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

For screen – CON redacted

Technology appraisal committee C [3rd September 2024]

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Company: ViiV Healthcare

Cabotegravir for preventing HIV-1 in adults and young people

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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Background on HIV

Causes and classification

- HIV is a retrovirus that infects and destroys immune cells that play a key role in fighting infections
- Routes of transmission are via body fluids of people who are living with HIV who are not on effective treatment, including sexual contact, maternal-infant exposure, sharing needles for injection
- HIV-1 subtype is considered more prevalent and more transmissible than HIV-2

Epidemiology

- An estimated 106,890 people were living with HIV in the UK in 2020
- In 2022, 4,040 people were newly diagnosed with HIV in the UK
- UK government's HIV Action Plan for England (2022 to 2025) aims to achieve zero new HIV transmissions by 2030

Symptoms and prognosis

- Gradual weakening of the immune system makes people vulnerable to infections and some diseases
- Untreated HIV progresses to late-stage infection, known as acquired immunodeficiency syndrome (AIDS)
- Life expectancy of people living with HIV can range from a normal/near-normal life span to 30 years lower than the general population, depending on adherence to treatment and CD4 cell counts

Abbreviations: CD4, cluster of differentiation 4; HIV, human immunodeficiency virus

Community perspectives

Difficulties accessing PrEP can lead to poorer outcomes

Submissions from Terrence Higgins Trust, UK Community Advisory Board, National AIDS Trust and a community expert

- Living under burden of known HIV risk can lead to poorer outcomes in many aspects of life and wellbeing
- Often those most at risk of HIV have one or more minority identity or are marginalised in some way and there is stigma attached to living with HIV
- People living with HIV are more likely to experience poor mental health, substance misuse, unemployment, homelessness, and loneliness
- Current treatment options are high quality but difficult to access due to underfunding of services
- Unmet need for choice in PrEP drugs and person-centred service delivery models
- Unmet needs for people whose circumstances are not suited to daily antiretroviral medication or who need a discreet HIV prevention option

"PrEP is still only available from level 3 sexual health clinics."

"It is likely that offering a range of HIV prevention options, including long-acting methods, will increase number of people using effective HIV prevention."

"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… Some people … have reverted to self-sourcing and subsequently self-managing their ongoing monitoring."

Abbreviations: HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis

Clinical perspectives

Cabotegravir injections could address unmet needs

Submissions from British HIV Association, English HIV and Sexual Health Commissioners Group, HIV Pharmacy Association, NHS England and a clinical expert

- Oral formulations of PrEP are available as TDF/FTC and proprietary TAF/FTC
- PrEP is currently delivered within specialist sexual health services
    - Additional resource would be required to implement and deliver cabotegravir injections as PrEP
    - Cabotegravir users would need to engage in reviews, regular blood tests and a sexual health screen and have the injection
- Technology will likely benefit those for whom adherence to daily oral medication is complex and challenging
- Individuals in whom oral PrEP is not appropriate may be identified from the clinical history when detailing age, co-morbidities adherence, swallowing, absorption, tolerance issues or adverse events

"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."

"Not all people at risk of acquiring HIV are able to take oral medication, [reasons include]… a risk of compromised confidentiality,…domestic abuse or modern slavery, or those who may struggle with adherence."

"One centre in London has reported that many of their new HIV diagnoses are in people who have struggled with PrEP adherence."."

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

Equality considerations

- HIV disproportionately affects: people of Black African family background; people of certain sexual orientation such as gay or bisexual men
- Key populations most at risk of HIV acquisition may be reluctant to engage in healthcare systems or to access sexual health services. Cultural concerns or stigma may exacerbate health inequity.
- Long-acting injections may not suit people who cannot easily access or schedule the necessary clinic appointments
- Long-acting injections may benefit some young people who struggle with managing oral therapies
- Acknowledged inequity of access to PrEP in the UK for cis-gender women
- Eligibility for key cabotegravir trials excluded current or planned pregnancy or breastfeeding status

Are there any further equality considerations the committee should consider?

Abbreviations: HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis

Cabotegravir (Apretude, ViiV Healthcare)

Marketing authorisation	Apretude is indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection in high-risk adults and adolescents, weighing at least 35 kg
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
Administration	• Intramuscular injection every 2 months administered by a healthcare professional experienced in the management of HIV PrEP • Daily tablets for approximately 1 month (at least 28 days) can be used as optional oral lead-in to assess tolerability to cabotegravir
Price	• List price per pack of cabotegravir injections: [redacted] • List price per pack of oral cabotegravir tablets: [redacted] • There are existing simple PAS discounts in place for both cabotegravir intramuscular injections and oral cabotegravir tablets due to an existing technology appraisal (TA757)

Key issues

	Key issues	ICER impact
1	No PrEP as a comparator	Large
2	Generalisability of the trial populations	Unknown
3	Duration of HIV risk period and associated costs	Large
4	Baseline risk of HIV acquisition	Large
5	Transition from cabotegravir to TDF/FTC	Large
6	Improved persistence with cabotegravir	Large
7	Disutility of HIV	Large
8	Implementation of cabotegravir injections (other consideration)	N/A
	Other issues	
9	Population is narrower than the decision problem	Unknown
10	Adherence to TDF/FTC	Small
11	Starting age of participants	Small
12	Cabotegravir administrative costs	Small
13	Cabotegravir dosing schedule	Small
14	Indirect treatment comparison	N/A

