NICE National Institute for Health and Care Excellence

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Cabotegravir and rilpivirine for treating HIV-1 [ID3766]

Lead team presentation

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Company: ViiV Healthcare

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Experts: Duncan Churchill, Cheryl Gowar, Anna Kafkalias, Nadia Naous, Iain Reeves, Alex Sparrowhawk, Adele Torkington, Laura Waters.

Organisations: British HIV Association (BHIVA); HIV Clinical Reference Group, NHSE; HIV Pharmacy Association; Manchester University Foundation Trust; National Aids Trust; UK Community Advisory Board (UK CAB).

Overview of HIV-1

What is HIV?

- A retrovirus that attacks vital cells in the immune system such as CD4+ T cells and macrophages.
- HIV-1 subtype accounts for the majority of infections worldwide.
- Routes of transmission include sexual contact, maternal-infant exposure, and broken skin.
- If untreated, gradual weakening of the immune system makes people vulnerable to infections and some diseases.

What are the current treatments?

- Antiretroviral therapy

What are the goals of treatment?

- For affected individuals: Undetectable = Untransmissable.
- For the NHS: zero HIV transmissions by 2030

How many people are affected?

- 96,200 people in England are living with HIV, of whom 6% were undiagnosed. (2019)
- Some groups are disproportionately affected: gay and bisexual men, people of Black African family background, people from countries with a high community prevalence; people who inject drugs; people with unstable housing.

ART: antiretroviral therapy; HIV-1: Human immunodeficiency virus; PHE: public health England
Sources: Company submission document B, “Disease background” and “Epidemiology”

HIV treatment commissioning structure

What relevant guidance exists for HIV treatments?

- NICE has none to date.
- NHS England's HIV Clinical Reference Group has produced **Best Practice in HIV Prescribing and Multidisciplinary Teams** and this policy guides commissioning:
  - Everybody living with HIV should have access to ART.
  - Services promote principles of informed choice, facilitate shared decision-making, and support concordance with therapies.
  - Supports the sustainability of services by switching appropriate treatments to generic drugs.

What is the source of regional variation in commissioning?

- Banded regimens based on cost.
- Multidisciplinary team decision.

Expert input from Technical Engagement response

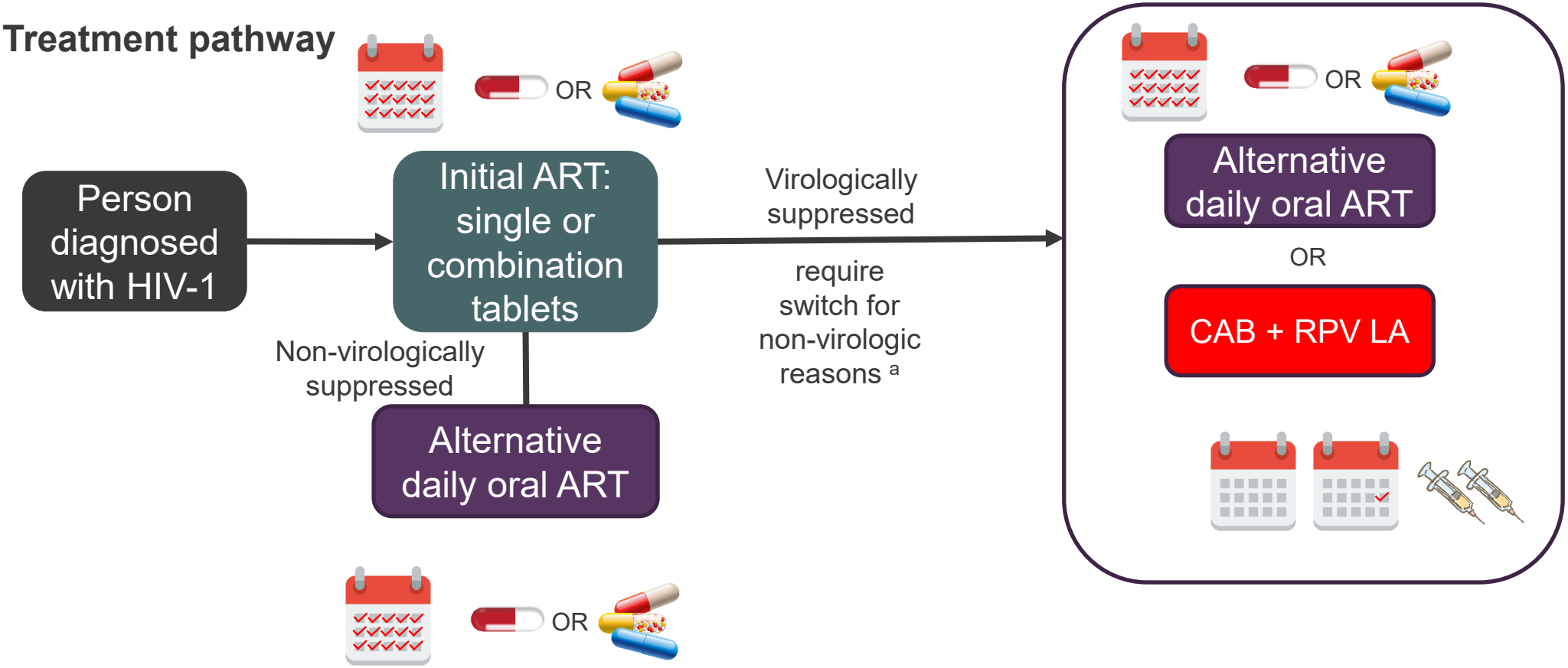
- Pathway of care is well defined. People living with HIV attend services in a commissioned hospital. Regular appointments until they are stable on a treatment routine and viral load drops. People visit 2 or 3 times per year for routine follow-up.
- When there are available treatment options, experts can consult specific regional guidelines based on the availability of generic medicines and commercial in confidence prices.

Treatment options and pathway

Current ART options overview

- •Nucleoside Reverse Transcriptase Inhibitors **(NRTIs)**
- •Non-Nucleoside Reverse Transcriptase Inhibitors (**NNRTIs**)
- •Protease Inhibitors (**PIs**)
- Fusion Inhibitors
- Integrase inhibitors (**INIs or INSTIs**)
- CCR5 antagonists

Treatment pathway



[a] Reasons to consider switching (from British HIV Association [BHIVA]): toxicity or intolerance, desire for once-daily dosing / reduced pill burden, drug–drug interactions, individual preference, cost.

Sources: Based on company submission document B, Figure 1 Anticipated place of CAB LA + RPV LA in the treatment pathway.

Perspectives on living with HIV-1 (1)

What is the unmet need?

> "there is no cure for HIV…people need to take their medication for life. High levels of treatment uptake do not equate to high levels of good health…"

What are the barriers?

> "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."

Stigma impacts every area of life

> "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."

> "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."

Burden of implementation

Everyday practicalities

Managing several health conditions

Perspectives on living with HIV-1 (2)

Trusting health and social care providers

People with HIV rated their GP practice an average 6.9/10, but HIV care team 9.3/10 (PHE, 2020).

“one in ten people with HIV have avoided seeking healthcare when needed due to fears of stigma.”

“[I had a skin infection and] 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”

”a long-term condition in addition to HIV has been diagnosed in more than half [of people living with HIV], with a third living with two or more.”

