acting injection does at least give protection against HIV acquisition for a prolonged period of time after it is given, vs little or no protection if inadequate or no oral medication is taken. The problem of generalisability from the HPTN studies is perhaps not very different from many randomised controlled trials. With respect to the population who might likely benefit more from injectable PrEP, the “real world” alternative to cabotegravir is likely to be no PrEP.
Inappropriateness of Baseline risk of HIV acquisition (section 4.7.1.1 of EAR)	No	No additional comment
Transition to TDF/FTC following discontinuation from cabotegravir (section 4.7.1.2 of EAR)	No	I am not sure of the clinical relevance of considering whether people taking TDF/FTC might transition to cabotegravir after discontinuing oral PrEP. As noted, most people in both arms offered choice in the OLE of 083 and 084 choose cabotegravir.
Adherence to TDF/FTC (section 4.7.1.5 of EAR)	Yes	I think the figures quoted form the UKHSA report for women first diagnosed in the UK (77% (301) born abroad and 31% (122) arriving in same year as diagnosis) are for all women diagnosed outside London. There were a further 171 women diagnosed in London, but the report does not give equivalent information about country of birth and year of arrival. For 2022, the UKHSA data tables indicate that there were 518 new HIV diagnoses among women, born in Africa, first diagnosed in England in 2022. For all new diagnoses in women born outside the UK and first made in England, UKHSA estimates that 37% were acquired in the UK. The report also notes lower testing rates in women in the UK so there is some uncertainty about the true rate of

		transmission among women in the UK. Oral PrEP uptake among women in the UK is very low and there are likely to be a number of barriers to this – some initial research into barriers for Black women in the UK was presented at the recent BHIVA conference (PowerPoint Presentation (bhiva.org) . Cultural beliefs and stigma as well as experiences of the healthcare system were identified as barriers. While not identical, there may be some similarities with the population recruited to HPTN 084.
Improved persistence to cabotegravir (section 4.7.1.3 of EAR)	No	I think it is very unlikely that an injection visit would take 60 minutes after a cabotegravir programme were established, and in any case some of this would be taken up with sexual health work which would be provided for people at risk of STI/HIV under usual circumstances. Health professionals are well versed in providing IM injections such as antibiotic and contraceptive injections, so additional training is likely to be minimal. A recall system would need to be introduced and there may be lower resource to actively recall patients than in a research trial setting, which may result in a higher number of missed / delayed injections.
Disutility for HIV infection (section 4.8.1.1 of EAR)	No	No comment
Starting age of Participants (section 4.7.1.4.1 of EAR)	No	Young people are likely to be a population where clinicians would look for opportunities to use cabotegravir, given lower adherence to all medication seen in this population. It may therefore be that the starting age for Cabotegravir is lower than the current PrEP population mean.
Duration of assumed aggregate risk period to reflect lifetime risk of sexually acquired HIV acquisition (section 4.7.1.4.2 of EAR)	No	No comment
Cabotegravir injection administrative costs (sections 4.9.2 and 4.9.2.1 of EAR)	No	There are a number of assumptions made. It is debatable that a senior clinician review would be required at every visit, especially once a patient is established on cabotegravir. A band 5 nurse is capable of reviewing symptoms, assessing STI risk, and performing the required tests under the direction of a prescriber. If the patient has more complex needs then this would appropriately use the skills of a more senior clinician. It is true that a cabotegravir programme would require the

		use of clinical resource within sexual health services that are already facing significant financial and resource constraints.
Drug acquisition and administration (sections 4.9.1 and 4.9.1.1 of EAR)	No	No comment
Other issue identified by NICE technical team: **Implementation of cabotegravir injections** In what clinical settings could/would cabotegravir injections be administered compared to where oral PrEP is currently administered?	No	Oral PrEP is only provided in specialist sexual health services in the UK, although there are ambitions to expand to community provision through pharmacies and primary care. Cabotegravir administration might present further opportunities for administration in women's health, primary care and other community settings, given that it does not need refrigeration and likely minimal requirements for toxicity-related blood monitoring. There are however, resource and cost implications for all these approaches, regardless of PrEP formulation. It seems likely that if introduced, cabotegravir would largely be delivered in specialist sexual health services.

Abbreviations: CAB-LA, cabotegravir injections; CS, company submission; HIV, human immunodeficiency virus; ITC, indirect treatment comparison; PrEP pre-exposure prohylaxis; TDF/FTC, tenofovir disoproxil fumarate with emtricitabine (oral PrEP)

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Sensitivity analyses around revised base case
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Single Technology Appraisal

Cabotegravir for preventing HIV-1 in adults and young people [ID6255]

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About you

Table 1 About you

Your name	[redacted], [redacted], [redacted], [redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	English HIV and Sexual Health Commissioners Group (EHSHCG) on behalf of ADPH: Stakeholder
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	NA
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	NA

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
The population is narrower than the decision problem (section 2.3 of EAR)	Yes	We agree with this issue. The biggest 'at risk' groups for HIV are MSM and Black African heterosexuals, yet Black African heterosexuals are not included within this modelling. In the UK the two groups most affected by HIV are gay and bisexual men and heterosexuals of Black African ethnicity. No effort to determine risks of heterosexual black Africans have been considered or whether they would benefit from receiving this form of PrEP treatment which we think is a gap: NAT-African-Communities-Report-June-2014-FINAL.pdf Clarification – are black African heterosexuals included in this? Another possible gap is people with complex lives/specific vulnerabilities e.g. injectable drug users, prison population, sex workers, who are at increased risk which is not specifically referenced. The population being considered should aim to mirror the population the BHIVA guidelines that identifies populations that are at risk of HIV and as such would benefit from having PrEP. See table on pg.52 of BHIVA PrEP Guidelines (2018) 2018-PrEP-Guidelines.pdf (bhiva.org)
Generalisability of the HPTN population (section 3.5.1.1 of EAR)	Yes/No	Agree this is a key issue that UK data isn't included when there is significant data available. It would be useful to compare to evidence from the PrEP Impact Trial.

Inclusion of studies in the ITC that were conducted in populations different from the population of interest as specified in the scope (section 3.4.1 of EAR)	Yes/No	See comment above re generalisability
Inclusion of studies in CS ITC that does not meet the specified population of interest as described in the NICE scope (section 3.5 of EAR)	Yes/No	See comment above re generalisability. Modelling may have benefitted from using the national PrEP indicator to inform need of PrEP who access specialist sexual health services. This indicator is used to determine PrEP need among people accessing specialist sexual health services (SHS). It assesses the proportion of all HIV negative people accessing specialist SHS who are at substantial HIV risk, and therefore could benefit from receiving PrEP: Public health profiles - OHID (phe.org.uk)
CS ITC analyses did not account for measurement error in adherence levels in the meta-regression of treatment effect on adherence to CAB-LA (section 3.4.1 of EAR)	Yes/No	Unable to comment
Restricting treatment costs to period of heightened risk (assumed 5-years in the CS base-case) over a life-time risk capping the treatment costs which could favour CAB-LA in cost-effectiveness (section 4.3 of EAR)	Yes/No	As PrEP has only been commissioned in Sexual Health services since 2020/21 it is difficult to say how long a 'typical' episode of PrEP would be. However, it is a fair assumption that individuals will access PrEP at different points in their life and have multiple episodes. Therefore a 5-year limit on this calculation feels very limiting. There will be variations in the need over a lifetime based on individual need.
Inappropriateness of "no PrEP" as a Comparator in the model (sections 4.4 and 4.5 of EAR)	Yes/No	Agree with this issue. However, the suggested remit is "To appraise the clinical and cost effectiveness of cabotegravir within its marketing authorisation as pre-exposure prophylaxis of HIV-1 infection in adults and young people". For this reason it may be appropriate to

		compare cabotegravir to both oral PrEP and “no PrEP”, as cabotegravir may still prove cost-effective compared to no PrEP, even if less cost-effective than oral PrEP. If more cost-effective than no-PrEP, this provides an alternative option for those who are deemed at high-risk in the population, for example those with complex lives, who are less likely to adhere to a daily tablet. For those where oral PrEP is not suitable, cabotegravir may also be an alternative option. Use BHIVA/BASHH table (B.1.3.4 /p23 of Technical Engagement papers) No-PrEP comparator – use BHIVA/BASHH table to identy PrEP need PHOF – PrEP need indicators -
Inappropriateness of Baseline risk of HIV acquisition (section 4.7.1.1 of EAR)	Yes/No	Rationale make sense but defer to clinical expertise.
Transition to TDF/FTC following discontinuation from cabotegravir (section 4.7.1.2 of EAR)	Yes/No	Rationale make sense but defer to clinical expertise. Note that TAF as an alternative does not seem to have been considered. Is this because it is not the SoC? However, as a second line option, cabotegravir may be a more cost-effective alternative to TAF for those who are not suitable for TDF/FTC.
Adherence to TDF/FTC (section 4.7.1.5 of EAR)	Yes/No	Agree with this issue. The eligible population has been framed incorrectly. Focus on MSM and cisgender women. Whilst there are studies on Black African communities these are based in sub-Saharan African studies rather UK population.
Improved persistence to cabotegravir (section 4.7.1.3 of EAR)	Yes/No	As sexual health commissioners we are unable to comment on this aspect. Clinical expertise should be sought.
Disutility for HIV infection (section 4.8.1.1 of EAR)	Yes/No	We would encourage UK data to be used to inform these figures.
Starting age of Participants (section 4.7.1.4.1 of EAR)	Yes/No	We disagree with using the median age of 33 as the data may be skewed due to the short time period that PrEP has been routinely available in the UK. As PrEP

		has only been routinely commissioned for 4 years, this means that those initiating PrEP now did not have the choice to start PrEP sooner as it was not available. Encouraging the whole eligible population to start PrEP (in line with HIV action plan) is likely to lead to a younger cohort accessing and offers opportunity to engage with the population sooner. Using the median starting age feels like an inappropriate indicator generally, especially when comparing to a trial where the socio-political factors and population demographics are likely to be vastly different from the UK population and where they can significantly impact the starting age of PrEP users. For example, in many sub-Saharan African countries, GBMSM individuals still face significant discrimination and stigma which will likely impact the starting age of PrEP due to fear of the consequences of being identified as GBMSM. For the two reasons above, if starting age were to be factored into the model of cost-effectiveness, rather than looking at the median age of PrEP users in the UK to try and be comparable to previous trials, it may prove more reliable and accurate to use the median/average starting age of new PrEP users in the UK.
Duration of assumed aggregate risk period to reflect lifetime risk of sexually acquired HIV acquisition (section 4.7.1.4.2 of EAR)	Yes/No	Agree to extend this to a 10-year risk period duration. A maximum is not realistic – some people may be on PrEP for much longer or may start and stop PrEP over their lifetime as their circumstances change. There should be some acknowledgement that a proportion of the population will continue to use PrEP for a potentially significantly longer period of time, for example those in long-term non-monogamous relationships. It may be beneficial to include a short-term, long-term, and life-long risk model to demonstrate cost-effectiveness which captures the wide variances in sexual behaviours/norms.
Cabotegravir injection administrative costs (sections 4.9.2 and 4.9.2.1 of EAR)	Yes/No	This new technology offers an opportunity to improve access amongst populations for whom oral PrEP may not be possible or acceptable therefore we welcome it as an additional treatment option. However, it is vital that there is consideration give

		to the funding of administration costs for cabotegravir injections. Whilst Local Authorities did receive a PrEP grant in 2020/21 and 21/22, this was specifically to support with costs of HIV PrEP drug will be met by NHS England in line with conditions set out in 'Supplying generic PrEP: NHS England contract requirements 2020/21' Reimbursement for the use of generic and second line drugs for Pre Exposure Prophylaxis (PrEP) for the prevention of HIV (2112) [230402P] (england.nhs.uk) This is based on generic TD-FTC being prescribed / supplied and approved in accordance with the appropriate provider arrangements for clinical governance and being the first-line therapy for PrEP. If this guidance changes to include cabotegravir then this grant allocation must be revised to reflect this. From initial economic analysis it seems that these additional administration costs could be significant. (caveat: below figures are suggested and unconfirmed Current PH commissioned annual activity costs for routine PrEP vary, but broadly annual cost per patient range £6-800 per annum. (Based on £214 first appointment x 1 and £186 x 3 follow up = £772). Early (unconfirmed) estimates suggest £1760 for year 1 and £1600 for year 2 based on the information provided with £675 discontinuation monitoring after cessation. At estimated £772 pa vs £1760 pa, this represents a 127.9% increased difference for activity costs and 87.45% for drug costs. Note that the overall drug costs for cabotegravir are less despite the increase due the less frequent administration (bimonthly rather than monthly)

		Current PH commissioned annual activity costs for routine PrEP vary, but broadly the annual cost per patient is around £800 per annum. (Based on £214 first appointment x 1 and £186 x 3 follow up = £772). Early (unconfirmed) estimates suggest *£2,300-£2,500* for year 1 and *£2,200* for year 2 based on the information provided with *£700* discontinuation monitoring after cessation. At estimated *£800 (or c.£1K)* pa vs *£2,400* pa, this represents *three (or 2.4) times increase in* activity costs. Potential implications of this are: • additional demand on already stretched sexual health services as additional appointments will be required (bi-monthly rather than quarterly, plus quarterly STI testing where this does not align with the bi-monthly dates). • Opportunity cost of sexual health services required to deliver these additional appointments – what won't/can't happen? • Workforce sustainability (existing pressure of Agenda for Change uplift being insufficient) If the administration costs are adequately funded then the above issues become less critical, as service provision will not be de-stabilised. Considerations/Questions: • What savings/efficiencies can be applied to these estimated activity costs? E.g.

		- Could clinical experts advise on if there is scope to align STI tests to existing appointments and (every 4 months) to minimise the additional burden of quarterly STI tests? - Is the appointment time accurate? We anticipate appointments would take less than 60+ minutes required post initiation? We would anticipate that this would likely be less than 60 minutes (but would defer to clinical expertise to advise). • Overall demand. It is unknown at this stage how many existing PrEP users would choose to transfer method of delivery from oral to injectable PrEP If they had the option. This is in addition to the new activity generated by the introduction of this new treatment option. • What clinical criteria will be applied to this new product? • Different delivery models at place. Local commissioning arrangements and models differ. Not all clinics will be offering nurse led clinics. Some may offer Dr/Consultant level based on local service models and workforce/skill capacity which would impact costs. In summary, we are supportive of the opportunity that cabotegravir offers for increasing access to PrEP and ultimately contributing towards the goal of the HIV Action Plan to achieve zero new transmissions by 2030. However, as Local Authority Commissioners it is vital to ensure that the costs of initiation, administration and discontinuation of cabotegravir are accurately reflected and funded to prevent destabilising already fragile specialist sexual health services.
Drug acquisition and administration (sections 4.9.1 and 4.9.1.1 of EAR)	Yes/No	For consistency across the system, we would support the NHSE calculation of weeks and days rather than months. Need to consider the impact of a patterns over a lifetime outside of the 5 (or 10) year window.

