NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Cabotegravir and rilpivirine for treating HIV-1 [ID3766]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Cabotegravir and rilpivirine for treating HIV-1 [ID3766]

Contents:

The following documents are made available to consultees and commentators:

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

1. **Company submission** from ViiV Healthcare

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions from:**
   a. UK Community Advisory Board (UK-CAB)
   b. National HIV Nurses Association (NHIVNA)

4. **Evidence Review Group report** prepared by Kleijnen Systematic Reviews Ltd

5. **Evidence Review Group – factual accuracy check**

6. **Technical engagement response** from ViiV Healthcare

7. **Technical engagement response & expert statement from experts:**
   a. Alex Sparrowhawk, expert nominated by The UK Community Advisory Board (UK-CAB),
   b. Dr Cheryl Gower, expert nominated by National AIDS Trust (NAT),
   c. Adele Torkington, expert nominated by HIV Pharmacy Association,
   d. Anna Kafkalias, expert, nominated by NHS England,

8. **Technical engagement response from consultees and commentators:**
   a. UK Community Advisory Board (UK-CAB)
   b. British HIV Association
   c. HIV Clinical Reference Group, NHS England
   d. HIV Pharmacy Association
   e. National HIV Nurses Association (NHIVNA)
   f. Gilead
   g. Janssen
   h. MSD

9. **Evidence Review Group critique of company response to technical engagement** prepared by Kleijnen Systematic Reviews Ltd

10. **Company addendum** from ViiV Healthcare
11. **ERG response to the company addendum**

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

Single technology appraisal

Long-acting cabotegravir plus long-acting rilpivirine (CAB LA+RPV LA) for the treatment of virologically suppressed patients with HIV-1 [ID3766]

Document B

Company evidence submission

February 2021

File name	Version	Contains confidential information	Date
ID3766_CAB_RPV_HIV_Document B_redacted	Final	No (redacted)	16/02/2021

Contents

Tables and figures

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List of abbreviations

Abbreviation	Definition
/r	Boosted with ritonavir
/c	Boosted with cobicistat
3TC	Lamivudine
ABC	Abacavir
ACCEPT	Chronic Treatment Acceptance Questionnaire
ADE	AIDS-defining events
AE	Adverse event
AF	Alafenamide
AIDS	Acquired immunodeficiency syndrome
ANCOVA	Analysis of covariance
ART	Antiretroviral therapy
ARV	Antiretroviral
ATLAS	Antiretroviral Therapy as Long-Acting Suppression
ATLAS-2M	Antiretroviral Therapy as Long-Acting Suppression Q2M
ATV	Atazanavir
AUC	Area under the concentration-time curve
BHIVA	British HIV Association
BMI	Body mass index
BMD	Bone mineral density
CAB	Cabotegravir
CD4+	Cluster of differentiation 4
CDC	Centers for Disease Control and Prevention
CFB	Change from Baseline
CI	Confidence interval
CMH	Cochran-Mantel Haenszel
CSR	Clinical study report
CVD	Cardiovascular disease
CVF	Confirmed virologic failure
DF	Disoproxil fumarate
DNA	Deoxyribonucleic acid
DTG	Dolutegravir
EACS	European AIDS Clinical Society
EFV	Efavirenz
ETR	Etravirine
EMA	European Medicines Agency
EVG	Elvitegravir
EQ-5D	EuroQol 5 Dimension questionnaire
FDA	US Food and Drug Administration
FLAIR	First Long-Acting Injectable Regimen

Abbreviation	Definition
FTC	Emtricitabine
GI	Gastrointestinal
HAT-QoL	HIV/AIDS Targeted Quality of Life
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL	high-density lipoprotein cholesterol
HIV	Human immunodeficiency virus
HIVTSQ(c)	HIV Treatment Satisfaction Questionnaire (change version)
HIVTSQ(s)	HIV Treatment Satisfaction Questionnaire (status version)
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IM	Intramuscular
INI	Integrase inhibitor
INSTI	Integrase strand transfer inhibitor
IQR	Interquartile range
ISR	Injection site reaction
ITT-E	Intent-to-treat exposed
IV	Intravenous
LA	Long-acting
LATTE	Long-Acting antireTroviral Treatment Enabling
LATTE-2	Long-Acting antireTroviral Treatment Enabling-2
LOCF	Last Observation Carried Forward
LY	Life year(s)
MSM	Men who have sex with men
MVC	Maraviroc
NA	Not applicable
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NRTTI	Nucleoside reverse transcriptase translocation inhibitor
PAS	Patient Access Scheme
PDVF	Protocol-defined virologic failure
PHE	Public Health England
PI	Protease inhibitor
PI/r	Ritonavir-boosted protease inhibitor
PIN	Perception of injection
PLHIV	People living with HIV
POLAR	Oral (PO) to Long-Acting (LA) Rollover
Q1M	Every month
Q2M	Every two months
QALY	Quality-adjusted life year

Abbreviation	Definition
QoL	Quality of life
RAL	Raltegravir
RNA	Ribonucleic acid
RPV	Rilpivirine
RT	Reverse transcriptase
RTV	Ritonavir
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SF-6D	Short form 6 dimension
SF-36	Short form 36 questionnaire
SLR	Systematic literature review
SmPC	Summary of product characteristics
SOC	Standard of care
TAF	Tenofovir alafenamide
TDF	Tenofovir disoproxil fumarate
TFV	Tenofovir
TPV/r	Ritonavir-boosted tipranavir
UK	United Kingdom
VL	Viral load

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

B.1.1. Decision problem

The submission covers the technology's full marketing authorisation for this indication.

The decision problem is presented in Table 1.

Table 1. The decision problem

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	"Adults with HIV-1 infection who are virologically suppressed on a stable regimen and who have not shown prior virological failure due to drug resistance to INTI/INIs" *[sic]*.	As per the marketing authorisation, i.e. adults who are virologically suppressed (HIV-1 RNA <50 copies /mL) on a stable antiretroviral regimen without present or past evidence of viral resistance to, and no prior virological failure with, agents of the NNRTI and INI class[1], who require a treatment switch due to non-virologic reasons.	Specificity added to align with the final marketing authorisation
Intervention	"Cabotegravir long-acting and rilpivirine long-acting injections with oral lead-in therapy"	As NICE scope	N/A
Comparator(s)	"Antiretroviral treatment (established clinical management such as an integrase inhibitor-based regimen)"	A basket of those antiretroviral regimens likely to be used as switch regimens for virally suppressed people living with HIV who are eligible for a switch to CAB LA + RPV LA, if CAB LA + RPV LA were not available.	These are considered as established ART for the population in question i.e. those people living with HIV who are most likely to benefit from a long-acting, non-oral alternative maintenance therapy.
Outcomes	"The outcome measures to be considered include: Maintenance of virological suppression CD4+ T-cell levels Treatment-emergent resistance Adherence to treatment regimen AIDS-defining events Mortality Comorbidities	As NICE scope, with the exception of comorbidities. Note that preference for and satisfaction with the long-acting regimen, as captured within the pivotal RCTs with patient-reported outcome instruments (PROs), is also included.	Treatment-related comorbidities are not considered as outcomes in the appraisal because with most regimens (including the intervention and the comparators) treatment-related comorbidities are no longer an important feature of treatment and do not generally feature in treatment decision-making.

	Adverse events (including inflammation) Health-related quality of life.”		
Economic analysis	“The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. 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 compared. Costs will be considered from an NHS and Personal Social Services perspective.”	As per reference case. To fully capture the survival benefits of a successful antiretroviral regimen, non-curative nature of treatment and the requirement for lifelong maintenance of treatment, a lifetime perspective (up to 80 years from model initiation) has been adopted (alternative time horizons are available [1–80 years]) The base case analysis is run until last participant has died, which is significantly less than 80 years.	N/A
Subgroups to be considered	“Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator. “	As NICE scope	N/A

B.1.2. Description of the technology being appraised

Details of the technology being appraised in this submission are summarised in Table 2. The Summary of Product Characteristics is attached as Appendix C.1.1.

ViiV Healthcare in partnership with Janssen Sciences Ireland UC (Janssen) are developing the cabotegravir (CAB) and rilpivirine (RPV) long-acting regimen for the treatment of HIV-1 infection. ViiV Healthcare is the Sponsor of the CAB + RPV clinical program.

Table 2. Technology being appraised

UK approved name and brand name	**Long-acting intramuscular injections** Approved name: Cabotegravir long acting (CAB LA) and rilpivirine long acting (RPV LA) Brand names: Vocabria (CAB LA) and Rekambys (RPV LA) **Oral lead-in** Note that prior to the initiation of CAB LA injection and RPV LA injection, oral cabotegravir (Vocabria) together with oral rilpivirine (Edurant, already licensed) should be taken for approximately one month (at least 28 days) to assess tolerability to CAB and RPV respectively[1, 2].
Mechanism of action	CAB LA + RPV LA is a 2-drug regimen that consists of LA formulations of the integrase strand transfer inhibitor (INSTI/INI) cabotegravir (CAB) and the non-nucleoside reverse transcriptase inhibitor (NNRTI) rilpivirine (RPV). CAB LA + RPV LA is administered at the same visit as two separate intramuscular injections. Each component is a prolonged release nanosuspension that undergoes slow absorption from the gluteal muscle into the systemic circulation resulting in sustained plasma concentrations[1, 2]. CAB inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration, which is essential for the HIV replication cycle[1]. RPV is a diarylpyrimidine NNRTI of HIV-1. RPV activity is mediated by non-competitive inhibition of HIV-1 reverse transcriptase (RT) and does not inhibit the human cellular DNA polymerases α, β and γ[2]. Neither CAB or RPV were antagonistic with each other or with other assessed antiretroviral agents when tested in combination[3].
Marketing authorisation status	EMA marketing authorisation was granted on 17 December 2020. UK launch is anticipated in 3Q 2021, initially in Scotland and subsequently in England and Wales. Note that only the every two month dosing (Q2M) for CAB LA + RPV LA will be made available in the UK (and the EU).

<table>
<tr><td>Indications and any restriction(s) as described in the summary of product characteristics (SmPC)</td><td>CAB injection is indicated, ‘in combination with RPV injection, for the treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen without present or past evidence of viral resistance to, and no prior virological failure with, agents of the NNRTI and INI class’[1, 2].

Prior to the initiation of CAB and RPV injections, oral CAB together with oral RPV should be taken for approximately one month (at least 28 days) to assess tolerability to CAB and RPV.

Note that oral RPV is already licensed (November 2011) “in combination with other antiretroviral medicinal products, for the treatment of HIV-1 infection in antiretroviral treatment-naïve patients 12 years of age and older with a viral load ≤ 100,000 HIV-1 RNA copies/mL”[4].</td></tr>
<tr><td>Method of administration and dosage</td><td>The recommended dosing schedule is as follows:[1, 2]
<table>
<tr><th></th><th>Oral lead-in</th><th>Initiation injections (one month apart)</th><th>Continuation injections (two months apart)</th></tr>
<tr><td>Drug</td><td>During Month 1 (at least 28 days)</td><td>At Month 2 and Month 3</td><td>Month 5 onward</td></tr>
<tr><td>CAB</td><td>30 mg once daily</td><td>600 mg (3mL)</td><td>600 mg (3mL)</td></tr>
<tr><td>RPV</td><td>25 mg once daily</td><td>900 mg (3mL)</td><td>900 mg (3mL)</td></tr>
</table>
Oral lead-in
• Prior to the initiation of CAB LA + RPV LA, oral CAB together with oral RPV should be taken for approximately one month (at least 28 days).
• When administered with RPV, CAB tablets should be taken with a meal.

Initiation injections
• On the final day of oral lead-in therapy
• Recommended initial dosage:
o Month 2: CAB LA 600 mg given as 1 x 3mL intramuscular injection + RPV LA 900 mg given as 1 x 3mL intramuscular injection
o Month 3: CAB LA 600 mg given as 1 x 3mL intramuscular injection + RPV LA 900 mg given as 1 x 3mL intramuscular injection
• Patients may be given the second CAB 600 mg (3 mL) and RPV 900 mg initiation injection up to 7 days before or after the scheduled dosing date.
• CAB LA + RPV LA should be administered at separate gluteal injection sites at the same visit.

Continuation injections
• After the initiation injections, the recommended continuation injection dosage in adults is:</td></tr>
</table>

	o CAB LA 600 mg given as 1 x 3mL intramuscular injection + RPV LA 900 mg given as 1 x 3mL intramuscular injection; Q2M. • CAB LA and RPV LA should be administered at separate gluteal injection sites at the same visit. Patients may be given injections up to 7 days before or after the date of Q2M injection schedule. **Oral bridging and missed 2-month doses** If a patient plans to miss a scheduled CAB LA + RPV LA injection visit by more than 7 days, oral therapy (one 30 mg cabotegravir tablet and one 25 mg rilpivirine tablet, once daily) may be used to replace one, 2-monthly injection visit. For oral therapy durations greater than two months, an alternative oral regimen is recommended. Full details of recommendations for dosing after missed injections are available in the SmPC. The first dose of oral therapy should be taken approximately two months (+/- 7 days) after the last injection doses of cabotegravir and rilpivirine. Injection dosing should be resumed on the day oral dosing completes, as recommended in the missed doses protocol set out in the respective SmPCs[1].
Additional tests or investigations	No additional tests or investigations are required beyond those routinely carried out for patients on ART.
List prices (TBC) and average cost of a course of treatment	Oral CAB: 30 x 30 mg tablets; [redacted](ex VAT) (month 1). Oral RPV (Edurant ®): 30 x 25 mg tablets; £200.27 (ex VAT) (month 1)[5]. CAB LA: 600 mg vial in 3 mL; [redacted] (ex VAT) (1 injection in month 2, 1 in month 3, then Q2M) RPV LA: 900 mg vial in 3mL; [redacted] (ex VAT) (1 injection in month 2, 1 in month 3, then Q2M)
Patient access scheme	Two separate simple patient access schemes have been submitted as follows: Oral CAB: 30 x 30 mg tabs; [redacted](ex VAT). CAB LA: 600 mg vial in 3 mL; [redacted](ex VAT). RPV LA: 900 mg vial in 3mL; [redacted](ex VAT).

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

B.1.3.1. Disease background

HIV is a retrovirus that attacks vital cells in the human immune system such as CD4+ T cells and macrophages. The virus enters macrophages and CD4+ T cells by the adsorption of glycoproteins on its surface to receptors on the target cell[6]. The HIV-1 subtype accounts for the majority of infections worldwide, and few HIV-2 cases are reported in the UK[7]. CAB LA + RPV LA is indicated for the treatment of HIV-1, and the term 'HIV' in this submission refers exclusively to HIV-1.

HIV may be transmitted through sexual contact, by maternal-infant exposure (during pregnancy or breastfeeding), and by percutaneous or intravenous inoculation (e.g. through sharing needles during recreational drug use or transfusion of unscreened blood)[8].

If untreated, HIV infection progresses through three stages: primary infection, clinical latency, and AIDS, although these may not always present as a continuum. Symptoms of primary infection occur soon after HIV acquisition and usually consist of flu-like symptoms, which then subside. Clinical latency is largely asymptomatic and can last for several years in untreated persons. During this stage, CD4+ levels gradually decrease and viraemia gradually rises[9]. HIV transmission may occur during all three stages. Reductions in CD4+ count are associated with decreasing health-related quality of life (HRQoL)[10, 11].

AIDS is the last stage of HIV infection and is defined by a CD4+ T-cell (CD4) count <200 cells/mm^3 and/or the occurrence of an AIDS-defining condition (certain cancers, infections or other manifestations of severe immune compromise)[9, 12]. People with AIDS are susceptible to a variety of opportunistic infections and neoplasms as CD4+ count falls (e.g. tuberculosis, cryptococcal meningitis, severe bacterial infections, and cancers such as certain lymphomas and Kaposi's sarcoma), and suffer progressively deteriorating health and HRQoL. Without treatment, survival is approximately 3 years[9].

The replication of HIV relies on enzymes produced by the virus itself, including reverse transcriptase, integrase and protease. These enzymes can be inhibited by antiretroviral drugs[13]. With successful antiretroviral therapy (ART), viral replication is suppressed (see Section B.1.3.4) such that viral load in the blood becomes undetectable (defined as HIV-1 RNA <50 copies/mL), and progression of disease is halted. Individuals with an undetectable viral load cannot sexually transmit the virus[14, 15].

B.1.3.2. Epidemiology

Based on estimates from Public Health England (PHE) for 2019[16]:

- 96,200 people in England were living with HIV infection, of whom 6% were undiagnosed. The median age of people living with HIV in the UK and receiving care (2018 data) is 41 years, and 40% are aged ≥50 years[17].
- There were 3,772 and 123 new HIV diagnoses in England and Wales, respectively[18]. The incidence of new HIV diagnoses has fallen since its peak of 6,278 in 2014[16].
- In the UK, 98% of people with a diagnosed HIV infection were receiving ART, and 97% of those on treatment were virally suppressed (defined as HIV-1 RNA <50 copies/mL).
- There were 622 deaths in people living with HIV in the UK. This represents a crude mortality rate of 631 per 100,000 living with diagnosed HIV infection.

Some populations are disproportionately affected by HIV: gay and bisexual men (GBM) accounted for approximately 50,300 (CrI 48,700 to 53,200) of the 105,200 (CrI 103,300 to 108,500) people living with HIV in the UK in 2019[16]. HIV infection also disproportionately affects

people of black African origin and people coming to the UK from countries with a high HIV prevalence (see Section B.1.4).

B.1.3.3. Life expectancy

While the advent of modern highly active ART has drastically improved the survival of people living with HIV, HIV is still an incurable infection and ART must be taken for a lifetime.

Early diagnosis and initiation of ART can result in life expectancy for people living with HIV close to that of the general population[19]. A UK study of people commencing ART between 2000 and 2010 found that life expectancy in men and women with an undetectable viral load and CD4+ count >350 cells/mm^3 was the same or slightly better than that for the general population[20, 21]. In 2018, the crude mortality rate in the UK among people living with HIV aged 15 to 59 years who were diagnosed promptly was 1.19 per 1,000, in line with the general population of the same age group (1.61 per 1,000)[17].

This means that people now initiating ART in their mid-20s will be taking treatment for many decades and must remain adherent to daily oral medication for life in order to maintain viral suppression. This reinforces the need for simple and convenient ART regimens that provide good tolerability and long-term safety for all people living with HIV, to promote long-term adherence and maximise HRQoL during long-term use.

B.1.3.4. Current pathway of care

Current standard of care treatments (consisting of life-long daily oral therapy with a combination of antiretroviral drugs, as either single- or multi-tablet regimens) provide extremely effective viral suppression. The latest Health Protection Report from Public Health England (2019 data) shows that nationally the Joint United Nations Programme on HIV and AIDS (UNAIDS) 90-90-90 targets were surpassed for the third consecutive year. The 90-90-90 targets stated that by 2020, 90% of all people living with HIV will know their HIV status, 90% of all people with diagnosed HIV infection will receive sustained antiretroviral therapy, and 90% of all people receiving antiretroviral therapy will have viral suppression[22].

Suppression of HIV currently requires life-long daily treatment. Having treatment options to suit individual needs is vital to reduce the physical and psychological impact of daily oral ART, which is heightened by HIV-specific challenges such as stigma, to enable improved HRQoL, adherence and maintenance of viral suppression.

People living with HIV have a choice of where they are treated in the UK, and care is usually centred within specialist HIV clinics. Primary care, specifically GPs, provides important additional support, although GPs are not able to prescribe HIV treatments. Whilst it is difficult to generalise, individuals will likely attend an HIV clinic 2-3 times per year, to see a healthcare provider, for blood tests and to collect medication. Individuals with HIV- or ART-related medical problems may need to be seen more frequently. A range of potential alternative regimens is available in the event of treatment failure or a requirement or desire to change therapy for other reasons.

B.1.3.4.1. *Goals of treatment*

British HIV Association (BHIVA) treatment guidelines state that the primary aim of ART is prevention of the mortality and morbidity associated with chronic HIV infection, at low cost of drug toxicity[21]. The guidelines also states that treatment should improve the physical and psychological well-being of people living with HIV.

Specific treatment goals include maximally and durably suppressing plasma HIV-1 RNA; reducing morbidity; prolonging the duration and improving the quality of survival; preserving or improving immunologic function; preventing drug-resistance mutations; and preventing HIV transmission[23].

Viral suppression is defined as achieving and maintaining HIV-1 RNA <50 copies/mL (also referred to as 'undetectable'), and virologic failure is defined as incomplete virologic response after commencing treatment or confirmed virologic rebound to >200 copies/mL[21]. Incomplete virologic response is defined as two consecutive results of >200 copies/mL after 24 weeks of treatment without ever achieving <50 copies/mL.

HIV cannot be sexually transmitted by persons on ART with an undetectable viral load (HIV-1 RNA <50 copies/mL) – the "undetectable = untransmissible" message[14, 15, 24, 25]. This reinforces the public health importance of maintaining full viral suppression over the long term.

To achieve these treatment goals, regimens should be tailored for the individual to enhance adherence and support long-term treatment success[21]. The regimen should be designed to promote adherence in order to maximise viral suppression, with consideration given to potential side-effects, comorbidities, drug-drug interactions, results of pre-treatment drug-resistance testing, and convenience of the regimen[23]. Issues that the BHIVA guidelines recommend should be discussed with people living with HIV in relation to ART include concerns with possible adverse social consequences, such as disclosure or interference with lifestyle; and socio-economic factors that could affect adherence, including, but not limited to, poverty, housing, or domestic violence[21]. The burden, challenges and unmet need associated with daily oral ART are described in detail in Section B.1.3.5.

B.1.3.4.2. *Treatment switching in virally suppressed individuals*

Switching ART regimen in virally suppressed individuals is common. In a structured survey carried out by IPSOS for ViiV Healthcare (the CARLA EU Unmet Need Survey[26]), of the 196 people living with HIV sampled in the UK, 61.2% reported two or more changes of ART since commencing treatment, and 21% reported 4-10 changes (the survey did not differentiate between virologic and non-virologic reasons for switching). For 46% of those who had switched, the most recent switch was in the last 1-3 years. The degree of switching reported suggests that people living with HIV continue to experience issues with ART[26]. In a separate UK sample of 123 people living with HIV in ViiV Healthcare's Positive Perspectives 2 study, only 29% said their current HIV medication meets their needs with little or no improvement required [27].

Reasons for considering switching, as cited in the BHIVA guidelines, include management of ART toxicity or intolerance; the individual's desire for a simpler regimen (e.g., once-daily dosing or reduced pill burden); management of potential drug–drug interactions; individual preference; and cost[21]. In the European AIDS Clinical Society (EACS) guidelines, minimising food restrictions and improving adherence are also listed among the potential indications for switching[28].

B.1.3.4.3. *Treatment guidelines*

HIV therapies have historically fallen outside the remit of NICE, so there are no NICE guidelines or technology appraisals for HIV treatment (in Wales HIV therapies have been appraised by the All Wales Medicines Strategy Group - AWMSG). Until a recent change as part of the new Voluntary Pricing and Access Scheme (VPAS) agreement, new antiretroviral therapies were made available in England through the NHS England Specialised Commissioning route (supported by the work of NICE's Commissioning Support Programme). Recent products such as Dovato®, Juluca® and Biktarvy® have been assessed through the NHS England Specialised Commissioning Priorities Advisory Group (CPAG).

Despite the many different ART regimens available, there is no single "standard of care" regimen, and selection of an appropriate ART regimen is individualised based on a broad range of clinical and non-clinical factors[29]. Without exception, current therapies are life-long daily oral regimens.

The principal UK HIV treatment guideline is the British HIV Association 2016 interim update[21], which is NICE-accredited. A summary of the relevant treatment recommendations is shown in Table 3 along with recommendations from more recent European guidelines where these cover details that current BHIVA guidelines do not. Some US guidelines[30] already recommend CAB LA + RPV LA although these are not detailed here.

Treatment is recommended for all people living with HIV and is generally initiated with two nucleoside reverse transcriptase inhibitors (NRTIs) and either a non-nucleoside reverse transcriptase inhibitor (NNRTI), a boosted protease inhibitor (bPI), or an integrase inhibitor (INSTI) [21]. Current initial regimens of choice contain two NRTIs plus one of the following: bPI, NNRTI or INSTI[21].

Two-drug regimens have gained acceptance in recent European[28] and US[23] guidelines, both as initial therapy and for switching (Table 3). These regimens are considered in an interim statement by the BHIVA (currently only available as brief slide deck)[29].

In March 2020 NHS England announced that the two-drug regimens dolutegravir/lamivudine[31] and dolutegravir/rilpirivine[32] would be included in routine commissioning. In its policy statement on the latter, NHS England notes in relation to two-drug regimens that, depending on the agents selected, "using fewer drugs could reduce the number of drug-related adverse events and interactions with other medications being taken," and "could also reduce the number of individual drugs or classes of drugs that the virus may become resistant to, saving more treatment options for the future."

BHIVA has also published a set of Standards of Care, setting out eight quality standards about the care that any adult living with HIV in the UK should expect to receive[33]. The BHIVA guidelines and standards state that people living with HIV should be given the opportunity to be involved in making decisions about their treatment[21] .

Table 3. Summary of relevant aspects of British HIV Association and other relevant guidelines

Guideline*	Recommendation	
BHIVA 2016 interim update[21]		
Initial therapy	ART containing two nucleoside reverse transcriptase inhibitors (NRTIs) plus one of the following: ritonavir-boosted protease inhibitor (PI/r), nonnucleoside reverse transcriptase inhibitor (NNRTI) or integrase inhibitor (INSTI)	
NRTI backbone	*Preferred* Tenofovir-DF and emtricitabine Tenofovir – AF and emtricitabine	*Alternative* Abacavir and lamivudine
Third agent	*Preferred* Atazanavir/r Darunavir/r Dolutegravir Elvitegravir/c Raltegravir Rilpivirine†	*Alternative* Efavirenz
Switching in virally suppressed individuals (general considerations)	*Reasons for considering switching* Management of ART drug toxicity or intolerance; desire for once-daily dosing and reduced pill burden; management of potential drug–drug interactions; individual preference; cost. Switching individual components of an ART regimen may well improve adherence and tolerability but should not be at the cost of virological efficacy.	
BHIVA 2019 interim statement on 2-drug regimens[29]		
Switching to 2-drug regimen	The statement suggests a PI/r + 3TC as an alternative to three-drug ART in individuals with viral suppression. The statement also covers recommended options for initial therapy with a 2DR	
EACS 2020 guidelines[28]		
Recommended initial regimens	2 NRTIs + INSTI; 1 NRTI + INSTI (DTG + 3TC) is listed as a recommended initial regimen in individuals who are HBsAg negative and have HIV-VL < 500,000 copies/mL).	

Indications for therapy switching[28]	*Indications include (but are not limited to):* **Documented toxicity** caused by one or more of the antiretrovirals included in the regimen. **Prevention of long-term toxicity.** This may include person's concerns about safety. **Avoidance of drug-drug interactions.** This includes ART switch when starting HCV treatment to avoid drug-drug interactions (DDIs). **Planned pregnancy or women wishing to conceive.** **Ageing and/or co-morbidity** with a possible negative impact of drug(s) in current regimen, e.g. on CVD risk, metabolic parameters. **Simplification:** to reduce pill burden, limit food restrictions, improve adherence and reduce monitoring needs. **Protection from HBV** infection or reactivation by including tenofovir in the regimen. **Regimen fortification:** Increasing the barrier to resistance of a regimen in order to prevent virological failure (e.g. in persons with reduced adherence). **Cost reduction:** switching to the generic form of their current regimen, if available. The primary concern when switching should be to sustain and not to jeopardise virological suppression.
Switching to 2-drug regimen	Several dual therapies are supported by large RCTs/meta-analyses.
NHS England: Best Practice in HIV Prescribing[34]	
Principles of HIV prescribing	Relevant principles include: • Promote, through the CRG and clinical services, the principles of informed choice, shared decision-making and supporting adherence to therapy. • Acknowledging the availability of generic alternatives to the branded formulation, seek to obtain the best clinical outcome for the lowest cost. • By promoting efficiency seeks to drive opportunities to consider new innovations, including those that cost more but offer significant clinical improvements over current treatment and care.

3TC: lamivudine, /r: boosted with ritonavir; /c: boosted with cobicistat; AF: alafenamide; CRG: Clinical Reference Group, DF: disoproxil fumarate; DTG: dolutegravir, NRTI: nucleoside reserve transcriptase inhibitors

*All currently available guideline editions were written before the publication of the ATLAS and FLAIR studies, and therefore do not discuss CAB LA + RPV LA or other new agents. The BHIVA interim statement on 2-drug regimens is currently only available as a brief slide deck.

†Only if baseline viral load ≤100,000 copies/mL; baseline viral load can be disregarded when used as a switch option in the context of viral load suppression

B.1.3.4.4. *Subsequent therapy after virologic failure*

People who experience virologic failure on ART are switched to another regimen as soon as possible to avoid accumulation of resistance mutations (preferably after results of resistance testing are available)[21]. According to BHIVA guidelines, the choice of the new ART regimen will primarily depend on the results of resistance testing (including how many drug classes the virus is resistant to), prior treatment history and the individual's preference, with comorbidities and future therapy options also taken into account. Thus, subsequent therapy is individualised as far as possible with the aim of constructing a fully suppressive regimen.

B.1.3.5. Daily oral ART: burden, challenges and unmet need

Modern ART regimens enable effective viral suppression and near-normal life expectancy for those who adhere to treatment [35]. Thus, a young person diagnosed with HIV today is likely to remain on ART for more than 40 years. However, close adherence to prescribed treatment is essential to achieve and maintain viral suppression and prevent emergence of viral resistance mutations, and life-long daily oral administration is currently the only treatment option available.

There is an unmet need for a long-acting treatment that can reduce the burden of ART, particularly for those who find daily oral ART challenging. People living with HIV rank less frequent dosing as one of their most desired improvements in HIV treatment[27], and showed a clear preference for long-acting injectable treatment over daily oral ART in clinical trials (see Section B.2.6.1.12).

The challenges associated with life-long daily oral ART can be broadly divided into psychological / emotional and medical factors, as elaborated below. All have the potential for negative effects on HRQoL and also on clinical outcomes, particularly through their potential adverse impact on adherence.

B.1.3.5.1. *Psychological / emotional challenges of daily oral ART*

The need to adhere to life-long daily oral ART is a constant reminder of a person's HIV status, and also provides evidence of their HIV that is visible to others in the form of their medication. This is problematic for some people for a number of reasons:

- **Stigma:** HIV differs from most other chronic diseases because of the stigma that remains associated with it. BHIVA notes that HIV-related stigma is widely reported and feared by people living with HIV[33]. For example, ongoing stigma was described by participants in the Public Health England Positive Voices survey[36], and in a sample of 123 UK people living with HIV who contributed to the ViiV Healthcare Positive Perspectives 2 study, 63% reported having chosen not to share their HIV status with someone out of fear that the person would see or treat them differently[27].

  HIV-related stigma can occur in various forms, such as self- or internalised stigma (negative self-beliefs based on HIV status), anticipated or perceived stigma (expecting negative treatment based on HIV status), and discrimination (experiencing negative and

devaluing treatment based on HIV status)[37]. These different forms of HIV-related stigma were captured in the People Living With HIV Stigma Survey. In a UK sample of 1,576 individuals (2015 survey), results showed that the lives of a significant number of people living with HIV in the UK continue to be adversely affected by all three forms of stigma[37].

Stigma and discrimination are experienced by many groups of people living with HIV in the UK, as revealed by the 2015 People Living With HIV Stigma Survey[38,39]. Another example is provided by The Sophia Forum, a UK charity for women living with HIV, who recently conducted a survey on women's experiences with stigma and discrimination. It found that "Stigma (including self-stigma, perceived stigma and discrimination) continues to play a role in the lives of women living with HIV. Many women both feared and experienced exclusion and negative treatment as a result of their HIV status"[40].

- **Fear of unwanted disclosure of HIV status through discovery of medication**: as a result of the stigma around HIV, some individuals report a fear of unwanted disclosure through discovery of their medication by others, including discovery of pills at home or in public settings[41, 42]. In the ViiV Healthcare Positive Perspectives 2 study, approximately half of the 123 people living with HIV sampled in the UK reported concerns about disclosure of their HIV status[27].

  This is a particular issue for people who live in a family, community or work environment where disclosure of their HIV status could have a negative impact on their lives. This includes the potential for domestic abuse or intimate partner violence, for example towards women whose HIV status is discovered during antenatal care. Fear of disclosure is also an issue for individuals travelling to countries where there is intolerance of people with HIV. In the EU Unmet Need study (a structured survey conducted for ViiV Healthcare that included 200 people living with HIV in the UK and 30 UK healthcare providers), 10.7% of the UK participants living with HIV reported worrying about this issue a lot or all of the time, and 46.4% reported hiding their treatment to avoid disclosure[26].

  Fear of disclosure may affect adherence: 10.2% of UK respondents living with HIV reported sometimes, often or very often missing a treatment dose because they were not in a situation where they felt comfortable taking medication[26].

- **Daily pill-taking as an unwanted reminder of HIV status**: in the EU Unmet Need study, 49% of UK respondents reported that their daily HIV treatment sometimes or often reminded them of their HIV status or of a mistake or bad memory from the past[26]. Such reminders can be distressing for those who feel stigma or shame in relation to having HIV (see above).

Other psychological / emotional challenges include:

- **Anxiety around daily medication**, including worry about missing doses: in the CARLA EU Unmet Need study, 52.6% of UK respondents living with HIV reported sometimes or often worrying about missing doses and consequently losing viral suppression[26].

- **Treatment fatigue** (defined as decreased desire and motivation to maintain vigilance in adhering to a treatment regimen among patients prescribed long-term therapy[43,44]) is a well-recognised phenomenon, both in HIV and other chronic conditions[43,44] and occurs even under modern simplified HIV treatment regimens[43]. Contributing factors include complicated regimens, food restrictions, inconvenience (transporting medication, planning for adequate supplies), the life-long nature of treatment, and side-effects[43].

These challenges have the potential to affect both adherence (see below, Section 1.3.5.3.) and HRQoL.

B.1.3.5.2. *Medical challenges of daily oral ART*

Daily oral ART can impose a substantial burden for those who have comorbidities or disease/treatment complications that interfere with administration. Many of these have a relatively high prevalence in people living with HIV compared with the general population: the list below includes prevalence rates reported by UK participants in the EU Unmet Need Study[26], where these are available. Medical challenges include:

- Malabsorption and other gastrointestinal (GI) conditions (estimated by clinician participants to make oral ART challenging for 9.4% and 8.4% of people living with HIV, respectively[26]).
- Dysphagia (difficulty swallowing, e.g. due to oesophageal pathology or neurological conditions) or pill aversion (26.5% of participants living with HIV reported some difficulty in swallowing pills[26]).
- Neurocognitive impairment, mental health and psychiatric disorders, and behavioural/addiction disorders (central nervous system disorders were estimated by clinician participants to make oral ART challenging for 11.4% of people living with HIV[26]).
- Polypharmacy due to comorbidities. Increases in life expectancy and above-average prevalence of comorbidities for their age mean that people living with HIV are now often required to take multiple non-HIV medications to treat age- and HIV-related comorbidities[45]: in a cohort of 4,630 people living with HIV in the UK, 17% were taking ≥5 non-ART medications, rising to 26.8% in those aged ≥50 years[46]. Polypharmacy is an established risk factor for decreased medication adherence[47].
- Drug-drug or drug-food interactions: 23.2% of people living with HIV in the UK reported they could not take antacids, proton pump inhibitors or histamine 2 blockers along with their HIV treatment, and 40.5% had to take food at the same time as their treatment[26].
- Drug toxicities: whilst ART is efficacious, tolerability and toxicity concerns are recognised across all classes of ART and chronic exposure to drug regimens can lead to both short- and long-term toxicities[21]. This illustrates the importance of having alternative treatment options. In the CARLA EU Unmet Need Study the most common reason for treatment switching (reported by 34.8% of participants who switched) was to reduce the severity or frequency of side-effects[26]).

B.1.3.5.3. *Adherence to daily oral ART*

Challenges in maintaining adherence

Achieving and maintaining optimal adherence to daily ART over the long term is challenging. Currently, people living with HIV in the UK take 1-4 tablets per day on their initial regimen[48]. HIV treatment must be taken at the same time each day and pills may have to be taken more than once a day, with some regimens having strict food/no food requirements. Thus, adherence to current ART requires sustained and consistent daily vigilance, regardless of the individual's other activities and commitments. In the Positive Perspectives study, 33% of the 123 people living with HIV in the UK who were questioned agreed that taking their HIV medication limits their everyday life [27].

BHIVA guidelines state that non-adherence is best understood as a variable behaviour with intentional and unintentional causes, and that most people taking medication are non-adherent some of the time. Unintentional non-adherence is linked to "limitations in capacity or resources that reduce the ability to adhere to the treatment as intended". Intentional non-adherence is the product of a decision informed by beliefs, emotions, and preferences[21].

Suboptimal adherence to daily oral ART is common: a targeted literature review found that estimates of its prevalence in the UK range from 10% (missing ≥2 doses in the last 7 days) to 57% (missing a dose or taking ≥1 dose incorrectly in last 7 days)[49 50-52]. Of people living with HIV in the UK sampled in the EU Unmet Need Study, 26% reported not taking pills exactly as prescribed sometimes or often (Table 4).

Many of the barriers to adherence result from the psychological and organisational burden of long-term daily pill-taking described in the previous section, as illustrated in Table 4. Eliminating the daily pill burden has the potential to increase the proportion who achieve optimal adherence to ART, reducing the potential for loss of viral suppression in the long-term and the consequent switches for virologic reasons, which may be more costly.

Once CAB LA + RPV LA has been administered, there is no possibility of suboptimal adherence (with its potential for adverse consequences; see below) for the remainder of the two-month period.

Table 4 Self-reported suboptimal adherence and five most frequently reported reasons for missing ART doses in the past month, UK people living with HIV

Adherence-related behaviours	% reporting* (N=196)
Not taking pills exactly as prescribed in last month	26.0
Reason for missing a dose in the last month	
Simply forgot	27.6
Away from home, traveling or on holiday	17.9
Felt depressed/overwhelmed	17.9
Bored of taking pills every day	10.2
Not in a situation where felt comfortable taking the pills (privacy/confidentiality)	10.2

*Sometimes, often or very often (3-5 on a 5-point scale, of which 1 = 'never' and 2 = 'rarely')
Source: EU Unmet Need Study, ViiV Healthcare[26]

Consequences of long-term suboptimal adherence

Suboptimal adherence to ART results in reduced treatment effectiveness[53-58], greater risk of resistance and onward transmission[21], and increased healthcare costs [59-61].

- In a 2016 meta-analysis of 43 studies (27,905 participants), the mean proportion of participants reporting optimal adherence was 63.4%. Suboptimal adherence was associated with a higher risk of virologic failure compared with optimal adherence (odds ratio for failure in optimal vs non-optimal adherence = 0.34; 95% CI: 0.26–0.44)[53].
- Several studies have shown that even small reductions in adherence are associated with increased risk of loss of virologic suppression[54-57]. Long-term (96-week) results from a recent phase 3 trial of two daily oral regimens (bictegravir combined with emtricitabine and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine) analysed treatment differences in proportion of participants with viral suppression (HIV-1 RNA <50 copies/mL) by adherence (<95% vs ≥95%) and found adherence had a statistically significant positive interaction (P=0.029) with suppression[58].
- Low adherence is associated with increased risk of drug resistance[21], which can emerge when HIV replication is not fully suppressed. This can limit treatment options for those experiencing virologic failure.
- Suboptimal adherence increases the risk of onward viral transmission due to the increased risk of loss of viral suppression, including potential transmission of a drug-resistant virus. In addition, transmission may occur from individuals who are normally suppressed, during viral blips (brief periods of increased viral load immediately preceded and followed by periods of viral suppression).

- A study of 228 individuals on ART during clinical trials reported that during the week prior to a blip in individuals who were otherwise virally suppressed, the mean number of days in which participants received prescribed doses of ART was 5.55; this was significantly lower than 6.22 days during matched periods when blips did not occur (P = 0.007)[62].
- Use of single viral load measurements has been shown to overestimate the proportion of individuals with stable suppressed viral load by 16% in a retrospective analysis of 10,942 in-care individuals:[63] 78.5% had a suppressed viral load based on a single test, whereas only 65.9% were virally suppressed on all tests during observation. The study did not report adherence data, but the authors noted that participants who had missed HIV primary care visits (no-shows without prior cancellation) during the 12 months of observation were less likely to exhibit stable viral suppression or maintenance of suppression.
- Poor adherence is associated with increased treatment cost[21]: those with poorer adherence have greater overall healthcare utilisation and costs than those with greater adherence[59-61].

The BHIVA guidelines state that: “given the multiple adverse consequences of treatment failure (risk of disease progression, increase in complexity and costs of treatment, and risk of HIV transmission) engaging people living with HIV in their treatment decisions and the monitoring and support of adherence are of paramount importance”[21].

In order to address the challenges described above, there is a need for additional treatment modalities that can overcome the barriers to adherence associated with daily oral ART and therefore the consequences of sub-optimal adherence over time.

B.1.3.6. CAB LA+ RPV LA in the treatment of virologically suppressed individuals with HIV-1

B.1.3.6.1. *Mechanism of action*

CAB (an INSTI) and RPV (an NNRTI; see Table 2 for definitions) are formulated as prolonged-release suspensions for injection[1]. After an oral lead-in period to assess tolerability, CAB LA and RPV LA injections are administered by a healthcare professional as two separate gluteal intramuscular injections, at separate sites at the same visit, every 2 months (Q2M).

Posology is described in Section B.1.2. CAB LA and RPV LA are absorbed slowly from the gluteal muscle into the systemic circulation, resulting in sustained plasma concentrations[1]. Each has a half-life of ≥40 days (vs ≤55 hours for commonly prescribed daily oral ART)[64]. Absorption from the gluteal muscle bypasses the GI tract, so there is no need for individuals to consider interaction with food or with indigestion treatments (antacids, histamine-2 blockers or proton pump inhibitors)[1].

CAB LA and RPV LA injections constitute a complete regimen and should not be administered with other antiretroviral medicinal products for the treatment of HIV[1].

B.1.3.6.2. *Place of CAB LA+RPV LA in the treatment pathway*

CAB LA + RPV LA is indicated for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen without present or past evidence of viral resistance to, and no prior virological failure with, agents of the NNRTI and INI class[2],[1]. Thus, it will be used in people who are switching from their current ART for non-virological reasons.

CAB LA + RPV LA is intended to provide an alternative treatment choice to daily oral ART for people living with HIV and their physicians. It will represent an additional treatment option, alongside current ART regimens, for those who would benefit from, or prefer, treatment in the form of injections Q2M rather than taking daily oral ART. The current pathway and the anticipated place of CAB LA + RPV LA is illustrated in Figure 1.

Adherence to the Q2M injection visit schedule is required. It is anticipated that individuals will only be offered CAB LA + RPV LA if they are able to commit to Q2M visits and a multidisciplinary team considers they are likely to fulfil this commitment. Individuals who do not keep to the visit schedule will be reassessed for suitability, as stipulated in the SmPC.[1]

Thus, the decision to switch to CAB LA + RPV LA will be limited to those individuals most likely to benefit from a long-acting treatment and who are able to adhere to the Q2M injection regimen. The key reasons to switch to long-acting injectable treatment are anticipated to be as follows:

- To ameliorate detrimental effects of HIV infection on psychological wellbeing that are exacerbated by daily oral treatment: for example, living with fear of disclosure of their HIV status and/or the stigma personally felt by the individual; the daily reminder of their HIV status; treatment fatigue or pill aversion; and anxiety around missing doses and the risk of disease progression or transmission to a partner if the viral load were to become detectable.

- To support an individual's adherence to treatment, in order to avoid suboptimal adherence and the associated risk of virologic failure. As previously detailed in Section B.1.3.5.3, adherence to life-long daily oral ART can be challenging. Although individuals are required to be virally suppressed when switching to CAB LA + RPV LA, they may have anxieties about their ability to maintain adherence to daily oral ART in the longer term.

- To provide individuals with medical conditions, including those that prevent the swallowing or absorption of tablets, and drug or food interactions, with an effective alternative treatment option.

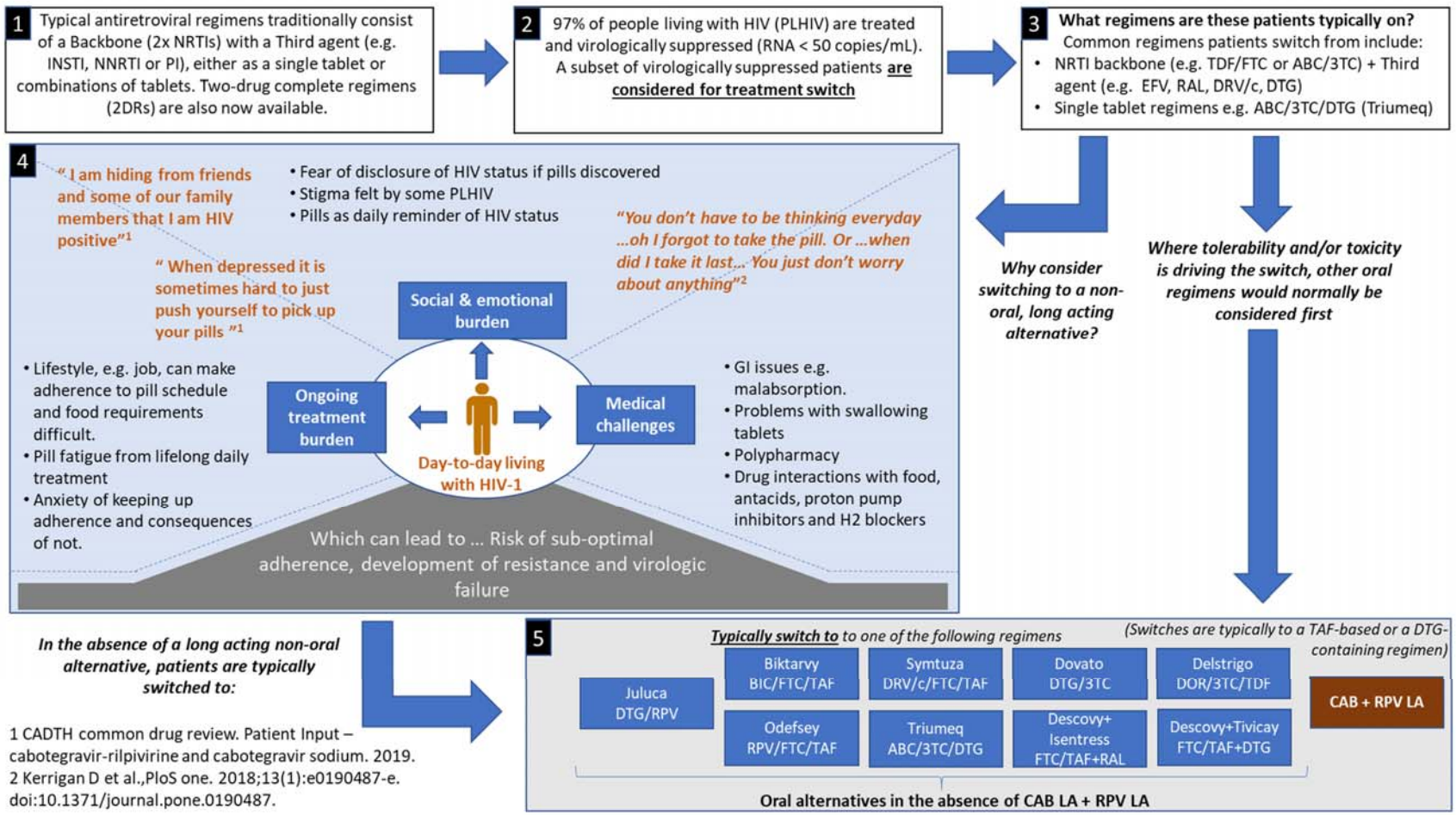


Figure 1 Schematic showing anticipated place of CAB LA + RPV LA in the treatment pathway

B.1.4. Equality considerations

People living with HIV are protected under the Equality Act 2010 on the grounds of Disability (HIV is a chronic health condition). Under the Equality 2010 Act there are a further two populations disproportionally affected by HIV, and therefore there are equality considerations associated with the subsequent guidance on the use of this technology.

- Race: HIV infection disproportionately affects people of black African origin and people coming to the UK from countries with a high HIV prevalence. For example, the estimated prevalence of HIV among heterosexual women and men aged 15 to 74 years in England in 2018 was 36.6 per 1,000 (CrI 36.0 to 37.3) among people of black African descent, compared with 1.10 per 1,000 (CrI 1.08 to 1.15) among the population in England as a whole[17].

- Sexual Orientation: HIV disproportionately affects gay and bisexual men (GBM), who accounted for approximately 50,300 (CrI 48,700 to 53,200) of the 105,200 (CrI 103,300 to 108,500) people living with HIV in the UK in 2019[16].

The availability of a long-acting treatment will provide an important new option for the management of their life-long need for ART. This is especially important for these groups, both of whom experience high rates of stigma.

Other important equality considerations are as follows:

- Financial insecurity: An estimated 46% of women and 32% of men with HIV live at or below the poverty line (income < £20,000 per household) and 53% of people living with HIV do not always have enough money to meet their basic needs (for example utilities, food, rent). An estimated 8% live in accommodation provided by friends or family or other temporary accommodation, including shared housing, where people may fear disclosure or may face difficulties with medicines storage or adherence[36].

- Stigma and discrimination: as stated earlier in the submission, HIV differs from most other chronic diseases because of the stigma that remains associated with it. Ongoing stigma was described by participants in the Public Health England Positive Voices survey[36]. In a sample of 123 people living with HIV in the UK who contributed to the ViiV Healthcare Positive Perspectives 2 study, 63% reported having chosen not to share their HIV status with someone out of fear that the person would see or treat them differently[27].

- Tackling stigma and discrimination (among other issues) will form part of the updated sexual and reproductive health strategy which the government committed to in October 2019[65].

This information further supports the importance of having a range of treatment options for people living with HIV.

B.2 Clinical effectiveness

Key points

- The clinical effectiveness of CAB LA + RPV LA Q2M was assessed in the ATLAS-2M trial, compared with Q1M administration[66].
    - CAB LA + RPV LA Q2M was highly efficacious in maintaining virologic suppression on the primary trial endpoint of virologic failure at Week 48 (intent-to-treat exposed [ITT-E] population), and was non-inferior to Q1M administration[66].
    - CAB LA + RPV LA Q1M was previously shown to be non-inferior to oral ART in the ATLAS and FLAIR trials[67, 68].
- CAB LA + RPV LA Q2M is non-inferior to oral ART: an indirect treatment comparison (ITC) using data from the ATLAS and FLAIR trials found that CAB LA + RPV LA Q2M is not statistically different to oral ART after 48 weeks on any of the efficacy or safety outcomes analysed[69].
- CAB LA + RPV LA Q2M is well tolerated. Injection site reactions (ISRs) are common but are almost always mild and rapidly resolving (median duration 3 days), and were well accepted by participants, with incidence declining over time[70].
- Levels of treatment satisfaction with CAB LA + RPV LA are high (by HIV Treatment Satisfaction Questionnaire [HIVTSQs] and General Acceptance scores), and trial participants expressed a strong preference for CAB LA + RPV LA over oral ART[70].
- CAB LA + RPV LA is associated with improved health state utility values compared with daily oral ART: a post-hoc analysis of SF-6D utility scores derived from the SF-12 items of ATLAS and FLAIR found a statistically significant utility difference of [redacted] in favour of CAB LA + RPV LA[71].

B.2.1. Identification and selection of relevant studies

A systematic literature review (SLR) was undertaken to identify the clinical effectiveness evidence (efficacy and safety) of interventions for the treatment of adults living with HIV-1 infection. Full details of the process and methods to identify and select the relevant clinical evidence are summarised in Appendix D.

B.2.2. List of relevant clinical effectiveness evidence

B.2.2.1. Overview of the clinical development programme

ViiV Healthcare in partnership with Janssen Sciences Ireland UC (Janssen) are developing the CAB LA + RPV LA regimen for the treatment of HIV-1 infection in adults who are virologically suppressed. ViiV Healthcare is the Sponsor of the CAB LA + RPV LA clinical programme, whose overall objective is to develop a novel, highly effective and well tolerated 2-drug long acting (LA) injectable regimen[72].

The CAB doses for the Phase 3 programme were selected on the basis of two Phase 2b studies: LATTE (oral CAB + RPV and proof of concept) and LATTE-2 (CAB LA + RPV LA)[72].

The efficacy and safety of CAB LA + RPV LA given every month (Q1M), following an oral lead in period to establish tolerability, was assessed in two Phase 3 randomised, multicentre, active-controlled parallel arm open label non-inferiority trials (ATLAS and FLAIR). The two studies were similar in design, enabling a pre-specified pooled analysis of non-inferiority[73]. The design of these studies, the pooling of the results, and the non-inferiority margin of the individual studies (6%) and of the pooled studies (4% pooling enabling a more reliable efficacy estimate) were agreed by the EMA[74].

ATLAS was conducted in virally suppressed participants who were switching from other current ART regimens[72]. FLAIR was conducted in participants who had not previously received ART; participants were required to achieve viral suppression in a 20-week oral induction with a 3-drug single-tablet ART regimen (dolutegravir/abacavir/lamivudine;Triumeq®) before being eligible for randomisation to either continue Triumeq® or switch to CAB LA + RPV LA (following an oral lead in period).

The efficacy and safety of CAB LA + RPV LA given Q2M, following an oral lead-in period for participants not previously exposed to CAB LA + RPV LA, was evaluated in ATLAS-2M, a Phase IIIb randomised, multicentre, parallel-arm open label non-inferiority study[72]. The CAB LA + RPV LA clinical development programme is summarised in Table 5.

Table 5 Overview of the clinical development programme

Study name, objective and population	Study design	Treatment arms and interventions
LATTE[75] Phase 2b trial evaluating oral CAB in combination with oral RPV ART-naïve at recruitment (N = 244)	Phase 2b, randomised, dose ranging multicentre, parallel-group, partially blinded, 2-part study	Induction Phase (24 weeks): CAB group: Oral CAB 10, 30, or 60 mg + ABC/3TC or TDF/FTC once daily Control group: EFV + ABC/3TC or TDF/FTC Maintenance Phase (72 weeks): CAB + RPV group: Oral CAB 10, 30, or 60 mg + oral RPV 25 mg once daily Control group: EFV + ABC/3TC or TDF/FTC Open-Label Phase (post 96 weeks): CAB 30 mg + RPV 25 mg
LATTE-2[76-78] Phase 2b trial evaluating CAB LA in combination with RPV LA compared with oral CAB in combination with 2 NRTIs to maintain virologic suppression ART-naïve at recruitment (N = 309)	Phase 2b, randomised, multicentre, parallel-group, open-label, dose ranging trial	Induction Phase (20 weeks): Oral CAB 30 mg + ABC/3TC once daily. With oral RPV 25 mg once daily for last 4 weeks Maintenance Phase (96 weeks): CAB + RPV Q1M group: CAB LA 800 mg +RPV LA 600 mg loading dose, CAB LA 400 mg + RPV LA 600 mg every 4 weeks CAB + RPV Q2M group: CAB LA 800 mg + RPV LA 900 mg loading dose, CAB LA 600 mg second loading dose, CAB LA 600 mg + RPV LA 900 mg every 8 Control group: Oral CAB 30 mg + ABC/3TC once daily
POLAR[79]	Phase 2b, multicentre, open-label, non-randomised, rollover study	Screening Phase Participants in LATTE, with HIV-1 RNA <50 copies/mL, who have received daily oral CAB (30 mg) + RPV (25mg) ≥312 weeks were enrolled. Maintenance Phase CAB LA + RPV LA Q2M group: CAB (600 mg) + RPV (900 mg) LA every 8 weeks current ART group: Single oral tablet dolutegravir (50mg) + RPV (25mg) once daily.
ATLAS[3, 67] Phase 3 trial to demonstrate non-inferior antiviral activity of switching to CAB LA in combination with RPV LA compared with remaining on current ART regimen ART-experienced, virologically suppressed on a stable regimen	Phase 3, randomised, open-label, active-controlled, multicentre, parallel-group, non-inferiority study	Maintenance Phase (52 Weeks): CAB + RPV group: Oral CAB 30 mg + RPV 25 mg once daily for 4-5 weeks, followed by IM CAB LA 600 mg + RPV LA 900 mg for the first IM dose and then CAB LA 400 mg + RPV LA 600 mg every 4 weeks Control group: 2 NRTIs + INSTI or 2 NRTIs + PI or 2 NRTIs + NNRTI.

containing 2 NRTIs plus an INSTI, NNRTI or a PI for at least 6 months (N = 618)		
FLAIR[68, 80] Phase 3 trial to demonstrate non-inferior antiviral activity of switching to CAB LA in combination with RPV LA compared with remaining on ABC/DTG/3TC ART-naïve (N = 566)	Phase 3, multiphase, randomised, open-label, active-controlled, multicentre, parallel-group, non-inferiority study	Induction Phase (20 weeks): Oral ABC/DTG/3TC FDC (NRTI substitution allowed) Maintenance Phase (100 weeks): CAB + RPV group: Oral CAB 30 mg + RPV 25 mg once daily for 4-5 weeks, followed by intramuscular CAB LA 600 mg + RPV LA 900 mg for the first IM dose and then CAB LA 400 mg + RPV LA 600 mg every 4 weeks Control group: oral ABC/DTG/3TC FDC once daily (or alternative DTG + 2 NRTIs)
ATLAS-2M[66, 70] Phase IIIb trial to demonstrate noninferiority of LA CAB + LA RPV Q2M compared with LA CAB + LA RPV Q1M ART-experienced, virally suppressed on a stable ART regimen (N =1,020)	Phase IIIb, randomised, open-label, active-controlled, multicentre, parallel-group, non-inferiority study	Maintenance Phase (52 Weeks): CAB + RPV Q1M group: CAB LA 600 mg + RPV LA 900 mg loading dose*, CAB LA 400 mg + RPV LA 600 mg every 4 weeks (±7 days) CAB + RPV Q2M group: CAB LA 600 mg + RPV LA 900 mg loading dose*, CAB LA 600 mg + RPV LA 900 mg second loading dose* administered 4 weeks after the initial loading dose, CAB LA 600 mg + RPV LA 900 mg every 8 weeks (±7 days) *Note: participants were either transitioned from ATLAS (CAB + RPV Q1M or current ART) or from their current ART. Those transitioning from current ART received oral CAB 30 mg + RPV 25 mg once daily for 4-5 weeks followed by appropriate loading doses. Those transitioning from CAB + RPV Q1M received oral lead in and loading doses during their participation in ATLAS and started maintenance doses on Day 1 of ATLAS-2M according to their randomisation assignment.

Abbreviations: ABC/DTG/3TC, abacavir/dolutegravir/lamivudine; ACTG A5359, AIDS Clinical Trials Group A5359; ART, antiretroviral therapy; ATLAS, Antiretroviral Therapy as Long-Acting Suppression; ATLAS-2M, Antiretroviral Therapy as Long-Acting Suppression Q2M; CAB, cabotegravir;; EFV, efavirenz; FLAIR, First Long-Acting Injectable Regimen; HIV, human immunodeficiency virus; IM, intramuscular; INSTI; integrase strand transfer inhibitor; LA, long-acting; LATTE, Long-Acting antireTroviral Treatment Enabling; LATTE-2, Long-Acting antireTroviral Treatment Enabling-2; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; POLAR, Oral (PO) to Long-Acting (LA) Rollover; Q1M, every 1 month; Q2M, every 2 months; RPV, rilpivirine

[a] 2 NRTIs = ABC/3TC 600 mg/300 mg or TDF/FTC 300 mg/200 mg. The 2 NRTIs were used in the induction phase, whereas RPV was used in the maintenance phase.

[b] All participants received CAB 30 mg orally with ABC/3TC 600 mg/300 mg as induction therapy before randomisation to one of the injectable therapy arms or the oral therapy arm.

[c] All participants who were receiving oral current ART at the time of entry into ATLAS-2M receive 4-week oral lead-in therapy consisting of CAB + RPV before they receive intramuscular injections.

[d] All participants who transition from the ATLAS study to ATLAS-2M do not receive a loading dose of CAB or RPV because their safety and tolerability has been established in ATLAS.

B.2.2.2. Evidence presented in the submission

The non-inferiority of CAB LA + RPV LA Q1M to oral current ART regimens was established in a pre-specified pooled analysis of the ATLAS and FLAIR Phase 3 studies[67, 68, 73, 81].

Having established the non-inferior efficacy of Q1M administration to current ART in maintaining virologic suppression, and in view of the potential added benefits for people living with HIV and health services of a longer administration interval, the efficacy (non-inferiority) and safety of CAB LA + RPV LA Q2M compared with Q1M was assessed in the LATTE-2 Phase 2b study (dose ranging) and the ATLAS-2M Phase IIIb study [66, 70, 76-78].

In this submission, evidence to support the effectiveness of CAB LA + RPV LA Q2M (the regimen available in the UK) for the treatment of HIV-1, in line with the licensed indication, is derived primarily from ATLAS-2M, summarised in Table 6 and described in more detail in Section B.2.6.1. The ATLAS and FLAIR studies are presented as supporting evidence. The efficacy (non-inferiority) of CAB LA + RPV LA Q2M versus oral current ART is estimated via an indirect treatment comparison, using data from the CAB LA + RPV LA Q1M arms of ATLAS and FLAIR (pooled) and ATLAS-2M – see Section B2.8. An overview of the phase 3 studies that inform the economic modelling is shown in Table 6 to Table 8.

Table 6. Clinical evidence - ATLAS-2M

Study	**ATLAS-2M (NCT03299049)**		
Study design	Phase IIIb Randomized, Multicenter, Active-controlled, Parallel-group, Non-inferiority, Open-label Study		
Population	HIV-1 infected ART-experienced adults who are virologically suppressed on a stable antiretroviral regimen		
Intervention(s)	CAB LA + RPV LA Q2M (switched from either Q1M arm of ATLAS or current ART; oral lead-in if no prior exposure to CAB LA + RPV LA)		
Comparator(s)	CAB LA + RPV LA Q1M (switched from either Q1M or current ART arm of ATLAS, or current ART; oral lead-in if no prior exposure to CAB LA + RPV LA)		
Indicate if trial supports application for marketing authorisation	Yes	Indicate if trial used in the economic model	Yes
Rationale for use/non-use in the model	Relevant population/outcomes reported		
Reported outcomes specified in the decision problem	Outcomes relating to the following aspects of the NICE scope were reported: - Proportion of participants with plasma HIV-1 RNA ≥50 copies/mL at week 48 (snapshot algorithm for the ITT-E population) - CD4+ T-cell levels		

	- Maintenance of viral suppression (proportion of participants with plasma viral load <50 copies/mL, per FDA Snapshot algorithm) - Adherence to treatment regimen - Mortality - Adverse effects of treatment - Health-related quality of life
All other reported outcomes	Proportion of participants with protocol defined confirmed virologic failure (CVF) Viral load changes from Baseline over time CD4+cell count changes from Baseline over time Incidence and severity of Adverse Events (AE) and laboratory abnormalities over time Proportion of participants who discontinue treatment due to AEs Change from Baseline in laboratory parameters Incidence of treatment emergent resistance through Week 48 and Week 96 Plasma pharmacokinetic parameters Demographic parameters Change from Baseline in HRQoL Change from Baseline in treatment satisfaction using HIV Treatment Satisfaction Status and Change Questionnaire HIVTSQs,c Change in Dimension scores of PIN Questionnaire Change in treatment acceptance Incidence of disease progression Subgroup analysis of defined CVF over time Subgroup analysis of change from Baseline in CD4+cell count Relationship between CAB and RPV concentration and virologic, immunologic response and occurrence of AEs over time Assessment of preference for CAB LA + RPV LA regimen Assessment of reason for switching Assessment of reason for continuation
Source: Clinical study report[70] and ClinicalTrials.gov[82]	

Table 7. Clinical evidence - ATLAS

Study	ATLAS (NCT02951052)
Study design	Phase 3, Randomized, Multicentre, Parallel-group, Non-inferiority, Open-label Study
Population	Participants virologically suppressed (stable on prior ART for at least 6 months)
Intervention(s)	CAB LA + RPV LA, oral lead-in then Q1M

Comparator(s)	Current anti-retroviral regimen (2 NRTIs plus an INSTI, NNRTI, or a PI)		
Indicate if trial supports application for marketing authorisation	Yes	Indicate if trial used in the economic model	Yes (via ITC)
Rationale for use/non-use in the model	Pooled evidence from ATLAS and FLAIR is used in an indirect treatment comparison (ITC) that informs the relative efficacy of CAB LA + RPV LA Q2M versus current ART in the model		
Reported outcomes specified in the decision problem	Outcomes relating to the following aspects of the NICE scope were reported: - Proportion of participants with plasma HIV-1 RNA ≥50 copies/mL at week 48 (snapshot algorithm for the ITT-E population). - CD4+ T-cell levels - Maintenance of viral suppression (proportion of participants with plasma viral load <50 copies/mL and <200c/mL, per FDA Snapshot algorithm) - Adherence to treatment regimen - Mortality - Adverse effects of treatment - Health-related quality of life		
All other reported outcomes	Proportion of participants with protocol defined confirmed virologic failure (CVF) Absolute values for plasma RNA and change from baseline Absolute values for CD4+ count and change from baseline Incidence of disease progression Incidence and severity of AEs over time Change from Baseline in laboratory parameters Proportions of participants who discontinue treatment due to AEs Incidence of treatment emergent resistance through Week 48 and Week 96 Plasma pharmacokinetic parameters Change from Baseline in treatment satisfaction using HIV Treatment Satisfaction Status and Change Questionnaire HIVTSQs,c Change in Dimension scores of PIN Questionnaire Change in treatment acceptance Change in tolerability Demographic parameters		
Source: Clinical study report[3] and ClinicalTrials.gov[83]			

Table 8. Clinical evidence - FLAIR

Study	**FLAIR (NCT02938520)**
Study design	Phase 3, Randomised, Multicentre, Parallel-group, Open-Label Study

Population	HIV-1 infected adults who were ART-naïve at recruitment (participants were required to achieve viral suppression on daily oral DTG-ABC-3TC (Triumeq®) for 20 weeks before randomisation to CAB LA + RPV LA Q1M or continuation of the induction regimen		
Intervention(s)	Oral induction with current ART, then oral lead-in with CAB + RPV, then CAB LA + RPV LA Q1M		
Comparator(s)	Daily oral DTG-ABC-3TC (continued from induction phase)		
Indicate if trial supports application for marketing authorisation	Yes	Indicate if trial used in the economic model	Yes (via ITC)
Rationale for use/non-use in the model	Pooled evidence from ATLAS and FLAIR is used in an indirect treatment comparison (ITC) that informs the relative efficacy of CAB LA + RPV LA Q2 M versus current ART in the model		
Reported outcomes specified in the decision problem	Outcomes relating to the following aspects of the NICE scope were reported: - Proportion of participants with plasma HIV-1 RNA ≥50 copies/mL at week 48 (snapshot algorithm for the ITT-E population). - CD4+ T-cell levels - Maintenance of viral suppression (proportion of participants with plasma viral load <50 copies/mL and <200c/mL, per FDA Snapshot algorithm - Adherence to treatment regimen - Mortality - Adverse effects of treatment - Health-related quality of life		
All other reported outcomes	Proportion of participants with CVF Absolute and change from Baseline in plasma HIV-1 RNA (log_{10} copies/mL) and CD4+ cell counts Incidence of disease progression Subgroup analysis participants with plasma viral load <50 copies/mL Subgroup analysis of virologic failure over time Safety and tolerability assessments including monitoring of AEs Incidence of treatment emergent genotypic and phenotypic resistance in participants experiencing CVF HIV-1 exploratory analysis Plasma pharmacokinetics concentrations Absolute values and change from Baseline in renal and bone biomarkers Change from Baseline in treatment satisfaction using HIV Treatment Satisfaction Status and Change Questionnaire HIVTSQs and c Change in Dimension scores of PIN Questionnaire Change in treatment acceptance		

Source: Clinical study report[80] and ClinicalTrials.gov[84]

The following additional studies were identified:

- LATTE-2: a phase 2b dose ranging study evaluating the efficacy and safety of CAB LA + RPV LA Q1M versus Q2M versus oral CAB + ABC/3TC[76-78]. ART-naïve adults initially received oral CAB + ABC/3TC. Those achieving viral suppression following 20 weeks of oral therapy were randomised 2:2:1 to CAB LA + RPV LA Q1M versus Q2M versus continuing with oral CAB + ABC/3TC[77].
- LATTE: a phase 2b dose-finding study of oral CAB (10 mg, 30 mg or 60 mg per day). Initially ART-naïve adults[75] received oral CAB (10 mg, 30 mg or 60 mg per day) or oral efavirenz 600 mg per day with two NRTIs. Those virologically suppressed by week 24 received a two-drug regimen of their CAB dose plus oral rilpivirine 25 mg or continued on their efavirenz-based regimen.
- POLAR: an ongoing phase 2b study of virally suppressed participants who participated in LATTE[79]. POLAR is described in Section B.2.11.

An overview of LATTE-2 is given in Section B.2.6.1.13 to support the phase 3 evidence for the Q2M regimen. It was not included in the economic model because it is superseded by the results of the ATLAS-2M phase 3 study; however, it provides long-term data on the durability of efficacy, safety and adherence, which is presented. The results of LATTE led to the setting up and progression of the ATLAS and FLAIR phase 3 studies. LATTE will not be described further in this submission.

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

The methodology of the relevant studies is summarised in Section B.2.6.

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

The statistical methods and definition of study groups for the relevant studies are summarised in Section B.2.6.

B.2.5. Quality assessment of the relevant clinical effectiveness evidence

The clinical effectiveness evidence provided in this submission is derived from large phase 3 trials conducted in line with the requirements of regulatory bodies. The complete quality assessments of ATLAS-2M, ATLAS and FLAIR are provided in Appendix D.

B.2.6. Clinical effectiveness results and methodology of the relevant trials

B.2.6.1. Trials of CAB LA + RPV LA Q2M (ATLAS-2M)

Key points from ATLAS-2M[70]

- Q2M dosing of CAB LA + RPV LA was highly efficacious and was non-inferior to Q1M dosing in maintaining virologic suppression on the primary endpoint - proportion of participants with HIV-RNA ≥50 copies/mL at Week 48 (defined by the USA FDA snapshot algorithm).
- Few participants experienced HIV-1 RNA ≥50 copies/mL: 1.7% and 1% in the Q2M and Q1M groups, respectively (upper bound of 95% CI for difference was 2.2%).
- Virologic suppression (HIV-1 RNA <50 copies/mL) was also non-inferior between the groups, maintained in 94.3% and 93.5% of those in the Q2M and Q1M arms, respectively (4.0% and 5.5% had no virologic data).
- The rate of confirmed virologic failure was low (1.5% and <1% for Q2M and Q1M, respectively).
- Participants expressed high satisfaction with treatment, and 94% (no prior Q1M experience) to 98% (with prior Q1M experience in ATLAS) of participants in the Q2M arm preferred CAB LA + RPV LA to daily oral ART.
- Results from ATLAS-2M support the option for people living with HIV who are virologically suppressed to switch to Q2M CAB LA + RPV LA injections for continued maintenance therapy.

B.2.6.1.1. *Study design*

ATLAS-2M is a phase IIIb, randomised, multicentre, parallel-group, non-inferiority, open-label study whose primary objective was to demonstrate the non-inferior antiviral activity of CAB LA + RPV LA Q2M compared with CAB LA + RPV LA Q1M over 48 weeks in antiretroviral therapy (ART)-experienced adults living with suppressed HIV-1 infection[66, 85].

Approximately half of the participants were enrolled from the ongoing ATLAS study, with additional participants enrolled in order to support a targeted total sample size of approximately 1,020. Participants randomised from current ART, including those enrolled to the current ART arm of ATLAS (following completion of the Week 52 visit at minimum), received a lead-in phase of oral therapy with CAB 30 mg + RPV 25 mg once daily at Baseline (Day 1) for 28 days (+/- 3 days) in order to assess tolerability before beginning treatment with CAB LA + RPV LA[66, 85].

Participants were randomised (1:1) to receive CAB LA + RPV LA Q1M, or CAB LA + RPV LA Q2M regimen for at least 100 weeks (the Maintenance Phase) [85]. The study design of ATLAS-2M is described in Figure 2.

A summary of methodology for ATLAS-2M is provided in Table 9. The sections that follow give additional information on eligibility criteria (Section B.2.6.1.3) and statistical methods (Section B.2.6.1.4.).

Table 9. Summary of trial methodology - ATLAS-2M

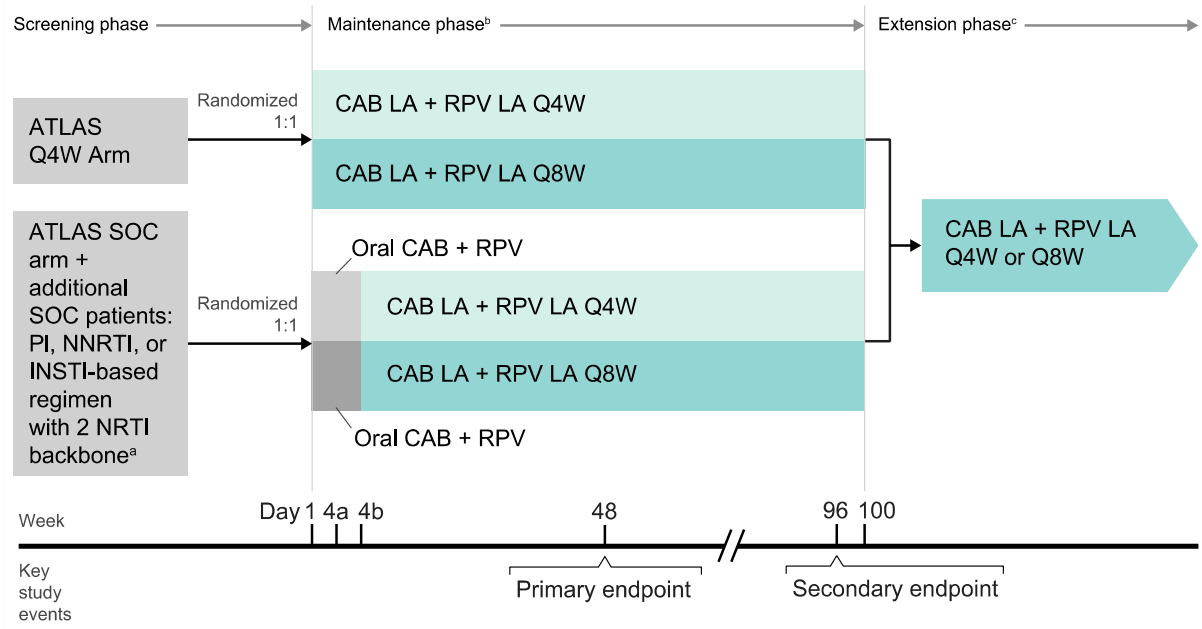
Trial name	ATLAS-2M
Location	North America, South America, Australia, Europe, Asia, Africa
Trial design	Randomised, multicentre, parallel-group, non-inferiority, open-label
Eligibility criteria for participants	HIV-1 infected antiretroviral therapy experienced adults who are virologically suppressed on a stable antiretroviral regimen. Additional details are provided in Table 10.
Settings and locations where data were collected	The study was conducted in ~90 academic centres and hospitals across 13 countries in North America, South America, Australia, Europe, Asia, Africa.
Study drugs	Oral CAB 30 mg + RPV 25 mg once daily at Day 1 for 28 days (±3 days) to determine individual safety and tolerability prior to receiving CAB LA + RPV LA. CAB LA + RPV LA: dosing regimens are described below.
Concomitant medications	The following concomitant medications or therapies are not permitted at any time during the study: - HIV immunotherapeutic vaccines - Other experimental agents, antiretroviral drugs not otherwise specified in the protocol, cytotoxic chemotherapy, or radiation therapy - Systemically administered immunomodulators - Acetaminophen (paracetamol) cannot be used in participants with acute viral hepatitis - Chronic use of systemic (oral or parenteral) glucocorticoids - A single dose of systemic dexamethasone is permitted - Hepatitis C infection therapy - Interferon-based HCV therapy
Primary outcome	Non-inferiority in the proportion of participants with HIV-RNA ≥50 copies/mL at Week 48 (defined by the USA FDA snapshot algorithm) - Assessed via the Abbott RealTime HIV-1 lower limit of detection (LLOD) 40 copies/mL
Other outcomes used in the economic model/specified in the scope	- Change from baseline in CD4+cell count (total lymphocyte counts, percentage and absolute CD4+ [collected Q2M] and CD8+ lymphocyte counts [collected every 6 months], ratios) - Adverse events - HRQoL (HAT-QoL, HIVTSQs and ACCEPT were assessed every 6 months) - Proportion of participants with plasma viral load <50 copies/mL(also pre-specified for non-inferiority assessment)

Other secondary outcomes	- Proportion of participants with protocol defined confirmed virologic failure (CVF) - Virologic failure at Week 96 - Viral load changes from Baseline over time - Incidence and severity of Adverse Events (AE) over time - Proportion of participants who discontinue treatment due to AEs - Change from Baseline in laboratory parameters - Incidence of treatment emergent resistance through Week 48 and Week 96 - Plasma pharmacokinetic parameters - Demographic parameters - Change from Baseline in HRQoL - Change from Baseline in treatment satisfaction using HIV Treatment Satisfaction Change Questionnaire HIVTSQc - Change from Baseline in treatment acceptance using the General Acceptance Domain of ACCEPT - Change from Baseline in Perception of Injection (PIN) - HIV-associated conditions were assessed according to the - 2014 CDC Revised Classification System for HIV Infection - Analyses for HIV-1 resistance was carried out on peripheral blood mononuclear cell (PBMC) samples collected at Baseline and/or on stored blood samples from other relevant time points
Pre-planned subgroups	Pre-specified subgroup analyses were carried out for the randomisation stratification factors: (prior exposure to CAB + RPV: 0 weeks, 1-24 weeks, and >24 weeks), and for demographic factors (age, gender, BMI, race), HIV-1 subtype, baseline viral load, baseline CD4+ lymphocyte count, and participating countries

ACCEPT: Chronic Treatment Acceptance Questionnaire, BMI: body mass index, CAB: cabotegravir, CD4+: cluster of differentiation 4, HAT-QoL: HIV/AIDS Targeted Quality of Life, HCV: hepatitis C virus, HIV: human immunodeficiency virus, HIVTSQ: HIV Treatment Satisfaction Questionnaire, INSTI: integrase strand transfer inhibitor, LA: long-acting, NNRTI: non-nucleoside reverse transcriptase inhibitor, RNA: ribonucleic acid, RPV: rilpivirine, Q1M: once a month, Q2M: every two months

Source: ATLAS-2M Protocol[85], Overton et al[66]

Figure 2. ATLAS-2M study design



ATLAS, Antiretroviral Therapy as Long-Acting Suppression; ATLAS-2M, Antiretroviral Therapy as Long-Acting Suppression Q2M; CAB, cabotegravir; HIV, human immunodeficiency virus; IM, intramuscular; INSTI, integrase strand transfer inhibitor; LA, long-acting; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; Q4W (Q1M), every 4 weeks; Q8W (Q2M), every 8 weeks; RPV, rilpivirine; SOC, standard of care (i.e. current ART).

[a] current ART participants not transitioning from the ATLAS study were required to continue their uninterrupted current regimen (either the initial or second current ART regimen) for at least 6 months before screening. Documented evidence was required of ≥2 plasma HIV RNA measurements <50 copies/mL in the 12 months before screening: one within the 6-12 month window, and one within 6 months before screening. Participants could not have a history of virologic failure or evidence of viral resistance based on the presence of any resistance-associated major INSTI or NNRTI mutation (except K103N) as well as no current or prior history of etravirine use.

[b] Participants who withdrew from the IM regimen were required to enter the 52-week long-term follow up phase if the randomised regimen was not yet locally approved and commercially available.

[c] During the optional extension phase, participants continued their randomised regimen of CAB LA + RPV LA Q1M or Q2M at Week 100

Source: ATLAS-2M Protocol[85]

B.2.6.1.2. *Study treatments*

Two groups of participants were randomized in a 1:1 ratio to:

- **Group 1:** Participants currently receiving current ART therapy, including those enrolled to the current ART arm of ATLAS (following completion of the Week 52 visit at minimum).

– Oral CAB 30 mg + RPV 25 mg once daily for 28 days (+/-3 days) followed by intramuscular injections of CAB + RPV (intramuscular CAB 600 mg + RPV 900 mg at Week 4b, intramuscular CAB 400 mg + RPV 600 mg at Week 8 and every 4 weeks thereafter). Participants were to receive intramuscular injections of CAB + RPV for at least 96 Weeks, or;

- Oral CAB 30 mg + RPV 25 mg once daily for 28 days (+/-3 days) followed by intramuscular injections of CAB + RPV (intramuscular CAB 600 mg + RPV 900 mg at Week 4b and Week 8 and every 8 weeks thereafter). Participants were to receive intramuscular injections of CAB + RPV for at least 96 Weeks.

- **Group 2:** Participants currently receiving intramuscular CAB + RPV Q1M in Study ATLAS (following completion of the Week 52 visit at minimum).

- intramuscular CAB 400 mg + RPV 600 mg Q1M for at least 100 Weeks, or:
- intramuscular CAB 600 mg + RPV 900 mg Q2M for at least 100 Weeks[66, 85].

B.2.6.1.3. *Eligibility criteria*

Key eligibility criteria for participants in ATLAS-2M are provided in Table 10.

Table 10. Key inclusion and exclusion criteria for ATLAS-2M

Key inclusion criteria	Key exclusion criteria

• Men and women of at least 18 years of age
• Participants receiving oral standard of care treatment for HIV-1 (not participating in ATLAS trial)
  - Must be on uninterrupted current regimen (either initial or second ART regimen) for at least 6 months prior to Screening
  - Acceptable stable (initial or second) ART regimens prior to Screening include 2 NRTIs plus:
  - INSTI (either the initial or second current ART regimen)
  - NNRTI (either the initial or second current ART regimen)
  - Boosted PI (or ATV unboosted) (must be either the initial current ART regimen or one historical within class switch is permitted due to safety/tolerability)
  - Documented evidence of at least two plasma HIV-1 RNA measurements <50 copies/mL in the 12 months prior to Screening
  - Plasma HIV-1 RNA <50 copies/mL at Screening
• Participants transitioning from ATLAS
  - Must have been on CAB LA 400 mg + RPV LA 600 mg Q1M or "Current ART" regimen through at minimum Week 52 of the ATLAS study as per ATLAS protocol dosing requirements and until Day 1 of the ATLAS-2M study.
	• Females who are pregnant or breast feeding
	• Evidence of active CDC stage 3 disease
	• Participants with moderate to severe hepatic impairment
	• Pre-existing physical or mental condition which, according to the investigator may interfere with the ability to comply with the trial
	• Participants with significant suicide risk
	• Further exclusion criteria can be found in the trial protocol

- Plasma HIV-1 RNA <50 copies/mL at Screening	

ART: antiretroviral, ATV: atazanavir, CAB: cabotegravir, , CDC: Centers for Disease Control and Prevention, HIV: human immunodeficiency virus, INSTI: integrase strand transfer inhibitor, LA: long-acting, NNRTI: non-nucleoside reverse transcriptase inhibitor, PI: protease inhibitor, RNA: ribonucleic acid, RPV: rilpivirine
Source: ATLAS-2M Protocol[85], Overton et al[66]

B.2.6.1.4. *Statistical analysis and definition of study groups*

A summary of the statistical analysis of ATLAS-2M is provided in Table 11.

Table 11. Statistical analysis and definition of study groups in ATLAS-2M

	ATLAS 2-M
Hypothesis objective	Demonstrate that the antiviral effect of Q2M dosing with CAB LA + RPV LA is non-inferior to Q1M dosing
Analysis populations	ITT-E population: all randomised participants who received at least one dose of study treatment; participants were assessed according to their randomised treatment, regardless of the treatment they received. Per protocol (PP) population: all those in the ITT-E population with the exception of major protocol violators. Safety population: All randomised participants who received at least one dose of study treatment; assessed according to treatment received.
Statistical analysis of primary endpoints	The primary analysis was based on the ITT-E population. The primary comparison was made at a one-sided 2.5% level of significance. Treatment with Q2M was declared non-inferior to Q1M if the upper end of a two-sided 95% confidence interval for the difference between the two groups (Q2M – Q1M) in the proportion of participants with plasma HIV-1 RNA ≥50 copies/mL at Week 48 (defined by the US FDA snapshot algorithm) was below 4%. The adjusted difference between the randomisation arms for the proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48 and its confidence interval was calculated according to a stratified analysis with CMH weights (to be adjusted for the randomisation strata according to prior exposure to CAB+RPV). The 95% CIs for the treatment differences were calculated using an unconditional exact method based on the two inverted 1-sided tests. The analysis described for the primary comparison was also performed using the Per-Protocol Population and the results were compared for consistency with the results from the ITT-E Population.
Non-inferiority margin	A non-inferiority margin of 4% was chosen because a snapshot proportion with plasma HIV-1 RNA ≥ 50 copies/mL at Week 48 in this range is considered clinically tolerable given the Q2M regimen will offer important advantages over the Q1M regimen such as reduced injection frequency and may offer better adherence and treatment satisfaction. This margin is also in concordance with the current FDA Guidance for Industry [23], which is the most current regulatory guidance from either the EMA or FDA and includes specific recommendations regarding switch studies.
Statistical analysis of key secondary endpoints	The key secondary efficacy analysis was performed to evaluate the proportion of plasma HIV-1 RNA <50 copies/mL per Snapshot at Week 48 based on the ITT-E Population using the same analysis method and

	stratification factors as specified for the primary analyses. A non-inferiority margin of -10% was used for this secondary comparison.
Statistical analysis of other relevant endpoints	The cumulative proportion of participants with confirmed virologic failure through Week 24 and other visits during the Maintenance Phase was also summarized. Absolute values and change from Baseline in plasma HIV-1 RNA and CD4+ lymphocyte count over time were summarised over time using descriptive statistics (mean, median, first and third quartiles, min and max).
Statistical analysis of safety endpoints	AEs and laboratory toxicities were summarised descriptively.
Sample size and power calculation	Assuming the true proportion with plasma HIV-1 RNA ≥50 copies/mL is 3% for the Q2M arm and 2% for the Q1M arm, a non-inferiority margin of 4%, and a 2.5% 1-sided significance level, the sample size of 510 participants per treatment arm would provide at least 85% power to show non-inferiority at Week 48 (using un-pooled Z test statistic). With this sample size, 90% power would be achieved assuming a 1% treatment difference and true proportions with plasma HIV-1 RNA ≥50copies/mL of 2.63% for the Q2M arm and 1.63% for the Q1M arm. With 510 participants per arm and assuming an observed proportion HIV-RNA ≥50 copies/mL is 2% for Q1M, the largest observed treatment difference to achieve non-inferiority with respect to a 4% margin is 1.92 percentage points. This equates approximately to observing an excess of 10 participants on the Q2M arm (10 participants on Q1M vs. 20 participants on Q2M).
Handling of missing data and participant withdrawals	In the Snapshot dataset, participants without HIV-1 RNA data in the assessment window for the visit of interest (due to missing data or discontinuation prior to the visit window) were not included in 'HIV-1 RNA < 50 copies/mL (or <200 copies/mL)'. The nature of this missing data was further classified in Snapshot summaries as either 'HIV-1 RNA ≥ 50 copies/mL' (or 'HIV-1 RNA ≥ 200 copies/mL') or 'No Virologic Data at Week X'[86]. For time-to-event analyses, follow-up time for participants who did not experience an event of interest were censored at time of early withdrawal or end of the Week 48 analysis window. The LOCF approach was used to impute missing values for the Health Outcomes analyses.
CAB: cabotegravir, CD4+: cluster of differentiation 4, CMH: Cochran-Mantel Haenszel, EMA: European Medicines Agency, HCV: hepatitis C virus, HIV: human immunodeficiency virus, INSTI: integrase strand transfer inhibitor, ITT-E: intention-to-treat exposed, LA: long-acting, NNRTI: non-nucleoside reverse transcriptase inhibitor, PP: per-protocol RNA: ribonucleic acid, RPV: rilpivirine, Q1M: once a month, Q2M: every two months Source: ATLAS-2M Protocol[85], Overton et al[66]	

B.2.6.1.5. *Participant disposition and baseline characteristics*

Participant disposition

A total of 1049 participants were randomised in the maintenance phase. Of these, 4 were randomised but did not receive the study treatments[70]. A summary of participant disposition is provided in Table 12.

- The proportion of participants who discontinued was low and comparable between the two treatment groups (Q2M: 36 [7%]; Q1M: 42 [8%])[70].
- For participants in the Q2M group, the most common reasons for withdrawal were AEs (12 participants [2%] and lack of efficacy (9 participants [2%] of which 8 had confirmed virologic failure). For participants in the Q1M group, the most common reasons for withdrawal were withdrawal by the participant (21 [4%]; mostly due to frequency of study visits or participant relocation and AEs (13 participant [2%]). All other reasons were reported by ≤1% of participants in either group[70].

Table 12. Participant disposition - ATLAS-2M

	CAB LA + RPV LA Q2M (N=522)	CAB LA + RPV LA Q1M (N=523)
Participant status		
Ongoing, n (%)	486 (93)	481 (92)
Completed, n (%)	0	0
Withdrawn, n (%)	36 (7)	42 (8)
Reason for withdrawal, n (%)		
AE	12 (2)	13 (2)
Lack of efficacy	9 (2)	3 (<1)
Protocol Defined CVF	8 (2)	2 (<1)
Insufficient viral load response	1 (<1)	1 (<1)
Protocol deviation	1 (<1)	1 (<1)
Prohibited medication use	0	1 (<1)
Non-compliance with study treatment	1 (<1)	0
Non-compliance with protocol procedures	1 (<1)	0
Protocol specified withdrawal criteria met	1 (<1)	3 (<1)
Pregnancy	1 (<1)	3 (<1)
Lost to follow-up	2 (<1)	0
Physician decision	5 (<1)	1 (<1)
Withdrawn by participant	6 (1)	21 (4)
Outcome of AEs resulting in study withdrawal		
Fatal	0	0
Non-fatal	12 (2)	13 (2)

AE: adverse event, CVF: confirmed virologic failure, Q2M: every two months, Q1M: once a month
a) Participant did not meet CVF at Week 48; the investigator withdrew the participant based on a viral load of 1038 copies/mL at Week 56.
Note: Participants may have only 1 primary reason for withdrawal. Percentages for sub reasons may sum to more or less than 100%. Participants may have more than 1 sub reason underneath a single primary reason. Participants are not required to indicate sub reasons.
Source: ATLAS-2M CSR[70], Overton et al[66]

Populations analysed

The populations analysed are shown in Table 13.

Table 13. Population Analysed - ATLAS-2M

	CAB LA + RPV LA Q2M	CAB LA + RPV LA Q1M	Total
Randomised Population	524	525	1049
ITT-E Population	522	523	1045
Safety Population	522	523	1045
PK Population	521	521	1042
CVF Population	8	2	10
CVF: Confirmed virologic failure, ITT: intention-to-treat exposed, PK: pharmacokinetic Source: Overton et al[66]			

Baseline characteristics

Demographic characteristics were broadly similar between the two treatment groups. The median age in both groups was 42 years, and 27% were aged ≥50. The majority of participants were male (Q2M: 74%, Q1M: 73%) and a majority were of white race (Q2M: 71%, Q1M: 75%). Median BMI was 25 in both treatment groups[66].

Over 99% of participants in both treatment groups had a viral load of <50 copies/mL at baseline. Mean CD4+ cell count was similar between the groups[66]. Baseline characteristics are summarised in Table 14.

Table 14. Baseline characteristics of participants, ATLAS-2M

Characteristic	CAB LA + RPV LA Q2M (N=522)	CAB LA + RPV LA Q1M (N=523)
Prior exposure to CAB + RPV, n (%)		
None	327 (63)	327 (63)
1-24 weeks	69 (13)	68 (13)
>24 weeks	126 (24)	128 (24)
Age (y)		
Mean (SD)	42.7 (11.16)	42.3 (10.58)
Median (range)	42 (20-83)	42 (19-75)
Age group (y), n (%)		
<35	137 (26)	145 (28)
35 to <50	242 (46)	239 (46)
≥50	143 (27)	139 (27)
Sex at birth, n (%)		
Female	137 (26)	143 (27)
Male	385 (74)	380 (73)
Race, n (%)		
White	370 (71)	393 (75)
Non-White	152 (29)	130 (25)

BMI (kg/m^2)		
Mean (SD)	26.677 (5.2)	26.782 (5.8)
Viral Load		
n	522	523
<50 copies/mL	519 (>99)	513 (98)
40<=<50 copies/mL	3 (<1)	69 (13)
<40 copies/mL and target detected	69 (13)	70 (13)
CD4+ cell count (cells per mm^3)		
Mean (SD)	681.8 (259.9)	729.8 (298.57)
Median (IQR)	642 (499 – 827)	688 (523 – 878)
<350	35 (7)	27 (5)
350 to <500	96 (18)	89 (17)
≥500	391 (75)	407 (78)
CDC Stage		
Stage 1	391 (75)	407 (78)
Stage 2	129 (25)	113 (22)
Stage 3	2 (<1)	3 (<1)
Hepatitis C co-infection		
n	522	522
Negative	517 (>99)	516 (99)
Positive	5 (<1)	6 (1)

BMI: body mass index, CAB: cabotegravir, CD4+: cluster of differentiation 4, CDC: Centers for Disease Control and Prevention, HIV: human immunodeficiency virus, IQR: interquartile range, NNRTI: non-nucleoside reverse transcriptase inhibitor, RNA: ribonucleic acid, RPV: rilpivirine, Q1M: once a month, Q2M: every two months
Source: ATLAS-2M CSR[70] Overton et al[66]

B.2.6.1.6. *Results: Plasma HIV-1 RNA ≥50 copies/mL at Week 48 (Snapshot Algorithm) ITT-E population (Primary endpoint)*

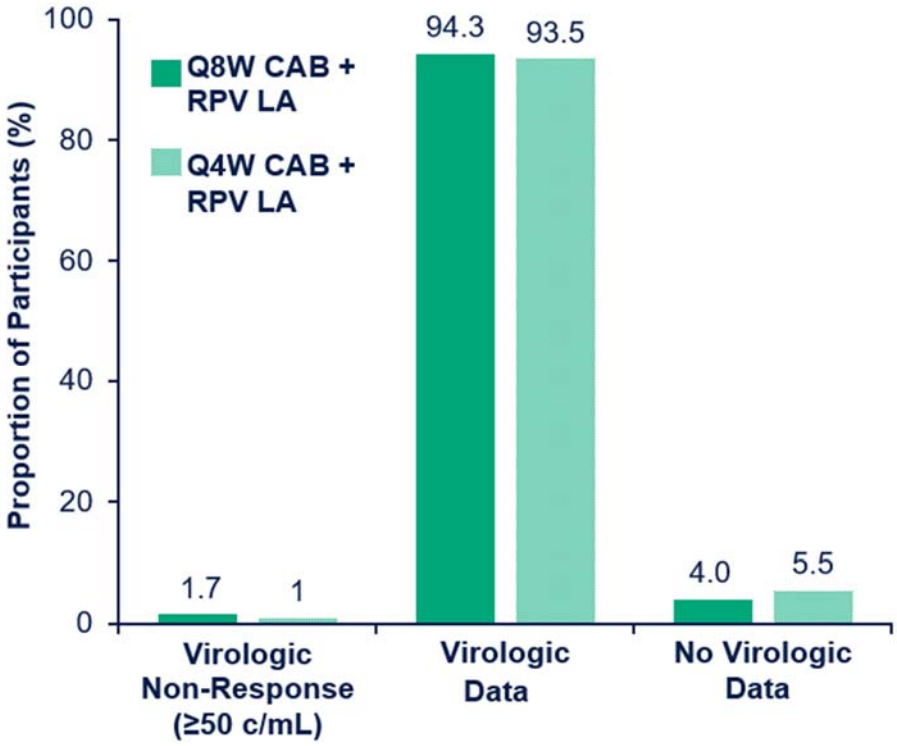
CAB LA + RPV LA Q2M was non-inferior to CAB LA + RPV LA Q1M in maintaining virologic suppression at Week 48 (Table 15, Figure 3). The upper bound of 95% CI for the adjusted treatment difference between Q2M and Q1M was 2.2%, which was less than the pre-defined non-inferiority margin of 4%[66, 70]. Results for the Per-Protocol (PP) population were similar to those for the ITT-E Population[70].

Table 15. Proportion of participants with Plasma HIV-1 RNA ≥50 copies/mL at Week 48 (Snapshot Algorithm) at Week 48 and Week 96, Snapshot algorithm, ITT-E population

		CAB LA + RPV LA Q2M (n=522)	CAB LA + RPV LA Q1M (n=523)
Week 48	**HIV RNA ≥ 50 copies/mL per total assessed (%)**	9/523 (1.7)	5/523 (1.0)
	Difference in proportion (95% CI)	0.8 (-0.6, 2.2)	
	Adjusted difference in proportion (95% CI)	0.8 (-0.6, 2.2)	
Week 96	**HIV RNA ≥ 50 copies/mL per total assessed (%)**	11 (2.1)	6 (1.1)
	Difference in proportion (95% CI)	-	
	Adjusted difference in proportion (95% CI)	1.0 (–0.6–2.5)	

CI: confidence interval, HIV: human immunodeficiency virus, RNA: ribonucleic acid, Q1M: once a month, Q2M: every 2 months
Source: ATLAS-2M CSR[70], Overton et al[66]

Figure 3. Proportion of participants with Plasma HIV-1 RNA ≥50 copies/mL at Week 48 (Snapshot Algorithm) at Week 48, ITT-E population



CAB: cabotegravir, LA: long-acting, RPV: rilpivirine, Q1M: every 4 weeks (i.e. once a month), Q2M: every 8 weeks (I.e. every 2 months)
Source: Overton et al.[87]

B.2.6.1.7. *Results: Plasma HIV-1 RNA <50 copies/mL at Week 48, Snapshot Algorithm*

The proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48 was similar for Q2M and Q1M CAB LA + RPV LA. The majority of participants remained suppressed (plasma HIV-1 RNA < 50 copies/mL: Q2M=94%, Q1M=93%)[66, 70]. Q2M is therefore non-inferior to Q1M for this endpoint as the lower end of the two-sided 95% confidence interval for the difference in proportions was above -10%. Results for the PP population were consistent with those for the ITT-E population[70].

Table 16. Proportion of participants with Plasma HIV-1 RNA <50 copies/mL at Week 48 and Week 96, Snapshot Algorithm, ITT-E population

		CAB LA + RPV LA Q2M (n=522)	CAB LA + RPV LA Q1M (n=523)
Week 48	**Plasma HIV-1 RNA <50 copies/mL (%)**	492/522 (94)	489/523 (93)
	Difference in proportion (95% CI)	0.8 (-2.2-3.7)	
	Adjusted difference in proportion (95% CI)	0.8 (-2.1-3.7)	
Week 96	**Plasma HIV-1 RNA <50 copies/mL (%)**	475 (91.0)	472 (90.2)
	Difference in proportion (95% CI)	-	
	Adjusted difference in proportion (95% CI)	0.8 (–2.8-4.3)	

CI: confidence interval, HIV: human immunodeficiency virus, RNA: ribonucleic acid, Q1M: once a month, Q2M: once every 2 months

Source: ATLAS-2M CSR[70], Overton et al[66]

B.2.6.1.8. *Results: Confirmed virologic failure*

The proportion of participants with confirmed virologic failure (CVF) through Week 48 (including those with dosing beyond Week 48) was 1.5% (8 participants) for the Q2M group and <1% (2 participants) for the Q1M group. Eight participants met criteria for confirmed virologic failure at or before Week 24[66, 70]. A post-hoc analysis was undertaken to explore the factors associated with CVF and is described below.

At Week 96, the proportion of participants with CVF was 1.7% (9 participants) and 0.4% (2 participants) in the Q2M and Q1M group, respectively.

B.2.6.1.9. *Post-hoc analysis on factors associated with confirmed virologic failure*

Multivariable analyses of pooled phase 3 studies (ATLAS, FLAIR and ATLAS-2M), including data from 1,039 HIV-infected adults with no prior exposure to CAB+RPV, examined the influence of baseline viral and participant characteristics, dosing regimen, and post-baseline plasma drug concentrations on CVF using regression modelling with a variable selection

procedure[1]. Through Week 48 in these studies, 13/1039 (1.25%) participants had CVF while receiving CAB LA + RPV LA.

Four covariates were significantly associated (P<0.05 for each adjusted odds ratio) with increased risk of CVF: rilpivirine resistance mutations at baseline identified by proviral DNA genotypic assay, HIV-1 subtype A6/A1 (associated with integrase L74I polymorphism), rilpivirine trough concentration 4 weeks following initial injection dose, body mass index of at least 30 kg/m^2 (associated with cabotegravir pharmacokinetics). Other variables including Q1M or Q2M dosing, female sex, or other viral subtypes (non A6/A1) had no significant association with CVF. No baseline factor, when present in isolation, was predictive of virologic failure. However, a combination of at least 2 of the following baseline factors was associated with an increased risk of CVF: rilpivirine resistance mutations, HIV-1 subtype A6/A1, or BMI ≥30 kg/m^2 (see Table 17)[1].

On the basis of these analyses, the following is included in the product SmPCs. “Before starting the regimen, it should be taken into account that multivariable analyses indicate that a combination of at least 2 of the following baseline factors may be associated with an increased risk of virological failure: archived rilpivirine resistance mutations, HIV-1 subtype A6/A1, or BMI ≥30 kg/m2. In participants with an incomplete or uncertain treatment history without pre-treatment resistance analyses, caution is warranted in the presence of either BMI ≥30 kg/m2 or HIV-1 A6/A1 subtype”[1, 2].

Table 17 Week 48 outcomes by presence of key baseline factors of rilpivirine resistance associated mutations, Subtype A6/A1 and BMI ≥30 kg/m^2

Baseline Factors (number)	Virologic Successes (%)[2]	Confirmed Virologic Failure (%)[3]
0	694/732 (94.8)	3/732 (0.41)
1	261/272 (96.0)	1/272 (0.37)[4]
2 ≥	25/35 (71.4)	9/35 (25.7)[5]
TOTAL (95% CI)	980/1039 (94.3) (92.74%, 95.65%)	13/1039 (1.25) (0.67%, 2.13%)

CI: confidence interval

[1] HIV-1 subtype A1 or A6 classification based on Los Alamos National Library panel from HIV Sequence database (June 2020)
[2] Based on the FDA Snapshot algorithm of RNA <50 copies/mL.
[3] Defined as two consecutive measurements of HIV-1 RNA >200 copies/mL.
[4] Positive Predictive Value (PPV) <1%; Negative Predictive Value (NPV) 98%; sensitivity 8%; specificity 74%
[5] PPV 26%; NPV 99.6%; sensitivity 69%; specificity 97.5%
Source: Vocabria SmPC[1]

B.2.6.1.10. *Results: CD4+ cell count*

The median baseline CD4+ cell count was 642 cells/mm^3 in the Q2M group and 688 cells/mm^3 in the Q1M group. Median CD4+ cell counts did not change from baseline in both treatment groups over time[66, 70].

Table 18. CD4+ cell count changes from baseline over time, ATLAS-2M

		CAB LA + RPV LA Q2M (n=522)	CAB LA + RPV LA Q1M (n=523)
Week 48	Median CD4+ cell count [cells/mm^3] at baseline (range)	642 (163-1737)	688 (114-2929)
	Median change from baseline in CD4+ cell count at Week 48	5 (-622-692)	-8 (-1049-1525)
CD4+: cluster of differentiation 4, Q1M: once a month, Q2M: every two months Source: ATLAS-2M CSR[70], Overton et al[66]			

B.2.6.1.11. *Results: disease progression or death*

Disease progression was defined as a progression from Baseline CDC Stage 1 or Stage 2 to CDC Stage 3 at any time during the Maintenance Phase based on the presence of new AIDS-defining conditions and/or lowest value of CD4+ counts and CD4+ percentages of total lymphocytes, per CDC criteria (2014)[70].

Rates of disease progression to CDC Stage 3 were similar in both treatment groups through Week 48 (including participants with dosing beyond Week 48)[70].

- 13 (2%) of participants in the Q2M group and 14 (3%) in the Q1M group had disease progression to CDC Stage 3 disease or death (n=1; Q2M group) during the Maintenance Phase. The reported cause of death was sepsis unrelated to underlying HIV[70].

- HIV-1 associated conditions reported during the Maintenance Phase were candidiasis of the oesophagus and Kaposi sarcoma (1 participant each)[70].

B.2.6.1.12. *Results: Health outcomes*

Key points

- [redacted]

B.2.6.1.12.1. HIV Treatment Satisfaction Questionnaire (HIVTSQ) status version

The HIV Treatment Satisfaction Questionnaire (HIVTSQ) was developed to evaluate treatment satisfaction specifically for people living with HIV. The HIVTSQ used in the trial is an adaptation of the validated 10-item HIVTSQ including two additional items to account for LA dosing. This 12-item questionnaire produces a treatment satisfaction total score (11 items) and 1 standalone item on pain and discomfort[85]. Both the status (HIVTSQs) and change (HIVTSQc) versions were used in ATLAS 2M.

For participants without prior exposure to CAB + RPV, baseline HIVTSQs mean total (SD) scores were similar between the two treatment groups at 57.73 (9.21) points for the Q2M and 56.72 (9.34) points for Q1M group[88].

- HIVTSQs total scores markedly improved from baseline at Weeks 24 and 48 for both treatment groups, after adjusting for baseline score, sex at birth, age, race, and third agent class (INSTI, PI, NNRTI)[88].
- The Q2M group had a significant increase in treatment satisfaction (adjusted mean change from baseline) at both timepoints compared with the Q1M group (Table 19)[88].

HIVTSQs mean total (SD) scores for participants with prior exposure to CAB + RPV (≥1 weeks) were high at baseline (62.22 [5.41] points for Q2M group and 61.98 [6.72] points for Q1M group) and remained stable across Weeks 24 and 48 after adjustment, without significant differences between the two groups (Table 19)[88].

Table 19. Change from Baseline (CFB) in Total HIVSTQs Score by Visit for participants with and without prior exposure to CAB + RPV (ITT-E Population)

	Without prior exposure				With prior exposure			
	Treatment	Adjusted Mean CFB (95% CI)	Adjusted Difference (Q2M-Q1M)	p-value (Q2M-Q1M)	Treatment	Adjusted Mean CFB (95% CI)	Adjusted Difference (Q2M-Q1M)	p-value (Q2M-Q1M)
Week 24	Q2M [redacted]	5.07 (4.36, 5.78)	1.07 (0.07, 2.07)	0.036	Q2M [redacted]	[redacted]	[redacted]	[redacted]
	Q1M [redacted]	4.00 (3.29, 4.70)			Q1M [redacted]	[redacted]		
Week 48	Q2M [redacted]	4.86 (4.02, 5.69)	1.74 (0.56, 2.91)	0.004	Q2M [redacted]	[redacted]	[redacted]	[redacted]
	Q1M [redacted]	3.12 (2.29, 3.95)			Q1M [redacted]	[redacted]		

CAB: cabotegravir, CFB: change from baseline, ITT: intention-to-treat, Q1M: once a month, Q2M: every two months, RPV: rilpivirine

Note: 12-item HIVTSQs min score: 0 (very dissatisfied); max score: 66 (very satisfied).

Source: ATLAS-2M CSR[70] and Chounta et al. 2020[88]

B.2.6.1.12.2. HIV Treatment Satisfaction (HIVTSQ) change version

The HIVTSQ change version (HIVTSQc) was designed to measure change in satisfaction with HIV treatment. The change version overcomes potential ceiling effects, i.e. when responders

score a maximum or near maximum satisfaction at baseline and can thus show little to no improvement at follow-up[89, 90].

HIVTSQ change version (HIVTSQc) was administered at Week 48 in both groups, to assess satisfaction with CAB + RPV approximately a year into the study compared to the ART participants were receiving prior to entering the study, with the intention to account for potentially high baseline values (ceiling effects) with HIVTSQs (Table 20)[70].

High total HIVTSQ change scores were reported in both treatment groups for participants without prior exposure to CAB + RPV at Week 48. [redacted] (Table 20)[70].

Table 20. Total HIVSTQc Score at Week 48 for Participants with and without prior exposure to CAB + RPV (ITT-E Population)

	Without prior exposure				With prior exposure			
	Treatment	Adjusted Mean CFB (95% CI)	Adjusted Difference Q2M-Q1M	p-value Q2M-Q1M	Treatment	Adjusted Mean CFB (95% CI)	Adjusted Difference Q2M-Q1M	p-value Q2M-Q1M
Week 48	Q2M [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Q1M [redacted]	[redacted]			[redacted]	[redacted]		

CAB: cabotegravir, CFB: change from baseline, ITT: intention-to-treat, Q1M: once a month, Q2M: every two months, RPV: rilpivirine

Note: 12-item HIVTSQs min score: 0 (very dissatisfied); max score: 66 (very satisfied).

Source: ATLAS-2M CSR[70]

B.2.6.1.12.3. Treatment Acceptance (General Acceptance Domain of ACCEPT)

The Chronic Treatment Acceptance (ACCEPT) questionnaire is a generic medication acceptance measure assessing how participants weigh advantages and disadvantages of long-term medications[91, 92]. The ACCEPT questionnaire consists of 25 items that capture six dimensions. However, in ATLAS-2M only the general acceptance dimension of ACCEPT was employed in order to not overburden participants[85].

For participants without prior exposure to CAB + RPV, baseline General Acceptance mean (SD) scores were similar between the two treatment groups at 81.5 (25.23) points for the Q2M group and 81.8 (25.98) points for the Q1M group[88].

- General Acceptance scores [redacted] from baseline at Weeks 24 and 48 for both treatment groups, after adjusting for baseline score, sex at birth, age, race (white, non-white)[70].
- [redacted] between Q2M and Q1M CAB LA + RPV LA groups in adjusted mean change from baseline in treatment acceptance were observed at any timepoint (Table 21)[70].

General Acceptance mean (SD) scores for participants with prior exposure to CAB + RPV were high at baseline (89.3 [20.03] points for the Q2M group and 91.2 [16.74] points for the Q1M group) and remained stable across Weeks 24 and 48 after adjustment, [redacted] between the two treatment groups (Table 21)[70, 88].

Table 21. Change from Baseline (CFB) in General Acceptance Score by Visit for Participants with and without prior exposure to CAB + RPV (ITT-E Population)

	Without prior exposure				With prior exposure			
	Treatment	Adjusted Mean CFB (95% CI)	Adjusted Difference (Q2M-Q1M)	p-value (Q2M-Q1M)	Treatment	Adjusted Mean CFB (95% CI)	Adjusted Difference (Q2M-Q1M)	p-value (Q2M-Q1M)
Week 24	Q2M [redacted]	[redacted]	[redacted]	[redacted]	Q2M [redacted]	[redacted]	[redacted]	[redacted]
	Q1M [redacted]	[redacted]			Q1M [redacted]	[redacted]		
Week 48	Q2M ([redacted])	6.8 (4.3, 9.3)	1.1 (-2.4, 4.6)	0.525	Q2M [redacted]	[redacted]	[redacted]	[redacted]
	Q1M [redacted]	5.7 (3.2, 8.1)			Q1M [redacted]	[redacted]		

CAB: cabotegravir, CFB: change from baseline, ITT: intention-to-treat, Q1M: once a month, Q2M: every two months, RPV: rilpivirine

Note: 12-item HIVTSQs min score: 0 (very dissatisfied); max score: 66 (very satisfied).

Source: ATLAS-2M CSR[70] and Chounta et al. 2020[88]

B.2.6.1.12.4. Treatment preference

A 3-item questionnaire assessed participant preference for CAB LA + RPV LA compared with daily oral CAB+RPV and preference for the Q2M or Q1M regimen. Treatment preference results were stratified by prior exposure to CAB + RPV and treatment group[70, 88].

At Week 48, 94% (n=179/191) of participants randomised to the Q2M arm and with prior CAB+RPV exposure preferred Q2M over oral daily dosing of CAB+RPV. Similarly, 98% (n=300/306) of participants without previous exposure to CAB+RPV who were receiving the Q2M regimen preferred this regimen over daily oral dosing. Within the Q1M arm, 94% (n=468/497) of participants preferred CAB LA + RPV LA Q1M over daily oral dosing[88].

Administration frequency and convenience were the most commonly reported reasons for preference[88].

B.2.6.1.12.5. Perception of Injection (PIN)

The Perception of Injection (PIN) questionnaire assesses the bother of pain at the injection site and ISR, anxiety before and after injection, willingness to receive an injectable treatment the following visit, satisfaction with the mode of treatment administration and perceptions associated with receiving injections. This instrument was adapted for gluteal IM administration from the earlier Vaccinees' Perception of Injection (VAPI) questionnaire but kept the same scoring system[92, 93].

The PIN questionnaire does not produce a total score but consists of 4 dimensions and 5 individually reported items. Acceptance of ISRs dimension consists of two items: acceptance of local reactions and acceptance of pain[93].

- Both treatment groups reported [redacted] acceptance of pain and acceptance of local reactions at Week 8 (in the Q2M group [redacted] and [redacted] of participants rated acceptance of local reactions and pain respectively as [redacted] proportions were very [redacted] in the Q1M group)[70]. Acceptance of ISRs [redacted] scores for the Acceptance of ISRs dimension [redacted] from Week 8 (first injection assessment) to Weeks 24 and 48 in both treatment groups [redacted] in Q2M group at Week 48 vs Week 8) [70].

Pre-specified statistical testing for improvement over time in scores was performed for the dimension of Acceptance of ISRs only to avoid multiplicity adjustment.

B.2.6.1.12.6. Life Satisfaction, Medication Concerns, Disclosure Worries (HAT-QoL)

The HIV/AIDS Targeted Quality of Life (HAT-QoL) instrument originally contained 42 items, grouped into nine dimensions, assessing overall function and well-being. For the purpose of ATLAS-2M, only the dimensions covering the concepts of interest were applied and contained 14 items grouped from the following dimensions: “life satisfaction”, “disclosure worries”, and “HIV medication”[70, 94].

Life Satisfaction scores for participants in both treatment groups were [redacted] in the Q2M group and [redacted] in the Q1M group for participants without prior CAB + RPV exposure; [redacted] in the Q2M group and [redacted] in the Q1M group for participants with prior exposure), and [redacted] after adjusting for prespecified covariates at Weeks 24 and 48. When comparing between the two groups for adjusted change from baseline in Life Satisfaction scores, a [redacted] of the Q1M dosing compared with Q2M dosing was observed, reaching [redacted] (Table 22)[70].

Even though relatively [redacted] in already virally suppressed participants would [redacted] it should be noted that these scores [redacted] the change to injections and the associated visits to HCPs and ISRs (see Section B.2.10).

Table 22. Change from Baseline in Life Satisfaction Score by Visit (ITT-E population)

	Without prior exposure				With prior exposure			
	Treatment	Adjusted Mean CFB (95% CI)	Adjusted Difference (Q2M-Q1M)	p-value (Q2M-Q1M)	Treatment	Adjusted Mean CFB (95% CI)	Adjusted Difference (Q2M-Q1M)	p-value (Q2M-Q1M)
Week 24	Q2M [redacted]	[redacted]	[redacted]	[redacted]	Q2M [redacted]	[redacted]	[redacted]	[redacted]
	Q1M [redacted]	[redacted]			Q1M [redacted]	[redacted]		
Week 48	Q2M [redacted]	[redacted]	[redacted]	[redacted]	Q2M [redacted]	[redacted]	[redacted]	[redacted]
	Q1M [redacted]	[redacted]			Q1M [redacted]	[redacted]		

CAB: cabotegravir, CFB: change from baseline, ITT: intention-to-treat, Q1M: once a month, Q2M: every two months, RPV: rilpivirine

Note: Life Satisfaction min score: 0 (none of the time); max score 100 (all of the time)

For participants without prior: Adjusted mean calculated from an ANCOVA model including the covariates: Baseline Score, sex at birth (female, male), age (<50, >=50 years) and race (white, non-white). For participants with prior: Adjusted mean calculated from an ANCOVA model including the covariates: Baseline Score, sex at birth (female, male), age (<50, >=50 years), race (white, non-white) and prior exposure to CAB + RPV (1 to 24, >24 weeks).

Source: ATLAS-2M CSR[70]

Medication Concerns scores for participants with and without prior exposure to CAB + RPV [redacted] from baseline [redacted] in the Q2M group and [redacted] in the Q1M group for participants without prior CAB + RPV exposure: [redacted] in the Q2M group and [redacted] in the Q1M group for those with prior exposure) following adjustment for prespecified covariates, with [redacted] between treatment groups were observed at Weeks 24 and 48 for participants with prior exposure to CAB + RPV and Week 24 for participants without prior CAB + RPV exposure. A [redacted] between Q2M and Q1M groups, [redacted] in adjusted change from baseline in HIV [redacted] in participants without prior exposure (Table 23)[70].

Table 23. Change from Baseline in Medication Concern Score by Visit (ITT-E population)

	Without prior exposure			With prior exposure			
	Treatment	Adjusted Mean CFB (95% CI)	Adjusted Difference (Q2M-Q1M)	p-value (Q2M-Q1M)	Treatment	Adjusted Mean CFB (95% CI)	Adjusted Difference (Q2M-Q1M)	p-value (Q2M-Q1M)
Week 24	Q2M [redacted]	[redacted]	[redacted]	[redacted]	Q2M [redacted]	[redacted]	[redacted]	[redacted]
	Q1M [redacted]	[redacted]			Q1M [redacted]	[redacted]		
Week 48	Q2M [redacted]	[redacted]	[redacted]	[redacted]	Q2M [redacted]	[redacted]	[redacted]	[redacted]
	Q1M [redacted]	[redacted]			Q1M [redacted]	[redacted]		

CAB: cabotegravir, ITT: intention-to-treat, Q1M: once a month, Q2M: every two months, RPV: rilpivirine
Note: Life Satisfaction min score: 0 (none of the time); max score 100 (all of the time)
For participants without prior: Adjusted mean calculated from an ANCOVA model including the covariates: Baseline Score, sex at birth (female, male), age (<50, >=50 years) and race (white, non-white). For participants with prior: Adjusted mean calculated from an ANCOVA model including the covariates: Baseline Score, sex at birth (female, male), age (<50, >=50 years), race (white, non-white) and prior exposure to CAB+RPV (1 to 24, >24 weeks).
Source: ATLAS-2M CSR[70]

Disclosure Worries scores for participants in both treatment groups, irrespective of prior CAB + RPV exposure, [redacted] from baseline ([redacted] in the Q2M group and [redacted] in the Q1M group for participants without prior CAB + RPV exposure; [redacted] in the Q2M group and [redacted] in the Q1M group for participants with prior exposure) across all visits, with [redacted] after adjusting for prespecified covariates at Weeks 24 and 48. [redacted] was observed between the two groups in adjusted change from baseline in [redacted] at any timepoint for participants with or without prior CAB + RPV exposure (Table 24)[70].

Table 24. Change from Baseline in Disclosure Worries Score by Visit (ITT-E population)

	Treatment	Without prior exposure			Treatment	With prior exposure		
		Adjusted Mean CFB (95% CI)	Adjusted Difference (Q2M-Q1M)	p-value (Q2M-Q1M)		Adjusted Mean CFB (95% CI)	Adjusted Difference (Q2M-Q1M)	p-value (Q2M-Q1M)
Week 24	Q2M [redacted]	[redacted]	[redacted]	[redacted]	Q2M [redacted]	[redacted]	[redacted]	[redacted]
	Q1M [redacted]	[redacted]			Q1M [redacted]	[redacted]		
Week 48	Q2M [redacted]	[redacted]	[redacted]	[redacted]	Q2M [redacted]	[redacted]	[redacted]	[redacted]
	Q1M [redacted]	[redacted]			Q1M [redacted]	[redacted]		

CAB: cabotegravir, ITT: intention-to-treat, Q1M: once a month, Q2M: every two months, RPV: rilpivirine
Note: Life Satisfaction min score: 0 (none of the time); max score 100 (all of the time)
For participants without prior: Adjusted mean calculated from an ANCOVA model including the covariates: Baseline Score, sex at birth (female, male), age (<50, >=50 years) and race (white, non-white). For participants with prior: Adjusted mean calculated from an ANCOVA model including the covariates: Baseline Score, sex at birth (female, male), age (<50, >=50 years), race (white, non-white) and prior exposure to CAB+RPV (1 to 24, >24 weeks).
Source: ATLAS-2M CSR[70]

B.2.6.1.13. *Long-term outcomes with CAB LA + RPV LA Q2M: evidence from LATTE-2*

Evidence from the LATTE-2 phase 2b study shows that CAB LA + RPV LA Q2M remained well tolerated and efficacious in maintaining virologic suppression at Week 256 (5 years).

Methods

LATTE-2 was a randomised, phase 2b, open-label, multicentre, non-inferiority, parallel-group study of CAB LA + RPV LA in initially ART-naïve adults. The trial consisted of a 20-week induction period, 96-week maintenance period, extension period, and long-term follow-up. It was not used to inform the economic model because it is superseded by the results of the ATLAS-2M phase 3 study and only included ART-naïve participants[76-78].

After the induction period, consisting of once-daily oral CAB (30 mg) plus abacavir/lamivudine (600/300 mg, once daily), participants with plasma HIV-1 RNA <50 copies/mL were randomised 2:2:1 to either CAB LA + RPV LA Q2M, CAB LA + RPV LA Q1M, or to continue their oral regimen in the Maintenance Period[76-78].

After the 96-week maintenance period, participants randomised to long-acting treatment continued their maintenance period regimen into the Extension Period. Participants randomised to oral therapy in the Maintenance Period were given the choice to switch to either CAB LA + RPV LA Q2M or Q1M in the Extension Period. At Week 256, further assessments of participants with virologic success (HIV-1 RNA <50 copies/mL) and protocol-defined virologic failure (PDVF; two consecutive plasma HIV-1 RNA measurements of at least 200 copies/mL) were conducted[76-78].

Results

At 32 weeks, CAB LA + RPV LA administered once monthly was as effective as daily oral ART (CAB 30 mg + ABC/3TC) and had an acceptable safety profile, with no drug-related SAEs and few AE-related withdrawals.

At Week 96, 87% of participants in the Q1M group and 94% in the Q2M group maintained virologic suppression, compared with 84% of those who continued oral CAB plus ABC/3TC. CAB LA + RPV LA was associated with high rates of adherence (98%), providing reassurance that participants were receiving their treatment as prescribed[77].

At Week 160, participants receiving CAB LA + RPV LA Q1M or Q2M successfully maintained virologic suppression (83% and 90%, respectively). Through 160 weeks, there were two protocol-defined virologic failures (PDVF), both in the Q2M arm; no additional failures occurred after Week 48 in any arm[78]. This demonstrates the long-term durability and tolerability of CAB LA + RPV LA Q2M.

At Week 256, 81% of participants randomised to LA therapy at Day 1 and 93% of participants who switched from oral therapy at Week 100 maintained virologic suppression. No participants had PDVF after Week 48 in any treatment arm, further demonstrating the durability of CAB LA +RPV LA as a maintenance therapy[95]. Similar to Week 96, CAB LA + RPV LA continued to be associated with high rates of adherence (96% of injections within the dosing window) across both dosing regimens, which provides further reassurance that participants received their treatment on time[96].

CAB LA + RPV LA was well tolerated through 5 years of treatment for both dosing regimens[95].

Long-term adherence to CAB LA + RPV LA

High rates of adherence to injection visits were maintained through 96 weeks of follow-up, with 98% of injections occurring within the +/- 7 day window[97].

B.2.6.1.14. *CAB LA + RPV LA Q2M: evidence from POLAR*

Evidence from the POLAR Phase 2b study shows that CAB LA + RPV LA Q2M remained efficacious in maintaining virologic suppression at Month 12[98].

Methods

POLAR is a Phase 2b, open-label, multicentre, non-randomised, rollover study of CAB LA + RPV LA Q2M in ART-experienced participants who received once daily CAB + RPV treatment in the LATTE study[79].

Virologically suppressed participants, who completed ≥ 312 weeks of oral CAB (30 mg) + RPV (25 mg) in LATTE, were enrolled and screened for POLAR. Participants were then given the option to choose treatment with either intramuscular injections of CAB LA + RPV LA Q2M or oral daily ART for the continued maintenance of virologic suppression. The primary endpoint of the study was proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Month 12[79].

Results

At Month 12, 98% of participants receiving CAB LA + RPV LA (2% had no virological data) and 100% of participants receiving daily oral ART maintained virological suppression. Of participants with available data, none had HIV-1 RNA ≥50 copies/mL and no participants had CVF in either arm[98].

CAB LA + RPV LA was well tolerated and had a favorable safety profile[98].

In total, 88% of participants who had previously received daily oral CAB + RPV expressed a preference for the injectable regimen during the 12 month maintenance period[98]. Participants stated increased convenience (69%) and the frequency of administration (57%) as their most common reasons for this preference[98].

B.2.6.2. Trials of CAB LA + RPV LA Q1M versus current daily oral ART (ATLAS and FLAIR)

The non-inferiority of CAB LA + RPV LA Q1M to current daily oral ART regimens was established in the ATLAS Phase 3 study in virally suppressed ART-experienced participants and the FLAIR Phase 3 study in those who were ART-naïve at enrolment and were required to achieve viral suppression on an induction regimen (Triumeq®) before randomisation to either CAB LA + RPV LA or continuation of Triumeq®. These studies had similar designs and a pooled analysis was prespecified. In the submission, the pooled analysis was used in an indirect treatment comparison to assess the efficacy of CAB LA + RPV LA Q2M relative to current daily oral ART (see Section B2.9).

Information on ATLAS and FLAIR is taken from the study publications where available, and from the clinical study report (CSR) where additional detail is required.

B.2.6.2.1. *Study design*

A summary of the methodology of ATLAS and FLAIR is provided in Table 25.

Table 25. Summary of trial methodology, ATLAS and FLAIR

Trial name	ATLAS	FLAIR
Location	North America, South America, Australia, Europe, Asia, Africa	North America, Europe, Asia, Africa
Trial design	Phase 3, Randomised, Multicentre, Parallel-group, Non-inferiority, Open-label Study	Phase 3, Randomised, Multicentre, Parallel-group, Non-inferiority, Open-Label Study
Eligibility criteria for participants	Eligible participants were 18 years of age or older and were HIV-1 infected antiretroviral therapy experienced adults who are virologically suppressed on a stable antiretroviral regimen	Eligible participants were 18 years of age or older, had not previously received antiretroviral therapy, and had a plasma HIV-1 RNA level of 1000 copies/mL or higher at screening.
Settings and locations where data were collected	The study was conducted in 115 locations across 13 countries.	The study was conducted in 108 study locations in 11 countries across North America, Europe (including the UK [7 sites]), Asia, and South Africa

Intervention	Oral CAB 30 mg + RPV 25 mg once daily for four weeks, intramuscular CAB LA 600 mg and RPV LA 900 mg for the first injection. From Week 4 CAB LA 400 mg + RPV LA 600 mg IM Q1M until withdrawal.	Induction therapy with ABC/DTG/3TC single-tablet regimen (Triumeq®). After viral suppression on induction: Oral CAB 30 mg + RPV 25 mg once daily for approximately 4 weeks. At Week 4 participants received CAB LA 600mg and RPV LA 900 mg. From Week 8 participants received CAB LA 600mg and RPV LA 900 mg Q1M.
Comparator	Current anti-retroviral regimen (2 NRTIs plus an INSTI, NNRTI, or a PI)	ABC/DTG/3TC single-tablet regimen (Triumeq®)
Concomitant medications	CAB and CAB LA were not to be co-administered with the following medicinal products - the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, phenytoin - the antimycobacterials rifampicin, rifapentine, rifabutin - St John's wort (Hypericum perforatum). Chronic use of oral glucocorticoids must be avoided. (Full list available in study protocol)	The following concomitant medications or therapies were not permitted at any time during the study: - HIV immunotherapeutic vaccines - Other experimental agents, ART drugs not otherwise specified in the protocol, - Systemically administered immunomodulators - Chronic use of systemic (oral or parenteral) glucocortioids must be avoided - Hepatitis C infection therapy is prohibited during the Maintenance Phase before Week 48; interferon-based HCV therapy is prohibited throughout the study. (Full list available in study protocol)
Primary outcomes	Proportion of participants with HIV-1 RNA ≥50 copies/mL as per FDA snapshot algorithm at Week 48 (ITT-E population).	Percentage of participants with HIV-1 RNA ≥50 copies/mL as per FDA snapshot algorithm at Week 48 (ITT-E population).
Other outcomes used in the economic model/specified in the scope	Other outcomes reported are summarised in Table 7. The outcomes used to inform the ITC were: - HIV-1 RNA <50 copies/mL - HIV-1 RNA ≥50 copies/mL - CD4+ cell change from baseline - Discontinuations	Other outcomes reported are summarised in Table **8**. The outcomes used to inform the ITC were: - HIV-1 RNA <50 copies/mL - HIV-1 RNA ≥50 copies/mL - CD4+ cell change from baseline

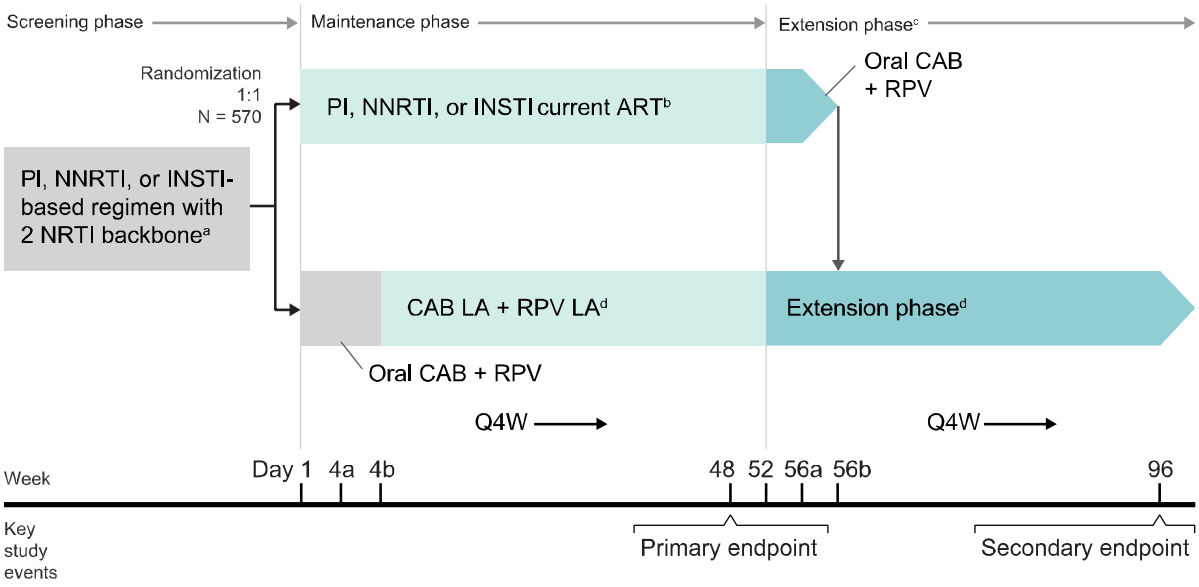
	- Discontinuations due to AEs - Grade 3-5 non-ISR AEs	- Discontinuations - Discontinuations due to AEs - Grade 3-5 non-ISR AEs
Pre-planned subgroups	The proportion of participants with virologic failure over time including Week 48 and Week 96 was analysed by important demographic and baseline characteristic subgroups factors (e.g. age, gender, BMI, race, HIV-1 subtype, and Baseline CD4+ cell counts). Changes from baseline in CD4+ lymphocyte count at Week 48 and Week 96.	The proportion of participants with virologic failure over time including Week 48 and Week 96 was analysed by important demographic and baseline characteristic subgroups factors (e.g. age, gender, BMI, race, HIV-1 subtype, and Baseline CD4+ cell counts). Changes from baseline in CD4+ lymphocyte count at Week 48 and Week 96.
ART: antiretroviral therapy, BMI: body mass index, CAB: cabotegravir, CD4+: cluster of differentiation 4, FDA: Food and Drug Administration, HCV: hepatitis C virus, LA: long acting, RPV: rilpivirine, Q1M: once a month, Q2M: every two months Source: ATLAS protocol[99], FLAIR protocol[100], Swindells et al.[67], Orkin et al.[68]		

B.2.6.2.1.1. ATLAS

ATLAS is a phase 3, randomised, open-label, multicentre, parallel-group, non-inferiority study designed to assess the antiviral activity and safety of CAB LA + RPV LA regimen every 4 weeks (Q1M) compared with maintenance of current ART[67, 99].

The primary objective of ATLAS was to establish if individuals virally suppressed on current oral ART remain suppressed upon switching to CAB LA + RPV LA. Participants were randomised (1:1) into the Maintenance Phase to either continue current ART or switch to initiate oral therapy with CAB 30mg + RPV 25 mg once daily for four weeks followed by monthly CAB LA + RPV LA injections. Following the Maintenance phase at Week 52, those who were randomised to continue their current ART regimen were given an option to switch to CAB LA + RPV LA injections. Participants who switched, started the transition with 4 weeks of oral CAB + RPV therapy at Week 52, and received the first CAB LA + RPV LA injections at Week 56. The primary endpoint of ATLAS was virologic failure at Week 48[67, 99]. The study design of ATLAS is shown in Figure 4.

Figure 4. ATLAS study design schematic



Abbreviations: ART, antiretroviral therapy; ATLAS, Antiretroviral Therapy as Long-Acting Suppression; CAB, cabotegravir; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; LA, long-acting; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; Q4W, every 4 weeks (Q1M); RPV, rilpivirine.

[a] Must be receiving uninterrupted current regimen (either the initial or second combination ART regimen) for at least 6 months before screening. Documented evidence of at least 2 plasma HIV RNA measurements <50 copies/mL in the 12 months before screening: one within the 6- to 12-month window, and one within 6 months before screening. No history of virologic failure. No evidence of viral resistance based on the presence of any resistance-associated major INSTI or NNRTI mutation (except K103N) from prior genotype assay results. No current or prior history of etravirine use.

[b] INSTI-based regimen excludes abacavir/dolutegravir/lamivudine (Triumeq®), and INSTI therapy was capped at approximately 40% of study enrolment for current ART.

[c] Optional extension phase to CAB LA + RPV LA at Week 52 for participants randomised to current ART. Most participants in the extension phase rolled over to the ATLAS-2M trial.

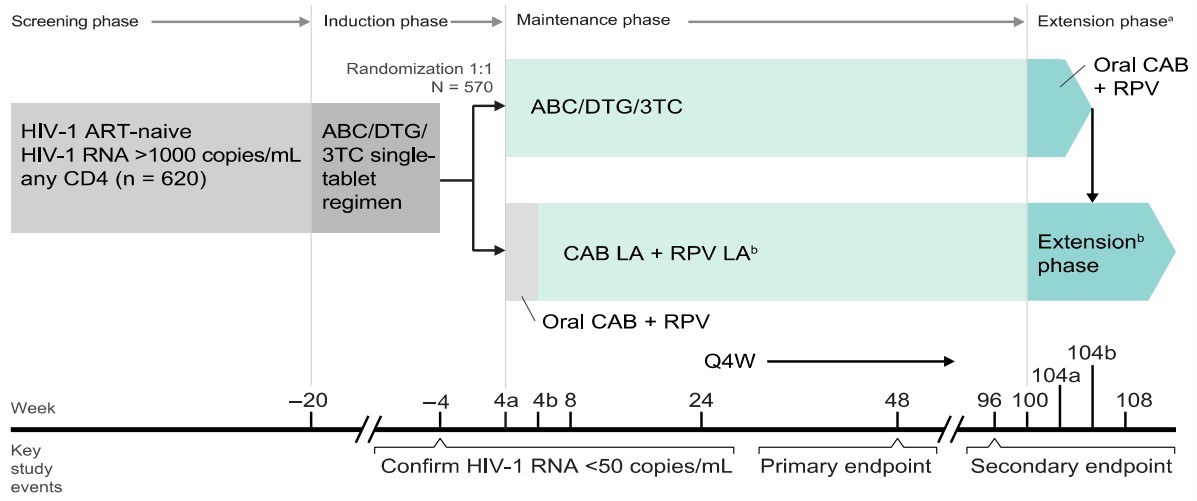
[d] Participants who withdrew from CAB LA + RPV LA arm were required to go into a 52-week long-term follow up phase.

Source: ATLAS protocol[99]

B.2.6.2.1.2. FLAIR

FLAIR is a phase 3, multiphase, randomised, open-label, multicentre, parallel-group, non-inferiority study in adults who were ART-naïve at recruitment. Participants who achieved virologic suppression on the ABC/DTG/3TC single-tablet regimen (Triumeq®) in the induction phase were randomised to receive CAB LA 400mg + RPV LA 600mg every 4 weeks (Q1M; after oral lead-in) or continue on the induction regimen. The primary endpoint was the proportion of participants defined as virologic failures by the Snapshot algorithm at 48 weeks[68, 100]. Study design of FLAIR is shown in Figure 5.

Figure 5. FLAIR Study design schematic



ABC/DTG/3TC, abacavir/dolutegravir/lamivudine; ART, antiretroviral therapy; CAB, cabotegravir; CD4, cluster of differentiation 4; FLAIR, First Long-Acting Injectable Regimen; HIV-1, human immunodeficiency virus type 1; LA, long-acting; RNA, ribonucleic acid; RPV, rilpivirine; Q4W, every 4 weeks (Q1M).