Advantages of long-acting

Reduction in burden of implementation

Reduction in sharing status

Eligibility and access

“[If I’m] perceived to be “doing well with HIV”… reflect on what “bad” or “very bad” could look like.”

“HIV population in England want to see the commissioning of the technology”

Professional perspectives (1)

What is the unmet need?

"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."

What are the barriers?

Need to bring people to multidisciplinary teams for discussion especially in complex cases where choice of drug therapy is not straightforward and varies due to individual clinical and non-clinical factors.

"Because it is vital the people living with HIV maintain their medication regime to prevent viral rebound and drug resistance…they must have a good relationship with their HIV clinician to ensure that they are able to take effective and tolerable antiretroviral therapy."

"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."

Stage of life and lifestyle affect suitability of options

More than two in five people with HIV are aged 50 or over.

In the UK 15-24 year olds have the lowest rate of viral suppression at 91% (PHE, 2020).

Complex work or living arrangements.

Professional perspectives (2)

Advantages of long-acting

Reduction in burden of implementation.

“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.”

“antiretrovirals via NG/PEG route, who would prefer injections there could be reduced complications of not requiring these tubes.”

Eligibility and access

“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.”

“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.”

“Real world data…will be reflective of experienced patients who struggle with oral therapy for many reasons.”

Cabotegravir and rilpivirine (Vocabria and Rekambys, ViiV Healthcare)

Mechanism of action

Cabotegravir (CAB) long acting (LA) + Rilpivirine (RPV)(LA) is a 2-drug intramuscular injectable regimen.
CAB: Integrase strand transfer inhibitor (INI). Blocks strand transfer step of retroviral deoxyribonucleic acid (DNA) integration.
RPV: Diarylpyrimidine non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV. Non-competitive inhibition of HIV-1 reverse transcriptase.

Marketing authorisation

CAB + RPV in combination: treatment of HIV 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.

Dosage and Administration

	Oral lead-in	Initiation injections (1 month apart)	Continuation injections (2 months apart)
Drug	During Month 1 (at least 28 days)	Month 2 and Month 3	Month 5 onward
CAB	30 mg once daily	600 mg (3mL)	600 mg (3mL)
RPV	25 mg once daily	900 mg (3mL)	900 mg (3mL)

Price

Oral CAB: 30 x 30 mg tablets; £638.57 (ex VAT) (month 1) List price

Oral RPV (Edurant): 30 x 25 mg tablets; £200.27 (ex VAT) List price

CAB LA: 600 mg vial in 3 mL; £1,197.02 (ex VAT) List price

RPV LA: 900 mg vial in 3mL; £440.47 (ex VAT) List price

Year 1 cost: £10,676.01 List price Year 2: £9,824.94 List price

INI: Integrase inhibitor NNRTI: Non-nucleoside reverse transcriptase inhibitor Sources: Company submission document B, Table 2 “Technology being appraised”.

Decision problem

	Final scope	Company submission	Rationale for difference
Population	Adults with HIV-1 infection, virologically suppressed, on a stable regimen and who have not shown prior virological failure due to drug resistance to INIs	Adults, virologically suppressed (HIV-1 RNA <50 copies /ml) on a stable ART 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 intramuscular injections with oral lead-in therapy		N/A
Comparator	ART (established clinical management such as an INI)	A basket of ART used as switch regimens for virally suppressed people living with HIV who are eligible for a switch to CAB LA + RPV LA	ART for people with HIV who are most likely to benefit from a long-acting therapy
Outcomes	Maintenance of virological suppression, CD4+ T-cell levels, treatment-emergent resistance, adherence to treatment regimen, mortality, comorbidities, adverse events (including inflammation), and health-related quality of life	As NICE scope excluding comorbidities and adding preference & satisfaction for long-acting regimen	Treatment-related comorbidities are no longer an important feature of treatment and do not generally feature in treatment decision-making

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ART: antiretroviral therapy INI: Integrase inhibitor NNRTI: Non-nucleoside reverse transcriptase inhibitor Sources: Company submission document B, Table 1.

Treatment options and pathway

Current ART options overview

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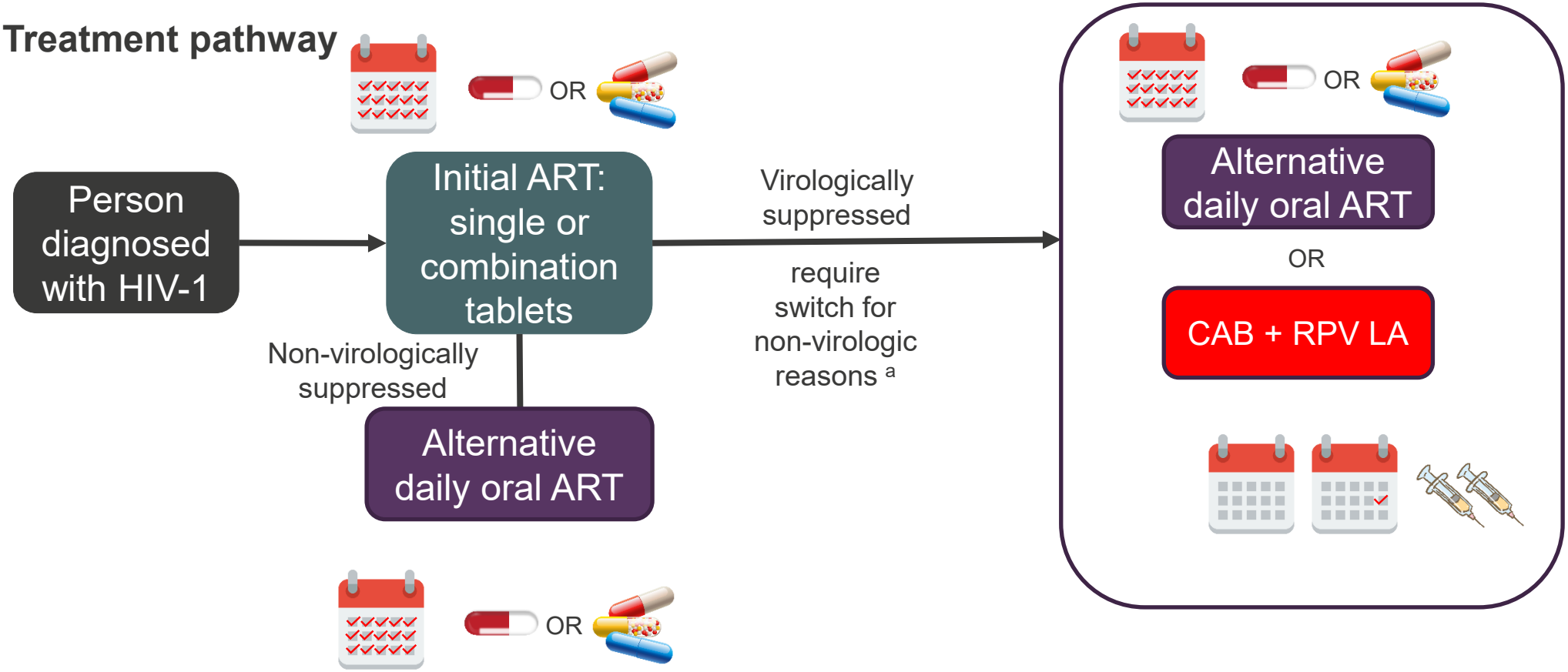
Treatment pathway



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Sources: Based on company submission document B, Figure 1 Anticipated place of CAB LA + RPV LA in the treatment pathway.