Other issue identified by NICE technical team: **Implementation of cabotegravir injections** In what clinical settings could/would cabotegravir injections be administered compared to where oral PrEP is currently administered?	Yes/No	At the moment sexual health services are the only commissioned providers to prescribe oral PrEP. There is the potential for PrEP (oral and injectable) to be available in other settings to improve access, however this would require additional funding and a nationally agreed framework. Additional settings include: Pharmacy Primary Care Drug and Alcohol Services Online (oral only)

Abbreviations: CAB-LA, cabotegravir injections; CS, company submission; HIV, human immunodeficiency virus; ITC, indirect treatment comparison; PrEP pre-exposure prohylaxis; TDF/FTC, tenofovir disoproxil fumarate with emtricitabine (oral PrEP)

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the EAR	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the EAR	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the EAR	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
PLEASE DESCRIBE HERE

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Cabotegravir for preventing HIV-1 in adults and young people [ID6255]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for comments is **5pm** on **Monday 10 June**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	NHS England Specialised Commissioning
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	**None**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**None**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
The population is narrower than the decision problem (section 2.3 of EAR)	Yes	We agree with the EAG's comment that the population in the company submission is narrower than that in NICE's scope, which has consequence on the assumed HIV incidence. Clinical expert opinion is that CAB-LA will be a good prevention option especially for women at higher risk of HIV infection, with one of the two key trials conducted in women (HPTN-084). We know that women are an underserved population, and so the availability of CAB-LA as PrEP will have a positive impact on health inequalities by reducing inequity to PrEP access. The following paragraphs were extracted from the UKHSA Official Statistics on HIV testing, PrEP, new HIV diagnoses and care outcomes for people accessing HIV services: 2023 report, which is the annual official statistics data release based on data to the end of Dec 2022 (link: HIV testing, PrEP, new HIV diagnoses and care outcomes for people accessing HIV services: 2023 report - GOV.UK (www.gov.uk); updated 6 Oct 2023). They show the PrEP need among sexual health clinic attendees and demonstrate that not all PrEP need had been met, especially in heterosexual men and women.

		"In 2022, the proportion of HIV negative people who were defined as having PrEP need, by gender and sexual orientation, remained highest in GBMSM at 69% (98,565 of 143,657) compared to 1.8% (4,156 of 228,668) in heterosexual men and 0.8% (4,602 of 595,303) in heterosexual and bisexual women (Figure 5 and Figure 6). Among HIV negative people, by gender and sexual orientation, the age group with the highest proportion of PrEP need were those aged 35 to 49 in GBMSM (69%, 30,129 of 43,654), 50 to 64 in heterosexual men (2.3%, 415 of 18,219), and 65 and over in heterosexual and bisexual women (1.8%, 46 of 2,500). Among people with PrEP need, the proportion who had their need identified during a clinical consultation increased slightly from 82% (58,464 of 71,581) in 2021 to 84% (83,223 of 98,565) in 2022 in GBMSM; there were larger increases in heterosexual men from 50% (1,554 of 3,125) in 2021 to 63% (2,607 of 4,156) in 2022 and in heterosexual and bisexual women from 34% (1,022 of 3,041) in 2021 to 59% (2,695 of 4,602) in 2022 (Figure 5 and Figure 6). Among people with PrEP need, by gender and sexual orientation, the age group with the highest proportion of their need identified were those aged 50 to 64 in GBMSM (88%, 9,730 of 11,058) and heterosexual and bisexual women (65%, 187 of 288), and 65 and over in heterosexual men (83%, 66 of 80). Among people with PrEP need, the proportion who initiated or continued PrEP rose slightly in GBMSM from 72% (51,689 of 71,581) in 2021 to 74% (72,457 of 98,565) in 2022; there were larger increases in heterosexual men from 35% (1,080 of 3,125) in 2021 to 39% (1,599 of 4,156) in 2022 and in heterosexual and bisexual women from 24% (716 of 3,041) in 2021 to 36% (1,676 of 4,602) in 2022 (Figure 5 and Figure 6). Among people with PrEP need, by gender and sexual orientation, the age group with the highest proportion of PrEP initiated or continued, were those aged 35 to 49 (78%, 23,426 of 30,129) as well as 50 to 64 (78%, 8,598 of 11,058) in GBMSM, those aged 50 to 64 years in heterosexual

		and bisexual women (45%, 130 of 288), and those aged 65 years and over in heterosexual men (46%, 37 of 80). These rises are likely due to a combination of an increase in PrEP service delivery as well as improvements in the coding and reporting of PrEP activity at SHSs.
Generalisability of the HPTN population (section 3.5.1.1 of EAR)	Yes	The HIV incidence in the HPTN population will be different to that in England. The HPTN 083 trial was conducted in the US, Thailand, Vietnam, Argentina, Brazil, Peru, and South Africa (link: Microsoft Word - SuppAppendix_Final_090221_Revised.docx (nejm.org)) and the HPTN 084 trial was conducted in seven countries in sub-Saharan Africa where the burden of HIV in women is high (ie, Botswana, Eswatini, Kenya, Malawi, South Africa, Uganda, and Zimbabwe) (link: Cabotegravir for the prevention of HIV-1 in women: results from HPTN 084, a phase 3, randomised clinical trial – The Lancet). HIV incidence in England is different from these two key trials. And the incidence is also changing due to ongoing efforts to achieve an 80% reduction in new HIV infections in England by 2025 (see Towards Zero: the HIV Action Plan for England - 2022 to 2025 - GOV.UK (www.gov.uk)). There is routine surveillance of HIV epidemiology in England led by UKHSA. The team at UKHSA has published incidence rate estimates in the following paper, 1. HIV incidence in an open national cohort of men who have sex with men attending sexually transmitted infection clinics in England - Desai - 2017 - HIV Medicine - Wiley Online Library

		2. HIV incidence among sexual health clinic attendees in England: First estimates for black African heterosexuals using a biomarker, 2009-2013 (lshtm.ac.uk) In addition, the HIV Synthesis Model (UCL) is another relevant information source, whereby it recreates the lifetime HIV risks, of MSM population in the UK. Their recent publication suggests the substantial effect on HIV incidence as a result of HIV prevention efforts in the form of oral PrEP HIV testing with ART initiation at diagnosis, and condom use. The publication also noted UKHSA's CD4 back calculation model estimated an 80% chance of a decline in incidence between 2019 and 2021 in this population. The publication can be found here The effect of combination prevention strategies on HIV incidence among gay and bisexual men who have sex with men in the UK: a model-based analysis - The Lancet HIV
Inclusion of studies in the ITC that were conducted in populations different from the population of interest as specified in the scope (section 3.4.1 of EAR)	Yes/No	We agree with the EAG's comments.
Inclusion of studies in CS ITC that does not meet the specified population of interest as described in the NICE scope (section 3.5 of EAR)	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
CS ITC analyses did not account for measurement error in adherence levels in the meta-regression of treatment effect on adherence to CAB-LA (section 3.4.1 of EAR)	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses

Restricting treatment costs to period of heightened risk (assumed 5-years in the CS base-case) over a life-time risk capping the treatment costs which could favour CAB-LA in cost-effectiveness (section 4.3 of EAR)	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Inappropriateness of "no PrEP" as a Comparator in the model (sections 4.4 and 4.5 of EAR)	Yes/No	We agree with the EAG's comments.
Inappropriateness of Baseline risk of HIV acquisition (section 4.7.1.1 of EAR)	Yes	The baseline risk of HIV acquisition needs to be based on the latest epidemiology in England and reflect that of the target population. Incidence will need to also reflect whether the target population is currently on oral PrEP, which will have reduced HIV risk as a consequence of oral PrEP. Using HIV incidence in people with a recent rectal bacterial infection only represents the highest risk group. As evident in Table 2 of Desai et al., 2017 (HIV incidence in an open national cohort of men who have sex with men attending sexually transmitted infection clinics in England - Desai - 2017 - HIV Medicine - Wiley Online Library), this group has the highest HIV incidence. In addition, HIV incidence is different among sexual health clinic attendees in England, as reported in Aghaizu et al., 2018 (HIV incidence among sexual health clinic attendees in England: First estimates for black African heterosexuals using a biomarker, 2009-2013 (lshtm.ac.uk)). This broader population is aligned to the population in NICE's scope and their corresponding HIV incidence should be considered. Finally, HIV incidence has reduced over time as a result of combination prevention strategies, as presented in Figure 2 of Cambiano et al., 2023 (The effect of

		combination prevention strategies on HIV incidence among gay and bisexual men who have sex with men in the UK: a model-based analysis - The Lancet HIV). The ongoing reduction in HIV incidence should be reflected in the cost-effectiveness model, this means that the HIV incidence is already lower than the estimates provided in earlier publications (Desai et al., 2017) and will likely reduce over time i.e. not fixed for the whole 5 years duration of high risk behaviour (as presented in the company submission base case).
Transition to TDF/FTC following discontinuation from cabotegravir (section 4.7.1.2 of EAR)	Yes	In addition to/besides oral PrEP, when an individual discontinues CAB-LA, they have to have quarterly HIV tests, including both the antigen/antibody test and the HIV RNA test. Individuals will need to continue to attend their sexual health clinics for blood sample collection. In addition, recall mechanisms will be required to be put in place to support and ensure continuity of care up to 12 months post-CAB-LA discontinuation.
Adherence to TDF/FTC (section 4.7.1.5 of EAR)	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Improved persistence to cabotegravir (section 4.7.1.3 of EAR)	Yes/No	Clinician expert advice suggests that persistence / adherence to cabotegravir could be higher for CAB-LA than oral PrEP due to the proactive approach (i.e. recall) that will be required to ensure continuity of care.
Disutility for HIV infection (section 4.8.1.1 of EAR)	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Starting age of Participants (section 4.7.1.4.1 of EAR)	Yes	The starting age differs by gender and sexual orientation. This is reported in the HIV testing, PrEP, new HIV diagnoses and care outcomes for people accessing HIV services: 2023 report - GOV.UK (www.gov.uk) which stated the following about age group with highest PrEP need. “Among people with PrEP need, by gender and sexual orientation, the age group with the highest proportion of PrEP initiated or continued, were those aged 35 to

		49 (78%, 23,426 of 30,129) as well as 50 to 64 (78%, 8,598 of 11,058) in GBMSM, those aged 50 to 64 years in heterosexual and bisexual women (45%, 130 of 288), and those aged 65 years and over in heterosexual men (46%, 37 of 80)."
Duration of assumed aggregate risk period to reflect lifetime risk of sexually acquired HIV acquisition (section 4.7.1.4.2 of EAR)	Yes	Changing HIV incidence over time needs to be reflected in the model to reflect anticipated background reduction in risk of infection. See The effect of combination prevention strategies on HIV incidence among gay and bisexual men who have sex with men in the UK: a model-based analysis - The Lancet HIV
Cabotegravir injection administrative costs (sections 4.9.2 and 4.9.2.1 of EAR)	Yes	We agree with the EAG's comment about administration cost being underestimated. Clinical experts suggested that initial assessment of CAB-LA eligibility requires MDT input, which consists of consultant medical doctors, and could take c.50 minutes for consultation, eligibility assessment, prescription writing, and to account for clinical time for declined CAB-LA offers. Additionally, 5 minutes of a Band 6 pharmacist time should be factored in for CAB-LA considering that this is a more complex intervention compared with oral PrEP. Clinical experts have advised that CAB-LA administration may initially be conducted by medical consultants and progress to staff nurses (Bands 6/7/8a) over time. A blend of registrar/medical consultant will need to be accounted for all subsequent prescribing activities. At the second appointment, it is anticipated that a blend of registrar/medical consultant will spend 30 minutes to review side effects and to prescribe CAB-LA. From the third administration onwards, this clinical input time reduces to 20 minutes. Five minutes of pharmacist time will need to be factored in for each administration. There will be heterogeneity in how services are delivered.

		In addition, the HIV testing cost used in the CS is lower than anticipated. The latest NIHR interactive costing tool suggests initial test cost is now £18. In addition to HIV antigen/antibody test, HIV RNA tests are necessary, this cost £52 for laboratory processing (from NIHR interactive costing tool, code 87534; cost for 2024/25; source: interactive-costing-tool-tariff-data-2024-25 v1.xlsx (live.com) There are other costs associated with each of the laboratory tests, including staff costs (5 minutes of a blend of scientific and professional staff pay bands 4 to 9; unit costs 2022/23; source: PSSRU 2023) for blood sample collection, disposables, and the cost for positive/reactive result management. Clinical expert suggests that 10% of individuals may require a second HIV viral load test. There will be additional time for medical consultant, nurses, and administration/clerical support to manage test results. The total estimated additional costs is c.£25 plus HIV antigen/antibody test £18 and HIV RNA test £52, giving a total pathway cost of c.£95. The HIV screening frequency is every 2 months, which is more frequent than the quarterly STI screening. In practice, individuals given CAB-LA could be offered STI tests alongside their CAB-LA injection appointments, which means more frequent STI screening compared to the counterfactual and increased corresponding resource use. CAB-LA levels have been detected in patients for up to 12 months, or longer in some cases. The Centers for Disease Control and Prevention (CDC) recommends that individuals who have discontinued CAB-LA require follow-up visits quarterly for 12 months, including antigen/antibody and HIV-1 RNA tests (https://www.cdc.gov/stophivtogether/library/topics/prevention/brochures/cdc-lsht-prevention-brochure-clinicians-quick-guide-what-is-injectable-hiv-prep.pdf). If the

		same recommendations apply in England, these monitoring costs need to be accounted for. This means that for 12 months, individuals will need to have their bloods taken for HIV antigen/antibody and HIV RNA tests every 3 months, therefore a minimum of 5 additional visits. Finally, the impact of setting up a recall mechanism to ensure follow-up and continuity of care post CAB-LA discontinuation should not be underestimated, since this will require additional staff time.
Drug acquisition and administration (sections 4.9.1 and 4.9.1.1 of EAR)	Yes	The MHRA licence for CAB-LA confirms that continuation injections are to be administered every 2 months.
Other issue identified by NICE technical team: **Implementation of cabotegravir injections** In what clinical settings could/would cabotegravir injections be administered compared to where oral PrEP is currently administered?	Yes	We have been advised by the service commissioners that CAB-LA PrEP will be administered in the same settings that oral PrEP is currently delivered i.e. Level 3 sexual health clinics. This includes sexual health providers that are co-located with NHSE commissioned HIV providers, as well as a number of independent, non-NHS sexual health providers.