[a] Optional switch to CAB LA + RPV LA at Week 100 for participants randomised to ABC/DTG/3TC.

[b] Participants who withdrew from intramuscular CAB LA + RPV LA treatment were required to enter the 52-week long-term follow up phase.

Source: FLAIR protocol[100]

B.2.6.2.2. *Eligibility criteria*

Key eligibility criteria for ATLAS and FLAIR are provided in Table 26 and Table 27, respectively.

Table 26. Inclusion and exclusion criteria for ATLAS

Key inclusion criteria	Key exclusion criteria
• HIV-1 positive, men or women aged 18 years or greater • On uninterrupted current regimen (either the initial or second ART regimen) for at least 6 months prior to Screening. Any prior switch must NOT have been done for treatment failure (HIV-1 RNA ≥400 copies/mL). • Documented evidence of at least 2 plasma HIV-1 RNA measurements <50 copies/mL in the 12 months prior to Screening: o 1 within the 6- to 12-month window, and o 1 within 6 months prior to Screening • Plasma HIV-1 RNA <50 copies/mL at Screening • Capable of giving signed informed consent	• Pregnant, breastfeeding or planning to become pregnant or breastfeed during the study • Within 6 months prior to Screening and after confirmed suppression to <50 copies/mL on current ART regimen, any plasma HIV-1 RNA measurement ≥50 copies/mL • Within the 6- to 12-month window prior to Screening and after confirmed suppression to <50 copies/mL, any plasma HIV-1 RNA measurement >200 copies/mL, or 2 or more plasma HIV-1 RNA measurements ≥50 copies/mL • Any drug holiday during the window between initiating first HIV ART and 6 months prior to Screening, except for brief periods (less than 1 month) where all ART

	was stopped due to tolerability and/or safety concerns • Any switch to a second-line regimen due to virologic failure to therapy • Abacavir/dolutegravir/lamivudine, (ABC/DTG/3TC) as current ART regimen • A history of use of any regimen consisting of only single NNRTI therapy, or only single or dual NRTI therapy prior to starting current ART • Any evidence at screening of active CDC stage 3 disease; known moderate to severe hepatic impairment, unstable liver disease, history of liver cirrhosis, evidence of HBV infection; any pre-existing physical or mental condition that may interfere with the participant's ability to comply with the dosing schedule; ongoing malignancy other than cutaneous Kaposi's sarcoma, basal cell carcinoma, resected non-invasive cutaneous squamous cell carcinoma, or cervical, anal or penile intraepithelial neoplasia; any condition that may interfere with the absorption, distribution, metabolism or excretion of the drug or render the participant unable to receive study medication; ALT ≥3 times ULN; clinically significant cardiovascular disease • Exposure to an experimental drug and/or experimental vaccine within 28 days or 5 half-lives of the test agent • Any evidence of primary resistance to NNRTIs or any known resistance to INSTIs • Any verified Grade 4 laboratory abnormality; any acute laboratory abnormality at screening; estimated creatinine clearance <50 mL/min/1.73 m^2 • Current participation in another interventional study
ALT: alanine aminotransferase, ART: antiretroviral therapy, ATLAS: Antiretroviral Therapy as Long-Acting Suppression, CDC: Centers for Disease Control and Prevention, HBV: hepatitis B virus, HIV: human immunodeficiency virus, INSTI: integrase strand transfer inhibitor, NNRTI: non-nucleoside reverse transcriptase inhibitor, RNA: ribonucleic acid, TB: tuberculosis, ULN: upper limit of normal Source: ATLAS protocol[99], Swindells et al.[67]	

Table 27. Inclusion and exclusion criteria for FLAIR

Key inclusion criteria	Key exclusion criteria
• HIV-1 infected, ART-naive men or women aged 18 years or greater • HIV-1 infection as documented by Screening plasma HIV-1 RNA ≥1000 copies/mL	• Women who are pregnant, breastfeeding or plan to become pregnant or breastfeed during the study • Any evidence at screening of an active CDC Stage 3 disease; known moderate to severe

• Antiretroviral-naïve (≤ 10 days of prior therapy with any ART following a diagnosis of HIV-1 infection) • Female participants were to be non-pregnant, non-lactating and had to be either of non-reproductive potential or of reproductive potential and agree to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential • Capable of giving signed informed consent	hepatic impairment; unstable liver disease; history of liver cirrhosis; any pre-existing physical or mental condition that may interfere with the participant's ability to comply with the dosing schedule; evidence of HBV infection; ongoing malignancy other than cutaneous Kaposi's sarcoma, basal cell carcinoma, resected non-invasive cutaneous squamous cell carcinoma, or cervical, anal or penile intraepithelial neoplasia; any condition that may interfere with the absorption, distribution, metabolism or excretion of the drug or render the participant unable to receive study medication; ALT ≥3 times ULN; clinically significant cardiovascular disease • Exposure to an experimental drug and/or experimental vaccine within 28 days or 5 half-lives of the test agent • Any evidence of primary resistance to NNRTIs or any known resistance to INSTIs • Any verified Grade 4 laboratory abnormality; any acute laboratory abnormality at screening; estimated creatinine clearance <50 mL/min/1.73 m^2 • Current participation in other interventional study
ALT: alanine aminotransferase, ART: antiretroviral therapy, CAB: cabotegravir, CD4: cluster of differentiation 4, CDC: Centers for Disease Control and Prevention, HBV: hepatitis B virus, FLAIR: First Long-Acting Injectable Regimen, HIV: human immunodeficiency virus, INSTIs: integrase strand transferase inhibitors, LA: long-acting, NNRTI: non-nucleoside reverse transcriptase inhibitor, RNA: ribonucleic acid, RPV: rilpivirine, TB: tuberculosis, ULN: upper limit of normal Source: FLAIR Protocol[100], Orkin et al.[68]	

B.2.6.2.3. *Statistical analysis and definition of study groups*

A summary of the statistical analysis of ATLAS and FLAIR is provided in Table 28.

Table 28. Statistical analysis and definition of study groups in ATLAS and FLAIR

	ATLAS	FLAIR
Hypothesis objective	To demonstrate the non-inferior antiviral activity of switching to intramuscular CAB LA + RPV LA every 4 weeks (monthly) compared to continuation of current first line antiretroviral regimen over 48 weeks in HIV-1 infected antiretroviral therapy (ART)-experienced participants.	To demonstrate that the antiviral effect of oral ABC/DTG/3TC (current ART) followed by intramuscular CAB LA + RPV LA regimen was non-inferior to continuation of ART at Week 48 of maintenance treatment.
Analysis populations	The primary analysis set for efficacy endpoints was based on the ITT-E population consisting of all randomly assigned participants	The primary analysis set for efficacy endpoints was based on the ITT-E population consisting of all randomly assigned participants who receive at

	who receive at least one dose of study drug. Participants were assessed according to their randomised treatment, regardless of the treatment they received.	least one dose of study drug. Participants were assessed according to their randomised treatment, regardless of the treatment they received.
Statistical analysis of primary endpoints	Comparison at a one-sided 2.5% level of significance. Treatment with CAB-LA+RPV LA was declared non-inferior to current ART if the upper end of a two-sided 95% CI for the difference between the two groups in virologic failure rates at Week 48 lies below 6%. Adjusted estimates of the difference in the rate of failures between the two arms was presented along with CIs based on a stratified analysis using CMH weight.	Comparison at a one-sided 2.5% level of significance. Treatment with CAB LA + RPV LA was declared non-inferior to current ART if the upper end of a two-sided 95% CI for the difference between the two groups in virologic failure rates at Week 48 lies below 6%. Adjusted estimates of the difference in the rate of failures between the two arms was presented along with CIs based on a stratified analysis using CMH weight.
Statistical analysis of key secondary endpoints	Evaluation of the proportion of responders (HIV-1 RNA <50 copies/mL per Snapshot) at Week 48 using a CMH test stratified by baseline third agent class (INSTI, NNRTI, or PI) and sex at birth. A non-inferiority margin of -10% was used for this secondary comparison, where if the lower limit of the 95% CI of the difference in responder rate between the two study arms is greater than minus 10%, non-inferiority was demonstrated.	Evaluation of the proportion of responders (HIV-1 RNA <50 copies/mL per Snapshot) at Week 48 using the same analysis method and stratification factors as specified for the primary endpoint. A noninferiority margin of -10% was used for this secondary comparison, where if the lower limit of the 95% CI of the difference in responder rate between the two treatment groups was greater than minus 10%, non-inferiority would be demonstrated.
Statistical analysis of safety endpoints	Descriptive summary	Descriptive summary
Sample size and power calculation	This study planned to randomise approximately 285 participants per arm. Assuming the true virologic failure rate is 3% for the CAB LA + RPV LA injectable regimen and 2% for current ART arm, a non-inferiority margin of 6%, and a 2.5% one-sided significance level, this provided approximately 97% power to show non-inferiority for the proportion of participants with virologic failure (per FDA's snapshot algorithm for assessing HIV-1 RNA ≥50 copies/mL) at Week 48. This sample size also provided at least 90% power to show non-inferiority in the proportion of participants with plasma HIV-1	This study planned to randomise approximately 285 participants per treatment group. Assuming the true proportion of participants with Snapshot HIV-1 RNA ≥50 copies/mL was 3% for the CAB LA + RPV LA treatment group and 2% for the current ART group, a non-inferiority margin of 6%, and a 2.5% 1-sided significance level, this provided approximately 97% power to show non-inferiority for the proportion of participants with Snapshot HIV-1 RNA ≥50 copies/mL at Week 48. The sample size of 285 participants per arm also provides at least 90% power to show non-inferiority in the proportion of participants with plasma HIV-1 RNA <50 copies/mL (per FDA's Snapshot algorithm) at Week 48 over a range of true response rates, based on a -10%

	RNA <50 copies/mL (per FDA's snapshot algorithm) at Week 48 over a range of true response rates, on the basis of a -10% non-inferiority margin and 2.5% one-sided significance level. Assuming true response rates for the CAB LA + RPV LA arm and current ART arm are both 87%, the power is at least 94% to show non-inferiority for this key secondary endpoint.	non-inferiority margin and 2.5% one-sided significance level. Assuming true response rates for the CAB LA + RPV LA arm and current ART arm were both 87%, the power is at least 94% to show non inferiority for this key secondary endpoint.
Combined analysis	Data from this study was combined with that of FLAIR to assess non-inferiority using a 4% non-inferiority margin. The combined sample size from both studies (570 pooled per arm) provided 90% power, under the assumptions described above, to show non-inferiority for the proportion of participants with virologic failure (per FDA's snapshot algorithm for assessing HIV-1 RNA ≥ 50 copies/mL) at Week 48.	The combined sample size from both studies (570 pooled per group) provided 90% power, under the assumptions described, to show non-inferiority for the proportion of participants with Snapshot HIV-1 RNA ≥50 copies/mL at Week 48.
Handling of missing data and participant withdrawals	LOCF imputation	LOCF imputation
ART: antiretroviral therapy, CAB: cabotegravir, CMH: Cochran-Mantel Haenszel, FLAIR: First Long-Acting Injectable Regimen, HIV: human immunodeficiency virus, INSTIs: integrase strand transferase inhibitors, LA: long-acting, NNRTI: non-nucleoside reverse transcriptase inhibitor, LOCF: last observation carried forward, RNA: ribonucleic acid, RPV: rilpivirine, TB: tuberculosis, ULN: upper limit of normal Source: ATLAS Protocol[99] and CSR[3], FLAIR Protocol[100] and CSR[80], Swindells et al.[67], Orkin et al.[68]		

B.2.6.2.4. *Participant disposition and baseline characteristics*

B.2.6.2.4.1. ATLAS

A total of 618 participants were randomised (1:1) to receive CAB+RPV (n=310) or continue current ART (N=308) during the Maintenance phase. The ITT and safety populations included 616 participants (N=308 at each group).

A summary of participant disposition is provided in Table 29. The proportion of participants withdrawn during the maintenance phase was low and comparable between the two treatment groups (Q1M: 26 participants [8%]; oral ART: 18 participants [6%]). For participants in the Q1M group, the most common reasons for withdrawal were AEs (13 participants [4%] and protocol deviations (5 participants [2%]). For participants in the current ART group, the most common reasons for withdrawal were withdrawal by participant (5 participants [2%]); AEs (5 participants [2%]), and lack of efficacy (4 participants [1%])[3, 67].

Baseline characteristics of participants are summarised in Table 30.

Table 29. Participant disposition - ATLAS

	CAB + RPV (N=308)	current ART (N=308)
Participant status, n (%)		
Ongoing	1 (<1)	0
Completed	281 (91)	290 (94)
Withdrawn	26 (8)	18 (6)
Primary/sub-reason for study withdrawal, n (%)		
AE	13 (4)	5 (2)
Lack of efficacy	3 (<1)	4 (1)
Protocol Defined CVF	3 (<1)	4 (1)
Protocol deviation	5 (2)	3 (<1)
Non-compliance with study treatment	1 (<1)	0
Non-compliance with protocol procedures	2 (<1)	2 (<1)
Pregnancy	2 (<1)	1 (<1)
Protocol specified withdrawal criteria met, n (%)	1 (<1)	0
Participant met the GSK-defined liver chemistry stopping criteria	1 (<1)	0
Lost to follow-up, n (%)	1 (<1)	1 (<1)
Physician decision	2 (<1)	0
Withdrawn by participant	1 (<1)	5 (2)
Outcome of adverse events which led to study withdrawal, n (%)		
Fatal	0	1 (<1)
Non-fatal	13 (4)	4 (1)

ART: antiretroviral therapy, CAB: cabotegravir, CVF: collagen volume fraction, RPV: rilpivirine

a. Participants may have only 1 primary reason for withdrawal.

b. Percentages for sub reasons may sum to more or less than 100%. Participants may have more than 1 sub reason underneath a single primary reason. Participants are not required to indicate sub reasons.

Source: ATLAS CSR[3] , Swindells et al.[67]

Table 30. Baseline characteristics in ATLAS

Characteristic	CAB+RPV (N=308)	Current ART (N=308)
Age (years), n		
Mean (SD)	41.6 (9.99)	43.2 (11.43)
Min, max.	21,74	18,82
Age group (years), n (%)		
<35	80 (26)	80 (26)
35 to <50	162 (53)	132 (43)
≥50	66 (21)	96 (31)
Sex at birth, n (%)		
Female	99 (32)	104 (34)
Male	209 (68)	204 (66)
Race, n (%)		
White	214 (69)	207 (67)
Non-White	94 (31)	101 (33)
BMI (kg/m^2)		
Mean (SD)	26.2 (5.1)	26.7 (5.8)

ART: antiretroviral therapy, BMI: body mass index, CAB: cabotegravir, RPV: rilpivirine
Source: ATLAS CSR[3], Swindells et al. (2020)[101]

B.2.6.2.4.2. FLAIR

A total of 631 participants entered the Induction phase, of which 566 completed the phase and were randomised into the Maintenance Phase (CAB + RPV 283 participants; current ART 283 participants). At the time of the data cut for the CSR, the number of participants ongoing in the Maintenance Phase was similar in both treatment groups (CAB + RPV 258 [91%]; current ART 261 participants [92%])[68].

A summary of patient disposition is shown in Table 31. The proportion of participants withdrawn during the Maintenance Phase was low and comparable between the two treatment arms (CAB + RPV 25 [9%]; current ART 22 [8%]). For the CAB + RPV group, the most common reasons for withdrawal were AEs (9 participants [3%]), lack of efficacy (5 participants [2%]) and withdrawal by participant (7 participants [2%]). For the current ART group, the most common reasons for withdrawal were physician decision (5 participants [2%)]) and withdrawal by participants (7 participants [2%])[80, 102].

Table 31. Participant disposition - FLAIR

	CAB + RPV (N=283)	current ART (N=283)
Participant status, n (%)		
Ongoing	258 (91)	261 (92)
Completed	0	0
Withdrawn	25 (9)	22 (8)
Primary/sub-reason for study withdrawal, n (%)		
AE	9 (3)	4 (1)
Lack of efficacy	5 (2)	3 (1)
Protocol Defined CVF	5 (2)	3 (1)
Protocol deviation	0	1 (<1)
Prohibited medication use	0	1 (<1)
Lost to follow-up	2 (<1)	2 (<1)
Physician decision	2 (<1)	5 (2)
Pregnancy	0	1 (<1)
Other	2 (<1)	4 (1)
Withdrawal by participant	7 (2)	7 (2)
Lost to follow-up	2 (<1)	2 (<1)
Outcome of adverse events which led to study withdrawal, n (%)		
Fatal	0	0
Non-fatal	9 (3)	4 (1)

ART: antiretroviral therapy, CAB: cabotegravir, CVF: collagen volume fraction, RPV: rilpivirine

a. Participants may have only 1 primary reason for withdrawal.
b. Percentages for sub reasons may sum to more or less than 100%. Participants may have more than 1 sub reason underneath a single primary reason. Participants are not required to indicate sub reasons.

Source: FLAIR CSR[80], Orkin et al[68]

Table 32. Baseline characteristics in FLAIR

Characteristic	CAB + RPV (N=283)	Current ART (N=283)
Age (years), n		
Mean (SD)	35.9 (10.17)	36.0 (9.82)
Min, max.	19, 68	18, 68
Age group (years), n (%)		
<35	143 (51)	145 (51)
35 to <50	107 (38)	109 (39)
≥50	33 (12)	29 (10)
Sex at birth, n (%)		
Female	63 (22)	64 (23)
Male	220 (78)	219 (77)
Race, n (%)		
White	216 (76)	201 (71)
Non-White	67 (24)	80 (28)
Missing	0	2 (<1)
BMI (kg/m^2)		
Mean (SD)	25.1 (4.4)	24.9 (4.9)

ART: antiretroviral therapy, BMI: body mass index, CAB: cabotegravir, RPV: rilpivirine
Source: FLAIR CSR[80], Orkin et al[68]

B.2.6.2.5. *Results: HIV-1 RNA ≥50 copies/mL at Week 48 (primary endpoint)*

Results are presented for the pooled analysis. This analysis was pre-specified in the study protocols (see Table 28). The pooled analysis demonstrated that Q1M CAB LA + RPV LA is non-inferior to current ART in maintaining virologic suppression in participants with HIV-1 infection at Week 48 (Table 33). The non-inferiority endpoint was achieved, with the upper bound of the 95% CI for the adjusted treatment difference below 4%[81].

Table 33. Proportion of participants with HIV-1 RNA ≥50 copies/mL at Week 48, ITT-E population

		Pooled ATLAS + FLAIR	
		Q1M (N=591)	**Current ART (N=591)**
Week 48	**HIV-1 RNA ≥ 50 copies/mL per total assessed (%)**	11/591 (1.9)	10/591 (1.7)
	Difference in proportion (95% CI)	0.17 (−1.34-1.68)	
	Adjusted difference in proportion (95% CI)	0.16 (−1.35-1.67)	
ART: antiretroviral therapy, HIV: human immunodeficiency virus, Q1M: once a month, RNA: ribonucleic acid Source: Rizzardini et al.[81]			

B.2.6.2.6. *Results: HIV-1 RNA <50 copies/mL, ITT-E population*

Q1M CAB LA + RPV LA was non-inferior to current ART on the endpoint of viral load <50 copies/mL at Week 48 (Table 34). These results are consistent with the results of the primary endpoint analysis (above)[81].

Table 34. Proportion of participants with viral load <50 copies/mL at Week48, ITT-E population

		Pooled ATLAS + FLAIR	
		Q1M (N=591)	**Current ART (N=591)**
Week 48	**Plasma HIV-1 RNA <50 copies/mL (%)**	550/591 (93)	558/591 (94)
	Difference in proportion (95% CI)	-1.35 (-4.11-1.41)	
	Adjusted difference in proportion (95% CI)	-1.37 (-4.12-1.39)	
ART: antiretroviral therapy, HIV: human immunodeficiency virus, Q1M: once a month, RNA: ribonucleic acid Source: Rizzardini et al.[81]			

B.2.6.2.7. *Results: Health-related quality of life and patient-reported outcomes*

SF-12 and SF-6D

HRQoL in ATLAS and FLAIR was assessed with the 12-item Short Form Health Survey (SF-12), which measures general health status and degree of mental health distress[103]. Physical and mental component SF-12 scores for ATLAS and FLAIR at Week 24 and Week 48 are shown in Table 35 and Table 36, respectively.

Table 35. Treatment difference in SF-12 (Physical Component) scores – FLAIR and ATLAS

	ATLAS			FLAIR		
	Treatment	**Adjusted Mean (95% CI)**	**Adjusted Difference (95% CI)**	**Treatment**	**Adjusted Mean (95% CI)**	**Adjusted Difference (95% CI)**
Week 24	CAB + RPV (n= 286)			CAB + RPV (n= 251)		
	current ART (n=288)			current ART (n=253)		
Week 48	CAB + RPV (n=288)			CAB + RPV (n=252)		
	current ART (n=295)			current ART (n=258)		

ART: antiretroviral therapy, CAB: cabotegravir, SD: standard deviation, RPV: rilpivirine
Source: ATLAS CSR[3], FLAIR CSR[80]

Table 36. Treatment difference in SF-12 (Mental Component) scores – FLAIR and ATLAS

	ATLAS			FLAIR		
	Treatment	**Adjusted Mean (95% CI)**	**Adjusted Difference (95% CI)**	**Treatment**	**Mean (SD)**	**Median (Range)**
Week 24	CAB + RPV (n= 289)			CAB + RPV (n= 251)		
	current ART (n=286)			current ART (n=253)		
Week 48	CAB + RPV (n=291)			CAB + RPV (n=252)		
	current ART (n=293)			current ART (n=258)		

ART: antiretroviral therapy, CAB: cabotegravir, SD: standard deviation, RPV: rilpivirine
Source: ATLAS CSR[3], FLAIR CSR[80]

In a post hoc analysis, SF-12 values from the trials were used to derive SF-6D (SF-12) utilities via a published algorithm. Between-treatment differences in SF-6D values were then explored as a post-hoc analysis[71]. Full details of the post hoc analysis are provided in Appendix N. In brief, the algorithm by Brazier and Roberts (2004)[104] was applied to SF-12 values captured in ATLAS and FLAIR.

Derived SF-6D scores for pooled ATLAS and FLAIR are presented in Table 37. An ANCOVA model was selected to perform statistical analysis of the treatment difference in SF-6D utility scores, adjusting for covariates: age, sex, race, and CD4+ count. At baseline [redacted] between treatment groups was observed in SF-6D scores [redacted] in SF-6D scores favouring CAB LA + RPV LA were observed at Week 24 and Week 48, showing a utility advantage of [redacted] points [redacted] for CAB LA + RPV LA vs daily oral treatment with current ART (Table 38).

Table 37. Derived SF-6D scores - Pooled ATLAS and FLAIR (ITT-E Population)

	Treatment	Mean (SD)	Median (Range)
Baseline	CAB + RPV (n= 556)	[redacted]	[redacted]
	current ART (n=552)	[redacted]	[redacted]
Week 24	CAB + RPV (n= 572)	[redacted]	[redacted]
	current ART (n=552)	[redacted]	[redacted]
Week 48	CAB + RPV (n=544)	[redacted]	[redacted]
	current ART (n=552)	[redacted]	[redacted]
CAB: cabotegravir, SD: standard deviation, RPV: rilpivirine			

Table 38. Treatment difference in SF-6D utility scores – Pooled ATLAS and FLAIR (ITT-E Population)

	Treatment	Adjusted Mean (95% CI)	Adjusted Difference (CAB +RPV - Current ART)	p-value (CAB +RPV - Current ART)
Week 24	CAB + RPV (n= 535)	[redacted]	[redacted]	[redacted]
	current ART (n=546)	[redacted]		
Week 48	CAB + RPV (n=500)	[redacted]	[redacted]	[redacted]
	current ART (n=548)	[redacted]		
ART: antiretroviral therapy, CAB: cabotegravir, CI: confidence interval, RPV: rilpivirine				

Other patient-reported outcomes

Participants treated with CAB LA + RPV LA reported statistically significant improvements in treatment satisfaction compared with participants treated with current ART for the HIVSTQs Score, HIVSTQs Score change and the ACCEPT score (Table 39 to Table 41). An overview of these instruments is given in Section B.2.6.1.12, where their use in ATLAS-2M is described.

In ATLAS at Week 48, 86% (n= 266/308) of participants preferred monthly CAB LA + RPV LA over the daily oral treatment they received prior to study entry[3]. Out of the subjects who completed the preference question, 97% (n=266/273) selected CAB LA + RPV LA over daily oral therapy as their preferred HIV treatment at Week 48[3].

Table 39. Change from Baseline (CFB) in Total HIVSTQs Score by Visit –Pooled ATLAS and FLAIR (ITT-E Population)

	Treatment	Adjusted Mean CFB (95% CI)	Adjusted Difference (CAB + RPV - Current ART)	p-value (CAB + RPV - Current ART)
Week 24	CAB + RPV (n= 557)	[redacted]	[redacted]	[redacted]
	Current ART (n=552)	[redacted]		
Week 44	CAB + RPV (n=557)	[redacted]	[redacted]	[redacted]
	Current ART (n=552)	[redacted]		
ART: antiretroviral therapy, CAB: cabotegravir, CFB: change from baseline, RPV: rilpivirine Source: Integrated Summary of Efficacy[73]				

Table 40. Total HIVSTQc Score Change at Week 48 – Maintenance Phase (ITT-E Population)

	Treatment	Adjusted Mean CFB (SE)	Adjusted Difference (CAB +RPV - Current ART)	p-value (CAB +RPV - Current ART)
Week 48	CAB + RPV (n= 263)	29.6 (0.49)	4.1 (2.8-5.5)	<0.001
	current ART (n=266)	25.5 (0.48)		
ART: antiretroviral therapy, CAB: cabotegravir, CFB: change from baseline, RPV: rilpivirine Source: Integrated Summary of Efficacy[73], EPAR[74]				

Table 41. Change from Baseline (CFB) in General Acceptance Domain of the ACCEPT – Pooled ATLAS and FLAIR (ITT-E Population)

	Treatment	Adjusted Mean CFB (95% CI)	Adjusted Difference (CAB +RPV - Current ART)	p-value (CAB +RPV - Current ART)
Week 8	CAB + RPV (n= 555)	[redacted]	[redacted]	[redacted]
	current ART (n=546)	[redacted]		
Week 24	CAB + RPV (n=558)	[redacted]	[redacted]	[redacted]
	current ART (n=552)	[redacted]		
Week 48	CAB + RPV (n=557)	[redacted]	[redacted]	[redacted]
	current ART (n=562)	[redacted]		
ART: antiretroviral therapy, CAB: cabotegravir, CFB: change from baseline, RPV: rilpivirine Source: Integrated Summary of Efficacy[73]				

B.2.6.2.8. *Long-term efficacy data from ATLAS and FLAIR*

Long-term follow-up shows that high efficacy and treatment satisfaction are maintained over time. Of the participants in ATLAS who completed the Maintenance Phase (to Week 52) in either treatment arm, almost all decided to remain on or switch to LA therapy and participate in the Extension Phase. Most participants then transitioned to ATLAS-2M as they became

eligible, but of the 52 remaining in ATLAS at week 96, only 1 had HIV-1 RNA ≥50 copies/mL at the Week 96 data analysis (HIV-1 RNA of 173 copies/mL at Week 92) and none met the criteria for confirmed virologic failure.

In FLAIR, CAB LA + RPV LA demonstrated high efficacy through Week 96 and 124 and was non-inferior to the continuation of daily oral current ART[105]. At Week 96, virologic failure was confirmed in 4 participants (1.4%) receiving CAB LA + RPV LA and 4 participants (1.4%) receiving daily oral current ART, with no new cases of virologic failure in participants receiving CAB LA + RPV LA after Week 48. CAB LA + RPV LA was associated with a high rate of adherence at Week 96, with 97% of injections given to participants within the ± 7 day allowed dosing window[96]. Of the participants in FLAIR who completed the Maintenance Phase (to Week 100) in either treatment arm, almost all decided to remain on or switch to LA therapy and participate in the Extension Phase[105]. At Week 124, only 1 participant (0.4%) in the direct to injection group of the Extension Switch Population had confirmed virologic failure, while none in the oral lead-in group showed virologic failure[106, 107].

Treatment satisfaction and preference for the long-acting regimen remained high in both trials[106, 108].

B.2.7. Subgroup analyses

B.2.7.1. Prespecified subgroup analyses in ATLAS-2M

In ATLAS-2M, pre-specified subgroup analyses were carried out for the primary endpoint and the plasma HIV-1 RNA <50 copies/mL at Week 48 Snapshot Algorithm secondary endpoint. Subgroups analysed were randomisation stratification factors (prior exposure to CAB + RPV: 0 weeks, 1-24 weeks, and >24 weeks), and demographic and baseline characteristics (demographic factors, baseline viral load, baseline CD4+ lymphocyte count, and participating countries)[70].

- Treatment differences for the primary endpoint and the Week 48 Snapshot endpoint for each randomisation stratification stratum support the non-inferiority of Q2M vs. Q1M dosing.
- No statistically significant difference between the two treatment arms was observed for the proportion of participants with HIV-1 RNA ≥50 (Snapshot algorithm) at 48 Weeks in any of these subgroups.
- The relatively small sample size limits the ability to make a robust conclusion regarding subgroup analyses.

A summary of the results for protocol-specified subgroups in ATLAS-2M is presented in Appendix E. The effect of third agent in the previous regimen was addressed as part of the indirect treatment comparison presented in Section B.2.9.

B.2.7.2. Post-hoc analysis of outcomes in women

Women are often under-represented in clinical trials of ART in HIV. A post-hoc analysis examining the efficacy, safety, and treatment satisfaction outcomes for women (i.e. those of

female sex at birth) participating in the ATLAS-2M study vs men at Week 48 was published as a conference presentation[109].

CAB LA + RPV LA Q2M and Q1M demonstrated high and similar rates of efficacy in women and men:

- Proportions of women and men with HIV-1 RNA ≥50 copies/mL were similar between groups (adjusted differences [95% CI], 3.5% [0.4 to 6.6] for women and −0.3% [−1.8 to 1.3] for men).
- HIV-1 RNA <50 copies/mL was maintained in the majority of women and men in each group (adjusted differences [95% CI], 0.4% [−6.2 to 7.1] for women and 0.8% [−2.3 to 4.0] for men).
- There were no notable or statistically significant differences between women and men in safety, tolerability or treatment satisfaction.

Female sex at birth had no significant association with confirmed virologic failure in the multivariable analysis described in Section B.2.6.1.9 above.

B.2.8. Meta-analysis

B.2.8.1. Pooled analysis of ATLAS and FLAIR

The results of the pooled analysis of key virologic endpoints in ATLAS and FLAIR are presented in Section B.2.6.2.5 and B.2.6.2.6. This analysis was pre-specified in the study protocols (see Table 28), and formed part of the Integrated Summary of Efficacy prepared for regulatory purposes.

B.2.9. Indirect and mixed treatment comparisons

Key points

- CAB LA + RPV LA Q2M is not statistically different to current ART after 48 weeks on any of the outcomes analysed (virologic suppression, change from baseline in CD4+ cell count, AE-related outcomes) [69].
- Further, there were no significant differences in virologic suppression or lack of virologic suppression for any baseline third active drug class subgroups.
- CAB LA + RPV LA Q2M was thus found to be non-inferior to daily oral ART.

No trial-based comparison between CAB LA + RPV LA Q2M and daily oral standard of care ART is available, and an indirect treatment comparison (ITC) was therefore required to inform the economic modelling.

B.2.9.1. Indirect treatment comparison

To inform the economic modelling, an ITC was performed to compare CAB LA + RPV LA Q2M with current oral ART in virologically suppressed treatment-experienced HIV-infected individuals for snapshot endpoints at 48 weeks after treatment switch[69]. The ITC was published at a recent conference[69] and is to be submitted for journal publication. The methodology is described in full in Appendix D.

B.2.9.1.1. *Identification and selection of studies*

Relevant articles were identified from PubMed/MEDLINE, Embase, and clinicaltrials.gov via previous and current systematic reviews (see Appendix D). The comparator of interest to CAB LA + RPV LA Q2M is current oral ART. The ATLAS-2M trial compares CAB LA + RPV LA Q2M with CAB LA + RPV LA Q1M. ATLAS and FLAIR are the only trials, which include a CAB LA + RPV LA Q1M arm to provide a link between Q2M and current oral ART (Table 42). The characteristics of these trials are reported in Section B.2.6.2.

Pooled data from ATLAS and FLAIR studies (n=591 per treatment group), and data from participants with no prior CAB + RPV exposure (n=327 per treatment group) in the ATLAS-2M trial, were used to inform the analysis.

Table 42 Summary of the trials used to carry out the ITC

Trial	Oral current ART	CAB LA + RPV LA Q1M	CAB LA + RPV LA Q2M
ATLAS-2M	No	Yes	Yes
ATLAS	Yes	Yes	No
FLAIR	Yes	Yes	No

B.2.9.1.2. *Methods*

Full details of the methodology for the indirect comparison are provided in Appendix D. In brief, an anchored ITC of CAB LA + RPV LA Q2M with daily current oral ART was conducted applying Bucher's methodology according to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines[110], with CAB LA + RPV LA Q1M as the common comparator.[69] Pooled data from ATLAS and FLAIR and the ATLAS-2M subgroup with no prior CAB LA + RPV LA exposure was included in the analysis, given the similarities in baseline characteristics between these participants[69].

Baseline characteristics between the Q1M arms of ATLAS/FLAIR and ATLAS-2M showed no significant differences or differences were not judged to be clinically relevant. The exception to this was that the proportion of participants switching from INSTIs and NNRTIs to study treatment was unmatched between the pooled ATLAS/FLAIR and ATLAS-2M trials. Therefore, a subgroup analysis of virologic suppression stratified by baseline third drug class was undertaken to assess the impact of this on the findings of the main analysis[69].

B.2.9.1.3. *Results*

The ITC found that CAB LA + RPV LA Q2M is not statistically different to current ART after 48 weeks on any of the key efficacy or safety outcomes in terms of relative risk, odds ratio, and risk difference (Table 43, Figure 6)[69]. Indirect comparison results of CAB LA + RPV LA Q2M relative to current ART stratified by baseline treatment class are shown in

Table **44** and Figure 7.

Additionally, the interpretation of non-inferiority study results should not focus on the point estimate, but rather the lower or upper bounds of the confidence interval of the delta, i.e. the difference between the study endpoints rather than the individual arms estimates for those who lost viral response and those who maintained it.

Interpretation of the point estimates alone is inappropriate, as the design does not facilitate comparisons of this nature.

Table 43 Summary of results of the indirect comparison of CAB LA + RPV LA Q2M relative to current ART

	Comparative effect measure (95% CI)		
	Relative risk	**Risk difference, %**	**Odds ratio**
HIV-1 RNA <50 copies/mL at Week 48	1.01 (0.95, 1.06)	0.5 (−4.40, 5.3)	1.04 (0.49, 2.22)
HIV-1 RNA ≥50 copies/mL at Week 48	1.10 (0.25, 4.90)	0.2 (−2.20, 2.60)	1.10 (0.24, 5.03)
CD4 cell count change from baseline, per μL[a] at Week 48	--	−5.1 (−40.0, 29.7)	--
No virologic data at Week 48	0.95 (0.42, 2.15)	−0.7 (−4.90, 3.60)	0.94 (0.40, 2.24)
Discontinuations due to AEs at Week 48	1.48 (0.40, 5.46)	0.5 (−2.5, 3.5)	1.49 (0.39, 5.65)
Grade 3–5 AEs (excluding ISR) maintenance phase	1.68 (0.78, 3.61)	3.3 (−1.3, 7.8)	1.74 (0.77, 3.92)

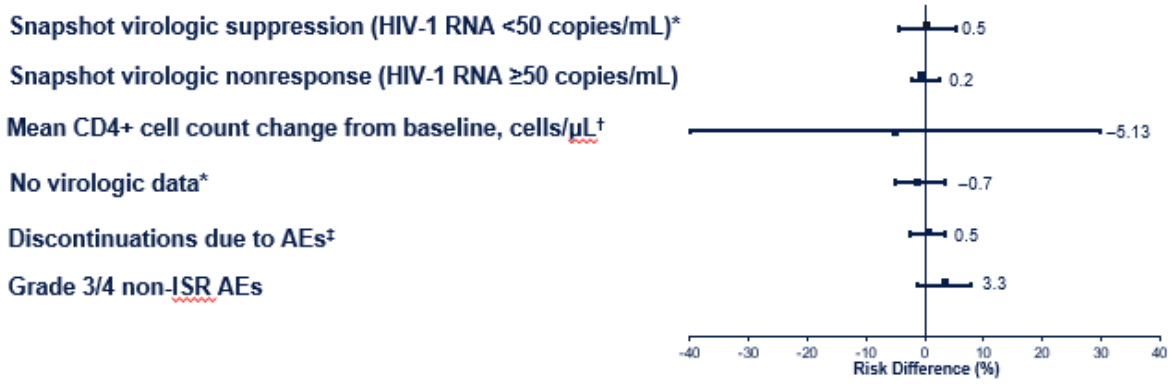
[a]Mean difference
AE, adverse event; CAB, cabotegravir; CI, confidence interval; HIV-1, human immunodeficiency virus type 1; ISR, injection-site reaction; Q8W, every 8 weeks; RNA, ribonucleic acid; RPV, rilpivirine; ART, antiretroviral therapy

Table 44 Indirect comparison results of CAB LA + RPV LA Q2M relative to current ART, stratified by baseline treatment class

	Comparative effect measure (95% CI)		
	Relative risk	Risk difference, %	Odds ratio
HIV-1 RNA <50 copies/mL at Week 48 by baseline third active drug class			
INSTI	1.04 (0.96, 1.13)	3.8 (−3.6, 11.2)	1.62 (0.57, 4.60)
NNRTI	0.96 (0.89, 1.04)	−4.0 (−11.4, 3.3)	0.50 (0.13, 1.99)
PI	1.01 (0.83, 1.24)	1.0 (−17.0, 19.1)	0.96 (0.11, 8.12)
HIV-1 RNA ≥50 copies/mL at week 48 by baseline third active drug class			
INSTI	1.03 (0.13, 7.97)	0 (−3.7, 3.7)	1.03 (0.13, 8.27)
NNRTI	2.07 (0.08, 52.49)	1.3 (−2.2, 4.9)	2.09 (0.08, 54.86)
PI[a]	--	1.1 (−7.8, 10.0)	--

[a]Values could not be calculated for RR and OR as value for ART in ATLAS/FLAIR was 0

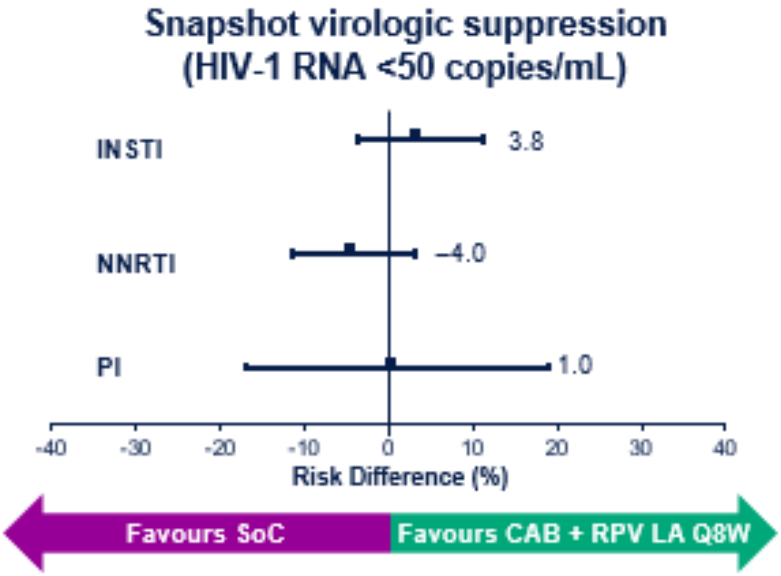
AE, adverse event; CAB, cabotegravir; CI, confidence interval; HIV-1, human immunodeficiency virus type 1; INSTI, integrase strand inhibitor; ISR, injection-site reaction; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; Q8W, every 8 weeks; RNA, ribonucleic acid; RPV, rilpivirine; ART, antiretroviral therapy



‡Participants with no virologic data at Week 48 who discontinued due to AEs.
AE, adverse event; CAB, cabotegravir; CI, confidence interval; ISR, injection site reaction; LA, long-acting; Q2M, every two months; RPV, rilpivirine

Source: Chounta 2020[69]

Figure 6. Forest Plot of Risk Difference (95% CI) for CAB LA + RPV LA Q2M vs. current ART at Week 48



SOC; standard of care, i.e. current ART

Source: Chounta 2020[69]

Figure 7. Forest Plots of Risk Difference (95% CI) for CAB LA + RPV LA Q2M vs. current ART at Week 48 Stratified by Baseline Third Active Drug Class

B.2.9.1.4. *Results of the assessment of heterogeneity*

Details of the assessment of heterogeneity are supplied in Appendix D. Of note, a pooled analysis of the ATLAS and FLAIR trials was previously conducted[111], and no significant heterogeneity was found between the two trials in terms of trial or participant characteristics that might modify the treatment effect.

B.2.9.2. Uncertainties in the indirect and mixed treatment comparisons

While indirect comparisons provide useful insights in the absence of direct trial-based comparisons, they cannot replace evidence from head-to-head studies, which remain the gold standard. The main area of uncertainty resulted from the unmatched distribution of participants switching from INSTIs and NNRTIs to study treatment between the pooled ATLAS/FLAIR and ATLAS-2M trials, which had the potential to be clinically relevant. Therefore, a subgroup analysis on virologic suppression was carried out to assess any potential effects of this unmatched distribution. The subgroup analysis found that there were no statistically significant differences on virologic suppression or lack of virologic suppression for any of the baseline third active drug classes assessed, implying that the overall conclusions of the main analyses are robust and unaffected by differences in baseline third drug class across trials.

B.2.9.3. Feasibility of pairwise indirect comparison

Key points

- There is substantial evidence supporting the assumption of comparable effectiveness for HIV therapies, particularly in people with HIV who are virologically suppressed. This is supported by recommendations from relevant clinical guidelines (outlined in Section B.1.3.4.3) and the significant body of non-inferiority research, and is aligned to opinions from clinical experts.
- The HIV evidence is based on non-inferiority studies, which are the foundation of the clinical commissioning of HIV treatments in England. Non-inferiority margins in HIV trials are established with narrow ranges, rather than a proportional acceptable loss of efficacy to the active treatment.
- NMA methodology is not appropriate for use with non-inferiority studies; the output, a ranking of interventions, has limited meaning in the context of non-inferiority evidence and limited practical application. In spite of the methodological limitations, if an NMA was progressed the result would be no more certain than the output of the Bucher ITC presented previously.
- The primary comparator – as outlined in the NICE scope - is established ART, rather than individual ART regimens. Hence, the ITC for CAB LA + RPV LA Q2M versus daily oral ART (described in Section B.2.9.1.2) can be considered the most informative to decision-making.

B.2.9.3.1. *Evidence supporting the assumption of comparable effectiveness between HIV therapies*

As previously described, an ITC was undertaken for CAB LA + RPV LA Q2M versus daily oral ART regimens, and demonstrates that the efficacy of CAB LA + RPV LA Q2M is not different to the oral ART regimens in the ATLAS and FLAIR studies. The geometry for this network of evidence is presented in Figure 8.

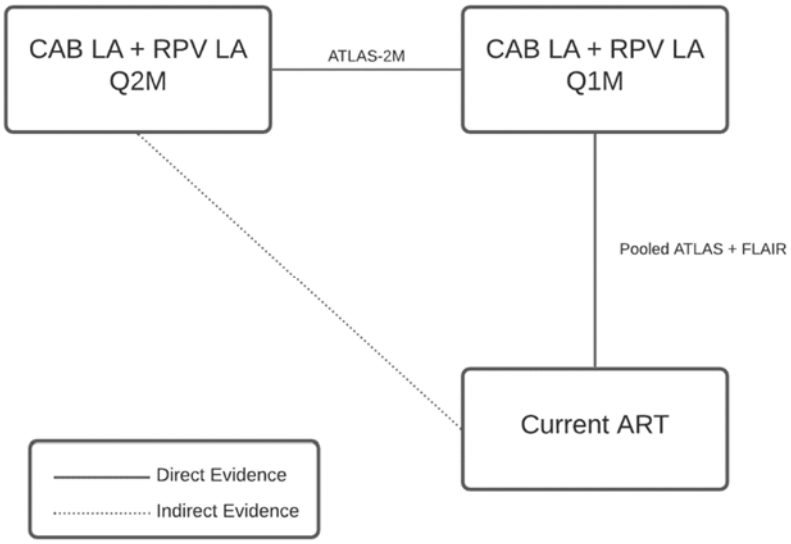


Figure 8 Network of evidence from trials of CAB LA + RPV LA

Specific oral ART regimens have been identified that would comprise standard of care in the absence of CAB + RPV Q2M. It is not anticipated that these therapies would have different efficacy to the pooled oral ARTs assessed during ATLAS and FLAIR. On the contrary, clinicians consulted for the submission confirm that for the purposes of clinical decision-making, all modern approved ART regimens are assumed to have equivalent efficacy. This is supported by recommendations from relevant clinical guidelines (outlined in Section B.1.3.4.3) and the clinical evidence. Hence, all available evidence supports the assumption of comparable effectiveness between comparators of interest and the ATLAS/FLAIR ART arm.

There is no single "standard of care" regimen, and selection of an appropriate ART regimen is individualised based on a broad range of clinical and non-clinical factors[29]. Within the guidelines, regimens should be tailored for the individual to enhance adherence and support long-term treatment success[21]. Regimens may offer different benefits depending on individual need, based on personal preference, lifestyle, underlying health risks and co-morbidities.

This is well aligned to the clinical evidence identified in the SLR described in Appendix D. Almost all regimens are associated with rates of viral suppression exceeding 90%, with the exception of dose-finding studies and switch studies. This is summarised in Figure 9 for ARTs of interest (including CAB LA + RPV LA, shown in the top rows of the graph). It is of note that included SLR studies required all enrolled participants to be virologically suppressed (<50 copies/ml) at baseline, so that high efficacy rates can be anticipated. Further, as outlined in Table 45, minor variation is observed for mean change in CD4 levels. However, this should be viewed in the context of the absolute values at baseline and at week 48, in which case values can be considered similar.

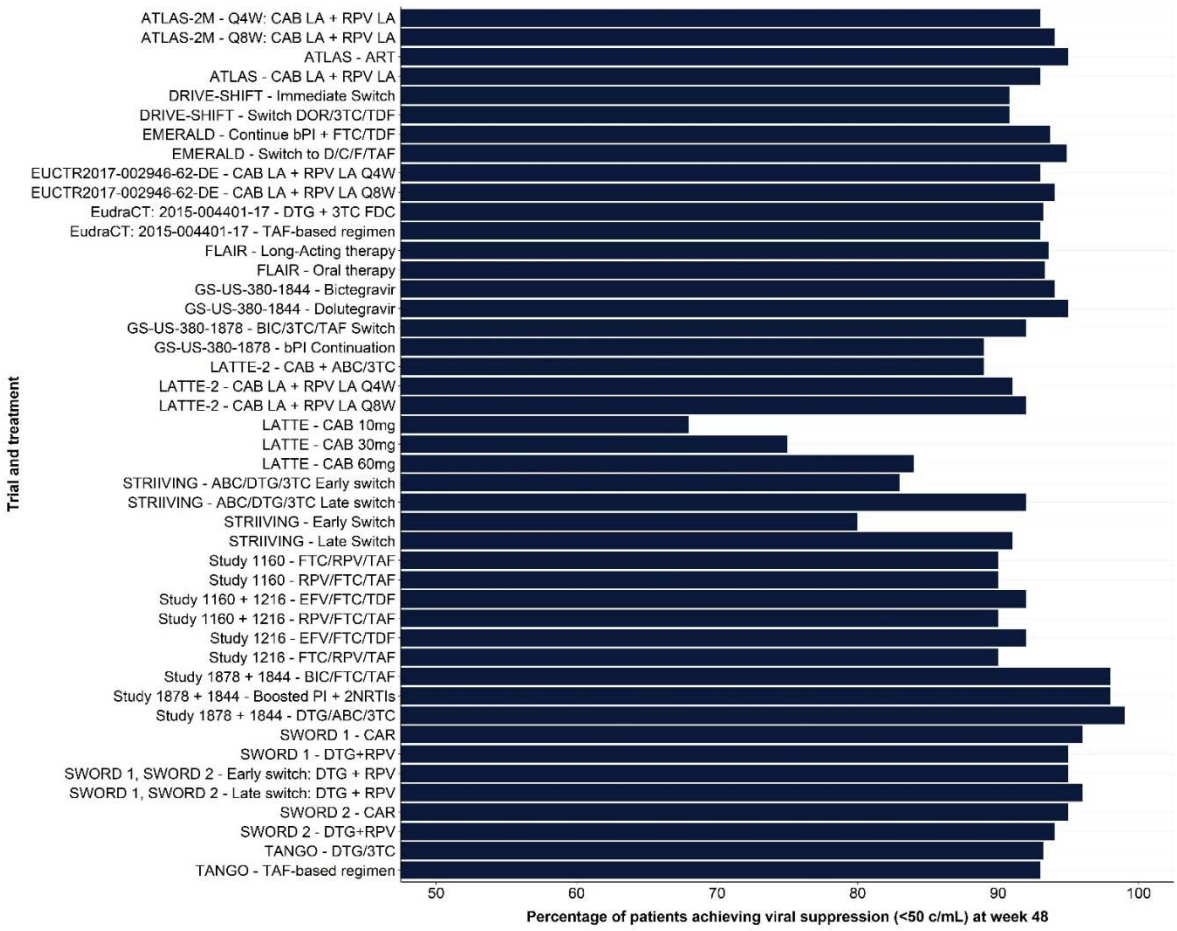


Figure 9. Virologic suppression at week 48 from studies exploring ART regimens of interest

Table 45. CD4 cell count at baseline and at week 48 for ART regimens of interest

Author, year	Clinical trial/study ID	Study arm	Number of participants (ITT)	Median CD4 T cell count (cells/mm^3)	CD4 T cell change from baseline at Week 48 (cells/mm^3)
FLAIR CSR[271], Orkin 2020[272]	FLAIR	CAB/RPV	283	624	40.2
		ART	283	625	79.9
ATLAS CSR[273], Swindells 2020[274]	ATLAS	CAB/RPV	308	654	4
		ART	308	653	13.5
Overton 2020[276]	ATLAS-2M	CAB/RPV (Q8W)	522	642	5
		CAB/RPV (Q4W)	523	688	-8
van Wyk et al, 2020 [254]	TANGO	3TC/DTG	369	682	22.5
		TAF/ART	372	720	11
Llibre et al, 2018 [121]	SWORD 1, SWORD 2	DTG/RPV	513	611	28
		ART	511	638	22
Molina et al, 2018 [154]	GS-US-380-1844	BIC/FTC/TAF	282	732	-31
		3TC/ABC/DTG	281	661	4
Daar et al, 2018 [54]	GS-US-380-1878	3TC/BIC/TAF	290	617	25
		PI	288	626	0
Johnson et al, 2019 [107]	DRIVE-SHIFT	3TC/DOR/TDF	447	633	5
		ART	233	625	19
Orkin et al, 2018 [178]	EMERALD	DRV/FTC/TAF	763	630	18.7
		ART	378	624	4.9

B.2.9.3.1.1. Previously published HIV NMAs

A targeted review was conducted to identify published NMAs in potentially relevant HIV populations. This comprised a non-systematic hand searching of published resources, with clinical expert guidance. Relevant NMAs included at least two comparators with a focus on treatment efficacy outcomes. The objective was to describe initial insights into the methodological approaches, challenges and limitations of NMAs in HIV participants, based on the published literature.

Five publications[112-116] were identified, of which only one, Kanters et al. (2017)[112], was in treatment-experienced people with HIV; the remainder covered initial treatment in treatment-naïve persons, and three focused on use of dolutegravir. No NMAs in virally suppressed participants switching treatment for non-virologic reasons were identified.

The Kanters publication[112], which covered studies in persons who switched ART after failure of an NNRTI-based first-line regimen, was undertaken to inform the revision of the WHO Guidelines. This NMA used a standard Bayesian approach and cited NICE Decision Support Unit guidelines. Assessment of non-inferiority was based on a pre-defined margin of 15% for the proportion with HIV-1 RNA < 50 copies mL, but no rationale was provided for this definition and no reference was made as to the methodological foundations of choosing this value or approach within an NMA framework. Twelve publications met inclusion criteria, representing eight studies, of which one study was excluded as it included participants who had not failed first-line regimens. The study authors note that most studies reported viral suppression at a

level of <50 copies/mL, but one endpoint was viral load <200 copies/mL. Additional outcomes or timepoints were more sparsely reported. Limitations of the NMA reflected the evidence base: differences in treatment history, endpoint definition and reporting of evidence may introduce uncertainty in the outcomes.

Of note, the Kanters study[112] reported on non-inferiority of therapies: ritonavir-boosted lopinavir plus raltegravir was considered non-inferior to ritonavir-boosted protease inhibitor plus two NNRTIs, while estimates of efficacy for ritonavir-boosted darunavir were too imprecise to determine non-inferiority.

The objective of the analysis in this submission differs from that of Kanters[112] in terms of the population and treatments of interest. The Kanters study[112] was interested in a population with known and the same treatment history (NNRTI-based first line regimen failures), whereas ATLAS did not have such a restriction. Further, the Kanters study[112] examined specific regimens switching to ritonavir-boosted regimens, while ATLAS included a wider pool of current ART regimens.

B.2.9.3.2. Absence of established methods for synthesis of non-inferiority evidence

The appropriateness, robustness and relevance of current NMA methodology to an evidence base which entirely consists of non-inferiority trials has not been fully explored in the literature. To inform the approach, a review was conducted of the methodological literature as it pertains to non-inferiority trials and indirect comparisons.

Two studies were identified which examined the topics of non-inferiority trials and meta-analysis/NMA. The focus for each study was not directly relevant to the context for CAB LA + RPV LA. Schmidli et al.[117] address the question as to whether the test treatment would have shown superior efficacy compared to placebo, had placebo been included in the trial. The authors propose a network meta-analytic-predictive approach to assess the relative efficacy to placebo. While demonstrating a successful application of their proposed approach, the authors conclude that interpretation, evaluation and synthesis of non-inferiority trials remains challenging. Lin et al.[118] proposed a generalisation of the Schmidli et al. approach, using power priors to place weights on the active controls available and Dirichlet process priors to enable a more flexible modelling approach. The authors state that is it possible to conduct a comparative effectiveness analysis for all the active treatments included in the NMA, recognising that the assumption of consistency in the common comparator across all trials is necessary. Crucially, both Schmidli et al. and Lin et al. assume a common comparator in all of the active control (historical) and non-inferiority trials.

B.2.9.3.3. *Assessment of NMA feasibility*

Despite the evidence supporting the assumption of comparable effectiveness, the feasibility and appropriateness of conducting an NMA (or pairwise indirect comparisons) utilising the wider clinical evidence base identified in the SLR was assessed through a review of previously published NMAs in HIV (as described in Section B.2.9.3.1.1) and an assessment of NMA feasibility based on SLR evidence[111] (see Appendix D). Studies identified using the SLR described in Appendix D were assessed for feasibility of forming an NMA network, as well as

the appropriateness of the resulting network. Details of the assessment are given in Appendix D. A summary table is shown below (Table 46).

The most significant obstacle was considered to be the composition of the pooled ART arm, which varied between comparator studies. An NMA could be conducted (notwithstanding the limitations in interpretation) if the explicit assumption is made that ART regimens have similar efficacy at this point in the treatment pathway. Whilst this is likely to be the case (as described in Section B.2.9.3.1), this approach is unlikely to reduce uncertainty compared with the presented ITC.

Outside of the feasibility of undertaking an NMA, the appropriateness and relevance of undertaking an NMA for non-inferiority evidence studies was assessed, as described in Section B.2.9.3.2. **In summary, it is not clear that an NMA would provide additional support for decision making beyond the ITC for CAB LA + RPV LA Q2M versus current ART that is presented in Section B.2.9.1.**

Table 46. Feasibility of pairwise comparisons

Criteria for assessing appropriateness versus CAB LA + RPV LA Q2M	Emtricitabine/ tenofovir alafenamide plus dolutegravir (Descovy® plus Tivicay®)	Emtricitabine/ tenofovir alafenamide plus raltegravir (Descovy® plus Isentress®)	Abacavir/ dolutegravir/ lamivudine (Triumeq®)	Dolutegravir/ lamivudine (Dovato®)	Dolutegravir/ rilpivirine (Juluca®)	Bictegravir/ emtricitabine/ tenofovir alafenamide (Biktarvy®)	Doravirine/ lamivudine/ tenofovir disoproxil fumarate (Delstrigo®)	Darunavir/ cobicistat/ emtricitabine/ tenofovir alafenamide (Symtuza®)	Emtricitabine/ rilpivirine/ tenofovir alafenamide (Odefsey®)
Comparative evidence available?	No Appendix D Section B.7.2	No Appendix D Section B.7.2	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Connected comparator arms?	NA	NA	1 study* (STRIIVING)	1 study (TANGO)	2 studies (SWORD 1 and 2)	2 studies (GS-US-380-1844; GS-US-380-1878)	1 study (DRIVE-SHIFT)	1 study (EMERALD)	No Appendix D Section D.7.3.1
Similar treatments in comparator arms?	NA	NA	No, significant differences in pooled ART Appendix D D.7.3.1	No, significant differences in pooled ART Appendix D Section D.7.3.1	No, significant differences in pooled ART Appendix D Section D.7.3.1	No, significant differences in pooled ART Appendix D Section D.7.3.1	No, significant differences in pooled ART Appendix D Section D.7.3.1	No, significant differences in pooled ART Appendix D Section D.7.3.1	Not assessed
Similar treatment doses/schedule?	NA	NA	Unclear**	Unclear**	Unclear**	Unclear**	Unclear**	Unclear**	Not assessed
Similar outcomes/outcome definitions and study design?	NA	NA	No Appendix D Section D.7.3.3	Yes	Yes	Yes	No Appendix D Section D.7.3.3	Yes	Not assessed
Similar patient characteristics and baseline risk?	NA	NA	Not assessed	Unclear	Unclear	Unclear	Not assessed	Unclear	Not assessed
Similar observed treatment effects?	NA	NA	Not assessed	Yes	Yes	Yes	Not assessed	Yes	Not assessed

* Pairwise comparison for FLAIR versus GS-US-380-1844 considered less informative than direct comparison provided by FLAIR

** Studies using pooled ART typically allowed patients to continue their suppressive regimen. This is anticipated to reflect locally licensed dosing and scheduled. Hence, it can reasonably be suggested that treatment dosing and schedules are comparable between studies. However, it should be noted as a limitation for any pairwise comparison.

B.2.10. Adverse reactions

Key points[3, 66-68, 70, 80]

- CAB LA + RPV LA is well tolerated, consistent with other switch studies in adults with virally suppressed HIV.
- Injection site reactions (ISR) were the most frequently reported AEs but were mostly mild (in ATLAS-2M 98% were grade 1 or 2), rarely led to discontinuation (≤2% of participants in each arm in ATLAS-2M) and reduced over time.
- Acceptability of injections as measured by the PIN questionnaire (see Section B.2.6.1.12.5) was high: (in the Q2M group 81% and 68% of participants rated acceptance of local reactions and pain respectively as totally or very acceptable).

B.2.10.1. ATLAS-2M

CAB LA + RPV LA was generally well tolerated at both dosing frequencies. The proportion of participants reporting any AE or any drug-related AE was similar between the treatment groups. The overall summary of AEs in ATLAS-2M is shown in Table 47.

Table 47. Overall summary of adverse events - Maintenance Phase (Safety Population)

	Q2M (N=522) n (%)	Q1M (N=523) n (%)
Any AE	473 (91)	482 (92)
Drug-related AEs	400 (77)	399 (76)
Any Grade 2 to 5 AEs	272 (52)	287 (55)
Drug-related Grade 2 to 5 AEs	156 (30)	164 (31)
AEs leading to withdrawal	12 (2)	13 (2)
Drug-related AEs leading to withdrawal	8 (2)	11 (2)
Any SAE	27 (5)	19 (4)
Drug-related SAEs[a]	3 (<1)	1 (<1)
Fatal SAEs	1 (<1)	0
Drug-related fatal SAEs	0	0

a. Drug related SAEs were injection site abscess, presyncope, and acute pancreatitis in the Q2M group and hypersensitivity in the Q1M group.
Source: Source: ATLAS-2M CSR[70], Overton et al[66]

The frequency of individual common AEs (≥5%) was generally comparable between the treatment groups (Table 48), however, the Q1M group had slightly greater frequency of

injection site nodule, upper respiratory tract infection, pyrexia, cough, gastroenteritis, pharyngitis, and fatigue; only the treatment difference in the incidence of fatigue and injection site nodule was notable, with lower frequency in the Q2M group.

Most of the drug-related AEs were ISRs and the most frequently reported drug-related AE was injection site pain in both treatment groups. Drug-related AEs are shown in Table 49

Table 48. Summary of Common AEs (≥5% in either Treatment Group) – Maintenance Phase (Safety Population)

Preferred Term	Q2M (N=522) n (%)	Q1M (N=523) n (%)
Any event	473 (91)	482 (92)
Injection site pain	371 (71)	363 (69)
Nasopharyngitis	71 (14)	74 (14)
Injection site nodule	54 (10)	89 (17)
Upper respiratory tract infection	50 (10)	71 (14)
Injection site induration	41 (8)	39 (7)
Injection site discomfort	36 (7)	41 (8)
Pyrexia	28 (5)	44 (8)
Headache	35 (7)	36 (7)
Diarrhoea	33 (6)	37 (7)
Injection site swelling	32 (6)	27 (5)
Back pain	28 (5)	29 (6)
Injection site pruritus	27 (5)	25 (5)
Cough	17 (3)	29 (6)
Fatigue	13 (2)	25 (5)
Gastroenteritis	16 (3)	28 (5)
Pharyngitis	16 (3)	28 (5)
Source: ATLAS-2M CSR[70], Overton et al[66]		

Table 49. Summary of Common Drug related AEs (≥1%) in Either Treatment Group During the Maintenance Phase (Safety Population)

Preferred Term	Q2M (N=522) n (%)	Q1M (N=523) n (%)
Any drug-related event	[redacted]	[redacted]
Injection site pain	[redacted]	[redacted]
Injection site nodule	[redacted]	[redacted]
Injection site induration	[redacted]	[redacted]
Injection site discomfort	[redacted]	[redacted]
Injection site pruritus	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Injection site erythema	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Injection site bruising	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Chills	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Injection site warmth	[redacted]	[redacted]
Malaise	[redacted]	[redacted]
Body temperature increased	[redacted]	[redacted]
Injection site haematoma	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Pain	[redacted]	[redacted]
Influenza like illness	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]

Source: ATLAS-2M CSR[70]

Injection site reactions

Overall, injections with CAB LA + RPV LA were well tolerated. ISRs were reported frequently (Table 49) but were most commonly comprised of mild (Grade 1 or 2), short-lived, self-resolving pain due to IM administration. Few ISRs (Q2M 4%; Q1M 6%) lasted more than 14 days, and the median duration was 3 days[66, 70].

Two percent of ISRs for each treatment group were Grade 3 events. ISRs seldom led to discontinuation (Q2M, n=6 [1%]; Q1M, n=11 [2%]) and health outcomes data measured via the PIN questionnaire (see Section B.2.6.1.12.5) demonstrated consistent and high levels of acceptability of injections[66, 70].

Serious AEs and withdrawal

The incidences of SAEs and AEs leading to withdrawal were low and similar between treatment groups. Individual SAEs occurred with a frequency of <1% and there were no discernible patterns of SAE by preferred term. There was 1 fatal SAE, sepsis as a result of complications of acute pancreatitis, which occurred 98 days after the final injection and was not classed as drug-related[70].

Overall, the AEs reported were consistent with the established safety profiles of CAB LA and RPV LA. Events of injection site abscess (drug-related SAE in the Q2M group), pyrexia and body temperature increase (drug-related Grade 3 AEs in the Q2M group), fatigue (drug-related Grade 3 AE in the Q1M group), and transaminase increase (drug-related Grade 3 AE in the Q2M group); associated with possible drug-induced liver injury [DILI] during oral lead in were observed and are included in the labelling for CAB and RPV[70].

B.2.10.2. ATLAS and FLAIR

Overall, CAB LA + RPV LA was well tolerated in these studies[74]. AEs were reported more frequently for the switch arm (CAB LA + RPV LA) compared with the current ART arm; this is consistent with other switch studies in virologically suppressed HIV-1 participants. Injection site pain was the most frequently reported type of ISR; however, few participants (<1% in each group) had ISRs that led to withdrawal. Overall, 1% of participants in the Q2M group and 2% in the Q1M group withdrew from the study due to intolerability of the injections. Pooled results for non-ISR AEs are shown in Table 50 and ISR AEs in Table 51.

Table 50. ATLAS and FLAIR: Overall Summary of Non-Injection Site Reaction AEs During the maintenance phase (Pooled Safety Population)

Type of AE	CAB LA + RPV LA Q1M (n = 591)	Current ART (n = 591)
Any AE	510 (86)	445 (75)
Any Grade 3 to 5 AEs	47 (8)	35 (6)
AEs leading to withdrawal	17 (3)	9 (2)
Any serious AE	31 (5)	26 (4)
Fatal serious AEs	0	1 (<1)
Drug-related AEs	166 (28)	36 (6)
Any drug-related Grade 3 to 5 AEs	8 (1)	1 (<1)
Drug-related serious AEs	1 (<1)	1 (<1)
Drug-related fatal serious AEs	0	0

Abbreviations: AE, adverse event; ART, antiretroviral therapy; ATLAS, Antiretroviral Therapy as Long-Acting Suppression; CAB, cabotegravir; FLAIR, First Long-Acting Injectable Regimen; LA, long-acting; RPV, rilpivirine.

Note: Data are presented as n (%). Current ART refers to ABC/DTG/3TC in FLAIR.

Source: EPAR[74]

Table 51. ATLAS and FLAIR: Summary of Injection Site Reaction AEs During the maintenance phase (Safety Population)

	CAB LA + RPV LA Q1M (n = 591) N (%)
Number of participants with injections	581 (98)
Number of participants with ISR event	489 (84)
Any grade[a]	
Grade 1	437 (75)
Grade 2	211 (36)
Grade 3	22 (4)
AEs leading to withdrawal/drug withdrawn	6 (1)
Maximum duration	
1-7 days	291 (50)
8-14 days	95 (16)
>14 days	101 (17)
Not applicable	2 (<1)

Abbreviations: AE, adverse event; ATLAS, Antiretroviral Therapy as Long-Acting Suppression; CAB, cabotegravir; FLAIR, First Long-Acting Injectable Regimen; IM, intramuscular; LA, long-acting; Q1M, every 1 month; RPV, rilpivirine.

Note: With the exception of the last row, data are presented as n (%). The denominator for all percentages is based on the total number of events. Any injection site reaction reported more than once by the same participant was counted more than once.

[a] No serious, fatal or Grade 4 or 5 injection site reactions were reported.

Source: Source: EPAR[74]

B.2.11. Ongoing studies

An overview of relevant ongoing studies is provided in Table 52. There are additional planned and ongoing real-world studies, including post marketing authorisation commitments, that will not report within the next 12 months; details are available upon request.

Table 52. Ongoing studies

Study name	Study type	Study objective	Study population	Study report expected
LATITUDE[121] NCT03635788	Phase 3 RCT	To evaluate the efficacy, safety, and durability of LA ART with RPV and CAB LA versus current ART.	Persons living with HIV with a history of sub-optimal adherence.	Estimated primary completion date September 2022.
SOLAR[122]	Phase IIIb, randomised multicenter, active-controlled, non-inferiority, open-label study	To evaluate the efficacy, safety and tolerability of switching to CAB LA + RPV LA versus bictegravir/emtricitabine/tenofovir alafenamide Single Tablet Regimen.	Virally suppressed.	TBC
C2C: COMBINE-2 for Cabotegravir + Rilpivirine LA Regimen - A Prospective Cohort Study to Monitor Effectiveness, Adherence and Resistance	Prospective Cohort Study within NEAT ID sites	Description of population initiating CAB LA + RPV LA; and assessment of adherence, durability and discontinuation and clinical effectiveness; monitoring for resistance.	New users of the CAB LA + RPV LA regimen, inclusion criteria in line with marketing authorisation.	March 2027 (interim study results annually).
Drug Utilization, Adherence, Effectiveness and Resistance: A Prospective Observational Cohort Study in People living with HIV (PLWH) initiating ARV regimen CAB+RPV LA in Collaboration with EuroSIDA Category 1 Post Authorization Safety Study (PASS)	Prospective Observational Cohort Study nested within the EuroSIDA study	Description of usage patterns of CAB LA and/or RPV LA-containing regimens; and assessment of adherence, durability and discontinuation and clinical effectiveness; monitoring for resistance.	1. Treatment experienced PLWH over the age of 18 years 2. New users of CAB and/or RPV LA containing regimens	March 2027 (interim study results annually)

B.2.12. Innovation

CAB LA + RPV LA is the first and only long-acting maintenance treatment for HIV infection

CAB LA + RPV LA is a prolonged-release nanosuspension administered by intramuscular gluteal injection Q2M, following an oral lead-in and initiation injections. It is the first and only long-acting HIV treatment regimen and the first complete HIV treatment regimen to offer an alternative to life-long daily oral ART. It has been shown to be non-inferior to oral 3-drug ART in maintaining virologic suppression after 48 weeks of treatment, with a comparable safety profile [3, 80 69, 85].

- CAB LA + RPV LA is administered Q2M with a flexible dosing window of 7 days before and 7 days after the planned injection date.
- Provided individuals attend for scheduled injections Q2M, there is no longer a daily requirement to take oral ART. The individual remains virally suppressed without the need for further treatment until the next visit, with no possibility of suboptimal adherence during the two-month period and no evidence of their HIV treatment visible to others.

The desirability of long-acting ART is evidenced by the fact that several such products are in development by other manufacturers, and reflects a general trend towards long-acting medications across many therapy areas[123].

CAB LA + RPV LA is the first and only alternative to life-long daily ART

CAB LA + RPV LA provides people living with HIV with the first alternative to life-long daily oral ART. Life-long daily ART remains a significant challenge for people living with HIV, even with modern simplified treatment regimens. The evidence on the burden of current ART is presented in Section B.1.3.5.

While most people living with HIV are virally suppressed on daily oral ART this does not represent optimisation of their care given the issues that remain around stigma (leading to fear of disclosure if medication is discovered), treatment fatigue, the anxiety and inconvenience some individuals experience around daily scheduling of ART (including the need to schedule treatment around food intake and work and lifestyle commitments), and the effect on psychological wellbeing of the daily reminder of their HIV status. In addition, some people living with HIV have medical conditions making daily oral treatment difficult, and as the population living with HIV ages, high comorbidity rates and the associated polypharmacy compound the challenges. Thus, CAB LA + RPV LA addresses important unmet needs in the management of HIV and provides a choice of treatment modality.

CAB LA + RPV LA has the potential to prevent the adverse consequences of suboptimal long-term adherence to daily oral antiretroviral therapy

This range of challenges with life-long daily ART has an impact on adherence, with potential consequences for viral suppression, development of treatment resistance, and onward transmission. Estimates of suboptimal adherence in the UK range from 10% to 57%[49 50-52] (see Section B.1.3.5.3).

The BHIVA 2016 guidelines state that “Given the multiple adverse consequences of treatment failure (risk of disease progression, increase in complexity and costs of treatment, and risk of

HIV transmission) engaging people living with HIV in treatment decisions and the monitoring and support of adherence are of paramount importance[21]".

Giving individuals and their physicians the option to prescribe long-acting treatment in the form of CAB LA + RPV LA will remove the barriers to adherence associated with the burden of daily pill-taking. Adherence to the every-2-month injection visit schedule is required. It is anticipated that individuals will only be offered CAB LA + RPV LA by their physicians if they commit to visits Q2M and a multidisciplinary team considers they are likely to fulfil this commitment. Individuals who do not keep to the visit schedule will be reassessed for suitability, as stipulated in the SmPC[1].

Facilitating optimal adherence increases the likelihood that people living with HIV will remain virally suppressed and reduces the potential for HIV-related morbidity, HIV transmission and the emergence of drug resistance. Any reduction in transmission has important benefits for public health, both reducing harm and saving the costs associated with treating new infections.

CAB LA + RPV LA offers people living with HIV and physicians the choice of a completely different treatment modality, with increased patient satisfaction

Current BHIVA guidelines recommend that people living with HIV should be given the opportunity to be involved in making decisions about their treatment [21].

Satisfaction with treatment is a critical component in maintaining high levels of adherence to treatment, and is particularly important from a patient wellbeing perspective when treatment must be taken for life. In the case of HIV there is also the public health imperative of ensuring that people living with HIV remain both on treatment and virally suppressed, in order to prevent transmission. Satisfaction with treatment is positively associated with better adherence to ART[124, 125]. Providing individuals with treatment options that address their treatment preferences and promote adherence may help England and Wales to continue meeting the UNAIDS 95-95-95 (a fast track strategy to end the AIDS epidemic by 2030) target[126] over the long term.

Participants in ATLAS-2M reported very high levels of satisfaction with CAB LA + RPV LA (see Section B.2.6.1.12). Evidence from two surveys suggests that many people living with HIV believe that a long-acting ART would address some of the challenges they face with daily oral ART:

- Participants in an international survey of people living with HIV (the Positive Perspectives study, N = 1,111) ranked longer-lasting treatment with less frequent dosing among their most important priorities for therapy improvements, second only to long-term safety concerns[127].
- In the CAB LA + RPV LA EU Unmet Need study,[128] people living with HIV in the UK indicated that such a regimen would lessen the emotional and psychological burden of treatment: 88% of 143 UK respondents who had hidden their pills said the regimen would help with their confidentiality concerns and 93% said it would help with the stress and anxiety related to confidentiality concerns. Among those reporting a negative impact of HIV treatment on emotional wellbeing (107 of 196), 82% said it would help reduce emotional burden/treatment fatigue[26].

- In the same study, out of 107 people living with HIV in the UK who reported suboptimal adherence in the previous month, 81% thought that a regimen with the characteristics of CAB LA + RPV LA would improve their current level of treatment adherence [26].

Two other innovative aspects are noteworthy:

- CAB LA + RPV LA is a directly observed therapy administered by a healthcare professional, providing HIV care teams with certainty about their patients' adherence and protection. In addition, this increased opportunity for contact and screening may be beneficial as people living with HIV are more at risk of developing other diseases. Bridging therapy using CAB and RPV tablets can be prescribed for individuals who plan to miss a scheduled injection visit or who miss an appointment, providing additional flexibility[1].
- CAB LA + RPV LA is a NRTI-sparing regimen, offering the choice of a regime that avoids well-recognised NRTI-related toxicities as well as NRTI-class-related resistance.

CAB LA + RPV LA is a step-change in the treatment of HIV

CAB LA + RPV LA represents a step-change in the treatment of HIV for those individuals who would benefit from an alternative to life-long daily oral ART. It is expected to provide substantial benefits over and above those captured in the QALY calculation, including effects on wellbeing that are not captured by generic preference-based utility measures. Second generation INSTIs (such as cabotegravir) continue the innovation that protease inhibitors introduced by rarely being associated with the development of resistance, but go further by having few drug-drug and drug-food interactions. These are likely to be characteristics of new antiretrovirals in the future. Making long-acting ART available to people living with HIV in England and Wales will enable clinicians to prescribe an effective alternative for people living with HIV for whom daily oral ART is suboptimal. CAB LA + RPV LA is potentially life-changing for selected individuals, offering them choice and empowerment in the management of this life-long condition.

B.2.13. Interpretation of clinical effectiveness and safety evidence

As with all approved ART products, the efficacy evidence for CAB LA + RPV LA is predicated on non-inferiority; non-inferiority design is now the norm in trials of ART and is accepted by the EMA and the FDA. It is increasingly implausible and unnecessary to demonstrate superiority versus the highly efficacious standard of care treatments. The historical measure of efficacy in HIV trials is maintenance of viral suppression, and the relative success of most treatments in achieving this endpoint creates a ceiling effect where newer drugs can hardly better those already achieving success rates of ≥90%. Newer treatments, instead, offer benefits in terms of safety, tolerability, convenience and other clinical advantages that can improve the treatment experience for people living with HIV. An important and understated goal of modern therapy is to help people *live well* with HIV.

Furthermore, the non-inferiority evidence base for virological efficacy is the foundation of the clinical commissioning of HIV treatments in the NHS today, and is the evidence base upon

which this submission and its comparisons rest. The trials underpinning the submission have been designed (powering and sample size, definition of non-inferiority margin), and analysed (significance testing, handling of missing information) in line with the requirements of the regulatory authorities.

Long-acting ART represents a paradigm shift in the treatment of HIV for those individuals who desire and would benefit from it. CAB LA + RPV LA was initially developed as a once-monthly injection. Once its non-inferiority to standard ART was established, the decision was made to explore the efficacy of a Q2M formulation in the ATLAS-2M study, to improve convenience for people living with HIV and healthcare providers. ATLAS-2M showed that the virological efficacy of Q2M administration is non-inferior to Q1M. The clinical evidence base thus confirms that CAB LA + RPV LA Q2M is effective, well tolerated and associated with a high degree of patient satisfaction.

B.2.13.1. Principal findings from the clinical evidence

CAB LA + RPV LA Q2M is non-inferior to current daily oral ART in maintaining virologic suppression

The efficacy of CAB LA + RPV LA Q2M was demonstrated in the ATLAS-2M trial (Section B.2.6.1). It showed high efficacy throughout the trial and was non-inferior to Q1M CAB LA + RPV LA in maintaining virologic suppression at Week 48. Few participants (<2%) had plasma HIV-1 RNA ≥50 copies/mL at this time point (per the Snapshot Algorithm) in either group (ITT-E population). The upper bound of 95% CI for the adjusted treatment difference between Q2M and Q1M was 2.2%, which was less than the pre-defined non-inferiority margin of 4%. Results for the PP population were similar to those for the ITT-E population.

Non-inferiority of the Q1M regimen to daily oral ART was shown in the ATLAS and FLAIR trials (Section B.2.6.2), and non-inferiority of the Q2M dosing to oral ART was demonstrated via an indirect treatment comparison (see Section B.2.9). In its appraisal the EMA confirms that “the SAG [scientific advisory group] experts were confident that both regimens could be equally considered for the management of HIV based on the clinical demonstration available.”[74]

As noted above, the evidence base for all approved ART products is predicated on non-inferiority of maintenance of virologic suppression, which is now the norm in trials of ART and is accepted by the EMA and the FDA. The non-inferiority margin of the individual studies (6%) and of the pooled studies (4%, pooling enabling a more reliable efficacy estimate) were agreed by the EMA[74] and FDA and are in concordance with the current FDA Guidance for Industry[23].

Integrase inhibitors have set high standards of efficacy in ART and are recommended as preferred treatments in international HIV treatment guidelines. A large proportion of current ART in the UK is based on these agents. CAB LA + RPV LA Q2M maintains these standards, showing efficacy in ATLAS-2M similar to that observed in other recent integrase inhibitor switch studies in virologically suppressed individuals, such as the SWORD-1 and SWORD-2 studies of dolutegravir/rilpivirine vs current ART[129]; study NCT02603120 of switching to bictegravir, emtricitabine and tenofovir alafenamide from dolutegravir, abacavir and lamivudine[130]; and study NCT02603107 of switching from therapy based on a boosted protease inhibitor to bictegravir, emtricitabine and tenofovir alafenamide[131].

Long-term follow-up from the ATLAS[108] and FLAIR[105] studies shows that high efficacy and treatment satisfaction are maintained over time (Section B.2.6.2.8).

Taken together, with the ITC performed, the clinical evidence demonstrates that switching to the CAB LA + RPV LA Q2M injectable regimen is effective in maintaining viral suppression and is non-inferior to current daily oral ART.

CAB LA + RPV LA is well tolerated

CAB LA + RPV LA was well tolerated. Although injection site reactions (ISRs) were reported frequently, the great majority were mild (Grade 1 or 2), short-lived and self-limiting. Few ISRs (4% with the Q2M regimen in ATLAS-2M) lasted more than 14 days, and the median duration in the trial was 3 days. Only 2% of ISRs for each treatment group were Grade 3 events, and ISRs seldom led to discontinuation (Q2M, n=6 [1%]; Q1M, n=11 [2%]).

Importantly, health outcomes data demonstrated consistent and high levels of acceptability of injections. Rates of acceptance of injection in ATLAS-2M, including ISRs, were high at baseline (as measured by the Perception of Injection questionnaire) and improved over time. Together with the strong preference expressed for CAB LA + RPV LA over daily oral ART and the high levels of treatment satisfaction (see below), this strongly suggests that participants did not consider ISRs to be a significant issue in their experience of treatment.

CAB LA + RPV LA is associated with improved HRQoL and treatment satisfaction

Participants in ATLAS-2M reported very high levels of satisfaction with CAB LA + RPV LA at Week 48, both for Q1M and Q2M dosing. For participants with prior CAB + RPV (oral + intramuscular) exposure, baseline treatment satisfaction (i.e. satisfaction with Q1M dosing) was approximately 62 out of a possible 66 points on the HIVTSQs) and remained high throughout the study for both dosing groups. Participants without prior exposure to CAB + RPV showed a significant increase from baseline in treatment satisfaction across all timepoints, significantly favouring the Q2M group [70].

There was a strong preference for CAB LA + RPV LA compared with daily oral treatment with the same regimen. Of participants who had experienced treatment with all three modalities (Q2M injections, Q1M injections and daily oral) and had a preference response (191 of 195 participants), 94% selected Q2M CAB LA + RPV LA as their preferred option, with only 2% selecting daily oral treatment. The most common reasons for their preference were mode and frequency of administration, and convenience [70].

HRQoL for people living with HIV treated with CAB LA + RPV LA Q1M compared with daily oral ART was measured in the ATLAS [3] and FLAIR [80] studies using the SF-12 instrument. In both studies, participants receiving the long-acting treatment had a positive (i.e. favourable) difference in point estimates for mean change from baseline in mental component summary score (MCS) at 48 weeks (adjusted mean difference 0.676 [95% CI -0.56, 1.91] and 1.103 [-0.248, 2.453] for ATLAS and FLAIR, respectively); however, these differences did not reach statistical significance. In a post-hoc analysis to further explore HRQoL, SF-12 values were used to derive SF-6D utility values (see Section B.2.6.2.7 and Appendix N). Statistically significant differences in SF-6D scores favouring CAB LA + RPV LA were observed at Week

24 and Week 48, showing a utility advantage of [redacted] points for CAB LA + RPV LA vs daily oral treatment with current ART[71].

B.2.13.2. Strengths and limitations of the clinical evidence base

B.2.13.2.1. *Limitations of the clinical evidence*

The principal limitation of the evidence base is the absence of a direct trial-based comparison between CAB LA + RPV LA Q2M and standard oral ART. This has been addressed via an indirect treatment comparison, using the CAB LA + RPV LA Q1M arm that is common to the ATLAS, FLAIR and ATLAS-2M trials to indirectly estimate the comparative effectiveness of CAB LA + RPV LA Q2M vs current ART.

A further limitation is that the regimens that constituted standard of care ART at the time of recruitment into ATLAS and FLAIR are not fully representative of current ART regimens, as prescribing patterns have changed and additional regimens have been introduced. However, as noted earlier in this section, the efficacy seen with CAB LA + RPV LA Q2M is similar to that seen in other recent integrase inhibitor switch studies in virologically suppressed individuals (see Section B.2.9.1).

B.2.13.2.2. *Strengths of the clinical evidence*

The efficacy and tolerability of CAB LA + RPV LA are supported by an extensive evidence base (three phase 3 trials and a phase 2 programme) in a diverse range of participants. A recruitment goal of ATLAS-2M was to enrol at least 25% women, who are typically underrepresented in HIV-1 clinical studies, and to provide sufficient data to determine whether sex is correlated with treatment response. This recruitment goal was achieved, with 26.8% of participants being female. Older people living with HIV (≥50 years of age) were also well represented, accounting for 27% of participants. The study also included a wide range of body types based on BMI, ranging from underweight to obese. The diverse demographics and baseline characteristics, including a broad range of prior HIV treatments and participants from 13 countries, broadens the applicability of the data across HIV treatment-experienced individuals.

The evidence base was further strengthened by post hoc multivariable analyses (across ATLAS, FLAIR and ATLAS-2M) that were undertaken to explore the baseline factors that were associated with early virologic failure in the small proportion (1.25%) of trial participants who experienced confirmed virologic failure with CAB LA + RPV LA in these studies. These analyses indicate that a combination of at least two of the following baseline factors may be associated with an increased risk of virological failure: archived RPV resistance mutations, HIV-1 subtype A6/A1, or BMI >30 kg/m^2 [1]. This enabled the following information to be added to the SmPC to aid patient selection: “In patients with an incomplete or uncertain treatment history without pre-treatment resistance analyses, caution is warranted in the presence of either BMI >30 kg/m^2 or HIV-1 A6/A1 subtype”[1].

B.2.13.3. Relevance of the evidence base to the decision problem

The endpoints covered in the evidence base (virologic failure, viral suppression, CD4+ cell count, safety and tolerability and patient-reported outcomes) are highly relevant to the decision problem. Viral suppression is the fundamental measure of treatment efficacy in ART, and maintenance of this is the primary consideration when switching ART in virally suppressed people living with HIV to ensure there is no impact on virologic efficacy[21]. In chronic conditions requiring life-long treatment, safety, tolerability and acceptability of treatment are all key outcomes, and are comprehensively addressed by the clinical evidence.

The evidence base does not deal specifically with the comparators used in the decision problem, because of the large number of different ART regimens available across the countries participating in ATLAS and FLAIR, and the introduction of new regimens since recruitment into the trials took place. However, the efficacy of the basket of comparators used in the economic modelling can be considered not different to the pooled efficacy of the range of therapies that made up 'current ART' in ATLAS and FLAIR. Clinical experts consider that efficacy in terms of maintenance of viral suppression is comparable between therapies. This is supported by several subsequent non-inferiority trials, which compare newer agents with older ones and conclude they are no less efficacious. The regimens used as comparators in the economic analysis were chosen on the basis that they represent ART regimens currently in use in the NHS in the switch setting. Some of these were among the regimens used in ATLAS and FLAIR, whereas others have been launched since.

As previously noted, the evidence base is predicated on non-inferiority trials. This is the norm in modern trials of ART in HIV and is accepted by the EMA and the FDA. The design of the clinical studies was discussed with regulators in both jurisdictions.

B.2.13.4. External validity of study results to patients in routine clinical practice

The ATLAS-2M study had a diverse study population, including a wide age range (median 42 years, 73% aged ≥35 years), good representation of women (26.8% of participants were of female sex at birth), a wide range of BMI (from underweight to obese) and approximately 18% of black or African American race. Approximately 61% had homosexual contact as an HIV risk factor and 36% cited heterosexual contact. Injection drug use was cited by 3-4%. This diverse study population has a somewhat higher representation of male homosexual acquisition than the population of people living with HIV in clinical practice in England: in 2018, an estimated 47.6% were gay and bisexual men, 47.6% had heterosexual acquisition and 1.9% had exposure through injecting drugs[17]. This difference in proportion is not considered to affect generalisability. Overall, the patient population of this diverse study is such that the results are considered to be generalisable to individuals in routine practice in England and Wales.

ATLAS-2M was conducted in people living with HIV who were virally suppressed on daily oral ART or CAB LA + RPV LA Q1M. This corresponds to the licensed indication (individuals must be virally suppressed) and also to the great majority of diagnosed individuals in the UK, of whom 98% are receiving treatment and 97% of those receiving treatment are virally suppressed[16]. However, treatment switching in virally suppressed individuals is common, and some people living with HIV will benefit from switching to a long-acting treatment, as discussed in Section B.1.3.5.

As discussed above, the regimens that constituted standard of care ART at the time of recruitment into ATLAS and FLAIR are not fully representative of current ART regimens used in England and Wales. This is to be expected given the wide range of regimens and formulations that are available, differences in commissioning priorities between countries, and the introduction of new regimens/formulations leading to changes in market share over time. However, the regimens used as comparators in ATLAS and FLAIR are considered to have comparable efficacy to currently used regimens, given that non-inferiority trials are the norm for ART in HIV.

In summary, the results of the phase 3 clinical studies of CAB LA + RPV LA are considered to be valid for individuals in routine clinical practice in England and Wales, with no major concerns identified regarding generalisability.

B.3 Cost effectiveness

Base case analysis

- Results of the cost-effectiveness analysis show that switching from daily oral ART to long-acting injectable treatment with CAB LA + RPV LA Q2M is cost-effective in the UK, based on the proposed PAS cost of CAB LA + RPV LA.

Sensitivity analysis

- Sensitivity analysis on the deterministic results conclude that results are robust to the structural assumptions and variations in input parameters.

B.3.1. Published cost-effectiveness studies

In line with the NICE Guide to the methods of technology appraisal 2013,[132] an SLR was conducted to identify cost-effectiveness studies for the treatment of HIV infection. In brief, electronic database searches (MEDLINE, Embase, the Cochrane library and EconLit) were conducted on 24 April 2020. Publications describing economic evaluations of interventions aimed at managing people living with HIV were considered to inform the conceptualisation of the economic model. Full details of the process and methods to identify and select the relevant cost-effectiveness evidence are summarised in Appendix G. A total of 92 studies were identified (see Appendix G), of which 9 were in the UK setting (across 10 publications). Results of the UK studies are summarised in Table 53. Cost-effectiveness modelling has not been routinely carried out for HIV therapies commissioned for use in England, as they have not previously fallen within the remit of NICE.

Table 53 Summary list of published cost-effectiveness studies

Study	Year	Model Structure	Patient population	Intervention (intervention, comparator)	QALY (intervention, comparator)	LY (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY/LY gained)
Published economic evaluations with UK NHS perspective: full publications								
Simpson et al.[133]	2012	Markov	TN	ATV/r, LPV/r	Incremental: 0.031	NR	Incremental: £3,558	£149,270/QALY
			TE		Incremental: 0.31		Incremental: £1,445	LPV/r dominant
Wilkins et al.[134]	2016	Markov	TN	TDF/FTC+EFV, ABC/3TC+EFV, TDF/FTC+ATV/r, ABC/3TC+ATV/r	6.30, 5.02, 6.45, 5.26	6.77, 5.39, 6.93, 5.66	£112,579, £82,560, £125,010, £96,570	£21,806/LY £22,446/QALY £23,355/LY £23,785/QALY
Published economic evaluations with UK public finance perspective: full publications								
Miners et al.[135]	2001	Markov	TN	Dual NRTI, HAART	11.7, 9.3	14.5, 11.6	£119,190, £77,135	£17,698/QALY
Trueman et al.[136]	2000	Markov	HIV	ZDV+3TC+ABC, ZDV+3TC	8.6, 7.7	10.8, 9.6	£87,965, £78,161	£8,419/LY £10,254/QALY
Published economic evaluations with UK NHS perspective: abstract only								
Girod et al.[137]	2012	Markov	TN	RPV+BR, EFV+BR	13.650 13.582	NR	£214,869 £217,860	- RPV dominates
Simpson et al.[138]	2012b	Markov	TN (WOCBA)	ATV+RTV, LPV/r	Incremental: 0.2 days	NR	Incremental: £3,003	NR
Published economic evaluations with Scottish perspective: abstract only								
Leen et al.[139]	2009	Markov	TN	ATV/r, LPV/r	Incremental: 0.24	Incremental: 0.14	Incremental: £17,633	91% cost effective at £20,000/QALY
Published economic evaluations with multiple perspectives including UK: full publications								
Moereman et al.[140]	2010a	Markov	TE (UK)	DRV/r+OBR LPV/r+OBR	10.396, 9.846	11.232 10.718	€251,210, €243,088	€15,825/LY €14,778/QALY
Moereman et al.[141]	2010b	Markov	TE (UK)	DRV/r, PI(s)	8.317, 7.226	9.253, 8.193	€244,328, €226,395	€16,908/LY €16,438/QALY
Simpson et al.[142]	2007	Markov	TE (UK)	ATV/r, LPV/r (tablets/capsules)	Incremental: 4.6 months	NR	5/10-year savings: Tablets: £3,000, £2,867 Capsules: £2,311 £3,000	- Tablets: €11,094/QALY

3TC: lamivudine; ABC: abacavir; ATV: atazanavir; ATV/r: atazanavir/ritonavir; AZT: zidovudine; BR: background regimen; d4T: stavudine; DRV: darunavir; DRV/r: darunavir/ritonavir; EFV: efavirenz; FTC: emtricitabine; LPV: lopinavir; LPV/r: lopinavir/ritonavir; NR: not reported; NRTI: nucleoside reverse-transcriptase inhibitor; OBR: optimised background regimen; PI: protease inhibitor; QALY: quality-adjusted life year; RTV: ritonavir; TDF: tenofovir disoproxil fumarate; TE: treatment experienced; TN: treatment naïve; WOCBA: women of childbearing age

B.3.2. Economic analysis

The economic case presented in this submission is based on conventional cost-utility analysis, assessing the use of CAB LA + RPV LA versus a pooled basket of 9 comparators for the treatment of adults living with HIV. The model is a deterministic hybrid Markov state-transition model, rather than a microsimulation model. Clinical inputs were informed by the ITC described in Section B.2.9. Key assumptions were validated with UK clinical experts specialising in HIV. The methods related to the economic methodology were based on the most recent NICE reference case.

The following principles underpinned the model development:

- Modelling of health states reflecting differences in patient health outcomes or costs
- Building in options for scenario analysis, in the context of known uncertainty
- Assessment of all clinical benefits relevant to the NHS, physicians and people with HIV
- Availability of evidence.

The ATLAS and FLAIR studies established that the clinical effectiveness of CAB LA + RPV LA Q1M in terms of maintaining virological suppression is *not inferior* to that of current ART, and the Q2M formulation was confirmed as not inferior to current ART via an ITC (see Section B.2.9.2). For the purposes of modelling, *not inferior* is interpreted as comparable (i.e. the ART regimens are as effective as one another in maintaining virological suppression). The non-inferiority evidence base is not in itself considered a limitation; indeed, non-inferiority study design is the norm in modern trials of ART in HIV. It is also well understood that non-inferiority studies are not equivalence studies, having different hypotheses, analyses and interpretations.

However, clinicians consulted for the submission confirm that for the purposes of clinical decision-making, all modern approved ART regimens are assumed to have equivalent efficacy (within the eligible populations stipulated in their marketing authorisations), and this approach has been carried through into the economic modelling. Because the pivotal studies for both CAB LA + RPV LA and the comparators were powered to demonstrate non-inferiority in viral suppression, any differences in point estimates within the non-inferiority margins for the primary (% of participants with plasma HIV-1 RNA ≥50 copies/mL) or key secondary endpoints (% of participants with plasma HIV-1 RNA <50 copies/mL) do not imply statistically significant differences in efficacy (as the trial design does not allow for this), and are not considered to be clinically relevant. Consistent with the above interpretation, no differences in primary (% of individuals with plasma HIV-1 RNA ≥50 copies/mL) or key secondary endpoints (% of individuals with plasma HIV-1 RNA <50 copies/mL) are assumed between treatment arms in the model.

Structurally, a deterministic Markov cohort model was considered preferable to a microsimulation as it can be run with a single set of mean input values, dramatically reducing run times compared with a microsimulation, and allowing for more robust scenario and sensitivity analyses.

People living with HIV are at risk of experiencing treatment failure, resulting in discontinuation of their current regimen. Treatment failure can occur for either virologic reasons (failure to achieve HIV RNA level <50 copies/mL or viral rebound to HIV RNA ≥50 copies/mL after

virologic suppression) or non-virologic reasons (adverse events [AEs] or other non-virologic reasons for discontinuation). To capture this complexity, a traditional Markov process was combined with a decision tree process, which manages treatment allocation and aggregates results across treatment lines. An internal decision process (the decision-making code of the model, which determines how individuals move through the health states) is also employed to distinguish between individuals switching for virologic versus non-virologic reasons.

The model also contains separate adherence and transmission modules, as these are both important aspects for consideration when evaluating HIV treatments. Life-long adherence to daily oral ART is challenging, as discussed in Section B.1.3.5.3. The nature of administration of CAB LA + RPV LA (i.e. long-acting injections administered Q2M by a healthcare professional) removes the requirement to adhere to daily oral therapy and the associated risk of suboptimal adherence over the long term. CAB LA + RPV LA is administered by HCPs (directly-observed therapy), providing them with certainty about their patients' adherence and protection provided that individuals attend within the dosing window (see Section B.1.3.5 for details). The literature indicates that suboptimal adherence to daily oral ART is common, and is associated with reductions in viral suppression[53, 55-57].

An example of the extent to which suboptimal adherence to daily oral ART can affect treatment efficacy can be seen in the long-term (96-week) results from a recent phase 3 trial of two daily oral regimens (bictegravir combined with emtricitabine and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine) which analysed treatment differences in proportion of individuals with viral suppression (HIV-1 RNA <50 copies/mL) by cumulative adherence (<95% vs ≥95%) and found adherence had a statistically significant interaction (P=0.029) with suppression[58]. Even in a trial setting, a considerable proportion of individuals had suboptimal adherence, and this was associated with lower suppression rates.

Table 54 differences in HIV-1 RNA <50 copies/mL at week 96 by subgroup

	Bictegravir, emtricitabine, and tenofovir alafenamide (n=314)	**Dolutegravir, abacavir, and lamivudine (n=315)**	**Test for interaction P-Value**
Study drug adherence (%)			0.029
<95	71/96 (74.0%)	103/120 (85.8%)	
≥95	205/216 (94.9%)	180/195 (92.3%)	

Source: Wohl et al. 2019, supplementary appendix[58]

Reduced viral suppression will in turn increase the risk of onward transmission[21]. To capture the potential benefits in terms of reduced transmission that may derive from avoidance of suboptimal adherence through use of long-acting therapy, an onward transmission component is also incorporated into the model. This attempts to capture the reduced cost and higher HRQoL resulting from new HIV infections avoided due to reduced onward transmission from the modelled cohort.

Finally, the model also incorporates a utility benefit for long-acting treatment, based on data from the ATLAS and FLAIR studies (see Section B.3.4.3). Lifetime daily oral ART exerts a burden for a number of reasons, including the effects of HIV-related stigma (fear of unwanted

disclosure of HIV status, the daily reminder of HIV status), and the anxiety and inconvenience around daily scheduling of ART around food intake, work and lifestyle commitments (see Section B.1.3.5 for full discussion of treatment burden).

B.3.2.1. Description of analyses

The analyses presented within this submission are informed by the ATLAS-2M trial[70] (which established non-inferiority of CAB LA + RPV LA Q2M to Q1M administration) and an indirect treatment comparison showing non-inferiority of Q2M dosing to current daily oral ART based on pooled results from the ATLAS and FLAIR trials (Section B.2.2.2). In addition, pooled data from the ATLAS and FLAIR trials provide evidence of a difference in utility between the injectable and daily oral treatments at 24 and 48 weeks. In the analyses, CAB LA + RPV LA Q2M is compared with a pooled basket of 9 comparator regimens.

In the context of HIV and the innovation associated with a long-acting injectable, it is essential that any cost-effectiveness analyses reflect the full value to people living with HIV and the NHS of offering an alternative to life-long daily oral therapy. In order to do this, the model incorporates three key concepts, namely no difference in clinical efficacy between treatments; a utility benefit for long-acting treatment vs daily oral ART; and improved adherence to long-acting versus vs daily oral ART, which in turn is assumed to lead to a reduction in onward transmission:

- Virological efficacy (achievement of HIV-1 RNA <50 copies/mL) is assumed to be not different between intervention and comparator arms in each treatment line (Section B.3.3.2.1). This is consistent with the conclusions of the ITC and the non-inferiority trials that underpin it, described in Section B.2.9, and with the opinion of clinical experts consulted for the submission. The justification for this assumption is discussed further in Section B.2.9.3.

- Life-long daily oral ART exerts a burden for a variety of reasons, including stigma-related issues, such as a fear of unwanted disclosure of HIV status, and the daily reminder of HIV status. As such, a utility advantage is applied to long-acting treatment with CAB LA + RPV LA compared with daily oral ART; this is derived from the trial HRQoL data, as discussed in Section B.3.4.

- As a directly observed therapy administered Q2M, CAB LA + RPV LA is expected to improve treatment adherence relative to self-administered daily oral ART over the long term. Suboptimal adherence to daily oral ART in clinical practice is common and is associated with reduced viral suppression[53-58], leading to an increased likelihood of viral rebound and of developing resistance to ART[21]. To model the potential adherence-related benefit associated with CAB LA + RPV LA, adjustments are made to reduce the probability of viral suppression and increase the probability of viral rebound as treatment adherence reduces. Improved adherence is associated with improved likelihood of viral suppression with effective treatments.

- HIV cannot be sexually transmitted by persons with an undetectable viral load (defined as HIV-1 RNA <50 copies/mL)[14, 15]. Improving the proportion of individuals who achieve and maintain viral suppression has the potential to reduce the risk of onward

transmission of HIV, and this is captured in an onward transmission module (see Section B.3.2.5.1.2).

All analyses have been conducted in line with the reference case as presented in the NICE Methods Guide 2013.[132] Model parameters are set such that they are most relevant to a UK population and can facilitate decision making by NICE.

B.3.2.2. Intervention technology and comparators

The intervention arm comprises CAB LA + RPV LA, administered as intramuscular injections Q2M, following a 30-day oral lead-in period and initiation injections.

A virologically suppressed population switching for non-virological reasons – current status quo

Of the 98% of persons diagnosed with HIV and on ART attending a consultation with their HCP, it is estimated that approximately [redacted] require a treatment switch. The BHIVA guidelines[21, 29] state that clinical reasons for considering switching include managing toxicity or intolerance, participants' desire for a reduced pill burden, management of drug-drug interactions, and individual preference (see Section B.1.3.4.3). The switch could be to a completely new regimen, a change of backbone or a change of third agent. The decision is led by the individual needs of that person after a thorough review and discussion with the HCP and in some cases with a multi-disciplinary team (MDT).

Commissioning of ART is led by Best Practice in HIV Prescribing[34], an NHS England Policy which sets out the Clinical Reference Group's principles for providing clinical advice to NHS England on HIV prescribing, including the role of the MDT. The Policy sets out a series of principles on:

- Providing timely access to ART
- Informed treatment choice, shared decision-making and the importance of life-long adherence
- Supporting opportunities for cost-savings where generic alternatives are clinically appropriate for use

Previously, the purchase price of ART has been subject to renewal negotiation (through a tendering process). Further, there is variation in the purchase price for ART across the regions of England; regional tenders typically drive regional prescribing guidelines which are often based on cost banding structures (also shared at the initial Scoping Meeting in August 2020). Typically, oral antiretrovirals are considered similar in their ability to maintain virological suppression and where clinically appropriate for the individual, the lowest cost regimen would be utilised.

The types of ART people living with HIV are switching to can be accessed from market data and this is presented in Table 56. The ART switched to by line of therapy is not available. Rows shaded in blue are regimens identified as the most relevant comparators for CAB LA + RPV LA.

Table 55. Switch share by regimen (Market overview for patients switching off stable regimens)

Brand Name	Generic name	Of those survey % by regimen
Biktarvy	BIC/FTC/TAF	[redacted]
Symtuza	DRV/Cobi/FTC/TAF	[redacted]
Dovato or Tivicay + Epivir	DTG/3TC or DTG+3TC	[redacted]
Delstrigo	DOR/3TC/TDF	[redacted]
Triumeq	DTG/ABC/3TC	[redacted]
Odefsey	RPV/FTC/TAF	[redacted]
Truvada+Tivicay	FTC/TDF+DTG	[redacted]
Descovy+Tivicay	FTC/TAF+DTG	[redacted]
Desovy+Isentress	FTC/TAF+RAL	[redacted]
Stribild	EVG/c/FTC/TDF	[redacted]
Juluca* or Tivicay + Rilpivirine	DTG/RPV or DTG+RPV	[redacted]
Eviplera	RPV/FTC/TDF	[redacted]
Genvoya	EVG/c/FTC/TAF	[redacted]
Truvada+Isentress	FTC/TDF+RAL	[redacted]
Descovy+DRV/r	FTC/TAF+DRV/r	[redacted]
Truvada+DRV/r	FTC/TDF+DRV/r	[redacted]
Tivicay + Other	DTG+other	[redacted]

*Not identified as a clinically relevant comparator through market data; clinical consensus suggested inclusion as a comparator was important; Juluca is viewed as the most clinically aligned oral version of CAB LA + RPV LA.

Source: ActOne Lime Data (09/12/2020)

Choice of appropriate clinical comparator for CAB LA + RPV LA

A switch to CAB LA + RPV LA can address important additional needs above and beyond those addressed by current switch regimens, as described in Section B.1.3.6. These include the social and emotional burden (i.e., fear of disclosure, daily reminder of HIV status, organisational burden of treatment with regard to work, travel and daily life, anxiety over maintaining adherence and pill fatigue), as well as medical barriers to oral treatment.

Even though alternative oral treatment options exist for individuals who switch for non-virological reasons, arguably these cannot satisfy the true unmet need of some people living with HIV for a non-daily, non-oral treatment that has a smaller impact (for all the reasons outlined above).

The clinically relevant comparators to CAB LA + RPV LA were based on a review of the market switch data (as shown in Table 56). We reviewed the list of ART regimens most commonly switched to and chose an arbitrary cut-off of 2.5% (of those surveyed by percentage regimen) as an initial inclusion parameter. We then sought feedback from clinical experts on this list of regimens relative to the decision problem for CAB LA + RPV LA.

- Truvada (TDF/FTC) +Tivicay was excluded. This regimen represents one of the lower cost regimens within the regional bandings and as such would likely have been used early on in treatment to achieve viral suppression. Persons living with HIV would likely be switching away from this regimen for known toxicity reasons associated with Truvada, many to the single tablet regimen, Biktarvy.

- Excluded regimens (<2.5%) were considered less relevant because they are less commonly used in current practice in a suppressed switch setting and/or were one of the lower cost regimens within the regional bandings and as such would likely have been used early on in treatment to achieve viral suppression.

One exception to this, as a result of clinician feedback, was the decision to include Juluca as a relevant comparator (despite <2.5%). Juluca is a 2-drug regimen of dolutegravir and rilpivirine, and was identified as clinically relevant for this appraisal because it is deemed a 'close' oral alternative to CAB LA + RPV LA.

All nine regimens are viewed as comparable in terms of their ability to maintain virological suppression. Each may offer different benefits depending on individual need based on personal preference, lifestyle, underlying health risks and co-morbidities.

Whilst we have sought strong alignment on the likely oral ART regimens that would be considered at this stage for a non-virological treatment switch in the absence of CAB LA + RPV LA, we are unable to access estimated market shares across these nine comparators that would be representative of reasons related specifically to the challenges of oral therapy. For this reason, the cost of the comparator, termed 'basket of comparators' refers to the average list price across these nine regimens (rather than the weighted average). Maintenance of virological suppression is assumed comparable across the comparators and also versus CAB LA + RPV LA.

B.3.2.3. Model perspective

The analysis was conducted from the perspective of the NHS and Personal Social Services (PSS) in England and Wales in line with the NICE reference case.

B.3.2.4. Patient population

In line with the ATLAS-2M trial population and the licensed indication, the economic evaluation considers the use of CAB LA + RPV LA, administered Q2M, for the treatment of adults with virologically suppressed HIV infection (HIV-1 RNA < 50 copies/mL) on a stable antiretroviral regimen.

In the base case, the economic analysis evaluates the ATLAS-2M trial population, reflecting individuals with chronic HIV infection, treated and virologically suppressed on their current regimen, in line with the details of the population who are initialised in the cost-effectiveness model as shown in Section B.3.3.1.

B.3.2.5. Model structure

The model developed to evaluate the cost-effectiveness of CAB LA + RPV LA is a deterministic hybrid Markov state-transition model. People living with HIV are at risk of experiencing treatment failure (predominantly due to failure to achieve or maintain virologic suppression or adverse events), resulting in the development of viral resistance and discontinuation of current therapy. To capture this complexity, a traditional Markov process

was combined with a decision tree process, which manages treatment allocation and aggregates results across treatment lines. An internal decision process (the decision-making code of the model, which determines how individuals move through the health states) is also employed to differentiate between those discontinuing for virologic and non-virologic reasons. Schematics depicting the treatment pathways modelled and the within-treatment-line health states are presented in Figure 10.

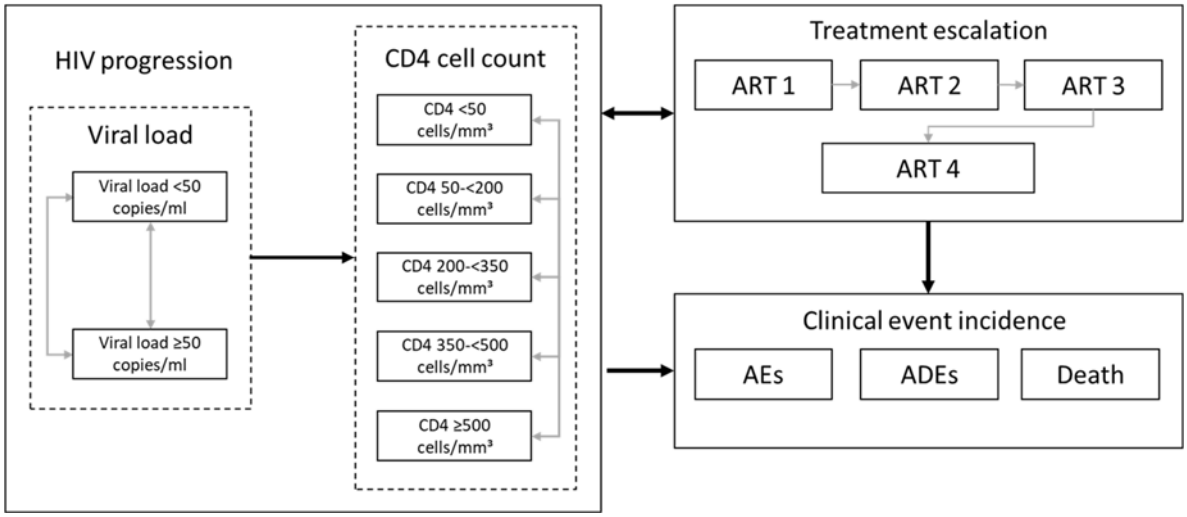


Figure 10. Conceptual model schematic
AE: adverse events, ADE: AIDS-defining event, ART: antiretroviral therapy, CD4+: cluster of differentiation 4

Health states included in the model are based upon treatment line, virologic response and CD4+ cell count, with death as an absorbing state. Whilst not defined as explicit health states, individuals are also subject to the risk of AIDS-defining events (ADEs; i.e. certain cancers, opportunistic infections and other manifestations of immunosuppression, defined according to the CDC Classification for HIV-1 Infection (2014)[144] as used in ATLAS-2M) and treatment-related AEs.

Four treatment lines are incorporated: first modelled line ART; two subsequent modelled, defined ART regimens; and one unspecified 4th modelled line treatment line (Figure 10). Individuals cannot skip any of the defined ART treatment lines; all individuals receive three lines of defined ART, followed by one line of 4th line treatment, depending on their treatment pathway and reasons for discontinuation. ART regimens are associated with a specific monthly cost of therapy, while the efficacy profiles account for all treatment-associated clinical parameters modelled inclusive of viral suppression, CD4+ cell count (Section B.3.3.2 and B.3.3.2.1) and AEs (Section B.3.3.5).

Upon model initiation, individuals begin on the initial ART (1st modelled line), comprised of either CAB LA + RPV LA or a comparator regimen (see Section B.3.2.5 for comparators). Individuals may then discontinue from the initial ART, moving to a second or a third modelled ART line. Reasons for discontinuation ('non-virologic' and 'virologic') determine subsequent treatment efficacy. A proportion of individuals discontinuing for 'virologic' reasons are assumed to develop resistance, or will be switched to a less well-tolerated regimen with a risk

of reduced adherence, and as such have a lower probability of viral suppression in subsequent lines of therapy. The term 'stable switch' indicates that an individual has discontinued for non-virologic reasons, and as such is not expected to experience the same reduction in the probability of achieving virologic suppression as a patient discontinuing for virologic reasons.

To account for differing levels of resistance at entry to the 4th therapy line, individuals may receive one of three 4th line therapy efficacy profiles, depending on the nature of their previous reasons for discontinuation. Further description of the impact of discontinuation is provided in Section B.3.3.2.2. Efficacy outcomes for subsequent treatment lines are described in Section B.3.3.2.1, while costs associated with subsequent treatment lines are described in Section B.3.5.2.

Upon initiation of a given treatment line, individuals enter the Markov process. Consistent with previous economic models[145][141], health states included are based on viral load (<50 copies/mL, ≥50 copies/mL) and CD4+ cell count (>500 cells/mm^3, 350–500 cells/mm^3, 200–<350 cells/mm^3, 50–<200 cells/mm^3, <50 cells/mm^3) and death.

During each monthly cycle, individuals' CD4+ cell count and viral status may improve, decline or remain constant. For a given treatment, this is represented by transitions between health states, as determined by treatment-specific transition matrices. Death is an absorbing state. In general, individuals within each health state are assumed to be homogenous, with movements between treatment lines determined by virologic status at the point of current and previous discontinuations.

In any of the first three modelled treatment lines, individuals may discontinue treatment due to virologic failure (failure to achieve HIV RNA <50 copies/mL), viral rebound (viral failure after initially achieving suppression) or non-virologic reasons. Individuals receiving treatment within the 4th therapy line are assumed to remain there for the remainder of the modelled horizon, with the 4th line therapy acting as an absorbing health state with respect to treatment options and assumed to contain all potential therapies post-3rd line treatment.

Rationale for model structure

Patient-level simulations are extremely computationally expensive for problems such as this, where clinical differences are very small, and so are not considered appropriate for use. Instead, computational time may be better devoted to additional scenario analyses to explore uncertainty.

By contrast, Markov models applying health states based on CD4+ cell count are commonly described in the literature (see Appendix G), as CD4+ cell count is a strong predictor of clinical progression, resource use (and therefore cost) and HRQoL. Indeed, all UK-relevant full text cost-effectiveness studies identified were Markov models with health states based on CD4+ cell count (Table 53). Two studies (Miners 2001[135] and Trueman (2000)[136] considered CD4+ cell counts with less granularity than the cost-effectiveness model used in the current submission; CD4+ cell count boundaries defining health states were considerably wider. Two other studies (Simpson 2012[133, 138] and Wilkins 2016[134]) used CD4+ cell count definitions of health states that were in line with the current model; one (Simpson 2012) included virologic measurements and cardiovascular-related events while the other (Wilkins 2016) considered regimen failure (stratified by reason for discontinuation as in the submitted model), and

mortality for both HIV and non-HIV related events. Therefore, the cost-effectiveness model used in the submission is considered in line with previously published models in the same indication with the inclusion of components from all identified relevant literature. Cost-effectiveness modelling has not been routinely carried out for HIV therapies commissioned for use in England, as they have not previously fallen within the remit of NICE.

However, an important limitation of strict Markov models is that a Markov model does not allow for additional components relevant to modelling HIV, including treatment lines and treatment options, development of resistance and reasons for discontinuation. This limitation can be addressed by incorporating a decision tree element into the Markov model structure to create a hybrid model.

A monthly cycle length is commonly applied in HIV models, as outlined in the SLR (Appendix G) and is used here too. As HIV can be a rapidly changing disease if uncontrolled, longer cycles may not capture all clinically important events.

Table 56. Features of the economic analysis

Feature	Current appraisal	
	Chosen values	**Justification**
Time horizon	Lifetime (maximum 80 years)	Clinical guidelines note durable long-term survival and HRQoL benefits for individuals receiving an effective antiretroviral regimen.[146] To fully capture the survival benefits of a successful antiretroviral regimen, non-curative nature of treatment and the requirement for lifelong maintenance of treatment, a lifetime perspective (up to 80 years from model initiation) has been adopted. Within the model, alternative time horizons are available (1–80 years) and may be evaluated to assess the impact of this parameter on model results. The maximum time horizon (80 years) is employed to facilitate scenario analysis and sensitivity analysis; the base case analysis is run until last patient has died, which is significantly less than 80 years.
Cycle length	One month	A cycle length of one month is utilised to make adequate provision for the timing of treatment switching, virologic response, CD4+ cell count increases, and the prediction of AIDS-defining events (ADEs), with the associated cost and quality of life implications. The adoption of a one-month cycle length is consistent with several previous cost-effectiveness models.[147-150]
Source of utilities	Kauf et al. (2008)[151]	As the model health states are CD4+ count-dependent, a source of utility values stratified by CD4+-count was required. The values published by Kauf et al. (2008) were derived from five open-label studies in individuals treated with highly active ART and have been widely used in other studies, allowing for comparison. Country-specific utility values for a UK HIV population by CD4+ count were not available (see Section B.3.4.2).
Source of costs	Beck et al. (2011)[152]	Beck et al. reports a UK-based cost-effectiveness analysis, it was deemed the most suitable source of costs given its specificity to the UK, the granularity of costs reported and the wide use of these costs in other UK studies; costs were inflated to current values (see Section B.3.5.3).
Discounting	3.5% on costs and benefits	In line with NICE reference case[132]

Discontinuation due to virologic failure is managed by the internal decision modelling process (the decision-making code of the model, which determines how individuals move through the health states):

- **Virologic failure:** In order that a cohort does not indefinitely remain on a failing treatment regimen, an internal memory process identifies those who have occupied the non-suppressed viral load state (≥50 copies/mL) for a three-month period. Individuals who have failed to achieve virologic suppression within this period discontinue their current therapy. This assumption was considered a reasonable simplification by clinical experts consulted (see Section B.3.6.2 for further details on rationale for assumptions). Individuals discontinuing due to virologic failure remain in the same CD4+ health state in the subsequent treatment arm, whilst also remaining in the non-suppressed viral load state.

Discontinuation due to viral rebound and non-virologic reasons is managed through treatment-specific transition matrices:

- **Virologic rebound:** All individuals who initially achieve viral suppression face a monthly probability of experiencing virologic rebound (i.e. a return to HIV RNA ≥50 copies/mL). Individuals experiencing virologic rebound are assigned to the non-suppressed viral load state in a subsequent treatment line.
- **Non-virologic reasons**: All individuals face a monthly probability of discontinuing their current line of therapy due to non-virologic reasons. Patients who discontinue through this process remain in their existing CD4+ and viral load health state.

A graphic representation of the treatment switching processes is presented in Figure 11. Patients who discontinue one regimen are assumed to immediately start a new regimen, in line with clinical guidelines.

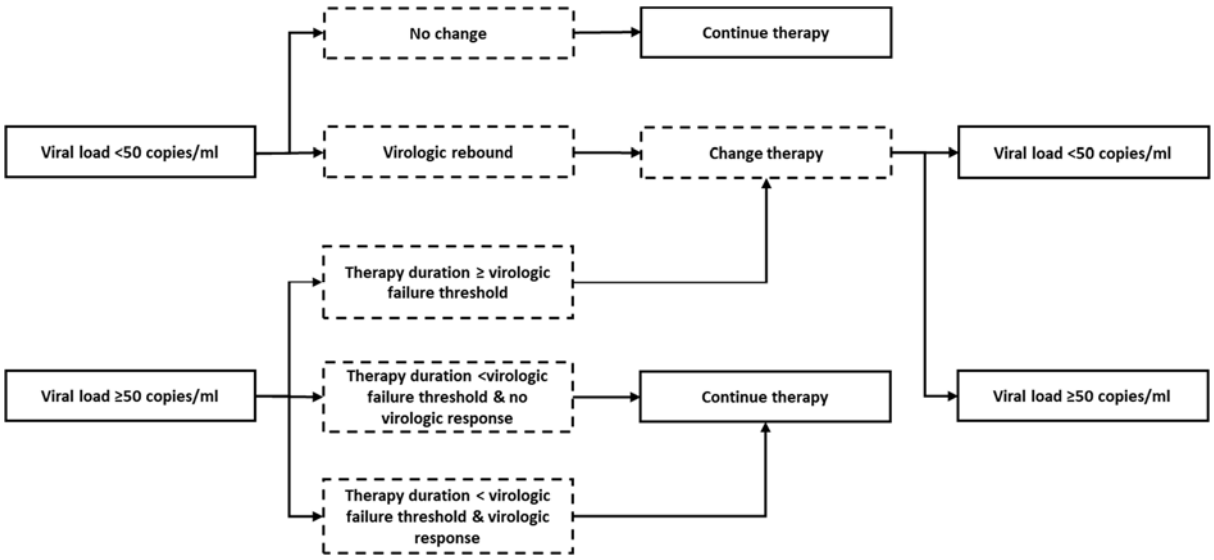


Figure 11. Treatment switching decision process

Where treatment switching is necessary, the decision tree allocates individuals to the appropriate subsequent treatment. Once analyses have been completed for all treatment

permutations, the decision tree aggregates the results to inform the overall cohort results, as presented in Figure 12.

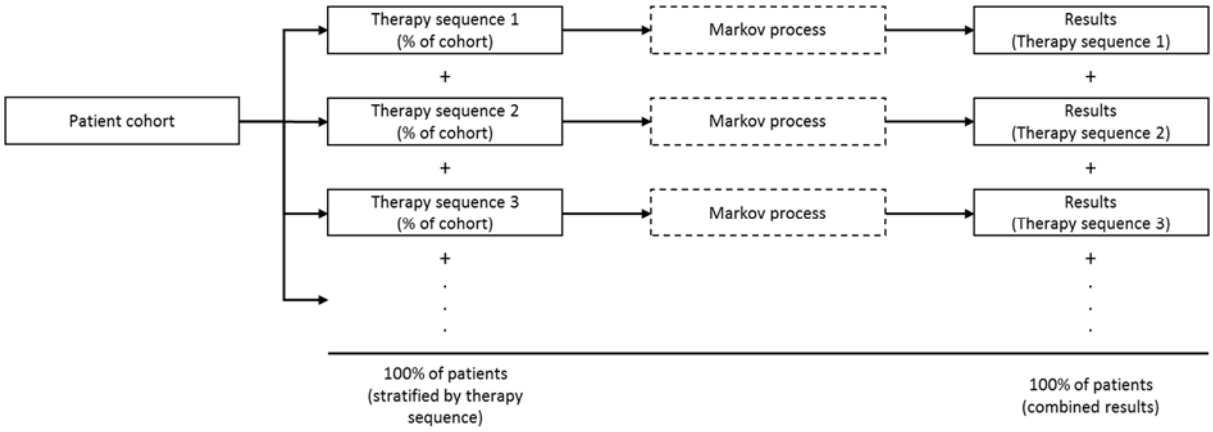


Figure 12. Decision tree process

B.3.2.5.1. *Modelling of adherence and onward viral transmission*

B.3.2.5.1.1. Adherence

As a directly observed therapy administered Q2M, CAB LA + RPV LA is expected to improve treatment adherence relative to self-administered daily oral therapy, because it removes the possibility of suboptimal adherence, provided that individuals attend for administration of their injections within the required time window.

The effectiveness of CAB LA + RPV LA in clinical practice is assumed to have been quantified in ATLAS 2M (i.e. adherence to long-acting injectables in clinical practice is not expected to be different from trial settings); this assumption is backed up by long-term data from CAB LA + RPV LA trials, which found adherence rates of 96-98% at 96 weeks' follow-up[96, 97]

Adherence to long-term oral therapy in the real-world setting is difficult to quantify, and all of the methods for doing so (e.g. patient recall, medicine possession ratio) are associated with limitations. However, the literature indicates that suboptimal adherence to daily ART is common[53 55-57, 61]. A targeted literature review on adherence to ART found that adherence data from the UK are sparse, but the UK studies identified indicated that suboptimal adherence occurs in approximately 10-57% of treated individuals (see Section B.1.3.5.3).

Reduced adherence is associated with reduced treatment effectiveness[53-58] leading to an increased likelihood of viral rebound and of developing resistance to ART. To model the potential adherence-related benefit associated with CAB LA + RPV LA, adherence-related adjustments are made in the comparator arm to reduce the probability of viral suppression and increase the probability of viral rebound. This is explained below.

B.3.3.2.3Adjustments to the adherence inputs (described in B.3.3.2.3) are based on a study by Ross et al.,[153] which evaluates the clinical and cost-effectiveness of long-acting

antiretroviral therapy using the widely published CEPAC HIV microsimulation model. The Ross study reports the relationship between viral suppression at 6 months from ART initiation and medication possession ratio (MPR), using data from the VOLTART cohort[146], which reported long-term virological outcomes on ART in people with HIV in Cote d'Ivoire. In this study, the proportion of individuals achieving HIV RNA suppression on daily ART was assumed to range from 0% to 91% depending on adherence, vs a proportion of 91% on long-acting ART. Variations in adherence, efficacy and loss to follow-up were explored in sensitivity analyses. [154] The following equation was fitted to the observed data to calculate the estimated viral suppression at different adherence levels, calculated from the x and y coordinates in the supplementary material of Ross et al.:

$$Viral\ suppression = 1.01111 \cdot Adherence - 0.05056$$

Subsequently, this equation is used in the model to estimate anticipated viral suppression at different levels of adherence, as follows:

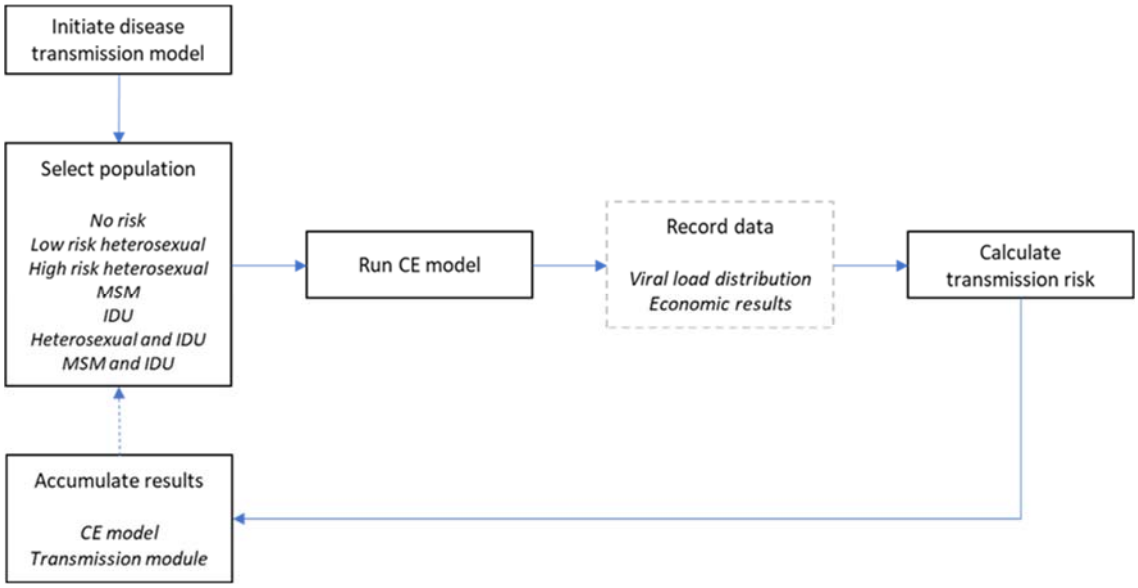
- The comparator arm (daily oral ART) is assumed to exhibit 74.4% adherence (consistently over the treatment duration), derived from a UK-based study of adherence to ART (SWEET[52]; see Section B.3.3.2.3). From this, the equation produces a viral suppression estimate of 70.17%. This is then divided by the suppression estimate of 96.06% derived from the equation for a perfectly adherent cohort (100% adherence). This gives an adjustment factor of 0.73, which is applied in the model base case to the probability of viral suppression in the comparator arm.

- In the CAB LA + RPV LA arm, no adherence-related adjustment is applied in the base case, i.e. the model assumes no reduction to the suppression that was achieved with the adherence reported in the ATLAS-2M trial (i.e. 98% adherence). Thus, for the purposes of modelling the adherence observed for CAB LA + RPV LA in ATLAS-2M is taken as 100% adherence, and decrements applied to the comparator arm are relative to this.

B.3.2.5.1.2. Onward viral transmission

Given the impact of treatment adherence on viral load, differences in adherence between treatment options can also be expected to influence onward viral transmission. The likelihood of onward transmission of HIV is dependent on several factors, predominantly the presence of behaviour conducive to disease transmission (e.g. unsafe sexual activity or injection drug use) and individuals' viral load. This aspect is captured in the economic model through a disease transmission module. This module utilises effectiveness data estimated through the cost-effectiveness model, alongside disease transmission parameters, to estimate the total number of onward infections attributable to the modelled cohort. Outcomes due to differences in new HIV cases resulting from onward transmission are then incorporated into cost-effectiveness estimates. Further description is available in Appendix M. An overview of the model process is provided in Figure 13.

Of note, individuals with an undetectable viral load (classed as HIV-1 RNA <50 copies/mL) cannot sexually transmit HIV[14, 15, 24, 25]. Transmission that occurs as a result of treatment failure may involve transmission of a resistant viral strain, leading to fewer treatment options and higher costs for the newly infected individuals.



CE: cost-effectiveness, IDU: intravenous drug users, MCM: men who have sex with men

Figure 13. Overview of onward transmission disease module and its interaction with the cost-effectiveness model

Individuals in the module are stratified into risk groups**CE: cost-effectiveness, IDU: intravenous drug users, MCM: men who have sex with men**

Figure 13 (Appendix P, Table 1), the majority of which potentially contribute to onward transmission of HIV. Based on these core transmission risk populations, a conceptual model design was developed (Figure 14). The heterosexual risk population was further stratified in to low-risk and high-risk behaviour categories and transmission from multiple sources was permitted (e.g. heterosexual transmission in the injecting drug use transmission risk group). Full details of risk groups and associated transmission probabilities are provided in Appendix M.

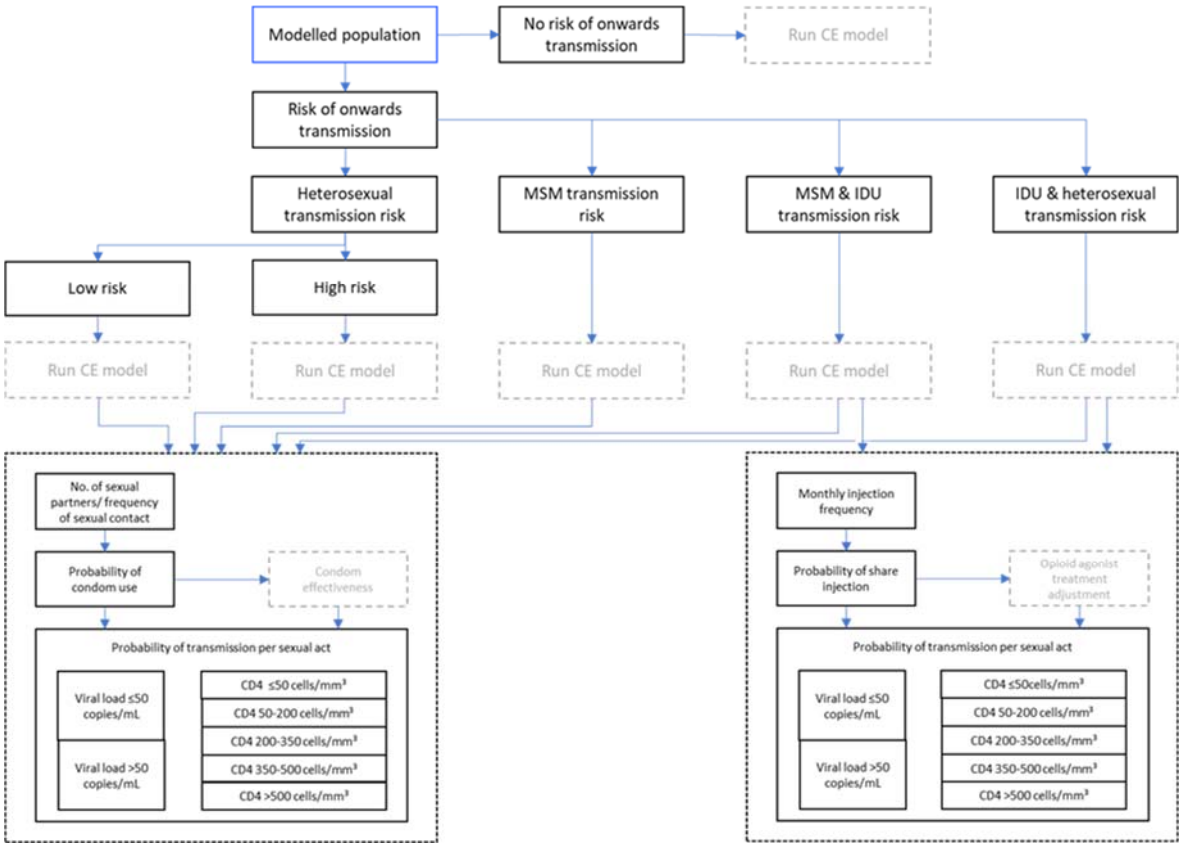


Figure 14. Disease transmission module flow diagram
CD4: cluster of differentiation 4; CE: cost-effectiveness; IDU: injecting drug use; MSM: men who have sex with men

The modelled cohort is initially distributed across each of the risk groups, where patient baseline characteristics may be specified individually by group. The cost-effectiveness model is subsequently used to estimate lifetime outcomes for each of the risk groups. Consistent with a typical cost-effectiveness analysis, lifetime costs, life years and quality-adjusted life years (QALYs) associated with HIV disease progression in the modelled cohort are accrued and recorded.

To estimate the number of onward infections, the lifetime viral load health state occupancy of each risk group is recorded. It is assumed that the modelled cohort may only contribute to onward HIV infections if they have a viral load ≥50 copies/mL; in line with clinical evidence, those with viral load below this threshold cannot infect others. It was necessary to make the simplifying assumption that all individuals in the HIV-1 RNA ≥50 copies/mL stated are capable of transmitting HIV; in reality, clinical evidence suggests that a somewhat higher viral load (approx. 200-400 copies/mL or greater) is required for transmission. Subsequently, time spent in the higher viral load states is combined with the time-dependent risk of transmission (based on risk group-specific behaviour characteristics) to estimate the number of onward HIV infections attributed to the initial cohort.

Total lifetime costs, life years and QALYs for each onward infection are estimated and incorporated within the initial cohort cost-effectiveness calculation. Only direct infections (i.e.

those transmitted by the original modelled cohort, not infections subsequently passed on by the newly infected persons) are considered within the model.

B.3.2.5.2. *Resistance*

Treatment failure while a patient is receiving an antiretroviral regimen may be associated with the development of resistance. A proportion of individuals discontinuing treatment for virologic reasons are assumed to develop resistance, which is reflected in the efficacy profiles used for 2nd and 3rd line modelled treatment and will determine their eligibility for future regimens. For simplicity, additional resistance is not explicitly modelled from third-line treatment onwards.

Patients who discontinue for virologic reasons in the first modelled line but then discontinue their second modelled line for non-virologic reasons will receive the same third modelled line efficacy under default settings as those who failed first and second modelled line for non-virologic and virologic reasons respectively; the assumption is that there has been resistance at some point in the treatment pathway irrespective of when this happened, so outcomes would be expected to be similar.

B.3.2.5.3. *Outcome measures*

The primary model output is the incremental cost-effectiveness ratio (ICER) expressed as incremental costs per QALY gained, in line with the reference case. The model also provides an overview of other outcomes, such as total and incremental life years, and disaggregated QALYs and costs.

As HIV is a complex disease area with numerous clinically important measures, a number of clinical outcomes are also calculated in the model and displayed to aid decision-making. The incidence of clinical outcomes such as adverse events and AIDS-defining events are displayed. The model also shows graphically the proportion of the cohort who are expected to achieve viral suppression and the mean CD4+ cell count over time for each comparator and intervention. The time on treatment (intervention and comparator) and the time in each viral load health state is also displayed graphically. Clinical outcomes and details relating to model outputs are shown in Table 57.

Table 57: Clinical outcomes estimated by the Company cost-effectiveness model

Clinical outcomes estimated	Key Notes
Adverse Events	Only injection site reactions (ISRs) are considered in this model. This is due to similar AE profiles between arms (with the exception of ISRs). This is detailed further in Section B.3.3.5.
AIDS defining Events (ADE)	Events considered and contributing to the overall incidence of captured ADEs: Acute viral opportunistic infection (OI) Acute bacterial OI Acute fungal OI Acute protozoan OI Other OI Further description is given in Section B.3.3.3

B.3.2.5.4. *Discount rate*

A 3.5% discount rate was applied to both costs and outcomes, in line with NICE guidelines on the reference case.[132] Sensitivity analyses have been provided applying a 1.5% discount rate. As noted in the NICE reference case, where treatment restores people to full or near full health who would otherwise die or have a very severely impaired life, and when this is sustained over a very long period (normally at least 30 years), cost-effectiveness analyses are very sensitive to the discount rate used. Effective HIV treatment is key to providing health benefits, in terms of extension to life, return to near full health and preventing onward transmission, and the consequences of this are magnified over the longer term. Hence, a scenario analysis applying a 1.5% rate is provided.[132]

B.3.3. Clinical parameters and variables

B.3.3.1. Patient parameters

Baseline patient parameters in the cost-effectiveness model (Table 58) are informed by the baseline characteristics of participants in ATLAS-2M. As outlined in B.2.2.2, participants enrolled in ATLAS-2M were broadly comparable to the other studies used to inform the ITC. Further, as described in Section B.2.13.4, the population in ATLAS-2M is adequately generalisable to the UK HIV population. The modelled baseline viral status is also derived from ATLAS-2M and is specified in Table 59.