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

Treatment pathway

= established treatment
= proposed positioning

People at risk of sexually acquired HIV-1 infection

Treatments delivered in Level 3 SHS

- Cabotegravir injections
- Oral TDF/FTC
- Oral TAF/FTC

HIV exposure

HIV acquisition

Treatments delivered in secondary care

- Antiretroviral treatment
- Cabotegravir with rilpivirine injections (NICE TA757)

- TDF/FTC and TAF/FTC are both forms of oral PrEP
- The majority of oral PrEP users in the UK will receive TDF/FTC
- TAF/FTC is used for individuals that are intolerant or contraindicated to TDF/FTC (NHS Clinical Commissioning Policy 2023)
- For the pre-exposure prophylaxis of HIV, TAF/FTC is only licensed in MSM

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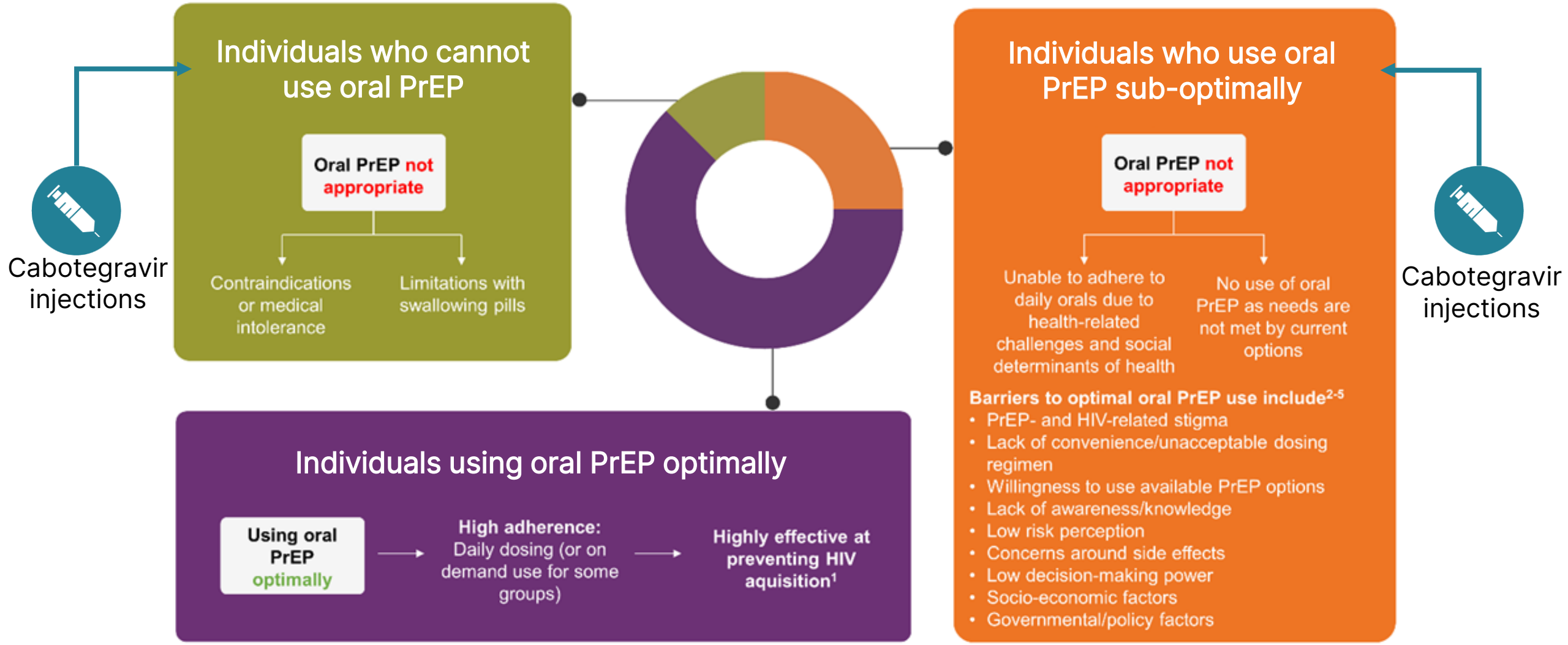
Abbreviations: HIV, human immunodeficiency virus; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; SHS, sexual health services; TAF/FTC, tenofovir alafenamide/emtricitabine; TDF/FTC, tenofovir disoproxil/emtricitabine

Populations with PrEP needs



Sources: 1. Sullivan et al, 2023; 2. Calabrese et al, 2020; 3. Coukan et al, 2023; 4. Sidebottom et al, 2018; 5. National AIDS trust

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Abbreviations: HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis

= proposed positioning of cabotegravir

Key issue: No PrEP as a comparator

Background

- Company and EAG disagree on whether 'no PrEP' is an appropriate comparator for this appraisal

Company

- No PrEP is an appropriate comparator, as there is no established clinical management for individuals who cannot take oral PrEP but are otherwise eligible
- Oral PrEP may not be appropriate for all who are eligible; this population is captured in the clinical trials, reflected by some participants sub-optimally adhering to oral PrEP
- In England, 15% of people who have a PrEP need identified, do not initiate or continue oral PrEP

EAG comments

- No PrEP is not an appropriate comparator
- In trial data, company combines population who do not initiate oral PrEP with those sub-optimally adherent
- PrEP eligible individuals sub-optimally adherent to oral PrEP are captured in comparison to TDF/FTC
- No evidence that those who do not initiate oral PrEP would accept cabotegravir injections and be fully adherent (as per model assumption)

Other considerations

- NHSE: Agree with EAG comments

Is 'no PrEP' an appropriate comparator? Are there some people who are not having oral PrEP who would have cabotegravir?

