CADTH

CADTH COMMON DRUG REVIEW

Clinical Review Report

CABOTEGRAVIR TABLETS, CABOTEGRAVIR EXTENDED-RELEASE INJECTABLE SUSPENSION, AND RILPIVIRINE EXTENDED-RELEASE INJECTABLE SUSPENSION (VOCABRIA, CABENUVA)

(ViiV Healthcare ULC)

Indication: HIV-1 infection

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

ACCEPT	Chronic Treatment Acceptance Questionnaire
ABC	abacavir
ACO	AIDS Committee of Ottawa
AE	adverse event
ART	antiretroviral therapy
ARV	antiretroviral
ASAAP	Alliance for South Asian AIDS Prevention
AUC	area under the curve
CAB	cabotegravir
CAB + RPV	cabotegravir plus rilpivirine
CART	current antiretroviral therapy
CBR	Community-Based Research Centre
CD4+	cluster of differentiation 4 positive
CDR	CADTH Common Drug Review
CI	confidence interval
CTAC	Canadian Treatment Action Council
CVF	confirmed viral failure
DHHS	Department of Health and Human Services (US)
DTG	dolutegravir
eGFR	estimated glomerular filtration rate
EMHC	Edmonton Men's Health Collective
FDC	fixed-dose combination
HAT-QoL	HIV/AIDS-targeted quality of life
HCV	hepatitis C virus
HIV-1	HIV type 1
HIVTSQs/c	HIV Treatment Satisfaction Questionnaire status/change version
HRQoL	health-related quality of life
ICC	intraclass correlation coefficient
IM	intramuscular
INI	integrase inhibitor
INSTI	integrase strand transfer inhibitor

ISR	injection site reaction
ITT-E	intention-to-treat–exposed
MID	minimal important difference
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NRS	Numeric Rating Scale
OL	open label
PI	protease inhibitor
PIN	perception of injection
PP	per protocol
RCT	randomized controlled trial
RNA	ribonucleic acid
ROC	receiver operating characteristic
RPV	rilpivirine
SAE	serious adverse event
SD	standard deviation
SF-12	Short Form (12) Health Survey
STR	single-tablet regimen
TDF	tenofovir disoproxil fumarate
WDAE	withdrawal due to adverse event
3TC	lamivudine

Drug	Cabotegravir tablets (Vocabria), cabotegravir extended-release injectable suspension, and rilpivirine extended-release injectable suspension (Cabenuva)
Indication	Cabotegravir tablets are indicated, in combination with rilpivirine tablets, as a complete regimen for short-term treatment of HIV-1 infection in adults who are virologically stable and suppressed (HIV type 1 [HIV-1] ribonucleic acid [RNA] < 50 copies/mL) as: • an oral lead-in therapy to assess tolerability of cabotegravir prior to initiating cabotegravir and rilpivirine extended release injections; • oral bridging therapy for missed cabotegravir and rilpivirine extended release injections. Cabotegravir and rilpivirine extended-release injectable suspensions are indicated: • as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in patients who are virologically stable and suppressed (HIV-1 RNA < 50 copies/mL).
Reimbursement request	As per indication
Dosage form(s) and route of administration) and strength(s)	Oral: cabotegravir tablets (30 mg) Intramuscular injection: cabotegravir (600 mg/3 mL, 400 mg/2 mL) and rilpivirine (900 mg/3 mL, 600 mg/2 mL) long-acting suspensions
Health Canada review pathway	Standard
NOC date	February 14, 2020 (anticipated)
Sponsor	ViiV Healthcare ULC

Executive Summary

Introduction

HIV type 1 (HIV-1) is one of the two types of viruses that cause HIV infection and is responsible for the majority of HIV infections worldwide.[1] HIV-1 is transmitted via body fluids such as blood, semen, genital secretions, and breast milk, and most commonly from unprotected sexual intercourse or through sharing contaminated needles and syringes with an infected person.[2] HIV-1 gradually weakens the immune system by selectively destroying cluster of differentiation 4 positive (CD4+) immune cells, thereby compromising the immune system's ability to mount an effective immunological response to opportunistic pathogens over time.[3] In 2017, the reported incidence rate of HIV-1 was 6.5 per 100,000 in Canada, translating to 2,402 newly reported cases per year.[4] Ontario (38.9%) and Quebec (27.9%) accounted for the highest proportion of HIV-1 cases in 2017, while Saskatchewan (15.5 per 100,000) and Quebec (8.0 per 100,000) had the two highest diagnosis rates across the provinces. Of the different demographic and high-risk features, the 30 to 39 year age group, White, males, and gay, bisexual, and other men who have sex with men constituted the highest proportion of reported cases.[4]

People with HIV-1 are primarily treated with antiretroviral therapy (ART), which helps to lower the level of HIV-1 in the body, slow the spread of the virus, and facilitate the function of the immune system.[5] According to the US Department of Health and Human Services (DHHS) Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV, the goals of antiretroviral (ARV) regimens are to: maximally and durably suppress plasma HIV-1 ribonucleic acid (RNA) below detectable limits (< 50 copies/mL); restore and preserve immunologic function (increase CD4+ cell counts); reduce HIV-1–associated

morbidity; prolong the duration and quality of survival; and prevent HIV-1 transmission. For treatment-experienced patients with viral suppression, the DHHS guidelines recommend selecting a new ARV regimen based on the patient's previous ART history, including virologic responses, past ART-associated toxicities and intolerances, resistance test results, drug-drug interactions, and pill burden, in addition to other non-clinical considerations. ART is a lifelong commitment and requires a high degree of adherence.[5] To reduce pill burden and ensure long-term resistance, a number of single-tablet regimens (STR) of two- or three-drug combinations of ARTs have been developed and are currently marketed in Canada.

The objective of this systematic review was to evaluate the beneficial and harmful effects of the cabotegravir plus rilpivirine (CAB + RPV) regimen for the treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA < 50 copies/mL). The CAB + RPV regimen consists of separate once-monthly injections with CAB and RPV preceded by an oral lead-in phase during which oral CAB tablets are taken in combination with RPV tablets (RPV tablets are marketed in Canada as Edurant) for at least 28 days. CAB is an integrase strand transfer inhibitor (INSTI) that inhibits HIV-1 integrase by binding to the integrase active site and blocking the strand transfer step of retroviral DNA integration which is essential for the HIV-1 replication cycle.[6] RPV is a diarylpyrimidine non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. RPV activity is mediated by non-competitive inhibition of HIV-1 reverse transcriptase.[6] CAB tablets are indicated in combination with RPV tablets (marketed in Canada as Edurant) as a complete regimen for short-term treatment of HIV-1 infection in adults who are virologically stable and suppressed (HIV-1 RNA < 50 copies/mL) as:

- an oral lead-in to assess tolerability of CAB prior to initiating CAB and RPV injections
- oral bridging therapy for missed CAB and RPV injections.

CAB and RPV extended release injectable suspensions are indicated:

- as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in patients who are virologically stable and suppressed (HIV-1 RNA < 50 copies/mL).[6]

The Health Canada–recommended dosing for the CAB + RPV regimen consists of three distinct phases:

1. Oral lead-in phase: one CAB 30 mg tablet taken together with one RPV 25 mg tablet
2. Initiation injections of CAB + RPV (600 mg + 900 mg, 3 mL each)
3. Continuation injections of CAB + RPV (400 mg + 600 mg, 2 mL each)

Stakeholder Engagement

Patient Input

Five patient group submissions were received from the following organizations: the Canadian Treatment Action Council (CTAC), the AIDS Committee of Ottawa (ACO), the Alliance for South Asian AIDS Prevention (ASAAP), and a joint submission from four non-profit groups working in sectors of gay and queer men's health with a focus on HIV prevention. Patient perspectives were obtained from a consultation workshop in Toronto, online surveys, and informally from staff and patients through personal experiences and community-based work. The following is a summary of key input from the perspective of the patient groups.

Patients are generally able to manage their symptoms and disease progression; however, they are susceptible to inflammation and noninfectious comorbidities. Patients indicated that stigma, discrimination, and resulting stress are major obstacles to their well-being. The physical and mental state of patients can often be exacerbated by various social determinants of health, including access to treatment, experience of health care professionals in treating patients with HIV-1, and the availability of resources.

Patients noted that their treatments were generally effective at suppressing viral load and resulted in improved health-related quality of life (HRQoL) and ability to engage in daily activities. Adhering to a daily medication is a challenge according to patients, which in part, is attributable to medication fatigue. Instances of treatment-associated side effects and failure to achieve viral suppression despite trying multiple treatments were noted; thus, the patient input emphasized the importance of having the maximum possible treatment options available.

The expectations from CAB + RPV were similar across the five submissions. Patients welcomed the idea of a once-monthly injection, which is expected to reduce stigma by providing patients with more privacy and discretion around living with HIV-1. In addition, patients expected that a reduction in pill burden would improve adherence and consequently improve viral suppression. One patient group included the experience of a patient on CAB + RPV, who reported having fewer side effects, and the ability to be more socially engaged both in the workplace and their private life, which led to improved self-esteem.

The joint submission from ACT, MAX, Edmonton Men's Health Collective (EMHC), and Community-Based Research Centre (CBRC, Vancouver) also brought forward a concern about a lack of service providers and questions about implementation of the CAB + RPV regimen. They wanted to know how the health system will ensure that the service is delivered by properly trained providers.

Clinician Input[1]

There are many available ARV STRs and other ARV combinations currently on the Canadian market that are effective, tolerable, and potentially convenient. There are no major gaps in treatment in terms of tolerability or effectiveness.

The CAB + RPV regimen would likely be most used by patients already doing well on oral therapy who wish to be freed from taking daily oral therapy. Less frequently, but perhaps more importantly, this combination would likely be used as first-line or switch therapy for those with proven or anticipated difficulties with adherence, which may be the result of mental health problems, chaotic lifestyle, and so forth. Undetectable HIV-1 viral load can be used to determine whether a patient is responding to treatment in clinical practice. In addition, patient adherence and satisfaction should be considered when assessing clinically meaningful response to treatment. It would be reasonable to assess treatment response every six months. The discontinuation of injectable CAB + RPV would lead to prolonged suboptimal drug levels in the blood, with the potential for the development of virologic resistance to either component of the therapy and related drugs. As such, discontinuation of this therapy mandates the use of effective alternative (oral) ARV therapy for approximately six months.

[1] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

Overall, the CAB + RPV regimen appears to be an effective, safe, and well-tolerated therapy for HIV-1. The convenience of a monthly injection may be offset by the inconvenience and cost of administering the injections, the need for reasonable adherence at the initiation of treatment (the oral treatment phase), and the care taken with discontinuation, as the risk of developing virologic resistance to the NNRTIs and/or INSTIs would be significant if the injections were stopped and no other therapy provided.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

Two similarly designed phase III trials were included in the review: FLAIR[7] (N = 566) and ATLAS[8] (N = 618). Both were multi-centre, active-controlled, open-label (OL), noninferiority, randomized controlled trials (RCTs) conducted in HIV-1 infected adults. FLAIR enrolled ART-naive patients whereas ATLAS enrolled ART-experienced patients who were on a stable ARV regimen. Patients in both trials initiated the CAB + RPV regimen after viral suppression with ART was achieved. Treatment-naive patients in FLAIR underwent a 20-week induction phase at the beginning of the trial, during which they received abacavir/dolutegravir/lamivudine (ABC/DTG/3TC) or DTG with a non-ABC nucleoside reverse transcriptase inhibitor (NRTI) backbone (among HLA-b5701 positive patients) for 20 weeks. Patients who achieved virologic suppression (HIV-1 RNA < 50 copies/mL) at the end of the induction phase entered the maintenance phase. The ATLAS trial enrolled ART-experienced patients who were on a stable ARV regimen (containing two NRTIs plus an integrase inhibitor [INI], NNRTI, or a protease inhibitor [PI]) and did not have an induction phase; eligible patients directly entered the maintenance phase. During the maintenance phase of both trials, patients were randomized (1:1) to continue their current ART (CART) or were switched to the CAB + RPV regimen. The CAB + RPV treatment regimen in the switch group was implemented in three stages: an oral lead-in period, in which patients received oral CAB + RPV (30 mg + 25 mg) once daily for at least four weeks, followed by intramuscular (IM) initiation injection of CAB + RPV (600 mg + 900 mg), and continuation doses of CAB + RPV (400 mg + 600 mg) every four weeks thereafter. Randomization was stratified by the following factors: sex at birth (both trials), HIV-1 RNA level at induction baseline (FLAIR only), and baseline third agent class (ATLAS only).

The primary efficacy outcome in both trials was the proportion of patients with virologic failure (HIV-1 RNA ≥ 50 copies/mL) at week 48, using the FDA-defined Snapshot algorithm (Missing, Switch, or Discontinuation = Failure; intention-to-treat–exposed [ITT-E] population). The noninferiority margin was set at 6% for the primary efficacy outcome. In addition, the following secondary efficacy outcomes were measured: the proportion of patients that achieved virologic suppression (HIV-1 RNA < 50 copies/mL) as per the snapshot algorithm (with noninferiority margin of –10%), CD4+ cell count over time, and a number of HRQoL end points, including HIV Treatment Satisfaction Questionnaire status and change version (HIVTSQs and HIVTSQc), Perception of Injection (PIN), Chronic Treatment Acceptance Questionnaire (ACCEPT), HIV/AIDS-targeted quality of life (HAT-QoL), Short Form (12) Health Survey (SF-12), and Numeric Rating Scale (NRS). The duration of the maintenance phase was 100 weeks in FLAIR and 52 weeks in ATLAS, following which patients in both trials entered an extension phase and: (a) continued to receive the CAB + RPV regimen; (b) switched to the CAB + RPV regimen from CART; or (c) discontinued from the study (currently ongoing, data not available).

The sponsor conducted a pre-planned pooled analysis of the FLAIR and ATLAS trials, and the data informed the economic analysis in the CADTH pharmacoeconomic report. The individual FLAIR and ATLAS trials were not sufficiently powered for a 4% noninferiority margin as recommended by the FDA for switch trials in HIV-1; the recommended noninferiority margin of 4% was applied to the pooled analysis. Detailed results of the pooled analysis are presented in Appendix 3.

Efficacy Results

The treatment period relevant for this review is the maintenance phase up to week 48, including the oral lead-in and the IM injection period. Accordingly, data for all outcomes are presented from maintenance baseline (i.e., assessments occurring at or after randomization in the maintenance phase).

Overall, the treatment arms in each trial had comparable virologic responses. Virologic failure (HIV-1 RNA ≥ 50 copies/mL at week 48 using the FDA Snapshot algorithm) was seen in 2.1% and 2.5% patients in the CAB + RPV and CART groups in FLAIR, respectively, and 1.6% and 1.0% patients in the CAB + RPV and CART groups in ATLAS, respectively. The between-treatment differences were –0.4% (95% confidence interval [CI], −2.8 to 2.1) and 0.6% (95% CI, −1.2 to 2.5), respectively. In both cases, the pre-specified noninferiority margin of 6% was met, as the upper bound of the 95% CI for the adjusted treatment difference between CAB + RPV and CART was below 6%. Per-protocol (PP) analyses supported the conclusion of noninferiority.

A similar proportion of patients with virologic suppression (HIV-1 RNA < 50 copies/mL at week 48 using the FDA Snapshot algorithm) was also seen in both treatment groups across trials. The proportion of patients with virologic suppression was 94% versus 93% in the CAB + RPV and CART groups, respectively, in FLAIR, and 93% versus 95% between CAB + RPV and CART, respectively, in ATLAS. Treatment differences in FLAIR and ATLAS were 0.4% (95% CI, –3.7 to 4.5) and –3.0% (95% CI, –6.7 to 0.7), respectively. Both trials met the pre-specified noninferiority margin of 10% since the lower limit of the 95% CI of the difference in virologic suppression rate between the two treatment groups was greater than –10%. These findings were consistent in the PP population.

Subgroups of interest in this review included sex at birth, CD4+ cell count, and HIV-1 RNA level prior to suppressive ARV regimen, all of which were assessed in FLAIR since patients in this trial were ART-naive at enrolment. None of the three subgroups showed any statistically significant difference between the treatment groups with respect to virologic failure or virologic suppression. In ATLAS sex at birth did not show any statistically significant difference between treatment groups for virologic failure or suppression.

CD4+ cell counts increased from baseline in all patients, irrespective of treatment arms. The average increase in FLAIR was 40.2 and 79.9 cells/mm^3 from baseline in the CAB + RPV and CART groups, respectively. In ATLAS, the mean change from baseline at week 48 was 9.9 and 19.4 cells/mm^3 in the CAB + RPV and CART groups, respectively. However, between-treatment differences within trials were not assessed statistically.

A number of HRQoL measures were included in both trials. Of these, the assessment of HIVTSQs total score between the treatment groups and the change from baseline in the PIN questionnaire within the CAB + RPV group were part of the pre-specified statistical testing hierarchy. The remaining HRQoL outcomes are discussed in the Results section of this report. The HIVTSQ is a HIV-specific questionnaire that assesses treatment satisfaction in patients with the disease, with higher scores indicative of a greater level of

satisfaction. In both trials, the HIVTSQs total score was comparable between the treatment groups at baseline. The adjusted mean differences in HIVTSQs score at week 44 between the two treatment groups were 0.7 (95% CI, –0.4 to 1.9; P = 0.22) and 5.68 (95% CI, 4.37 to 6.98; P < 0.001) in FLAIR and ATLAS, respectively.