Abbreviations: CAB-LA, cabotegravir injections; CS, company submission; HIV, human immunodeficiency virus; ITC, indirect treatment comparison; PrEP pre-exposure prohylaxis; TDF/FTC, tenofovir disoproxil fumarate with emtricitabine (oral PrEP)

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: HIV management costs	4.9.4	Yes	The company submission used list price estimates for HIV treatment drug cost published in Ong et al. (2019) and inflated these published costs from 2016/17 to 2023. There are two issues here. Firstly, it is clear in Figure 3 of the paper that many ARV would have lost market exclusivity since 2018 and generics are available on NHSE framework. The average treatment cost per HIV person is much lower now compared with 2015. NHSE figures suggests the current ARV cost per patient per year is £3,370 based on the latest data (confidential information to be shared with NICE). Secondly, ARV list prices for products that are still within their marketing exclusivity period in England have not changed over time. The government's 2024 Voluntary Scheme for Branded Medicines Pricing, Access and Growth sets out the criteria for any NHS List Price Increases (p.58 of 97, link: 2024 Voluntary Scheme for Branded Medicines Pricing, Access and Growth (publishing.service.gov.uk)).

Additional issue 2: What is the HIV incidence in a comparator arm of people who are on oral PrEP?	Did not identify specific section	Yes	It is not entirely clear what is the HIV risk if the comparator is oral PrEP. This value will need to reflect the changing disease epidemiology in England, as presented in published UKHSA HIV data and estimated change in risk over time as estimated by Cambiano et al., 2023 The effect of combination prevention strategies on HIV incidence among gay and bisexual men who have sex with men in the UK: a model-based analysis - The Lancet HIV.
Additional issue 3: Table 31 Unit costs of monitoring tests	4.9.3	Yes	The NIHR interactive costing tool tariff has been updated for 2024/25 and the latest costs should be used as they have changed at a faster rate than inflation, see interactive-costing-tool-tariff-data-2024-25 v1.xlsx (live.com)

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the EAR	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the EAR	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the EAR	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
PLEASE DESCRIBE HERE

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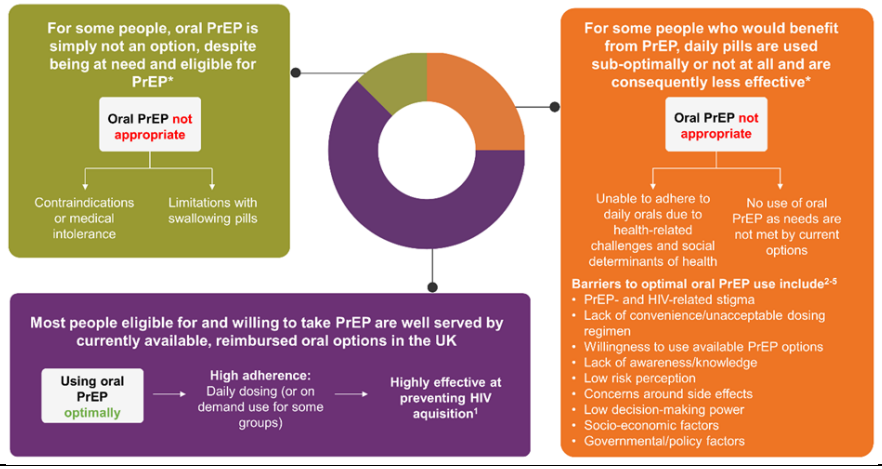
Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 1: Key issues

Key issue	New evidence, data or analyses ?	Response	EAG response
Issue 1: The population is narrower than the decision problem (section 2.3 of EAR)	No	***The company believe that the EAG have misinterpreted the description of the decision problem population in the CS. For some individuals with a PrEP need identified, oral PrEP options are not appropriate either because they cannot take oral PrEP or because they are unable to optimally adhere to an oral PrEP regimen.*** **Distinction between being eligible for oral PrEP and oral PrEP not being appropriate** The decision problem population (i.e., individuals for whom oral PrEP is not appropriate), while narrower, is aligned with the NICE scope[1] and the marketing authorisation for cabotegravir for PrEP.[2] In several key issues, the EAG have misinterpreted the description of the population in the decision problem, instead referring to "ineligibility" for oral PrEP. It is essential to understand that the population in the decision problem consists of individuals at high risk of acquiring HIV-1 for whom oral PrEP is not appropriate, which does not use the word "ineligible". PrEP eligibility, as described within the BHIVA/BASHH guidelines[3], is based on population level indicators, clinical indicators, sexual behaviour and sexual network indicators, drug use, sexual health autonomy or other factors that may affect sexual health autonomy. Individuals can meet these criteria and be eligible for oral PrEP, but that does not mean oral PrEP will be an appropriate option to meet their HIV prevention needs.	***The EAG have not misinterpreted the description of the population but agree that the use of the term 'ineligible' is not helpful. The company describes those*** **'for whom oral PrEP is not appropriate' :** **'1) Cannot take oral PrEP (comparison vs no PrEP)'** • ***These people are not represented in the HPTN 083 and 084 trials (as all participants could and did take oral PrEP)*** **'2) Can and are taking oral PrEP but have challenges resulting in sub-optimal adherence to it (comparison vs TDF/FTC), which may be for a variety of health, social or structural reasons*.'** • ***The trials included people who adhered optimally and people who had suboptimal adherence, however this was determined retrospectively.***

		The Company's decision problem population considers individuals who have a PrEP need identified (and are eligible for PrEP) but whose HIV prevention need is not met by current options, either because they cannot take oral PrEP or because they are unable to optimally adhere to it. **Population represented in the cost-effectiveness analysis** The population considered in the economic model represents individuals at high-risk of HIV acquisition who are eligible for oral PrEP in accordance with BHIVA/BASHH guidelines[3], for whom oral PrEP is not appropriate, including those who: 1) Cannot take oral PrEP (comparison vs no PrEP) 2) Can and are taking oral PrEP but have challenges resulting in sub-optimal adherence to it (comparison vs TDF/FTC), which may be for a variety of health, social or structural reasons. **Clinical efficacy data used in the economic analysis** The EAG expressed concerns with the population within both the HPTN trials not meeting the criteria outlined in the decision problem (i.e., people for whom oral PrEP is not appropriate), indicating that neither trial included eligibility criteria based on the ability/inability to take oral PrEP. Whilst the ability / inability to take oral PrEP was not a trial inclusion criterion, TDF/FTC adherence levels reported in the HPTN 083 and HPTN 084 trials demonstrate that oral PrEP was not used optimally by all participants. Irrespective of potential motivation for research participation, it is common to observe suboptimal adherence in oral PrEP studies as demonstrated in a systematic review and meta-analysis[4]. The proportion of participants in HPTN 083 and HPTN 084 with undetectable TDF/FTC, as measured by plasma TFV concentrations <0.31 ng/mL, was 14% and 44%, respectively. These data indicate that the trials represent a broad group of oral PrEP users, including some participants exhibiting sub-optimal adherence to daily TDF/FTC; therefore, within the trials it was observed that oral PrEP was not appropriate to meet some of the participants' HIV prevention needs. Because oral PrEP adherence is required for oral PrEP to be effective, this aligns with the population within the decision problem of people for whom oral PrEP is not appropriate.	***The final scope published by NICE for this appraisal describes the population of interest as "people at risk of sexually acquired HIV-1 infection." The company's decision problem (Section B.1.1 of the CS) describes the population as "adults and adolescents (weighing at least 35 kg) at risk of sexually acquired HIV for whom oral PrEP is not appropriate." The two populations are clearly different - the latter could be considered a subgroup of the former. Therefore, the EAG did not misinterpret the description of the decision problem.*** ***The company's original economic model structure allows for a proportion (set at [redacted] in the original base-case) of people in the CAB-LA arm of the model to transition to an oral PrEP regime within the 5-year heightened risk period. It is not logical coherent in the model to let people transition from CAB-LA to oral PrEP if oral PrEP is not appropriate for them in the first place. The model structure is thus consistent with the EAG's assessment that the company's description of the decision problem population is different from the population considered in the economic model (Section B.1.1 of the CS).***

		The EAG also comment that the main evidence submitted by the company for the comparison of cabotegravir with TDF/FTC is limited to adults aged ≥18 years in specific populations, i.e., men who have sex with men / transgender women, or cisgender women <45 years. These populations are representative of the majority of individuals who are expected to receive cabotegravir in the UK. **Unmet need** While the proposed reimbursement population of "individuals at high risk of HIV-1 acquisition for whom oral PrEP is not appropriate" is narrower than the marketing authorisation for "individuals at high risk of HIV-1 acquisition", this is suitable for NHS clinical and commissioning pathways for PrEP. This is because oral PrEP meets the HIV prevention needs of many people who have a PrEP need identified (purple box in Figure 1). However, there remains a quantifiable unmet need in England (green and orange boxes in Figure 1), which is driven by suboptimal uptake, adherence, and persistence to oral PrEP; therefore, new innovations are required to meet the needs of people at high risk of HIV-acquisition who are underserved by current oral options, and to reach the UK HIV Action Plan's target of zero new transmissions by 2030[5]. **Figure 1: HIV PrEP unmet need**  	

		***The green and orange boxes represent the anticipated positioning of cabotegravir.** Sources: 1. Sullivan et al, 2023[6]; 2. Calabrese et al, 2020[7]; 3. Coukan et al, 2023[8]; 4. Sidebottom et al, 2018[9]; 5. National AIDS trust[10]. Abbreviations: HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis; UK, United Kingdom.	
Issue 2: Generalisability of the HPTN population (section 3.5.1.1 of EAR)	No	***There are no UK patients in the HPTN trials; this issue is acknowledged but not considered a significant limitation given that the effectiveness of cabotegravir will be consistent across settings as demonstrated in the ITC. The effectiveness of TDF/FTC is driven by adherence and the economic model considers suboptimal adherence to TDF/FTC, in line with the population in the decision problem.*** **Extrapolation of HIV prevention trial data to other settings is frequent according to UK clinical experts** Although the HPTN studies did not include UK sites, this is not uncommon in NICE appraisals. HCPs have confirmed that within the fields of HIV prevention and treatment, they are comfortable with extrapolating data from different settings, and do this often.[11] They also noted that evidence of PrEP efficacy in cisgender women is limited and the data from HPTN 084 is highly valuable.[11] In addition, the reasons for engaging with oral PrEP for HIV prevention will be transferable regardless of the setting, as evidenced by high proportions of post-migration HIV acquisition in Western Europe.[12] **The definition of HIV acquisition risk in the HPTN trials is consistent with UK clinical guidelines** While the Company acknowledge that some differences between the trial populations and individuals potentially receiving PrEP in the UK may exist, these differences (such as sites, location, ethnicity, and socioeconomic factors) are not unique to these trials and are present in the majority of HIV prevention and treatment studies. However, when considering the definition of PrEP eligibility there is a significant degree of overlap between the trials and UK clinical practice.	***The absence of UK patients in the HPTN trials presents challenges in generalising the findings to NHS patients. This uncertainty about the applicability of HPTN trial data to economic decision model of UK populations remains an EAG issue. While the HPTN trials are the main source of effectiveness data, the absence of UK-specific data introduces significant uncertainties. These uncertainties could influence the cost-effectiveness analysis. Quantifying the impact without UK-specific data remains a challenge.***

The BHIVA/BASHH guidelines criteria for PrEP eligibility and the trial inclusion criteria are consistent, describing people at high risk of HIV acquisition (Table 2).

Table 2: HPTN 083, HPTN 084 inclusion criteria and BHIVA/BASHH criteria for PrEP eligibility

	HPTN 084	BHIVA/BASHH
ndomless receptive anal rse in the 6 months prior to nt (condomless anal rse within monogamous HIV ative concordant relationship t meet this criterion) an 5 partners in the 6 months enrolment (regardless of use and HIV serostatus, as by the enrolee) nulant drug use in the 6 prior to enrolment r urethral gonorrhoea or dia or incident syphilis in the s prior to enrolment S, a SexPro score of ≤16 o applied, which essentially ises the above criteria	• Born female • 18–45 years at the time of screening • Willing and able to provide informed consent • Willing and able to undergo all required study procedures • Non-reactive HIV test results at Screening and Enrolment • Sexually active (i.e., vaginal intercourse on a minimum of two separate days in the 30 days prior to Screening) • Score of >5 using a modified VOICE risk score • No plans to re-locate or travel away from the site for >8 consecutive weeks during study participation • CrCl ≥60 mL/min • HBsAg negative and accepts vaccination	• HIV-negative men who hav with men and transgender who report condomless ana the previous 6 months and condomless anal sex • HIV-negative individuals ha condomless sex with partn are HIV positive, unless the has been on ART for at lea months and their plasma vi <200 copies/mL

Abbreviations: ART, antiretroviral therapy; BHIVA/BASHH, British HIV Association/British Association for Sexual Health and HIV; CrCl, creatinine clearance; HBsAg, Hepatitis B surface antigen; HIV, human immunodeficiency virus; US, United States.

Conclusions from the indirect treatment comparison support that geographical location is not a treatment effect modifier

The ITC reported [redacted] estimates of effectiveness for cabotegravir versus no PrEP in the analyses in men who have sex with men and transgender women (the HPTN 083 study population) and cisgender women (the HPTN 084 study population) despite the differences in setting ([redacted] and [redacted], respectively). These observations support the generalisability of the results of the HPTN trials to other populations. Furthermore, the meta-regression establishing the relationship between adherence and effectiveness of TDF/FTC confirms that

		adherence is the true determinant of TDF/FTC effectiveness estimates. The level of adherence to TDF/FTC considered in the economic analysis, and therefore the resulting effectiveness of TDF/FTC, reflects those observed in the HPTN 083 and HPTN 084 clinical trials. Effectiveness is determined by the level of adherence observed in the population, regardless of the geographical location. **Comparing the populations of the HPTN trials with the IMPACT trial population is not appropriate and could lead to bias** Although the EAG suggest comparing the HPTN population with the PrEP IMPACT population, this would likely cause bias. There are substantial PrEP IMPACT trial inequities that widened post-commissioning of oral PrEP in England,[13] across gender, ethnicity, and region of residence, especially those of older age, women of Black ethnicity and those outside of London[8], with Black women being underserved with the largest PrEP equity gap[8] and 278-fold post-commissioning difference in PrEP to need ratio for Black African women (0.3) compared with White men (96.0).[8, 13] Additionally, the demographics of the PrEP IMPACT study[6] reflect people who are most activated and engaged in HIV prevention, with the majority of study participants being white men who have sex with men, born in the UK, and not experiencing deprivation. Therefore, the PrEP IMPACT study evaluating implementation does not fully reflect the wider HIV prevention needs of people across the UK, particularly where there are disparities in opportunities to prevent HIV acquisitions,[14] and among those who are more likely to acquire HIV and have unmet PrEP needs[15]. However, the HPTN trials intentionally recruited ethnically diverse men who have sex with men and transgender women, and Black cisgender women who have sex with men, reflecting populations with unmet PrEP need in the UK.	
Issue 3: Inclusion of studies in the ITC that were conducted in	No	***The studies included in the ITC and the population considered in the appraisal comprise individuals who are eligible for PrEP; not all individuals eligible for PrEP take oral PrEP or use it optimally, as evidenced by the inclusion of placebo arms and trials reporting suboptimal oral PrEP adherence. The relationship between adherence and oral PrEP effectiveness is informed by the meta-regression, and the ITC is used to estimate the relative effectiveness of cabotegravir or TDF/FTC versus no PrEP. The HPTN trials were well conducted multi-national trials and there***	***As stated in the EAG's response to issue 1 (please see above), the EAG did not misunderstand the company's description of the modelled population in the decision problem statement (CS Section B.1.1).*** ***Key issue 3 is related to the inclusion of the Bangkok Tenofovir study, which was conducted in a population of drug users, representing a***

<table>
<tr>
<td>populations different from the population of interest as specified in the scope (section 3.4.1 of EAR)</td>
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is no reason to believe that the effectiveness of cabotegravir is not transferable to settings not directly represented within the trials.