See appendix – Population is narrower than the decision problem

Abbreviations: ITC, indirect treatment comparison; PrEP, pre-exposure prophylaxis; TDF/FTC, tenofovir disoproxil/emtricitabine

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Key clinical trials

Clinical trial designs and outcomes

	HPTN 083	HPTN 084
Design	Phase 2b/3 RCT	Phase 3 RCT
Population	Adult (≥18 years) cisgender men and transgender women who have sex with men at risk of acquiring HIV	Adults (aged 18–45 years) assigned female sex at birth at risk of acquiring HIV
Intervention	Active cabotegravir with TDF/FTC placebo	
Comparator(s)	Active TDF/FTC with cabotegravir placebo	
Duration	Start date: December 2016 Estimated completion date: July 2024	Start date: November 2017 Estimated completion date: November 2024
Primary outcomes	Number of documented incident HIV acquisitions; adverse effects of treatment	Number of documented incident HIV acquisitions
Key secondary outcomes	Changes in renal function, liver function and bone mineral density; incidence of resistance mutations	Adverse effects of treatment; changes in renal function and liver function; incidence of resistance mutations
Locations	Argentina, Brazil, Peru, South Africa, Thailand, United States, Vietnam	Botswana, Kenya, Malawi, South Africa, Swaziland, Uganda, Zimbabwe
Used in model?	Yes	Yes

Abbreviations: HIV, human immunodeficiency virus; RCT, randomised controlled trial; TDF/FTC, tenofovir disoproxil/emtricitabine

Key clinical trials

Clinical trial results

HPTN 083* - trial conducted in Latin American and SE Asian countries, the US and South Africa in MSM and TGW

	Cabotegravir (N=2,280)	Daily oral TDF/FTC (N=2,281)
Number of HIV acquisitions	13	39
Person-years	3,211	3,193
Incidence rate/100 PY	0.40 [redacted]	1.22 [redacted]
Unadjusted HR; superiority p value	[redacted]	
Bias-adjusted HR; superiority p value	0.34 (0.18, 0.62); [redacted]	

HPTN 084* - conducted in sub-Saharan African countries in CGW

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

*Analysis from Steps 1 and 2 for the clinical trials (153 weeks)

Abbreviations: HIV, human immunodeficiency virus; HR, hazard ratio; PY, person-years; TDF/FTC, tenofovir disoproxil/emtricitabine
CGW, cisgender women; MSM, men who have sex with men; TGW, transgender women

Results of indirect treatment comparison

Parameter	Log Relative Risk		% 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]

Company

- The predicted effectiveness of cabotegravir versus TDF/FTC is [redacted] for the CGW population (HPTN 084 trial) ([redacted]) versus the MSM and TGW population (HPTN 083 trial) ([redacted])
- Corresponds with lower adherence to TDF/FTC observed in HPTN 084 (56%), compared with HPTN 083 (86%)
- 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 CGW population (HPTN 084 trial) and [redacted] for the MSM and TGW population (HPTN 083 trial)

Abbreviations: CGW, cisgender women; HIV, human immunodeficiency virus; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; TDF/FTC, tenofovir disoproxil/emtricitabine; TGW, transgender women

Key issues: Generalisability of the trial populations

Background
- HPTN 083 conducted in 43 sites in US, Latin America, Asia and Africa
- HPTN 084 conducted in 20 sites in 7 countries in sub-Saharan Africa

Company
- No UK patients in HPTN trials acknowledged but not considered a significant limitation
- Effectiveness of cabotegravir consistent across settings as demonstrated in ITC
- Effectiveness of TDF/FTC is driven by adherence and model considers suboptimal adherence to TDF/FTC

EAG comments
- The absence of UK-specific data introduces significant uncertainties in relation to risk of HIV acquisition, uptake, and adherence
- Uncertainties could influence the cost-effectiveness analysis but quantifying the impact is a challenge

Clinical expert
- HPTN studies have diverse populations reflective of UK population at risk of HIV acquisition
- Some groups were under-represented such as those that identify as non-binary, under 18s, TGW, PWID

Is the company's clinical trial data generalisable to UK clinical practice?

See appendix – Trial baseline characteristics and Adherence to TDF/FTC

Abbreviations: ITC, indirect treatment comparison; PWID, people who inject drugs; TDF/FTC, tenofovir disoproxil/emtricitabine; TGW, transgender women

Key issues: Duration of HIV risk period and associated costs

Background
- Company and EAG disagree on the appropriate at-risk period for HIV acquisition (5 years vs 10 years)

Company
- An at-risk period of 5 years is appropriate
- RWE on persistence to oral PrEP demonstrates a high rate of discontinuation (over 40% at 12 months)
- UK clinical experts indicated PrEP is mostly used for short-term periods ranging from 6 months to 2 years
- No data available on mean duration of at-risk period, but RWE on rate of PrEP discontinuations indicates mean duration may be shorter than 5 years and unlikely to be longer

EAG comments
- An at-risk period of 10 years is preferred to account for uncertainties associated with a single risk period
- Company's model assumes that a single period of PrEP use represents lifetime of PrEP use
- But individuals eligible for PrEP may have multiple short-term engagement with PrEP over their lifetime
- Mean duration of PrEP users with the highest risk of HIV acquisition is more appropriate but was not implemented in the model
- This would effectively cap the cost of treatment to five years which would favour cabotegravir

Other considerations
- EHSCG: Agree with EAG extension to a 10-year risk period duration

What is the most appropriate at-risk period?