The PIN questionnaire evaluates patients' perception of pain and injection site reactions (ISRs) following injections and was administered only to patients in the CAB + RPV group since the comparator group received oral ARV therapy and therefore was not susceptible to ISRs. The total score for PIN was not calculated; pre-specified statistical testing was performed for the domain of acceptability of ISRs. In both trials, a statistically significant change in the above domain of PIN was found at week 48 from baseline (mean score change from week 5: –0.40 and –0.54 in FLAIR and ATLAS, respectively; P < 0.001 in both cases); however, the P value for FLAIR could not be declared statistically significant due to failing multiple testing sequence in the hypothesis prior. The remaining HRQoL outcomes suggest an improvement in patients' HRQoL associated with CAB + RPV treatment compared with CART or compared with baseline. However, analyses of these statistical comparisons were not controlled for multiplicity. Additionally, a minimum important difference was not found for any of these measures, presenting additional challenges in interpreting the results.

Among other efficacy end points, resistance to the study medications occurred infrequently. Adherence to the planned treatment schedule for CAB + RPV administration was high in both trials (98% of the CAB + RPV injections were administered within seven days of the planned treatment window), with few injections administered outside of the allowable treatment period.

Harms Results

This review focuses on safety results through the maintenance phase, including the oral lead-in and injection periods (safety outcomes specific to the oral lead-in period are summarized in Table 15). Patients in the CAB + RPV group reported more adverse events (AEs) (> 90%) compared with the CART group (range 71% to 80%) across trials. Overall, the most frequent AEs (incidence of ≥ 10% in any group) across the trials included injection site pain, nasopharyngitis, injection site nodule, headache, upper respiratory tract infection, injection site induration, and diarrhea. The imbalance in AEs in the CAB + RPV group was, in part, due to ISRs resulting from the monthly IM injections (overall frequency 86% and 83% in FLAIR and ATLAS, respectively). However, the incidence of non-ISR AEs also occurred at a higher frequency in the CAB + RPV group (87% versus 80% between CAB + RPV and CART in FLAIR, respectively; and 86% versus 71% between CAB + RPV and CART in ATLAS, respectively). This may be explained by the selection of patients in both trials, where patients receiving CART had been on a stable ARV regimen for more than six months (ATLAS) or may have developed tolerance through CART induction treatment (FLAIR), both resulting in a longer exposure to CART compared to CAB + RPV to develop tolerance.

There were no fatal serious adverse events (SAEs) across the trials and the incidence of nonfatal SAEs and withdrawal from the study due to adverse events (WDAEs) was low (≤ 6%) and comparable between the treatment groups. More patients in the CAB + RPV group withdrew from the study, primarily due to ISRs. Two cases of deaths were registered through the duration of the two trials; one case of possible homicide during the induction phase in FLAIR (patients in the CAB + RPV group), and one case of methamphetamine overdose during the maintenance phase in ATLAS (patient in the CART group). Notable

harms identified in the CADTH review protocol included ISRs, depressive disorders, hepatotoxicity, skin reactions, hypersensitivity, bone-related AEs, and renal function. ISRs were reported for the CAB + RPV group only, and were the most frequently reported AEs in patients receiving CAB + RPV. Injection site pain (> 75%), nodules (12% to 16%), and induration (10% to 13%) were the three most common forms of ISR events. The majority of ISRs (88%) were resolved within seven days, and were grade 1 or 2 in severity. In both trials, the incidence of ISRs decreased over time resulting from a reduction in the number of patients reporting pain. These patterns were consistent with the clinical expert's speculation for CAB + RPV injection. The remaining notable safety end points occurred in a small number of patients, or were absent in either group. Laboratory biomarkers remained stable and showed no signs of abnormal patterns over time.

Table 1: Summary of Key Results from Pivotal and Protocol Selected Studies

Outcomes	FLAIR		ATLAS	
	CAB + RPV	CART	CAB + RPV	CART
Virologic failures				
HIV-1 RNA ≥ 50 copies/mL at week 48, n/N (%) (ITT-E population)[a]	6/283 (2.1)	7/283 (2.5)	5/308 (1.6)	3/308 (1.0)
Adjusted difference in proportion, % (95% CI)	–0.4 (–2.8 to 2.1) NI met at 6%		0.6 (–1.2 to 2.5) NI met at 6%	
Reasons for virologic failures, n (%): Data in window not below threshold Discontinued for lack of efficacy Discontinued for other reason Change in background therapy	 2 (0.7) 4 (1.4) 0 0	 2 (0.7) 3 (1.1) 2 (0.7) 0	 1 (0.3) 3 (1.0) 1 (0.3) 0	 1 (0.3) 2 (0.6) 0 0
Virologic suppression				
HIV-1 RNA < 50 copies/mL at week 48, n/N (%) (ITT-E population)[a]	265/283 (94)	264/283 (93)	285/308 (93)	294/308 (95)
Adjusted difference in proportion, % (95% CI)	0.4 (–3.7 to 4.5) NI met at –10%		–3.0 (–6.7 to 0.7) NI met at –10%	
HIVTSQs – Change from baseline in total treatment satisfaction score in ITT-E population – (adjusted, LOCF)				
Baseline, n	259	266	302	298
Baseline, mean (SD)	59.3 (7.37)	59.1 (7.55)	55.25 (9.14)	55.40 (8.68)
Week 44, n	281	275	306	303
Week 44 score, mean (SD)	60.9 (7.25)	59.6 (7.64)	61.31 (6.63)	56.03 (9.83)
Adjusted change from baseline at week 44, n	257	256	300	294
Adjusted mean [SD] (95% CI)	1.3 [8.63] (0.5 to 2.1)	0.5 [7.33] (–0.3 to 1.4)	6.12 (5.21 to 7.03)	0.44 (–0.48 to 1.37)
Difference (95% CI); P value	0.7 (0.4 to 1.9); P = 0.22		5.68 (4.37 to 6.98); P < 0.001	
PIN[b] – Change from week 5[c] in the acceptability of ISRs[d] domain scores in ITT-E population – (LOCF)				
Week 5, n	270	NA	296	NA
Week 5 score, mean (SD)	2.08 (1.03)		2.10 (1.03)	
Week 48, n	278		303	
Week 48 score, mean (SD)	1.66 (0.78)		1.56 (0.80)	
Change from week 5, n	270		296	
Change from week 5, mean (SD)	–0.40 (0.94)		–0.54 (1.08)	
P value	< 0.001		< 0.001	

Outcomes	FLAIR		ATLAS	
	CAB + RPV	CART	CAB + RPV	CART
Harms[e]				
AEs, n/N (%)	267/283 (94)	225/283 (80)	294/308 (95)	220/308 (71)
SAEs, n/N (%)	18/283 (6)	12/283 (4)	13/308 (4)	14/308 (5)
WDAEs, n/N (%)	9/283 (3)	4/283 (1)	13/308 (4)	5/308 (2)
Deaths, n/N (%)[f]	0	0	0	1

AE = adverse event; CAB + RPV = cabotegravir plus rilpivirine; CART = current antiretroviral treatment; CI = confidence interval; HIV-1 = HIV type 1; HIVTSQs = HIV Treatment Satisfaction Questionnaire status version; ISR = injection site reaction; ITT-E = intention-to-treat–exposed population; LOCF = last observation carried forward; NI = noninferiority; PIN = Perception of Injection; RNA = ribonucleic acid; SAE = serious adverse event; SD = standard deviation; WDAE = withdrawal due to adverse event.

[a] Using the FDA Snapshot algorithm.

[b] Only applicable to the CAB + RPV group since they received injection only.

[c] Baseline for PIN; this was the first week that patients assigned to the CAB + RPV group received the injectable formulation.

[d] Only domain in PIN that was compared statistically and controlled for multiplicity.

[e] Safety data presented for maintenance phase, not separated by oral lead-in and injection period.

[f] In addition to one death observed during the maintenance phase in ATLAS, one death occurred during the induction phase in FLAIR in a patient in the CAB + RPV group. The cause of death was possible homicide.

Source: FLAIR Clinical Study Report,[7] ATLAS Clinical Study Report.[8]

Critical Appraisal

The two studies included in this review, FLAIR and ATLAS, were generally conducted well with sound methodology. The main limitation is that both trials were OL in design, which may bias the results if assessment of the trial outcomes are impacted by known treatment assignment. However, efficacy and safety end points measured in blood or plasma were measured in an objective manner, and therefore less likely to be affected by reporting and recall bias. Nonetheless, the possibility remains that ascertainment of treatment allocation influenced patient reporting of subjective outcomes (especially HRQoL).

Both trials assessed a number of HRQoL outcomes; however, most of these measures had limited to no evidence of validity or responsiveness and were lacking an established minimal important difference (MID), particularly in patients with HIV-1. Evidence of reliability was documented for ACCEPT, HAT-QoL, and HIVTSQ (both versions) but not for the other instruments used to measure HRQoL. There is a potential for bias in the assessment of HRQoL outcomes, especially those administered exclusively to the CAB + RPV group that are focused on assessing the patient's experience with the CAB and RPV injections. There is potential for patients to rate their answer to the HRQoL scales worse on the first exposure to injection due to relative unfamiliarity with the regimen and the higher volume of the initial injection; scores on the HRQoL measure may become more positive as patients become more comfortable with the injections as treatment progresses. Overall, the changes in various HRQoL scores at week 44 or 48 compared to that at baseline were relatively small and were likely suffering from random error and/or missing data. Moreover, the between-group differences were highly inconsistent across the two trials despite of the similarity of trial design, duration, and identical outcome measures.

According to the clinical expert consulted by CADTH, the baseline demographic and clinical characteristics in FLAIR and ATLAS were generally reflective of treatment-experienced, virologically suppressed patients in a Canadian setting. However, it was noted that the proportion of injectable drug users constituted no more than 5% of the trial population; a higher proportion of injectable drug users are seen in clinical practice. It was also noted that patients in ATLAS were likely to be treatment adherent and fairly homogeneous, whereas FLAIR likely included a broad selection of patients with unknown adherence record prior to the trial.

The comparators used in the trials included many of the recent ARV regimens commonly prescribed in clinical practice. Patients in the comparator arm in FLAIR primarily received ABC/DTG/3TC through the maintenance phase. The ATLAS trial compared the CAB + RPV regimen against a combination of oral ARTs; therefore, the comparative efficacy and safety of individual ARTs are unknown. However, this is unlikely to affect the generalizability of the trial as patients had exposure to a wide variety of oral ARTs.

Conclusions

Results from two OL RCTs (FLAIR and ATLAS) in HIV-1 infected virologically suppressed patients demonstrated that once-monthly injections of CAB + RPV are noninferior to oral CART with respect to virologic failure (HIV-1 RNA ≥ 50 copies/mL) and virologic suppression (HIV-1 RNA < 50 copies/mL) at week 48. CAB + RPV may be associated with small benefits of HRQoL over CART, including patient's satisfaction and acceptance of treatment; however, the HRQoL results are inconclusive and associated with many uncertainties. The safety profile of CAB + RPV did not show any additional signs of concern. While patients in the CAB + RPV group reported more AEs, the majority were a result of ISRs, which were mostly resolved within a week, and not of concern according to the clinical expert.

Long-term trials of the CAB + RPV regimen are ongoing, with a planned duration of 120 to 148 weeks. Results of these trials will provide more conclusive evidence of the durability of the IM CAB + RPV regimen. Overall, CAB + RPV is an effective regimen with no major safety concerns and could be a new treatment option in virologic-suppressed patients.

Introduction

Disease Background

HIV-1 is one of the two types of viruses that cause HIV infection and is responsible for the majority of HIV infections worldwide.[1] HIV-1 is transmitted via body fluids such as blood, semen, genital secretions, and breast milk.[2] HIV-1 gradually weakens the immune system by selectively destroying CD4+ immune cells, which are critically important in helping the body fight infection. This compromises the immune system's ability to mount an effective immunological response to opportunistic pathogens over time.[3] HIV-1 infection can progress to AIDS and ultimately death if left untreated. The fatality of HIV-1 has been significantly reduced since the mid-1990s after the invention of highly active forms of ART.[5] Treatments are aimed at lowering the level of HIV-1 in the body, thereby slowing the spread of the virus and helping the immune system respond to other infections. Treatment with ART has provided patients an opportunity to live a longer, healthier life with a decreased risk of transmitting the virus to others. Newer ARTs have significantly reduced HIV-1–associated morbidity and mortality and HIV-1 is largely considered a manageable chronic condition. Starting treatment early can increase the probability of living a near-normal lifespan.[5] Patients consulted for this review indicated that stigma and HRQoL are still a major concern despite the clinical improvements in treatment.

A recently published HIV-1 surveillance report[4] estimated that, in Canada, the incidence rate of HIV-1 was 6.5 per 100,000, or 2,402 newly reported cases in 2017. There was an increase in incidence rate of 3% compared with 2016 and an increase of 17.1% since 2014.[4] Overall, there was a decrease in the annual diagnosis rate between 1996 and 2000 (14.2 per 100,000 to 10.2 per 100,000), followed by an increase in 2001 (10.6 per 100,000), and a plateau until 2008 (11.7 per 100,000).[4] A slight decrease in the national rate followed until 2014 (8.8 per 100,000). Since then, a slight increase has been observed (9.9 per 100,000 in 2017). Ontario accounted for the highest number and proportion of reported HIV-1 cases in 2017 (38.9%), followed by Quebec (27.9%), Alberta (11.7%), and British Columbia (7.8%).[4] The provincial and territorial HIV-1 diagnosis rates varied notably across the country, with the highest diagnosis rates found in Saskatchewan (15.5 per 100,000) and Quebec (8.0 per 100,000), followed by Manitoba, Alberta, and Ontario (6.6 per 100,000 in each province).[4] In 2017, the diagnostic rate for males (9.9 per 100,000 population) was higher than for females (3.2 per 100,000 population).[4] The 30 to 39 year old age group represented the highest number of new HIV-1 cases (31.2%), followed by 50 years or older (22.9%), and 40 to 49 years (22.4%). Among adults with known exposure (60.2% of all cases), the most common exposure categories were "gay, bisexual, and other men who have sex with men" (46.4%), followed by heterosexual contact (28.7%), and injection drug use (16.3%).[4] Race and ethnicity distribution showed that the following races accounted for the most commonly reported HIV-1 cases: White/Caucasian (34.5%), Black (25.3%), and Indigenous (20.1%).[4]

Standards of Therapy

The clinical expert consulted for this review indicated that the DHHS Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV[5] inform clinical practice in Canada. According to the recommendations, ARV regimens for treatment-naive patients generally consist of two NRTIs in combination with a third active ARV drug from one of

three classes: an INSTI, an NNRTI, or a PI with a pharmacokinetic enhancer (booster) such as cobicistat or ritonavir.[5]

Once initiated, ARTs should be continued with the following key treatment goals to: maximally and durably suppress plasma HIV-1 RNA below detectable limits (< 50 copies/mL); restore and preserve immunologic function (increase CD4+ cell count); reduce HIV-1–associated morbidity; prolong the duration and quality of survival; and prevent HIV-1 transmission. Current ARTs are not curative; they require lifelong administration and therefore high levels of adherence to achieve treatment goals. To simplify ARV regimens and support long-term adherence, several STRs are available, alongside non-STRs, providing clinicians and patients with an array of therapeutic options.[5]

For treatment-experienced patients with viral suppression, the DHHS guidelines do not provide a list of recommended therapies; the selection of a new ARV regimen should be based instead on patients' previous ART histories, including virologic responses, past ART-associated toxicities and intolerances, resistance test results, drug-drug interactions, and pill burden, in addition to other non-clinical considerations. For switching to a two-drug regimen, the DHHS guidelines include two regimen options with strong supporting evidence: a boosted PI plus emtricitabine or 3TC, or DTG plus RPV. Switching to a monotherapy regimen is not recommended due to a lack of efficacy and development of treatment resistance.[5] Table 2 summarizes currently available ARV treatments across Canada and includes a range of single- and multi-tablet regimens.

Drug

The objective of this systematic review was to evaluate the beneficial and harmful effects of the CAB + RPV regimen for the treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA < 50 copies/mL). The CAB + RPV regimen consists of separate once-monthly injections with CAB and RPV preceded by an oral lead-in phase during which oral CAB tablets are taken in combination with RPV tablets (currently available in Canada) for at least 28 days.

CAB tablets are indicated in combination with RPV tablets as a complete regimen for short-term treatment of HIV-1 infection in adults who are virologically stable and suppressed (HIV-1 RNA < 50 copies/mL) as:

- an oral lead-in to assess tolerability of CAB prior to initiating CAB and RPV injections
- oral bridging therapy for missed CAB and RPV injections.