Table 58. Baseline parameters

Variable	ATLAS-2M (base case)		
	Mean value	SE	Source
Age of cohort (years)	42.7	0.49	ATLAS-2M CSR[70]
Percentage of cohort that are female (%)	26%	1.92%	ATLAS-2M CSR[70]
SE: standard error			

Table 59. Baseline viral status

Viral load (copies/mL)	CD4+ cell count category (cells/mm3)	ATLAS-2M		
		Mean	SE	Source
<50	≥500	74.90%	1.90%	Derived from ATLAS-2M CSR[70]
	350–<500	18.39%	1.70%	
	200–<350*	6.70%	1.09%	
	50–<200	0.00%	0.00%	
	<50	0.00%	0.00%	
≥50**	≥500	0.00%	0.00%	
	350–<500	0.00%	0.00%	
	200–<350	0.00%	0.00%	
	50–<200	0.00%	0.00%	
	<50	0.00%	0.00%	
SE: standard error *Assumed that all participants with CD4+ <350 (as defined in the ATLAS-2M CSR) fall within this category ** No participants were in this category at baseline as users are required to be virally suppressed before commencing CAB LA + RPV LA				

B.3.3.2. Health state occupancy

Health states are defined by CD4+ cell count and viral suppression, with patients moving between health states based on treatment- and time-specific transition matrices and viral suppression data. Patients' CD4+ cell count status may improve, decline or remain constant, represented by transitions through the respective health states.

The rate at which individuals transition between health states is determined by treatment- and time-specific transition matrices defined by the efficacy data selected. The pooled ATLAS-2M ITC profiles (see Section B.2.9 and Appendix M) are used to define the efficacy for the first modelled line. Death is included in the model as an absorbing state. In general, individuals within each health state are assumed to be homogenous, except those who experience virologic failure (this is detailed further in Section B.3.3.2.2).

In any of the first three modelled treatment lines, individuals may discontinue treatment due to virologic failure or other non-virologic reasons. Patients receiving treatment within the 4th therapy line are assumed to remain there for the remainder of the modelled horizon, with the 4th therapy line acting as an absorbing health state with respect to treatment options and assumed to contain all potential therapies post-3rd line treatment.

B.3.3.2.1. *Efficacy*

ART efficacy is measured by virologic response, defined as the maintenance of a viral load (HIV-1 RNA) <50 copies/mL, and immunological response, defined as the average increase in CD4+ cell count. These measurements inform transition matrices that are used in the model to control individuals' movement between viral load and CD4+ cell count health states. Efficacy parameters used in the derivation of transition matrices for each efficacy profile used in the model are presented in Appendix M.

In the base case analysis, it is assumed that virological efficacy is not affected by therapy applied (i.e. no difference in virological efficacy is assumed between therapies); this assumption is in line with the published literature, and with the ITC described in Section B.2.9. However, efficacy is assumed to be dependent on therapy line, treatment history (i.e. previous virological failures) and development of resistance.

The first modelled line uses efficacy from the Q2M arm of ATLAS-2M for CAB LA + RPV LA; comparator efficacy is assumed to be equivalent, based on the ITC. In the second and third modelled lines of therapy, the 'stable switch' efficacy profile is used for those who discontinued their previous treatment and changed therapy for non-virologic reasons; the 'failing switch' efficacy profile is used for those who subsequently changed therapy as a result of virologic failure. Clinical experts noted that although this was an acceptable assumption for modelling, many individuals would not experience a reduction in efficacy in the stable switch scenario; the effect of assuming a zero reduction in efficacy after stable switch was explored in a sensitivity analysis. In the final line of modelled therapy, efficacy profiles were applied based on the number of previous virologic failures.

Data used to populate the efficacy profiles in the model are shown in Table 60. The Kanters (2017)[113] paper used to inform 2L and 3L failing switch was identified from a targeted literature

review of NMAs, where it was the only NMA identified that analysed outcomes in individuals who switched from initial treatment because of virologic failure. The Baril (2016)[155] paper was considered an appropriate source because it provides a systematic review of the efficacy of switching regimen in virally suppressed individuals. The Cooper (2008)[156] and Steigbigel (2008)[157] papers were selected to inform efficacy in the 4th modelled line as they were the only papers identified that provide the required data stratified by number of resistance classes in an appropriate patient population. The effects of alternative assumptions and inputs for the respective modelled treatment lines were explored in scenario analyses (see Section B.3.8.3.1).

Table 60. Efficacy profile parameters

Therapy line	Treatment arm	Source	Virologic suppression at 48 weeks Mean (SE)	Baseline CD4+ count Mean (SD)	Change in CD4+ cell count at 48 weeks Mean (SD)
Initial modelled line	CAB LA + RPV LA	Q2M arm from ATLAS-2M	94.3%	681.8 (259.9)	5.3 (168.62)
	Comparators	Assumed equivalent to Q2M arm from ATLAS-2M			
Second modelled line	Stable switch	Baril (2016)[155]	74.82% (3.74%)	540.02 (232.46)	69.25 (149.14)
	Failing switch	Kanters (2017)[113]	73.78% (3.69%)	168.67 (155.07)	176.35 (149.30)
Third modelled line	Stable switch	Baril (2016) [155]	74.82% (3.74%)	540.02 (232.46)	69.25 (149.14)
	Failing switch	Kanters (2017)[113]	73.78% (3.69%)	168.67 (155.07)	176.35 (149.30)
Fourth modelled line	No ART resistance	Cooper 2008[156] & Steigbigel 2008[157]	71.04% (7.10%)	151.00 (141.00)	119.00 (132.73)
	Resistance to one ART class	Cooper 2008[156] & Steigbigel 2008[157]	60.58% (6.06%)	151.00 (141.00)	111.00 (146.31)
	Resistance to two ART classes	Cooper 2008[156] & Steigbigel 2008[157]	50.80% (5.08%)	151.00 (141.00)	71.00 (100.78)
NB: Failing switch refers to people who switch for virologic reasons. Stable switch refers to people who switch for non-virologic reasons.					

Table 61. Virologic and non-virologic discontinuations

Therapy line	Treatment arm	Source	Time point	Virologic discontinuation at 48 weeks Mean (SE*)	Non-virologic discontinuation at 48 weeks Mean (SE*)
Initial modelled line	CAB LA + RPV LA	ATLAS-2M	Year 1	1.72%	4.02%
			Year 2	1.72%	4.02%
			Year 3	1.72%	4.02%
	Comparators	ATLAS-2M	Year 1	1.72%	4.02%
			Year 2	1.72%	4.02%
			Year 3	1.72%	4.02%
Second modelled line	Stable switch	Baril (2016)[155]	All years	5.74%	8.39%
	Failing switch	Kanters (2017)[113]	All years	16.79%	2.67%
Third modelled line	Stable switch	Baril (2016)[155]	All years	5.74%	8.39%
	Failing switch	Kanters (2017)[113]	All years	16.79%	2.67%
Fourth modelled line	No ART resistance	Cooper 2008[156] & Steigbigel 2008[157]	All years	2.2%	13.0%
	Resistance to one ART class	Cooper 2008[156] & Steigbigel 2008[157]	All years	2.2%	13.0%
	Resistance to two ART classes	Cooper 2008[156] & Steigbigel 2008[157]	All years	2.2%	13.0%
*SE assumed 10% of the mean Proportion discontinuing are calculated using the standard rate to probability formulae as displayed in Section B.3.3.4					

B.3.3.2.2. *Treatment discontinuation*

As described in Section B.3.3.2.2, individuals can discontinue therapy for virologic (failure, rebound) or non-virologic reasons. Following therapy discontinuation, they switch to a subsequent therapy determined by the reasons for discontinuation. Discontinuation rates are provided in Table 61.

B.3.3.2.3. *Adherence*

As described in Section B.3.2.5.1.1, CAB LA + RPV LA is expected to improve treatment adherence relative to self-administered daily oral ART. A targeted literature review undertaken to identify studies reporting adherence to ART in the UK found few publications. Reported rates of non-adherence ranged from 10% (missing ≥2 doses in the last 7 days) to 57% (missing a dose or taking ≥1 dose incorrectly in last 7 days).[49-52] The reduction in adherence applied to daily oral ART is taken from the UK-based SWEET trial.[52] SWEET was considered to be the most appropriate source to inform the modelling because it was a formal clinical trial with a relatively large population size.

SWEET measured adherence to two daily oral ART regimens in virally suppressed participants with HIV using the Medication Adherence Self-Report Inventory (MASRI). Patients indicated the percentage of ART medication taken over the previous month on a visual analogue scale (VAS). Low adherence was defined as taking <95% of their prescribed ART medication over the past month, and was reported by 25.6% of patients in one therapy arm and 37.6% in the other arm at Week 48 (study population N=117 per arm). The 25.6% reduction from 100% of patients having perfect adherence was applied to daily oral ART in the base case analysis, as this represented the more conservative choice. This corresponds well with the findings of the EU Unmet Need Study, in which 26% of people living with HIV surveyed in the UK (N=196) reported not taking pills exactly as prescribed sometimes or often (see Section B.1.3.5].[26] The relationship of adherence to viral suppression in the model is described in Section B.3.2.5.1.1.

In the base case it is assumed that CAB LA + RPV LA in clinical practice is associated with 100% of the adherence seen in ATLAS-2M, because attendance to injections can be verified by the healthcare provider (directly observed therapy), and any participants who do not attend as required for appointments will be reviewed and therapy with CAB LA + RPV LA discontinued, as per the SmPC[1]. Thus, no reduction in adherence is applied; the rationale is described in full in Section B.3.2.5.1.1. Supportive evidence for the assumption that in-trial rates of adherence to CAB LA + RPV LA are maintained over time is provided by long-term data from the phase 2 LATTE-2 study, which found that high rates of adherence to injection visits were maintained through 96 weeks of follow-up, with 98% of injections occurring within the +/- 7 day window[97]. Similarly, adherence of >96% was seen in 96-week follow-up from ATLAS and FLAIR[96].

B.3.3.3. AIDS Defining Events

AIDS Defining Events (ADEs) are important clinical considerations for people living with HIV that reflect the progression of disease and affect mortality, cost of disease management and HRQoL. In each cycle (one month), individuals are at risk of experiencing an ADE. The

probability of experiencing specific ADEs is a factor of both CD4+ cell count and time since model initiation (time on treatment). The incidence of ADEs in the model influences mortality and HRQoL and indirectly, disease management costs.

Five ADEs have been modelled, all of which are opportunistic infections (OIs):

- Acute viral
- Acute bacterial
- Acute fungal
- Acute protozoan
- Other OI

These were chosen as the most appropriate ADEs to model because the risk of occurrence is dependent on both CD4+ cell count and the time on, and status of treatment. Probabilities included in the model can be found in Table 62. The ARAMIS study report[150] describes ADE probabilities over time and observed that in some cases risk of ADE increased with increasing CD4+ cell count; in order to better replicate known disease progression, the lowest probability by CD4+ cell count was carried forward, so that improving health states does not yield a higher likelihood of ADEs.

Table 62. Incidence of AIDS-defining events

Time on treatment	Opportunistic infection	Probability of experiencing an ADE (mean value)					Source
		CD4+ <50	CD4+ 50-200	CD4+ 200-350	CD4+ 350-500	CD4+ >500	
0-6 months	Acute viral OI	0.0071	0.0033	0.0008	0.0008	0.0008	ARAMIS technical report[150]; Lowest value for each time-point by CD4+ cell count carried forward
	Acute bacterial OI	0.0070	0.0022	0.0006	0.0004	0.0004	
	Acute fungal OI	0.0049	0.0022	0.0003	0.0001	0.0001	
	Acute protozoal OI	0.0021	0.0006	0.0002	0.0001	0.0001	
	Other OI	0.0036	0.0020	0.0000	0.0000	0.0000	
7-12 months	Acute viral OI	0.0039	0.0010	0.0003	0.0003	0.0002	
	Acute bacterial OI	0.0027	0.0009	0.0001	0.0001	0.0001	
	Acute fungal OI	0.0018	0.0013	0.0002	0.0002	0.0001	
	Acute protozoal OI	0.0018	0.0004	0.0001	0.0001	0.0001	
	Other OI	0.0022	0.0014	0.0007	0.0003	0.0003	
13-24 months	Acute viral OI	0.0019	0.0005	0.0002	0.0002	0.0001	
	Acute bacterial OI	0.0022	0.0008	0.0001	0.0001	0.0001	
	Acute fungal OI	0.0016	0.0011	0.0002	0.0002	0.0001	
	Acute protozoal OI	0.0015	0.0004	0.0001	0.0001	0.0001	
	Other OI	0.0014	0.0009	0.0004	0.0002	0.0002	
25-36 months	Acute viral OI	0.0005	0.0001	0.0000	0.0000	0.0000	
	Acute bacterial OI	0.0012	0.0004	0.0000	0.0000	0.0000	
	Acute fungal OI	0.0015	0.0011	0.0001	0.0001	0.0001	
	Acute protozoal OI	0.0008	0.0002	0.0000	0.0000	0.0000	
	Other OI	0.0009	0.0006	0.0003	0.0001	0.0001	
36 months+	Acute viral OI	0.0005	0.0001	0.0000	0.0000	0.0000	
	Acute bacterial OI	0.0012	0.0004	0.0000	0.0000	0.0000	
	Acute fungal OI	0.0015	0.0011	0.0001	0.0001	0.0001	
	Acute protozoal OI	0.0008	0.0002	0.0000	0.0000	0.0000	
	Other OI	0.0009	0.0006	0.0003	0.0001	0.0001	

ADE: AIDS-defining event; OI: opportunistic infection
SE assumed to be 10% of mean for all inputs

B.3.3.4. Mortality

All modelled individuals are at risk of all-cause mortality, with health state and the incidence of ADEs resulting in increased rates of mortality, as described in B.3.3.3. Increased rates of mortality are typically applied through the application of relative risks. Relative risks are applied to rates (after conversion from the input probability) before conversion back to probabilities. The following formulae are used to convert probabilities to rates, and rates to probabilities, respectively:

$$\text{Rate} = \text{LN}(1 - \text{Probability}) / \text{Time}$$

$$\text{Probability} = 1 - \text{Exp}(-\text{Rate} \times \text{Time})$$

B.3.3.4.1. *Composite all-cause and adjusted HIV mortality*

The model accounts for all-cause mortality using age- and gender-specific mortality rates, derived from UK life tables[158], describing the annual probability that a person aged *x* years will die before reaching age *x+1*. The probability of mortality at age 101 is assumed to be equal to 1; i.e. once individuals reach 100 years in age, they are assumed to die in the next model cycle. The model has been populated with values from 2016-18 UK life-tables.[158]

To reflect the additional mortality in the HIV population, relative risks, stratified by CD4+ cell count states (Table 63), are applied to all-cause mortality probabilities. These are derived from the study by Lewden et al.[159] which quantified the relative risk of mortality by CD4+ cell count compared with general population mortality. Although based on the French population, this is considered to be an appropriate source, as relative risk compared with general population mortality can be assumed to be generalisable from one western European country to another. Of note, studies of large cohorts of individuals with low CD4+ counts were conducted in the era before highly effective modern therapies; recent studies are therefore not available.

Table 63. Risk of death relative to all-cause mortality

Relative risk of death by CD4+ cell count	Mean	SE	Source
>500	2.50	1.515	Lewden (2007)[159]
350-500	3.50	1.515	Lewden (2007)[159]
200-350	5.60	0.280	Lewden (2007)[159]
50-200	30.30*	0.175*	Lewden (2007)[159]
<50	30.30*	0.175*	Lewden (2007)[159]
CVD	1.00	0.10	Assumption
CVD: cardiovascular disease; SE: standard error SEs assumed 10% of mean * Assumed to be the same as the ≤200 state in the Lewden study[159]			

B.3.3.4.2. *ADE mortality*

Patients experiencing ADEs face an increased risk of mortality. This heightened risk is accounted for using additional ADE-specific mortality probabilities. These monthly probabilities are applied in an additive manner to adjusted all-cause mortality rates and are

applied for the duration that the ADE is experienced (ADEs are assumed to last one cycle). Default values, presented in Table 64, are derived from the Multicenter AIDS Cohort Study (MACS); initiated in 1984, MACS provides information on the natural history of HIV/AIDS in the absence of treatment and has been used in previously published cost-effectiveness analyses.[160, 161]

Table 64. AIDS Defining Event related mortality

Risk of death	Mean	SE	Source
Acute viral OI	0.0492	0.0049	ARAMIS DTG Technical Report[150]; MACS[161]
Acute bacterial OI	0.0460	0.0046	
Acute fungal OI	0.0362	0.0036	
Acute protozoan OI	0.2009	0.0201	
Other OI	0.0440	0.0044	
OI: opportunistic infection; SE: standard error			

B.3.3.5. Adverse events

AEs are incorporated via monthly, treatment-specific probabilities, and are associated with a per event cost and a monthly utility decrement. The base case analysis only considered AE rates for injection site reactions, since all other AEs are assumed equivalent between intervention and comparator, in line with evidence from the ITC described in Section B.2.9.1. For injection site reaction grade 3/4 the probability for CAB LA + RPV LA Q2M is 0.51% (SE 0.31%). For injection site reactions grade 1/2 the probability for CAB LA + RPV LA Q2M is 29.09% (SE 1.99%). There is no probability of injection site reaction for current ART since it is administered orally.

AEs are modelled only in the first therapy line. As subsequent lines consist of oral ART, ISRs are not relevant and the assumption that other AEs are not different between arms would continue to be valid as the same efficacy profiles are applied to each arm regardless of the initial modelled efficacy.

B.3.4. Measurement and valuation of health effects

As described in Appendix H, an SLR was conducted to identify health-related quality-of-life studies. In brief, electronic database searches (MEDLINE, Embase and the Cochrane library) were conducted in April 2020. Publications describing health-related quality of life in individuals receiving interventions aimed at managing HIV infection were considered. Of the publications presenting de novo utility values stratified by CD4+ count in line with the model structure, the most relevant was considered to be the study by Kauf et al.[151], as described in Section B.3.4.2 below.

Full details of the process and methods to identify and select the relevant cost-effectiveness evidence are summarised in Appendix H.

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

HRQoL data in the form of SF-12 were collected from the ATLAS and FLAIR clinical trials and are presented in Section B.2.6.2.7. No generic HRQoL instrument was used in ATLAS-2M. In a post hoc analysis, SF-12 data from ATLAS and FLAIR were used to derive SF-6D utility scores via the algorithm by Brazier and Roberts[104] and differences between CAB LA + RPV LA and current ART treatment arms were explored (see Appendix N). The trial HRQoL data was not stratified by CD4+ cell count and therefore was not suitable to inform utility values for the modelled health states. However, the utility advantage applied to long-acting treatment with CAB LA + RPV LA was derived from the trial data (see Section B.3.4.2.3).

B.3.4.2. Health-related quality-of-life data used in the cost-effectiveness analysis

Health state utilities are defined by CD4+ cell count category for application during all treatment lines. As the model health states are CD4+ count-dependent, a source of utility values stratified by CD4+ count was required. The values used are those published by Kauf et al [151]; these were derived from five open-label studies in individuals treated with highly active ART. Kauf et al. is considered an appropriate source as these values have been widely used and their use allows for comparison with previous studies. Country-specific utility values for a UK HIV population by CD4+ count were not available.

Utilities are representative of time-point specific SF-36 measurements and were estimated by Kauf et al. as a function of patient demographics, regimen attributes, disease status and AEs using a mixed effects maximum likelihood model.

Table 65. Health state utility values

CD4+ cell count category (cells/mm^3)	Mean	SE	Source
>500	0.798	0.052	Kauf (2008)[162]
350–500	0.784	0.059	
200–350	0.778	0.053	
50–200	0.750	0.058	
<50	0.742	0.058	
SE: standard error			

B.3.4.2.1. *Age-dependent utility decrement*

Age-dependent utility decrements are applied in the model through the application of general population age-dependent utility estimates[163]. Age-dependent adjustments are applied additively relative to a patient's starting age. For example, a cohort with a starting age of 50 and a corresponding general population utility of 0.850 would incur a cumulative utility decrement of 0.031 by the time they are 60 (general population utility estimate of 0.819).

B.3.4.2.2. *Adverse event utility decrements*

No utility decrement is applied for AEs, given that the ITC (see Section B.2.9.2) showed no significant difference in AE profile between CAB LA + RPV LA and daily oral ART. The only exception to this is injection site reactions, which occur only with injectable treatment. Any impact of injection site reactions is assumed to have been captured in the assessment of SF-6D utilities. Of note, data on acceptability of injections, treatment satisfaction and treatment acceptance were collected in ATLAS-2M (see Section B.2.6.1.11), and individuals reported high levels of acceptance and satisfaction that increased over time. Furthermore, the SF-6D analysis (see next section) showed that CAB LA + RPV LA was associated with a statistically significant improvement in HRQoL compared with daily oral treatment. These observations are supportive of the decision not to apply a utility decrement for injection site reactions.

B.3.4.2.3. *Utility advantage associated with long-acting treatment*

Patients commonly express a desire for a long-acting treatment due to the disadvantages associated with daily oral medication[98]. Patients may experience psychological challenges to life-long daily ART, including stigma-related issues, such as a fear of unwanted disclosure of HIV-1 status, and the psychological burden of the daily reminder of their HIV status (see Section B.1.3.5).

A post hoc analysis of pooled SF-6D utility data derived from the ATLAS and FLAIR trials demonstrates that at both 24 and 48 weeks, there is a mean utility difference of [redacted] between daily oral therapy and CAB LA + RPV LA Q1M. Between-treatment differences in SF-6D utility scores derived from the trial SF-12 data were analysed using an ANCOVA model, adjusted for age, sex and CD4+ cell count as covariates. At week 24 a statistically significant difference between treatment groups was reported (adjusted mean treatment difference in SF-6D: [redacted] points; 95% CI: [redacted]). At week 48 results were consistent with those at 24 weeks, indicating

a durable difference (Table 66). The considered covariates did not exert a significant influence on the results at either time point. The analysis report is provided in Appendix N.

Due to the relatively short follow-up in the trials relative to a lifetime of daily treatment, and the low sensitivity of generic instruments such as SF-12 to HIV-specific issues such as stigma, this is considered an underestimate of the likely true utility gain associated with such a fundamental change in the treatment paradigm for those individuals who desire a switch to long-acting treatment (those who prefer daily oral ART will not be considered for CAB LA + RPV LA). Another reason why the trial-derived advantage may be conservative is that it relates to Q1M treatment with CAB LA + RPV LA (SF-12 was not used in ATLAS-2M); Q2M dosing offers additional convenience and was preferred to Q1M dosing by ATLAS-2M participants who had experienced both[164].

In line with this finding, and to reflect the burden of daily oral treatment on people with HIV, a utility advantage of [redacted] is applied to CAB LA + RPV LA in the cost-effectiveness analysis. This is applied as an annual utility.

Table 66: Pooled ATLAS and FLAIR Utility Analysis Results at Week 48

Treatment	CAB LA + RPV LA (Q1M)	Daily oral ART
N	591	591
n	500	548
Adjusted Mean (SF-6D score)	[redacted]	[redacted]
95% CI of adjusted mean	[redacted]	[redacted]
Adjusted difference in SF-6D score	[redacted]	
95% CI of treatment difference	[redacted]	
P value for model	[redacted]	
ART: Antiretroviral therapy; CAB: Cabotegravir; CI: Confidence Interval; LA: long-acting; RPV: Rilpivirine;		

B.3.4.3. AIDS-defining event utility decrements

Utility decrements associated with ADEs are applied upon occurrence, for the duration of the cycle of incidence. The values used in the model were derived from a study by Paltiel et al.[165], and are presented in Table 67.

Table 67. AIDS-defining event utility decrements

ADE	Mean	SE*	Source
Acute viral OI	0.141	0.014	Paltiel (1998)[165]
Acute bacterial OI	0.232	0.023	
Acute fungal OI	0.141	0.014	
Acute protozoal OI	0.232	0.023	
Other OI	0.232	0.023	
ADE: AIDS-defining event; OI: opportunistic infection; SE: standard error *SEs assumed 10% of mean Note: Utility decrements associated with ADEs were derived as the mean utility across CD4+ cell health states (including post-failure) minus ADE utility as presented in the Paltiel study[165]			

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

B.3.5.1. Published cost and healthcare resource identification, measurement and valuation studies

An SLR was conducted to identify cost and healthcare resource use studies. In brief, electronic database searches (MEDLINE, Embase and the Cochrane library) were conducted in April 2020. Publications describing cost and healthcare resource use in individuals receiving interventions aimed at managing HIV infection were considered. Full details of the process and methods to identify and select the relevant cost and resource use evidence are summarised in Appendix I.

B.3.5.2. Intervention and comparator costs and resource use

B.3.5.2.1. *CAB LA + RPV LA acquisition costs*

CAB and RPV tablets are administered for 30 days of the first model cycle. Subsequently, the costs of CAB LA + RPV LA, including drug procurement and administration, are applied once every two months based on acquisition costs detailed in Table 13.

NHSE and CCGs are responsible for commissioning Outpatient HIV services in England; in Wales this falls to the Health Boards. The PbR currency for HIV activity is an annual 'year of care' (not including ART) stratified into three separate patient groupings – category 1 (new), category 2 (stable) and category 3 (complex) – details are supplied in Appendix O. Category 2 (stable) includes individuals changing ART for toxicity / simplification / adherence issues whilst maintaining an undetectable load, i.e. those for whom CAB LA + RPV LA may be an option.

Whilst it is possible that the administration of CAB LA + RPV LA could be subsumed within the PbR currency for this patient category, an additional 15 minutes of Band 5 nurse time per

administration has been included in the economic model to account for the potential that there is an additional cost to some providers of administering the CAB LA + RPV LA injections every two months. The cost, shown in

Table 69, is applied for cycles where the injectable (2 intramuscular injections) is administered.

Table 68. CAB LA + RPV LA dosing and acquisition cost (exc. VAT)

Dosing	Oral lead in month one, followed by two initial injections in month two and month three, to then subsequently be administered intramuscularly at same visit every two months model cycle (Q2M administration)
Cost at list prices (TBC)	[redacted] per set of injections, with an initial oral lead in treatment of [redacted] per 30 days (cabotegravir [redacted] and rilpivirine £200.27 oral lead in)
Cost per treatment cycle (list prices, TBC)*	[redacted]
Administration costs	**£9.25 (Q2M; assumed as detailed in** Table 69)
Year 1 Cost (excl. admin costs, TBC)	[redacted]
Year 2 Cost (excl. admin costs, TBC)	[redacted]

*** For daily treatments, 30 day costs are converted to calendar months in the economic model**

Table 69. Administration costs for CAB LA + RPV LA

Component	Cost	Source
15 minutes – Band 5 Nurse*	£9.25	PSSRU 2019[166]

* considered in addition to the current commissioning (CG1) pathway

B.3.5.2.2. *Patient Access Scheme*

- [redacted]

The total costs are shown in Table 70.

Table 70: CAB LA + RPV LA dosing and acquisition cost (including PAS, exc. VAT)

Dosing	Oral lead in month one, followed by two initial injections in month two and month three, to then subsequently be administered intramuscularly at same visit every two months model cycle (Q2M administration)
Cost (including PAS)	[redacted] per set of injections, with an initial oral lead in treatment of [redacted] per 30 days (cabotegravir [redacted] and rilpivirine £200.27 [list] oral lead in)
Cost per treatment cycle*	[redacted]
Administration costs	£9.25 (assumed as detailed in Table 69)
Year 1 Cost (excl. admin costs)	[redacted]
Year 2 Cost (excl. admin costs)	[redacted]

*** For daily treatments, 30 day costs are converted to calendar months in the economic model**

B.3.5.2.3. *Comparator acquisition costs*

The proposed comparator regimen is a pooled regimen based on those regimens deemed most likely to be switched to by virologically suppressed individuals in the UK who would otherwise be considered for a switch to CAB LA + RPV LA if it were available.

The rationale for the choice of comparators is given in Section B.3.2.2; in brief, usage data were consulted to ascertain which regimens are currently used in individuals likely to be considered for switching to CAB LA + RPV LA, and the list was validated by UK clinicians consulted for the submission. Following conversation with UK clinicians, the following therapies are considered relevant to the patient population:

- Emtricitabine/tenofovir alafenamide plus dolutegravir (Descovy® plus Tivicay®)
- Emtricitabine/tenofovir alafenamide plus raltegravir (Descovy® plus Isentress®)
- Abacavir/dolutegravir/lamivudine (Triumeq®)

- Dolutegravir/lamivudine (Dovato®)
- Dolutegravir/rilpivirine (Juluca®)
- Bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy®)
- Doravirine/lamivudine/tenofovir disoproxil fumarate (Delstrigo®)
- Darunavir/cobicistat/emtricitabine/tenofovir alafenamide (Symtuza®)
- Emtricitabine/rilpivirine/tenofovir alafenamide (Odefsey®)

The costs of these comparators were pooled and the mean used to derive the monthly cost for the model (Table 72). The pooled cost of £721.34 is for 30 tablets (derivation detailed in Table 71) and is adjusted to a monthly cost of £731.86 (accounting for the variation in days per month). The same cost is attributed to further lines of treatment for both arms. This assumption is made as clinical advice has indicated that people would typically switch to and from the listed treatments. Therefore, as people move through treatment lines, they may on average be expected to accrue the same acquisition costs.

Table 71: Derivation of Pooled Comparator cost

Brand name	Generic name	Pack size	30 day list price[5]
Single tablet regimens			
Delstrigo®	DOR/3TC/TDF	30	£578.55
Symtuza®	DRV/Cobi/FTC/TAF	30	£672.97
Odefsey®	RPV/FTC/TAF	30	£525.95
Biktarvy®	BIC/FTC/TAF	30	£879.51
Triumeq®	DTG/ABC/3TC	30	£798.16
Dovato®	DTG/3TC	30	£656.26
Juluca®	DTG/RPV	30	£699.02
Multi-tablet regimens			
Descovy®+Isentress®	FTC/TAF+RAL	30	£827.14
Descovy®+Tivicay®	FTC/TAF+DTG	30	£854.48
Average			
Pooled comparator		30	£721.34

Table 72. Comparator cost and subsequent therapy costs

Therapy	Monthly cost*	Source
Pooled comparator	£731.86	BNF[5]
2nd line therapy	£731.86	Assumed as Pooled Comparator
3rd line therapy	£731.86	Assumed as Pooled Comparator
4th line therapy	£731.86	Assumed as Pooled Comparator

*Costs are shown adjusted for calendar month

B.3.5.3. Health-state unit costs and resource use

The model includes costs associated with ART, HIV-specific costs (including opportunistic infection treatment costs), AE treatment costs and end of life care costs.

The SLR for health and cost resource use yielded 4,556 unique studies. Of these, 27 included qualitative data relevant to the UK. A number of studies reported drug costs or resource use that was sourced from MIMs, BNF, PSSRU or the NHS costs (Hill[167, 168], Nagakawa[169, 170], Ong[171], Wilkins[134]). Alternatively, one study only reported drug costs (Mandalia[172]) and other

studies provided only very limited data or were only available as conference abstracts. Of the remaining studies, the majority use costs published by Beck et al. (2008)[152] in a UK-based cost-effectiveness analysis. Indeed, the source chosen to inform the majority of the included costs in the company cost-effectiveness model was sourced from the utilities SLR and references the same analyses. Given the wide use of the Beck et al. analyses, the granularity of costs reported and the relevance to a UK submission, Beck et al. was deemed to be the most representative for the decision problem. Costs in the model are applied on either a monthly or per event basis and are discounted at the specified annual discount rates. All costs presented are in Pounds Sterling and inflated where necessary to 2019 values.

Reflective of the additional resource use and healthcare costs associated with HIV infection, all-cause health encounter costs have been included across the following resource categories:

- Outpatient visits to HIV primary care provider
- Day ward costs
- Inpatient days
- CD4+ cell count test and other procedures
- HIV-1 RNA test
- Non-HIV medication

Although viral load is prognostic of disease progression, CD4+ cell count categories are representative of a patient's physiology and therefore are likely to be reflected in their costs and utility outcomes. Resource use associated with all-cause health encounters is expected to vary significantly between CD4+ cell count health states. As such, the above parameters are stratified by the model's CD4+ cell count health states (CD4+ >500 cells/mm^3; CD4+ 350-500 cells/mm^3; CD4+ 200-<350 cells/mm^3; CD4+ 50-<200 cells/mm^3; CD4+ <50 cells/mm^3).

Values included in the model (Table 73) represent a composite mean monthly CD4+ health state cost and are comprised of the costs associated with HIV clinic visits, HIV-related specialist visits as an outpatient and inpatient, non-HIV medication and all laboratory testing (CD4+ cell count, viral load, HIV genotypic resistance testing, serological tests, haematology and routine chemistry testing). These costs were assumed to include the cost of ADEs due to the inclusion of both inpatient and outpatient visits and non-HIV medication. As such, specific ADE costs are not included to avoid double counting. Further, due to their inclusion in the composite costs, CD4+ cell count, viral load and HIV genotypic resistance testing costs are also excluded to avoid double counting.

End of life care costs are reflective of the additional resource use incurred by individuals in the months prior to death and are applied in the final month of life. This cost is sourced from a cost-effectiveness evaluation in HIV by Moeremans et al (2010)[140] inflated to 2019 costs using CPI-HLTH and converted to Pounds Sterling (£13,352.92, SE £1,335.29).

HIV-related health encounter costs were taken from a cost-effectiveness evaluation in HIV by Beck et al 2011[152], inflated to 2019 costs using CPI-HLTH.

Table 73. HIV-related health encounter costs

Variable	CD4+ cell count category (cells/mm^3)	Mean		SE	Source
Outpatient care		CD4+ ≤50	£87.99	£0.51	Beck 2011[152]
		CD4+ 50-200	£87.99	£0.51	
		CD4+ 200-350	£79.58	£0.40	
		CD4+ 350-500	£79.58	£0.40	
		CD4+ > 500	£79.58	£0.40	
Non-HIV medication		CD4+ ≤50	£355.71	£3.56	
		CD4+ 50-200	£355.71	£3.56	
		CD4+ 200-350	£218.14	£2.18	
		CD4+ 350-500	£218.14	£2.18	
		CD4+ > 500	£218.14	£2.18	
Day ward Costs		CD4+ ≤50	£56.44	£0.85	
		CD4+ 50-200	£56.44	£0.85	
		CD4+ 200-350	£37.52	£0.51	
		CD4+ 350-500	£37.52	£0.51	
		CD4+ > 500	£37.52	£0.51	
Inpatient Days		CD4+ ≤50	£166.12	£0.79	
		CD4+ 50-200	£166.12	£0.79	
		CD4+ 200-350	£78.03	£1.52	
		CD4+ 350-500	£78.03	£1.52	
		CD4+ > 500	£78.03	£1.52	
CD4+ tests and other procedures		CD4+ ≤50	£87.77	£0.88	
		CD4+ 50-200	£87.77	£0.88	
		CD4+ 200-350	£63.97	£0.64	
		CD4+ 350-500	£63.97	£0.64	
		CD4+ > 500	£63.97	£0.64	

HIV-1: human immunodeficiency virus type 1; NA: not applicable; OI: opportunistic infection; RNA: ribonucleic acid; SE: standard error

SEs assumed 10% of mean

B.3.5.4. Adverse reaction unit costs and resource use

Costs associated with the management of AEs are applied as a per-event cost in the cycle of incidence. The AE profile between therapy arms in the ATLAS and FLAIR trials is consistent, except for injection site reactions. Grade 1 and 2 ISRs are assumed not to incur additional costs in the model (as they are usually managed symptomatically – e.g. cold/warm compress, paracetamol, ibuprofen). Grade 3 and 4 injection site reactions have been incorporated at a

cost of £139.45 per event, based on NHS reference costs (N18AF, Specialist Nursing, face to face). All other AEs are assumed to incur zero cost.

B.3.6. Summary of base-case analysis inputs and assumptions

B.3.6.1. Summary of base-case analysis inputs

Table 74. Summary of variables applied in the economic model

Variable			Value (SD)	Measurement of uncertainty and distribution	Section
Baseline parameters					
Average baseline age of cohort (years)			42.7 (0.49)	Normal	B.3.3.1
Percentage of cohort that are female (%)			0.26 (0.02)	Beta	B.3.3.1
Starting Distribution	Viral load ≤ 50 (copies/mL)	CD4+ ≤50	0% (0%)	Beta	B.3.3.1
		CD4+ 50-200	0% (0%)	Beta	B.3.3.1
		CD4+ 200-350	6.7% (1.09%)	Beta	B.3.3.1
		CD4+ 350-500	18.39% (1.7%)	Beta	B.3.3.1
		CD4+ > 500	74.9% (1.9%)	Beta	B.3.3.1
	Viral load > 50 (copies/mL)	CD4+ ≤50	0% (0%)	Beta	B.3.3.1
		CD4+ 50-200	0% (0%)	Beta	B.3.3.1
		CD4+ 200-350	0% (0%)	Beta	B.3.3.1
		CD4+ 350-500	0% (0%)	Beta	B.3.3.1
		CD4+ > 500	0% (0%)	Beta	B.3.3.1
Utilities					
Utility - CD4+ cell count ≤50 cells/mm3			0.742 (0.06)	Beta	B.3.4.2
Utility - CD4+ cell count 50-200 cells/mm3			0.75 (0.06)	Beta	B.3.4.2
Utility - CD4+ cell count 200-350 cells/mm3			0.778 (0.05)	Beta	B.3.4.2
Utility - CD4+ cell count 350-500 cells/mm3			0.784 (0.06)	Beta	B.3.4.2
Utility - CD4+ cell count >500 cells/mm3			0.798 (0.05)	Beta	B.3.4.2
Utility advantage of CAB LA + RPV LA over daily oral therapy			[redacted]	Beta	B.3.4.2.3
Costs					
Costs - Outpatient visits		CD4+ ≤50	£87.99 (£0.51)	Gamma	B.3.5.3
		CD4+ 50-200	£87.99 (£0.51)	Gamma	B.3.5.3
		CD4+ 200-350	£79.58 (£0.4)	Gamma	B.3.5.3
		CD4+ 350-500	£79.58 (£0.4)	Gamma	B.3.5.3
		CD4+ > 500	£79.58 (£0.4)	Gamma	B.3.5.3
Costs – Day ward		CD4+ ≤50	£56.44 (£0.85)	Gamma	B.3.5.3
		CD4+ 50-200	£56.44 (£0.85)	Gamma	B.3.5.3
		CD4+ 200-350	£37.52 (£0.51)	Gamma	B.3.5.3
		CD4+ 350-500	£37.52 (£0.51)	Gamma	B.3.5.3

Variable		Value (SD)	Measurement of uncertainty and distribution	Section
	CD4+ > 500	£37.52 (£0.51)	Gamma	B.3.5.3
Costs - inpatient days	CD4+ ≤50	£166.12 (£0.79)	Gamma	B.3.5.3
	CD4+ 50-200	£166.12 (£0.79)	Gamma	B.3.5.3
	CD4+ 200-350	£78.03 (£1.52)	Gamma	B.3.5.3
	CD4+ 350-500	£78.03 (£1.52)	Gamma	B.3.5.3
	CD4+ > 500	£78.03 (£1.52)	Gamma	B.3.5.3
Costs - CD4+ test and other test and procedures	CD4+ ≤50	£87.77 (£0.88)	Gamma	B.3.5.3
	CD4+ 50-200	£87.77 (£0.88)	Gamma	B.3.5.3
	CD4+ 200-350	£63.97 (£0.64)	Gamma	B.3.5.3
	CD4+ 350-500	£63.97 (£0.64)	Gamma	B.3.5.3
	CD4+ > 500	£63.97 (£0.64)	Gamma	B.3.5.3
Cost - non-HIV medication	CD4+ ≤50	£355.71 (£3.56)	Gamma	B.3.5.3
	CD4+ 50-200	£355.71 (£3.56)	Gamma	B.3.5.3
	CD4+ 200-350	£218.14 (£2.18)	Gamma	B.3.5.3
	CD4+ 350-500	£218.14 (£2.18)	Gamma	B.3.5.3
	CD4+ > 500	£355.71 (£3.56)	Gamma	B.3.5.3
Injection site reaction cost		£139.45 (£13.94)	Gamma	B.3.5.4
End of life care		£13,352.92 (£1335.29)	Gamma	B.3.5.3
Adherence reduction		25.6%	Beta	B.3.3.2.3

B.3.6.2. Assumptions

A summary of the main assumptions applied within the economic model is provided in Table 75.

Table 75. Assumptions applied within the economic model

Model input and cross reference	Source/assumption	Justification
Clinical efficacy	No difference is assumed in the efficacy of HIV therapies.	The non-inferiority evidence base is the foundation of the clinical commissioning of HIV treatments in the NHS today. BHIVA

B.3.3.2.1		guidelines[120] provide a set of recommended regimens based on the available clinical evidence and support the broad comparability of the different ART backbones in terms of efficacy, as does the published literature. Further, CAB LA + RPV LA has demonstrated similar efficacy to that of other INSTI-based regimens in virologically suppressed persons (Figure 8). Consultation with UK expert clinicians indicated that this assumption is reasonable, and that efficacy is not a major consideration in prescribing decisions as all approved/commissioned regimens are considered highly effective. The ITC described in Section B.2.9. showed that there was no statistically significant difference in efficacy between CAB LA + RPV LA and current ART, and equivalent efficacy is applied in the model.
Clinical efficacy B.3.3.2.2	Viral load ≥50 copies/mL is considered as treatment failure, as defined in ATLAS-2M, and individuals switch treatments when moving into this viral load state.	Clinical experts indicated that in clinical practice a single measurement of viral load ≥50 copies/mL would not automatically be considered a failure or warrant a switch of treatment. However, repeated measures above 50 copies/mL may, and so the model will hold patients in this failing state for a maximum of three months before movement. This was considered an acceptable simplifying assumption for the purposes of modelling.
Clinical efficacy B.3.3.2.2	A proportion of individuals discontinuing for 'virologic' reasons are assumed to develop resistance, and as such have a lower probability of viral suppression in subsequent lines of therapy.	The predominant factors relating to virologic failure include drug resistance, drug toxicity and poor adherence to ART. Hence, when switching due to virologic failure, it is reasonable to assume that a proportion of individuals develop drug resistance, resulting in lower efficacy in subsequent arms. Consultation with UK clinical experts confirmed that the efficacy profiles identified from the literature were appropriate.

Clinical efficacy B.3.3.2.1	Efficacy is not affected by therapy arm; however, efficacy is dependent on therapy line, treatment history (i.e. previous virological failures) and development of resistance.	This assumption is in line with the published literature, and with the ITC described in Section B.2.9. Consultation with UK clinical experts confirmed that it is reasonable to apply reduced efficacy to later treatment lines and that the efficacy profiles identified from the literature were appropriate. However, they indicated that many individuals would not experience a drop in efficacy when switching for non-virologic reasons. The effect of use/non-use of this efficacy decrement was therefore explored in a sensitivity analysis.
Adherence B.3.3.2.3	CAB LA + RPV LA is assumed to be associated with 100% adherence (100% being defined as the adherence level seen in ATLAS-2M).	CAB LA + RPV LA is a directly observed therapy so adherence can be verified. Patients who miss an appointment have a 7-day window either side in which to receive the injections, and those who plan to miss a scheduled visit by >7 days can receive oral bridging therapy[1, 2]. The assumption that in-trial rates of adherence to CAB LA + RPV LA are maintained over time is supported by long-term data from the phase 2 LATTE-2 study, where high rates of adherence to injection visits were maintained through 96 weeks of follow-up, with 98% of injections occurring within the +/- 7 day window[97], and by long-term adherence rates of >96% seen in 96-week follow-up from other relevant studies[96] (See Section B.2.6.1.13 and B.2.6.2.8) Expert UK clinicians further indicated that this was an appropriate assumption for modelling.
Adherence B.3.3.2.3	Daily oral ART is assumed to be associated with a reduction in adherence of 25.6%.	Adherence to daily oral ART over a lifetime of treatment is rarely perfect. The assumed reduction in adherence to current ART is 25.6%, taken from the UK-based SWEET trial[52]. After a literature review of UK-based studies reporting adherence, this was deemed the most appropriate source

		because it was a relatively large-scale study that provided evidence directly relevant to the modelled data.
Utility B.3.4.2.3	CAB LA + RPV LA is associated with a utility advantage of [redacted] relative to daily oral ART.	Life-long adherence to daily oral ART imposes a psychological and organisational burden on treated individuals. This includes stigma-related issues, such as a fear of unwanted disclosure of HIV-1 status through discovery of medication and the burden of the daily reminder of their HIV-1 status, among other challenges (described in Section B.1.3.5). This is likely to affect HRQoL, as observed in an analysis of the pooled ATLAS and FLAIR data, where CAB LA + RPV LA therapy was associated with a utility benefit of [redacted] compared with daily oral ART.
Transmission B.3.2.5.1.2	A disease transmission module utilises effectiveness data estimated through the cost-effectiveness model, alongside disease transmission parameters, to estimate the total number of onward infections attributable to the modelled cohort.	One of the key benefits of long-acting injectables is the anticipated impact on long-term adherence which is expected to have a positive impact on onward transmission of HIV. However, clinical trials do not capture information on onward transmission, limiting the data available to quantify this benefit. The impact of clinical outcomes on onward transmission is modelled using published literature values. It was necessary to make the simplifying assumption that all persons with HIV-1 RNA ≥50 copies/mL are capable of transmitting HIV; in reality, clinical evidence suggests that a somewhat higher viral load (approx. 200-400 copies/mL or greater) is required for transmission.

B.3.7. Base-case results

B.3.7.1. Base-case incremental cost-effectiveness analysis results

In the context of HIV and the innovation associated with a long-acting injectable administered Q2M, it is essential that any cost-effectiveness analyses reflect the full value brought to people

living with HIV and to the NHS, including the value of improved HRQoL and the potential for improved adherence and reduced onward transmission. Hence, the base case reflects each component that represents the innovative nature of CAB LA + RPV LA and its value to the NHS.

Results are included in Table 76 and indicate that the introduction of CAB LA + RPV LA is cost-effective; CAB LA + RPV LA is estimated to dominate the daily oral therapy. The results are driven by gains in QALYs over the time horizon with CAB LA + RPV LA, and cost savings estimated to be [redacted] per person living with HIV over a lifetime horizon. These results are based on a comparison with the net price for CAB LA + RPV LA and the list price for the comparator basket.

Table 76. Summary of cost-effectiveness base case scenario

	CAB+RPV-Q2M (net price)	Pooled comparator (list price)	Incremental
Life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]	[redacted]
ICER (£/QALY)			-65,850.02
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year			

B.3.7.2. Summary of base case analysis

Detailed results for all analyses are included in Table 77 and Table 78 and show that switching to a long-acting injectable HIV regimen is cost-effective in the UK (based on the proposed PAS cost of CAB LA + RPV LA and list price of the comparator). The base case analysis demonstrates that CAB LA + RPV LA is associated with an additional [redacted] LYs ([redacted] LYs versus [redacted] LYs) and an additional [redacted] QALYs ([redacted] QALYs versus [redacted] QALYs). By contrast, there is lower accrual of costs in the CAB LA + RPV LA arm [redacted] so that the resulting incremental cost-effectiveness ratio (ICER) is dominant, at −£65,850.

Table 77. Detailed clinical outcomes from base case analysis

		Base Case Analysis	
		CAB LA + RPV LA	**Comparator**
QALYs gained (discounted)		[redacted]	[redacted]
Time on treatment (years, undiscounted)	Initial modelled line	[redacted]	[redacted]
	Second modelled line	[redacted]	[redacted]
	Third modelled line	[redacted]	[redacted]
	Fourth modelled line	[redacted]	[redacted]
Time in health states (years, undiscounted)	CD4+ <50	[redacted]	[redacted]
	CD4+ 50-200	[redacted]	[redacted]
	CD4+ 200-350	[redacted]	[redacted]
	CD4+ 350-500	[redacted]	[redacted]
	CD4+ >500	[redacted]	[redacted]
QALYs gained (discounted)	CD4+ <50	[redacted]	[redacted]
	CD4+ 50-200	[redacted]	[redacted]
	CD4+ 200-350	[redacted]	[redacted]
	CD4+ 350-500	[redacted]	[redacted]
	CD4+ >500	[redacted]	[redacted]
	Onward Transmission	[redacted]	[redacted]
QALY decrements (discounted)	ADEs	[redacted]	[redacted]
	Treatment Disutility	[redacted]	[redacted]
Incidence of AEs		0.11	0.12

Table 78. Detailed cost outcomes from base case analysis

		Base Case Analysis	
		CAB LA + RPV LA (net price)	**Comparator (list price)**
Total costs (discounted)		[redacted]	[redacted]
	Health state costs	[redacted]	[redacted]
Costs (£)	Initial modelled line therapy costs	[redacted]	[redacted]
	Initial modelled line administration	[redacted]	[redacted]
	Second and third line	[redacted]	[redacted]
	Fourth modelled line	[redacted]	[redacted]
	AE	[redacted]	[redacted]
	End of Life	[redacted]	[redacted]
	Onward Transmission	[redacted]	[redacted]

B.3.8. Sensitivity analyses

B.3.8.1. Probabilistic sensitivity analysis

Results from 1,000 iterations of the model using probabilistic values can be seen in Table 79 and show results that are in line with the deterministic analysis. The scatterplot shows that although there is an expected spread of values, these appear predominantly in the south east quadrant (Figure 15). Importantly, none appear in the northern quadrants indicating that in all iterations run, CAB LA + RPV LA is associated with a cost saving. In very few iterations is CAB LA + RPV LA associated with a loss of QALYs.

Table 79: Probabilistic Sensitivity Analysis Results

	CAB+RPV-Q2M (net price)	**Pooled comparator (list price)**	**Incremental**
Life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]	[redacted]
ICER (£/QALY)			£-72,043.42
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year			

[redacted]

Figure 15: Probabilistic Sensitivity Analysis Scatterplot (CIC)

B.3.8.2. Deterministic sensitivity analysis

DSA results indicate the parameters that influence the results and conclusions of the decision problem to the greatest degree (Table 80 and Figure 16). Adherence to oral ART is the most influential parameter, which is to be expected as this impacts the efficacy of all lines. Indeed, the degree to which efficacy is reduced in the first modelled line for both arms is also influential to results as is the time horizon. It is important to note that while these parameters may be influential, there are no variations in the parameters that result in CAB LA + RPV LA being deemed not cost-effective.

Table 80: Deterministic Sensitivity Analysis Results

Scenario	Parameter variation	Incremental			ICER
		Costs	QALY	LYG	
Adherence modelling	On	[redacted]	[redacted]	[redacted]	-£65,850.02
	Off	[redacted]	[redacted]	[redacted]	-£168,089.16
Variation of adherence to first line ART – treatment arm	Base case –20%	[redacted]	[redacted]	[redacted]	-£118,309.16
	Base case (100% of trial)	[redacted]	[redacted]	[redacted]	-£65,850.02
Model time horizon (months)	120 months	[redacted]	[redacted]	[redacted]	-£113,752.25
	240 months	[redacted]	[redacted]	[redacted]	-£93,060.50
Variation of adherence to first line ART – control arm	80% of base case	[redacted]	[redacted]	[redacted]	-£47,453.28
	120% of base case	[redacted]	[redacted]	[redacted]	-£103,265.43
Discount, outcomes (%)	Lower (0%)	[redacted]	[redacted]	[redacted]	-£36,680.63
	Upper (6%)	[redacted]	[redacted]	[redacted]	-£91,370.81
Treatment-related utility advantage (Intervention)	Lower (120% of base case)	[redacted]	[redacted]	[redacted]	-£73,520.05
	Upper (80% of base case)	[redacted]	[redacted]	[redacted]	-£83,212.40
Costs discount (%)	Lower (0%)	[redacted]	[redacted]	[redacted]	-£80,486.15
	Upper (6%)	[redacted]	[redacted]	[redacted]	-£56,851.18
Age (years)	Lower (80% base case)	[redacted]	[redacted]	[redacted]	-£75,182.90
	Upper (120% base case)	[redacted]	[redacted]	[redacted]	-£58,182.14

Health state utilities	Lower (80% of base case)	[redacted]	[redacted]	[redacted]	-£74,231.84
	Upper (120% of base case)	[redacted]	[redacted]	[redacted]	-£59,169.00
Percentage of cohort that are female (%)	Lower (0%)	[redacted]	[redacted]	[redacted]	-£64,410.81
	Upper (100%)	[redacted]	[redacted]	[redacted]	-£71,198.42
Variation of adherence to second 4L therapy line	Lower (80% of base case)	[redacted]	[redacted]	[redacted]	-£60,775.89
	Upper (120% of base case)	[redacted]	[redacted]	[redacted]	-£69,727.48
Probability of non-virologic discontinuation of CAB+RPV Q2M	Lower (80% of base case)	[redacted]	[redacted]	[redacted]	-£70,157.87
	Upper (120% of base case)	[redacted]	[redacted]	[redacted]	-£61,872.99
Treatment-related utility advantage (Comparator)	Lower (80% of base case)	[redacted]	[redacted]	[redacted]	-£70,081.43
	Upper (120% of base case)	[redacted]	[redacted]	[redacted]	-£62,100.48
Probability of virologic discontinuation of CAB+RPV Q2M	Lower (80% of base case)	[redacted]	[redacted]	[redacted]	-£62,131.94
	Upper (120% of base case)	[redacted]	[redacted]	[redacted]	-£69,975.62
Risk of death (relative to all cause mortality)	Lower (80% of base case)	[redacted]	[redacted]	[redacted]	-£69,046.40
	Upper (120% of base case)	[redacted]	[redacted]	[redacted]	-£63,325.37
Administration costs associated with injectables	Lower (£5)	[redacted]	[redacted]	[redacted]	-£65,209.51
	Upper (£20)	[redacted]	[redacted]	[redacted]	-£63,287.99
Other resource costs associated with injectables	Lower (80% of base case)	[redacted]	[redacted]	[redacted]	-£65,209.51
	Upper (120% of base case)	[redacted]	[redacted]	[redacted]	-£63,287.99
Treatment disutility (4L 3)	Lower (80% of base case)	[redacted]	[redacted]	[redacted]	-£67,931.67

	Upper (120% of base case)	[redacted]	[redacted]	[redacted]	-£63,892.16
Variation of adherence to second line ART (discontinuation due to viral failure/rebound)	Lower (80% of base case)	[redacted]	[redacted]	[redacted]	-£64,867.65
	Upper (120% of base case)	[redacted]	[redacted]	[redacted]	-£67,005.04
Variation of adherence to second line ART (discontinuation due to virologic reasons)	Lower (80% of base case)	[redacted]	[redacted]	[redacted]	-£64,990.04
	Upper (120% of base case)	[redacted]	[redacted]	[redacted]	-£65,850.02
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.					

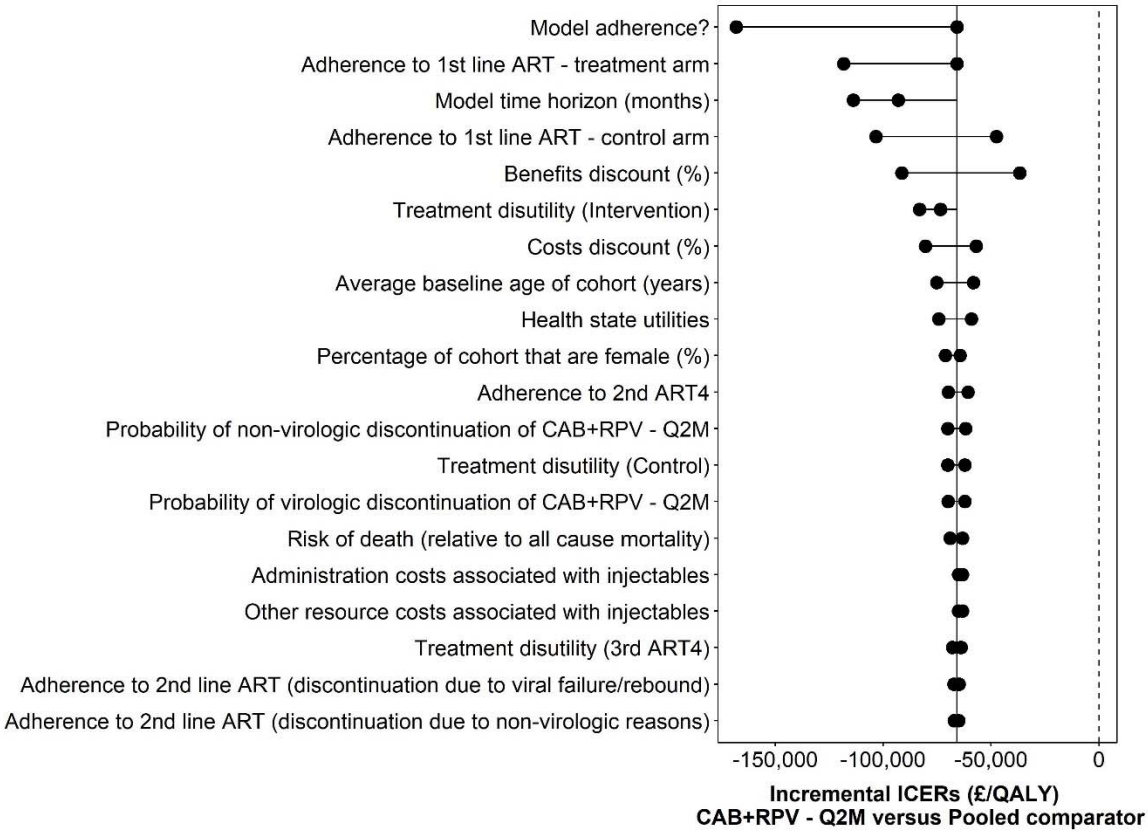


Figure 16 Tornado plot showing results of deterministic sensitivity analysis

B.3.8.3. Scenario analysis

Scenario analysis was undertaken to examine the impact of structural and input assumptions that are necessary when building cost-effectiveness models. In all scenarios examined, while the degree to which there is a utility benefit or cost saving associated with the introduction of CAB LA + RPV LA can change, the decision as to whether it is cost-effective does not change.

B.3.8.3.1. *Alternative efficacy in further lines*

The base case assumes that individuals who discontinue into the further modelled lines experience a reduced efficacy when compared with the first modelled line. In addition, it is assumed that individuals who discontinue due to virologic reasons experience worse outcomes than those who discontinue due to non-virologic reasons. The fourth modelled line assumes a decline in efficacy again depending on whether there have been one or more discontinuations due to virologic reasons.

Clinicians advised that this may not be true for all individuals because of the heterogenous nature of the modelled group. In order to address the impact of this assumption, two scenarios were examined where the reason for discontinuation in second and third modelled line efficacy are not assumed to be different; both are assumed to be associated with the efficacy profile that represents those who experience non-virologic discontinuation in the base case.

Where there is no assumed difference in efficacy between those who discontinue for virologic or non-virologic reasons in the second and third modelled line, CAB LA + RPV LA is estimated to be dominant over the pooled comparator (Table 81). There are slightly reduced QALY gains when compared to the base case although there is no change in the decision.

Table 81: Cost-effectiveness results where there is no assumed difference in efficacy associated with reason for discontinuation

	CAB+RPV-Q2M	Pooled comparator	Incremental
Life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]	[redacted]
ICER (£/QALY)			-£73,730.38
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year			

B.3.8.3.2. *Alternative discounting*

In anticipation of potential revisions to the reference case, the results where discounting for cost and benefits is 1.5% is also presented (Table 82). CAB LA + RPV LA is estimated to be cost-effective in this scenario and there is no difference in the decision from the base case analysis.

Table 82: Cost-effectiveness results where discounting is assumed to be 1.5%

	CAB+RPV-Q2M	Pooled comparator	Incremental
Life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]	[redacted]
ICER (£/QALY)			-£54,039.37
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year			

B.3.8.3.3. *Variability in utility advantage associated with CAB LA + RPV LA*

Analysis of trial data showed a significant difference in the utility between daily oral ART and CAB LA + RPV LA, which is attributed to treatment modality; there are anticipated to be substantial benefits for individuals using long-acting injectable treatment with CAB LA + RPV LA as opposed to daily oral therapy (see Section B.3.4.2.3). This is supported by the results of a time trade-off (TTO) elicitation study performed to examine potential utility differences between treatment modalities.[173] The TTO study, which was conducted in people living with HIV in the UK using relevant health state vignettes, found that in individuals who showed a preference for long-acting injectable treatment over daily oral treatment, the utility advantage was up to [redacted] in some subgroups; thus, the advantage derived from the trial may be conservative. This is expected as generic HRQoL instruments such as the SF-12 (from which the trial-based utility advantage was derived), have limited sensitivity to HIV-specific issues such as stigma. Of note, only individuals who express a desire for long-acting injectable treatment rather than daily oral treatment will switch to CAB LA + RPV LA in clinical practice; those who do not wish for injectable treatment will not form part of the user population.

There are currently no other long-acting injectables available that could be used to validate these utility findings. As such, it is important to examine how the decision might change if the utility advantage were varied, and analyses were therefore carried out to assess this (Table 83). Across all variations of the utility advantage tested, CAB LA + RPV LA remained dominant and no change in the decision with respect to the base case would be warranted.

Table 83: Cost-effectiveness results where utility advantage associated with long-acting injectable treatments is varied

Utility Advantage	Incremental QALYs	Incremental LYs	Incremental Costs (£)	ICER (£)
0.005	[redacted]	[redacted]	[redacted]	-£94,532.43
0.01	[redacted]	[redacted]	[redacted]	-£82,547.33
0.015	[redacted]	[redacted]	[redacted]	-£73,259.30
0.025	[redacted]	[redacted]	[redacted]	-£59,801.80
0.03	[redacted]	[redacted]	[redacted]	-£54,771.15
0.035	[redacted]	[redacted]	[redacted]	-£50,521.21
0.04	[redacted]	[redacted]	[redacted]	-£46,883.32
0.045	[redacted]	[redacted]	[redacted]	-£43,734.14
0.05	[redacted]	[redacted]	[redacted]	-£40,981.40
0.055	[redacted]	[redacted]	[redacted]	-£38,554.67
0.06	[redacted]	[redacted]	[redacted]	-£36,399.28
0.065	[redacted]	[redacted]	[redacted]	-£34,472.11
0.07	[redacted]	[redacted]	[redacted]	-£32,738.76
0.075	[redacted]	[redacted]	[redacted]	-£31,171.37
0.08	[redacted]	[redacted]	[redacted]	-£29,747.21
Base case ([redacted])	[redacted]	[redacted]	[redacted]	-£65,850.02
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year				

B.3.8.3.4. *Variability in adherence reduction with daily oral treatments*

There is no gold standard way to measure adherence, and the variable nature of measuring and reporting makes definitive assessment of adherence difficult. Therefore, results are presented where the reduction in adherence applied to daily oral ART is varied in order to assess the impact of using the base case estimate (Table 84). In all scenarios, the decision as to whether CAB LA + RPV LA is cost-effective is not changed. CAB LA + RPV LA is always associated with cost savings and a utility gain.

Table 84: Cost-effectiveness results where reduction in adherence for daily oral treatment is varied

Adherence reduction	Incremental QALYs	Incremental LYs	Incremental Costs (£)	ICER (£)
5%	[redacted]	[redacted]	[redacted]	-£135,015.53
10%	[redacted]	[redacted]	[redacted]	-£110,802.54
15%	[redacted]	[redacted]	[redacted]	-£92,504.99
20%	[redacted]	[redacted]	[redacted]	-£78,307.60
25%	[redacted]	[redacted]	[redacted]	-£67,044.29
30%	[redacted]	[redacted]	[redacted]	-£57,938.16
35%	[redacted]	[redacted]	[redacted]	-£50,454.61
40%	[redacted]	[redacted]	[redacted]	-£44,215.07
Base case	[redacted]	[redacted]	[redacted]	-£65,850.02
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year				

B.3.8.4. Summary of sensitivity analyses results

Sensitivity analysis on the deterministic results conclude that results are robust to the structural assumptions and variations in input parameters. In all scenarios run, in variations of input parameters and in the vast majority of probabilistic iterations, CAB LA + RPV LA remains dominant over the pooled comparator.

B.4 Subgroup analysis

No subgroup analysis was performed as the trial results are representative of the whole eligible population as defined by the marketing authorisation.

B.4.1. Validation

Demonstrating the validity and credibility of health economic models is a vital component in ensuring their adequacy to support health economic decision making.[174] The base model from which the current customisation for NICE is made has previously been subject to a series of external consistency validation exercises, designed to determine whether values predicted by the cost-effectiveness model are consistent with previously published outcomes. Details of the external validation are provided below, with validation exercises also presented at ISPOR conference proceedings.[175-177]

Further, internal verification of the functions employed by the model were performed to ensure they were consistent with the model specification.

B.4.1.1. External validity of Cost-Effectiveness Model

B.4.1.1.1. *Method*

Studies to which the economic model's outcomes could be compared were identified from a review of previous cost-effectiveness studies in HIV[145], in addition to a search of grey literature. These studies were not identified in the subsequent SLR accompanying this submission which specified relevance to the UK setting (see Appendix G), whereas this prior search did not. Studies that used models whose structure differed significantly from the CAB LA + RPV LA model were excluded; i.e., only models with structures that the CAB LA + RPV LA model could adequately replicate (minimum four therapy lines, three definable ART lines and a 4th line of therapy) were considered in the validation. Studies providing insufficient information regarding model inputs were also excluded.

For each validation exercise, model inputs (demographics, baseline risk factors, HIV disease status, costs, and quality of life values) corresponding to published profiles were entered into the CAB LA + RPV LA cost-effectiveness model workbook. Where required model inputs were not reported, default model inputs were used, or reasonable assumptions were made.

Details of included studies and assumptions made can be found in Table 85.

Table 85. Validation studies and associated assumptions

Study	Assumptions/Notes
Despiegel (2015)[178] Cost-Effectiveness of Dolutegravir in HIV-1 Treatment Naïve and Treatment-Experienced Patients in Canada.	Baseline viral status: Initial health state distribution was imputed by fitting normal distributions to mean and SD values to the CD4+ and viral load values presented for the initiated cohort. Mortality relative risks: Relative risk factors associated with CVD were assumed as model defaults.
Brogan (2014)[179] Cost Effectiveness of Darunavir/ritonavir Combination Antiretroviral Therapy for Treatment-Naïve adults with HIV-1 Infection in Canada.	Baseline viral status: The initial health state distribution of the cohort was assumed equal to the values derived by imputing a normal distribution using mean and SD viral load values presented in the ARTEMIS trial and by multiplying by the proportion of the cohort in each CD4+ health state at baseline.
Brogan (2011)[180] Cost-Effectiveness of Nucleoside Reverse Transcriptase Inhibitor Pairs in Efavirenz-Based Regimens for Treatment-Naïve Adults with HIV Infection in the United States	Baseline viral status: Initial health state distribution was imputed by fitting normal distributions to mean and SD values to the CD4+ and viral load values presented for the initiated cohort. Transition matrices: Derived based on patient virologic response at 48 weeks. Mortality: Relative risk applied to all-cause mortality equally across all CD4+ cell count states. Additional mortality as a result of HIV infection modelled through AIDS-defining events.
Walenksy (2013)[181] Economic Savings Versus Health Losses: The Cost-Effectiveness of Generic Antiretroviral Therapy in the United States	Mortality relative risks: Relative risk factors associated with CD4+ cell count were assumed as model defaults. AIDS-defining events: Probability of experiencing AIDS-defining events and associated mortality assumed as model defaults. CD4+ state utility: Utility values associated with CD4+ cell count states were assumed as model defaults.
Peng (2015)[182] Cost-effectiveness of DTG + ABC/3TC versus EFV/ TDF/FTC for first-line treatment of HIV-1 in the United States	CD4+ state utility: Utility values associated with CD4+ cell count states were assumed as model defaults.

B.4.1.1.2. *Goodness of fit*

For each validation exercise, predicted values for total costs, QALYs and ICERs, were compared with the published (expected) values. Consistent with previously published health economic validation studies, goodness of fit was measured using the coefficient of determination (R^2), mean absolute percentage error (MAPE) and the root mean square percentage error (RMSPE). MAPE and RMSPE were calculated using the following equations:

$$MAPE = \frac{1}{n}\sum_{i=1}^{n}\left|\left(\frac{Y_i - X_i}{Y_i}\right) \times 100\right|$$

$$RMSPE \sqrt{\frac{\sum_{i=1}^{n}(X_i - Y_i)^2}{n}}$$

In which, X_1, X_2,…, X_n correspond to endpoints as predicted by the HIV CAB LA + RPV LA cost-effectiveness model, Y_1, Y_2,… Y_n correspond to endpoints as observed in the published literature, where *n* represents the sample size (i.e. the number of validation endpoints). The residuals *Z* are defined as the differences between the two outcomes: For i = 1,2,…,n, Z = Y – X for.

Further, we present a scatterplot of the observed versus predicted outcomes along the coefficient of determination.

B.4.1.1.3. *Results*

With an Overall R^2 value of 0.937, a high degree of linear correlation is observed between predicted and expected endpoints. Further, with RMSPE and MAPE values of 14.7% and 17.7%, respectively, the HIV CAB LA + RPV LA cost-effectiveness model exhibits a high degree of consistency with previously published cost-effectiveness analyses.

A graphical representation of the relationship between the observed and predicted endpoints of the individual studies has been presented in Figure 17.

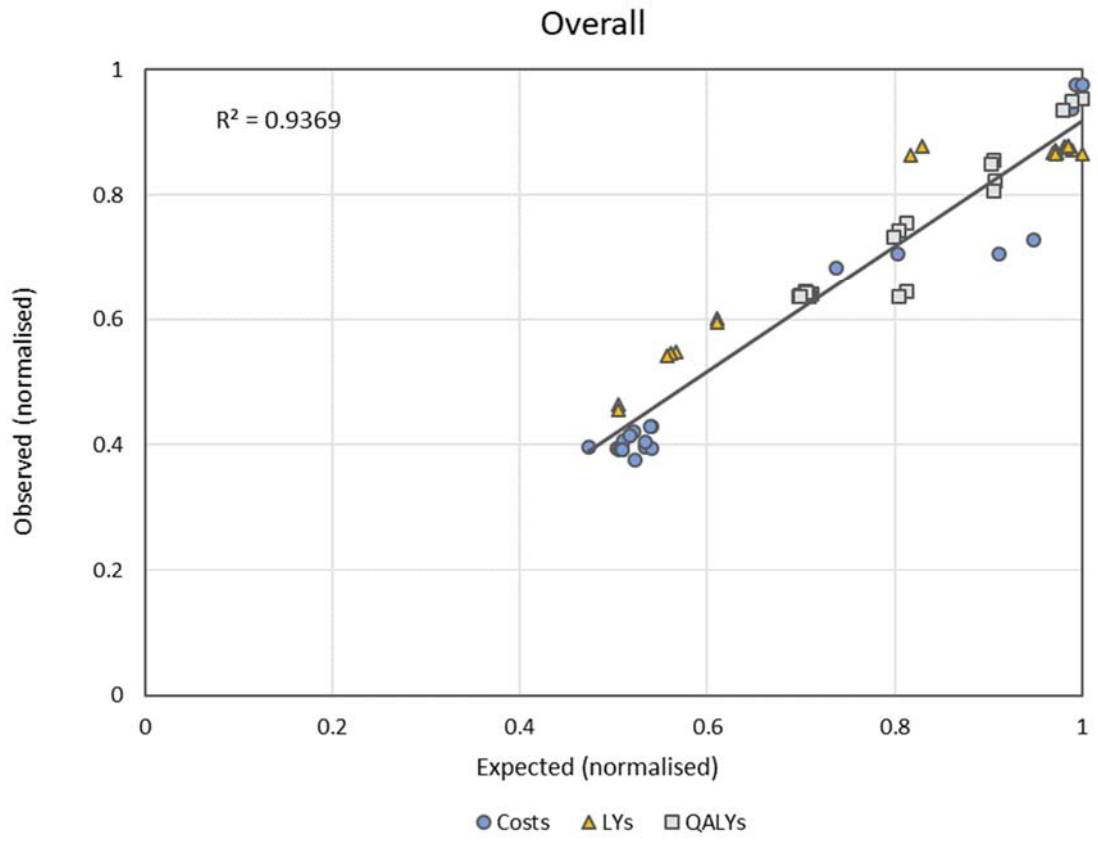


Figure 17. Normalised observed (model predicted) versus expected (published results) validation results for costs, life years (LYs) and quality adjusted life years (QALYs) from the HIV CAB LA + RPV LA cost-effectiveness model

B.4.1.2. Internal validity

The Company cost-effectiveness model has been thoroughly examined for calculation and application errors. Multiple senior analysts have been involved in a quality assessment of functionality of the model and input of relevant parameters.

B.4.2. Interpretation and conclusions of economic evidence

The cost-utility model presented, set out to evaluate the cost-effectiveness of CAB LA + RPV LA compared with a pooled basket of clinically relevant ART comparators to demonstrate the value of introducing the first long-acting injectable regimen, for the maintenance of virological suppression in adults living with HIV from the NHS perspective.

The model sought to capture the key clinical outcomes; virologic suppression and CD4+ cell count and follow a typical treatment pathway. The model design incorporates a semi-Markov structure with a decision tree element, which is an important progression from previous HIV models because it more accurately represents the journey of a person living with HIV. Not all people who discontinue a therapy will move on to receive the same treatment afterwards (selection depends on history and other baseline characteristics) and as such, may not have the same outcomes. The model structure allows this heterogeneity to be captured. In addition, the model has internal functionality to prevent individuals from remaining indefinitely in a failing state. In this way, the model better reflects real-world treatment pathways.

Evidence for this evaluation has where possible, been sought from the most relevant sources; in this case the FLAIR, ATLAS and ATLAS-2M trials. These studies were used to inform the model baseline characteristics and the results of the indirect treatment comparison (CAB LA + RPV LA Q2M versus oral ART) which underpins the modelled efficacy profiles. This ensures that the evidence is directly relevant to the decision population.

Strengths of the modelling approach

The model design has been carefully considered to reflect important clinical outcomes. Where there is a non-inferiority evidence base around universally high efficacy, the benefit and added value of innovative new treatments is unlikely to be in the efficacy of treatment but rather in other components, such as utility, adherence and onward transmission.

Importantly, modelling is consistent with previous modelling approaches but has been developed to advance these; the model is able to capture CD4+ cell count in greater granularity than other published models and at the same time capture virologic suppression. The decision tree allows for virologic and non-virologic failure, which are both considered as important decision points. In addition to these features, the impact of adherence on clinical outcomes and onward transmission is considered. Onward transmission is an important component from a public health perspective.

Results for base model components can be validated against previously published studies. Literature has been consulted for the most appropriate inputs where direct evidence is not available.

HIV is a very complex indication and treatment decisions are, in reality, made on an individual basis with no single well-defined pathway. This necessitates simplifying assumptions to be made during modelling. Simplifying assumptions are present in all analyses and do not limit their usefulness; reflecting complex health situations through modelling is crucial to quantifying their cost and health outcomes. However, the evidence base must be considered alongside the results. The range of sensitivity analysis performed on the base case helps to qualify uncertainty, and a range of scenario analyses have been performed to address structural uncertainty introduced through model design and necessary assumptions. All of these point to CAB LA + RPV LA being dominant in these analyses over the pooled comparator at the prices modelled.

Limitations

There are several limitations to the economic evidence. Ideally, modelling with a patient-level simulation would be considered, but the extremely large computational requirement means this is impractical and therefore unhelpful for decision making. As CAB LA + RPV LA is novel, there are limited studies that can inform certain parameters; for example, adherence inputs cannot be verified against other long-acting injectables for HIV as there are no others. HRQoL trial data was not available for every health state included in the model so literature values were used instead. Survey data was used to inform some parameters. This is often considered to be a less reliable form of evidence, although due to the particularly niche area that these inform (for example, sexual and injecting drug behaviour), it is unlikely that there is a more reliable way to collect information.

In conclusion, the economic evidence can be considered strong and reflective of the patient experience, despite inevitable limitations.

Conclusions from economic evidence

Throughout the range of scenarios and sensitivity analyses, CAB LA + RPV LA dominates the pooled comparator representing current daily oral ART. This indicates that the structural and parameter uncertainties potentially presented do not affect the decision.

In conclusion, CAB LA + RPV LA is a cost-effective use of NHS resources, bringing increased life years and QALYs and reduced lifetime costs compared with current daily oral ART.

Life-long daily ART remains a significant challenge for people living with HIV. In spite of the modern simplified treatment regimens, issues remain around stigma, treatment fatigue, the anxiety and inconvenience some individuals experience around daily scheduling of ART and the effect on psychological wellbeing of the daily reminder of HIV status. CAB LA + RPV LA addresses important unmet needs in the management of HIV and provides a meaningful choice of treatment modality.

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B.6 List of appendices provided as separate documents

Appendix number	Appendix Title
C	SmPC and EPAR
D	Clinical systematic literature review report and NMA feasibility assessment
E	Subgroup analyses (Appendix empty as information provided in main submission)
F	Adverse events (Appendix empty as information provided in main submission)
G	Cost-effectiveness systematic literature review
H	HRQoL systematic literature review
I	Healthcare resource use systematic literature review
J	Clinical outcomes and disaggregated results from the model
K	Checklist of confidential information
L	Indirect treatment comparison report
M	Transition rates and onward transmission probabilities applied in the model
N	Utility analysis report
O	National HIV Clinical Pathway
P	Model technical document and code guide

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Long-acting cabotegravir plus long-acting rilpivirine (CAB LA+RPV LA) for the treatment of virologically suppressed patients with HIV-1 [ID3766]

Clarification questions

March 2021

File name	Version	Contains confidential information	Date
ID3766_CAB_RPV_LA_HIV_ERG CQs_ACIC redacted	V0.1	No	25/03/2021

Notes for company

Highlighting in the template

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Section A: Literature searches

A.1. Please explain the rationale for limiting the literature searches reported in Appendices D, G, H and I to English language only (cf. question B2).

Given the high volume of evidence gathered when applying the English language only limit, expanding the search to other languages was very unlikely to bring new evidence which would diverge from the overall picture drawn from the studies in English language.

A.2. Please explain the rationale for limiting the searches reported in Appendices D, G, H and I by date to 2000 to 2020 (cf. question B2).

Given the high volume of evidence gathered applying the date filter, expanding the search to studies over 20 years old was very unlikely to bring new evidence which would diverge from the overall picture drawn from the studies published in 2000-2020. Further, HIV regimens have been continually developing since the advent of highly-active ART in 1995; thus, studies of treatment regimens more than 20 years old are unlikely to be representative of modern clinical practice.

A.3. Please provide full details of the searches of conference proceedings referred to in Appendices D.1.5, G.1.5, H.1.5 and I.1.5 including the specific resources searched, the search strategies or search terms used, and results.

The list of conference proceedings to search was pre-determined and listed in the protocol for each SLR:

- British HIV Association conference (https://www.bhiva.org/Conferences-Events)
- National HIV Prevention Conference (https://www.cdc.gov/nhpc/index.html)
- The International AIDS Society (IAS) conferences (https://iasociety.org/Conferences)
- Conference on Retroviruses and Opportunistic Infections (CROI; http://www.croiconference.org/)
- HIV drug therapy conferences (http://hivglasgow.org/)
- NICE conference (http://www.niceconference.org.uk/)
- International Society for Pharmacoeconomics and Outcomes (ISPOR) conference (for economic SLRs only; https://www.ispor.org/conferences-education/conferences)

For each conference website listed, the abstract list of the conferences held between 2017 and 2020 were obtained, and were hand searched, through the word-find function, using keywords similar to those used in the searches of electronic databases: HIV, immunodeficiency, AIDS. Abstracts that met eligibility criteria were included in the relevant review. Results of the overall additional sources of evidence (conference proceedings, clinical trial websites, HTA bodies websites, and reference lists of systematic literature reviews identified through database searches) are included in the PRISMA diagram ("Additional records identified through other sources" box), with a further breakdown in Table 1.

A.4. Please provide full search strategies for the clinical trial registries searches (clinicaltrials.gov, World Health Organization (WHO) International

Clinical Trials Registry Platform (ICTRP) and European Union (EU) Clinical Trials Register) in Appendices D.1.5, H.1.5 and I.1.5.

The list of clinical trial registries to search was pre-determined and listed in the protocol for each SLR:

- ClinicalTrials.gov (http://clinicaltrials.gov/)
- International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/)
- European Union's Clinical Trials Register (http://www.clinicaltrialsregister.eu/)

Each clinical trial registry website was hand searched, through the search function available from each website, using keywords similar to those used in the searches of electronic databases: HIV, immunodeficiency, AIDS. Trials that met eligibility criteria were included in the relevant review. Results of the overall additional sources of evidence (conference proceedings, clinical trial websites, HTA bodies websites, and reference lists of systematic literature reviews identified through database searches) are included in the PRISMA diagram ("Additional records identified through other sources" box), with a further breakdown in Table 1.

A.5. Please provide full details of the searches of health technology assessment organisations referred to in Appendices D.1.5, G.1.5, H.1.5 and I.1.5, including the specific resources searched, the search strategies or search terms used, and results.

The list of HTA bodies to search was pre-determined and listed in the protocol for each SLR:

- National Institute for Health and Care Excellence (NICE), Scottish Medicines Consortium (SMC) and All Wales Medicines Strategy Group (AWMSG) in UK
- Canadian Agency for Drugs and Technologies in Health (CADTH) in Canada

Each HTA website was hand searched, through the search function available from each website, using keywords similar to those used in the searches of electronic databases: HIV, immunodeficiency, AIDS. HTA documents that met eligibility criteria were included in the relevant review. For the clinical SLR (Appendix D),

HRQoL/Utilities SLR (Appendix H) and HCRU SLR (Appendix I), the relevant HTA documents were used to review the reference list for each SLR, with a view to identify any potential trials not captured through the database searches. Results of the overall additional sources of evidence (conference proceedings, clinical trial websites, HTA bodies websites, and reference lists of systematic literature reviews identified through database searches) are included in the PRISMA diagram ("Additional records identified through other sources" box), with a further breakdown in Table 1.

It should be noted that reporting was limited for previous HTAs.

Table 1. Records identified through grey literature searches across SLRs

	Conferences	Clinical trials	HTA	Other
Clinical	45	48	0	54
HRQoL/utilities	6	1	0	37
Cost and resource use	0	0	0	0
Cost effectiveness	1	NA	0	0

A.6. Please provide full details of the targeted literature review of network meta-analyses (NMAs) referred to in section B.2.9.3.1.1; and the review of 'the methodological literature as it pertains to non-inferiority trials and indirect comparisons" referred to in section B.2.9.3.2.

A pragmatic literature search was performed using search terms to identify English-language articles that specifically reported on NMAs with at least two comparators focusing on HIV-related treatment efficacy outcomes. The database search was restricted to PubMed, with no time limitation. Full texts were obtained and reviewed and clinical experts were consulted to determine study relevance.

With regards to methodological literature as it pertains to non-inferiority trials and indirect comparison, this included a hand search of the literature using the following keywords: non-inferiority trials, superiority trials, equivalence trials, trial design, methods, analysis, indirect treatment comparison.

A.7. Please provide full details of the targeted literature review of adherence to daily oral antiretroviral therapy (ART) referred to in sections B.1.3.5.3 and B.3.2.5.1.1.

A systematic update of a targeted literature review was undertaken in 2020 assessing the relationship between efficacy and adherence to HIV therapy. The original literature review report has been provided as part of this response (please refer to Appendix A7b).

For the purposes of this submission, we collated SLR-identified studies reporting UK adherence but without efficacy data (i.e. excluded from SLR, but relevant to this use); UK-specific adherence data were considered most relevant because adherence has cultural dimensions. These studies were assessed for suitability to inform the economic model. Further information on our examination of the UK studies identified there, and other studies published subsequently, are presented in Appendix A7a.

A.8. Please provide full details of the targeted literature review of viral transmission in Appendix P, section 3.6; and the "pragmatic targeted review of published literature" referred to in Appendix P, section 5.2.1.

A literature search was performed using predetermined search terms to identify English-language articles that reported on HIV transmission models. This was a targeted review and the database search was restricted to PubMed, with the search limited to publications from 01 January 2008 until 01 January July 2018. Full texts were obtained and reviewed to determine study eligibility based on predefined inclusion and exclusion criteria.

Studies identified within this targeted literature review were further used to validate the transmission module. The search strategy is presented in Table 2 and the study characteristics are presented in Table 3.

Table 2: Proposed PubMed search strategy (as of 02/07/2018)

#	Search terms		Number of hits
1	human immunodeficiency virus[MeSH Terms]	**HIV terms**	91,301
2	HIV Infections[MeSH Terms]		259,161
3	(HIV Infections[Title/Abstract] OR HIV[Title/Abstract] OR HIV?1*[Title/Abstract] OR HIV?2*[Title/Abstract] OR HIV		279,960

	infect*[Title/Abstract] OR human immuno?deficiency virus[Title/Abstract] OR human immune?deficiency virus[Title/Abstract])		
4	(human immun*[Title/Abstract]) AND deficiency virus[Title/Abstract]		580
5	(acquired immuno?deficiency syndrome[Title/Abstract] OR AIDS[Title/Abstract] OR acquired immunedeficiency syndrome[Title/Abstract] OR acquired immune deficiency[Title/Abstract])		139,876
6	(acquired immun*[Title/Abstract]) AND deficiency syndrome[Title/Abstract]		5,645
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6		396,060
8	disease transmission, infectious[MeSH Terms]	**Disease transmission terms**	60,149
9	transmission[Title/Abstract] OR infectiousness[Title/Abstract] OR acquisition[Title/Abstract] OR infectivity[Title/Abstract] OR exposure[Title/Abstract] OR transmissibility[Title/Abstract] OR incidence[Title/Abstract]		1,740,143
10	#8 OR #9		1,773,473
11	"transmission model*"[Title/Abstract] OR "epidemic model*"[Title/Abstract] OR "mathematical model*"[Title/Abstract] OR "cost effectiveness"[Title/Abstract] OR "cost-effectiveness"[Title/Abstract])	**Model terms**	77,676
12	#7 AND #10 AND #11	**Combined**	1,260
13	Date Publication: 2008 to present	**Date limit**	815

Table 3. Study characteristics

Author	Year	Country	Study type	Model type	Cohort	Population	Time horizon	Model outcomes
Alistar et al.[1]	2014	Russia and Uganda	Disease transmission	Compartmental/ Markov model	Population level	IDUs and non-IDUs	10 years	IDU prevention funding increase; People on treatment, Prevention costs per year; Treatment costs per year; Reduction in HIV cases between 2007 - 2020
Bezemer et al.[2]	2015	Netherlands and Curaçao	Observational study*	Individual/Monte Carlo simulation	Patient level	MSM	10 years	Reproduction numbers within each MSM cluster
Bezemer, et al.[3]	2008	Netherlands	Observational study *	Compartmental/ Markov model	Patient level	MSM	25 years	Reproduction number R(t)
Birger et al.[4]	2014	USA	Disease transmission	Compartmental/ Markov model	Population level	General population	10 years	Incidence; Mortality
Bobashev et al.[5]	2014	Russia	Observational study *	Individual/Monte Carlo simulation	Patient level	IDU serodiscordant couples	3 years	Probability of getting infected within 6 months
Cassels et al.[6]	2009	USA	Observational study *	Compartmental/ Markov model	Cohort level	MSM	NR	Prevalence; Risk behavior
Goldman et al.[7]	2014	USA	Disease transmission	Compartmental/ Markov model	Population level	General population	14 years	Incidence; Avoided losses of life expectancy; Value of life-years saved through early treatment
Gopalappa et al.[8]	2012	USA	Cost-effectiveness	Individual/Monte Carlo simulation	Cohort level	General population	Lifetime	Lifetime number of HIV transmissions averted per index person; Life expectancy; Onset of AIDS; Discounted values of total lifetime costs of HIV
Graw et al.[9]	2012	Latvia	Disease transmission	Compartmental/ Markov model	Population level	IDUs, MSM, HET, SW	10 years	Cumulative incidence for the sub-epidemics in MSM, IDU and HET
Gray et al.[10]	2017	Australia	Observational study*	Risk equation model	Cohort level	Temporary but legal citizens in Australia, MSM and non-MSM	5 years	Annual infections after 5 years; Cumulative infections; Infections averted; Cost of providing care and ART; Lifetime care and ART costs; Reduction in lifetime care and ART costs
Gurski and Hoffman[11]	2016	USA	Disease transmission	Compartmental/ Markov model	Population level	General population	10 years	Incidence; Prevalence
Herbeck et al.[12]	2014	UK	Disease transmission	Stochastic agent-based HIV epidemic model	Patient level	General population	100 years	The variability of set point viral load (a prognostic factor for AIDS progression) over time
Heymer and Wilson[13]	2011	Australia	Disease transmission	Compartmental/ Markov model	Population level	MSM	5 years	Expected number of HIV diagnoses among MSM/infections averted under status quo and ideal scenarios
Hoare et al.[14]	2008	Australia	Disease transmission	Compartmental/ Markov model	Population level	MSM	20 years	Trends in clinical and behavioral parameters and HIV transmission (Prevalence)

Author	Year	Country	Study type	Model type	Cohort	Population	Time horizon	Model outcomes
Holtgrave[15]	2010	USA	Disease transmission	Compartmental/ Markov model	Population level	General population	Lifetime	Reproductive rate (R0): the number of HIV transmissions from one person living with HIV to HIV-seronegative partners over the HIV-seropositive person's lifetime
Holtgrave et al.[16]	2012	USA	Disease transmission and cost-effectiveness	Compartmental/ Markov model	Population level	General population	10 years	Incidence; Prevalence; Transmission rate; Cumulative infections averted; Cumulative quality-adjusted-life years (QALYs) saved; Cumulative cost of policy implementation; Downstream medical costs avoided due to HIV infections averted; Ratio of savings to costs; Net cost per QALY saved
Lazenby et al.[17]	2014	USA	Cost-effectiveness	Decision tree	Cohort level	General population	1 year	Costs saved; Costs for screening and treatment; Costs of new HIV cases; Rate of HIV transmission from infected women to men
Letchumanan et al.[18]	2015	Canada	Cost-effectiveness	Compartmental/ Markov model	Cohort level	HET serodiscordant couples **	Lifetime	ICER; QALYs; Probability of giving birth to a healthy child
Lima et al.[19]	2015	USA	Disease transmission	Compartmental/ Markov model	Population level	Black MSM with a history of incarceration	10 years	Cumulative HIV incidence
Lima et al.[20]	2010	Canada	Disease transmission	Compartmental/ Markov model	Population level	MSM, IDU, SW	40 years	Incidence; Infections averted; Costs avoided
Lin et al.[21]	2016	USA	Cost-effectiveness and disease transmission	Bernoulli process model	Population level	MSM, IDU and sexually active HET	NR	Reduction in annual risk of HIV transmission or acquisition
Long et al.[22]	2010	USA	Cost-effectiveness	Compartmental/ Markov model	Population level	High-risk (IDU, MSM) and low-risk individuals	20 years and lifetime (costs and QALYs)	HIV infections; Discounted costs; Discounted quality-adjusted life years; Incremental cost-effectiveness ratios
Mabileau et al.[23]	2015	France	Cost-effectiveness and disease transmission	Compartmental/ Markov model	Cohort level	HIV-serodiscordant couples desiring a child ■	1 year	Cumulative risk of HIV heterosexual transmission to HIV negative partner and mother-to-child transmission; Risk of birth defects; Life expectancy of both woman and child; Costs; Incremental cost-effectiveness ratios
Marseille et al.[24]	2011	USA	Cost-effectiveness and disease transmission	Compartmental/ Markov model	Population level	General population	Lifetime	Number of transmissions averted among participants in each intervention type
Maulsby et al.[25]	2017	USA	Cost-effectiveness	Observational trial-based costing analysis	Cohort level	Multiple populations***	1 year	HIV transmission averted

Author	Year	Country	Study type	Model type	Cohort	Population	Time horizon	Model outcomes
McCabe et al.[26]	2010	USA and Europe	Cost-effectiveness	Monte Carlo simulation	Cohort level	Pregnant women	NR	Average costs; Percentage requiring c-section; Percentage of mother-to-child HIV transmission; Infants quality-adjusted life expectancy; ICER
Mills et al.[27]	2013	Russia	Disease transmission	Compartmental/ Markov model	Cohort level	IDU, non IDUs and their partners	25 years	Transmission rates
Miltz et al.[28]	2017	UK and Europe	NHS policy report	Individual/Monte Carlo simulation	Patient level	MSM	NR	Incidence; ICER; QALYs
Nichols et al.[29]	2015	Netherlands	Disease transmission	Compartmental/ Markov model	Population level	MSM	5-year scenario and 10-year scenario	Cumulative infections averted; Cost-effectiveness
Nosyk et al.[30]	2015	Canada	Disease transmission and cost-effectiveness	Compartmental/ Markov model	Population level	MSM, IDU, MSM-IDU, HET	25 years	Incidence; Prevalence; Mortality; Costs; QALYs
Nosyk et al.[31]	2017	Canada	Disease transmission and cost-effectiveness	Compartmental/ Markov model	Population level	MSM, IDU, MSM-IDU, HET	7 years	Incidence; Prevalence; Mortality; Costs; QALYs
Pinkerton et al.[32]	2011	NR	Disease transmission	Compartmental/ Markov model	Patient level	General population	NR	Risk of HIV infection
Shah et al.[33]	2016	USA	Disease transmission	Compartmental/ Markov model	Population level	HET, MSM, IDU	10 years	Incidence; Prevalence; Mortality; Costs
Shah et al.[34]	2016	USA	Disease transmission and cost-effectiveness	Compartmental/ Markov model	Population level	HET, MSM, IDU	20 years	Incidence; Prevalence; Mortality; Costs
Shen et al.[35]	2017	USA	Disease transmission	Infection-age-structured transmission model	Cohort level	MSM	20 years	Total and drug-resistant HIV incidence
Song et al.[36]	2015	USA	Disease transmission and cost-effectiveness	Compartmental/ Markov model	Population level	IDU	10 years	Incidence prevented; Incidence; Prevalence; QALYs; Medical costs
Sood et al.[37]	2013	USA	Disease transmission	Compartmental/ Markov model	Cohort level	MSM	10 years	Incidence; mortality; AIDS incidence; multi-drug resistance
Sorensen et al.[38]	2012	USA	Disease transmission	Compartmental/ Markov model	Cohort level	MSM	20 years	Reduction in incidence
Tuckwell et al.[39]	2008	NR	Disease transmission	Simple mathematical model	Cohort level	General population	NR	Probability and time dependence that one or more HIV virions successfully infect target cells

Author	Year	Country	Study type	Model type	Cohort	Population	Time horizon	Model outcomes
Vrancken et al.[40]	2015	NR	Disease transmission	Transmission model and Bayesian hierarchical phylogenetic model (HPM)	Population level	MSM, HET, direct BC	NR	Viral evolutionary histories and bottleneck size differences
Vrancken et al.[41]	2014	NR	Disease transmission	Bayesian genealogical inference framework	Observed patient cohort	General population	15 years	Viral evolutionary histories and bottleneck size differences
White et al.[42]	2014	UK	Disease transmission	Individual/Monte Carlo simulation	Patient level	MSM	3 months following infection	Number of transmission events that would have occurred from each study participant during the 3-month period after infection
Wilson et al.[43]	2010	Australia	Disease transmission	Compartmental/ Markov model	Cohort level	MSM	NR	Relative risk of HIV acquisition associated with serosorting
Xia et al.[44]	2015	USA	Disease transmission	Compartmental/ Markov model	Population level	General population	30 years	Case finding; Incidence
Xiridou et al.[45]	2010	Netherlands	Disease transmission	Compartmental/ Markov model	Population level	African/ Caribbean migrants, local Dutch population	20 years	Prevalence among migrants and overall; Percentage of new infections via sexual transmission; percentage of newly infected Dutch people
Xiridou et al.[46]	2011	Netherlands	Disease transmission	Compartmental/ Markov model	Population level	African/ Caribbean migrants, local Dutch population	20 years	Incidence
Zaric et al[47].	2008	USA	Disease transmission	Compartmental/ Markov model	Population level	MSM	20 years	Incidence, Costs, QALYs

AIDS: acquired immunodeficiency syndrome; BC: blood contact; HET: heterosexual; ICER: incremental cost-effectiveness ratio; IDU: injecting drug user; MSM: men-who-have-sex-with-men; QALY: quality adjusted life year; SW: sex worker.
* supplemented with mathematical mod
** The male partner is HIV positive
***African-America rural residents; Substance users; Homeless; Transgender women; Individuals living in poverty and sub-optimally housed; Women who have experienced trauma
■ With the male partners being treated for HIV with undetectable blood viral load and the female partners HIV negative

A.9. Please provide the missing search strategies in Appendix G 1.1, Table 3 (National Health Service (NHS)-Economic Evaluation Database) and Table 4 (EconLIT via EBSCO).

The two search strategies are as follows:

Table 4. (National Health Service (NHS)-Economic Evaluation Database) search strategy

#	Terms	# hits
1	MeSH DESCRIPTOR HIV EXPLODE ALL TREES IN NHSEED	97
2	MeSH DESCRIPTOR HIV infection EXPLODE ALL TREES IN NHSEED	636
3	#1 OR #2	636
4	((HIV) OR (HIV infections)) AND ((Economic evaluations:ZTD and Bibliographic: ZPS) OR (Economic evaluation:ZTD and Abstract: ZPS) IN NHSEED	723
5	MeSH DESCRIPTOR acquired immunodeficiency syndrome EXPLODE ALL TREES IN NHSEED	47
6	((acquired immune deficiency syndrome) OR (acquired immune-deficiency syndrome) OR (acquired immunodeficiency syndrome)) AND ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT AND Abstracts:ZPS) IN NHSEED	45
7	#4 OR #5 OR #6	736
8	#3 OR #7	745

Table 5. (EconLIT via EBSCO) search strategy

#	Terms	# hits
1	human immunodeficiency virus OR HIV	2,044
2	Cost effectiveness	6,509
3	#1 AND #2	74

Section B: Clarification on effectiveness data

Treatment pathway

B1. Priority question. Section B.1.3.6.2 of the company submission (CS) provides information on the place of long-acting cabotegravir (CAB LA) + long-acting rilpivirine (RPV LA) in the treatment pathway.

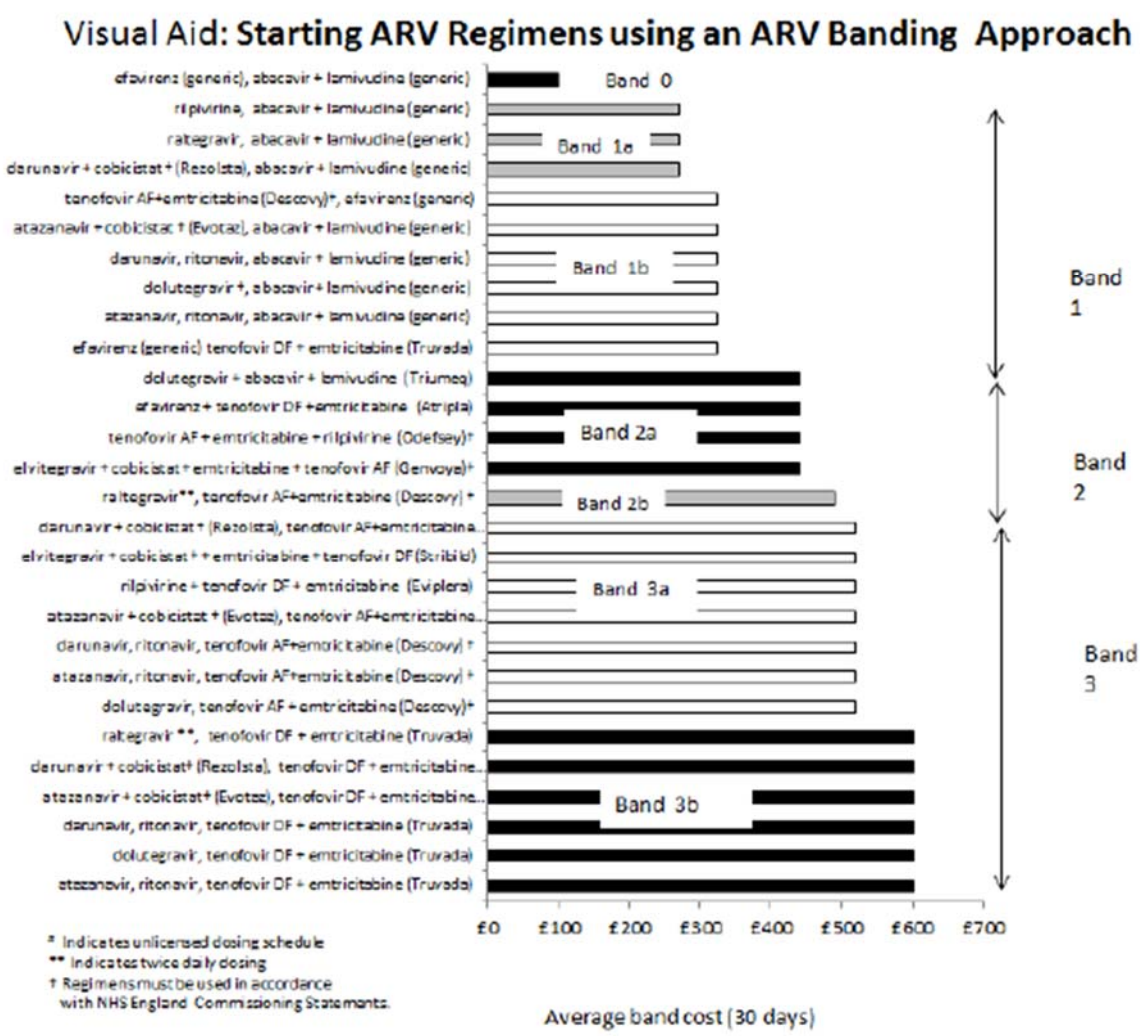
a. **The choice of oral alternatives in the absence of CAB LA + RPV LA (box 5 of Figure 1) is not clearly described. Please provide more details on the methods of establishing the alternative treatments as well as for which patient population that applies to and reference any sources from which the information was gathered.**

b. Please provide a simplified version of Figure 1 focussing on the treatment pathway, e.g. without statements made by patients etc. This should include all interventions and comparators mentioned in both, the National Institute for Health and Care Excellence (NICE) final scope as well as the decision problem addressed in the CS, and should indicate whether a treatment is considered to be first-line, second-line etc.

a. Although international treatment guidelines are somewhat prescriptive in their recommendations for initial therapy in antiretroviral naïve individuals, there are no specific guidelines or pathways for individuals switching treatment. Where a change of therapy is warranted for a virally-suppressed individual, multiple factors are taken into consideration, including the presence of underlying ARV resistance, and whether the switch is for toxicity, adherence concerns, drug-drug interactions or co-morbidities. The complexity and heterogeneity of individuals across these categories means that there is no "average" patient or pathway that can be applied to this group of individuals.

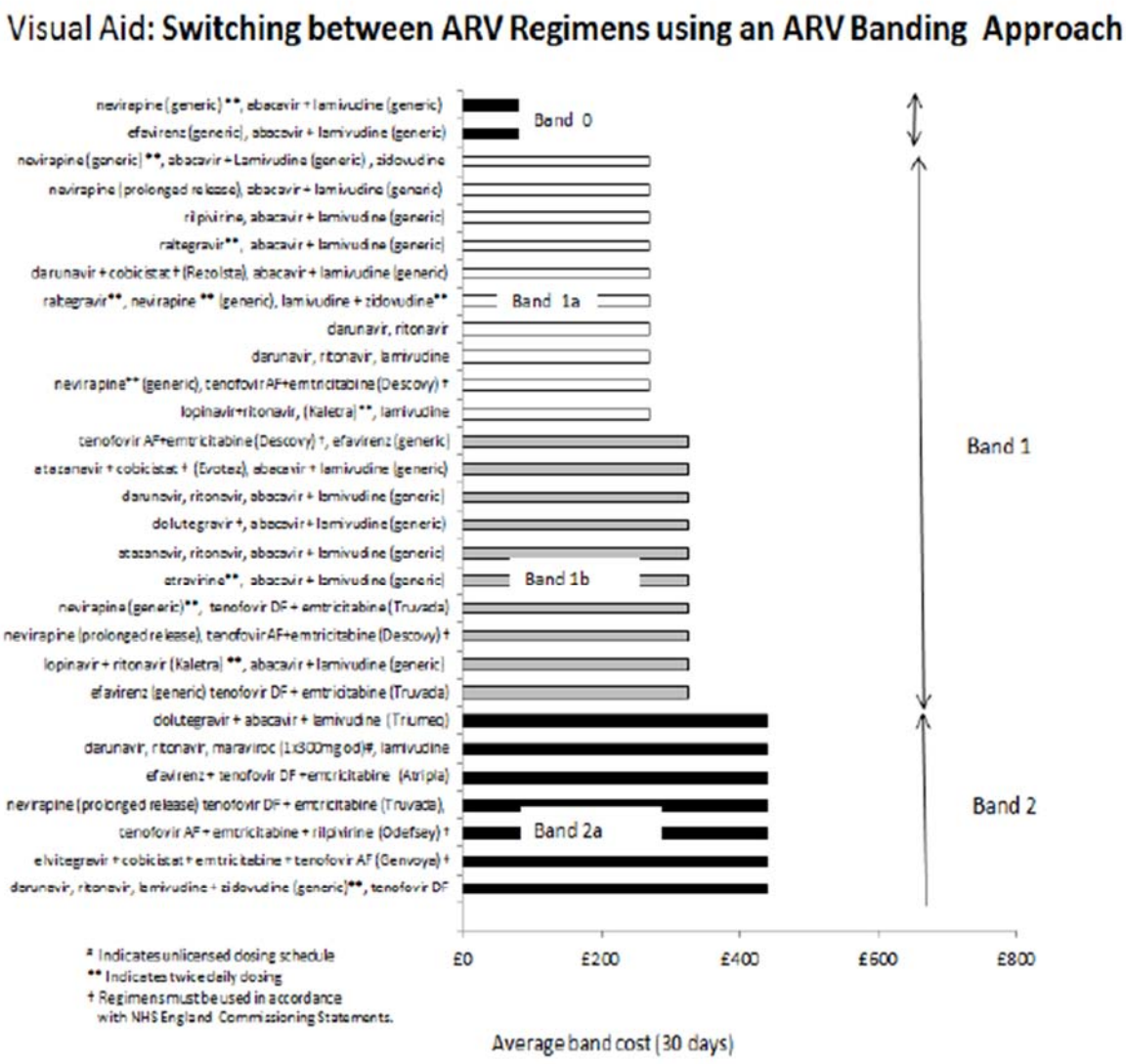
Commissioning policies in England have an influence, too; since they consider treatment affordability.[48] Regimens are grouped into their price bands and clinicians are encouraged to prescribe from lower cost bands (e.g. 0 & 1) early on, or switch to them where clinically appropriate. Switching within band 1 regimens or cost saving/cost neutral switches do not require multidisciplinary team approval, whilst moving from a low to a higher cost option usually does.[48]

Figure 1 to Figure 3, for example, show the ARV price bands as applicable to the Midlands and East region for starting and switching ARV treatment.[49] We expect CAB LA + RPV LA to fall into band 2, in general an option where “a regimen within the same, or lower, band would not provide the desired clinical response”.[49] This was discussed with NICE during the scoping workshop for this appraisal.



This is not an exhaustive list and only includes some of the more commonly used drug regimens.

Figure 1. Antiretroviral banding for starting antiretroviral regimens[49]



This is not an exhaustive list and only includes some of the more commonly used drug regimens.

Figure 2. ***Antiretroviral banding for switching antiretroviral regimens (Bands 1 and 2)[49]***

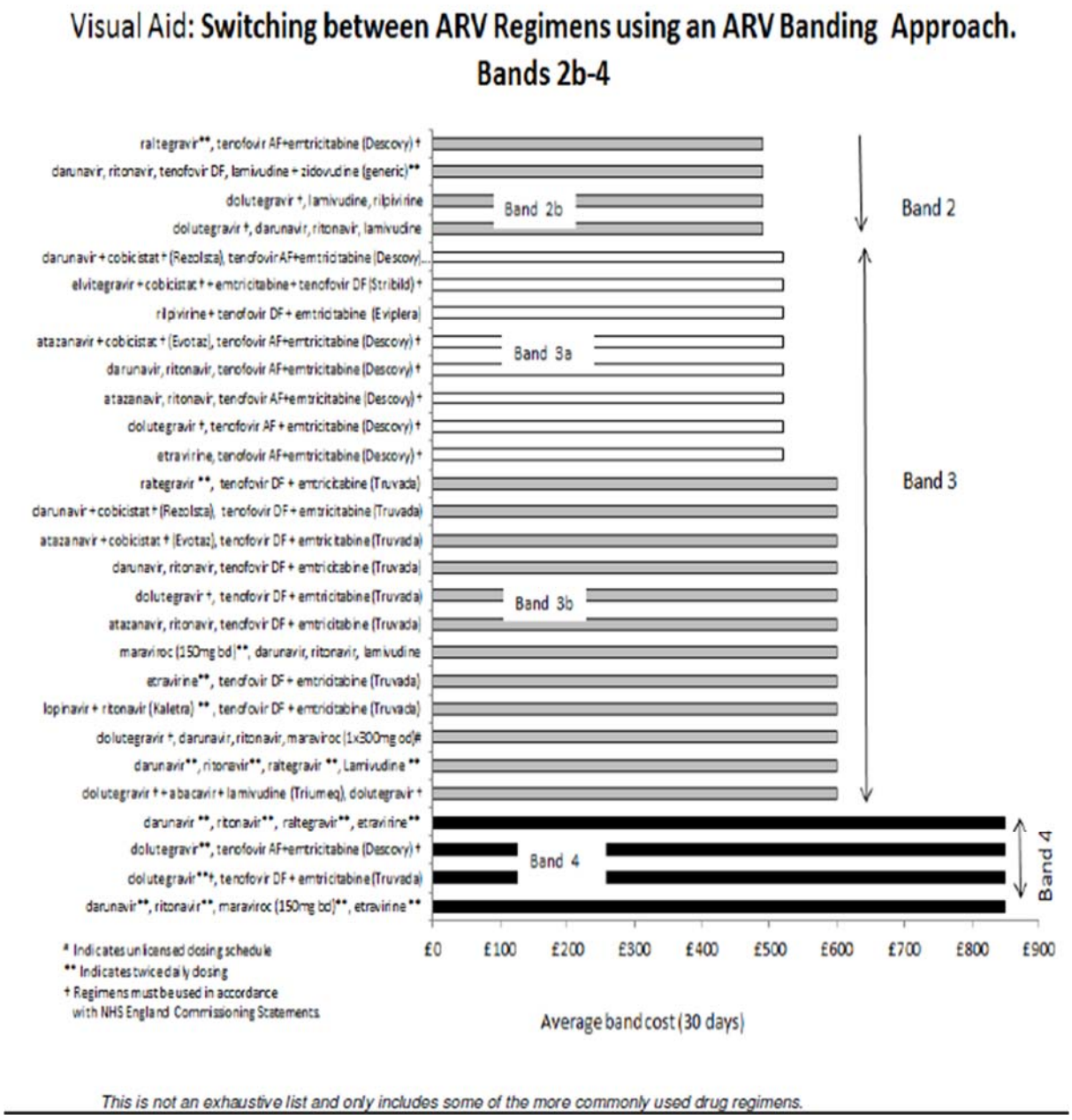


Figure 3. ***Antiretroviral banding for switching antiretroviral regimens (Bands 2,3 and 4)[49]***

The regimens called out in the company submission (Box 5 of Figure 1), i.e. the comparators in this appraisal, were drawn from market data for a 'stable switch' population as described in Section B.3.2.2. of the company submission. The data source was ActOne market research, which collects data from 10-14 hospital accounts across England in the form of Patient Record Forms (PRFs). There are 4-6 Healthcare Professionals from each account providing a total of 183 PRFs per month. Approximately 60% of the hospital accounts are London based with the remaining 40% coming from the rest of England. These data allow analysis of switch share by regimen since they reflect the treatments **to** which virally suppressed patients are currently switching. ViiV applied a pragmatic 2.5% share cut off below which were less relevant comparators. The resulting shortlist was refined with clinical experts who advised us that given the way that regimens are commissioned (the price bands described above). Truvada based regimens (e.g. Truvada + Tivicay) are not a likely alternative to CAB LA + RPV LA and should be excluded since the majority (>50%) of people on HIV treatment in England and Wales are receiving such therapy. Given then that most patients will likely have already received, or be currently receiving a Truvada based regimen, they are more likely to be switching *away* from these and onto one of the basket of comparators we have listed or onto CAB LA + RPV LA. Clinicians also advised that Juluca (dolutegravir plus rilpivirine [DTG + RPV]) be included as its components match CAB LA + RPV LA more closely than other oral regimens.

The market data are not stratified by the reason for the switch, so we acknowledge the approach isn't perfect. However, the precise distribution of relevant comparators for CAB LA + RPV LA is unknowable in part because those whose issues can be solved by a switch to a *non-oral and/or a non-daily* treatment are not represented (as no such option exists). We are confident that our approach – starting with market data and engaging prescribers in a face validity check – is appropriate. Further, the simple mean cost of the comparator basket is more appropriate in this context where we are unable to map the reason for switching in today's market to the reasons that CAB LA + RPV LA may be an alternative.

b. As described above, there is no simple treatment pathway in HIV. Instead, the comprehensive list of available regimens has the lower cost ones listed upfront to be

used, where clinically appropriate, ahead of higher cost regimens. Considerable heterogeneity sits behind every treatment decision because of the variability in the population of people living with HIV, their treatment history, experience and needs. We believe the value of Figure 1 (in the submission) as it stands is to illustrate this. Patient quotes have been used to show what conversations may sit behind the decision to consider CAB LA + RPV LA as a treatment option. We do not feel they distract from or overcomplicate the figure, given how patient-centric the treatment decision making is. We prefer to retain them in the schematic.

Systematic review

B2. Priority question. Table 5 of Appendix D of the CS details the eligibility criteria for the identification of human immunodeficiency virus (HIV) clinical effectiveness studies.

a. **The population inclusion criteria differ slightly between Table 5 of Appendix D and Table 1 of document B of the CS, i.e. the decision problem (Table 1) refers to "adults who are virologically suppressed (HIV-1 RNA [ribonucleic acid] <50 copies /mL) on a stable antiretroviral regimen without present or past evidence of viral resistance to, and no prior virological failure with, agents of the NNRTI [nucleoside reverse transcriptase translocation inhibitor] and INI [integrase inhibitor] class[1], who require a treatment switch due to non-virologic reasons" whereas Table 5 does not mention this population. Please clarify whether this criterion was applied in the review, e.g. by referring to relevant sections of the CS or CSRs.**

b. **As noted in section A, there are restrictions for date ("Studies published from 01 January 2000 to 24 April 2020") as well as language ("English language only"). Please justify these restrictions and, if possible, provide a list of excluded studies based on these criteria. Alternatively, please discuss if potentially relevant studies might have been missed.**

c. **Please provide a justification for the exclusion of observational case-control studies.**

a. The SLR inclusion criteria is slightly broader than the licensed indication for CAB LA + RPV LA in order to encompass the potential comparator population. The correspondence between the SLR inclusion criteria and the CAB LA + RPV LA licensed indication is provided below:

    - "adults who are virologically suppressed (HIV-1 RNA <50 copies /mL) on a stable antiretroviral regimen": This aligns with the SLR inclusion criteria, as stated in Appendix D Table 5 from the company submission.

    - "without present or past evidence of viral resistance to, and no prior virological failure with, agents of the NNRTI and INI class": This criterion was not applied during the SLR. However, inclusion criteria were captured at the data extraction stage and, where inclusion criteria are available, all switch studies specified that participants should not have resistance to study antiretrovirals. Hence, the SLR studies align with the population of interest for CAB LA + RPV LA. Further, this methodology ensures that relevant data for comparator therapies was captured, particularly where studies may specify resistance to other classes (e.g. PIs).

    - "who require a treatment switch due to non-virologic reasons": As patients are virally suppressed on current regimen, this criterion is aligned to the patient population in SLR inclusion criteria.

b. The majority of HIV randomised controlled trials are published in English. Given the high volume of evidence gathered applying the English language only limit, and the date limit, expanding the search to other languages or to older studies was very unlikely to bring new evidence which would diverge from the overall picture drawn from the studies in English language.

c. The search strategy included observational study designs such as longitudinal studies and retrospective studies. However, as the literature search retrieved a very large number of randomised controlled trials (RCTs), which are of higher quality compared to observational studies, these studies were not extracted. Case control studies were not eligible for inclusion in the SLR, due to the lower quality of evidence to inform comparative effectiveness. Given the

high volume of RCTs, the inclusion of case-control studies is very unlikely to add new evidence that would diverge from the overall picture drawn from RCTs.

As outlined in B3 below, the updated data extraction table (Appendix B3D3) and a list of eligible observational and single-arm studies (Appendix B3D5) has been provided.

B3. Priority question. Figure 1 of Appendix D provides information on 289 randomised controlled trials (RCTs) that were found through the literature search and also refers to 160 "unique studies" (included studies box).

a. **Table 7 of Appendix D suggests that some references belong to the same study, e.g. Arribas et al. 2012 (reference 19) and Arribas et al. 2010 (reference 25) both relate to the MONET trial (NCT00458302). Please update Figure 1 of document D so that the numbers of papers and trials are clearly differentiated for the included RCT records.**

b. **Please also edit the information in Table 7 so that papers relating to the same research evaluation are grouped together (currently the papers are listed alphabetically according to first author surname).**

c. **Table 8 of Appendix D (Baseline characteristics of participants from eligible randomised controlled trials) lists 173 RCTs. This relates to neither the number of RCT records (n=289) nor the number of unique studies (n=160) shown in Figure 1 of Appendix D. Please explain this discrepancy and/or update Table 8 so that it relates to the total number of unique studies.**

d. **Document 4 embedded on page 122 of Appendix D (Quality assessment of eligible randomized controlled trials) lists 158 RCTs. This number is discrepant with other parts of Appendix D, e.g. Figure 1, Table 7 and Table 8. Please explain these discrepancies or correct Figure 1, Document 4, Table 7 and/or Table 8 as required.**

a. Figure 1 has been updated for clarity to reflect the distinction between the number of RCT records (n=266) and the number of unique RCT studies (n=160), as well as reflecting the number of observation/single-arm records (n=300). Please refer to appendix B3a for the updated figure.

b. Table 7 has been updated to show the 266 RCTs, grouping the studies by the trial name/ID. Please refer to appendix B3b for the updated table.

c. Table 8 has now been updated to reflect the unique trials (n=160). Please refer to appendix B3c for the updated table.

d. The QA table has been updated to reflect quality assessments for the 160 unique studies. Please refer to appendix B3d for the updated spreadsheet.

To reflect points a-d, we have also updated the data extraction table (D3) and list of eligible observational and single-arm studies (D5). Please refer to appendix B3D3 and appendix B3D5, respectively.

B4. Priority question. Table 1 (The decision problem) lists a "basket of those antiretroviral regimens" and states that "these are considered as established ART for the population in question".

Please support this statement, e.g. by referring to a relevant clinical guideline.

Please see our response to Question B1.a, which is relevant here. Guideline recommendations, particularly for switch situations, are not particularly prescriptive. There are many different ART regimens available and no single "standard of care" or treatment pathway. In part this is as a consequence of the significant evolution in treatment over a number of decades. No guideline lists a bounded set of options or a preferred treatment sequence for virologically suppressed people wishing to change their therapy. This is positive as it means that individuals and their prescribers are able to tailor treatment to life circumstances and to psychosocial and other needs, alongside medical needs. Despite the considerable choice of available regimens (>50), treatment decisions are primarily based on medical need, while not ignoring commissioning policy.

Virally supressed switch market data and clinical expert opinion have guided the selection of the basket of comparator antiretroviral regimens in this appraisal. We are confident that this selection represents the current established ART options in the population under consideration (namely virologically suppressed people switching away from their current treatment regimen).

B5. The NICE final scope and Table 1 of document B of the CS (The decision problem) both list acquired immunodeficiency syndrome (AIDS)-defining events and health-related quality of life as outcomes. However, neither of these outcomes are shown in Table 5 of Appendix D (Eligibility criteria for the identification of HIV clinical effectiveness studies).

Please clarify whether these outcomes were included in the review. If they were included, please provide all results. If they were excluded, please justify the exclusion.

The outcomes in the clinical efficacy and safety systematic review, reported in Appendix D, are limited to clinical efficacy and safety. AIDS-defining events is an outcome listed and extracted in the cost-effectiveness systematic review and reported in Appendix G; health-related quality of life outcomes were included and extracted in the health effects systematic review and reported in Appendix H.

B6. Table 6 of Appendix D (Variables extracted from studies meeting the review criteria for identification of clinical efficacy in HIV maintenance treatment) mentions 'Subgroup – Description of subgroup included' under 'Patient characteristics'. A single population without subgroups is mentioned in the NICE final scope and Table 1 of document B of the CS (The decision problem): "Adults with HIV-1 infection who are virologically suppressed on a stable regimen and who have not shown prior virological failure due to drug resistance to INTI/INIs" (INTI probably referring to Integrase strand transfer inhibitor (INSTI)). The Evidence Review Group (ERG) noted reference to some pre-specified subgroups within specific RCTs: e.g., subgroups according to randomisation stratification factors ("prior exposure to CAB + RPV: 0 weeks, 1-24 weeks, and >24 weeks"), and demographic and baseline characteristics (demographic factors, baseline viral load, baseline

CD4+ (cluster of differentiation 4) lymphocyte count, and participating countries) in ATLAS-2M (section B.2.7.1 of the CS).

Please clarify whether any participant subgroups were pre-specified for the systematic review and meta-analysis. If any pre-specified subgroups were defined for the review/ meta-analysis, please provide the justification for this and present all available results.

There were no subgroups pre-specified for the systematic review. Sometimes, the results of a trial were stratified by age, or ethnic background, or CD4 count, and these were listed as subgroups as reported by the authors. If the outcomes are for a specific subgroup rather than for the overall population, details are reported in the study arm column throughout the tables in Appendix D.

B7. Document 4 embedded on page 122 of Appendix D presents the "quality assessment of eligible randomized controlled trials".

a. **Please provide supporting information explaining the risk of bias tool used to assess the eligible RCTs.**

b. **Please explain how the risk of bias assessment was undertaken, e.g. the number of reviewers involved and how any discrepancies were resolved.**

a. Studies included in the clinical SLR were assessed using the Cochrane Risk of Bias Assessment Tool 1.0 (Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928)[50]. This reference has been provided along with response, as Appendix B7.

b. Quality assessment was conducted by two independent reviewers and any discrepancies between the two reviewers was resolved by consensus or involvement of a third reviewer, as needed.

Clinical trials

B8. Priority question. Section B.2.6.2 of the CS provides details of the supporting trials, i.e. trials of CAB LA + RPV LA Q1M versus current daily oral ART (ATLAS and FLAIR).

a. **Table 25 in section B.2.6.2.1 of the CS summarises the trial methodology for ATLAS and FLAIR. The dosing schedule in the FLAIR study under subheading "Intervention" for week 8 and onwards ("From Week 8 participants received CAB LA 600 mg and RPV LA 900 mg Q1M") differs from information in Table 5 in section B.2.2.1 of the CS ("…CAB LA 400 mg + RPV LA 600 mg every 4 weeks"). Please clarify which dosing schedule is correct and refer to relevant section of the clinical study report (CSR) of the FLAIR trial.**

The correct dosing schedule for participants in FLAIR from week 8 and onwards was CAB LA 400 mg + RPV LA 600 mg Q1M.[51] The dosing schedule is described in further detail on page 18 of the protocol for FLAIR. We acknowledge the error in reporting the dosing schedule in Table 25.

b. **In Table 25 in section B.2.6.2.1, the comparator treatment in the FLAIR study is clearly described (ABC/DTG/3TC single-tablet regimen [Triumeq®]), however, it is unclear what ART regimens were given to patients participating in ATLAS study. Please provide details of ART regimens of all participants of ATLAS who were included in the pooled sample of participants from the ATLAS and FLAIR studies, including references to relevant sections of the CSR.**

A range of ART regimens were given to participants in ATLAS. This can be located in the supplementary material of Swindells et al. (2020)[52] in Table S1 (p.18), which presents regimens for the ITT and safety populations i.e. 616 participants. This has been provided as Appendix B8.

c. **Sections B.6.2.2.5 to B.2.6.2.8 of the CS reports the results of the primary and secondary outcomes of pooled analysis of participants included in**

the ATLAS and FLAIR studies. However, the CS does not present the methods used for pooling the data from two separate trials.

- **Please provide the details on the methods used for pooling the participant data from the ATLAS and FLAIR studies and reference relevant sources of information.**

The statistical strategy, including definition of the non-inferiority (NI) margin for the pooled analysis, was agreed by the EMA 'scientific advices'. Rizzardini et al (2020)[53] provides further information on the approach that was taken to pooling data from the underlying trials.

- **Please provide results for the separate studies.**

The primary efficacy endpoints for ATLAS and FLAIR separately are presented in Table 6 - Table 9. Results for further endpoints are available in the respective CSRs for ATLAS and FLAIR.

Table 6. Proportion of participants with HIV-1 RNA ≥50 copies/mL at Week 48, ITT-E population - ATLAS

		ATLAS	
		Q1M	**Current ART**
Week 48	**HIV-1 RNA ≥ 50 copies/mL per total assessed (%)**	5/308 (1.6)	3/308 (1.0)
	Difference in proportion (95% CI)	0.6 (−1.1-2.4)	
	Adjusted difference in proportion (95% CI)	0.6 (−1.2-2.5)	
ART: antiretroviral therapy, HIV: human immunodeficiency virus, Q1M: once a month, RNA: ribonucleic acid Source: Swindells et al.[52]			

Table 7. Proportion of participants with HIV-1 RNA ≥50 copies/mL at Week 48, ITT-E population -FLAIR

		FLAIR	
		Q1M	**Current ART**
Week 48	**HIV-1 RNA ≥ 50 copies/mL per total assessed (%)**	6/283 (2.1)	7/283 (2.5)
	Difference in proportion (95% CI)	-0.4 (−2.8-2.1)	
	Adjusted difference in proportion (95% CI)	-0.4 (−2.8-2.1)	
ART: antiretroviral therapy, HIV: human immunodeficiency virus, Q1M: once a month, RNA: ribonucleic acid Source: Orkin et al.[54]			

Table 8. Proportion of participants with viral load <50 copies/mL at Week48, ITT-E population - ATLAS

		ATLAS	
		Q1M	**Current ART**
Week 48	**Plasma HIV-1 RNA <50 copies/mL (%)**	285/308 (93)	294/308 (95)
	Difference in proportion (95% CI)	-2.9 (-6.7-0.8)	

	Adjusted difference in proportion (95% CI)	-3.0 (-6.7-0.7)
ART: antiretroviral therapy, HIV: human immunodeficiency virus, Q1M: once a month, RNA: ribonucleic acid Source: Swindells et al.[52]		

Table 9. Proportion of participants with viral load <50 copies/mL at Week48, ITT-E population - FLAIR

		FLAIR	
		Q1M	**Current ART**
Week 48	**Plasma HIV-1 RNA <50 copies/mL (%)**	265/283 (93.6)	264/283 (93.3)
	Difference in proportion (95% CI)	0.4 (-3.7-4.4)	
	Adjusted difference in proportion (95% CI)	0.4 (-3.7-4.5)	
ART: antiretroviral therapy, HIV: human immunodeficiency virus, Q1M: once a month, RNA: ribonucleic acid Source: Orkin et al.[54]			

B9. Table 50 of document B of the CS provides an "Overall Summary of Non-Injection Site Reaction AEs During the maintenance phase" (cf. question C.13).

a. Please provide further details on the differences in drug-related adverse events (AEs), i.e. by providing a Table with detailed results.

In the pooled ATLAS (201585) and FLAIR (201584) analysis, the most frequently reported, Grade 2 to 4, drug-related, non-ISR AEs in the CAB + RPV LA group were headache (5 participants [<1%]), diarrhoea (5 participants [<1%]), fatigue (4 participants [<1%]) and pyrexia (4 participants [<1%]). The summary table from the EPAR is shown in Table 10 below.

Overall, more drug-related AEs were reported in FLAIR (n=28 ([10%]) compared with ATLAS (n=8 [3%]).

Table 10 Table of drug-related adverse events, from EPAR (EPAR p.108)

Table 43 **Most Common Drug-Related Adverse Events (Reported in >=1% of Subjects in Any Treatment Group) by Preferred Term during the Maintenance Phase for Study 201584, Study 201585, and Pooled Data (Safety Population)**

	201584		201585		POOLED	
	CAB + RPV (N=283)	CAR (N=283)	CAB + RPV (N=308)	CAR (N=308)	CAB + RPV (N=591)	CAR (N=591)
ANY EVENT, n (%)	236 (83)	28 (10)	255 (83)	8 (3)	491 (83)	36 (6)
Injection site pain	221 (78)	0	227 (74)	0	448 (76)	0
Injection site nodule	43 (15)	0	36 (12)	0	79 (13)	0
Injection site induration	37 (13)	0	29 (9)	0	66 (11)	0
Injection site swelling	22 (8)	0	22 (7)	0	44 (7)	0
Headache	14 (5)	4 (1)	11 (4)	0	25 (4)	4 (<1)
Injection site erythema	12 (4)	0	12 (4)	0	24 (4)	0
Pyrexia	13 (5)	0	11 (4)	0	24 (4)	0
Injection site pruritus	16 (6)	0	7 (2)	0	23 (4)	0
Nausea	4 (1)	6 (2)	11 (4)	0	15 (3)	6 (1)
Fatigue	4 (1)	5 (2)	11 (4)	0	15 (3)	5 (<1)
Injection site bruising	6 (2)	0	10 (3)	0	16 (3)	0
Injection site warmth	8 (3)	0	6 (2)	0	14 (2)	0
Asthenia	7 (2)	0	6 (2)	0	13 (2)	0
Body temperature increased	8 (3)	0	4 (1)	0	12 (2)	0
Myalgia	4 (1)	1 (<1)	6 (2)	0	10 (2)	1 (<1)
Dizziness	4 (1)	1 (<1)	5 (2)	0	9 (2)	1 (<1)
Injection site hematoma	4 (1)	0	6 (2)	0	10 (2)	0
Abnormal dreams	4 (1)	0	3 (<1)	2 (<1)	7 (1)	2 (<1)
Anxiety	4 (1)	1 (<1)	4 (1)	0	8 (1)	1 (<1)
Insomnia	0	0	8 (3)	1 (<1)	8 (1)	1 (<1)
Diarrhea	5 (2)	1 (<1)	2 (<1)	0	7 (1)	1 (<1)
Creatinine renal clearance decreased	2 (<1)	3 (1)	2 (<1)	0	4 (<1)	3 (<1)
Malaise	5 (2)	0	2 (<1)	0	7 (1)	0
Influenza like illness	0	0	5 (2)	0	5 (<1)	0
Pain	1 (<1)	0	4 (1)	0	5 (<1)	0
Chills	0	0	4 (1)	0	4 (<1)	0
Depression	3 (1)	0	0	1 (<1)	3 (<1)	1 (<1)
Vitamin D deficiency	3 (1)	1 (<1)	0	0	3 (<1)	1 (<1)

b. Please discuss any differences.

Please refer to the response in B9a above. The largest difference in drug related non-ISR AEs is between the current antiretroviral regimen (CAR) arms of the two trials. This can be explained by the fact that participants in FLAIR were new to ARVs and would be expected to have higher rates of AEs than those on ATLAS who had been on treatment for several years.

Indirect treatment comparison (ITC)

B10. Priority question. Details on the indirect treatment comparison are reported in Appendix L.

a. **Please clarify the hypothesis of the ITCs including details on the non-inferiority margin.**

b. **Kindly provide the corresponding data for each analysis.**

a. This analysis was designed to estimate the relative efficacy and uncertainty between CAB LA + RPV LA and standard of care. No specific hypotheses testing to demonstrate non-inferiority was performed. Instead, the statistical methodology published by Bucher et al[55] was used to calculate the 95% CI of indirect treatment effects (odds ratio [OR], relative risk [RR], risk difference [RD], mean difference [MD]), which are shown to be not statistically significant different for the efficacy and safety endpoints analysed (Table 4 Appendix L).

b. The data used for each analysis are provided in Table 11 below.

Table 11. Key snapshot outcomes, other efficacy and safety outcomes used to inform the ITC from pooled ATLAS/FLAIR and the ATLAS-2M studies

	ATLAS/FLAIR		ATLAS-2M*	
Outcome	**Current ART (n=591)**	**CAB+RPV LA Q1M (n=591)**	**CAB+RPV LA Q2M (n=327)**	**CAB+RPV LA Q1M (n=327)**
Snapshot outcomes				
HIV-1 RNA <50 copies/mL, n (%)	558 (94)	550 (93)	306 (94)	300 (92)
HIV-1 RNA ≥50 copies/mL, n (%)	10 (2)	11 (2)	5 (2)	5 (2)
Data in window not <50 copies/mL	3 (<1)	3 (<1)	1 (<1)	2 (<1)
Discontinued for lack of efficacy	5 (<1)	7 (1)	4 (1)	2 (<1)
Discontinued for other reasons while not <50 copies/mL	2 (<1)	1 (<1)	0	1 (<1)
No virologic data, n (%)	23 (4)	30 (5)	16 (5)	22 (7)
Discontinued for AE	6 (1)	19 (3)	6 (2)	11 (3)
Discontinued for death	1 (<1)†	0	0	0
Discontinued for other reasons	16 (3)	11 (2)	10 (3)	11 (3)
Other efficacy outcomes				
Mean CD4+ cell count change from baseline (SD), cells/μL	48.2 (182.1)	24.5 (191.3)	–0.7 (150.6)	–19.2 (204.9)
Safety outcomes				
Discontinuations due to AEs, n (%)	7 (1)	19 (3)	6 (2)	11 (3)
Grade 3/4 non-ISR AEs, n (%)	35 (6)	47 (8)	16 (5)	20 (6)

AE: adverse event, ART: antiretroviral therapy, CAB: cabotegravir, CD4: Cluster of differentiation 4, HIV: human immunodeficiency virus, ISR: injection site reaction, SD: standard deviationQ1M: once a month, RPV: rilpivirine, RNA: ribonucleic acid, Q1M: every month, Q2M: every two months
*Participants with prior CAB+RPV LA exposure in ATLAS-2M were excluded.
†Death was due to a methamphetamine overdose and was considered not related to the study treatment.
Source: Chounta et al. 2020[56]

B11. Table 25 of the CS describes participants in the FLAIR trial as follows "eligible participants were 18 years of age or older, had not previously received antiretroviral therapy, and had a plasma HIV-1 RNA level of 1000 copies/mL or higher at screening" whereas the first sentence in "Participants and treatment" of Appendix L states that "eligible participants from the ATLAS, FLAIR, and ATLAS-2M trials were all

treatment-experienced individuals with virologically suppressed HIV, and a viral load of <50 HIV-1 ribonucleic acid (RNA) copies/mL".

a. **Please clarify and justify if the sentence in 'Participants and treatment' of the Appendix L refers to the participants included in the FLAIR trial and provide any missing data, if needed.**

The statements highlighted by the ERG in this question are not discrepant. The first describes the participants in the FLAIR trial (treatment naïve but were required to achieve viral suppression on an induction regimen (Triumeq®) before randomisation to either CAB LA + RPV LA or continuation of Triumeq®[57, 58]), whilst the second describes the participants in the indirect treatment comparison (ITC), i.e. study results utilised in the ITC were all from "treatment-experienced individuals with virologically suppressed HIV, and a viral load of <50 HIV-1 ribonucleic acid (RNA) copies/mL.

Section C: Clarification on cost-effectiveness data

Model Structure

C1. Priority question. Please provide a detailed explanation of how patients may transition through the model, including health states based on CD4 count, HIV RNA copy levels being either above or below 50 per ml, probabilities of discontinuation due to virologic and non-virologic reasons and subsequent treatment lines.

Model Overview

The diagram showing the model structure in document B, section 3.2.5 (figure 10) provides a broad overview of individual movement through the model and the events that they can experience. Specifically, the health states are stratified by both viral load (measured in copies/mL) and by CD4+ cell count (a type of white blood cell with a role in fighting infection). Values for each of these health states apply from the first modelled line to the final modelled line. In all states, individuals may also experience

events (including AEs Adverse events; ADEs AIDS-defining events and death) shown in Figure 4.