Overview of key CAB LA + RPV LA clinical trials

	ATLAS	FLAIR	ATLAS-2M
Phase	3	3	3b
Design	Non-inferiority	Non-inferiority	Non-inferiority
Setting	North America, South America, Australia, Europe, Asia, Africa	North America, Europe, Asia, Africa	North America, South America, Australia, Europe, Asia, Africa
Population	Virologically suppressed adults on ART	Virologically suppressed adults prior CAB LA + RPV LA	Virologically suppressed adults on ART
Intervention	CAB LA + RPV LA monthly	CAB LA + RPV LA monthly	CAB LA + RPV LA every two months
Comparator	Current ARTs (2 NRTIs + INSTI, NNRTI or PI)	ABC/DTG/3TC single-tablet regimen (Triumeq)	CAB LA + RPV LA monthly
Duration in weeks	52	100	• 100 ATLAS monthly • 96 after induction
Primary outcome	Proportion of participants with HIV-1 RNA ≥50 copies/ml at Week 48		
Used in ITC?	✓ (pooled data)		✓
Supporting evidence	LATTE (phase 2b) , LATTE-2 (phase 2b) and POLAR (phase 2b)		

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Source: ERG report Table 3.4 and company submission document B Table 5.
ABC: abacavir; DTG: dolutegravir; 3TC:lamivudine.

ATLAS-2M study design

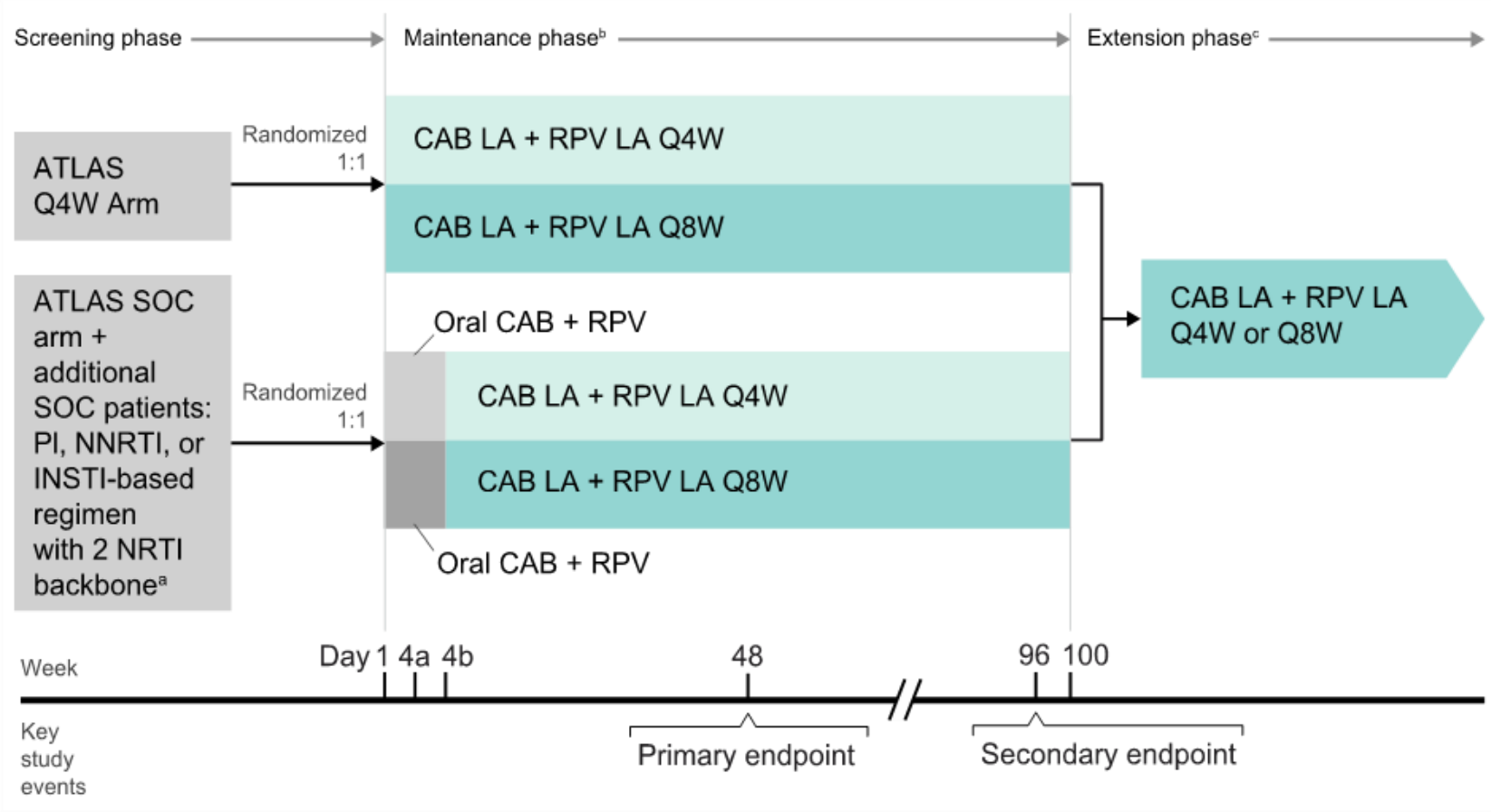
Randomised, multicentre, parallel-group, open-label study to demonstrate non-inferior antiviral activity of CAB LA+ RPV LA every 2 months compared with every 1 month

Population

- Adults with HIV-1 on ART who are virologically suppressed

Key exclusions:

- History of virologic failure
- Evidence of viral resistance based on any resistance-associated major INSTI or NNRTI mutation (except K103N)



Primary Endpoint (Used in economic model)
Non-inferiority in proportion with HIV-RNA ≥50 copies/ml at Week 48

Q4W: every 4 weeks; Q8W: every 8 weeks; SOC: standard of care.
Source: Company submission doc B, clinical effectiveness results and methodology of the relevant trials, Figure 2.

Key efficacy results from pooled ATLAS + FLAIR and ATLAS-2M

Proportions with plasma HIV-1 RNA ≥50 and <50 copies/ml at Weeks 48 and 96

		Pooled ATLAS + FLAIR		ATLAS-2M	
		CAB LA + RPV LA monthly (N=591)	**Current ART** (N=591)	**CAB LA + RPV LA 2 months** (n=522)	**CAB LA + RPV LA monthly** (n=523)
Week 48	**HIV RNA ≥ 50 copies/ml per total assessed (%)**	11/591 (1.9)	10/591 (1.7)	9/522 (1.7)	5/523 (1.0)
	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)
	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)
	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)
	Adjusted difference in proportion (95% CI)		NR		0.8 (-2.8 to 4.3)

Source: ERG report, efficacy results table 3.12

Red box = in model

Plasma HIV-1 RNA <50 copies/ml at Week 48 similar between long acting injectables (monthly) and ART (pooled ATLAS and FLAIR) and between different regimens in ATLAS- 2M with a non inferiority margin of -10%.