CAB and RPV extended release injectable suspensions are indicated:

- as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in patients who are virologically stable and suppressed (HIV-1 RNA < 50 copies/mL).[6]

The Health Canada–recommended dosing for the CAB + RPV regimen consists of three distinct phases:

1. Oral lead-in phase: One CAB 30 mg tablet taken together with one RPV 25 mg tablet, orally and once daily
2. Initiation injection of CAB + RPV (600 mg + 900 mg, 3 mL each)
3. Continuation injections with CAB + RPV (400 mg + 600 mg, 2 mL each)

CAB in combination with available RPV tablets are recommended to be administered for approximately one month (at least 28 days) prior to the initiation of injection to assess tolerability of the patient to CAB. CAB in combination with RPV tablets should be taken with a meal. The final oral doses of CAB and RPV should be taken on the same day injections with CAB + RPV are started. If a patient plans to miss a scheduled injection visit by more than seven days, oral CAB and RPV tablets may be used once daily to replace up to two consecutive planned missed monthly injection visits. The recommended initial injection doses of CAB + RPV in adults are a single 3 mL (600 mg) IM injection of CAB and a single 3 mL (900 mg) IM injection of RPV. One month following the initiation injections, the recommended continuation injection doses of CAB + RPV in adults are a single 2 mL (400 mg) IM injection of CAB and a single 2 mL (600 mg) IM injection of RPV monthly. CAB and RPV injections should be administered at separate gluteal sites during the same visit.[6] Reimbursement is being sought by the sponsor in accordance with the indication.

CAB is an INSTI that inhibits HIV-1 integrase by binding to the integrase active site and blocking the strand transfer step of retroviral DNA integration which is essential for the HIV-1 replication cycle. RPV is a diarylpyrimidine NNRTI of HIV-1. RPV activity is mediated by non-competitive inhibition of HIV-1 RT. RPV does not inhibit the human cellular DNA polymerases alpha, beta, and gamma.[6]

A table describing key characteristics of STRs and other commonly recommended ARV regimens is presented in Table 2.

Table 2: Key Characteristics of Commonly Recommended Antiretroviral Therapy Regimens[a]

Comparator regimens	Brand	Dosage strengths	Indications[b]	Key side effects/safety issues
Single tablet regimens				
DTG/3TC	Dovato	**DTG:** 50 mg **3TC:** 300 mg	A complete regimen for the treatment of HIV-1 infection in adults and adolescents aged ≥ 12 years and weighing ≥ 40 kg	**DTG**: insomnia, headache, depression, early benign increase in SCr[9,10] **3TC**: generally well tolerated[9]
DOR/TDF/3TC	Delstrigo	**DOR:** 100 mg **TDF:** 300 mg **3TC:** 300 mg	A complete regimen for the treatment of HIV-1 infection in adults without past or present evidence of viral resistance to doravirine, lamivudine, or tenofovir.	**DOR:** dizziness, abnormal dreams, insomnia, nightmares, headache, sleepiness, nausea, diarrhea, vomiting, feeling tired and weak, depression[9] **TDF**: renal toxicity, decreased BMD, increased osteoporotic fractures, reports of lactic acidosis, hepatotoxicity[9] **3TC**: generally well tolerated[9]
BIC/TAF/FTC	Biktarvy	**BIC:** 50 mg **FTC:** 200 mg **TAF:** 25 mg	A complete regimen for the treatment of HIV-1 infection in adults with no known substitution associated with resistance to the individual components of Biktarvy[11]	**BIC:** diarrhea, nausea, headache, fatigue, abnormal dreams, dizziness, and insomnia[11] **FTC**: discoloration of skin (hands/feet)[10] **TAF:** similar to TDF, but may have less renal and bone toxicity[12]
DTG/ABC/3TC	Triumeq	**DTG**: 50 mg **ABC**: 600 mg **3TC**: 300 mg	Treatment of HIV-1 infection in adults and adolescents aged ≥ 12 years and weighing ≥ 40 kg[13]	**DTG**: insomnia, headache, depression, early benign increase in SCr[9,10] **ABC**: risk of severe hypersensitivity reaction in genetically susceptible

Comparator regimens	Brand	Dosage strengths	Indications[b]	Key side effects/safety issues
				patients, possible increased risk for MI[9,10] **3TC**: generally well tolerated[9]
EVG/c/TAF/FTC	Genvoya[c]	**EVG**: 150 mg **c**: 150 mg **FTC**: 200 mg **TAF**: 10 mg	A complete regimen for the treatment of HIV-1 infection in adults and pediatric patients aged ≥ 12 years (and weighing ≥ 35 kg) and with no known RAMs to the individual components of Genvoya[14]	**EVG:** nausea, diarrhea, insomnia, headache, depression; early benign increase in SCr[9,10] **c**: can falsely increase SCr[10] **FTC**: discoloration of skin (hands/feet)[10] **TAF:** similar to TDF, but may have less renal and bone toxicity[12]
RPV/TAF/FTC	Odefsey[c]	**RPV**: 25 mg **TAF**: 25 mg **FTC**: 200 mg	A complete regimen for the treatment of adults infected with HIV-1 with no known RAMs to the NNRTI class, tenofovir, or FTC, and with a VL ≤ 100,000 copies/mL[15]	**RPV**: depression, insomnia, rash, headache; early benign increase in SCr[9] **TAF:** similar to TDF, but may have less renal and bone toxicity[12] **FTC**: discoloration of skin (hands/feet)[10]
DTG/RPV	Juluca	**DTG:** 50 mg **RPV:** 25 mg	A complete regimen to replace the current antiretroviral regimen for the treatment of HIV-1 infection in adults who are virologically stable and suppressed (HIV-1 RNA < 50 copies/mL)[16]	**DTG**: insomnia, headache, depression; early benign increase in SCr[9,10] **RPV**: depression, insomnia, rash, headache, early benign increase in SCr[9]
DRV/c/TDF/FTC	Symtuza	**DRV:** 800 mg **c**: 150 mg **TAF**: 10 mg **FTC**: 200 mg	Indicated as a complete regimen for the treatment of HIV-1 infection in adults and adolescents (aged 12 years and older with body weight at least 40 kg) and with no known mutations associated with resistance to the individual components of Symtuza[17]	**DRV:** diarrhea, nausea, headache, rash, hyperlipidemia; drug-induced hepatotoxicity in DRV/r (rare); all PIs: risk of ECG abnormalities (i.e., PR interval prolongation)[9,10] **c**: can falsely increase SCr[10] **TAF:** similar to TDF, but may have less renal and bone toxicity[12] **FTC**: discoloration of skin (hands/feet)[10]
EVG/c/TDF/FTC	Stribild[c]	**EVG**: 150 mg **c**: 150 mg **FTC**: 200 mg **TDF**: 300 mg	A complete regimen for the treatment of adults aged ≥ 18 years infected with HIV-1 with no known mutations to the INSTI class, tenofovir, or FTC[18]	**EVG:** nausea, diarrhea, insomnia, headache, depression, early benign increase in SCr[9,10] **c**: can falsely increase SCr[10] **FTC**: discoloration of skin (hands/feet)[10] **TDF**: renal toxicity, decreased BMD, increased osteoporotic fractures, reports of lactic acidosis, hepatotoxicity[9]
RPV/TDF/FTC	Complera[c]	**RPV**: 25 mg **TDF**: 300 mg **FTC**: 200 mg	A complete regimen for the treatment of adults infected with HIV-1 with no known RAMs to the NNRTI class, tenofovir, or FTC, and with a VL ≤ 100,000 copies/mL[19]	**RPV**: depression, insomnia, rash, headache, early benign increase in SCr[9] **TDF**: renal toxicity, decreased BMD, increased osteoporotic fractures, reports of lactic acidosis, hepatotoxicity[9]

Comparator regimens	Brand	Dosage strengths	Indications[b]	Key side effects/safety issues
				FTC: discoloration of skin (hands/feet)[10]
EFV/TDF/FTC	Atripla[d]	**EFV**: 600 mg **TDF**: 300 mg **FTC**: 200 mg	For use alone as a complete regimen or in combination with other ARV agents for the treatment of HIV-1 infection in adults[20]	**EFV**: insomnia, vivid dreams, depressed mood, dizziness, headache, rash; avoid in patients with history of anxiety, depression, or psychosis. Contraindicated in first trimester of pregnancy[9,10] **TDF**: renal toxicity, decreased BMD, increased osteoporotic fractures, reports of lactic acidosis, hepatotoxicity[9] **FTC**: discoloration of skin (hands/feet)[10]
Additional relevant comparator regimens				
DRV/c + TAF/FTC	Prezcobix[c] Descovy	**DRV/c**: 800 mg/150 mg **TAF/FTC**: 10 mg/200 mg 25 mg/200 mg	In combination with other ARV agents for the treatment of HIV infection in treatment-naive and in treatment-experienced patients without DRV RAMs[21] In combination with other ARVs (such as NNRTIs or PIs) for the treatment of HIV-1 infection in adults and pediatric patients aged ≥ 12 years (and weighing ≥ 35 kg)[22]	**DRV**: diarrhea, nausea, headache, rash, hyperlipidemia, drug-induced hepatotoxicity in DRV/r (rare); all PIs: risk of ECG abnormalities (i.e., PR interval prolongation)[9,10] **c**: can falsely increase SCr[10] **TAF**: similar to TDF, but may have less renal and bone toxicity[12] **FTC**: discoloration of skin (hands/feet)[10]
DTG + TAF/FTC	Tivicay Descovy	**DTG**: 50 mg **TAF/FTC:** 10 mg/200 mg 25 mg/200 mg	Treatment of HIV-1 infection in adults and in INSTI-naive children weighing ≥ 30 kg[23] In combination with other ARVs (such as NNRTIs or PIs) for the treatment of HIV-1 infection in adults and pediatric patients aged ≥ 12 years (and weighing ≥ 35 kg)[22]	**DTG**: insomnia, headache, depression, early benign increase in SCr[9,10] **TAF:** similar to TDF, but may have less renal and bone toxicity[12] **FTC**: discoloration of skin (hands/feet)[10]
DRV+ r + TDF/FTC	Prezista[c]	**DRV**: 800 mg	Co-administered with 100 mg ritonavir and with other ARV agents for the treatment of HIV-1 infection[24]	**DRV**: diarrhea, nausea, headache, rash, hyperlipidemia; drug-induced hepatotoxicity in DRV/r (rare); all PIs: risk of ECG abnormalities (i.e., PR interval prolongation)[9,10] **r**: diarrhea, nausea, headache, paresthesias, rash, hyperlipidemia, drug-induced hepatotoxicity in DRV/r (rare); all PIs: risk of ECG abnormalities (i.e., PR interval prolongation)[9,10] **TDF**: renal toxicity; decreased BMD, increased osteoporotic fractures; reports of lactic acidosis, hepatotoxicity[10]
	Norvir[c]	**r:** 100 mg	In combination with other ARV agents for the treatment of HIV infection when therapy is warranted[25]	
	Truvada, generics	**TDF**: 300 mg **FTC**: 200 mg	In combination with other ARV agents (such as NNRTIs or PIs) for the treatment of HIV-1 infection in adults[26]	

Comparator regimens	Brand	Dosage strengths	Indications[b]	Key side effects/safety issues
				FTC: discoloration of skin (hands/feet)[10]
DTG + TDF/FTC	Tivicay	**DTG**: 50 mg	Treatment of HIV-1 infection in adults and in INSTI-naive children weighing ≥ 30 kg[23]	**DTG**: insomnia, headache, depression, early benign increase in SCr[9,10] **TDF**: renal toxicity, decreased BMD, increased osteoporotic fractures, reports of lactic acidosis, hepatotoxicity[9] **FTC**: discoloration of skin (hands/feet)[10]
	Truvada, generics	**TDF**: 300 mg **FTC**: 200 mg	In combination with other ARV agents (such as NNRTIs or PIs) for the treatment of HIV-1 infection in adults[26]	

3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; BIC = bictegravir; BMD = bone mineral density; c = cobicistat; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; ECG = electrocardiogram; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; HIV-1 = HIV type 1; INSTI = integrase strand transfer inhibitor; MI = myocardial infarction; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PR interval = the time from the beginning of the P wave, indicating atrial depolarization, to the beginning of the QRS complex; r = low-dose ritonavir; RAM = resistance-associated mutation; RNA = ribonucleic acid; RPV = rilpivirine; SCr = serum creatinine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; VL = viral load.

[a] All regimens are administered orally once daily.[30]

[b] Health Canada indication.

[c] Must be taken with food or a meal.[30]

[d] Must be taken on an empty stomach.[30]

Source: Dovato product monograph,[27] Delstrigo product monograph,[28] Biktarvy product monograph,[11] Prezcobix product monograph,[21] Tivicay product monograph,[23] Descovy product monograph,[22] Genvoya product monograph,[14] Odefsey product monograph,[15] Triumeq product monograph,[13] Truvada product monograph,[26] Prezista product monograph,[24] Norvir product monograph,[25] Stribild product monograph,[18] Complera product monograph,[19] Atripla product monograph,[20] Juluca product monograph,[16] Symtuza product monograph,[29] e-CPS,[9] RxFiles,[10] AIDSinfo.[30]

Stakeholder Engagement

Patient Group Input

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Groups Supplying Input

Five patient group submissions were received for this review. The CTAC is a national, non-governmental organization that aims to engage community members, service providers, policy-makers, and other stakeholders to identify, develop, and implement policy and program solutions for people living with HIV-1 and hepatitis C (HCV). Realize is a national, charitable organization focused on integrating research, education, policy, and practice to improve the health and well-being of people living with HIV-1 and other episodic disabilities. ACO is a community agency that provides support, prevention, education, and outreach services to those living with, affected by, or at risk of HIV/AIDS in Ottawa. A joint submission from four non-profit groups working in sectors of gay and queer men's health with a focus on HIV-1 prevention, including ACT (Toronto), MAX (Ottawa), EMHC (Edmonton), and CBRC (Vancouver) was received. ACT, EMHC, and MAX Ottawa are community-based organizations that provide support and education services for the health and wellness of gay, bisexual, transgender, and two-spirit men, including HIV-1 prevention. The CBRC promotes the health of gay men through research and intervention development. ASAAP provides support services to South Asian communities in the Greater Toronto Area regarding HIV/AIDS and sexual health, in a culturally appropriate way.

All the patient group submissions were written independently. Each of the patient groups, with the exception of ASAAP and ACO, reported having received funding from ViiV Healthcare; however, ASAAP has ViiV Healthcare listed as a funder on their website (www.ASAAP.com).

2. Condition-Related Information

CTAC invited people living with HIV-1 to participate in a patient input consultation workshop in Toronto. An overview of the CADTH patient input process and key findings from the CAB + RPV clinical trials were provided. They also conducted a survey that was available for approximately two weeks in 2019. The workshop and online survey had seven and 15 participants, respectively, all of whom identified as HIV-1 positive and were currently receiving treatment for HIV-1 (ranging from eight months to 35 years). More than half (59%) of the participants identified as male, and the age of participants ranged from less than 20 years to greater than 60 years. In addition, participants identified by various sexual orientations, including bisexual and non-binary. The other four patient groups collected information for their submission informally, based on personal experiences and those shared with them through their community-based work. The ACO community received feedback from clients at their drop-in centre through informal conversations with staff and volunteers. The joint submission (ACT, MAX, EMHC, and CBRC) gathered information from staff and service users. Realize collected stories of personal experiences from national members living with HIV-1 collected over a period of three months.

Patient groups described HIV-1 as a serious, life-threatening illness that threatens the immune system. If untreated, HIV-1 infection may compromise a person's immune system to the point where they can no longer fight off opportunistic infections. Access, administration of, and adherence to highly active antiretroviral treatment can control

progression of HIV-1 such that patients generally manage their condition as a chronic illness. Successful treatment or viral suppression is linked to marked improvement in long-term health outcomes and drastically reduces the possibility of transmitting HIV-1 to sexual partners. The patient input also noted the loss in labour productivity associated with living with HIV-1, as well as a loss in quality of life. One respondent stated “I am worried about the fact that HIV is now viewed as a chronic, manageable disease. I still have good and bad days but, if HIV is now seen as something other than a disability, will I be forced to go back to work, even when I’m not well?” The ability to participate in the work force may impact a patient’s sense of identity, financial security, and access to health insurance.

There is also a stigma associated with living with HIV-1 that remains and continues to be a challenge for patients. This was a common theme among all five submissions. Patient groups described discrimination based on their HIV-1 status, which impacts their access to social support and health services. Even within the medical community, patients reported “local doctors feel ill-equipped to treat HIV due to inexperience because of low patient caseloads with the condition.” They also noted that “unless they're familiar, doctors still see HIV as something more difficult to live with than it actually is.” Patient groups also highlighted intersecting vulnerabilities experienced by patients living with HIV-1, shaped by social determinants of health. Limited funding or services for addictions, mental health, housing, and food security can impact a patient’s HIV-1 treatment.

Regarding social support, patients described feelings of shame and guilt associated with living with HIV-1, which makes it difficult to be open with friends and families about their condition. One person noted that “hiding from friends and some of our family members that I am HIV positive” has been extremely difficult and hindered the ability to acquire a social safety net. Adhering to a daily medication is a challenge in itself and hiding treatment from friends and families creates an additional barrier, which was also described by all of the patient groups. Many of those living with HIV-1 also experience negative mental health outcomes, whether as a side effect from treatment, or from facing stigma, discrimination, and related stress. One participant explained how their depression can have an effect on whether they adhere to their medication, “When depressed it is sometimes hard to just push yourself to pick up your pills.”