Alignment of studies included in the ITC and the Company's decision problem population

The EAG are concerned about disparities between the intended and actual populations modelled, and the inclusion of trials recruiting individuals eligible for oral PrEP in the ITC. As described in response to key issue 1, there is a misunderstanding of the Company's decision problem population (people for whom oral PrEP is not appropriate) and the definition of PrEP eligibility. The trials included in the ITC correspond to the clinical SLR PICOS criteria described in Table 3 that also specifically reported adherence on the basis of plasma samples.

Table 3: Clinical efficacy SLR eligibility criteria
<table>
<tr><td></td><td>Cisgender women, men who have sex with men, and transgender women ag
18 years and older who are at an increased risk of acquiring HIV-1
Adolescents who are at an increased risk of acquiring HIV-1</td></tr>
<tr><td>n/
rs</td><td>Long-acting injectable PrEP (including e.g. cabotegravir for PrEP)
Oral PrEP (including e.g. TDF/FTC, TAF/FTC)
Placebo or no PrEP</td></tr>
<tr><td></td><td>Incidence of HIV acquisition; cases of HIV averted; adherence to PrEP; AEs; of other STIs; behavioural changes (including condom use); drug resistance</td></tr>
<tr><td>gn</td><td>RCTs</td></tr>
<tr><td></td><td>English Language only</td></tr>
<tr><td colspan="2">Abbreviations: AE, adverse event; HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis; RCT, randomised controlled trial; SLR, systematic literature review; STI, sexually transmitted infection; TAF/FTC, tenofovir alafenamide/emtricitabine; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.</td></tr>
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The trials included in the ITC and the population considered in the appraisal consist of individuals eligible for PrEP; this does not mean that all individuals eligible for PrEP are taking oral PrEP or are using oral PrEP optimally, resulting in oral PrEP not being appropriate for their HIV prevention needs. Indeed, this is evidenced by trials including placebo arms and trials reporting suboptimal levels
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<td>
different mode of HIV infection to sexually acquired HIV infection. Additionally, the IPERGAY study was excluded in the EAG assessment because the TDF/FTC arm was described a" being used on an as-required basis, not daily oral PrEP usage", which is out of scope.

The comparison with placebo is irrelevant to the population for whom oral PrEP is or is not appropriate. This is because participants in the placebo-controlled trials, like the HPTN trials, could be randomised to receive TDF/FTC, and there was no reported a priori assessment of eligibility based on the appropriateness of oral PrEP.
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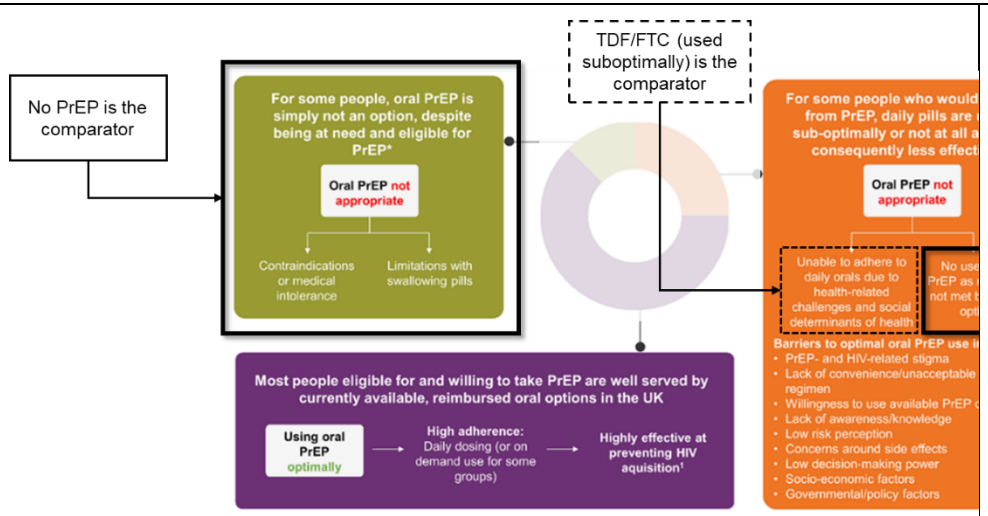
		of TDF/FTC adherence (as described in Table 19 and Table 20, section B.2.9.3 of the CS Document B). **The meta-regression is used to inform the relationship between adherence and effectiveness of oral PrEP and the ITC is used to estimate the relative effectiveness of cabotegravir or TDF/FTC versus no PrEP** As described in CS document B section 2.9, it is well established that adherence will be the primary determinant of effectiveness of TDF/FTC, and that differences observed between populations would primarily be mediated by differences in adherence. In the economic analysis versus TDF/FTC, the TDF/FTC adherence levels reported in the HPTN trials (86% of individuals sampled had detectable TDF in plasma in HPTN 083 and 56% in HPTN 084]) are used to inform TDF/FTC adherence and effectiveness in the economic model. Reflecting the observed adherence and effectiveness levels from the HPTN 083 trial in the Company's base-case analysis is conservative ([redacted] have TDF/FTC concentration corresponding to high adherence).[4] Populations who are underserved by current SoC may have lower levels of adherence to TDF/FTC than observed in clinical trials, which can be explored using the meta-regression relationship specified. Indeed, with lower adherence, effectiveness of TDF/FTC would be lower, leading to a greater differential in effectiveness between TDF/FTC and cabotegravir and greater cost-effectiveness of cabotegravir than presented in the base case for underserved populations. The ITC included trials with placebo arms that are used to inform the efficacy of interventions compared with 'no PrEP'. The efficacy of the 'no PrEP' comparator in the economic model is informed with UK data corresponding to the underlying risk of HIV acquisition for individuals who are eligible for PrEP (have a PrEP need identified) but are not taking oral PrEP.[3] **Extraction and calculation of adherence data** While the EAG noted in Section 3.2.6.3 of their report that there were concerns regarding the extraction and calculation of adherence data from the original publications of some studies in the ITC, the estimated adherence rates accounted for adherence in the sampled participants for both those who acquired HIV and those who did not. The Company estimated the weighted average according to the proportion of trial participants who acquired HIV. As the	

		proportions of patients who acquired HIV in these trials were low, the weighted average was close to the adherence in the sample of patients who did not acquire HIV.	
Issue 4: Inclusion of studies in CS ITC that does not meet the specified population of interest as described in the NICE scope (section 3.5 of EAR)	No	***Studies conducted outside of the NICE scope were included in the ITC base-case analysis; however, this is not necessarily a material issue given the results of the ITC are robust to the inclusion or exclusion of certain studies.*** The Company's ITC included data from the Bangkok Tenofovir study and the IPERGAY study, which were excluded by the EAG in their analyses. The results of the ITC are robust to the inclusion or exclusion of the PROUD, IPERGAY, and Bangkok studies as demonstrated in the Company's sensitivity analyses, and with the EAG analysis yielding similar results to the Company's ITC. The EAG also acknowledged that the differences observed between the ITC analyses and the Company's analyses, when applied to the economic model, are unlikely to substantially alter the magnitude of cost-effectiveness of cabotegravir compared with TDF/FTC produced from the Company's base case. It is therefore important to consider this key issue in the context of the EAG's conclusion that the analysis generated similar results to the Company's ITC. Although the Bangkok study was conducted in a different population, it is informative in an analysis examining the relationship between adherence and effectiveness. The Company note there may be other differences between this study and the other study populations; therefore, it was excluded in a sensitivity analysis. PROUD and IPERGAY were also excluded in sensitivity analyses due to differences between these and the remaining studies in terms of assessment of adherence and mode of PrEP administration. As stated above, the results of the ITC were robust in these sensitivity analyses.	***See our response to issue 3 which addresses this issue. We agree that the ITC analysis remained robust to the exclusion of these studies in this particular instance; however, the EAG assessment uses best practice in the conduct of systematic reviews, which dictates that the inclusion/exclusion criteria be applied to minimise bias.***
Issue 5: CS ITC analyses did not account for measur	No	***The Company agree with the EAG's approach to account for measurement error in adherence levels in the meta-regression of treatment effect and are reassured that the modification causes minimal changes, confirming the robustness of the ITC results.*** The robustness of the analysis is demonstrated by the fact that the EAG's analysis yielded similar results to the Company's. The Company treated the observed adherence as a fixed value as per the previous published meta-	***Again, we agree that the ITC results were robust to conducting the appropriate analysis for the data. The ERG raised this concern in the context of best practice, as it not possible to tell* a priori *what the likely impact would be on findings of the meta-analysis of formulating an incorrect statistical model for the relationship***

ement error in adherence levels in the meta-regression of treatment effect on adherence to CAB-LA (section 3.4.1 of EAR)		regressions.[16-18] Adherence measured by detectable plasma levels was chosen, as self-report was felt not to be reliable (self-reported measures are subject to multiple biases including social desirability and recall bias),[19, 20] and pill count data were infrequently available. This approach also aligns with the other published studies.[16, 17] The Company agree that the EAG's approach, formulating a binomial distribution for the number of people adherent to oral PrEP in the TDF/FTC arm of each trial, represents an incremental improvement in the analysis and are reassured that the modification causes a minimal change in results. This analysis, and the conclusions further corroborate the overall conclusion that the ITC is robust and suitable for decision making. As part of the critique of the Company's approach to adherence measurement, the EAG state in Section 3.4.2, Page 106 of their report that "incorrect estimates of adherence were applied in the Company's ITC for four trials (Partners PrEP,[9] iPrEx,[10] FEM-PrEP,[11] and PROUD[12] and corrected them in the EAG re-analyses of the ITC data." However, the EAG did not account for the preferential sampling of individuals who acquired HIV in the adherence studies. The EAG's 'corrected' values do not account for this and hence are biased. The CS used weighted averages to account for this and therefore the Company consider the ITC analysis used in their base case cost-effectiveness to be appropriate.	***between the treatment effect and a covariate measured with mirror.***
Issue 6: Restricting treatment costs to period of heightened risk (assumed 5-years in the CS	No	***Based on real-world data on PrEP persistence and UK clinical expert opinion, an assumed at-risk period of no longer than 5 years is deemed reasonable and appropriate for decision making where the purpose of the modelling analysis is to compare use of PrEP modalities.*** **Real-world evidence demonstrates a high rate of discontinuation** The EAG indicate a preference for a model allowing the at-risk period to be varied across a much broader range of values, while the Company's model allowed the at-risk period to vary from one to a maximum of 10 years; treatment costs are applied in both arms for all who remain on prophylactic care during the defined at-risk period. The real-world evidence used to inform persistence to oral PrEP in the economic model demonstrates a high rate of discontinuation (over 40% of people at 12 months).[21] Extrapolation of the real-world persistence data in the economic	***The company appears to base their modelling of cabotegravir on clinical expert opinion suggesting short-term use of PrEP. The EAG agrees that PrEP is mostly used for short-term periods. Expert opinion provided by NICE and submitted as part of this consultation supported the of short-term use of PrEP.*** ***To clarify, the company's model assumes that a single period of PrEP use represents lifetime of PrEP use. However, the EAG, supported by expert opinion, argues that individuals eligible for PrEP may have multiple short-term engagement with PrEP over their lifetime.***

base-case) over a life-time risk capping the treatment costs which could favour CAB-LA in cost-effectiveness (section 4.3 of EAR)		model leads to a decreasing proportion of individuals on PrEP and an increasing proportion of individuals on no PrEP over time so that in both the TDF/FTC and cabotegravir arms, the proportion of individuals who remain on PrEP after 5 years is 15% or lower. Single periods over which people are at-risk beyond 5 years, in combination with the available data on discontinuation, imply high levels of disengagement with PrEP provision, which are not consistent with data in the UK indicating that the majority of people with an assessed need for PrEP are accessing PrEP. In addition, UK clinical experts indicated that PrEP is mostly used for short-term periods ranging from 6 months to 2 years, while only a small percentage use it for longer durations, corroborating that a 5-year period of elevated risk may be considered as an upper limit and hence conservative. In summary, there are no data to support modelling an extended period of time beyond 5 years of elevated risk and as such receiving associated prophylactic care.	***Hence, a 5-year risk model is inadequate to support lifetime use of PrEP in individuals at high-risk of HIV acquisition.***
Issue 7: Inappropriateness of "no PrEP" as a Comparator in the model (sections 4.4 and 4.5 of EAR)	No	***The Company consider no PrEP to be an appropriate comparator, as there is no established clinical management, or alternative biomedical HIV prevention for individuals who cannot take oral PrEP but are otherwise eligible for PrEP. This population is quantifiable from UKHSA GUMCAD data (i.e., those with a PrEP need identified who do not initiate or continue PrEP).*** **No PrEP is a valid comparator in this appraisal** The Company consider no PrEP to be an appropriate comparator, and do not believe that it is "beyond the scope of the decision problem" as suggested by the EAG. The NICE final scope states that comparators are "established clinical management including tenofovir disoproxil or alafenamide in combination with emtricitabine or tenofovir alone" and does not explicitly exclude no PrEP as a comparator. For individuals who cannot have oral PrEP, there is no 'established clinical management' or alternative biomedical HIV prevention and as such 'no PrEP' is an appropriate comparator for these individuals.	***The trial data provided in the company submission captures the non-adherent population. The company combines the population who do not initiate oral PrEP i.e. 'no PrEP' population (are either unable to take oral PrEP or do not take oral PrEP) with the population who are either sub optimally adherent or persistent to oral PrEP. The costs and health outcomes of the population that sub optimally adhere or persist to oral PrEP were accounted for in the comparison with TDF/FTC as seen in the relatively lower adherence and persistence to oral PrEP compared with cabotegravir (full adherence was assumed for the cabotegravir arm).***