Abbreviations: EHSCG, English HIV and Sexual Health Commissioners Group; HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis; RWE, real-world evidence

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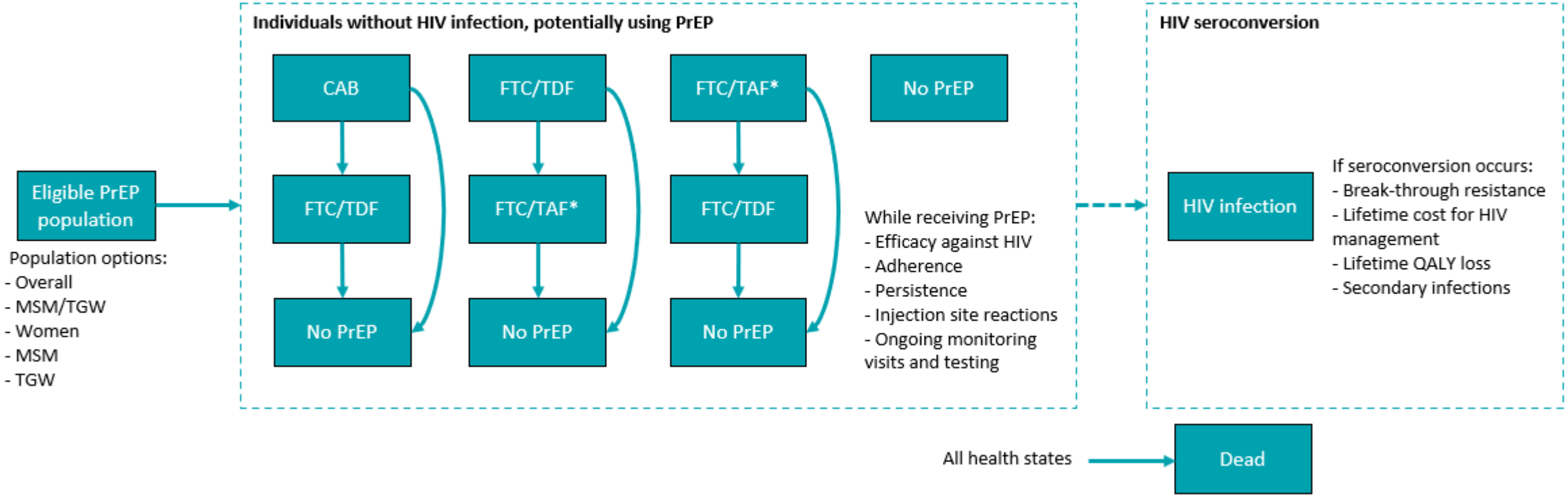
Company's model structure

Model structure



* FTC/TAF is only available for MSM and TGW subpopulations.

Abbreviations: CAB, cabotegravir; CGW, cisgender women; HIV, human immunodeficiency virus; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; FTC/ TAF, tenofovir alafenamide/emtricitabine; FTC/TDF, tenofovir disoproxil/emtricitabine; TGW, transgender women

Key Issue: Baseline risk of HIV acquisition

Background

- Company and EAG disagree on baseline value for HIV acquisition (4.9 per 100 PY vs 3.9 per 100 PY)
- Reducing risk of HIV acquisition considerably increases the ICER

Company

- 4.9 HIV acquisitions per 100 PY is an appropriate value for baseline risk of HIV acquisition
- Value limits risk of bias resulting from not capturing those with limited current utilisation of SHS
- Estimated background risk of HIV acquisition derived from ITC for HPTN 083 population is within a range of [redacted] HIV acquisitions per 100 PY in men who have sex with men

EAG comments

- Company's risk of HIV acquisition is biased by potential inclusion of people who may already have HIV at when tested (36% of new HIV diagnosis in England in 2022 were for those previously diagnosed abroad)
- BHIVA/BASHH estimated 3.9 HIV acquisitions per 100 PY for MSM who had a rectal bacterial STI and an HIV test in past 12 months. This removes potential bias of those who may have HIV at time of testing
- Unclear about source and nature of bias from not capturing those with limited current utilisation of SHS

Clinical expert

- Support EAG's comment around using the incident rate of 3.9 per 100 person-years

What is the most plausible value for baseline risk of HIV acquisition?

Abbreviations: BHIVA/BASHH, British HIV Association/British Association for Sexual Health and HIV; HIV, human immunodeficiency virus; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; MSM, men who have sex with men; PY, person-years; SHS, sexual health services; STI, sexually transmitted infection

Key issue: Transition from cabotegravir to TDF/FTC

Background

- Company and EAG disagree on whether modelled participants should transition to TDF/FTC (oral PrEP) after discontinuation of cabotegravir (allowing transition vs not allowing transition)

Company

- [redacted] of people in the cabotegravir arm who were also sub-optimally adherent to oral PrEP transition to TDF/FTC
- Discontinuation rate of [redacted] monthly is applied so only a small proportion are still on TDF/FTC after 1 year
- This is in line with cabotegravir SmPC recommendation of taking alternative not long-acting forms of PrEP in the months following discontinuation of cabotegravir
- Agree those who cannot take oral PrEP should not transition to TDF/FTC after cabotegravir discontinuation

EAG comments

- Not logical for people in cabotegravir arm to transition to oral PrEP if it is not appropriate for them
- Company does not make a similar assumption for people in the oral TDF/FTC arm transitioning to cabotegravir, which biases ICERs in favour of cabotegravir
- EAG prefers no transitioning from cabotegravir to TDF/FTC

Clinical expert

- Transition to TDF/FTC on stopping cabotegravir is unlikely to be possible for majority of this population

Is it appropriate to allow participants to transition to TDF/FTC after discontinuing cabotegravir?