3. Current Therapy-Related Information

According to patient groups, the complex nature of living with and treating HIV-1 necessitates having as many treatment options available as possible. The patients who participated in the workshop and survey hosted by CTAC had been on their current therapy for the treatment of HIV-1 for approximately two months to 12 years, with minor changes made due to other health problems or development of resistance. Respondents indicated having experience with regimens containing: darunavir, DTG, FTC, RPV, 3TC, and/or tenofovir; and treatments including: Viread, Intelence, Triumeq, Genvoya, Norvir, and/or Biktarvy. Although currently most people can achieve viral suppression, treatment adherence and drug class resistance are still an issue for some patients. They acknowledged that the currently available treatments have fewer side effects than in the past, although not eliminated completely as one patient noted “I’ve been on treatments in the past that resulted in me having severe mood swings, and I wasn’t able to sleep at all. I’m very concerned about the side effects of new medications, especially because I’m older and have a lot of comorbidities to consider.”

The joint submission from ACT, MAX, EMHC, and CBRC noted that adherence to a daily pill regimen is a significant barrier to certain groups as well, particularly youths, whether it

be the result of a lack of stable housing, mental illness, HIV-1 stigma, or intimate partner violence. All of the patient input groups highlighted a desire or need for discretion with treatments for HIV-1, due to the social and cultural discrimination and challenges associated with living with HIV-1.

4. Expectations About the Drug Being Reviewed

The expectations that patients have for CAB + RPV were similar across the five submissions. The reduction of stigma associated with living with HIV-1 was a predominant theme. Patients believe that decreasing the frequency with which they need to take their medication may reduce stigma by providing patients with more privacy and discretion around living with HIV-1. They would not have to hide their HIV-1 pills from friends and families whom they have not disclosed their HIV-1 status to, which was reported as a source of anxiety for patients. The joint submission also noted that the discretion that a long-acting treatment can provide would also be beneficial for those who travel to countries where they may be discriminated against and forbidden to travel to for using HIV-1 medications.

The option for a once-monthly regimen rather than daily was appealing to all, as patients felt it would reduce pill burden and improve adherence and consequently improve viral suppression. This is particularly true for those who find difficulty in taking pills daily, such as elderly patients who have reported different levels of dementia as noted by the joint submission. The reduced frequency of treatment would also be helpful for those who are living in precarious housing conditions, or with mental illness, or for those who fear partner violence or employment discrimination.

All of the patient groups also expressed a desire for fewer side effects with new medications and low potential for drug-drug interactions. One patient also reported that they were interested in the injectable form of the medication as they are “really bad at taking medications.”

Realize was the only patient group that reported capturing patients who had experience with CAB + RPV. Patients reported having fewer side effects, and the ability to be more socially engaged both in the workplace and their private lives, which led to improved self-esteem. The joint submission provided second-hand feedback from a staff member who attended a panel with participants of the “injectables trial.” They reported that patients described the drug as having helped reduce stigma and anxiety, and that many are looking forward to having a long-acting option.

5. Additional Information

The cost and affordability of a new long-acting treatment for HIV-1 was another common theme among each of five patient group submissions. They highlighted that it is important for patients to have options, but the options also need to be affordable, especially considering that some of the more marginalized members of the community would be among those who benefit the most from this option.

The joint submission from ACT, MAX, EMHC, and CBRC also brought forward a concern about a lack of service providers and questions about implementation of CAB + RPV. They wanted to know how the health system will ensure that the service is delivered by properly trained providers and noted that it would be beneficial if nurse practitioners were able to prescribe this drug for those with difficulty accessing a physician. In addition, they mentioned that the cultural history with injectable drugs in certain communities, such as Indigenous communities, should be considered. In summary, they want to ensure that an

injectable treatment for HIV-1 would benefit the more marginalized living with HIV-1 and not work against them.

Clinician Input

All CADTH review teams include at least one clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol; assisting in the critical appraisal of clinical evidence; interpreting the clinical relevance of the results; and providing guidance on the potential place in therapy). The following input was provided by one clinical specialist with expertise in the diagnosis and management of HIV-1.

Description of the Current Treatment Paradigm for the Disease

The current main treatment for HIV-1 is ARV therapy. This suppresses HIV-1 replication and, through this, restores the immune system to near-normal health. This allows normal or near-normal life-expectancy and HRQoL. ARV therapy typically consists of three (less commonly two) individual ARV drugs, given together as a STR (to optimize adherence). ARV therapy is started as soon as possible after HIV-1 diagnosis, and lifelong therapy is anticipated.

Treatment Goals

The ideal treatment would result in complete and persistent suppression of HIV-1 replication, which would translate into a restored immune system, freedom from HIV-1–associated illness, and prolonged life. The medication should be convenient and free of short- and long-term adverse effects. Treatment should be non-intrusive; in other words, it should be a minimal part of the person's life and allow for overall "normality."

Unmet Needs

There are many available STR ARV therapies, and many other potentially convenient, effective, and tolerable combinations consisting of two to four tablets once or twice daily. There are no major gaps in treatment in terms of tolerability or effectiveness. There is a subset of patients who have difficulties with adherence, which is the result of mental health problems, chaotic lifestyle, or otherwise. For these individuals, a long-acting depot formulation of ARV could enhance adherence.

Place in Therapy

The CAB + RPV regimen would likely be most used by patients already doing well on oral therapy who wish to be freed from taking daily oral therapy. Less frequently, but perhaps more importantly, this combination would likely be used as first-line or switch therapy for those with proven or anticipated difficulties with adherence. This would include those with mental health issues or more chaotic lifestyles (IV drug users, homeless, and so forth).

Patient Population

Assuming a lack of genotypic resistance to either component of this regimen, most patients would likely respond well to CAB + RPV virologically. Those best suited to use this therapy would be those with anticipated or demonstrated difficulties with adhering to daily oral therapy.

Patients would be identified though clinical assessment by their treating physicians and nurses. As well, those with detectable HIV-1 viral loads on therapy, especially if supported

by pharmacy records or a stated history of nonadherence, would be evident as candidates for this treatment.

Only those who have resistance to a component of this therapy, or could not adhere to once-monthly injections, would be inappropriate candidates for this therapy.

Assessing Response to Treatment

Undetectable HIV-1 viral load can be used to determine whether a patient is responding to treatment in clinical practice. In addition, patient adherence and satisfaction should be considered when assessing clinically meaningful response to treatment.

Optimal virologic response would be expected in those with a non-resistant virus (identified with HIV-1 genotyping, or clinically as demonstrated by a medical history lacking virologic treatment failures and HIV-1 suppression on standard single oral therapy) who would be able to adhere to the once-monthly injections.

It would be reasonable to assess treatment response every six months.

Discontinuing Treatment

The discontinuation of injectable CAB + RPV would lead to prolonged suboptimal drug levels in the blood, with the potential for the development of virologic resistance to either component of the therapy and related drugs. As such, discontinuation of this therapy mandates the use of effective alternative (oral) ARV therapy for some six months.

Prescribing Conditions

Any HIV-1–treating physician should be able to prescribe CAB + RPV. A specialist in HIV-1 treatment should always be involved in the ARV treatment of a patient infected with HIV-1. The CAB and RPV injections would not be self-administered; they would likely be provided through home care or at a treatment centre, an HIV clinic/walk-in clinic, or at the office of a family physician.

Additional Considerations

The CAB + RPV regimen appears to be an effective, safe, and well-tolerated therapy for HIV-1. The convenience of a monthly injection is offset somewhat by the inconvenience and cost of getting the injections, the need for reasonable adherence at the start of treatment (the oral treatment phase), and the care needed with discontinuation, as the risk of developing virologic resistance to the NNRTIs and/or INSTIs would be significant if the injections were stopped and no other therapy provided.

Clinical Evidence

The clinical evidence included in the review of CAB + RPV is presented in three sections. The first section is the Systematic Review, which includes pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those studies that were selected according to an a priori protocol. The second section is intended to include indirect evidence from the sponsor (if submitted) and indirect evidence selected from the literature that met the selection criteria specified in the review. However, no indirect evidence was submitted by the sponsor nor was any indirect evidence that met the selection criteria specified in the review identified from the literature. The third section is intended to include long-term extension studies and additional studies submitted by the sponsor that were considered to address important gaps in the evidence included in the systematic review; however, no such evidence was submitted.

Systematic Review (Pivotal and Protocol Selected Studies)

Objectives

To perform a systematic review of the beneficial and harmful effects of the CAB + RPV regimen for the treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA < 50 copies/mL). The CAB + RPV regimen consists of oral CAB tablets (30 mg) during the oral lead-in phase in combination with RPV tablets (25 mg; currently available in Canada), and injection of CAB (600 mg and 400 mg) in combination with RPV injection (900 mg and 600 mg) during the initiation injection and continuation injection phases.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the sponsor's submission to CDR and Health Canada, as well as those meeting the selection criteria presented in Table 3.

Of note, the systematic review protocol was established prior to the granting of a Notice of Compliance from Health Canada.

Table 3: Inclusion Criteria for the Systematic Review

Patient population	Adults (≥ 18 years) with HIV-1 infection who are virologically suppressed (HIV-1 RNA < 50 copies/mL) Subgroups: • Baseline viral load prior to suppressive ARV regimen • Baseline CD4+ count prior to suppressive ARV regimen • Biological sex at birth
Intervention	As a complete regimen including the following: • Oral lead-in: CAB (30 mg) + RPV (25 mg) administered once daily for approximately 1 month (at least 28 days); followed by: • IM initiation injection: single dose of CAB (600 mg) + RPV (900 mg) administered at the end of month 1 and then; • IM continuation injection: CAB (400 mg) + RPV (600 mg) administered monthly, 1 month following the initiation injections.
Comparators	Standard of care triple ARV regimens for HIV-1 infection: either 2 NRTIs + 1 INSTI; 2 NRTIs + 1 NNRTI; or 2 NRTIs + 1 PI (boosted with ritonavir or cobicistat) or other Health Canada–approved ARV, including 2-drug ARV regimens
Outcomes	**Efficacy outcomes:** • Viral load (e.g., proportion of patients with HIV-1 RNA ≥ and < 50 copies/mL) • Change in CD4+ count • HRQoL[a] • Resistance • Adherence[a] **Harms outcomes:** • Mortality • AEs[a] • SAEs • WDAEs • Notable harms (e.g., bone-related AEs [fractures, BMD], renal function, injection site reactions, depressive disorders, hepatotoxicity, skin reactions, hypersensitivity)
Study design	Published and unpublished Phase III and IV RCTs

AE = adverse event; ARV = antiretroviral; BMD = bone mineral density; CAB = cabotegravir; CD4+ = cluster of differentiation 4 positive; HIV-1 = HIV type 1; HRQoL = health-related quality of life; IM = intramuscular; INSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RCT = randomized controlled trial; RNA = ribonucleic acid; RPV = rilpivirine; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups.

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the PRESS Peer Review of Electronic Search Strategies checklist (https://www.cadth.ca/resources/finding-evidence/press).[31]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were cabotegravir and rilpivirine. Clinical trial registries were searched: the US National Institutes of Health's clinicaltrials.gov and the WHO's International Clinical Trials Registry Platform (ICTRP) search portal.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on September 19, 2019. Regular alerts updated the search until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on January 15, 2020.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters: A Practical Tool For Searching Health-Related Grey Literature checklist (https://www.cadth.ca/grey-matters):[32]

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug And Device Regulatory Approvals
- Advisories And Warnings
- Drug Class Reviews
- Clinical Trials Registries
- Databases (Free).

Google was used to search for additional internet-based materials. These searches were supplemented by reviewing bibliographies of key papers and through contacts with appropriate experts. In addition, the sponsor of the drug was contacted for information regarding unpublished studies. See Appendix 1 for more information on the grey literature search strategy.

Indirect Evidence

No indirect evidence was submitted by the sponsor; an independent search for indirect evidence conducted by CADTH did not result in any published indirect treatment comparison being found.

Other Relevant Studies

At the time of preparation of the protocol, no other studies included in the sponsor's submission were considered of relevance to the CADTH review.

Findings from the Literature

A total of 41 studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4. A list of excluded studies is presented in Appendix 2.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

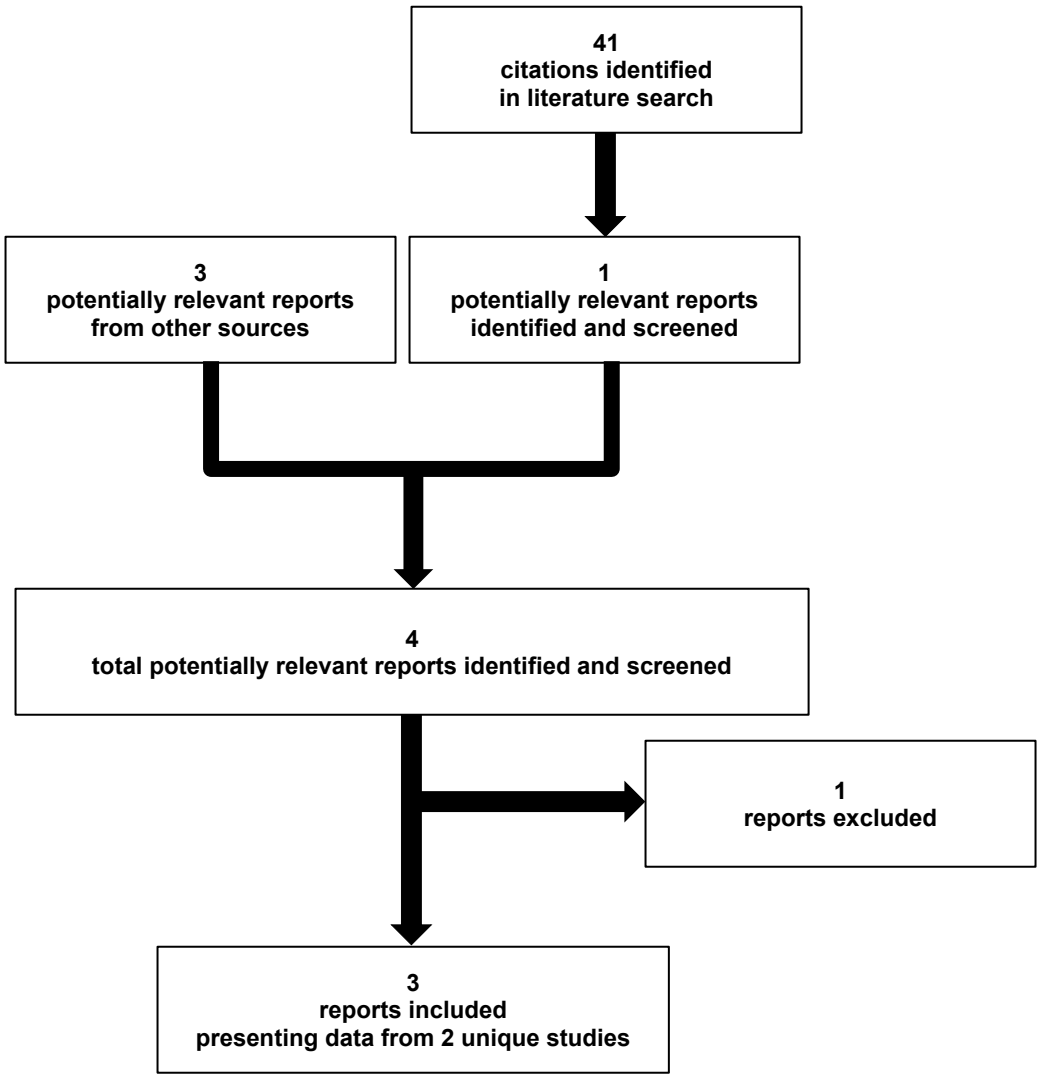


Table 4: Details of Included Studies

		FLAIR	ATLAS
Designs and Populations	**Study design**	Open-label, active-control, noninferiority RCTs	
	Locations	108 centres in 11 countries: Canada, France, Germany, Italy, Japan, Netherlands, Russia, South Africa, Spain, UK, and US	115 centres in 13 countries: Argentina, Australia, Canada, France, Germany, Italy, Korea, Mexico, Russia, South Africa, Spain, Sweden, and US
	Randomized (N)	566 (1:1)[a]	618 (1:1)
	Inclusion criteria	Patients with screening plasma HIV-1 RNA ≥ 1,000 copies/mL and ART-naive (≤ 10 days of prior therapy with any ART)	Stable (≥ 6 months prior to screening) and uninterrupted current regimen (either the initial or second ARV regimen of 2 NRTIs + INI/NNRTI/PI) Treatment switch not related to virologic failure (HIV-1 RNA ≥ 400 copies/mL after initial suppression to < 50 copies/mL) HIV-1 RNA < 50 copies/mL prior to and at screening
		HIV-1 infected male and female (nonpregnant, nonlactating, and practising adequate contraception) adults (≥ 18 years)	
	Exclusion criteria	Previous exposure to an HIV-1 integrase inhibitor or NNRTI	HIV-1 RNA ≥ 50 copies/mL after confirmed suppression to < 50 copies/mL Any treatment discontinuation that was not temporary (≤ 1 month) Any switch to a second-line regimen, ABC/DTG/3TC as ART regimen, only single NNRTI therapy, or only single or dual NRTI therapy
		Any CDC-defined stage 3 disease[b], syphilis, moderate to severe hepatic impairment, unstable liver disease, suicidal behaviour and/or ideation, tattoo or other dermatological condition, or any physical (e.g., CVD, malignancy, seizures, ongoing malignancy), allergy, or mental condition precluding participation HBV and symptomatic HCV infection Resistance to any of the drug components Laboratory abnormality	
Drugs	**Intervention**	**Maintenance phase intervention:** Oral CAB 30 mg + RPV 25 mg q.d. for 4 weeks; followed by IM injection of CAB (600 mg) + RPV (900 mg); thereafter IM injection of CAB (400 mg) + RPV (600 mg) q.4.w.	
	Comparator(s)	Continuation of ART (ABC/DTG/3TC or alternative non-ABC NRTI backbone)	Continuation of ART (2 NRTIs + an INI, NNRTI, or a PI)
Duration	**Phase**		
	Screening	Up to 35 days	
	Induction phase	20 weeks	–
	Maintenance phase	96 weeks (CAB+RPV) or 100 weeks (ART)	52 weeks
	Extension phase	Indefinite period[c]	Up to 96 weeks