		The EAG also state that the population "ineligible for oral PrEP" is poorly defined in the decision problem and "for a no PrEP population to be considered, the characteristics of the population need to be clearly and explicitly outlined" and "sufficiently distinct from the population currently on oral PrEP". However, as discussed in response to key issue 1, the Company's decision problem population is defined as individuals for whom oral PrEP is not appropriate, which includes those who are otherwise eligible for but do not or cannot take oral PrEP for a variety of reasons. These individuals are distinct from individuals who are currently on oral PrEP in the UK. In England, 15% of people who have a PrEP need identified, do not initiate or continue oral PrEP.[22] This reflects both an unmet need, and a population of people with a need for HIV prevention that are not accessing or using oral PrEP. This quantifiable "no PrEP" population in the UKHSA GUMCAD data (i.e. those with a PrEP need identified who do not initiate or continue PrEP) alongside continued new HIV acquisitions in England, with 3,805 new HIV diagnoses in England in 2022, demonstrates there are people in England who require HIV prevention who would fall into the category of "no PrEP".[15] Figure 2 describes the population groups considered in the decision problem and the relevant comparators. **Oral PrEP may not be appropriate for all individuals who are eligible for PrEP; this population is captured in the clinical trials, reflected by some participants sub-optimally adhering to oral PrEP** The clinical trials include people who are eligible for PrEP but are not limited to people for whom oral PrEP is appropriate; this is reflected by the adherence levels in the trial, which demonstrated that oral PrEP was not appropriate for every individual (see response to key issue 3 for further details). **Figure 2: Cabotegravir comparators**	***PrEP eligible individuals who are sub optimally adherent or persistent to oral PrEP due to various reasons such as drug intolerability, begin oral PrEP but discontinue are non-adherent (this population is already captured in the comparison to TDF/FTC).*** ***The 'no PrEP' cohort are assumed to be on no PrEP from the first cycle. The EAG believes this population corresponds to company's a subset of "15% of people who have a PrEP need identified, (but) do not initiate or continue oral PrEP".[22] The EAG could not find the evidence to support the assumption that individuals who do not initiate oral PrEP for various reasons would accept CAB-LA and be fully adherent to.***



***The green and orange boxes represent the anticipated positioning of cabotegravir.**
Sources: 1. Sullivan et al, 2023;[6] 2. Calabrese et al, 2020;[7] 3. Coukan et al, 2023;[8] 4. Sidebottom et al, 2018;[9] 5. National AIDS trust[10] Abbreviations: HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine; UK, United Kingdom.

The Company's updated cost-effectiveness analysis removes the assumption of [redacted] transition onto TDF/FTC for individuals who cannot take oral PrEP (comparison vs no PrEP)

The EAG state that the "[redacted] of patients who stop taking cabotegravir transition to daily oral PrEP undermines arguments on the use of cabotegravir in patients whom oral PrEP is inappropriate and the comparison to oral PrEP." As described in response to key issue 9, the modelling of this transition reflects the SmPC recommendation following discontinuation of cabotegravir and the Company has removed this transition in the comparison versus no PrEP, reflecting people who cannot take oral PrEP, in its updated cost-effectiveness analysis.

Issue 8: Inappropriateness of Baseline risk of HIV acquisition (section 4.7.1.1 of EAR)	No	***The Company maintain an HIV incidence of 4.9 HIV acquisitions per 100 person years (PY) to be the most appropriate value; this limits the risk of bias resulting from not capturing those with limited current utilisation of sexual health services (SHS) and is aligned with evidence reporting HIV incidence in a population of individuals at high-risk of HIV acquisition. This value is supported by the results of the ITC.*** The baseline risk of HIV acquisition considered in the Company's economic model reflects the HIV incidence in England and Wales for individuals at high risk of HIV acquisition who are not receiving PrEP. In the BHIVA/BASHH guidelines,[3] incidence is reported of 4.9 HIV acquisitions per 100 PY for men who have sex with men who had a rectal bacterial STI in the previous 12 months, and 3.9 HIV acquisitions per 100 PY for men who have sex with men who had a rectal bacterial STI and an HIV test in the previous 12 months. The EAG argue that the latter estimate of 3.9 per 100 PY is more appropriate because the HIV test in the previous year ensures that the HIV acquisition is recent. It is important to recognise that in practice, whilst a negative HIV test at PrEP initiation is required, clinical experts consulted confirmed an additional negative test in the year prior to initiation is not a PrEP eligibility criterion. To avoid creating bias through not capturing those with limited current utilisation of SHS, the Company consider an incidence of 4.9 per 100 PY to be representative of the decision problem population. The estimated background risk of HIV acquisition derived from the ITC for the HPTN 083 population is within a range of [redacted] HIV acquisitions per 100 PY in men who have sex with men). The ITC results support the Company's preferred value to inform the HIV incidence for individuals on no PrEP in the economic model. HIV incidence should also be considered in the context of rising new HIV and STI diagnoses in England. Despite reductions in new HIV acquisitions in previous years, new HIV diagnoses in England are rising alongside large increases in STIs, which may reflect sexual behaviour with increased risk for HIV acquisition. New HIV diagnosis increased by 3% from 3,026 in 2020 to 3,118 in 2021, and by 22% from 3,118 in 2021 to 3,805 in 2022.[15] Additionally, the number of HIV diagnoses first made in England are rising in certain groups including heterosexual men and women living in London (14% rise from 284 in 2021 to 325 in 2022) and outside London (11% rise from 586 to 651), gay and bisexual men who have sex with men of Asian (17% from 75 to 88) and mixed or	***The company TE response states: "whilst a negative HIV test at PrEP initiation is required, clinical experts consulted confirmed an additional negative test in the year prior to initiation is not a PrEP eligibility criterion. To minimise bias from not capturing those with limited current utilisation of SHS, the company consider an incidence of 4.9 per 100 PY to be representative of the decision problem population". The EAG is unclear about the source and nature of bias that the company is alluding to.*** ***The BHIVA/BASHH guidelines reports multiple incidences estimates of HIV in England and Wales for men who have sex with men. The incidence rate used by the company is biased by the potential inclusion of people who may already be HIV positive at the time of testing given that 36% of all new HIV diagnosis in England in 2022 were among individuals previously diagnosed abroad (a rise from 21% in 2021).[26] While a previous HIV test is not a requirement for PrEP initiation, individuals who are HIV positive are ineligible for PrEP. Hence, the BHIVA/BASHH estimated 3.9 HIV acquisition per 100 PY for men who have sex with men who had a rectal bacterial STI and an HIV test in the previous 12 months removes the potential bias of individuals who may be HIV positive at the time of testing.*** ***If CAB-LA was proven to be cost-effective and was adopted by the NHS for high-risk groups, it could lead to a rapid reduction in HIV***

		other ethnicity (25% from 71 to 89), and a rise that is particularly steep in women living outside London who were exposed through sex with men (31% from 300 in 2021 to 393 in 2022). This rising trend is mirrored by rising incidence of STIs,[23] which may be considered as a proxy for the risk of HIV acquisition (indicator for condomless sex). The diagnosis of new STIs increased among people in England by 23.8% between 2021 and 2022 (392,453 new diagnoses in 2022 compared to 317,022 new diagnoses in 2021).[23] In 2022 there were large increases in the number of new diagnoses of gonorrhoea (50.3%, from 54,961 to 82,592), chlamydia (24.3%, from 160,279 to 199,233) and infectious syphilis (primary, secondary, and early latent stages; 15.2%, from 7,543 to 8,692) compared with 2021. The number of gonorrhoea diagnoses in 2022 is the largest annual number reported since records began, and the number of syphilis diagnoses the largest annual number reported since 1948.[23, 24] The UK government has acknowledged that the UKHSA data on STIs in 2022 is deeply concerning and identified that despite access to PrEP being highly effective in some groups, the focus on men had created inequality with a 26% increase in HIV diagnoses among heterosexual women.[25] Finally, the Company does not consider the EAG's scenario testing (using 1.9 per 100 PY) to be appropriate for the decision problem (individuals with a high risk of HIV acquisition). This incidence rate does not represent the population under consideration as they do not have the marker of high risk (recent STI as a proxy for condomless anal sex in the previous 6 months). It is vital to follow the guidelines definition to ensure that the underlying risk is reflective of the population considered in the appraisal.	***acquisition over time, resulting in a concomitant reduction in HIV incidence. Consequently, CAB-LA could become less cost-effective in future reassessments due to its success in reducing HIV infections to negligible levels.***
Issue 9: Transition to TDF/FTC following discontinuation from	Yes	***The transition from cabotegravir to TDF/FTC in the comparison versus TDF/FTC intends to model the PK tail following discontinuation of cabotegravir as recommended in the SmPC. The Company agree that in comparison versus no PrEP, for individuals who cannot take oral PrEP, 0% of individuals should transition to TDF/FTC after discontinuing cabotegravir. This is reflected in the Company's updated base-case analysis of cabotegravir versus no PrEP.*** In the economic model, the transition from cabotegravir to TDF/FTC represents the use of an alternative PrEP modality (not long-acting) in the PK tail as recommended in the SmPC, "Residual concentrations of cabotegravir may	***The EAG disagree with the company's rationale on transitioning to TDF/FTC following discontinuation from CAB-LA in the comparison to oral PrEP. The company's rational increases the ICERs. The company justified the transition on the basis that "Residual concentrations of cabotegravir may remain in the systemic circulation of individuals for prolonged periods (up to 12 months or longer)" following discontinuation. This justification infers that the***

cabotegravir (section 4.7.1.2 of EAR)		remain in the systemic circulation of individuals for prolonged periods (up to 12 months or longer); therefore, the prolonged release characteristics of Apretude injection should be taken into consideration when the medicinal product is discontinued and alternative not long-acting forms of PrEP are taken, as long as or at any time the risk of acquiring HIV is present in the months after discontinuation of Apretude".[2] It is important to distinguish this approach from modelling sequences where alternative longer-term PrEP modalities are considered upon discontinuation of cabotegravir or TDF/FTC. Furthermore, the comparator arm in the economic model should not include cabotegravir as a follow-on medicine if the model is to address this decision problem, which is specifically to assess the cost-effectiveness of the introduction of cabotegravir. Hence, a transition from oral PrEP to cabotegravir would not be appropriate in the oral PrEP comparator arm. In the population of individuals who are sub-optimally adherent to oral PrEP, the model considers that only [redacted] of individuals will receive TDF/FTC in the PK tail and applies a high rate of discontinuation of [redacted] monthly so that only a small proportion of individuals are still on TDF/FTC after 1 year. The Company maintains its original approach, which is in line with the SmPC recommendation of alternative not long-acting forms of PrEP to be taken in the months following discontinuation of cabotegravir. In the population of individuals who cannot take oral PrEP, the company accepts and agrees with the EAG that individuals would not receive TDF/FTC in the PK tail and has provided an updated cost-effectiveness comparison of cabotegravir versus no PrEP.	***residual concentration that remaisn in circulation offer some level of protection from HIV acquisition. The EAG could not locate the evidence that demonstrates the extent to which diminishing residual concentrations of cabotegravir protects from HIV acquisition.***
Issue 10: Adherence to TDF/FTC (section 4.7.1.5 of EAR)	No	***The company has provided evidence that disagrees with the EAG's assumption of equivalent adherence in men who have sex with men and transgender women, and cisgender women populations.*** While the EAG argue for equivalent adherence in men who have sex with men and transgender women, and cisgender women populations, clinical expert opinion and published evidence support that adherence for cisgender women is lower than in men who have sex with men and transgender women.[9, 16, 27, 28] For example, as noted by Sidebottom et al, both the FEM-PrEP and VOICE trials failed in young African women, and these trials are associated with poor	***The company states that it has provided evidence that disagrees with the EAG's assumption of equivalent adherence in men who have sex with men and transgender women, and cisgender women populations. However, the company does not provide any evidence that the adherence rates provided are generalisable to the UK setting:***

		adherence to oral PrEP (24% and 29% of non-seroconvertors, respectively, had detectable TDF).[29, 30] In a global systematic review, the pooled estimate of suboptimal adherence among cisgender women and girls who continued PrEP was 56.1% (95% CI: 44.0, 67.5),[4] and in a pooled analysis of 11 studies including 6,296 cisgender women less than 40% achieved high protection through consistently taking at least 4 doses per week with dramatic declines in adherence by Week 96.[27] In addition, cis-gender women have less PrEP options compared with men who have sex with men and transgender women, as they are not able to use TAF/FTC or event-based dosing.[3, 31] The EAG's assumption of equal adherence in these populations is not substantiated by any evidence. The company accepts that there is a lack of evidence on adherence to oral PrEP amongst cisgender women in England and Wales. The company would argue that the data from HPTN 084 on adherence in cisgender women outside the UK is a better estimate of adherence of cisgender women in England and Wales than data from a population of men who have sex with men and transgender women in HPTN 083. The Company note that 38% of HIV acquisitions in England in 2022 in cisgender women occurred in women of Black African ethnicity.[15] It is also worth noting that 36% of people newly diagnosed with HIV in England in 2022 were previously diagnosed abroad and that in 49% of cases, the region of origin was Africa. Consequently, there are cultural similarities between many cisgender women eligible for PrEP in the UK and the trial population in HPTN 084.	***Ref 9. The studies of cisgender women included in the Sidebottom 2018 systematic review were conducted in African countries.[9]*** ***Ref 4 Zhang 2022 systematic review: the company notes the pooled estimate of suboptimal adherence among cisgender women and girls who continued PrEP was 56.1% (95% CI: 44.0, 67.5).[4] The EAG notes that this is based on one study of 66 participants. Among all studies (including those of men who have sex with men) suboptimal adherence was higher in Sub-Saharan (51.7%) and Asia and Pacific (53.2%) regions than in North America (34.2%), Europe (28.6%) and South America (26.1%), suggesting that the setting is important.*** ***Ref 28 Marrazzo 2024: the company states that in a* 'pooled analysis of 11 studies including 6,296 cisgender women less than 40% achieved high protection through consistently taking at least 4 doses per week with dramatic declines in adherence by Week 96'.[27] *The EAG notes that of the 6296 participants, 46% were from Kenya, 28% were from South Africa, 21% were from India, 2.9% were from Uganda, 1.6% were from Botswana, and 0.8% were from the US.***
Issue 11: Improved persistence to caboteg	No	***Recently published real-world evidence has been provided that demonstrates a high persistence to cabotegravir, further supporting the assumption of 20% improved persistence versus oral PrEP applied in the economic model.*** **Real-world evidence supports the assumption of improved persistence with cabotegravir**	***Both referenced studies are published as abstracts only (posters available).*** ***The evidence cited by the company (Mills et al, 2024) is sensitive to the definition of discontinuation which is > or = 128 days (i.e. 18.2 weeks or 4.2 months) without cabotegravir injections.[32] This threshold might be too high***