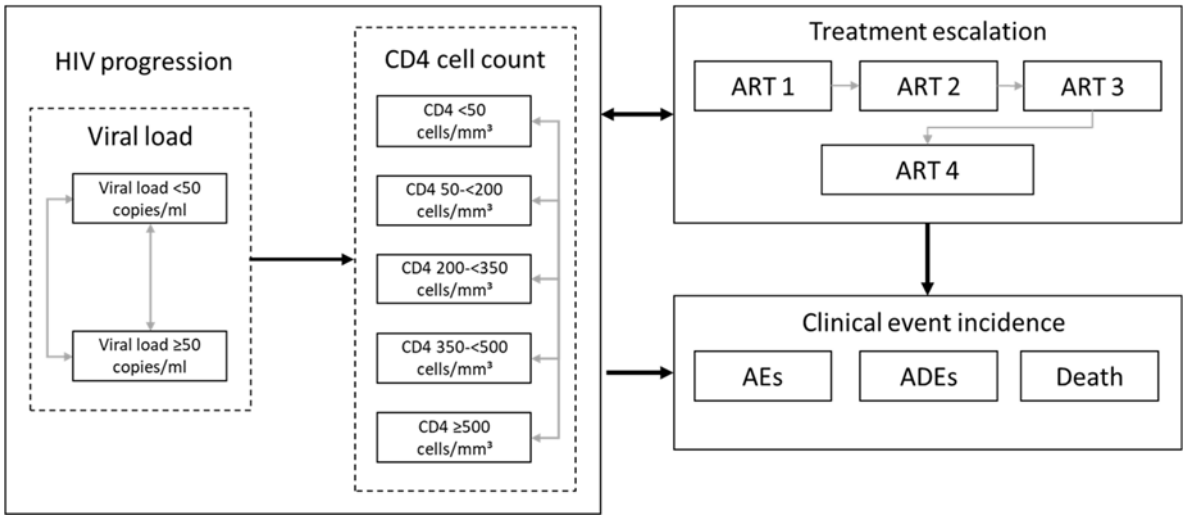


Figure 4: Health states, treatment lines and events included in the cost-effectiveness model

Initiation

Individuals enter the model in start states defined on the "Non-Treatment Specific Inputs" worksheet Range I37:I46 as shown in Table 12.

Table 12: Starting distribution of patients in the cost-effectiveness model

Health state Category		Proportion present at initiation
Viral load < 50 (copies/mL)	CD4 <50	0.0%
	CD4 50-200	0.0%
	CD4 200-350	6.7%
	CD4 350-500	18.4%
	CD4 ≥ 500	74.9%
Viral load ≥ 50 (copies/mL)	CD4 <50	0.0%
	CD4 50-200	0.0%
	CD4 200-350	0.0%
	CD4 350-500	0.0%
	CD4 ≥ 500	0.0%

These values were sourced from the ATLAS-2M CSR to describe how treatment experienced people are distributed at model initiation. As expected, 100% of

participants are in the virologically supressed state (a viral load of < 50 copies/mL) initially as this is in line with the requirements for treatment with CAB LA + RPV LA and will describe those who would receive treatment in clinical practice. All individuals who experience a virologic failure are assumed to change treatment (see Figure 4, treatment escalation box), hence no patients should have a viral load ≥50 whilst in the first modelled line.

People will transition, in month long cycles, between CD4 states based on the matrices found in “Efficacy Profiles”, specific to each treatment line and arm of treatment. They may also transition to a new treatment either due to virologic or non-virologic failure (also found in “Efficacy Profiles”).

The matrices for the first modelled line (both CAB LA + RPV LA and current combination antiretroviral therapy [cART]) are assumed to be identical in terms of virologic efficacy and CD4+ cell count stratification, and consist of a matrix that is applied monthly, that informs movement in an initial 48-week period (Table 13) and a matrix that informs movement in all subsequent periods (Table 14). People who do not fail treatment or experience a death event, have their CD4+ state determined by these matrices.

Table 13. Transition matrix for individuals receiving CAB LA+RPV LA (initial 48 week period): CAB LA+RPV LA Q2M (ATLAS-2M ITC) - Trial analysis data

		To									
Viral load*		<50					≥50				
CD4 cell count^		<50	50-199	200-349	350-500	>500	<50	50-199	200-349	350-500	>500
From	<50	0.9318	0.0649	0.0011	0.0011	0.0011	0.9318	0.0649	0.0011	0.0011	0.0011
	50-199	0.0204	0.9231	0.0558	0.0003	0.0003	0.0204	0.9231	0.0558	0.0003	0.0003
	200-349	0.0001	0.0232	0.9300	0.0466	0.0001	0.0001	0.0232	0.9300	0.0466	0.0001
	350-500	0.0001	0.0001	0.0250	0.9258	0.0491	0.0001	0.0001	0.0250	0.9258	0.0491
	>500	0.0000	0.0000	0.0000	0.0095	0.9905	0.0000	0.0000	0.0000	0.0095	0.9905

*Viral load in copies/mL

^CD4 cell count in cells/mm^3

Table 14. Transition matrix for individuals receiving CAB LA+RPV LA (subsequent period): CAB LA+RPV LA Q2M (ATLAS-2M ITC) - Trial analysis data

		To									
Viral load*		<50					≥50				
CD4 cell count^		<50	50-199	200-349	350-500	>500	<50	50-199	200-349	350-500	>500
From	<50	0.8844	0.1119	0.0012	0.0012	0.0012	0.8844	0.1119	0.0012	0.0012	0.0012
	50-199	0.0280	0.9095	0.0619	0.0003	0.0003	0.0280	0.9095	0.0619	0.0003	0.0003
	200-349	0.0001	0.0268	0.9202	0.0527	0.0001	0.0001	0.0268	0.9202	0.0527	0.0001
	350-500	0.0001	0.0001	0.0296	0.9216	0.0487	0.0001	0.0001	0.0296	0.9216	0.0487
	>500	0.0000	0.0000	0.0000	0.0089	0.9911	0.0000	0.0000	0.0000	0.0089	0.9911

*Viral load in copies/mL

^CD4 cell count in cells/mm^3

Both virologic and non-virologic discontinuation is assumed to be applied evenly across all CD4+ and viral load health states. From the first modelled treatment line, this means that 0.16% of participants across all CD4+ states discontinue into the ≥50 viral load states and 0.37% discontinue into the <50 viral load states in the second line ART, remaining in the same CD4+ state they would have otherwise been in. For example; if an individual was in the health state defined as CD4+ 350-500 and in a viral load category of ≥50 copies/mL, they would discontinue into the same health state in the subsequent treatment line. More detail is given on the movements at the first modelled line in the answers to C5 and C8.

This means the individuals moving on to ART 2 who are virologically suppressed will represent 0.37% of those in each CD4 state within this cycle on ART 1 whilst individuals moving on to ART 2 who are not virologically suppressed will represent 0.16% of those in each CD4 state within this cycle on ART 1.

People who fail virologically are discontinued to the ART2 Virologic efficacy line which uses the inputs found in the “Failing Switch” efficacy profile. Those who fail non virologically are discontinued to the ART2 Non-virologic efficacy line which uses the inputs found in the “Stable Switch” efficacy profile.

Once in ART 2 the respective stable and failing switch matrices found in the efficacy profiles are adjusted by virologic and non-virologic discontinuation along with 48 week viral suppression in order to produce two matrices. Those having previously failed virologically have their movement through CD4 and viral load states determined by the matrices in ‘Active Inputs’ Sheet, cells D130:M139 and D144:M153 (Figure 5)

ART2 - Virologic - Efficacy

ART2 to ART2

Pooled comparator	Failing Switch	Viral load ≤ 50					Viral load > 50				
		CD4 < 50	CD4 50-200	CD4 200-350	CD4 350-500	CD4 > 500	CD4 < 50	CD4 50-200	CD4 200-350	CD4 350-500	CD4 > 500
Viral load ≤ 50	CD4 < 50	0.6603	0.3142	0.0001	0.0001	0.0001	0	0	0	0	0
	CD4 50-200	0.0038	0.8411	0.1301	0.0000	0.0000	0	0	0	0	0
	CD4 200-350	0.0000	0.0052	0.8700	0.0996	0.0000	0	0	0	0	0
	CD4 350-500	0.0000	0.0000	0.0073	0.8986	0.0690	0	0	0	0	0
	CD4 > 500	0.0001	0.0001	0.0001	0.0089	0.9657	0	0	0	0	0
Viral load > 50	CD4 < 50	0.0619	0.0043	0.0000	0.0000	0.0000	0.8490	0.0596	0.0000	0.0000	0.0000
	CD4 50-200	0.0023	0.0614	0.0025	0.0000	0.0000	0.0321	0.8425	0.0340	0.0000	0.0000
	CD4 200-350	0.0000	0.0030	0.0617	0.0016	0.0000	0.0000	0.0405	0.8465	0.0216	0.0000
	CD4 350-500	0.0000	0.0000	0.0039	0.0613	0.0010	0.0001	0.0001	0.0536	0.8407	0.0142
	CD4 > 500	0.0000	0.0000	0.0000	0.0047	0.0615	0.0004	0.0004	0.0004	0.0639	0.8436

ART2 to ART3

		Viral load ≤ 50					Viral load > 50				
		CD4 < 50	CD4 50-200	CD4 200-350	CD4 350-500	CD4 > 500	CD4 < 50	CD4 50-200	CD4 200-350	CD4 350-500	CD4 > 500
Viral load ≤ 50	CD4 < 50	0.0017	0.0008	0.0000	0.0000	0.0000	0.0153	0.0073	0.0000	0.0000	0.0000
	CD4 50-200	0.0000	0.0021	0.0003	0.0000	0.0000	0.0001	0.0195	0.0030	0.0000	0.0000
	CD4 200-350	0.0000	0.0000	0.0022	0.0003	0.0000	0.0000	0.0001	0.0202	0.0023	0.0000
	CD4 350-500	0.0000	0.0000	0.0000	0.0023	0.0002	0.0000	0.0000	0.0002	0.0208	0.0016
	CD4 > 500	0.0000	0.0000	0.0000	0.0000	0.0024	0.0000	0.0000	0.0000	0.0002	0.0224
Viral load > 50	CD4 < 50	0.0002	0.0000	0.0000	0.0000	0.0000	0.0233	0.0016	0.0000	0.0000	0.0000
	CD4 50-200	0.0000	0.0002	0.0000	0.0000	0.0000	0.0009	0.0231	0.0009	0.0000	0.0000
	CD4 200-350	0.0000	0.0000	0.0002	0.0000	0.0000	0.0000	0.0011	0.0232	0.0006	0.0000
	CD4 350-500	0.0000	0.0000	0.0000	0.0002	0.0000	0.0000	0.0000	0.0015	0.0230	0.0004
	CD4 > 500	0.0000	0.0000	0.0000	0.0000	0.0002	0.0000	0.0000	0.0000	0.0018	0.0231

Figure 5: Screenshot from cost-effectiveness model showing the efficacy matrices for ART2

As can be observed, all people who fail virologically are assumed to change treatments. Each CD4 state row of ART2 to ART 2 and ART 2 to ART 3 combine to add up to 1 so all patients on ART 2 are accounted for. People who discontinue ART 2 are put through an identical set of matrices for ART 3, with ART4 following. The flow chart on the 'Treatment Algorithms' sheet shows where people move through the model depending on their reason for switch and allows the user to assign cost and efficacy profiles accordingly. Figure 6 shows the base case assumptions:

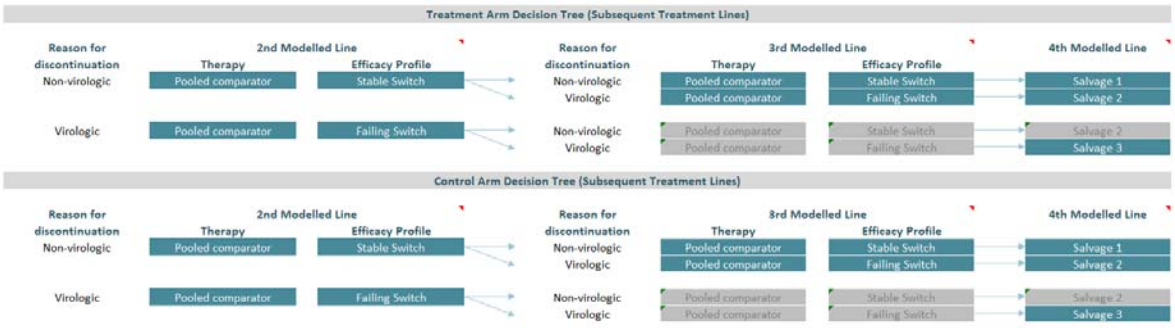


Figure 6: Screenshot from the cost-effectiveness model showing the treatment pathways assumed in the base case

'Salvage' (i.e. ART4 or fourth modelled line as described in the CS) is the absorbing state and individuals can go onto salvage 1, 2 or 3 depending on their history of virologic/non-virologic discontinuation in the model so far. 'Salvage' is the only treatment where people can transition to having a viral load ≥50 but remain on the same treatment. This is an absorbing state that is assumed to represent any and all

further lines of treatment, recognising that this is a heterogenous group. People at this treatment line transition based on the calculated matrix found in the 'Active Inputs' sheet, starting at line 288 (Figure 7).

Salvage 1

		Salvage 1 to Salvage 1									
		Viral load ≤ 50					Viral load > 50				
		CD4 < 50	CD4 50-200	CD4 200-350	CD4 350-500	CD4 > 500	CD4 < 50	CD4 50-200	CD4 200-350	CD4 350-500	CD4 > 500
Viral load ≤ 50	CD4 < 50	0.7525	0.2452	0.0001	0.0001	0.0001	0.0015	0.0005	0.0000	0.0000	0.0000
	CD4 50-200	0.0065	0.9083	0.0832	0.0000	0.0000	0.0000	0.0018	0.0002	0.0000	0.0000
	CD4 200-350	0.0000	0.0092	0.9267	0.0621	0.0000	0.0000	0.0000	0.0019	0.0001	0.0000
	CD4 350-500	0.0001	0.0001	0.0136	0.9479	0.0364	0.0000	0.0000	0.0000	0.0019	0.0001
	CD4 > 500	0.0003	0.0003	0.0003	0.0202	0.9768	0.0000	0.0000	0.0000	0.0000	0.0020
Viral load > 50	CD4 < 50	0.0604	0.0039	0.0000	0.0000	0.0000	0.8782	0.0574	0.0000	0.0000	0.0000
	CD4 50-200	0.0020	0.0602	0.0021	0.0000	0.0000	0.0290	0.8764	0.0303	0.0000	0.0000
	CD4 200-350	0.0000	0.0028	0.0602	0.0013	0.0000	0.0000	0.0408	0.8763	0.0186	0.0000
	CD4 350-500	0.0000	0.0000	0.0042	0.0594	0.0007	0.0001	0.0001	0.0613	0.8646	0.0096
	CD4 > 500	0.0001	0.0001	0.0001	0.0062	0.0578	0.0013	0.0013	0.0013	0.0909	0.8409

Figure 7: Screenshot from the cost-effectiveness model showing the efficacy matrices for ART4

Similar to previous treatments these matrices use the input matrices in the "Efficacy profiles" worksheet combined with viral discontinuation/viral suppression at 48 weeks. Viral discontinuation does not lead to a discontinuation at this stage in the model, it leads to those in the virally suppressed health states transitioning to those with viral loads ≥50.

Inputs affecting mortality are all found on the 'Life Tables & ADEs' worksheet. All-cause, age-related mortality from the lifetables acts as a base from which risk of death (relative to all-cause mortality), by CD4 health state, is applied as a multiplier. In addition to this, ADE related mortality is applied based on the rate of ADE occurrence, which changes based on time on treatment.

C2. Priority question. Appendix M is cited in several places as providing information about the onward transmission model, e.g. "Outcomes due to differences in new HIV cases resulting from onward transmission are then incorporated into cost-effectiveness estimates. Further description is available in Appendix M" on page 122 of CS Doc B. However, Appendix M only contains transition matrices for CD4 health states. No information on the parameters

included in the disease transmission model, their sources or any relevant assumptions could be found in the CS.

Please provide all details of the estimation and sources of all parameters included and assumptions made in the onward disease transmission model, including all parameters in the "Disease Transmission" sheet of the model and any other relevant parameters.

Upon review of the submitted material, ViiV Healthcare would like to confirm that in error, this information was not provided and as such, offer an apology. All parameters relating to the disease transmission module of the cost-effectiveness model are included below in Table 15 to Table 21, with notes on relevant assumptions. Where possible, these were sourced from UK specific literature, however for clinical parameters (such as the risk of transmission dependent on CD4+ cell count) it was assumed that this would not change dependent on country so it was not necessary to restrict inputs to UK specific.

Table 15: Modelled population distribution

No risk of transmission	0.000	PHE National HIV Surveillance data tables (Table 2) 2019[59]
Non-IDU transmission	0.974	
Heterosexual transmission	0.463	
Low risk	0.900	
High risk	0.100	
MSM transmission	0.537	
IDU transmission	0.026	
MSM & IDU	0.537	
Heterosexual & IDU	0.463	
Notes: Source did not differentiate between high and low risk – values are assumed where not provided. IDU+MSM/IDU+Heterosexual is estimated to be the same ratio as MSM to heterosexual transmission The adjusted total population was used as the overall cohort (4400) and values were taken as a proportion of this. Key: IDU: Intravenous drug user; MSM: Men who have sex with men		

Table 16: Behavioural parameters – Sexual Transmission

Sexual transmission parameters	Low risk heterosexual transmission	Source	High risk heterosexual transmission	Source	MSM transmission	Source	Notes
Average no. of partners over remainder of life	10.000	Assumed	10.000	Assumed	10.000	Assumed	Required for method 2. Assumption fits with data from table 35 of UK survey of sexual attitudes.[60]
Average partnership duration (months)	10.435	National Survey of Sexual Attitudes and Lifestyles (Natsal-3)[60] Reference tables	0.058	House of Commons Home Affairs Committee (2016) report[61] on prostitution listed 25 clients per week as the average	6.667	National Survey of Sexual Attitudes and Lifestyles (Natsal-3)[60] Reference tables	Required for method 3. Low risk heterosexual and MSM values are sourced from the National Surveys of Sexual attitudes from the UK 2011-Table 33 and Table 29. For high risk the UK house of commons report
Average no. of unique sexual partners (per month)	0.096	National Survey of Sexual Attitudes and Lifestyles (Natsal-3)[60] Reference tables	17.170		0.150	National Survey of Sexual Attitudes and Lifestyles (Natsal-3)[60] Reference tables	
Age at which no further new partners are observed (years)	70.000	Assumed	70.000	Assumed	70.000	Assumed	
No. of sexual acts per partner per month	4.150	National Survey of Sexual Attitudes and Lifestyles	1.000	Assumed	3.600	National Survey of Sexual Attitudes and	Taken from survey of sexual attitudes from the UK 2011[60]- Table 18 for heterosexual. For same-sex sexual acts table 39 was used.

		(Natsal-3)[60] Reference tables				Lifestyles (Natsal-3)[60] Reference tables	Table 39 groups same and opposite sex together
Probability of condom use	0.779	Lampe et al. (2016)[62]	0.779	Assumed	0.618	Lampe et al. (2016) [62]	Taken from UK cross sectional study (2011-2012). Table 2 condomless sex numbers were used to inform this variable. Heterosexual was assumed to be an average of heterosexual men and women. As the data listed is condomless sex, the inverse was taken to obtain probability of sex with a condom.
Transmission HR for condom use	0.100	Nosyk et al. (2017)[63]	0.100	Nosyk et al. (2017)[63]	0.100	Nosyk et al. (2017)[63]	In appendix it lists condom effectiveness as 0.9. table A3: Supplementary Appendix for "The relative impacts of antiretroviral therapy and harm reduction initiatives on HIV incidence in British Columbia, Canada: 1996-2013"
Transmission risk behaviour HR for age ≤30 years	1.000	Twenge et al. (2017) [64]	1.000	Assumed as low-risk heterosexual	1.000	Assumed as low-risk heterosexual	Calculated based on 2010-2014 changes in sexual frequency by age, taken from table 2 of Twenge et al (2017). For 60+ age categories 60-69 and 70+ were combined and weighted by the number in each cohort (n).
Transmission risk behaviour HR for age 30-40 years	0.992		0.992		0.992		
Transmission risk behaviour HR for age 40-50 years	0.805		0.805		0.805		
Transmission risk behaviour	0.488		0.488		0.488		

HR for age 50-60 years							
Transmission risk behaviour HR for age >60 years	0.234		0.234		0.234		

Table 17: Behavioural parameters – IDU transmission

IDU transmission parameters	IDU transmission	Source
Max no. of transmissions per patient per month	1.000	Assumed
Monthly injection frequency	17.800	Nosyk et al. (2017)[63] table A3 number of injections monthly at baseline
Probability of shared injection	0.180	National Infections Service, Public Health England[65] (Table 5-2018)
Probability of opioid agonist treatment	0.313	Nosyk et al. (2017)[63] Table A5 2013 Derived OAT coverage
Transmission HR for opioid agonist treatment	0.750	Nosyk et al. (2017)[63] Table A3 Reduced injections due to OAT
Transmission risk behaviour HR for age ≤30 years	1.000	Assumed
Transmission risk behaviour HR for age 30-40 years	1.000	
Transmission risk behaviour HR for age 40-50 years	1.000	
Transmission risk behaviour HR for age 50-60 years	1.000	
Transmission risk behaviour HR for age >60 years	0.000	

Table 18: Probability of transmission - Heterosexual (low risk)

Heterosexual transmission probability per sexual act (Low risk)	Viral load health state		Source
	<50 copies/mL	≥50 copies/mL	Public Health Agency of Canada[66]
CD4 <50	0.000025	0.000405	
CD4 50-200	0.000025	0.000405	
CD4 200-350	0.000025	0.000405	
CD4 350-500	0.000025	0.000405	
CD4 > 500	0.000025	0.000405	

Table 19: Probability of transmission - Heterosexual (high risk)

Heterosexual transmission probability per sexual act (High risk)	Viral load health state		Source
	<50 copies/mL	≥50 copies/mL	Public Health Agency of Canada[66]
CD4 <50	0.000025	0.000405	
CD4 50-200	0.000025	0.000405	
CD4 200-350	0.000025	0.000405	
CD4 350-500	0.000025	0.000405	
CD4 > 500	0.000025	0.000405	

Table 20: Probability of transmission - MSM

MSM transmission probability per sexual act	Viral load health state		Source
	<50 copies/mL	≥50 copies/mL	Public Health Agency of Canada[66]
CD4 <50	0.000314	0.0043	
CD4 50-200	0.000314	0.0043	
CD4 200-350	0.000314	0.0043	
CD4 350-500	0.000314	0.0043	
CD4 > 500	0.000314	0.0043	

Table 21: Probability of transmission - IDU

IDU transmission probability per shared injection	Viral load health state		Source
	<50 copies/mL	≥50 copies/mL	Bayoumi et al (2008)[67] <50 copies/ml assumed zero.
CD4 <50	0	0.008	
CD4 50-200	0	0.008	
CD4 200-350	0	0.008	
CD4 350-500	0	0.008	
CD4 > 500	0	0.008	

Expected outcomes associated with newly infected individuals were generated by a run of the model under base case settings (except for disease transmission, which was turned off) and inclusive of the cost of Triumeq® rather than the pooled comparator used in the base case. These outputs from the model are then assumed to be the cost, LY and QALYs attributable to a newly infected patient. Expected outcomes associated with an equivalent non-HIV infected person are estimated using National life tables and general population utility and assume no marginal cost.[68]

C3. Priority question. Page 123 of the CS states that "individuals with an undetectable viral load (classed as HIV-1 RNA <50 copies/mL) cannot sexually transmit HIV".

Please clarify why in the model sheet "Disease transmission" the probability of transmission for MSM (men who have sex with men) per sexual act with ≤50 copies/mL is 0.031%

As detailed in the answer to question C2, the data source, considered the most appropriate data source, indicates that there is a small risk of transmission in

individuals who have a VL of <50 copies/mL.[66] It was not considered sensible to ignore data suggesting a potential risk of transmission, even if extremely small. However, the Company acknowledges that this has been superseded by later studies which have led to widespread acceptance that persons with an undetectable viral load (<50 copies/mL) cannot sexually transmit HIV.[69, 70] The company has therefore run a scenario where the risk of transmission for all patient groups with a viral load of <50 copies/mL is zero (Table 22). This scenario shows that there is little impact on the model results.

Table 22: Scenario analysis results - zero probability of transmission for individuals with a VL <50 copies/mL

	CAB+RPV-Q2M (net price)	Pooled comparator (list price)	Incremental
Life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]	[redacted]
ICER (£/QALY)			-£65,771.35
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year			

C4. Priority question. In the disease transmission model, patients can transmit HIV if they have >50 copies but Table 75 of the CS states that "clinical evidence suggests that a somewhat higher viral load (approx. 200-400 copies/mL or greater) is required for transmission".

Please clarify the likely impact of this on results and implement appropriate scenarios where the threshold is 200 or 400 copies/ml to examine the impact of this assumption on results.

As described in Document B, the use of the boundary of 50 copies/mL was a simplifying assumption for calculating transmissibility, based on data availability. It is acknowledged that undetectable, and therefore sexually untransmissible viral load may be at a threshold of 200 copies/mL, and potentially as high as 400 copies/mL.

In response to question C3, a scenario was provided where no transmission was permitted for patients with a viral load of <50 copies/mL. This scenario shows that there is limited impact on the results when these parameters are changed. Given the time constraints with which to provide clarification responses, it was not considered

feasible to make substantial structural changes to the model. Despite this, demonstration of the stability of results when changes are made to the transmission parameters increases confidence that the impact of assuming a threshold around 200 copies/mL is unlikely to considerably change the model results.

Additionally, the most relevant available information source (used in the base case) was not able to provide data that would allow any further stratification other than has been used. Data for clinical parameters (and particularly transmission) is not considered to change between countries and therefore limits any concern with using non-UK specific inputs. Data about the risk of transmission was only available stratified by the following copies/mL counts: 10, 40, 400, 1000, 10,000 and 50,000 (Figure 8).[66]

Therefore, further stratifying the model to consider viral load categories of less than or greater than 400 copies/mL, or indeed 200 copies/mL, would not have resulted in a different application. Specifically, if the states were split by a viral load of less than or greater than 400 copies/mL, exactly the same stratification and pooling of data would have been used.[66]

	RISK OF TRANSMISSION PER VIRAL LOAD IN COPIES/ML % RISK PER ACT					
TYPE OF SEX ACT	10	40	400	1000	10,000	50,000
Insertive vaginal	0.001	0.002	0.007	0.010	0.029	0.062
Receptive vaginal	0.002	0.005	0.013	0.020	0.059	0.124
Insertive anal	0.002	0.005	0.013	0.020	0.059	0.124
Receptive anal	0.036	0.069	0.199	0.304	0.881	1.854

Abbreviations: HIV, human immunodeficiency virus.

[a] Calculated with methods used by Wilson et al., 2008 (63). Assumes that each $\log_{10}$ increase in plasma HIV-1 RNA increases the per-act risk of transmission 2.9-fold (19) for all types of sex acts. Assumes risk of transmission per act in the absence of treatment of 0.05% for insertive vaginal intercourse; 0.1% for receptive vaginal intercourse, as used by Wilson et al (2008) (63); 1.5% for receptive anal intercourse (10, 11, 17); and 0.1% for insertive anal intercourse (13, 17, 18).

Figure 8: Table 4 from Public Health Agency Canada detailing the risk of transmission per viral load in copies/mL

C5. Please explain the apparent discrepancy between there being no patients in the ART1 Markov traces having HIV RNA levels above 50/ml although patients are at risk of virologic failure, which is defined as having levels above 50/ml and

which they can have for (a user-defined time period of) several months before transitioning to subsequent treatment lines.

Aligned with the ATLAS 2M, ATLAS and FLAIR studies and indeed the licensed population for CAB LA + RPV LA, the initial cohort are individuals who have their virus suppressed, i.e., within the virological suppression state (virus levels of <50 copies per mL). Once individuals experience virologic failure (virus levels changing to ≥50 copies per mL), they are assigned to the higher viral load state in a subsequent treatment regimen and not within their current first line treatment. It is in these subsequent regimens where individuals who are in the higher viral load state (those with virologic failure) can stay for three months or any user defined time (in months) before transitioning to subsequent treatment lines. This is described in Appendix P in section 3.2. Therefore we do not believe there to be a discrepancy.

Patients in first line ART in this model already have virologic suppression; this is aligned with the CAB LA + RPV LA licensed indication and are reflective of the patients enrolled in ATLAS-2M. By contrast, in subsequent treatment lines, individuals may have failed previous treatment and so enter the state without virologic suppression. In addition, given the short time for which people are considered able to remain in a failing state (three months in the base case) and the dosing schedule for CAB LA + RPV LA (once every two months), it was not considered feasible to model this movement in first line as it would result in moving to a subsequent line while still within a time of active treatment with CAB LA + RPV LA. In order to address concerns about the impact of this decision, a scenario has been considered where the time spent in a failing state is zero (i.e. individuals would be switched to subsequent therapy as soon as the viral load increases above 50 copies/mL). As can be seen (Table 22), this has little impact on the model results.

Treatment effectiveness

C6. Priority question. In ATLAS-2M virologic failure is defined as having two sequential measures of ≥200 HIV RNA copies per ml as determined using the Snapshot algorithm in which measurements are performed at week 24 and week 48 of treatment. The model defines a monthly probability

of (discontinuation due to) virologic failure, based on a threshold level of 50 HIV RNA copies per ml.

a. **Please justify the choices for implementation of virologic failure in the model and their relation to clinical practice.**

b. **Please explain whether all studies that are used to inform model parameters use the same definition of virologic failure as stated above, in terms of threshold level and measurements of HIV RNA copies.**

c. **Please implement a scenario where the threshold is 200 HIV RNA copies per ml.**

a) Viral suppression is defined as achieving and maintaining HIV-1 RNA <50 copies/mL (also referred to as 'undetectable'). Virologic failure is defined by BHIVA as incomplete virologic response after commencing treatment or confirmed virologic rebound to >200 copies/mL. Incomplete virologic response is defined as two consecutive results of >200 copies/mL after 24 weeks of treatment without ever achieving <50 copies/mL. Thus, virologic failure is a separate endpoint from viral suppression.

The primary reason for implementing the threshold of ≥50 copies/mL as 'virologic failure' in the Company cost-effectiveness model is discussed in the submission document (Document B: assumptions table, p 148). This implementation was a simplifying assumption, necessary because the model can only differentiate between two health states with regard to viral load: <50 copies/mL, or ≥ 50 copies/mL. It was decided to base modelling around viral suppression (viral load <50 copies/mL), because achieving and maintaining viral suppression using this definition is the guideline-recognised goal of treatment, and aligns with a key clinical endpoint of the studies (proportion with viral load or ≥ 50 copies/mL and <50 copies/mL).[71] In addition, much of the evidence (as discussed in response to previous questions) is available in this stratification, limiting the number of further assumptions that need to be made.

The model is based on virally suppressed/unsuppressed health states and including additional health states based on the virologic failure criteria would have introduced excessive complexity and computational requirements. In order that individuals were

not considered to be failing treatment after a single measurement of ≥50 copies/mL, the model will hold people in this failing state for three months (if no discontinuation for other reasons) before movement to another treatment line. This was considered by clinicians to be an acceptable simplifying assumption for the purposes of modelling.

In clinical practice, patients are generally tested for viral suppression every 6 months, unless there is cause for concern, in which case testing would be more frequent. Thus, sampling in the model (monthly) is more frequent than in clinical practice. A 6-monthly or 2-monthly model cycle was not considered appropriate. This decision is described in Appendix P, section 2.3 and in Document B, section 3.2.5 and Table 56, but in summary, aligns with previously published models and the granularity required to capture important clinical events, monitoring and disease progression.

b) Yes, all the trials used to inform the model (ATLAS, FLAIR and ATLAS-2M) used the same definition of confirmed virologic failure. In ATLAS-2M, HIV-RNA measurements were taken at baseline and Weeks 4, 8, 16, then every 8 weeks until Week 48 (the primary endpoint). From week 52 these measurements were taken every 8 weeks until week 96 (Clinical Study Protocol, p. 108). Confirmed virologic failure was defined as having had two sequential measurements ≥200 copies/mL after prior suppression to <200 c/mL. In ATLAS and FLAIR the same definition was used, but measurements were taken every four weeks. Expert clinicians confirm that this definition also reflects clinical practice.

c) As the virological efficacy is considered to be equal for each arm in the model for all lines, the assumption has, by definition, been applied in the same way to each arm. Therefore, regardless of the definition chosen, this would not be expected to change the incremental results. In addition, as described, the assumption that virologic failure relates to a threshold of 50 copies/mL is a simplifying assumption necessary for construction of the model and to limit the requirement for additional complexity and align to data availability. As such, it would not be possible within the time constraints to rebuild and populate a model where the definitions of virologic failure were altered. As described previously, because the underlying assumption

throughout treatment is one of equal efficacy, such an activity would not be expected to significantly impact the model results.

C7. Priority question. Please provide a detailed explanation on how each transition matrix in the model was derived, which sources were used to inform the transition probabilities, as well as how the probabilities for discontinuation for both virologic and non-virologic reasons were estimated and informed.

Table 23 and Table 24 show the available data for each parameter required for calculation of the transition matrices. Where data were not directly reported, every effort was made to source these data from the original articles. For first and fourth modelled lines, the respective trials were used to inform all required parameters. Specifically, these were: proportion supressed, proportion experiencing virologic failure, proportion experiencing non-virologic failure, CD4+ cell count change, the SD of the CD4+ cell count change, the CD4+ cell count change at baseline and the SD of the CD4+ cell count change at baseline.

For stable and failing switch, not all parameters were reported by all papers. Table 23 and Table 24 show, for stable and failing switch profiles respectively, which studies were able to contribute to the estimate of each parameter. In these instances, the average was estimated from the available values.

CAB LA + RPV LA and comparator oral ART was informed by a network meta-analysis (NMA) including ATLAS, FLAIR and ATLAS-2M data. This data is reported in section 2.9 of Document B.

Stable Switch (Baril 2016[72])

Table 23: Studies informing parameters necessary for estimation of Stable Switch efficacy profile

Study	Arm	Supression	VF	NVF	CD4+ change	CD4+ Change SD	Baseline CD4+ count	Baseline CD4+ SD
BATAR	ATV/r+RAL	Yes	Yes	Yes	Yes	No	No	No
	ATV/r+RAL	Yes	Yes	Yes	Yes	No	No	No
	ATV/r+TDF/FTC	Yes	Yes	Yes	Yes	No	No	No
Ruane	ATV+RAL	Yes	Yes	Yes	Yes	No	No	No
SPARE	DRV/r+RAL	Yes	Yes	Yes	No	No	Yes	Yes
	LPV/r+TDF/FTC	Yes	Yes	Yes	No	No	Yes	Yes
Calza	DRV/r+RAL	Yes	Yes	Yes	Yes	No	No	No

KITE	LPV/r+RAL	Yes	Yes	Yes	Yes	No	Yes	Yes
	HAART	Yes	Yes	Yes	Yes	No	Yes	Yes
ATLAS	ATV/r+3TC	Yes	Yes	Yes	Yes	No	No	No
A5116	EFV+LPV/r	Yes	Yes	Yes	Yes	Yes	No	No
	EFV+2 NRTI	Yes	Yes	Yes	Yes	Yes	No	No
NEKA	LPV/r+NVP	No	No	No	Yes	Yes	Yes	Yes
	LPV/r+2 NRTI	No	No	No	Yes	Yes	Yes	Yes
Reliquet	RAL+NVP	Yes	Yes	Yes	No	No	No	No
Calin	RAL+ETR	Yes	Yes	Yes	No	No	No	No
No Nuc No Boost	RAL+MVC	Yes	Yes	Yes	Yes	No	No	No
ROCnRAL	RAL+MVC	No	No	No	No	No	Yes	Yes

VF Virological failure; NVF No virological failure

Failing Switch (Kanters 2017[73])

Table 24: Studies informing parameters necessary for estimation of Failing Switch efficacy profile

Study	Arm	Supression	VF	NVF	CD4+ change	CD4+ Change SD	Baseline CD4+ count	Baseline CD4+ SD
2LADY	LPV/r + 2 NRTI	Yes					Yes	Yes
HIV STAR	LPV/r + 2 NRTI	Yes					Yes	Yes
Laker et al.	LPV/r + 2 NRTI	Yes			Yes	Yes	Yes	Yes
EARNEST	LPV/r + 2 NRTI	Yes			Yes	Yes	Yes	Yes
SECOND-LINE	LPV/r + 2 NRTI	Yes	Yes	Yes	Yes	Yes	Yes	Yes
SELECT	LPV/r + 2 NRTI	Yes	Yes	Yes	Yes	Yes	Yes	Yes

VF Virological failure; NVF No virological failure

Fourth modelled lines 1-3 were informed by BENCHMRK 1&2 studies, where data was pooled.

The workbook used to generate the CD4+ cell trajectories relies on use of a random number seed. While this random number seed has been replicated for derivation of matrices used for 1L treatments in the model, this random number seed was not captured for 2L matrices, so that the efficacy matrices for 2L onward cannot be replicated exactly. However, they can be recalculated with the information detailed above such that they are sufficiently close to the values included in the model. Given that the application of efficacy is equal to both arms throughout, any updates do not impact on cost-effectiveness conclusions for CAB LA + RPV LA. This is supported by scenarios conducted for the submission documentation (Document B, Section

3.8.3.1) where no change in efficacy between stable and failing switch efficacy was assumed and there was minimal movement in the ICER. This demonstrates that the cost-effectiveness outcomes are robust to any changes in further lines due to the underlying assumption that this is the same regardless of the first line treatment.

C8. Priority question. For CAB LA + RPV LA transition probabilities between health states based on CD4 count are provided, both for patients above and below the HIV RNA threshold level of 50 per ml.

a. Please explain what the transition probabilities for CAB LA + RPV LA for patients above the HIV RNA threshold level of 50 per ml are used for in the model, since no such patients enter the model and those who experience virologic failure (i.e. those who go from below to above the threshold level) move on to subsequent treatment lines.

b. Please explain whether the model precludes the possibility of patients experiencing viral re-suppression when remaining on the same treatment (for a user-specified time) after experiencing a virologic failure.

c. Please explain why the transition probabilities for CAB LA + RPV LA are the same regardless of patients being above and below the HIV RNA threshold level of 50 per ml, whereas they are different for oral ART regimens depending on whether patients are above and below the HIV RNA threshold level of 50 per ml, and justify the clinical plausibility of these transition probabilities being the same for CAB LA + RPV LA.

a. As described in the answer to C5, transition matrices informing movement for those with a viral load ≥50 copies/mL are inert in the first modelled line. They are placed in the model because of its standardised structure for efficacy profiles and although unused, have been filled out with identical values for individuals below the HIV RNA threshold of 50 copies/mL. However, they can be set to zero if this increases confidence in the application. Currently, they are filled with the same transition probabilities as for those with a VL <50 copies/mL

but are not used explicitly by the model; this can be seen more clearly in the 'Active Inputs' sheet, in cells I8:M12, I22:M26 and D27:H31.

b. As described in the answer to question C5, people in subsequent treatment lines can remain in a failing state for three months. If they experience a virologic failure and subsequent suppression within these three months, they remain in the same treatment line (until the threshold time).
c. In first line, the transition probabilities for CAB LA + RPV LA are the same regardless of being above or below the threshold of 50 copies/mL as described above in the response to part a. This is not different for the first line comparator treatment efficacy as the same efficacy is assumed for both arms and the same transitions are used. Subsequent lines however, do have different transition probabilities above and below this threshold as people may remain in the failing health state for up to three months and therefore these transitions are required. This assumption is detailed more thoroughly in the answer to question C5 and relates to the potential for patients in later lines being able to enter without viral suppression.

C9. Priority question. Please explain whether all evidence on viral suppression for oral ART treatments that is used to inform the model is based on optimal, 100% adherence. If it is not, then please justify the appropriateness of using an adjustment factor for suboptimal adherence.

Adherence to oral ART in ATLAS and FLAIR was not reported, only adherence to CAB LA + RPV LA. Individuals had to be virally suppressed on their oral regimen for inclusion in the trials (or before randomisation to the main trial phase in the case of FLAIR), but there were no inclusion/exclusion criteria relating to adherence. Regardless of the actual adherence to oral ART in the trial (a 48-week period), it is reasonable to expect that adherence would be somewhat lower over a lifetime of treatment in the real-world setting; this is described further in the answer to question C10.

These are the principles upon which the model makes its assumptions. Importantly, it does not assume that adherence for either arm is 100%. Rather it makes explicit the relationship between the trial results (efficacy) and the fact that they are based on some underlying level of adherence (whether measured or not), i.e. 100% ***trial***

adherence). Since it is reasonable to expect that adherence over a lifetime of treatment in clinical practice will be lower than that seen in the trial, reductions are made relative to this trial baseline. So, although adherence to oral ART was not measured in the trials, it is not required for this calculation or assumption. Whatever the absolute adherence , the model simply assumes initially that 100% of that adherence level generated the reported efficacy and makes a reduction to this based on what might reasonably be seen in real life. Since reductions in adherence are *relative* to an assumed 100%, the absolute adherence value would have no application.

C10. Priority question. As stated on page 122 of the CS, the relationship between adherence and viral suppression was estimated using data from the supplementary material from the article by Ross et al. 2015.

a. **Please provide a detailed explanation on how this relationship was estimated, and justify its applicability to the current appraisal.**

b. **Please explain whether other sources were considered to inform the relation between adherence and viral suppression, e.g. the article by Bezabhe et al. 2016 (also referenced in the CS) notes on page 6 that patients with a near perfect adherence do not necessarily have better virologic outcomes than patients with an adherence of ≥80-90%.**

c. **Please conduct a literature review to appraise other sources of evidence and conduct scenario analyses with those other values if considered appropriate**

In response to a) and b), a number of studies have demonstrated that adherence can reduce over time for people who are taking oral ART. Specifically, this may not appear immediately but can be expected over a lifetime. Ross et al.(2015)[74] looked at the benefits that long-acting ART could have on adherence to treatment regimens and in turn, the impact on outcomes. Ross et al. [74] concluded that the benefits of long-acting therapy could result in additional life-years. Ross et al. [74] used medication possession ratios (MPR) to determine the relationship between adherence and virologic suppression from the long-term outcomes of people taking

daily oral therapies and found that suppression rates were dependent on adherence levels.

As the current decision problem examines daily oral ART and compares it with an innovative long-acting therapy over a life time horizon, this evidence can be considered directly relevant to the population in question. CAB LA + RPV LA eliminates the need for strict adherence to daily dosing and therefore it is not expected that the adherence seen in clinical practice would decrease from that seen in the trial. However, it is generally recognised that individuals taking daily self-administered treatment over the long term in clinical practice will have a reduction in adherence compared with that seen over the short term, as part of a clinical trial setting. Given this, the evidence derived by Ross et al. [74] was incorporated into the model so as to accurately reflect the outcomes for people taking long-term daily oral ART. The derived relationship between adherence and viral suppression is displayed in the supplementary materials of Ross (figure S2). The line of best fit displays coordinates (0.95,0.91) and (0.05,0). These were used to quantify the relationship using the standard y=mx+c approach. The resulting formula is the one that is used in the model.

In response to question b and c), Bezabhe et al. (2016)[75] was also considered a potential source and reported a pooled OR for adherence on viral suppression to be 0.55 although, when subcategorised, this was as low as 0.33 in groups relevant to this decision problem. In conclusion, though literature was available, with data reported as ORs, these were quite different from one another despite all potentially being relevant. There are a number of reasons why this may happen such as varying quality of studies and definitions of the adherence measure but it highlights that measuring adherence is challenging.

An additional problem with using ORs is that they limit modelling flexibility offered by the equation sourced from Ross et al.[74]. Using a single and invariable OR would also restrict the capability of the model to perform sensitivity analysis and indeed, user variation. In contrast, the equation sourced from Ross et al. [74], is not limited in this way.

To check the face validity of our approach, Ross et al's. equation was used to derive the corresponding OR so it could be compared with other sources. In second line ART, the OR is approximately 0.41. This is between the pooled and relevant category stratification values presented by Bezabhe et al.[75]. It was therefore concluded that this provided a credible estimate of the relationship between suboptimal adherence and viral suppression and further, the application increased model flexibility without limiting functionality and adaptability.

In direct response to c), given the time constraints for clarification of any parts of the submission, it is not considered feasible to conduct any additional literature review further to the evidence already provided. As adherence in the model is calculated via a flexible equation, rather than an OR, it would not be feasible within the time frame to make substantial changes to the model to accommodate scenarios with ORs.

C11. Priority question. Please explain for which AIDS-defining events (ADEs) the ARAMIS study report showed the risk of ADE increased with increasing CD4+ cell count and what adjustments had to be made by the company. Please provide the full report for the reference of the ERG, as it is not included in the CS Doc B reference pack.

Within the ARAMIS study report, provided in the reference pack (Folder 'References to Documents A and B'; Reference: 'ARAMIS dolutegravir model report TN Global'), the opportunistic infection (OI) risk matched with CD4+ cell count and time can be found in Table 6 on page 39.

As can be seen in Table 6 of the ARAMIS report there are instances where a higher CD4+ cell count leads to a higher probability of ADE i.e. going from CD4+ cell count of 350-500 to CD4+ cell count of >500 results in a higher probability of every single type of OI. This is not intuitive in that it is unlikely that people in more favourable health states would experience worse outcomes. This may be due to underlying low patient numbers leading to inflated probabilities.

To address the face validity of these assumptions, all values from 25-36 months were repeated for 36 months+. In addition, some other values were repeated, highlighted in Table 25 for clarity.

Table 25: Probability of experiencing an ADE used in the Company CE model

Time on treatment	Opportunistic infection	Probability of experiencing an ADE (mean value)					Source
		CD4 <50	CD4 50-200	CD4 200-350	CD4 350-500	CD4 >500	
0-6 months	Acute viral OI	0.0071	0.0033	0.0008	0.0008	0.0008	ARAMIS technical report[19] Lowest value for each time-point by CD4 cell count carried forward
	Acute bacterial OI	0.0070	0.0022	0.0006	0.0004	0.0004	
	Acute fungal OI	0.0049	0.0022	0.0003	0.0001	0.0001	
	Acute protozoal OI	0.0021	0.0006	0.0002	0.0001	0.0001	
	Other OI	0.0036	0.0020	0.0000	0.0000	0.0000	
7-12 months	Acute viral OI	0.0039	0.0010	0.0003	0.0003	0.0002	
	Acute bacterial OI	0.0027	0.0009	0.0001	0.0001	0.0001	
	Acute fungal OI	0.0018	0.0013	0.0002	0.0002	0.0001	
	Acute protozoal OI	0.0018	0.0004	0.0001	0.0001	0.0001	
	Other OI	0.0022	0.0014	0.0007	0.0003	0.0003	
13-24 months	Acute viral OI	0.0019	0.0005	0.0002	0.0002	0.0001	
	Acute bacterial OI	0.0022	0.0008	0.0001	0.0001	0.0001	
	Acute fungal OI	0.0016	0.0011	0.0002	0.0002	0.0001	
	Acute protozoal OI	0.0015	0.0004	0.0001	0.0001	0.0001	
	Other OI	0.0014	0.0009	0.0004	0.0002	0.0002	
25-36 months	Acute viral OI	0.0005	0.0001	0.0000	0.0000	0.0000	
	Acute bacterial OI	0.0012	0.0004	0.0000	0.0000	0.0000	
	Acute fungal OI	0.0015	0.0011	0.0001	0.0001	0.0001	
	Acute protozoal OI	0.0008	0.0002	0.0000	0.0000	0.0000	
	Other OI	0.0009	0.0006	0.0003	0.0001	0.0001	
36 months+	Acute viral OI	0.0005	0.0001	0.0000	0.0000	0.0000	
	Acute bacterial OI	0.0012	0.0004	0.0000	0.0000	0.0000	
	Acute fungal OI	0.0015	0.0011	0.0001	0.0001	0.0001	
	Acute protozoal OI	0.0008	0.0002	0.0000	0.0000	0.0000	
	Other OI	0.0009	0.0006	0.0003	0.0001	0.0001	

ADE: AIDS-defining event; OI: opportunistic infection
SE assumed to be 10% of mean for all inputs

C12. Page 133 of the CS states that "these were chosen as the most appropriate ADEs to model because the risk of occurrence is dependent on both CD4+ cell count and the time on, and status of treatment".

Were other ADEs experienced by participants in the trials or in clinical practice excluded? If so, please provide details of the incidence of excluded events, justification for exclusion and provide the option in the model to include these.

The ATLAS-2M trial does not provide a breakdown of specific ADEs, but does provide reporting on the number of transitions to CDC stage 3 (AIDS), although this was not stratified by CD4 count. In addition, development of AIDS is considered to be a clinical outcome which can be derived and estimated from the model output. Further inclusion of AIDS development as a specific ADE would be considered double counting. Note that information regarding the development of AIDS was collected in ATLAS-2M but not in the pooled ATLAS and FLAIR data, nor was it included as a specific outcome in the supporting NMA – therefore any differences between arms are not quantifiable.

It is considered that the base case inclusion of ADEs, with accompanying disutilities and costs is conservative. Additionally, clinical advice indicates that the vast majority of ADEs that may be observed would be opportunistic infections, i.e. those included in the base case analysis. However, in the answer to question C15, a scenario was provided where ADEs were not included at all and it is not influential on the results.

C13. Priority question. Please include all drug-related AEs which affect ≥5% of patients in either arm in the model (cf. question B9).

In Table 26 the drug related adverse events observed in the pooled ATLAS and FLAIR data can be seen; with those occurring in over 5% of the patients highlighted. Table 27 shows the same data that was observed in the ATLAS-2M trial with highlighting following a similar format. This confirms that the only AEs observed in over 5% of the population are injection site reactions (ISRs), of varying description. The exception to this is that in the Q4W arm of the ATLAS-2M trial, 5% experience Pyrexia; this arm is not considered in this analysis and would likely be treated at home and therefore not incur additional cost. The base case analysis has used this data to inform the included AEs and included only the ISRs as these were the only substantive difference between arms. Using the criteria described in the question,

the Company is confident that the base case analysis satisfies the answer to this question.

Table 26: Summary of Common Drug related AEs in Either Treatment Group During the Maintenance Phase - pooled ATLAS-FLAIR data

Table 29 Most Common Drug-Related AEs (Reported in ≥1% in Any Treatment Group) by Preferred Term during the Maintenance Phase for Study 201584, Study 201585, and Pooled Data (Safety Population)

	201584		201585		POOLED	
	CAB + RPV (N=283)	CAR (N=283)	CAB + RPV (N=308)	CAR (N=308)	CAB + RPV (N=591)	CAR (N=591)
ANY EVENT, n (%)	236 (83)	28 (10)	255 (83)	8 (3)	491 (83)	36 (6)
Injection site pain	221 (78)	0	227 (74)	0	448 (76)	0
Injection site nodule	43 (15)	0	36 (12)	0	79 (13)	0
Injection site induration	37 (13)	0	29 (9)	0	66 (11)	0
Injection site swelling	22 (8)	0	22 (7)	0	44 (7)	0
Headache	14 (5)	4 (1)	11 (4)	0	25 (4)	4 (<1)
Injection site erythema	12 (4)	0	12 (4)	0	24 (4)	0
Pyrexia	13 (5)	0	11 (4)	0	24 (4)	0
Injection site pruritus	16 (6)	0	7 (2)	0	23 (4)	0
Nausea	4 (1)	6 (2)	11 (4)	0	15 (3)	6 (1)
Fatigue	4 (1)	5 (2)	11 (4)	0	15 (3)	5 (<1)
Injection site bruising	6 (2)	0	10 (3)	0	16 (3)	0
Injection site warmth	8 (3)	0	6 (2)	0	14 (2)	0
Asthenia	7 (2)	0	6 (2)	0	13 (2)	0
Body temperature increased	8 (3)	0	4 (1)	0	12 (2)	0
Myalgia	4 (1)	1 (<1)	6 (2)	0	10 (2)	1 (<1)
Dizziness	4 (1)	1 (<1)	5 (2)	0	9 (2)	1 (<1)
Injection site hematoma	4 (1)	0	6 (2)	0	10 (2)	0
Abnormal dreams	4 (1)	0	3 (<1)	2 (<1)	7 (1)	2 (<1)
Anxiety	4 (1)	1 (<1)	4 (1)	0	8 (1)	1 (<1)
Insomnia	0	0	8 (3)	1 (<1)	8 (1)	1 (<1)
Diarrhoea	5 (2)	1 (<1)	2 (<1)	0	7 (1)	1 (<1)
Creatinine renal clearance decreased	2 (<1)	3 (1)	2 (<1)	0	4 (<1)	3 (<1)
Malaise	5 (2)	0	2 (<1)	0	7 (1)	0
Influenza like illness	0	0	5 (2)	0	5 (<1)	0
Pain	1 (<1)	0	4 (1)	0	5 (<1)	0
Chills	0	0	4 (1)	0	4 (<1)	0
Depression	3 (1)	0	0	1 (<1)	3 (<1)	1 (<1)
Vitamin D deficiency	3 (1)	1 (<1)	0	0	3 (<1)	1 (<1)

Data Source: Mod5.3.5.3/209522 Output/Tab3.26.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

Table 27: Summary of Common Drug related AEs in Either Treatment Group During the Maintenance Phase - ATLAS-2M data

Table 30 Summary of common drug related AEs (≥1%) in either treatment group during the maintenance phase

Preferred Term	Q8W (N=522) n (%)	Q4W (N=523) n (%)
Any drug-related event	400 (77)	399 (76)
Injection site pain	364 (70)	358 (68)
Injection site nodule	54 (10)	87 (17)
Injection site induration	40 (8)	37 (7)
Injection site discomfort	34 (7)	40 (8)
Injection site swelling	32 (6)	26 (5)
Injection site pruritus	26 (5)	24 (5)
Pyrexia	19 (4)	25 (5)
Injection site erythema	12 (2)	15 (3)
Asthenia	12 (2)	6 (1)
Injection site bruising	10 (2)	11 (2)
Headache	10 (2)	11 (2)
Dizziness	10 (2)	5 (<1)
Chills	9 (2)	6 (1)
Diarrhea	8 (2)	3 (<1)
Fatigue	7 (1)	19 (4)
Injection site warmth	7 (1)	7 (1)
Malaise	7 (1)	6 (1)
Body temperature increased	7 (1)	8 (2)
Injection site hematoma	3 (<1)	14 (3)
Nausea	5 (<1)	12 (2)
Pain	5 (<1)	10 (2)
Influenza like illness	5 (<1)	8 (2)
Back pain	2 (<1)	6 (1)
Insomnia	1 (<1)	6 (1)

Data Source: Table 3.12.

Mortality

C14. Priority question. Please explain in detail how the relative risks of death were derived from the study by Lewden et al. 2007, where in the model these are applied to calculate the composite all-cause mortality, and make sure that these do not include the same error in the conversion from probabilities to rates and back to probabilities as in the transition matrices on the Active Input sheet (i.e. as mentioned in question C25).

The risks of death were taken directly from the Standardized Mortality Ratios (SMR) in Table 2 of Lewden et al.[76] and were applied as a multiplier to age-based mortality in the model (Figure 9). This can be found in the 'Life Tables & ADEs' sheet in the cost-effectiveness model. There is no error in the estimation of probabilities from rates in the transition matrices, as detailed in the response to C25. In addition, no transformation was made to the values extracted from the published literature. The

presented values are SMRs and so are applicable in the sense that they describe the excess mortality that can be attributed to disease and disease severity.

TABLE 2. Mortality Rates and SMRs in HIV-Infected Adults, ANRS CO8 APROCO-COPILOTE and ANRS CO3 AQUITAINE Cohorts, 1997 to 2005, According to Cumulated Time Spent Within Each Category of CD4 Cell Count

	Patients (N)	Median Time Spent (y)	IQR	PYs	Deaths (n)	Rates (per 100 PYs)	(95% CI)	SMR	(95% CI)
CD4 count ≥500 cells/mm^3	1208	4.5	(2.1 to 7.0)	5402	37	0.7	(0.5 to 0.9)	2.5	(1.8 to 3.5)
CD4 count 350 to 499 cells/mm^3	1263	2.0	(1.0 to 4.0)	3446	40	1.2	(0.8 to 1.5)	3.5	(2.5 to 4.8)
CD4 count 200 to 349 cells/mm^3	1296	2.0	(0.6 to 3.9)	3178	56	1.8	(1.3 to 2.2)	5.6	(4.2 to 7.2)
CD4 count <200 cells/mm^3	1118	0.6	(0.2 to 2.7)	1928	155	8.0	(6.8 to 9.3)	30.3	(25.8 to 35.5)

Figure 9: Table 2 from Lewden et al. describing standard mortality ratios used in the cost-effectiveness model

C15. Priority question. Please justify that mortality probabilities need to be included for ADEs in addition to the relative risks of death as derived from Lewden et al. 2007, which would imply that Lewden et al. 2007 excluded these additional probabilities in their estimates, and provide the option in the model to exclude these additional probabilities for ADEs from the analysis.

Lewden et al. [76] do not explicitly state whether mortality related to ADEs is excluded and it is not possible to separate out ADE-specific and any other cause of death, the decision was made to include both.

It is important to note that while the risk of death could be marginally overinflated with this method, the efficacy and risks are equally applied to both arms, so this assumption does not favour one arm or the other and would not be expected to affect the model results. In response to this question, a scenario has been conducted, where the probability of experiencing ADEs is set to zero (Table 28) and it shows, as expected, limited impact on the model result.

Table 28: Scenario analysis results - no ADE risk considered

	CAB+RPV-Q2M (net price)	Pooled comparator (list price)	Incremental
Life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]	[redacted]
ICER (£/QALY)			-£66,203.34
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year			

Health-related quality of life (HRQoL)

C16. Priority question. Please provide additional evidence supporting the assumption that injection site reactions would have been captured in the short form (SF)-12 trial data collected, including:

a. **When was HRQoL measured in relation to cabotegravir injections given in the ATLAS and FLAIR?**

b. **How long did injection site reactions last on average?**

c. **Please provide the per dimension perception of injection (PIN) questionnaire scores for the Q2M (every two months) group, separately for each available measurement (including week 8, 24 and 48). In light of these data, please consider the likelihood that injection site reactions were captured in the SF-12 data collections at weeks 24 and 48.**

a. Injection site reactions (ISRs) were assessed at every study visit from Week 4 to the primary endpoint, and every visit thereafter (reference: ATLAS and FLAIR protocols). The SF-12 was administered at baseline and Weeks 24 and 48, and refers to recollections in the last 4 weeks. With the exception of the Numeric Rating Scale (NRS) and Perception of Injection (PIN), all patient-reported outcome questionnaires were recommended to be administered at the beginning of the visit before any other assessments were conducted. The NRS and PIN were administered post injection.

b. In the pooled analysis of ATLAS & FLAIR: Injection site reactions had a median duration of 3 days; most ISRs resolved within 14 days but 17% of subjects experienced ISRs lasting more than 14 days (EPAR p121). On average, ISRs lasted for 5.5 days (mean duration). Fewer than 5% of subjects experienced ISRs of Grade 3 or higher, and the proportion of subjects who withdrew from study due to ISRs was very low (<1%) (EPAR p. 110).

c. SF-12 was not administered in the ATLAS-2M study so was not captured for participants on a Q2M regimen, only for those on a Q1M regimen (i.e. in ATLAS and FLAIR). In terms of PIN data in the two studies in which SF-12 was administered, PIN was administered at Weeks 5, 41 and 48. Scores are tabulated below. At the

visits where SF-12 was administered on the same day as PIN (i.e. Week 48), average PIN summary scores indicated that ISRs were ‘totally’ or ‘very’ acceptable and the bother of ISRs fell between ‘not at all’ and ‘a little’. Average individual item scores were in a similar range. It is reasonable to suppose that participants’ responses to the SF-12 at the Week 48 visit would have been influenced by their perception of ISRs at that same visit. From the PIN data it can be seen that any effect on their HRQoL being experienced due to ISRs at that time would be extremely small, as the average perception of ISRs signalled high acceptance and no or little bother. Further, the high acceptance and low/no bother, together with the short median duration and low grade of ISRs, support the decision not to impose a separate disutility for ISRs.

The likelihood that injection site reactions are captured in the SF-12 data collections at weeks 24 and 48 is high because the questions in the SF-12 questionnaire specifically mention a period of 4 weeks (e.g. “During the past 4 weeks, how much of the time have you accomplished less than you would like with your work or other regular daily activities as a result of your physical health?”) which covers the average duration of ISRs in ATLAS/FLAIR between the monthly injections. Four weeks is standard in generic HRQoL instruments such as the SF-12 because people can remember well their experience over a 4-week period. For instance, in **Error! Reference source not found.** below (Table 50 from CSR), the independent PIN item measuring “Pain” (2) is well captured by the following SF-12 question: “During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?”. Finally, the different dimensions of the PIN instrument refer to different time periods such as “the anxiety before the injection”, “the anxiety after the injection”, and the overall satisfaction and willingness for an injectable treatment.

Table 29 PIN Tables from ATLAS CSR

Table 29 PIN Tables from ATLAS CSR

Table 30. PIN tables from FLAIR CSR

Table 31. PIN tables from FLAIR CSR

C17. Priority question. Please provide a full list of studies identified which provided utility values stratified by CD4 count and justify why the study by Kauf et al. 2008 was chosen for the base-case.

The table below shows studies that report original utilities identified in the utility SLR. A number of other studies were identified which use utilities reported in these original publications. Those studies are not listed here.

Of the studies identified, Kauf et al. [77]was considered the most relevant as it derived utility values from data collected in 5 clinical trials, resulting in a large analysis population and these were measured using the SF-36 instrument. In addition, some trials reported using stratifications that were not ideally suited to the Company cost-effectiveness model health states which would have necessitated further assumptions to use these. Table 32 shows the original studies identified in the literature review and the criteria used for determining the appropriateness for either use in the base case or scenario analysis.

The only identified study which may lend well for sensitivity analysis was Marcellusi, 2016. However, this study used data from the Kauf paper to derive the utility values, alongside another study which used EQ-5D data. Since the authors do not state explicitly how these values were pooled or merged, it is not possible to say whether these are compatible or relevant.

Table 32 Studies reporting utility/disutility values

Author, year	Country specific or UK/multinational values	Health state alignment to model	Instrument alignment to ATLAS-2M trial	Reference
Chaudhary, 2009[78] Taken from Simpson 2004	× Country Specific	✓	× EQ-5D	Simpson (2004) HIV Clin Trials 5:294–304.[79]
Colombo, 2011[80]	× Country Specific	× Insufficient granularity a low CD4+ cell counts	× EQ-5D	NR
Contreras-Hernandez, 2010[81] SCHACKMAN 2002	× Country Specific	✓	× SF-6D	Schackman (2002) Med Decis Making;22:27–38.[82]
Hornberger, 2006[83]	× Country Specific	× Incompatible stratification	× Medical Outcomes Study HIV questionnaire	NR
Hornberger, 2005[84]	× Country Specific	× Incompatible stratification	× Medical Outcomes Study HIV questionnaire and the Subcutaneous Injection Survey	NR
Hubben, 2007[85]	× Country Specific	✓	× EQ-5D	NR
Marcellusi, 2016[86] • Sourced from a mixture of data from Kauf and Simpson 2004	× Country Specific	× Incompatible stratification	SF-36 (broadly compatible with SF-12)	NR
Pialoux, 2018[87]	× Country Specific	✓	× EQ-5D	NR
Simpson, 2008[88] Taken from Simpson 2004	× Country Specific	✓	× EQ-5D	NR
Simpson, 2013[89]	×	✓	×	NR

• Sourced from Simpson et al. 2011	Country Specific		Not explicitly stated (or in source paper)	
Trueman, 2000[90] RISEBOROUGH 2009	✓ Multinational (including UK)	× Incompatible stratification	× Not explicitly stated	Risebrough (1999) Sixth Conference on Retroviruses and Opportunistic Infections;[91]

Costs

C18. Priority question. The model uses cost input parameters that were informed by Beck et al. 2011, which is based on costs from the cost year 2008 and which were inflated using consumer price index for health (CPI-HLTH).

a. **Please replace inflated costs with costs sourced from NHS Reference costs 2018/2019 for all unit costs for which this is possible.**

b. **Please use the NHS Cost Inflation Index (NHSCII) from Personal Social Services Research Unit (PSSRU) 2019 for inflating costs that cannot be sourced from NHS Reference costs 2018/2019 and provide the calculations for this in the model.**

In order to facilitate this scenario, costs for the relevant input parameters were sourced from the NHS Reference costs and inflated using the NHSCII from the PSSRU and a microcosting approach taken. Clinicians were consulted to determine the appropriate level of resource use for each health state cost category included in the model.

Clinicians advised that they would not expect that patients with a VL <50 copies/mL would require additional inpatient, outpatient and day ward care over and above that that would be already accounted for by ADE incidence and cost in the model and testing costs. Therefore, for this scenario, a zero cost was applied for all health state costs other than non-HIV medication and CD4+ tests and other procedures.

The non-HIV medication costs were advised to contain exclusively prophylaxis for opportunistic infections for patients with a CD4+ cell count <200. Azithromycin was assumed to be used at a dosage of 1250mg once per week, in line with clinical advice is only costed for patients with CD4+ cell count <50.

Fluconazole was assumed to be used at the same dosages as for prevention of relapse of cryptococcal meningitis in HIV-infected patients after completion of primary therapy. This involves an oral dose of 200mg daily. This is costed for all patients with CD4+ cell count <200.

Co-trimoxazole was assumed to be used at the same dosages as for Prophylaxis of Pneumocystis jirovecii (Pneumocystis carinii) infections. This is listed as being 960 mg once daily, reduced if not tolerated to 480 mg once daily, alternatively 960 mg once daily on alternate days, alternate day dose to be given 3 times weekly, alternatively 960 mg twice a day on alternate days, alternate day dose to be given 3 times weekly. In the costing this is assumed to be 960mg once a day for three days every week. This is costed for all patients with CD4+ cell count <200.

Additionally, testing costs were examined. The NHS reference costs do not list detailed test prices. They only list broad pathology test categories with Integrated blood services including clinical biochemistry, haematology and immunology. The unit cost for this item is £1.76 though this is inflation adjusted to £1.80 using the NHS cost inflation index (NHSCII). The following resource use was assumed in costing as described by clinical experts;

- CD4+ cell count >350: Viral load testing every 6 months = £0.30 per cycle
- CD4+ cell count 200-350: CD4+ cell count testing every 12 months = £0.15 per cycle, and viral load testing every 6 months = £0.30 per cycle
- CD4+ cell count 50-200: CD4+ cell count testing every 3-6 months (6 months assumed in the model) = £0.30 per cycle, and viral load testing every 6 months = £0.30 per cycle
- CD4+ cell count <50: CD4+ cell count testing every 3-6 months (3 months assumed in the model) = £0.60 per cycle, and viral load testing every 6 months = £0.30 per cycle

In addition to the above costs, the following non-HIV specific tests would be required for all CD4+ cell categories:

- Twice per year (all assumed £0.30 per cycle):
    - Full blood count
    - Renal function test
    - Liver function test

    - Bone profile assessment
    - Dipstick urinalysis
- Annually (all assumed £0.15 per cycle):
    - Urine protein/creatine ratio
    - Lipid profile assessment
    - HbA1c testing
    - Hepatitis A/B/C infection/immunity status

Combining the information above leads to the health state costs seen in Table 33.

Table 33. Health state costs

Variable	CD4+ cell count category (cells/mm^3)	Mean (per month)	SE	Source	Resource use assumption
Non-HIV medication	CD4+ <50	£30.19	£3.02	eMIT	-
	CD4+ 50-200	£27.41	£2.74	eMIT	-
	CD4+ 200-350	£-	£-		
	CD4+ 350-500	£-	£-		
	CD4+ > 500	£-	£-		
CD4+ tests and other procedures	CD4+ <50	£3.00	£0.30	NHS reference costs	All tests assumed to be covered under "Integrated Blood Services".
	CD4+ 50-200	£2.70	£0.28	NHS reference costs	
	CD4+ 200-350	£2.55	£0.26	NHS reference costs	
	CD4+ 350-500	£2.40	£0.24	NHS reference costs	
	CD4+ > 500	£2.40	£0.24	NHS reference costs	
HIV-1: human immunodeficiency virus type 1; NA: not applicable; RNA: ribonucleic acid; SE: standard error SEs assumed 10% of mean					

When these costs are used in the model under base case settings, there is little impact on the results from the base case (Table 34).

Table 34. Scenario analysis results: Alternate health state costs

	CAB+RPV-Q2M (net price)	Pooled comparator (list price)	Incremental
Life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]	[redacted]
ICER (£/QALY)			-£68,694.40
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year			

C19. Priority question. As explained on pages 114 and 115 of the CS, some comparator drugs were excluded on the basis that these were of relatively low costs and would therefore have been used earlier in treatment than at the time CAB LA + RPV LA would be considered. Please provide the option in the model to use a cost estimate for the basket of comparator drugs that includes these low cost drugs.

Please see our response to Question B1.a which is relevant here. An initial arbitrary cut off of 2.5% share of the stable switch market was applied to market data to derive a short list of potential alternatives to CAB LA + RPV LA. Clinical experts assessing the face validity of this approach then advised on the exclusion of Truvada (TDF/FTC) + Tivicay (3% market share) and the inclusion of Juluca (1.9% market share). TDF/FTC is the most frequently used NRTI backbone regimen and tends to be prescribed in first-line, in part because of its lower cost compared to TAF/FTC.

Drug cost per se was not an explicit consideration in deriving the comparators; some low cost branded single tablet regimens such as Triumeq® and Dovato® are included. The fact that some of the 'lower cost' regimens were switch options in fewer than 2.5% of virologically suppressed individuals illustrates the point made in the submission that they are treatments more likely used early on. In other words they would be heavily represented in a list of treatments that people were switching from.

Therefore we do not think it is appropriate to provide a cost estimate based on a basket of comparator drugs which includes these low cost regimens. Doing so would

suggest that they are appropriate in the CAB LA + RPV LA clinical setting which we strongly believe not to be the case.

C20. Priority question. The cost of the basket of comparator drugs is based on a simple average of the drugs that were considered relevant, and on page 115 of the CS it is explained that this is because of the inability "to access estimated market shares across these nine comparators that would be representative of reasons related specifically to the challenges of oral therapy".

a. **Please explain what is meant by "reasons related specifically to the challenges of oral therapy".**

Please see our response to Question B1.a which is relevant here. In summary, there are several reasons why a switch away from an efficacious ART may be undertaken. For tolerability or toxicity reasons, there may be options within currently available ART for example by switching or removing the backbone NRTIs or by switching the choice of the core agent. For people who want a non-daily, or a non-oral therapy, there are currently no alternatives (CAB LA + RPV LA is the first). The following patient quotes may help to provide a flavour of the types of challenges faced by people receiving existing ART:

"It's less and less stigmatized with the injection, because I don't feel like I'm reminding myself of [HIV]. . .with the injection you go through days and weeks. . .two months not having to worry about that, so it's less stigmatized"

"I love it because I don't have to take a daily medication, so that's just one less thing on my plate that I have to worry about. . . I definitely feel there's less pressure. I like the injection because it's not a daily, in my face, I have to do this."

We anticipate that CAB LA + RPV LA will provide an option for individuals for whom a switch to an alternative oral regimen would not address a specific need, such as those implicit in the quotes above. We invite the ERG to review additional commentary from people about their experience of long acting injectables in Kerrigan et al. 2018 [92] from where these were selected (provided in the submitted reference pack for documents A&B). The market data that guided the selection of comparator regimens in this appraisal reported treatments to which virally suppressed individuals are currently switching. No details are available on the reason for switching, so it is

impossible to know whether individuals in the sample were switching for a reason that makes CAB LA + RPV LA an option. Our statement 'reasons related specifically to the challenges of oral therapy' implies this.

b. Please provide the option in the model to use a cost estimate for the basket of comparator drugs that is based on a weighted average using the "Switch share by regimen" that is provided in Table 55 of the CS.

For the reasons outlined above, we do not consider a weighted average cost to be an appropriate method here as it implicitly assumes that the current switch market represents the future market. This may be true of the total numbers switching, but the forecasted distribution across the options is in fact unknowable since CAB LA + RPV LA will be the only non-oral and/or a non-daily treatment.

In spite of these reservations we have estimated the weighted cost of the 9 comparators as requested (weighted by the market share in Table 55 in the company submission). By this method, the cost is £730.88 is for 30 tablets, adjusted to a monthly cost of £741.54 (accounting for the variation in days per month). The fact that it is only marginally different than the simple mean cost implies it will have little real impact in the analyses (Table 35).

Table 35: Scenario Analysis Results: Weighted pooled comparator cost

	CAB+RPV-Q2M (net price)	Pooled comparator (list price)	Incremental
Life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]	[redacted]
ICER (£/QALY)			-£68,199.44
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year			

C21. Priority question. The model includes the costs of non-HIV medication that were sourced from Beck et al. 2011, based on the cost year 2008 and inflated to 2018/2019 values. Please justify that this cost estimate from 2008 is still valid today, also considering the likeliness that generic versions of drugs that were patented in 2008 may have become available in current times.

Beck et al. do not state all of the drug treatments that were given in the "other drug" categories so it would not be possible to check whether some of these treatments have become available as generic alternatives. However, it is reasonable to assume that the composition of treatments may not have changed (only the cost). As the

other cost categories cover large proportions of care such as in and outpatient care and testing costs, the “non-HIV medication” category of cost reflects only medication costs outside the other categories such as medication for co-morbidities. These factors are considered unlikely to have changed amongst a HIV positive population, but it is acknowledged that the cost of drugs may have changed since the publication of the informing study.

To facilitate decision making a scenario has been provided below where the cost of non-HIV medication has been arbitrarily halved to account for any treatments that comprised this cost category that may be now available as generic medications (Table 36). In addition, a scenario has been provided where these are removed in entirety; this scenario reflects the possibility that some treatments included are now priced so low that they would be overrepresented in the scenario where costs are halved (Table 37). In both scenarios, there is little impact on the base case analysis.

Table 36: Scenario analysis results - Non-HIV medication costs halved

	CAB+RPV-Q2M (net price)	**Pooled comparator (list price)**	**Incremental**
Life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]	[redacted]
ICER (£/QALY)			-£66,466.04
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year			

Table 37: Scenario analysis results - Non-HIV medication costs not included

	CAB+RPV-Q2M (net price)	**Pooled comparator (list price)**	**Incremental**
Life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]	[redacted]
ICER (£/QALY)			-£67,082.06
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year			

C22. Priority question. On page 140 of the CS, an explanation is provided on payment by result (PbR) currency for HIV regarding how it is stratified and what it could possibly include. This includes a reference to an appendix O. This explanation appears to be provided in support of the assumption that administration costs consist of 15 minutes of a Band 5 nurse, as detailed in Table 69 of the CS. This Table 69 also provides a note that this is considered in addition to the current commissioning (CG1) pathway.

a. **Please explain how PbR currencies are used to inform the analysis, and whether no corresponding cost estimates from NHS Reference costs 2018/2019 are available.**

b. **Please explain whether it can be assumed that no additional costs for outpatient visits in relation to treatment administration are relevant for the analysis, or provide the option to include these costs, e.g. by replacing the costs of 15 minutes of nurse time by those for a nurse-led outpatient visit based on NHS Reference costs 2018/2019.**

c. **Please provide Appendix O. Currently, an Appendix Q is provided under the filename Appendix O.**

a. The explanation of PbR currencies in Document B section 3.5.2.1 describes HIV activity for a year of care (for new, stable and complex patients). HIV has a national currency with no assumed national price.[93] NHS Reference costs are available for 2018/2019 based on HIV-related activity for that year. The PbR currencies for service are reflected in the model and health states. The assumed resource and costs by health state (viral load and CD4 count) are taken from Beck et al.

b. We acknowledge that it is unclear whether the current allocation of service activities will cover administration of injectables.

   In Document B section 3.5.2.1 the Company is clear that it does not assume that no additional costs for outpatient visits in relation to treatment administration should be considered, "*Whilst it is possible that the administration of CAB LA + RPV LA could be subsumed within the PbR currency for this patient category, an additional 15 minutes of Band 5 nurse*

time per administration has been included in the economic model to account for the potential that there is an additional cost to some providers of administering the CAB LA + RPV LA injections every two months". This was not sourced from the NHS Reference costs, rather the PSSRU 2019 (detailed in Table 68 of Document B). This was done so as not to assume that there are no additional costs although this approach is considered conservative. As described, it is possible that the cost would be subsumed within the PbR currency. The NHS Reference costs do not detail a nurse-led outpatient visit and so the PSSRU cost is considered to be more relevant to the decision problem.

c.

Appendix O is the correct document and was titled appendix Q in error.

C23. Priority question. The health state cost estimates from Beck et al. 2011 pertain to patients with a CD4+ cell count above or below a threshold of 200. Please justify that no further distinction in costs applies when health states are defined based on the further subdivision of CD4+ cell counts as is used in the model, or provide the option in the model to assume a further subdivision of costs in line with the definition of the health states based on CD4+ cell counts as is used in the model.

Data provided by Beck et al was stratified by CD4+ cell counts that were less than or greater than 200. As such, it was assumed that the costs for a CD4+ cell count under 50 and between 50-200 were the same. Similarly, all health state categories above a CD4+ cell count of 200 were assumed to be the same. As such, it is reasonable to expect that the cost provided is an average of all stratifications for a CD4+ cell count under or over 200. Given that in the base case less time is spent in the lower CD4+ cell count health states in the CAB LA + RPV LA arm than in the comparator arm over a life time, it is not expected that any change or further stratification would significantly impact the result. Indeed, this is considered a conservative assumption.

Clinical advice indicated that once people have a CD4+ cell count above 200, there is unlikely to be any significant difference in costs attributed to any of the stratifications.

It is important to consider that individuals in this model spend the vast majority of modelled time with a viral load of <50 copies/mL. In the oral treatment and CAB LA + RPV LA arms over a lifetime, people are expected to spend only 1.7 and 1.3 LYs respectively in with a viral load over 50 copies/mL and are therefore likely to be in reasonably good health. A total of 0.78 and 0.94 life years are spent in CD4+ cell counts <200 for CAB LA + RPV LA and oral comparator arms respectively. This is very likely to align with times in virologically failing health states further confirming that people represented in the model are likely to be in good health.

C24. Please justify that the costs of testing for HIV RNA copies / viral load is included in the cost component "CD4+ tests and other procedures" at a frequency that corresponds to an assumed number of tests that is in line with the assumptions for the model regarding the detection of changes in viral load that are the basis for treatment switching (i.e. if the model assumes a monthly probability of changes in viral load, then that would imply monthly costs of testing for this), and provide the option in the model to explicitly include these costs in case there is a possibility that the costs as currently included do not match the underlying assumptions in the model.

Clinical opinion, along with guidelines from BHIVA has indicated that testing would likely be conducted approximately every six months for CD4 cell count and viral load testing, and other biochemical testing either annually or every six months. Using NHS reference costs, this amounts to a total of £2.40 – 3.00 per month as detailed in the answer to C18. The amount used in the base case is £87.77 or £63.97 per month dependent on the CD4+ cell count category. It is therefore reasonable to conclude, that the frequency of testing was captured by Beck et al.

An average monthly cost was assumed because this aligns with the probability of changes in viral load or CD4+ cell count and therefore would reflect the costs associated with a proportion of people experiencing changes in either viral load or CD4+ cell count. In clinical practice, it is not usual to test every month as this would be both prohibitively invasive and expensive. Therefore, to implement these costs

such that they occur every month would not reflect clinical practice and so would not contribute to the decision problem.

It is always necessary to make simplifying assumptions during modelling; specifically, in this model, a proportion of individuals may require testing each month due to changes in clinical outcomes and as such, they are attributed a cost adjusted to a monthly figure. As stated in the question, the model assumes a monthly probability of changes in viral load and therefore, there is a proportionally representative cost associated.

Model functionality and results

C25. Priority question. There appears to be an error in cells on the Active Input sheet, where the '-' (i.e. minus)-sign has been omitted in the formulas;

=OFFSET('Efficacy Profiles'!AW17;A5-1;0)*IF(I36=1;1;(1-EXP(LN(1-I36)/11)))

instead of

=OFFSET('Efficacy Profiles'!AW17;A5-1;0)*IF(I36=1;1;(1-EXP(-LN(1-I36)/11)))

, which applies to cells D13:M17, D27:M31, D81:M85, D95:M99, D135:D139, D149:D153, D189:M193, D203:M207, D243:M247, D257:M261, D297:M301, D336:M340 and D375:M379. Please check whether this is indeed an error and, if so, correct it in all relevant cells.

We have doubled checked the highlighted calculation and can confirm that this is not an error, rather the removal of a double negative. We have used the formulae listed below, where r denotes the rate parameter, t the time parameter and P the probability parameter:

Rate → -[ln(1-P)]/t

Probability → 1-exp{-rt}

When these formulae are combined, the full formula becomes =1-EXP{-(-[LN(1-P)]/t)t} where the double negatives are removed and one of the time elements is 1 (as it has already been transformed). This in turn becomes 1-EXP{([lLN(1-P)])t}. Correspondingly **p** and **t** are emboldened in the following formula: **(**1-EXP(LN(1-**I36**)/**11**))).

C26. Priority question. The run time for the model is slow when trying to see the impact of changing a single parameter. This is likely due to the fact that the Run Model button (Control sheet D40) is also connected to the probabilistic sensitivity analysis (PSA).

Is there any way to allow a deterministic run without PSA in order to improve deterministic run time?

A requirement of the model is to store information about previous model cycles and the number of model cycles that need to be stored is dependent on a number of user amendable settings. This is computationally expensive and therefore it can take several minutes to perform one run with mean values. This is not related to the PSA and unfortunately not something which can be easily addressed within the time frame available.

C27. Priority question. The sum of the disaggregated costs that are listed in Table 78 in the CS does not match the total costs for CAB LA + RPV LA. On the "Results" sheet in the model, the sums of absolute disaggregated costs and quality-adjusted life years (QALYs) calculated by the ERG do not match total costs or QALYs (except for costs for the pooled comparator). Disaggregated incrementals also do not match the total incrementals used in the calculation of the incremental cost effectiveness ratio (ICER). The same is observed in the sheet Intervention: E29≠ΣE30-E40, F60≠ΣF61-F71.

Please provide the correct total costs for CAB LA + RPV LA, make sure that all cost-effectiveness results (incl. PSA, OWSA, and scenario results) are based on the correct total costs and ensure that the correct values are displayed for all relevant cells in the model.

Total costs in the base case include those attributed to onward transmission. When including onward transmission in the results, the model should direct the user to the 'DTx Results' sheet for results rather than the standard 'Results' sheet. Therefore the total cost is the total cost displayed in E100 'Results' and F8 'DTx Results' added to the total cost of onward transmission displayed in J8 'DTx Results'. Similarly, the same applies to the QALYs except these are *lost* and are therefore subtracted from the total QALYs seen in Table 77 of the CS.

This discrepancy in the disaggregated results stems from a referencing error in the model which fails to apply the confidential PAS discount in the disaggregated first line costs. The total cost is the correct value (as is being sourced from a separate trace column) but the Initial modelled line therapy costs (found in table 78 of document B) has a value of the costs with no PAS applied. This can be seen where each section obtains costs from the "Treatment Trace" as disaggregated 1st line admin costs is taken from column JI which uses in calculation, numbers that extract treatment costs from the "Treatment Specification" worksheet without applying dblPAS. On the other hand, "total costs" is taken from rows BI to BT which are cost results input directly from the VBA code (which is where the PAS is applied to 1st line treatment costs).

The corrected discounted 1st line therapy cost with DTx turned off should be £[redacted]. This error does not impact any further results and the total costs presented in the submission are correct. Importantly, the total cost used in the calculation of the ICER is correct and no adjustment is required.

C28. Priority question. Please explain the functionality of cell H5 on Sheet "DTx".

Cell H5 on the "DTx Results" Sheet allows the user to view results either per patient (when selecting "Patient-Level") or for the entire cohort (when selecting "Cohort-Level").

Section D: Textual clarification and additional points

D1. According to section B.1.3.4.3 of the CS, "HIV therapies have historically fallen outside the remit of NICE".

Please elaborate on this point, e.g. by providing a reference supporting the statement.

In England, HIV services, including treatment, have until recently been commissioned by NHSE through specialised commissioning. In Wales, the All Wales Medicines Strategy Group has historically appraised new ARVs. NICE has not assessed any HIV treatments through its technology appraisal programme. As described in the response to B. 1a, commissioning policy plays an important part in the market.

Following the conclusion of negotiations between DHSC and the Association of the British Pharmaceutical Industry in 2018/2019, it was agreed and stated in the new voluntary scheme for branded medicines (VPAS)[94], that all new medicines or indications will have the option of a NICE appraisal. This submission for CAB LA + RPV LA is the first of its kind, the first occasion where the cost-effectiveness of an HIV treatment is being assessed for use in NHS England and Wales. The context is a market place in which treatments are considered to have comparable efficacy (in terms of viral suppression) and where pricing has been negotiated through national and regional tendering.

D2. Section B.2.11 of the CS refers to "additional planned and ongoing real-world studies, including post marketing authorisation commitments, that will not report within the next 12 months" for which "details are available upon request".

Please provide details for these studies.

Additional detail of the post-marketing authorisation studies for CAB LA + RPV LA are provided in Table 38 below. Please note that these are still under discussion with regulators and are academic in confidence.

Table 38: Post-authorisation studies

Study Name	Study Type	Study Objective	Study population	Study report expected
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Study Name	Study Type	Study Objective	Study population	Study report expected

D3. On page 123 of document B of the CS there is some strange formatting in the paragraph below Figure 13. Please clarify whether any text is missing here.

This is a formatting issue related to the caption of Figure 13. The company can clarify that no text is missing. The paragraph should read as follows:

"Individuals in the module are stratified into risk groups, Figure 13 (Appendix P, Table 1), the majority of which potentially contribute to onward transmission of HIV. Based on these core transmission risk populations, a conceptual model design was developed (Figure 14). The heterosexual risk population was further stratified in to low-risk and high-risk behaviour categories and transmission from multiple sources

was permitted (e.g. heterosexual transmission in the injecting drug use transmission risk group). Full details of risk groups and associated transmission probabilities are provided in Appendix M. “

D4. The CS includes many abbreviations that are not provided in full wording nor included in the list of abbreviations.

Please make sure that all abbreviations are provided in full wording at first instance and are included in the list of abbreviations.

Please make sure that all abbreviations are provided in full wording at first instance and are included in the list of abbreviations.

Please find an updated list of abbreviations below.

Abbreviation	Definition
/r	Boosted with ritonavir
/c	Boosted with cobicistat
3TC	Lamivudine
ABC	Abacavir
ACCEPT	Chronic Treatment Acceptance Questionnaire
ADE	AIDS-defining events
AE	Adverse event
AF	Alafenamide
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ART	Antiretroviral therapy
ARV	Antiretroviral
ATLAS	Antiretroviral Therapy as Long-Acting Suppression
ATLAS-2M	Antiretroviral Therapy as Long-Acting Suppression Q2M
ATV	Atazanavir
AUC	Area under the concentration-time curve
AWMSG	All Wales Medicines Strategy Group
AZT	Zidovudine
BHIVA	British HIV Association
BIC	Bictegravir
BMI	Body mass index
BMD	Bone mineral density
BNF	British National Formulary
BR	Background regimen
bPI	Boosted protease inhibitor
C	Cobicistat
CAB	Cabotegravir

CAR	Current antiretroviral regimen
CCG	Clinical care group
CD4+	Cluster of differentiation 4
CDC	Centers for Disease Control and Prevention
CE	Cost effectiveness
CFB	Change from Baseline
CI	Confidence interval
CMH	Cochran-Mantel Haenszel
CPAG	Commissioning Priorities Advisory Group
CPI-HLTH	Consumer price index for health
CRG	Clinical reference group
CSR	Clinical study report
CVD	Cardiovascular disease
CVF	Confirmed virologic failure
DRV	Darunavir
d4T	Stavudine
DILI	Drug-induced liver injury
DF	Disoproxil fumarate
DNA	Deoxyribonucleic acid
DOR	Doravirine
DRV	Darunavir
DSA	Deterministic sensitivity
DTG	Dolutegravir
EACS	European AIDS Clinical Society
EFV	Efavirenz
ETR	Etravirine
EMA	European Medicines Agency
EVG	Elvitegravir
EQ-5D	EuroQol 5 Dimension questionnaire
FDA	US Food and Drug Administration
FDC	Fixed dose combination
FLAIR	First Long-Acting Injectable Regimen
FTC	Emtricitabine
GBM	Gay and bisexual men
GI	Gastrointestinal
GP	General practitioner
HAT-QoL	HIV/AIDS Targeted Quality of Life
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HCP	Healthcare professional
HDL	high-density lipoprotein cholesterol
HIV	Human immunodeficiency virus
HIVTSQ(c)	HIV Treatment Satisfaction Questionnaire (change version)
HIVTSQ(s)	HIV Treatment Satisfaction Questionnaire (status version)
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment

ICER	Incremental cost-effectiveness ratio
IM	Intramuscular
IDU	Intravenous drug user
INI	Integrase inhibitor
INSTI	Integrase strand transfer inhibitor
INTI	Integrase inhibitor
IQR	Interquartile range
ISR	Injection site reaction
ITC	Indirect treatment comparison
ITT-E	Intent-to-treat exposed
IV	Intravenous
LA	Long-acting
LATTE	Long-Acting antireTroviral Treatment Enabling
LATTE-2	Long-Acting antireTroviral Treatment Enabling-2
LLOD	Lower limit of detection
LOCF	Last Observation Carried Forward
LPV	Lopinavir
LY	Life year(s)
MACS	Multicenter AIDS cohort study
MAPE	Mean absolute percentage error
MCS	Mental component summary score
MDT	Multi-disciplinary team
MIMS	Monthly Index of Medical Specialties
MPR	Medication possession ratio
MSM	Men who have sex with men
MVC	Maraviroc
NA	Not applicable
NHS	National Healthcare System
NHSE	National Healthcare System England
NICE	National Institute for Healthcare and Excellence
NMA	Network meta-analysis
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NRTTI	Nucleoside reverse transcriptase translocation inhibitor
OBR	Optimised background regimen
OI	Opportunistic infection
PAS	Patient Access Scheme
PbR	Payment by results
PBMC	Peripheral blood mononuclear cell
PDVF	Protocol-defined virologic failure
PHE	Public Health England
PI	Protease inhibitor
PIN	Perception of injection
PK	Pharmacokinetic
PI/r	Ritonavir-boosted protease inhibitor
PLHIV	People living with HIV

POLAR	Oral (PO) to Long-Acting (LA) Rollover
PP	Per-protocol
PRO	Patient reported outcome
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
Q1M	Every month
Q2M	Every two months
QALY	Quality-adjusted life year
QoL	Quality of life
R^2	Coefficient of determination
RAL	Raltegravir
RCT	Randomised control trial
RMSPE	Root mean square percentage error
RNA	Ribonucleic acid
RPV	Rilpivirine
RT	Reverse transcriptase
RTV	Ritonavir
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SF-6D	Short form 6 dimension
SF-36	Short form 36 questionnaire
SLR	Systematic literature review
SmPC	Summary of product characteristics
SOC	Standard of care
SOLAR	Switch Onto Long Acting Regimen
TAF	Tenofovir alafenamide
TB	Tuberculosis
TDF	Tenofovir disoproxil fumarate
TE	Treatment experience
TFV	Tenofovir
TN	Treatment naïve
TPV/r	Ritonavir-boosted tipranavir
TTO	Time trade-off
ULN	Upper limit of normal
UK	United Kingdom
UNAIDS	United Nations Programme on HIV and AIDS
VAPI	Vaccinees Perception of Injection
VL	Viral load
VPAS	Voluntary Pricing and Access Scheme
WHO	World Health Organisation
WOCBA	Women of childbearing age
ZDV	Zidovudine

D5. In case the company base-case model is updated in response to the ERG's clarification questions in a way that leads to a change in results, then please provide updated results (i.e. including base-case, PSA, one-way sensitivity analysis (OWSA) and scenario analysis results) alongside the company's response to clarification and provide details of all changes made (also indicating which cells in the model were amended.

After review of all included clarifications, the Company does not feel that any corrections to the base case are required other than clarification on the disaggregated costs mentioned in the response to C27.

D6. The front sheet of the model mentions in cell N25 that a user guide is available for the model, please provide this user guide.

The Company is happy to provide the user guide. The guide has been supplied together with the response document. Please see appendix D6 provided with this response.

Appendices

Appendices provided with this response are described in Table 39.

Table 39. Overview of appendices

Question	Appendix number	Document title
A7	A7a	UK adherence summary
A7	A7b	Adherence SLR report
B3	B3a	Figure 1 PRISMA flow diagram
B3	B3b	Table 7 Study characteristics RCTs
B3	B3c	Table 8 Baseline characteristics RCTs
B3	B3d	Quality assessment
B3	B3D3	Data extraction
B3	B3D5	Observational and single-arm studies
B7	B7	Cochrane Risk of Bias Assessment Tool
B8	B8	Swindells 2020 Supplementary appendix Table S1
C7	C7a	Transition matrix generator workbook
C7	C7b	CD4MatrixGenerator_example
D6	D6	UK Cabotegravir user guide

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Cabotegravir and rilpivirine for treating HIV-1 [ID3766]

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 patient 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 Community Advisory Board (UK-CAB)
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The UK-CAB is a network for community HIV treatment advocates across the UK. The UK-CAB has three main aims: 1. To develop and strengthen a UK network of HIV treatment advocates. We do this using a confidential email forum that links all members. 2. To provide expert training on current treatment issues. This includes the chance to meet with doctors, researchers and pharmaceutical companies. We do this with regular training workshops and by publishing all related material online. 3. To ensure there is effective community representation on formal structures that affect our care. This includes guideline panels, research studies and national commissioning groups. All representatives, including on the Steering Group, are elected by CAB members. The UK-CAB is funded by grant-awarding charities and pharmaceuticals. Our funders play no role in our strategy and aims. Our Steering Group independently set out the agenda of the CAB with feedback from our membership, which totals more than 800 HIV treatment advocates, who are connected to more than 80 organisations who work in and with the HIV sector.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant	All UK-CAB funding is to support our interactive member/training meetings to enhance HIV advocates knowledge of the latest developments in HIV research and treatment and its duration is ongoing unless otherwise stated. The UK-CAB received funding from the following organisations: • The manufacturer, ViiV Healthcare UK Ltd: £10,000 And the following comparator organisations: • Gilead Sciences, Ltd: £12,987 • Janssen UK: £8,000 • Merck Sharp & Dohme (UK) Limited: £29,087 – in addition to the above we received an honorarium to provide advice and support for the company's current HIV and ageing project. The total figure

manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	also includes a grant awarded for a Virtual HIV Treatment Activism training programme running during 2021. Mylan UK Healthcare Limited: £960 honorarium for an European Advisory Board meeting.
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 patients and carers to include in your submission?	Our submission is shaped with the views of members and with input from the following sector partners: HIV i-Base, Positively UK, NAM (aidsmap), NAT (National AIDS Trust) and AAF (Africa Advocacy Foundation). Content for this submission was collated via our membership's online network and our ongoing meetings of the UK-CAB, the most recent of which was held 12.02.2021. We have followed this treatment technology throughout its development process. Where beneficial to our submission we have included evidence from these reports by Public Health England (PHE): • Positive Voices 2017: survey report, PHE, 2020. • Trends in HIV testing, new diagnoses and people receiving HIV-related care in the United Kingdom: data to the end of December 2019, PHE, 2020

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	HIV is a manageable long-term condition, people diagnosed today can expect to start treatment immediately and have a life expectancy no different to those who live without the virus. The treatment also provides protection from onwards transmission, meaning people with HIV can protect themselves and their sexual partners. However, HIV is a complex condition and no two people with the virus are the same or share the same experiences. Stigma, especially internalised or self-stigma, are key barriers to people with HIV living fulfilled and happy lives. People with HIV still face discrimination and prejudice from friends, family, their employers or when trying to access a variety of services or facilities – from NHS healthcare to tattoo parlours. Public Health England's Positive Voices report identified that one in ten people with HIV have avoided seeking healthcare when needed due to fears of stigma. Stigma cannot be underestimated: 13% of people with HIV have not shared their HIV status with anyone outside a healthcare setting (PHE, 2020). As people with HIV live longer comorbidities are playing an increasing role in their health. More than one third are diagnosed with a clinical mental health disorder in their lifetime; a long-term condition in addition to HIV has been diagnosed in more than half, with a third living with two or more (PHE, 2020). People with HIV can often live well and happy lives until specific touch points, such as starting new relationships, changing jobs, needing to access healthcare. The stress of ordinary life changes can be amplified by a person's HIV status and all that entails. Sharing your HIV status doesn't happen once, it is a constant throughout your life, and requires an individual to be resilient and confident with their diagnosis, characteristics which not all people with HIV are privileged to maintain all of the time.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	The past decade has seen a number of changes to how treatment is provided. The SMART, START and PARTNER studies impacted people by advising: • Treatment should be for life, with no intervals or gaps in the therapy • To start treatment immediately upon diagnosis

	• That treatment protects you AND your sexual partners At the same time once daily pills have become more popular. To some the only reminder of HIV is their clinic appointments and taking their daily medication. People with HIV trust and have more confidence in their HIV care team than other areas of the NHS. People with HIV rated their GP practice an average 6.9 out of 10, but they rate their HIV on average 9.3 out of 10 (PHE, 2020).
8. Is there an unmet need for patients with this condition?	There are approximately 19,200 people with HIV who are not virally suppressed (15%). Of these 6,600 are not aware of their status (PHE, 2020). Amongst the remaining 12,600 there are potential candidates to receive this treatment technology for the reasons listed in this submission, as well as many who are on existing treatment. It is important to remember that there is no cure for HIV and that people need to take their medication for life. High levels of treatment uptake do not equate to high levels of good health, especially good mental health. Positive Voices identified many areas of unmet need amongst the population: 20% of HIV-related needs were unmet; 45% of other health-related needs were unmet; and 62% of social and welfare needs were unmet. Additionally 33% said that services had been become more difficult to access over the past 2 years (PHE, 2020).
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Impact on stigma • Removing the fear of pill-based treatment being discovered by people in the same household/workplace etc. by replacing it with confidential and private clinic visits. • Increasing accessibility to treatment for BAME groups and young people. Impact on mental health/wellbeing

	• Improving mental wellbeing/internalised stigma by removing the **daily** reminder of HIV for those with mental health concerns, depression, low mood and anxiety. Treatment: • Providing an alternative HIV treatment to people who find it difficult to swallow pills, or to those with a high pill burden (both from HIV and non-HIV pill-based regimens for other conditions) • Some people with HIV would simply prefer an injectable than taking a daily pill. Since the technology was authorised in Europe and the USA it has become a 'hot topic' of conversation and many people living with HIV are keen to see it made available in England. • Potential to reduce common gastro-intestinal side effects by switching away from oral medications, as well as the challenges of some drug-drug interactions that may be reduced by a switch to non-oral regime.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Reasons why someone may not want to use the treatment include: • The number of their clinic visits increasing from ~two per year to at least six. • Concerns about needing to switch treatments following a recent dose, i.e. how long would the tail of the drugs used in this technology be, affecting the length of time in between switching medication or being able to access a medication for a different condition where there is a drug/drug interaction? • A common question is where this treatment could be accessed. Ideally we would like to see patient choice exercised e.g. administered in community locations not just HIV clinical services.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	The overarching theme which connects the people who would benefit from the technology is those who struggle with taking daily pills: • Young adults who were born with HIV. In the UK 15-24 year olds have the lowest rate of viral suppression at 91% (PHE, 2020). This group has a different and complex relationship with their HIV. • People who find it difficult to swallow pills. • People with multiple comorbidities and an existing high pill burden which could be eased by their HIV medication being delivered via a long-acting injectable. • People living with HIV who fear daily pills will reveal their HIV status. This is often more prominent in Black and minority ethnic populations, or in shared accommodation i.e. immigrant or homeless populations. • The greater flexibility this might afford people with complex lifestyles where they may regularly travel across time-zones and to countries where carrying their medication may be problematic. • Stigma: People with poor mental health or wellbeing who struggle with the reminder of HIV when they take their pill on a daily basis.
Equality	
12. Are there any potential equality issues that should be taken into account when	In the UK, HIV disproportionately impacts marginalised communities, most notably gay and bisexual men, Black African men and women, and transgender women. Just under a third of people with HIV in the UK are women. More than two in five people with HIV are aged 50 or over (PHE, 2020). There is anecdotal evidence that a concern to keep HIV status confidential may be particularly prevalent among Black and minority ethnic populations, so the technology may be particularly beneficial for them.

considering this condition and the technology?	Similarly, the higher rates of viral non-suppression in young people may suggest potential benefits in this group.
Other issues	
13. Are there any other issues that you would like the committee to consider?	This is the first HIV treatment to undergo the NICE appraisal process and therefore, our first and only experience of engaging with NICE in this way and completing this submission.
14. To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] if there are none delete highlighted rows and renumber below	

Key messages
15. In up to 5 bullet points, please summarise the key messages of your submission: • HIV is a long-term manageable condition but people with HIV still experience significant issues, especially regarding stigma. • There are no alternatives to pill-based treatment or methods for people to take their treatment more privately or confidentially. • This technology will benefit marginalised groups, especially those experiencing stigma, mental health or wellbeing issues. • There are few disadvantages to the technology, and none are of severe concern. • It is abundantly clear that the HIV population in England want to see the commissioning of the technology.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Cabotegravir and rilpivirine for treating HIV-1 [ID3766]

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

- 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 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	National HIV Nurses Association (NHIVNA)
3. Job title or position	**HIV Clinical Services Manager and Advanced Clinical Nurse Practitioner (respectively)**

4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	NHIVNA represents HIV nurses in the UK. Its members are nurses and other allied professionals whose work supports people living with HIV. We provide support and education and encourage research amongst members.
4b. 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.	Funding received from ViiV: £1377.89 Purpose: ViiV travel bursary Funding received from ViiV: £30,000 Purpose: Sponsorship of NHIVNA Conference 2020 (funding for ViiV exhibition stand and ViiV conference delegates and sponsorship of venue, catering, and equipment). NOTE: NHIVNA annual conference 2020 was cancelled due to the COVID-19 pandemic and funds were held over for spend on NHIVNA virtual conference 2021, held on 16–17 June 2021.

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 suppress HIV infection and therefore preserve an individual's immune function • To stop progression of HIV infection into AIDS • To prevent onward transmission of HIV infection • To improve and maintain good quality of life for people living with 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.)	• A reduction in HIV viral load to <200 copies • Maintenance of CD4 cell count >200 • Reduction in HIV incidence in a population • Reduction in number of individuals whose HIV infection develops into AIDS
8. In your view, is there an unmet need for patients and	• Yes, for some patients. A small number of individuals are unable to, or have difficultly, adhering to daily oral ART. These patients will, on the whole, not meet the criteria for long acting injectables and yet they would benefit greatly from this form of ART.

healthcare professionals in this condition?	
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	In specialist centres that provide treatment and care for people living with HIV. This includes: • The provision of oral ART • Blood test monitoring • Screening for opportunistic infections and STIs • Support around living with HIV and support around adherence to ART, if needed • Support from HIV community nurses (in some areas)
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	• British HIV Association treatment guidelines • NHSE Service Specification for HIV
• 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.)	• Services are run in line with NHSE Service Specification which aims to harmonise services across the country • BHIVA provide guidelines for ART prescribing but services also follow local policy, e.g., in the local area and/or hospital trust • There are often individual differences of opinion regarding ART prescribing based on professional experience and experience within individual organisations

• What impact would the technology have on the current pathway of care?	• Patients routinely attend an HIV service twice a year. This technology would require patients to attend every two months, which would have an impact on number of staff needed, space required and the amount of time patients spend in a service or with a clinician.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	• It will still be used within the current service specification for HIV clinical practice but this approach to providing ART is different to current practice. Current practice involves prescribing oral ART which a patient self-administers outside of the service and is monitored every six months. As this technology requires administration of an IM injection, it will alter the way treatment is administered and taken by patients. As mentioned above, as the number of patients who use this technology increases and so will the number of staff, and amount of time and resources.
• How does healthcare resource use differ between the technology and current care?	• As mentioned above, there will be a potential need for more staff, time and space to introduce this technology into HIV clinical practice.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	• Predominantly in specialist HIV services but there is definite potential for this technology to be used in the community (in patients' homes, for example) particularly for people who may have difficulty attending a hospital.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	• Potential need for initial investment in training as the new technology is introduced • The technology is likely to be administered by nurses (either in a clinic or the community) and so increased investment in the nursing workforce would be needed • If patients are to be attending a service more than twice a year (current practice), then an investment in space to accommodate this increase in numbers would be needed.
11. Do you expect the	• Current HIV care in England is of a high standard and most people adhere to oral ART well. This

technology to provide clinically meaningful benefits compared with current care?	is reflected in the high uptake of ART and retention in care across HIV services in the country. • This technology may provide benefits for people who are, for a variety of reasons, unable to adhere to oral ART.
• Do you expect the technology to increase length of life more than current care?	• For those who already take oral ART well – no • For a small number of individuals who do not take oral ART – potentially.
• Do you expect the technology to increase health-related quality of life more than current care?	• As above. • Some patients feel that a daily dose of oral ART is a 'daily reminder' of their HIV status so removing this may improve QoL for some patients.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	• This technology may be useful for people who are unable to tolerate oral ART or may prefer not to take a daily oral tablet. We believe this to be a small number of people living with HIV in England. • We certainly believe the technology has the potential, with the support of specialist clinicians, to benefit the lives of people with complex needs (such as homelessness, chronic mental health issues, drug and alcohol dependency), which are impacting on their ability to adhere to daily oral ART.
• The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare	• Likely more difficult than current care due to the increase in resources needed as mentioned above. • Extra contacts with a clinician (either in a clinic or the community) might be more difficult for

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.)	patients to schedule. • Some patients might find having an injection more 'difficult' than taking an oral medication although conversely some people might find this 'easier' due to adherence issues mentioned above. • Patients prescribed this technology will be required to have contact with a clinician on a regular and routine basis. This will require careful monitoring by the clinician and the patient (e.g., to ensure that the injections are administered at the correct time intervals) and appropriate follow-up if a patient does not adhere to the recommended treatment plan. At present, patients are routinely monitored every six months but this technology may increase the amount of monitoring needed (blood tests being the main way of monitoring HIV treatment), which may affect patient acceptability.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	• Initially, patients will be required to start with a course of oral treatment to check for side effects and tolerability of the ART regimen. This may be inappropriate and/or unacceptable to some patients due to the issues mentioned above. • If a patient misses an injection date they may 'bridge' with oral treatment (if acceptable/ appropriate) but if they are subsequently 'lost to follow-up' and not taking any ART, then further testing (particularly for drug resistance) would be required.
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?	For a small number of patients, with specialist support, this technology has the potential to improve health-related benefits. For example, NHIVNA members were involved in initiating a patient onto injectable ART. This patient was accepted on compassionate grounds. For the first time they reached undetectable levels and the injectable ART were administered in the patient's home each month. This has transformed the patient's life and significantly reduced the risk of onward transmission.
• Is the technology a 'step-change' in the management of the condition?	Potentially, for a small number of patients but not for the majority of people who adhere well to oral ART.
• Does the use of the technology address any particular unmet need of the patient population?	As above.
17. How do any side effects or adverse effects of the technology affect the management of the condition	Intramuscular injections carry the risk of infection site pain, swelling and infection. These may impact on a patients' QoL.

and the patient's quality of life?	
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	In term of outcomes measured, yes; however, this is the first time that an injectable medication has been used as routine ART so it is hard to compare the results directly to current practice. It is reassuring that, in terms of viral suppression, this technology is as effective as oral ART.
• 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?	Viral suppression Patient satisfaction with and acceptability of the technology
• 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?	

19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
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?	People who may benefit from this technology may be marginalised due to gender, sexuality, ethnicity, socio-economic status and other social determinants that impact on their health and/or ability to access HIV services. We believe that it is vital that any implementation of this technology prioritises these marginalised people over those living with HIV who might be considered 'stable', i.e., they have no problem with, and are happy taking, oral ART.
21b. Consider whether these issues are different from issues with current care and why.	New and innovative technologies are often taken up by people who are well informed and fully engaged with a service. Although this technology may be useful for a small number of people in this group, we believe that its main potential lies in its ability to engage the small number of people with HIV in England who do not, or will not, take oral ART and have difficulty engaging with HIV services because of this.

Key messages
24. In up to 5 bullet points, please summarise the key messages of your submission. • Investment in nursing workforce needed if widespread use of the technology is to be introduced. • Use of this technology in patients with complex needs is vital, as is the specialist support to ensure this. • Most people with HIV in England adhere well to oral ART and are likely to continue to do so. • This technology will increase the amount and level of resources needed to deliver an HIV service. • Ensuring equality and access to this technology in marginalised groups is vital.

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in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Cabotegravir and rilpivirine for treating HIV-1

Produced by Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Declared competing interests of the authors

None.

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Commercial in confidence (CiC) data are highlighted in blue throughout the report.

Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Confidential comparator prices are highlighted in green throughout the report.

Any de-personalised data are highlighted in pink throughout the report.

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.

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Contributions of authors

Robert Wolff acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Pim Wetzelaer acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Hannah Penton, Steve Ryder, and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Edyta Ryczek and Susan O'Meara acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Sean Harrison acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Steven Duffy critiqued the search methods in the submission and contributed to the writing of the report. Maiwenn Al acted as health economist on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

3TC	Lamivudine
ABC	Abacavir
ABC/DTG/3TC	Abacavir/dolutegravir/lamivudine
ACCEPT	Chronic Treatment Acceptance Questionnaire
ADE	AIDS-defining event
AE	Adverse event
AiC	Academic in confidence
AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
ARV	Antiretroviral
ATLAS	Antiretroviral Therapy as Long-Acting Suppression
ATLAS-2M	Antiretroviral Therapy as Long-Acting Suppression Q2M
ATV	Atazanavir
AWMSG	All Wales Medicines Strategy Group
BC	Base-case
BHIVA	British HIV Association
BIC	Bictegravir
BMI	Body mass index
BNF	British National Formulary
C	Cobicistat
CAB	Cabotegravir
CADTH	Canadian Agency for Drugs and Technologies in Health
CD	Cluster of differentiation
CDC	Centers for Disease Control and Prevention
CE	Cost effectiveness
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CEPAC	Cost-Effectiveness of Preventing AIDS complications
CFB	change from baseline
CI	Confidence interval
CiC	Commercial in confidence
CINAHL	Cumulative Index to Nursing & Allied Health
CMH	Cochran-Mantel Haenszel
CPI HLTH	Consumer price index for health
CRD	Centre for Reviews and Dissemination
CROI	Conference on Retroviruses and Opportunistic Infections
CS	Company submission
CSR	Clinical study report
CVF	Confirmed virological failure
DOR	Doravirine
DRV	Darunavir
DSA	Deterministic sensitivity analysis
DTG	Dolutegravir
EED	Economic Evaluation Database
EFV	Efavirenz
EMA	European Medicines Agency
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D-3L	European Quality of Life-5 Dimensions-3 levels
ERG	Evidence Review Group
ESHPM	Erasmus School of Health Policy & Management
EUCTR	European Union Clinical Trials Register
EUR	Erasmus University Rotterdam

EVG	Elvitegravir
FDA	Food and Drug Administration
FLAIR	First Long-Acting Injectable Regimen
FTC	Emtricitabine
HAT-QoL	HIV/AIDS Targeted Quality of Life
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HIV-1	Human immunodeficiency virus type 1
HIVDR	HIV drug resistance
HIVDT	HIV drug therapy
HIVTSQ	HIV Treatment Satisfaction Questionnaire
HRQoL	Health-related quality of life
HSUV	Health state utility value
HTA	Health technology assessment
IAS	International AIDS Society
IAS-USA	International Antiviral Society, United States of America
ICER	Incremental cost effectiveness ratio
ICTRP	International Clinical Trials Registry Platform
IDU	Injecting drug use
INI	Integrase inhibitor
INSTI	Integrase strand transfer inhibitor
IQR	Interquartile range
ISPOR	International Society for Pharmacoeconomics and Outcomes
ISR	Injection site reaction
ITC	Indirect treatment comparison
ITT	Intention to treat
ITT-E	Intention-to-treat exposed
KSR	Kleijnen Systematic Reviews
LA	Long-acting
LATTE	Long-Acting antireTroviral; Treatment Enabling
LATTE-2	Long-Acting antireTroviral Treatment Enabling-2
LOCF	Last observation carried forward
LYG	Life years gained
MAIC	Match-adjusted indirect comparison
MAPE	Mean absolute percentage error
MeSH	Medical subject headings
mITT	Modified intention-to-treat
ml	Millilitre
mm	Millimetre
MPR	Medication possession ratio
MSM	Men who have sex with men
NA	Not applicable
NHIVP	National HIV Prevention
NHS	National Health Service
NHSCII	NHS Cost Inflation Index
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NMA	Network meta-analysis
NR	Not reported
NRTI	Nucleoside reverse transcriptase inhibitor
NVP	Nevirapine
OI	Opportunistic infection
PAS	Patient access scheme

PbR	Payment by Results
PHE	Public Health England
PI	Protease inhibitor
PIN	Perception of Injection
POLAR	Oral (PO) to Long-Acting (LA) Rollover
PP	Per-protocol
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
RAL	Raltegravir
Q1M	Given every one month
Q2M	Given every two months
Q4W	Given every four weeks
QALY	Quality adjusted life year
R^2	Coefficient of determination
RCT	Randomised controlled trial
RD	Risk difference
RMSPE	Root mean square percentage error
RNA	Ribonucleic acid
RPV	Rilpivirine
RR	Relative risk; Risk ratio
SAE	Serious adverse event
ScHARRHUD	School of Health and Related Research Health Utility Database
SD	Standard deviation
SE	Standard error
SF-6D	Short form – six dimensions
SF-12	12-item Short Form Health Survey
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
STA	Single technology appraisal
TAF	Tenofovir alafenamide
TB	Tuberculosis
TDF	Tenofovir disoproxil fumarate
TTO	Time trade-off
UK	United Kingdom
ULN	Upper limit of normal
WHO	World Health Organization
WTP	Willingness-to-pay

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1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. If possible, it also includes the ERG's preferred assumptions and the resulting incremental cost effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 presents the key model outcomes. Section 1.3 discusses the decision problem, Section 1.4 issues related to the clinical effectiveness, and Section 1.5 issues related to the cost effectiveness. Other key issues are discussed in Section 1.6 while a summary in presented in Section 1.7.

Background information on the condition, technology and evidence and information on key as well as non-key issues are in the main ERG report, see sections 2 (decision problem), 3 (clinical effectiveness), and 4 (cost effectiveness) for more details.

All issues identified represent the ERG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the ERG's key issues

Table 1.1: Summary of key issues

ID	Summary of issue	Report sections
1	Concerns regarding English language and date limits used in the literature searches, the sensitivity of the search strategies, and the currency of the literature searches	**Executive summary**: Table 1.2 **Main report**: Sections 3.1.1 and 4.1.1
2	Lack of head-to-head evidence and limited reporting of evidence between CAB LA + RPV LA (Q2M) and ART therapy	**Executive summary**: Table 1.3 **Main report**: Section 3.2.1 and 3.2.5
3	Unclear generalisability of the results to patients in the UK NHS setting	**Executive summary**: Table 1.5 **Main report**: Section 3.6
4	Exclusion of case-control studies from the clinical effectiveness (effectiveness and safety) review	**Executive summary**: Table 1.6 **Main report**: Section 3.1.2
5	Pooling of ATLAS and FLAIR	**Executive summary**: Table 1.7 **Main report**: Section 3.3

ID	Summary of issue	Report sections
6	All oral ARTs are assumed to have a similar efficacy	**Executive summary**: Table 1.8 **Main report**: Section 3.3
7	Non-significance interpreted as non-inferiority	**Executive summary**: Table 1.9 **Main report**: Section 3.4
8	Cost of basket of comparators	**Executive summary**: Table 1.10 **Main report**: Section 4.2.9
9	Adherence assumptions	**Executive summary**: Table 1.11 **Main report**: Section 4.2.6.4
10	Utility advantage for patients taking CAB LA + RPV LA	**Executive summary**: Table 1.12 **Main report**: Section 4.2.8.2
ART = antiretroviral therapy; CAB = cabotegravir; LA = long-acting; NHS = National Health Service; NNRTI = non-nucleoside reverse transcriptase inhibitor; Q2M = given every 2 months; RPV = rilpivirine; UK = United Kingdom		

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). ICER refers to the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing time spent in higher cluster of differentiation (CD) four count health states
- Reducing the incidence of AIDS-defining events (ADEs)
- Increased utility due to preference for long-acting treatment over standard antiretroviral therapy (ART)

Overall, the technology is modelled to affect costs by:

- Lower drug acquisition costs than current treatments
- Increasing time spent in higher CD4 count health states

The modelling assumptions that have the greatest effect on the outcomes are:

- Assumptions regarding adherence
- The cost of the basket of comparators

- Reduction or removal of the utility advantage for long-acting cabotegravir (CAB LA) + long-acting rilpivirine (RPV LA)

1.3 The decision problem: summary of the ERG's key issues

The decision problem addressed in the company submission (CS) is broadly in line with the final scope issued by NICE.

However, there were some notable differences:

- The population addressed in the decision problem is narrower as it requires a "treatment switch due to non-virologic reasons", see section 4.2.3 for further details. As detailed in section 3.2.3, mutation K103N was allowed in the three studies informing large parts of the CS.
- The relevant comparator treatment regimen consists of the variety of oral ART regimens that are given as second-line (or further) treatment to patients who switched their first-line (or other previous) treatment due to non-virologic reasons related specifically to the challenges of oral therapy, see sections 4.2.4, 4.2.9.1, and 6.1.3.1 of the main body of the report as well as key issue 8 (Table 1.9).
- A number of outcomes specified in the NICE scope were not assessed in the trials included in the CS, including treatment-emergent resistance, acquired immunodeficiency syndrome (AIDS)-defining events, and comorbidities (see Table 3.11 in section 3.2.5).

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

The ERG identified a number of concerns with the evidence presented on the clinical effectiveness:

- Key issue 1 – Concerns regarding the literature searches (see Table 1.2)
- Key issue 2 – Lack of evidence (see Table 1.3)
- Key issue 3 – Unclear generalisability to United Kingdom (UK) National Health Service (NHS) setting (see Table 1.4)
- Key issue 4 – Exclusion of case-control studies (see Table 1.5)
- Key issue 5 – Pooling of ATLAS and FLAIR (see Table 1.6)
- Key issue 6 – Assumption that all oral ARTs have similar efficacy (see Table 1.7)
- Key issue 7 – Non-significance interpreted as non-inferiority (see Table 1.8)

Table 1.2: Key issue 1 – Concerns regarding English language and date limits used in the literature searches, the sensitivity of the search strategies, and the currency of the literature searches

Report section	Sections 3.1.1 and 4.1.1
Description of issue and why the ERG has identified it as important	The ERG identified a number of issues regarding the search strategies: • Limiting searches to English language may have introduced language bias • Only studies published 2000 and later were included • Combining five search facets of search terms reduced the sensitivity of the searches • Only generic antiretroviral drug terms were included, i.e. no named drugs were included, including the two of specific interest to this submission: cabotegravir and rilpivirine

Report section	Sections 3.1.1 and 4.1.1
	• Relevant EMTREE indexing terms were missing from the Embase search strategy, e.g. 'Human immunodeficiency virus/' • Inclusion of more synonyms would have improved the sensitivity of the searches • Use of study design filters in the Cochrane Library unnecessarily restricted the retrieved results • No separate search for safety outcomes was conducted, cf. key issue 5 • The searches were conducted in April 2020, no update was performed before the submission Potentially relevant studies might have been missed.
What alternative approach has the ERG suggested?	Searches should have been performed prior to submission. Conduct and reporting should have followed best practice.
What is the expected effect on the cost effectiveness estimates?	Uncertain as it is unclear how many publications, if any, have been missed and what these reported.
What additional evidence or analyses might help to resolve this key issue?	Update searches following best practice would increase the likelihood that the submission is based on the best available evidence, including separate searches for safety outcomes.
ART = antiretroviral therapy; CAB = cabotegravir; ERG = Evidence Review Group; LA = long-acting; Q2M = given every 2 months; RPV = rilpivirine	

Table 1.3: Key issue 2 – Lack of head-to-head evidence between CAB LA + RPV LA (Q2M) and ART therapy

Report section	Sections 3.2.1 and 3.2.5
Description of issue and why the ERG has identified it as important	The decision problem (sections 2.2 and 2.3; Table 2) specifies the comparison between CAB LA + RPV LA (with oral lead-in therapy) and ART therapy. Furthermore, the company specifies that, in accordance with current marketing authorisation, only the every two month dosing schedule (Q2M) will be made available in the UK. However, the company did not identify any studies which included the comparison of CAB LA + RPV LA (Q2M) and ART therapy. Lack of head-to-head comparison restricts the comparability of the interventions. Moreover, the CS reports limited evidence for the outcomes included in the NICE scope allowing the comparison between CAB LA + RPV LA (Q2M) and ART therapy.
What alternative approach has the ERG suggested?	Future studies should include the comparison of interest to assess the clinical effectiveness and safety of intervention.
What is the expected effect on the cost effectiveness estimates?	The direct comparison between the intervention and control, in a well performed clinical study, can reduce the uncertainty around the clinical effectiveness and safety estimates used to inform the economic model.
What additional evidence or analyses might help to resolve this key issue?	Use of direct evidence rather than indirect evidence will help reducing the uncertainty of the estimates.

Report section	Sections 3.2.1 and 3.2.5
ART = antiretroviral therapy; CAB = cabotegravir; CS = company submission; ERG = Evidence Review Group; LA = long-acting; NICE = National Institute for Health and Care Excellence; Q2M = given every 2 months; RPV = rilpivirine; UK = United Kingdom	

Table 1.4: Key issue 3 – Unclear generalisability of the results to patients in the UK NHS setting

Report section	Section 3.6
Description of issue and why the ERG has identified it as important	As discussed in the CS (section B.2.13.4), the regimens used in ATLAS and FLAIR studies are not fully representative of currently used ART regimens in the UK NHS setting. This can substantially affect the generalisability of the results for the comparison of ART therapy vs. CAB LA + RPV LA (Q2M). The company states, however, that "(…) *the regimens used as comparators in ATLAS and FLAIR are considered to have comparable efficacy to currently used regimens, given that non-inferiority trials are the norm for ART in HIV*."
What alternative approach has the ERG suggested?	ERG suggests providing additional evidence (if available) to confirm that comparators in ATLAS and FLAIR trials are comparable to currently used regimens in the UK NHS setting.
What is the expected effect on the cost effectiveness estimates?	The cost effectiveness estimates could be not applicable to the UK NHS setting in situations where comparability between comparators of ATLAS and FLAIR studies and currently used regimens in the UK NHS setting cannot be established.
What additional evidence or analyses might help to resolve this key issue?	The ERG suggests providing additional evidence (if available) to confirm that comparators in ATLAS and FLAIR trials are comparable with currently used regimens in the UK NHS setting.
ART = antiretroviral therapy; CAB = cabotegravir; CS = company submission; ERG = Evidence Review Group; LA = long-acting; NHS = National Health Service; Q2M = given every 2 months; RPV = rilpivirine; UK = United Kingdom	

Table 1.5: Key issue 4 – Exclusion of case-control studies

Report section	Section 3.1.2
Description of issue and why the ERG has identified it as important	Table 5 in Appendix D of the CS indicated that case-control studies were not eligible for inclusion in the clinical effectiveness review. The objectives of the clinical effectiveness review included evaluation of both effectiveness and safety outcomes. It is possible that relevant data on safety were missed through the exclusion of case-control studies and therefore the presented evidence may not be complete.
What alternative approach has the ERG suggested?	It would be preferable to allow the inclusion of case-control studies for the clinical effectiveness review.
What is the expected effect on the cost effectiveness estimates?	Since no utility decrements were applied for safety (adverse events), it is likely that the cost effectiveness estimates derived from the company's submitted model would not change with additional available data on safety. However, a more complete review of the safety data, i.e. including evidence from case-control studies, may provide information to suggest that a different approach is required to account for differences between intervention and comparator groups in terms of safety.

Report section	Section 3.1.2
What additional evidence or analyses might help to resolve this key issue?	The ERG suggests that relevant evidence on safety from case-control studies should be included in order to have access to all available, relevant evidence.
CS = company submission; ERG = Evidence Review Group	

Table 1.6: Key issue 5 – Pooling of ATLAS and FLAIR

Report section	Section 3.3
Description of issue and why the ERG has identified it as important	An indirect treatment comparison (ITC) combined the patients in ATLAS and FLAIR into a single larger population for analysis. As there are substantial differences between the two studies, including the comparator treatment and use of a run-in period, this is an inappropriate analysis method. It is likely that the standard error of all effect estimates derived from the ITC are underestimated as a result. While the ERG recognises that the pooled analysis was pre-planned, the studies should have been meta-analysed rather than pooled.
What alternative approach has the ERG suggested?	The effect estimates for ATLAS and FLAIR should be combined in a random-effects meta-analysis, rather than combined as a single analytic population.
What is the expected effect on the cost effectiveness estimates?	Unknown. Any effect estimates are unlikely to change substantially, but the standard errors on all estimates may increase.
What additional evidence or analyses might help to resolve this key issue?	The ERG suggests using random-effects meta-analysis to combine ATLAS and FLAIR in the ITC, rather than using results from a pooled analysis.
ERG = Evidence Review Group; ITC = indirect treatment comparison	

Table 1.7: Key issue 6 –All oral ARTs are assumed to have a similar efficacy

Report section	Section 3.3
Description of issue and why the ERG has identified it as important	The CS assumes all oral ARTs have a similar efficacy. Given the very high efficacy of all current ART, the ERG has no specific issues with this statement and as such believe the use of a match-adjusted indirect comparison (MAIC) without a full network meta-analysis (NMA) is likely justified in this case. However, should the efficacy of ART used in the NHS be shown to be different to the ART used in ATLAS/FLAIR, then a NMA would be indicated.
What alternative approach has the ERG suggested?	No other approach at this time, though a full NMA would be indicated if the efficacy of ART used in the NHS is shown to be different to the efficacy of ART used in ATLAS/FLAIR.
What is the expected effect on the cost effectiveness estimates?	Unknown, it would depend on whether the efficacy of ART used in the NHS is higher or lower than the ART used in ATLAS/FLAIR.
What additional evidence or analyses might help to resolve this key issue?	Without further evidence showing the ART used in the NHS is different to ART used in ATLAS/FLAIR, the ERG believes no additional evidence or analyses are necessary. However, if such evidence becomes available, then a full NMA may be indicated to compare the efficacy of cabotegravir with all ARTs currently used in the NHS.

Report section	Section 3.3
ART = antiretroviral therapy; CS = company submission; ERG = Evidence Review Group; MAIC = match-adjusted indirect comparison; NHS = National Health Service; NMA = network meta-analysis	

Table 1.8: Key issue 7 – Non-significance interpreted as non-inferiority

Report section	Section 3.4
Description of issue and why the ERG has identified it as important	The company refers to the results as showing that CAB + RPV LA Q2M was, in fact, non-inferior or not different to *"current ART"*. As the ITC is imprecise, and as the ITC was not designed as a non-inferiority analysis with defined non-inferiority margins, non-significance cannot be interpreted as non-inferiority, only imprecision. From the ITC, we believe the interpretation should be that there is no current evidence that CAB + RPV LA Q2M is inferior to *"current ART"*, and that we cannot be certain that CAB + RPV LA Q2M is non-inferior to *"current ART"*.
What alternative approach has the ERG suggested?	The ERG suggests that the company replaces all claims in the CS that the ITC demonstrates CAB + RPV LA Q2M is non-inferior or not different to *"current ART"* with appropriate claims, i.e. that the ITC neither demonstrates that CAB + RPV LA Q2M is non-inferior nor inferior to *"current ART"*, and interpret the effect estimates and confidence intervals appropriately.
What is the expected effect on the cost effectiveness estimates?	None – this issue is the interpretation rather than estimation of effect estimates.
What additional evidence or analyses might help to resolve this key issue?	Appendix L of the company submission states that *"a head-to-head study assessing non-inferiority in efficacy of CAB + RPV Q8W [LA Q2M] versus bictegravir/emtricitabine/tenofovir alafenamide is currently planned"*. This planned study would ideally provide evidence of the non-inferiority or otherwise of CAB + RPV LA Q2M.
ART = antiretroviral therapy; CAB = cabotegravir; CS = company submission; ERG = Evidence Review Group; ITC = indirect treatment comparison; LA = long-acting; Q2M = given every 2 months	

1.5 The cost effectiveness evidence : summary of the ERG's key issues

The company's cost effectiveness results are presented in section 5, the ERG's summary and detailed critique in section 4, and the ERG's amendments to the company's model and results are presented in section 6. A full summary of the cost effectiveness evidence review conclusions can be found in section 6.4 of this report. The key issues in the cost effectiveness evidence are discussed in Tables 1.9 to 1.11.

Table 1.9: Key issue 8 – Cost of basket of comparators

Report section	Sections 4.2.4 and 4.2.9
Description of issue and why the ERG has identified it as important	Cost of 'basket of comparators' is uncertain. The cost savings associated with the use of CAB LA + RPV LA depend on assumptions regarding the cost of the 'basket of comparators'. The ERG is not aware of such evidence being available on the specific treatments that are currently provided to patients that would otherwise receive CAB LA + RPV LA if it

Report section	Sections 4.2.4 and 4.2.9
	were available, and therefore the average cost of these treatments remains uncertain.
What alternative approach has the ERG suggested?	The ERG performed a series of scenario analyses where alternative costs are assumed for the 'basket of comparators', which are based on the cost bands of ART regimens used by patients who switch treatment in the Midlands and East region.
What is the expected effect on the cost effectiveness estimates?	In these scenarios the incremental costs varied between [redacted] and [redacted] when using the lowest and highest alternative costs for the 'basket of comparators', respectively. CAB LA + RPV LA remained dominant over oral ARTs in all scenarios except when using the costs of Band 0, Band 1 or Bands 0, 1, 2, 3 and 4 (weighted average excluding Truvada-based regimens) which resulted in ICERs of [redacted], [redacted] or [redacted] per QALY gained, respectively. This highlights the sensitivity of the results to alternative assumptions on the costs of the 'basket of comparators'.
What additional evidence or analyses might help to resolve this key issue?	This issue could be resolved if evidence would be available on the specific treatments that are currently provided to patients that would otherwise receive CAB LA + RPV LA if it were available, and which proportion of patients would receive each treatment.
ART = antiretroviral therapy; CAB = cabotegravir; ERG = Evidence Review Group; LA = long-acting	

Table 1.10: Key issue 9 – Adherence assumptions

Report section	Section 4.2.6.4
Description of issue and why the ERG has identified it as important	Uncertainty regarding assumptions on the reduction in adherence for oral ART regimens. The company used an estimate for the proportion of patients not meeting a predefined cut-off value for adherence of ≥95% as an input for an estimated linear relationship between an individual's percentage adherence and percentage of patients experiencing viral suppression. Literature indicates that adequate viral suppression may still be achieved with adherence levels that are substantially lower than 95%. The reduction in adherence for the first modelled treatment line appears to have been modelled as a monthly probability of viral rebound (inadequate suppression) and switching treatment regimen. This is the single determinant of the difference between intervention and comparator in how patients transition through the model, but no explanation nor justification was provided by the company on this important aspect.
What alternative approach has the ERG suggested?	The ERG has used a lower estimate for the reduction in adherence, which is based on a stricter definition of suboptimal adherence that would correspond to a cut-off value of 71%. However, the appropriateness of using this value as an input for the estimated relationship between adherence and viral suppression remains uncertain. The appropriateness of using the reduction in adherence as a monthly probability of viral rebound and switching treatment regimen remains uncertain.

Report section	Section 4.2.6.4
What is the expected effect on the cost effectiveness estimates?	CAB LA + RPV LA remained dominant over oral ART regimens, both when the lower estimate was used and when no reduction in adherence was assumed.
What additional evidence or analyses might help to resolve this key issue?	This issue could be resolved if evidence would be available on either: • the proportions of patients in the UK not meeting a predefined cut-off for adherence and the proportion of patients not achieving adequate viral suppression above and below that cut-off, or • the proportion of patients achieving different levels of individual adherence plus the relationship between individual adherence and adequacy of viral suppression. The ERG is not aware of such evidence being available. Explanation and justification should be sought from the company on the apparent implementation of the reduction in adherence for the first modelled treatment line.
ART = antiretroviral therapy; CAB = cabotegravir; ERG = Evidence Review Group; LA = long-acting; UK = United Kingdom	

Table 1.11: Key issue 10 – Utility advantage for patients taking CAB LA + RPV LA

Report section	Section 4.2.8.2
Description of issue and why the ERG has identified it as important	Between-treatment differences in short form – six dimensions (SF-6D) utility scores of [redacted] were observed between patients taking CAB LA + RPV LA versus ART in the ATLAS/FLAIR data. The ERG felt the presence/size of this utility advantage was uncertain due to potential biases in this estimate which could favour CAB LA + RPV LA, including higher drop-out in HRQoL reporting in the CAB LA + RPV LA group versus the ART group and that injection site reactions may have been missed in the HRQoL data collection. Reducing or removing the utility advantage for cabotegravir has a substantial impact on the incremental QALYs gained.
What alternative approach has the ERG suggested?	The ERG did not remove this assumption from the base-case, as a difference is suggested by the HRQoL data. The ERG simply wanted to raise and examine potential uncertainties and biases in the data.
What is the expected effect on the cost effectiveness estimates?	Halving the size of the utility advantage resulted in the incremental QALYs dropping from [redacted] to [redacted]. Removing the treatment related utility advantage altogether decreased the incremental QALYs to [redacted], although CAB LA + RPV LA still remained dominant in all scenarios, with incremental QALYs remaining positive.
What additional evidence or analyses might help to resolve this key issue?	This uncertainty would be reduced by improved HRQoL data collection in the future.
ART = antiretroviral therapy; CAB = cabotegravir; ERG = Evidence Review Group; HRQoL = health-related quality of life; LA = long-acting; QALY = quality-adjusted life year; SF-6D = short form-six dimensions; UK = United Kingdom	

1.6 Other key issues: summary of the ERG's view

All key issues have been summarised above.

1.7 Summary of the ERG's view

Table 1.13 provides the incremental results of both the company's and ERG's preferred base-cases, as well as the impact of each ERG assumption change applied individually to the company base-case. The ERG base-case change which had the largest impact was reducing the assumed reduction in adherence for oral ART relative to CAB LA + RPV LA from 25.6% to 10.1%. The probabilistic results were consistent with the deterministic results.

The scenarios which had the largest impact on results were those surrounding adherence assumptions, the cost of the basket of comparators and reducing or removing the utility advantage applied to patients receiving CAB LA + RPV LA.

Table 1.12: Summary of ERG's preferred assumptions and ICER

Scenario	Incremental cost	Incremental QALYs	ICER
Company's base case	[redacted]	[redacted]	Dominant
Reducing the assumed reduction in adherence to oral ART from 25.6% to 10.1%	[redacted]	[redacted]	Dominant
Probability of onwards transmission for MSM patients with an undetectable viral load from 0.031% to 0%	[redacted]	[redacted]	Dominant
ERG's preferred base-case	[redacted]	[redacted]	Dominant

ART = antiretroviral therapy; ICER = incremental cost effectiveness ratio; MSM = men who have sex with men; QALY = quality adjusted life year

2. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 2.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	"Adults with HIV-1 infection who are virologically suppressed on a stable regimen and who have not shown prior virological failure due to drug resistance to INTI/INIs" [sic].	As per the marketing authorisation, i.e. adults who are virologically suppressed (HIV-1 RNA <50 copies /ml) on a stable antiretroviral regimen without present or past evidence of viral resistance to, and no prior virological failure with, agents of the NNRTI and INI class 1, who require a treatment switch due to non-virologic reasons.	Specificity added to align with the final marketing authorisation	The population addressed in the decision problem is narrower as it requires a "treatment switch due to non-virologic reasons". It should be noted that patients with K103N (NNRTIs resistance-associated) mutation were included. See section 2.1 for details.
Intervention	"Cabotegravir long-acting and rilpivirine long-acting injections with oral lead-in therapy"	As NICE scope	N/A	No comment
Comparator(s)	"Antiretroviral treatment (established clinical management such as an integrase inhibitor-based regimen)"	A basket of those antiretroviral regimens likely to be used as switch regimens for virally suppressed people living with HIV who are eligible for a switch to CAB LA + RPV LA, if CAB LA + RPV LA were not available.	These are considered as established ART for the population in question i.e. those people living with HIV who are most likely to benefit from a long-acting, non-oral alternative maintenance therapy.	The company used a basket of antiretroviral treatments as comparator which adds uncertainty, see section 2.3 for details.
Outcomes	"The outcome measures to be considered include: • Maintenance of virological suppression	As NICE scope, with the exception of comorbidities. Note that preference for and satisfaction with the long-acting	• Treatment-related comorbidities are not considered as outcomes in the appraisal because with most regimens (including the intervention	A number of outcomes specified in the NICE scope have not been addressed, as detailed in section 2.4.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
	• CD4+ T-cell levels • Treatment-emergent resistance • Adherence to treatment regimen • AIDS-defining events • Mortality • Comorbidities • Adverse events (including inflammation) • Health-related quality of life.”	regimen, as captured within the pivotal RCTs with patient-reported outcome instruments (PROs), is also included.	and the comparators) treatment-related comorbidities are no longer an important feature of treatment and do not generally feature in treatment decision-making.	
Economic analysis	“The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. 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 compared. • Costs will be considered from an NHS and Personal Social Services perspective.”	As per reference case. To fully capture the survival benefits of a successful antiretroviral regimen, non-curative nature of treatment and the requirement for lifelong maintenance of treatment, a lifetime perspective (up to 80 years from model initiation) has been adopted (alternative time horizons are available [1–80 years]) • The base case analysis is run until last participant has died, which is significantly less than 80 years.	N/A	The economic analysis was in line with the NICE reference case.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Subgroups to be considered	"Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator. "	As NICE scope	N/A	Although not pre-specified, results for some subgroups were reported, see section 2.5.
Special considerations including issues related to equity or equality	None specified.	Not reported.	N/A	No comment

Based on Table 1 of the CS[1]

ART = antiretroviral therapy; CAB = cabotegravir; CD = cluster of differentiation; CS = company submission; ERG = Evidence Review Group; HIV-1 = human immunodeficiency virus type 1; INI = integrase inhibitor; INSTI = integrase strand transfer inhibitor; LA = long-acting; N/A = not applicable; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PRO = patient-reported outcome; RNA = ribonucleic acid; RPV = rilpivirine

2.1 Population

The population addressed in the decision problem is narrower as it requires a "treatment switch due to non-virologic reasons", see section 4.2.3 for further details.