Median CD4+ cell counts did not change from baseline in ATLAS or ATLAS-2M over time.

Indirect comparison of CAB LA + RPV bimonthly versus daily oral ART

- No trial-based comparison between CAB LA + RPV LA bimonthly and daily oral standard of care ART is available, and an indirect treatment comparison (ITC) was therefore required to inform the economic modelling.
- Pooled data from ATLAS and FLAIR and the ATLAS-2M subgroup with no prior CAB LA + RPV LA exposure was included in the analysis.
- Current oral ART is based on ATLAS and FLAIR clinical trials, comprised of 2 NRTIs plus an INSTI, NNRTI or a PI and ABC/DTG/3TC respectively.
- CAB LA + RPV LA bimonthly not statistically different to current ART after 48 weeks across any key efficacy or safety outcome.

Results of the indirect comparison of CAB LA + RPV LA bimonthly relative to current ART

	Odds ratio (95% CI)
HIV-1 RNA <50 copies/mL at Week 48	1.04 (0.49, 2.22)
HIV-1 RNA ≥50 copies/mL at Week 48	1.10 (0.24, 5.03)
No virologic data at Week 48	0.94 (0.40, 2.24)
Discontinuations due to AEs at Week 48	1.49 (0.39, 5.65)
Grade 3–5 AEs (excluding ISR) maintenance phase	1.74 (0.77, 3.92)
Source: Company submission document B, Indirect treatment comparison, table 43	

Also see Issue 5: ERG recommended combining ATLAS and FLAIR in a network meta-analysis

Adverse Events

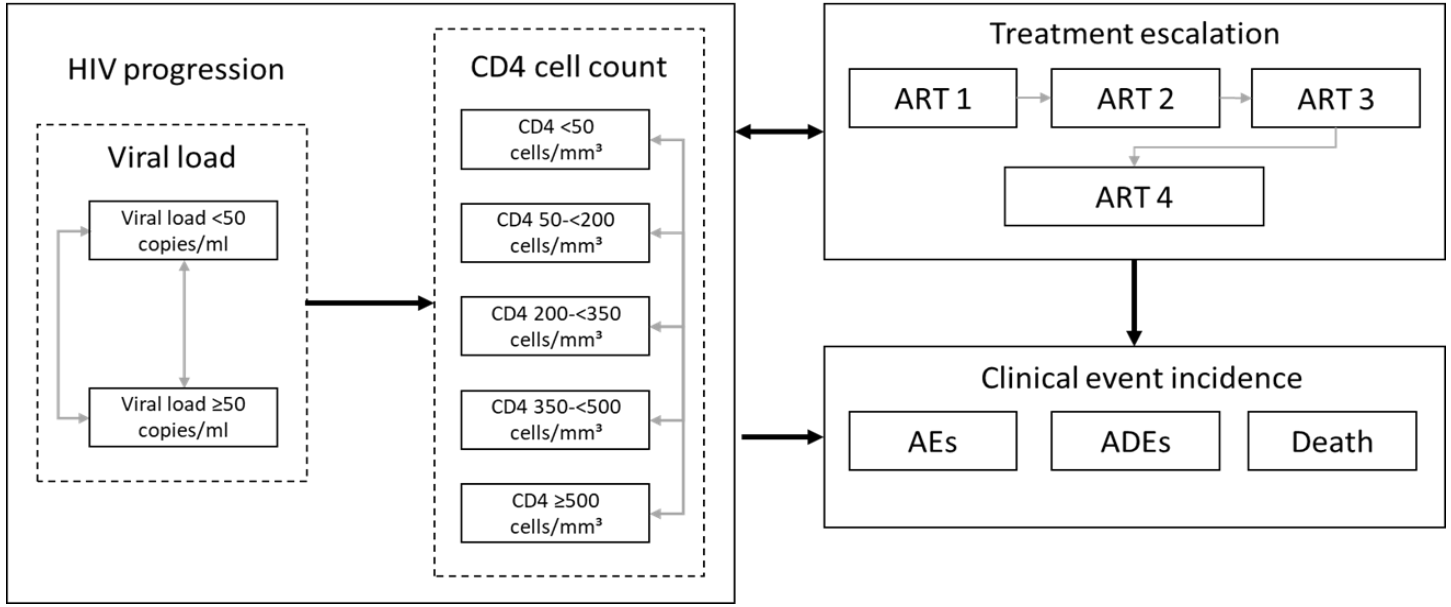
	ATLAS		FLAIR		ATLAS-2M	
Frequency & type of administration	Combination daily oral ART	1 x 4 weeks	Single daily oral ART	1 x 4 weeks	1 x 4 weeks	1 x 8 weeks
						
						
Any adverse events		↑ Higher (pooled with FLAIR)		↑ Higher (pooled with ATLAS)	= Similar in both arms	
Drug-related		↑ Considerably (pooled with FLAIR)		↑ Considerably (pooled with ATLAS)	= Similar in both arms	
Grade 2-5					↑ Slightly	
Injection site abscess						↑ Higher
Overall adverse events (AEs)	Similar proportions of participants had: drug-related AEs –> withdrawal; any serious AEs; drug-related, fatal or drug-related fatal SAEs, in all treatment arms of all studies					
	Most commonly reported CAB LA + RPV LA related AEs were injection site pain, injection site nodule and induration					
	Majority of participants in trials reported injection site reactions (ISRs) related to injection of CAB LA + RPV LA – mostly mild (grade 1 or 2)					

Overview of company's model (1)

Model characteristics

- Deterministic hybrid Markov state-transition model (Decision tree process)
- Health states (HS) based on viral load and CD4+ cell count
- 4 treatment lines (4th line is an absorbing HS in treatment options)
- Monthly cycle lengths
- People with HIV are at risk of experiencing either treatment failure, achieve/ maintain virologic suppression or AE. Potentially leads to viral resistance or discontinuation of therapy.
- Internal decision process in the model can differentiate between those discontinuing for virologic and non-virologic reasons.