Abbreviations: ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; PK, pharmacokinetic; PrEP, pre-exposure prophylaxis; TDF/FTC, tenofovir disoproxil/emtricitabine; SmPC, summary of product characteristics

Key issue: Improved persistence with cabotegravir

Background

- Company and EAG disagree on whether persistence with cabotegravir improves relative to TDF/FTC (20% improvement vs no improvement)
- **Persistence** refers to the willingness to continue taking a prescribed treatment for a given length of time

Company

- RWE supports assumption of 20% improved persistence with cabotegravir compared with oral PrEP
  - Two US-based real-world studies showed 93% and 94% persistence for cabotegravir injections
- UK clinical experts indicated that a 20% persistence advantage over oral PrEP was a reasonable assumption, and that they would expect up to 50% improvement in persistence

EAG comments

- Prefers a conservative approach to assume persistence to cabotegravir is equivalent to oral PrEP
- There are limitations associated with real-world evidence cited by the company (see appendix)

Clinical expert

- Expect a higher persistence for individuals taking cabotegravir injections compared with oral PrEP
- Given concerns around residual efficacy of cabotegravir after discontinuation, service providers will be keen to ensure that anyone who has had a cabotegravir injection are actively recalled where required

Is it plausible to assume that cabotegravir injections will improve persistence compared to oral PrEP?

See appendix – Improved persistence to cabotegravir evidence

Abbreviations: ICER, incremental cost-effectiveness ratio; PrEP, pre-exposure prophylaxis; TDF/FTC, tenofovir disoproxil/emtricitabine

Discontinuation probability of oral PrEP and cabotegravir

Company calculated probabilities of discontinuation for cabotegravir injections and oral PrEP

Treatment	Cabotegravir injections	Oral PrEP (TDF/FTC)
Monthly discontinuation probability over the first 6 months	2.82%	5.73%
Monthly discontinuation probability after 6 months	3.30%	3.30%

Company

- A US-based study (Oglesby 2021) (n=24,232) reported persistence of oral PrEP at 6 and 12 months as 70.2% and 57.4%
- SLR (Zhang 2022) also 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)
- US cost-effectiveness analysis of cabotegravir (Brogan 2024) was used to generate the probabilities of monthly discontinuation for cabotegravir

Abbreviations: CI, confidence interval; PrEP, pre-exposure prophylaxis; SLR, systematic literature review; TDF/FTC, tenofovir disoproxil/emtricitabine;

Key issue: Disutility of HIV

Background

- Company assumes a disutility associated with HIV of –0.11 (Miners 2014), compared to EAG's value of –0.05 (Positive Voices Survey 2022)

Company

- 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

EAG comments

- Positive Voices Survey 2022 is more likely to reflect current disutility related to HIV, accounting for improvement in anti-HIV treatments with fewer side effects and less pill burden

Community expert

- There is still stigma attached to living with HIV, even for groups with high HIV awareness such as GBMSM
- HIV diagnosis can have devastating effects on a person's life, relationships, and general wellbeing
- Some CGW report being minoritised and marginalised due to their HIV status, which is emotionally taxing

Is the company's or EAG's estimate for disutility of living with HIV more appropriate?

See appendix – Comparison of disutility values

Abbreviations: CGW, cisgender women; EQ-5D, EuroQol 5 Dimension; GBMSM, gay, bisexual and men who have sex with men; HIV, human immunodeficiency virus; HRQoL, health-related quality of life

Summary of company and EAG base cases

Exact results are reported in part 2

- Cost-effectiveness results are confidential because there is a confidential PAS for cabotegravir, and TDF/FTC and TAF/FTC have confidential MPSC prices
- Cost-effectiveness analyses include company and EAG base cases, EAG deterministic scenario analyses and the impact of individual EAG assumptions on the company base case (see next slide)

Company base case

- Cabotegravir is more costly and generated more QALYs than TDF/FTC
- ICER for cabotegravir is dominant over TDF/FTC
- ICER for cabotegravir is dominant over no PrEP
- Probabilistic results similar to deterministic results

EAG base case

- Cabotegravir is more costly and generated more QALYs than TDF/FTC
- ICER for cabotegravir vs TDF/FTC is considerably higher than £30,000 per QALY gained
- Probabilistic results similar to deterministic results

Abbreviations: ICER, incremental cost-effectiveness ratio; ; MPSC, Medicines Procurement and Supply Chain; PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life year; TAF/FTC, tenofovir alafenamide/emtricitabine; TDF/FTC, tenofovir disoproxil/emtricitabine