ravir (section 4.7.1.3 of EAR)		There is real-world evidence demonstrating the high persistence to cabotegravir: • In one study, 93% persistence (7% discontinuation; defined as ≥128 days without a cabotegravir LA injection) was observed over a median of 7 months follow-up (IQR: 4.7 to 9.5) in the OPERA cohort of routine clinical care in the US[32] • In another, 94% persistence (aka: continuation) and no missed injections was reported in the 12-month TRIO cohort of routine clinical care in the US. Among 43 individuals with ≥3 injections, 27 (63%) had all injections after their second on time injection[33] In addition, UK clinical experts we consulted indicated that a 20% persistence advantage over oral PrEP was a reasonable assumption, and further commented that they would expect up to 50% improvement in persistence. **The EAG's assumption of reduced persistence to cabotegravir versus oral PrEP is misaligned with recently published real-world evidence** Recently published evidence (described above) confirms that real-life persistence with cabotegravir is high. Therefore, the Company considers the EAG's scenario of reduced persistence versus oral PrEP to be implausible and not justified. The EAG's rationale for assuming persistence to be lower with cabotegravir than oral PrEP is based on the "significant burden on both individuals and healthcare systems in ensuring on-time injections and the additional inconvenience of injection site reactions (ISRs) to patients." The population considered in the decision problem is individuals for whom oral PrEP is not appropriate. It is implausible to state that people who are receiving a more suitable PrEP modality are less likely to persist than individuals who are receiving a PrEP option that is not meeting their needs. Indeed, recently published evidence demonstrates that providing PrEP modalities that meet peoples' needs improves outcomes, including increased biomedical covered time and reduced HIV incidence.[34] The implementation of cabotegravir persistence in the model is likely conservative. It is important to note that in the CS, a 20% increase in persistence was applied to the proportion of people persisting with cabotegravir treatment at six and 12 months. The resulting monthly discontinuation rates are reduced in the first 6	***given that cabotegravir is administered every 8 weeks. The median follow up was 7 months which is inadequate to support a long-term effect.*** ***Furthermore, the study also reported that 11% of participants missed on-time injections in contrast to the company's assumption of full adherence to the on time injections in the economic model. PrEP users who miss on-time injections are required to take cabotegravir tablets for 30 days (and fully adhere to dosage requirements) before normal injections can resume. None of these scenarios were accounted for in the economic model.*** ***The second study cited by the company[33] as evidence of 94% persistence to cabotegravir was inaccurately described by the company. Individuals were followed up for 2 years and 5 months from PrEP initiation. 84 individuals had at least one documented injection of CAB LA for PrEP. Of these, 64 individuals had ≥ 2 cabotegravir PrEP, and only 48 of these 64 individuals had on time second injection (75%). Of 43 individuals with ≥ injections, only 27 (63%) had all injections after their second on-time. The 94% persistence cited by the company in their response actually refers to 94% of the 27 individuals (i.e. 25 individuals) who had all injections after their second on-time injection. Accounting for those began PrEP, the actual persistence is 29% (25/85) after 2 and 5 months of follow-up.***

		months for cabotegravir compared with oral PrEP, but thereafter are equal across the two arms. Hence, the assumption of increased persistence does not impact the discontinuation rate beyond 6 months. Whilst real-world implementation data for cabotegravir for PrEP is only available for a limited time-period, recently published real-world evidence (described above) demonstrates that persistence to cabotegravir is high and is supportive of a lower probability of discontinuation over this time relative to oral PrEP. It is likely that persistence improvements will be maintained beyond the 6 months post-initiation and so the Company's approach to modelling persistence can be considered conservative. As described in section B.3.3.9 (CS document B), long-acting interventions are commonly associated with improvements in persistence. This is observed with long-acting contraceptives, where matching women's preferred modality increased persistence (82). Clinical experts consulted confirmed they would expect comparable improvement in persistence with long-acting contraceptives and HIV prevention modality.	***Given the evidence above, it is a conservative approach to assume that persistence to cabotegravir is equivalent to oral PrEP.***
Issue 12: Disutility associated with living with HIV (section 4.8.1.1 of EAR)	No	***Clinical and methodological arguments presented by the Company strongly disagree with the EAG's decision to inform the HIV disutility with EQ-5D-5L data. The disutility value used by the Company is estimated with EQ-5D-3L in line with the NICE reference case[35]*** The EAG have assumed a disutility associated with living with HIV of –0.05 from the 2022 Positive Voice survey results.[36] The disutility preferred by the EAG uses the EQ-5D-5L instrument and applies the 5L tariff estimated by Devlin et al, which NICE does not currently recommend.[35] Conversely, Miners et al, 2014[37] preferred by the Company, uses the EQ-5D-3L version of the questionnaire and the NICE recommended UK 3L valuation set. A study published by Popping et al.[38] analysing the Positive Voices 2017 survey results allows us to compare the distributions per domain between the EQ-5D-5L of the Positive Voice survey and the EQ-5D-3L in Miners et al.[37] The importance of choosing either the EQ-5D-5L or EQ-5D-3L to estimate a disutility can be demonstrated by comparing the absolute differences between the proportion of responses by people living with HIV and the general populations on each of the domains, for each study (Table 4).	***We strongly disagree with the company's rationale for their choice of utility values based on the use of the EQ-5D-5L. It is incorrect to state that the tariff developed by Devlin et al was used to value EQ-5D-5L responses in the study reported by Positive Voices. It is also incorrect to state that using the EQ-5D-3L to estimate utility is in line with NICE reference case. NICE recommends the EQ-5D-5L as the preferred measure for health related quality of life.[43] NICE released a statement on the use of the mapping function developed by Devlin et al in 2019 recommending the use of the van Hout et al 2012 mapping function in place of the mapping algorithm developed by Devlin et al (Position statement on use of the EQ-5D-5L value set for England (updated October 2019)).[44] Since then, a mapping function for the EQ-5D-5L developed by Alava et al in 2022[45] has been***

For example, in Popping et al., 81% and 72% of the general population and people living with HIV respectively reported no problems with mobility, leading to an absolute difference of 9%. In Miners 2014, the corresponding proportions are 80% and 73%, leading to a difference of 7%. With the exception of the anxiety and depression domain, the absolute differences in domain responses are very similar across the studies. Overall, this suggests that it is the choice of 5L or 3L tariff that is driving the difference in disutility score, not that newer treatments have improved HRQoL.

Table 4: Comparison of disutility values in Popping 2021 and Miners et al, 2014

	No problems (absolute % difference)		Most severe level (absolute % difference)	
	Popping	**Miners**	**Popping**	**Miners**
Mobility	9	7	–1	0
Self-care	8	8	1	0
Usual act.	11	12	0	1
Pain	2	2	0	2
Anxiety/dep.	19	23	2	7

Note: the values for Popping relate to the 40–60-year age group, which is the closest age match to Miners, 2014.
Abbreviations: Dep., depression; act, activities.

The two Positive Voices surveys indicate that HRQoL in people living with HIV is lower than the general population and this has not improved between 2017 and 2022; there has been little change in the proportion of people reporting problems across all EQ-5D-5L domains since the original 2017 survey, except for pain and discomfort, which has increased.[36] HRQoL scores for people living with HIV in England are largely driven by lower scores in the anxiety/depression domain of the EQ-5D-5L,[36, 39, 40] and HIV prevalence in people in contact with mental health services is 2.5 times higher compared with the general population.[41] Stigma is associated with higher rates of depression.[42]

developed and is currently the recommended value set (NICE Decision Support Unit, 2022). Using the same argument as the company, the value set used by Miners et al[46] that informed disutility estimate would be invalid as it relied on a currently unrecommended mapping function.

The EAG's argument for the use of the more recent utility values is based on improvement in the drugs given to HIV positive individuals, which has led to fewer side effects and less pill burden. This has led to relatively better quality of life for HIV positive individuals who are actively managed. The new treatment guidelines were introduced in 2016 and utility values from the Positive Voices Survey are more likely reflect current disutility related to HIV infection than values from 2011.

Comparing responses to the individual domains of the EQ-5D instrument reported in the company TE responses is uninformative as profile scores are valued using general population preferences. Furthermore, the EQ-5D-5L has 5 levels and hence more discriminant validity than the EQ-5D-3L with 3 levels.

Issue 13: Starting age of Participants (section 4.7.1.4.1 of EAR)	Yes	***The Company agree with using UK data to inform the median age in the economic model. Using the latest UKSHA data available, the Company consider a revised median age of 31 for men who have sex with men and transgender women, and 29 years for cisgender women in the updated base case analysis.*** The EAG have stated that "the starting age of the cohort should reflect the median starting age of PrEP users in the UK rather than the median age of participants in non-UK trials". The Company agree that UK data may be more appropriate to inform age in the economic analysis and that the UKHSA is the appropriate source. Data from the UKHSA indicate that the median age of those accessing oral PrEP for both men who have sex with men and transgender women, and cisgender women falls within the groups aged 25–34. Assuming a uniform distribution of ages within this age group, the company estimates the median age for men who have sex with men and transgender women is 33.8 years. The corresponding figure for cisgender women is 31.1 years. The Company suggest that the midpoint of this range should align with the cohort age at the midpoint of the 5-year period of elevated risk modelled. Hence, the Company argue that the starting age for cohorts in the model should be 2.5 years less than the median age estimated from the UKHSA data. The Company's base case cost-effectiveness analysis has been updated to reflect a period of elevated risk commencing at age 31 for a cohort of men who have sex with men and transgender women, and 29 for cisgender women.	***The EAG could not verify the information provided by the company in calculating a median age of 25-34 years. The UKHSA cited by the company to support their analysis state: "Among those first diagnosed in England in 2022, 9% (232) were aged between 15 to 24, 31% (750) were aged between 25 to 34, 37% (904) were aged between 35 to 49, 19% (467) were aged between 50 to 64 and 4% (91) were aged 65 and over".[15] Stating that the median age of PrEP users in the UK falls within the age group 25-34 is factually incorrect. Indeed, the UKHSA sates "Among HIV negative people, by gender and sexual orientation, the age group with the highest proportion of PrEP need were those aged 35 to 49 in GBMSM (69%, 30,129 of 43,654)".[15] Given the company's population being restricted to people with highest risk of HIV acquisition, the median age of PrEP users in their defined population is likely to be higher than the starting age assumed by both the company and the EAG. Hence, the EAG followed a conservative approach in assuming a starting age of 33 years.***
Issue 14: Duration of assumed aggregate risk period to reflect lifetime	No	***The Company consider the simplified model structure to be appropriate for decision-making; the model in the CS captures the relevant costs of PrEP and the downstream impacts of HIV acquisition during a period over which people would be eligible for PrEP.*** As discussed in response to key issue 6, extending the risk period to 10 years is not appropriate based on real-world evidence of persistence. Indeed, the model's persistence factor implies that most people who are not living with HIV and could still benefit from PrEP would have already discontinued PrEP and returned to their baseline risk after approximately 3.5 years. This also represents	***The EAG could not verify the company's statement that most people who could still benefit from PrEP would have discontinued it by 3.5 years. After 3.5 years, 28% of people remain on cabotegravir PrEP (25.47% on cabotegravir + 2.51% on TDF/FTC) compared to only 21% on oral PrEP. Clinical opinion from the English HIV and Sexual Health Commissioners Group stated as part of the consultation process: "There should be some acknowledgement that a proportion of the population will continue to use***

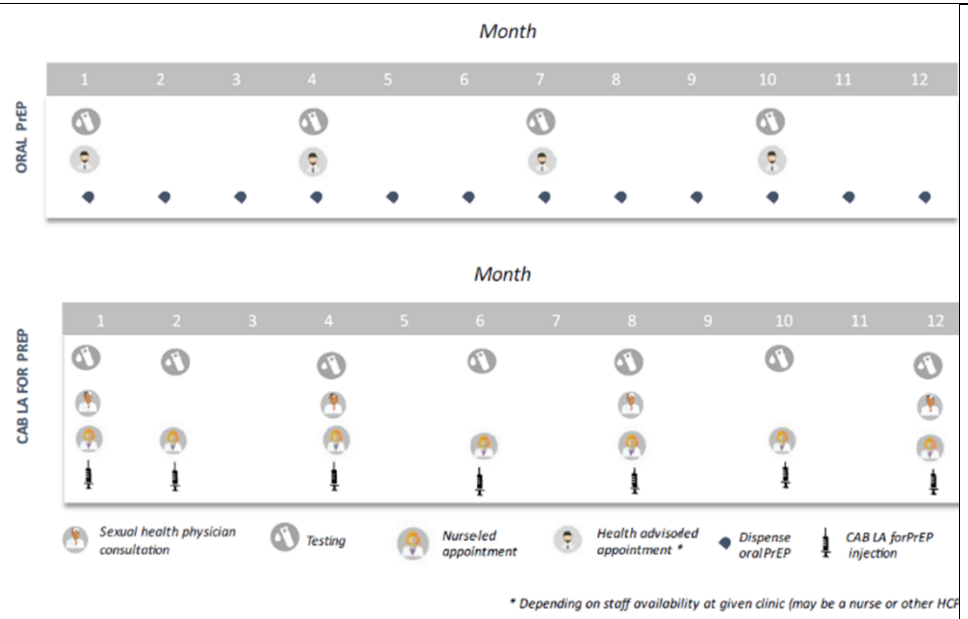
risk of sexually acquired HIV acquisition (section 4.7.1.4.2 of EAR)		poor coverage of the PrEP programme, with significant periods of high risk over the lifetime not covered by a PrEP intervention. The Company's model captures the relevant costs of PrEP and the downstream impacts of HIV acquisition during a period over which people would be eligible for PrEP. This duration will vary between individuals and no data on the mean duration could be found. The Company remain aligned with the assumptions on the mean duration presented in their original submission. Whilst no direct evidence on the duration is available, the real-world evidence on the rate of discontinuation and the proportion of people with an assessed need for oral PrEP who are accessing oral PrEP would indicate that the mean duration may be shorter than 5 years and is highly unlikely to be longer, which is consistent with clinical expert opinion (as reported in response to key issue 6).	***PrEP for a potentially significantly longer period of time, for example those in long-term non-monogamous relationships. It may be beneficial to include a short-term, long-term, and life-long risk model to demonstrate cost-effectiveness which captures the wide variances in sexual behaviours/norms".*** ***Allowing the at-risk period to be varied beyond 10 years would allow the EAG to explore the cost-effectiveness of differences in sexual and behavioural norms. The EAG agrees with the company that the duration of risk will vary between individuals and there is no data on mean duration. However, while risk duration might vary, mean duration on PrEP is not appropriate for this appraisal. Rather, the mean duration of PrEP users with the highest risk of HIV acquisition is more appropriate for the model population. Individuals at high risk of HIV acquisition are likely to stay on PrEP longer than the average PrEP user. Hence, the EAG maintains the 5-year risk period is insufficient to model lifetime risk of HIV acquisition. A higher risk duration is consistent with the company base case modelling assumption, defined population, and expert opinion from English HIV and Sexual Health Commissioners Group.***
Issue 15: Cabotegravir injection administrative	Yes	***The Company's updated base case analysis considers administration of cabotegravir requires two 30-minute initiation injection appointments, with 20-minute appointments for subsequent injections.*** The EAG's assumption overestimates the cabotegravir long-acting (LA) administration time. In a previous HTA of cabotegravir as treatment for HIV (cabotegravir + rilpivirine), NICE previously considered the assumption of a 15-minute administration time to be acceptable,[47] However, real-world evidence	***The company states that implementation of cabotegravir and rilpivirine involves a 5 step process which includes review by a physician. Evidence cited by the company from SHARE LAI-net also showed that injections take between 30-60 mins.[48] Despite the evidence cited by the company, the company's economic***