Conceptual model schematic

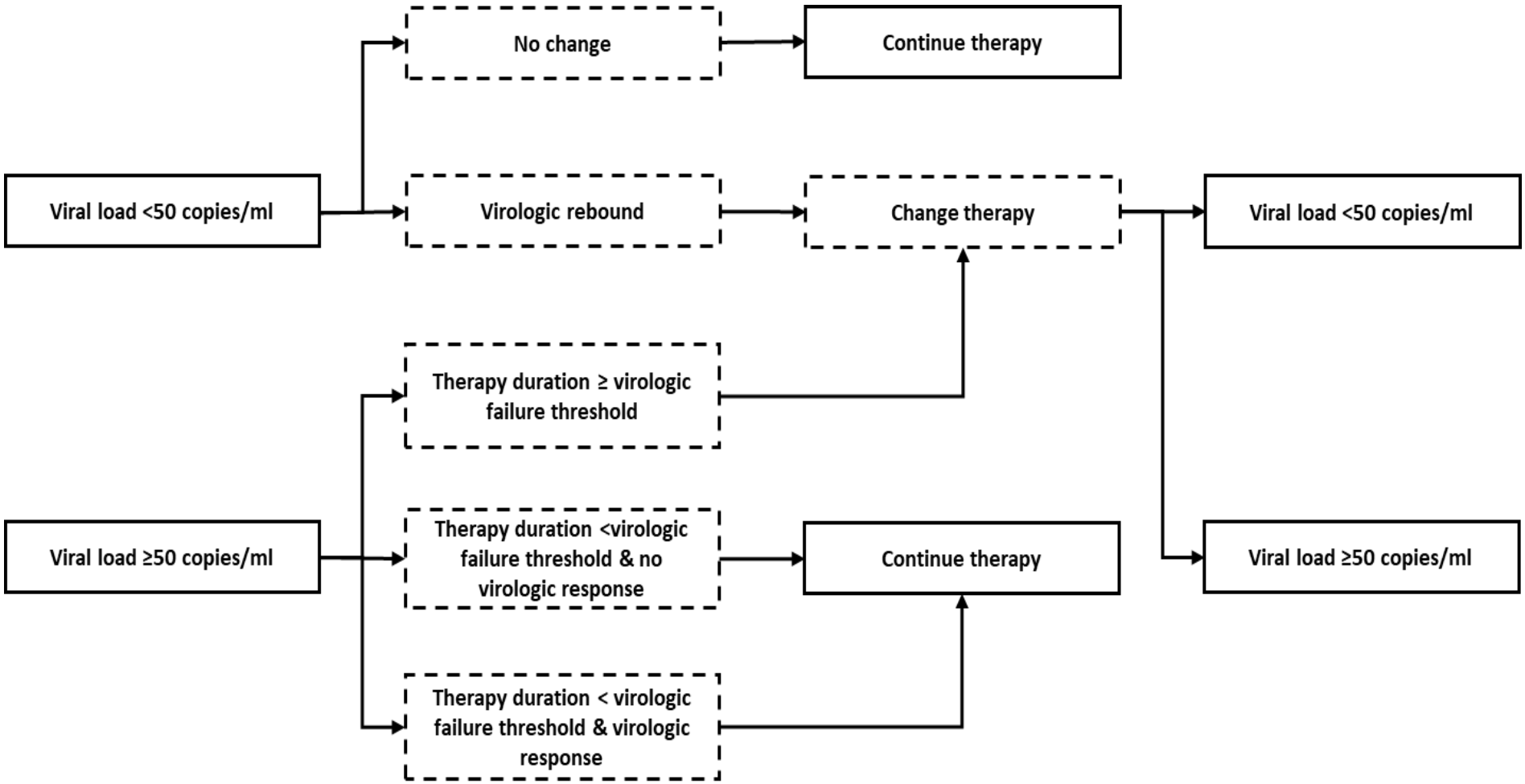


Source: Company submission document B, Model structure, figure 10

AE: Adverse events, ADE: AIDS-defining event, ART: antiretroviral therapy, CD4+: cluster of differentiation 4

Overview of company's model (2)

Treatment switching decision process



The treatment switching decision process is allocated by the decision tree. It transitions individuals to the appropriate subsequent treatment and informs the overall cohort results.

Source: Company submission document b, model structure, figure11 and 12.

Overview of company's model (3)

Clinical efficacy	Driven by virologic response (viral load <50 copies/mL) + immunological response (increase in CD4+ cells)
	No difference in efficacy between intervention and comparator
	Efficacy dependent on therapy line, treatment history (i.e. previous virological failures) and development of resistance
	Key data source: ATLAS-2M, CAB LA + RPV LA bimonthly arm
Discontinuation	Individuals may discontinue treatment due to virologic failure or other non-virologic reasons
Adherence	Reduced adherence is associated with reduced treatment effectiveness, likelihood of viral rebound and resistance to ART
	CAB LA + RPV LA is assumed to be associated with 100% adherence Evidence source: ATLAS 2M, LATTE-2
	Daily oral ART is assumed to be associated with a reduction in adherence of 17.85% Evidence source: (Midway point between ERG's preference 10.1% and company's original base-case 25.6%)

Overview of company's model (4)

AIDS defining events	Clinical consideration that reflect the progression of disease and mortality, cost of disease management and HRQoL. Opportunistic infections due to virus, bacteria, fungi, protozoan, and others
Mortality	Individuals are at risk of all-cause mortality, with health state and the incidence of ADEs resulting in increased rates of mortality
Adverse events	Only injection site reactions – other AEs excluded because assumed equivalent between treatments
Utilities	Trial HRQoL data not stratified by CD4+ cell count so not suitable for modelled health states
	SF-6D utilities obtained from literature based on CD4+ cell count (Kauf et al. 2008)
	Utility advantage of XXX applied to CAB LA + RPV LA derived from ATLAS and FLAIR trials
Costs	Health state and resource use costs from Beck et al. (2011) UK-based cost-effectiveness analysis
	Costs, benefits discounted at 3.5% pa

Issues after technical engagement

Key Issues identified prior to technical engagement	Impact	Status
1) Concerns regarding English language and date limits used in the literature searches		Partially resolved
2) Lack of head-to-head evidence between CAB LA + RPV LA (bimonthly) and ART may restrict the comparability of the interventions		Unresolved
3) Unclear generalisability of the results to people in the UK NHS setting		Unresolved
4) Exclusion of case-control studies: relevant data on safety may have been missed		Partially resolved
5) Pooling of ATLAS and FLAIR. Inappropriate analysis method as there are substantial differences between the two studies		Partially resolved
6) All oral ARTs are assumed to have a similar efficacy		Unresolved
7) Non-significance interpreted as non-inferiority. The ITC was not designed as a non-inferiority analysis with defined non-inferiority margins		Unresolved
8) Cost of basket of comparators		Unresolved
9) Adherence assumptions		Unresolved
10) Reducing or removing the utility advantage for CAB LA + RPV LA has a substantial impact on the incremental QALYs gained		Partially resolved

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Key: Model driver; Unknown impact; Small/moderate impact

Issue 1: Literature searches

Impact =

Background: summary of issue from ERG report

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. Potentially relevant studies might have been missed.

Company technical engagement response

- Searches were updated to cover the period between April 2020 and June 2021.
- The interventions were restricted to the specific comparators that make up the 'comparator basket' in the economic model.
- These updated searches yielded 9 additional studies.
- An updated network metanalysis to include new studies **would not** provide additional support for decision making beyond the ITC for CAB LA + RPV LA bimonthly versus current ART.

Stakeholder technical engagement responses

- Majority of peer reviewed research papers of impact are in English.
- Unlikely that any relevant studies were missed.

ERG views after technical engagement

- Company's rationale for more specific search strategies reasonable (HIV is an extensively studied and well-defined area).
- Fewer search facets would have been preferred, but unlikely to have missed any included studies.

Issue 2: Lack of head-to-head evidence and limited reporting of evidence between CAB LA + RPV LA bimonthly and ART

Impact =

Background: summary of issue from ERG report

- Company did not identify any studies comparing CAB LA + RPV LA bimonthly and ART.
- Lack of head-to-head comparison restricts the comparability of the interventions.