Summary of company and EAG base case assumptions

Differing assumptions with a large impact on the ICER

Assumption	Company base case	EAG base case
No PrEP as a comparator	Appropriate comparator	Not an appropriate comparator
Baseline risk of HIV acquisition	4.9 per 100 person-years	3.9 per 100 person-years
Transitioning from cabotegravir to oral PrEP	[redacted] of individuals transition from cabotegravir to oral PrEP	No transitioning from cabotegravir to oral PrEP
Persistence to cabotegravir	20% improved persistence for cabotegravir over oral PrEP	Persistence to cabotegravir equal to oral TDF/FTC
Duration of risk period	5 years	10 years
Disutility for HIV	–0.11	–0.05

See appendix – Differing assumptions with a small impact on the ICER

Abbreviations: HIV, human immunodeficiency virus; ICER, incremental cost-effectiveness ratio; PrEP, pre-exposure prophylaxis; TDF/FTC, tenofovir disoproxil/emtricitabine

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Implementation of cabotegravir injections

Background

- PrEP is currently administered in Level 3 SHS
- Note that commercial arrangements may affect implementation of cabotegravir in practice

Company

- Anticipate cabotegravir injections for PrEP will be administered in Level 3 SHS in England
- SHS in England provide risk assessment, initiation and clinical follow up and monitoring of HIV PrEP
- Individuals must be tested for HIV-1 prior to initiating cabotegravir and at each subsequent injection
- 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 result of the HIV-RNA-based test will become available after cabotegravir injection

NHSE

- Service commissioners have advised that cabotegravir injections 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

British HIV Association

- Cabotegravir programme would require clinical resource within SHS that already face constraints

In what clinical setting are cabotegravir injections most likely to be administered?

Abbreviations: HIV, human immunodeficiency virus; PAS, patient access scheme; PrEP, pre-exposure prophylaxis; RNA, ribonucleic acid; SHS, sexual health services

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Key issues

Key issue	ICER impact	Slide
No PrEP as a comparator	Large	11
Generalisability of the trial populations	Unknown	16
Duration of HIV risk period and associated costs	Large	17
Baseline risk of HIV acquisition	Large	20
Transition from cabotegravir to TDF/FTC	Large	21
Improved persistence to cabotegravir	Large	22
Disutility of HIV	Large	24

Abbreviations: HIV, human immunodeficiency virus; ICER, incremental cost-effectiveness ratio; PrEP, pre-exposure prophylaxis; TDF/FTC, tenofovir disoproxil/emtricitabine

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Supplementary appendix

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HPTN 083 baseline characteristics

Characteristic	Cabotegravir injections (n=2,282)	Oral PrEP (TDF/FTC) (n=2,284)
Median age (IQR)	26 years (22–32)	26 years (22–32)
Gender identity		
CGM who have sex with men	2,013 (88.2%)	1,979 (86.6%)
TGW who have sex with men	266 (11.7%)	304 (13.3%)
Preferred not to answer	304 (13.3%)	304 (13.3%)
Geographic region		
US	849 (37.2%)	849 (37.2%)
Argentina	169 (7.4%)	168 (7.4%)
Brazil	395 (17.3%)	401 (17.6%)
Peru	416 (18.2%)	415 (18.2%)
Thailand	275 (12.1%)	278 (12.2%)
Vietnam	100 (4.4%)	99 (4.3%)
Africa	78 (3.4%)	74 (3.2%)

Are these baseline characteristics generalisable to NHS clinical practice?

Link to – Generalisability of the trial populations

NICE

Abbreviations: CGM, cisgender men; IQR, interquartile range; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; TDF/FTC, tenofovir disoproxil/emtricitabine; TGW, transgender women

HPTN 084 baseline characteristics

Characteristic	Cabotegravir injections (n=1,614)	Oral PrEP (TDF/FTC) (n=1,610)
Median age (IQR)	25 years (22–30)	25 years (22–30)
Gender identity		
Female	1,612 (99.9%)	1,607 (99.8%)
Male	0 (0.0%)	3 (0.2%)
Transgender male	2 (0.1%)	0 (0.0%)
Country		
Botswana	46 (2.9%)	45 (2.8%)
Eswatini	80 (5.0%)	80 (5.0%)
Kenya	31 (1.9%)	35 (2.2%)
Malawi	113 (7.0%)	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%)

Are these baseline characteristics generalisable to NHS clinical practice?

Link to – Generalisability of the trial populations

Abbreviations: IQR, interquartile range; PrEP, pre-exposure prophylaxis; TDF/FTC, tenofovir disoproxil/emtricitabine

Improved persistence to cabotegravir evidence

Company

- **Mills 2024:** 93% persistence (7% discontinuation; defined as ≥128 days without a cabotegravir injection) was observed over a median of 7 months follow-up (IQR: 4.7 to 9.5) in OPERA cohort of routine clinical care in US
- **Mayer et al.:** 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

EAG comments – Mills 2024

- Study is sensitive to the definition of discontinuation which is ≥128 days without cabotegravir injections. This threshold might be too high as cabotegravir is administered every 8 weeks.
- Median follow up of 7 months is inadequate to support a long-term effect
- 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 and fully adhere to cabotegravir tablets for 30 days before injections can resume. None of these scenarios were accounted for in the economic model

EAG comments – Mayer et al.