costs (sections 4.9.2 and 4.9.2.1 of EAR)		from clinical practice is now available to support the administration timings used in the updated model: A UK multi-centre service evaluation of cabotegravir and rilpivirine pathways (SHARE LAI-net) demonstrates appointment length was between 30 to 60 minutes, with an appointment length of ≤40 minutes in 78% (n=7/9) of NHS HIV clinics (note: cabotegravir + rilpivirine requires two injections with rilpivirine requiring cold chain storage).[48] [redacted]A lead nurse from a large urban sexual health clinic has advised that for compassionate use of cabotegravir for PrEP a 30-minute appointment would be appropriate; suggesting the injection itself is quick to draw up and administer and considered very similar to giving a treatment for gonorrhoea, which requires a slow plunge of the syringe for around 5-10 seconds. In UK SHS, penicillin antibiotic syphilis injections are intramuscular injections, similar to cabotegravir. The UK syphilis guidelines (BASHH 2015) state that "*all patients should be kept on clinic premises for 15 minutes after receiving the first injection to observe for immediate adverse reactions*".[49] Given all the above information, the Company believe that assuming two initial 30-minute appointments and then subsequent 20-minute appointments for the administration of cabotegravir LA is reasonable.	***model assumes cabotegravir administration is performed by a band 5 nurse and take only 20 mins for subsequent injections. It should be noted that the evidence cited by the company relates to the administration of cabotegravir and rilviripine. The EAG still maintains its base case assumptions and calls for clinical expert opinion to provide greater clarity on the administrative costs of cabotegravir PrEP injections.***
Issue 16: Drug acquisition and administration (sections 4.9.1 and	No	***In line with NICE reference case, final scope,[1, 50] the Company consider it is appropriate to model the cabotegravir dosing schedule in line with its marketing authorisation.*** **Cabotegravir dosing schedule** The Company modelled costs associated with cabotegravir acquisition, visits and administration following the dosing schedule as described in the SmPC, in line with the NICE reference case,[50] which states "*When we recommend medicines we expect that healthcare professionals will prescribe or advise their use within the terms of their UK marketing authorisations, as described in*	***Cabotegravir dosing schedule*** ***The company conflates a two month and an 8-week time period. The EAG does not dispute the wording of the SmPC which recommends administration of cabotegravir every 2 months. However, in the pivotal trial that formed the evidence base for cabotegravir use (HPTN 083 and HPTN 084), and in cases where cabotegravir has been used in the UK, doses are administered***

4.9.1.1 of EAR)		*manufacturers' SmPCs.*"[50] In addition, the NICE final scope states 'Guidance will only be issued in accordance with the marketing authorisation' hence cabotegravir has been modelled this way".[1] The EAG consider an alternative dosing schedule informed by an NHSE submission. At the technical engagement call, the EAG clarified that consulted clinical experts had been using cabotegravir following the clinical trials schedule. The Company acknowledge that in practice, there may be some variability in administration date (the SmPC indicates that individuals may be given injections up to 7 days before or after the date of the target injection date;https://www.medicines.org.uk/emc/product/15696/smpc (last accessed May 2024)[2]; however, best practice is to administer cabotegravir in line with the SmPC recommendation that is, continuation injections administered every 2 months following initiation injections. ***The EAG's approach to model incremental costs that could incur if restarting cabotegravir during the modelled risk-period without considering effects on health outcomes is inappropriate and misaligned with the model structure.*** **Multiple treatment cycles due to discontinuation and restarting over an individual's lifetime** The EAG have noted that the model does not explicitly represent discontinuation and restarting of PrEP over an individual's lifetime, and that this could further impact drug acquisition and administration costs. The EAG propose to illustrate this in the economic model by applying a 5% incremental cost to cabotegravir. Considering the model structure, modelling costs associated with people resuming PrEP is not appropriate without considering effect on health outcomes. The model captures the costs associated with cabotegravir initiation within the first 2 months. In practice, it is plausible that individuals may have several periods of elevated risk throughout a lifetime but there is no evidence reporting the average frequency of these periods throughout individuals' lifetimes. Furthermore, attempting to model multiple risk periods (which may be highly variable amongst individuals) would require a complex modelling approach without improving the clinical validity of the model structure to the decision problem.	***every 8 weeks after the initial two doses. In fact, the EAG is unaware of any study or real-world use of cabotegravir PrEP where an 8-weekly dosing schedule was not used after the initial two doses. The dosing schedule reflects both evidence from the NHSE and the clinical trials conducted by the company. Actual administration time may vary due to injections being given 7 days before or after 8-weekly target injection date.*** ***Six injections a year translates to 48 weeks of PrEP coverage leaving 4 weeks unaccounted for. This is more than the recommended time between injection doses.*** ***Assuming an 8 weekly dosing schedule after the initial two doses doubles the ICER as shown in the EAG report. Failure to accurately reflect the frequency of cabotegravir administration goes against NICE guidance that all direct costs and health effects be accounted for.*** ***Using an alternative dosing schedule to that used in a real-world setting undervalues the real cost of cabotegravir use and produces an incorrect ICER.*** ***Multiple treatment cycles due to discontinuation and restarting over an individual's lifetime*** ***The EAG agrees with the company's description of the complexity of implementing a dynamic risk of HIV acquisition within the framework of the***

		The model captures the increased initial costs of cabotegravir within the first 2 months and then utilises real-world evidence of persistence to inform the rate of discontinuation of PrEP. Thus, the model captures the full cost and benefits of cabotegravir use over a period of elevated risk. If individuals subsequently restart PrEP, this would be considered as a separate period of risk. The company would argue that the modelled single time period is representative of each period of elevated risk an individual may experience during their lifetime. The company argues that explicit modelling of increased costs and benefits of cabotegravir throughout multiple single time periods is unlikely to be materially different from the cost-effectiveness of cabotegravir than what is presented. As individuals must be HIV negative to be eligible for PrEP, prior periods of risk would not influence the characteristics of the individuals entering the modelled population/decision problem. There is no reason to believe that the costs and benefits do not scale proportionally leaving the ICER essentially the same. Indeed, the age distribution of current PrEP users does in fact represent a cross-sectional snapshot of periods of elevated risk across the lifetime of those engaged in the PrEP programme, and we reflect this distribution though using the median age in the model. The EAG's approach to inflating costs associated with cabotegravir acquisition, administration and visits, effectively assumes that patients are stopping and restarting PrEP during the period of persistence indicated by the real-world evidence. This would indicate true discontinuation rates much higher than those used in the model, which are informed by real-world data. The Company consider this approach to be overly simplistic, poorly aligned with the available real-world evidence and not appropriate to evaluate the cost-effectiveness of multiple cycles of cabotegravir use with varying risk patterns over an individual's lifetime.	***model and decision problem. The EAG however, disagrees that modelling increased costs through multiple time periods is unlikely to be different to the cost-effectiveness results already presented. Currently, the benefits of multiple time periods are currently captured in the model as individuals on PrEP receive have a significantly lower risk of HIV acquisition over the on-risk time period. However, the costs associated with multiple risk periods is not captured as restarting cabotegravir requires two initial doses before an 8 weekly dosing schedule is resumed.*** ***Furthermore, assuming risk of HIV acquisition changes when individuals stop and restart cabotegravir, the ICER is likely to be significantly higher than currently calculated by both the company and EAG due to the impact of cabotegravir in reducing HIV incidence rates.*** ***The EAG's simplistic approach in accounting for the costs of multiple risk period is a conservative estimate and accounts for the implicit assumptions in the company's model structure. According to their model, individuals cannot take PrEP or acquire HIV beyond 36 years of age. The EAG proposes the exploration of a scenario that reflects a lifetime use of PrEP and thus eliminates the need to model multiple risk periods.***

Other issue identified by NICE technical team: **Implementation of cabotegravir injections** In what clinical settings could/would cabotegravir injections be administered compared to where oral PrEP is currently administered?	No	***Injectable PrEP will be administered in SHS, which have experience in administering intragluteal injections for infectious diseases.*** **Administration setting** We anticipate commissioning policy and service specifications to state that cabotegravir for PrEP (Apretude) injections will be administered in Level 3 SHS in England, which is where oral PrEP is currently administered[51] • Level 3 (specialist) SHS in England provide risk assessment, initiation and clinical follow up and monitoring of HIV PrEP.[52] • SHSs providing specialist services in England, including HIV prevention, are commissioned by local authorities.[53] **Injectables competency** Level 3 SHSs have extensive experience of administering intramuscular injections, for example injectable antibiotics for syphilis and gonorrhoea.[54] In addition, several HCPs have reported similarities with the administration of injectable contraceptives, including both injection administration and setup of regular appointments for the recipient and the clinic (12-weekly appointments for injectable contraception), **Administration process and resource capacity** Cabotegravir LA is to be administered as a single 3mL intramuscular gluteal injection, with the first two injections administered 1 month apart and subsequent injections administered every 2 months. An optional 1-month oral lead-in and bridging during which cabotegravir 30 mg tablets can be taken orally once daily is also available to assess tolerability.[2] **Differences in patient pathway between oral PrEP and cabotegravir** Comparison to the current oral PrEP treatment environment is described in Figure 3. **Figure 3: Current oral PrEP environment**	***Committee points***



Source: EMA 2009[55]; EMC 2024[2, 56]
Abbreviations: PrEP, pre-exposure prophylaxis.

Due to the mode and frequency of administration, cabotegravir will require certain changes to the current patient pathway:

- **Mode of Administration** – compared to oral PrEP options, which are self-administered, cabotegravir LA is an injection administered by an HCP, with nurses likely to be the main staff group administering intramuscular injections.
- **Frequency of Administration** – administration for cabotegravir LA will be every 2 months after initiation[2]
- **HIV testing (and potentially different type of test)** – prior to receiving PrEP, individuals must have a recently documented negative HIV test. For oral PrEP, HIV testing is recommended using combined HIV antigen/antibody test (plus point of care test if same

			day initiation is preferable) before initiation and monitoring tests performed every 3 months.[3] For cabotegravir LA, individuals must be tested for HIV-1 prior to initiating cabotegravir and at each subsequent injection of cabotegravir. A combined antigen/antibody test as well as an HIV-RNA-based test should both be negative. Prescribers are advised to perform both tests, even if the result of the HIV-RNA-based test will become available after cabotegravir injection.[2]	

Abbreviations: BHIVA/BASHH, British HIV Association/British Association for Sexual Health and HIV; CI, confidence interval; CS, company submission; EAG, evidence assessment group; GUMCAD, Genitourinary Medicine Clinical Activity Dataset; HCP, healthcare professional; HIV, human immunodeficiency virus; HPTN, HIV Prevention Trials Network; HRQoL, health-related quality of life; HTA, health technology assessment; ICER, incremental cost-effectiveness ratio; IQR, interquartile range; ISR, injection site reaction; ITC, indirect treatment comparison; LA, long acting; NHS, National Health Service; NHSE, National Health Service England; NICE, National Institute for Health and Care Excellence; PICOS, population, intervention, comparison, outcomes, study design; PK, pharmacokinetic; PrEP pre-exposure prophylaxis; PY, person-years; RNA, ribonucleic acid; SHS, sexual health services; SLR, systematic literature review; SmPC, summary of product characteristics; SoC, standard of care; STI, sexually transmitted infection; TDF/FTC, tenofovir disoproxil fumarate with emtricitabine; TFV, tenofovir; UK, United Kingdom; UKHSA, United Kingdom Health Security Agency; US, United States.