Company technical engagement response

- Agree with the ERG that indirect treatment comparisons (ITCs) cannot replace evidence from head-to-head studies.
- An ITC was conducted to determine the relative efficacy of CAB LA + RPV LA bimonthly vs daily oral ART.
- SOLAR trial (NCT04542070) is currently recruiting and it will assess the antiviral activity and safety of CAB LA + RPV LA bimonthly compared with maintenance of the oral regimen Biktarvy.
- Interim results are expected in the first half of 2022 and analysis of the primary endpoint in the second half of 2022.

Stakeholder technical engagement responses

- The efficacy of CAB LA + RPV LA is high therefore it is uncertain if a direct comparison would be useful.

ERG views after technical engagement

- Key issue remains.

Does the lack of head-to-head evidence limit the comparability of interventions?

Issue 3: Unclear generalisability of the results to people in the UK NHS setting (1)

Impact =

Background: summary of issue from ERG report

- The regimens used in ATLAS and FLAIR studies are not fully representative of currently used ART regimens in the UK NHS setting.
- Can affect generalisability of results for the comparison of ART vs. CAB LA + RPV LA (bimonthly).

Company technical engagement response

- 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 (BHIVA, 2016).
- Company's clinical systematic review pooled different ART arms and all can be considered relatively similar to UK clinical practice.
- Differences in pooled ART composition did not show an impact on clinical outcomes, any differences are not expected to impact on the generalisability of ATLAS and FLAIR to UK.

Stakeholder technical engagement responses

- The studies included UK centres.
- The exact agents are relevant for cost-effectiveness estimates because of the large variation in prescribing due to regional costs and guidelines.
- The majority of individuals will take an NRTI as backbone and an NNRTI, INSTI or PI like in ATLAS.

ERG views after technical engagement

- 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.

Issue 3: Unclear generalisability of the results to people in the UK NHS setting (2)

Impact =

Company provided additional information in response to technical engagement

Figure 1: Third agents in UK HIV market (England, February 2011)

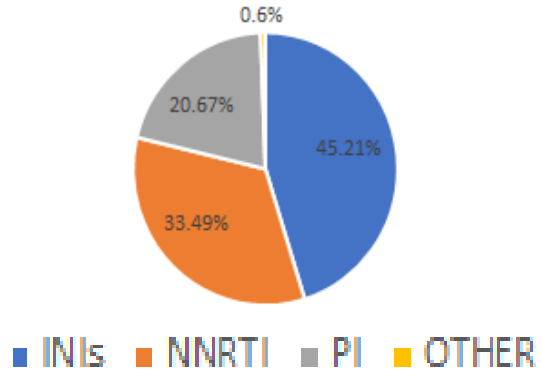
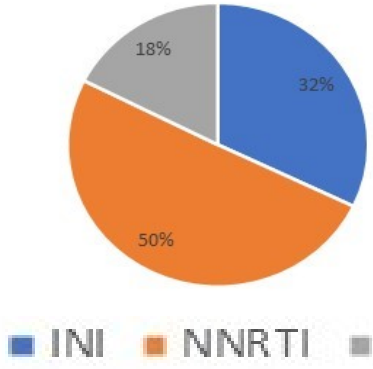


Figure 2: Third agents in ATLAS comparator arm



Company

- Treatments used in England (Figure 1) and comparator arm of ATLAS (Figure 2) broadly comparable and there is a reasonable overlap in class of third agent.
- Differences due to the ATLAS study design.
- ATLAS excluded people treated with Triumeq and had a cap on recruitment of people receiving INI as a third agent.
- Current regimens frequently include dolutegravir which is one of the active ingredients of Triumeq.
- Consulted experts have no reservations about the generalisability of the results of the FLAIR trial to UK practice.

Source: Company response to technical engagement, issue 3, figure1.

Issue 4: Exclusion of case-control studies from the clinical effectiveness (effectiveness and safety) review

Impact = 

Background: summary of issue from ERG report

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.

Company technical engagement response

- 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 lead to different conclusions.

Stakeholder technical engagement responses

- The evidence comes from randomised control-trials which is the “gold standard”.

ERG views after technical engagement

- Would have preferred searches specifically for safety data.
- Given the large HIV literature about safety data it is unlikely anything new would have been identified.

Was it appropriate for the company to exclude case-control studies from the clinical effectiveness evidence?

Issue 5: Pooling of ATLAS and FLAIR

Impact =

Background: summary of issue from ERG report

- Company's ITC combined participants in ATLAS and FLAIR into single larger population for analysis.
- Substantial differences between the two studies, including the comparator treatment and use of a run-in period.
- Studies should have been meta-analysed rather than pooled.

Company technical engagement response

- Pooling was pre-specified and trials were designed with this purpose in mind.
- The alternative approach suggested by the ERG, with ATLAS and FLAIR combined in a meta-analysis within the ITC, was conducted.
- The analyses produced very similar relative risks for viral load.
- Results for adverse events not comparable between the 2 ITCs – ITC using non-pooled data included injection site reactions (ISRs), ITC using pooled data excluded ISRs.

Outcomes from ITC 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	xxx [xxx, x.xx]	1.01 [0.95, 1.06]
Viral load ≥ 50 c/mL at week 48	xxx [xxx, xxx]	1.10 [0.25, 4.90]
AEs leading to discontinuation	xxx[xxx; xxx],	1.48 [0.40, 5.46]

ERG views after technical engagement

- Key issue remains.
- As results are similar, there are no changes to the cost effectiveness model required.
- Noted difference between ITCs for 'AEs leading to discontinuation'.

NICE

Was it appropriate for the company to pool data from ATLAS and FLAIR?

Issue 6: All oral ARTs are assumed to have a similar efficacy

Impact = 

Background: summary of issue from ERG report

- Company assumes all ARTs have similar efficacy.
- ERG satisfied with company's approach, and use of a match-adjusted indirect comparison (MAIC) without a full network meta-analysis (NMA) likely justified.
- But if the efficacy of ART used in the NHS is different to the ART used in ATLAS/FLAIR, then a NMA would be indicated.

Company technical engagement response

- Assumption that oral ART regimens have similar efficacy supported by breadth of non-inferiority studies and by clinical experts consulted by the company.
- ART used in ATLAS/FLAIR trials generalisable to ART used in the NHS, so efficacies would be similar.

Stakeholder technical engagement responses

- All first line therapies in the UK have high efficacy however the success is determined by adherence which is driven by side effects (psychosocial issues contribute).
- General agreement that all oral ARTs have similar efficacy.

ERG views after technical engagement

- Key issue remains.

Issue 7: Non-significance interpreted as non-inferiority

Impact = 

Background: summary of issue from ERG report

- Based on ITC, company concludes CAB LA + RPV LA bimonthly is non-inferior or not different to current ART.
- ITC is imprecise and not designed as non-inferiority analysis with defined non-inferiority margins – non-significance cannot be interpreted as non-inferiority, only imprecision.
- No current evidence that CAB LA + RPV LA bimonthly is inferior to current ART and cannot be certain that CAB + RPV LA bimonthly is non-inferior to current ART.

Company technical engagement response

- Guidance on the interpretation of non-inferiority within the context of ITC methodology is still in development, and there is no single accepted method.
- The ITC used the statistical methodology published by Bucher et al. 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.
- ITC demonstrates equivalent efficacy to current ART and 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.

Stakeholder technical engagement responses

- Unlikely to change the clinical view of the utility of these medicines.

ERG views after technical engagement

- Key issue remains.