		FLAIR	ATLAS
	Long-term follow-up	52 weeks	52 weeks
Outcomes	**Primary end point**	Proportion of patients with virologic failure, (i.e., plasma HIV-1 RNA ≥ 50 copies/mL as per FDA Snapshot algorithm [Missing, Switch, or Discontinuation = Failure] at week 48) Noninferiority margin: < 6%	
	Secondary and exploratory end points	**Secondary (all measured at week 48):** Proportion of patients with plasma HIV-1 RNA < 50 copies/mL (with a noninferiority margin of –10%) and using FDA Snapshot algorithm Proportion of patients with plasma HIV-1 RNA < 200 copies/mL using FDA Snapshot algorithm Proportion of patients with confirmed virologic failure (2 consecutive plasma HIV-1 RNA levels ≥ 200 copies/mL after prior suppression to < 200 copies/mL) Absolute values and change from baseline in plasma HIV-1 RNA (log_{10} copies/mL) Absolute values and changes from baseline in CD4+ cell counts over time Incidence of disease progression (HIV-associated conditions, AIDS, and death) **HRQoL Outcomes Assessments/End Points:** Change from baseline (or week of first administration) in total and individual item/domain scores of the HIVTSQs/HIVTSQc and PIN questionnaire Proportion of participants considering pain and local reactions following injection to be extremely or very acceptable based on the acceptability score over time using PIN Change from baseline in HAT-QoL, SF-12, ACCEPT, NRS, and Preference questionnaire through week 96 (or withdrawal) **Exploratory:** Proportion of patients by subgroup(s) (e.g., by age, sex at birth, BMI, race, HIV-1 subtype, baseline CD4+, baseline third agent treatment class) with virologic failure, HIV-1 RNA < 50 copies/mL, and CD4+ cell counts over time **Safety Assessments/End Points:** Incidence and severity of AEs and laboratory abnormalities over time Proportion of participants who discontinue treatment due to AEs over time Absolute values and changes in laboratory parameters over time Change from baseline in fasting lipids over time	
Notes	**Publications**	None	None

ABC = abacavir; ABC/DTG/3TC = abacavir/dolutegravir/lamivudine; ACCEPT = Chronic Treatment Acceptance Questionnaire; AE = adverse event; ART = antiretroviral therapy; BMI = body mass index; CAB + RPV = cabotegravir plus rilpivirine; CD4+ = cluster of differentiation 4 positive; CDC = Centers for Disease Control and Prevention; CVD: cardiovascular disease; HAT-QoL = HIV/AIDS-targeted quality of life; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV-1 = HIV type 1; HIVTSQs/HIVTSQc = HIV Treatment Satisfaction Questionnaire status/change version; HRQoL = health-related quality of life; INI = integrase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NRS = Numeric Rating Scale; PI = protease inhibitor; PIN = Perception of Injection; q.4.w. = every 4 weeks; q.d. = daily; RCT = randomized controlled trial; RNA = ribonucleic acid; SF-12 = Short Form (12) Health Survey.

Note: Three additional reports were included: FLAIR Clinical Study Report,[7] ATLAS Clinical Study Report,[8] and Pooled Clinical Study Report.[33]

[a] Number represents patients randomized to the maintenance phase of the study.

[b] Stage 3 CDC disease excludes cutaneous Kaposi's sarcoma not requiring systemic therapy and historical or current CD4+ cell counts less than 200 cells/mm^3.

[c] Indefinite period represents a period until CAB and RPV injections are either locally approved and commercially available, the participant no longer derives clinical benefit, the participant meets a protocol-defined reason for discontinuation, or until development of either CAB or RPV injection is terminated.

Source: FLAIR Clinical Study Report,[7] ATLAS Clinical Study Report.[8]

Description of Studies

Two trials met the inclusion criteria for this review (Table 3). Study-specific details are listed in Table 4, and schematics of the trial designs are included in Figure 2 and Figure 3.

FLAIR (N = 566) and ATLAS (N = 618) were similarly designed phase III, randomized, multi-centre, OL, parallel-group, active-controlled, noninferiority trials conducted in HIV-1 infected adults. The objective of both trials was to demonstrate the noninferior antiviral activity of switching to long-acting CAB + RPV (400 mg + 600 mg) every four weeks for 48 weeks compared with the continuation of current antiretroviral treatment (CART) among virologically suppressed adults or ARTs. FLAIR enrolled ART-naive patients, all of which were subject to an ART induction regimen, whereas ATLAS included only ART-experienced patients who were stable on an ARV regimen. Both trials had patients initiate the CAB + RPV regimen after viral suppression was achieved at the end of induction phase or confirmed at baseline. A centrally conducted block randomization method was implemented in both trials, with a computer-generated randomization schedule. Details of the study design are described below, with additional details on treatment schedule given in the intervention section.

The FLAIR trial enrolled ART-naive patients, who underwent a 35-day screening phase to assess eligibility, during which approximately 22% were classified as screening failures primarily due to not meeting eligibility criteria. Eligible patients were enrolled in the induction phase, during which they received ABC/DTG/3TC or DTG with a non-ABC NRTI backbone (among HLA-b5701 positive patients) for 20 weeks. Patients who achieved virologic suppression (HIV-1 RNA < 50 copies/mL) at the end of the induction phase entered the maintenance phase. Patients eligible for the maintenance phase were randomized (1:1) to continue CART through 100 weeks or were switched to the CAB + RPV regimen through 96 weeks. The treatment regimen in the switch arm was implemented in two stages: oral lead-in period, in which patients received oral CAB + RPV (30 mg + 25 mg) once daily for at least four weeks; followed by one IM initiation injection of CAB + RPV (600 mg + 900 mg); and continuation doses of CAB + RPV (400 mg + 600 mg) every four weeks thereafter. Randomization was stratified by patient's HIV-1 RNA level at induction baseline (< 100,000 copies/mL or ≥ 100,000 copies/mL) and sex at birth.

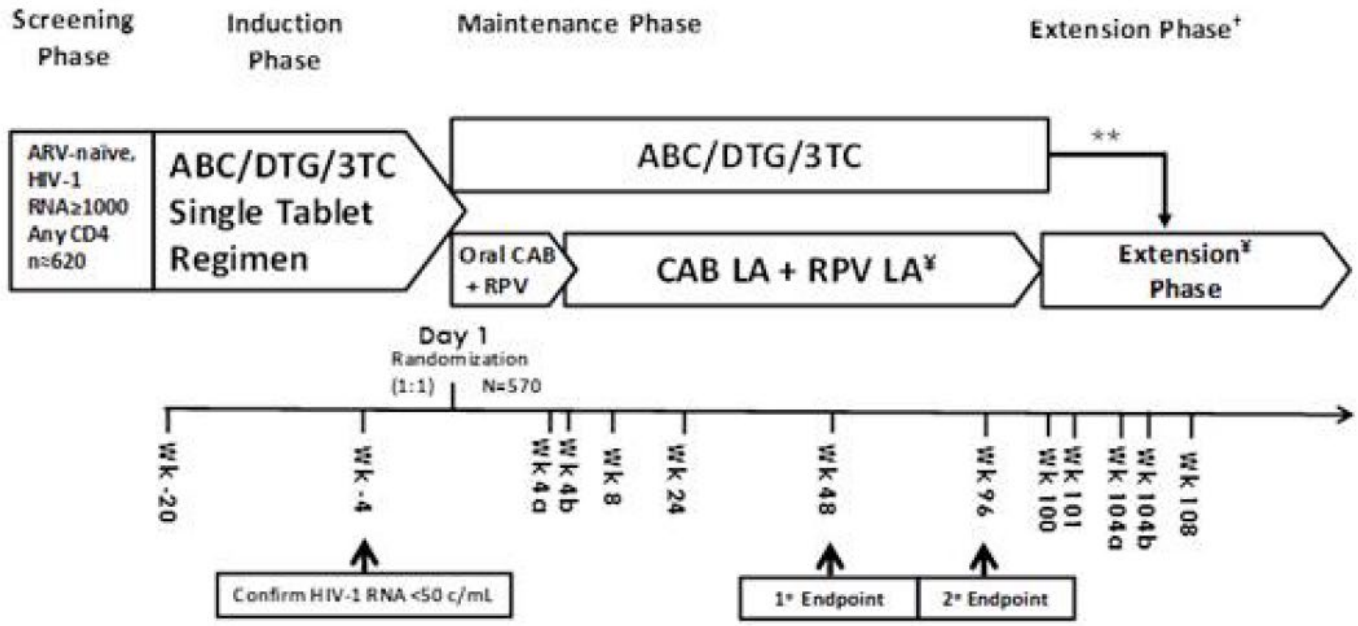
The ATLAS trial enrolled ART-experienced patients who were on a stable ARV regimen (containing two NRTIs plus an INI, NNRTI, or a PI) and did not have an induction phase. Eligible patients directly entered the maintenance phase following the assessment of eligibility and a 35-day screening phase. The maintenance phase was similar to FLAIR in which patients were randomized (1:1) to continue CART or were switched to the CAB + RPV regimen with a four-week oral lead-in dose followed by 52 weeks of IM dose as previously described. Randomization was stratified by baseline third agent class (PI, INI, or NNRTI) and sex at birth.

Each trial included an extension phase. Following the maintenance phase, patients receiving CAB + RPV in both trials continued the same treatment during the extension phase, whereas those who successfully completed CART treatment (i.e., without meeting study defined withdrawal criteria and who remained virologically suppressed) were allowed to switch to the IM CAB + RPV arm in the extension phase (with or without the oral lead-in dose in FLAIR and with the oral lead-in dose in ATLAS) or be withdrawn from the study. The extension phase lasted for 96 weeks in ATLAS and for an indefinite period in FLAIR (until long-acting CAB + RPV is either locally approved and commercially available, the patients no longer gain clinical benefit, the patients meet a protocol-defined reason for

discontinuation, or until development of either CAB or RPV long-acting formulation is terminated). Due to the minimal data available for the extension period of each trial, this review will be limited to the duration of the maintenance study. Finally, patients in either trial who received at least one IM dose of CAB + RPV and discontinued the regimen entered a 52-week long-term follow-up phase. All patients remained on suppressive highly active antiretroviral therapy for an additional 52 weeks after the last CAB + RPV injection.

FLAIR and ATLAS were conducted in parallel with the aim to pool data. Results of the pooled analysis informed the economic analysis in the pharmacoeconomic report. Details of the pooled analysis and results are described in Appendix 3.

Figure 2: Study Design of the FLAIR Trial



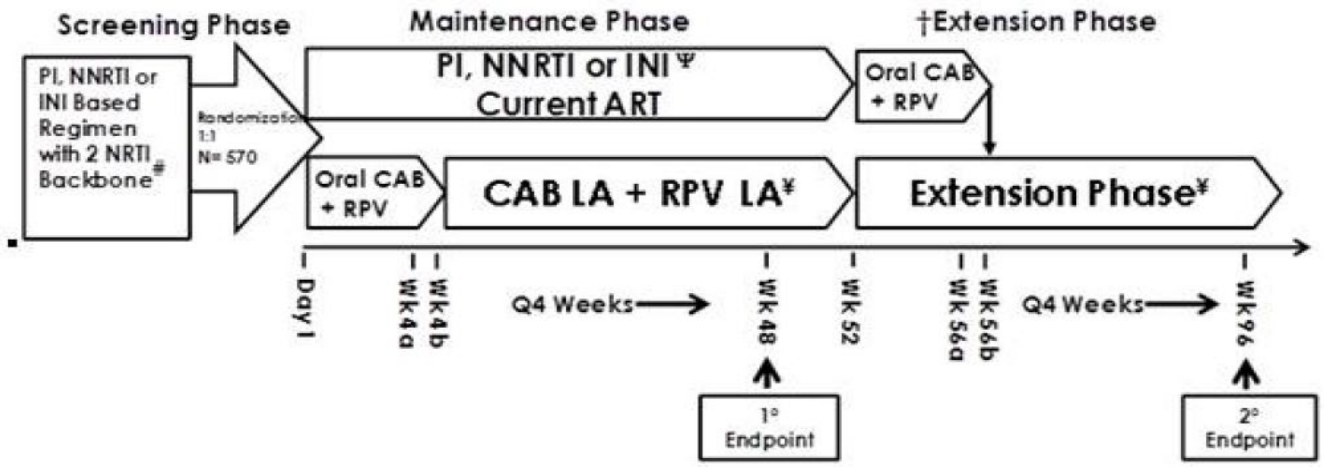
ABC/DTG/3TC = abacavir/dolutegravir/lamivudine; CAB + RPV = cabotegravir plus rilpivirine; CD4 = cluster of differentiation 4; HIV-1 = HIV type 1; LA = long acting; RNA = ribonucleic acid;

** Optional oral lead-in (investigator discretion) available from week 100 to week 104b.

¥ Patients who withdrew from CAB + RPV LA must enter 52-week long-term follow-up phase.

Source: FLAIR Clinical Study Report.[7]

Figure 3: Study Design of the ATLAS Trial



ABC/DTG/3TC = abacavir/dolutegravir/lamivudine; ART = antiretroviral therapy; CAB + RPV = cabotegravir plus rilpivirine; CART = current antiretroviral therapy; INI = integrase inhibitor; LA = long acting; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; Q4 = every 4; Wk = week.

Ψ INI-based regimens excluded ABC/DTG/3TC (Triumeq), an INI therapy, and was capped at approximately 40% of study enrolment for CART.

† Optional extension phase to CAB + RPV at week 52 for patients randomized to CART.

¥ Patients who withdrew from the CAB + RPV group had to go into the long-term follow-up phase.

Source: ATLAS Clinical Study Report.[8]

Populations

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria of FLAIR and ATLAS are described in Table 4. The main difference between the trials was the inclusion of ART-naive patients in FLAIR, defined as 10 days or less of prior therapy with any ARV agent (including an INI or NNRTI) following a diagnosis of HIV-1 infection. Patients with a screening plasma HIV-1 RNA of 1,000 copies/mL or greater only were eligible for the study induction and patients who achieved virologic suppression (HIV-1 RNA < 50 copies/mL) at the end of the induction phase entered the maintenance phase. In contrast, ATLAS included patients on an uninterrupted ARV regimen (either first- or second-line, with treatment switch not related to virologic failure (i.e., HIV-1 RNA ≥ 400 copies/mL) for at least six months prior to screening, with a plasma HIV-1 RNA < 50 copies/mL at screening. Both trials enrolled HIV-1 positive patients aged 18 years or older with screening for HIV-1 RNA levels ≥ 1,000 copies/mL, and without any exclusionary laboratory values. Notable exclusion criteria included having an active Centre for Disease Control (CDC) stage 3 disease, moderate to severe hepatic impairment or liver disease, pre-existing and disease-interfering physical or mental condition, high risk of seizures and suicide, tattoo or other dermatological condition in the gluteus region, evidence of hepatitis B virus infection, chronic and symptomatic HCV infection, untreated syphilis, and ongoing malignancy. Additionally, patients treated with an HIV-1 immunotherapeutic vaccine within 90 days of screening, and those with evidence of a primary resistance to INI or NNRTI were excluded. The ATLAS trial excluded patients on ABC/DTG/3TC; however, no such restriction was placed in the FLAIR trial; in fact this was the primary treatment received in the CART arm.

Baseline Characteristics

Data presented in Table 5 represents the baseline characteristics at the beginning of the maintenance phase, unless otherwise specified. Baseline patient demographic and disease characteristics appeared balanced between the treatment groups in both trials. Patients in ATLAS were older on average compared with FLAIR, with a mean age of approximately 42 and 36 years, respectively. There was a predominance of male patients (66% to 78%) compared with female patients (22% to 34%) in both trials. Only patients in FLAIR had a measurable viral load at the beginning of the induction phase (induction baseline), since these patients were ART-naive at the outset. The majority of these patients had a HIV-1 RNA level of 1,000 to less than 200,000 copies/mL at induction baseline. Viral load at maintenance baseline was not assessed in either trial, since all patients had low or undetectable plasma HIV-1 RNA levels prior to the start of this phase. CD4+ cell count was similar at the beginning of the maintenance phase across the trials and ranged from between 645 cells/mm^3 and 693 cells/mm^3. Approximately one-third of the patients in both trials were classified as having stage 1 HIV-1 infection, one-half had same-sex contact, and no more than 5% were injectable drug users. Patients with HCV did not exceed 10% in either trial. The majority (> 65%) of the patients had current and previous comorbidities, and greater than 70% were on concomitant medications. In ATLAS, one-half of the patients had an NNRTI as the third drug class during screening, followed by approximately one-third an INI, and the remaining a PI. However, the ARV distribution during the maintenance phase was not provided.