- 94% persistence to cabotegravir inaccurately described by the company. Of 43 individuals with ≥3 injections, only 27 (63%) had all injections after their second on-time. The 94% persistence cited by the company in their response refers to 94% of the 27 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

Abbreviations: IQR, interquartile range; PrEP, pre-exposure prophylaxis

Link to – Improved persistence to cabotegravir

Comparison of disutility values in Popping 2021 and Miners 2014

	No problems (absolute % difference)		Most severe level (absolute % difference)	
	Popping 2021	Miners 2014	Popping 2021	Miners 2014
Mobility	9	7	-1	0
Self-care	8	8	1	0
Usual activities	11	12	0	1
Pain	2	2	0	2
Anxiety/depression	19	23	2	7

Company

- Popping 2021 analysing the Positive Voices 2017 survey results allows comparison of the distributions per domain between the EQ-5D-5L of the Positive Voice survey and the EQ-5D-3L in Miners 2014
- Importance of choosing either EQ-5D-5L or EQ-5D-3L shown by comparing absolute differences between the proportion of responses by people living with HIV and general populations on each of the domains
- Indicates choice of 5L or 3L tariff drives difference in disutility score, not that newer treatments improved HRQoL

EAG comments

- Comparing responses to individual domains of the EQ-5D instrument is uninformative as profile scores are valued using general population preferences
- EQ-5D-5L has 5 levels and hence more discriminant validity than the EQ-5D-3L with 3 levels

NICE

Abbreviations: EQ-5D, EuroQol 5 Dimension; HIV, human immunodeficiency virus; HRQoL, health-related quality of life

Link to – Disutility of HIV

Other issues

Other issue	ICER impact	Slide
Population is narrower than the decision problem	Unknown	37
Adherence to TDF/FTC	Small	39
Starting age of participants	Small	40
Cabotegravir administrative costs	Small	41
Cabotegravir dosing schedule	Small	42
Indirect treatment comparison	Small	43

Abbreviations: ICER, incremental cost-effectiveness ratio; TDF/FTC, tenofovir disoproxil/emtricitabine

Other issues: Population is narrower than the decision problem

Background

- EAG notes misalignment between appraisal population (adults in specific populations e.g. MSM and TGW) and NICE scope (adults and adolescents at risk of sexually acquired HIV)

Company

- Population is narrower because oral PrEP meets HIV prevention needs of many people
- Population considered in economic model represents individuals who have a PrEP need but cannot take oral PrEP or are taking oral PrEP but have challenges resulting in sub-optimal adherence
- Evidence submitted representative of majority of individuals who are expected to receive cabotegravir in the UK (MSM / TGW aged ≥18 years, or cisgender women <45 years)

EAG comments

- Those who can't take oral PrEP weren't represented in HPTN trials
- Company's description of decision problem population is different from population in the model

Clinical expert

- Challenge extrapolating data from HPTN trials in individuals who were not necessarily identified as having pre-determined or pre-detected issues with oral medication
- Some of those enrolled in the studies would have struggled with oral medication

Is the company's appraisal population appropriate for decision making?

Link to – No PrEP as a comparator

NICE

Abbreviations: CGW, cisgender women; HIV, human immunodeficiency virus; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; TGW, transgender women

Decision problem population

	Final scope	Company	EAG comments
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. Rationale: 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. A new drug class, modalities, and or dosing frequencies, such as cabotegravir, will help to address the unmet needs for these individuals	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. 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.

Abbreviations: CAB-LA, cabotegravir injection; HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis; SoC, standard of care; TDF/FTC, tenofovir disoproxil/emtricitabine

Other issue: Adherence to TDF/FTC

Background

- Company and EAG disagree on whether TDF/FTC adherence differs in MSM, TGW and CGW populations

Company

- Clinical opinion and published evidence support that adherence for CGW is lower than in MSM and TGW
- Sidebottom 2018, Zhang 2022 and Marrazzo 2024 show poor adherence to oral PrEP in cisgender women
- Cultural similarities exist between many CGW eligible for PrEP in the UK and the population in HPTN 084

EAG comments

- Company does not provide evidence that adherence rates provided are generalisable to UK setting
- Evidence for cisgender women in Sidebottom 2018 and Marrazzo 2024 was not UK-based
- Zhang 2022 showed suboptimal adherence was higher in Sub-Saharan (51.7%) and Asia and Pacific (53.2%) regions compared to Europe (28.6%), suggesting that the setting is important
- HPTN 084 trial was conducted in sub-Saharan African countries where there are differences to UK settings
- EAG prefers to set adherence for cisgender women equal to transgender women and MSM

BHIVA

- Oral PrEP uptake among women in the UK is very low and there are likely to be a number of barriers such as cultural beliefs, stigma and experiences of the healthcare system

Is it appropriate to assume that TDF/FTC adherence for CGW is lower than in MSM and TGW?

Abbreviations: CGW, cisgender women; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; TDF/FTC, tenofovir disoproxil/emtricitabine; TGW, transgender women

Other issue: Starting age of participants

Background

- Company and EAG disagree on appropriate starting age of model cohort (31 and 29 years vs 33 years)

Company

- Starting age of 31 for MSM and transgender women, and 29 years for cisgender women is appropriate
- Agree that UKHSA data is appropriate to inform age in economic analysis
- Median age of those accessing oral PrEP for both MSM and TGW, and CGW within the groups aged 25–34

EAG comments

- UKHSA sates for those without HIV, the highest proportion of PrEP need were those aged 35 to 49 in GBMSM (69%, 30,129 of 43,654)
- Company's population is restricted to people with highest risk of HIV acquisition, so median age of PrEP users in population is likely to be higher than assumed by both company and EAG
- A starting age of 33 is an appropriate and conservative estimate

Other considerations

- BHIVA: 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
- NHSE: UKHSA sates highest proportion of PrEP initiated or continued were those aged 35 to 49 (78%)

Is the company's or EAG's starting age for the model cohort more appropriate?