The decision problem addressed in the CS included participants without present or past evidence of viral resistance to, and no prior virological failure with, agents of the non-nucleoside reverse transcriptase inhibitor (NNRTI) and integrase inhibitor (INI) class 1. However, mutation K103N was allowed in the three studies informing large parts of the CS. It should be noted that K103N as a single mutation can affect other NNRTIs such as nevirapine (NVP) or efavirenz (EFV), as detailed in section 3.2.3.

2.2 Intervention

The ERG does not have specific comments on the intervention addressed in the decision problem of the CS.

2.3 Comparators

The relevant comparator treatment regimen consists of the variety of oral ART regimens that are given as second-line (or further) treatment to patients who switched their first-line (or other previous) treatment due to non-virologic reasons related specifically to the challenges of oral therapy. As detailed in section 4.2.4, this was largely based on market data apart from two exceptions.

As detailed in section 4.2.9.1, the ERG considers the use of a basket of comparators to be problematic. The uncertainty linked to the use of a basket of comparators was explored in a number of scenario analyses (see section 6.1.3.1).

2.4 Outcomes

A number of outcomes specified in the NICE scope were not assessed in the trials included in the CS, including treatment-emergent resistance, AIDS-defining events, and comorbidities (see Table 3.11 in section 3.2.5).

The justification for these omissions was not always clear. For example, the company stated that *"treatment-related comorbidities are not considered as outcomes in the appraisal because with most regimens (including the intervention and the comparators) treatment-related comorbidities are no longer an important feature of treatment and do not generally feature in treatment decision-making"* without providing supporting evidence.[1]

A number of outcomes, which were not included in the NICE scope, were reported in the CS. An overview of these outcomes can be found in section 3.2.5.9 but these have not been assessed in detail.

2.5 Other relevant factors

Following a request for clarification, the company explained that no subgroups were pre-specified for the systematic review, however, data were extracted where trial results were stratified by factors such as age, ethnicity or CD4 count, such instances being listed as subgroups reported by the trial authors, see section 3.1.2.6 for details.[2]

3. CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company conducted a systematic review to evaluate the evidence on clinical effectiveness (efficacy and safety) of long-acting cabotegravir plus long-acting rilpivirine (CAB LA + RPV LA) for the treatment of adults living with human immunodeficiency virus type 1 (HIV-1) infection.[1] Section 3.1 critiques the methods of the review including: the search strategy; study inclusion criteria; data extraction; assessment of risk of bias; and data synthesis.

3.1.1 Searches

Appendix D of the CS provided details of the systematic literature searches used to identify clinical efficacy and safety evidence.[3] Database searches were conducted on 24 April 2020. A summary of the resources searched is provided in Table 3.1.

Table 3.1: Resources searched for clinical efficacy and safety.

Resource	Host/source	Date range	Date searched
Electronic databases			
Embase	Not reported	01 January 2000 to 24 April 2020	24 April 2020
PubMed	-	01 January 2000 to 24 April 2020	24 April 2020
Cochrane Library (CENTRAL)	Not reported	01 January 2000 to 24 April 2020	24 April 2020
University of York Centre of Reviews and Dissemination (CRD)	Not reported	01 January 2000 to 24 April 2020	24 April 2020
Conference proceedings			
BHIVA	https://www.bhiva.org/Conferences-Events	2017-2020	Not reported
NHIVP	https://www.cdc.gov/nhpc/index.html	2017-2020	Not reported
IAS	https://iasociety.org/Conferences	2017-2020	Not reported
CROI	http://www.croiconference.org/	2017-2020	Not reported
HIVDT	http://hivglasgow.org/	2017-2020	Not reported
NICE	http://www.niceconference.org.uk/	2017-2020	Not reported
ISPOR (for economic SLRs only)*	https://www.ispor.org/conferences-education/conferences	2017-2020	Not reported
Clinical trial registries			
ClinicalTrials.gov	https://clinicaltrials.gov		Not reported
WHO ICTRP	http://www.who.int/ictrp/en/		Not reported
EUCTR	http://www.clinicaltrialsregister.eu/		Not reported
HTA websites			
NICE	Not reported		Not reported

Resource	Host/source	Date range	Date searched
SMC	Not reported		Not reported
AWMSG	Not reported		Not reported
CADTH	Not reported		Not reported
Reference lists from relevant primary studies identified were visually scanned to identify further studies that met eligibility criteria. Additionally, recent systematic reviews (published 2017-2020) were visually scanned to ensure that all relevant information was obtained. * As reported by the company. AIDS = acquired immunodeficiency syndrome; AWMSG = All Wales Medicines Strategy Group; BHIVA = British HIV Association; CADTH = Canadian Agency for Drugs and Technologies in Health; CENTRAL = Cochrane Central Register of Controlled Trials; CRD = Centre of Reviews and Dissemination; CROI = Conference on Retroviruses and Opportunistic Infections; EUCTR = European Union Clinical Trials Register; HIV = human immunodeficiency virus; HIVDT = HIV drug therapy; HTA = health technology assessment; IAS = International AIDS Society; ICTRP = International Clinical Trials Registry Platform; ISPOR = International Society for Pharmacoeconomics and Outcomes; NHIVP = National HIV Prevention; NICE = National Institute for Health and Care Excellence; SLR = systematic literature review; SMC = Scottish Medicines Consortium; WHO ICTRP = World Health Organization			

ERG comment:

- The selection of databases searched was satisfactory. The database name and date searched were provided. The host platform was not provided for any of the databases, and it was not clearly reported which database was searched in the University of York Centre for Reviews and Dissemination (CRD). The database issue number was not provided for CENTRAL in the Cochrane Library, and the database date range was not clearly reported for any of the databases searched: the 'date span' provided, 01 January 2000 to 24 April 2020, does not indicate if records were identified by publication date or database entry date.
- Conference proceedings were searched. Full details of the conferences searched, search strategies or search terms used, and results were not reported in the CS. Further details of the conference proceedings searches were provided in response to the ERG clarification letter, including the methods used to search abstract books and the search terms used.[2]
- Trials registers were searched, but details of the search strategies or search terms used, dates of searches, and results were not reported in the CS. Further details of the trials registers searches were provided in response to the ERG clarification letter: *"Each clinical trial registry website was hand searched, through the search function available from each website, using keywords similar to those used in the searches of electronic databases: HIV, immunodeficiency, AIDS. Trials that met eligibility criteria were included in the relevant review. Results of the overall additional sources of evidence (conference proceedings, clinical trial websites, HTA bodies websites, and reference lists of systematic literature reviews identified through database searches) are included in the PRISMA diagram ('Additional records identified through other sources' box), with a further breakdown in Table 1"*.[4]
- HTA organisation websites were searched, but details of the search terms used, dates of searches, and results were not reported in the CS. Full details of the HTA searches were provided in response to the ERG clarification letter, including an explanation that *"the relevant HTA documents were used to review the reference list for each SLR, with a view to identify any potential trials not captured through the database searches"*.[2]
- The ERG was concerned that limiting the searches to English language may have introduced potential language bias. Current best practice suggests that whenever possible review authors should attempt to identify and assess for eligibility all possibly relevant reports of trials irrespective of language of publication[5] and that research related to language bias supports the inclusion of non-

English studies in systematic reviews.[6-8] In response to the ERG clarification letter the company replied that *"given the high volume of evidence gathered when applying the English language only limit, expanding the search to other languages was very unlikely to bring new evidence which would diverge from the overall picture drawn from the studies in English language"*.[2]

- Five facets of search terms were combined in the search strategy: 1) Population, 2) Interventions of interest, 3) Disease stage, 4) Outcomes and 5) Study type. Combining this number of search facets reduced the sensitivity of the searches.
- The intervention facet of search terms only included generic antiretroviral drug terms. There were no named drugs, including the two of specific interest to this submission: cabotegravir and rilpivirine.
- Numerous MeSH (Medical Subject Heading) terms were inaccurate in the PubMed search strategy, though fortunately PubMed maps terms to the closest matching MeSH term. Relevant EMTREE indexing terms were missing from the Embase search strategy, e.g. 'Human immunodeficiency virus/'
- The inclusion of more synonyms would have improved the search strategies and their sensitivity, particularly in the population, intervention and disease stage search facets.
- Study design search filters were included for randomised controlled trials (RCTs) and observational studies. The search strategies grouped each facet under a heading, and the Study type heading included in brackets, SIGN. This suggests that the study design filters used were based on the Scottish Intercollegiate Guidelines Network (SIGN) search filters (https://www.sign.ac.uk/what-we-do/methodology/search-filters/). It is good practice to indicate whether published search filters were used (as originally designed or modified), and it would have been more transparent and helpful if the search filters had been cited in detail in the methods section.[9] The study design filters did not match those provided on the SIGN website, and search terms used in the MEDLINE filter, including medical subject headings (MeSH), were used in the Embase search strategy.
- The ERG noted that an RCT filter was included in the Cochrane Library search. As this resource consists of prefiltered databases of clinical trials and systematic reviews the ERG believes including this facet may have resulted in unnecessarily restricting of the results retrieved. Further, the Cochrane search included a SIGN study design filter, but there are no Cochrane SIGN filters.
- Search terms for safety were included in the outcomes facet of the search strategies and combined with the study design filter. Ideally, a search for adverse effects should be carried out alongside the search for effectiveness.[10]
- Truncation was used inconsistently throughout, and proximity operators were only occasionally used. Better use of these powerful search tools would have enhanced the search strategies, making them more sensitive and may have identified more potentially useful studies. There were numerous redundant search terms throughout the strategies, as well as inconsistent use of field tags, e.g. title, abstract.
- The searches were limited by date from 2000 to 2020. In response to the ERG clarification letter the company explained that *"given the high volume of evidence gathered applying the date filter, expanding the search to studies over 20 years old was very unlikely to bring new evidence which would diverge from the overall picture drawn from the studies published in 2000-2020. Further, HIV regimens have been continually developing since the advent of highly-active ART in 1995; thus, studies of treatment regimens more than 20 years old are unlikely to be representative of modern clinical practice"*.[2]
- The searches were conducted in April 2020. An update of the searches immediately prior to submission to NICE would have been appropriate and could have identified potentially relevant records published since April 2020.

- The CS referred to a targeted literature review of network meta-analyses (NMAs) and a review *"of the methodological literature as it pertains to non-inferiority trials and indirect comparison"*. It was not clear if the literature reviews were conducted by the company or referred to other publications, as full details of the targeted literature reviews were not reported. Further details of the targeted literature reviews were provided in response to the ERG clarification letter: *"A pragmatic literature search was performed using search terms to identify English-language articles that specifically reported on NMAs with at least two comparators focusing on HIV-related treatment efficacy outcomes. The database search was restricted to PubMed, with no time limitation. Full texts were obtained and reviewed and clinical experts were consulted to determine study relevance. With regards to methodological literature as it pertains to non-inferiority trials and indirect comparison, this included a hand search of the literature using the following keywords: non-inferiority trials, superiority trials, equivalence trials, trial design, methods, analysis, indirect treatment comparison"*.[2]

3.1.2 Inclusion criteria

As stated above, the company performed a systematic review to evaluate the evidence on clinical effectiveness (efficacy and safety) of CAB LA + RPV LA for the treatment of adults living with HIV-1 infection.[1] The study eligibility criteria for the systematic review are summarised in Table 3.2 below.

Table 3.2: Eligibility criteria used in the systematic review of clinical effectiveness evidence

	Inclusion criteria	Exclusion criteria
Population	• Patients with HIV-1 that is stabilised based on current therapy, defined as HIV-1 RNA <50 copies /ml • Adults (≥18 years old) • Above patients requiring treatment switch for non-virological reasons*	• Children and young people (under 18 years) • Patients with HIV-2 • Patients without HIV-1 • Patients uncontrolled on current therapy • Animal studies
Interventions & comparators	Any intervention for the maintenance of response in stable HIV-1, defined as HIV-1 RNA <50 copies /ml	Interventions not aimed at maintaining response in stable HIV
Outcomes	• Viral load • Virological failure • Virological resistance • Virological response • Change in CD4 cell count from baseline • Change in CD8 cell count from baseline • Discontinuation • Weight change • Adherence • Adverse events	Outcomes of interest not reported
Study design	• Randomised controlled trials • Non-randomised controlled trials • Longitudinal cohort studies	• Case-control studies • Pharmacokinetics studies • Cost effectiveness studies

	Inclusion criteria	Exclusion criteria
	• Observational studies (retrospective, prospective, cohort studies, longitudinal studies)	• Clinical trial registry entry only • Narrative reviews, editorials, letters or comments, notes, short surveys, case series or reports • Animal or *in vitro* studies
Language restriction	English language only (studies published in languages other than English but with an abstract available in English will be included)	Studies published in languages other than English
Date restriction	Studies published from 1 January 2000 to 24 April 2020	Studies published before 1 January 2000

Based on Table 5 of Appendix D of the CS[3]
* Information provided by the company in their response to the ERG's clarification letter.[2]
CD = cluster of differentiation; CS = company submission; ERG = Evidence Review Group; HIV = human immunodeficiency virus; RNA = ribonucleic acid

ERG comment: As detailed below, the ERG has a number of comments.

3.1.2.1 Differences in inclusion criteria reported in the CS

The ERG noted that the population inclusion criteria differed slightly between Table 5 of Appendix D and Table 1 of document B of the CS (The Decision Problem).[1, 3] The latter refers to *"adults who are virologically suppressed (HIV-1 RNA [ribonucleic acid] <50 copies /mL) on a stable antiretroviral regimen without present or past evidence of viral resistance to, and no prior virological failure with, agents of the NNRTI [nucleoside reverse transcriptase translocation inhibitor] and INI [integrase inhibitor] class, who require a treatment switch due to non-virologic reasons"* whereas Table 5 of Appendix D does not mention this population.

In response to the request for clarification, the company explained that the study eligibility criteria for the systematic review were slightly broader than those shown in the licensed indication for CAB LA + RPV LA in order to capture the potential comparator population.[2] The company pointed out that the first part of the criterion is common across both documents: *"adults who are virologically suppressed (HIV-1 RNA [ribonucleic acid] <50 copies /mL) on a stable antiretroviral regimen"*.[2] The company stated that the second part of the criterion was not applied during the systematic review of clinical effectiveness evidence (*"...without present or past evidence of viral resistance to, and no prior virological failure with, agents of the NNRTI and INI class"*) but that where available, this information was extracted from each trial's description of participant selection criteria.[2] The trials evaluating switch to CAB LA + RPV LA from oral ART specified that participants should not have resistance to ART. Finally, the company stated that the third part of the criterion (*"...who require a treatment switch due to non-virologic reasons"*) had been applied since participants were virally suppressed on their current regimen.[2]

3.1.2.2 Inclusion restricted by time and language of publication

The ERG queried the rationale for restricting study selection to trials published from 1 January 2000 to 24 April 2020 in the English language.[11] The company responded that even with these limitations, the volume of relevant evidence retrieved was large and it was not anticipated that additional relevant evidence had been missed.[2] The ERG agreed that a large volume of evidence had been retrieved. The updated Figure 1 in Appendix B3a (PRISMA diagram) indicated that 12,170 bibliographic records

were retrieved following deduplication, 2,046 full-text reports were assessed for eligibility and 160 unique RCTs were considered for inclusion.[4] However, given the global distribution of HIV/AIDS, it is possible that relevant studies were missed because of being reported in languages other than English. It is also possible that some relevant studies may have been published before the year 2000.

3.1.2.3 Exclusion of observational case-control studies

The ERG asked why observational case-control studies had been excluded from the review.[11] The company replied that although such evaluations were allowed for in the search strategy, they were ultimately excluded in light of the large number of retrieved RCTs. Since RCTs provide higher quality evidence in terms of evaluating treatment effectiveness, the company did not feel that the addition of data from observational studies would add useful information to the review.[2] Appendix B3D5 suggests that 300 eligible observational and single-arm studies were identified[12] and the same number is also shown in the updated PRISMA diagram (Figure 1 in Appendix B3a).[4] The ERG noted that evaluation of safety of the study interventions was a review objective and therefore it is possible that relevant material could have been missed through the exclusion of case-control studies.

In considering the study selection criteria overall, the ERG suggests that relevant evidence may have been omitted from the review on the basis of restrictions according to date of publication, language of report or study design. The extent of the omitted material, and its impact on the review are uncertain.

3.1.2.4 Discrepant numbers of eligible RCTs

In the CS, Table 7 in Appendix D (Study characteristics of eligible randomised controlled trials) listed each eligible RCT record separately, ordered alphabetically according to the first author's surname.[3] Of note, this is not the full data extraction tables but a list of basic trial characteristics including: trial ID; title of article; country; and details of trial design and phase.

The ERG noted instances of multiple records relating to the same RCT and requested to update Figure 1 of Appendix D (PRISMA diagram) in order to clearly differentiate between the number of included RCTs and the number of included RCT records.[3] The company provided an updated PRISMA diagram that shows this information more clearly.[4] Related to this, the ERG also asked for Table 7 in Appendix D to be updated so that records relating to the same RCT were grouped together.[3] The company provided this, with records presented first by alphabetical order of the study ID/trial ID and secondly by alphabetical order of references (usually surname of first author) for RCTs with multiple references.[13]

The ERG noticed discrepant numbers reported for the number of eligible RCTs between Table 8 of Appendix D (Baseline characteristics of participants from eligible randomised controlled trials; n=173 RCTs) and Figure 1 of Appendix D (PRISMA diagram; n=289 RCT records and n=160 unique RCTs) and therefore requested that the incorrect documentation be updated.[3, 11] The company provided an updated version of Table 8 that now summarises the baseline data for 160 unique RCTs. However, this table does not appear to have been ordered by any particular system therefore navigation to any specific RCT would have to be done via the 'Find' facility in Microsoft Word.[14]

The ERG pointed out that document 4 embedded within Appendix D (Quality assessment of eligible randomised controlled trials) listed 158 RCTs and that this number was discrepant with other parts of the same appendix (Figure 1, Table 7 and Table 8).[3] The ERG asked for the incorrect documentation to be updated. The company provided an updated version of document 4 that summarises the quality assessment information for the 160 unique RCTs.[15]

In light of the above-mentioned updated documents[4, 13-15] the company also provided updated versions of the data extraction table for the eligible unique RCTs (n=160 extracted)[16] and the list of eligible observational and single-arm studies (n=300 listed).[12] Scrutiny of these two documents suggested that all relevant studies from those identified had been included in the review.[12, 16]

3.1.2.5 Omission of AIDS-defining events and HRQoL

The ERG queried why the outcomes of AIDS-defining events and health-related quality of life (HRQoL) were not shown in Table 5 of Appendix D (Eligibility criteria for the identification of HIV clinical effectiveness studies) when both were mentioned in the NICE final scope and Table 1 of Document B of the CS.[1, 3, 17]

The company replied that the outcome of AIDS-defining events had been listed and extracted in the systematic review of cost effectiveness evaluations as reported in Appendix G.[2, 18] Scrutiny of Appendix G confirmed that this outcome was listed as being eligible (Table 3, Eligibility criteria for the identification of HIV cost effectiveness studies).[18] Furthermore, mentions of AIDS-defining events were noted in the Excel spreadsheet embedded in section G.2.2 in Appendix G (which appears to represent the data extraction of cost effectiveness studies).[18] It is still not clear why this outcome was omitted from the clinical effectiveness systematic review when it was included in the NICE final scope. This issue has also been noted within section 3.2.5.5 (AIDS-defining events).

Furthermore, the company explained that HRQoL outcomes were included and extracted in the health effects systematic review (in relation to the cost effectiveness analysis), as reported in Appendix H.[2] Information in Appendix H indicates that a dedicated literature search was carried out to identify studies reporting HRQoL as an outcome (Section 1) and that these outcome data were used to generate utility estimates for the economic analysis (see Table 4.2 in section 4.1.1).[19] The ERG notes that HRQoL data from the ATLAS, ATLAS-2M and FLAIR trials were presented as part of the clinical effectiveness review, as outlined in section 3.2.5.8.

3.1.2.6 Eligibility of subgroups

The ERG asked whether any pre-specified participant subgroups had been defined for the systematic review of clinical efficacy and safety. This query arose from information that appeared to be conflicting, i.e. subgroups mentioned in Table 6 of Appendix D (Variables extracted from studies meeting the review criteria for identification of clinical efficacy in HIV maintenance treatment) whereas the NICE final scope and Table 1 of Document B of the CS referred to a single population group (*"Adults with HIV-1 infection who are virologically suppressed on a stable regimen and who have not shown prior virological failure due to drug resistance to INTI/INIs"*).[1, 3, 17] The ERG noted reference to some pre-specified subgroups within specific RCTs, e.g. subgroups defined according to randomisation stratification factors or demographic/baseline characteristics relevant to the disease (e.g. in section B.2.7.1 of the CS).[1]

The company replied that no subgroups were pre-specified for the systematic review, however, data were extracted where trial results were stratified by factors such as age, ethnicity or CD4 count, such instances being listed as subgroups reported by the trial authors.[2] The company explained further that where the outcomes were reported for a specific subgroup rather than for the overall population, details were recorded in the study arm column throughout the tables in Appendix D.[3]

3.1.2.7 Process of study selection

The approach taken for the study selection process is outlined in section D.1.7 of Appendix D.[3] Two reviewers independently assessed titles and abstracts for relevance (first stage) and full text reports for

eligibility (second stage). At both stages, disagreements were resolved by discussion or if necessary by consulting a third reviewer.[3]

3.1.3 Critique of data extraction

The layout of the data extraction table suggested that a standardised template had been used.[16] The extracted details related clearly to all of the domains indicated in Tables 5 and 6 of Appendix D, respectively (Eligibility criteria for the identification of HIV clinical effectiveness studies; and Variables extracted from studies meeting the review criteria for identification of clinical efficacy in HIV maintenance treatment).[3] Further information (in section D.1.8. of Appendix D) outlined that data were extracted by one reviewer and checked for accuracy and completeness by a second reviewer (it was not stated whether the reviewers worked independently).[3] Any disagreements between the two reviewers were resolved by discussion.[3]

This process is not considered as optimal, best practice being dual data extraction performed by two independent reviewers.[20] This means that there is some potential for errors and missing data.

3.1.4 Quality assessment

The ERG requested information on the risk of bias tool used to assess the eligible RCTs and also details of the tool application process.[21] The company replied that the original Cochrane Risk of Bias Assessment Tool for RCTs (1.0) was used.[2, 22] Whilst this tool is appropriate for assessing RCTs, the ERG noted that the current version of the Cochrane Handbook for Systematic Reviews of Interventions recommends that the updated version of the Cochrane Risk of Bias Assessment Tool for RCTs (2.0) is used.[20, 23]

Furthermore, the company stated that the risk of bias assessment was conducted by two independent reviewers with any discrepancies resolved by consensus or if necessary, by consulting a third reviewer. This process reflects best practice in systematic reviewing.[20] Therefore the ERG is satisfied that the risk of bias assessment was conducted in a satisfactory fashion.

3.1.5 Evidence synthesis

No details on the methods of pooling the data between ATLAS and FLAIR was reported in the CS.[1]

ERG comment: The results for the ATLAS and FLAIR trials are only reported for the pooled sample of both studies with no data available separately for each study. In the clarification letter, the company was asked to provide the details of the methods used for pooling the participant data from the ATLAS and FLAIR studies and reference relevant sources of information; as well as to provide results for the separate studies. The company's response[2] provided the reference to published and peer-reviewed paper which includes methods for pooling data from the underlying trials (Rizzardini et al. 2020).[24] The company provided the data for ATLAS and FLAIR separately for the primary efficacy endpoints only (proportion of participants with HIV-1 RNA ≥50 copies/ml and with viral load <50 copies/ml at week 48) and referred to CSRs for other outcomes (no relevant sections provided). With regards to the primary efficacy outcomes at 48 weeks, the adjusted difference in proportion and corresponding 95% CI between CAB LA + RPV LA (Q1M) and the current ART therapy lied within the margin of non-inferiority (6%) as described in section 3.2.2.

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

The CS identified six RCTs of CAB LA + RPV LA as relevant to the submission:

1. LATTE[25]
2. LATTE-2[26-28]
3. POLAR[29]
4. ATLAS[30, 31]
5. FLAIR[32, 33]
6. ATLAS-2M[34, 35]

The CAB doses for phase 3 studies were selected based on the two phase 2b studies: LATTE and LATTE-2. The POLAR study was an extension study to LATTE. Two phase 3 randomised, multicentre, active-controlled parallel arm open label non-inferiority trials, i.e. ATLAS and FLAIR, provided the data of the efficacy and safety of CAB LA + RPV LA given every month (Q1M), following an oral lead in period to establish tolerability. Due to the similarity in the study designs, their results were used in the pooled analysis of non-inferiority of CAB LA + RPV (Q1M) vs. current ART therapy in maintaining virologic suppression. The efficacy and safety of CAB LA + RPV LA given every two months (Q2M), following an oral lead-in period for participants not previously exposed to CAB LA + RPV LA, was evaluated in ATLAS-2M, a phase 3b randomised, multicentre, parallel-arm open label non-inferiority study. The efficacy and safety of CAB LA + RPV LA (Q2M) vs. ART therapy was estimated via an indirect treatment comparison using the results of CAB LA + RPV LA (Q1M) arms of ATLAS-2M and pooled arms from ATLAS and FLAIR. The results of LATTE-2 and POLAR studies are provided as supportive evidence.

A summary of these studies is provided in Table 3.3.

Table 3.3: Overview of the clinical effectiveness evidence for CAB LA + RPV LA

Study	LATTE[25]	LATTE-2 [26-28]	POLAR[29]	ATLAS (NCT02951052)[30, 31, 36]	FLAIR (NCT02938520)[32, 33, 37]	ATLAS-2M (NCT03299049) [34, 35, 38]
Study design	Phase 2b, randomised, dose ranging multicentre, parallel-group, partially blinded, 2-part study	Phase 2b, randomised, multicentre, parallel-group, open-label, dose ranging trial	Phase 2b, multicentre, open-label, non-randomised, rollover study	Phase 3, randomised, open-label, active-controlled, multicentre, parallel-group, non-inferiority study	Phase 3, multiphase, randomised, open-label, active-controlled, multicentre, parallel-group, non-inferiority study	Phase 3b, randomised, open-label, active-controlled, multicentre, parallel-group, non-inferiority study
Objective	Phase 2b trial evaluating oral CAB in combination with oral RPV	Phase 2b trial evaluating CAB LA in combination with RPV LA compared with oral CAB in combination with 2 NRTIs to maintain virologic suppression	NA	Phase 3 trial to demonstrate non-inferior antiviral activity of switching to CAB LA in combination with RPV LA compared with remaining on current ART regimen	Phase 3 trial to demonstrate non-inferior antiviral activity of switching to CAB LA in combination with RPV LA compared with remaining on ABC/DTG/3TC	Phase 3b trial to demonstrate noninferiority of LA CAB + LA RPV Q2M compared with LA CAB + LA RPV Q1M
Population	ART-naïve at recruitment (N=244)	ART-naïve at recruitment (N=309)	NA	ART-experienced, virologically suppressed on a stable regimen containing 2 NRTIs plus an INSTI, NNRTI or a PI for at least 6 months (N=618)	ART-naïve (N=566)	ART-experienced, virally suppressed on a stable ART regimen (N=1,020)

Study	LATTE[25]	LATTE-2 [26-28]	POLAR[29]	ATLAS (NCT02951052)[30, 31, 36]	FLAIR (NCT02938520)[32, 33, 37]	ATLAS-2M (NCT03299049) [34, 35, 38]
Intervention	CAB LA + RPV LA (Q1M; oral only)	CAB LA + RPV LA (Q1M; injection) or CAB LA + RPV LA (Q2M; injection)	CAB LA + RPV LA (Q2M; injection)	CAB LA + RPV LA, oral lead-in then Q1M	Oral induction with current ART, then oral lead-in with CAB + RPV, then CAB LA + RPV LA Q1M	CAB LA + RPV LA Q2M (switched from either Q1M arm of ATLAS or current ART; oral lead-in if no prior exposure to CAB LA + RPV LA)
Comparator	control (EFV/NRTIs)	control (3TC/ABC/CAB)	control (dolutegravir + oral RPV)	Current anti-retroviral regimen (2 NRTIs plus an INSTI, NNRTI, or a PI)	Daily oral DTG-ABC-3TC (continued from induction phase)	CAB LA + RPV LA Q1M (switched from either Q1M or current ART arm of ATLAS, or current ART; oral lead-in if no prior exposure to CAB LA + RPV LA)
Supports marketing authorisation	NA			Yes		
Used in economic model				Yes (via ITC)		Yes
Rationale for use/non-use in the model				Pooled evidence from ATLAS and FLAIR is used in an ITC that informs the relative efficacy of CAB LA + RPV LA Q2M versus current ART in the model		Relevant population/ outcomes reported
Key outcomes (specified in the decision problem)				Proportion of participants with plasma HIV-1 RNA ≥50 copies/ml at week 48 (snapshot algorithm for the ITT-E population). CD4+ T-cell levels Maintenance of viral suppression (proportion of participants with plasma viral load <50		Proportion of participants with plasma HIV-1 RNA ≥50 copies/ml at week 48 (snapshot algorithm for the ITT-E population) CD4+ T-cell levels

Study	LATTE[25]	LATTE-2 [26-28]	POLAR[29]	ATLAS (NCT02951052)[30, 31, 36]	FLAIR (NCT02938520)[32, 33, 37]	ATLAS-2M (NCT03299049) [34, 35, 38]
				copies/ml and <200c/ml, per FDA Snapshot algorithm) Adherence to treatment regimen Mortality Adverse effects of treatment Health-related quality of life		Maintenance of viral suppression (proportion of participants with plasma viral load <50 copies/ml, per FDA Snapshot algorithm) Adherence to treatment regimen Mortality Adverse effects of treatment Health-related quality of life

Based on Tables 5-8 of the CS[1]

ABC/DTG/3TC = abacavir/dolutegravir/lamivudine; ART = antiretroviral therapy; ATLAS = Antiretroviral Therapy as Long-Acting Suppression; ATLAS-2M = Antiretroviral Therapy as Long-Acting Suppression Q2M; CAB = cabotegravir; CD = cluster of differentiation; EFV = **efavirenz**; FDA = Food and Drug Administration; FLAIR = First Long-Acting Injectable Regimen; HIV-1 = human immunodeficiency virus type 1; INSTI = integrase strand transfer inhibitor; ITC = indirect treatment comparison; ITT-E = intention-to-treat exposed; LA = long-acting; LATTE = Long-Acting antireTroviral; Treatment Enabling; LATTE-2 = Long-Acting antireTroviral Treatment Enabling-2; NA = not applicable; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; POLAR = Oral (PO) to Long-Acting (LA) Rollover; Q1M = every 1 month; Q2M = every 2 months; RNA = ribonucleic acid; RPV = rilpivirine

ERG comment: The included RCTs (ATLAS, FLAIR and ATLAS-2M) are discussed in more detail in sections 3.2.1 to 3.2.4. The supporting evidence from POLAR and LATTE-2 are discussed in section 3.2.5 ("Maintenance of virological suppression" and "Adherence to treatment regimen").

3.2.1 Details of included CAB LA + RPV LA RCTs

The appropriate doses of CAB were established in phase 2 studies i.e. LATTE-2 and LATTE with its extension study POLAR and the results are used as a supporting evidence. The three main RCTs of interest are ATLAS, FLAIR and ATLAS-2M with the summary of each study methodology presented in Table 3.4. The evidence supporting the effectiveness of CAB LA + RPV LA (Q2M), the regimen available in the UK, is derived primarily from ATLAS-2M and the results compared to the pooled results of ATLAS and FLAIR to establish non-inferiority of the Q2M treatment regimen with ART therapy (via an indirect treatment comparison using arm data from CAB LA + RPV LA [Q1M]).

All studies were conducted in multiple countries around the world and recruited HIV-1 infected adults only (>18 years of age). Patients in the ATLAS and ATLAS-2M studies were antiviral therapy experienced and virologically supressed on a stable antiretroviral regimen. Patients in the FLAIR study were antiretroviral therapy-naïve with high levels of HIV-1 RNA levels (≥1000 copies/ml). The details on the drug schedule for the main three RCTs is reported in Table 3.5 and for the supporting trials (i.e. LATTE, LATTE-2 and POLAR) in section 3.2.5.9. All studies included an induction phase (oral lead-in therapy) of CAB and RPV. The drug doses in the CAB LA + RPV LA arm given every month (Q1M) in all studies were the same with the dosing changing for Q2M arm in ATLAS-2M. The study population of the ATLAS-2M was composed of patients switching from either Q1M arm of ATLAS or current ART who received oral lead-in if no prior exposure to CAB LA + RPV LA. Chronic use of systemic glucocorticoids was not permitted at any time during the ATLAS, FLAIR and ATLAS-2M studies. The primary outcome was consistent across the studies, i.e. the proportion/percentage of participants with HIV-RNA ≥50 copies/ml at week 48 (defined by the United Stated Food and Drug Administration (FDA) snapshot algorithm; no reference provided in the CS).

Table 3.4: Summary of study methodology for included RCTs

Trial name	ATLAS[31, 39]	FLAIR[32, 40]	ATLAS-2M[34, 41]
Location	North America, South America, Australia, Europe, Asia, Africa	North America, Europe, Asia, Africa	North America, South America, Australia, Europe, Asia, Africa
Trial design	Phase 3, Randomised, Multicentre, Parallel-group, Non-inferiority, Open-label Study	Phase 3, Randomised, Multicentre, Parallel-group, Non-inferiority, Open-Label Study	Randomised, multicentre, parallel-group, non-inferiority, open-label (phase 3b)
Eligibility criteria for participants	Eligible participants were 18 years of age or older and were HIV-1 infected antiretroviral therapy experienced adults who are virologically suppressed on a stable antiretroviral regimen	Eligible participants were 18 years of age or older, had not previously received antiretroviral therapy, and had a plasma HIV-1 RNA level of 1000 copies/ml or higher at screening.	HIV-1 infected antiretroviral therapy experienced adults who are virologically suppressed on a stable antiretroviral regimen.
Settings and locations where data were collected	The study was conducted in 115 locations across 13 countries.	The study was conducted in 108 study locations in 11 countries across North America, Europe (including the UK [7 sites]), Asia, and South Africa	The study was conducted in ~90 academic centres and hospitals across 13 countries in North America, South America, Australia, Europe, Asia, Africa.
Study drugs	Intervention: Oral CAB 30 mg + RPV 25 mg once daily for four weeks, intramuscular CAB LA 600 mg and RPV LA 900 mg for the first injection. From Week 4 CAB LA 400 mg + RPV LA 600 mg IM Q1M until withdrawal. Comparator: Current anti-retroviral regimen (2 NRTIs plus an INSTI, NNRTI, or a PI)	Intervention: Induction therapy with ABC/DTG/3TC single-tablet regimen (Triumeq®). After viral suppression on induction: Oral CAB 30 mg + RPV 25 mg once daily for approximately 4 weeks. At Week 4 participants received CAB LA 600mg and RPV LA 900 mg. From Week 8 participants received CAB LA 600mg and RPV LA 600 mg Q1M. Comparator: ABC/DTG/3TC single-tablet regimen (Triumeq®)	Oral CAB 30 mg + RPV 25 mg once daily at Day 1 for 28 days (±3 days) to determine individual safety and tolerability prior to receiving CAB LA + RPV LA (Q1M vs. Q2M). CAB LA + RPV LA: dosing regimens are described in Table 3.5.

Trial name	ATLAS[31, 39]	FLAIR[32, 40]	ATLAS-2M[34, 41]
Concomitant medications	CAB and CAB LA were not to be co-administered with the following medicinal products: the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, phenytoin the antimycobacterials rifampicin, rifapentine, rifabutin St John's wort (Hypericum perforatum). Chronic use of oral glucocorticoids must be avoided. Full list available in study protocol.[39]	The following concomitant medications or therapies were not permitted at any time during the study: HIV immunotherapeutic vaccines Other experimental agents, ART drugs not otherwise specified in the protocol, Systemically administered immunomodulators Chronic use of systemic (oral or parenteral) glucocorticoids must be avoided Hepatitis C infection therapy is prohibited during the Maintenance Phase before Week 48; interferon-based HCV therapy is prohibited throughout the study. Full list available in study protocol.[40]	The following concomitant medications or therapies are not permitted at any time during the study: HIV immunotherapeutic vaccines Other experimental agents, antiretroviral drugs not otherwise specified in the protocol, cytotoxic chemotherapy, or radiation therapy Systemically administered immunomodulators Acetaminophen (paracetamol) cannot be used in participants with acute viral hepatitis Chronic use of systemic (oral or parenteral) glucocorticoids A single dose of systemic dexamethasone is permitted Hepatitis C infection therapy Interferon-based HCV therapy
Primary outcome	Proportion/percentage of participants with HIV-1 RNA ≥50 copies/ml as per FDA snapshot algorithm at Week 48 (ITT-E population).		
Other outcomes used in the economic model/specified in the scope	The outcomes used to inform the ITC were: HIV-1 RNA <50 copies/ml HIV-1 RNA ≥50 copies/ml CD4+ cell change from baseline Discontinuations Discontinuations due to AEs Grade 3-5 non-ISR AEs		Change from baseline in CD4+cell count (total lymphocyte counts, percentage and absolute CD4+ [collected Q2M] and CD8+ lymphocyte counts [collected every 6 months], ratios) Adverse events HRQoL (HAT-QoL, HIVTSQs and ACCEPT were assessed every 6 months)

Trial name	ATLAS[31, 39]	FLAIR[32, 40]	ATLAS-2M[34, 41]
			Proportion of participants with plasma viral load <50 copies/ml(also pre-specified for non-inferiority assessment)
Pre-planned subgroups	The proportion of participants with virologic failure over time including Week 48 and Week 96 was analysed by important demographic and baseline characteristic subgroups factors (e.g. age, gender, BMI, race, HIV-1 subtype, and Baseline CD4+ cell counts). Changes from baseline in CD4+ lymphocyte count at Week 48 and Week 96.		Pre-specified subgroup analyses were carried out for the randomisation stratification factors: (prior exposure to CAB + RPV: 0 weeks, 1-24 weeks, and >24 weeks), and for demographic factors (age, gender, BMI, race), HIV-1 subtype, baseline viral load, baseline CD4+ lymphocyte count, and participating countries

Based on Tables 9 and 25 of the CS[1]

ACCEPT = Chronic Treatment Acceptance Questionnaire, AIDS = acquired immunodeficiency syndrome; ART = antiretroviral therapy, BMI = body mass index, CAB = cabotegravir, CD = cluster of differentiation, FDA = Food and Drug Administration, HAT-QoL = HIV/AIDS Targeted Quality of Life, HCV = hepatitis C virus, HIV = human immunodeficiency virus, HIVTSQ = HIV Treatment Satisfaction Questionnaire, HRQoL = health-related quality of life; INSTI = integrase strand transfer inhibitor, ITTE-E = intention-to-treat exposed; LA = long acting, NNRTI = non-nucleoside reverse transcriptase inhibitor, PI = protease inhibitor; RNA = ribonucleic acid, RPV = rilpivirine, Q1M = given every 1 month, Q2M = given every 2 months; UK = United Kingdom

Table 3.5: Overview of the dosing schedule in the main clinical effectiveness trials for CAB LA + RPV LA

Study (phase; comparison)		ATLAS (III; Q1M vs. ART[^*])			FLAIR (III; Q1M vs. 3TC/ABC/DTG[$*])			ATLAS-2M (IIIb; Q1M vs. Q2M)				
length/drug		**length (weeks)**	**CAB LA (Q1M)**	**RPV LA (Q1M)**	**length (weeks)**	**CAB LA (Q1M)**	**RPV LA (Q1M)**	**length (weeks)**	**CAB LA (Q1M)**	**CAB LA (Q2M)**	**RPV LA (Q1M)**	**RPV LA (Q2M)**
induction phase		4-5	oral 30 mg	oral 25 mg	20 + 4-5	oral ABC/DTG /3TC FDC[**] for 20 + oral CAB 30 mg for 4-5	oral ABC/DTG/3 TC FDC[**] for 20 + oral RPV 25 mg for 4-5	4-5 (only CAB/RPV naïve)	oral 30 mg		oral 25 mg	
maintenance phase	loading dose 1 (within 2h from final oral dose)	up to 52	600 mg	900 mg	100	600 mg	900 mg	100 (ATLAS Q1M patients) or 96 (after induction phase)	600 mg	600 mg	900 mg	900 mg
	loading dose 2 (4 weeks after dose 1)		-	-		-	-		-	600 mg	-	900 mg
	Thereafter		400 mg (every 4)	600 mg (every 4)		400 mg (every 4)	600 mg (every 4)		400 mg (every 4)	600 mg (every 8)	600 mg (every 4)	900 mg (every 8)
extension phase		onwards	400 mg (every 4)	600 mg (every 4)	onwards	400 mg (every 4)	600 mg (every 4)	onwards	400 mg (every 4)	600 mg (every 8)	600 mg (every 4)	900 mg (every 8)

Based on the CSR of the studies[39-41] and Table 5 of the CS[1]

[*] patients in the comparator arm were able to switch to intramuscular CAB LA + RPV LA after the maintenance phase and if eligible (oral lead-in CAB 30 mg + oral RPV 25 mg; 1st dose: CAB LA 600mg/RPV LA 900 mg; 2nd, 3rd and onwards every 4 weeks: CAB LA 400mg/RPV LA 600 mg; [**] NRTI substitution allowed; [^] 2 NRTIs + INSTI or 2 NRTIs + PI or 2 NRTIs + NNRTI; [$]oral ABC/DTG/3TC FDC once daily (or alternative DTG + 2 NRTIs

ABC/DTG/3TC = abacavir/dolutegravir/lamivudine; ART = antiretroviral therapy; ATLAS = Antiretroviral Therapy as Long-Acting Suppression; ATLAS-2M = Antiretroviral Therapy as Long-Acting Suppression Q2M; CAB = cabotegravir; CSR = clinical study report; FLAIR = First Long-Acting Injectable Regimen; INSTI = integrase strand transfer inhibitor; LA = long-acting; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; Q1M = given every 1 month; Q2M = given every 2 months; RPV = rilpivirine

ERG comment:

- The ERG highlights that there are currently no studies comparing CAB LA + RPV LA administered every second month (Q2M), a regimen which will be available in the UK upon successful decision by NICE, with ART therapy.
- The ERG agrees that the methodology of the trials included in this submission is appropriate for this disease area. The CS highlighted that the design of the studies, the pooling of the results, and the non-inferiority margins were agreed by the European Medicines Agency (EMA).[1, 42]
- The company was asked to clarify the correct dosing schedule used in FLAIR study (question B8.a of the request for clarification).[11] The error was acknowledged by the company and the correct dosing is provided in Tables 3.4 and 3.5 in this report.[2]
- In question B8.b of the request for clarification, the company was asked to provide supporting information regarding the ART regimens given to participants in the ATLAS study.[11] The company's response[2] referred to the supplementary Table S1 of already published paper by Swindells et al. 2020.[31, 43]

3.2.2 Statistical analysis of the included RCTs

The analysis populations for ATLAS, ATLAS-2M and FLAIR consisted of intention-to-treat-exposed (ITT-E) populations. In all three instances, ITT-E was defined as the population of all randomised participants who had received at least one dose of the trial drug who were analysed according to randomised treatment, regardless of the treatment actually received (cf. Table 11 of the CS).[1] This appears to be a similar strategy to modified ITT (mITT) which can take different definitions, including the above. The recommended approach has been suggested as an analysis based on all randomised participants within their allocated groups, regardless of actual treatment and whether any treatment was received. Therefore, ITT-E and mITT are not optimal methods of analysis.[44] This said, based on the easily accessible data, it appears that the difference between randomised participants and the ITT-E population per arm is small for each RCT therefore the impact in terms of risk of bias is likely to be low (Table 3.6).

The details of the trial hypotheses, endpoints, sample size calculation and statistical analysis methods are provided in Table 3.7. The ATLAS and FLAIR study hypothesised the non-inferiority between CAB LA + RPV LA (Q1M) and the ART therapy whereas the ATLAS-2M study focused on the non-inferiority between different dosing of CAB LA + RPV LA, i.e. Q1M vs. Q2M.

Table 3.6: Summary of randomised versus ITT-E numbers

Study	Trial group	Randomised	ITT-E	Difference
ATLAS-2M	Overall	1,049	1,045	0.38%
	CAB LA + RPV LA Q2M	524	522	0.38%
	CAB LA + RPV LA Q1M	525	523	0.38%
ATLAS	Overall	618	616	0.32%
	CAB LA + RPV LA	?	308	?
	Oral ART	?	308	?
FLAIR	Overall	?	566	?
	CAB LA + RPV LA	?	283	?
	Oral ART	?	283	?

Study	Trial group	Randomised	ITT-E	Difference
Based on Table 13 of the CS,[1] the trial registry record for ATLAS,[36] and Murray et al. 2020[45] ART = antiretroviral therapy; CAB = cabotegravir; CS = company submission; ITT-E = intention-to-treat exposed; LA = long-acting; Q1M = given every 1 month; Q2M = given every 2 months; RPV = rilpivirine				

The safety population consisted of all randomised participants who received at least one dose of study treatment and assessed according to treatment received. The non-inferiority margin in the statistical analysis of primary endpoints in the ATLAS and FLAIR was established at 6% whereas in the ATLAS-2M at 4%. However, the combined data from the ATLAS and FLAIR used non-inferiority margin of 4% and an adequate sample size calculation was performed. The methods used in the ATLAS and FLAIR studies were comparable with the exception of statistical analysis of the primary and secondary endpoints due to different stratification factors.

Table 3.7: Summary of statistical analyses for included RCTs

	ATLAS[30, 31, 39]	FLAIR[32, 33, 40]	ATLAS-2M[34, 41]
Hypothesis objective	To demonstrate the non-inferior antiviral activity of switching to intramuscular CAB LA + RPV LA every 4 weeks (monthly) compared to continuation of current first line antiretroviral regimen over 48 weeks in HIV-1 infected antiretroviral therapy (ART)-experienced participants.	To demonstrate that the antiviral effect of oral ABC/DTG/3TC (current ART) followed by intramuscular CAB LA + RPV LA regimen was non-inferior to continuation of ART at Week 48 of maintenance treatment.	Demonstrate that the antiviral effect of Q2M dosing with CAB LA + RPV LA is non-inferior to Q1M dosing
Analysis populations	ITT-E population: all randomised participants who received at least one dose of study treatment; participants were assessed according to their randomised treatment, regardless of the treatment they received. Per protocol (PP) population: all those in the ITT-E population with the exception of major protocol violators. Safety population: All randomised participants who received at least one dose of study treatment; assessed according to treatment received.		
Statistical analysis of primary endpoints	Comparison at a one-sided 2.5% level of significance. Treatment with CAB-LA+RPV LA was declared non-inferior to current ART if the upper end of a two-sided 95% CI for the difference between the two groups in virologic failure rates at Week 48 lies below 6%. Adjusted estimates of the difference in the rate of failures between the two arms was presented along with CIs based on a stratified analysis using CMH weight (according to the baseline third agent class [INI, NNRTI, or PI] and gender at birth.	Comparison at a one-sided 2.5% level of significance. Treatment with CAB LA + RPV LA was declared non-inferior to current ART if the upper end of a two-sided 95% CI for the difference between the two groups in virologic failure rates at Week 48 lies below 6%. Adjusted estimates of the difference in the rate of failures between the two arms was presented along with CIs based on a stratified analysis using CMH weight (based on participants' Baseline HIV-1 RNA [<100,000, ≥100,000 c/ml] and gender at birth)	The primary analysis was based on the ITT-E population. The primary comparison was made at a one-sided 2.5% level of significance. Treatment with Q2M was declared non-inferior to Q1M if the upper end of a two-sided 95% confidence interval for the difference between the two groups (Q2M – Q1M) in the proportion of participants with plasma HIV-1 RNA ≥50 copies/ml at Week 48 (defined by the US FDA snapshot algorithm) was below 4%. The adjusted difference between the randomisation arms for the proportion of participants with HIV-1 RNA ≥ 50 copies/ml at Week 48 and its confidence interval was calculated according to a stratified analysis with CMH weights (to be adjusted for the randomisation strata according to prior exposure to CAB+RPV). The 95% CIs for the treatment differences were calculated using an unconditional exact method based on the two inverted 1-sided tests.

	ATLAS[30, 31, 39]	FLAIR[32, 33, 40]	ATLAS-2M[34, 41]
			The analysis described for the primary comparison was also performed using the Per-Protocol Population and the results were compared for consistency with the results from the ITT-E Population.
Non-inferiority margin	Data from the ATLAS study was combined with that of FLAIR to assess non-inferiority using a 4% non-inferiority margin. The combined sample size from both studies (570 pooled per arm) provided 90% power, under the assumptions described above, to show non-inferiority for the proportion of participants with virologic failure (per FDA's snapshot algorithm for assessing HIV-1 RNA ≥ 50 copies/ml) at Week 48.		A non-inferiority margin of 4% was chosen because a snapshot proportion with plasma HIV-1 RNA ≥ 50 copies/ml at Week 48 in this range is considered clinically tolerable given the Q2M regimen will offer important advantages over the Q1M regimen such as reduced injection frequency and may offer better adherence and treatment satisfaction. This margin is also in concordance with the current FDA Guidance for Industry,[46] which is the most current regulatory guidance from either the EMA or FDA and includes specific recommendations regarding switch studies.
Statistical analysis of key secondary endpoints	Evaluation of the proportion of responders (HIV-1 RNA <50 copies/ml per Snapshot) at Week 48 using a CMH test stratified by baseline third agent class (INSTI, NNRTI, or PI) and sex at birth. A non-inferiority margin of -10% was used for this secondary comparison, where if the lower limit of the 95% CI of the difference in responder rate between the two study arms is greater than minus 10%, non-inferiority was demonstrated.	Evaluation of the proportion of responders (HIV-1 RNA <50 copies/ml per Snapshot) at Week 48 using the same analysis method and stratification factors as specified for the primary endpoint. A noninferiority margin of -10% was used for this secondary comparison, where if the lower limit of the 95% CI of the difference in responder rate between the two treatment groups was greater than minus 10%, non-inferiority would be demonstrated.	The key secondary efficacy analysis was performed to evaluate the proportion of plasma HIV-1 RNA <50 copies/ml per Snapshot at Week 48 based on the ITT-E Population using the same analysis method and stratification factors as specified for the primary analyses. A non-inferiority margin of -10% was used for this secondary comparison.
Statistical analysis of	NR		The cumulative proportion of participants with confirmed virologic failure through Week 24 and other visits during the Maintenance Phase was also summarized. Absolute values

	ATLAS[30, 31, 39]	FLAIR[32, 33, 40]	ATLAS-2M[34, 41]
other relevant endpoints			and change from Baseline in plasma HIV-1 RNA and CD4+ lymphocyte count over time were summarised over time using descriptive statistics (mean, median, first and third quartiles, min and max).
Statistical analysis of safety endpoints	Descriptive summary		
Sample size and power calculation	This study planned to randomise approximately 285 participants per treatment group. Assuming the true proportion of participants with Snapshot HIV-1 RNA ≥50 copies/ml was 3% for the CAB LA + RPV LA treatment group and 2% for the current ART group, a non-inferiority margin of 6%, and a 2.5% 1-sided significance level, this provided approximately 97% power to show non-inferiority for the proportion of participants with Snapshot HIV-1 RNA ≥50 copies/ml at Week 48. The sample size of 285 participants per arm also provides at least 90% power to show non-inferiority in the proportion of participants with plasma HIV-1 RNA <50 copies/ml (per FDA's Snapshot algorithm) at Week 48 over a range of true response rates, based on a -10% non-inferiority margin and 2.5% one-sided significance level. Assuming true response rates for the CAB LA + RPV LA arm and current ART arm were both 87%, the power is at least 94% to show non inferiority for this key secondary endpoint.		Assuming the true proportion with plasma HIV-1 RNA ≥50 copies/ml is 3% for the Q2M arm and 2% for the Q1M arm, a non-inferiority margin of 4%, and a 2.5% 1-sided significance level, the sample size of 510 participants per treatment arm would provide at least 85% power to show non-inferiority at Week 48 (using un-pooled Z test statistic). With this sample size, 90% power would be achieved assuming a 1% treatment difference and true proportions with plasma HIV-1 RNA ≥50copies/ml of 2.63% for the Q2M arm and 1.63% for the Q1M arm. With 510 participants per arm and assuming an observed proportion HIV-RNA ≥50 copies/ml is 2% for Q1M, the largest observed treatment difference to achieve non-inferiority with respect to a 4% margin is 1.92 percentage points. This equates approximately to observing an excess of 10 participants on the Q2M arm (10 participants on Q1M vs. 20 participants on Q2M).
Handling of missing data and participant withdrawals	LOCF imputation		In the Snapshot dataset, participants without HIV-1 RNA data in the assessment window for the visit of interest (due to missing data or discontinuation prior to the visit window) were not included in 'HIV-1 RNA < 50 copies/ml (or <200 copies/ml)'. The nature of this missing data was further classified in Snapshot summaries as either 'HIV-1 RNA ≥ 50

	ATLAS[30, 31, 39]	FLAIR[32, 33, 40]	ATLAS-2M[34, 41]
			copies/ml' (or 'HIV-1 RNA ≥ 200 copies/ml') or 'No Virologic Data at Week X'.[47] For time-to-event analyses, follow-up time for participants who did not experience an event of interest were censored at time of early withdrawal or end of the Week 48 analysis window. The LOCF approach was used to impute missing values for the Health Outcomes analyses.

Based on Tables 11 and 28 of the CS[1]

ART = antiretroviral therapy, ATLAS = Antiretroviral Therapy as Long-Acting Suppression, ATLAS-2M = Antiretroviral Therapy as Long-Acting Suppression Q2M; CAB = cabotegravir, CD = cluster of differentiation, CMH = Cochran-Mantel Haenszel, CS = company submission; EMA = European Medicines Agency, FLAIR = First Long-Acting Injectable Regimen, HCV = hepatitis C virus, HIV = human immunodeficiency virus, INSTI = integrase strand transfer inhibitor, ITT-E = intention-to-treat exposed, LA = long-acting, LOCF = last observation carried forward, NNRTI = non-nucleoside reverse transcriptase inhibitor, NR = not reported, PP = per-protocol; Q1M = given every 1 month, Q2M = given every 2 months, RNA = ribonucleic acid, RPV = rilpivirine, TB = tuberculosis, ULN = upper limit of normal,

ERG comment: The non-inferiority margin in the ATLAS and FLAIR trials was established at 6% whereas in the ATLAS-2M at 4%. However, for the adjusted treatment differences of the pooled sample of patients from the ATLAS and FLAIR trials, the CS utilises the margin of 4%.

3.2.3 Trial participant characteristics

The key inclusion and exclusion criteria for the ATLAS, FLAIR and ATLAS-2M studies are summarised in Table 3.8. All patients had to be infected with HIV-1 and ≥18 years of age. Patients included in ATLAS and ATLAS-2M studies had to have plasma HIV-1 RNA <50 copies/ml at screening whereas HIV treatment-naïve patients in the FLAIR study plasma HIV-1 RNA ≥1000 copies/ml documented at screening. Separate inclusion criteria in the ATLAS-2M were provided for patients previously participating in the ATLAS trial and those on previous oral therapy. Pregnant and breastfeeding women were excluded from all three RCTs with most of the other exclusion criteria being similar between studies. However, the use of abacavir/dolutegravir/lamivudine (ABC/DTG/3TC) as current ART regimen was an exclusion criterion in the ATLAS study which was the ART regimen used as the control treatment in the FLAIR study.

The ERG noticed, upon checking the protocols for ATLAS, FLAIR and ATLAS-2M,[39-41] that patients with any evidence of primary resistance based on the presence of any major known NNRTIs resistance-associated mutations were excluded from the studies. However, mutation K103N was allowed in all three studies. The company referenced the document published by the International Antiviral Society-USA (IAS-USA) which states that K103N as a single mutation will not impact susceptibility to RPV[48]. Based on data from the HIV drug resistance database[49] and FDA's Guidance for Industry[50], K103N as a single mutation can affect other NNRTIs such as nevirapine (NVP) or efavirenz (EFV). Those NNRTIs were used by 5% and 34% of patients, respectively, in the ART arm of the ATLAS study.[43] However, based on the information from CSRs for FLAIR{ViiV Healthcare, 2019 #115}, ATLAS{ViiV Healthcare, 2019 #115} and ATLAS-2M{ViiV Healthcare, 2019 #112}, none of the patients experiencing treatment failure were carriers of the baseline K103N mutation in any of the treatment arms.

With regards to patient disposition, the proportion of participants who discontinued ATLAS-2M study was low and comparable between treatment arms (CAB LA + RPV LA [Q1M]: n=42 [8%] and CAB LA + RPV LA [Q2M]: n=36 [7%]). The reasons for withdrawal from the study did not substantially differ between treatment arms. Thirteen (2%) and 12 patients (2%) withdraw due to non-fatal adverse events in CAB LA + RPV LA (Q1M) and CAB LA + RPV LA (Q2M) treatment arms, respectively. Similarly, the proportion of participants who discontinued ATLAS (CAB LA + RPV LA [Q1M]: n=26 (8%) and current ART therapy: n=18 [6%]) or FLAIR study (CAB LA + RPV LA [Q1M]: n=25 (9%) and current ART therapy: n=22 [8%]) was comparable between treatment arms. Withdrawal due to adverse events were the most common reason in ATLAS (CAB LA + RPV LA [Q1M]: n=13 (4%) and current ART therapy: n=5 [2%]; only one fatal case in the control arm) and FLAIR study (CAB LA + RPV LA [Q1M]: n=9 (3%) and current ART therapy: n=4 [1%]; all non-fatal).

Table 3.8: Key inclusion and exclusion criteria for included RCTs

	ATLAS[30, 31, 39]	FLAIR[32, 33, 40]	ATLAS-2M[34, 41]
Inclusion criteria	• HIV-1 positive, men or women aged 18 years or greater • On uninterrupted current regimen (either the initial or second ART regimen) for at least 6 months prior to Screening. Any prior switch must NOT have been done for treatment failure (HIV-1 RNA ≥400 copies/ml). • Documented evidence of at least 2 plasma HIV-1 RNA measurements <50 copies/ml in the 12 months prior to Screening: o 1 within the 6- to 12-month window, and o 1 within 6 months prior to Screening • Plasma HIV-1 RNA <50 copies/ml at Screening • Capable of giving signed informed consent	• HIV-1 infected, ART-naive men or women aged 18 years or greater • HIV-1 infection as documented by Screening plasma HIV-1 RNA ≥1000 copies/ml • Antiretroviral-naïve (≤10 days of prior therapy with any ART following a diagnosis of HIV-1 infection) • Female participants were to be non-pregnant, non-lactating and had to be either of non-reproductive potential or of reproductive potential and agree to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential • Capable of giving signed informed	• Men and women of at least 18 years of age • Participants receiving oral standard of care treatment for HIV-1 (not participating in ATLAS trial) o Must be on uninterrupted current regimen (either initial or second ART regimen) for at least 6 months prior to Screening o Acceptable stable (initial or second) ART regimens prior to Screening include 2 NRTIs plus: o INSTI (either the initial or second current ART regimen) o NNRTI (either the initial or second current ART regimen) o Boosted PI (or ATV unboosted) (must be either the initial current ART regimen or one historical within class switch is permitted due to safety/tolerability) o Documented evidence of at least two plasma HIV-1 RNA measurements <50 copies/ml in the 12 months prior to Screening o Plasma HIV-1 RNA <50 copies/ml at Screening

	ATLAS[30, 31, 39]	FLAIR[32, 33, 40]	ATLAS-2M[34, 41]
			• Participants transitioning from ATLAS o Must have been on CAB LA 400 mg + RPV LA 600 mg Q1M or "Current ART" regimen through at minimum Week 52 of the ATLAS study as per ATLAS protocol dosing requirements and until Day 1 of the ATLAS-2M study. o Plasma HIV-1 RNA <50 copies/ml at Screening
Exclusion criteria	• Pregnant, breastfeeding or planning to become pregnant or breastfeed during the study • Within 6 months prior to Screening and after confirmed suppression to <50 copies/ml on current ART regimen, any plasma HIV-1 RNA measurement ≥50 copies/ml • Within the 6- to 12-month window prior to Screening and after confirmed suppression to <50 copies/ml, any plasma HIV-1 RNA measurement >200 copies/ml, or 2 or more plasma HIV-1 RNA measurements ≥50 copies/ml • Any drug holiday during the window between initiating first HIV ART and 6 months prior to Screening, except for brief periods (less than 1 month) where all ART was stopped due to tolerability and/or safety concerns • Any switch to a second-line regimen due to virologic failure to therapy • Abacavir/dolutegravir/lamivudine, (ABC/DTG/3TC) as current ART regimen	• Women who are pregnant, breastfeeding or plan to become pregnant or breastfeed during the study • Any evidence at screening of an active CDC Stage 3 disease; known moderate to severe hepatic impairment; unstable liver disease; history of liver cirrhosis; any pre-existing physical or mental condition that may interfere with the participant's ability to comply with the dosing schedule; evidence of HBV infection; ongoing malignancy other than cutaneous Kaposi's sarcoma, basal cell carcinoma, resected non-invasive cutaneous squamous cell carcinoma, or cervical, anal or penile intraepithelial neoplasia; any condition that may interfere	• Females who are pregnant or breast feeding • Evidence of active CDC stage 3 disease • Participants with moderate to severe hepatic impairment • Pre-existing physical or mental condition which, according to the investigator may interfere with the ability to comply with the trial • Participants with significant suicide risk • Further exclusion criteria can be found in the trial protocol

	ATLAS[30, 31, 39]	FLAIR[32, 33, 40]	ATLAS-2M[34, 41]
	• A history of use of any regimen consisting of only single NNRTI therapy, or only single or dual NRTI therapy prior to starting current ART • Any evidence at screening of active CDC stage 3 disease; known moderate to severe hepatic impairment, unstable liver disease, history of liver cirrhosis, evidence of HBV infection; any pre-existing physical or mental condition that may interfere with the participant's ability to comply with the dosing schedule; ongoing malignancy other than cutaneous Kaposi's sarcoma, basal cell carcinoma, resected non-invasive cutaneous squamous cell carcinoma, or cervical, anal or penile intraepithelial neoplasia; any condition that may interfere with the absorption, distribution, metabolism or excretion of the drug or render the participant unable to receive study medication; ALT ³3 times ULN; clinically significant cardiovascular disease • Exposure to an experimental drug and/or experimental vaccine within 28 days or 5 half-lives of the test agent • Any evidence of primary resistance to NNRTIs or any known resistance to INSTIs • Any verified Grade 4 laboratory abnormality; any acute laboratory abnormality at screening; estimated creatinine clearance <50 ml/min/1.73 m^2 • Current participation in another interventional study	with the absorption, distribution, metabolism or excretion of the drug or render the participant unable to receive study medication; ALT ³3 times ULN; clinically significant cardiovascular disease • Exposure to an experimental drug and/or experimental vaccine within 28 days or 5 half-lives of the test agent • Any evidence of primary resistance to NNRTIs or any known resistance to INSTIs • Any verified Grade 4 laboratory abnormality; any acute laboratory abnormality at screening; estimated creatinine clearance <50 ml/min/1.73 m^2 • Current participation in other interventional study	

Based on Tables 10, 26 and 27 of the CS[1]
ALT = alanine aminotransferase, ART = antiretroviral, ATLAS = Antiretroviral Therapy as Long-Acting Suppression, ATLAS-2M = Antiretroviral Therapy as Long-Acting Suppression Q2M; ATV = atazanavir, CAB = cabotegravir, CD = cluster of differentiation, CDC = Centers for Disease Control and Prevention, CS = company submission; FLAIR = First Long-Acting Injectable Regimen, HBV = hepatitis B virus, HIV = human immunodeficiency virus, INSTI = integrase strand transfer inhibitor, LA = long-acting, NNRTI = non-nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, RNA = ribonucleic acid, RPV = rilpivirine, TB = tuberculosis, ULN = upper limit of normal

ERG comment:

- One of the exclusion criteria for patients in the ATLAS trial was the use of abacavir/dolutegravir/lamivudine (ABC/DTG/3TC) as current ART regimen which was the ART treatment used as the control group in the FLAIR study. The company provided more information on the ART regimens used in the control group of the ATLAS trial and is discussed in the ERG comment in section 3.2.1.[2] The patient characteristics in the included RCTs are presented in Table 3.9. Patients' baseline characteristics within trials are comparable between arms.
- Based on the study protocols, patients with evidence of K103N mutation (NNRTIs resistance-associated genetic mutation) were eligible for inclusion in ATLAS, FLAIR and ATLAS-2M studies. However, there is no evidence for any of the patients experiencing treatment failure in the studies to be the carrier of the baseline K103N mutation in any of the treatment arms.

Table 3.9: Baseline characteristics of the RCTs

Characteristic	ATLAS[30, 51]		FLAIR[32, 33]		ATLAS-2M[34, 35]	
	CAB+RPV (Q1M; N=308)	Current ART (N=308)	CAB + RPV (Q1M; N=283)	Current ART (N=283)	CAB LA + RPV LA Q2M (N=522)	CAB LA + RPV LA Q1M (N=523)
Prior exposure to CAB + RPV, n (%)						
None	NR	NR	NR	NR	327 (63)	327 (63)
1-24 weeks	NR	NR	NR	NR	69 (13)	68 (13)
>24 weeks	NR	NR	NR	NR	126 (24)	128 (24)
Age (y)						
Mean (SD)	41.6 (9.99)	43.2 (11.43)	35.9 (10.17)	36.0 (9.82)	42.7 (11.16)	42.3 (10.58)
Median (range)	NR	NR	NR	NR	42 (20 to 83)	42 (19 to 75)
Min, max.	21,74	18,82	19, 68	18, 68	NR	NR
Age group (y), n (%)						
<35	80 (26)	80 (26)	143 (51)	145 (51)	137 (26)	145 (28)
35 to <50	162 (53)	132 (43)	107 (38)	109 (39)	242 (46)	239 (46)
≥50	66 (21)	96 (31)	33 (12)	29 (10)	143 (27)	139 (27)
Sex at birth, n (%)						
Female	99 (32)	104 (34)	63 (22)	64 (23)	137 (26)	143 (27)
Male	209 (68)	204 (66)	220 (78)	219 (77)	385 (74)	380 (73)
Race, n (%)						
White	214 (69)	207 (67)	216 (76)	201 (71)	370 (71)	393 (75)
Non-White	94 (31)	101 (33)	67 (24)	80 (28)	152 (29)	130 (25)
Missing	NR	NR	0	2 (<1)	NR	NR

Characteristic	ATLAS[30, 51]		FLAIR[32, 33]		ATLAS-2M[34, 35]	
	CAB+RPV (Q1M; N=308)	Current ART (N=308)	CAB + RPV (Q1M; N=283)	Current ART (N=283)	CAB LA + RPV LA Q2M (N=522)	CAB LA + RPV LA Q1M (N=523)
BMI (kg/m^2)						
Mean (SD)	26.2 (5.1)	26.7 (5.8)	25.1 (4.4)	24.9 (4.9)	26.677 (5.2)	26.782 (5.8)
Viral Load						
n	NR	NR	NR	NR	522	523
<50 copies/ml	NR	NR	NR	NR	519 (>99)	513 (98)
≥40 to <50 copies/ml	NR	NR	NR	NR	3 (<1)	69 (13)
<40 copies/ml and target detected	NR	NR	NR	NR	69 (13)	70 (13)
CD4+ cell count (cells per mm^3)						
Mean (SD)	NR	NR	NR	NR	681.8 (259.9)	729.8 (298.57)
Median (IQR)	NR	NR	NR	NR	642 (499 to 827)	688 (523 to 878)
<350	NR	NR	NR	NR	35 (7)	27 (5)
350 to <500	NR	NR	NR	NR	96 (18)	89 (17)
≥500	NR	NR	NR	NR	391 (75)	407 (78)
CDC Stage						
Stage 1	NR	NR	NR	NR	391 (75)	407 (78)
Stage 2	NR	NR	NR	NR	129 (25)	113 (22)
Stage 3	NR	NR	NR	NR	2 (<1)	3 (<1)
Hepatitis C co-infection						
n	NR	NR	NR	NR	522	522
Negative	NR	NR	NR	NR	517 (>99)	516 (99)
Positive	NR	NR	NR	NR	5 (<1)	6 (1)

Based on Tables 14, 30, and 32 of the CS[1]

ART = antiretroviral therapy, ATLAS = Antiretroviral Therapy as Long-Acting Suppression, ATLAS-2M = Antiretroviral Therapy as Long-Acting Suppression Q2M; BMI = body mass index, CAB = cabotegravir, CD = cluster of differentiation, CDC = Centers for Disease Control and Prevention, CS = company submission; FLAIR = First Long-Acting Injectable Regimen, HIV = human immunodeficiency virus, IQR = interquartile range, NNRTI = non-nucleoside reverse transcriptase inhibitor, Q1M = given every 1 month, Q2M = given every 2 months RNA = ribonucleic acid, RPV = rilpivirine; SD = standard deviation

3.2.4 Quality assessment of included RCTs

The tool and methods used for quality assessment of included RCTs is provided in section 3.1.4. The results of quality assessment of relevant trials are provided in Table 3.10.

Table 3.10: The quality assessment of included RCTs

Trial name (clinical ID)	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
ATLAS (NCT02951052)	Unclear risk	Unclear risk	High risk	Unclear risk	Low risk	Low risk
FLAIR (NCT02938520)	Low risk	Low risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
ATLAS-2M (NCT03299049)	Unclear risk	Unclear risk	High risk	Unclear risk	Unclear risk	Low risk

Based on Table D.4 in the Appendix D of the CS[3]
ATLAS = Antiretroviral Therapy as Long-Acting Suppression, ATLAS-2M = Antiretroviral Therapy as Long-Acting Suppression Q2M, CS = company submission; FLAIR = First Long-Acting Injectable Regimen; Q2M = given every 2 months

ERG comment:

- The results of quality assessment were only provided for three phase 3 trials: ATLAS, FLAIR and ATLAS-2M. No further justification for the decisions or discussion on summary risk of bias in the trials was provided.
- No information about the quality assessment of supporting trials, i.e. LATTE, LATTE-2 and POLAR, was provided nor discussed in the CS.[1]

3.2.5 Efficacy results

Table 3.11 lists the main outcomes, relevant to NICE scope (see Table 2.1), and studies which provide relevant information.

Table 3.11: The outcomes included in the NICE scope that were reported in the CS

Outcome	Source of information	Section of the CS[1]	Section of the ERG report
Maintenance of virological suppression	ATLAS-2M; ATLAS and FLAIR; LATTE-2 and POLAR	B.2.6.1.6 - B.2.6.1.9; B.2.6.1.13; B.2.6.1.14; B.2.6.2.5; B.2.6.2.6	3.2.5.1
CD4+ T-cell levels	ATLAS-2M	B.2.6.1.10	3.2.5.2
Treatment-emergent resistance	none	-	3.2.5.3

Outcome	Source of information	Section of the CS[1]	Section of the ERG report
Adherence to treatment regimen	FLAIR; LATTE-2	B.2.6.1.13; B.2.6.2.8	3.2.5.4
AIDS-defining events	none	-	3.2.5.5
Mortality	ATLAS-2M	B.2.6.1.11	3.2.5.6
Comorbidities	none	-	3.2.5.7
HRQoL	ATLAS-2M; ATLAS and FLAIR	B.2.6.1.12.6; B.2.6.2.7	3.2.5.8

AIDS = Acquired immunodeficiency syndrome, ATLAS = Antiretroviral Therapy as Long-Acting Suppression, ATLAS-2M = Antiretroviral Therapy as Long-Acting Suppression Q2M, CD4 = cluster of differentiation, CS = company submission; FLAIR = First Long-Acting Injectable Regimen, HRQoL = health-related quality of life, LATTE = Long-Acting antireTroviral Treatment Enabling, LATTE-2 = Long-Acting antireTroviral Treatment Enabling-2, POLAR = Oral (PO) to Long-Acting (LA) Rollover

3.2.5.1 Maintenance of virological suppression

3.2.5.1.1 Proportion of participants with Plasma HIV-1 RNA ≥50 copies/ml at Week 48 (primary endpoint) and Week 96 and HIV-1 RNA copies <50 copies/ml at Week 48 and Week 96

The results of the primary endpoint, i.e. the proportion of HIV-1 RNA ≥50 copies/ml at week 48 (Snapshot algorithm; ITT-E population) for pooled ATLAS and FLAIR as well as the ATLAS-2M study is provided in Table 3.12. The analysis demonstrated the non-inferiority of CAB LA + RPV LA (Q1M) to current ART therapy in maintaining virologic suppression in participants with HIV-1 infection at week 48 assuming the non-inferiority margin of 4% (adjusted difference in proportion 0.16, 95% CI -1.35 to 1.67). Similarly, non-inferiority was showed between CAB LA + RPV LA given every month (Q1M) or every second month (Q2M) with the same non-inferiority margin of 4% (adjusted difference in proportion 0.8, 95% CI -0.6 to 2.2). However, the patients with lack of virologic data at week 48 in the ATLAS-2M study were assumed to have HIV-1 RNA <50 copies/ml (Figure 3.1) with no information provided for the pooled ATLAS and FLAIR. The non-inferiority between treatment arms for the same outcome (the proportion of patients with plasma HIV-1 RNA <50 copies/ml) at week 96 was not available for pooled ATLAS and FLAIR studies maintained for the ATLAS-2M (Q1M vs. Q2M adjusted difference in proportion 1.0, 95% CI -0.6 to 2.5).

The proportion of participants with plasma HIV-1 RNA <50 copies/ml at week 48 was similar between CAB LA + RPV LA (Q1M) and ART therapy as reported in pooled ATLAS and FLAIR (adjusted difference in proportion -1.37, 95% CI -4.12 to 1.39) and between different regimens of CAB LA + RPV LA (Q1M vs. Q2M) as reported in the ATLAS-2M (adjusted difference in proportion 0.8, 95% CI -2.1 to 3.7) assuming the non-inferiority margin of 4%. However, at week 96, the non-inferiority between different regimens of CAB LA + RPV LA (Q1M vs. Q2M) could not be confirmed as 95% CI included the non-inferiority margin of 4% (adjusted difference in proportion 0.8, 95%CI -2.8 to 4.3).

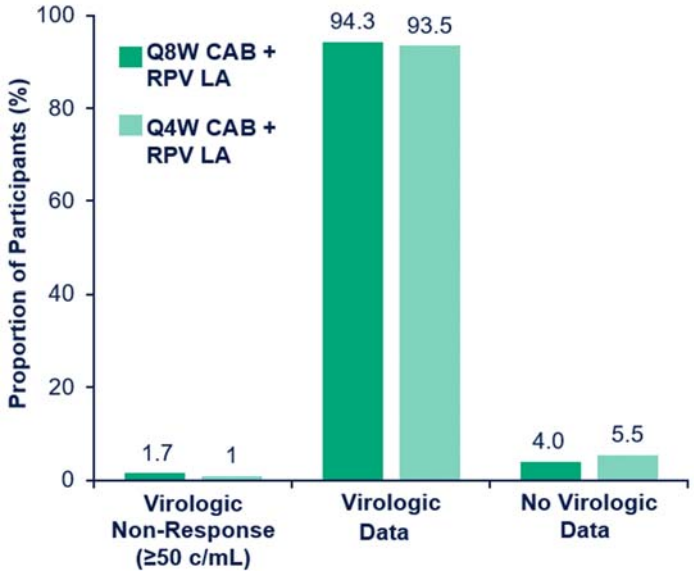
Most of the patients included in ATLAS transitions to ATLAS-2M, however, at week 96 of data analysis only one out of 52 patients had HIV-1 RNA ≥50 copies/ml.

Table 3.12: Proportion of participants with Plasma HIV-1 RNA ≥50 copies/ml at Week 48 (primary endpoint) and Week 96 and HIV-1 RNA copies <50 copies/ml at Week 48 and Week 96 (ITT-E population of pooled ATLAS and FLAIR or ATLAS-2M studies)

		Pooled ATLAS + FLAIR[24]		ATLAS-2M[34, 35]	
		Q1M (N=591)	Current ART (N=591)	CAB LA + RPV LA Q2M (n=522)	CAB LA + RPV LA Q1M (n=523)
Week 48	***Primary endpoint:*** **HIV RNA ≥ 50 copies/ml per total assessed (%)**	11/591 (1.9)	10/591 (1.7)	9/522 (1.7)	5/523 (1.0)
	Difference in proportion (95% CI)	0.17 (-1.34 to 1.68)		0.8 (-0.6 to 2.2)	
	Adjusted difference in proportion (95% CI)	0.16 (-1.35 to 1.67)		0.8 (-0.6 to 2.2)	
	Plasma HIV-1 RNA <50 copies/ml (%)	550/591 (93)	558/591 (94)	492/522 (94)	489/523 (93)
	Difference in proportion (95% CI)	-1.35 (-4.11 to 1.41)		0.8 (-2.2 to 3.7)	
	Adjusted difference in proportion (95% CI)	-1.37 (-4.12 to 1.39)		0.8 (-2.1 to 3.7)	
Week 96	**HIV RNA ≥ 50 copies/ml per total assessed (%)**	NR	NR	11 (2.1)	6 (1.1)
	Difference in proportion (95% CI)	NR		-	
	Adjusted difference in proportion (95% CI)	NR		1.0 (-0.6 to 2.5)	
	Plasma HIV-1 RNA <50 copies/ml (%)	NR	NR	475 (91.0)	472 (90.2)
	Difference in proportion (95% CI)	NR		-	
	Adjusted difference in proportion (95% CI)	NR		0.8 (-2.8 to 4.3)	

Based on Tables 15, 16, 33, and 34 of the CS[1]
ATLAS = Antiretroviral Therapy as Long-Acting Suppression, ATLAS-2M = Antiretroviral Therapy as Long-Acting Suppression Q2M, ART = antiretroviral therapy, CI = confidence interval, CS = company submission; FLAIR = First Long-Acting Injectable Regimen, HIV = human immunodeficiency virus, NR = not reported, Q1M = given every 1 month, Q2M = given every 2 months, RNA = ribonucleic acid

Figure 3.1: Proportion of participants with Plasma HIV-1 RNA ≥50 copies/ml at Week 48 (Snapshot Algorithm; ITT-E population) in the ATLAS-2M study



Based on Figure 3 of the CS[1]
CAB = cabotegravir, CS = company submission; ITT-E = intention-to-treat exposed; LA = long-acting, Q1M =given every 1 month, Q2M = given every 2 months; RPV = rilpivirine

3.2.5.1.2 Confirmed virological failure (CVF)

For the ATLAS-2M study, the CS reported that through week 48, including dosing beyond week 48, there were eight participants (1.5%) in the CAB LA + RPV LA (Q2M) and two participants (<1%) in the CAB LA + RPV LA (Q1M) with CVF. At week 96, there was nine (1.7%) and two (0.4%) participants with CVF in the CAB LA + RPV LA Q2M and Q1M, respectively.

No patients met the criteria for CVF at week 96 in 52 patients in the ATLAS study who did not transitioned to ATLAS-2M. In the FLAIR study at week 96, CVF was confirmed in four (1.4%) of participants in CAB LA + RPV LA (Q1M; all before week 48) and in four (1.4%) of participants receiving ART therapy. At week 124 (the extension phase after the FLAIR study), one participant (0.4%) had CVF with no participant in the ART therapy.

The company provided post-hoc analysis of pooled ATLAS, FLAIR and ATLAS-2M studies focused on factors associated with CVF and the results can be found in section B.2.6.1.9 of the CS.[1]

3.2.5.1.3 Long-term outcomes from LATTE-2 and POLAR

The CS included the evidence from phase 2b LATTE-2 study evaluating CAB LA + RPV LA (Q1M or Q2M) versus ART therapy in maintaining virological suppression (for study details see Table 3.4).[1] The CS stated that at week 96, virologic suppression was maintained in 87% and 94% of participants receiving CAB LA + RPV LA Q1M or Q2M, respectively and at week 160, in 83% and 90% of participants, respectively. In CAB LA + RPV LA (Q2M) there were two protocol-defined virological failures at week 160 with no other events after week 48 in any arm. At week 256, 81% and 93% participants randomised to LA therapy at day 1 and participants who switched from oral therapy at week 100, respectively, maintained virological suppression.

The evidence from phase 2b POLAR study evaluating CAB LA + RPV LA (Q2M) versus ART therapy showed that at month 12, 98% and 100% participants, respectively, maintained virological suppression.

In CAB LA + RPV LA (Q2M), 2% of patients did not have virological data. In patients with data available, none had HIV-1 RNA ≥50 copies/ml or CVF in either arm.

ERG comment:

- The outcomes of the ATLAS-2M study were reported for ITT-E population. The results for the per-protocol population were only mentioned and compared to the results of ITT-E. Appropriate reference was provided for the clinical study report (CSR) of ATLAS-2M where relevant data can be found.
- No definition for CVF was provided in the CS.
- No results regarding CVF are provided for patients included in the ATLAS study even though three and four participants in the CAB LA + RPV LA (Q1M) and ART therapy, respectively had CVF (Table 29 of the CS).[1] For patients in FLAIR study, the number of patients with CVF (four in each study arm) does not match the information in the Table 31 of the CS reporting participant disposition (i.e. five participants with CVF in the CAB LA + RPV LA [Q1M] and three in current ART therapy.[1]

3.2.5.2 CD4+ T-cell levels

The CD4+ T-cell levels are reported in the Table 3.13. Median CD4+ cell counts did not change substantially from baseline to week 48 in CAB LA + RPV LA treatment regimens (Q1M and Q2M).

Table 3.13: CD4+ cell count changes from baseline over time in the ATLAS-2M study

		ATLAS-2M[34, 35]	
		CAB LA + RPV LA Q2M (n=522)	**CAB LA + RPV LA Q1M (n=523)**
Week 48	Median CD4+ cell count [cells/mm^3] at baseline (range)	642 (163 to 1737)	688 (114 to 2929)
	Median change from baseline in CD4+ cell count at Week 48	5 (-622 to 692)	-8 (-1049 to 1525)

Based on Table 18 of the CS[1]
ATLAS-2M = Antiretroviral Therapy as Long-Acting Suppression Q2M, CD = cluster of differentiation, CS = company submission; Q1M = given every 1 month, Q2M = given every 2 months

ERG comment: No data were provided for the comparison between CAB LA + RPV LA (Q1M or Q2M) vs. ART therapy. However, this outcome was included in the ITC (see sections 3.3 and 3.4) for risk difference estimate in the indirect comparison between CAB LA + RPV LA (Q2M) and ART therapy.

3.2.5.3 Treatment-emergent resistance

Treatment-emergent resistance was included in the NICE scope, but not covered by the CS. No rationale was provided for the reasons of not including this outcome in the submission.

ERG comment: Based on the WHO HIV drug resistance report 2019, *"HIV drug resistance (HIVDR) is caused by one or more changes (mutation/s) in the genetic structure of HIV that affects the ability of a specific drug or combination of drugs to block replication of the virus. All current antiretroviral (ARV) drugs, including newer classes, are at risk of becoming partly or fully inactive because of the emergence of drug-resistant virus"*.[52] In the ATLAS-2M, CVF was defined as *"rebound as indicated by two consecutive plasma HIV-1 RNA levels ≥200 c/mL after prior suppression to <200 c/mL"*.[41] Furthermore, the CSR of ALTAS-2M states: *"For all participants who meet CVF, baseline*

and suspected virologic failure plasma samples with HIV-1 RNA level ≥200 c/mL will be analyzed in an attempt to obtain genotype/phenotype data on as many samples as possible. (…) Participants may continue to receive study drug at the discretion of the investigator until results of resistance testing are available at which time the participant must be discontinued from the study".[41] Table 13 of the CS states that 10 participants (eight in CAB LA + RPV LA [Q2M] and two in CAB LA + RPV LA [Q1M]) had CVF, but no more details on the results of any genotype/phenotype testing was provided in the CS, thus, the outcomes was not covered.[1]

3.2.5.4 Adherence to treatment regimen

The CS reported long-term data from the FLAIR study.[1] CAB LA + RPV LA (Q2M) was associated with high adherence rate of 97% at week 96 with injection given within the +/- seven day window.

The long-term data from the LATTE-2 study stating high adherence (98%) to treatment with CAB LA + RPV LA with the injections received within the +/- seven day window. Similarly, at week 256, CAB LA + RPV LA treatment was associated with high rates of adherence, i.e. 96% of injections within the dosing window across both dosing regimens, i.e. Q1M and Q2M.

ERG comment: The ERG highlights that the CS did not provide any evidence for this outcome from the trials of interest, i.e. ATLAS and ATLAS-2M.

3.2.5.5 AIDS-defining events

AIDS-defining events were included in the NICE scope, but not covered by the CS. No rationale was provided for the reasons of not including this outcome in the submission.

ERG comment: The company was asked to provide information if this outcome was included in the SLR. For more information on the company's response please see section 3.1.2.5.

3.2.5.6 Mortality

The CS reported the results for the disease progression or death from the ATLAS-2M trial. Disease progression was defined as a progression from baseline CDC stage 1 or stage 2 to CDC stage 3 at any time during the Maintenance Phase based on the presence of new AIDS-defining conditions and/or lowest value of CD4+ counts and CD4+ percentages of total lymphocytes, per CDC 2014 criteria.[53]

Disease progression rates to CDC stage 3 were similar in both treatment groups through week 48, including participants with dosing beyond week 48, i.e. 14 participants (3%) receiving CAB LA + RPV LA Q1M and 13 (2%) participants in Q2M (including n=1 death due to sepsis unrelated to HIV).

ERG comment: No data were provided for the comparison between CAB LA + RPV LA (Q1M or Q2M) vs. ART therapy.

3.2.5.7 Comorbidities

Comorbidities were included in the NICE scope, but not covered by the CS. The company provided the justification stating: *"Treatment-related comorbidities are not considered as outcomes in the appraisal because with most regimens (including the intervention and the comparators) treatment-related comorbidities are no longer an important feature of treatment and do not generally feature in treatment decision-making".*[1]

ERG comment: For the ERG response, please see section 2.4.

3.2.5.8 HRQoL

In the ATLAS-2M study, 14 items (out of 42) of the HIV/AIDS Targeted Quality of Life (HAT-QoL) instrument related to "life satisfaction", "disclosure worries", and "HIV medication" were used. The results are provided in Table 3.14.

Life satisfaction scores [redacted] and after adjusting for prespecified covariates at weeks 24 and 48. [redacted] between two CAB LA + RPV LA regimens was visible [redacted] Q1M, when compared to Q2M, but the difference [redacted].

[redacted] were visible between two CAB LA + RPV LA treatment regimens (Q1M and Q2M) at [redacted] in results for Medication Concern Score. [redacted] was observed between treatment groups at week 24 for patients with and without prior exposure [redacted] and at week 48 for patients with prior exposure [redacted]). At week 48, [redacted] was reported [redacted] for participants without prior exposure [redacted]).

Scores for disclosure worries [redacted] from baseline to the study endpoints for participants in both treatment groups irrespective of prior exposure to CAB LA + RPV LA. [redacted] was observed between treatment groups at week 24 [redacted] and week 48 [redacted].

In ATLAS and FLAIR, HRQoL was assessed with the 12-item Short Form Health Survey (SF-12; measures general health status and degree of mental health distress). The results are provided in Table 3.15. The CS did not provide comparison between treatment arms for both components of the scale. The CS includes a post-hoc analysis in which SF-12 values were used to derive SF-6D (SF-12) utilities via published algorithm. The results are provided in section B.2.6.2.7 of the CS.[1]

Table 3.14: Change from baseline in life satisfaction, medication concern and disclosure worries score of HAT-QoL by visit (ITT-E population) in the ATLAS-2M study

ATLAS-2M[35]									
			Without prior exposure			Treatment	With prior exposure		
		Treatment	Adjusted Mean CFB (95% CI)	Adjusted Difference (Q2M-Q1M)	p-value (Q2M-Q1M)		Adjusted Mean CFB (95% CI)	Adjusted Difference (Q2M-Q1M)	p-value (Q2M-Q1M)
Life satisfaction	Week 24	Q2M [redacted]	[redacted]	[redacted]	[redacted]	Q2M [redacted]	[redacted]	[redacted]	[redacted]
		Q1M [redacted]	[redacted]			Q1M [redacted]	[redacted]		
	Week 48	Q2M [redacted]	[redacted]	[redacted]	[redacted]	Q2M [redacted]	[redacted]	[redacted]	[redacted]
		Q1M [redacted]	[redacted]			Q1M [redacted]	[redacted]		
Medication concern	Week 24	Q2M [redacted]	[redacted]	[redacted]	[redacted]	Q2M [redacted]	[redacted]	[redacted]	[redacted]
		Q1M [redacted]	[redacted]			Q1M [redacted]	[redacted]		
	Week 48	Q2M [redacted]	[redacted]	[redacted]	[redacted]	Q2M [redacted]	[redacted]	[redacted]	[redacted]
		Q1M [redacted]	[redacted]			Q1M [redacted]	[redacted]		
Disclosure worries	Week 24	Q2M [redacted]	[redacted]	[redacted]	[redacted]	Q2M [redacted]	[redacted]	[redacted]	[redacted]
		Q1M [redacted]	[redacted]			Q1M [redacted]	[redacted]		
	Week 48	Q2M [redacted]	[redacted]	[redacted]	[redacted]	Q2M [redacted]	[redacted]	[redacted]	[redacted]
		Q1M [redacted]	[redacted]			Q1M [redacted]	[redacted]		

Based on Tables 22 to 24 of the CS[1]
Note: Life Satisfaction min score: 0 (none of the time); max score 100 (all of the time)
For participants without prior: Adjusted mean calculated from an ANCOVA model including the covariates: Baseline Score, sex at birth (female, male), age (<50, >=50 years) and race (white, non-white).
For participants with prior: Adjusted mean calculated from an ANCOVA model including the covariates: Baseline Score, sex at birth (female, male), age (<50, >=50 years), race (white, non-white) and prior exposure to CAB + RPV (1 to 24, >24 weeks).
ATLAS-2M = Antiretroviral Therapy as Long-Acting Suppression Q2M, CAB = cabotegravir, CFB = change from baseline, CS = company submission; ITT = intention-to-treat, Q1M = given every 1 month, Q2M = given every 2 months, RPV = rilpivirine

Table 3.15: Treatment difference in SF-12 (physical and mental component) scores – FLAIR and ATLAS

		ATLAS[30]			FLAIR[33]		
		Treatment	**Adjusted Mean (95% CI)**	**Adjusted Difference (95% CI)**	**Treatment**	**Adjusted Mean (95% CI)**	**Adjusted Difference (95% CI)**
Physical component	**Week 24**	CAB + RPV (n= 286)	[redacted]	[redacted]	CAB + RPV (n= 251)	[redacted]	[redacted]
		current ART (n=288)	[redacted]	[redacted]	current ART (n=253)	[redacted]	[redacted]
	Week 48	CAB + RPV (n=288)	[redacted]	[redacted]	CAB + RPV (n=252)	[redacted]	[redacted]
		current ART (n=295)	[redacted]	[redacted]	current ART (n=258)	[redacted]	[redacted]
Mental component	**Week 24**	CAB + RPV (n= 289)	[redacted]	[redacted]	CAB + RPV (n= 251)	[redacted]	[redacted]
		current ART (n=286)	[redacted]	[redacted]	current ART (n=253)	[redacted]	[redacted]
	Week 48	CAB + RPV (n=291)	[redacted]	[redacted]	CAB + RPV (n=252)	[redacted]	[redacted]
		current ART (n=293)	[redacted]	[redacted]	current ART (n=258)	[redacted]	[redacted]

Based on Tables 35 and 36 of the CS[1]

ATLAS = Antiretroviral Therapy as Long-Acting Suppression, ART = antiretroviral therapy, CAB = cabotegravir, CS = company submission; FLAIR = First Long-Acting Injectable Regimen, RPV = rilpivirine, SD = standard deviation

ERG comment:

- The HRQoL in the ATLAS and FLAIR was investigated using different measurement tool (SF-12) than in the ATLAS-2M (14 items of HAT-QoL) which restricts the comparability of the results.
- Only 14 out of 42 items included in HAT-QoL instrument, focused on life satisfaction, disclosure worries and HIV medication, were used in the ATLAS-2M.
- It is unclear what covariates were used to calculate the adjusted mean and difference in SF-12 scores (Physical and Mental Component). There is no comparison between the treatment arms (CAB LA + RPV LA [Q1M] and ART therapy) for the ATLAS and FLAIR studies with regards to SF-12 scores.

3.2.5.9 Other outcomes and information reported in the CS

The CS reported outcomes other than those included in the NICE scope (see section 2.4) and the results can be found in the CS, as detailed in Table 3.16.[1] The dosing schedule of the trials providing supporting evidence, i.e. LATTE, LATTE-2 and POLAR, is provided in Table 3.17.

Table 3.16: Other outcomes reported in the CS, but not included in the NICE scope

Outcome (measurement tool)	Study	Section in the CS
Treatment satisfaction (HIVSTQ status and change version)	Pooled ATLAS and FLAIR ATLAS-2M	B.2.6.1.12.1, B.2.6.1.12.2, B.2.6.2.7 B.2.6.2.8
Treatment acceptance (general domain of the ACCEPT)	Pooled ATLAS and FLAIR ATLAS-2M	B.2.6.1.12.3, B.2.6.2.7
Treatment preference (NR; a 3-item questionnaire)	ATLAS & FLAIR ATLAS-2M	B.2.6.1.12.4 B.2.6.2.8
Perception of injection (the PIN questionnaire)	ATLAS-2M	B.2.6.1.12.5

ACCEPT = Chronic Treatment Acceptance Questionnaire, ATLAS = Antiretroviral Therapy as Long-Acting Suppression, ATLAS-2M = Antiretroviral Therapy as Long-Acting Suppression Q2M, CS = company submission; FLAIR = First Long-Acting Injectable Regimen; HIVSTQ = HIV Treatment Satisfaction Questionnaire (change version); PIN = Perception of Injection

Table 3.17: Overview of the dosing schedule in the supporting clinical effectiveness trials for CAB LA + RPV LA

Study (phase; comparison)		**LATTE** (2b; Q1M vs. EFV/NRTIs)			**LATTE-2** (2b; Q1M vs. Q2M vs. 3TC/ABC/CAB*)					**POLAR** (2b; Q2M vs. DTG/RPV)		
length/drug		**length (weeks)**	**CAB LA (Q1M)**	**RPV LA (Q1M)**	**length (weeks)**	**CAB LA (Q1M)**	**CAB LA (Q2M)**	**RPV LA (Q1M)**	**RPV LA (Q2M)**	**length (weeks)**	**CAB LA (Q2M)**	**RPV LA (Q2M)**
induction phase		24	oral 10, 30, or 60 mg + ABC/3TC or TDF/FTC	-	20	oral CAB 30mg + ABC/3TC		oral 25 mg (last 4 weeks)		LATTE patients with ≥312 weeks of treatment	oral 30 mg	oral 25 mg
maintenance phase	loading dose 1 (within 2h from final oral dose)	72	oral 10, 30, or 60 mg	oral 25 mg	96	800 mg	800 mg	600 mg	900 mg	NR	600 mg	900 mg
	loading dose 2 (4 weeks after dose 1)					-	600 mg	-	-		-	-
	thereafter					400 mg (every 4)	600 mg (every 8)	600 mg (every 4)	900 mg (every 8)		600 mg (every 8)	900 mg (every 8)
extension phase		onwards (open label)	oral 30 mg	oral 25 mg	onwards	400 mg (every 4)	400 mg (every 8)	600 mg (every 4)	600 mg (every 8)	-	-	-

Based on Table 5 of CS[1]

* patients in the comparator arm were able to switch to intramuscular CAB LA + RPV LA after the maintenance phase and if eligible (oral 3TC/ABD/CAB for 4 weeks; for Q1M 1st loading dose: CAB LA 600 mg/RPV LA 900 mg; 2nd onwards every 4 weeks: CAB LA 400 mg/RPV LA 600 mg and Q2M 1st and 2nd loading dose: CAB LA 600 mg/RPV LA 900 mg and onwards every 8 weeks CAB LA 600 mg/RPV LA 900 mg)

3TC/ABC/CAB = Lamivudine/Abacavir/Cabotegravir; CAB = cabotegravir; CS = company submission; DTG = dolutegravir; EFV = efavirenz; FTC = emtricitabine; LA = long-acting; LATTE = Long-Acting antireTroviral; Treatment Enabling; LATTE-2 = Long-Acting antireTroviral Treatment Enabling-2; NRTI = nucleoside reverse transcriptase inhibitor; POLAR = Oral (PO) to Long-Acting (LA) Rollover; Q1M = given every 1 month; Q2M = given every 2 months; RPV = rilpivirine; TDF = tenofovir disoproxil fumarate

3.2.6 Safety results

This section considers the information about adverse events provided in the CS.[1] The overall summary of adverse events (AEs) for ATLAS-2M is summarised in Table 3.18. The proportion of patients in ATLAS-2M experienced similar numbers of any AEs or drug-related AEs in both treatment arms and slight increase in number of any grade 2 to 5 AEs in CAB LA + RPV LA (Q1M) arm. The summary of non-injection and injection site AEs for pooled sample of ATLAS and FLAIR is summarised in Table 3.19. For non-injection site reaction AEs, substantially more patients in the CAB LA + RPV LA (Q1M) experienced any AE or drug-related AE when compared to current ART arm. No comparable data exist for injection site reaction (ISR) AEs for CAB LA + RPV LA (Q1M) and ART therapy. It is unclear if data from Tables 3.18 and 3.19 is comparable; no overall summary of AEs was reported for pooled ATLAS and FLAIR.

The CS reported that in ATLAS-2M only 4% and 6% of ISRs lasted more than 14 days in CAB LA + RPV LA Q2M and Q1M arm, respectively. However, substantially more patients in CAB LA + RPV LA (Q1M) arm of pooled ATLAS and FLAIR experienced ISRs of >14 days (17%; Table 3.18). It should be noted that some patients included in ATLAS-2M study were previously participating in ATLAS study (CAB LA + RPV LA [Q1M] arm) which could impact the length of ISRs. Similar number of grade 3 ISRs (pooled ATLAS and FLAIR, Q1M arm: 4%; ATLAS-2M, Q2M: 2% or Q1M: 2%) were reported in the CS[1] with small number leading to study discontinuation (pooled ATLAS and FLAIR, Q1M arm: 1%; ATLAS-2M, Q2M: 1% or Q1M: 2%). The company highlighted that based on the data from ATLAS-2M, events of injection site abscess (drug-related SAE in the Q2M group), pyrexia and body temperature increase (drug-related grade 3 AEs in the Q2M group), fatigue (drug-related grade 3 AE in the Q1M group) and transaminase increase (drug-related grade 3 AE in the Q2M group); associated with possible drug-induced liver injury during oral lead in were observed and are included in the labelling for CAB LA + RPV LA.

The summary of common AEs (≥5% in either arm) of ATLAS-2M is summarised in Table 3.20. The information was not reported for pooled sample of ATLAS and FLAIR studies. The Q1M arm of ATLAS-2M experienced slightly higher frequency of injection site nodule, upper respiratory tract infection, pyrexia, cough, gastroenteritis, pharyngitis, and fatigue.

The summary of common drug-related AEs (≥1% in either arm) of pooled ATLAS and FLAIR as well as ATLAS-2M is summarised in Table 3.21. Substantially less patients in current ART arm of pooled ATLAS and FLAIR studies experienced any drug-related event. The most often reported common CAB LA + RPV LA related AEs were injection site pain (pooled ATLAS and FLAIR, Q1M arm: 76%; ATLAS-2M, Q2M: 70% or Q1M: 68%), injection site nodule (pooled ATLAS and FLAIR, Q1M arm: 13%; ATLAS-2M, Q2M: 10% or Q1M: 17%) and induration (pooled ATLAS and FLAIR, Q1M arm: 11%; ATLAS-2M, Q2M: 8% or Q1M: 7%).

The CS states that CAB LA + RPV LA was well tolerated in patients included in LATTE-2 and POLAR, however, no further data were provided.[1]

Table 3.18: Overall summary of AEs reported in ATLAS-2M (maintenance phase; safety Population)

Type of AE	ATLAS-2M[34, 35]	
	Q2M (N=522), n (%)	Q1M (N=523), n (%)
Any AE	473 (91)	482 (92)
Drug-related AEs	400 (77)	399 (76)
Any Grade 2 to 5 AEs	272 (52)	287 (55)
Drug-related Grade 2 to 5 AEs	156 (30)	164 (31)
AEs leading to withdrawal	12 (2)	13 (2)
Drug-related AEs leading to withdrawal	8 (2)	11 (2)
Any SAE	27 (5)	19 (4)
Drug-related SAEs	3 (<1)	1 (<1)
Fatal SAEs[a]	1 (<1)	0
Drug-related fatal SAEs	0	0

Based on Table 47 of the CS[1]
[a.] One fatal SAEs due to sepsis as a result of complications of acute pancreatitis, which occurred 98 days after the final injection and was not classed as drug-related
AE = adverse event; ATLAS-2M = Antiretroviral Therapy as Long-Acting Suppression Q2M; CS = company submission; Q1M = given every 1 month; Q2M = given every 2 months; SAE = serious adverse event

Table 3.19: Overall summary of AEs (non-injection and injection site) of the pooled ATLAS and FLAIR studies (maintenance phase; pooled safety population)

Type of AE		Pooled ATLAS + FLAIR[42]	
		Q1M (N=591) n (%)	Current ART (N=591) n (%)
Non-injection site reaction AEs	Any AE	510 (86)	445 (75)
	Drug-related AEs	166 (28)	36 (6)
	Any Grade 3 to 5 AEs	47 (8)	35 (6)
	Any drug-related Grade 3 to 5 AEs	8 (1)	1 (<1)
	AEs leading to withdrawal	17 (3)	9 (2)
	Any SAE	31 (5)	26 (4)
	Drug-related SAEs[a]	1 (<1)	1 (<1)
	Fatal SAEs	0	1 (<1)
	Drug-related fatal SAEs	0	0
Injection site reaction AEs	Number of participants with injections	581 (98)	NA
	Number of participants with ISR event	489 (84)	NA
	Any grade[b]		
	Grade 1	437 (75)	NA
	Grade 2	211 (36)	NA
	Grade 3	22 (4)	NA
	AEs leading to withdrawal/drug withdrawn	6 (1)	NA

Type of AE		Pooled ATLAS + FLAIR[42]	
		Q1M (N=591) n (%)	Current ART (N=591) n (%)
	Maximum duration		
	1-7 days	291 (50)	NA
	8-14 days	95 (16)	NA
	>14 days	101 (17)	NA
	Not applicable	2 (<1)	NA

Based on Tables 50 and 51 of the CS[1]
Notes: Current ART refers to ABC/DTG/3TC in FLAIR. With the exception of the last row, data are presented as n (%). The denominator for all percentages is based on the total number of events. Any injection site reaction reported more than once by the same participant was counted more than once.
[a.] Drug related SAEs were injection site abscess, presyncope, and acute pancreatitis in the Q2M group and hypersensitivity in the Q1M group; [b.] No serious, fatal or Grade 4 or 5 injection site reactions were reported.
AE = adverse event, ART = antiretroviral therapy, ATLAS = Antiretroviral Therapy as Long-Acting Suppression, CS = company submission; FLAIR = First Long-Acting Injectable Regimen, ISR = injection site reaction, NA = not available, Q1M = given every 1 month

Table 3.20: Summary of common AEs (≥5% in either treatment group) in ATLAS-2M (maintenance phase, safety population)

Preferred Term	ATLAS-2M[34, 35]	
	Q2M (N=522) n (%)	Q1M (N=523) n (%)
Any event	473 (91)	482 (92)
Injection site pain	371 (71)	363 (69)
Nasopharyngitis	71 (14)	74 (14)
Injection site nodule	54 (10)	89 (17)
Upper respiratory tract infection	50 (10)	71 (14)
Injection site induration	41 (8)	39 (7)
Injection site discomfort	36 (7)	41 (8)
Pyrexia	28 (5)	44 (8)
Headache	35 (7)	36 (7)
Diarrhoea	33 (6)	37 (7)
Injection site swelling	32 (6)	27 (5)
Back pain	28 (5)	29 (6)
Injection site pruritus	27 (5)	25 (5)
Cough	17 (3)	29 (6)
Fatigue	13 (2)	25 (5)
Gastroenteritis	16 (3)	28 (5)
Pharyngitis	16 (3)	28 (5)

Based on Table 48 of the CS[1]

Preferred Term	ATLAS-2M[34, 35]	
	Q2M (N=522) n (%)	Q1M (N=523) n (%)

ATLAS-2M = Antiretroviral Therapy as Long-Acting Suppression Q2M; CS = company submission; Q1M = given every 1 month; Q2M = given every 2 months

Table 3.21: The summary of common drug related AEs (≥1%) in treatment groups of ATLAS-2M and pooled ATLAS and FLAIR studies (maintenance phase; safety population)

Preferred Term	Pooled ATLAS + FLAIR		ATLAS-2M[35]	
	Q1M (N=591) n (%)	Current ART (N=591) n (%)	Q2M (N=522) n (%)	Q1M (N=523) n (%)
Any drug-related event	491 (83)	36 (6)	[redacted]	[redacted]
Injection site pain	448 (76)	0	[redacted]	[redacted]
Injection site nodule	79 (13)	0	[redacted]	[redacted]
Injection site induration	66 (11)	0	[redacted]	[redacted]
Injection site discomfort	NA	NA	[redacted]	[redacted]
Injection site pruritus	23 (4)	0	[redacted]	[redacted]
Pyrexia	24 (4)	0	[redacted]	[redacted]
Injection site erythema	24 (4)	0	[redacted]	[redacted]
Asthenia	13 (2)	0	[redacted]	[redacted]
Injection site bruising	16 (3)	0	[redacted]	[redacted]
Headache	25 (4)	4 (<1)	[redacted]	[redacted]
Dizziness	9 (2)	1 (<1)	[redacted]	[redacted]
Chills	4 (<1)	0	[redacted]	[redacted]
Diarrhoea	7 (1)	2 (<1)	[redacted]	[redacted]
Fatigue	15 (3)	5 (<1)	[redacted]	[redacted]
Injection site warmth	14 (2)	0	[redacted]	[redacted]
Malaise	7 (1)	0	[redacted]	[redacted]
Body temperature increased	12 (2)	0	[redacted]	[redacted]
Injection site haematoma	10 (2)	0	[redacted]	[redacted]
Nausea	15 (3)	6 (1)	[redacted]	[redacted]
Pain	5 (<1)	0	[redacted]	[redacted]
Influenza like illness	5 (<1)	0	[redacted]	[redacted]
Back pain	NA	NA	[redacted]	[redacted]
Insomnia	8 (1)	1 (<1)	[redacted]	[redacted]
Injection site swelling	44 (7)	0	[redacted]	[redacted]
Myalgia	10 (2)	1 (<1)	[redacted]	[redacted]
Abnormal dreams	7 (1)	2 (<1)	[redacted]	[redacted]
Anxiety	8 (1)	1 (<1)	[redacted]	[redacted]

Preferred Term	Pooled ATLAS + FLAIR		ATLAS-2M[35]	
	Q1M (N=591) n (%)	Current ART (N=591) n (%)	Q2M (N=522) n (%)	Q1M (N=523) n (%)
Creatinine renal clearance decreased	4 (<1)	3 (<1)	[redacted]	[redacted]
Depression	3 (<1)	1 (<1)	[redacted]	[redacted]
Vitamin D deficiency	3 (<1)	1 (<1)	[redacted]	[redacted]

Based on Table 49 of the CS[1] and the company's response to question B9 of the Clarification Letter[2]
ATLAS = Antiretroviral Therapy as Long-Acting Suppression; ATLAS-2M = Antiretroviral Therapy as Long-Acting Suppression Q2M, CS = company submission; FLAIR = First Long-Acting Injectable Regimen, NA = not available, Q1M = given every 1 month, Q2M = given every 2 months

ERG comment:

- In the request for clarification, the company was asked to provide more details on the differences in drug-related AEs for ATLAS and FLAIR.[11] The company's response (question B9) included separate results for ATLAS and FLAIR studies as well as pooled results.[2] Only the latter were included in Table 3.21. Considering ATLAS and FLAIR separately, more drug-related AEs were reported in FLAIR (n=28 ([10%]) compared with ATLAS (n=8 [3%]).
- It is unclear if the overall summary results from ATLAS-2M and pooled ATLAS and FLAIR (Tables 3.18 and 3.19) are comparable. No overall summary of AEs for pooled ATLAS and FLAIR studies was reported.
- The summary results of common AEs (≥5% in either arm) were not reported for pooled ATLAS and FLAIR studies.
- Overall, the majority of participants in trials reported ISR related to injection of CAB LA + RPV LA, however, there were mostly mild AEs (grade 1 or 2). A small number of grade 3 AEs resulted in discontinuation of study drug. Substantially less patients in current ART arm of pooled ATLAS and FLAIR studies experienced any drug-related event.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The company reported an indirect treatment comparison (ITC), using data from the pooled ATLAS and FLAIR studies[30-33] and the ATLAS-2M study[34, 35]. The main outcome in the ITC was viral suppression of the HIV-1 virus at 48 weeks, defined as having <50 copies of HIV-1 RNA copies/ml, though other outcomes were assessed. The aim of the ITC was to compare CAB + RPV LA Q2M with *"current ART"*, using CAB + RPV LA Q1M as an intermediate treatment.

ERG comment: There is likely a high enough degree of similarity in the ATLAS-2M and ATLAS/FLAIR patient populations and treatment arms that the ITC could provide meaningful results, in the absence of a direct comparison between CAB + RPV LA Q2M and *"current ART"*. Additionally, the ERG believes use of non-inferiority trials to conduct the ITC is justified as the aim of the ITC is to assess relative efficacy of *"current ART"* and CAB + RPV LA Q2M. However, there remain two main issues with the ITC, namely regarding differences in comparators (see below) and the interpretation of the ITC (see section 3.4).

While the ATLAS and FLAIR studies both included CAB + RPV Q4W as the treatment arm, the comparator arms were different: continued ART therapy (two nucleoside reverse transcriptase

inhibitors (NRTIs) plus an integrase strand transfer inhibitor (INSTI), NNRTI, or a protease inhibitor (PI)) in ATLAS and dolutegravir (DTG) + abacavir (ABC) + lamivudine (3TC) in FLAIR. Throughout the CS, the company references the FLAIR comparator arm as *"current ART"*, which the ERG considers to be erroneous: all participants of FLAIR were commenced on DTG + ABC + 3TC at the beginning of a 20-week induction phase, i.e. patients in FLAIR are not on *"current ART"* but a specific ART that may have been different from their previous ART.

Therefore, the implicit assumption in pooling ATLAS and FLAIR patients is that there is no meaningful difference in treatment outcomes between the *"current ART"* received by patients in ATLAS and DTG + ABC + 3TC. Given this difference in comparator arms and appreciating any other difference between the ATLAS and FLAIR populations (including treatment regimens), these studies should not have been pooled to give a single patient population, but rather analysed as two separate studies using meta-analysis.

Additionally, it is uncertain whether the comparator in the ITC can be described as *"current ART"*, given almost half of the patients in this arm were potentially changed to DTG + ABC + 3TC from a different ART.

Furthermore, the use of *"current ART"* has the implicit understanding that all current antiretroviral therapies for HIV have similar efficacy, otherwise a full network meta-analysis (NMA) would be warranted to compare the efficacy of cabotegravir to all other ART. The company states in section B.2.9.3.1 of the company submission that *"it is not anticipated that these therapies would have different efficacy to the pooled oral ARTs assessed during ATLAS and FLAIR. On the contrary, clinicians consulted for the submission confirm that for the purposes of clinical decision-making, all modern approved ART regimens are assumed to have equivalent efficacy. This is supported by recommendations from relevant clinical guidelines (outlined in Section B.1.3.4.3) and the clinical evidence. Hence, all available evidence supports the assumption of comparable effectiveness between comparators of interest and the ATLAS/FLAIR ART arm"*.

Given the very high efficacy of all current ART, the ERG has no specific issues with this statement and as such believe the use of a match-adjusted indirect comparison (MAIC) without a full NMA is likely justified in this case. However, should the efficacy of ART used in the NHS be shown to be different to the ART used in ATLAS/FLAIR, then a NMA would be indicated.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

The ITC *"was designed to estimate the relative efficacy and uncertainty between CAB LA + RPV LA and standard of care"*.[2] Therefore, the ITC was not designed to test whether CAB + RPV LA Q2M was non-inferior to *"current ART"*, but the company refers to the results as showing that CAB + RPV LA Q2M was, in fact, non-inferior or not different to *"current ART"*, for example *"As previously described, an ITC was undertaken for CAB LA + RPV LA Q2M versus daily oral ART regimens, and demonstrates that the efficacy of CAB LA + RPV LA Q2M is not different to the oral ART regimens in the ATLAS and FLAIR studies"*.[54] These statements are factually incorrect.

The ERG believes the issue stems from the finding from the ITC that there is no statistically significant difference between CAB + RPV LA Q2M and *"current ART"* in terms of viral suppression at 48 weeks. This finding alone is insufficient to draw conclusions about non-inferiority: rather, the effect estimate and 95% confidence interval (CI) should be interpreted, as with the ATLAS/FLAIR studies where the non-inferiority margin was 4%. For viral suppression, the relative risk (RR) of CAB + RPV LA Q2M relative to *"current ART"* was 1.01 (95% CI 0.95 to 1.06), the risk difference (RD) was 0.5% (95%

CI -4.40% to 5.3%), and the odds ratio (OR) was 1.04 (95% CI 0.49 to 2.22). Given viral suppression was achieved in 92% to 94% of all patients in ATLAS/FLAIR and ATLAS-2M, the CIs are relatively imprecise (and above the non-inferiority margin for ATLAS/FLAIR), indicating that CAB + RPV LA Q2M could be substantially (4% to 5%) worse at maintaining viral suppression than *"current ART"*, though it could also be substantially better (by the same amount). As the ITC is imprecise, non-significance cannot be interpreted as non-inferiority, only imprecision. From the ITC, we believe the interpretation should be that there is no current evidence that CAB + RPV LA Q2M is inferior to *"current ART"*, and that we cannot be certain that CAB + RPV LA Q2M is non-inferior to *"current ART"*.

Appendix L of the company submission states that *"a head-to-head study assessing non-inferiority in efficacy of CAB + RPV Q8W [LA Q2M] versus bictegravir/emtricitabine/tenofovir alafenamide is currently planned"*.[54] This planned study would ideally provide evidence of the non-inferiority or otherwise of CAB + RPV LA Q2M.

3.5 Additional work on clinical effectiveness undertaken by the ERG

No additional work was conducted by the ERG.

3.6 Conclusions of the clinical effectiveness section

The participant selection criteria applied in the review were slightly broader than those reflected in the licensed indication information for CAB LA + RPV LA. The ERG did not see this as a threat to the validity of the review. Study selection was restricted on the basis of language (English language reports only), date (publication year 2000 onwards only) and study design (case-control studies were excluded). The ERG suggest that these restrictions could have resulted in relevant evidence being missed from the review. However, the extent of the omitted material and its impact on the results of the review are uncertain. Whilst the processes used for study selection and assessing risk of bias were satisfactory, the data extraction approach (extraction by one reviewer and checking by a second reviewer) was not optimal and could have resulted in missing or inaccurate data.

No head-to-head evidence exist for the comparison of CAB LA + RPV LA (Q2M), the regimen that will be used in the UK upon positive response from NICE, and current standard of care, which is some form of oral ART therapy. Instead, the CS provided data for three phase 3 non-inferiority trials, i.e. ATLAS and FLAIR and ATLAS-2M. The pooled results from ATLAS and FLAIR were used to establish non-inferiority of CAB LA + RPV (Q1M) vs. current ART therapy in maintaining virologic suppression. The efficacy and safety of CAB LA + RPV LA (Q2M) versus CAB LA + RPV LA (Q1M) was evaluated in ATLAS-2M. The efficacy and safety of CAB LA + RPV LA (Q2M) vs. ART therapy was therefore estimated via an indirect treatment comparison involving ATLAS-2M and the pooled results of ATLAS and FLAIR. In addition, the results of phase II trials, i.e. LATTE, LATTE-2 and POLAR, were provided as supporting evidence. The ERG agrees that methodology of the trials is appropriate for the disease area. The impact of permitting inclusion of patients with K103N mutation is unclear.

Focusing on the results of the main trials, the analysis demonstrated the non-inferiority of CAB LA + RPV LA (Q1M) vs. ART therapy as well as CAB LA + RPV LA (Q1M) vs. CAB LA + RPV LA (Q2M) in maintaining virologic suppression in participants with HIV-1 infection at week 48 assuming the non-inferiority margin of 4% (primary outcome). Limited evidence allowing the comparison between CAB LA + RPV LA (Q2M) and ART therapy exists for other outcomes defined in the NICE scope (see Tables 2.1 and 3.11) with no information in the clinical effectiveness section regarding treatment-

emergent resistance, AIDS-defining events and comorbidities. The CS presented additional outcomes that were not included in the NICE scope (see Table 3.16).

Considering the safety results, the majority of patients in the trials reported ISR related to injection of CAB LA + RPV LA, however, there were mostly mild AEs (grade 1 or 2). A small number of grade 3 AEs resulted in discontinuation of study drug. However, it was unclear from the CS if the overall summary results from ATLAS-2M and pooled ATLAS and FLAIR are comparable. The summary of common AEs (≥5% in either arm) were not reported for pooled ATLAS and FLAIR studies. The committee will need to decide if the evidence provided by the company is sufficient to demonstrate the safety of CAB LA + RPV LA (Q2M).

The CS highlighted that standard of care (i.e. ART therapy) at the time of recruitment to ATLAS and FLAIR studies might not fully represent currently used regimens in England and Wales. The company stated that the comparators used in ATLAS and FLAIR *"are considered to have comparable efficacy to currently used regimens, given that non-inferiority trials are the norm for ART in HIV"*.[1] No evidence was provided to support this statement.

The ITC did not demonstrate conclusively that CAB + RPV LA Q2M was inferior, non-inferior or superior to *"current ART"*, and the confidence intervals on the main outcome (viral suppression) allow for CAB + RPV LA Q2M to be materially better and worse than *"current ART"*. However, there is likely a high enough degree of similarity in the ATLAS-2M and ATLAS/FLAIR patient populations and treatment arms that, in the absence of a direct comparison between CAB + RPV LA Q2M and *"current ART",* the ITC provides useful information.

4 COST EFFECTIVENESS

4.1 ERG comment on company's review of cost effectiveness evidence

Three systematic literature searches were performed to identify cost effectiveness studies (CS Appendix G); health-related quality of life studies (CS Appendix H); and costs and healthcare resource use studies (CS Appendix I).[18, 19, 55]

The following tables and paragraphs contain summaries and critiques of all searches related to cost effectiveness reported in the CS.

4.1.1 Searches performed for cost effectiveness section.

Appendix G of the CS reported the literature searches used to identify cost effectiveness studies.[18] Searches were conducted on 24 April 2020. A summary of the resources searched is provided in Table 4.1.

Table 4.1: Resources searched for cost effectiveness studies.

Resource	Host/source	Date range	Date searched
Electronic databases			
Embase	Not reported	01 January 2000 to 24 April 2020	24 April 2020
PubMed	-	01 January 2000 to 24 April 2020	24 April 2020
NHS EED	Not reported	01 January 2000 to 24 April 2020	24 April 2020
EconLit	EBSCO	01 January 2000 to 24 April 2020	24 April 2020
Conference proceedings			
BHIVA	https://www.bhiva.org/Conferences-Events	2017-2020	Not reported
NHIVP	https://www.cdc.gov/nhpc/index.html	2017-2020	Not reported
IAS	https://iasociety.org/Conferences	2017-2020	Not reported
CROI	http://www.croiconference.org/	2017-2020	Not reported
HIVDT	http://hivglasgow.org/	2017-2020	Not reported
NICE	http://www.niceconference.org.uk/	2017-2020	Not reported
ISPOR (for economic SLRs only)	https://www.ispor.org/conferences-education/conferences	2017-2020	Not reported
HTA websites			
NICE	Not reported		Not reported
SMC	Not reported		Not reported
AWMSG	Not reported		Not reported
CADTH	Not reported		Not reported

AIDS = acquired immunodeficiency syndrome; AWMSG = All Wales Medicines Strategy Group; BHIVA = British HIV Association; CADTH = Canadian Agency for Drugs and Technologies in Health; CROI = Conference on Retroviruses and Opportunistic Infections; HIV = human immunodeficiency viruses; IAS = International AIDS Society; NHS EED = NHS Economic Evaluation Database; HIVDT = HIV drug therapy; ISPOR = International Society for Pharmacoeconomics and Outcomes; NHIVP = National HIV Prevention;

Resource	Host/source	Date range	Date searched
NHS = National Health Service; NICE = National Institute for Health and Care Excellence; SLR = systematic literature review; SMC = Scottish Medicines Consortium			

ERG comment:

- The selection of databases searched was satisfactory. The database name and date searched were provided. The host platform was not provided for all databases except EconLit (EBSCO). The company reported searching NHS EED and EconLit but did not provide the full search strategies. Full details of the NHS EED and EconLit searches were provided in response to the ERG clarification letter.[2]
- The NHS EED database is no longer updated, having ceased in March 2015, and was probably not worth searching.
- Conference proceedings were searched. Full details of the conferences searched, search strategies or search terms used, and results were not reported in the CS. Further details of the conference proceedings searches were provided in response to the ERG clarification letter, including the methods used to search abstract books and the search terms used.[2]
- HTA organisation websites were searched, but details of the search terms used, dates of searches, and results were not reported in the CS. Full details of the HTA searches were provided in response to the ERG clarification letter, including an explanation that *"the relevant HTA documents were used to review the reference list for each SLR, with a view to identify any potential trials not captured through the database searches"*.[2]
- The intervention facet of search terms only included generic antiretroviral drug terms. There were no named drugs, including the two of specific interest to this submission: cabotegravir and rilpivirine.
- The inclusion of more synonyms would have improved the search strategies and their sensitivity, particularly in the population, intervention and disease stage search facets.
- The ERG was concerned that limiting the searches to English language may have introduced potential language bias. Current best practice suggests that whenever possible review authors should attempt to identify and assess for eligibility all possibly relevant studies irrespective of language of publication[5] and that research related to language bias supports the inclusion of non-English studies in systematic reviews.[6-8] In response to the ERG clarification letter, the company replied that *"given the high volume of evidence gathered when applying the English language only limit, expanding the search to other languages was very unlikely to bring new evidence which would diverge from the overall picture drawn from the studies in English language"*.[2]
- Study design search filters were included for economic studies. The search strategies grouped each facet under a heading: Population, Interventions of interest and Study type. The Study type heading included in brackets, SIGN. This suggests that the economic filters used were based on the SIGN search filters (https://www.sign.ac.uk/what-we-do/methodology/search-filters/). However, in the methods section the CS stated that *"search filters were adopted from previously used filters, CRD filters and those used in other HTA publication"*. It is good practice to indicate whether published search filters were used (as originally designed or modified), but it would have been more transparent and helpful if the search filters had been cited and more detail provided in the methods section.[9] The economic study design filters did not match those provided on the SIGN website.
- The 'Exclusion' facet of search terms included 'controlled clinical trials' and 'observational study'. By excluding these studies there was a good chance the searches missed studies where an RCT and economic evaluation occurred in tandem, or where clinical data were used in the economic evaluation. Furthermore, the exclusion facet heading had SIGN in brackets suggesting that this is

where the facet was derived from, but neither of the MEDLINE and Embase economic filters have any exclusion terms. Only the CINAHL economic search filter has exclusion terms, none of which were used in the CS search strategies.

- Truncation was used inconsistently throughout, and proximity operators were only occasionally used. Better use of these powerful search tools would have enhanced the search strategies, making them more sensitive and may have identified more potentially useful studies. There were numerous redundant search terms throughout the strategies, as well as inconsistent use of field tags, e.g. title, abstract.
- The searches were limited by date from 2000 to 2020. No reason was given for this decision in the CS. In response to the ERG clarification letter the company explained that *"given the high volume of evidence gathered applying the date filter, expanding the search to studies over 20 years old was very unlikely to bring new evidence which would diverge from the overall picture drawn from the studies published in 2000-2020. Further, HIV regimens have been continually developing since the advent of highly-active ART in 1995; thus, studies of treatment regimens more than 20 years old are unlikely to be representative of modern clinical practice"*.[2]
- The searches were conducted in April 2020. An update of the searches immediately prior to submission to NICE would have been appropriate and could have identified potentially relevant records published since April 2020.

Appendix H of the CS reported the literature searches used to identify health-related quality of life (HRQoL) studies.[19] Searches were conducted on 5 May 2020. A summary of the resources searched is provided in Table 4.2.

Table 4.2: Resources searched for HRQoL studies

Resource	Host/source	Date range	Date searched
Electronic databases			
Embase	Embase interface	01 January 2000 to 05 May 2020	5 May 2020
PubMed	-	01 January 2000 to 05 May 2020	5 May 2020
NHS EED	University of York interface	01 January 2000 to 05 May 2020	5 May 2020
Conference proceedings			
BHIVA	https://www.bhiva.org/Conferences-Events	2017-2020	Not reported
NHIVP	https://www.cdc.gov/nhpc/index.html	2017-2020	Not reported
IAS	https://iasociety.org/Conferences	2017-2020	Not reported
CROI	http://www.croiconference.org/	2017-2020	Not reported
HIVDT	http://hivglasgow.org/	2017-2020	Not reported
NICE	http://www.niceconference.org.uk/	2017-2020	Not reported
Clinical trial registries			
ClinicalTrials.gov	https://clinicaltrials.gov		Not reported
WHO ICTRP	http://www.who.int/ictrp/en/		Not reported
EUCTR	http://www.clinicaltrialsregister.eu/		Not reported

Resource	Host/source	Date range	Date searched
HTA websites			
NICE	Not reported		Not reported
SMC	Not reported		Not reported
AWMSG	Not reported		Not reported
CADTH	Not reported		Not reported
In line with the Cochrane Handbook for Systematic Reviews, bibliographies of relevant studies and recent reviews (published 2017-2020) were searched to ensure all relevant studies were identified.[56] AIDS = acquired immunodeficiency syndrome; AWMSG = All Wales Medicines Strategy Group; BHIVA = British HIV Association; CADTH = Canadian Agency for Drugs and Technologies in Health; CROI = Conference on Retroviruses and Opportunistic Infections; EUCTR = European Union Clinical Trials Register; HIV = human immunodeficiency viruses; HIVDT = HIV drug therapy; HRQoL = health-related quality of life; IAS = International AIDS Society; ISPOR = International Society for Pharmacoeconomics and Outcomes; NHIVP = National HIV Prevention; NHS EED = NHS Economic Evaluation Database; NICE = National Institute for Health and Care Excellence; SMC = Scottish Medicines Consortium; WHO ICTRP = World Health Organization International Clinical Trials Registry Platform			

ERG comment:

- The selection of databases searched was satisfactory. The database name and date searched were provided. The host platform was provided for all databases, though it is not clear what 'Embase Interface' referred to.
- The NHS EED database is no longer updated, having ceased in March 2015, and was probably not worth searching. Alternative resources might have been a useful addition to the searches for HRQoL: Cost Effectiveness Analysis (CEA) Registry (www.cearegistry.org) and ScHARRHUD (http://www.scharrhud.org/).
- Conference proceedings were searched. Full details of the conferences searched, search strategies or search terms used, and results were not reported in the CS. Further details of the conference proceedings searches were provided in response to the ERG clarification letter, including the methods used to search abstract books and the search terms used.
- HTA organisation websites were searched, but details of the search terms used, dates of searches, and results were not reported in the CS. Full details of the HTA searches were provided in response to the ERG clarification letter, including an explanation that "*the relevant HTA documents were used to review the reference list for each SLR, with a view to identify any potential trials not captured through the database searches.*"
- Trials registers were searched, but details of the search strategies or search terms used, dates of searches, and results were not reported in the CS. Further details of the trials register searches were provided in response to the ERG clarification letter. It is not clear why trials registers were searched to identify HRQoL data.
- The intervention facet of search terms only included generic antiretroviral drug terms. There were no named drugs, including the two of specific interest to this submission: cabotegravir and rilpivirine. The search strategies might have benefited by not including this facet of terms, searching instead more sensitively for HRQoL studies in HIV/AIDS.
- Study design search filters were included for HRQoL and utilities studies. The search strategies grouped each search facet under a heading: disease, therapy and study design. The study design heading included in brackets, SIGN. This suggests that the study design filters used were based on the SIGN search filters (https://www.sign.ac.uk/what-we-do/methodology/search-filters/).

However, there are no HRQoL/utilities search filters on the SIGN website, so it is not clear where the filters were derived from.

- The NHS EED search included a facet of terms for cost and healthcare utilities. As this is an economics database it was not necessary to include this facet, as this may have resulted in unnecessarily restricting the results retrieved.
- Truncation was used inconsistently throughout, and proximity operators were only occasionally used. Better use of these powerful search tools would have enhanced the search strategies, making them more sensitive and may have identified more potentially useful studies.

Appendix I of the CS reported the literature searches used to identify cost and resource use studies. Searches were conducted on 27 April 2020.[55] A summary of the resources searched is provided in Table 4.3.

Table 4.3: Resources searched for cost and healthcare resource identification, measurement and valuation data

Resource	Host/source	Date range	Date searched
Electronic databases			
Embase	Embase Interface	01 January 2000 to 27 April 2020	27 April 2020
PubMed	-	01 January 2000 to 27 April 2020	27 April 2020
NHS EED	University of York	01 January 2000 to 27 April 2020	27 April 2020
EconLit	Not reported	01 January 2000 to 27 April 2020	27 April 2020
Conference proceedings			
BHIVA	https://www.bhiva.org/Conferences-Events	2017-2020	Not reported
NHIVP	https://www.cdc.gov/nhpc/index.html	2017-2020	Not reported
IAS	https://iasociety.org/Conferences	2017-2020	Not reported
CROI	http://www.croiconference.org/	2017-2020	Not reported
HIVDT	http://hivglasgow.org/	2017-2020	Not reported
NICE	http://www.niceconference.org.uk/	2017-2020	Not reported
ISPOR (for economic SLRs only)	https://www.ispor.org/conferences-education/conferences	2017-2020	Not reported
Clinical trial registries			
ClinicalTrials.gov	https://clinicaltrials.gov		Not reported
WHO ICTRP	http://www.who.int/ictrp/en/		Not reported
EUCTR	http://www.clinicaltrialsregister.eu/		Not reported
HTA websites			
NICE	Not reported		Not reported
SMC	Not reported		Not reported
AWMSG	Not reported		Not reported
CADTH	Not reported		Not reported

Resource	Host/source	Date range	Date searched
Reference lists from relevant studies visually scanned to identify further studies that may have met eligibility criteria. AIDS = acquired immunodeficiency syndrome; AWMSG = All Wales Medicines Strategy Group; BHIVA = British HIV Association; CADTH = Canadian Agency for Drugs and Technologies in Health; CROI = Conference on Retroviruses and Opportunistic Infections; EUCTR = European Union Clinical Trials Register; HIV = human immunodeficiency viruses; HIVDT = HIV drug therapy; HTA = health technology assessment; IAS = International AIDS Society; ISPOR = International Society for Pharmacoeconomics and Outcomes; NHS EED = NHS Economic Evaluation Database; NHIVP = National HIV Prevention; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; SLR = systematic literature review; SMC = Scottish Medicines Consortium; WHO ICTRP = World Health Organization International Clinical Trials Registry Platform			

ERG comment:

- The selection of databases searched was satisfactory. The database name and date searched were provided. The host platform was not provided for EconLit; it was provided for Embase, though it is not clear what 'Embase Interface' referred to; and was reported incorrectly for NHS EED. NHS EED is no longer available via the Cochrane Library, and the search syntax would suggest that the NHS EED search was conducted via the CRD interface.
- The NHS EED database is no longer updated, having ceased in March 2015, and was probably not worth searching.
- Conference proceedings were searched. Full details of the conferences searched, search strategies or search terms used, and results were not reported in the CS. Further details of the conference proceedings searches were provided in response to the ERG clarification letter, including the methods used to search abstract books and the search terms used.[2]
- HTA organisation websites were searched, but details of the search terms used, dates of searches, and results were not reported in the CS. Full details of the HTA searches were provided in response to the ERG clarification letter, including an explanation that *"the relevant HTA documents were used to review the reference list for each SLR, with a view to identify any potential trials not captured through the database searches"*.[2]
- Trials registers were searched, but details of the search strategies or search terms used, dates of searches, and results were not reported in the CS. Further details of the trials register searches were provided in response to the ERG clarification letter.[2] It is not clear why trials registers were searched to identify costs and healthcare resource use data.
- The Intervention facet of search terms only included generic antiretroviral drug terms. There were no named drugs, including the two of specific interest to this submission: cabotegravir and rilpivirine. The search strategies might have benefited by not including this facet of terms, searching instead more sensitively for costs and healthcare resource use in HIV/AIDS.
- Study design search filters were included for cost and healthcare resource use. The search strategies grouped each facet under a heading and the Study design heading included in brackets, SIGN. This suggests that the study design filters used were based on the SIGN search filters (https://www.sign.ac.uk/what-we-do/methodology/search-filters/). It is good practice to indicate whether published search filters were used (as originally designed or modified), and it would have been more transparent and helpful if the search filters had been cited with more detail in the methods section.[9]
- Table 2 of Appendix I reported that PubMed was searched for 'In-process' records, but the search strategy did not include the 'in-process' limit, '*inprocess[sb]*'.[55]

- The NHS EED search included a facet of terms for costs and healthcare resources. As this is an economics database it was not necessary to include this facet, as this may have resulted in unnecessarily restricting the results retrieved.
- The search strategies included a countries of interest facet. It is not clear why this facet was included. The methods sections reported that *"for the purposes of this appendix we report only UK costs and resource use in-line with NICE requirements"*.
- Truncation was used inconsistently throughout, and proximity operators were only occasionally used. Better use of these powerful search tools would have enhanced the search strategies, making them more sensitive and may have identified more potentially useful studies.
- The CS referred to a targeted literature review of adherence to daily oral ART. It was not clear if this targeted literature review was conducted by the company or referred to another publication, as full details of the targeted literature review were not reported. In response to the ERG clarification letter the company provided further details: *"A systematic update of a targeted literature review was undertaken in 2020 assessing the relationship between efficacy and adherence to HIV therapy. The original literature review report has been provided as part of this response (please refer to Appendix A7b).[57] For the purposes of this submission, we collated SLR-identified studies reporting UK adherence but without efficacy data (i.e. excluded from SLR, but relevant to this use); UK-specific adherence data were considered most relevant because adherence has cultural dimensions. These studies were assessed for suitability to inform the economic model. Further information on our examination of the UK studies identified there, and other studies published subsequently, are presented in Appendix A7a."*[2, 58]
- In Section B.4.1.1 (External validity of Cost-Effectiveness Model) it was reported that *"studies to which the economic model's outcomes could be compared were identified from a review of previous cost-effectiveness studies in HIV[59]"*.[1] The studies included in that review were not identified in the CS SLR of cost effectiveness studies as this review specified studies in the UK setting only (Appendix G).[18] There was no limit to UK studies in the search strategy, and although the inclusion criteria did not mention anything, it appears that only UK specific studies were included after the search results had been screened.
- The cost effectiveness model technical report (Appendix P) reports that data sources for validation of the viral transmission module were identified from the clinical efficacy SLR and that other sources of data were identified through a pragmatic targeted literature review.[60] Full details of the pragmatic literature review were not reported. In response to the ERG clarification letter the company provided further details: *"A literature search was performed using predetermined search terms to identify English-language articles that reported on HIV transmission models. This was a targeted review and the database search was restricted to PubMed, with the search limited to publications from 01 January 2008 until 01 January July 2018. Full texts were obtained and reviewed to determine study eligibility based on predefined inclusion and exclusion criteria. Studies identified within this targeted literature review were further used to validate the transmission module"*.[2] The full PubMed search strategy and a detailed table of study characteristics were also provided.

4.1.2 Inclusion/exclusion criteria

In- and exclusion criteria for the reviews on cost effectiveness studies, utilities and costs and resource use are presented in Tables 4.4, 4.5 and 4.6, respectively.