Additional issues

Not applicable.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 5: Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Issue 15: Cabotegravir injection administrative costs (sections 4.9.2 and 4.9.2.1 of EAR)	No RNA testing included	Cost of RNA testing included for patients on cabotegravir: 7 tests in Year 1, followed by 6 tests in Year 2+	• ICER vs oral PrEP: £8,844 ○ Change of +58% • ICER vs no PrEP: Dominant (–£43,407; South-East quadrant) ○ Change of +2%
Other issue identified by NICE technical team: **Implementation of cabotegravir injections**	Antigen/antibody HIV testing included 6 tests in Year 1, followed by 4 tests in Year 2+ for patients on cabotegravir	Antigen/antibody HIV testing included at every injection administration for patients on cabotegravir: 7 tests in Year 1, followed by 6 tests in Year 2+	• ICER vs oral PrEP: £5,783 ○ Change of +4% • ICER vs no PrEP: Dominant (–£44,440; South-East Quadrant) ○ Change of 0%
Issue 13: Starting age of Participants (section 4.7.1.4.1 of EAR)	Starting age of 26 for men who have sex with men and transgender women, starting age of 25 for cisgender women	Starting age of 31 for men who have sex with men and transgender women, starting age of 29 for cisgender women	• ICER vs oral PrEP: £7,778 ○ Change of +39% • ICER vs no PrEP: Dominant (–£42,966; South-East quadrant) ○ Change of +3%

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Issue 15: Cabotegravir injection administrative costs (sections 4.9.2 and 4.9.2.1 of EAR)	Administration time of 15 minutes for all administrations of cabotegravir LA	Administration time of 30 minutes for first two administrations of cabotegravir LA, followed by administration time of 20 minutes for all subsequent administrations of cabotegravir LA	• ICER vs oral PrEP: £5,902 ○ Change of +6% • ICER vs no PrEP: Dominant (–£44,400; South-East quadrant) ○ Change of 0%
Issue 9: Transition to TDF/FTC following discontinuation from cabotegravir (section 4.7.1.2 of EAR)	[redacted] of individuals transition to TDF/FTC after discontinuing cabotegravir in the comparison with no PrEP	0% of individuals transition to TDF/FTC after discontinuing cabotegravir in the comparison with no PrEP	• ICER vs oral PrEP: £5,580 ○ Change of 0% • ICER vs no PrEP: Dominant (–£42,872; South-East quadrant) ○ Change of +4%
Company's revised base case following technical engagement	Incremental QALYs vs oral PrEP: [redacted] Incremental QALYs vs no PrEP: [redacted]	Incremental costs vs oral PrEP: [redacted] Incremental costs vs no PrEP: [redacted]	• ICER vs oral PrEP: £11,616 ○ Change of +108% • ICER vs no PrEP: Dominant (–£39,932; South-East quadrant) ○ Change of +10%

Abbreviations: ICER, incremental cost-effectiveness ratio; HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life year; RNA, ribonucleic acid; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

Sensitivity analyses around revised base case

Probabilistic sensitivity analysis

Table 6: PSA base case cost-effectiveness results for cabotegravir versus TDF/FTC

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus baseline (£/QALY)	Incr. NHB at £20,000 per QALY	Incr. NHB at £30,000 per QALY
TDF/FTC	[redacted]	[redacted]	–	–	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	£10,924	0.09	0.12

Abbreviations: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

Figure 4: Cost-effectiveness scatterplot of cabotegravir versus TDF/FTC

Abbreviations: QALY, quality-adjusted life year; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

Figure 5: Cost-effectiveness acceptability curve of cabotegravir versus TDF/FTC

Abbreviations: QALY, quality-adjusted life year; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

Table 7: PSA base case cost-effectiveness results for cabotegravir versus no PrEP

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus baseline (£/QALY)	Incr. NHB at £20,000 per QALY	Incr. NHB at £30,000 per QALY
No PrEP	[redacted]	[redacted]	–	–	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	–£43,616	1.66	1.28

Abbreviations: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; PrEP, pre-exposure prophylaxis; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

Figure 6: Cost-effectiveness scatterplot of cabotegravir versus no PrEP

Abbreviations: PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life year.

Figure 7: Cost-effectiveness acceptability curve of cabotegravir versus no PrEP

Abbreviations: PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life year.

Deterministic sensitivity analysis

Figure 8: Tornado diagram with cabotegravir versus TDF/FTC

Abbreviations: ARV, antiretroviral; cabotegravir LA, cabotegravir long-acting; CI, confidence interval; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; MSM, men who have sex with men; NRTI, nucleoside reverse transcriptase inhibitor; PK, pharmacokinetic; PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life year; SMR, standardised mortality ratio; TDF/FTC, Tenofovir disoproxil fumarate with emtricitabine.

Figure 9: Tornado diagram with cabotegravir versus no PrEP

Abbreviations: ARV, antiretroviral; CI, confidence interval; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; MSM, men who have sex with men; PK, pharmacokinetic; PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life year; SMR, standardised mortality ratio; TDF/FTC, Tenofovir disoproxil fumarate with emtricitabine.

Scenario analysis

Table 8: Probabilistic scenario analysis for cabotegravir compared with TDF/FTC and cabotegravir compared with no PrEP

Scenario	Base case parameter	Value in scenario analysis	Rationale	ICER versus TDF/FTC	ICER versus no PrEP
Base case	–	–	–	£10,924	Dominant (–£43,616; SE quadrant)
Cisgender women population	3.14% of the population	100% of the population	Clarify cost-effectiveness in this part of the population	£14,098	Dominant (–£14,744; SE quadrant)
Men who have sex with men and transgender women population	96.86% of the population	100% of the population		£12,366	Dominant (–£44,560; SE quadrant)
Men who have sex with men and transgender women on TDF/FTC receive TAF/FTC each month	0%	0.0077%	In real-world, a small proportion of men who have sex with men and transgender women may receive TAF/FTC	£11,138	–
Persistence for cabotegravir compared with TDF/FTC	Increased persistence of 20%	Increased persistence of 35%	Increased convenience of cabotegravir is likely to improve persistence but the extent is unknown	Dominant (–£32; SE quadrant)	Dominant (–£43,890; SE quadrant)
Percentage of individuals requiring oral lead in	[redacted]	5%	An oral lead-in is recommended in the SmPC but may not be implemented	£10,103	Dominant (–£44,301; SE quadrant)
	[redacted]	95%		£13,418	Dominant (–£42,802; SE quadrant)
Drug wastage for TDF/FTC	No wastage	Missed TDF/FTC doses are wasted	Wastage is unknown but likely	£10,491	Dominant (–£43,640; SE quadrant)
Discount rate for costs and outcomes	3.5%	1.5%	A value of 1.5% has been advocated for use in public health interventions [57]	Dominant (–£20,646; SE quadrant)	Dominant (–£54,065; SE quadrant)

Abbreviations: PrEP, pre-exposure prophylaxis; SE, South-East; TAF/FTC, tenofovir alafenamide/emtricitabine; TDF/FTC, Tenofovir disoproxil fumarate with emtricitabine; SmPC, summary of product characteristics.

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Prices used in the following analyses:
[redacted] – list price for cabotegravir prolonged release injection vials 600mg/3 mL

[redacted] – list price for cabotegravir oral 30mg tablets (pack size:30)

£34.20 – list price for Tenofovir disoproxil / emtricitabine (TDF/FTC) 200 mg/245 mg tablets (pack size:30)

£355.73 – list price for Tenofovir disoproxil / alafenamide (TAF/FTC) 10 mg/200 mg or 25 mg/200 mg (pack size: 30)

Company base cases

Table 1: Company deterministic and probabilistic base cases using list prices for cabotegravir and TDF/FTC

Model	Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company base case deterministic	TDF/FTC (list price)	[redacted]	[redacted]	-	-	-
	Cabotegravir (list price)	[redacted]	[redacted]	[redacted]	[redacted]	£11,615.67
Company base case probablistic	TDF/FTC (list price)	[redacted]	[redacted]	-	-	-
	Cabotegravir (list price)	[redacted]	[redacted]	[redacted]	[redacted]	£10,924

EAG base cases

Table 2: EAG deterministic and probabilistic base cases using list prices for cabotegravir and TDF/FTC

Model	Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
EAG base case deterministic	TDF/FTC (list price)	[redacted]	[redacted]	-	-	-
	Cabotegravir (list price)	[redacted]	[redacted]	[redacted]	[redacted]	£352,928
EAG base case probablistic	TDF/FTC (list price)	[redacted]	[redacted]	-	-	-
	Cabotegravir (list price)	[redacted]	[redacted]	[redacted]	[redacted]	£363,504.88

EAG changes made to the company model

The changes made to the company model are described below.

EAG 01: No PrEP is an inappropriate comparator and should not be considered in the cost-effectiveness analyses.

Based on the reasons outlined in Section 3.2.3, comparisons between cabotegravir and no PrEP is not presented in the EAG analyses.

EAG 02: Baseline risk of HIV acquisition

Due to the uncertainty around the estimate used for the baseline risk of HIV acquisition, the EAG prefers a baseline risk of 3.9 per 100 person-years. This incidence rate reflects the HIV incidence of individuals with recent HIV test and rectal bacterial STI infection.

EAG 03: Patients who stop cabotegravir PrEP do not transition to receive oral PrEP

The company argues that the population considered for cabotegravir PrEP are those for whom oral PrEP is inappropriate while simultaneously assuming that [redacted] of patients on stop cabotegravir PrEP subsequently go on to receive oral PrEP. A similar assumption is not made in the oral TDF/FTC group which biases the ICER in favour of cabotegravir. The EAG prefers no transitioning from cabotegravir to oral PrEP.

EAG 04: **Adherence to TDF/FTC**

Due to the lack of evidence showing gender-based differences in adherence to oral PrEP in the UK, and the unreliability of adherence data from the HPTN 084 study which was conducted in participants from sub-Saharan Africa, the EAG prefers to set adherence for cisgender women equal to transgender women and men who have sex with men.

EAG 05: Persistence to cabotegravir

Due to the lack of evidence on the company's base case assumption of improved persistence of cabotegravir compared to oral PrEP, the EAG considers no relative improvement in persistence to cabotegravir compared to oral PrEP.

EAG 06: Per cycle application of ISR costs and disutility

Costs of treating ISR was also applied per cycle rather than as a one-off cost. A disutility value of –0.015 was assumed for ISR and applied per cycle.

EAG 07: Duration of risk period

Duration of on-risk period changed from 5 years to 10 years to account for uncertainties associated with a shorter risk period.

EAG 08: Cabotegravir administration costs

Administration costs for cabotegravir costs changed from company base case to an hour of activity in the clinic (i.e. 20 mins band 5 nurse for observation, 40 mins clinical activity representing the weighted average a pharmacist, consultant, and clinical nurse specialist wage.

EAG 09: Cabotegravir dosing schedule

Cabotegravir was assumed to be administered every 8 weeks rather than 2 months in the company base case. EAG preferred frequency of visit was applied to cabotegravir administration costs and cabotegravir HIV antigen tests cost.

EAG 10: Cabotegravir acquisition costs

Drug acquisition and administration costs for cabotegravir increased by 5% to account for potential increases in lifetime costs of cabotegravir administration during to changing risk patterns over the lifetime of the cohort.

EAG 11: Starting age of model

The starting age of the model cohort was increased from 26 years to 33 years to match the median age of PrEP users in the UK

EAG 12: Disutility for HIV

Disutility for HIV changed from –0.11 to -0.05 based on reasons outlined in Section 4.8.1.1

Table 3: Impact of individual EAG preferred model assumptions on ICER using list prices for cabotegravir and TDF/FTC

Model	Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company base case deterministic	TDF/FTC (list price)	[redacted]	[redacted]	-		
	Cabotegravir (list price)	[redacted]	[redacted]	[redacted]	[redacted]	£11,615.67
EAG02	TDF/FTC (list price)	[redacted]	[redacted]	-	-	-
	Cabotegravir (list price)	[redacted]	[redacted]	[redacted]	[redacted]	£30,093
EAG03:	TDF/FTC (list price)	[redacted]	[redacted]	-	-	-
	Cabotegravir (list price)	[redacted]	[redacted]	[redacted]	[redacted]	£28,911
EAG04:	TDF/FTC (list price)	[redacted]	[redacted]	-	-	-
	Cabotegravir (list price)	[redacted]	[redacted]	[redacted]	[redacted]	£13,050
EAG05:	TDF/FTC (list price)	[redacted]	[redacted]	-	-	
	Cabotegravir (list price)	[redacted]	[redacted]	[redacted]	[redacted]	£39,319
EAG06:	TDF/FTC (list price)	[redacted]	[redacted]	-	-	
	Cabotegravir (list price)	[redacted]	[redacted]	[redacted]	[redacted]	£11,640
EAG07:	TDF/FTC (list price)	[redacted]	[redacted]	-	-	
	Cabotegravir (list price)	[redacted]	[redacted]	[redacted]	[redacted]	£24,175
EAG08:	TDF/FTC (list price)	[redacted]	[redacted]	-	-	-
	Cabotegravir (list price)	[redacted]	[redacted]	[redacted]	[redacted]	£14,268
EAG09:	TDF/FTC (list price)	[redacted]	[redacted]	-	-	-
	Cabotegravir (list price)	[redacted]	[redacted]	[redacted]	[redacted]	£15,751
EAG10:	TDF/FTC (list price)	[redacted]	[redacted]	-	-	-
	Cabotegravir (list price)	[redacted]	[redacted]	[redacted]	[redacted]	£15,651
EAG 11:	TDF/FTC (list price)	[redacted]	[redacted]	-	-	
	Cabotegravir (list price)	[redacted]	[redacted]	[redacted]	[redacted]	£12,657
EAG 12:	TDF/FTC (list price)	[redacted]	[redacted]	-	-	

	Cabotegravir (list price)	[redacted]	[redacted]	[redacted]	[redacted]	£22,622
EAG Base Case	TDF/FTC (list price)	[redacted]	[redacted]	-	-	-
	Cabotegravir (list price)	[redacted]	[redacted]	[redacted]	[redacted]	£352,928

EAG scenario analyses

Scenario 1: Alternative alpha and beta parameters were estimated to reflect the EAG concerns with uncertainties around the ITC conducted by the company.

Scenario 2: Given the significant logistical challenges of implementing reliable recall systems in clinics administering cabotegravir, the potential impact of severe injection site reaction and the potential challenges to patients in meeting on-time injections, persistence to cabotegravir was assumed to be 10% lower than oral TDF/FTC.

Scenario 3: Alternative baseline HIV incidence rate was assumed using estimates from the men who have sex with men population with recent HIV tests and bacterial STI infection. A baseline HIV incidence rate of 3.3 per 100 person years was assumed.

Scenario 4: Alternative baseline incidence rate of 1.9 per 100 person years was assumed to reflect HIV incidence in the men who have sex with men population with HIV test done in the previous year.

Table 4: Impact of EAG scenarios on EAG base case using list prices for cabotegravir and TDF/FTC

Model	Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
EAG base case deterministic	TDF/FTC (list price)	[redacted]	[redacted]	-	-	-
	Cabotegravir (list price)	[redacted]	[redacted]	[redacted]	[redacted]	£352,928
Scenario 1	TDF/FTC (list price)	[redacted]	[redacted]	-	-	
	Cabotegravir (list price)	[redacted]	[redacted]	[redacted]	[redacted]	£312,250
Scenario 2	TDF/FTC (list price)	[redacted]	[redacted]	-	-	
	Cabotegravir (list price)	[redacted]	[redacted]	[redacted]	[redacted]	£624,111
Scenario 3	TDF/FTC (list price)	[redacted]	[redacted]	-	-	
	Cabotegravir (list price)	[redacted]	[redacted]	[redacted]	[redacted]	£424,994
Scenario 4	TDF/FTC (list price)	[redacted]	[redacted]	-	-	
	Cabotegravir (list price)	[redacted]	[redacted]	[redacted]	[redacted]	£766,287

No PrEP as a comparator analyses

Table 5: Scenario analyses based on EAG's and company's preferred base-case assumptions with 'no PrEP' as the comparator

Model	Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Comparison between Cabotegravir and Prep (EAG preferred assumptions)						
Scenario with 'no PrEP' as comparator	'no PrEP'	[redacted]	[redacted]	-	-	-
	Cabotegravir (list price)	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Comparison between Cabotegravir and Prep (Company preferred assumptions)						
Scenario with 'no PrEP' as comparator	'no PrEP'	[redacted]	[redacted]	-	-	-
	Cabotegravir (list price)	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Note: The EAG does not believe that 'no PrEP' is an appropriate comparator. The results in Table 5 were produced following NICE request.

EAG base case ICER plane

EAG base case: cost-effectiveness acceptability curve