Table 5: Summary of Baseline Characteristics

Characteristic	FLAIR		ATLAS	
	CAB + RPV N = 283	CART N = 283	CAB + RPV N = 308	CART N = 308
Age (years), n (%)				
Mean (SD)	35.9 (10.17)	36.0 (9.82)	41.6 (9.99)	43.2 (11.43)
≤ 35	143 (51)	145 (51)	80 (26)	80 (26)
35 to 50	107 (38)	109 (39)	162 (53)	132 (43)
≥ 50	33 (12)	29 (10)	66 (21)	96 (31)
Sex, n (%)				
Female	63 (22)	64 (23)	99 (32)	104 (34)
Male	220 (78)	219 (77)	209 (68)	204 (66)
Race, n (%)				
White	216 (76)	201 (71)	214 (69)	207 (67)
Black	47 (17)	56 (20)	62 (20)	77 (25)
American Indian or Alaska Native	3 (1)	6 (2)	8 (3)	8 (3)
Asian-Central/South Asian heritage	2 (< 1)	1 (< 1)	1 (< 1)	0
Asian-East Asian heritage	1 (< 1)	2 (< 1)	13 (4)	8 (3)
Asian-Japanese heritage	8 (3)	12 (4)		
Asian-South-East Asian heritage	1 (< 1)	0	8 (3)	5 (2)
Native Hawaiian or Other Pacific Islander	1 (< 1)	0	0	1 (< 1)
Multiple	4 (1)	3 (1)	2 (< 1)	2 (< 1)
Missing	0	2 (< 1)		
Induction baseline[a] HIV-1 RNA (log_{10} copies/mL), mean (SD)	4.43 (0.69)	4.39 (0.69)		
Induction baseline HIV-1 RNA (copies/mL), n (%)				
< 1,000	9 (3)	5 (2)		
1,000 to < 10,000	64 (23)	71 (25)		

Characteristic	FLAIR		ATLAS	
	CAB + RPV N = 283	CART N = 283	CAB + RPV N = 308	CART N = 308
10,000 to < 50,000 50,000 to < 100,000 100,000 to < 200,000 ≥ 200,000	95 (34) 59 (21) 30 (11) 26 (9)	113 (40) 38 (13) 33 (12) 23 (8)		
Time from first plasma HIV-1 RNA < 50 copies/mL[b]/ART[c] until maintenance phase, weeks[b]/months[c], mean (SD)	14.53 (3.37)	14.93 (2.88)	64.7 (41.97)	65.1 (45.23)
Maintenance baseline CD4+ count (cells/mm^3) Mean (SD)	666.4 (272.14)	645.7 (253.44)	678.5 (257.11)	692.8 (288.74)
HBV and HCV test results at induction Baseline, n (%) HBV only HCV only HBV and HCV Neither	 0 18 (6) 1 (< 1) 264 (93)	 0 9 (3) 0 274 (97)	 0 23 (7) 0 285 (93)	 0 31 (10) 0 277 (90)
CDC category, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
HIV risk factors, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Current medical conditions, n (%)	204 (72)	185 (65)	235 (76)	202 (66)
Concomitant medication (maintenance phase)	243 (86%)	235 (83%)	255 (83%)	217 (70%)
Concomitant ART at end of induction phase	[redacted]	[redacted]		
ARTs taken during screening PI + NRTIs NNRTI + NRTIs INI + NRTIs			 51 (17%) 155 (50%) 102 (33%)	 54 (18%) 155 (50%) 99 (32%)

ART = antiretroviral therapy; CAB + RPV = cabotegravir plus rilpivirine; CART = current antiretroviral treatment; CD4+ = cluster of differentiation 4 positive; CDC = Centers for Disease Control and Prevention; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV-1 = HIV type 1; INI = integrase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RNA = ribonucleic acid; SD = standard deviation.

[a] Induction baseline (week –20) refers to the last available value prior to and including the date of first Induction phase dose of study drug.

[b] Applies to FLAIR only.

[c] Applied to ATLAS only.

Source: FLAIR Clinical Study Report,[7] ATLAS Clinical Study Report.[8]

Interventions

Both trials were OL in nature, therefore no blinding was conducted. Treatment during each study period is described as follows.

Induction phase: This initial treatment phase is applicable to FLAIR only. All patients received oral ABC/DTG/3TC (600 mg/50 mg/300 mg, available as an STR) or DTG with a non-ABC NRTI backbone (among HLA-b5701 positive patients) once daily for 20 weeks, with or without food, with the aim to lower their plasma HIV-1 RNA to less than 50 copies/mL.

Maintenance phase: Patients in both trials were randomized (1:1) to remain on oral CART or switch to the CAB + RPV regimen. In the FLAIR study, patients in the CART group continued on the same treatment they received during the induction phase of ABC/DTG/3TC or DTG plus the alternative non-ABC backbone. In ATLAS, patients in the CART group continued their regular ARV regimen (initial or second regimen) prior to screening, which included two NRTIs in addition to one of the following: INI with the exception of ABC/DTG/3TC (NNRTI), or boosted PI (or atazanavir, unboosted). The CAB + RPV treatment regimen in the switch group was implemented in three stages:

- Oral lead-in: During this period, oral CAB + RPV (30 mg/25 mg, one tablet each) was administered once daily for at least four weeks, at approximately the same time each day with a meal
- IM injection: Patients received an initiation dose of CAB + RPV (600 mg/900 mg, one 3 mL injection each) during their first IM injection visit (within two hours of the final oral dose), followed by CAB + RPV (400 mg/600 mg, one 2 mL injection each) every four weeks thereafter.

Extension phase: During this period, patients in the CAB + RPV group continued their IM dosing as per usual, and those transitioning to CAB + RPV from the CART group followed the same treatment regimen (with or without oral lead-in as shown in Figure 2 and Figure 3, followed by IM injection).

CART regimen was administered without regard to food throughout the study, whereas no such information was provided for IM injection. No dose reductions, modifications, or changes in the frequency of any drug components were allowed during the study. There was a provision to allow a short-term oral treatment with CAB + RPV (30 mg + 25 mg), termed “oral bridging,” among patients who missed their first scheduled IM CAB + RPV injections following the oral lead-in period. In certain circumstances (following the greater than four-week oral bridge and prior to continuation dosing), repeating the initiation doses of CAB + RPV was allowed. Oral bridging was done in consultation with the medical monitor.

Concomitant, permitted, and prohibited medications: All concomitant medications, blood products, and vaccines, whether prescribed or over-the-counter, were evaluated for potential drug-drug interactions. Notable classes of concomitant medications included the following, with appropriate dosing and timing per investigator’s discretion and guideline: antacid and H_2-antagonists, non–HIV-1 vaccines, metformin, methadone, and hormonal contraception. According to the clinical expert consulted by CADTH, concomitant medications permitted during the trials would not be expected to confound the efficacy of the study treatments. The following medications or therapies were not permitted at any time during the study: HIV-1 immunotherapeutic vaccines, systemic immunomodulators, acetaminophen (if acute viral hepatitis present), chronic use of systemic glucocorticoids,

HCV therapy, certain antibiotics, concurrent administration of medications that decrease concentration of any study drug components, and other experimental agents, ARV drugs (not otherwise specified), cytotoxic chemotherapy, or radiation therapy.

Outcomes

Table 6: Outcome Measures Included in Each Study

Outcome measure	FLAIR	ATLAS
Virologic failure (plasma HIV-1 RNA ≥ 50 copies/mL)	Primary	Primary
Virologic suppression (plasma HIV-1 RNA < 50 copies/mL)	Secondary	Secondary
Confirmed virologic failure (2 consecutive plasma HIV-1 RNA levels ≥ 200 copies/mL after prior suppression to < 200 copies/mL)	Secondary	Secondary
CD4+ cell count	Secondary	Secondary
HRQoL measures (HIVTSQ, PIN, ACCEPT, HAT-QoL, SF-12, and NRS)	Secondary	Secondary
Subgroup analysis by baseline stratification factors	Exploratory	Exploratory

ACCEPT = Chronic Treatment Acceptance Questionnaire; CD4+ = cluster of differentiation 4 positive; HAT-QoL = HIV/AIDS-targeted quality of life; HIV-1 = HIV type 1; HIVTSQ = HIV Treatment Satisfaction Questionnaire; HRQoL = health-related quality of life; NRS = Numeric Rating Scale; PIN = Perception of Injection; RNA = ribonucleic acid; SF-12 = Short Form (12) Health Survey.

Source: FLAIR Clinical Study Report,[7] ATLAS Clinical Study Report.[8]

The primary efficacy outcome in FLAIR and ATLAS was the proportion of patients with virologic failure (i.e., HIV-1 RNA ≥ 50 copies/mL at week 48, as determined by the FDA-defined Snapshot algorithm). Under this approach, all missing data were treated as failures.

A number of secondary and exploratory outcomes were assessed, of which the ones identified in the review protocol (Table 3) are listed as follows: virologic suppression, CD4+ cell count, drug resistance, adherence, and HRQoL (Table 6). Virologic suppression was defined as the proportions of patients with HIV-1 RNA of less than 50 copies/mL at week 48, as determined by the FDA Snapshot algorithm. In addition to the cut-off based on 50 copies/mL, viral load based on a 200 copies/mL cut-off was also measured. Changes in plasma HIV-1 RNA (log_{10} copies/mL) and CD4+ cell count from baseline were estimated at week 48. The magnitude and direction of the CD4+ cell count was compared with the baseline value rather than a pre-established cut-off.

Genotypic and phenotypic resistance testing to the study drugs (including CAB, RPV, and other on-study ART) was performed by a central laboratory. Data were summarized for patients who met the criteria for confirmed viral failure (CVF). Patients were classified as CVF if they experienced a rebound (i.e., two consecutive plasma HIV-1 RNA levels ≥ 200 copies/mL after prior suppression to < 200 copies/mL).

Both FLAIR and ATLAS measured a number of patient-reported HRQoL end points, of which the ones relevant as per the review protocol (Table 3) are discussed as follows.

The HIVTSQ is a HIV-specific questionnaire that assesses treatment satisfaction in patients with the disease. The scale has two versions, status and change (termed HIVTSQs and HIVTSQc, respectively), and is comprised of 10 and 12 items, respectively. HIVTSQc is used to address potential ceiling effects associated with HIVTSQs. Both versions are rated on a seven-point Likert scale. The status version ranges from 0 (very dissatisfied) to 6 (very

satisfied), with a total score from 0 to 66. The change version ranges from –3 (much less satisfied) to 3 (much more satisfied), with a total score ranging from –33 to 33. Higher scores indicate a greater improvement in treatment satisfaction with the new treatment, and a score of 0 represents no change in satisfaction. Both versions were found to have internal consistency. The status version has evidence of weak to moderate construct validity.[34] Evidence of responsiveness and MID was not identified for either version.

The PIN questionnaire evaluates patients' perception of pain and ISRs following injections. This questionnaire consists of four dimensions (Bother from ISRs, Leg Movement, Sleep, and Acceptance of ISRs), and 21 items in total. Both dimensions and items are scored on a Likert scale ranging from 1 (most favourable option) to 5 (least favourable). Evidence of validity, reliability, responsiveness, and MID was not identified for this scale.

The ACCEPT questionnaire is a generic measure of medication acceptance, consisting of 25 items within seven domains. Each item is rated on a three-point Likert scale, where a higher score indicates greater acceptance. The General Acceptance domain of the ACCEPT questionnaire was selected for inclusion in the studies, and has three items and produces a total score of 100. The scale showed high reliability, and some evidence of convergent validity.[35] However, evidence of responsiveness and MID was not identified in the literature.

The HAT-QoL is an instrument designed to assess HRQoL of people with HIV/AIDS. The scale has 42 items, grouped into nine dimensions. Three out of the nine dimensions were selected for inclusion in the two studies (life satisfaction, disclosure worries, and HIV medication concerns), which used a 14-item adapted version of the scale. Each item is rated on a five-point Likert scale from 1 to 5, which are added to obtain dimension scores (range = 0 to 100; higher scores indicate better function and well-being). There is evidence of acceptable construct validity and reliability[36,37] (internal consistency and test-retest) for the 42-item original version; however, no information on responsiveness and MID were identified.

The NRS measures the level of pain experienced following injections. This is a one-item scale answered on an 11-point scale from 0 (no pain) to 10 (extreme pain). The scale is widely used and validated in other diseases and clinical situations; however, evidence of validity, reliability, responsiveness, and MID in patients living with HIV-1 was not identified.

The SF-12 is a generic measure of HRQoL based on the 36-item version of the survey (SF-36). The scale is composed of eight concepts, categorized as physical and mental component scores (PCS and MCS, respectively). Both PCS and MCS range from 0 to 100, where a higher score indicates better HRQoL. Limited evidence of discriminant validity for the PCS, but not the MCS, was identified.[38] There was no evidence of reliability, responsiveness, and MID for patients with HIV-1 identified from the literature.

Harms outcomes included the monitoring of all AEs, ISRs, clinical laboratory tests, vital signs, electrocardiograms, HIV-1–associated conditions, and bone and renal markers. An AE was defined as "any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product."

Statistical Analysis

Noninferiority Margin

In both FLAIR and ATLAS, a noninferiority margin of 6% for virologic failure was used. Therefore, the CAB + RPV arm in each trial was considered to be noninferior to the comparator arm if the upper bound of the two-sided 95% CI for the primary outcome (difference in the proportion of patients with HIV-1 RNA ≥ 50 copies/mL) was less than 6%. The FDA Guidance to Industry report[39] recommends the use of a 4% noninferiority margin for virologic failure in switch trials. However, data from the two studies were pooled to assess noninferiority for the primary efficacy end point, and a 4% margin was used there (described in Appendix 3).

In contrast to virologic failure, a noninferiority margin of –10% was used for virologic suppression, where noninferiority would be demonstrated if the lower limit of the 95% CI of the difference in responder rate between the two treatment groups was greater than –10%.

Sample Size

Both studies assumed a true virologic failure rate (HIV-1 RNA ≥ 50 copies/mL) to be 3% for the CAB + RPV group and 2% for the CART group, corresponding to approximately 97% power to demonstrate noninferiority at 6% at a 2.5% one-sided significance level for the primary analysis. This resulted in approximately 285 patients per treatment group. This sample size was also estimated to provide at least 90% power to demonstrate noninferiority in the proportion of patients with HIV-1 RNA of less than 50 copies/mL over a range of true response rates on the basis of a –10% noninferiority margin and a 2.5% one-sided significance level (key secondary end point). Additionally, 285 patients in each group allowed noninferiority of the key secondary end points to be shown with at least 94% power, assuming a true response rate of 87% in both treatment groups.

The failure rate for the CAB + RPV group was informed by two phase IIb studies (LATTE and LATTE-2) and the failure rate for the comparator or control arm was based on a number of recent switch studies involving treatment-naive and experienced patients.

Statistical Analysis for Efficacy End Points

The protocol-specified objectives were planned to be analyzed at three timepoints for FLAIR (week 48, 96, and 124) and two timepoints for ATLAS (week 48 and 96). All statistical tests were conducted at a one-sided 2.5% level of significance unless otherwise indicated. In both trials, the primary outcome (between-group difference in HIV-1 RNA ≥ 50 copies/mL at week 48) was calculated based on stratum-adjusted proportions using Cochran–Mantel–Haenszel weights. For the primary comparison, the analysis was stratified by HIV-1 RNA at induction baseline (<100,000 copies/mL or ≥ 100,000 copies/mL) and sex at birth in FLAIR and by baseline third agent class (INI, NNRTI, or PI) and sex at birth in ATLAS. Treatment heterogeneity across randomization strata was assessed individually using the weighted least squares chi-square statistics and a one-sided alpha level of 10%. The key secondary virologic end point (proportion of responders [i.e., HIV-1 RNA < 50 copies/mL per snapshot at week 48]) was analyzed using the same analysis method and stratification factors as previously noted.

The primary and key secondary efficacy end points were assessed in various per-specified subgroups defined by demographic and baseline characteristics. Two of the subgroups relevant to this review, baseline plasma viral load and baseline CD4+ cell count prior to

ARV regimen, were applicable to FLAIR only as patients in ATLAS enrolled in the study having experienced with a stable ARV regimen. Among other subgroups identified in the CADTH review protocol, biologic sex at birth was assessed in both trials. The 95% CIs for the treatment differences were calculated using an unconditional exact method based on two inverted one-sided tests.

Sensitivity analyses for the primary and key secondary efficacy end points were conducted using the PP population, which were compared for consistency with the results from the primary intention-to-treat–exposed (ITT-E) population analysis.

The following additional secondary efficacy end points were analyzed over time during the maintenance phase: HIV-1 RNA using a cut-off of 200 copies/mL and CVF. All time-to-event analyses of failure were performed using the Kaplan–Meier nonparametric method. The estimated proportion of patients without any of these events at week 48 for each treatment group, and the treatment difference with 95% CI were presented. Finally, absolute values and change from maintenance baseline in all continuous efficacy variables (including virologic and immunologic end points) were summarized over time using descriptive statistics.

Genotypic and phenotypic resistance data from patients with CVF (defined as two consecutive plasma HIV-1 RNA levels ≥ 200 copies/mL after prior suppression to < 200 copies/mL) were summarized descriptively.