Is the company's interpretation of non-inferiority appropriate? Is this likely to impact results?

Issue Issue 8: Cost of basket of comparators (1)

Impact =

Background: summary of issue from ERG report

- The average cost of the current treatments remains uncertain.
- Cost savings associated with CAB LA + RPV LA depend on cost of basket of comparators.
- Not aware of evidence on the treatments currently provided to people who would receive CAB LA + RPV LA if it were available, therefore average cost of comparator remains uncertain.

Company technical engagement response

Summary of treatments included in company's basket of comparators:

- 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 comparators are a basket of those ART most frequently 'switched to' for virologically suppressed people living with HIV, who would be eligible to switch to CAB LA + RPV LA.
- Cost of basket based on simple average of costs of included treatments.
- Costs used in economic evaluation cannot be shown because they include confidential discounts.

Issue 8: Cost of basket of comparators (2)

Impact =

Company technical engagement response

- Those treatments with a share of ≥2.5% (an arbitrary cut-off) were discussed with clinical experts prior to submission.
- Truvada + Tivicay was removed as individuals normally switch away from this regimen rather than into it because there are toxicity concerns.
- Company acknowledges that imprecision remains because the reason for the switches is unknown, and is likely to be critical in the consideration of transitioning to a long-acting regimen.
- 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 but depends on individual characteristics and local practice.
- Cost not an explicit consideration in deriving comparators – some low-cost branded single tablet regimens are included.
- Provided scenario using weighted average based on market share data at clarification (backup slide).

Stakeholder technical engagement responses

- Important to consider that individuals with side effects and tolerability problems, drug-drug interactions/drug resistance, and difficulty in managing oral formulations may take more expensive regimens than considered.

ERG views after technical engagement

- Uncertainty remains whether the current basket of comparators is representative of the treatment options for people living with HIV for whom CAB LA + RPV LA would be considered.

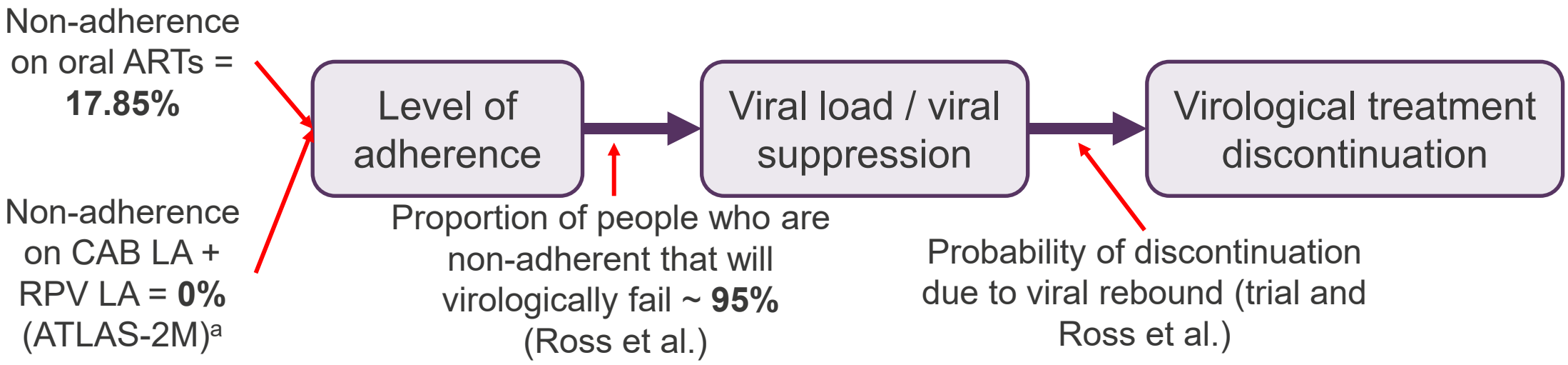
NICE

Is the company's approach to costing the basket comparator appropriate for decision making?

Issue 9: Adherence assumptions (1)

Impact =

Overview of how adherence is implemented in company's model



Background: ERG summary of issue

The link between adherence and efficacy is a twofold:

a) For people who switch to a subsequent treatment line due to virological failure, the probability of achieving viral suppression is reduced using the adjustment factor based on the assumed linear relationship between adherence and viral suppression (Ross et al).

b) For all people using ARTs the probability of experiencing viral rebound is increased using the same adjustment factor.

- Company non-adherence input 17.85%: company updated value following technical engagement. Used mid-point between ERG-assumption (10.1%) and company's original base-case (25.6%)
- ERG non-adherence input is 10.1% from Sherr et al (2010) (based on >2 missed doses in 7 days)
- Uncertainty of the appropriate value to represent average lifetime adherence in the UK

[a] Adherence reported in ATLAS-2M was 98%.

Issue 9: Adherence assumptions (2)

Impact = 

Company technical engagement response

- Adherence input affects viral suppression, which then impacts the monthly probability of viral rebound.
  - Reduced adherence = higher probability of viral rebound (and treatment switching) each month
  - Not immediate, and not experienced by all individuals with less than optimal adherence
- No definitive estimate of long-term adherence to oral ART in UK.
- SWEET study measures adherence with a formal tool (MASRI). It uses a 1-month recall period and in here low adherence is defined as taking less than 95% of oral ART.
  - 25.6% of people in SWEET reported low adherence – used in the original company's model
- Sherr et al (2010) recommended by the ERG uses adherence based on doses missed during a 7 day period – estimates non-adherence in 10.1% of people.
  - Company considers it is a less effective picture of long term adherence patterns due to its short recall period.
- After technical engagement, the company considered it reasonable to adjust its adherence input to a midway value of 17.85% between the ERG's preferred value and the company's original base-case.

Issue 9: Adherence assumptions (3)

Impact = 

Stakeholder technical engagement responses

- RCTs recruit motivated individuals, in ATLAS & FLAIR, participants had to demonstrate good adherence by maintaining an undetectable viral load to get the long-acting drug.
- Literature demonstrate that modern ART do not require very high levels of adherence (>95%) to remain effective.
- The tolerability of drugs and the rate of side effects is an important determinant of adherence.
- Self-reported adherence over-estimates adherence compared to pill count or drug levels in blood so a <95% self-reported adherence may represent a lower true value (Spinelli et al, 2020).
- Oral adherence principles cannot be extrapolated to injectables and in the absence of real-world data it is impossible to predict what the real-life impact of delayed or missed doses will be.

ERG views after technical engagement

- The ERG retains their value of 10.1% reduction in adherence for their base-case.
- ERG agrees that Sherr et al (2010) is problematic for its short recall period.
- A range of 87-93% for average lifetime adherence is plausible (ERG's preferred value 89.9%).
- Uncertainty regarding the appropriate UK estimate for lifetime adherence in the UK.
- Uncertainty about functional form of the relationship between adherence and viral suppression.
- Uncertainty of the generalisability of data used to estimate the relationship between adherence and viral suppression.
- Uncertainty in adherence estimate based on a proportion of people meeting a pre-defined cut off value as an input for average adherence and viral suppression at individual level.

NICE

Is the company's approach to modelling adherence appropriate?
Is the company's or ERG's adherence input most appropriate?