NICE

Abbreviations: CGM, cisgender men; GBMSM, gay, bisexual and men who have sex with men; HIV, human immunodeficiency virus; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; TGW, transgender women; UKHSA, United Kingdom Health Security Agency

Other issue: Cabotegravir administration costs

Background

- Company and EAG disagree on costs associated with administering cabotegravir injections (EAG's higher)

Company

- Administration of cabotegravir requires two 30-minute initiation injection appointments, with 20-minute appointments for subsequent injections
- UK multi-centre service evaluation of cabotegravir and rilpivirine pathways shows appointments took 30-60 minutes and ≤40 minutes in 78% of NHS HIV clinics
- 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

EAG comments

- Costs based on 1 hour of clinic time (20 mins band 5 nurse for observation, 40 mins clinical activity)
- Despite evidence stating time appointments took, 30-60 minutes company model assumes cabotegravir administration is performed by a band 5 nurse and take only 20 mins for subsequent injections

Other considerations

- Clinical expert: Extra time must be factored in at each appointment for PrEP user to be reviewed
- BHIVA: Cabotegravir programme would require clinical resource within SHS that already face constraints

What is an appropriate amount of time to assume for cabotegravir injections to be administered?

Abbreviations: BHIVA, British HIV Association; HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis; SHS, sexual health services

Other issue: Cabotegravir dosing schedule

Background
- Company and EAG disagree on dosing schedule and acquisition costs for cabotegravir

Company
- Cabotegravir should be administered in line with the SmPC – every 2 months following initiation injections
- Modelled single time period is representative of each period of elevated risk an individual may experience during their lifetime
- Explicit modelling of increased costs and benefits of cabotegravir throughout multiple single time periods is unlikely to be materially different from the cost-effectiveness results already presented

EAG comments
- HPTN 083 and HPTN 084 trials 8-weekly dosing schedule is used
- Assuming an 8-weekly dosing schedule doubles the ICER compared to a 2-monthly schedule
- The benefits of multiple time periods are currently captured in the model, but the costs are not
- A 5% increase should be applied to cabotegravir acquisition and administration costs to account for discrepancy in frequency of administration and changing risk patterns over the lifetime of the cohort

Clinical expert
- Most clinicians will be confident following the 2-monthly schedule

Is it appropriate to add a 5% increase to cabotegravir acquisition and administration costs?

Abbreviations: ICER, incremental cost-effectiveness ratio; SmPC, summary of product characteristics

Other issue: Indirect treatment comparison

Background

- EAG raised some methodological issues with company's ITC of cabotegravir versus TDF/FTC
- Differences between company and EAG ITC analyses are unlikely to substantially impact the ICER

EAG comments

- Exclude Bangkok Tenofovir and IperGay studies from ITC due to population or intervention incompatibility
- Formulating a binomial distribution for the number of people adherent to oral PrEP in the TDF/FTC arm of each trial, would address the issue of measurement error in adherence levels
- Agree that company's ITC results are robust to conducting the appropriate analysis

Company

- Company's ITC base-case analysis results are were not considerably impacted by the exclusion of the Bangkok Tenofovir and IperGay studies, demonstrated by the EAG's ITC and company sensitivity analysis
- Agree with EAG's approach to account for measurement error in adherence levels in the meta-regression of treatment effect, but causes a minimal change in company ITC results
- ITC base-case analysis results robust and suitable for decision making

Are the company's ITC results appropriate for decision making?

Abbreviations: ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; PrEP, pre-exposure prophylaxis; TDF/FTC, tenofovir disoproxil/emtricitabine

Company's model overview

Technology affects **QALYs** by:

- Assumption of improved persistence to cabotegravir
- Transition to TDF/FTC following discontinuation from cabotegravir
- Duration of assumed aggregate risk period
- Adherence to PrEP regimens

Technology affects **costs** by:

- Drug acquisition and administration costs
- Cabotegravir administration frequency
- Adverse events costs
- HIV management costs

Assumptions with greatest ICER effect:

- 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

Abbreviations: HIV, human immunodeficiency virus; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; PrEP, pre-exposure prophylaxis; TDF/FTC, tenofovir disoproxil/emtricitabine

Summary of company and EAG base case assumptions

Differing assumptions with a small impact on the ICER

Assumption	Company base case	EAG base case
Adherence to TDF/FTC	Adherence for CGW is lower than TGW and MSM	Adherence for CGW is equal to TGW and MSM
Per cycle application of injection site reaction (ISR) costs & disutility	No disutility value applied for ISR	Disutility value of –0.015 applied per cycle for ISR
Cabotegravir administration costs	Based on two 30-minute initiation appointments and 20-minute subsequent appointments	Based on an hour of clinic activity
Cabotegravir dosing schedule	Every 2 months	Every 8 weeks
Cabotegravir acquisition costs to account for change in risk patterns	No increase	Increased by 5%
Starting age of model cohort	31 years for MSM and TGW; 29 years for CGW	33 years

Link to – Differing assumptions with a large impact on the ICER

Abbreviations: CGW, cisgender women; ISR, injection site reaction; MSM, men who have sex with men; TDF/FTC, tenofovir disoproxil/emtricitabine; TGW, transgender women