Table 4.4: Eligibility criteria for the cost effectiveness systematic literature review

	Inclusion criteria	Exclusion criteria
Population	• Patients with HIV-1 • Adults (≥ 18 years old)	• Children and young people (under 18 years) • Patients with HIV-2 • Patients without HIV-1
Intervention and comparators	Any intervention for the treatment of HIV-1	• Interventions not aimed at treating HIV-1 (e.g. screening) • Therapies that are not antiretroviral agents
Outcomes	• Model structure and any health economic outcome, including (but not restricted to) QALYs, ICERs, LYG • Methods of modelling adherence in HIV-1 • Resource use and/or cost for the following model inputs: • Antiretroviral therapy (must be specified) • Salvage therapy • Disease management/monitoring • Adverse events • AIDS-defining events	Outcomes of interest not reported
Study design	• Economic evaluation, pharmacoeconomic evaluation, cost-effectiveness study, cost-utility study, cost-benefit study, or cost minimisation study • Studies modelling adherence in HIV will be extracted	Randomised clinical trial, non-randomised clinical trial, prospective study, longitudinal study, retrospective study, guideline, cohort study, case reports, letter, editorial, review, retracted publications
Language restrictions	English language only (studies published in languages other than English but with abstract available in English will be included)	Studies published in languages other than English
Date restriction	Studies published from 1 January 2000 to 24 April 2020	Studies published before 1 January 2000

Based on Table 3 of Appendix G of the CS[18]
AIDS = acquired immunodeficiency syndrome; CS = company submission; HIV = human immunodeficiency virus; ICER = incremental cost effectiveness ratio; LYG = life years gained; QALY = quality adjusted life year

A list of included and excluded cost effectiveness studies can be found in section 2.2 and section 3 of Appendix G of the CS.[18]

Table 4.5: Eligibility criteria for the utility systematic literature review

	Inclusion criteria	Exclusion criteria
Population	• Patients with HIV-1 • Adults (≥ 18 years old)	• Children and young people (under 18 years) • Patients with HIV-2 • Patients without HIV-1

	Inclusion criteria	Exclusion criteria
Intervention and comparators	Any intervention for the treatment of HIV-1	Interventions not aimed at treating HIV-1 (e.g. screening)
Outcomes	Utility, disutility and HRQoL values for relevant model health states and inputs including: • CD4-specific values • AIDS-defining events • Cardiovascular events • Adverse events • Treatment satisfaction	Outcomes of interest not reported
Study design	Studies that report eligible HRQoL/utility values by instruments e.g. EQ-5D, TTO or direct elicitation	Studies that do not report HRQoL/utility values
Language restrictions	English language only (studies published in languages other than English but with abstract available in English will be included)	Studies published in languages other than English
Date restriction	Studies published from 1 January 2000 to 5 May 2020	Studies published before 1 January 2000

Based on Table 4 of Appendix H of the CS[19]
CS = company submission; EQ-5D = European Quality of Life- 5 dimensions; HRQoL = heath-related quality of life; TTO = time trade-off

A list of included and excluded HRQoL studies can be found in section 2.2 and section 4 of Appendix H of the CS.[19]

Table 4.6: Eligibility criteria for the cost and resource use systematic literature review

	Inclusion criteria	Exclusion criteria
Population	• Patients with HIV-1 • Adults (≥ 18 years old)	• Children and young people (under 18 years) • Patients with HIV-2 • Patients without HIV-1 • Animal studies
Intervention and comparators	Any intervention for the treatment of HIV	Interventions not aimed at treating HIV (e.g. screening)
Outcomes	• Costs (direct and indirect) and healthcare resource data for relevant health states • Costs associated with implementation of novel treatment in HIV-1	Outcomes of interest not reported
Study design	Studies that report eligible cost and healthcare resource data	Studies that do not report eligible costs and healthcare resource data
Language restrictions	English language only (studies published in languages other than English but with abstract available in English will be included)	Studies published in languages other than English
Date restriction	1 January 2000 to 27 April 2020	Prior to 1 January 2000

	Inclusion criteria	Exclusion criteria
Other restrictions	Study conducted in the UK, EU, Canada, or Australia	Study conducted outside of the UK, EU, Canada and Australia setting
Based on Table 5 of Appendix I of the CS[55] CS = company submission; EU = European Union; HIV = human immunodeficiency virus; UK = United Kingdom		

A list of included and excluded cost and resource use studies can be found in section 2.2 and section 3 of Appendix I of the CS.[55]

4.1.3 Conclusions of the cost effectiveness review

The CS provides an overview of the included cost effectiveness, utility and resource use and costs studies, but no specific conclusion was formulated. The inclusion/exclusion criteria appear generally appropriate.

4.2 Summary and critique of company's submitted economic evaluation by the ERG

4.2.1 NICE reference case checklist

Table 4.7: NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	According to NICE reference case
Perspective on costs	NHS and PSS	According to NICE reference case
Type of economic evaluation	Cost utility analysis with fully incremental analysis	According to NICE reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	According to NICE reference case
Synthesis of evidence on health effects	Based on systematic review	According to NICE reference case
Measuring and valuing health effects	Health effects should be expressed in quality adjusted life years (QALYs). The EQ-5D is the preferred measure of health-related quality of life in adults.	Health effects were expressed in QALYs, but measured using the SF-36 (HSUVs) and SF-12 (treatment differential)
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	According to NICE reference case
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	SF-36 and SF-12 data was converted to utilities using UK specific scoring algorithms based on representative general population data.[61, 62]

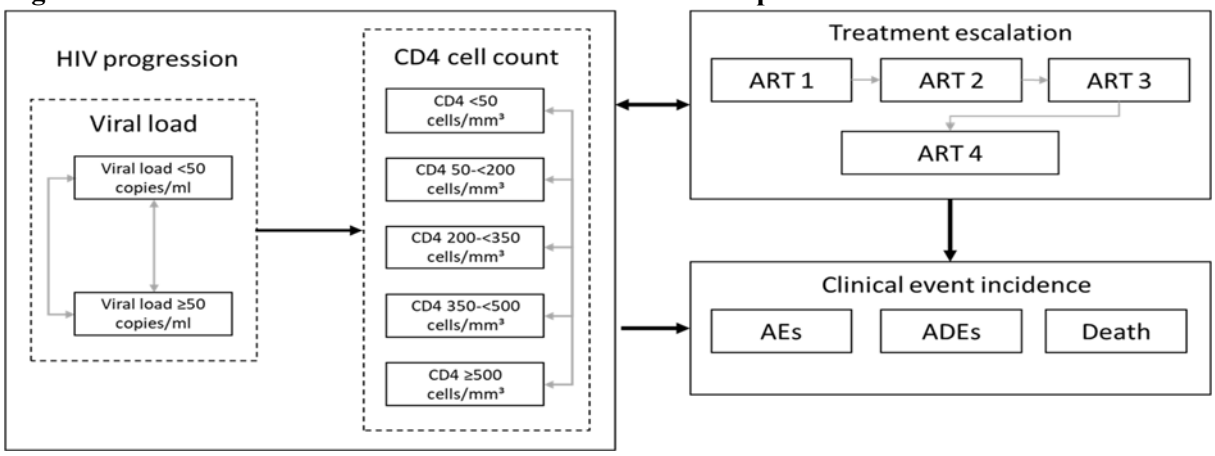
Element of health technology assessment	Reference case	ERG comment on company submission
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	According to NICE reference case
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	According to NICE reference case
Discounting	The same annual rate for both costs and health effects (3.5%)	According to NICE reference case

EQ-5D = European Quality of Life-5 Dimensions; HRQoL = health-related quality of life; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = personal social services; QALY = quality-adjusted life year; UK = United Kingdom

4.2.2 Model structure

The company developed a hybrid cost effectiveness model consisting of a Markov state transition model, a decision tree process, and a disease transmission module. The health states in the model are based on CD4+ cell counts, with five different health states for CD4+ cell counts <50, 50 to <200, 200 to <350, 350 to <500 and ≥500, respectively, and viral load, which refers to the number of plasma HIV RNA copies per ml, of either <50 or ≥50. Death is an absorbing health state. The decision tree process refers to patients switching treatment due to virologic failure (i.e. transitioning from a viral load <50 to ≥50) or non-virologic reasons (i.e. AEs or other non-virologic reasons) for a maximum of four different treatment lines. A schematic of the Markov state transition model and decision tree process is provided in Figure 4.1 below. The disease transmission module serves to capture the outcomes associated with new HIV cases that result from onward transmission. Model cycles have a duration of one month.

Figure 4.1: Markov state transition model and decision tree process schematic



Based on Figure 10 of the CS[1]

AE = adverse event; ADE = AIDS-defining event; ART = antiretroviral therapy; CD = cluster of differentiation; CS = company submission; ml = millilitre; mm = millimetre

All patients start the model with a viral load <50 copies/ml, in line with the requirements for treatment with CAB LA + RPV LA and ATLAS-2M. The starting distribution of patients over the health states based on CD4+ cell count is provided in Table 59 of the CS and in section 4.2.3.[1] In subsequent model cycles, patients may remain in the same CD4+ cell count-based health state or transition to a different

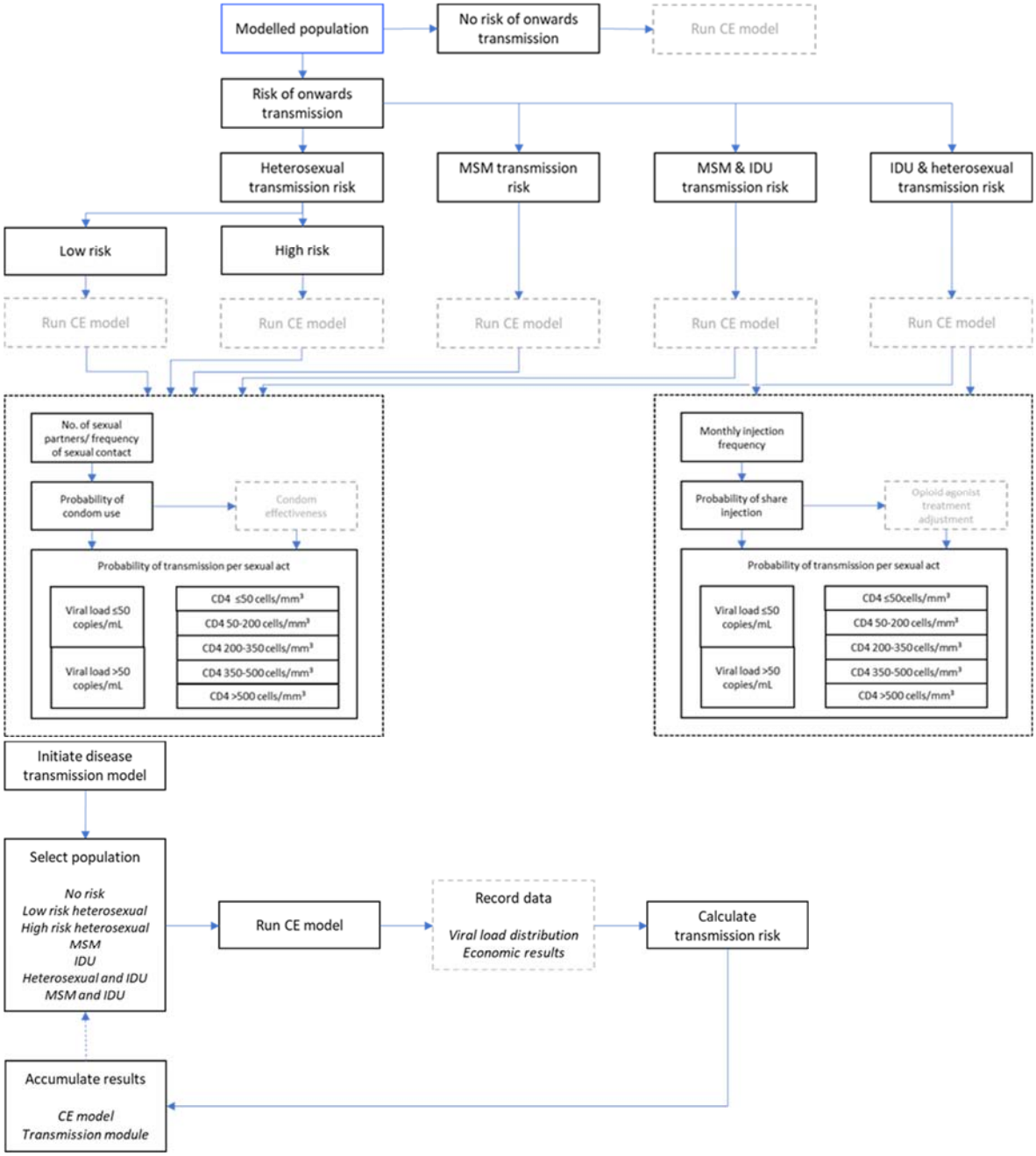
CD4+ cell count-based health state in accordance with the efficacy profile of their current treatment line. The development of viral resistance is modelled as a reduction in efficacy from the second line onwards for patients who switch treatment due to virologic failure, termed a failing switch, in comparison to those who switch for non-virological reasons, termed a stable switch.

Patients who switch treatment start their new treatment in the same CD4+ cell count-based health state as they were in during the previous model cycle. Patients who switch treatment due to virologic failure start their new treatment with viral load ≥50. In subsequent model cycles, patients who started their second or third treatment line with a viral load ≥50 can experience viral suppression and transition to a health state with a viral load <50 or remain in a health state with a viral load ≥50 for a maximum of three model cycles. Patients who have been in a health state with a viral load ≥50 for three model cycles switch to the next treatment line.

A reduced efficacy profile is assumed for the second and third treatment lines (i.e. the same for both) in comparison to the first treatment line. Clinical experts noted this as an acceptable assumption, but also noted that many patients would not experience a reduction in efficacy after a stable switch. The company therefore performed a scenario analysis that assumed a zero reduction after a stable switch. Once patients enter the fourth treatment line, also called salvage therapy, they remain there for the remainder of the model time horizon. Three different efficacy profiles are used for salvage therapy to reflect reduced efficacy for patients who developed resistance (i.e. experienced virologic failure) to one or more of the prior treatments they received: one for patients who did not develop resistance, one for patients who developed resistance to one prior treatment, and one for patients who developed resistance to two prior treatments. Details on the efficacy profiles that are used for the intervention, comparators and treatment line are provided in section 4.2.6.

The company model also includes an onwards transmission module. Long-acting treatment is assumed to improve adherence, which should decrease the likelihood of sub-optimal viral suppression, and therefore reduce onward disease transmission.[1, 63] The likelihood of onward transmission of HIV is predominantly dependent on the presence of behaviour conducive to disease transmission, e.g. unsafe sexual activity or injection drug use, and individuals' viral load.[1] This aspect is captured in the economic model through a disease transmission module, which utilises effectiveness data estimated through the cost-effectiveness model, alongside disease transmission parameters, to estimate the total number of onward infections attributable to the modelled cohort. Outcomes due to differences in new HIV cases resulting from onward transmission are then incorporated into cost-effectiveness estimates. The model process is shown in Figure 4.2.

Figure 4.2: Disease transmission module flow diagram



Based on Figure 13 of the CS[1]

CD = cluster of differentiation 4; CE = cost effectiveness; CS = company submission; IDU = intravenous drug use; MSM = men who have sex with men

ERG comment: The ERG agrees that the model structure is appropriate to capture all relevant benefits and costs that are associated with the intervention and comparators.

4.2.3 Population

The patient population that is used to inform the cost effectiveness analysis is based on the trial population of ATLAS-2M and consists of adults with virologically suppressed HIV infection (HIV-1 RNA<50 copies/ml) on a stable antiretroviral regimen, without evidence of primary resistance based on the presence of any major known INI or NNRTI resistance-associated mutation, except for K103N which was allowed, and who have not previously switched ART regimen due to virologic failure. This

is in line with the final scope by NICE, except for specifying the allowance of the K103N resistance-associated mutation. In their specification of the population for the decision problem that is addressed in the CS,[1]

The company furthermore added that the relevant patients are those who require a treatment switch due to non-virologic reasons. The latter addition to the specification of the population was not mentioned in the final scope by NICE, and not mentioned as a criterion for eligibility to participate in the ATLAS-2M trial.[17] An estimated [redacted] of the 98% of persons diagnosed with HIV and on ART attending a consultation with their healthcare professional require a treatment switch,[64] with clinical reasons including managing toxicity or intolerance, participants' desire for a reduced pill burden, management of drug-drug interactions, and individual preference.[63, 65]

Only data from patients in ATLAS-2M without prior exposure to CAB + RPV (n=327 or 63% in both treatment arms) were used to inform the analysis. A detailed overview of the baseline characteristics of all patients in ATLAS-2M is provided in Table 14 of the CS.[1] Baseline characteristics that are used to inform the model are provided in Table 58 and Table 59 of the CS,[1] and include a mean age of 42.7 (standard error (SE) 0.49) years, percentage female of 26% (SE 1.92%), and proportions of patients with the following CD4+ cell counts/mm^3: 74.90% (SE 1.90%) ≥500, 18.39% (SE 1.70%) 350 to <500, and 6.70% (SE 1.09%) <350 (the latter patients are all assumed to fall in the 200 to <350 category). No patients were assumed to have a CD4+ cell count/mm^3 of 50 to <200 or <50, and all patients are virally suppressed with a viral load <50 copies per ml, i.e. in line with the requirements for starting the CAB LA + RPV LA treatment regimen at baseline.

ERG comment: The ERG agrees that the patient population that is used to inform the cost effectiveness analysis is in line with the licensed indication and the Final Scope by NICE,[17] except for specifying the allowance of the K103N resistance-associated mutation in ATLAS-2M. As described in section 3.2.3, the presence of this mutation would not affect susceptibility to RPV, however, at least 39% of patients on the ART therapy in the ATLAS study (receiving EFV or NVP) were at risk of developing resistance if they were carriers of K103N mutation.

As discussed in the CS (Section B.2.13.4),[1] the regimens used in ATLAS and FLAIR studies are not fully representative of currently used ART regimens in the UK NHS setting. This can substantially affect the generalisability of the results for the comparison of ART therapy vs. CAB LA + RPV LA (Q2M). The company stated, however, that *"(...) the regimens used as comparators in ATLAS and FLAIR are considered to have comparable efficacy to currently used regimens, given that non-inferiority trials are the norm for ART in HIV"*.[1]

4.2.4 Interventions and comparators

The intervention consists of CAB LA + RPV LA, administered as intramuscular injections Q2M, following a 30-day oral lead-in period and initiation injections. The oral lead-in is given as 30 mg CAB and 25 mg RPV once daily during the first month, initiation injections are given as 600 mg CAB as 1x 3 ml and 900 mg RPV 1x 3 ml during month 2 and month 3 (i.e. one month apart), and continuation injections are given as 600 mg CAB as 1x 3 ml and 900 mg RPV 1x 3 ml from the fifth month onwards once per two months. Injections of CAB LA and RPV LA are administered at separate gluteal injection sites at the same visit.

The relevant comparator treatment regimen consists of the variety of oral ART regimens that are given as second-line (or further) treatment to patients who switched their first-line (or other previous) treatment due to non-virologic reasons related specifically to the challenges of oral therapy. Based on

market data on the types of ART patients are switching to, the company identified relevant comparators using a criterion of ≥2.5% of patients switching to a specific type of ART (Table 4.8). Two exceptions were made to this: Truvada + Tivicay (emtricitabine/tenofovir + dolutegravir), was excluded since it is a low cost regimen and therefore was assumed to be used as first-line treatment (in accordance with NHS England Policy to use lowest cost regimens where clinically appropriate), and Juluca (dolutegravir/rilipivirine) was included (despite <2.5% switching to it) since clinician feedback indicated it as a close oral alternative to CAB LA + RPV LA. All possible comparators that were considered are listed in Table 55 of the CS,[1] with the comparators that were identified as relevant shaded in blue. All nine relevant regimens are assumed to have the same ability to maintain virological suppression. However, each regimen may offer different benefits depending on individual need based on personal preference, lifestyle, underlying health risks and co-morbidities. No further information is provided regarding which regimen offers which benefits. The company notes that market data are not available for types of ART switched to by line of therapy, nor for types of ART switched to by reasons related specifically to the challenges of oral therapy.

Table 4.8: Switch share by regimen (market overview for patients switching off stable regimens)

Brand Name	Generic name	Of those survey % by regimen	Included?
Biktarvy	BIC/FTC/TAF	[redacted]	Yes
Symtuza	DRV/Cobi/FTC/TAF	[redacted]	Yes
Dovato or Tivicay + Epivir	DTG/3TC or DTG+3TC	[redacted]	Yes
Delstrigo	DOR/3TC/TDF	[redacted]	Yes
Triumeq	DTG/ABC/3TC	[redacted]	Yes
Odefsey	RPV/FTC/TAF	[redacted]	Yes
Truvada+Tivicay	FTC/TDF+DTG	[redacted]	No
Descovy+Tivicay	FTC/TAF+DTG	[redacted]	Yes
Desovy+Isentress	FTC/TAF+RAL	[redacted]	Yes
Stribild	EVG/c/FTC/TDF	[redacted]	No
Juluca* or Tivicay + Rilpivirine	DTG/RPV or DTG+RPV	[redacted]	Yes
Eviplera	RPV/FTC/TDF	[redacted]	No
Genvoya	EVG/c/FTC/TAF	[redacted]	No
Truvada+Isentress	FTC/TDF+RAL	[redacted]	No
Descovy+DRV/r	FTC/TAF+DRV/r	[redacted]	No
Truvada+DRV/r	FTC/TDF+DRV/r	[redacted]	No
Tivicay + Other	DTG+other	[redacted]	No

Based on Figure 10 of the CS[1]

3TC = lamivudine; ABC = abacavir; BIC = bictegravir; C = cobicistat; CS = company submission; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; EVG = elvitegravir; FTC = emtricitabine; RAL = raltegravir; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

ERG comment: In line with the company's explanation, the ERG is uncertain whether the 'basket of comparators' consists of the treatments that are relevant comparators to CAB LA + RPV LA in the context of the current submission. The ERG is also uncertain whether all included comparator regimens

are relevant for consideration as certain lines of therapy, and whether they are in line with reasons for switching that relate to the specific challenges of oral therapy.

In the clarification phase, the ERG asked the company to provide the option in the model to also include low cost ART regimens in the 'basket of comparators'.[11] The company did not comply with the ERG's request indicating that they strongly believed this would not be appropriate in light of the notion that lower cost regimens are used early in treatment.[2] Furthermore, the company indicated that drug cost per se was not an explicit consideration in deriving the comparators which was illustrated by still having included some low cost regimens. According to the company, the fact that some of the lower cost regimens were switch options in fewer than 2.5% of patients illustrates the point that these are used early on in treatment. In the absence of more information on types of ART switched to by line of therapy or types of ART switched to by reasons related specifically to the challenges of oral therapy, the ERG considers it plausible that with the availability of several low cost regimens a switch could be made from one low cost regimen to another. Since all included oral ART regimens are assumed to have equal efficacy, the uncertainty on this aspect is only relevant in determining the appropriate cost of the comparator. The ERG performed a series of scenario analyses where alternative costs were assumed for the 'basket of comparators' (see section 6.1.3.1).

4.2.5 Perspective, time horizon and discounting

The analysis is performed from an National Health Service (NHS) and Personal Social Services (PSS) perspective, in line with the NICE reference case.[66] The base-case analysis is run until the last patient has died (up to 80 years from model initiation), which represents a lifetime time horizon as per the NICE reference case.[66] All costs and benefits, i.e. life years and QALYs gained, are discounted at 3.5% per annum, which is in line with the NICE reference case.[66] In addition, a scenario analysis is performed using a 1.5% discount rate for costs and benefits (see section 5.2.3.2).

4.2.6 Treatment effectiveness, AIDS-defining events and mortality

Treatment effectiveness is modelled through various efficacy profiles that consist of transition matrices that determine CD4+ cell count-based health state occupancy, probability of viral suppression for those starting a treatment line with a viral load ≥50 HIV RNA copies per ml, probability of discontinuing due to virological failure (i.e. failing switch), and probability of discontinuing due to non-virologic reasons (i.e. stable switch). The ability for maintenance of virological suppression is assumed the same across the treatment regimens contained in the 'basket of comparators' as well as versus CAB LA + RPV LA. However, the development of resistance is modelled as a reduced efficacy profile for second- and third-line treatments in patients who have made a failing switch. The same reduced efficacy profiles are used in second- and third-line treatments for patients who have made either one or two failing switches in first- or second-line treatments, respectively. For the fourth-line treatments, different reduced efficacy profiles are used for patients who have made either one or ≥2 failing switches in previous treatment lines. For patients making one or more stable switches a reduced efficacy profile is used as well, with the same efficacy profile used for second- and third-line treatments for patients who have not made a failing switch in previous treatment lines, and a reduced efficacy profile for the fourth treatment line for patients who have only made stable switches up to that point. The reduction in efficacy is larger in second- and third-line treatment for patients who have made a failing switch compared to those who made one or two stable switches. In the fourth treatment line the reduction in efficacy is smallest for patients who only made stable switches, followed by a larger reduction for patients who have made one failing switch previously, and the largest reduction for patients who made two failing switches previously.

Transition matrices that determine CD4+ cell count-based health state occupancy were estimated using data from the ITC of CAB LA + RPV LA versus oral ART, described in sections 3.3 and 3.4, for the first-line treatments, and data from published articles for the second- to fourth-line treatments. Details regarding the data and their sources used to derive the various transition matrices for each treatment line are provided below.

In general, transition matrices were derived by means of simulating the trial cohort based on available summary statistics as explained in Appendix M of the CS.[67] These simulations were performed in such a way that the initial (i.e. at baseline) CD4+ cell count distribution converges on the distribution at the end of the trial. For this, the initial CD4+ cell count for each patient is drawn from a normal distribution based on the mean and SD CD4+ cell count at baseline. Subsequently, each month a change in CD4+ cell count is sampled from a normal distribution based on the change in CD4+ cell count over 48 weeks. After the cohort of patients is simulated using this approach, an empirical distribution of transitions between CD4+ cell count-based health states is generated to which a multinomial distribution is fitted to generate a matrix of transition probabilities. This process is then repeated based on changes in CD4+ cell counts from week 48 onwards to 96 weeks.

The efficacy profile parameters for all modelled treatment lines are provided in Table 4.9, and the probabilities of virologic and non-virologic discontinuation for all modelled treatment lines are provided in Table 4.10.

4.2.6.1 First-line treatments

Transition matrices for the first treatment line are derived using parameters from the ITC described in sections 3.3 and 3.4, containing data from ATLAS-2M, ATLAS and FLAIR. The transition matrix for the initial 48 week period is derived using data specific to the CAB LA + RPV LA Q2M arm, whereas the subsequent 48 week periods are derived using pooled data from both the CAB LA + RPV LA Q2M arm and the daily oral treatment. The efficacy of CAB-LA + RPV LA is assumed to be equivalent to the comparator regimens. Therefore, the same transition matrices (one for the initial 48 week period and one for the subsequent period) are used for both treatments. The probabilities for discontinuing due to virologic failure and discontinuing due to non-virologic reasons are also assumed to be the same for both treatments.

Table 4.9: Efficacy profile parameters

Therapy line	Treatment arm	Source	Virologic suppression at 48 weeks Mean (SE)	Baseline CD4+ count Mean (SD)	Change CD4+ cell count at 48 weeks Mean (SD)
Initial modelled line	CAB LA + RPV LA	Q2M arm from ATLAS-2M	94.3% (0.77%)	681.8 (259.9)	5.3 (168.62)
	Comparators	Assumed equivalent to Q2M arm from ATLAS-2M			
Second and third modelled line	Stable switch	Baril et al. 2016[68]	74.82% (3.74%)	540.02 (232.46)	69.25 (149.14)
	Failing switch	Kanters et al. 2017[69]	73.78% (3.69%)	168.67 (155.07)	176.35 (149.30)

Therapy line	Treatment arm	Source	Virologic suppression at 48 weeks Mean (SE)	Baseline CD4+ count Mean (SD)	Change CD4+ cell count at 48 weeks Mean (SD)
Fourth modelled line	No ART resistance	Cooper et al. 2008[70] and Steigbigel et al. 2008[71]	71.04% (7.10%)	151.00 (141.00)	119.00 (132.73)
	Resistance to one ART class		60.58% (6.06%)		111.00 (146.31)
	Resistance to two ART classes		50.80% (5.08%)		71.00 (100.78)

Based on Table 60 of the CS[1]
NB: Failing switch refers to people who switch for virologic reasons. Stable switch refers to people who switch for non-virologic reasons.
ART = antiretroviral therapy; CAB LA = cabotegravir long-acting; CS = company submission; RPV LA = rilpivirine long-acting; Q2M = given every 2 months; SD = standard deviation; SE = standard error

Table 4.10: Virologic and non-virologic discontinuations

Therapy line	Treatment arm	Source	Virologic discontinuation at 48 weeks Mean	Non-virologic discontinuation at 48 weeks Mean
Initial modelled line	CAB LA + RPV LA	ATLAS-2M	1.72%	4.02%
	Comparators		1.72%	4.02%
Second and third modelled line	Stable switch	Baril et al. 2016[68]	5.74%	8.39%
	Failing switch	Kanters et al. 2017[69]	16.79%	2.67%
Fourth modelled line	Independent of ART resistance	Cooper et al. 2008[70] and Steigbigel et al. 2008[71]	2.2%	13.0%

Based on Table 61 of the CS[1]
ART = antiretroviral therapy; CAB LA = cabotegravir long-acting; CS = company submission; RPV LA = rilpivirine long-acting

4.2.6.2 Second- and third-line treatments

For patients making a stable switch from their first- and/or second-line treatment, the transition matrices were derived using data from Baril et al. 2016.[68] This data source is a systematic review of the efficacy of switching regimen in virally suppressed patients. Table 23 in the response to the request for clarification provided an overview of the different studies that were identified by Baril et al. 2016 and the data they provide to inform the parameters necessary for estimating the stable switch efficacy profile for second- and third-line treatment.[2] For patients making a failing switch from their first- and/or second-line treatment, the transition matrices were derived using data from Kanters et al. 2017.[69] This data source was identified as the only one from a targeted literature review of network meta-analyses (NMAs) that provided data on patients who switched from their initial treatment due to virologic failure. Table 24 in the response to request for clarification provided an overview of the different studies that were identified by Kanters et al. 2017 and the data they provide to inform the

parameters necessary for estimating the failing switch efficacy profile for second- and third-line treatment.[2]

4.2.6.3 Fourth-line treatments

The efficacy profiles for fourth-line treatments (i.e. salvage therapies), which are different for patients having developed resistance to none, one, or two previous therapies are based on Cooper et al. 2008,[70] and Steigbigel et al. 2008.[71] These were the only papers that the company identified that provide the required data stratified by number of resistance classes in an appropriate patient population.

All transition matrices are provided in Tables 1 to 9 in Appendix M of the CS.[67] These are combined in the model with monthly probabilities of discontinuing due to virologic failure and discontinuing due to non-virologic reasons, and probabilities of viral suppression. As such, they determine the transitions of patients between CD4+ cell count-based health states as well as to subsequent treatment lines with a viral load that is either <50 (i.e. stable switch) or ≥50 (i.e. failing switch) HIV RNA copies per ml.

ERG comment: If the model were implemented following the company's explanation (as provided in the CS,[1] Appendix M,[67] technical report,[72] user guide and in response to the ERG's clarification questions[2]) there would be no difference between treatments regarding how patients transition through the model. This is because the same efficacy profile is used for both the intervention and the comparator. However, it can be seen from the Markov traces in the model that a substantial proportion of patients is switching from their first-line oral ART regimen to the second-line treatment with a viral load of ≥50 HIV RNA copies per ml, already after the first month of treatment.

Using a deductive approach, in absence of any information provided by the company on this aspect, the ERG noticed that the proportion of patients making this failing switch from first- to second-line oral ART corresponds to a monthly probability of non-adherence (i.e. calculated from an assumed 25.6% of patients not meeting a ≥95% adherence cut-off), in addition to the probability of patients discontinuing due to virologic failure and minus the probability of dying. In other words, it appears that the company assumed that all patients with an adherence below 95% experience virologic failure within one month and switch treatment due to virologic failure. No justification, nor any general explanation on this aspect being implemented in the model as such is provided by the company. The ERG considers it implausible that all patients who are less than 95% adherent experience a virologic failure within one month and therefore switch treatment. However, given the emphasis that is placed in the CS on differences in adherence between CAB LA + RPV LA and oral ART regimens the ERG assumes that the lack of explanation and justification for this aspect of the model is an erroneous omission. The ERG has reviewed the literature that the company refers to in relation to the assumptions on adherence, a summary of which is provided below in the ERG comment of section 4.2.6.4.

4.2.6.4 Adherence

An important advantage of CAB LA + RPV LA compared to oral ART regimens that is put forward by the company relates to improved treatment adherence. Provided that patients timely attend appointments with the health care provider to receive their injections, the possibility for suboptimal adherence to daily oral self-administration of ART is removed. In ATLAS-2M, adherence rates were 96-98% at 96 weeks. It is assumed that that adherence in clinical practice will not differ from the adherence observed in a trial setting. The company refers to literature on adherence to oral ART at various occasions in the CS,[1] which indicates that suboptimal adherence (most often defined as adherence below 95%) is common.[73-77] Based on the results from a targeted literature review, data on adherence to oral ART in the UK are sparse and the studies identified indicate that suboptimal adherence occurs in approximately 10-57% of patients.

The company assumed that suboptimal adherence is associated with reduced treatment effectiveness and development of viral resistance that makes viral rebound more likely to occur. [73-76, 78, 79] To model the reduced treatment effectiveness of oral ART due to suboptimal adherence, an attempt was made to quantify the relationship between adherence and viral suppression. The company assumed a linear relationship between individual percentage adherence measured as medication possession ratio (MPR: i.e. a measure of patient-level adherence, not a proportion of patients meeting a predefined threshold of adherence) and the proportion of patients achieving HIV RNA suppression at 6 months from ART. This was based on a straight line showing this relationship in Figure S2 from the supplementary materials for the article by Ross et al. 2015, estimated using data from the VOLTART cohort of patients with HIV from the Ivory Coast,[80] and used to inform the Cost-Effectiveness of Preventing AIDS complications (CEPAC) model.[81] The quantification of the slope and intercept of this line resulted in the following estimates for the linear relationship between adherence and suppression:

Viral suppression = 1.01111 * Adherence – 0.05056

This equation is used to calculate an adjustment factor, which was applied to (multiplied with) the probability of viral suppression estimated from the trial data. The factor was calculated as percentage viral suppression of 70.17% based on assumed adherence of 74.4% for oral ART, as reported in the UK-based SWEET study on oral ART adherence by Cooper et al. 2011, divided by a viral suppression of 96.06% based on perfect (100%) adherence for CAB LA + RPV LA.[82] However, those figures of 74.4% and 100% are the percentage of patients achieving at least 95% adherence as opposed to the average individual percentage adherence, which was the variable on which the relationship was originally estimated in the Ross et al. 2015 study.[81] In the model, viral suppression is only relevant starting from the second-line treatments and onwards since all individuals that enter the model are virally suppressed when they initiate first-line treatment and switch to the next treatment after virological failure.

ERG comment: An underlying assumption of the model is the assumed relationship between treatment adherence and viral suppression. To exemplify the extent to which suboptimal adherence affects viral suppression rates, the company refers on p. 111 of the CS to the findings from a study by Wohl et al. 2019 indicating that patients with an adherence below 95% have a substantially lower viral suppression rate than patients with an adherence of 95% or higher.[1, 79] However, the company did not include the explanation for this result as provided in the article by Wohl et al. 2019 that *"the difference was driven by participants who did not have available data in the analysis window and whose last on-treatment assessment of HIV-1 RNA was less than 50 copies per mL (appendix pp 5–6), rather than any evidence of virological failure"*.[79] In other words, in both treatment arms of the study by Wohl et al. all or nearly all of the patients who were not confirmed to have less than 50 copies per ml were those for whom data was missing.[79] Therefore, this study does not provide any evidence that an adherence below 95% is associated with reduced viral suppression.

On page 112 of the CS, the company repeated the statement that suboptimal adherence is associated with reduced viral suppression with reference to a series of articles. For example, both Bezabhe et al. 2016 and Gordon et al. 2015 indeed report that an optimal adherence is associated with a lower risk of virologic failure.[73, 78] However, the same papers also noted that the threshold for optimal adherence appears to be wider than the commonly used cut-off of ≥95% adherence and that adherence levels of 80-90% may be adequate for viral suppression. Konstantopoulos et al. 2015 did indeed find a trend that lower adherence levels were associated with lower levels of viral suppression, but the differences were not statistically significant.[74] O'Connor et al. 2015 did find statistically significant differences between suboptimal adherence (which was based on a descriptive, self-report measure of adherence) and viral

rebound, but also noted an overall low risk of viral rebound even in patients with suboptimal adherence.[75] O'Connor et al. 2015 also provided some possible explanations for this indicating on the one hand the possibility that episodes of suboptimal adherence or viral rebound were relatively short-lived, and on the other hand the possibility that many modern regimens are successful at adherence levels of 70–80%. Glass et al. 2015 did find a statistically significant association between nonadherence and an increased risk of viral failure.[76]

In summary, it is undisputable that optimal or near optimal adherence is associated with the lowest risk of virologic failure. At the same time, there is considerable uncertainty to what extent a certain degree of suboptimal adherence increases the risk for virologic failure or, in other words, reduces viral suppression. Similar uncertainty exists regarding the use of a cut-off value of ≥95% adherence as a threshold for optimal adherence, with several studies indicating that a substantially lower threshold may be appropriate to assume adequate viral suppression.

The company assumed an adherence level of 74.4% for daily oral ART that is based on a UK-based study by Cooper et al. 2011.[82] This estimate pertains to adherence after 48 weeks on treatment, is the lowest from a declining series over time, and refers to the proportion of subjects that meet the threshold for optimal adherence of ≥95%. In light of what was described in the preceding paragraph, this does not necessarily mean that the remaining 25.6% of patients do not have adequate viral suppression or an increased risk of viral rebound. In addition, the 25.6% of patients with suboptimal adherence also includes patients with missing data (i.e. they were defined as suboptimal adherence) and patients who discontinued treatment. It is important that the figure of 74.4% is interpreted as a proportion of patients that did meet the strict threshold for optimal adherence of ≥95%, and not as an average adherence level.

To quantify the relationship between adherence and viral suppression, the company derived a slope and intercept from a line estimated in the Ross et al. 2015 study.[81] This linear function describes the relationship between individual percentage MPR and the proportion of patients achieving HIV RNA suppression at six months from ART initiation. The ERG has serious concerns regarding the appropriateness of using this function in combination with the adherence figure of 74.4% from Cooper al. 2011, since the latter corresponds to a proportion of patients with optimal adherence of ≥95% which is a different concept to the MPR or individual percentage adherence.[82] The average MPR for ART in the UK is unknown, but if 74.4% is the percentage of patients achieving an MPR above 95%, then the value that should be used as an input, which is the average MPR for all patients, would be 74.4%*average MPR above 95% plus (100-74.4)%*average MPR below 95%. Therefore, the average MPR must be much higher than the 74.4% input into the linear equation to estimate percentage of patients achieving adequate viral suppression. This can be demonstrated by assuming the lowest value of average MPR for those who achieve at least 95% MPR, which is 95%: this implies an average MPR for those who fail to achieve this MPR of only14% in order for average MPR to be 74.4%. Even if the average MPR for those whose MPR is below 95% was as low as 50%, the average MPR for all patients would be 83%, which is quite a bit higher than 74.4%.

The company justifies the validity of the 74.4% adherence estimate by comparing it to the results from the EU Unmet Need Study, in which 26% of UK patients reported *"not taking pills exactly as described sometimes or often"*.[83] The ERG notes that not taking pills to meet an adherence level of ≥95% (i.e. the definition used for suboptimal adherence by Cooper et al. 2011) does not mean the same as not taking pills exactly as described (i.e. the definition used in the EU Unmet Need Study). Therefore, the ERG does not agree that the findings from the EU Unmet Need Study can be used to justify the validity of the findings from the study by Cooper et al. 2011.[82, 83]

The company performed a targeted literature review to identify adherence estimates that pertain to patients from the UK. They found estimates for the prevalence of suboptimal adherence in the UK ranging from 10% to 57%. These values were reported by Sherr et al. 2010 and were based on a multi-clinic study in the UK that included 486 patients and assessed levels of self-reported adherence using a variety of definitions for suboptimal adherence.[84] A value of 10.1% pertains to patients who reported having missed ≥2 doses in the last seven days and a value of 57.2% pertains to patients who reported having missed ≥1 dose or taking ≥1 dose incorrectly in last seven days. The ERG considers taking a dose incorrectly does not mean the same as missing a dose and considers a definition of suboptimal adherence that could plausibly be assumed to be associated with a reduction in viral suppression as most relevant in the current context. As such, the ERG considers the 10.1% estimate based on ≥2 missed doses in the last seven days the most appropriate measure for use in the model, since this would correspond to a level of suboptimal adherence at or below which viral suppression can be assumed to be reduced, i.e. taking into account statements in the literature that is referenced by the company in the CS and reviewed by the ERG above which indicates that adequate viral suppression may still be achieved in patients with certain levels of suboptimal adherence.

In summary, the ERG identified several issues that are related to the company's assumptions on treatment adherence and implementation of adherence in the model:

- Firstly, the assumptions regarding suboptimal adherence are mostly derived from studies that use a measure of adherence that is defined as the proportion of patients who do not meet a predefined adherence level of ≥95%. However, several of the articles that report findings based on this cut-off value indicate that substantially lower levels of adherence are still likely to be associated with adequate viral suppression.
- Secondly, the company uses a value of suboptimal adherence that is defined as described above as an input for an estimated linear relationship between adherence at the individual level and viral suppression. The ERG notes that a proportion of patients not meeting a cut-off value for adherence of ≥95% is an entirely different concept than a measure of adherence that is defined as individual adherence based on MPR, and therefore the two cannot be used interchangeably. As such, the ERG does not consider the use of the estimate by Cooper et al. 2011 as an input for the estimated relationship between MPR and viral suppression appropriate.[82]
- Thirdly, as described in the ERG comment in section 4.2.6.3, it appears (in absence of any explanation provided on this aspect) that the company has used the proportion of patients not meeting an adherence level of ≥95% to model a monthly probability for the transition of patients in first-line treatment to switch to second-line treatment with a viral load of ≥50 HIV RNA copies per ml. The ERG considers that an explanation and justification of this modelling aspect should have been provided in the CS, in particular because it is the sole determinant of differences between intervention and comparator regarding the way patients transition through the model and considers it unlikely that all patients with an adherence below 95% experience viral rebound within one month and immediately switch treatments due to that reason.

In light of these issues, the ERG has used a different reduction in adherence for oral ART compared to CAB LA + RPV LA in their base-case model than the 25.6% that the company used. The ERG considers a value of 10.1% suboptimal adherence that is based on the findings from Sherr et al. 2010 a more appropriate value to use, since it is based on a UK study and defined as a proportion of patients who self-report having missed two or more doses in a time period of one week (i.e. assuming a once daily dosing schedule, that would equate to a cut-off value for optimal adherence of 71%).[84] At such a level of suboptimal adherence the ERG considers it plausible to assumed that viral suppression is no longer adequate. Despite their aforementioned reservations regarding the use of a proportion of patients not

meeting a predefined cut-off value of adherence as an input for the estimated relationship between individual levels of adherence and viral suppression, the ERG agrees to use the value of a 10.1% reduction in adherence as an input to calculate an adjustment factor for viral suppression. By using this value as such, the ERG considers the company's (presumed) implementation of patients with suboptimal adherence switching to a subsequent treatment line with a viral load above 50 copies per ml plausible. To address uncertainty regarding the use of the adherence parameter in the model and to represent a situation where viral suppression is adequate in all patients, i.e. even in those with suboptimal adherence, the ERG has performed a scenario analysis that assumes 100% adherence in all patients so that the maximum viral suppression is assumed for all patients.

4.2.6.5 Disease transmission

The company report in the CS that the transmission module is based on several key assumptions: that individuals with an undetectable viral load (classed by the company as HIV-1 RNA <50 copies/ml) cannot sexually transmit HIV[85-88] (although this statement does not align with the transmission probabilities presented in the clarification response or the model[2]) and that transmission which occurs as a result of treatment failure may involve transmission of a resistant viral strain, leading to fewer treatment options and higher costs for the newly infected individuals.[1]

Individuals in the transmission module were stratified into risk groups, the majority of which can contribute to onward transmission, as shown in Figure 4.2. The heterosexual risk population was further stratified into low-risk and high-risk behaviour categories and transmission from multiple sources was permitted, e.g. heterosexual transmission in the injecting drug use transmission risk group. Presumably, women who have sex with women are assumed to part of the heterosexual group in this context.

The modelled cohort was initially distributed across each of the risk groups, as shown in Table 4.11. The behavioural parameters for sexual and IDU transmission are shown in Tables 16 and 17 of the clarification response.[2] The probabilities of transmission for each risk group per sexual act or per shared injection, based on CD4 state and viral load are displayed in Table 4.12. The cost effectiveness model is subsequently used to estimate lifetime outcomes for each of the risk groups. Consistent with a typical cost effectiveness analysis, lifetime costs, life years and quality-adjusted life years (QALYs) associated with HIV disease progression in the modelled cohort are accrued and recorded.

Table 4.11: Modelled transmission population distribution

Risk group	Distribution	Source
No risk of transmission	0.000	PHE National HIV Surveillance data tables (Table 2) 2019[89]
Non-IDU transmission	0.974	
Heterosexual transmission	0.463	
Low risk	0.900	
High risk	0.100	
MSM transmission	0.537	
IDU transmission	0.026	
MSM & IDU	0.537	
Heterosexual & IDU	0.463	

Based on Table 15 of the response to request for clarification[2]
Notes: The source did not differentiate between high and low risk – values are assumed where not provided. IDU+MSM/IDU+Heterosexual is estimated to be the same ratio as MSM to heterosexual transmission. The adjusted total population was used as the overall cohort (4400) and values were taken as a proportion of this.
HIV = human immunodeficiency virus; IDU = intravenous drug user; MSM = men who have sex with men; PHE = Public Health England

Table 4.12: Probability of transmission per act

Viral load (copies/ml)	Low risk heterosexual (per sexual act)	High risk heterosexual (per sexual act)	MSM (per sexual act)	IDU (per shared injection)
<50	0.000025	0.000025	0.000314	0*
≥50	0.000405	0.000405	0.0043	0.008
Source	Public Health Agency of Canada[90]			Bayoumi et al. 2008[91]

Based on Tables 18 to 21 of the response to request for clarification[2]
* <50 copies/ml assumed zero
CD = cluster of differentiation; IDU = intravenous drug user; MSM = men who have sex with men.

To estimate the number of onward infections, the lifetime viral load health state occupancy of each risk group is recorded. The CS states that it is assumed that the modelled cohort may only contribute to onward HIV infections if they have a viral load ≥50 copies/ml, in line with clinical evidence, individuals with viral load below this threshold cannot infect others. The company reported that it was necessary to make the simplifying assumption that all individuals with viral load ≥50 copies/ml are capable of transmitting HIV, but in reality, clinical evidence suggests that a somewhat higher viral load (approx. 200-400 copies/ml or greater) is required for transmission. Subsequently, time spent in the higher viral load states is combined with the time-dependent risk of transmission (based on risk group-specific behaviour characteristics) to estimate the number of onward HIV infections attributed to the initial cohort. Total lifetime costs, life years and QALYs for each onward infection are estimated and incorporated within the initial cohort cost-effectiveness calculation. Only direct infections (i.e. those transmitted by the original modelled cohort, not infections subsequently passed on by the newly infected persons) are considered within the model.

ERG comment: There was some mismatch between parameters applied in the model, those values reported in the response to the request for clarification and the description of the transmission model in the company submission.[1, 2] The probability of transmission per sexual act for heterosexual patients with a viral load ≤50 copies of 0.000025% provided in the clarification response does not match with the assumed 0% in the model.[2] It is unclear which value the company intended to apply. The company state several times in in the CS that the modelled cohort may only contribute to onward HIV infections if they have a viral load ≥50 copies/ml, therefore the ERG assumes that they intended a value of 0%. In the model a per act transmission probability of 0.0314% is applied to the MSM group with a viral load of ≤50 copies/ml. The ERG requested clarification on this point during the clarification phase.[11] The company responded that the source of data used indicates that there is a small risk of transmission in individuals who have a viral load of <50 copies/ml.[2, 90] Therefore they included this probability in the model, despite more recent large studies which have led to widespread acceptance that persons with an undetectable viral load (defined as <200 copies/ml in these newer studies) cannot sexually transmit HIV.[85, 86] Given this more recent data, the ERG decided to assume a 0% probability of transmission in MSM individuals with a viral load of <50 copies/ml in their base-case, also to remain consistent with the 0% assumed by the company for heterosexual couples (where the source data used by the company had also identified a very small risk of transmission in heterosexual acts with a viral load of <50 copies/ml).

The ERG cannot fully verify the probabilities reported in the CS for the probabilities of transmission per sexual act for individuals with viral loads <50 and >50 copies/ml, as while the Public Health Canada report does contain a table from which the relationship between sexual acts and viral load can be estimated, these are split between insertive and receptive vaginal and anal acts and it is unclear how the company merged these probabilities into combined heterosexual and MSM probabilities.[90] From trial-and-error calculations, the assumed probability of MSM transmission per act is approximately equivalent to the probability of receptive anal transmission at around 2,000 copies/ml, while the assumed probability per heterosexual act roughly is equivalent to the probability of receptive vaginal transmission at around 4,000 copies/ml. The expected distribution or mean level of viral load for patients in the >50 copies/ml group is unknown and therefore it is unclear to the ERG how appropriate the assumed per act probabilities of transmission are. However, the lack of information makes it difficult for the ERG to propose any change in base-case.

The fact that more recent studies have shown a 0% probability of transmission in individuals with a viral load <200 copies/ml calls into question the reliability of the mathematical relationship between viral load and probability of transmission estimated in the Public Health Canada report and used by the company in the base-case, which suggests a probability of transmission at a viral load as low as 10 copies/ml, despite no transmissions having been observed in the data in treated individuals with a viral load <400 copies/ml.[90] However the ERG could not replace these probabilities with alternative literature sources as the cut-off of 50 copies/ml used in the model does not match the more recent data available and therefore this source could not be used.[85, 86]

Given the low numbers of onward transmissions estimated by the transmission model, assumptions within this section of the model are not the main drivers of results. The DSA conducted by the company on transmission model parameters shows that the parameters which have the largest impact on outcomes are the assumed lifetime cost and QALY outcomes for newly infected patients relative to the assumed equivalent uninfected individual. However, when increasing the lifetime QALYs estimated for a new infected patient by 20%, the final ICER decreased by less than 1,000. Therefore, uncertainties in this section of the model are not considered key issues.

4.2.6.6 AIDS-defining events (ADEs)

ADEs are important clinical events in HIV which reflect disease progression and affect costs, QALYs and mortality. The probability of experiencing a specific ADE is dependent on CD4 count, time on treatment and treatment status. Five opportunistic infection (OI) ADEs have been included in the model: acute viral; acute bacterial; acute fungal; acute protozoan; other OI. The per cycle probability of experiencing each OI are displayed in Table 4.13. These probabilities were taken from the ARAMIS study report.[92] The company reported that in some cases over time, risk of ADE increased with increasing CD4+ cell count. In order to better replicate known disease progression, the company carried forward the lowest probability by CD4+ cell count, so that improving health states did not yield a higher likelihood of ADEs.

Table 4.13: Incidence of ADEs

Time on treatment	Opportunistic Infection	Probability of experiencing an ADE per CD4 count				
		<50	50-200	200-350	350-500	>500
0-6 months	Acute viral	0.0071	0.0033	0.0008	**0.0008**	**0.0008**
	Acute bacterial	0.0070	0.0022	0.0006	0.0004	**0.0004**
	Acute fungal	0.0049	0.0022	0.0003	0.0001	**0.0001**
	Acute protozoal	0.0021	0.0006	0.0002	0.0001	**0.0001**
	Other	0.0036	0.0020	**0.0000**	**0.0000**	**0.0000**
7-12 months	Acute viral	0.0039	0.0010	0.0003	**0.0003**	0.0002
	Acute bacterial	0.0027	0.0009	0.0001	**0.0001**	0.0001
	Acute fungal	0.0018	0.0013	0.0002	0.0002	0.0001
	Acute protozoal	0.0018	0.0004	0.0001	0.0001	0.0001
	Other	0.0022	0.0014	0.0007	0.0003	**0.0003**
13-24 months	Acute viral	0.0019	0.0005	0.0002	0.0002	0.0001
	Acute bacterial	0.0022	0.0008	0.0001	**0.0001**	**0.0001**
	Acute fungal	0.0016	0.0011	0.0002	0.0002	0.0001
	Acute protozoal	0.0015	0.0004	0.0001	0.0001	0.0001
	Other	0.0014	0.0009	0.0004	0.0002	**0.0002**
25-36 months	Acute viral	0.0005	0.0001	0.0000	0.0000	0.0000
	Acute bacterial	0.0012	0.0004	0.0000	**0.0000**	0.0000
	Acute fungal	0.0015	0.0011	0.0001	0.0001	0.0001
	Acute protozoal	0.0008	0.0002	0.0000	0.0000	0.0000
	Other	0.0009	0.0006	0.0003	0.0001	0.0001
36+ months	Acute viral	0.0005	0.0001	0.0000	0.0000	0.0000
	Acute bacterial	0.0012	0.0004	0.0000	0.0000	0.0000
	Acute fungal	0.0015	0.0011	0.0001	0.0001	0.0001
	Acute protozoal	0.0008	0.0002	0.0000	0.0000	0.0000
	Other	0.0009	0.0006	0.0003	0.0001	0.0001

Based on Table 62 of the CS, sourced by the company from the ARAMIS Technical Report[1, 92]
Lowest value for each time-point by CD4+ cell count carried forward. SE assumed to be 10% of mean for all inputs. Bolded values were amended using last value carried forward.

Time on treatment	Opportunistic Infection	Probability of experiencing an ADE per CD4 count				
		<50	50-200	200-350	350-500	>500
ADE = AIDS-defining event; CD = cluster of differentiation; CS = company submission; OI = opportunistic infection; SE = standard error						

ERG comment: The ERG considers that given the very low probabilities at which values were adjusted using lowest value carried forward, this is unlikely to have had a large impact on results and the company's adjustment approach seems plausible.

At clarification, the ERG requested information on any ADEs which were seen in the trials, but not included in the model. The company reported that ATLAS-2M did not provide a breakdown of specific ADEs but does report the number of transitions to CDC stage 3 (AIDS), but this was not stratified by CD4 count. The pooled ATLAS/FLAIR data did not report the development of AIDS therefore it was not included in the NMA and differences between arms were not quantifiable. The company reported that the development of AIDS was considered to be a clinical outcome which can be derived and estimated from model outputs. Additional inclusion of AIDS as an ADE would result in double counting. The ERG concurs with the decision not to include AIDS as ADE. In terms of other ADEs, clinical advice sought by the company indicated that the vast majority of ADEs that may be observed would be opportunistic infections, as included in the base-case. Additionally, removing the ADEs from the model had minimal impact on results.

4.2.6.7 Mortality

All-cause mortality was modelled based on age- and gender-specific mortality rates derived from 2016 to 2018 UK life tables.[79] A maximum age of 100 years is applied in the model, after which all patients die in the next model cycle. Additional HIV-related mortality was modelled using relative risks of mortality by CD4+ cell counts as estimated in a French population-based study by Lewden et al. 2007.[93] These estimates are provided in Table 63 of the CS.[1] To reflect an additional risk of mortality for patients experiencing ADEs, a monthly probability of dying due to ADEs is added to the adjusted all-cause mortality for the duration of the model cycle that an ADE occurs. The probabilities of dying due to ADEs were based on values derived from the Multicentre AIDS Cohort Study,[92] which are provided in Table 64 of the CS.[1]

ERG comment: During the clarification phase, the ERG requested justification for the use of additional monthly probabilities of dying due to ADEs since that would imply that this additional risk was excluded in the study by Lewden et al. 2007.[11, 93] The ERG also requested the company to provide the option in the model to exclude these additional probabilities from the analysis.[11] The company did not comply to the latter and indicated that it was unclear whether the study by Lewden et al. 2007 included or excluded these additional probabilities of dying due to ADEs.[2, 93] The company did perform a scenario analysis in which these additional probabilities were excluded, the results of which are provided in section 5.2.3.6 and indicate that this has limited impact on the results. Given this limited impact, the ERG agrees to include the additional probabilities of dying in their preferred base-case model.

4.2.7 Adverse events

The company only included injection site reaction AEs in their base-case, assuming all other AEs were equivalent between intervention and comparator, in line with evidence from the ITC described in section B.2.9.1 of the CS.[1] For CAB LA + RPV LA Q2M the monthly probabilities of injection site reaction grade 3/4 and grade 1/2 are 0.51% (SE 0.31%) and 29.09% (SE 1.99%), respectively. There is

no probability of injection site reaction for current ART since it is administered orally. AEs are modelled only in first line therapy as subsequent lines consist of oral ARTs (where injection site reactions are not applicable) and the assumption that other AEs are not different between arms would continue to be valid as the same efficacy profiles are applied to each arm regardless of the initial modelled efficacy.

ERG comment: The ERG requested that all drug-related AEs which affected ≥5% of patients in either treatment arm be included in the model as although the ITC may show insignificant difference in the incidence of grade 3/4 adverse events across treatment groups, this may disguise differences in the AEs experienced within the profile across groups, which may have differing impact in terms of costs and utility.[11] In Tables 29 and 30 of the clarification response, the company showed all drug-related AEs that occurred in greater than 1% of either arm from the pooled ATLAS FLAIR data and the ATLAS-2M data.[2] This showed that the only AE which occurred in ≥5% of patients was injection site reactions (already included in the model), with the exception of pyrexia, which occurred in 5% of the once every four weeks (Q4W) arm of the ATLAS-2M trial. The company did not include pyrexia stating that the Q4W arm was not considered in this analysis and pyrexia would likely be treated at home and therefore not incur additional cost. Given that the incidence is fairly similar in the other arms (4%), the ERG consider that this exclusion would have minimal impact on results.

It is possible that relevant data on safety were missed through the exclusion of case control studies and therefore the presented evidence regarding AEs may not be complete (see section 3.1.2). However, if the potentially missed AEs are of relatively short duration, they will probably have limited to no impact on the cost effectiveness.

4.2.8 Health-related quality of life

HRQoL data was collected in the ATLAS and FLAIR trials at baseline and weeks 24 and 48, using the SF-12 version with a four week recall period. The scoring algorithm by Brazier and Roberts was used to derive SF-6D utilities from this trial data.[62] However the trial data was not stratified by CD4+ cell counts, as required by the model health states and therefore these trial utilities were only used in the model to explore differences in utility between long-acting CAB LA + RPV and current ART treatments.

4.2.8.1 Health state utility values

The company searched the literature for utility values defined by CD4+ counts for use as HSUVs in the model. They selected values published by Kauf et al. 2008, derived from five open-label studies in 1,327 patients treated with highly active ART.[94] HRQoL was measured using the SF-36 and utilities were generated using the Brazier et al. 2002 SF-6D UK mapping algorithm.[61] Utilities were estimated as a function of patient demographics, regimen attributes, disease status and AEs using a mixed effects maximum likelihood model.[94] The company reported that this source of values has been widely used and allows for comparison with previous studies, without providing any citations though. The HSUVs used in the model are displayed in Table 4.14.

Table 4.14: Health state utility values

CD4+ cell count category (cells/mm^3)	Mean	SE	Source
>500	0.798	0.052	Kauf et al. 2008[94]
350–500	0.784	0.059	
200–350	0.778	0.053	
50–200	0.750	0.058	
<50	0.742	0.058	
CD = cluster of differentiation; SE = standard error			

Utilities were adjusted for age in the model through the application of general population age-dependent utility estimates from Szende and Janssen 2014.[95] Age-dependent adjustments were applied additively relative to a patient's starting age. For example, a cohort with a starting age of 50 years and a corresponding general population utility of 0.850 incurred a cumulative utility decrement of 0.031 by the time they were 60 years (general population utility estimate of 0.819).

ERG comment: The CD4 boundaries defined in Kauf et al. 2008 differed slightly from those in the model, with the lowest category being 0-99 and the next being 100-199 in Kauf.[94] This may mean that the utility of patients in the model categories <50 and 50-200 would be slightly lower in reality, as both model categories include a higher proportion of patients with lower CD4 than in the source paper.

HSUVs were not measured using the EQ-5D as preferred by NICE, either in the company's trial or in the literature source selected. During the clarification phase, the ERG requested the company to provide a full list of studies identified in their SLR which provided utility values stratified by CD4 count.[11] The company provided a list of 11 studies, of which five were stated to use the EQ-5D.[2] From this list, the ERG identified a series of potentially useful alternative literature sources and HSUVs which could be considered for use in the model, as shown in Table 4.15. Simpson et al. 2007 provides EQ-5D-3L values for matching CD4 categories, with multiple values per category depending on viral load.[96] These utilities were estimated from a pooled sample of 21,000 responses from patients in five clinical trials of protease-based ART regimens. The utility values obtained in Simpson et al. 2007 are quite high, ranging from 0.954-0.781 for individuals with CD4 counts >500 to <50 and the ERG could not access the underlying 2004 publication, referenced in the paper by Simpson et al. 2007, to trace what value set was used to estimate utilities.[96] Alternative EQ-5D values are also available from Marcellusi et al. 2016,[97] Pialoux et al. 2018[98] and Stavem et al. 2005[99]. Stavem et al. 2005 measured HRQoL in 59 patients in Norway, using the EQ-5D-3L valued using the UK tariff.[99] Pialoux et al. 2018 reported utilities estimated from EQ-5D data measured in three trials (SINGLE, SPRING-2, and FLAMINGO), but provided no information on which country-specific tariff was used for valuation.[98] Marcellusi et al. 2016 utilised both the Simpson and Kauf data, although details on how these were pooled are not available.[97] Only the Simpson study provided utilities which exactly matched the CD4 count health states in the model, although multiple estimates were available for each health state for different viral load cut-offs. The ERG considered that all sources had potential advantages and disadvantages, with none clearly better suited to the base-case than others. Therefore, no base-case change was made, but scenarios were run with the remaining sources.

Table 4.15: Base-case and scenario HSUVs

CD4+ cell count category (cells/mm^3)	Kauf 2008 [94]	Simpson 2007[96]	Marcellusi 2016 [97]	Pialoux 2018 [98]	Stavem 2005[99]
>500	0.798	0.954-0.938*	0.872	0.9	0.86
350–500	0.784	0.934-0.931*	0.859		0.87
200–350	0.778	0.929-0.933*	0.855		
50–200	0.750	0.863-0.826*	0.788	50-100=0.86 10-200=0.87	0.73
<50	0.742	0.781		0.83	0.55
HRQoL measurement	SF-36	EQ-5D-3L	Pooled utilities from Simpson and Kauf	EQ-5D-3L	EQ-5D-3L
HRQoL valuation	SF-6D UK algorithm	Tariff unknown		Tariff unknown	UK tariff

* Dependent on level of viral copies/ml

CD = cluster of differentiation; EQ-5D-3L = European Quality of Life-5 Dimensions-3 levels; HRQoL = health-related quality of life; HSUVs = health state utility values.

4.2.8.2 Treatment-related utility advantage

The SF-6D utility data derived from FLAIR and ATLAS was used to examine the impact on utility of receiving long-acting injectable therapy versus daily oral treatment.[1] Between-treatment differences in SF-6D utility scores derived from the trial SF-12 data were analysed using an ANCOVA model, adjusted for age, sex and CD4+ cell count as covariates. At week 24, a statistically significant difference between treatment groups was reported (adjusted mean treatment difference in SF-6D: [redacted] points; 95% CI [redacted]). At week 48, results were consistent with those at 24 weeks (adjusted mean treatment difference in SF-6D: [redacted] points; 95% CI [redacted]). The considered covariates did not exert a significant influence on the results at either time point. This utility advantage of [redacted] was applied to patients receiving CAB LA + RPV LA in the model as an annual utility.

The company argued that due to the relatively short follow-up in the trials relative to a lifetime of daily treatment, and the low sensitivity of generic instruments such as SF-12 to HIV-specific issues such as stigma, this is considered an underestimate of the likely utility gain associated with the important change in treatment administration for those individuals who desire a switch to long-acting treatment (those who prefer daily oral ART will not be considered for CAB LA + RPV LA).[1] Another reason why the trial-observed utility impact may be conservative is that it relates to Q1M treatment with CAB LA + RPV LA rather than Q2M which was preferred by ATLAS-2M participants who had experienced both, but SF-12 was not collected in ATLAS-2M.[100]

ERG comment: This utility advantage favouring CAB LA + RPV LA in the model has quite some impact on model results in terms of incremental utility gain. Therefore, the ERG wanted to carefully examine this assumption and the analysis for any potential biases:

1. The ERG considered whether differences in baseline characteristics between the ART and CAB groups in the pooled ATLAS/FLAIR data may have influenced results, however the baseline characteristics shown in Table 2 of Appendix L of the CS appear well balanced.[54]

2. The ERG considered whether differences in efficacy over time, in terms of maintaining CD4 counts may have affected results, as if this were driving the difference in utility observed, this would be double counted as CD4 health states should already be capturing the impact of CD4 on utility. However, CD4 count at each visit was included in the utility analysis as a covariate, so this should have already been captured within the utilities.
3. One uncertainty that remains is that drop-out over time was higher in the reporting of HRQoL in the CAB LA + RPV LA arm versus the ART arm (CAB n=556, 535 and 500 at baseline, week 24 and week 48 respectively versus ART n=552, 546 and 548).[101] If participants who failed to report their HRQoL were more likely to be those with worse HRQoL, this could have increased the difference in utility observed between the groups.

In general, given that a difference in utility is observed between patients receiving CAB LA + RPV LA and standard ART and given the clear preference of trial patients for long-acting treatment over daily treatment, a small difference in utility does seem appropriate, as long-acting treatment may easy anxieties over suboptimal adherence and loss of suppression, or may ease daily living where dosing schedules or concern over taking pills in public make usual activities more difficult. However, uncertainties over the size of the utility advantage remain and alternatives will be tested in scenario analysis.

4.2.8.3 AIDS-defining event and AE utility decrements

Utility decrements were applied to ADE for the duration of the cycle of incidence. The decrements applied, displayed in Table 4.16, were derived from a study by Paltiel et al. 1998.[102]

Table 4.16: AIDS-defining event utility decrements

ADE	Mean	SE*	Source
Acute viral OI	0.141	0.014	Paltiel 1998[102]
Acute bacterial OI	0.232	0.023	
Acute fungal OI	0.141	0.014	
Acute protozoal OI	0.232	0.023	
Other OI	0.232	0.023	

* SEs assumed 10% of mean

Note: Utility decrements associated with ADEs were derived as the mean utility across CD4+ cell health states (including post-failure) minus ADE utility as presented in the Paltiel study

ADE = AIDS-defining event; OI = opportunistic infection; SE = standard error.

No utility decrements were applied for AEs, as the ITC showed no significant difference in AE profile between CAB LA + RPV LA and daily oral ART. The company noted a difference in injection site reactions, which occurred only with CAB LA + RPV LA, but this difference was assumed to be captured in the assessment of SF-6D utilities within the trials. The company reported that data on acceptability of injections, treatment satisfaction and treatment acceptance were collected in ATLAS-2M, and individuals reported high levels of acceptance and satisfaction that increased over time. Furthermore, the SF-6D analysis showed that CAB LA + RPV LA was associated with a statistically significant improvement in HRQoL compared with daily oral treatment. They considered these findings supportive of the decision not to apply a utility decrement for injection site reactions.

ERG comment: Given that SF-12 was only measured at baseline and weeks 24 and 48, only injection site reactions which occurred due to injections at week 20 and 44 would have been captured within the four week recall of the SF-12. Given that scores on the PIN questionnaire showed improvement over

time between weeks 8 and 24 and 48, it is likely that the impact of injection site reactions was larger for earlier injections which are not covered by the SF-12 data collection. However, given that in the pooled analysis of ATLAS and FLAIR the mean duration of injection site reactions was 5.5 days, fewer than 5% of patients experienced ISRs of ≥Grade 3 and mean scores on the PIN were fairly positive, it is likely that the impact of including ISRs would be minimal. In the company's literature review they identified one cost effectiveness study which included a disutility for injection site reactions of 0.01 (assumed to be the same as the disutility for rash estimated in Kauf et al. 2008 used for the HSUVs[94]).[19, 103] The ERG also identified another study where injection site reactions were associated with a disutility of 0.011 in a study of type 2 diabetes patients, which provides support for this disutility.[104] Combined with a mean duration of 5.5 days, a disutility of 0.011 would imply a QALY loss of 0.000151 per event. The impact of including these events would therefore be minimal but would favour the comparator. Given the rarity and similarity in incidence of the remaining AEs observed their inclusion would likely also have minimal impact on results.

4.2.9 Resources and costs

The following cost categories were included in the model: drug acquisition costs, drug administration costs (CAB LA + RPV LA only), health state costs (consisting of HIV infection-associated and all cause health care resource use, disease monitoring and non-HIV medication), management of ISRs and end of life costs.

4.2.9.1 Drug acquisition costs

Drug acquisition costs for CAB LA + RPV LA pertain to the costs of the oral tablets during the 30 day lead in period, and subsequent initiation and continuation injections. At list price, tablets per 30 day oral lead in cost [redacted] ([redacted] for cabotegravir and £200.27 for rilpivirine) and per set of injections CAB LA + RPV LA costs [redacted]. In the model, a cost of [redacted] per calendar month is applied for oral lead in tablets, followed by the cost per set of initiation injections in months 2 and 3, and the cost per set of continuation injections every two months thereafter (i.e. in months 5, 7, 9, etc.). This amounts to an annual cost of [redacted] in year 1 and [redacted] from year 2 onwards.

[redacted]

As explained in section 4.2.4, CAB LA + RPV LA is compared to a pooled 'basket of comparator regimens' that consists of those oral ART regimens deemed most likely to be switched to by virologically suppressed individuals in the UK who would otherwise be considered for a switch to CAB LA + RPV LA if it were available. In consultation with UK clinicians, the following oral ART regimens were included in the 'basket of comparator regimens':

- Emtricitabine/tenofovir alafenamide plus dolutegravir (Descovy® plus Tivicay®)
- Emtricitabine/tenofovir alafenamide plus raltegravir (Descovy® plus Isentress®)
- Abacavir/dolutegravir/lamivudine (Triumeq®)
- Dolutegravir/lamivudine (Dovato®)
- Dolutegravir/rilpivirine (Juluca®)
- Bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy®)

- Doravirine/lamivudine/tenofovir disoproxil fumarate (Delstrigo®)
- Darunavir/cobicistat/emtricitabine/tenofovir alafenamide (Symtuza®)
- Emtricitabine/rilpivirine/tenofovir alafenamide (Odefsey®)

The list prices of these comparator regimens were sourced from the British National Formulary (BNF) and are provided in Table 4.17.[105] A simple (i.e. non-weighted) average price of £731.86 per calendar month (adjusted from 30-day average of £721.34) was calculated for the 'basket of comparator regimens', which was used in the model as the cost for all oral ART regimens irrespective of treatment line.

Table 4.17 Comparator costs

Brand name	Generic name	Pack size	30 day list price in BNF 2020[105]
Single tablet regimens			
Delstrigo®	DOR/3TC/TDF	30	£578.55
Symtuza®	DRV/C/FTC/TAF	30	£672.97
Odefsey®	RPV/FTC/TAF	30	£525.95
Biktarvy®	BIC/FTC/TAF	30	£879.51
Triumeq®	DTG/ABC/3TC	30	£798.16
Dovato®	DTG/3TC	30	£656.26
Juluca®	DTG/RPV	30	£699.02
Multi-tablet regimens			
Descovy®+Isentress®	FTC/TAF+RAL	30	£827.14
Descovy®+Tivicay®	FTC/TAF+DTG	30	£854.48
Average			
Pooled comparator		30	£721.34

Based on Table 71 of the CS[1]
3TC = lamivudine; BIC = bictegravir; BNF = British national formulary, C = cobicistat; CS = company submission; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; FTC = emtricitabine; RAL = raltegravir; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

ERG comment: In absence of information about the extent to which the treatment regimens included in the 'basket of comparators' are representative of those that are given as second-line (or further) treatments to patients who switched their first-line treatment due to non-virologic reasons related specifically to the challenges of oral therapy (see section 4.2.4), the company calculated a simple (i.e. non-weighted) average cost for the 'basket of comparators'. During the clarification phase, the ERG requested the company to provide options in the model 1) to use a cost estimate for a 'basket of comparator drugs' in which also low cost regimens were included, and 2) to use a cost estimate for a 'basket of comparator drugs' that was based on a weighted average cost by market share.[11]

As explained in section 4.2.4, the company did not comply with the first request. Regarding the second request, the company did not provide this option in the model but did provide the results of a scenario analysis using a cost estimate for the 'basket of comparator drugs' that was based on a weighted average cost by market share. These results are provided in section 5.2.3.8 and indicate that an approach using a weighted average only led to a marginal difference in the cost of the comparator and therefore a limited impact on the results.

The ERG considers the use of a basket of comparators in general problematic, as a cost effectiveness analysis should ideally compare to the treatment being replaced. But given the wide variety of treatment options that may be used in various sequences, depending on multiple factors such as patient preferences and drug interactions, the ERG acknowledges that the current approach has its merits. However, it is clear that substantial uncertainty exists about the composition of the basket, and the associated costs. The ERG will explore this uncertainty in series of scenario analyses using a set of different cost estimates for the comparator based on the information provided by the company during clarification on the drugs that are contained in different price bands and are used by patients after regimen switching in the Midlands and East region (see section 6.1.3.1).

4.2.9.2 Drug administration costs

Drug administration costs were included for CAB LA + RPV injections, based on an assumed 15 minutes of time for a nurse to administer the two intramuscular injections. The cost of a Band 5 nurse was sourced from the Personal Social Services Research Unit (PSSRU) 2019, and amounts to £37 per working hour or £9.25 per 15 minutes.[106]

The company indicated that the administration costs could possibly already be subsumed within the Payment by Results (PbR) category 2 currency for patients with HIV who are stable and switching ART due to toxicity, simplification or adherence issues whilst maintaining an undetectable viral load.

4.2.9.3 Health state costs

Health state costs were sourced from Beck et al. 2011 and include the following cost components: outpatient care, day ward costs, inpatient days, non-HIV medication, CD4+ tests and other procedures.[107] The company used the same distinction in costs as Beck et al. 2011 based on CD4+ cell counts being either <200 or ≥200 cells per mm^3, with no further distinction applied in relation to the five health states as defined in the model based on CD4+ cell counts. The health state costs as used in the model are provided in Table 4.18. It was assumed that costs for the treatment of ADEs, CD4+ cell counts, viral load and HIC genotypic resistance testing were included in the health state costs, i.e. no additional costs were included specifically for these items. The costs as reported by Beck et al. 2011 were based on 2008 prices and were inflated to 2019 costs using the consumer price index for health (CPI-HLTH).

Table 4.18 HIV-related health encounter costs

Variable	CD4+ cell count	Mean	SE	Source
Outpatient care	CD4+ ≤200	£87.99	£0.51	Beck et al. 2011[107]
	CD4+ > 200	£79.58	£0.40	
Non-HIV medication	CD4+ ≤200	£355.71	£3.56	
	CD4+ > 200	£218.14	£2.18	
Day ward Costs	CD4+ ≤200	£56.44	£0.85	
	CD4+ > 200	£37.52	£0.51	
Inpatient Days	CD4+ ≤200	£166.12	£0.79	
	CD4+ > 200	£78.03	£1.52	
CD4+ tests and other procedures	CD4+ ≤200	£87.77	£0.88	
	CD4+ > 200	£63.97	£0.64	

Based on Table 73 of the CS[1]
CD4 = cluster of differentiation; CS = company submission; HIV = human immunodeficiency virus; SE = standard error

ERG comment: In the clarification phase, the ERG requested the company to replace the inflated cost estimates from Beck et al. 2011 with costs sourced from the NHS Reference costs 2018/2019 and use the NHS Cost Inflation Index (NHSCII) from PSSRU 2019 to inflate any costs that could not be sourced from the NHS Reference costs 2018/2019.[11] In response to this request, the company reported the results of a scenario analysis in which a zero cost was applied to all health state costs other than non-HIV medication and CD4+ test and other procedures.[2] This scenario was justified by referring to consultation with clinicians that indicated that virally suppressed patients do not require additional inpatient, outpatient and day ward care over and above what was already accounted for by costs due to non-HIV medication for the treatment of ADEs and testing costs.

For patients with a CD4+ cell count below 50, the prophylactic use of azithromycin was assumed at a dosage of 1250 mg once a week to prevent opportunistic infections. For patients with a CD4+ cell count below 200 the use of fluconazole and co-trimoxazole was assumed. A daily dosage of 200 mg was assumed for fluconazole, which is the same dosage as used for prevention of relapse of cryptococcal meningitis in HIV-infected patients after completion of primary therapy. A dosage of 960 mg once a day for three days every week was assumed for co-trimoxazole, which is the same as for prophylaxis of Pneumocystis jirovecii (Pneumocystis carinii) infections. This is listed as being 960 mg once daily, reduced if not tolerated to 480 mg once daily, alternatively 960 mg once daily on alternate days, alternate day dose to be given 3 times weekly, alternatively 960 mg twice a day on alternate days, alternate day dose to be given 3 times weekly.

In addition, the company sourced a unit cost for testing procedures from the NHS Reference costs 2018/2019 of £1.76 (Currency code DAPS03 'Integrated Blood Services') and inflated it to 2019/2020 costs using the NHSCII from PSSRU 2020 resulting in a unit cost of £1.80. This was applied as a monthly (i.e. per model cycle) cost for CD4+ cell count and viral load testing, based on the following frequencies as indicated by clinical experts:

- CD4+ cell count >350: Viral load testing every six months = £0.30 per cycle
- CD4+ cell count 200-350: CD4+ cell count testing every 12 months = £0.15 per cycle, and viral load testing every six months = £0.30 per cycle
- CD4+ cell count 50-200: CD4+ cell count testing every three to six months (six months assumed in the model) = £0.30 per cycle, and viral load testing every six months = £0.30 per cycle
- CD4+ cell count <50: CD4+ cell count testing every three to six months (three months assumed in the model) = £0.60 per cycle, and viral load testing every six months = £0.30 per cycle

Other testing procedures that were costed in the model at a frequency of twice (i.e. £0.30 per cycle) per year for all patients, irrespective of CD4+ cell count, were the following: full blood count, renal function test, liver function test, bone profile assessment, and dipstick urinalysis. The following test procedures were costed at a frequency of once per year (i.e. £0.15 per cycle): urine protein/creatine ratio, lipid profile assessment, HbA1c testing and Hepatitis A/B/C infection/immunity status. The resulting health state cost estimates that were used for this scenario were provided in Table 34 in the response to request for clarification.[2] The results of this scenario are provided in section 5.

The ERG notes that the model implicitly assumes a monthly frequency of testing for CD4+ cell counts and viral load, since patients are at a monthly risk of transitioning between CD4+ cell count based health states and viral loads below or above 50 copies per ml. During the clarification phase, the company confirmed that a monthly frequency of testing does not represent clinical practice. The ERG agrees that the application of a monthly cost for testing proportional to frequencies that are in line with clinical

practice is reasonable, but this issue clearly exposes a problem in the model, where patients may change treatment much more frequent than that they are tested.

The health care resource estimates provided during clarification were based on clinician advice that assumed that costs for the treatment of ADEs were already accounted for in the model. However, this is not the case. The health care resource estimates provided in the original CS assumed that these did include costs associated with the treatment of ADEs. For this reason, and in the absence of separate estimates for the costs of managing ADEs, the ERG chose to use the estimates from the original CS for their base-case analysis.

4.2.9.4 ISR management cost

The company did not include any costs for the management of AEs other than ISRs. This was justified by referring to the consistency in AE profile between therapy arms in ATLAS and FLAIR, except for ISRs.[1] Grade 1 and 2 ISRs were assumed not to incur any additional costs since they are usually managed symptomatically, for example using a cold/warm compress, paracetamol or ibuprofen. Grade 3 and 4 ISRs were assumed to be managed at a cost of £139.45 per event, sourced from the NHS Reference costs 2018/2019 (Currency code N18AF 'Specialist Nursing, HIV/AIDS Nursing Services, Adult, Face to face').[108] The monthly probability of a Grade 3/4 ISR is 0.51% (SE 0.31%), which only applies to CAB LA + RPV LA.

4.2.9.5 End of life cost

End of life costs are included in the model in the final month of life, which were sourced from a cost effectiveness analysis by Moeremans et al. 2010, inflated to 2019 costs using CPI-HLTH and converted to Pounds Sterling.[109] This resulted in an estimate of £13,352.92 (SE £1,335.29).

ERG comment: The article by Moeremans et al. 2010 is on a cost effectiveness analysis of darunavir/ritonavir in Belgium, Italy, Sweden and the UK and does not provide details on the end of life cost estimate.[109] The article states that the end of life cost estimate was used in the Belgian analysis, but not in their analyses for Italy, Sweden and the UK. It is therefore uncertain whether this estimate is appropriate for use in the context of the UK.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The company base-case incremental cost effectiveness results, provided in Table 5.1, indicate that CAB LA + RPV LA is dominant over oral ART regimens. Total costs associated with CAB LA + RPV LA were estimated at [redacted] (including [redacted] from the onwards transmission module) and total costs associated with oral ART regimens were estimated at [redacted] (including [redacted] from the onwards transmission module), indicating that CAB LA + RPV is cost saving at an incremental cost of [redacted]. Total QALYs associated with CAB LA + RPV LA were estimated at [redacted] (including [redacted] QALYs lost from the onwards transmission module) and total QALYs associated with oral ART regimens were estimated at [redacted] (including [redacted] QALYs lost from the onwards transmission module), indicating an incremental number of [redacted] QALYs gained with CAB LA + RPV LA.

Table 5.1: Company base-case deterministic cost effectiveness results (discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
CAB LA + RPV LA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Oral ART regimens	[redacted]	[redacted]	[redacted]				

Based on company version of the electronic model submitted alongside the CS[72]
ART = antiretroviral therapy; CAB LA = cabotegravir long-acting; CS = company submission; ICER = incremental cost effectiveness ratio; LYG = life years gained; RPV LA = rilpivirine long-acting; QALY = quality adjusted life year

5.2 Company's sensitivity analyses

5.2.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was performed using 1,000 iterations and probabilistic values for input parameters based on uncertainty estimates and parametric distributions as detailed in Table 74 of the CS.[1] The PSA results were consistent with the deterministic results and are provided in Table 5.2 below indicating that CAB LA + RPV LA is dominant over oral ART regimens. Total costs associated with CAB LA + RPV LA were estimated at [redacted] and total costs associated with oral ART regimens were estimated at [redacted], indicating that CAB LA + RPV is cost saving at an incremental cost of [redacted]. Total QALYs associated with CAB LA + RPV LA are estimated at [redacted] and total QALYs associated with oral ART regimens are estimated at [redacted], indicating an incremental number of [redacted] QALYs gained with CAB LA + RPV LA.

Table 5.2: Company base-case probabilistic cost effectiveness results (discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
CAB LA + RPV LA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Oral ART regimens	[redacted]	[redacted]	[redacted]				

Based on Table 79 of the CS[1]
ART = antiretroviral therapy; CAB LA = cabotegravir long-acting; CS = company submission; ICER = incremental cost effectiveness ratio; LYG = life years gained; RPV LA = rilpivirine long-acting; QALY = quality adjusted life year

The cost effectiveness (CE) plane and cost effectiveness acceptability curve (CEAC) are shown in Figure 5.1 and Figure 5.2, respectively. At incremental cost effectiveness ratio (ICER) thresholds of £20,000 and £30,000, CAB LA + RPV LA has a 100% probability of being cost effective relative to oral ART regimens.

Figure 5.1: Cost effectiveness plane

Based on Figure 15 of the CS[1]
CS = company submission; QALY = quality adjusted life year

Figure 5.2: Cost effectiveness acceptability curve

Based on the electronic model submitted by the company alongside the CS[72]
CAB LA = cabotegravir long-acting; CS = company submission; ICER = incremental cost effectiveness ratio; RPV LA = rilpivirine long-acting.

5.2.2 Deterministic sensitivity analysis

The company performed a series of deterministic sensitivity analyses to assess the impact of alternative assumptions on the cost effectiveness results. A summary of which assumptions were altered and how is provided in Table 5.3 below alongside their corresponding impacts on incremental costs, QALYs and life years gained.

Table 5.3: Deterministic sensitivity analyses and results

Scenario	Parameter variation	Incremental			ICER
		Costs	QALYs	LYG	
Adherence modelling	On	[redacted]	[redacted]	[redacted]	Dominant
	Off	[redacted]	[redacted]	[redacted]	Dominant
Variation of adherence to first line ART – treatment arm	Base case – 20%	[redacted]	[redacted]	[redacted]	Dominant
	Base case (100% of trial)	[redacted]	[redacted]	[redacted]	Dominant
Model time horizon (months)	120 months	[redacted]	[redacted]	[redacted]	Dominant
	240 months	[redacted]	[redacted]	[redacted]	Dominant
Variation of adherence to first line ART – control arm	80% of base case	[redacted]	[redacted]	[redacted]	Dominant
	120% of base case	[redacted]	[redacted]	[redacted]	Dominant
Discount, outcomes (%)	Lower (0%)	[redacted]	[redacted]	[redacted]	Dominant
	Upper (6%)	[redacted]	[redacted]	[redacted]	Dominant
Treatment-related utility advantage (Intervention)	Lower (120% of base case)	[redacted]	[redacted]	[redacted]	Dominant
	Upper (80% of base case)	[redacted]	[redacted]	[redacted]	Dominant
Cost's discount (%)	Lower (0%)	[redacted]	[redacted]	[redacted]	Dominant
	Upper (6%)	[redacted]	[redacted]	[redacted]	Dominant
Age (years)	Lower (80% base case)	[redacted]	[redacted]	[redacted]	Dominant
	Upper (120% base case)	[redacted]	[redacted]	[redacted]	Dominant
Health state utilities	Lower (80% of base case)	[redacted]	[redacted]	[redacted]	Dominant
	Upper (120% of base case)	[redacted]	[redacted]	[redacted]	Dominant
Percentage of cohort that are female (%)	Lower (0%)	[redacted]	[redacted]	[redacted]	Dominant
	Upper (100%)	[redacted]	[redacted]	[redacted]	Dominant
Variation of adherence to second 4L therapy line	Lower (80% of base case)	[redacted]	[redacted]	[redacted]	Dominant
	Upper (120% of base case)	[redacted]	[redacted]	[redacted]	Dominant

Scenario	Parameter variation	Incremental			ICER
		Costs	QALYs	LYG	
Probability of non-virologic discontinuation of CAB LA + RPV LA Q2M	Lower (80% of base case)	[redacted]	[redacted]	[redacted]	Dominant
	Upper (120% of base case)	[redacted]	[redacted]	[redacted]	Dominant
Treatment-related utility advantage (Comparator)	Lower (80% of base case)	[redacted]	[redacted]	[redacted]	Dominant
	Upper (120% of base case)	[redacted]	[redacted]	[redacted]	Dominant
Probability of virologic discontinuation of CAB LA + RPV LA Q2M	Lower (80% of base case)	[redacted]	[redacted]	[redacted]	Dominant
	Upper (120% of base case)	[redacted]	[redacted]	[redacted]	Dominant
Risk of death (relative to all-cause mortality)	Lower (80% of base case)	[redacted]	[redacted]	[redacted]	Dominant
	Upper (120% of base case)	[redacted]	[redacted]	[redacted]	Dominant
Administration costs associated with injectables	Lower (£5)	[redacted]	[redacted]	[redacted]	Dominant
	Upper (£20)	[redacted]	[redacted]	[redacted]	Dominant
Other resource costs associated with injectables	Lower (80% of base case)	[redacted]	[redacted]	[redacted]	Dominant
	Upper (120% of base case)	[redacted]	[redacted]	[redacted]	Dominant
Treatment disutility (4L 3)	Lower (80% of base case)	[redacted]	[redacted]	[redacted]	Dominant
	Upper (120% of base case)	[redacted]	[redacted]	[redacted]	Dominant
Variation of adherence to second-line ART (discontinuation due to viral failure/rebound)	Lower (80% of base case)	[redacted]	[redacted]	[redacted]	Dominant
	Upper (120% of base case)	[redacted]	[redacted]	[redacted]	Dominant
Variation of adherence to second-line ART (discontinuation due to non-virologic reasons)	Lower (80% of base case)	[redacted]	[redacted]	[redacted]	Dominant
	Upper (120% of base case)	[redacted]	[redacted]	[redacted]	Dominant

Based on Table 80 of the CS[1]

ART = antiretroviral therapy; CAB LA = cabotegravir long-acting; CS = company submission; ICER = incremental cost effectiveness ratio; LYG = life years gained; RPV LA = rilpivirine long-acting; Q2M = given every 2 months; QALY = quality adjusted life year

The parameters that influence the results and conclusions of the decision problem to the greatest degree are adherence to oral ART, the efficacy of the first modelled line for both arms, and the time horizon. No variations in any of the parameters resulted in CAB LA + RPV LA being deemed not cost effective.

5.2.3 Scenario analyses

The company performed a series of scenario analyses to examine the impact of structural and input assumptions, the details and results of which are summarised below. The first four sets of scenarios below were provided in the CS,[1] and a series of additional scenario analyses were provided in the company's response to the ERG's clarification questions.

5.2.3.1 Alternative efficacy in further lines

To address concerns raised by clinicians consulted by the company who indicated that it may not be true for all individuals to experience a reduced efficacy in further treatment lines compared to the first modelled line, a scenario analysis was performed where the same efficacy profile for second and third modelled treatment line is assumed to be the same for all patients, using the efficacy profiles that represent those switching due to non-virologic reasons. This scenario resulted in a slight reduction in incremental life years and QALYs gained, as shown in Table 5.4.

Table 5.4: Cost effectiveness results for scenario assuming the same efficacy for second and third treatment lines in all patients

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
CAB LA + RPV LA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Oral ART regimens	[redacted]	[redacted]	[redacted]				

Based on Table 81 of the CS[1]
ART = antiretroviral therapy; CAB LA = cabotegravir long-acting; CS = company submission; ICER = incremental cost effectiveness ratio; LYG = life years gained; RPV LA = rilpivirine long-acting; QALY = quality adjusted life year

5.2.3.2 Alternative discounting

To anticipate a potential revision of the NICE Reference case that prescribes the use of an annual discount rate of 3.5% for costs and effects, a scenario analysis was performed where a discount rate of 1.5% is used for costs and effects. This scenario resulted in higher estimates of total costs and effects but did not change the results of CAB LA + RPV LA being cost effective. These results are provided in Table 5.5.

Table 5.5: Cost effectiveness results for scenario assuming 1.5% discount rate for costs and effects

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
CAB LA + RPV LA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Oral ART regimens	[redacted]	[redacted]	[redacted]				

Based on Table 82 of the CS[1]
ART = antiretroviral therapy; CAB LA = cabotegravir long-acting; CS = company submission; ICER = incremental cost effectiveness ratio; LYG = life years gained; RPV LA = rilpivirine long-acting; QALY = quality adjusted life year

5.2.3.3 Variability in utility advantage associated with CAB LA + RPV LA

To address the impact of variability in the utility advantage that is offered by the long-acting injectable over daily oral therapy, the company performed a series of scenario analyses in which the utility advantage is varied using a range of 0.005 to 0.08. A value of [redacted] is used for the base case analysis, which was derived from the analysis of trial data as described in Section 4.2.8. To illustrate how the utility advantage may vary, the company refers to the results of a time trade-off (TTO) elicitation study performed to examine potential utility differences between treatment modalities.[110] The TTO study, which was conducted in people living with HIV in the UK using relevant health state vignettes, found that in individuals who showed a preference for long-acting injectable treatment over daily oral treatment, the utility advantage was up to [redacted] in some subgroups; thus, the estimated advantage derived from the trial may be conservative. The company notes this is expected as generic HRQoL instruments such as the SF-12 (from which the trial-based utility advantage was derived), have limited sensitivity to HIV-specific issues such as stigma. Of note, only individuals who express a desire for long-acting injectable treatment rather than daily oral treatment will switch to CAB LA + RPV LA in clinical practice; those who do not wish for injectable treatment will not form part of the user population. There are currently no other long-acting injectables available that could be used to validate these utility findings. CAB LA + RPV LA remained dominant across all variations of the utility advantage tested, as shown in Table 5.6 below.

Table 5.6: Cost effectiveness results for scenario where the utility advantage associated with long-acting injectable treatments is varied

Utility advantage	Incremental QALYs	Incremental LYG	Incremental costs (£)	ICER
[redacted] (Base-case)	[redacted]	[redacted]	[redacted]	Dominant
0.005	[redacted]	[redacted]	[redacted]	Dominant
0.01	[redacted]	[redacted]	[redacted]	Dominant
0.015	[redacted]	[redacted]	[redacted]	Dominant
0.025	[redacted]	[redacted]	[redacted]	Dominant
0.03	[redacted]	[redacted]	[redacted]	Dominant
0.035	[redacted]	[redacted]	[redacted]	Dominant
0.04	[redacted]	[redacted]	[redacted]	Dominant
0.045	[redacted]	[redacted]	[redacted]	Dominant
0.05	[redacted]	[redacted]	[redacted]	Dominant
0.055	[redacted]	[redacted]	[redacted]	Dominant

Utility advantage	Incremental QALYs	Incremental LYG	Incremental costs (£)	ICER
0.06	[redacted]	[redacted]	[redacted]	Dominant
0.065	[redacted]	[redacted]	[redacted]	Dominant
0.07	[redacted]	[redacted]	[redacted]	Dominant
0.075	[redacted]	[redacted]	[redacted]	Dominant
0.08	[redacted]	[redacted]	[redacted]	Dominant

Based on Table 83 of the CS[1]
CS = company submission; ICER = incremental cost effectiveness ratio; LYG = life years gained; QALY = quality adjusted life year

5.2.3.4 Variability in adherence reduction with daily oral treatments

To address the uncertainty caused by the variable nature of measuring and reporting adherence, the company performed a scenario analysis where the reduction in adherence applied to daily oral ART is varied. CAB LA + RPV LA remained cost effective and was associated with cost savings and a utility gain with all values tested, as shown in Table 5.7 below.

Table 5.7: Cost effectiveness results for scenario where the reduction in adherence for daily oral treatment is varied

Utility advantage	Incremental QALYs	Incremental LYG	Incremental costs (£)	ICER
25.6% (Base-case)	[redacted]	[redacted]	[redacted]	Dominant
5%	[redacted]	[redacted]	[redacted]	Dominant
10%	[redacted]	[redacted]	[redacted]	Dominant
15%	[redacted]	[redacted]	[redacted]	Dominant
20%	[redacted]	[redacted]	[redacted]	Dominant
25%	[redacted]	[redacted]	[redacted]	Dominant
30%	[redacted]	[redacted]	[redacted]	Dominant
35%	[redacted]	[redacted]	[redacted]	Dominant
40%	[redacted]	[redacted]	[redacted]	Dominant

Based on Table 84 of the CS[1]
CS = company submission; ICER = incremental cost effectiveness ratio; LYG = life years gained; QALY = quality adjusted life year

5.2.3.5 Zero probability of HIV transmission for individuals with an undetectable viral load

During the clarification phase, the ERG asked why the company assumed a 0.0031% probability for HIV transmission for MSM despite stating that individuals with an undetectable viral load (i.e. classed as <50 HIV RNA copies per ml) cannot sexually transmit HIV.[11] In the response, the company acknowledged the widespread acceptance that individuals with an undetectable viral load cannot sexually transmit HIV and provided the results of a scenario analysis where a zero probability of transmission was assumed for these individuals.[2] These results are provided in Table 5.8 below, showing that changing this assumption had little impact on the results, with only slight changes in total costs and the same small increases in total life years and QALYs for both arms.

Table 5.8: Cost effectiveness results for scenario assuming a zero probability of HIV transmission for individuals with an undetectable viral load

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
CAB LA + RPV LA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Oral ART regimens	[redacted]	[redacted]	[redacted]				

Based on Table 22 in the response to request for clarification[2]
ART = antiretroviral therapy; CAB LA = cabotegravir long-acting; CS = company submission; ICER = incremental cost effectiveness ratio; LYG = life years gained; RPV LA = rilpivirine long-acting; QALY = quality adjusted life year

5.2.3.6 Additional mortality probabilities for ADEs excluded

The company base-case assumed mortality probabilities for ADEs in addition to the relative risks of death for different CD4+ classes, as derived from Lewden et al. 2007, which would imply that Lewden et al. excluded these additional probabilities in their estimates.[93] In response to the ERG's request to provide the option in the model to exclude these additional probabilities, the company performed a scenario analysis (i.e. instead of providing the option in the model) where the probability of experiencing ADEs is set to zero. This only had a limited impact on the results, as shown in Table 5.9 below, with only slight increases in total costs for both arms and the same small increases in total life years and QALYs for both arms.

Table 5.9: Cost effectiveness results for scenario assuming zero probabilities of experiencing ADEs

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
CAB LA + RPV LA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Oral ART regimens	[redacted]	[redacted]	[redacted]				

Based on Table 28 in the response to request for clarification[2]
ART = antiretroviral therapy; CAB LA = cabotegravir long-acting; CS = company submission; ICER = incremental cost effectiveness ratio; LYG = life years gained; RPV LA = rilpivirine long-acting; QALY = quality adjusted life year

5.2.3.7 Alternative health care resource use estimates

As described in the ERG comment in section 4.2.9.3, the company performed a scenario analysis where alternative health care resource use estimates were used that correspond to clinician advice. These results were provided in response to the ERG's clarification questions and are shown in Table 5.10. The use of these alternative health care resource use estimates had little impact on the incremental costs, although the estimates of total costs in each treatment arm decreased substantially.

Table 5.10: Cost effectiveness results for scenario assuming alternative health care resource use estimates

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
CAB LA + RPV LA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Oral ART regimens	[redacted]	[redacted]	[redacted]				

Based on Table 35 of the response to request for clarification[2]
ART = antiretroviral therapy; CAB LA = cabotegravir long-acting; CS = company submission; ICER = incremental cost effectiveness ratio; LYG = life years gained; RPV LA = rilpivirine long-acting; QALY = quality adjusted life year

5.2.3.8 Cost of 'basket of comparators' based on weighted average of 'switch share by regimen'

In response to the ERG's request during the clarification phase to provide the option in the model to use an average cost for the 'basket of comparators' weighted by the 'switch share by regimen', as provided in Table 55 of the CS, the company performed a scenario analysis (i.e. instead of providing the option in the model) in which a weighted adjusted average monthly cost of £741.54 was used instead of the £731.86 that was used for the base case.[2, 11] The results of this scenario are provided in Table 5.11, and show that changing this assumption had little impact on the results.

Table 5.11: Cost effectiveness results for scenario assuming a weighted average cost for the 'basket of comparators'

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
CAB LA + RPV LA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Oral ART regimens	[redacted]	[redacted]	[redacted]				

Based on Table 36 of the response to request for clarification[2]
ART = antiretroviral therapy; CAB LA = cabotegravir long-acting; CS = company submission; ICER = incremental cost effectiveness ratio; LYG = life years gained; RPV LA = rilpivirine long-acting; QALY = quality adjusted life year

5.2.3.9 Alternative costs for non-HIV medication

During the clarification phase, the ERG requested justification for the validity of the cost estimates derived from Beck et al. 2011 for non-HIV medication which were based on 2008 costs.[107] In response to this request, the company provided the results of two sets of scenario analyses: one where the original estimates for the costs were halved, and one where the costs of non-HIV medication were excluded.[2] These results are provided in Tables 5.12 and 5.13, respectively, showing that these alternative estimates had little impact on the incremental costs despite decreasing the total costs per treatment.

Table 5.12: Cost effectiveness results for scenario where non-HIV medication costs were halved

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
CAB LA + RPV LA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Oral ART regimens	[redacted]	[redacted]	[redacted]				
Based on Table 37 of the response to request for clarification[2] ART = antiretroviral therapy; CAB LA = cabotegravir long-acting; CS = company submission; ICER = incremental cost effectiveness ratio; LYG = life years gained; RPV LA = rilpivirine long-acting; QALY = quality adjusted life year							

Table 5.13: Cost effectiveness results for scenario where non-HIV medication costs were excluded

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
CAB LA + RPV LA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Oral ART regimens	[redacted]	[redacted]	[redacted]				
Based on Table 38 of the response to request for clarification[2] ART = antiretroviral therapy; CAB LA = cabotegravir long-acting; CS = company submission; ICER = incremental cost effectiveness ratio; LYG = life years gained; RPV LA = rilpivirine long-acting; QALY = quality adjusted life year							

5.2.3.10 Summary of scenario analyses results

All the scenario analyses that were performed by the company show that the base-case cost effectiveness results are robust to alternative structural assumptions and variations in input parameters.

5.3 Model validation and face validity check

5.3.1 Technical verification

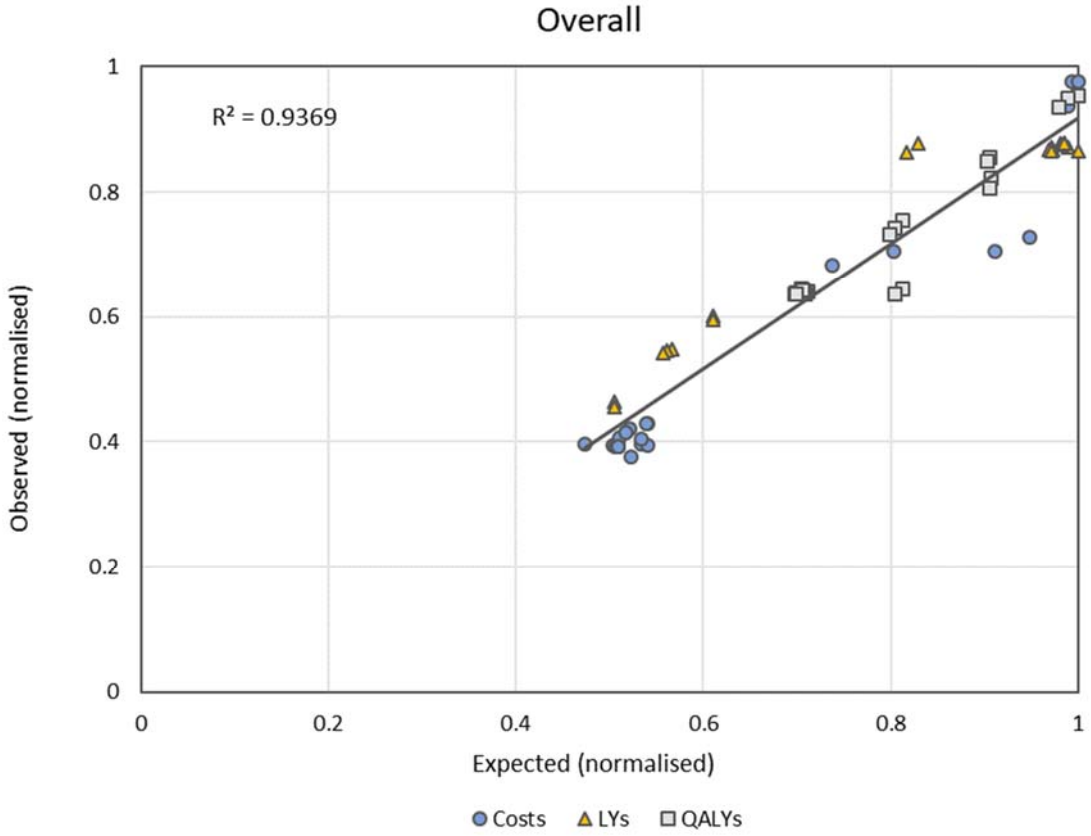
The CS reported that the model had been thoroughly examined for calculation and application errors and that multiple senior analysts have been involved in a quality assessment of functionality of the model and input of relevant parameters.

5.3.2 Comparisons with other cost effectiveness studies

Studies to which the economic model's outcomes could be compared were identified from a grey literature search and a review of previous cost effectiveness studies in HIV.[59] Only models with structures that the CAB LA + RPV LA model could adequately replicate (minimum four therapy lines, three definable ART lines and a 4th line of therapy) were considered in the validation.[1] For each validation exercise, model inputs (demographics, baseline risk factors, HIV disease status, costs, and quality of life values) corresponding to published profiles were entered into the CAB LA + RPV LA cost-effectiveness model workbook. Where required inputs were not reported, default model inputs were used, or reasonable assumptions were made. Details of the five validation studies included and assumptions made can be found in Table 85 of the CS.[1] Goodness of fit of predicted values for total costs, QALYs and ICERs compared with the published values was measured using the coefficient of determination (R^2), mean absolute percentage error (MAPE) and the root mean square percentage error (RMSPE).[1]

The HIV CAB LA + RPV LA cost effectiveness model was found to exhibit a high degree of consistency with previously published cost effectiveness analyses with an overall R^2 value of 0.937 and RMSPE and MAPE values of 14.7% and 17.7%, respectively, the HIV CAB LA + RPV LA. A graphical representation of the relationship between the observed and predicted endpoints of the individual studies is shown in Figure 5.3.

Figure 5.3: Normalised observed (model predicted) versus expected (published results) validation results for costs, life years (LYs) and quality adjusted life years (QALYs) from the HIV CAB LA + RPV LA cost effectiveness model



Based on Figure 17 of the CS[1]
CS = company submission; HIV = human immunodeficiency virus; LYs = life years; QALYs = quality adjusted life years

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the ERG

6.1.1 Explanation of the company adjustments after the request for clarification

No changes in the model were implemented by the company in response to the ERG's clarification questions.

6.1.2 Explanation of the ERG adjustments

The changes that the ERG can make (to the model received with the response to the clarification letter) were subdivided into the following three categories (according to Kaltenthaler et al. 2016[111]):

- Fixing errors (correcting the model where the company's electronic model was unequivocally wrong).
- Fixing violations (correcting the model where the ERG considered that the NICE reference case, scope or best practice has not been adhered to).
- Matters of judgement (amending the model where the ERG considered that reasonable alternative assumptions are preferred).

In the current assessment, only matters of judgement played a role. After the proposed changes were implemented in the company's model, additional scenario analyses were explored by the ERG in order to assess the impact of alternative assumptions on the cost effectiveness results.

6.1.2.1 Fixing errors

No errors were corrected by the ERG in the model provided in response to the clarification letter.

6.1.2.2 Fixing violations

No violations were applicable to this appraisal.

6.1.2.3 Matters of judgement

The ERG's preferences regarding reasonable alternative assumptions led to the following changes to the company model:

- The ERG changed the reduction in adherence for oral ART relative to CAB LA + RPV LA from 25.6% to 10.1% (see Section 4.2.6.4).
- The ERG assumed a zero probability of onwards transmission for patients with an undetectable viral load (see section 4.2.6.5).

The overview of the changes and the bookmarks for the justification of the ERG changes are presented in Table 6.1.

Table 6.1: Company and ERG base-case preferred assumptions

Base-case preferred assumptions	Company	ERG	Justification for change
Reduction in adherence for oral ART	25.6%	10.1%	Section 4.2.6.4
Probability of onwards transmission for patients with an undetectable viral load	0.031%	0%	Section 4.2.6.5
ART = antiretroviral therapy; ERG = Evidence Review Group			

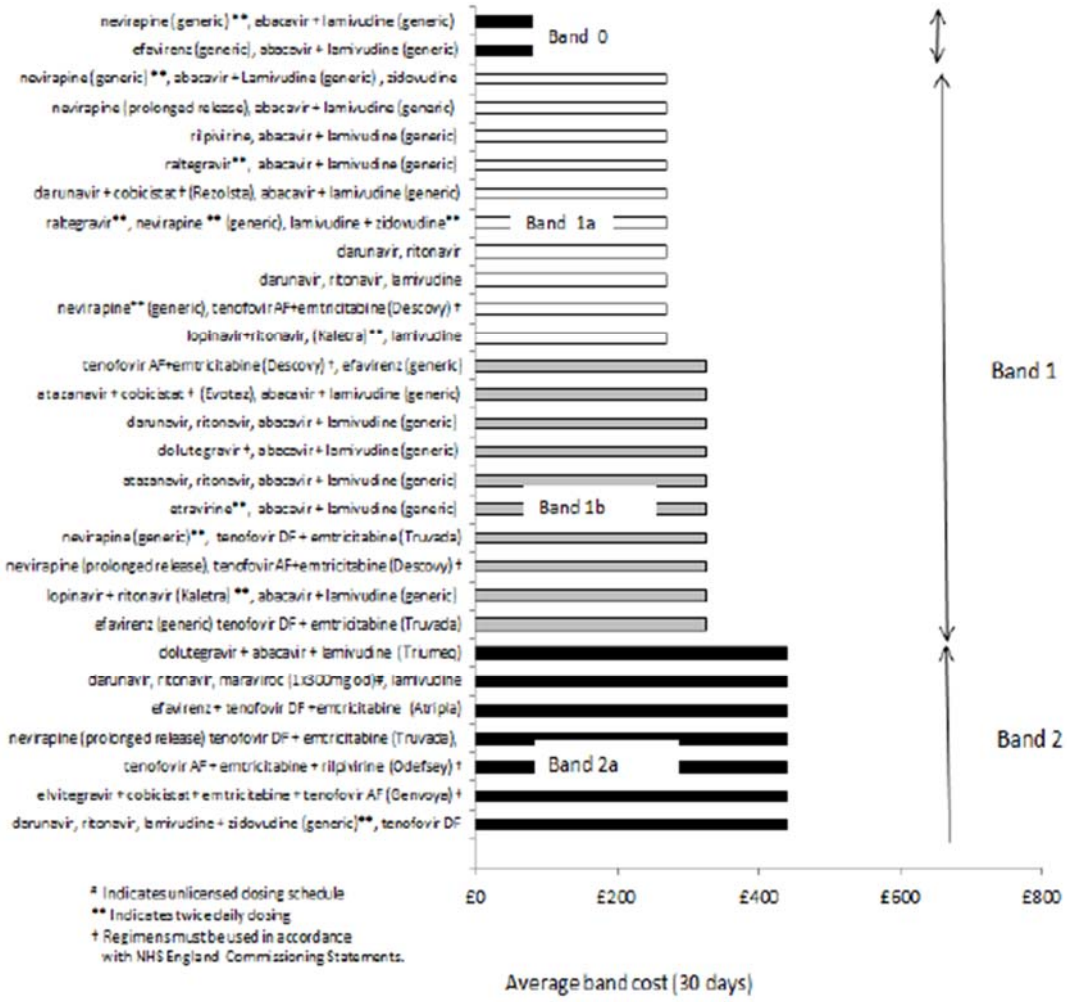
6.1.3 Additional scenarios conducted by the ERG

The ERG conducted a series of scenario analyses to explore the impact of key assumptions and uncertainties within the cost effectiveness analyses. These uncertainties were related to the cost of the 'basket of comparators', assumptions regarding adherence, health-related quality of life and the disease transmission model.

6.1.3.1 Scenario set 1: Alternative costs for the 'basket of comparators'

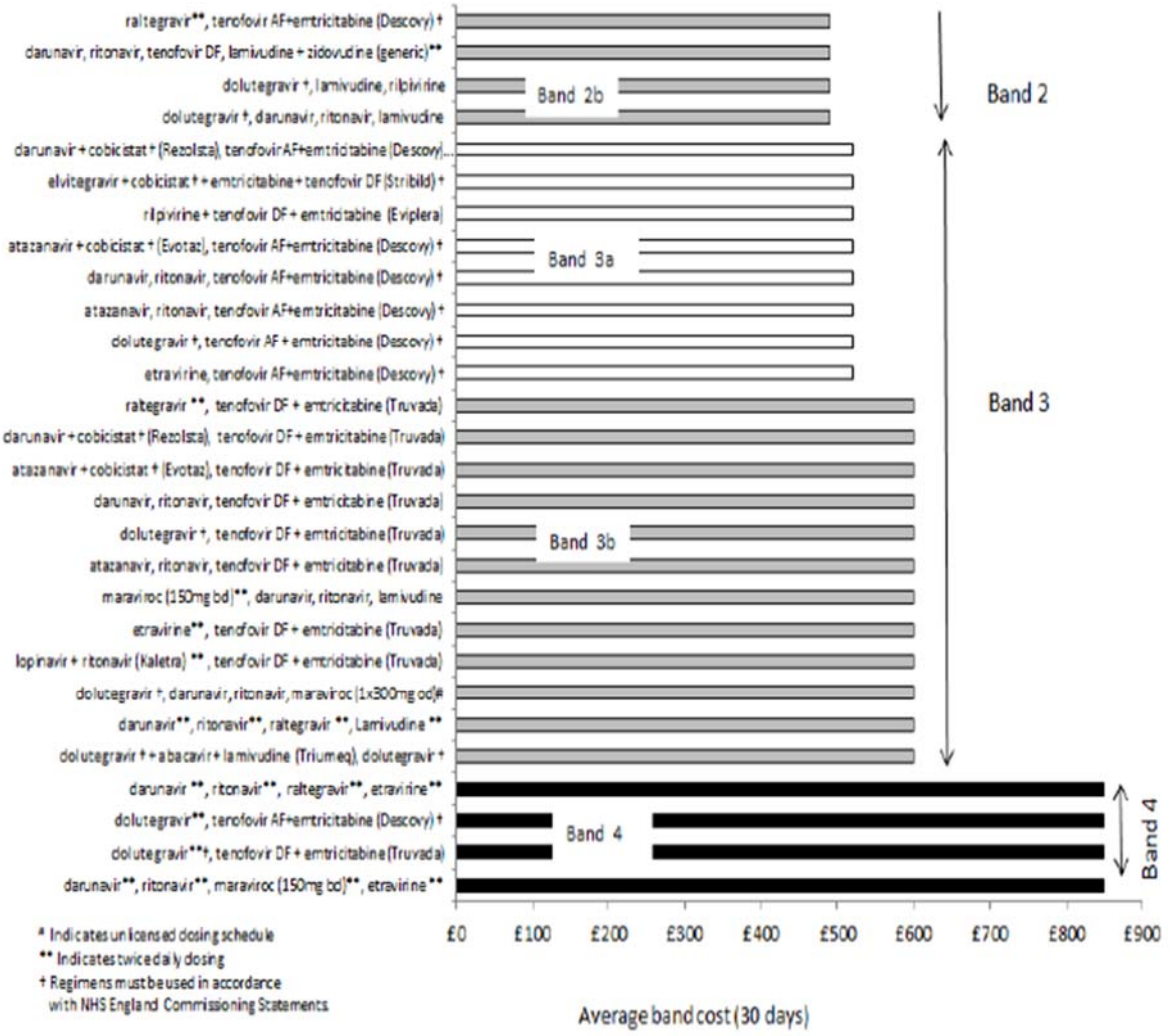
A series of scenario analyses was performed where various alternative costs are assumed for the costs of the 'basket of comparators'. These costs were derived from the information provided by the company in response to the ERG's clarification question B1 on commonly used ART regimens used by patients who switch regimen in the Midlands and East region, as shown in Figures 6.1 and 6.2 below.[2] The ERG calculated the average cost per calendar month for ART regimens in Band 0, Band 1 (weighted average of 1a and 1b), Band 2 (weighted average of 2a and 2b), Band 3 (weighted average of 3a and 3b) and Band 4, a weighted average over Bands 0-4, a weighted average over Bands 0-4 whilst excluding Truvada-based regimens, a weighted average over Bands 2-4, and a weighted average over Bands 2-4 whilst excluding Truvada-based regimens. Averages were weighted by the number of regimens contained in each cost band (Table 6.2). Note that the costs per band were reported in 2017, and only from one of the four main regions, thus, this scenario mainly explores the impact of various choices for the costs of the comparator on the cost-effectiveness of CAB LA + RPV LA.

Figure 6.1: Commonly used ART regimens used by patients who switch regimen in the Midlands and East region (part 1)



Based on Figure 2 of the response to request for clarification[2], ART = antiretroviral therapy

Figure 6.2: Commonly used ART regimens used by patients who switch regimen in the Midlands and East region (part 2)



Based on Figure 3 of the response to request for clarification[2], ART = antiretroviral therapy

Table 6.2: Alternative costs for the 'basket of comparators'

Cost per calendar month for 'basket of comparators'	Value
ERG and company base-case	£731.86
Scenario 1a: Band 0	£87
Scenario 1b: Band 1 (weighted average of 1a and 1b)	£304
Scenario 1c: Band 2 (weighted average of 2a and 2b)	£466
Scenario 1d: Band 3 (weighted average of 3a and 3b)	£580
Scenario 1e: Band 4	£869
Scenario 1f: Bands 0, 1, 2, 3 and 4 (weighted average)	£464
Scenario 1g: Bands 0, 1, 2, 3 and 4 (weighted average excluding Truvada-based regimens)	£435
Scenario 1h: Bands 2, 3 and 4 (weighted average)	£577
Scenario 1i: Bands 2, 3 and 4 (weighted average excluding Truvada-based regimens)	£560
ERG = Evidence Review Group	

6.1.3.2 Scenario set 2: 100% adherence assumed for oral ARTs

In section 4.2.6.4, it was mentioned that a scenario analysis that assumes 100% adherence in all patients (so that the maximum viral suppression is assumed for all patients) was performed. This is done to address uncertainty regarding the use of the adherence parameter in the model and to represent a situation where viral suppression is adequate in all patients (i.e. even in those with suboptimal adherence). On the one hand, this assumption ensures that no adjustment factor is applied to reduce viral suppression for patients on oral ARTs, and on the other hand, this prevents the occurrence of non-adherent patients on oral ARTs in the first modelled treatment line switching to the next therapy line. As such, there is no difference between intervention and comparator in the way that patients transition through the model. The ERG notes that this should be regarded as an extreme scenario since a certain level of suboptimal adherence can be expected for patients on oral ARTs.

6.1.3.3 Scenario set 3: Health-related quality of life

Different sources of HSUVs by CD4 count identified in the literature were explored in a range of scenarios to examine the impact on results of using HSUVs from Kauf et al. 2008[94] The utility values assumed in each HSUV scenario are shown in Table 6.3. Bolded values show where the ERG had to make an adjustment to values identified in the literature, where either multiple values were available per CD4 category (in Simpson et al. 2007 and Pialoux et al. 2018[96, 98]) or the utilities reported in the literature did not maintain a consistent trend in improved HRQoL with improved CD4 count (as was the case for one value from Stavem et al 2005[99]). Given the uncertainty in the size and presence of the utility advantage of [redacted] for CAB LA + RPV LA over comparator ARTs, the ERG tested scenarios of [redacted] and 0 utility advantages, to explore the potential that higher drop out in the reporting of utility in CAB LA + RPV LA patients and the exclusion of injection site reactions may have biased the utilities in favour of CAB LA + RPV LA.

Table 6.3: HRQoL scenario

CD4+ cell count category (cells/mm^3)	Kauf 2008[94]	Simpson 2007[96]	Marcellusi 2016[97]	Pialoux 2018[98]	Stavem 2005[99]
<50	0.742	0.781	0.788	0.83	0.55
50-200	0.75	**0.8445***	0.788	**0.865***	0.73
200–350	0.778	**0.931***	0.855	0.9	0.87
350–500	0.784	**0.9325***	0.859	0.9	0.87
>500	0.798	**0.946***	0.872	0.9	**0.87****

Original values reported in the literature can be seen in Table 4.15. Adjusted values are bolded.
* Average value used; ** Last value carried forward to maintain consistent trend
CD = cluster of differentiation; HSUVs = health state utility values

6.1.3.4 Scenario set 4: Disease transmission mode scenarios

Several sets of assumptions from the transmission model were also tested, to explore various uncertainties in this analysis. First, the ERG reinstated the non-zero probability of MSM transmission in individuals with a viral load <50 copies/ml, while simultaneously including the non-zero probabilities of heterosexual transmission in the same viral load group, as reported in the clarification response. In two other scenarios the lifetime QALYs of a newly infected patients were increased by 20% and lifetime costs of newly infected patients were decreased to 80% of their assumed value to examine the impact of these parameter on results, as these were found to be the most influential parameters in the disease transmission DSA conducted by the company.

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

6.2.1 Results of the ERG preferred base-case scenario

The ERG preferred base-case incremental cost effectiveness results, provided in Table 6.4, indicate that CAB LA + RPV LA is dominant over oral ART regimens. Total costs associated with CAB LA + RPV LA were estimated at [redacted] (including [redacted] from the onwards transmission module) and total costs associated with oral ART regimens were estimated at [redacted] (including [redacted] from the onwards transmission module), indicating that CAB LA + RPV is cost saving at an incremental cost of [redacted]. Total QALYs associated with CAB LA + RPV LA were estimated at [redacted] (including [redacted] QALYs lost from the onwards transmission module) and total QALYs associated with oral ART regimens were estimated at [redacted] (including [redacted] QALYs lost from the onwards transmission module), indicating an incremental number of [redacted] QALYs gained with CAB LA + RPV LA. In comparison to the company's base-case results, the ERG preferred base-case estimated total costs slightly lower for both arms and total life years and QALYs higher. The incremental costs estimate was only slightly decreased but estimates of incremental life years and QALYs were substantially reduced.

Table 6.4: ERG preferred base-case deterministic cost effectiveness results (discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
CAB LA + RPV LA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Oral ART regimens	[redacted]	[redacted]	[redacted]				

Based on ERG preferred version of the electronic model
ART = antiretroviral therapy; CAB LA = cabotegravir long-acting; ICER = incremental cost effectiveness ratio; LYG = life years gained; RPV LA = rilpivirine long-acting; QALY = quality adjusted life year

The ERG preferred probabilistic cost effectiveness results, provided in Table 6.5, are consistent with the deterministic results and also indicate that CAB LA + RPV LA is dominant over oral ART regimens. Total costs associated with CAB LA + RPV LA were estimated at [redacted] (including [redacted] from the onwards transmission module) and total costs associated with oral ART regimens were estimated at [redacted] (including [redacted] from the onwards transmission module), indicating that CAB LA + RPV is cost saving at an incremental cost of [redacted]. Total QALYs associated with CAB LA + RPV LA were estimated at [redacted] (including [redacted] QALYs lost from the onwards transmission module) and total QALYs associated with oral ART regimens were estimated at [redacted] (including [redacted] QALYs lost from the onwards transmission module), indicating an incremental number of [redacted] QALYs gained with CAB LA + RPV LA. The CE-plane and CEAC are provided in Figures 6.3 and 6.4. At incremental cost effectiveness ratio (ICER) thresholds of £20,000 and £30,000, CAB LA + RPV LA has a 100% probability of being cost effective relative to oral ART regimens.

Table 6.5: ERG preferred probabilistic cost effectiveness results (discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
CAB LA + RPV LA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Oral ART regimens	[redacted]	[redacted]	[redacted]				

Based on ERG preferred version of the electronic model
ART = antiretroviral therapy; CAB LA = cabotegravir long-acting; ICER = incremental cost effectiveness ratio; LYG = life years gained; RPV LA = rilpivirine long-acting; QALY = quality adjusted life year

Figure 6.3: Cost effectiveness plane

[redacted]

Based on ERG preferred version of the electronic model
CE = cost effectiveness; CI = confidence interval; QALY = quality adjusted life years; WTP = willingness to pay

Figure 6.4: Cost effectiveness acceptability curve

[redacted]

Based on ERG preferred version of the electronic model
CAB LA = cabotegravir long-acting; RPV LA = rilpivirine long-acting.

6.2.2 Results of the ERG additional exploratory scenario analyses

6.2.2.1 Scenario set 1 results: Alternative costs for the 'basket of comparators'

The results of scenario analyses set 1, using various alternative inputs for the cost of the 'basket of comparators' based on different ART regimen cost bands, are provided in Table 6.6 below. In these

scenarios, the incremental costs varied between [redacted] and [redacted] when using the lowest and highest alternative costs for the 'basket of comparators' respectively. CAB LA + RPV LA remained dominant over oral ARTs in all scenarios except when using the costs of Band 0, Band 1 or Bands 0, 1, 2, 3 and 4 (weighted average excluding Truvada-based regimens) which resulted in ICERs of [redacted], [redacted] or [redacted] per QALY gained respectively. This highlights the sensitivity of the results to alternative assumptions on the costs of the 'basket of comparators'

Table 6.6: Scenario set 1: Alternative costs for the 'basket of comparators'

Scenario	CAB LA + RPV LA		Oral ART regimens		Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs			
ERG base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Scenario 1a: Band 0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	146,638
Scenario 1b: Band 1 (weighted average of 1a and 1b)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	60,115
Scenario 1c: Band 2 (weighted average of 2a and 2b)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Scenario 1d: Band 3 (weighted average of 3a and 3b)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Scenario 1e: Band 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Scenario 1f: Bands 0, 1, 2, 3 and 4 (weighted average)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Scenario 1g: Bands 0, 1, 2, 3 and 4 (weighted average excluding Truvada-based regimens)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	7,958
Scenario 1h: Bands 2, 3 and 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Scenario	CAB LA + RPV LA		Oral ART regimens		Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs			
(weighted average)							
Scenario 1i: Bands 2, 3 and 4 (weighted average excluding Truvada-based regimens)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Based on ERG preferred version of the electronic model
ART = antiretroviral therapy; CAB LA = cabotegravir long-acting; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; RPV LA = rilpivirine long-acting; Incr. = incremental; QALY = quality adjusted life year

6.2.2.2 Scenario set 2: 100% adherence assumed for oral ARTs

The results of scenario 2, assuming 100% adherence (i.e. no reduction) for oral ART regimens, are provided in Table 6.7 below. In this scenario CAB LA + RPV LA remained dominant over oral ARTs, with a slight decrease in incremental costs and a decrease in incremental QALYs gained.

Table 6.7: Scenario 2 results: 100% adherence assumed for oral ARTs

Adherence reduction for oral ART regimens	CAB LA + RPV LA		Oral ART regimens		Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs			
10.1% (ERG base-case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Based on ERG preferred version of the electronic model
ART = antiretroviral therapy; CAB LA = cabotegravir long-acting; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; RPV LA = rilpivirine long-acting; Incr. = incremental; QALY = quality adjusted life year

6.2.2.3 Scenario set 3: Health-related quality of life

Scenario results in Table 6.8 demonstrate that the values selected by the company in the base-case actually result in the most conservative incremental QALY estimate, with the largest difference seen when using the HSUVs from Simpson et al., which increases the QALYs gained by 0.016.[112]

Reducing the size of the assumed utility advantage for patients taking CAB LA + RPV LA over standard ART of [redacted] had a much larger impact on the incremental QALYs. Halving the size of the utility advantage resulted in the incremental QALYs dropping from [redacted] to [redacted]. Removing the treatment related utility advantage altogether decreased the incremental QALYs to [redacted], although CAB LA + RPV LA still remained dominant in all scenarios, with incremental QALYs remaining positive.

Table 6.8: HRQoL scenarios results

Source of utilities	CAB LA + RPV LA		Oral ART regimens		Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs			
HSUVs							
Kauf (BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Simpson	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Marcellusi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Pialoux	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Stavem	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
CAB LA + RPV LA utility advantage							
[redacted] (BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

ERG preferred base case, applied in electronic model from the response to the clarification letter[112]

ART = antiretroviral therapy; BC = base-case; ERG = Evidence Review Group; HSUV = health state utility value; ICER = incremental cost-effectiveness ratio; Incr. = incremental; QALY = quality adjusted life year

6.2.2.4 Scenario set 4: Disease transmission model

Table 6.9 shows that assuming the non-zero probabilities of transmission in patients with <50 copies/ml which were presented in the clarification response had a minimal impact on the ICER. The impact of increasing the lifetime QALYs per newly infected patient or decreasing the assumed lifetime costs was larger, but the impact remained small. As these lifetime cost and QALY assumptions were shown by the company to be the most influential on the results of the disease transmission model, this demonstrates that assumptions in the disease transmission model are not drivers of overall costs.

Table 6.9: Disease transmission model scenario results

Disease transmission model	CAB LA + RPV LA		Oral ART regimens		Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs			
Zero <50 copies/ml transmission probabilities per sex act (BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Non-zero <50 copies/ml transmission probabilities per sex act	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Disease transmission model	CAB LA + RPV LA		Oral ART regimens		Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs			
Lifetime QALYs per newly infected patients 120% of BC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Lifetime costs per newly infected patients 80% of BC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
ERG preferred base case, applied in electronic model from the response to the clarification letter[112]							
ART = antiretroviral therapy; BC = base-case; ERG = Evidence Review Group; ICER = incremental cost-effectiveness ratio; Incr. = incremental; QALY = quality adjusted life year							

6.3 ERG's preferred assumptions

Table 6.10 below displays the step-by-step changes which the ERG made to the company base-case alongside the cumulative impact of each change added to the previous changes on results. The change which had the largest impact on results was applying a reduction in adherence for oral ART regimens of 10.1%, instead of the 25.6% assumed by the company. This decreased the incremental QALYs to [redacted]. The ERG preferred assumption of a zero probability of onwards transmission for patients with an undetectable viral load had a minimal impact on the results.

Table 6.10: Incremental impact of ERG preferred assumptions

Preferred assumption (Section in ERG report)	CAB LA + RPV LA		Oral ART regimens		Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs			
Company base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
+ Reduction in adherence for oral ART regimens of 10.1%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
+ Zero probability of onwards transmission for patients with an	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Preferred assumption (Section in ERG report)	CAB LA + RPV LA		Oral ART regimens		Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs			
undetectable viral load							
Based on ERG preferred version of the electronic model ART = antiretroviral therapy; CAB LA = cabotegravir long-acting; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; RPV LA = rilpivirine long-acting; Incr. = incremental; QALY = quality adjusted life year							

6.4 Conclusions of the cost effectiveness section

The key uncertainties that underlie the cost effectiveness results are related to the assumptions regarding adherence of patients on oral ARTs, the costs of the 'basket of comparators' and lack of transparency about the implementation of important aspects and their underlying assumptions in the model.

Regarding adherence, the uncertainties relate to:

1. which level of adherence can be assumed for patients on oral ARTs in the UK,
2. the appropriateness of expressing the adherence level in the current context as a proportion of patients who do not meet a predefined cut-off value of adherence that is commonly defined as ≥95%, i.e. also considering literature that indicates that a substantially lower level of adherence could still be assumed to provide adequate viral suppression,
3. the use of an adherence estimate that is defined as a proportion of patients who do not meet a predefined cut-off value as an input for an estimated linear relationship between adherence measured at the individual level and viral suppression, and
4. the model implementation (for which no explanation or justification was provided) that non-adherent patients experience viral rebound and switch to the next treatment line within one month. For their base-case analysis, the ERG assumed a reduction in adherence for patients on oral ARTs of 10.1% instead of the 25.6% that was assumed by the company. The estimate of 10.1% is derived from a UK multi-clinic study and based on a definition of suboptimal adherence as 'having missed ≥2 doses in the past seven days' that would correspond, assuming a single daily dose, to a cut-off value of 71% adherence. The ERG has more confidence in the assumption that viral suppression is reduced in patients who do not meet this level of adherence than in patients who do not meet an adherence level of ≥95% (i.e. which was the cut-off value used in the study by Cooper et al. 2011 that the company used to estimate the reduction in adherence).[82]

The ERG also performed an extreme case scenario that assumed 100% adherence for patients on oral ARTs, which implies that no reduction is applied to viral suppression for oral ARTs and which removes the possibility of non-adherent patients on oral ARTs in the first modelled treatment line experiencing viral rebound and switching treatment within one month. As such, in the scenario with 100% adherence patients transition through the model in exactly the same way for intervention and comparator. This scenario resulted in a slight decrease in incremental costs and a decrease in incremental QALYs gained (0.18) compared to the ERG base case, and CAB LA + RPV LA still being dominant over oral ART regimens.

Regarding the costs of the 'basket of comparators', it is uncertain which ART regimens patients facing the challenges of oral ART (i.e. patients for whom CAB LA + RPV LA could be considered if it were

available) are switching to. As such, it is also uncertain which drug acquisition costs are appropriate to assume for the comparator arm. The ERG performed a series of scenario analyses where various alternative costs are assumed for the 'basket of comparators', which were based on the costs of drugs in different Bands of ART regimens that are commonly used in patients who switch regimen in the Midlands and East region. In these scenarios the incremental costs varied between [redacted] and [redacted] when using the lowest and highest alternative costs for the 'basket of comparators', respectively. CAB LA + RPV LA remained dominant over oral ARTs in all scenarios except when using the costs of Band 0, Band 1 or Bands 0, 1, 2, 3 and 4 (weighted average excluding Truvada-based regimens) which resulted in ICERs of [redacted], [redacted] or [redacted] per QALY gained respectively. This highlights the sensitivity of the results to alternative assumptions on the costs of the 'basket of comparators'.

Regarding the lack of transparency about the implementation of important aspects and their underlying assumptions in the model, the ERG considers it important that no explanation and justification was provided for how the company has appeared to model the reduction in adherence for oral ART regimens as a monthly probability of patients in the first modelled treatment line experiencing viral rebound and switching to the second modelled treatment line. The implementation of this aspect is the single determinant of there being a difference in the way that patients transition through the model. The ERG further notes that no documentation was provided of clinical opinion consulted by the company to inform assumptions, so that these aspects could not be reviewed by the ERG.

In summary, the cost effectiveness of CAB LA + RPV LA relative to oral ARTs was evaluated using a hybrid model that consists of a Markov model for transitions between health states based on CD4+ cell counts in combination with a decision tree process for deciding which patients switch to subsequent treatment lines, with a maximum of four lines in total, with each subsequent treatment line having different efficacy profiles in relation to the reasons for switching and development of viral resistance to previous treatment lines. In the first modelled treatment line, a proportion of patients with suboptimal adherence on oral ARTs was assumed to experience viral rebound and switch to the next treatment line. For the second and further modelled treatment lines, suboptimal adherence was assumed to be associated with a reduction in viral suppression for patients on oral ARTs. The model also included an onwards transmission module to account for the risk of patients who are not virally suppressed transmitting HIV onwards. An important simplification that was made in the model relates to the monthly probabilities of patients transitioning to different health states, viral loads and treatments which would imply that such changes are detected through testing of CD4+ cell counts, viral load, and clinical consultation at a monthly frequency in clinical practice, which is not realistic. The monthly health care resource use estimates that are applied in the model are therefore proportional to the frequencies of use that are assumed to correspond to clinical practice.

In the disease transmission model, there were several inconsistencies between the model parameters reported in the clarification response, the parameters implemented in the model and the assumptions reported in the CS. The CS reportedly stated that it was assumed that individuals with a viral load<50 copies/ml could not transmit HIV. However, in the clarification response, non-zero transmission probabilities were provided per sexual act for individuals with a viral load<50 copies/ml, estimated using a mathematical relationship reported in a report by Public Health Canada.[90] However, in the model, zero-probabilities were assumed for the heterosexual group, but non-zero probabilities were assumed for the MSM group. Given more recent large studies which showed that no transmissions occurred in individuals with viral loads <200 copies/ml, the ERG assumed probabilities of zero for all individuals with a viral load<50 copies/ml and question the reliability of the data and probabilities used

by the company in the base-case. However, scenarios show that the disease transmission model is not a driver of results and therefore these are not considered key issues.

HRQoL was measured in the ATLAS and FLAIR trials, but not in ATLAS-2M. The ATLAS/FLAIR SF-12 data were valued using the SF-6D UK scoring algorithm, but the trial data was not stratified by CD4 count and therefore could not be used for the HSUVs required in the model. HSUVs were assumed from Kauf et al 2008, measured using the SF-36 and valued using a UK SF-6D algorithm. Alternative EQ-5D values per CD4 category were available in the literature, but either based on UK tariffs from a small sample, or based on a large sample, with an unknown country-specific tariff. However, scenarios showed that the choice of HSUVs had a limited impact on results and therefore this was not considered a key issue.

The company also modelled a utility advantage for CAB LA + RPV LA over oral ARTs of [redacted], due to an observed difference of this size between groups in the ATLAS/FLAIR data. While the ERG acknowledge that it is possible that patients may have slightly better HRQoL while taking CAB LA + RPV LA, if they experience anxieties related to maintaining sufficient adherence on standard ARTs or if dosing schedules cause difficulties with usual activities or anxieties about regular pill taking in public, the ERG also feels there are uncertainties in the application of this utility advantage annually over the duration of treatment as drop-out in HRQoL reporting was higher in the CAB LA + RPV LA arm and if those with poorer HRQoL are more likely to fail to provide a measurement, this would bias the difference in favour of CAB LA + RPV LA. Additionally, the company assumed that the impact of injection site reactions were included in the ALTAS and FLAIR trial data. Given that SF-12 was only measured at baseline and weeks 24 and 48, only injection site reactions which occurred due to injections at week 20 and 44 would have been captured within the 4-week recall of the SF-12. Given that scores on the PIN questionnaire showed improvement over time between weeks 8, 24, and 48, it is likely that the impact of injection site reactions was larger for earlier injections which are not covered by the SF-12 data collection. Given the rarity of reactions ≥grade 3 and the short duration of each episode, the impact of excluding additional disutilities on QALYs lost is likely to be quite small. However, the ERG considers that again this choice may bias the utility analysis in favour of CAB LA + RPV LA. Reducing the size of the utility advantage for CAB LA + RPV LA substantially reduced the incremental QALY gain observed for CAB LA + RPV LA.

Costs and resource use were modelled including drug acquisition costs, drug administration costs, health state unit costs that include the costs of outpatient, day ward and inpatient attendances, non-HIV medication and testing procedures, costs for the management of injection site reactions, and end-of-life costs.

Only grade 3/4 injection site reactions were included in the model as adverse events. The costs of treatment for injection site reactions were included, but no utility decrement was applied for this. AIDS-defining events were included in the model through increased risks of mortality and utility decrements, whilst the costs of treatments for ADEs were assumed to be included within health care resource use estimates used to estimate CD4+ cell count-based health states. All-cause mortality was based on UK life tables and adjusted for increased HIV-related mortality based on CD4+ cell counts. End of life costs were applied to all patients in the final month of life.

In all ERG and company base-case and sensitivity analyses CAB LA + RPV was dominant over oral ART regimens in terms of cost-effectiveness, except when the costs for the 'basket of comparators' was assumed to correspond to the cost of a Band 0, Band 1 or Bands 0, 1, 2, 3 and 4 (weighted average excluding Truvada-based regimens) ART regimen. Relative to oral ART regimens, the use of CAB

LA + RPV would lead to savings in costs and QALY gains, except when the costs for the ‘basket of comparators’ corresponds to the cost of various Bands, as detailed before.