HRQoL Outcomes Analyses

All HRQoL outcomes were continuous variables and were summarized by visit. Changes from baseline were calculated at different timepoints (week 24, 41, 44, and 48) depending on the week a particular HRQoL outcome was last assessed, with baseline defined as the week that the HRQoL outcome was first assessed. Additionally, the HRQoL end points that are designed to evaluate injection-associated AEs (PIN and NRS) were assessed in the CAB + RPV group only. A statistical comparison between treatment groups was performed at each visit for HAT-QoL, HIVTSQs and HIVTSQc, ACCEPT, and SF-12 using an analysis of covariance model with the following covariates as fixed effects: treatment, age, sex at birth, race, baseline score value (except for HIVTSQc), induction baseline viral load (only for FLAIR), and baseline third agent class (only for ATLAS).

Multiple Comparisons and Multiplicity

Multiple statistical testing was carried out in a hierarchical manner, as shown in Table 7. The following efficacy end points were tested in a sequential manner, such that testing was stopped with the first of these tests failing to reach statistical significance and no subsequent tests were considered statistically significant. The simultaneous assessment of noninferiority and superiority for the primary outcome negated the necessity for multiple comparison adjustment to assess superiority of CAB + RPV IM every four weeks over CART. Superiority favouring CAB + RPV was declared if the upper end of the CI was below 0% for the primary efficacy end point of virologic suppression. The P value for superiority was only calculated if superiority was declared. The overall one-sided type I error rate in testing these hypotheses was controlled at a nominal level. Finally, analysis at week 96 was considered supportive of the primary end point, therefore, no adjustment for multiplicity was conducted.

Table 7: Statistical Testing Hierarchy for Multiplicity

Testing sequence	Alpha level
Noninferiority of CAB + RPV q.4.w. IM to CART for HIV-1 RNA ≥ 50 copies/mL at week 48 (using US FDA Snapshot algorithm)	1-sided 2.5% level of significance
Superiority of CAB + RPV q.4.w. IM to CART for HIV-1 RNA ≥ 50 copies/mL at week 48 (using US FDA Snapshot algorithm)	2-sided 5% level of significance
Noninferiority of CAB + RPV q.4.w. IM to CART for HIV-1 RNA < 50 copies/mL at week 48 (using US FDA Snapshot algorithm)	2-sided 5% level of significance
Superiority of CAB + RPV q.4.w. IM to CART for change from maintenance baseline HIVTSQs total score at week 44	2-sided 5% level of significance
Changes in the PIN acceptance score from week 5 to week 41 (FLAIR only) and change from week 5 to week 48 (both trials)	2-sided 5% level of significance

CAB + RPV = cabotegravir plus rilpivirine; CART = current antiretroviral therapy; HIV-1 = HIV type 1; HIVTSQs = HIV Treatment Satisfaction Questionnaire status version; IM = intramuscular; PIN = Perception of Injection; q.4.w. = every 4 weeks; RNA = ribonucleic acid.

Source: FLAIR Clinical Study Report,[7] ATLAS Clinical Study Report.[8]

Missing Data

The primary approach for missing data handling was consistent with the FDA Snapshot approach, in which all missing data were considered treatment failures regardless of reasons. All non-completers as well as those with an HIV-1 RNA measurement of 50 copies/mL or more were therefore considered virologic failures. Only patients with an HIV-1 RNA level of less than 50 copies/mL within the pre-specified time window of the OL phase were classified as virologic successes.

The last observation carried forward approach was used for other health outcomes data (e.g., HRQoL). In the last observation carried forward approach, missing values were carried forward from the previous, non-missing, available, on-treatment assessment from the same dimension.

Statistical Analysis for Safety End Points

Data for safety end points were collected through week 48 in the maintenance phase. Data beyond week 48 were available for a smaller proportion of patients, therefore this review is limited to data up to week 48. Safety parameters including most notable safety end points (listed in Table 3) were summarized using descriptive statistics. Changes from baseline in renal and bone biomarkers were summarized by treatment and visit.

Analysis Populations

Results are reported for the following populations in the FLAIR and ATLAS trials:

- ITT-E: All randomly assigned patients who received at least one dose of study drug during the maintenance phase of the study. Patients were assessed according to their randomized treatment, regardless of the treatment they received; the primary efficacy analysis was based on the ITT-E population.
- PP Population: All patients in the ITT-E population with the exception of those with important protocol deviations; the PP population was used for sensitivity analysis of the primary and key secondary efficacy end points.
- Safety Population: All randomized patients who received at least one dose of study drug; patients were assessed according to actual treatment received and unless otherwise stated, the safety population was used for safety analyses.

- CVF Population: All patients in the ITT-E population who met the CVF criteria, (i.e., rebound as indicated by two consecutive plasma HIV-1 RNA levels ≥ 200 copies/mL after prior suppression to < 200 copies/mL).

Results

Patient Disposition

A summary of patient disposition in the two trials by study period is given in Table 8. Of the patients who were screened for study participation, 22% patients in FLAIR and 12% patients in ATLAS were considered screening failures, primarily due to not meeting eligibility criteria. In FLAIR, among the patients who entered the 20-week induction period, 10% did not complete, primarily due to a lack of efficacy (5%). In both trials, the proportion of patients who withdrew from the study during the maintenance phase was low (< 10%) and comparable between the treatment groups (range 6% to 9%). The most common causes for study discontinuation were AEs, lack of efficacy, and patient withdrawal. Of note, five patients in each trial discontinued during the oral lead-in period prior to receiving any CAB + RPV injection. At the time of the data cut-off, more than 90% of the patients in both trials were continuing through or completed the maintenance phase. In ATLAS, a total of 61 patients remained ongoing during the extension phase (25 in CAB + RPV; 36 in CART); 496 patients (n = 252 in CAB + RPV; n = 244 in CART) transitioned into Study 207966. Approximately 5% to 7% patients in both trials discontinued treatment after starting CAB + RPV regimen, and subsequently entered the long-term follow-up phase.

Table 8: Patient Disposition

	FLAIR		ATLAS	
	CAB + RPV	CART	CAB + RPV	CART
Screened, N	809		705	
Screen failures, n (%)	178 (22)		87 (12)	
Did not meet eligibility criteria	149 (18)		74 (10)	
Lost to follow-up	8 (< 1)		5 (< 1)	
Physician decision	13 (2)		2 (< 1)	
Withdrawal by subject	9 (1)		7 (< 1)	
Induction phase, N			NA	NA
Entered		631		
Received study drug		629		
Completed		566 (90)		
Withdrawn, n (%)		63 (10)		
Lack of efficacy		30 (5)		
Adverse events		4 (< 1)		
Lost to follow-up		5 (< 1)		
Physician decision		5 (< 1)		
Protocol deviation		11 (2)		
Protocol-specified withdrawal criterion met		2 (< 1)		
Withdrawal by subject		10 (2)		

	FLAIR		ATLAS	
	CAB + RPV	CART	CAB + RPV	CART
Maintenance phase, N (%)				
Randomized	283	283	310	308
Discontinued	25 (9)	22 (8)	26 (8)	18 (6)
Reason for discontinuation, N (%)				
Adverse events	9 (3)	4 (1)	13 (4)	5 (2)
Lack of efficacy (CVF)	5 (2)	3 (1)	3 (< 1)	4 (1)
Protocol deviation	0	1 (< 1)	5 (2)	3 (< 1)
Protocol-specified withdrawal criterion met			1 (< 1)	0
Lost to follow-up	2 (< 1)	2 (< 1)	1 (< 1)	1 (< 1)
Physician decision	2 (< 1)	5 (2)	2 (< 1)	0
Withdrawal by patient	7 (2)	7 (2)	1 (< 1)	5 (2)
Nonfatal AEs resulting in study withdrawal	9 (3)	4 (1)	13 (4)	4 (1)
Ongoing/completed, n (%)	258 (91)	261 (92)	281 (91)	290 (94)
Long-term follow-up, n (%)	14 (5)	0	23 (7)	3 (< 1)
ITT-E, N	283 (100)	283 (100)	308 (99)	308 (100)
PP, N	278 (98)	282 (> 99)	294 (95)	292 (95)
Safety, N	283 (100)	283 (100)	308 (99)	308 (100)

AE = adverse event; CAB + RPV = cabotegravir plus rilpivirine; CART = current antiretroviral treatment; CVF = confirmed virologic failure; ITT-E = intention-to-treat–exposed; NA = not applicable; PP = per protocol.

Source: FLAIR Clinical Study Report,[7] ATLAS Clinical Study Report.[8]

Exposure to Study Treatments

Table 9: Exposure in the FLAIR and ATLAS Trials – Maintenance Phase (Safety Population)

Exposure	FLAIR		ATLAS	
	CAB + RPV[a] N = 283	CART[b] N = 283	CAB + RPV[c] N = 308	CART N = 308
Overall exposure, days mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Weeks, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	
[redacted]	[redacted]		[redacted]	

CAB + RPV = cabotegravir plus rilpivirine; CART = current antiretroviral treatment; SD = standard deviation.

Source: FLAIR Clinical Study Report,[7] ATLAS Clinical Study Report.[8]

[redacted]

Efficacy

Only those efficacy outcomes and analyses of subgroups identified in the review protocol are reported below. Unless otherwise specified, this review is focused on the maintenance phase of the trials (up to week 48), including the oral lead-in and the IM injection period. Accordingly, assessment of outcomes is done from maintenance baseline (i.e., assessments occurring at or after randomization [day 1]).

Viral Load

Overall, the treatment arms in each trial had comparable virologic responses at week 48 (Table 10). Virologic failure, defined as HIV-1 RNA of 50 copies/mL or greater at week 48, was seen in 2.1% and 2.5% patients in the CAB + RPV and CART groups in FLAIR, respectively. In ATLAS, 1.6% patients in the CAB + RPV group had virologic failure compared with 1.0% patients in the CART group. Treatment differences in FLAIR and ATLAS were –0.4% (95% CI, −2.8 to 2.1) and 0.6% (95% CI, −1.2 to 2.5), respectively. In both cases, the pre-specified noninferiority margin of 6% was met, as the upper bound of 95% CI for the adjusted treatment difference between CAB + RPV and CART was below

6%. CAB + RPV was not found to be superior over CART, since the upper end of the CI was below 0%. The secondary analyses (using PP population) supported the primary analyses. The primary reason for virologic failure was patient discontinuation due to lack of efficacy. Approximately 4% to 6% of patients across the studies had no virologic data at week 48. Among the patients with no virologic data, more patients in the CAB + RPV group discontinued due to AEs.

In both trials, more than 90% of randomized patients at baseline achieved the FDA-defined Snapshot algorithm of HIV-1 RNA of less than 50 copies/mL at week 48. The proportions of patients with HIV-1 RNA of less than 50 copies/mL using the FDA-defined Snapshot approach were 94% versus 93% between CAB + RPV and CART, respectively, in FLAIR, and 93% versus 95% between CAB + RPV and CART, respectively, in ATLAS. Treatment differences in FLAIR and ATLAS were 0.4% (95% CI, –3.7 to 4.5) and –3.0% (95% CI, –6.7 to 0.7), respectively. Both trials met the pre-specified noninferiority margin of 10% since the lower limit of the 95% CI of the difference in responder rate between the two treatment groups was greater than –10%. These findings were consistent in the PP population.

The proportion of patients with CVF or those who discontinued due to treatment-related reasons or lack of efficacy did not exceed 4% at or before week 48 in either trial. No more than four patients in either trial had CVF and a plasma HIV-1 RNA level of 200 copies/mL or greater. Among the patients with CVF, the mean plasma HIV-1 RNA level ranged between 2.7 and 3.4 $\log_{10}$ copies/mL across trials. Among all other patients, the mean plasma HIV-1 RNA level was approximately 1.5 $\log_{10}$ copies/mL at the start of the maintenance phase, which remained at the same level through week 48 (Table 10).

In FLAIR, all the review protocol-specified subgroups were assessed for the virologic end points, since patients in this trial were ART-naive at enrolment. None of the three subgroups (e.g., sex at birth, CD4+ cell count, and HIV-1 RNA level prior to ARV regimen) showed any statistically significant difference between the treatment groups with respect to virologic failure. A similar pattern was found for virologic suppression; the treatment groups did not show any statistically significant difference based on the aforementioned subgroups. In ATLAS, sex at birth did not show any statistically significant difference between treatment groups for virologic failure or suppression (Table 11).

Table 10: Virologic Efficacy Outcomes in FLAIR and ATLAS – Maintenance Phase

Virologic efficacy outcomes	FLAIR		ATLAS	
	CAB + RPV	CART	CAB + RPV	CART
Virologic failure				
ITT-E population at week 48				
HIV-1 RNA ≥ 50 copies/mL at week 48, n/N (%)	6/283 (2.1)	7/283 (2.5)	5/308 (1.6)	3/308 (1.0)
Difference in proportion[a], % (95% CI)	–0.4 (–2.8 to 2.1)		0.6 (–1.1 to 2.4)	
Adj. difference in proportion[b], % (95% CI)	–0.4 (–2.8 to 2.1) NI met at 6%		0.6 (–1.2 to 2.5) NI met at 6%	
Reasons for virologic failures, n (%): • **Data in window not below threshold** • **Discontinued for lack of efficacy** • **Discontinued for other reason** • **Change in background therapy**	 2 (0.7) 4 (1.4) 0 0	 2 (0.7) 3 (1.1) 2 (0.7) 0	 1 (0.3) 3 (1.0) 1 (0.3) 0	 1 (0.3) 2 (0.6) 0 0
No virologic data, n (%):	12 (4.2)	12 (4.2)	18 (5.8)	11 (3.6)

Virologic efficacy outcomes	FLAIR		ATLAS	
	CAB + RPV	CART	CAB + RPV	CART
• Discontinued study due to AE or death • Discontinued for other reason • On study but missing data in window	8 (2.8) 4 (1.4) 0	2 (0.7) 10 (3.5) 0	11 (3.6) 7 (2.3) 0	5 (1.6) 6 (1.9) 0
PP population at week 48				
HIV-1 RNA ≥ 50 copies/mL at week 48, n/N (%)	6/278 (2.2)	7/282 (2.5)	4/294 (1.4)	3/292 (1.0)
Difference in proportion[a], % (95% CI)	–0.3 (–2.8 to 2.2)		0.3 (–1.4 to 2.1)	
Adj. difference in proportion[b], % (95% CI)	–0.3 (–2.8 to 2.2)		0.3 (–1.4 to 2.1)	
Virologic suppression				
ITT-E population at week 48				
HIV-1 RNA < 50 copies/mL at week 48, n/N (%)	265/283 (94)	264/283 (93)	285/308 (93)	294/308 (95)
Difference in proportion[a], % (95% CI)	0.4 (–3.7 to 4.4)		–2.9 (–6.7 to 0.8)	
Adj. difference in proportion[b], % (95% CI)	0.4 (–3.7 to 4.5) NI met at –10%		–3.0 (–6.7 to 0.7) NI met at –10%	
PP population at week 48				
HIV-1 RNA < 50 copies/mL at week 48, n/N (%)	260/278 (94)	263/282 (93)	276/294 (94)	280/292 (96)
Difference in proportion[a], % (95% CI)	0.3 (–3.9 to 4.4)		–2.0 (–5.6 to 1.6)	
Adj. difference in proportion[b], % (95% CI)	0.3 (–3.8 to 4.4)		–2.0 (–5.6 to 1.5)	
Treatment/Efficacy-related discontinuation with or without confirmed viral failure (= failure)				
ITT-E population at week 48				
CVF or discontinuation due to treatment related reasons[c] at or prior to week 48, n/N (%)	9/283 (3.2)	5/283 (1.8)	13/308 (4)	5/308 (2)
Proportion of subjects without CVF or not discontinued due to treatment-related reasons at or prior to week 48, K-M estimate (95% CI)	96.7 (93.8 to 98.3)	98.2 (95.7 to 99.2)	95.7 (92.7 to 97.5)	98.3 (96.1 to 99.3)
Difference in proportions, estimated difference[a] (95% CI)[d]	–1.5 (–4.1 to 1.2)		–2.7 (–5.4 to 0.1)	
CVF or discontinuation due to CVF or lack of efficacy at or prior to week 48, n/N (%)	5/283 (1.8)	3/283 (1.1)	3/308 (< 1)	4/308 (1)
Proportion of subjects without CVF or not discontinued due to lack of efficacy at or prior to week 48, K-M estimate (95% CI)	98.2 (95.7 to 99.2)	98.9 (96.7 to 99.7)	99.0 (96.9 to 99.7)	98.7 (96.5 to 99.5)
Difference in proportions, estimated difference[a] (95% CI)[d]	–0.8 (–2.8 to 1.3)		0.3 (–1.4 to 2.0)	
Confirmed virologic failure (2 consecutive HIV-1 RNA levels ≥ 200 copies/mL after prior suppression to < 200 copies/mL)				
Confirmed virologic failure, n (%)	4 (1.4)	3 (1.1)	3 (1.0)	4 (1.3)
Confirmed virologic failure HIV-1 RNA (log_{10} copies/mL), mean (SD)	2.74 (0.30)	2.86 (0.48)	3.36 (1.00)	3.00 (0.68)
HIV- 1 RNA ≥ 200 copies/mL	4 (1.4)	2 (0.7)	3 (1.0%)	2 (0.6%)
Summary of plasma HIV-1 RNA levels (log_{10} copies/mL)				
Maintenance baseline, n	283	283	308	308
Maintenance baseline, mean (SD)	1.52 (0.09)	1.52 (0.17)	1.51 (0.17)	1.50 (0.04)
Week 48, n	248	263	265	292
Week 48, mean (SD)	1.51 (0.09)	1.52 (0.11)	1.50 (0.05)	1.52 (0.11)
Week 52, n			126	36

Virologic efficacy outcomes	FLAIR		ATLAS	
	CAB + RPV	CART	CAB + RPV	CART
Week 52, mean (SD)			1.51 (0.08)	1.504 (0.02)

Adj = adjusted; AE = adverse event; CAB + RPV = cabotegravir plus rilpivirine; CART = current antiretroviral treatment; CI = confidence interval; CMH = Cochran–Mantel–Haenszel; CVF = confirmed virologic failure; HIV-1 = HIV type 1; INI = integrase inhibitor; ITT-E = intention-to-treat–exposed population; K-M = Kaplan–Meier; NI = noninferiority; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PP = per protocol; RNA = ribonucleic acid; SD = standard deviation.