Issue 10: Utility advantage for people taking CAB LA + RPV LA

Impact =

Background: summary of issue from ERG report

- CAB LA + RPV LA has utility advantage of xxx versus ART in ATLAS/FLAIR data.
- Presence/size of utility advantage uncertain due to potential biases in estimate – could favour CAB LA + RPV LA:
  a) Higher drop-out in HRQoL reporting in the CAB LA + RPV LA group versus the ART group
  b) Injection site reactions (ISRs) may have been missed in the HRQoL data collection (N.B. decrement for ISRs not included – assumed to be captured in SF-6D utilities).
- Reducing or removing utility advantage has a substantial impact on the incremental QALYs gained.

Company technical engagement response

- A) Difference not due to drop outs but in the number of participants who had data available for all the necessary covariates in the analysis. ANCOVA model used age, sex and CD4+ as covariates, individuals with missing data on this variables were not included.
- B) HRQoL measured prior to intervention, study physician states that intervention-related adverse events apply to both trial arms. Injection site reactions not likely to have a considerable impact on quality of life due to short duration (median 3 days in ATLAS-2M).
- Utility likely to be underestimated, SF-6D does not captures stigma issues neither lifestyle related benefits.

Stakeholder technical engagement responses

- People affected by HIV-related stigma and less motivated to engage in treatment might be under-represented in the clinical trials population. However, this group might benefit most from injectables.

Issue 10: Utility advantage for people taking CAB LA + RPV LA

Impact = 

ERG views after technical engagement

a) No longer an issue given that the missing data is not due to drop out but to missing covariates.
b)

- ISRs only apply to the CAB LA + RPV LA arm.
- ISRs likely to be under captured in HRQoL data but agrees that it does not have a large impact due to their short duration.
- Model results are sensitive to differences in utility between CAB LA + RPV LA and oral ART.
- No data beyond 48 weeks, unclear whether utility advantage would change over time.
- Lack of evidence on how stigma-related issues and lifestyle-related benefits are captured by SF-12. Therefore, difficult to know whether the benefits are being undervalued.

Is the utility advantage for CAB LA + RPV LA appropriate?

Innovation and Equality considerations

Innovation: Company view

- CAB LA + RPV LA is the first and only alternative to life-long daily ART
- Offers a choice of an injection over daily oral therapy
- Can prevent the consequences of suboptimal adherence to ARTs
- Directly observed administration ensures certainty of adherence

Innovation: Stakeholder's view

- May reduce adherence issues when transitioning from children's services to adult services.
- May reduce stigma in care homes, if staff are not aware of the resident's health status.

Equalities issues

- People living with HIV who also have protected characteristics might benefit by modifying one source of stigma from their lives.
- Long acting may not be suitable for people living with HIV who cannot easily access their specialist HIV clinic and attend an appointment because of their geographical location, work or other commitments.
- Long acting may not be available to homeless people affected by the additive impact of structural inequalities and who struggle with the practicalities of adherence to oral ART.
- In the UK, HIV disproportionately affects gay and bisexual men, people from Black African family backgrounds, and trans people.

Issues after technical engagement

Key Issues identified prior to technical engagement	Impact	Status
1) Concerns regarding English language and date limits used in the literature searches		Partially resolved
2) Lack of head-to-head evidence between CAB LA + RPV LA (bimonthly) and ART may restrict the comparability of the interventions		Unresolved
3) Unclear generalisability of the results to people in the UK NHS setting		Unresolved
4) Exclusion of case-control studies: relevant data on safety may have been missed		Partially resolved
5) Pooling of ATLAS and FLAIR. Inappropriate analysis method as there are substantial differences between the two studies		Partially resolved
6) All oral ARTs are assumed to have a similar efficacy		Unresolved
7) Non-significance interpreted as non-inferiority. The ITC was not designed as a non-inferiority analysis with defined non-inferiority margins		Unresolved
8) Cost of basket of comparators		Unresolved
9) Adherence assumptions		Unresolved
10) Reducing or removing the utility advantage for CAB LA + RPV LA has a substantial impact on the incremental QALYs gained		Partially resolved

NICE

Key: Model driver; Unknown impact; Small/moderate impact

Company and ERG base case preferred assumptions

Base-case preferred assumptions	Company	ERG	ERG justification for change
Reduction in adherence for oral ART	17.85%	10.1%	**Based on the findings from Sherr et al. 2010 which is a UK based study and defined as a proportion of people who self-report having missed two or more doses in a time period of one week.** **The company's input changed from 25.6% to 17.85% to meet the ERG's preferred value at a midpoint.**
ERG report, Table 6.1			

The probability of onward transmission was not identified by the ERG as a key issue and is not a key driver of results.

Cost-effectiveness results

The results are based on the net price for CAB LA + RPV LA and the commercial liaison unit (CMU) prices for the comparator basket (oral ART).

Exact cost-effectiveness results are confidential and will be discussed in private session of the appraisal committee meeting

	ICER (£/QALY)	
	Company	ERG
Oral ART (Basket) vs CAB LA+ RPV LA	£20,000 to £30,000	>£30,000 (deterministic) >£30,000 (probabilistic)
Source: ERG confidential appendix, Tables 1.2, 1.3 and 1.6		

Cost-effectiveness results

Scenario analysis using the lowest and the highest CMU prices.

Exact cost-effectiveness results are confidential, and will be discussed in private session of the appraisal committee meeting

	ICER (£/QALY)	
Oral ART (Basket) vs CAB LA+ RPV LA	Company	ERG
CMU average prices	**£20,000 to £30,000**	**>£30,000**
CMU lowest prices	**>£30,000**	**>£30,000**
CMU highest prices	**£20,000 to £30,000**	**>£30,000**
Source: ERG confidential appendix, Table 1.7 and 1.8		

Scenario analysis: varying adherence reduction for oral ART regimens assumptions

Exact cost-effectiveness results are confidential, and will be discussed in private session of the appraisal committee meeting

Adherence reduction for oral ART regimens	Effect on base case		
	CMU average	CMU lowest	CMU highest
0% (ERG scenario)	>£30,000	>£30,000	>£30,000
10.1% (ERG base-case)	>£30,000	>£30,000	>£30,000
17.85% (company's updated base case)	£20,000 to £30,000	>£30,000	£20,000 to £30,000
25.6% (company's original base case)	£20,000 to £30,000	>£30,000	£20,000 to £30,000
Scenarios were run by the ERG			

Scenario analysis: Combinations of CMU prices and alternative utility advantage values scenario results

Exact cost-effectiveness results are confidential, and will be discussed in private session of the appraisal committee meeting

	ICER (£/QALY)		
	CMU average	CMU lowest	CMU highest
Scenarios based on ERG base case (10.1% adherence assumption)			
xxx utility advantage (ERG base-case)	>£30,000	>£30,000	>£30,000
xxx utility advantage	>£30,000	>£30,000	>£30,000
0 utility advantage	>£30,000	>£30,000	>£30,000
Source: ERG confidential addendum, Table 1.14.			

BACK-UP SLIDES

Switch share by regimen: Market overview for people living with HIV who switch off stable regimen

Brand Name	Generic name	% 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]

Source: Company submission document B, Table 55.

- The table shows the types of ART that people living with HIV typically switch to when changing oral ART regimens.
- The information illustrates the switches captured by market data.