7 END OF LIFE

The CS did not include any statements regarding CAB LA + RPV LA (Q2M) meeting the end of life criteria defined by NICE, therefore this is not applicable.[1]

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National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Cabotegravir and rilpivirine for treating HIV-1 [ID3766]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG 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 11 May 2021** 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 separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'de-personalised data' in pink.

Issue 1 Adherence assumptions

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Table 1.11, page 20 The ERG state that: *"The appropriateness of using the reduction in adherence as a monthly probability of viral rebound and switching treatment regimen remains uncertain."* This contradicts earlier acknowledgements (see 'justification for amendments' section).	This sentence should be removed or rephrased to better describe the method of modelling adherence. Adherence assumptions are not implemented as a monthly probability of viral rebound. The modelling approach is more accurately described as: "The appropriateness of using an assumed reduction in adherence to model a reduction in the ART's effectiveness at virological suppression remains uncertain."	Currently, this statement suggests that adherence produces a probability of viral rebound, as opposed to reducing the effectiveness of an ART at preventing rebound. Further, the ERG acknowledges later in the document, in 4.2.6.4, that "*it is undisputable that optimal or near optimal adherence is associated with the lowest risk of virologic failure.*" Given that this relationship between adherence and virologic failure is acknowledged, regardless of whether the current values used in the model are appropriate, it should be included in the model. Virologic failure in the model is treated equally (i.e. leads to a treatment switch) regardless of the cause, as there is no evidence to suggest virologic failure due to poor adherence is less likely to result in a treatment switch.	Unclear whether this is a factual inaccuracy The ERG feels justification is needed why it is assumed that patients who become less than 95% adherent will immediately need to switch therapy and will immediately experience a viral load >50 HIV RNA copies per ml. The ERG considers it more plausible that it would require a longer period of adherence below the 95% threshold (potentially below a lower threshold) before the viral load increases and the patient is switched to another treatment.

Table 1.11, page 20 The ERG state that: *"This is the single determinant of the difference between intervention and comparator in how patients transition through the model, but no explanation nor justification was provided by the company on this important aspect."*	This sentence should be revised as it inaccurately communicates a failure by the company to explain or justify the methodology employed for modelling adherence.	A detailed explanation regarding why and how adherence was modelled is given in the CS, in Sections B.3.2.1, B.3.2.5, B.3.2.5.1 and B.3.3.2.3 and in Appendix P of the CS, in Sections 3.4 and 3.6. As highlighted above, it is incorrect to imply that the adherence was modelled as a probability of viral rebound.	Not a factual inaccuracy: Although the ERG agrees that the company has provided an explanation at several instances regarding how adherence affects viral suppression for those patients with a viral load above 50 HIV RNA copies per ml (i.e. after having switched treatment), the explanation does not include details regarding adherence and the probability of experiencing viral rebound before switching treatment. Using a deductive approach by interpreting the values in the Markov traces and back-calculation, it appears that this probability of experiencing viral rebound and switching treatment is derived from the assumed reduction in adherence.

			However, the ERG is uncertain whether this is indeed the way that the company intended to model this aspect and feels that it should be explained in more detail and that justification is needed for any underlying assumptions (see above) that this is based on. This in particular true given that it is the single determinant of the difference between intervention and comparator in how patients transition through the model.
Section 4.2.6 Page 93 The ERG report states: *"If the model were implemented following the company's explanation (as provided in the CS,[1] Appendix M,[2] technical report,[3] user guide and in response to the ERG's clarification questions[4]) there would be no difference between treatments*	The description of the methodology is inaccurate. The following is an appropriate summary of the method (as described in several instances in the CS); the ERG should rephrase wording in this section accordingly. "The company assumed that the proportion of people with sub-optimal adherence (from a review-identified study and defined as below 95%) approximates *mean adherence over the lifetime* and the capacity of oral	It is not the case that "all patients with an adherence below 95% experience virologic failure within one month and switch treatment due to virologic failure". This would imply that the 25.6% of people in the model (who were 'sub-optimally' adherent) instantly failed and switched therapy, which is not the case. This comment conflates the application of two separate assumptions in the model (i.e. what adherence might be over the life of	Unclear whether this is a factual inaccuracy. No details explainomh how viral rebound (i.e. before treatment switching) and its relationship to adherence is implemented in the model were provided, nor were its underlying assumptions justified. Regarding the company's statement *"Patients experiencing virological*

regarding how patients transition through the model." *"In other words, it appears that the company assumed that all patients with an adherence below 95% experience virologic failure within one month and switch treatment due to virologic failure"*	ART to suppress the virus is reduced (by a modelled relationship between adherence level and viral suppression) when adherence is suboptimal. Patients experiencing virological failure as a result of this reduced adherence are assumed to switch therapies each month, including in month one."	a patient and what impact suboptimal adherence has). The economic model uses the proportion of patients with suboptimal adherence over their lifetime (defined as <95% adherence) and derives a reduction in viral suppression, using a published relationship. This is calculated over 48 weeks (based on the virologic suppression rate at 48 weeks from the clinical trials) and converted to a monthly probability of virologic failure. This is aligned to clinical practice, where people may exhibit suboptimal adherence and discontinue treatment more frequently than every 48 weeks.	*failure as a result of this reduced adherence are assumed to switch therapies each month, including in month one"* in the description of the proposed amendment in this section, the ERG feels that it is exactly this aspect for which more details should be provided in terms of the probability of experiencing viral rebound in relation to adherence (i.e. before treatment switching) and justification is needed regarding the plausibility of the assumed timeframe in which viral rebound occurs in non-adherent patients and the requirement for treatment switching. Note that in our sentence starting with *"in other words, …"* we were not implying that all non-adherence takes place in month one, it is clear to the ERG the overall non-adherence is spread out over a 48 weeks, and each month

			a smaller number of patients become non-adherent.
Section 4.2.6.3 Page 93 The ERG report states: "*In other words, it appears that the company assumed that all patients with an adherence below 95% experience virologic failure within one month and switch treatment due to virologic failure. No justification, nor any general explanation on this aspect being implemented in the model as such is provided by the company."* **A related statement is made on Page 96:** *"Thirdly, as described in the ERG comment in section 4.2.6.3, it appears (in absence of any explanation provided on this aspect) that the company has used the proportion of patients not meeting an adherence level of ≥95% to model a monthly probability for the transition of patients in first-line treatment to switch to second-line treatment with a viral load of ≥50 HIV RNA copies*	The sentence: "*No justification, nor any general explanation on this aspect being implemented in the model as such is provided by the company"* should be removed. Similarly, on p.96 the following sentence should be removed: *"The ERG considers that an explanation and justification of this modelling aspect should have been provided in the CS, in particular because it is the sole determinant of differences between intervention and comparator regarding the way patients transition through the model and considers it unlikely that all patients with an adherence below 95% experience viral rebound within one month and immediately switch treatments due to that reason."*	A justification was in fact provided. The paper Ross et al.[5] has a cut-off effect of 95% adherence. This paper, as stated in the CQs, was preferred for two primary reasons: 1. This paper specifically compared to LA treatments as opposed to others which compared to optimal and suboptimal adherence on oral regimens. 2. Ross et al.[5] provided a probability link between adherence and viral suppression from an ART as opposed to most other papers which only provided an odds ratio. An explanation and justification for the approach is provided in Section B.3.3.2.3 and B.3.2.5.1.1.	Not a factual inaccuracy. The ERG feels justification is needed why it is assumed that patients who become less than 95% adherent will immediately need to switch therapy and will immediately experience a viral load >50 HIV RNA copies per ml. The ERG considers it more plausible that it would require a longer period of adherence below the 95% threshold (potentially below a lower threshold) before the viral load increases and the patient is switched to another treatment.

per ml. The ERG considers that an explanation and justification of this modelling aspect should have been provided in the CS, in particular because it is the sole determinant of differences between intervention and comparator regarding the way patients transition through the model and considers it unlikely that all patients with an adherence below 95% experience viral rebound within one month and immediately switch treatments due to that reason."		See C10 in ERG CQs for a more detailed explanation.	
Section 4.2.6 Page 96 The ERG chose to use a value reported by Sherr et al. 2010[6] to represent the proportion of people who may be sub-optimally adherent over the lifetime of the model. The ERG acknowledge two reported values from Sherr et al.: 10.1% and 57.2%. They justified not using the value of 57.2% given that the definition of suboptimal adherence pertaining to this value includes having missed or incorrectly taken one or more doses in the past 7 days and "*The ERG considers*	The adherence should be changed to 21.0% or justification should be given as to why this value was not used, given it was identified in the ERG's preferred study and has an 'acceptable' definition of suboptimal (per the ERG's concerns), or it should replace the adherence currently used in the ERGs base case.	Sherr et al 2015 includes three definitions of suboptimal adherence: at least one dose missed or taken incorrectly in the past seven days (57.2% of patients); at least one dose missed in the past seven days (21.0% of patients); and at least two doses missed in the past seven days (10.1% of patients). In line with the ERG report methodology, these definitions can be used to derive a percentage adherence, assuming once daily dosing. The definition of at least one dose missed in the past seven days	Not a factual inaccuracy. The ERG has used a percentage of non-adherence (i.e. 10.1% of patients who missed at least two doses in the past seven days; which would correspond to an adherence level of 71% or less) that is based on a proportion of patients with a level of suboptimal adherence for which it can more reliably assumed that viral suppression is indeed reduced than the definition

taking a dose incorrectly does not mean the same as missing a dose and considers a definition of suboptimal adherence". Instead the ERG prefer to use the value of 10.1% in their revised base case. The ERG have not described a further adherence threshold identified in Sherr et al, which sits in the middle of these two extremes and is based on a definition of suboptimal adherence as "one or more doses missed in the prior 7 days" (21.0%). When converted to a percentage adherence value for comparison purposes, this definition would equate to an adherence threshold 86% (assuming once-daily dosing, in line with ERG assumptions).		is broadly comparable to 86% adherence, under these assumptions. While there is discussion about the optimal threshold for adherence as it pertains to virologic suppression, the majority of studies apply definitions of optimal adherence >95%. However, the definition of adherence used by Sherr et al 2015 (one missed dose in the past seven days, i.e. 86% when expressed as a percentage) is closer to the lowest definitions of optimal adherence assessed in Bezabhe et al. 2016 and Gordon et al. 2015 (i.e. >80-90%). It should also be noted that the Bezabhe et al.[8] meta analysis only identified two studies with thresholds less than 90% and only six studies when including studies where adherence was defined as >90%. Hence, the Sherr 2015 definition of adherence (one missed dose in the past seven days, i.e. 86% when expressed as a percentage) is on the lower end of definitions in the published literature.	proposed by the company at which 21% of patients are non-adherent (i.e. at least one dose missed in the past seven days; which would correspond to 86% adherence, for which the literature indicates that at this level of adherence viral suppression can still be assumed to be adequate). For this aspect, it could also be relevant to consider the statement by O'Connor et al. 2015 regarding *"the possibility that many modern regimens are successful at adherence levels of 70–80%"*.

		Further, the ERG has provided a justification why one definition in Sherr 2015 was not used. Hence, it seems unreasonable that other definitions that could also be considered conservative were not used and no justification was provided.	

Issue 2 Eligibility of study participants with K103N mutation

Background statement: The presence of a resistance-associated major INI or NNRTI mutation, except K103N, from prior genotype assay results was an explicit exclusion criterion in both the ATLAS and FLAIR studies. The ERG raise some concerns about whether there is a bias in the trial in favour of the CAB LA + RPV LA arm linked to the possibility that NNRTI resistance (associated with K103N mutation) may be present in, and impact only or more so, those individuals taking nevirapine or efavirenz in the comparator arm (since the presence of K103N is not associated with viral resistance to RPV but is associated with resistance to efavirenz and nevirapine).

However, it is important to note that all individuals starting or continuing CAB LA + RPV LA had suppressed viral loads regardless of the presence or absence of K103N, and that at failure, no individuals in either arm of the ATLAS trial who failed treatment were identified as having pre-existing K103N mutations on retrospective HIV DNA resistance testing. This demonstrates that individuals in the comparator arm were not at an efficacy disadvantage compared to those in the CAB LA + RPV LA arm.

It is also noteworthy that the SPCs for both Vocabria and Rekambys specify that the indication for their use is in individuals without present or past evidence of viral resistance to, and no prior virological failure with agents of the NNRTI and INI class as a whole and do not make an exception for individuals in whom K103N is present. Therefore, in clinical practice, all individuals with these mutations at baseline, including K103N would be excluded from treatment with CAB LA + RPV LA.

NB: **ERG comment** in the Table below.			
Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG comment**
Section 3.2.3, page 50 and in Table 1.4 page 16: *"However, if the patient is a carrier of K103N, he is at risk of developing resistance to other NNRTIs such as NVP or EFV."*	This sentence should be removed/rephrased.	We would like to clarify that it is the virus - rather than the patient - which carries the mutation and it is therefore important to rephrase this sentence. Additionally, the context in which the phrase is written implies that this mutation is a concern for the population under consideration in this appraisal. This is not accurate given that the population is virally suppressed (i.e. treatment is working whether or not K103N is present). It is acknowledged that people with K103N mutation were eligible for entry into ATLAS, FLAIR and ATLAS 2M. However, all trial participants in ATLAS, including those on EFV and NVP were virologically suppressed at baseline and during the course of the trial indicating that they were on effective treatment. It should also be noted that, unlike for individuals with a detectable viral load, testing in virally suppressed people is performed on DNA in peripheral blood mononuclear cells (PBMCs) and is not performed routinely, limiting the applicability of this testing. Although genotypic assays were not available for study participants at baseline, resistance testing was	The key issue was removed from the ERG report.

		conducted on baseline samples (as described above) in patients who failed treatment. During ATLAS, four participants in the oral-therapy group had confirmed virologic failure (two consecutive plasma HIV-1 RNA measurements of ≥200 copies per ml), and reverse-transcriptase mutations were detected in three of these participants: one had the M184I mutation, one had M184V plus G190S, and one had M230M/I.[13] None of these participants had resistance caused by K103N mutation either at baseline or at failure. When discussing the K103N mutation, it should be noted that resistance testing and mutation analysis are routinely undertaken following previous regimen failures and would have been taken into account when making the decision to use the regimens that patients were receiving at baseline. Therefore, participants were excluded from the study if they had previously failed an NNRTI or INI containing regimen or if NNRTI mutations other than K103N were identified.	
Table 1.4 Page 16 The ERG report states: *"Development of NNRTI resistance in patients in e.g. the ART arm of ATLAS study could affect the clinical effectiveness*	This statement and any concern about the impact of K103N should be revised / removed as it is inaccurate.	There is no bias in favour of CAB LA + RPV LA results from inclusion of participants regardless of K103N mutation. • All trial participants in ATLAS, including those on EFV and NVP were virologically suppressed at baseline	After checking the CSR documents for FLAIR, ATLAS and ATLAS-2M

estimates used to inform the economic model." The statement is factually inaccurate in its claim that clinical effectiveness estimates could be affected (see the justification) and in its suggestion that the model would be impacted (since no difference in virological efficacy is assumed between therapies).		and during the course of the trial indicating that they were on effective treatment. • It is possible that if the K103N mutation is detectable on resistance testing, other, undetected, mutations may also be present and under the right circumstances these may in combination, result in virological failure. However, this is equally true for CAB LA + RPV LA as it is for oral NNRTI regimens. • There is no evidence of baseline K103N mutations in any subject experiencing treatment failure in ATLAS or FLAIR (regardless of treatment arm). The model base case analysis assumes that virological efficacy is not affected by therapy applied (i.e. no difference in virological efficacy is assumed between therapies). Hence, there would be no impact on the cost-effectiveness analysis even if there were a bias linked to baseline mutations.	studies, ERG agrees with the company's justification. The issue was removed from the ERG report and the text in section 3.2.3 updated to include more information.

Table 2.1 Page 23 The ERG states: *"It should be noted that patients with K103N (NNRTIs resistance-associated) mutation were included"*	This statement should be amended to: It should be noted that participants with evidence of K103N (NNRTIs resistance-associated) mutation from historical testing were eligible for inclusion.	Given that genotyping was not undertaken to screen participants for entry into the studies, the suggested statement – which highlights reliance on prior genotypic test results - is more accurate.	The key issue was removed from the ERG report.

Issue 3 Comparator evidence and generalisability to UK practice

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Table 1.5, page 16 The ERG report states: *"As discussed in the CS (section B.2.13.4), the regimens used in ATLAS and FLAIR studies are not fully representative of currently used ART regimens in the UK NHS setting. This can substantially affect the generalisability of the results for the comparison of ART therapy vs. CAB LA + RPV LA (Q2M)."*	The italicised statement should be replaced with the following proposed amendment: As discussed in the CS (section B.2.13.4), the regimens used in ATLAS and FLAIR studies are not fully representative of currently used ART regimens in the NHS setting today (given factors including changes in market share over time) for this specific decision problem; i.e. where a long-acting non-oral alternative may be considered.	The ARTs included in the cART arms of ATLAS and FLAIR are reflective of NHS practice; i.e. all of these regimens, both older and more recent ARTs are used across naïve, maintenance and switching persons with HIV. Please see the additional detail in the row below. Commentary in the CS on the generalisability is in relation to the specific decision problem, and the basket of comparators deemed most typical, regimens to switch **to** based on market share. In the feasibility for a NMA assessment provided in the CS, the	Not a factual inaccuracy

		presented evidence across these comparators shows similar high levels of maintenance of virological suppression.	
Figure 1 below shows the distribution of the different third agents used (with two NRTI backbones) across the whole of today's treated HIV population in England (data from February 2021, IQVIA HPA). Figure 2 alongside presents the corresponding breakdown by third agent in the ATLAS trial. The profiles are broadly comparable and there is a reasonable overlap in class of third agent. The differences that are seen are explained by study design (ATLAS excluded people treated with Triumeq and had a cap on recruitment of people receiving INI as a third agent), evolution of research/change in availability of treatments over time, and the fact that ATLAS was conducted in multiple countries. All ARTs are assumed to have equivalent efficacy in the model, so even these understandable differences have no consequence for the economic argument.			Not a factual inaccuracy.

Figure 1: Third agents in UK HIV market (all patients, England February 2021)

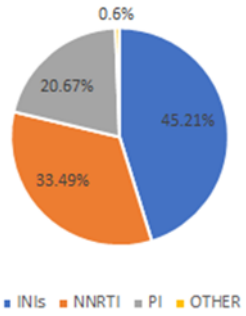
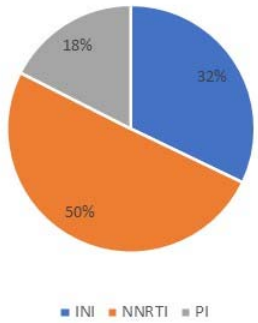


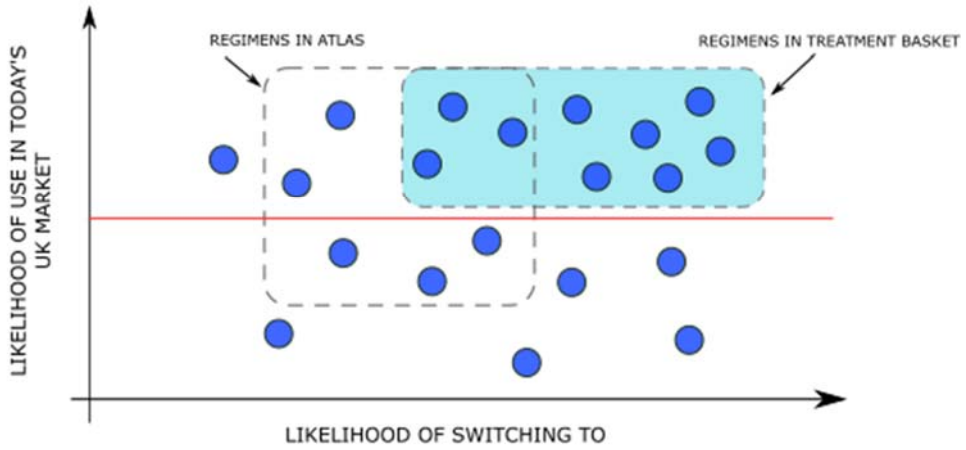
Figure 2: Third agents in ATLAS comparator arm



The identification of a comparator basket was purely to define a cost of the comparator arm for modelling purposes. The most reliable source of information for this is a dataset, which would not be expected to overlap with the two above (given that it is a subset of the market who have particular challenges with their treatment in spite of its efficacy). In itself this too is an imperfect dataset because it is impossible to know whether the reasons

virologically suppressed people switch in the current market are ones that can be resolved by a long-acting treatment (this is why we do not support the use of a weighted average price when using these data).

The following illustration may be a useful conceptual description of how the comparator basket overlays the trial comparator populations (across ATLAS and FLAIR).



The Y axis corresponds to the evolution of the market as modern treatments replace those previously used or divides the market in England and Wales into treatments that practitioners are more or less likely to prescribe for other reasons. The X axis indicates the reality that some regimens are more likely to be used early on in treatment. Across England and Wales, these are commonly the lower cost regimens in line with commissioning policies. The ATLAS trial included regimes that straddle these two dynamics. The regimens selected by the company to represent the comparator basket (for cost purposes) can only be a subset of these given that they are derived from **current** stable switch market data. This is a nuanced issue, but if we accept the assumption of

comparable efficacy of the oral ARTs, it has no consequence on estimates of benefit (in the trials or the model). It has been necessary to derive a comparator cost and we would ask the Committee to take a pragmatic approach to this given the dynamics of the switch market and the 'unknowability' of how this will look should a long-acting treatment become an alternative to a daily, oral therapy.			
Section 3.3 Page 72 The ERG report states: *"Throughout the CS, the company references the FLAIR comparator arm as "current ART", which the ERG considers to be erroneous: all participants of FLAIR were commenced on DTG + ABC + 3TC at the beginning of a 20-week induction phase, i.e. patients in FLAIR are not on "current ART" but a specific ART that may have been different from their previous ART."*	This statement should be deleted. Alternatively, the statement should be amended to reflect that participants are stabilised on the ART that they are currently receiving at time of entering the randomised phase of FLAIR.	Participants in the FLAIR study were ART naïve at study entry. All FLAIR study participants received a 20-week induction phase consisting of DTG + ABC + 3TC. At week -4, participants who had an HIV-1 RNA <50 copies/ml were eligible to continue to the randomised phase of the study, where they continued to receive DTG + ABC + 3TC or switched to receive CAB LA + RPV LA Q1M. Hence, at week -4, these study participants are stabilised on their "current ART," and may be switched to an alternative or continue to receive DTG + ABC + 3TC.	Not a factual inaccuracy. The term "Current ART" implies a variety of therapies dependent on the time and location of the study in question, incorporating patient preference and tolerances. In ATLAS, patients continued the ART they were using prior to entering the study, so "current ART" is valid. This was not true of FLAIR, where the study required that all participants take the same ART. While no patients in FLAIR had taken a previous ART and therefore did not switch to DTG/ABC/3TC from a different ART, neither was that ART representative of the variety of ARTs the patients would have taken had they not been recruited into FLAIR.
Section 3.6 Page 74 *"The summary of common AEs (≥5% in either arm) were not reported for pooled ATLAS and FLAIR studies. The*	This sentence should be removed or rephrased.	The information specified (i.e. sufficient evidence to demonstrate the	Not a factual inaccuracy. The ERG acknowledges that the company provided the summary of drug related AEs reported in ≥1% in

committee will need to decide if the evidence provided by the company is sufficient to demonstrate the safety of CAB LA + RPV LA (Q2M).”		safety of CAB LA + RPV LA) has been supplied. A summary of the most common drug related AEs reported in ≥1% in any treatment group in ATLAS, FLAIR and the pooled analysis was provided in the CQs, Table 10. This gives information on common AEs that is more comprehensive than a table of those occurring in ≥5% would be.	any treatment group in ATLAS, FLAIR, and the pooled analysis. However, the company reported the summary of common AEs (≥5% in either treatment group) only for the ATLAS-2M study. ERG was not able to compare the results for this outcome between ATLAS-2M and pooled ATLAS and FLAIR. Moreover, ERG was not able to compare the results for the rates of AEs experienced by ≥5% and ≥1% of patients.
Section 3.6 Page 74 The company stated that the comparators used in ATLAS and FLAIR *“are considered to have comparable efficacy to currently used regimens, given that non-inferiority trials are the norm for ART in HIV”*. No evidence was provided to support this statement.	The statement that “No evidence was provided to support this statement” should be removed.	Evidence to support this was presented in the CS, Appendix D, Table 36.	Not a factual inaccuracy. Of note, Table 36 does not present evidence that comparators used in ATLAS and FLAIR have comparable efficacy to currently used regimens.

Issue 4 Clinical effectiveness evidence

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Table 1.7, page 17 The ERG report states: "*As there are substantial differences between the two studies, including the comparator treatment and use of a run-in period, this is an inappropriate analysis method."* *"While the ERG recognises that the pooled analysis was pre-planned, the studies should have been meta-analysed rather than pooled."*	This sentence should be amended to acknowledge that both methods are appropriate.	The statistical strategy, including the pre-specified pooling and definition of the non-inferiority (NI) margin for the pooled analysis, was agreed by the EMA and other international 'scientific advices'. Note that ATLAS and FLAIR were intentionally designed such that the protocols, subject management, conduct and analyses of each study were very similar from Day 1 (i.e., Randomization) onwards – with the express purpose of pooling them for reporting. Rizzardini et al (2020) provides further information on the approach that was taken to pooling data from the underlying trials. This approach was accepted by the EMA. All three trials (ATLAS, FLAIR and ATLAS-2M) were comparable (by PICOS). The pooled analysis of the ATLAS and FLAIR trials showed no significant heterogeneity between the two trials in terms of trial or participant characteristics for the treatment effect. In the ITC itself, people who had prior LA (in ATLAS 2M) were excluded from the analysis	Not a factual inaccuracy The ERG was not commenting on the validity of using an ITC, rather, only on the validity of using a pooled analysis, treating ATLAS and FLAIR as a single study rather than distinct studies that should be analysed separately and combined with meta-analysis. It is not relevant that other "scientific advices" have accepted pooling of ATLAS and FLAIR as a single study to whether it is scientifically justifiable to do so. There are differences between ATLAS and FLAIR in population (including the countries in which the studies were performed and inclusion/exclusion criteria), trial protocol (FLAIR had a run-in period, ATLAS did not) and comparator treatment (it is an assumption that all oral ARTs have exactly the same efficacy, but even if they did, the

		and subgroup analyses of viral suppression by baseline treatment were conducted to assess what impact, if any, these differences had on the conclusions. Both a meta-analysis and an indirect treatment comparison are appropriate methods for this analysis, and so the text should be amended to reflect this. The ERG's concern about 'substantial differences between the two studies' likely stems from comments elsewhere about differences in the comparator arms. However, an assumption of comparable efficacy (in terms of viral suppression) of oral ART underpins this and other analyses in the submission.	people who do no, for whatever reason, tolerate DTG/ABC/3TC would not be included in FLAIR but could be included in ATLAS, and this may cause effect modification). Given the scope for effect modification, ATLAS and FLAIR should be analysed separately, then combined in meta-analysis. Even in the absence of effect modification, the standard error of the pooled ATLAS/FLAIR effect estimate is overly precise, given ATLAS and FLAIR are not the same trial.
Table 1.3, page 16 The ERG state that: *"the CS reports limited evidence for the outcomes included in the NICE scope."*	This sentence should be rephrased.	The outcomes included in the NICE scope were reported from the ATLAS-2M, ATLAS and FLAIR trials, with the exception of co-morbidities, which were not considered in the appraisal because with most regimens, treatment-related comorbidities are no longer an important feature of treatment and do not generally feature in treatment decision-making. The ITC conducted does not consider all of the endpoints in the NICE scope, however, it does consider both viral suppression and adverse events, as described in Appendix L of the CS.	The sentences in Table 1.3 and section 3.6 were rephrased to highlight that there is limited evidence allowing the comparison between CAB LA + RPV LA (Q2M) and ART therapy.

		The efficacy outcomes that are relevant to the decision problem, including viral suppression, CD4+ T-cell levels, adherence, and HRQoL, are reported in Sections B.2.6.1.6-12 of the CS from the ATLAS-2M trial, and Sections B.2.6.2.5-8 from the ATLAS and FLAIR trials. Safety outcomes, including adverse events and mortality, are reported in Section B.2.10 of the CS.	

Issue 5 Systematic literature review issues

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Table 1.2, page 14 The ERG recommends: *"Update searches following best practice would increase the likelihood that the submission is based on the best available evidence, including separate searches for safety outcomes."*	This sentence should be revised.	The searches were conducted in accordance with guidance from the Centre for Reviews and Dissemination (CRD),[18] which specifies that separate safety search is not required by NICE.	Not a factual inaccuracy. CRD guidance states that *"if a search for effectiveness studies included only terms for the population and intervention with no search filters for study design, no terms for the outcomes, …then it may be sufficient to scan the results of the effectiveness searches for information on adverse effects.* *If the effectiveness searches were limited to RCTs and the adverse effects sought are*

			long-term, rare or unanticipated, then additional searches will be required."
Section 3.1.1 Page 29 The ERG report states: *"Five facets of search terms were combined in the search strategy: 1) Population, 2) Interventions of interest, 3) Disease stage, 4) Outcomes and 5) Study type. Combining this number of search facets reduced the sensitivity of the searches."*	This sentence should be amended as it is unknown whether this search strategy would have reduced the sensitivity of the searches, and as the searches were conducted in-line with CRD guidance, they can be considered appropriate.	CRD guidance states that constructing an effective combination of search terms involves breaking down the review question into 'concepts,' and using the Population, Intervention, Comparator, and Outcomes elements from PICOS can help to structure the search, but it is not essential that every element is used.[18]	Not a factual inaccuracy. The more search facets there are, the more precise the search strategy and the less sensitive the search results. That does not mean any studies were missed but does make it more likely. CRD guidance suggests that *"it is not necessary to include all of the PICOS concepts in the search strategy. It is preferable to search for those concepts that can be clearly defined and translated into search terms. Concepts that are poorly defined, not likely to be included in journal abstracts, or not indexed in a consistent way will be difficult to identify from database searches. If this is the case, using a broader search and then sifting through the identified studies may be preferable. This may apply*

			particularly to the outcome(s) of studies as these are frequently not referred to in either the title or abstract of a database record".
Table 1.6, page 17 The ERG reports: *"It is possible that relevant data on safety were missed through the exclusion of case-control studies and therefore the presented evidence may not be complete."*	This sentence should be removed.	The user guide for company evidence submission template states: Evidence from comparative RCTs and regulatory summaries is preferred, but findings from non-comparative trials may sometimes be relevant.[19] Hence, case-control studies are not required.	Not a factual inaccuracy. The case-control studies are not required, but NICE do not limit the evidence to evidence from RCTs only. Case-control studies can provide useful information on the safety of the treatment of interest and ERG's sentence is justified.
Section 4.1.2 Page 84 The ERG report states: "*It is unclear whether relevant studies will have been missed due to the English language and date restrictions across all three SLRs or the geographical restrictions in the cost and resource SLR*."	This sentence should be removed as the searches were conducted in-line with NICE guidance and should not have missed any studies relevant to clinical practice in the UK.	Geographical restrictions: The Single technology appraisal: User guide for company evidence submission template states: If the systematic search yields limited data for England, the search strategy may be extended to capture data from other countries.[19] HIV is a well studied area and the SLR for cost and resource use assessed several countries relevant to NHS England. Hence, there was no requirement to extend	The ERG removed this statement as the response to a query about date and language limits is included in section 4.1.1.

		the SLR to capture data from other countries. Date limits: HIV regimens have evolved substantially over the past 30 years. Key therapies were only licensed in the late 1990s (e.g. efavirenz in 1999) through to early 2000s (e.g. atazanavir in 2004). Use of highly active retroviral regimens was also evolving through this time. As a result, earlier data would not have been a true reflection of clinical practice. Further, a comparison between a current and historical switch study in virologically suppressed people would not have been a like for like comparison.	

Issue 6 Non-inferiority of CAB LA + RPV LA Q2M

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Table 1.9, page 18 The ERG states that: *"From the ITC, we believe the interpretation should be that there is no current evidence that CAB + RPV LA Q2M is inferior to*	The following sentence should be added: "However, given the lack of statistical certainty inherent in the wider HIV evidence base, which is largely predicated on non-inferiority trials, this element of uncertainty does not negate the assumption that modern approved HIV	To ensure the conclusions on comparative effectiveness for CAB LA + RPV LA are appropriately interpreted in the context of HIV regimens and the basis for their efficacy today.	Not a factual inaccuracy.

"current ART", and that we cannot be certain that CAB + RPV LA Q2M is non-inferior to "current ART"."	therapies have essentially 'equivalent' efficacy".		

Issue 7 Cost of comparators

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Table 6.2, page 124 This table lists the 30-day costs for various bands of the 'basket of comparators,' except for the ERG base case which uses the 30.4375 day (monthly exactly) cost. Using these inputs, we are unable to replicate the results found in Table 6.6.	The costs should be listed to 2 dp and Table 6.2 should be labelled as 'cost per 30 days,' assuming the data comes from Figures 6.1 and 6.2 , and contain the 30 day cost for the pooled comparator (£721.34) . The scenarios should be run with the 30-day costs (i.e. inputs should be 30 days costs which are automatically adjusted to calendar months in the model).	This will make the data consistent with the data source and will make the values consistent with the formatting of the base case results. This additional clarity would also allow the results to be replicated.	Not a factual inaccuracy. The ERG can confirm that the values in Table 6.2 pertain to those per calendar month instead of 30-day costs, whilst the 30-day costs were used as inputs for the model. The costs were read off from Figures 6.1 and 6.2, which does not allow for a level of preciseness to specify them at 2 decimal points.
Section 4.2.4 Page 90 'According to the ERG, the fact that lower cost regimens were switch options in fewer than 2.5% of patients who switch therefore could undermine the notion that	Suggest removal of sentence.	The fact that lower cost options were switch options in fewer than 2.5% does not undermine the notion that preference is given to lower cost regimens when possible, it instead more reflects that PLHIV will have likely 'cycled' through an older (and typically a lower cost)	The ERG has removed the sentence.

preference is given to the lower cost regimens when possible'		regimen earlier. This is evident in the total market share for the HIV population in England and Wales where a relatively high percentage of patients are on older (i.e. lower cost) regimens vs newer ones.	

Issue 8 Utility for LA therapies

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Table 1.12, page 21 The ERG state that: *"The ERG felt the presence/size of this utility advantage was uncertain due to potential biases in this estimate which could favour CAB LA + RVP LA, including higher drop-out in HRQoL reporting in the CAB LA + RVP LA group versus the ART group and that injection site reactions may have been missed in the HRQoL data collection."*	This sentence should be removed or rephrased.	The company believes the ERG's statements in relation to bias favouring CAB LA + RPV LA to be factually inaccurate. To the contrary, we argue in the report that the estimate used in the model is an underestimate of the true value and should only be considered as a lower limit. Drop out: (1) At baseline and week 24 the missing values are almost the same between CAB LA + RPV LA and oral ART (baseline 6% vs 5%, week 24 9% vs 8%) whereas a slightly larger difference is observed at week 48 (15% vs 7%). Since the difference in utility values is consistent between w24 and w48	Not a factual inaccuracy. Drop out in HRQoL reporting was higher in the CAB group as can be seen by the numbers of observations over time (note that following a correction of a reporting error in Appendix N from the company in a later FAC issue, the numbers of patients providing HRQoL observations over time in each group has been updated to CAB n=556, 535 and 500 at baseline, week 24 and week 48 respectively versus ART n=552, 546 and 548). The fact that the difference in utility values is consistent

		we can assume that the missing values are random. (2) Trial investigators follow strict procedures during the visits and PRO questionnaires are required from all participants. Therefore, missing values should be random with no impact on the PRO results. Visit timing: While HRQoL data in the form of SF-12 was not collected at every visit, at the visits where SF-12 was administered on the same day as the Perception of Injection instrument (PIN; i.e. Week 48), average PIN summary scores indicated that ISRs were 'totally' or 'very' acceptable and the bother of ISRs fell between 'not at all' and 'a little'. Average individual item scores were in a similar range. From the PIN data it can be seen that any effect on HRQoL due to ISRs would be extremely small, as the average perception of ISRs signalled high acceptance and no or little bother. Further, the likelihood that injection site reactions are captured in the	between w24 and w48 or that trial investigators followed strict protocols does not mean we can assume that values were missing at random. In response to the argument that injection site reactions would have been captured in the SF-12 reporting at w24 and w48, the ERG acknowledges that these time points will have captured some injection site reactions in the report, which states *"Given that SF-12 was only measured at baseline and weeks 24 and 48, only injection site reactions which occurred due to injections at week 20 and 44 would have been captured within the four week recall of the SF-12"*. However, given that scores on the PIN questionnaire showed improvement over time between weeks 8 and 24 and 48, it is likely that the impact of injection site reactions was larger for earlier injections which are not covered by the

		SF-12 data collections at weeks 24 and 48 is high because the questions in the SF-12 questionnaire specifically mention a period of 4 weeks (e.g. "During the past 4 weeks, how much of the time have you accomplished less than you would like with your work or other regular daily activities as a result of your physical health?") which covers the average duration of ISRs in ATLAS/FLAIR between the monthly injections. This issue is explained more fully in the CQ document Section C16 (p. 59-60).	SF-12 data collection and therefore some of the impact will have been missed. The ERG does not claim that either the effect of missed injection site reactions or the larger drop out in the CAB reporting of HRQoL would have had a very large impact on group utilities and the difference between them over time, but given that we are dealing with a small ([redacted]) group difference, which has a large impact on results, it is important to consider what impact biases, even small ones, may be having on results.
Table 6.8, page 130 The ERG's CAB LA + RPV LA utility advantage scenarios, with results reported in table 6.8, appear to have been incorrectly run. These have only applied the oral disutility of 0.01 and 0 to the pooled comparator but not the salvage lines (which are also oral ARTs).	This scenario should be rerun, applying the disutility to salvage as well as the pooled comparator. For clarity, cells L82, L84 and L86 on the 'Treatment Specification' worksheet should be updated with the value from cell L29.	The utility advantage associated with long-acting treatment needs to be applied to all oral treatments irrespective of treatment line. As it is now, in both these scenarios salvage maintains a disutility of 0.02 whilst the pooled comparator has the disutility of 0.01 or 0 applied.	The ERG thank the company for noting this and have updated the scenario results as suggested.

Issue 9 Decision problem population

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG comment</th></tr>
<tr>
<td>Table 2.1 page 23

Section 2.1 page 26

It is not accurate to state that the population addressed in the company submission is narrower than the decision problem. The company have simply specified the requirement for ‘treatment switch due to non-virologic reasons’ to support the understanding of the wording of the final NICE scope (‘virologically suppressed’).</td>
<td>This should be deleted wherever noted.</td>
<td>A comparison of the NICE decision problem and licensed indication is provided below. As can be seen, the two are comparable.

The company submission notes that CAB LA + RPV LA Q2M should be used in people who require a treatment switch due to non-virologic reasons. While not explicitly stated in either the NICE decision problem or licensed indication, it is implicitly captured by the requirement for switching to occur in people who are virologically suppressed (i.e. there is no virologic reason for switching)

<table>
<tr><th>NICE decision problem</th><th>Licensed indication</th></tr>
<tr><td>Adults</td><td>Adults</td></tr>
<tr><td>HIV-1 infection</td><td>HIV-1 infection</td></tr>
</table>
</td>
<td>Not a factual inaccuracy.</td>
</tr>
</table>

		Virologically suppressed	Virologically suppressed (HIV-1 RNA <50 copies/mL)	
		On a stable regimen	On a stable antiretroviral regimen	
		Who have not shown prior virological failure due to drug resistance to INTI/INIs	Without present or past evidence of viral resistance to, and no prior virological failure with agents of the NNRTI and INI class	

Issue 10 Fear of disclosure

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 4.2.3 Page 88 The ERG report states: *"As stated at several instances in the CS, the company considers a fear of disclosure of HIV status if medication is discovered as an*	This paragraph should be removed or rephrased.	The company do not agree that a similar fear of disclosure would operate in relation to healthcare appointments. While it is possible that disclosure might come about through discovery of a healthcare appointment, the degree of risk of	In rereading the statement the ERG realizes that 'a similar fear' could be read as a suggestion that the number of patients for whom a fear of detection is reason to switch from oral to injection

important reason for switching treatment regimen in patients currently on an oral ART regimen. The ERG considers it plausible that a similar fear of disclosure could apply to CAB LA + RPV LA in relation to the requirement of attending a healthcare provider once every two months to receive the injections and the substantial probability of experiencing injection site reactions (ISR; see section 4.2.7).”		disclosure is far greater with oral ART: • All people with HIV who are on-treatment attend HIV-specific healthcare appointments. Many people who fear disclosure of their HIV status travel to clinics far from their place of residence, even to a different city, to avoid being seen by people they know. • A person can obfuscate the reason for a healthcare appointment, for example, because many HIV services exist within a hospital setting, it is usually easy to convince questioners that an HIV clinic appointment is for something else, should it be discovered. Further, injections may be received not just in HIV clinics, but in alternative injection facilities (e.g. GPs). However, discovery of HIV medication is an undeniable disclosure.	administration is the same as the number of patients who might switch from injection to oral because of fear of detection. However, this was not what the ERG wanted to convey, and given that this topic has no bearing on the rest of the report, we have deleted this paragraph.

		• Discovery of medication is more likely than discovery of an HIV clinic appointment. • The circumstances in which discovery of medication could force disclosure are wider than those where a person's healthcare appointments are discovered; e.g. carrying medication while travelling. • Patients themselves state the risk of disclosure as one of the key reasons for wanting the long-acting regimen.[20]	

Issue 11 Cost source for alternative basket of comparators

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 6.1.3.1 Page 123 'The ERG present a series of scenario analyses where alternative costs are assumed for the 'basket of comparators'. These costs were derived by the ERG from the information provided by the company in response to the ERG's clarification question B1 on	We propose that the ERG seek up to date information on current ARTs by banding directly from NHS E, since these vary by region, and source the corresponding list prices from BNF.	The Company provided the algorithm from the Midland and East Region to illustrate the existence of the banding system only (reflecting the way it was used at the NICE Scoping Meeting). Since the document is dated from 2017 and the lists of ARTs are not exhaustive, derived costs using	The issue mentioned by the company is not a factual inaccuracy. The ERG feels that the information provided by the company on the costs bands of various ART regimens that patients switch to was sufficiently appropriate for use as an illustration of the uncertainty that surrounds the costs of comparator drugs and

commonly used ART regimens in patients who switch regimen in the Midlands and East region, as shown in Figures 6.1 and 6.2.' The use of these figures in the way proposed by the ERG is problematic.		these tables may be considered inaccurate.	its impact on the cost-effectiveness results. We have added text to section 6.1.3 to make the data of the cost data more clear and to highlight the purpose of the scenarios.

Issue 12 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Table 1.1 Page 13 **ID 11:** Utility advantage for patients taking CAB LA + RVP LA Error in the abbreviation of rilpivirine in several places in the document	Utility advantage for patients taking CAB LA + RPV LA	Correction of error in the abbreviation used to describe rilpivirine	The report was checked and corrected for any errors in the rilpivirine abbreviation.
Table 2.1, page 23 The "rationale if different from the final NICE scope" column for the outcomes is a repeat of the final scope issued by NICE column instead of the rationale provided in the CS.	The text should be updated to align with the rationale presented in the CS: Treatment-related comorbidities are not considered as outcomes in the appraisal because with most regimens (including the intervention and the comparators) treatment-related comorbidities are no longer an	The company's rationale for any departure from the NICE scope should be presented (Table 1, page 11).	This has been corrected-

	important feature of treatment and do not generally feature in treatment decision-making.		
Table 2.1, page 24 The "rationale if different from the final NICE scope" column for the economic analysis is a repeat of the final scope issued by NICE column instead of the rationale provided in the CS.	The text should be updated to align with the rationale presented in the CS: N/A	The economic analysis in the CS does not differ from the NICE scope and so no rationale is required. This should be updated as reported in the CS (Table 1, page 12).	This has been corrected-
Table 2.1, page 25 The "rationale if different from the final NICE scope" column for the subgroups to be considered is a repeat of the final scope issued by NICE column instead of the rationale provided in the CS.	The text should be updated to align with the rationale presented in the CS: N/A	The subgroups considered in the CS do not differ from the NICE scope and so no rationale is required. This should be updated as reported in the CS (Table 1, page 12).	This has been corrected-
Section 3.2.5.1.1, page 57 The Q1M vs. Q2M adjusted difference in proportion is given as 1.0, 95% CI 0.6 to 2.5.	The CI should be corrected to include the sign (-0.6 to 2.5).	In the CS, the CI is given as -0.6 to 2.5 (Table 15).	The report was updated with the correct value (-0.6).
Page 105, bullet point 3 "*One uncertainty that remains is that drop-out over time was higher in the reporting of HRQoL in the CAB LA + RPV LA arm versus the*	n = 561 should be updated to 552.	The value for the number of people receiving ART at baseline is incorrect (n = 552, not 561, Page 78, CS)	The number of HRQoL observations at baseline in the ART group was reported as 561 in the SF-6D analysis in Appendix N. However this value has been updated in the

ART arm (CAB n=556, 535 and 500 at baseline, week 24 and week 48 respectively versus ART n=561, 546 and 548).”			ERG report following the company’s clarification.
Section 5.1, page 111, text and Table 5.1 The total costs associated with CAB LA + RPV LA have been incorrectly rounded down to [redacted].	This value should have been rounded up to [redacted] in the text and in Table 5.1.	[redacted] should be rounded up from [redacted] (Table 76, CS).	Not a factual inaccuracy; as indicated in the table these values were taken from the model (calculated by the ERG since the company’s version of the model did not provide these results) and pertain to a value of [redacted] that was rounded to [redacted].
Section 5.1, Table 5.1, page 111 The total LYG for Oral ART regimens is given as [redacted].	The value of [redacted] should be corrected to 16.22 in Table 5.1.	The value should be [redacted] as given in Table 76, CS.	Not a factual inaccuracy; as indicated in the table these values were taken from the model (calculated by the ERG since the company’s version of the model did not provide these results) and pertain to a value of [redacted] that was rounded to [redacted].
Section 5.2.3.8 page 119 ***“…** as provided in Table 55 of the CS, the company performed a scenario analysis (i.e. instead of providing the option in the model) in which a weighted average monthly cost of £741.54 was used*	This should be amended to read:”…..as provided in Table 55 of the CS, the company performed a scenario analysis (i.e. instead of providing the option in the model) in which a weighted average adjusted monthly cost of £741.54 was used instead of the £731.86 that was used for the base case.”	This is factually accurate but for consistency this should read ‘adjusted monthly cost’ as it is not the 30-day pack cost.	The ERG agrees with the company and has amended the sentence accordingly.

instead of the £731.86 that was used for the base case."			
Page 115 Section 5.2.2 *ERG comment: In absence of more details on which parameters were varied and how, it is not clear to the ERG how the two last scenarios in Table 5.3, i.e. 'Variation of adherence to second-line ART (discontinuation due to viral failure/rebound)' and 'Variation of adherence to second-line ART (discontinuation due to virologic reasons)', differ in terms of which parameters were varied.*	This was a typographical error in the original table in the company submission, the parameter that read 'Variation of adherence to second-line ART (discontinuation due to virologic reasons)' should be altered to 'Variation of adherence to second-line ART (discontinuation due to non-virologic reasons)'.	This was an error in the original submission, the parameter was correctly labelled and run in the originally submitted model but the document B table was mislabelled. These parameters, *'Variation of adherence to second-line ART (discontinuation due to viral failure/rebound)'* and *'Variation of adherence to second-line ART (discontinuation due to non-virologic reasons)',* alter the adherence for patients who are currently on second line ART having failed first line for virologic and non-virologic reasons respectively.	The ERG agrees to correct this error in the company submission and has amended the label in Table 5.3 accordingly and deleted the corresponding ERG comment.

Issue 13 Change to the proposed list price for LA RPV

Section 4.2.9.1 Page 106 **Drug acquisition**	Change the submitted list price for RPV LA from [redacted] to [redacted]. Change the submitted list cost per set of injections from [redacted] to [redacted] Note this should still be marked as CIC.	As a result of discussions following the RPV LA list price submission to the Department of Health and Social Care, the list price for RPV LA has been changed to [redacted].	The ERG agreed to amend the text accordingly.

costs (List) for RPV LA	There are amendments to be made therefore to the reporting of list prices (and annual prices based on list), as follows: This amounts to an annual cost of [redacted] in year 1 and [redacted] from year 2 onwards. [redacted]	Note that this does not affect the submitted net prices (although the level of discount for RPV LA will be revised to maintain the net price submitted to PASLU) and therefore has no impact on the presented cost-effectiveness analysis and results. Any inconsistencies are due to rounding.	

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NICE National Institute for Health and Care Excellence

Technical engagement response form

Cabotegravir and rilpivirine for treating HIV-1 [ID3766]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments **18 June 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report 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 appraisal, 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.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. 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.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- 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 under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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	Nneka Nwokolo and Claire Gait
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 past or current, direct or indirect links to, or funding from, the tobacco industry.	None

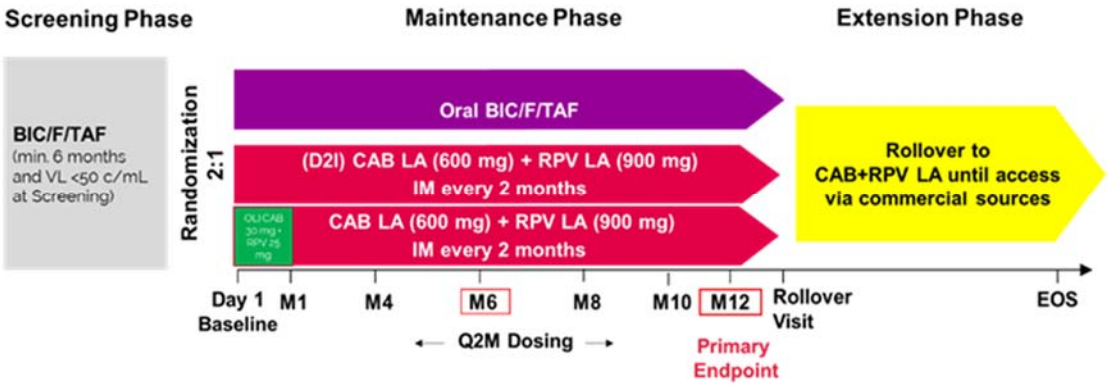
Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Concerns regarding English language and date limits used in the literature searches, the sensitivity of the search strategies, and the currency of the literature searches	Yes, with no update to base case analysis	***Searches have been updated to cover the period between April 2020 and June 2021; there are no additional studies to incorporate into the base case.*** The company agrees that literature searches should be conducted to a high quality, following appropriate guidance to yield all of the evidence relevant to the submission. As such, the searches in the company submission (CS) were conducted according to guidance from the Centre for Reviews and Dissemination (CRD),[1] and retrieved a high volume of evidence. Given the substantial number of publications gathered when applying the 'English- language-only' limit, expanding the search to other languages was very unlikely to identify new evidence relevant to a UK setting. Similarly, given the high volume of evidence gathered, by applying the 'Date' filter, and expanding the search to studies over 20 years old was very unlikely to bring relevant evidence. Over the past 30 years, new HIV regimens have evolved substantially, with key highly active antiretroviral therapies only being licensed in the late 1990s to early 2000s. As a result, earlier data would not have been a true reflection of more 'current' clinical practice. Further, a comparison between a current and historical switch study (i.e. more than 20 years old and used prior to licensing of the first highly active antiretroviral treatment) in virologically suppressed people would not have been a like for like comparison. The ERG expressed concerns regarding the number of search facets that were combined in the search strategy, which they say may have reduced the sensitivity of

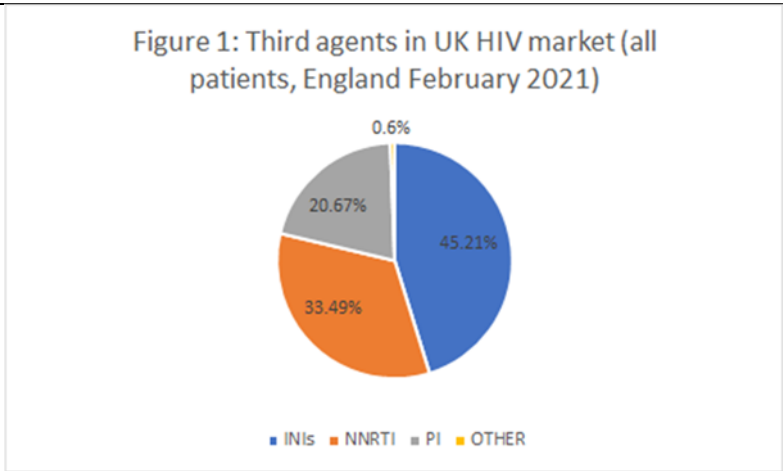
		the search results. The company conducted the searches in line with CRD guidance, which states that constructing an effective combination of search terms involves breaking down the review question into 'concepts,' and that using the Population, Intervention, Comparator, and Outcomes elements from PICOS can help to structure the search, but it is not essential that every element is used.[1] While the company agree that combining search facets like this may reduce the ability of the search to identify concepts that are poorly defined or identify outcomes that were not included in either the title or abstract, in an extensively studied area such as HIV, more uniform definitions have been applied across study publications and were included in the search strategy. Therefore, it is unlikely that the searches would have missed these publications. ***Search update*** The company agrees with the ERG that the timing of the reviews, 10 months prior to submission, may have resulted in more recent publications being missed. CRD guidance recommends that if the initial searches were conducted some time before the final analysis, such as six months, it may be necessary to re-run the searches.[1] Therefore, the company re-ran the initial searches for the SLRs, restricting the date from April 2020, when the searches were initially conducted, to June 2021. A report is supplied as a separate document (Addendum 1). For this update, the interventions were restricted to the specific comparators that make up the 'comparator basket' in the economic model. These updated searches yielded 193 results, of which 21 publications were deemed to meet the inclusion criteria, describing nine studies identified in the original SLR and nine additional studies. No additional studies were identified describing CAB LA + RPV LA. Studies identified using the updated review were assessed for feasibility of informing an indirect comparison, as well as the appropriateness of the resulting network. Details of the assessment are given in Addendum 1B. As described in the company submission, the most significant obstacle was considered to be the composition of the pooled ART arm, which varied between comparator studies. As with the results of the previous searches, an NMA could be conducted (notwithstanding the limitations in interpretation) if the explicit assumption is made that ART regimens have similar efficacy at this point in the treatment pathway. Whilst this is likely to be the case (as

		described in the company submission), this approach is unlikely to reduce uncertainty compared with the presented ITC. In summary, it was determined that an NMA would not provide additional support for decision making beyond the ITC for CAB LA + RPV LA Q2M versus current ART that is presented in the company submission. The additional nine studies therefore add little in terms of comparative evidence.
Key issue 2: Lack of head-to-head evidence between Cabotegravir and rilpivirine (CAB LA + RPV LA) and antiretroviral therapy (ART) therapy	No	***There are currently no head-to-head trials comparing CAB LA + RPV LA Q2M and daily oral standard of care ART; this issue is acknowledged but not considered a significant limitation particularly given the accepted position that the modern treatments are similar in terms of their capacity to suppress the virus (an assumption which is made in the model).*** An indirect treatment comparison was conducted to determine the relative efficacy of CAB LA + RPV Q2M vs daily oral ART. This was conducted applying Bucher's methodology according to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines,[2] with CAB LA + RPV LA Q1M as the common comparator.[3] The ITC is discussed further under Issue 5. The company agree with the ERG that while indirect comparisons provide useful insights in the absence of direct trial-based comparisons, they cannot replace evidence from head-to-head studies. To note, the SOLAR trial (NCT04542070)[4] is currently recruiting and it will assess the antiviral activity and safety of a two-drug regimen of CAB LA + RPV LA Q2M compared with maintenance of the oral regimen Biktarvy® (BIK). This is a Phase IIIb, randomised, open-label, active-controlled, multicentre, parallel-group, non-inferiority study (SOLAR: Switch Onto Long Acting Regimen). It is designed to assess the antiviral activity and safety of CAB LA + RPV LA (Q2M) compared with maintenance of BIK. Approximately 654 adult HIV-1 infected participants who are on the stable ARV regimen BIK will be randomised in a 2:1 ratio to either be switched to the CAB LA + RPV LA regimen or continue BIK through 12 months. Participants will be offered the option to start with a month long oral lead in (OLI) or to start long acting intramuscular injections (D2I). The study will continue with an Extension Phase after Month 12 for individuals in the OLI

		group and on BIK and from Month 11 for the D2I group. [4] (see schematic of study design, below).  The primary endpoint is the proportion of participants with plasma HIV-RNA ≥50 copies/mL as per FDA Snapshot algorithm at Months 6 and 12 (OLI and BIK)/Months 5 and 11 (D2I) (ITT-E population). Recruitment to the study closed [redacted] Evidence from this study will not be available during the timeframe of the submission. Interim results are expected in the first half of 2022 and analysis of the primary endpoint in the second half of 2022.

Key issue 3: Unclear generalisability of the results to patients in the UK NHS setting	Yes	***The comparator regimens in ATLAS and FLAIR overlap considerably with current UK practice. Clinical experts consulted as part of this response consider that the differences are not unexpected given the evolution in therapy since the studies were conducted; they have no concerns about the generalisability of study results to the UK setting*** The ERG are concerned about generalisability since the regimens used in the ATLAS and FLAIR studies are not **fully** representative of currently used ART regimens in the NHS, for this specific decision problem, i.e. virologically suppressed persons for whom a switch to LA ART may be appropriate. As emphasised in the CS, it is important to note that there is no single 'standard of care' regimen and selection of an appropriate ART regimen is individualised based on a broad range of clinical and non-clinical factors.[5] The principal UK HIV treatment guideline, the British HIV Association 2016 interim update,[6] found no difference in the virological efficacy of PI/r or NNRTIs, for virologically suppressed people switching antiretroviral therapy,[6] and recommend that when switching, consideration should be given to other factors, such as the difference in side-effect profiles, drug-drug interactions, pill burden and food effect. Further, it should be noted that Appendix D of the Company Submission details evidence derived from the clinical SLR, wherein studies for relevant comparators included vastly different pooled ART comparator arms. Despite these differences, these pooled ART arms can all be considered relatively similar to UK clinical practice, with no inappropriate ARTs included. Further, it should be noted that these differences in pooled ART composition did not impact on clinical outcomes. Hence, any differences are not expected to impact on the generalisability of ATLAS and FLAIR to UK clinical practice. **ATLAS study**

		The issue of generalisability of regimens was discussed at the clinical advisory board held to inform the Technical Engagement responses (see Addendum 2). The advisors agreed that the treatments in the comparator arm of the ATLAS study are broadly representative of treatments used today. In instances where specific regimens in ATLAS do not overlap with today's options, they agreed that this is due to evolution in treatment landscape since the study was conducted, the multi-country nature of the study, and the variability in specific populations / subgroups (who may have different profiles and needs). The significant variations in patient backgrounds and needs within HIV populations make discussion of 'the average patient' difficult and potentially meaningless. They also felt that not all treatments are options in all cases (i.e. subsets of the full spectrum of treatments become alternatives for individuals depending on their reasons for changing therapy). Figure 1 shows the distribution of the different third agents used with two NRTI backbones across the whole treated HIV population in England (data from February 2021, IQVIA HPA). Figure 2 presents the corresponding breakdown by third agent in the ATLAS trial. The profiles are broadly comparable and there is a reasonable overlap in class of third agent. The differences observed here can be explained by study design, where ATLAS excluded people treated with Triumeq® and had a cap on recruitment of people receiving INI as a third agent. This is in addition to the reasons for differences discussed above. It is important to note that as all ARTs are assumed to have equivalent efficacy in the model, any differences would not affect the modelling of treatment efficacy, reported QALYs and LYs.



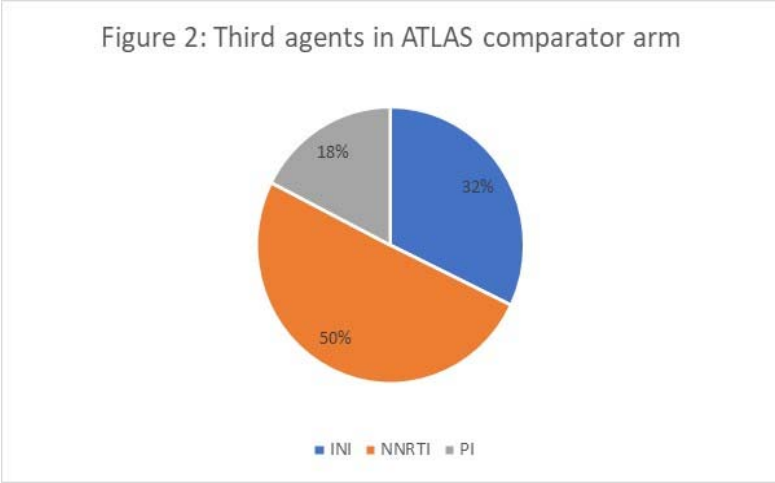


Figure 1: Third agents by market share and in ATLAS comparator arm

		FLAIR study The ERG considers the term 'current ART' to be erroneous in the case of FLAIR. It states that: '*the term "Current ART" implies a variety of therapies dependent on the time and location of the study in question, incorporating patient preference and tolerances. In ATLAS, patients continued the ART they were using prior to entering the study, so "current ART" is valid. This was not true of FLAIR, where the study required that all participants take the same ART. While no patients in FLAIR had taken a previous ART and therefore did not switch to DTG/ABC/3TC from a different ART, neither was that ART representative of the variety of ARTs the patients would have taken had they not been recruited into FLAIR.'* The company acknowledges that this description of FLAIR is correct. However, given that all modern approved ART regimens are assumed to have comparable efficacy (see Key issue 7 for discussion of this), the fact that patients in FLAIR switched from one particular (commonly used and guideline recommended) ART is not considered to materially affect either the efficacy results obtained for CAB LA + RPV LA or the generalisability of the evidence base for CAB LA + RPV LA to patients in the NHS. Further, the company considers that 'current ART' is an adequate and meaningful description of the comparator in the overall trial evidence base, despite the fact that patients in FLAIR did not have a free choice of regimen. FLAIR provides additional information to ATLAS in that ATLAS did not contain many patients on a dolutegravir (DTG) based regimen (most were on an NNRTI (EFV) regimen). Today, DTG- based regimens are the most frequently used regimens. In FLAIR, patients are suppressed on Triumeq® and then switch to CAB LA + RPV LA, which can be viewed as more representative of the typical switch seen today for patients being considered for the long acting treatment. Most importantly, consulted experts have no reservations about the generalisability of the results of the FLAIR trial to UK practice (see Addendum 2).
Key issue 4: Exclusion of case-control studies	No	***Case-control studies were excluded from the company submission; however this is not necessarily a material issue given the significant body of higher level evidence (RCTs) that was included***

		The company agrees with the ERG that case-control studies can provide useful information on the safety of the treatment of interest. However, as the literature search retrieved a very large number of randomised controlled trials (RCTs), which are of higher quality compared to observational studies,[7] data from non-RCT studies were not extracted but provided as Section D.5 of Company submission Appendix D; this does not include case-control studies, which were excluded from the SLR. Case-control studies represent lower quality of evidence than RCTs to inform comparative effectiveness and given the high volume of RCTs and observational studies, priority was given to RCTs. The inclusion of case-control studies would be very unlikely to add new evidence that would diverge from the overall picture drawn from RCTs. Additional safety data from the CAB LA + RPV LA EPAR has been provided – see Additional Issue 2.
Key issue 5: Pooling of ATLAS and FLAIR	Yes	**The ITC combined the patients in the ATLAS and FLAIR trials into a single larger population for analysis. Whilst we recognise the theoretical limitations of using pooled datasets for ITCs, there is limited concern here given that the pooling was pre-specified and the trials were designed with this purpose in mind.** The ERG felt that due to the differences between the trials, such as the different comparator treatments and use of a run-in period, pooling was an inappropriate analysis method and recommended an alternative approach of combining ATLAS and FLAIR in a meta-analysis within the ITC. They also commented that *"Even in the absence of effect modification, the standard error of the pooled ATLAS/FLAIR effect estimate is overly precise, given ATLAS and FLAIR are not the same trial."* The company recognises the theoretical limitations of using pooled datasets in the conduct of ITCs. However, the assumption of trial homogeneity was deemed appropriate for ATLAS and FLAIR given they were designed to be pooled. In theory, we would expect to see a difference using a random-effects meta-analysis due to

trial heterogeneity; however, in practice it can be observed that the impact of this is minimal. Further, it should be noted that standard meta-analysis methods typically account for mean values, variance and sample size when synthesising data; in this case, where the studies are similar and were designed to be pooled, those factors are inherently captured by the pooling method, as it incorporates all participant data.

In preparing responses for an IQWiG submission in Germany, the alternative approach suggested by the ERG, with ATLAS and FLAIR combined in a meta-analysis within the ITC, was conducted. A fixed effects meta-analysis was presented in the main submission and accepted by IQWiG. In accordance with their guidance 'In the case of very few studies, the heterogeneity cannot be reliably estimated. Therefore, if fewer than 5 studies are available, the use of a model with a fixed effect or a qualitative summary should also be considered'. Like the ITC presented in the CS, the subsequent ITC analysis was also conducted using Bucher's methodology. The results based on both a fixed effects and random effects model are provided in Appendix D of this document.

As shown in Table 1, the different analyses to compare the relative effectiveness of CAB LA + RPV LA Q2M to current ART produced very similar relative risks (point estimates and confidence intervals) for viral load. Note that results for adverse events could not be compared directly between the two analyses; the ITC using the non-pooled data included ISRs whereas the ITC using the pooled data excluded ISRs.

Table 1. Comparison of the outcomes from the ITCs using pooled and separate ATLAS and FLAIR trial data

	ITC using non-pooled data Relative Risk [95% CI]	ITC from CS (using pooled data) Relative Risk [95% CI]
Viral load < 50 c/mL at week 48	[redacted]	1.01 [0.95, 1.06]
Viral load ≥ 50 c/mL at week 48	[redacted]	1.10 [0.25, 4.90]

		AEs leading to discontinuation [redacted] 1.48 [0.40, 5.46]
Key issue 6: All oral ARTs are assumed to have a similar efficacy	No	***The model assumption that oral ART regimens have similar efficacy is supported by a breadth of non-inferiority studies, by clinical experts consulted by the Company and is not of particular concern to the ERG (providing there are no issues about trial generalisability – discussed above); this is not considered to be a particularly controversial assumption.*** In the factual accuracy check, Table 36 in CS Appendix D was cited by the company as evidence for the statement that the comparators used in ATLAS and FLAIR have comparable efficacy to currently used regimens. The ERG noted that the table does not present such evidence. This was an error by the company: the statement should have referred to Figure 3 in Appendix D. Figure 3 shows virologic suppression at Week 48 in relevant studies identified in the SLR. It shows that almost all studies reported virological suppression exceeding 90% at week 48, with the exception of dose finding studies and switch studies. This figure is reproduced in an appendix to this form (Appendix B). The ERG agreed with the CS that given the very high efficacy of all current ART, that all oral ARTs have a similar efficacy, but believed the use of a match-adjusted indirect comparison (MAIC) without a full network meta-analysis (NMA) was likely to be justified. However, they concluded that no additional evidence or analyses were necessary. They were concerned that should the efficacy of ART used in the NHS be shown to be different to the ART used in ATLAS/FLAIR, then an NMA would be indicated. As demonstrated in the discussion of Key Issue 3 above, the company believe that the ART used in ATLAS/FLAIR trials are generalisable to the ART used in the NHS,

		and so their efficacies would be the similar, and, in agreement with the ERG, the company do not believe that a full NMA is necessary in this situation.
Key issue 7: Non-significance interpreted as non-inferiority	No	***The ERG has clarified that this is an issue relating to semantics/interpretation. We agree with the ERG that there is ambiguity in the literature surrounding interpretation of non-inferiority studies. As with the point above, there is no material impact of this issue on the outcomes of the analyses.*** The ITC conducted during the CS (B.2.9) found that CAB LA + RPV LA Q2M is not statistically different to current ART after 48 weeks on any of the key efficacy or safety outcomes, in terms of relative risk, odds ratio and risk difference. The ERG highlighted that *'the company refers to the results as showing that CAB + RPV LA Q2M was, in fact, non-inferior or not different to* "current ART." *As the ITC is imprecise, and as the ITC was not designed as a non-inferiority analysis with defined non-inferiority margins, non-significance cannot be interpreted as non-inferiority*.' Guidance on the interpretation of non-inferiority within the context of ITC methodology is still in development, and there is no single accepted method. However, while no specific hypotheses testing to demonstrate non-inferiority was performed, the ITC used the statistical methodology published by Bucher et al.[8] to calculate the 95% CI of indirect treatment effects, which are shown to be not statistically significant different for the efficacy and safety endpoints analysed. Given the lack of statistical certainty inherent in the wider HIV evidence base, which is largely predicated on non-inferiority trials, the element of uncertainty does not negate the assumption that modern approved HIV therapies have essentially 'equivalent' efficacy. Therefore, while the ITC conducted during the CS did not test for non-inferiority, it demonstrates equivalent efficacy to current ART, and so can be considered equivalent to modern approved HIV therapies. The conclusions on comparative effectiveness for CAB LA + RPV LA have been appropriately interpreted in the context of HIV regimens and the basis for their efficacy today.

Key issue 8: Cost of basket of comparators	No	***The company has used the only source of information of relevance to the current market to inform the selection of comparators (for cost purposes) in the submission – i.e. current market share information which indicate the treatments that virologically suppressed individuals 'switch to'; we acknowledge the data are not perfect (since they do not stratify by reasons for switch) but consulted clinical experts – both prior and post submission - agree they are a reasonable representation of likely comparators for long-acting injectables (see Addendum 2)*** There are many different ART regimens available and no single "standard of care" or treatment pathway. This is partly due to the significant evolution in treatment over a number of decades. None of the current guidelines list a bounded set of options or a preferred treatment sequence for virologically suppressed people wishing to change their therapy. This allows individuals and their prescribers to tailor treatment to individual circumstances alongside their medical needs. Despite the considerable choice of available regimens, treatment decisions are primarily based on medical need and commissioning policies. The comparators in the decision problem were a basket of those antiretroviral regimens shown to be most frequently 'switched to' for virologically suppressed people living with HIV, who would be eligible to switch to CAB LA + RPV LA, if CAB LA + RPV LA. The company considers this dataset to be the most appropriate starting point. Those treatments with a share of ≥2.5% (an arbitrary cut-off) were discussed with clinical experts prior to submission. Clinicians advised the addition of Juluca®, as this is a two-drug regimen of dolutegravir and rilpivirine that was identified as clinically relevant for this appraisal because it represents a 'close' oral alternative to CAB LA + RPV LA). Further, clinicians suggested removal of Truvada® (TDF/FTC) + Tivicay®, as patients typically switch away from this regimen rather than onto it, because of toxicity concerns.

		The company acknowledges that imprecision remains in the data since the reason for the switches is unknown, and this reason is likely to be critical in the consideration of transitioning a virally suppressed individual to a long-acting alternative. The choice of comparators was also raised with clinical experts post submission, and they agreed that the selected comparators are largely representative of clinical practice (see Addendum 2), although the various different options will be more or less commonly used depending on patient characteristics and local policies and practice. The choice of switch therapy is individualised based on a range of factors including previous treatment history, underlying health risks and co-morbidities, and considerations relating to lifestyle and individual preference. Drug cost was not an explicit consideration in deriving the comparators and some low-cost branded single tablet regimens, such as Triumeq® and Dovato®, are included. The use of some of the 'lower cost' regimens in fewer than 2.5% of virologically suppressed individuals relates to the fact that these treatments are more likely to be used early on, i.e. are more likely to be treatments that people were switching from. Alternative approaches to identifying comparators, e.g. the ERG's use of the Midland and East Region commissioning policy, have shortcomings given regional variation in pricing and policies, and the date of the algorithm.
Key issue 9: Adherence assumptions NB: From CS: A targeted literature review undertaken to identify studies reporting adherence to ART in the UK found few publications.	NO	***It is reasonable to assume that as a directly observed therapy, improved adherence is an advantage of long-acting injectable treatment. The company accepts there is uncertainty in how this is modelled given availability of data (both on levels of adherence to lifetime daily oral ART and on the consequence of suboptimal adherence on treatment effectiveness).*** ***The company now realise that the ERG has misinterpreted the way the adherence assumptions are implemented in the model (assuming these directly affect the probability of viral rebound and treatment switching, which***

Reported rates of non-adherence ranged from 10% (missing ≥2 doses in the last 7 days) to 57% (missing a dose or taking ≥1 dose incorrectly in last 7 days). SWEET was considered to be the most appropriate source to inform the modelling because it was a formal clinical trial with a relatively large population size. SWEET measured adherence to two daily oral ART regimens in virally suppressed participants with HIV using the Medication Adherence Self-Report Inventory (MASRI). Patients indicated the percentage of ART medication taken over the previous month on a visual analogue scale (VAS). Low adherence was defined as taking <95% of their prescribed ART medication over the past month, and was reported by 25.6% of patients in one therapy arm and 37.6% in the other arm at Week 48 (study population N=117 per arm). The 25.6% reduction from 100% of		***is not the case). Since the ERG's preference for a more conservative approach to adherence is underpinned by this understanding of the model function, we provide in this response an additional step by step, visual guide to the application of adherence assumptions (see Addendum 3)*** **Context** Treatment of HIV currently involves life-long adherence to daily oral therapy in order to achieve and maintain viral suppression. At any one time, levels of adherence and virological success are generally high in the UK. However, adherence can fluctuate, sometimes significantly, within and between individuals in a population. Unexpected disruptions in life can impact even those who have generally high adherence levels. For the purposes of economic modelling, this real-world complexity and variation must be simplified into two key inputs – the degree of suboptimal adherence over a lifetime (for an average person) and the consequences thereof (i.e. the link between adherence and viral suppression). Neither can be quantified with full certainty, as HIV medications requires life-long adherence and there is no universally accepted way to define or quantify adherence. In particular, published estimates of adherence are subject to relatively short measurement periods which do not necessarily reflect individuals' adherence over many years of treatment. Further, there is the added complication that adherence is not the only factor impacting on suppression, but is one of many drivers: a person who is fully adherent to medication may still experience viral rebound. The company acknowledge the uncertainty highlighted by the ERG around economic model inputs for adherence and impact of adherence. Following receipt of the ERG report, the Company conducted an advisory board to discuss adherence in depth with a clinical expert panel; a summary is supplied (Addendum 2). The clinical experts agreed that it is reasonable to expect a relationship between adherence and treatment efficacy, and for them to be positively associated (i.e. better adherence is linked to better efficacy outcomes). They confirm that in their

patients having perfect adherence was applied to daily oral ART in the base case analysis, as this represented the more conservative choice.		practices, levels of adherence are high at any one time. They described variation within and between individuals in a population, highlighting the impact of life events and unexpected life disruptions. The experts acknowledged the complexity related to extrapolating the experiences of a cross section of patients at any one point in time to the lifetime / longitudinal framing for an average patient that is required for NICE decision making. In the context of the company's economic model, the single input representing the proportion who are 'sub-optimally adherent' must summarise significant variation across a population (due to unpredictable life disruptions) and average this over the lifetime (due to the lifetime nature of treatments). Whilst there is inevitable uncertainty, it is reasonable to expect that the lifetime 'average' adherence will be lower than the level of adherence seen in a population snapshot at a single point in time. **Implementation of adherence in the model** Following the ERG's response to the Company's factual inaccuracy check and Technical Engagement call it appears the ERG have misinterpreted the way that adherence is implemented in the model, specifically its impact on 'downstream' consequences of non-adherence. Adherence or non-adherence does not impact on treatment outcomes directly in clinical practice: less than optimal adherence results in a slightly lower probability of achieving viral suppression. It is essential to understand that: • Individuals who are completely adherent will predominantly achieve viral suppression; however, some may still experience viral rebound due to unknown factors. • In clinical practice, not all individuals with less than optimal adherence will experience viral rebound or fail to achieve viral suppression in clinical practice, as modern regimens may maintain their efficacy at lower levels of adherence than older regimens.

		• Not all individuals with less than optimal adherence will discontinue current treatment and move to subsequent treatment. During economic model conceptualisation, these factors were discussed with clinical experts and the model design was developed with this in mind. Hence, to address any misunderstandings, the company has provided a step-by-step guide to implementation of adherence in the model (see Addendum 3). To model the potential adherence-related benefit associated with CAB LA + RPV LA, adherence-related adjustments are made to treatment efficacy in the pooled ART arm, indirectly increasing the probability of viral rebound. Although in clinical practice, adherence does not directly impact on treatment discontinuation, the relationship between adherence and treatment effectiveness is captured in the model by adjustment of the monthly risk of discontinuation for individuals with reduced adherence. Further, it should be noted that the following ERG comment is inaccurate: "The ERG feels justification is needed why it is assumed that patients who become less than 95% adherent will immediately need to switch therapy and will immediately experience a viral load >50 HIV RNA copies per ml". The economic model adjusts viral suppression as a result of the adherence input which has a consequence on the monthly probability of viral rebound. Thus, these individuals with reduced adherence experience a higher probability of viral rebound (and hence treatment switching) each month, but this is not immediate and it is not experienced by all individuals with less than optimal adherence. **Evidence to describe the relationship between adherence and viral suppression** The experts at the advisory board were asked if they were aware of additional evidence sources on the relationship between adherence and viral suppression in a UK population, beyond those already identified by the company and discussed in the CS. They highlighted the potential value of the UK Collaborative HIV Cohort (UK CHIC) study (Jose et al, 2018)[8], which reports a range of outcomes in a cohort of people with HIV in the UK. However, on further investigation, no published outputs from this study were suitable for use in the economic modelling. While the UK CHIC

		study reports on long-term outcomes, UK CHIC does not report any quantitative data on adherence or the relationship of adherence to viral suppression. The company therefore remains of the opinion that the existing implementation of the relationship between adherence and efficacy in the model, although subject to limitations, remains the most suitable approach given the available evidence. **Choice of adherence inputs** As noted above, there is no definitive estimate of long-term adherence to oral ART in the UK because of differences in the method of assessing adherence, the time period over which it is measured, and the threshold used to define suboptimal adherence. As reported in the CS, a targeted literature review undertaken to identify studies reporting adherence to ART in the UK found few publications. Reported rates of non-adherence ranged from 10% (where non-adherence was defined as missing ≥2 doses in the last 7 days) to 57% (missing a dose or taking ≥1 dose incorrectly in last 7 days). The SWEET study[9] was considered to be the most appropriate source to inform the modelling because it was a formal clinical trial with a relatively large population size, and used a formal adherence measurement tool (MASRI) with a 1-month recall period. Low adherence was defined as taking <95% of their prescribed ART medication over the past month, and was reported by 25.6% of patients in one therapy arm and 37.6% in the other arm at Week 48. The more conservative of the two adherence results (i.e. the lower non-adherence value, 25.6%) was used; the ERG states that this would correspond to 86% adherence. The Company remains of the opinion that SWEET, whilst not definitive, is the most suitable estimation of UK adherence levels that is available. The ERG recommended the use of an adherence value from Sherr et al. 2010 of 10.1% of patients (Sherr) who missed at least two doses in the past seven days; the ERG states this would correspond to an adherence level of 71% or less); the ERG states that this may be more reflective of an adherence value below which it can more reliably assumed that viral suppression is indeed reduced, given that

		modern regimens may maintain their efficacy at lower levels of adherence than older regimens. The Company considers Sherr et al. to be a less suitable source because it uses a single snapshot of adherence based on doses missed during a 7-day recall period. In contrast, SWEET uses a 1-month recall period and patients had been taking their regimen for 48 weeks at the time of questioning (treatment duration was not specified in Sherr et al). In the company's opinion the Sherr et al. study is a less effective picture of long-term adherence patterns, because of the short recall period, which is likely to miss many fluctuations in adherence. It does not therefore provide any greater degree of certainty, particularly as the true relationship between adherence and efficacy of the comparator regimens remains unknown due to lack of data. The company acknowledges the uncertainty around quantifying adherence, and therefore addressed this in sensitivity analyses in the CS whereby the modelled reduction in adherence was varied in 5% increments from 5% to 40%. Importantly, the ERG prefer the more conservative assumption of lifetime adherence - at least in part - to underwrite their concerns that the model functionality lacks clinical justification. However, as described above, we believe the ERG has misunderstood how adherence is modelled. It is hoped that the clarifications presented in this submission will help reconcile the preferred assumptions. It is acknowledged that the impact on viral suppression of fluctuations in adherence to oral ART over a lifetime is in reality complex with many interdependencies and day-to-day challenges for individuals. An economic analysis can in no way reflect all patterns, scenarios and complexities. However, the base case approach has been developed in collaboration with clinical experts and HIV advocacy groups to reflect a pragmatic, clinically plausible simplification of these factors. Alternative methodologies should not be judged solely on their conservative nature, but should incorporate similar pragmatism and ensure that clinical plausibility is the key determinant of approach.

Key issue 10: Utility advantage for patients taking CAB LA + RVP LA	**YES**	• ***The company are able to resolve one of the ERG's concerns relating to utility (drop-outs); this should no longer be an issue (see below).*** • ***Injection site reactions (ISRs) – the ERG's second concern - were of short duration (median 3 days in ATLAS-2M) and would not have materially impacted PROs; this is reflected in the Perception of Injection data which indicates high acceptance and little or no bother with injections and is supported by a clinical expert who was consulted on the topic (see Addendum 2).*** • ***In summary we agree with the ERGs overall view that these two 'issues' have limited impact; the company goes one step further and considers that the modelled 0.02 utility benefit associated with a Q2M, long-acting treatment versus daily, oral ART is a likely underestimate.*** The ERG expressed two separate concerns regarding the uncertainty around the size of the utility advantage associated with CAB LA + RPV LA: • They highlighted the higher incidence of what appeared to be 'missing data' in the HRQoL reporting in the CAB LA + RPV LA group, compared to the oral ART group; this led to concern that data may have been missing non-randomly due to different 'drop-out' rates in the two arms. • The ERG felt that ISRs may have been missed during the HRQoL data collection (given that the SF-12 questionnaire was administered before participants received injections). We acknowledge that neither of these concerns led to a change in the utility assumption in the ERG's basecase. **'Missing data'** After further follow-up with the trial statisticians, the Company can now clarify the reason for the slightly lower number of patients in the CAB LA + RPV LA arm who had SF-6D data analysed, compared with the comparator (daily oral ART) arm. The difference in numbers was not due to missing patients (i.e. drop-outs); rather, it was due to differences in the numbers of patients who had data available for all the necessary covariates in the analysis. As detailed in the CS Appendix N, the

		ANCOVA model was adjusted for age, sex and CD4+ cell count as covariates. Subsequently, one model was created per visit (total three models [baseline, week 24 and week 48]) and CD4+ categories and SF-6D data at the same visit were used in each model. Patients with a missing covariate were not included. As these patients had some data available (but not all covariates), the missingness is not related to drop-out and can be considered random. To further investigate the effect of these variations on the SF-6D analysis, the Company has produced a summary of SF-6D score at each visit, broken down by patients with and without missing covariates (see Appendix C). It can be seen that the mean SF-6D scores at Week 48 are in fact slightly higher in patients with missing covariates, in both treatment arms. At Week 24, this holds true for the CAB LA + RPV LA arm (though not the comparator arm). These findings show that the analysis leading to the 0.02 utility advantage for CAB LA + RPV LA was not biased and the ERG's concern should now be addressed. **ISRs** The ERG was concerned that the timing of the PRO instruments, i.e. prior to receiving the intervention, may have missed effects of ISRs on SF-12 scores. However, a study physician consulted post-submission pointed out that any concern that the timing of the PRO instruments may miss intervention-related adverse events applies to both trial arms (not just long-acting treatment). They also agreed that ISRs are not likely to have a big impact on quality of life given their short duration (median 3 days in ATLAS-2M) and that overall there is high acceptability of injections to participants (as shown by the Perception of Injection data). **Summary** The Company accepts and agrees with the ERG's observation that these issues have little impact on the modelled utility. The company additionally considers that the utility difference between the two groups as captured by SF-6D (0.02) is conservative and is very likely to be an underestimate of the true utility gain associated with CAB LA + RPV LA compared with daily oral ART. This is because of the recognised limitations associated with generic HRQoL instruments (including

		the SF-12, on which the utility values are based) in capturing disease-specific factors such as stigma-related issues (e.g. fear of disclosure, daily reminder of HIV status) and lifestyle-related benefits such as convenience (which can in turn influence adherence). This view is supported by clinical expert opinion (a study physician) sought on this topic for this response (see Addendum 2). Thus the company believes that there are significant HRQoL benefits that are not captured in the QALY in this submission, and that 0.02 should be considered as a lower limit of the difference. Furthermore, long-acting regimens are generally recognised to have advantages for the patient over daily regimens, and their development is a priority in a number of therapy areas. In comparable situations when patients are offered a choice between a daily oral therapy and a less frequent, long-acting injectable therapy, such as with contraception and anti-psychotics, patients experience greater treatment satisfaction due to the increased choice and empowerment that having different treatment modalities offers.[9-11] Similarly, patients benefit from the assured adherence offered by a long-acting treatment and in the case of anti-psychotics report better disease management and fewer sudden symptoms.[9] The desirability of long-acting ART is evidenced by the fact that other HIV pharmaceutical companies are currently developing similar products, and reflects a general trend towards long-acting therapies across several therapy areas.[12]

Additional issues

Please use the table below to respond to additional issues in the ERG report 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 appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Eligibility of study participants with K103N mutation	Pages: 12, 23, 26, 73, 87-88	No	***Eligibility for trial participation of those with baseline K103N mutation was removed by the ERG as a major issue. The company consider it unnecessary to retain reference to K103N at all in the report since there is no bias against oral ART associated with it. All trial participants were virally suppressed and none of the treatment failures (in either arm) had a baseline K103N mutation.*** In the original ERG report, the ERG stated that patients who were a carrier of K103N were at risk of developing resistance to other NNRTIs, such as NVP or EFV. During the factual accuracy check, the company clarified that this mutation is not a concern for the population under consideration, given that the population is virally suppressed. Additionally, it should be noted that none of the participants who experienced virologic failure in ATLAS or FLAIR, in either treatment arm, had this mutation at baseline; this provides further reassurance that this issue is not clinically relevant to the submission.

<table>
<tr>
<td>Additional issue 2:
Comparator safety evidence</td>
<td>Section 3.6, page 74</td>
<td>Yes</td>
<td>As highlighted by the ERG, the CS did not report a summary of the common AEs (≥5% in either arm) for the pooled ATLAS and FLAIR studies. To allow like for like naïve comparison on safety across ATLAS 2M, ATLAS and FLAIR, and thereby ensure the committee can fully assess the safety of CAB LA + RPV LA (Q2M), this evidence has been provided with this form (Appendix A). The table below summarises the location of safety data within the CS and subsequent documents.
<table>
<tr><th></th><th>ATLAS-2M</th><th>ATLAS</th><th>FLAIR</th><th>ATLAS & FLAIR</th></tr>
<tr><td>Overall Summary</td><td>Document B B.2.10.1</td><td>Technical Engagement Appendix A</td><td>Technical Engagement Appendix A</td><td>Technical Engagement Appendix A</td></tr>
<tr><td>Common AEs (≥5%)</td><td>Document B B.2.10.1</td><td>Technical Engagement Appendix A</td><td>Technical Engagement Appendix A</td><td>Technical Engagement Appendix A</td></tr>
<tr><td>Drug related AEs (≥1%)</td><td>Document B B.2.10.1</td><td>Clarification questions Table 10</td><td>Clarification questions Table 10</td><td>Clarification questions Table 10</td></tr>
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Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

NOT APPLICABLE: no changes were made.

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Addendum 1: Updated search strategies and results

This is supplied as a separate document.

Addendum 2: Summary of additional advisory boards

This is supplied as a separate document.

Addendum 3: Guide to implementation of adherence in the economic model

This is supplied as a separate document.

Appendices

Appendices are supplied on the pages that follow.

Appendix A Additional safety information from the EPAR

Table 1: Overview of all adverse events during the maintenance phase, pooled Phase III studies (safety population)

	201584		201585		Pooled	
	CAB LA + RPV LA (n=283) n (%)	CAR (n=283) n (%)	CAB LA + RPV LA (n=308) n (%)	CAR (n= 308) n (%)	CAB LA + RPV LA (n=591) n (%)	CAR (n=591) n (%)
Any AE	267 (94)	225 (80)	294 (95)	220 (71)	561 (95)	445 (75)
Any Grade 3/4/5 AE	31 (11)	11 (4)	35 (11)	24 (8)	66 (11)	35 (6)
Any drug related AE	236 (83)	28 (10)	255 (83)	8 (3)	491 (83)	36 (6)
Any Grade 3/4/5 drug related AE	14 (5)	0	14 (5)	1 (<1)	28 (5)	1 (<1)
Any AEs leading to withdrawal	9 (3)	4 (1)	13 (4)	5 (2)	22 (4)	9 (2)
Any SAE	18 (6)	12 (4)	13 (4)	14 (5)	31 (5)	26 (4)
SAEs related to study treatment	1 (<1)	0	0	1 (<1)	1 (<1)	1 (<1)
Fatal SAEs	0	0	0	1 (<1)	0	1 (<1)
Fatal SAEs related to study treatment	0	0	0	0	0	0

The CAB LA + RPV LA group is listed as Q4W IM. For study 201584, CAR = ABC/DTG/3TC
3TC: lamivudine; ABC: abacavir; AE: adverse event; CAB: cabotegravir; CAR: current antiretroviral regimen; DTG: dolutegravir; LA: long acting; RPV: rilpivirine; SAE: serious adverse event;
Source: Vocabria EPAR[13]

Table 2: Overall summary of non-ISR adverse events during the maintenance phase for pooled data (safety population)

	201584		201585		Pooled	
	CAB LA + RPV LA (n=283) n (%)	CAR (n=283) n (%)	CAB LA + RPV LA (n=308) n (%)	CAR (n= 308) n (%)	CAB LA + RPV LA (n=591) n (%)	CAR (n=591) n (%)
Any AE	246 (87)	225 (80)	264 (86)	220 (71)	510 (86)	445 (75)
Any Grade 3/4/5 AE	22 (8)	11 (4)	25 (8)	24 (8)	47 (8)	35 (6)
Any drug related AE	79 (28)	28 (10)	87 (28)	8 (3)	166 (28)	36 (6)
Any Grade 3/4/5 drug related AE	4 (1)	0	4 (1)	1 (<1)	8 (1)	1 (<1)
Any AEs leading to withdrawal	8 (3)	4 (1)	9 (3)	5 (2)	17 (3)	9 (2)
Any SAE	18 (6)	12 (4)	13 (4)	14 (5)	31 (5)	26 (4)
SAEs related to study treatment	1 (<1)	0	0	1 (<1)	1 (<1)	1 (<1)
Fatal SAEs	0	0	0	1 (<1)	0	1 (<1)
Fatal SAEs related to study treatment	0	0	0	0	0	0

AE: adverse event; CAB: cabotegravir; CAR: current antiretroviral regimen; ISR: injection site reaction; LA: long-acting; RPV: rilpivirine; SAE: serious adverse event;
Source: Vocabria EPAR[13]

Table 3: Most common adverse events (reported in ≥5% of subjects in any treatment group) by preferred term during the maintenance phase for Study 201584, study 201585 and pooled data (safety population)

	201584		201585		Pooled			
	CAB LA + RPV LA (n=283) n (%)	CAR (n=283) n (%)	CAB LA + RPV LA (n=308) n (%)	CAR (n= 308) n (%)	CAB LA + RPV LA (n=591) n (%)	AE rate per 100 subject years	CAR (n=591) n (%)	AE rate per 100 subject years
Any event	267 (94)	225 (80)	294 (95)	220 (71)	561 (95)	542.03	445 (75)	221.25
Injection site pain	227 (80)	0	231 (75)	0	458 (77)	231.27	0	0.00
Nasopharyngitis	56 (20)	48 (17)	51 (17)	42 (14)	108 (18)	20.31	90 (15)	29.51
Upper respiratory tract infection	38 (13)	28 (10)	32 (10)	25 (8)	70 (12)	12.32	53 (9)	17.27
Headache	39 (14)	21 (7)	34 (11)	17 (6)	73 (12)	13.07	38 (6)	12.36
Diarrhoea	32 (11)	25 (9)	22 (7)	15 (5)	54 (9)	9.43	40 (7)	12.81
Injection site nodule	44 (16)	0	37 (12)	0	81 (14)	14.51	0	0.00
Influenza	25 (9)	20 (7)	17 (6)	14 (5)	42 (7)	7.19	34 (6)	10.87
Injection site induration	38 (13)	0	30 (10)	0	68 (12)	12.28	0	0.00
Back pain	22 (8)	13 (5)	21 (7)	10 (3)	43 (7)	7.36	23 (4)	7.40
Pyrexia	22 (8)	4 (1)	21 (7)	9 (3)	43 (7)	7.42	13 (2)	4.22
Vitamin D deficiency	23 (8)	13 (5)	8 (3)	12 (4)	31 (5)	5.30	25 (4)	8.14
Respiratory tract infection	13 (5)	12 (4)	11 (4)	17 (6)	24 (4)	4.03	29 (5)	9.45
Cough	10 (4)	12 (4)	16 (5)	14 (5)	26 (4)	4.40	26 (4)	8.50
Injection site swelling	23 (8)	0	23 (7)	0	46 (8)	8.00	0	0.00
Nausea	16 (6)	11 (4)	14 (5)	5 (2)	30 (5)	5.13	16 (3)	5.15
Pharyngitis	15 (5)	9 (3)	8 (3)	12 (4)	23 (4)	3.86	21 (4)	6.80
Fatigue	7 (2)	8 (3)	22 (7)	6 (2)	29 (5)	4.93	14 (2)	4.52
Gastroenteritis	15 (5)	11 (4)	5 (2)	10 (3)	20 (3)	3.36	21 (4)	6.79
Dizziness	15 (5)	3 (1)	9 (3)	5 (2)	24 (4)	4.05	8 (1)	2.58
Haemorrhoids	16 (6)	3 (1)	4 (1)	2 (<1)	20 (3)	3.36	5 (<1)	1.61
Injection site pruritus	16 (6)	0	7 (2)	0	23 (4)	3.86	0	0.00

The CAB LA + RPV LA group is listed as Q4W IM. For study 201584, CAR = ABC/DTG/3TC
3TC: lamivudine; ABC: abacavir; CAB: cabotegravir; CAR: current antiretroviral regimen; DTG: dolutegravir; LA: long acting; RPV: rilpivirine;
Source: Vocabria EPAR[13]

Appendix B Virologic suppression at Week 48 in comparable studies

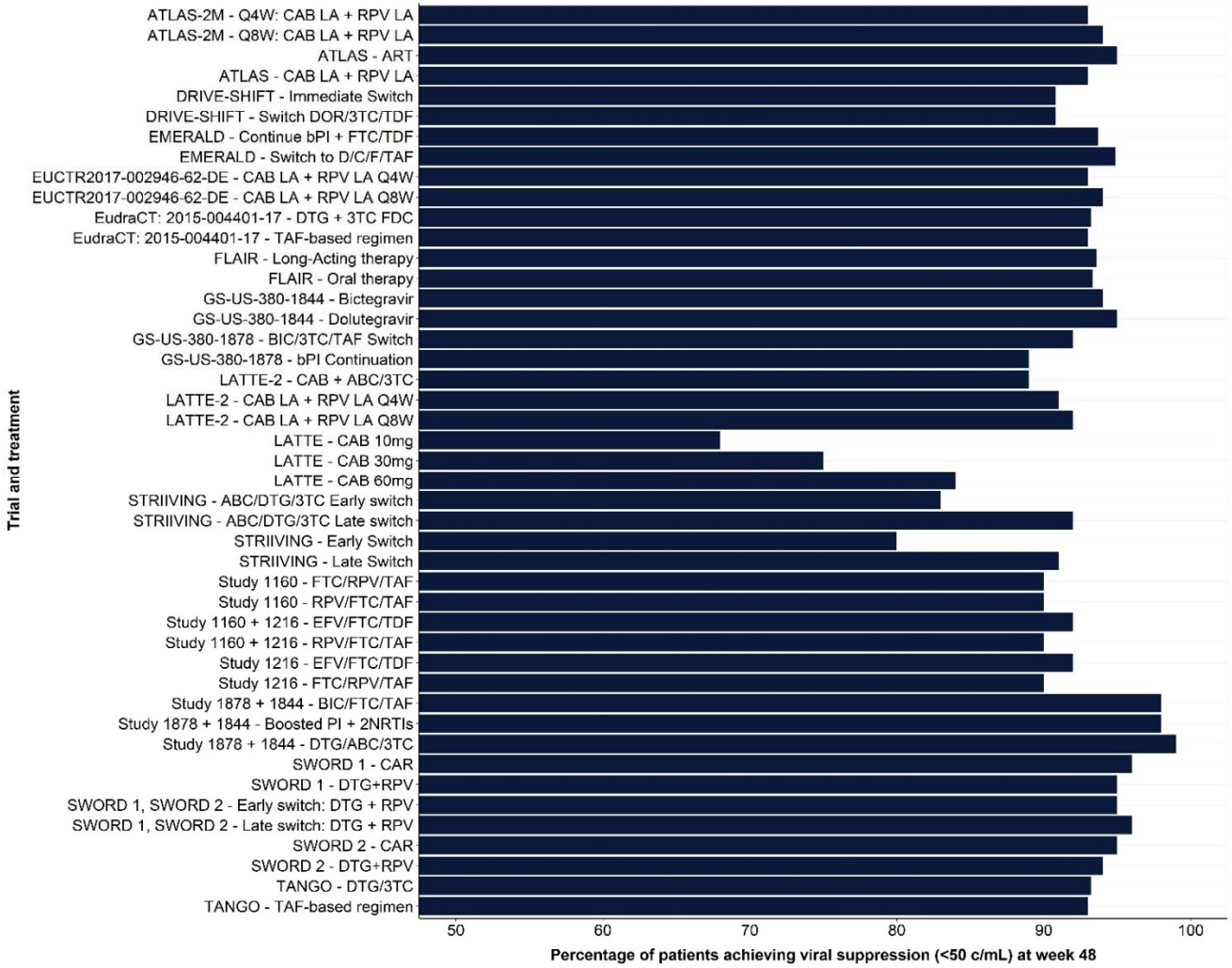

Figure 1 Virologic suppression at Week 48 from relevant studies in the SLR (Reproduced from CS Appendix D, Figure 3).

Appendix C Additional information on SF-6D analysis

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Population: Intent-to-Treat Exposed

Table 1.5
Summary of SF6D Score by Visit Baseline, Week 24 and Week 48
(by Missing and Non-Missing Covariates)

Subgroup	Category	Treatment	N	Analysis Visit	n	Mean	SD	Median	Q1	Q3	Min.	Max.
Missing Covariate(s)	No	Q4W	591	Baseline	556	0.832	0.1275	0.863	0.723	0.922	0.48	1.00
				Week 24	535	0.836	0.1363	0.863	0.723	0.922	0.44	1.00
				Week 48	500	0.839	0.1353	0.863	0.723	0.922	0.45	1.00
		CAR	591	Baseline	561	0.827	0.1241	0.859	0.723	0.922	0.51	1.00
				Week 24	546	0.816	0.1369	0.859	0.669	0.922	0.43	1.00
				Week 48	548	0.821	0.1349	0.859	0.708	0.922	0.38	1.00
	Yes	Q4W	591	Week 24	37	0.799	0.1237	0.801	0.695	0.922	0.54	1.00
				Week 48	44	0.848	0.1339	0.863	0.723	1.000	0.59	1.00
		CAR	591	Baseline	2	0.961	0.0552	0.961	0.922	1.000	0.92	1.00
				Week 24	20	0.825	0.1693	0.922	0.674	1.000	0.53	1.00
				Week 48	14	0.822	0.1322	0.860	0.782	0.922	0.54	1.00

Appendix D. Indirect treatment comparison - HTA assessment in Germany

Tabelle 1: Ergebnisse der Meta-Analyse für Viruslast < 50 Kopien/ml zu Woche 48 aus RCT für indirekte Vergleiche

	Relatives Risiko CAB+RPV Q1M vs. CAR [95% KI], p-Wert
[redacted]	
Modell mit festen Effekten [fixed effects]	[redacted]
Modell mit zufälligen Effekten [random effects]	

Abkürzungen: CAB = Cabotegravir, RPV = Rilpivirin, Q1M = einmal monatlich, CAR = current antiretroviral regimen, KI= Konfidenzintervall

Tabelle 2: Ergebnis des indirekten Vergleichs für Viruslast < 50 Kopien/ml zu Woche 48

	Relatives Risiko [95%-KI] p-Wert
CAB+RPV Q2M vs. CAB+RPV Q1M[a]	[redacted]
CAB+RPV Q1M vs. CAR[b]	[redacted]
indirekter Vergleich: CAB+RPV Q2M vs. CAR	[redacted]

[a] Ergebnis der Studie ATLAS-2M
[b] Ergebnis der Meta-Analyse der Studien FLAIR und ATLAS

Abkürzungen: CAB = Cabotegravir, RPV = Rilpivirin, Q2M = einmal alle zwei Monate, Q1M = einmal monatlich, CAR = current antiretroviral regimen, KI = Konfidenzintervall

Tabelle 3: Ergebnisse der Meta-Analyse für Viruslast ≥ 50 Kopien/ml zu Woche 48 aus RCT für indirekte Vergleiche

	Relatives Risiko CAB+RPV Q1M vs. CAR [95% KI], p-Wert
[redacted]	
Modell mit festen Effekten [fixed effects]	[redacted]
Modell mit zufälligen Effekten [random effects]	[redacted]
Abkürzungen: CAB = Cabotegravir, RPV = Rilpivirin, Q1M = einmal monatlich, CAR = current antiretroviral regimen, KI= Konfidenzintervall	

Tabelle 0-4: Ergebnis des indirekten Vergleichs für Viruslast ≥ 50 Kopien/ml zu Woche 48

	Relatives Risiko [95%-KI] p-Wert
CAB+RPV Q2M vs. CAB+RPV Q1M[a]	[redacted]
CAB+RPV Q1M vs. CAR[b]	[redacted]
indirekter Vergleich: CAB+RPV Q2M vs. CAR	[redacted]
[a] Ergebnis der Studie ATLAS-2M [b] Ergebnis der Meta-Analyse der Studien FLAIR und ATLAS Abkürzungen: CAB = Cabotegravir, RPV = Rilpivirin, Q2M = einmal alle zwei Monate, Q1M = einmal monatlich, CAR = current antiretroviral regimen, KI = Konfidenzintervall	

Tabelle 0-5: Ergebnisse der Meta-Analyse für unerwünschte Ereignisse bis Woche 48, die zum Therapieabbruch geführt hatten, aus RCT für indirekte Vergleiche [AEs leading to discontinuation]

	Relatives Risiko CAB+RPV Q1M vs. CAR [95% KI], p-Wert
[redacted]	
Modell mit festen Effekten	[redacted]
Modell mit zufälligen Effekten	
Abkürzungen: CAB = Cabotegravir, RPV = Rilpivirin, Q1M = einmal monatlich, CAR = current antiretroviral regimen, KI= Konfidenzintervall	

Tabelle 0-6: Ergebnis des indirekten Vergleichs für unerwünschte Ereignisse bis Woche 48, die zum Therapieabbruch geführt hatten [AEs leading to discontinuation]

	Relatives Risiko [95%-KI] p-Wert
CAB+RPV Q2M vs. CAB+RPV Q1M[a]	[redacted]
CAB+RPV Q1M vs. CAR[b]	[redacted]
indirekter Vergleich: CAB+RPV Q2M vs. CAR	[redacted]
[a] Ergebnis der Studie ATLAS-2M [b] Ergebnis der Meta-Analyse der Studien FLAIR und ATLAS Abkürzungen: CAB = Cabotegravir, RPV = Rilpivirin, Q2M = einmal alle zwei Monate, Q1M = einmal monatlich, CAR = current antiretroviral regimen, KI = Konfidenzintervall	

NICE National Institute for Health and Care Excellence

Expert statement and technical engagement response form

Cabotegravir and rilpivirine for treating HIV-1 [ID3766]

Thank you for agreeing to give us your views on this treatment 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.

About this Form
In **part 1** we are asking you to complete questions about living with or caring for a person with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a lived experience 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.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

NICE National Institute for Health and Care Excellence

Please return this form by **5pm** on **Friday 18th June 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Please use this questionnaire with our hints and tips for patient 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. The text boxes will expand as you type.

Important information on completing this expert statement

- 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 want 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 15 pages.

PART 1 – Living with or caring for a person with HIV-1 and current treatment options	
About you	
1.Your name	**Alex Sparrowhawk**
2. Are you (please tick all that apply):	☒ a person living with HIV-related illness (or disease)? ☐ a person with experience of the treatment being evaluated? ☐ a carer of a person living with with HIV-related illness (or disease)? ☒ a community organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	UK Community Advisory Board (UK-CAB)
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete an 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/experience (e.g. I am drawing on others' experiences). Please specify what other experience: ☒ 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
Living with HIV-1	
6. What is your experience of living with HIV-1? If you are a carer (for someone with HIV-1) please share your experience of caring for them.	I was diagnosed in November 2009 at the age of 24, I started treatment within a few weeks due to the impact the virus had already made on my immune system. My first treatment consisted of four pills taken at daily at the same time, one of which was kept in the fridge, I lived with a friend so the decision to keep my status private from them was largely removed at the time. I was lucky enough to find them supportive and decided to tell close friends within the same time period so I had a support network around me. Living in Manchester I had access to a local support service, George House Trust, and I was able to join some of their support groups and 'newly diagnosed course'. Unfortunately there was high demand for their counselling service, a couple of months into my diagnosis I was offered to join another waiting list with LGBT Foundation (then LGF) but I was too worried about more people knowing my status and declined, despite a history of depression and mental health issues – largely connected to my sexuality and not fitting in during my school years. It took me two years to tell my family because I was concerned about how they would react, they have supported me ever since, the fear of rejection was so

	powerful and then I had to handle the guilt of thinking ill of them when they were supportive. I still struggled with mental health issues but did not seek support, largely due to my distrust and poor past counselling experiences, in February 2012 I took an overdose which included my HIV medication and was taken to hospital. However, this incident provoked me to tackle the things I was unhappy with in my life, including my HIV status. I made a decision to speak out about my HIV status later that year, I was tired of the burden of keeping it private, and the control other people had in knowing the information, and also the hold I felt the virus had on me. I've been open about my HIV status ever since. Stigma played a big factor in my decision to speak openly about HIV, realising that things couldn't change unless people could show others that people living with HIV are just like everyone else, and deserve respect, love and support. A number of stigmatising experiences meant that I was keen to remove the control others have over you, and the constant fear that my status could be shared without my knowledge. Most stigma I've experienced is in relation to romantic and sexual rejection. At the other extreme in my first few months with HIV I was blackmailed into having an ongoing sexual relationship with a regular-casual partner who said they would tell people otherwise. I've experienced stigma in the health service, the first time this related to a skin injection which was eventually diagnosed by my HIV team, my GP was insistent on testing for syphilis despite my recent sexual history and testing ruling it out, it was clear they were making assumptions based on my HIV status. I've encountered other bad experiences where a lack of knowledge of HIV is evident, such as being prescribed other drugs which I then found out interacted with my medication.

Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for HIV-1 on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	I've been on a daily pill regimen for about seven years now, the same drug apart from a six month period where I tried something else which I stopped using due to side effects. I've had ongoing gastro issues since my diagnosis, but it is unclear whether this is connected to inflammation caused by HIV, side effects, or just coincidence. One of the ongoing battles for people living with HIV is working out whether their health needs are HIV-related, would have happened anyway, and whether this matters – personally for psychological reasons I believe it does. I've mostly been happy with my care since my diagnosis. I trust my HIV team much more than the primary are staff at my GP practice, mostly around their knowledge, and the lack of training primary care professionals receive about the condition. The HIV population is varied and diverse, people are mostly concerned that their treatment works, and it keeps them undetectable – especially since the release of the PARTNER study, showing people with an undetectable viral load can't pass HIV on to sexual partners. However, I do know people who have struggled at times in their lives to take the treatment when their mental health has been poor. I'm also familiar of people living in accommodation with people – both strangers and even their own families – who do not know they have HIV. There is an excitement and 'buzz' around injectable treatment, more and more people are asking when they can start it, and how much longer until they can 'stop taking the pills' etc.
8. If there are disadvantages of **current NHS treatments** for people living with HIV-1 (for example how the treatment is given or taken, side effects of treatment etc) please describe these	It can be difficult even with an app or alarm to remember if I have taken them – or worry about double dosing. The issue of people knowing or spotting you taking them can be difficult. I used to take my original combination at 10pm, I wouldn't want to take four pills with me on a night out, it is not much better with one – I would leave them on my pillow and hope I would remember them when I got home drunk. I know people who have been thrown out of clubs/bars (including gay venues which you might expect to have better knowledge or understanding)

	because they've been accused of taking recreational drugs when it was the time to take their HIV meds. HIV meds are easily searchable online so people who hide them can get worried about them being found by people who do not know their status. I know of people who put them in vitamin containers – which is potentially dangerous if someone else were to mistake them.
Advantages of this treatment	
9a. If there are advantages of cabotegravir and rilpivirine over current treatments on the NHS please describe these. For example, the impact on 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 and rilpivirine help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	Injectable treatment is reducing treatment dosing from 365 down to 12 or even 6 days a year (post oral lead-in period) – that would benefit many people who do not like the daily reminder pills have that they have HIV. It would be highly beneficial for people who have not shared their status with people they live with. Injectable treatment provides privacy, you do not have to worry about forgetting pills. The ability for people to access treatment without fear of their status being discovered, and the balance to mental wellbeing (especially considering people with HIV are twice as likely as general population to experience depression and anxiety) injectable treatment can bring are the factors I would consider most important. Hopefully it is obvious these benefits counter and provide a solution to the issues described in the above section.

Disadvantages of this treatment	
10. If there are disadvantages of cabotegravir and rilpivirine over current treatments on the NHS please describe these? For example, are there any risks with cabotegravir and rilpivirine? If you are concerned about any potential side affects you have heard about, please describe them and explain why.	There is the potential for some side effects which would be different to those of pill-based treatment, i.e. reactions at the injection site. If these occurred people may need to get used to them, but I have not seen this a concern in the community, and it would not put me off using injectable treatment. This treatment would not be for everyone, and some will want to stick to pills, preferring not to need to see a health professional at regular intervals etc.
Community population	
11. Are there any groups of people living with HIV-1 who might benefit more from cabotegravir and rilpivirine or any who may benefit less? If so, please describe them and explain why. Consider, for example, if people living with HIV-related illness (or disease) also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	People living with HIV are diverse and varied, there is no one 'demographic' that would benefit from this treatment – but there are people, often in vulnerable circumstances who would. • People who are taking a lot of pills and worry about pill burden • People who live with others who do not know they have HIV • People who find it hard to take a daily pill due to physical and mental wellbeing issues.

Equality	
12. Are there any potential equality issues that should be taken into account when considering HIV-1 and cabotegravir and rilpivirine? 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 More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-	In the UK, HIV disproportionately impacts marginalised communities, most notably gay and bisexual men, people of Black African ethnicity, and transgender women. Just under a third of people with HIV in the UK are women. More than two in five people with HIV are aged 50 or over (PHE, 2020). There is anecdotal evidence that a concern to keep HIV status confidential may be particularly prevalent among racially minoritised populations, so the technology may be particularly beneficial for them. Similarly, the higher rates of viral non-suppression in young people (15-24) may suggest potential benefits in this group (PHE, 2020).

real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	1. This submission details my personal experiences as a queer person, aged 24-36, who is white, middleclass, degree-level educated, who has received the support of friends and family during my diagnosis. I would ask the committee to put themselves in the shoes of other people who are living with this virus who do not have the same societal privileges as I do, and consider if these are the experiences of someone in that situation and who is perceived to be "doing well with HIV" then to reflect on what "bad" or "very bad" could look like. 2. This is the first HIV treatment to undergo the NICE appraisal process and therefore, our first and only experience of engaging with NICE in this way and completing this submission.

PART 2 – Technical engagement questions for experts
Issues arising from technical engagement
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to the community has been missed in the ERG report, 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 appraisal committee meeting. For information: the organisation that nominated you has 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 ERG report, these will also be considered by the committee.

14a. Which antiretroviral treatments are used in the NHS for treating HIV-1? 14b. What are the most important factors when choosing a treatment for HIV-1? 14c. What are the most important aims of treatment for HIV-1?	• There are multiple treatments available to the population. At present these are largely all in pill-based form. An illustrated guide is available here: https://i-base.info/guides/starting/arvs - this was published in 2019 and does not necessarily reflect all the medications available. HIV medications are used in combination, some like the one undergoing the appraisal are dual-therapy, but some people can take up to four or five different drugs, and these may or may not be combined into one or more tablets. • The most important factors are that the treatment works, that side effects are few or easy to manage, and that the medication is as discreet as possible. Further factors include that there are no issues with interactions with other medication a person living with HIV is taking, and that the medication can be taken to fit in with their lifestyle/employment etc. i.e. consider whether medication can be taken with/without food; whether it might impact productivity or lethargy etc. Resistance to some medication is an issue to some people, especially those who have been living with HIV for a long time. • The most important aim of HIV treatment is to reduce the person's viral load (amount of virus) down to an undetectable level: 1) to provide the best opportunity for that person to have a healthy life by reducing the impact of the virus on the immune system; 2) to ensure that the health of their sexual partners, or unborn baby is protected. An undetectable viral load means someone can't pass it on through sexual contact or vertically during pregnancy and birth.
15a. Is lack of adherence to current oral antiretrovirals an issue in HIV-1?	• A not insignificant number of people can find it hard to adhere to treatment at vulnerable periods of their life. It would be difficult to comment further from a community perspective, but support services do focus on this issue to provide help and information to ensure people know how to take their medication and when. Many people living with HIV rely on alarms and apps to remind them. • This could be due to multiple factors: mental health and wellbeing issues, including wanting to avoid a daily reminder that they have HIV when it becomes too much to deal with; no place to adequately store or hide medication due to homelessness or not fixed accommodation; fear of the treatment itself, or a reluctance to take it due to misinformation – sometimes this stems from 'AIDS

15b. If any, what are the reasons for lack of adherence to oral treatment?	denialism' or conspiracy theories on the internet, people exploiting people with HIV when they are vulnerable in an effort to sell natural or herbal [false] 'cures', and can also come from those in power in their communities such as faith leaders. Some people also may find themselves in circumstances where they are afraid of their medication being found so they stop taking it.
16. Does changing from daily oral therapy to injections every two months have any advantages or disadvantages for people with HIV-1?	• No one would be forced to switch so there are no disadvantages, but the treatment would not suit everyone's routine or lifestyle, and some people may be afraid of needles for example. • To many people the simple freedom from daily pills is enough of a reason to want to start using injectable treatment. Those who would meaningfully benefit include people who are afraid people will find out their HIV status by finding medication because they live in stigmatised circumstances, or with people they do not know, those who struggle with the mental health impact from the daily reminder of pills, and people who struggle to take pill-based medicines.
17. Are there any important issues that have been missed in the ERG report?	• The COVID-19 pandemic has impacted the treatment and care of many people living with HIV. It has also brought forward many people who had been lost from care, who engaged their care again and started treatment once more because they were afraid of becoming sick. It was clear during the pandemic that many people found themselves in stressful situations, largely in trying to hide their treatment and virtual care from people who they were confined to living with who did not know they had HIV. Injectable treatment would bring a relief and ease to these people should these type of circumstances occur again in future.

PART 3 - Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- HIV is a long-term manageable condition but people with HIV still experience significant issues, especially regarding stigma.
- There are no alternatives to pill-based treatment or methods for people to take their treatment more privately or confidentially.

- This technology will benefit marginalised groups, especially those experiencing stigma, mental health or wellbeing issues.
- There are few disadvantages to the technology, and none are of severe concern.
- It is abundantly clear that the HIV population in England want to see the commissioning of the technology.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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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.

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NICE National Institute for Health and Care Excellence

Expert statement and technical engagement response form

Cabotegravir and rilpivirine for treating HIV-1 [ID3766]

Thank you for agreeing to give us your views on this treatment 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.

About this Form
In **part 1** we are asking you to complete questions about living with or caring for a person with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a lived experience 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.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

NICE National Institute for Health and Care Excellence

Please return this form by **5pm** on **Friday 18th June 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Please use this questionnaire with our hints and tips for patient 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. The text boxes will expand as you type.

Important information on completing this expert statement

- 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 want 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 15 pages.

PART 1 – Living with or caring for a person with HIV-1 and current treatment options	
About you	
1.Your name	**Cheryl Gowar**
2. Are you (please tick all that apply):	☐ a person living with HIV-related illness (or disease)? ☐ a person with experience of the treatment being evaluated? ☐ a carer of a person living with with HIV-related illness (or disease)? ☐ a community organisation employee or volunteer? ☒ other (please specify): a national HIV rights charity
3. Name of your nominating organisation.	National AIDS Trust
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete an 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/experience (e.g. I am drawing on others' experiences). Please specify what other experience: National AIDS Trust works closely with the HIV community to conduct research and provide robust, evidenced policy recommendations. ☐ 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
Living with HIV-1	
6. What is your experience of living with HIV-1? If you are a carer (for someone with HIV-1) please share your experience of caring for them.	I am not living with HIV, nor do I provide direct care for anyone living with HIV. However, at National AIDS Trust I work closely with people living with HIV and HIV support services in our research work. My own research responsibilities at NAT include healthcare. I am well versed in the experience of healthcare for people living with HIV, including both the medical and psychosocial aspects of treatment

Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for HIV-1 on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	7a: Over the last 30 years we have made huge advances in HIV treatment which mean that people living with HIV have the same life expectancy as those who are HIV negative. However, those treatments can be accompanied by significant side effects, as well as problems such as drug resistance. Because it is vital the people living with HIV maintain their medication regime to prevent viral rebound and drug resistance (with both personal and potential public health consequences), they must have a good relationship with their HIV clinician to ensure that they are able to take effective and tolerable antiretroviral therapy (ART). According to Public Health England (Positive Voices) data, a very high percentage of people living with HIV do report good relationships with their HIV specialists. However, this is unfortunately not the case across the healthcare system, including in primary care, where lack of knowledge about HIV and HIV-related stigma are commonly experienced. This has significant harms for people living with HIV, especially for those who are living with other long term health conditions (72%, according to PHE) and need regular interaction with other, non-HIV healthcare professionals. Moreover, especially given the psychosocial impact of HIV (as reported in our *Why we need HIV Support Services: A Review of the Evidence*, 2017) there is generally insufficient provision of mental health services, peer support, and HIV specialist support services, even though these have been proven to be effective in maintaining the mental and physical health, including adherence, of people living with HIV. 7b: As a cohort, people living with HIV follow a variety of ART regimes. This variation can be due to efficacy, contraindication with medication for other

	treatments, experience of side effects, ability to swallow medications, lifestyle and capacity to maintain drug regimes etc. People living with HIV generally tell us that these decisions are made collaboratively between themselves and their clinicians. NAT's view on long-acting injectables is that they represent a real, positive change for people living with HIV, both practically and psychologically. This perspective has been developed through engaging with people living with HIV during our research and generally in ad hoc interaction. I am confident that our perspective echoes that of the active HIV community.
8. If there are disadvantages of **current NHS treatments** for people living with HIV-1 (for example how the treatment is given or taken, side effects of treatment etc) please describe these	People living with HIV have to take their medications at the same time every day, and under specific conditions (e.g. some tablets must be taken with food). This is not always easy to comply with. This may be especially true for those with more chaotic lifestyles. For example, we are occasionally called on to intervene, or to provide evidence in legal cases against the Home Office, where people have been taken into immigration detention without medication, and can go many days without medication. Obviously this is an extreme example, but the consequences (as well as the psychological impact of understanding the consequences) of missing medication are also significant for those who don't have such complex lives. A factor that is perhaps unique to HIV is the attached stigma, and people living with HIV have reported that their HIV status has been disclosed because people have identified their medications. People living with HIV routinely have to negotiate keeping medication readily available to be taken at the appropriate time, while also hiding it from people in their surroundings who are unaware of their status. In terms of side effects, different treatments have different impacts, but side effects can include day to day issues requiring management, such as loss of appetite,

	fatigue and diarrhoea, as well as issues such as lipodystrophy or elevated cholesterol.
Advantages of this treatment	
9a. If there are advantages of cabotegravir and rilpivirine over current treatments on the NHS please describe these. For example, the impact on 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 and rilpivirine help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	Injectable treatment on a monthly or bimonthly schedule would remove many of the practical difficulties that can be attached to people having to take daily pills according to a strict regimen. This would be an advantage for those with more chaotic lives who find it difficult to adhere to treatment (e.g. those with insecure housing, those in prison). It could also provide some degree of psychological relief from the constant reminder of living with HIV, as well as decreasing the practical burdens. We know that, generally, people living with HIV do what they can to remain adherent because they understand the importance of their ART. Access to long-acting injectables would make that a lot easier for many. It is possible that routine treatment would also encourage regular engagement with healthcare services, among those who find that difficult. Further, side effects can be easier to manage when they can be planned for, rather than a daily occurrence that must be managed. While NAT understands that cabotegravir + rilpivirine have limited side effects, it is likely that people would be able to negotiate their impact much better than they are able to with a daily regimen. All of these advantages respond directly to disadvantages listed above (practical burdens, chaotic lifestyles, stigma and management of side effects). In practice, the relative importance of these advantages will depend on the individual taking the ART.

Disadvantages of this treatment	
10. If there are disadvantages of cabotegravir and rilpivirine over current treatments on the NHS please describe these? For example, are there any risks with cabotegravir and rilpivirine? If you are concerned about any potential side affects you have heard about, please describe them and explain why.	We do know that their may be injection site reactions, which is common among injectable treatment for many other health conditions. It may be that some people need to discontinue the treatment because of these but, from the trial data, we don't expect that to be a significant number of people. We do not expect everyone living with HIV to want to switch to injectable treatment.
Community population	
11. Are there any groups of people living with HIV-1 who might benefit more from cabotegravir and rilpivirine or any who may benefit less? If so, please describe them and explain why. Consider, for example, if people living with HIV-related illness (or disease) also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	I wouldn't expect any particular key population affected by HIV to benefit more than any other. Rather it would be specific to the individual. These individual characteristics would include those who experience practical or psychological difficulties with maintaining their current regime; those who are affected by stigma and wish to maintain their confidentiality; those who have difficulty swallowing pills; those who have multiple other long-term conditions and have an existing pill burden. Moreover, due to treatment advances, the cohort of people living with HIV is getting older. In research conducted by NAT, many people living with HIV have been concerned about their capacity to look after themselves as they age. Although we haven't tested the idea of long-acting injectables specifically with older people living with HIV, there is good reason to suspect that this would aid treatment and care management for those who are ageing.

Equality	
12. Are there any potential equality issues that should be taken into account when considering HIV-1 and cabotegravir and rilpivirine? 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 More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-	The majority of people living with HIV in the UK are either men who have sex with men (MSM) or people with Black African or Black Caribbean heritage. Improving access to medication reduces health inequality among these protected groups. Although fewer in number, trans people living with HIV exist at the intersection of multiple aspects of subjectivity that are subject to stigma. They are especially likely to benefit significantly from being able to limit one potential dimension of stigma from their lives. Research by NAT has shown that HIV-related stigma in care homes can be attached to staff who are not associated with healthcare finding out residents' HIV status. Long acting injectables may be one mechanism for reducing this likelihood. Further, we know that transition out of children's services into adult services can be a time when adherence is especially problematic. Long acting injectables may provide one way of reducing this difficulty. Therefore, this treatment may benefit both ends of the age spectrum.

read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	No

PART 2 – Technical engagement questions for experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to the community has been missed in the ERG report, 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 appraisal committee meeting. For information: the organisation that nominated you has 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 ERG report, these will also be considered by the committee.	
14a. Which antiretroviral treatments are used in the NHS for treating HIV-1?	

14b. What are the most important factors when choosing a treatment for HIV-1? 14c. What are the most important aims of treatment for HIV-1?	
15a. Is lack of adherence to current oral antiretrovirals an issue in HIV-1? 15b. If any, what are the reasons for lack of adherence to oral treatment?	
16. Does changing from daily oral therapy to injections every two months have any advantages or disadvantages for people with HIV-1?	

17. Are there any important issues that have been missed in the ERG report?	

PART 3 - Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

-
-
-
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Your privacy

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NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Cabotegravir and rilpivirine for treating HIV-1 [ID3766]

Thank you for agreeing to comment on the ERG report for this appraisal, 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 ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal 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 to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having 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 return this form by **5pm** on **Friday 18th June 2021**

NICE National Institute for Health and Care Excellence

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

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- 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.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with HIV-1 and current treatment options	
About you	
1. Your name	**Adele Torkington**
2. Name of organisation	**Manchester University Foundation Trust**
3. Job title or position	**Clinical Pharmacy Services Manager**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition 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 didn't submit one, I don't 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	☐ yes

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.	
The aim of treatment for HIV-1	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Simply for patients to be virally suppressed with no adverse effects from their therapy and prevent morbidity and mortality associated with HIV. This will reduce the risk of opportunistic infections in the individual and prevent complications of AIDS. By being virally suppressed the individual can prevent onward transmission of HIV.
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.)	Patients to remain virally suppressed on therapy, in most centres in the UK this is a viral load <50 copies/ml.
10. In your view, is there an unmet need for patients and healthcare professionals in HIV-1?	Yes, for individuals who cannot take oral therapy due to psychological reasons or physiological reasons or social reasons, we need other routes to be available for continuing therapy and ensure viral suppression.
What is the expected place of cabotegravir and rilpivirine in current practice?	

11. How is HIV-1 currently treated in the NHS?	HIV is treated predominantly with oral antiretrovirals. In some instances, patients may use liquid medication via other routes. There are many combinations of HIV therapy and the regimen a patient will receive will be dependent on national and local guidelines, lifestyle factors, resistance factors and drug-drug interactions.
• Are any clinical guidelines used in the treatment of HIV-1, and if so, which?	Yes there are national guidelines from BHIVA which are accredited by NICE. Each region also has specific regional guidelines based on availability of generic medicines and commercial in confidence prices to guide clinicians in a more structured way when there are options available to the patient.
• 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 is well defined and supported by the BHIVA standards of Care 2018. There are subtle differences in pathways for patients dependent on how they present for care, how they would prefer to access care in the future, however care is always individualised as is their treatment.
• What impact would cabotegravir and rilpivirine have on the current pathway of care?	This will give clinicians options for patients who require a non oral route for routine care for many different reasons. It will also provide extra confidentiality for patients where taking tablets daily could be an issue due to disclosure of their status to people they may live with, work with.
12. Will cabotegravir and rilpivirine be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes the product like all HIV treatments will be individualised to the patient. The only difference is they will access the healthcare setting to receive the injection regularly rather than access oral medication every 6-12 months.
• How does healthcare resource use differ between cabotegravir and rilpivirine and current care?	There will need to be provision for clinics to administer the injections. The options for where this is done are endless however this will be an associated cost to clinics and NHS providers and drug dispensing costs. There will also need to be provision for emergency appointments if patients are late for their injection and therefore need bridging therapy.
• In what clinical setting should cabotegravir and rilpivirine be used? (For example,	Specialist clinics in secondary care would be the preferred option to ensure continuing HIV therapy and sexual health screening as required in the first instances. There will need to be innovative

primary or secondary care, specialist clinics.)	solutions in the future to ensure access for everyone as secondary care may cause barriers to accessing treatment in the future.
• What investment is needed to introduce cabotegravir and rilpivirine? (For example, for facilities, equipment, or training.)	There will need to be investment in staffing to administer the medication and due to the risks of missing the appointment, there will need to be admin support to ensure patients are contacted prior to remind them injections are due and not to miss appointments. There will need to be investment in clinic capacity and estates for clinics.
13. Do you expect cabotegravir and rilpivirine to provide clinically meaningful benefits compared with current care?	Yes for individuals who require this therapy and cannot take oral therapy.
• Do you expect cabotegravir and rilpivirine to increase length of life more than current care?	In certain individuals where they do not take oral therapy, then yes this will increase length of life rather than current care as they may either refuse current care or not be able to be adherent with oral therapy.
• Do you expect cabotegravir and rilpivirine to increase health-related quality of life more than current care?	In certain individuals where they do not take oral therapy then yes.
14. Are there any groups of people for whom cabotegravir and rilpivirine would be more or less effective (or appropriate) than the general population?	This therapy will not be effective in individuals who do not engage with routine follow up and miss injections in comparison to the general populations. However this group of individuals are likely to not be adherent with oral therapy either. This population may benefit the most, but careful structuring of care for them will be essential.
The use of cabotegravir and rilpivirine	

15. Will cabotegravir and rilpivirine 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.)	This therapy will require additional appointments and trained staff to administer the injection, administrative staff to chase individuals who do not attend on time. There is likely to be increased blood monitoring for these patients. This has a resource implication to treatment and detailed above.
16. Will any rules (informal or formal) be used to start or stop treatment with cabotegravir and rilpivirine? Do these include any additional testing?	Patients will need to be assessed and supported to be adherent with this therapy. There will need to be rules about stopping therapy if patients do not routinely attend for their injection on time to prevent resistance.
17. Do you consider that the use of cabotegravir and rilpivirine will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	I believe it will improve mental health for these individuals who cannot currently take oral medication who want to be on effective therapy that will control their HIV, and the intense follow up of two months will support them further. For individuals who take antiretrovirals via NG/PEG route, who would prefer injections there could be reduced complications of not requiring these tubes.

18. Do you consider cabotegravir and rilpivirine 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?	I do believe this is an innovative therapy that will show benefits in many individuals and will provide therapy for specific individuals who currently do not access medication due to inability to take oral medication routinely.
• Is cabotegravir and rilpivirine a 'step-change' in the management of the condition?	Yes
• Does the use of cabotegravir and rilpivirine address any particular unmet need of the patient population?	Yes, for those individuals who do not currently access therapy due to inability to take oral therapy routinely. Also attending a healthcare setting for regular injections will also be positive for these individuals who require a more patient centred approach.
19. How do any side effects or adverse effects of cabotegravir and rilpivirine affect the management of the condition and the patient's quality of life?	The adverse effects will not affect the management of the condition. The injection site reactions appear not to prevent patients adhering. "Real – world" data will inform us of other adverse effects and this will be shared within the HIV professional arena and with communities.
Sources of evidence	
20. Do the clinical trials on cabotegravir and rilpivirine reflect current UK clinical practice?	Yes
• 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?	HIV viral load, emerging resistance and tolerability of the injection.
• 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?	Not that I am aware of
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?	Real world data I suspect will be reflective of experienced patients who struggle with oral therapy for many reasons. The emergence of resistance and viral suppression in these individuals will be imperative post marketing in the UK. Data from the compassionate use programme shows experience in these vulnerable patients who often do not volunteer for studies or who are excluded.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

23b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
24a. Do you consider that the following oral antiretroviral (ART) regimens are representative of those given at second-line (or beyond) to people who switched their first-line treatment due to non-virologic reasons in the UK NHS setting (i.e. people who would be eligible to have cabotegravir and rilpivirine long-acting injections if available)? • Emtricitabine/tenofovir alafenamide plus dolutegravir (Descovy® plus Tivicay®) • Emtricitabine/tenofovir alafenamide plus raltegravir (Descovy® plus Isentress®) • Abacavir/dolutegravir/lamivudine (Triumeq®) • Dolutegravir/lamivudine (Dovato®) • Dolutegravir/rilpivirine (Juluca®)	Yes

• Bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy®) • Doravirine/lamivudine/tenofovir disoproxil fumarate (Delstrigo®) • Darunavir/cobicistat/emtricitabine/tenofovir alafenamide (Symtuza®) • Emtricitabine/rilpivirine/tenofovir alafenamide (Odefsey®)	
24b. What is the estimated market share of each oral ART regimen mentioned in your answer to 24a (i.e. those taken by people with HIV-1 who switched their first-line treatment due to non-virologic reasons)?	I do not know
24c. Is the efficacy of these different oral ARTs similar?	Yes as long as accounting for resistance mutations and viral load, drug interactions and patient factors
24d. Are there any expected differences in efficacy between the treatments used in the NHS and the treatments used as comparators in the ATLAS/FLAIR trials? (N.B. in ATLAS the comparator was 2 Nucleotide reverse transcriptase inhibitors plus an integrase	No, not for a high number of patients on standard of care. There will always be individuals who require more complex therapies due to resistance mutations, tolerability concerns, comorbidities.

strand transfer inhibitor, non-nucleoside reverse transcriptase inhibitors, or a protease inhibitor, and in FLAIR the comparator was abacavir/dolutegravir/lamivudine single-tablet regimen)	
25a. Does changing from daily oral therapy to injections every two months represent a benefit in the clinical management of people with HIV-1? 25b. Are there any groups for whom there are advantages or disadvantages associated with having an injection every two months instead of daily oral therapy (for example, people with mental health problems or other comorbidities)?	Yes There are advantages for individuals who cannot take oral therapy daily due to psychological reasons of a daily reminder of HIV and how they may have contracted it. It will reduce stigma in individuals who do not wish to share their status with people they live with or work with. It will benefit individuals who travel a lot for work and time zones make it difficult to keep track of therapy and when to take. There will be benefits for individuals who need to travel to countries where laws discriminate on the basis of HIV status. There will be benefits for individuals who have poor gastrointestinal absorption due severe illness, however there will still be an oral lead in required, so this will need to be managed effectively. It is hoped there will be benefits in individuals who do not adhere at certain time eg those who take recreational drugs and/or alcohol at the weekend however it will be important that individuals attend for the injections and take the lead in oral therapy correctly. There will potentially be a benefit in adolescents who are transitioning from paediatric care to adult care.

	There could be disadvantages to two monthly injections, if people notice that they require time away from work or home to receive their injection. Individuals they live with may notice injection site reactions if they have not disclosed their status.
26a. Is lack of adherence to oral ART an issue in HIV-1?	Yes
26b. If any, what are the reasons for lack of adherence to treatment?	There can be many, psychological issues with taking tablets due to reminders about their diagnosis, opportunistic infections that affect memory and cognitive function, social stigma to taking therapy, inability to have privacy to take medication. Some therapy is required to be taken with food, this can be a problem for individuals on a poor income, or who eat meals with others. Homelessness can be multifaceted, inability to attend clinics, inability to have food to take with therapy, drugs are lost or stolen, use of other street drugs or alcohol can affect memory to take on time. People's lifestyle can affect adherence, working long hours, and needing to take drugs to work, taking recreational drugs or alcohol which lead to forgetting to take. Some recreational drugs interact with some HIV therapies, so individuals may choose the recreational drugs over HIV drugs.
26c. Does lack of adherence affect the efficacy of oral treatment?	Yes in most cases. Some therapies require better adherence than others. This is usually taken into consideration when choosing therapy for an individual.

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, 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 appraisal committee meeting. For information: the professional organisation that nominated you has 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 ERG report, these will also be considered by the committee.	
Key issue 1: Concerns regarding English language and date limits used in the literature searches, the sensitivity of the search strategies, and the currency of the literature searches	No, most peer reviewed research papers and conference abstracts will be in English and therefore I do not believe there is any relevant data missing.
Key issue 2: Lack of head-to-head evidence between cabotegravir with rilpivirine and antiretrovirals (ART) therapy	No, as the ERG identifies there was comparators with monthly injections not two monthly. Given the high efficacy of the regimen I do not believe there is a benefit in having this extra information, however “real world” data will be collected post marketing to inform issues such as virological failures.
Key issue 3: Unclear generalisability of the results to patients in the UK NHS setting	No, there was representations from some UK study sites. First line therapies in the UK maybe different due to regional variations however I do not believe this is significant to this review, the majority of individuals will be taking an NRTI backbone with a third agent as shown in ATLAS.

Key issue 4: Exclusion of case-control studies	No, the evidence is from randomised controlled trials.
Key issue 5: Pooling of ATLAS and FLAIR	No, I do not believe this has any significant impact of how we will use this therapy and how it will benefit patients.
Key issue 6: Assumption that all oral ARTs have similar efficacy	No, the first line therapies across the UK all have high efficacy. What is important for individuals is adherence to these therapies.
Key issue 7: Non-significance interpreted as non-inferiority	No
Key issue 8: Cost of basket of comparators	No, It is however very difficult to compare therapies in the UK due to variations across regions with commercially sensitive prices and BNF/list prices rarely used in specialised commissioning in hospital settings. It is also important to consider that over time, individuals with tolerability concerns, side effects, drug-drug interactions and drug resistance, may take more expensive regimens than considered. It is also very important to consider the cost of therapy if individuals having the injection have virological failure, the resulting therapy will be more expensive than standard of care. I would also suggest that costs for the dispensing of the drug, the administration of the injection, the estates availability especially in centres where extended hours are provided for such clinics, the clinic administrative costs to ensure patients come to clinic and are contacted if they do not attend. It is important to note, most centres dispense oral HIV medication via a third party provider and therefore VAT is not paid. If this is to be dispensed by a hospital pharmacy, VAT will need to be paid.

	Currently most patients, and certainly during covid only attend clinic every 6 or 12 months and have bloods taken at the same time. It is likely blood monitoring costs will increase in these individuals until they are stable and clinicians feel more confident.
Key issue 9: Adherence assumptions	No, however it is worth noting that when this therapy becomes more widely available individuals with poor adherence to oral therapy may benefit but it will be essential to ensure good adherence for the oral lead in stage first.
Key issue 10: Utility advantage for patients taking cabotegravir with rilpivirine	No, however the quality of life for individuals who may receive this treatment in "real-life" could be further increased due to reduction in social stigma and confidentiality issues that would not have been assessed in study participants as these individuals rarely take part in research. It is important to note that the acceptability of this treatment will greatly depend on the efficiency and availability of the clinic settings to administer this drug. The clinic administrative support will be essential to ensure no patients miss their dose as this could lead to virological failure.

PART 3 - Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- This is an innovative HIV therapy that will greatly benefit individuals living with HIV
- There will need to be investment in infrastructure costs to deliver this therapy effectively to patients
- Real- world data of use in vulnerable populations will be closely monitored and will need to inform future practice
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

NHS commissioning expert statement

Cabotegravir and rilpivirine for treating HIV-1 [ID3766]

Thank you for agreeing to give us 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.

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. Your response should not be longer than 10 pages.

Information on completing this expert statement

- 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	Anna Kafkalias
2. Name of organisation	NHS England and NHS Improvement – Specialised Commissioning

3. Job title or position	National Programme of Care manager for Blood and Infection
4. Are you (please tick all that apply):	☐ commissioning services for a CCG or NHS England in general? ☒ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☐ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the 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 didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick	☐ yes

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
Current treatment of the condition in the NHS	
8. Are any clinical guidelines used in the treatment of the condition, and if so, which?	British HIV Association (BHIVA) Clinical guidelines Related policies: • Dolutegravir-rilpivirine for treating HIV-1 in adults • Elvitegravir/cobicistat/emtricitabine/tenofovir for treatment of HIV in adults • Dolutegravir / lamivudine for the treatment of Human Immunodeficiency Virus (HIV-1) infected adults and adolescents over 12 years of age • Immediate antiretroviral therapy for treatment of HIV-1 in adults and adolescents • Use of cobicistat as a booster in treatment of HIV infection (all ages) • Dolutegravir for treatment of HIV-1 infection (all ages) • Doravirine for the treatment of HIV-1 in adults • Tenofovir Alafenamide for treatment of HIV 1 in adults and adolescents • Bictegravir-emtricitabine-tenofovir alafenamide for the treatment of HIV-1 in adults

9. 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.)	On the whole the pathway of care is well defined. Patients attend a hospital which is commissioned to provide HIV care and are seen regularly - initially fortnightly, monthly until patient becomes stable on the drug and viral load drops. Patient is then seen every 4-6 months for routine testing of bloods, checking of side effects and adherence and ensuring that the virus is suppressed. The patient would come in for bloods first and then a week later would have their appointments with the doctor, nurse, pharmacist and/or health advisor. In terms of drug treatments, although the treatment approach is standard with the use of triple/dual therapy regimens, the choice of the drug will vary due to individual clinical and non-clinical factors. Overall the consensus between clinicians is the same. However, there is a need to bring many patients to MDT for discussion especially in complex cases where choice of drug therapy is not straightforward.
10. What impact would the technology have on the current pathway of care?	Minimal impact at present due to the limited capacity to set up clinics and resource to administer the injection within the HIV clinic setting. Feasibility of setting up new clinics to administer will be dependent on uptake. Integrated sexual health and HIV services may have more capacity to administer this within their clinics but this would need to be scoped. Criteria for use is patients who are stable and virologically suppressed; however, patients likely to benefit may also include those patients that are not able to comply with oral tablets, those who have hectic lifestyles and as a result who may struggle with taking tablets daily. This cohort of patients is unlikely to be stable and virologically suppressed and thus potentially ineligible for this new technology. The technology may be suitable for those patients who prefer an injectable because they struggle to swallow tablets and it removes the need to take a tablet every day. Many patients on the trial have expressed they prefer the injectable because it takes away the reminder that they are HIV positive by not having to then worry about taking tablets the rest of the month. Increased attendance to administer the drug may be too burdensome for the patient, therefore this may limit the uptake. If patients have compliance issues, they would also potentially have attendance issues –

	there will be questions around whether they will attend at least 6 times a year rather than the standard twice a year. This treatment may be suitable for those patients that are due to have planned surgery.
The use of the technology	
11. To what extent and in which population(s) is the technology being used in your local health economy?	Limited use at present and is within the trial setting or where it may have been offered it on a compassionate use basis by the manufacturer.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Whilst many patients currently attend hospital for injectable medicines, there are currently no other injectable HIV medicines available
• How does healthcare resource use differ between the technology and current care?	Resource and expertise needed for administration of injection every 1-2 months – no other injectables at present so this will be additional resource. Different skill mix of staff needed for the administration function rather than just a supply function.

• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Expected to be administered in secondary care specialist HIV clinics, although would be good to explore other models of drug administration. Other options may include off-site community centres with specialist HIV nurses/pharmacists administering the drug. Homecare delivery and nursing use may be an option however the patients' social circumstances would need to be considered. May be useful for rural areas.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Clinics may require additional staff and physical clinic space Clinic appointments (time) for administration of injection Training of staff who may not be accustomed to administering IM injections Other models of drug delivery may require additional resource and cost and a cost v. benefit analysis would be required.
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	Pregnancy test will be required in addition to tests routinely carried out for patients on antiretroviral therapy
13. What is the outcome of any evaluations or audits of the use of the technology?	n/a

Equality	
14a. Are there any potential equality issues that should be taken into account when considering this treatment?	This treatment may not suit certain individuals who cannot easily access their specialist HIV clinic and attend an appointment – due to geographical location, work / personal commitments etc.
14b. Consider whether these issues are different from issues with current care and why.	Currently patients, especially those who are stable and virologically suppressed, may only need to attend their specialist HIV clinic 2-3 times per year and possibly maintain virtual/online consultations- monthly or 2-monthly attendance is significantly different.
Topic-specific questions	
15 Is the treatment pathway described by the company in their submission an accurate representation of how people with HIV-1 are treated in the NHS?	Yes fairly accurate

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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The information that you provide on this form will be used to contact you about the topic above.

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NICE National Institute for Health and Care Excellence

Technical engagement response form

Cabotegravir and rilpivirine for treating HIV-1 [ID3766]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments **18 June 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report 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 appraisal, 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.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. 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.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- 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 under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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)	**UK Community Advisory Board (UK-CAB)**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

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Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Concerns regarding English language and date limits used in the literature searches, the sensitivity of the search strategies, and the currency of the literature searches	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 2: Lack of head-to-head evidence between Cabotegravir and rilpivirine (CAB LA + RPV LA) and antiretroviral therapy (ART) therapy	**NO**	From a community perspective we have outlined the need for the new technology undergoing the appraisal in our 'patient/carer' organisation submission earlier this year, and in the expert submission this week. We do not have concerns about the types of pill-based cART compared to the LA cART via injection. From our position the benefits are connected to quality of life, addressing stigmatising situations people can be vulnerable to, and improving mental wellbeing.
Key issue 3: Unclear generalisability of the results to patients in the UK NHS setting	**NO**	From a community perspective we have outlined the need for the new technology undergoing the appraisal in our 'patient/carer' organisation submission earlier this year, and in the expert submission this week. We do not have concerns about the types of pill-based cART compared to the LA cART via injection. From our position the benefits are connected to quality of life, addressing stigmatising situations people can be vulnerable to, and improving mental wellbeing.

Key issue 4: Exclusion of case-control studies	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 5: Pooling of ATLAS and FLAIR	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 6: All oral ARTs are assumed to have a similar efficacy	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 7: Non-significance interpreted as non-inferiority	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 8: Cost of basket of comparators	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 9: Adherence assumptions	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 10: Utility advantage for patients taking CAB LA + RVP LA	**YES/NO**	Please provide your response to this key issue, including any new evidence, data or analyses

Additional issues

Please use the table below to respond to additional issues in the ERG report 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 appraisal (e.g. at the clarification stage).

Issue from the ERG report	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 ERG report 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 ERG report 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]

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Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report 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 ICER**
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER
..	..	..	[INSERT / DELETE ROWS AS REQUIRED]
Company's preferred base case following technical engagement	**Incremental QALYs: [QQQ]**	**Incremental costs: [£££]**	**Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER**

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Technical engagement response form

Cabotegravir and rilpivirine for treating HIV-1 [ID3766]

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We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments **18 June 2021**

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- If you are the company involved in this appraisal, 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.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. 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.
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- 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 under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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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)	**British HIV Association**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Concerns regarding English language and date limits used in the literature searches, the sensitivity of the search strategies, and the currency of the literature searches	**No**	It is doubtful that broadening the search e.g. in terms of other languages would produce additional relevant studies. A repeated literature search to identify more recent information would likely yield the longer-term follow-up reports of the main studies, but these would probably not result in any major change to conclusions around safety and efficacy. As real-world evidence is lacking it will be important to ensure any experiences from countries where CAB LA + RPV LA is already in routine use (e.g. Canada) are captured.
Key issue 2: Lack of head-to-head evidence between Cabotegravir and rilpivirine (CAB LA + RPV LA) and antiretroviral therapy (ART) therapy	**N**o	The ERG report correctly identifies the issue that CAB LA + RPV LA given every 2 months has only been compared with the same regimen being given every month. The comparison was statistically non-inferior for viral load outcomes although there was a numerical difference in virological failure rates favouring the 1 monthly dosing. However, only CAB LA + RPV LA given monthly has been compared with oral treatment – either against dolutegravir/lamivudine/abacavir in the FLAIR study, or other standard oral therapies in the ATLAS study. It is true then, that the comparison of 2 monthly dosing with oral therapies is indirect. While a direct comparison might reduce uncertainty, given the very high efficacy of these treatment regimens, it is also uncertain whether this would generate helpful information for patients who might benefit from the treatment. What is more important is to understand why there are more virological failures in

		the 2 monthly arm and whether there are any predictive factors that will assist decision making. This will require careful monitoring of implementation trial, and real world, outcomes.
Key issue 3: Unclear generalisability of the results to patients in the UK NHS setting	**N**o	In ATLAS, those recruited at baseline were taking an NRTI backbone with: an NNRTI in 50% of cases, an INSTI in 33% and a PI in 17%. This mixture of different treatment regimens is broadly representative of treatment taken by people living with HIV in the UK. However, the exact agents used would have relevance to estimates of cost-effectiveness, given the widespread use of generic HIV drugs in the UK, as these are substantially cheaper than proprietary formulations. In addition, the discounted prices NHS England negotiates can be substantially lower than list prices.
Key issue 4: Exclusion of case-control studies	No	The available evidence comes from randomised controlled trials, performed to obtain a marketing license. Given that fact, it is hard to imagine how case-control studies could exist.
Key issue 5: Pooling of ATLAS and FLAIR	*No*	The ERG report suggests that a random effects meta-analysis is a more appropriate analysis method, while commenting that any change in effect sizes would likely be small, but the standard error might increase. It is uncertain whether this would be helpful in understanding clinical utility and the benefits for patients.
Key issue 6: All oral ARTs are assumed to have a similar efficacy	**N**o	All standard first line ART regimens used in the UK have high efficacy in clinical trials and the viral load results obtained in the ATLAS and FLAIR studies are in line with what would be expected in routine clinical practice in the UK. The chief determinant of treatment success with current oral regimens is adherence, which is partly driven by side effects, but with a substantial contribution of psychosocial issues. It is important to note that people experienced virological failure in ATLAS and FLAIR despite 100% adherence (something impossible to assess in trials of

		oral medication but straightforward when drug administration is by a health care professional) and that this was numerically greater in the 2-monthly arm after 48 weeks.
Key issue 7: Non-significance interpreted as non-inferiority	**N**o	The change in terminology suggested is noted as not affecting cost-effectiveness. It is unlikely to change the clinical view of the utility of these medicines.
Key issue 8: Cost of basket of comparators	No	It is an important point that the cost-effectiveness of this treatment is very sensitive to the cost of medication taken by people who might be suitable for long acting injectables. This raises a key issue about how the medication should be used in clinical practice and there are some areas of uncertainty which are not fully addressed by the available evidence. It is likely that the costlier ART regimens are used in people with HIV who have experienced more difficulty with ART, for example: side effects and tolerability; tablet number or swallowing of oral formulations, or difficulty managing oral daily dosing regimens. However, if the aim were to offer treatment choice to people living with HIV according to preference, then those who are highly adherent to standard, fully generic oral regimens could be regarded as ideal candidates for injectables. Clearly, the cost-effectiveness comparisons will likely be starkly different. Additionally, the costs of treatment amongst the small number of virological failures should be considered – since most people experiencing failure will develop resistance to two medication classes, subsequent lines of treatment are likely to be cost more. Importantly, injectables will differ markedly from current oral options in term of: 1) Drug dispensing costs 2) Drug administration costs (staff, estates) 3) Clinic admin costs (appointment booking, intensive recall if appointments missed) It also likely, until we have more data available, viral load monitoring will be more frequent (currently it's typically 6-monthly and lessons learned during COVID-19 will likely make this less frequent for at least some individuals). These must be considered when reviewing the financial impact of LA CAB + LA RPV.

Key issue 9: Adherence assumptions	**Y**es	Clinical trials tend to recruit very motivated participants and in the case of ATLAS and FLAIR, trial participants had to have demonstrated good adherence to treatment with maintenance of an undetectable viral load in order to receive the long-acting product. Moreover, individuals with a prior history of virological failure were excluded. These two factors will affect the generalisability to the broader clinic population. As noted in the ERG report, there is some literature demonstrating that more modern oral ART regimens do not require very high levels of adherence (>95%) to maintain effectiveness. The level of adherence needed likely varies according to pharmacokinetic and pharmacodynamic factors of specific drugs and the individuals taking them. The tolerability of drugs and the rate of side effects is an important determinant of adherence and likely plays an important role in driving adherence. It is important to note that when studies of modern oral ART assess adherence by pill count, an effect on virological response is demonstrated. In study GS-1489, a viral load <50 copies/ml was seen in 81% vs 97% in those taking bictegravir/emtricitabine/tenofovir alafenamide, with <95% vs >95% adherence (although this did not reach statistical significance) (Gallant et al 2017). The VL<50 outcomes for those taking dolutegravir/lamivudine/abacavir in this study were 86% vs 96% (again not statistically significant). In the GEMINI study of dolutegravir/lamivudine vs dolutegravir/emtricitabine/tenofovir-DF, virological response was 69% vs 91% and 65% vs 85%, respectively, with pill count adherence stratified by <90% vs >90% (Ait-Khaled M, 2020). Self-reported adherence is recognised to over-estimate adherence as measured by e.g., pill count, prescription refills or drug levels in blood or urine, so a <95% self-reported adherence figure may represent a lower “true” value (Spinelli et al, Curr HIV/AIDS Rep 17, 301-314, 2020). However, self-reported adherence will be the chief, if not only factor that can be assessed by clinicians in routine practice.

		O'Connor et al (Lancet HIV 2017; 4: e295–302) conducted an observational study of a large UK cohort which concluded that rates of viral rebound were low overall, and declined over time, reaching a plateau of 1.0% per year for men who have sex with men living with HIV. Of note 29% of observed viral rebounds above 200 copies/ml, re-suppressed to <50 at the next measurement with no change in treatment regimen. Treatment interruption was documented in 31% of viral rebounds. However, adherence principles for oral medication cannot be extrapolated to injectable and in the absence of real-world data it is impossible to predict what the real-life impact of delayed or missed LA CAB + LA RPV doses will be. ATLAS and FLAIR, where all people who developed virological failure were 100% adherent, cannot provide any information about what adherence thresholds would be associated with higher rates of virological failure. Adherence counselling is central to HIV care, and it will be important to counsel people switching to injectable treatment that even with 100% adherence to the injection schedule and avoidance of efficacy-limiting drug-drug interactions, there is still a small risk of treatment failure that will necessitate switch to oral medication that may be more complex than their previous regimen. It can be concluded that the majority of people living with HIV will achieve and sustain an undetectable viral load and that where single viral rebound occurs, it may not require regimen change. However, hidden within these figures are individuals, e.g., those who require treatment change or who interrupt treatment, who need high levels of support in order to maintain adequate adherence to oral treatment. These persons might gain particular adherence benefit and utility from long acting injectables though will also require appropriate counselling and support to ensure they adhere to the injection schedule.
Key issue 10: Utility advantage for patients taking CAB LA + RVP LA	**No**	Further information on quality of life would undoubtedly improve understanding of the utility of CAB LA + RPV LA. The clinical trials of these medications have likely recruited people motivated to take injectable therapy, in addition to the more

		general motivation to take part in research. The studies reported improved treatment satisfaction and acceptance of treatment in those on injectable therapy. While decreasing utility estimates will affect QALYs, it is also possible that the trial data under-estimates the quality of life improvement that might be seen in "real-life" clinical use. People more affected by HIV-related stigma and less motivated to engage in treatment might be under-represented in the population recruited to clinical trials. However, these people might benefit most from an innovative treatment that removes the need for home storage of medications as well as daily treatment that acts as a reminder of their health condition. It is likely that how and where injectables are delivered will impact patient satisfaction. Clinical trials tend to offer a staff:patient ratio far beyond that which is feasible of affordable in the NHS and the motivation for people living with HIV to attend busy NHS clinics may be less. It is also important to consider that the COVID accelerated move to more virtual care is not necessarily compatible with a treatment that needs to be administered by a health care professional and this may impact patients' willingness to attend 2-monthly. Support to deliver treatment outside traditional NHS settings will be essential. Any consideration of the cost and practicalities of injectable treatment must consider the resource burdens of administering treatment and the crucial element of ensuring patients attend for injections. It is likely that late or missed doses will result higher rates of virological failure, and consequently drug resistance, than those observed in clinical trials so enhanced adherence support will be central to the success of this novel and exciting treatment strategy.

Additional issues

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Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report 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 ERG report 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]

NICE National Institute for Health and Care Excellence

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Company's preferred base case following technical engagement	**Incremental QALYs: [QQQ]**	**Incremental costs: [£££]**	**Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER**

NICE National Institute for Health and Care Excellence

Technical engagement response form

Cabotegravir and rilpivirine for treating HIV-1 [ID3766]

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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)	**HIV Clinical Reference Group, NHSE**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**NIL**

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Key issues for engagement

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Key issue	**Does this response contain new evidence, data or analyses?**	Response
Key issue 1: Concerns regarding English language and date limits used in the literature searches, the sensitivity of the search strategies, and the currency of the literature searches	**no**	Nil additional comments
Key issue 2: Lack of head-to-head evidence between Cabotegravir and rilpivirine (CAB LA + RPV LA) and antiretroviral therapy (ART) therapy	**No**	Nil additional comments
Key issue 3: Unclear generalisability of the results to patients in the UK NHS setting	**No**	Profile of ART switch regimens used in NHS in settings comparable to Atlas and Flair could be extracted from HIV/AIDS Reporting System (HARS) data.
Key issue 4: Exclusion of case-control studies	No	Nil additional comments

Key issue 5: Pooling of ATLAS and FLAIR	**No**	Nil additional comments
Key issue 6: All oral ARTs are assumed to have a similar efficacy	No	While this is an unsafe assumption for initial regimens in individuals with higher viral loads, this is not unreasonable for suppressed switch scenarios.
Key issue 7: Non-significance interpreted as non-inferiority	**No**	
Key issue 8: Cost of basket of comparators	**No**	We agree that the basket of comparators used is critical. Several suitable regimens for example TDF/FTC/RAL, TDF/FTC/DTG have not been included. A clearer rationale for their exclusion should be sought. If reliable NHS data can be provided it would be reasonable to use a weighted basket in sensitivity analyses. In view of the proposed advantage of CBT/RPV in individuals seeking to reduce the impact of taking oral daily therapy it would be helpful to also compare against a basket of single tablet regimens.
Key issue 9: Adherence assumptions	**No**	This is a critical issue and the two treatment strategies (injectable vs daily oral) have not been treated equally in the analysis. Adherence to daily oral therapy is anticipated in the model to decline significantly leading to poorer health outcomes and onward transmissions while adherence to injectables is predicted to stay high. The literature supporting the first assumption is very limited and does not adequately take into account the resilience of newer ART regimens to maintain viral suppression with lower adherence. In defence of the assumptions related to injectables the longer term follow-up in Latte is cited. However what we don't have is real world data on individuals switched outside clinical trials. Longer term results in these cohorts may be significantly different.
Key issue 10: Utility advantage for patients taking CAB LA + RVP LA	**No**	No additional comments

Additional issues

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Additional issue 1: **Additional costs**	4.2.9.2	No	The additional costs of administering one dose of CBT/RPV extend significantly beyond 15 minutes of a band 5 nurse and include admin costs, additional dispensing costs, overheads utilities etc
Additional issue 2: Treatment emergent Drug resistance	2.4	No	Long-acting agents present very specific risks in individuals who are not compliant with follow-up due to the long half-life of drugs. There is the potential for the development of resistance due to differences in the pharmacokinetic "tail" of the two agents and hence functional monotherapy. This has not been included in the model.
Additional issue N: ***Population***	Table 2	No	It's stated that CBT/RPV is indicated in individuals "….and no prior virological failure with, agents of the NNRTI and INI class. Shouldn't this read agents of the NNRTI or INI class?

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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)	**HIV Pharmacy Association**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**nil**

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Key issues for engagement

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Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Concerns regarding English language and date limits used in the literature searches, the sensitivity of the search strategies, and the currency of the literature searches	**NO**	**The majority of peer reviewed research papers of impact English and it is therefore unlikely that any articles of relevance have been missed. The search terms are relevant and adequate.**
Key issue 2: Lack of head-to-head evidence between Cabotegravir and rilpivirine (CAB LA + RPV LA) and antiretroviral therapy (ART) therapy	**NO**	No comments on this issue
Key issue 3: Unclear generalisability of the results to patients in the UK NHS setting	**NO**	**UK centres participated in the studies and included appropriate controls. The marketing authorisation in the USA and Europe have different wording regarding resistance (cabotegravir and rilpivirine) or INSTI or NNRTI. The ERG have raised this as some studies have included patients with a K103N mutation. Generalisibility will be difficult in the UK as large variations in prescribing due to regional cost differences/guidelines**

Key issue 4: Exclusion of case-control studies	**NO**	No comments on this issue
Key issue 5: Pooling of ATLAS and FLAIR	**NO**	**There are sufficient data already to demonstrate non inferiority to the gold standard of care.**
Key issue 6: All oral ARTs are assumed to have a similar efficacy	**NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 7: Non-significance interpreted as non-inferiority	**NO**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 8: Cost of basket of comparators	**NO**	We agree with the ERG's concerns about basket of comparators as the financial advantage/ disadvantage will be dependent on this . This is often a problem when considering cost impact of new drugs which may sometimes be cost saving. This could be managed with a standard average cost per patient comparison, though this information would need to be sought from NHS England due to its commercially sensitive nature. Re. page 89 post FAC report we truvada dolutegravir was excluded but could be second line due to a switch from certain regmiments eg. Abacavir/lamivudine + efavirenz, raltegravir containing regimens, Of note Triumeq is included as a switch option, truvada/dolutegravir is equally likely to be used here. Prices in cost comparison are BNF/list price not contracted prices, as these are commercially sensitive. The contracted prices are substantially lower which will affect financial advantage, so we suggest using regional/national average drug cost per patient.

Key issue 9: Adherence assumptions	**NO**	In practice, full suppression is observed with less than 95% adherence although there is no peer reviewed literature we are aware of to support this.
Key issue 10: Utility advantage for patients taking CAB LA + RVP LA	**NO**	Please provide your response to this key issue, including any new evidence, data or analyses

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Additional issue 1: Cost of drug administration	Not applicable	**NO**	In addition to the drug acquisition cost there is the cost of administration which needs to be considered. Without a clear policy on how this will be administered, this is difficult to estimate as the cost of administering in a clinic will vary greatly depending on setting, market forces factor, however alternative models exist such as community based delivery at home by NHS and non-NHS providers, community based clinics, rather than those in secondary/tertiary care, and economies of scale could be achieved by concentrating numbers of those receiving injections to regional/local hubs, however ability to do this will be directly influenced on the commissioning policy and breadth of access.
Additional issue 2: Use of the drugs in special populations	B1.3.5.2	**YESCOMPASSIONATE USE OF LONG-ACTING (LA)** **Reference:** **CABOTEGRAVIR (CAB) AND RILPIVIRINE (RPV) FOR PATIENTS IN NEED OF PARENTERAL ANTIRETROVIRAL THERAPY.** 23rd International AIDS Conference; July 6-10, 2020; Virtual. D'Amico et al. AIDS 2020:	Although there are no randomised controlled trials in very specific populations that this regimen would be useful for, this life saving intervention in these groups must not be overlooked. This included those who are unable to take/absorb oral medicines. Although there is mention of switching for non virological reasons, further consideration is needed. Clinical trials exclude vulnerable populations including those whose adherence is seriously compromised by confidentiality and diagnosis disclosure issues, extremely vulnerable individuals with complex social and safeguarding concerns, limiting ability to store and take oral medication, those with compromised absorption, which in some cases if lifelong, those who cannot for

		Virtual. Poster PEB0263	medial or psychological reasons tolerate oral medication, particularly adolescents living with HIV with tablet phobia. No alternatives exist for these populations, and this intervention, as it the only parenteral complete regmimen available, should be considered life saving and access granted in these situations, as demonstrated by data form the compassionate use scheme.
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

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Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**National HIV Nurses Association**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**none**

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Key issue 2: Lack of head-to-head evidence between Cabotegravir and rilpivirine (CAB LA + RPV LA) and antiretroviral therapy (ART) therapy	**No**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 3: Unclear generalisability of the results to patients in the UK NHS setting	**No**	Although the evidence from ATLAS and FLAIR are promising it is currently unclear how injectable ART might be introduced in to current services given the need for extra resources (time, people, space)
Key issue 4: Exclusion of case-control studies	No	Please provide your response to this key issue, including any new evidence, data or analyses

Key issue 5: Pooling of ATLAS and FLAIR	**No**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 6: All oral ARTs are assumed to have a similar efficacy	**No**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 7: Non-significance interpreted as non-inferiority	**No**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 8: Cost of basket of comparators	**No**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 9: Adherence assumptions	**No**	The trials assume that people will 'adhere' to the treatment insomuch as they will attend, on time, for injections. Real world practice will likely differ from this as people may either forget to or are unable to book an appointment to continue their treatment. This may result in the patient having sub-optimal adherence to their ART regimen.
Key issue 10: Utility advantage for patients taking CAB LA + RVP LA	**No**	Please provide your response to this key issue, including any new evidence, data or analyses

Additional issues

Please use the table below to respond to additional issues in the ERG report 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 appraisal (e.g. at the clarification stage).

Issue from the ERG report	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 ERG report 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 ERG report 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]

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Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

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Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER
..	..	..	[INSERT / DELETE ROWS AS REQUIRED]
Company's preferred base case following technical engagement	**Incremental QALYs: [QQQ]**	**Incremental costs: [£££]**	**Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER**

NICE National Institute for Health and Care Excellence

Technical engagement response form

Cabotegravir and rilpivirine for treating HIV-1 [ID3766]

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Deadline for comments **18 June 2021**

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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)	• Gilead Sciences Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	• None

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Concerns regarding English language and date limits used in the literature searches, the sensitivity of the search strategies, and the currency of the literature searches	**N/A**	• No response
Key issue 2: Lack of head-to-head evidence between Cabotegravir and rilpivirine (CAB LA + RPV LA) and antiretroviral therapy (ART) therapy	**N/A**	• No response
Key issue 3: Unclear generalisability of the results to patients in the UK NHS setting	**N/A**	• The assumption that the comparators used in ATLAS and FLAIR are comparable to the current UK standard of care is an over-simplification and raises concerns over the applicability of results. • Gilead agree that the generalisability of the ATLAS and FLAIR trials to UK clinical practice with respect to the antiretroviral therapy (ART) comparators is therefore uncertain, and may influence the conclusions that can be made regarding the efficacy-safety profile of cabotegravir + rilpivirine (CAB+RPV)

		in the UK setting, relative to current standard of care.
Key issue 4: Exclusion of case-control studies	**N/A**	• No response
Key issue 5: Pooling of ATLAS and FLAIR	**N/A**	• No response
Key issue 6: All oral ARTs are assumed to have a similar efficacy	**N/A**	• As per the response to Key Issue 3, the assumption that all oral ARTs have a similar efficacy is an over-simplification. The different ARTs have different levels of effectiveness and safety profiles, and are available in different forms (for example as separate tablets, fixed dose combinations [FDCs] and single tablet regimens [STRs]) which affects adherence and therefore effectiveness. • Sensitivity analyses to explore the impact of this assumption of equal efficacy between all ARTs are warranted.
Key issue 7: Non-significance interpreted as non-inferiority	**N/A**	• Gilead agree with the conclusions from the Evidence Review Group (ERG) that, based on the evidence available, and particularly in light of the wide confidence intervals from the indirect treatment comparison (ITC), there are no data to conclude that CAB+RPV long-acting (LA) injectable given every 2 months (Q2M) is non-inferior to “current ART”.
Key issue 8: Cost of basket of comparators	**N/A**	• The base case cost-effectiveness analysis assumes a basket comparator of nine ARTs – the cost of these is calculated as a simple non-weighted average (based on list prices), resulting in an average cost per 30 days of £721.34. • Gilead consider this approach to be an over-simplification, given the differences in market shares of these therapies in

		current clinical practice. As a result, the comparator cost approach appears selective to branded and higher-cost regimens. • It is not clear why market share data have not been used to conduct a weighted average for the cost of the comparator, particularly given market share data were used to estimate which treatments should be included in the basket based on the proportion of patients switching therapies. Consideration of the full market would be more appropriate and consistent with previous NHS England (NHSE) decision-making regarding ARTs. • Further sensitivity analyses on the cost of the basket comparator are necessary to adequately explore the uncertainty introduced by the over-simplification of the approach taken in the base case.
Key issue 9: Adherence assumptions	**N/A**	• Adherence is an important determinant of ART efficacy, and as such should be appropriately considered in health economic modelling of therapies for HIV. • The company submission assumes optimal adherence to CAB+RPV, which Gilead believes to be unrealistic for a real-world setting where patients may skip appointments. • Furthermore, the company submission does not account for differences in adherence between multi-tablet regimens (MTRs) and STRs, which is an over-simplification of adherence in the comparator arm. For example, one 2019 systematic literature review (SLR) conducted by Altice, F. *et al.*[1] found that individuals treated with STRs had higher treatment adherence than those treated with than MTRs in 10/11 relevant studies included. Specifically, those on STRs

		had a 63% greater likelihood of ≥95% adherence (95% confidence interval [CI]: 1.52–1.74; p<0.001) and 43% greater likelihood of ≥90% adherence (95% CI: 1.21–1.69; p<0.001), and higher adherence was associated with higher levels of viral suppression in 13/18 studies. • In addition, the submitting company's choice of a predefined cut-off value for adherence of ≥95% is overly conservative. As noted by the ERG, published UK evidence (Sherr, L. *et al.* [2010][2]) suggests that assuming a single daily oral dose of ART, adherence of ≥71% is adequate to bring about virologic suppression. Whilst more recent estimates based on real-world evidence suggest an average adherence of 82% is sufficient,[3] the assumption of ≥95% remains overly conservative. • In the company submission, the publication used to adjust treatment efficacy by adherence (Ross *et al.* [2015][4]) is based on a study from Cote d'Ivoire (Messou *et al.* [2011][5]) which included patients who started treatment with an MTR (stavudine/zidovudine + lamivudine + nevirapine/efavirenz) in 2006-07. This adjustment is therefore based on old data that are not reflective of the current UK standard of care. • Given the uncertainties in adherence levels and the impact of adherence on efficacy, it would be beneficial to see more sensitivity analyses to test the impact of changing these assumptions on the health economic results.
Key issue 10: Utility advantage for patients taking CAB LA + RVP LA	**N/A**	• The base case cost-effectiveness analysis assumes an increase in utility of [redacted] for patients receiving CAB+RPV versus ART. Whilst it is acknowledged that CAB+RPV remains dominant in all scenarios even with the utility advantage

		removed, reducing or removing the utility advantage for CAB+RPV does have a substantial negative impact on the incremental QALYs gained. • Gilead support the ERG view that these data are uncertain and should be interpreted with caution, based on the reasons highlighted within the ERG report including potential drop-out rate differences and limited clinical trial follow-up. It also remains unclear whether the collection of health-related quality of life (HRQoL) data at Weeks 24 and 48 only, with a 4-week recall of HRQoL, will have accurately captured adverse effects such as injection site pain sufficiently. Indeed, Mantsios *et al.* (2021)[6] report one of the biggest drawbacks of the LA injectable to be the frequent clinic visits and injection site pain. • Moreover, as a new mode of administration, there is no precedent for the utility advantage with a LA injectable therapy versus oral ART. In the ATLAS-2M and FLAIR trials, patients were highly screened and only specific treatment-experienced patients with a history of good adherence and engagement in care were enrolled. This high engagement and interest in receiving CAB+RPV LA injectable prior to trial enrollment may have had an impact on the utility estimates.

Additional issues

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	and/or page(s)	analyses?	
Additional issue 1: Resistance	Section 3.2.5.3 (p 60)	**N/A**	• Although high rates of virologic suppression were reached in ATLAS, ATLAS-2M and FLAIR, adherence to CAB+RPV did not guarantee virologic success and multi-class resistance developed in some patients. The company submission reports that at Week 48 of ATLAS, ATLAS-2M and FLAIR, eight participants (1.5%) treated Q2M had confirmed virologic failure, despite the high levels of treatment adherence across the trials. • The benefits of CAB+RPV are at the cost of potential resistance development, even when adherence is very good. The implications of resistance are concerning both for the individual with HIV, since resistance leads to a loss of future treatment options, and a societal level through the potential for transmission of resistant HIV.
Additional issue 2: Appropriate population	Section 2.1 (p 26)	**N/A**	• The ATLAS, FLAIR and ATLAS-2M trials are considered to be associated with significant selection bias. The eligibility criteria are reflective of a highly selective population, whereby patients were highly screened prior to enrollment and only specific treatment-experienced patients with a history of good adherence and engagement in care were enrolled. Whilst CAB+RPV is recommended by the Department of Health and Human Services (DHHS) for similar patients, the summary of product characteristics for CAB(+RPV) includes a recommendation for patient adherence counselling, highlighting the importance of this being required in clinical practice. • Patients in the real-world setting can differ substantially from these trial populations, and patient behaviours in terms of

			adherence and engagement with care can change over time. • Moreover, as discussed in response to Key Issue 3, the generalisability of the ATLAS, FLAIR and ATLAS-2M trials to UK clinical practice should be highlighted due to the high selection bias in terms of the enrolled population – this not only potentially influences the results of the ITC and the utility estimates adopted within the cost-effectiveness analysis, but healthcare professionals should carefully consider the applicability of the data from these trials and in turn the suitability of CAB+RPV for their patients.
Additional issue 3: Administration costs and consideration of logistical/infrastructure change requirements	Section 4.2.9 (p 106)	**N/A**	• The administration cost of CAB+RPV was assumed to comprise 15 minutes for a (Band 5) nurse to administer the two intramuscular injections – based on PSSRU costs (£9.25 per 15 minutes). Gilead believe this administration cost represents the lowest case estimate. • CAB+RPV preparation is complex and internal Gilead experts understand this would take longer than 15 minutes (e.g. the therapies will need to be prescribed, dispensed, collected and stored in a drug fridge pending patient arrival, then retrieved 15 minutes ahead of the planned injection time). Whilst the injection can be carried out by a Band 5 nurse, higher grade nurses may need to be used in smaller clinics or due to staffing issues. • It is also important to highlight the overall complexity of CAB+RPV administration and associated resource use requirements that may include logistical and infrastructure changes, as well as the potential opportunity costs associated with these changes. These have been highlighted by Mantsios et al. (2021)[6] and do not appear to have been explicitly discussed thus far in this appraisal.

References

1. Altice F, Evuarherhe O, Shina S, et al. Adherence to HIV treatment regimens: systematic literature review and meta-analysis. Patient preference and adherence 2019;13:475.
2. Sherr L, Lampe FC, Clucas C, et al. Self-reported non-adherence to ART and virological outcome in a multiclinic UK study. AIDS Care 2010;22:939-45.
3. Byrd KK, Hou JG, Hazen R, et al. Antiretroviral Adherence Level Necessary for HIV Viral Suppression Using Real-World Data. Journal of acquired immune deficiency syndromes (1999) 2019;82:245-251.
4. Ross EL, Weinstein MC, Schackman BR, et al. The clinical role and cost-effectiveness of long-acting antiretroviral therapy. Clin Infect Dis 2015;60:1102-10.
5. Messou E, Chaix M-L, Gabillard D, et al. Association between medication possession ratio, virologic failure and drug resistance in HIV-1 infected adults on antiretroviral therapy in Côte d'Ivoire. Journal of acquired immune deficiency syndromes (1999) 2011;56:356.
6. Mantsios A, Murray M, Karver TS, et al. Multi-level considerations for optimal implementation of long-acting injectable antiretroviral therapy to treat people living with HIV: perspectives of health care providers participating in phase 3 trials. BMC Health Serv Res 2021;21:255.

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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)	**Janssen-Cilag**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nothing to disclose.**

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Key issues for engagement

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Key issue 1: Concerns regarding English language and date limits used in the literature searches, the sensitivity of the search strategies, and the currency of the literature searches	**No**	Janssen do not have any further comments or responses for this key issue.
Key issue 2: Lack of head-to-head evidence between Cabotegravir and rilpivirine (CAB LA + RPV LA) and antiretroviral therapy (ART) therapy	**No**	Janssen do not have any further comments or responses for this key issue.
Key issue 3: Unclear generalisability of the results to patients in the UK NHS setting	**No**	Janssen do not have any further comments or responses for this key issue.
Key issue 4: Exclusion of case-control studies	**No**	Janssen do not have any further comments or responses for this key issue.

Key issue 5: Pooling of ATLAS and FLAIR	**No**	Janssen do not have any further comments or responses for this key issue.
Key issue 6: All oral ARTs are assumed to have a similar efficacy	**No**	Janssen do not have any further comments or responses for this key issue.
Key issue 7: Non-significance interpreted as non-inferiority	**No**	Janssen do not have any further comments or responses for this key issue.
Key issue 8: Cost of basket of comparators	**No**	Janssen do not have any further comments or responses for this key issue.
Key issue 9: Adherence assumptions	**No**	Janssen do not have any further comments or responses for this key issue.
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..	..	..	[INSERT / DELETE ROWS AS REQUIRED]
Company's preferred base case following technical engagement	**Incremental QALYs: [QQQ]**	**Incremental costs: [£££]**	**Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER**

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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)	**MSD**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

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Key issues for engagement

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Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Concerns regarding English language and date limits used in the literature searches, the sensitivity of the search strategies, and the currency of the literature searches	NO	We note that where possible the evidence base should be updated within 6 months of the NICE submission as per the York CRD recommendations for systematic literature reviews[1]. However, we also note that this is unlikely to have affected the decision regarding feasibility for NMA to a great extent in this instance. We have no further comments with regards to the searches conducted by the company.
Key issue 2: Lack of head-to-head evidence between Cabotegravir and rilpivirine (CAB LA + RPV LA) and antiretroviral therapy (ART) therapy	NO	Well established statistical methods exist that can address the lack of head to head comparisons.
Key issue 3: Unclear generalisability of the results to patients in the UK NHS setting	NO	No additional comments.
Key issue 4: Exclusion of case-control studies	NO	We do not think that the exclusion of case-control studies is a major issue, given that, as stated in the submission, there is a high level of 'gold standard' evidence available from head-to-head RCTs.

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		The methodology followed in the submission aligns with NICE's preferred evidence sources (i.e. prioritising data from RCTs – NICE PMG9[2]).
Key issue 5: Pooling of ATLAS and FLAIR	NO	We note the differences in the patient populations between ATLAS and FLAIR relating to previous ART exposure. From a decision-making perspective, the NICE-recommended indirect treatment methodology for conducting evidence synthesis should be followed unless there is sufficient justification against this due to data limitations. NICE DSU have published a number of TSDs on evidence synthesis methodologies[3].
Key issue 6: All oral ARTs are assumed to have a similar efficacy	NO	No further comments. However, as already noted within the TE documents, justification on assumptions with regards to ART equivalence in terms of efficacy and/or safety may not always be appropriate without prior clinical expert input alongside a detailed feasibility assessment. This process should be reported transparently and completed for each submission.
Key issue 7: Non-significance interpreted as non-inferiority	NO	No additional comments.
Key issue 8: Cost of basket of comparators	NO	From a costing perspective, we consider scenarios whereby the comparator is comprised of a single ART band to not be reflective of the clinical practice. A more pragmatic approach may be the use of a mix of ART bands, as this may be more typical in UK clinical practice for decision making purposes. Additionally, any assumptions pertaining to the equivalence of ARTs should also be justified and validated by clinical experts.
Key issue 9: Adherence assumptions	NO	No additional comments.
Key issue 10: Utility advantage for patients taking CAB LA + RVP LA	NO	No additional comments.

1. Systematic Reviews: CRD's guidance for undertaking reviews in health care (york.ac.uk)

2. The reference case | Guide to the methods of technology appraisal 2013 | Guidance | NICE
3. Evidence Synthesis TSD series – NICE Decision Support Unit (nicedsu.org.uk)

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Additional issue 1: **N/A**	N/A	NO	No additional issues.

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Cabotegravir and rilpivirine for treating HIV-1 [ID3766]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments **18 June 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report 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 appraisal, 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.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. 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.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- 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 under 'commercial in confidence' in turquoise, all information submitted under academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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)	ViiV Healthcare
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

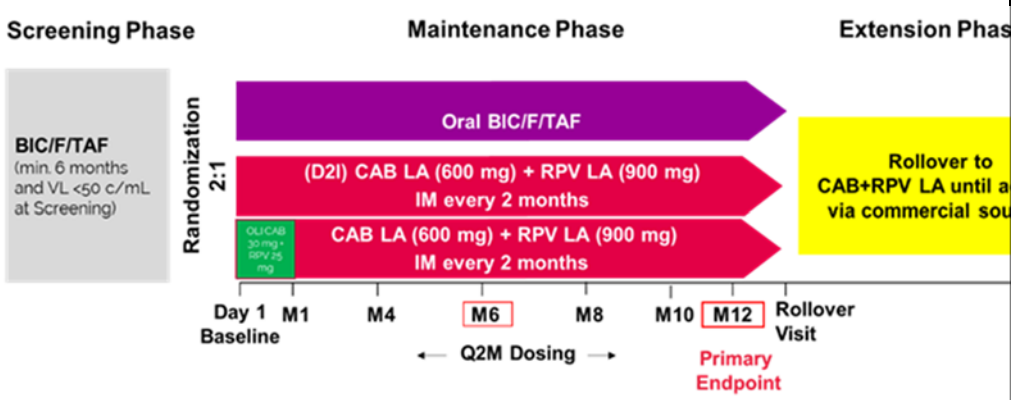
Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG comment
Key issue 1: Concerns regarding English language and date limits used in the literature searches, the sensitivity of the search strategies, and the currency of the literature searches	Yes, with no update to base case analysis	***Searches have been updated to cover the period between April 2020 and June 2021; there are no additional studies to incorporate into the base case.*** The company agrees that literature searches should be conducted to a high quality, following appropriate guidance to yield all of the evidence relevant to the submission. As such, the searches in the company submission (CS) were conducted according to guidance from the Centre for Reviews and Dissemination (CRD),[1] and retrieved a high volume of evidence. Given the substantial number of publications gathered when applying the 'English-language-only' limit, expanding the search to other languages was very unlikely to identify new evidence relevant to a UK setting. Similarly, given the high volume of evidence gathered, by applying the 'Date' filter, and expanding the search to studies over 20 years old was very unlikely to bring relevant evidence. Over the past 30 years, new HIV regimens have evolved substantially, with key highly active antiretroviral therapies only being licensed in the late 1990s to early 2000s. As a result, earlier data would not have been a true reflection of more 'current' clinical practice. Further, a comparison between a current and historical switch study (i.e. more than 20	Key issue partly addressed As suggested by the ERG and in line with best practice, an update of the searches was conducted. Full details of the update search strategies, including changes made, have been provided in Addendum 1. The search strategies were clearly reported to be 'pragmatic' and were adapted to include specific comparators in the intervention facet, rather than generic search terms for anti-HIV agents; two of the search facets were removed, 'Disease stage' and 'Outcomes', as well as dropping the 'Study type' facet

		years old and used prior to licensing of the first highly active antiretroviral treatment) in virologically suppressed people would not have been a like for like comparison. The ERG expressed concerns regarding the number of search facets that were combined in the search strategy, which they say may have reduced the sensitivity of the search results. The company conducted the searches in line with CRD guidance, which states that constructing an effective combination of search terms involves breaking down the review question into 'concepts,' and that using the Population, Intervention, Comparator, and Outcomes elements from PICOS can help to structure the search, but it is not essential that every element is used.[1] While the company agree that combining search facets like this may reduce the ability of the search to identify concepts that are poorly defined or identify outcomes that were not included in either the title or abstract, in an extensively studied area such as HIV, more uniform definitions have been applied across study publications and were included in the search strategy. Therefore, it is unlikely that the searches would have missed these publications. ***Search update*** The company agrees with the ERG that the timing of the reviews, 10 months prior to submission, may have resulted in more recent publications being missed. CRD guidance recommends that if the initial searches were conducted some time before the final analysis, such as six months, it may be necessary to re-run the searches.[1] Therefore, the company re-ran the initial searches for the SLRs, restricting the date from April 2020, when the searches were initially conducted, to June 2021. A report is supplied as a separate document (Addendum 1). For this update, the interventions were restricted to the specific comparators that make up the 'comparator basket' in the economic model. These updated searches yielded 193 results, of which 21 publications were deemed to meet the inclusion criteria, describing nine studies identified in the original SLR and nine additional studies. No additional studies were identified describing CAB LA + RPV LA.	from the CENTRAL search strategy; and the searches were not limited to English language. The company reiterated their reasons for using an English language limit as well as a date limit in the CS searches, providing a more detailed explanation of how HIV regimens have evolved over the past 30 years. This justification for a date limit is reasonable. The company refers to CRD guidance to reiterate why they included five facets in the CS search strategies, and provides further justification by explaining that HIV is an extensively studied and well-defined area, which allows for more specific search strategies. This is a reasonable explanation. Fewer facets would have been preferable, but, as the company point out, it is unlikely they would have missed any included studies. However, the update searches did remove two of the search facets, 'Disease stage' and 'Outcomes', as well as the 'Study

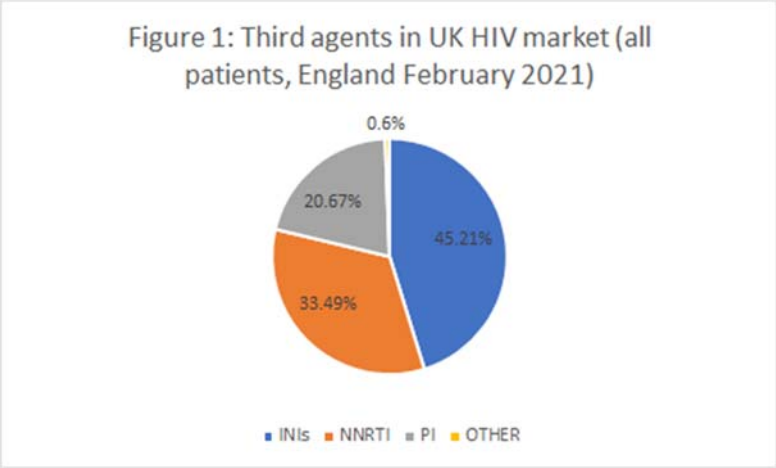
		Studies identified using the updated review were assessed for feasibility of informing an indirect comparison, as well as the appropriateness of the resulting network. Details of the assessment are given in Addendum 1B. As described in the company submission, the most significant obstacle was considered to be the composition of the pooled ART arm, which varied between comparator studies. As with the results of the previous searches, an NMA could be conducted (notwithstanding the limitations in interpretation) if the explicit assumption is made that ART regimens have similar efficacy at this point in the treatment pathway. Whilst this is likely to be the case (as described in the company submission), this approach is unlikely to reduce uncertainty compared with the presented ITC. In summary, it was determined that an NMA would not provide additional support for decision making beyond the ITC for CAB LA + RPV LA Q2M versus current ART that is presented in the company submission. The additional nine studies therefore add little in terms of comparative evidence.	type' facet from the CENTRAL search strategy.
Key issue 2: Lack of head-to-head evidence between Cabotegravir and rilpivirine (CAB LA + RPV LA) and antiretroviral therapy	No	***There are currently no head-to-head trials comparing CAB LA + RPV LA Q2M and daily oral standard of care ART; this issue is acknowledged but not considered a significant limitation particularly given the accepted position that the modern treatments are similar in terms of their capacity to suppress the virus (an assumption which is made in the model).*** An indirect treatment comparison was conducted to determine the relative efficacy of CAB LA + RPV Q2M vs daily oral ART. This was conducted applying Bucher's methodology according to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines,[2] with CAB LA + RPV LA Q1M as the common comparator.[3] The ITC is discussed further under Issue 5. The company agree with the ERG that while indirect comparisons provide useful insights in the absence of direct trial-based comparisons, they cannot replace evidence from head-to-head studies.	Key issue remains. There seems to be general agreement about (the lack of) head-to-head studies ("The company agree with the ERG that while indirect comparisons provide useful insights in the absence of direct trial-based comparisons, they cannot replace evidence from head-to-head studies").

(ART) therapy		To note, the SOLAR trial (NCT04542070)[4] is currently recruiting and it will assess the antiviral activity and safety of a two-drug regimen of CAB LA + RPV LA Q2M compared with maintenance of the oral regimen Biktarvy® (BIK). This is a Phase IIIb, randomised, open-label, active-controlled, multicentre, parallel-group, non-inferiority study (SOLAR: Switch Onto Long Acting Regimen). It is designed to assess the antiviral activity and safety of CAB LA + RPV LA (Q2M) compared with maintenance of BIK. Approximately 654 adult HIV-1 infected participants who are on the stable ARV regimen BIK will be randomised in a 2:1 ratio to either be switched to the CAB LA + RPV LA regimen or continue BIK through 12 months. Participants will be offered the option to start with a month long oral lead in (OLI) or to start long acting intramuscular injections (D2I). The study will continue with an Extension Phase after Month 12 for individuals in the OLI group and on BIK and from Month 11 for the D2I group. [4] (see schematic of study design, below).  The primary endpoint is the proportion of participants with plasma HIV-RNA ≥50 copies/mL as per FDA Snapshot algorithm at Months 6 and 12 (OLI and BIK)/Months 5 and 11 (D2I) (ITT-E population). Recruitment to the study closed [redacted]	

		Evidence from this study will not be available during the timeframe of the submission. Interim results are expected in the first half of 2022 and analysis of the primary endpoint in the second half of 2022.	

Key issue 3: Unclear generalisability of the results to patients in the UK NHS setting	Yes	***The comparator regimens in ATLAS and FLAIR overlap considerably with current UK practice. Clinical experts consulted as part of this response consider that the differences are not unexpected given the evolution in therapy since the studies were conducted; they have no concerns about the generalisability of study results to the UK setting*** The ERG are concerned about generalisability since the regimens used in the ATLAS and FLAIR studies are not **fully** representative of currently used ART regimens in the NHS, for this specific decision problem, i.e. virologically suppressed persons for whom a switch to LA ART may be appropriate. As emphasised in the CS, it is important to note that there is no single 'standard of care' regimen and selection of an appropriate ART regimen is individualised based on a broad range of clinical and non-clinical factors.[5] The principal UK HIV treatment guideline, the British HIV Association 2016 interim update,[6] found no difference in the virological efficacy of PI/r or NNRTIs, for virologically suppressed people switching antiretroviral therapy,[6] and recommend that when switching, consideration should be given to other factors, such as the difference in side-effect profiles, drug-drug interactions, pill burden and food effect. Further, it should be noted that Appendix D of the Company Submission details evidence derived from the clinical SLR, wherein studies for relevant comparators included vastly different pooled ART comparator arms. Despite these differences, these pooled ART arms can all be considered relatively similar to UK clinical practice, with no inappropriate ARTs included. Further, it should be noted that these differences in pooled ART composition did not impact on clinical outcomes. Hence, any differences are not expected to impact on the generalisability of ATLAS and FLAIR to UK clinical practice.	Key issue remains. As highlighted in the ERG report, the generalisability to the UK NHS setting is unclear, i.e. there is a potential risk from lack of generalisability. Regarding current treatment, no new evidence has been provided.

		ATLAS study The issue of generalisability of regimens was discussed at the clinical advisory board held to inform the Technical Engagement responses (see Addendum 2). The advisors agreed that the treatments in the comparator arm of the ATLAS study are broadly representative of treatments used today. In instances where specific regimens in ATLAS do not overlap with today's options, they agreed that this is due to evolution in treatment landscape since the study was conducted, the multi-country nature of the study, and the variability in specific populations / subgroups (who may have different profiles and needs). The significant variations in patient backgrounds and needs within HIV populations make discussion of 'the average patient' difficult and potentially meaningless. They also felt that not all treatments are options in all cases (i.e. subsets of the full spectrum of treatments become alternatives for individuals depending on their reasons for changing therapy). Figure 1 shows the distribution of the different third agents used with two NRTI backbones across the whole treated HIV population in England (data from February 2021, IQVIA HPA). Figure 2 presents the corresponding breakdown by third agent in the ATLAS trial. The profiles are broadly comparable and there is a reasonable overlap in class of third agent. The differences observed here can be explained by study design, where ATLAS excluded people treated with Triumeq® and had a cap on recruitment of people receiving INI as a third agent. This is in addition to the reasons for differences discussed above. It is important to note that as all ARTs are assumed to have equivalent efficacy in the model, any differences would not affect the modelling of treatment efficacy, reported QALYs and LYs.	



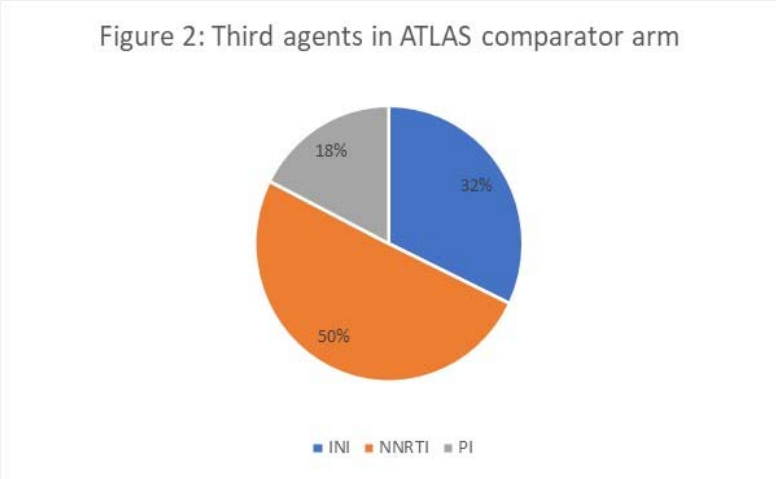


Figure 1: Third agents by market share and in ATLAS comparator arm

		FLAIR study The ERG considers the term 'current ART' to be erroneous in the case of FLAIR. It states that: '*the term "Current ART" implies a variety of therapies dependent on the time and location of the study in question, incorporating patient preference and tolerances. In ATLAS, patients continued the ART they were using prior to entering the study, so "current ART" is valid. This was not true of FLAIR, where the study required that all participants take the same ART. While no patients in FLAIR had taken a previous ART and therefore did not switch to DTG/ABC/3TC from a different ART, neither was that ART representative of the variety of ARTs the patients would have taken had they not been recruited into FLAIR.'* The company acknowledges that this description of FLAIR is correct. However, given that all modern approved ART regimens are assumed to have comparable efficacy (see Key issue 7 for discussion of this), the fact that patients in FLAIR switched from one particular (commonly used and guideline recommended) ART is not considered to materially affect either the efficacy results obtained for CAB LA + RPV LA or the generalisability of the evidence base for CAB LA + RPV LA to patients in the NHS. Further, the company considers that 'current ART' is an adequate and meaningful description of the comparator in the overall trial evidence base, despite the fact that patients in FLAIR did not have a free choice of regimen. FLAIR provides additional information to ATLAS in that ATLAS did not contain many patients on a dolutegravir (DTG) based regimen (most were on an NNRTI (EFV) regimen). Today, DTG- based regimens are the most frequently used regimens. In FLAIR, patients are suppressed on Triumeq® and then switch to CAB LA + RPV LA, which can be viewed as more representative of the typical switch seen today for patients being considered for the long acting treatment. Most importantly, consulted	

		experts have no reservations about the generalisability of the results of the FLAIR trial to UK practice (see Addendum 2).	
Key issue 4: Exclusion of case-control studies	No	***Case-control studies were excluded from the company submission; however this is not necessarily a material issue given the significant body of higher level evidence (RCTs) that was included*** The company agrees with the ERG that case-control studies can provide useful information on the safety of the treatment of interest. However, as the literature search retrieved a very large number of randomised controlled trials (RCTs), which are of higher quality compared to observational studies,[7] data from non-RCT studies were not extracted but provided as Section D.5 of Company submission Appendix D; this does not include case-control studies, which were excluded from the SLR. Case-control studies represent lower quality of evidence than RCTs to inform comparative effectiveness and given the high volume of RCTs and observational studies, priority was given to RCTs. The inclusion of case-control studies would be very unlikely to add new evidence that would diverge from the overall picture drawn from RCTs. Additional safety data from the CAB LA + RPV LA EPAR has been provided – see Additional Issue 2.	Key issue partly addressed The ERG would have preferred searches specifically for safety data. However, as higlighted by the company, given the large HIV literature with safety data it is unlikely anything new would have been identified
Key issue 5: Pooling of ATLAS and FLAIR	Yes	**The ITC combined the patients in the ATLAS and FLAIR trials into a single larger population for analysis. Whilst we recognise the theoretical limitations of using pooled datasets for ITCs, there is limited concern here given that the pooling was pre-specified and the trials were designed with this purpose in mind.** The ERG felt that due to the differences between the trials, such as the different comparator treatments and use of a run-in period, pooling was an inappropriate analysis method and recommended an alternative	Key issue remains. The comments made by the ERG are justified. However, the ERG appreciates that the company provided results from the meta-analysis suggested by

		approach of combining ATLAS and FLAIR in a meta-analysis within the ITC. They also commented that *"Even in the absence of effect modification, the standard error of the pooled ATLAS/FLAIR effect estimate is overly precise, given ATLAS and FLAIR are not the same trial."* The company recognises the theoretical limitations of using pooled datasets in the conduct of ITCs. However, the assumption of trial homogeneity was deemed appropriate for ATLAS and FLAIR given they were designed to be pooled. In theory, we would expect to see a difference using a random-effects meta-analysis due to trial heterogeneity; however, in practice it can be observed that the impact of this is minimal. Further, it should be noted that standard meta-analysis methods typically account for mean values, variance and sample size when synthesising data; in this case, where the studies are similar and were designed to be pooled, those factors are inherently captured by the pooling method, as it incorporates all participant data. In preparing responses for an IQWiG submission in Germany, the alternative approach suggested by the ERG, with ATLAS and FLAIR combined in a meta-analysis within the ITC, was conducted. A fixed effects meta-analysis was presented in the main submission and accepted by IQWiG. In accordance with their guidance 'In the case of very few studies, the heterogeneity cannot be reliably estimated. Therefore, if fewer than 5 studies are available, the use of a model with a fixed effect or a qualitative summary should also be considered'. Like the ITC presented in the CS, the subsequent ITC analysis was also conducted using Bucher's methodology. The results based on both a fixed effects and random effects model are provided in Appendix D of this document. As shown in Table 1, the different analyses to compare the relative effectiveness of CAB LA + RPV LA Q2M to current ART produced very	IQWiG and the ERG. As these results are similar, there are no changes to the cost effectiveness model required. Differences in results for the outcome "AEs leading to discontinuation" should be noted.

<table>
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<td>similar relative risks (point estimates and confidence intervals) for viral load. Note that results for adverse events could not be compared directly between the two analyses; the ITC using the non-pooled data included ISRs whereas the ITC using the pooled data excluded ISRs.

Table 1. Comparison of the outcomes from the ITCs using pooled and separate ATLAS and FLAIR trial data
<table>
<tr><th></th><th>ITC using non-pooled data
Relative Risk [95% CI]</th><th>ITC from CS (using pooled data)
Relative Risk [95% CI]</th></tr>
<tr><td>Viral load < 50 c/mL at week 48</td><td>[redacted]</td><td>1.01
[0.95, 1.06]</td></tr>
<tr><td>Viral load ≥ 50 c/mL at week 48</td><td>[redacted]</td><td>1.10
[0.25, 4.90]</td></tr>
<tr><td>AEs leading to discontinuation</td><td>[redacted]</td><td>1.48
[0.40, 5.46]</td></tr>
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<td>Key issue 6: All oral ARTs are assumed to have a similar efficacy</td>
<td>No</td>
<td>The model assumption that oral ART regimens have similar efficacy is supported by a breadth of non-inferiority studies, by clinical experts consulted by the Company and is not of particular concern to the ERG (providing there are no issues about trial generalisability – discussed above); this is not considered to be a particularly controversial assumption.

In the factual accuracy check, Table 36 in CS Appendix D was cited by the company as evidence for the statement that the comparators used in ATLAS and FLAIR have comparable efficacy to currently used regimens. The ERG noted that the table does not present such evidence.

This was an error by the company: the statement should have referred to Figure 3 in Appendix D. Figure 3 shows virologic suppression at Week 48 in relevant studies identified in the SLR. It shows that almost all studies reported virological suppression exceeding 90% at week 48, with</td>
<td>Key issue remains.

The ERG report highlights the uncertainty linked to this assumption.</td>
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		the exception of dose finding studies and switch studies. This figure is reproduced in an appendix to this form (Appendix B). The ERG agreed with the CS that given the very high efficacy of all current ART, that all oral ARTs have a similar efficacy, but believed the use of a match-adjusted indirect comparison (MAIC) without a full network meta-analysis (NMA) was likely to be justified. However, they concluded that no additional evidence or analyses were necessary. They were concerned that should the efficacy of ART used in the NHS be shown to be different to the ART used in ATLAS/FLAIR, then an NMA would be indicated. As demonstrated in the discussion of Key Issue 3 above, the company believe that the ART used in ATLAS/FLAIR trials are generalisable to the ART used in the NHS, and so their efficacies would be the similar, and, in agreement with the ERG, the company do not believe that a full NMA is necessary in this situation.	
Key issue 7: Non-significance interpreted as non-inferiority	No	***The ERG has clarified that this is an issue relating to semantics/interpretation. We agree with the ERG that there is ambiguity in the literature surrounding interpretation of non-inferiority studies. As with the point above, there is no material impact of this issue on the outcomes of the analyses.*** The ITC conducted during the CS (B.2.9) found that CAB LA + RPV LA Q2M is not statistically different to current ART after 48 weeks on any of the key efficacy or safety outcomes, in terms of relative risk, odds ratio and risk difference. The ERG highlighted that *'the company refers to the results as showing that CAB + RPV LA Q2M was, in fact, non-inferior or not different to* "current ART." *As the ITC is imprecise, and as the ITC*	Key issue remains. The ERG considers the comments and suggestions in the ERG report to still be relevant.

		was not designed as a non-inferiority analysis with defined non-inferiority margins, non-significance cannot be interpreted as non-inferiority.' Guidance on the interpretation of non-inferiority within the context of ITC methodology is still in development, and there is no single accepted method. However, while no specific hypotheses testing to demonstrate non-inferiority was performed, the ITC used the statistical methodology published by Bucher et al.[8] to calculate the 95% CI of indirect treatment effects, which are shown to be not statistically significant different for the efficacy and safety endpoints analysed. Given the lack of statistical certainty inherent in the wider HIV evidence base, which is largely predicated on non-inferiority trials, the element of uncertainty does not negate the assumption that modern approved HIV therapies have essentially 'equivalent' efficacy. Therefore, while the ITC conducted during the CS did not test for non-inferiority, it demonstrates equivalent efficacy to current ART, and so can be considered equivalent to modern approved HIV therapies. The conclusions on comparative effectiveness for CAB LA + RPV LA have been appropriately interpreted in the context of HIV regimens and the basis for their efficacy today.	
Key issue 8: Cost of basket of comparators	No	***The company has used the only source of information of relevance to the current market to inform the selection of comparators (for cost purposes) in the submission – i.e. current market share information which indicate the treatments that virologically suppressed individuals 'switch to'; we acknowledge the data are not perfect (since they do not stratify by reasons for switch) but consulted clinical experts – both prior and post submission - agree they are a reasonable representation of likely comparators for long-acting injectables (see Addendum 2)*** There are many different ART regimens available and no single "standard of care" or treatment pathway. This is partly due to the	The additional clinical expert opinion that was consulted by the company indicated agreement that the treatments used in the comparator arm of ATLAS are broadly representative of treatments that are currently being used, which the company interpreted as there being no concern about the generalisability of the results

		significant evolution in treatment over a number of decades. None of the current guidelines list a bounded set of options or a preferred treatment sequence for virologically suppressed people wishing to change their therapy. This allows individuals and their prescribers to tailor treatment to individual circumstances alongside their medical needs. Despite the considerable choice of available regimens, treatment decisions are primarily based on medical need and commissioning policies. The comparators in the decision problem were a basket of those antiretroviral regimens shown to be most frequently 'switched to' for virologically suppressed people living with HIV, who would be eligible to switch to CAB LA + RPV LA, if CAB LA + RPV LA. The company considers this dataset to be the most appropriate starting point. Those treatments with a share of ≥2.5% (an arbitrary cut-off) were discussed with clinical experts prior to submission. Clinicians advised the addition of Juluca®, as this is a two-drug regimen of dolutegravir and rilpivirine that was identified as clinically relevant for this appraisal because it represents a 'close' oral alternative to CAB LA + RPV LA). Further, clinicians suggested removal of Truvada® (TDF/FTC) + Tivicay®, as patients typically switch away from this regimen rather than onto it, because of toxicity concerns. The company acknowledges that imprecision remains in the data since the reason for the switches is unknown, and this reason is likely to be critical in the consideration of transitioning a virally suppressed individual to a long-acting alternative. The choice of comparators was also raised with clinical experts post submission, and they agreed that the selected comparators are largely representative of clinical practice (see Addendum 2), although the various different options will be more or less commonly used depending on patient characteristics and local policies and practice. The choice of	of the ATLAS and FLAIR trials to current UK clinical practice. However, the additional clinical expert opinion also confirmed the uncertainty that stems from the fact that choice of treatment is very much dependent on individual circumstances of patients that can vary significantly. As such, it remains uncertain whether and to what extent the current basket of comparators is representative of the treatments options that would be considered for persons living with HIV for whom CAB LA + RPV LA would be considered if it were available. The ERG acknowledges that this uncertainty also applies to the ERG's scenario analyses that are based on the Midland and East Region commissioning policy costs. However, the ERG emphasises that the aim of these scenario analyses was not to address the uncertainty regarding the contents of the

		switch therapy is individualised based on a range of factors including previous treatment history, underlying health risks and co-morbidities, and considerations relating to lifestyle and individual preference. Drug cost was not an explicit consideration in deriving the comparators and some low-cost branded single tablet regimens, such as Triumeq® and Dovato®, are included. The use of some of the 'lower cost' regimens in fewer than 2.5% of virologically suppressed individuals relates to the fact that these treatments are more likely to be used early on, i.e. are more likely to be treatments that people were switching from. Alternative approaches to identifying comparators, e.g. the ERG's use of the Midland and East Region commissioning policy, have shortcomings given regional variation in pricing and policies, and the date of the algorithm.	basket of comparator regimens but to assess the sensitivity of the results to the assumed cost of the basket of comparators. Importantly, neither the company base case nor the ERG preferred results that are presented in the ERG report reflect the cost of the basket of comparators to the NHS since these analyses did not include the PAS discounts that are currently in place for the oral ARTs that are included in the basket of comparators.
Key issue 9: Adherence assumptions NB: From CS: A targeted literature review undertaken to identify studies reporting adherence to ART in the UK found few publications. Reported rates of non-adherence ranged from 10% (missing ≥2 doses in the last 7 days) to 57% (missing a dose or taking ≥1	NO	***It is reasonable to assume that as a directly observed therapy, improved adherence is an advantage of long-acting injectable treatment. The company accepts there is uncertainty in how this is modelled given availability of data (both on levels of adherence to lifetime daily oral ART and on the consequence of suboptimal adherence on treatment effectiveness).*** ***The company now realise that the ERG has misinterpreted the way the adherence assumptions are implemented in the model (assuming these directly affect the probability of viral rebound and treatment switching, which is not the case). Since the ERG's preference for a more conservative approach to adherence is underpinned by this understanding of the model function, we provide in this response an additional step by step, visual guide to the application of adherence assumptions (see Addendum 3)***	See 'Appendix E. ERG's response to issue #9' at the end of this document.

dose incorrectly in last 7 days). SWEET was considered to be the most appropriate source to inform the modelling because it was a formal clinical trial with a relatively large population size. SWEET measured adherence to two daily oral ART regimens in virally suppressed participants with HIV using the Medication Adherence Self-Report Inventory (MASRI). Patients indicated the percentage of ART medication taken over the previous month on a visual analogue scale (VAS). Low adherence was defined as taking <95% of their prescribed ART medication over the past month, and was reported by 25.6% of patients in one therapy arm and 37.6% in		**Context** Treatment of HIV currently involves life-long adherence to daily oral therapy in order to achieve and maintain viral suppression. At any one time, levels of adherence and virological success are generally high in the UK. However, adherence can fluctuate, sometimes significantly, within and between individuals in a population. Unexpected disruptions in life can impact even those who have generally high adherence levels. For the purposes of economic modelling, this real-world complexity and variation must be simplified into two key inputs – the degree of suboptimal adherence over a lifetime (for an average person) and the consequences thereof (i.e. the link between adherence and viral suppression). Neither can be quantified with full certainty, as HIV medications requires life-long adherence and there is no universally accepted way to define or quantify adherence. In particular, published estimates of adherence are subject to relatively short measurement periods which do not necessarily reflect individuals' adherence over many years of treatment. Further, there is the added complication that adherence is not the only factor impacting on suppression, but is one of many drivers: a person who is fully adherent to medication may still experience viral rebound. The company acknowledge the uncertainty highlighted by the ERG around economic model inputs for adherence and impact of adherence. Following receipt of the ERG report, the Company conducted an advisory board to discuss adherence in depth with a clinical expert panel; a summary is supplied (Addendum 2). The clinical experts agreed that it is reasonable to expect a relationship between adherence and treatment efficacy, and for them to be positively associated (i.e. better adherence is linked to better efficacy outcomes).	

the other arm at Week 48 (study population N=117 per arm). The 25.6% reduction from 100% of patients having perfect adherence was applied to daily oral ART in the base case analysis, as this represented the more conservative choice.		They confirm that in their practices, levels of adherence are high at any one time. They described variation within and between individuals in a population, highlighting the impact of life events and unexpected life disruptions. The experts acknowledged the complexity related to extrapolating the experiences of a cross section of patients at any one point in time to the lifetime / longitudinal framing for an average patient that is required for NICE decision making. In the context of the company's economic model, the single input representing the proportion who are 'sub-optimally adherent' must summarise significant variation across a population (due to unpredictable life disruptions) and average this over the lifetime (due to the lifetime nature of treatments). Whilst there is inevitable uncertainty, it is reasonable to expect that the lifetime 'average' adherence will be lower than the level of adherence seen in a population snapshot at a single point in time. **Implementation of adherence in the model** Following the ERG's response to the Company's factual inaccuracy check and Technical Engagement call it appears the ERG have misinterpreted the way that adherence is implemented in the model, specifically its impact on 'downstream' consequences of non-adherence. Adherence or non-adherence does not impact on treatment outcomes directly in clinical practice: less than optimal adherence results in a slightly lower probability of achieving viral suppression. It is essential to understand that: • Individuals who are completely adherent will predominantly achieve viral suppression; however, some may still experience viral rebound due to unknown factors. • In clinical practice, not all individuals with less than optimal adherence will experience viral rebound or fail to achieve viral	

		suppression in clinical practice, as modern regimens may maintain their efficacy at lower levels of adherence than older regimens. • Not all individuals with less than optimal adherence will discontinue current treatment and move to subsequent treatment. During economic model conceptualisation, these factors were discussed with clinical experts and the model design was developed with this in mind. Hence, to address any misunderstandings, the company has provided a step-by-step guide to implementation of adherence in the model (see Addendum 3). To model the potential adherence-related benefit associated with CAB LA + RPV LA, adherence-related adjustments are made to treatment efficacy in the pooled ART arm, indirectly increasing the probability of viral rebound. Although in clinical practice, adherence does not directly impact on treatment discontinuation, the relationship between adherence and treatment effectiveness is captured in the model by adjustment of the monthly risk of discontinuation for individuals with reduced adherence. Further, it should be noted that the following ERG comment is inaccurate: "The ERG feels justification is needed why it is assumed that patients who become less than 95% adherent will immediately need to switch therapy and will immediately experience a viral load >50 HIV RNA copies per ml". The economic model adjusts viral suppression as a result of the adherence input which has a consequence on the monthly probability of viral rebound. Thus, these individuals with reduced adherence experience a higher probability of viral rebound (and hence treatment switching) each month, but this is not immediate and it is not experienced by all individuals with less than optimal adherence.	

		Evidence to describe the relationship between adherence and viral suppression The experts at the advisory board were asked if they were aware of additional evidence sources on the relationship between adherence and viral suppression in a UK population, beyond those already identified by the company and discussed in the CS. They highlighted the potential value of the UK Collaborative HIV Cohort (UK CHIC) study (Jose et al, 2018)[8], which reports a range of outcomes in a cohort of people with HIV in the UK. However, on further investigation, no published outputs from this study were suitable for use in the economic modelling. While the UK CHIC study reports on long-term outcomes, UK CHIC does not report any quantitative data on adherence or the relationship of adherence to viral suppression. The company therefore remains of the opinion that the existing implementation of the relationship between adherence and efficacy in the model, although subject to limitations, remains the most suitable approach given the available evidence. **Choice of adherence inputs** As noted above, there is no definitive estimate of long-term adherence to oral ART in the UK because of differences in the method of assessing adherence, the time period over which it is measured, and the threshold used to define suboptimal adherence. As reported in the CS, a targeted literature review undertaken to identify studies reporting adherence to ART in the UK found few publications. Reported rates of non-adherence ranged from 10% (where non-adherence was defined as missing ≥2 doses in the last 7 days) to 57% (missing a dose or taking ≥1 dose incorrectly in last 7 days). The SWEET study[9] was considered to be the most appropriate source to inform the modelling because it was a formal clinical trial with a relatively large population size, and used a formal adherence measurement tool (MASRI) with a 1-month recall period. Low	

		adherence was defined as taking <95% of their prescribed ART medication over the past month, and was reported by 25.6% of patients in one therapy arm and 37.6% in the other arm at Week 48. The more conservative of the two adherence results (i.e. the lower non-adherence value, 25.6%) was used; the ERG states that this would correspond to 86% adherence. The Company remains of the opinion that SWEET, whilst not definitive, is the most suitable estimation of UK adherence levels that is available. The ERG recommended the use of an adherence value from Sherr et al. 2010 of 10.1% of patients (Sherr) who missed at least two doses in the past seven days; the ERG states this would correspond to an adherence level of 71% or less); the ERG states that this may be more reflective of an adherence value below which it can more reliably assumed that viral suppression is indeed reduced, given that modern regimens may maintain their efficacy at lower levels of adherence than older regimens. The Company considers Sherr et al. to be a less suitable source because it uses a single snapshot of adherence based on doses missed during a 7-day recall period. In contrast, SWEET uses a 1-month recall period and patients had been taking their regimen for 48 weeks at the time of questioning (treatment duration was not specified in Sherr et al). In the company's opinion the Sherr et al. study is a less effective picture of long-term adherence patterns, because of the short recall period, which is likely to miss many fluctuations in adherence. It does not therefore provide any greater degree of certainty, particularly as the true relationship between adherence and efficacy of the comparator regimens remains unknown due to lack of data. The company acknowledges the uncertainty around quantifying adherence, and therefore addressed this in sensitivity analyses in the CS whereby the modelled reduction in adherence was varied in 5% increments from 5% to 40%.	

		Importantly, the ERG prefer the more conservative assumption of lifetime adherence - at least in part - to underwrite their concerns that the model functionality lacks clinical justification. However, as described above, we believe the ERG has misunderstood how adherence is modelled. It is hoped that the clarifications presented in this submission will help reconcile the preferred assumptions. It is acknowledged that the impact on viral suppression of fluctuations in adherence to oral ART over a lifetime is in reality complex with many interdependencies and day-to-day challenges for individuals. An economic analysis can in no way reflect all patterns, scenarios and complexities. However, the base case approach has been developed in collaboration with clinical experts and HIV advocacy groups to reflect a pragmatic, clinically plausible simplification of these factors. Alternative methodologies should not be judged solely on their conservative nature, but should incorporate similar pragmatism and ensure that clinical plausibility is the key determinant of approach.	
Key issue 10: Utility advantage for patients taking CAB LA + RVP LA	**YES**	• ***The company are able to resolve one of the ERG's concerns relating to utility (drop-outs); this should no longer be an issue (see below).*** • ***Injection site reactions (ISRs) – the ERG's second concern - were of short duration (median 3 days in ATLAS-2M) and would not have materially impacted PROs; this is reflected in the Perception of Injection data which indicates high acceptance and little or no bother with injections and is supported by a clinical expert who was consulted on the topic (see Addendum 2).*** • ***In summary we agree with the ERGs overall view that these two 'issues' have limited impact; the company goes one step further and considers that the modelled 0.02 utility benefit associated with a Q2M, long-acting treatment versus daily, oral ART is a likely underestimate.***	**Missing data** The ERG thanks the company for the additional explanation and analysis related to the apparent missing data in the HRQoL analysis. Given that these missing data were due to missing covariates and not drop out and that utilities were similar between those with missing covariates and those included in the analysis, the ERG no

		The ERG expressed two separate concerns regarding the uncertainty around the size of the utility advantage associated with CAB LA + RPV LA: • They highlighted the higher incidence of what appeared to be 'missing data' in the HRQoL reporting in the CAB LA + RPV LA group, compared to the oral ART group; this led to concern that data may have been missing non-randomly due to different 'drop-out' rates in the two arms. • The ERG felt that ISRs may have been missed during the HRQoL data collection (given that the SF-12 questionnaire was administered before participants received injections). We acknowledge that neither of these concerns led to a change in the utility assumption in the ERG's basecase. **'Missing data'** After further follow-up with the trial statisticians, the Company can now clarify the reason for the slightly lower number of patients in the CAB LA + RPV LA arm who had SF-6D data analysed, compared with the comparator (daily oral ART) arm. The difference in numbers was not due to missing patients (i.e. drop-outs); rather, it was due to differences in the numbers of patients who had data available for all the necessary covariates in the analysis. As detailed in the CS Appendix N, the ANCOVA model was adjusted for age, sex and CD4+ cell count as covariates. Subsequently, one model was created per visit (total three models [baseline, week 24 and week 48]) and CD4+ categories and SF-6D data at the same visit were used in each model. Patients with a missing covariate were not included. As these patients had some data available (but not all covariates), the missingness is not related to drop-out and can be considered random.	longer considers this to be an issue. **ISRs** In response to the comment that "any concern that the timing of the PRO instruments may miss intervention-related adverse events applies to both trial arms", the ERG would like to note that ISRs only apply to the long-acting arm as the comparators are oral treatments. The ERG still considers that the impact of ISRs have likely been under captured in the HRQoL data collection but continue to agree that this is unlikely to have a large impact on HRQoL, given the short duration of ISRs. However it remains that the small utility differential observed may underestimate the impact of ISRs, particularly

		To further investigate the effect of these variations on the SF-6D analysis, the Company has produced a summary of SF-6D score at each visit, broken down by patients with and without missing covariates (see Appendix C). It can be seen that the mean SF-6D scores at Week 48 are in fact slightly higher in patients with missing covariates, in both treatment arms. At Week 24, this holds true for the CAB LA + RPV LA arm (though not the comparator arm). These findings show that the analysis leading to the 0.02 utility advantage for CAB LA + RPV LA was not biased and the ERG's concern should now be addressed. **ISRs** The ERG was concerned that the timing of the PRO instruments, i.e. prior to receiving the intervention, may have missed effects of ISRs on SF-12 scores. However, a study physician consulted post-submission pointed out that any concern that the timing of the PRO instruments may miss intervention-related adverse events applies to both trial arms (not just long-acting treatment). They also agreed that ISRs are not likely to have a big impact on quality of life given their short duration (median 3 days in ATLAS-2M) and that overall there is high acceptability of injections to participants (as shown by the Perception of Injection data). **Summary** The Company accepts and agrees with the ERG's observation that these issues have little impact on the modelled utility. The company additionally considers that the utility difference between the two groups as captured by SF-6D (0.02) is conservative and is very likely to be an underestimate of the true utility gain associated with CAB LA + RPV LA compared with daily oral ART. This is because of the recognised limitations associated with generic HRQoL instruments (including the SF-12, on which the utility values are based) in capturing disease-specific factors such as stigma-related issues (e.g. fear of disclosure, daily reminder of HIV status) and lifestyle-related benefits such as convenience (which can in turn influence adherence). This view is	at the beginning of treatment where ISRs tended to be rated worse. While the impact is likely to be small, the model results are fairly sensitive to this utility differential parameter. As there is no evidence on the utility differential beyond 48 weeks, it is unclear whether the applied differential would change over the long term and in which direction. There is a lack of evidence on how well aspects such as stigma-related issues (e.g. fear of disclosure, daily reminder of HIV status) and lifestyle-related benefits such as convenience, are captured by SF-12 items asking about limitations in work and daily activities due to emotional problems; feeling downhearted and low and; physical and

		supported by clinical expert opinion (a study physician) sought on this topic for this response (see Addendum 2). Thus the company believes that there are significant HRQoL benefits that are not captured in the QALY in this submission, and that 0.02 should be considered as a lower limit of the difference. Furthermore, long-acting regimens are generally recognised to have advantages for the patient over daily regimens, and their development is a priority in a number of therapy areas. In comparable situations when patients are offered a choice between a daily oral therapy and a less frequent, long-acting injectable therapy, such as with contraception and anti-psychotics, patients experience greater treatment satisfaction due to the increased choice and empowerment that having different treatment modalities offers.[9-11] Similarly, patients benefit from the assured adherence offered by a long-acting treatment and in the case of anti-psychotics report better disease management and fewer sudden symptoms.[9] The desirability of long-acting ART is evidenced by the fact that other HIV pharmaceutical companies are currently developing similar products, and reflects a general trend towards long-acting therapies across several therapy areas.[12]	emotional problems interfering with social activities. Without any evidence it is difficult to say whether the benefits of long-acting treatment are being undervalued.

Additional issues

Please use the table below to respond to additional issues in the ERG report 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 appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response	ERG comment
Additional issue 1: Eligibility of study participants with K103N mutation	Pages: 12, 23, 26, 73, 87-88	No	*Eligibility for trial participation of those with baseline K103N mutation was removed by the ERG as a major issue. The company consider it unnecessary to retain reference to K103N at all in the report since there is no bias against oral ART associated with it. All trial participants were virally suppressed and none of the treatment failures (in either arm) had a baseline K103N mutation.* In the original ERG report, the ERG stated that patients who were a carrier of K103N were at risk of developing resistance to other NNRTIs, such as NVP or EFV. During the factual accuracy check, the company clarified that this mutation is not a concern for the population under consideration, given that the population is virally suppressed. Additionally, it should be noted that none of the participants who experienced virologic failure in ATLAS or FLAIR, in either treatment arm, had this mutation at baseline; this provides further reassurance that this issue is not clinically relevant to the submission.	No change required The ERG agreed to remove the key issue related to the eligibility for trial participation of those with baseline K103N mutation. Page 50 of the post-FAC ERG report highlighted that *"…none of the patients experiencing treatment failure were carriers of the baseline K103N mutation in any of the treatment arms"*. Therefore, the report

<table>
<tr><td></td><td></td><td></td><td></td><td>provides relevant information.

However, references to K103N have been removed from sections 1.3 and 2.1 as well as Table 2.1 of the revised ERG report.</td></tr>
<tr><td>Additional issue 2: Comparator safety evidence</td><td>Section 3.6, page 74</td><td>Yes</td><td>As highlighted by the ERG, the CS did not report a summary of the common AEs (≥5% in either arm) for the pooled ATLAS and FLAIR studies. To allow like for like naïve comparison on safety across ATLAS 2M, ATLAS and FLAIR, and thereby ensure the committee can fully assess the safety of CAB LA + RPV LA (Q2M), this evidence has been provided with this form (Appendix A). The table below summarises the location of safety data within the CS and subsequent documents.
<table>
<tr><th></th><th>ATLAS-2M</th><th>ATLAS</th><th>FLAIR</th><th>ATLAS & FLAIR</th></tr>
<tr><td>Overall Summary</td><td>Document B B.2.10.1</td><td>Technical Engagement Appendix A</td><td>Technical Engagement Appendix A</td><td>Technical Engagement Appendix A</td></tr>
<tr><td>Common AEs (≥5%)</td><td>Document B B.2.10.1</td><td>Technical Engagement Appendix A</td><td>Technical Engagement Appendix A</td><td>Technical Engagement Appendix A</td></tr>
<tr><td>Drug related AEs (≥1%)</td><td>Document B B.2.10.1</td><td>Clarification questions Table 10</td><td>Clarification questions Table 10</td><td>Clarification questions Table 10</td></tr>
</table></td><td>Report updated with newly provided evidence.

Sections 3.2.6 and 3.6 of the ERG report have been amended to incorporate these results.</td></tr>
</table>

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

NOT APPLICABLE: no changes were made.

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Addendum 1: Updated search strategies and results

This is supplied as a separate document.

Addendum 2: Summary of additional advisory boards

This is supplied as a separate document.

Addendum 3: Guide to implementation of adherence in the economic model

This is supplied as a separate document.

Appendices

Appendices are supplied on the pages that follow.

Appendix A Additional safety information from the EPAR

Table 1: Overview of all adverse events during the maintenance phase, pooled Phase III studies (safety population)

	201584		201585		Pooled	
	CAB LA + RPV LA (n=283) n (%)	CAR (n=283) n (%)	CAB LA + RPV LA (n=308) n (%)	CAR (n= 308) n (%)	CAB LA + RPV LA (n=591) n (%)	CAR (n=591) n (%)
Any AE	267 (94)	225 (80)	294 (95)	220 (71)	561 (95)	445 (75)
Any Grade 3/4/5 AE	31 (11)	11 (4)	35 (11)	24 (8)	66 (11)	35 (6)
Any drug related AE	236 (83)	28 (10)	255 (83)	8 (3)	491 (83)	36 (6)
Any Grade 3/4/5 drug related AE	14 (5)	0	14 (5)	1 (<1)	28 (5)	1 (<1)
Any AEs leading to withdrawal	9 (3)	4 (1)	13 (4)	5 (2)	22 (4)	9 (2)
Any SAE	18 (6)	12 (4)	13 (4)	14 (5)	31 (5)	26 (4)
SAEs related to study treatment	1 (<1)	0	0	1 (<1)	1 (<1)	1 (<1)
Fatal SAEs	0	0	0	1 (<1)	0	1 (<1)
Fatal SAEs related to study treatment	0	0	0	0	0	0

The CAB LA + RPV LA group is listed as Q4W IM. For study 201584, CAR = ABC/DTG/3TC
3TC: lamivudine; ABC: abacavir; AE: adverse event; CAB: cabotegravir; CAR: current antiretroviral regimen; DTG: dolutegravir; LA: long acting; RPV: rilpivirine; SAE: serious adverse event;
Source: Vocabria EPAR[13]

Table 2: Overall summary of non-ISR adverse events during the maintenance phase for pooled data (safety population)

	201584		201585		Pooled	
	CAB LA + RPV LA (n=283) n (%)	CAR (n=283) n (%)	CAB LA + RPV LA (n=308) n (%)	CAR (n= 308) n (%)	CAB LA + RPV LA (n=591) n (%)	CAR (n=591) n (%)
Any AE	246 (87)	225 (80)	264 (86)	220 (71)	510 (86)	445 (75)
Any Grade 3/4/5 AE	22 (8)	11 (4)	25 (8)	24 (8)	47 (8)	35 (6)
Any drug related AE	79 (28)	28 (10)	87 (28)	8 (3)	166 (28)	36 (6)
Any Grade 3/4/5 drug related AE	4 (1)	0	4 (1)	1 (<1)	8 (1)	1 (<1)
Any AEs leading to withdrawal	8 (3)	4 (1)	9 (3)	5 (2)	17 (3)	9 (2)
Any SAE	18 (6)	12 (4)	13 (4)	14 (5)	31 (5)	26 (4)
SAEs related to study treatment	1 (<1)	0	0	1 (<1)	1 (<1)	1 (<1)
Fatal SAEs	0	0	0	1 (<1)	0	1 (<1)
Fatal SAEs related to study treatment	0	0	0	0	0	0

AE: adverse event; CAB: cabotegravir; CAR: current antiretroviral regimen; ISR: injection site reaction; LA: long-acting; RPV: rilpivirine; SAE: serious adverse event;
Source: Vocabria EPAR[13]

Table 3: Most common adverse events (reported in ≥5% of subjects in any treatment group) by preferred term during the maintenance phase for Study 201584, study 201585 and pooled data (safety population)

	201584		201585		Pooled			
	CAB LA + RPV LA (n=283) n (%)	CAR (n=283) n (%)	CAB LA + RPV LA (n=308) n (%)	CAR (n= 308) n (%)	CAB LA + RPV LA (n=591) n (%)	AE rate per 100 subject years	CAR (n=591) n (%)	AE rate per 100 subject years
Any event	267 (94)	225 (80)	294 (95)	220 (71)	561 (95)	542.03	445 (75)	221.25
Injection site pain	227 (80)	0	231 (75)	0	458 (77)	231.27	0	0.00
Nasopharyngitis	56 (20)	48 (17)	51 (17)	42 (14)	108 (18)	20.31	90 (15)	29.51
Upper respiratory tract infection	38 (13)	28 (10)	32 (10)	25 (8)	70 (12)	12.32	53 (9)	17.27
Headache	39 (14)	21 (7)	34 (11)	17 (6)	73 (12)	13.07	38 (6)	12.36
Diarrhoea	32 (11)	25 (9)	22 (7)	15 (5)	54 (9)	9.43	40 (7)	12.81
Injection site nodule	44 (16)	0	37 (12)	0	81 (14)	14.51	0	0.00
Influenza	25 (9)	20 (7)	17 (6)	14 (5)	42 (7)	7.19	34 (6)	10.87
Injection site induration	38 (13)	0	30 (10)	0	68 (12)	12.28	0	0.00
Back pain	22 (8)	13 (5)	21 (7)	10 (3)	43 (7)	7.36	23 (4)	7.40
Pyrexia	22 (8)	4 (1)	21 (7)	9 (3)	43 (7)	7.42	13 (2)	4.22
Vitamin D deficiency	23 (8)	13 (5)	8 (3)	12 (4)	31 (5)	5.30	25 (4)	8.14
Respiratory tract infection	13 (5)	12 (4)	11 (4)	17 (6)	24 (4)	4.03	29 (5)	9.45
Cough	10 (4)	12 (4)	16 (5)	14 (5)	26 (4)	4.40	26 (4)	8.50
Injection site swelling	23 (8)	0	23 (7)	0	46 (8)	8.00	0	0.00
Nausea	16 (6)	11 (4)	14 (5)	5 (2)	30 (5)	5.13	16 (3)	5.15
Pharyngitis	15 (5)	9 (3)	8 (3)	12 (4)	23 (4)	3.86	21 (4)	6.80
Fatigue	7 (2)	8 (3)	22 (7)	6 (2)	29 (5)	4.93	14 (2)	4.52
Gastroenteritis	15 (5)	11 (4)	5 (2)	10 (3)	20 (3)	3.36	21 (4)	6.79
Dizziness	15 (5)	3 (1)	9 (3)	5 (2)	24 (4)	4.05	8 (1)	2.58
Haemorrhoids	16 (6)	3 (1)	4 (1)	2 (<1)	20 (3)	3.36	5 (<1)	1.61
Injection site pruritus	16 (6)	0	7 (2)	0	23 (4)	3.86	0	0.00

The CAB LA + RPV LA group is listed as Q4W IM. For study 201584, CAR = ABC/DTG/3TC
3TC: lamivudine; ABC: abacavir; CAB: cabotegravir; CAR: current antiretroviral regimen; DTG: dolutegravir; LA: long acting; RPV: rilpivirine;
Source: Vocabria EPAR[13]

Appendix B Virologic suppression at Week 48 in comparable studies

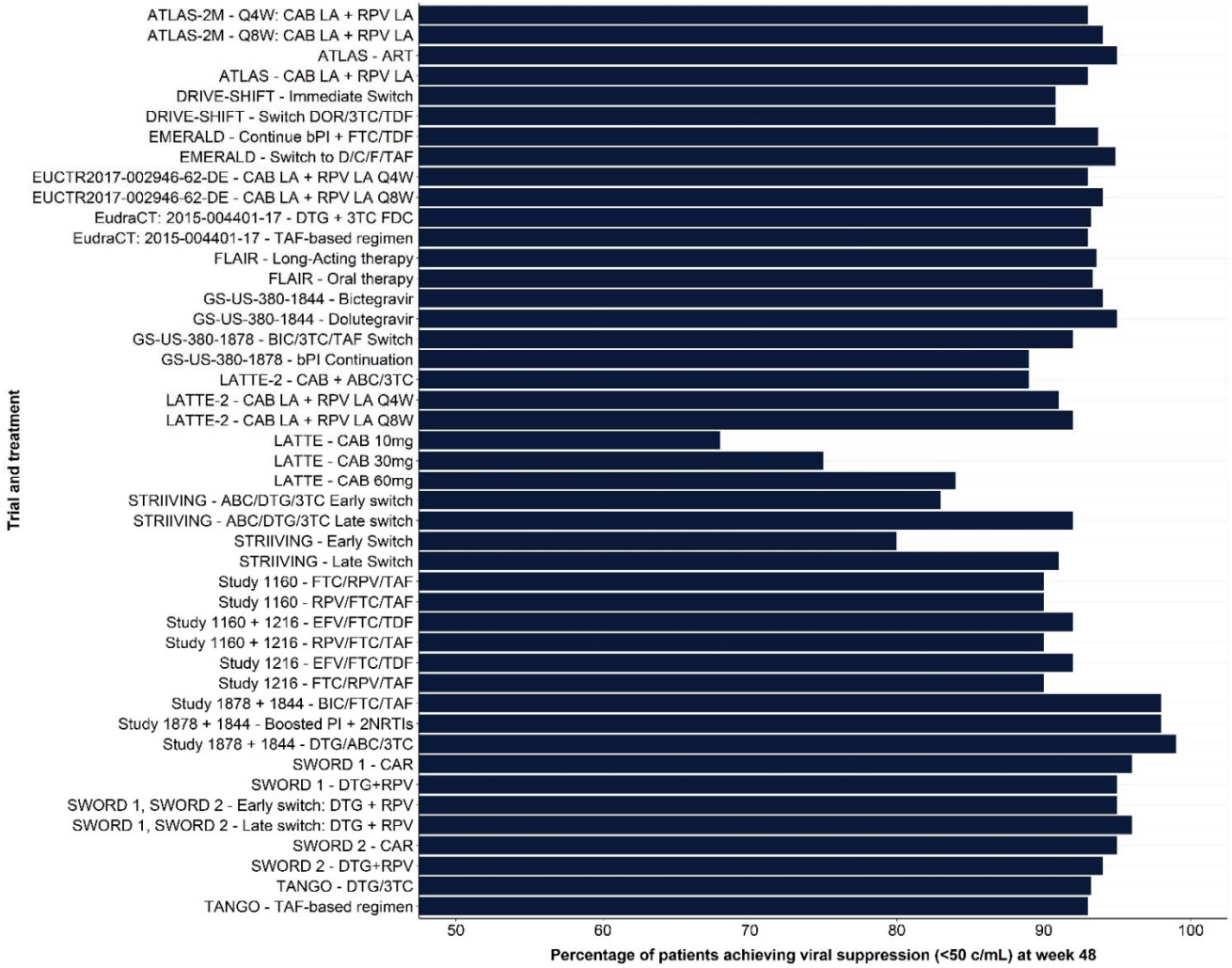

Figure 1 Virologic suppression at Week 48 from relevant studies in the SLR (Reproduced from CS Appendix D, Figure 3).

Appendix C Additional information on SF-6D analysis

Protocol: 209522
Population: Intent-to-Treat Exposed

Table 1.5
Summary of SF6D Score by Visit Baseline, Week 24 and Week 48
(by Missing and Non-Missing Covariates)

Subgroup	Category	Treatment	N	Analysis Visit	n	Mean	SD	Median	Q1	Q3	Min.	Max.
Missing Covariate(s)	No	Q4W	591	Baseline	556	0.832	0.1275	0.863	0.723	0.922	0.48	1.00
				Week 24	535	0.836	0.1363	0.863	0.723	0.922	0.44	1.00
				Week 48	500	0.839	0.1353	0.863	0.723	0.922	0.45	1.00
		CAR	591	Baseline	561	0.827	0.1241	0.859	0.723	0.922	0.51	1.00
				Week 24	546	0.816	0.1369	0.859	0.669	0.922	0.43	1.00
				Week 48	548	0.821	0.1349	0.859	0.708	0.922	0.38	1.00
	Yes	Q4W	591	Week 24	37	0.799	0.1237	0.801	0.695	0.922	0.54	1.00
				Week 48	44	0.848	0.1339	0.863	0.723	1.000	0.59	1.00
		CAR	591	Baseline	2	0.961	0.0552	0.961	0.922	1.000	0.92	1.00
				Week 24	20	0.825	0.1693	0.922	0.674	1.000	0.53	1.00
				Week 48	14	0.822	0.1322	0.860	0.782	0.922	0.54	1.00

Appendix D. Indirect treatment comparison - HTA assessment in Germany

Tabelle 1: Ergebnisse der Meta-Analyse für Viruslast < 50 Kopien/ml zu Woche 48 aus RCT für indirekte Vergleiche

	Relatives Risiko CAB+RPV Q1M vs. CAR [95% KI], p-Wert
[redacted]	
Modell mit festen Effekten [fixed effects]	[redacted]
Modell mit zufälligen Effekten [random effects]	

Abkürzungen: CAB = Cabotegravir, RPV = Rilpivirin, Q1M = einmal monatlich, CAR = current antiretroviral regimen, KI= Konfidenzintervall

Tabelle 2: Ergebnis des indirekten Vergleichs für Viruslast < 50 Kopien/ml zu Woche 48

	Relatives Risiko [95%-KI] p-Wert
CAB+RPV Q2M vs. CAB+RPV Q1M[a]	[redacted]
CAB+RPV Q1M vs. CAR[b]	[redacted]
indirekter Vergleich: CAB+RPV Q2M vs. CAR	[redacted]

[a] Ergebnis der Studie ATLAS-2M
[b] Ergebnis der Meta-Analyse der Studien FLAIR und ATLAS

Abkürzungen: CAB = Cabotegravir, RPV = Rilpivirin, Q2M = einmal alle zwei Monate, Q1M = einmal monatlich, CAR = current antiretroviral regimen, KI = Konfidenzintervall

Tabelle 3: Ergebnisse der Meta-Analyse für Viruslast ≥ 50 Kopien/ml zu Woche 48 aus RCT für indirekte Vergleiche

	Relatives Risiko CAB+RPV Q1M vs. CAR [95% KI], p-Wert
[redacted]	
Modell mit festen Effekten [fixed effects]	[redacted]
Modell mit zufälligen Effekten [random effects]	[redacted]
Abkürzungen: CAB = Cabotegravir, RPV = Rilpivirin, Q1M = einmal monatlich, CAR = current antiretroviral regimen, KI= Konfidenzintervall	

Tabelle 0-4: Ergebnis des indirekten Vergleichs für Viruslast ≥ 50 Kopien/ml zu Woche 48

	Relatives Risiko [95%-KI] p-Wert
CAB+RPV Q2M vs. CAB+RPV Q1M[a]	[redacted]
CAB+RPV Q1M vs. CAR[b]	[redacted]
indirekter Vergleich: CAB+RPV Q2M vs. CAR	[redacted]
[a] Ergebnis der Studie ATLAS-2M [b] Ergebnis der Meta-Analyse der Studien FLAIR und ATLAS Abkürzungen: CAB = Cabotegravir, RPV = Rilpivirin, Q2M = einmal alle zwei Monate, Q1M = einmal monatlich, CAR = current antiretroviral regimen, KI = Konfidenzintervall	

Tabelle 0-5: Ergebnisse der Meta-Analyse für unerwünschte Ereignisse bis Woche 48, die zum Therapieabbruch geführt hatten, aus RCT für indirekte Vergleiche [AEs leading to discontinuation]

	Relatives Risiko CAB+RPV Q1M vs. CAR [95% KI], p-Wert
[redacted]	
Modell mit festen Effekten	[redacted]
Modell mit zufälligen Effekten	
Abkürzungen: CAB = Cabotegravir, RPV = Rilpivirin, Q1M = einmal monatlich, CAR = current antiretroviral regimen, KI= Konfidenzintervall	

Tabelle 0-6: Ergebnis des indirekten Vergleichs für unerwünschte Ereignisse bis Woche 48, die zum Therapieabbruch geführt hatten [AEs leading to discontinuation]

	Relatives Risiko [95%-KI] p-Wert
CAB+RPV Q2M vs. CAB+RPV Q1M[a]	[redacted]
CAB+RPV Q1M vs. CAR[b]	[redacted]
indirekter Vergleich: CAB+RPV Q2M vs. CAR	[redacted]
[a] Ergebnis der Studie ATLAS-2M [b] Ergebnis der Meta-Analyse der Studien FLAIR und ATLAS Abkürzungen: CAB = Cabotegravir, RPV = Rilpivirin, Q2M = einmal alle zwei Monate, Q1M = einmal monatlich, CAR = current antiretroviral regimen, KI = Konfidenzintervall	

Appendix E. ERG's response to issue #9

The ERG appreciates now having been provided with a more complete explanation of how assumptions regarding adherence are implemented in the model, regarding persons with HIV with suboptimal adherence to oral ARTs having an increased probability of experiencing viral rebound in comparison to persons with (near) optimal adherence. In addition, the company consulted additional clinical expert opinion in relation to estimates of lifetime adherence to oral ARTs and the link between adherence and treatment efficacy.

The implementation of the link between adherence and efficacy (i.e. viral suppression) in the model is twofold:

1. for persons who switch to a subsequent line of oral ART treatment due to virological failure, the probability of achieving viral suppression is reduced using the adjustment factor that is based on the assumed linear relationship between adherence and viral suppression (Ross et al.), and

2. for all persons receiving oral ARTs, including in the first treatment line as a comparator to CAB LA + RPV LA, the probability of experiencing viral rebound (followed by a treatment discontinuation and switch in the same month) is increased using the same adjustment factor. For the second aspect, the company has used two different approaches for the first year and subsequent years of treatment. For the first year, a monthly probability of discontinuation due to viral rebound is estimated based on the difference between 48-week viral suppression as observed in the trial (injections) and 48-week viral suppression as assumed to occur with oral treatment (i.e. because of reduced adherence in comparison to the trial), where the latter was calculated by multiplying the trial results with the adjustment factor mentioned earlier. For the subsequent years a simpler approach was used by dividing the probability of viral rebound in the first 48 weeks as observed in the trial by the adjustment factor.

The additional clinical expert opinion consulted by the company indicated that whilst rates of both viral suppression and adherence can fluctuate, both are high overall in the UK. In addition, clinical experts expressed concerns about the generalisability of the data used to estimate the linear relationship between adherence and viral suppression (Ross et al) to the current context and considered the application of a linear relationship to be an over-simplification. The population lifetime average adherence was estimated at 80 – 90% and the 'tipping point' below which viral suppression is more significantly impacted was perceived to be around 70% adherence.

In summary of the issues raised by the company, the ERG and the clinical experts, the following aspects regarding adherence are surrounded by substantial uncertainty:

- The value to appropriately represent an estimate of average lifetime adherence in the UK.
- The functional form of the relationship between adherence and viral suppression.
- The generalizability of the data that was used to estimate the relationship between adherence and viral suppression to the current context.
- The use of an estimate of adherence based on a dichotomous definition of adherence (i.e. a proportion of patients meeting a pre-defined cut-off value) as an input into a relationship

between adherence based on a continuous definition (i.e. an average of adherence at the individual level) and viral suppression.

In the ERG report, the ERG preferred to use an estimate of 89.9% adherence by Sherr et al., 2010 that is based on a definition of non-adherence as persons with HIV having missed two or more doses of oral ART in a recall period of 7 days. This value equates to a cut-off value for adherence of 71% (i.e. patients are considered adherent if they take their oral medication according to prescription at least 71% of the time) and represents a level of suboptimal adherence at which the ERG felt more confident to assume that viral suppression would indeed be reduced and treatment might be discontinued. The perceived tipping point of 70% that was indicated by clinical experts confirms the plausibility of that assumption.

Upon reconsideration of the implementation of adherence assumptions in the model the ERG realises that a more appropriate input for the estimated relationship between adherence and viral suppression is one that is based on an estimate of average adherence at the individual level. Using an additional figure reported by Sherr et al. of 21% persons with HIV having missed one or more doses of oral ART in a recall period of 7 days (which equates to a cut-off value of 86%) and assuming that those persons who missed 2 or more doses on average missed 2.5 doses (which equates to a cut-off value of 64%), the average adherence in that study can be estimated as: (0.21 – 0.101) * 86% + 0.101 * 64% + (1 – 0.21) * 100% = 95% adherence. However, the ERG agrees with the company that the use of Sherr et al., 2010 as an estimate of lifetime adherence is problematic due to the short recall period that was used in that study.

The SWEET study by Cooper et al., 2011 that the company used for their base case analysis indicates an estimate of 74.4% of patients being adherent at the predefined cut-off value of 95%, that was assessed at 48 weeks post treatment initiation. Assuming that patients who meet the 95% cut-off value have an adherence of 95% and assuming an adherence of 64% (corresponding to having missed on average 2.5 doses per week; see above) for those who are considered as non-adherent, the average adherence in that study can be estimated as: 0.744 * 95 + 0.256 * 64 = 87%. If non-adherent patients on average have an adherence of 71% (corresponding to having missed on average 2 doses per week), the average adherence is 89%. A limitation to the use of the SWEET study is that missing data were scored as persons who did not meet the cut-off of 95% adherence. Although no information is available on the extent of missing data in the SWEET study, it appears that the largest number of patients becoming non-adherent or having missing data occurs in the first 4 weeks of the 48-week study period. As such, a more representative estimate of average lifetime adherence could perhaps be estimated by the number of persons who were adherent at 48 weeks divided by the number of persons who were still adherent at 4 weeks. This approach results in 91% of persons meeting the cut-off value of 95% and combined with the assumption that non-adherent patients have adherence levels of either 64% or 71%, this results in estimates for the average adherence level of 92% and 93%, respectively.

In conclusion, the ERG considers a range of 87% - 93% plausible as an estimate of the average lifetime adherence that is based on a definition that the ERG considers appropriate for use as an input into the estimated linear relationship between adherence and viral suppression. As such, the ERG considers the use of an adherence estimate of 89.9% (i.e. the ERG's preferred value in the ERG report) to be

both plausible and appropriate, though now the ERG arrives at this estimate by the above presented assumptions.

Finally, the ERG notes that the population under consideration is one that consists of persons who have been successful in achieving viral suppression with oral ARTs in the past. Although their adherence may not have been optimal during that time, it obviously was sufficient to achieve viral suppression. It could therefore be argued that there is no specific reason to expect that these patients will become less adherent when switching to a different oral ART. Such a scenario is approximated by assuming 100% adherence (i.e. no reduction) for oral ARTs, the results of which are available in the ERG report.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Long-acting cabotegravir plus long-acting rilpivirine (CAB LA+RPV LA) for the treatment of virologically suppressed patients with HIV-1 [ID3766]

ADDENDUM TO Document B
Base case with revised PAS

July 2021

File name	Version	Contains confidential information	Date
ID3766_CAB_RPV_LA_HIV_Document B_ACIC_RESULTS ADDENDUM	Final	Yes	27/07/2021

1. Background

ViiV Healthcare's original submission to NICE in February 2021 included the following PASLU approved simple patient access schemes:

Table 1: Originally submitted prices

	Cabotegravir	Rilpivirine
Previously submitted prices	List: • 30mg x 30 film coated tablets: £638.57 • Prolonged release suspension for injection: £1197.02 Fixed net prices: • 30mg x 30 film coated tablets: £[redacted] • Prolonged release suspension for injection: £[redacted] (every two months)	• Proposed list price: £480.66 • Proposed discount: [redacted] from proposed list price (=net price of £[redacted])
i.e. • List price of £1677.68 for CAB LA + RPV LA • Net price of £[redacted] for CAB LA + RPV LA		

Following Technical Engagement, ViiV Healthcare acknowledges there is some uncertainty in the likely lifetime adherence upside that will be associated with long-acting injectables (versus oral ART). The company base case proposed a lifetime value of suboptimal adherence with oral ART of 25.6% (based on a UK study) whilst the ERG have alternatively proposed 10.1%, a more conservative estimate but one which we believe provides no further certainty. ViiV has submitted a revised net price to PASLU on the basis that it is reasonable to 'meet in the middle' of these values.

We would like to expand upon the reasons for the revised patient access scheme. Adherence is a particularly complex parameter and in order to model it as a single input, significant heterogeneity and variability (both during a single person's lifetime and between individuals with differing circumstances) must be unavoidably oversimplified. It would be impossible to design a model which accurately accounts for and predicts all possible nuances that impact adherence over an individual's lifetime, let alone a population's.

We strongly defend our approach and the study we use to inform this input in the economic model. This was identified systematically and was deemed to be the most relevant of a selection of studies to the UK setting. We of course accept there are alternative sources to

support adherence assumptions, but they all have their limitations and we do not accept that any of them provide more certainty than we have proposed for the population under consideration.

We do however appreciate the decision making implications where imprecise estimates exist. We do not wish to see the Committee distracted by the current framing of this discussion as a debate between two ends of a spectrum; we believe this risks losing the key messages relating to the potential value of this new medicine.

Our revised PAS (submitted to PASLU (on 21/7/2021) aims to maintain a cost-effective proposition and meets the ERG midway in the adherence assumption, a concession we believe is worthwhile in order to support a more holistic discussion about the value of long-acting injectables for certain people living with HIV.

Table 2: Revised prices

	Cabotegravir	Rilpivirine
Current / new prices (long-acting)	• Prolonged release suspension for injection: Fixed net price of £[redacted] (representing a discount of [redacted]% from list price)	• Final list price: £440.47 (submitted to PASLU on 11/5/2021) • Revised discount: [redacted]% from list price (=net price of £[redacted])
i.e. • List price of £1637.49 for CAB LA + RPV LA • Net price of £[redacted] for CAB LA + RPV LA		

This addendum presents the revised base case results on the basis of the new net price for CAB LA + RPV LA.

2. Summary base case results

The following tables adjust the information presented in the company's original submission on the basis of the revised net price. Note that the table numbers from the original submission are referenced for convenience.

Revised Table 68: CAB LA + RPV LA dosing and acquisition cost (list price exc. VAT)

Dosing	Oral lead in month one, followed by two initial injections in month two and month three, to then subsequently be administered intramuscularly at same visit every two months model cycle (Q2M administration)

Cost at list prices (TBC)	[redacted] per set of injections, with an initial oral lead in treatment of [redacted] per 30 days (cabotegravir [redacted] and rilpivirine £200.27 oral lead in)
Cost per treatment cycle (list prices, TBC)*	[redacted]
Administration costs	£9.25 (Q2M; assumed as detailed in Table 69)
Year 1 Cost (excl. admin costs, TBC)	[redacted]
Year 2 Cost (excl. admin costs, TBC)	[redacted]

*** For daily treatments, 30 day costs are converted to calendar months in the economic model**

Revised Table 69: CAB LA + RPV LA dosing and acquisition cost (net price exc. VAT)

Dosing	Oral lead in month one, followed by two initial injections in month two and month three, to then subsequently be administered intramuscularly at same visit every two months model cycle (Q2M administration)
Cost (including PAS)	£[redacted] per set of injections, with an initial oral lead in treatment of £[redacted] per 30 days (cabotegravir £[redacted] and rilpivirine £200.27 [list] oral lead in)
Cost per treatment cycle*	[redacted]

Administration costs	£9.25 (assumed as detailed in Table 69)
Year 1 Cost (excl. admin costs)	[redacted]
Year 2 Cost (excl. admin costs)	[redacted]

*** For daily treatments, 30 day costs are converted to calendar months in the economic model**

Revised Table 76: Summary of cost-effectiveness base case scenario (net vs. list)

Results in Table 76 present the revised base case under the following assumptions:

- Analysis 1: 10.1% suboptimal adherence in oral ART arm (ERG's 'preferred' assumption)
- Analysis 2: 25.6% suboptimal adherence in oral ART arm (Company's 'preferred' assumption)
- Analysis 3: 17.85% suboptimal adherence: midway point between two prior assumptions

Note that the analyses have also been corrected for a (minor) erroneous risk of transmission between MSM that was included in the original company base case (and noted by ERG during technical engagement).

In these analyses, which compare the revised net price of CAB LA + RPV LA with the list price of the comparator, CAB LA + RPV LA remains a cost-effective treatment option in all three scenarios; CAB LA + RPV LA is estimated to dominate the daily oral therapy (with comparator at list price). The results are driven by gains in QALYs over the time horizon with CAB LA + RPV LA, and cost savings estimated to be [redacted] (analysis 1), £[redacted] (analysis 2) and £[redacted] (analysis 3) per person living with HIV over a lifetime horizon. These results are

based on a comparison with the **revised** net price for CAB LA + RPV LA and the **list** price for the comparator basket.

Table 76: Cost effectiveness of CAB LA + RPV LA under varying assumptions of adherence using revised net price

	Analysis 1: Suboptimal adherence @ 10.1% (ERG assumption)			Analysis 2: Suboptimal adherence @ 25.6% (Company base case)**			Analysis 3: Suboptimal adherence @ 17.85% (Revised company base case)		
	CAB+RPV-Q2M (net price)	**Pooled comparator (list price)**	**Incremental**	**CAB+RPV-Q2M (net price)**	**Pooled comparator (list price)**	**Incremental**	**CAB+RPV-Q2M (net price)**	**Pooled comparator (list price)**	**Incremental**
Life years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)			-£118,334.04			-£70,780.11			-£90,142.35

*NB: these analyses incorporate the revised net price for CAB LA + RPV LA (see Table 2 above)

**Note that the incremental QALYs and LYs differ to CS basecase due to the correction made to the risk of transmission between MSM

3. Detailed base case results (revised net price, Analysis 3)

For the purposes of this addendum, the revised base case aligns with the company's previous submission with the following changes:

- Revised net price of CAB LA + RPV LA
- Lifetime suboptimal adherence (to oral ART) assumption amended to 17.85%
- Model corrected for (minor) erroneous risk of transmission between MSM (noted by ERG during technical engagement)

Detailed results for the base case analyes are included in Table 77 and 78 below. The base case analysis demonstrates that CAB LA + RPV LA is associated with an additional 0.20 LYs (16.62 LYs versus 16.42 LYs) and an additional 0.34 QALYs (12.31 QALYs versus 11.97 QALYs). By contrast, there is lower accrual of costs in the CAB LA + RPV LA arm (£218,780 versus £249,643), so that the resulting incremental cost-effectiveness ratio (ICER) is dominant, at −£90,142.

Table 77. Detailed clinical outcomes from base case analysis

		Base Case Analysis	
		CAB LA + RPV LA	**Comparator**
QALYs gained (discounted)		[redacted]	[redacted]
Time on treatment (years, undiscounted)	Initial modelled line	[redacted]	[redacted]
	Second modelled line	[redacted]	[redacted]
	Third modelled line	[redacted]	[redacted]
	Fourth modelled line	[redacted]	[redacted]
Time in health states (years, undiscounted)	CD4+ <50	[redacted]	[redacted]
	CD4+ 50-200	[redacted]	[redacted]
	CD4+ 200-350	[redacted]	[redacted]
	CD4+ 350-500	[redacted]	[redacted]
	CD4+ >500	[redacted]	[redacted]
QALYs gained (discounted)	CD4+ <50	[redacted]	[redacted]
	CD4+ 50-200	[redacted]	[redacted]
	CD4+ 200-350	[redacted]	[redacted]
	CD4+ 350-500	[redacted]	[redacted]
	CD4+ >500	[redacted]	[redacted]

	Onward Transmission	[redacted]	[redacted]
QALY decrements (discounted)	ADEs	[redacted]	[redacted]
	Treatment Disutility	[redacted]	[redacted]
Incidence of AEs		[redacted]	[redacted]

Table 78. Detailed cost outcomes from base case analysis

		Base Case Analysis	
		CAB LA + RPV LA (net price)	**Comparator (list price)**
Total costs (discounted)		[redacted]	[redacted]
	Health state costs	[redacted]	[redacted]
Costs (£)	Initial modelled line therapy costs	[redacted]	[redacted]
	Initial modelled line administration	[redacted]	[redacted]
	Second and third line	[redacted]	[redacted]
	Fourth modelled line	[redacted]	[redacted]
	AE	[redacted]	[redacted]
	End of Life	[redacted]	[redacted]
	Onward Transmission	[redacted]	[redacted]

4. Probabilistic sensitivity analysis

Results from 1,000 iterations of the model using probabilistic values can be seen in Table 79 and show results that are in line with the deterministic analysis. The scatterplot shows that although there is an expected spread of values, these appear predominantly in the south east quadrant (Figure 15). Importantly, none appear in the northern quadrants indicating that in all iterations run, CAB LA + RPV LA is associated with a cost saving. In very few iterations is CAB LA + RPV LA associated with a loss of QALYs.

Table 79: Probabilistic Sensitivity Analysis Results

	CAB+RPV-Q2M (net price)	**Pooled comparator (list price)**	**Incremental**
Life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]	[redacted]
ICER (£/QALY)			-£97,680.10

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

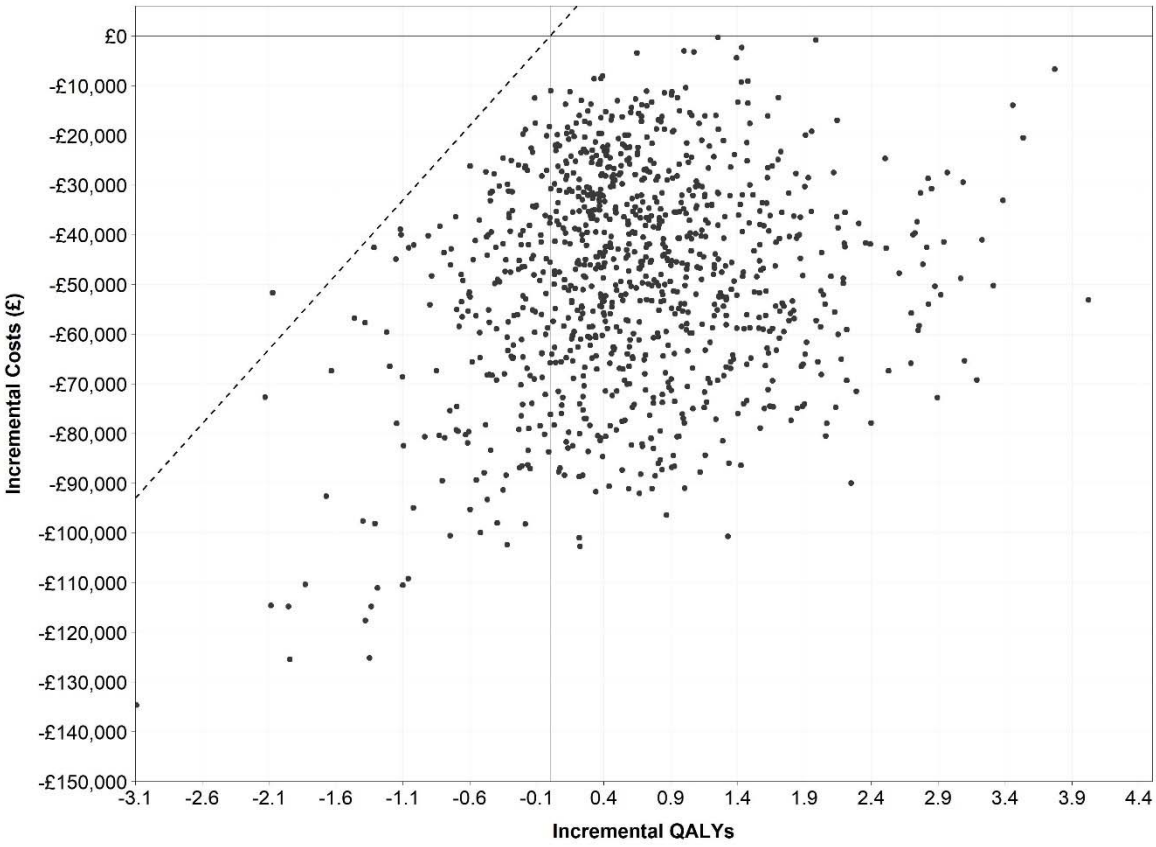

Figure 15: Probabilistic Sensitivity Analysis Scatterplot (CIC)

5. Deterministic sensitivity analysis

DSA results indicate the parameters that influence the results and conclusions of the decision problem to the greatest degree (Table 80 and Figure 16). Adherence to oral ART is the most influential parameter, which is to be expected as this impacts the efficacy of all lines. Indeed, the degree to which efficacy is reduced in the first modelled line for both arms is also influential to results as is the time horizon. It is important to note that while these parameters may be influential, there are no variations in the parameters that result in CAB LA + RPV LA being deemed not cost-effective.

Table 80: Deterministic Sensitivity Analysis Results

Scenario	Parameter variation	Incremental			ICER
		Costs	QALY	LYG	
Adherence modelling	On	[redacted]	[redacted]	[redacted]	-£90,142.35
	Off	[redacted]	[redacted]	[redacted]	-£180,143.61

Variation of adherence to first line ART – treatment arm	Base case – 20%	[redacted]	[redacted]	[redacted]	-£209,915.35
	Base case (100% of trial)	[redacted]	[redacted]	[redacted]	-£90,142.35
Model time horizon (months)	120 months	[redacted]	[redacted]	[redacted]	-£137,223.38
	240 months	[redacted]	[redacted]	[redacted]	-£119,041.42
Variation of adherence to first line ART – control arm	80% of base case	[redacted]	[redacted]	[redacted]	-£60,361.12
	120% of base case	[redacted]	[redacted]	[redacted]	-£167,303.82
Discount, outcomes (%)	Lower (0%)	[redacted]	[redacted]	[redacted]	-£51,713.14
	Upper (6%)	[redacted]	[redacted]	[redacted]	-£122,687.04
Treatment-related disutility (Intervention)	0.005	[redacted]	[redacted]	[redacted]	-£103,621.75
	0.01	[redacted]	[redacted]	[redacted]	-£121,841.24
Costs discount (%)	Lower (0%)	[redacted]	[redacted]	[redacted]	-£115,864.83
	Upper (6%)	[redacted]	[redacted]	[redacted]	-£76,317.07
Age (years)	Lower (80% base case)	[redacted]	[redacted]	[redacted]	-£99,200.62
	Upper (120% base case)	[redacted]	[redacted]	[redacted]	-£82,579.65
Health state utilities	Lower (80% of base case)	[redacted]	[redacted]	[redacted]	-£99,400.98
	Upper (120% of base case)	[redacted]	[redacted]	[redacted]	-£82,461.54
Percentage of cohort that are female (%)	Lower (0%)	[redacted]	[redacted]	[redacted]	-£88,705.95
	Upper (100%)	[redacted]	[redacted]	[redacted]	-£95,436.64
Variation of adherence to	Lower (80% of base case)	[redacted]	[redacted]	[redacted]	-£84,536.85

second 4L therapy line	Upper (120% of base case)	[redacted]	[redacted]	[redacted]	-£94,323.86
Probability of non-virologic discontinuation of CAB+RPV Q2M	Lower (80% of base case)	[redacted]	[redacted]	[redacted]	-£96,250.94
	Upper (120% of base case)	[redacted]	[redacted]	[redacted]	-£84,561.92
Treatment-related utility advantage (Comparator)	Lower (80% of base case)	[redacted]	[redacted]	[redacted]	-£98,407.09
	Upper (120% of base case)	[redacted]	[redacted]	[redacted]	-£83,158.29
Probability of virologic discontinuation of CAB+RPV Q2M	Lower (80% of base case)	[redacted]	[redacted]	[redacted]	-£83,927.30
	Upper (120% of base case)	[redacted]	[redacted]	[redacted]	-£97,259.83
Risk of death (relative to all-cause mortality)	Lower (80% of base case)	[redacted]	[redacted]	[redacted]	-£93,298.64
	Upper (120% of base case)	[redacted]	[redacted]	[redacted]	-£87,628.52
Administration costs associated with injectables	Lower (£5)	[redacted]	[redacted]	[redacted]	-£89,343.71
	Upper (£20)	[redacted]	[redacted]	[redacted]	-£86,947.78
Other resource costs associated with injectables	Lower (£5)	[redacted]	[redacted]	[redacted]	-£89,343.71
	Upper (£20)	[redacted]	[redacted]	[redacted]	-£86,947.78
Treatment disutility (4L 3)	Lower (80% of base case)	[redacted]	[redacted]	[redacted]	-£92,570.72

	Upper (120% of base case)	[redacted]	[redacted]	[redacted]	-£87,838.13
Variation of adherence to second line ART (discontinuation due to viral failure/rebound)	Lower (80% of base case)	[redacted]	[redacted]	[redacted]	-£88,732.70
	Upper (120% of base case)	[redacted]	[redacted]	[redacted]	-£92,206.91
Variation of adherence to second line ART (discontinuation due to non-virologic reasons)	Lower (80% of base case)	[redacted]	[redacted]	[redacted]	-£91,339.17
	Upper (120% of base case)	[redacted]	[redacted]	[redacted]	-£89,255.60
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.					

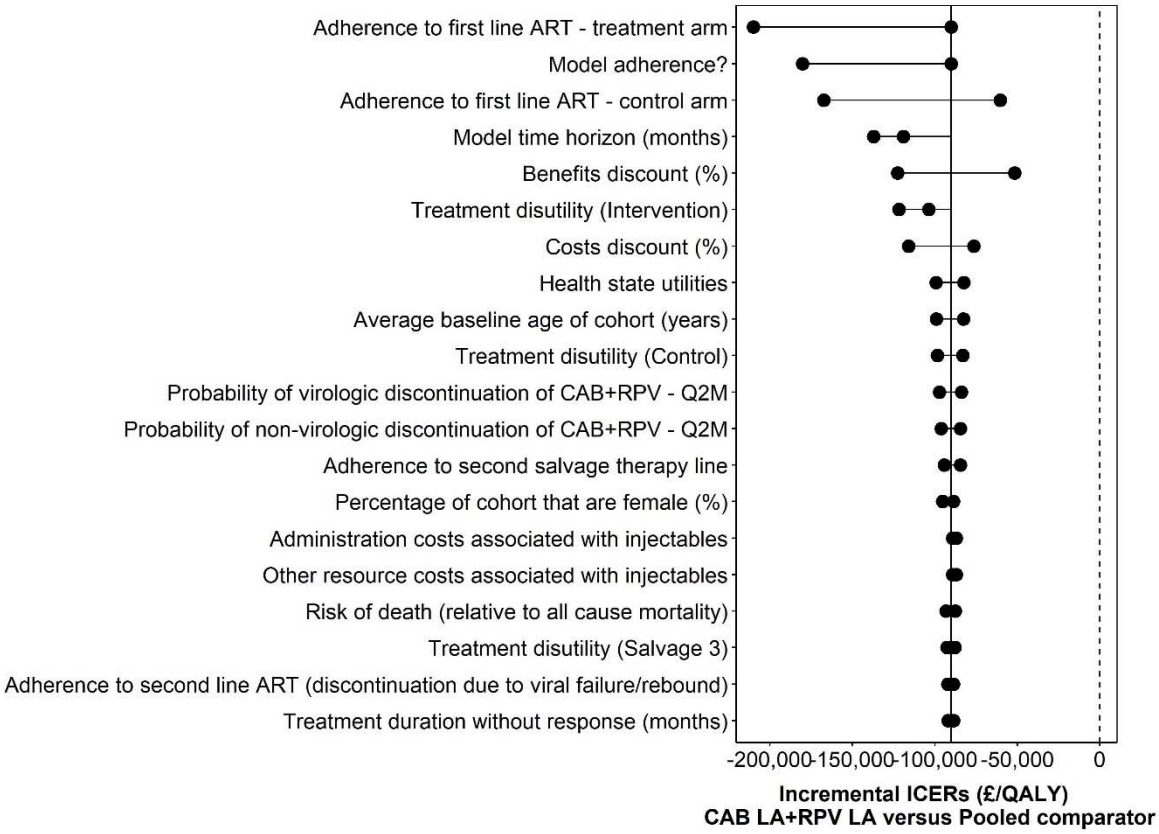

Figure 16 Tornado plot showing results of deterministic sensitivity analysis

6. Scenario analysis

Scenario analysis was undertaken to examine the impact of structural and input assumptions that are necessary when building cost-effectiveness models. In all scenarios examined, while the degree to which there is a utility benefit or cost saving associated with the introduction of CAB LA + RPV LA can change, the decision as to whether it is cost-effective does not change.

i. Alternative efficacy in further lines

The base case assumes that individuals who discontinue into the further modelled lines experience a reduced efficacy when compared with the first modelled line. In addition, it is assumed that individuals who discontinue due to virologic reasons experience worse outcomes than those who discontinue due to non-virologic reasons. The fourth modelled line assumes a decline in efficacy again depending on whether there have been one or more discontinuations due to virologic reasons.

Clinicians advised that this may not be true for all individuals because of the heterogenous nature of the modelled group. In order to address the impact of this assumption, two scenarios were examined where the reason for discontinuation in second and third modelled line efficacy are not assumed to be different; both are assumed to be associated with the efficacy profile that represents those who experience non-virologic discontinuation in the base case.

Where there is no assumed difference in efficacy between those who discontinue for virologic or non-virologic reasons in the second and third modelled line, CAB LA + RPV LA is estimated to be dominant over the pooled comparator (Table 81). There are slightly reduced QALY gains when compared to the base case although there is no change in the decision.

Table 81: Cost-effectiveness results where there is no assumed difference in efficacy associated with reason for discontinuation

	CAB+RPV-Q2M	Pooled comparator	Incremental
Life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]	[redacted]
ICER (£/QALY)			-£146,154.29
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year			

ii. Alternative discounting

In anticipation of potential revisions to the reference case, the results where discounting for cost and benefits is 1.5% is also presented (Table 82). CAB LA + RPV LA is estimated to be cost-effective in this scenario and there is no difference in the decision from the base case analysis.

Table 82: Cost-effectiveness results where discounting is assumed to be 1.5%

	CAB+RPV-Q2M	Pooled comparator	Incremental
Life years	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]	[redacted]
ICER (£/QALY)			-£77,064.13
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year			

iii. Variability in utility advantage associated with CAB LA + RPV LA

Analysis of trial data showed a significant difference in the utility between daily oral ART and CAB LA + RPV LA, which is attributed to treatment modality; there are anticipated to be substantial benefits for individuals using long-acting injectable treatment with CAB LA + RPV LA as opposed to daily oral therapy (see Section B.3.4.2.3). This is supported by the results of a time trade-off (TTO) elicitation study performed to examine potential utility differences between treatment modalities.173 The TTO study, which was conducted in people living with HIV in the UK using relevant health state vignettes, found that in individuals who showed a preference for long-acting injectable treatment over daily oral treatment, the utility advantage was up to 0.06 in some subgroups; thus, the advantage derived from the trial may be conservative. This is expected as generic HRQoL instruments such as the SF-12 (from which the trial-based utility advantage was derived), have limited sensitivity to HIV-specific issues such as stigma. Of note, only individuals who express a desire for long-acting injectable treatment rather than daily oral treatment will switch to CAB LA + RPV LA in clinical practice; those who do not wish for injectable treatment will not form part of the user population.

There are currently no other long-acting injectables available that could be used to validate these utility findings. As such, it is important to examine how the decision might change if the utility advantage were varied, and analyses were therefore carried out to assess this (Table 83). Across all variations of the utility advantage tested, CAB LA + RPV LA remained dominant and no change in the decision with respect to the base case would be warranted.

Table 83: Cost-effectiveness results where utility advantage associated with long-acting injectable treatments is varied

Utility Advantage	Incremental QALYs	Incremental LYs	Incremental Costs (£)	ICER (£)
0.005	[redacted]	[redacted]	[redacted]	-£145,948.10
0.01	[redacted]	[redacted]	[redacted]	-£120,982.05
0.015	[redacted]	[redacted]	[redacted]	-£103,309.77
0.025	[redacted]	[redacted]	[redacted]	-£79,952.01
0.03	[redacted]	[redacted]	[redacted]	-£71,831.65
0.035	[redacted]	[redacted]	[redacted]	-£65,208.69
0.04	[redacted]	[redacted]	[redacted]	-£59,703.93
0.045	[redacted]	[redacted]	[redacted]	-£55,056.21
0.05	[redacted]	[redacted]	[redacted]	-£51,079.85
0.055	[redacted]	[redacted]	[redacted]	-£47,639.17
0.06	[redacted]	[redacted]	[redacted]	-£44,632.76
0.065	[redacted]	[redacted]	[redacted]	-£41,983.28
0.07	[redacted]	[redacted]	[redacted]	-£39,630.73
0.075	[redacted]	[redacted]	[redacted]	-£37,527.84
0.08	[redacted]	[redacted]	[redacted]	-£35,636.88
Base case ([redacted])	[redacted]	[redacted]	[redacted]	-£90,142.35
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year				

iv. Variability in adherence reduction with daily oral treatments

There is no gold standard way to measure adherence, and the variable nature of measuring and reporting makes definitive assessment of adherence difficult. Therefore, results are presented where the reduction in adherence applied to daily oral ART is varied in order to assess the impact of using the base case estimate (Table 84). In all scenarios, the decision as to whether CAB LA + RPV LA is cost-effective is not changed. CAB LA + RPV LA is always associated with cost savings and a utility gain.

Table 84: Cost-effectiveness results where reduction in adherence for daily oral treatment is varied

Adherence reduction	Incremental QALYs	Incremental LYs	Incremental Costs (£)	ICER (£)
5%	[redacted]	[redacted]	[redacted]	-£144,686.65
10%	[redacted]	[redacted]	[redacted]	-£118,779.26

15%	[redacted]	[redacted]	[redacted]	-£99,227.62
20%	[redacted]	[redacted]	[redacted]	-£84,071.10
25%	[redacted]	[redacted]	[redacted]	-£72,054.02
30%	[redacted]	[redacted]	[redacted]	-£62,341.65
35%	[redacted]	[redacted]	[redacted]	-£54,360.72
40%	[redacted]	[redacted]	[redacted]	-£47,705.78
Base case	[redacted]	[redacted]	[redacted]	-£90,142.35
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year				

Summary of sensitivity analyses results

Sensitivity analysis on the deterministic results conclude that results are robust to the structural assumptions and variations in input parameters. In all scenarios run, in variations of input parameters and in the vast majority of probabilistic iterations, CAB LA + RPV LA remains dominant over the pooled comparator.

7. Conclusions

As described previously, the revised patient access scheme acknowledges the challenges to decision making where imprecise estimates exist.

In the context of the net versus list price analyses presented here, the revised discount makes a significant impact on the cost effectiveness of CAB LA + RPV LA relative to the pooled comparator. As can be observed in Table 3 below, costs increase dramatically if no PAS is applied. The [redacted] decrease that has been applied to net price in the latest analysis has resulted an incremental cost reduction of £2,148 due to the long life expectancy of patients taking oral ARTs.

Table 3: Impact of PAS prices (assumptions of Analysis 3)

CAB LA+RPV LA price used	Incremental QALYs	Incremental LYs	Incremental Costs (£)	ICER (£)
[redacted]	[redacted]	[redacted]	[redacted]	£34,910.19
[redacted]	[redacted]	[redacted]	[redacted]	-£83,870.04
[redacted]	[redacted]	[redacted]	[redacted]	-£90,142.35

Addendum: ERG response to updated company base-case

After the Technical Engagement phase, the company submitted the results of an updated version of their base-case model. This updated version was based on the updated Patient Access Scheme (PAS) discount for CAB LA + RPV LA, and was in line with the ERG-preferred version of the model except for the assumed reduction in adherence for oral ART regimens.

As the underlying rationale for changing the assumed reduction in adherence for oral ART regimens, the company indicated that they considered it reasonable to 'meet in the middle' between the ERG's preferred value of 10.1% and the value used in the company's original base-case of 25.6% given that the company increased their PAS discount. Therefore, the updated company base-case used a value of 17.85% for the reduction in adherence.

ERG comment:

The ERG considered the plausibility of the assumed value for the reduction in adherence as the main criterion for selecting an input value for this parameter. As explained in Appendix E in their response to Technical Engagement, the ERG considers a range of 87% - 93% adherence on oral ART regimens plausible. This range of estimates is based on the same study that the company used to inform their original base-case, and refers to adherence on the individual level (i.e. instead of a proportion that meets a pre-defined cut-off value) in order to enhance compatibility with use as an input for the company's estimated linear relationship between adherence (i.e. measured at the individual level) and viral suppression.

As such, the ERG prefers to retain their value of 10.1% reduction in adherence for their base-case. This estimate, as used in the ERG report, is within the range that the ERG considers plausible.