[a] Difference is the proportion of patients on CAB + RPV minus the proportion of patients on CART.

[b] Adjusted difference is based on the CMH-stratified analysis adjusting for baseline stratification factors of sex at birth, induction baseline (week –20), and HIV-1 RNA (≤ 100,000 copies/mL and > 100,000 copies/mL) in FLAIR, and sex at birth (male or female) and baseline third agent class (PI, NNRTI, INI) in ATLAS.

[c] Treatment-related reasons are drug-related AEs, intolerability of injection, protocol-defined safety stopping criteria, or lack of efficacy.

[d] Based on Greenwood's formula.

Source: FLAIR Clinical Study Report,[7] ATLAS Clinical Study Report.[8]

Table 11: Subgroup Analysis for Virologic Outcomes – Maintenance Phase

Subgroups/virologic efficacy outcomes	FLAIR		ATLAS	
	CAB + RPV	CART	CAB + RPV	CART
Virologic failure (HIV-1 RNA ≥ 50 copies/mL) in ITT-E population at week 48				
Sex at birth				
Female, n/N (%)	3/63 (4.8)	1/64 (1.6)	2/99 (2.0)	0/104
Difference in proportion[a], % (95% CI)	a3.2 (–4.3 to 12.0)		2.0 (–1.7 to 7.1)	
Male, n/N (%)	3/220 (1.4)	6/219 (2.7)	3/209 (1.4)	3/204 (1.5)
Difference in proportion[a], % (95% CI)	–1.4 (–4.7 to 1.6)		0.0 (–3.0 to 2.9)	
P value for test of homogeneity[b]	0.18		0.32	
CD4+ cell count (cells/mm^3) prior to induction ARV regimen				
< 200	1/16 (6.3)	2/23 (8.7)		
Difference in proportion[a], % (95% CI)	–2.4 (–22.7 to 22.6)			
200 to < 350	2/71 (2.8)	1/64 (1.6)		
Difference in proportion[a], % (95% CI)	1.3 (–5.9 to 8.7)			
350 to < 500	3/88 (3.4)	0/88		
Difference in proportion[a], % (95% CI)	3.4 (–0.9 to 9.6)			
≥ 500	0/108	4/108 (3.7)		
Difference in proportion[a], % (95% CI)	–3.7 (–9.2 to –0.1)			
HIV- 1 RNA (copies/mL) prior to induction ARV regimen				
< 100,000 copies/mL, n/N (%)	4/227 (1.8)	5/227 (2.2)		
Difference in proportion[a], % (95% CI)	–0.4 (–3.6 to 2.5)			
≥ 100,000 copies/mL, n/N (%)	2/56 (3.6)	2/56 (3.6)		
Difference in proportion[a], % (95% CI)	0.0 (–9.2 to 9.2)			
P value for test of homogeneity[b]	0.91			
Virologic suppression (HIV-1 RNA < 50 copies/mL) in ITT-E population at week 48				
Sex at birth				
Female, n/N (%)	58/63 (92)	61/64 (95)	92/99 (93)	98/104 (94)
Difference in proportion[a], % (95% CI)	–3.2 (–13.5 to 6.4)		–1.3 (–8.1 to 5.4)	
Male, n/N (%)	207/220 (94)	203/219 (93)	193/209 (92)	196/204 (96)
Difference in proportion[a], % (95% CI)	1.4 (–3.4 to 6.4)		–3.7 (–8.2 to 0.7)	

Subgroups/virologic efficacy outcomes	FLAIR		ATLAS	
	CAB + RPV	CART	CAB + RPV	CART
P value for test of homogeneity[b]	0.35		0.56	
CD4+ cell count (cells/mm^3) prior to ARV regimen				
< 200	15/16 (94)	21/23 (91)		
Difference in proportion[a], % (95% CI)	2.4 (–22.6 to 22.7)			
200 to < 350	65/71 (92)	60/64 (94)		
Difference in proportion[a], % (95% CI)	–2.2 (–12.1 to 7.8)			
350 to < 500	82/88 (93)	80/88 (91)		
Difference in proportion[a], % (95% CI)	2.3 (–6.3 to 11.2)			
≥ 500	103/108 (95)	103/108 (95)		
Difference in proportion[a], % (95% CI)	0.0 (–6.4 to 6.4)			
HIV- 1 RNA (copies/mL) prior to ARV regimen				
< 100,000 copies/mL, n/N (%)	215/227 (95)	211/227 (93)		
Difference in proportion[a], % (95% CI)	1.8 (–2.8 to 6.5)			
≥ 100,000 copies/mL, n/N (%)	50/56 (89)	53/56 (95)		
Difference in proportion[a], % (95% CI)	–5.4 (–17.5 to 5.6)			
P value for test of homogeneity[b]	0.21			

ARV = antiretroviral; CAB + RPV = cabotegravir plus rilpivirine; CART = current antiretroviral therapy; CD4+ = cluster of differentiation 4 positive; CI = confidence interval; HIV-1 = HIV type 1; ITT-E = intention-to-treat–exposed population; RNA = ribonucleic acid.

[a] Difference is proportion on CAB + RPV minus proportion on CART (unadjusted); 95% CIs were calculated using an unconditional exact method with two inverted one-sided tests based on the score statistic.

[b] One-sided P value from weighted least squares chi-squared statistic. A P value < 0.10 was used to indicate statistically significant evidence of heterogeneity in the difference in proportions across levels of each analysis strata.

Source: FLAIR Clinical Study Report,[7] ATLAS Clinical Study Report.[8]

CD4+ Cell Count

At the start of the maintenance phase, the mean CD4+ cell count ranged between 645 and 693 cells/mm^3 across the trials (Table 12). In both trials, patients had an increase in CD4+ cell count at weeks 48 (and at week 52 in ATLAS), regardless of treatment. The increase was more prominent in FLAIR, with an average increase of 40.2 and 79.9 cells/mm^3 from baseline in the CAB + RPV and CART groups, respectively. In ATLAS, the mean change from baseline at week 48 was 9.9 and 19.4 in the CAB + RPV and CART groups, respectively.

Results of ITT-E population for CD4+ cell count were available for the three protocol-specified subgroups in FLAIR and only for sex at birth in ATLAS. A formal statistical test for heterogeneity was not done in any case. Therefore, no statistical conclusion should be made with regard to the difference of the subgroups on CD4+ cell count. In FLAIR, both treatment groups showed a numeric increase in CD4+ cell count through week 48, irrespective of the subgroup. In ATLAS, female patients in both treatment groups showed a numeric increase in CD4+ cell count through week 48; however, only male patients receiving CART showed an increase.

Table 12: Immunologic Outcomes in FLAIR and ATLAS – Maintenance Phase

Immunologic outcomes	FLAIR		ATLAS	
	CAB + RPV	CART	CAB + RPV	CART
CD4+ cell count results (cells/mm^3)				
ITT-E population at week 48				
Baseline, n	283	283	308	308
Baseline, mean (SD)	666.4 (272.14)	645.7 (253.44)	678.5 (257.11)	692.8 (288.74)
Week 48, n	246	263	263	290
Week 48, mean (SD)	703.2 (285.75)	731.2 (272.49)	685.3 (262.97)	716.7 (292.85)
Change from baseline at week 48, mean (SD)	40.2 (195.17)	79.9 (194.55)	9.9 (187.24)	19.4 (168.80)
Week 52, n			280	284
Week 52, mean (SD)			711.5 (265.54)	718.7 (296.11)
Change from baseline at week 52, mean (SD)			28.0 (184.74)	17.3 (186.75)
Subgroup analysis: sex at birth				
Female, n	63	64	99	104
Baseline, mean (SD)	630.5 (334.98)	586.2 (225.68)	653.1 (275.25)	695.9 (272.53)
Week 48, n	59	60	86	97
Change from baseline at week 48, mean (SD)	19.1 (228.06)	112.2 (159.90)	41.4 (196.05)	20.1 (169.20)
Male, n	220	219	209	204
Baseline, mean (SD)	676.7 (251.23)	663.1 (258.90)	690.6 (247.83)	691.2 (297.31)
Week 48, n	187	203	177	193
Change from baseline at week 48, mean (SD)	46.8 (183.76)	70.3 (203.04)	–5.4 (181.41)	19.1 (169.04)
Subgroup analysis: HIV-1 RNA (copies/mL) prior to ARV regimen				
< 100,000 copies/mL				
Maintenance baseline, n	227	227		
Maintenance baseline, mean (SD)	684.9 (275.15)	664.0 (249.59)		
Week 48, n	201	209		
Change from baseline at week 48, mean (SD)	44.3 (202.12)	68.9 (196.60)		
≥ 100,000 copies/mL				
Maintenance baseline, n	56	56		
Maintenance baseline, mean (SD)	591.7 (248.08)	571.6 (257.70)		
Week 48, n	45	54		
Change from baseline at week 48, mean (SD)	21.8 (161.21)	122.5 (181.94)		

ARV = antiretroviral; CAB + RPV = cabotegravir plus rilpivirine; CART = current antiretroviral therapy; CD4+ = cluster of differentiation 4 positive; HIV-1 = HIV type 1; ITT-E = intention-to-treat–exposed population; RNA = ribonucleic acid; SD = standard deviation.

Source: FLAIR Clinical Study Report,[7] ATLAS Clinical Study Report.[8]

Health-Related Quality of Life

HIV Treatment Satisfaction Questionnaire Status/Change Version (HIVTSQs/HIVTSQc)

In both trials, HIVTSQs total score was comparable in both treatment groups at baseline. The higher scores indicate a greater level of satisfaction. At week 44, there was a slight increase in HIVTSQs score in both groups. The adjusted mean differences in each of the trials were 0.7 (95% CI, –0.4 to 1.9; P = 0.22) and 5.68 (95% CI, 4.37 to 6.98; P < 0.001) in

FLAIR and ATLAS, respectively. As shown in Table 13, the between-treatment difference in ATLAS was statistically significantly in favour of CAB + RPV group. The HIVTSQc was administered only at week 48, at which time patients receiving CAB + RPV and CART in FLAIR reported an adjusted mean score of 29.6 and 25.5, respectively (adjusted mean difference = 4.1; 95% CI, 2.8 to 5.5; P < 0.001) in treatment satisfaction from induction phase. In ATLAS, HIVTSQc was not assessed in the CART group, therefore, no between-treatment comparison was made (Table 13). Overall, the inconsistent changes were likely suffering from potential bias due to a large proportion of missing data at week 44 or 48, particularly for FLAIR.

Perception of Injection (PIN):

The PIN questionnaire was administered only to patients in the CAB + RPV group and change from week 5 (first time point of administration) was assessed at week 48. The total score for the PIN was not calculated, instead, scores for the four domains and five separate items (that do not belong in any domain) were provided individually. Of these, pre-specified statistical testing was performed for the domain of acceptability of ISRs. At week 48, patients receiving CAB + RPV in both trials showed an improvement from week 5 in the mean score of the acceptability of ISRs domain (mean score change from week 5 = –0.40 and –0.54 in FLAIR and ATLAS, respectively). However, since the hypothesis appearing prior to PIN in the testing hierarchy, namely HIVTSQs, failed in FLAIR, the P value associated with PIN assessment cannot be declared statistically significant in this trial. In contrast, the difference in PIN score compared to baseline can be considered statistically significant in ATLAS (P < 0.001). All the remaining domains and items showed either a numeric improvement or unchanged score through week 48; however, no statistical comparisons were made for these domains and items (Table 13).

HIV/AIDS-Targeted Quality of Life (HAT-QoL)

The HAT-QoL included three of the nine domains: Life Satisfaction, Disclosure Worries, and HIV Medication. A higher total score indicates better function, satisfaction, and well-being. At baseline, all three domain scores were comparable, irrespective of treatment groups or studies. [redacted]

Chronic Treatment Acceptance Questionnaire (ACCEPT)

At baseline, the mean General Acceptance domain score was similar for both treatment groups across the two trials. At week 48, the mean adjusted change from baseline was 2.2 and 1.3 in the CAB + RPV and CART groups (mean adjusted difference = 2.2; 95% CI, –1.4 to 5.8; P = 0.24) in FLAIR, respectively; and 13.3 and 3.4 in the two groups (adjusted mean difference = 10.7, 95% CI, 7.1 to 14.4; P < 0.001) in ATLAS, respectively (Table 14).

12-Item Short Form Health Survey (SF-12)

In both studies, no difference in the SF-12 component scores (PCS and MCS) were found between treatment groups. At week 48, the mean adjusted change from baseline in SF-12 PCS was –0.29 and –0.13 in the CAB + RPV and CART groups (mean adjusted difference = –0.17; 95% CI, –0.99 to 0.66; P = 0.69) in FLAIR, respectively; and 0.76 and 0.06 in the two groups (adjusted mean difference = 0.7; 95% CI, –0.11 to 1.50; P = 0.09) in ATLAS, respectively. For MCS, the mean adjusted change from baseline score was –0.01 and –1.12 in the CAB + RPV and CART groups (mean adjusted difference = 1.10; 95%CI, –0.25 to 2.45; P = 0.11) in FLAIR, respectively; and 0.26 and –0.37 in the two groups (adjusted mean difference = 0.63; 95% CI, –0.64 to 1.91; P = 0.33) in ATLAS, respectively (Table 14).

Numeric Rating Scale (NRS)

[redacted]

Table 13: Summary of HIVTSQ and PIN Questionnaire – Maintenance Phase

Characteristic	FLAIR		ATLAS	
	CAB + RPV N = 283	CART N = 283	CAB + RPV N = 308	CART N = 308
HIVTSQs – Change from baseline in total treatment satisfaction score in ITT-E population – (adjusted, LOCF)				
Baseline, n	259	266	302	298
Baseline score, mean (SD)	59.3 (7.37)	59.1 (7.55)	55.25 (9.14)	55.40 (8.68)
Week 44, n	281	275	306	303
Week 44 score, mean (SD)	60.9 (7.25)	59.6 (7.64)	61.31 (6.63)	56.03 (9.83)
Change from baseline, n	257	258	300	294
Change from baseline, mean (SD)	1.2 (8.63)	0.6 (7.33)	6.02 (10.80)	0.54 (9.88)
Adjusted change from baseline at week 44, n	257	256	300	294
Adjusted mean [SD] (95% CI)	1.3 [8.63] (0.5 to 2.1)	0.5 [7.33] (–0.3 to 1.4)	6.12 (5.21 to 7.03)	0.44 (–0.48 to 1.37)
Adjusted mean difference (95% CI)	0.7 (–0.4 to 1.9)		5.68 (4.37 to 6.98)	
P value	0.22		< 0.001	
HIVTSQc – Change from baseline in total treatment satisfaction score in ITT-E population – (adjusted, LOCF)				
Baseline score, mean (SD)	NR	NR	NR	NR
Week 48, n	263	268	275	
Week 48, mean (SD)	29.5 (4.86)	25.5 (10.27)		
Week 48, adjusted, n	263	266		
Week 48, adjusted mean (SE)	29.6 (0.49)	25.5 (0.48)	29.05 (6.98)	
Adjusted mean difference (95% CI)	4.1 (2.8 to 5.5)			
P value	< 0.001			
PIN[a] – Change from week 5[b] in domain scores and individual items scores in ITT-E population – (LOCF)				
Acceptability of ISRs				
Week 5, n	270	NA	296	NA
Mean (SD)	2.08 (1.03)		2.10 (1.03)	

Characteristic	FLAIR		ATLAS	
	CAB + RPV N = 283	CART N = 283	CAB + RPV N = 308	CART N = 308
Week 48, n	278		303	
Mean (SD)	1.66 (0.78)		1.56 (0.80)	
Change from week 5, n	270		296	
Change from week 5, mean (SD)	–0.40 (0.94)		–0.54 (1.08)	
P value	< 0.001		< 0.001	
Bother of ISRs				
Week 5, n	270		296	
Mean (SD)	1.62 (0.61)		1.58 (0.51)	
Week 48, n	278		303	
Mean (SD)	1.47 (0.50)		1.37 (0.43)	
Change from week 5, n	270		296	
Change from week 5, mean (SD)	–0.14 (0.64)		–0.21 (0.52)	
Leg movement				
Week 5, n	[redacted]		[redacted]	
Mean (SD)	[redacted]		[redacted]	
Week 48, n	[redacted]		[redacted]	
Mean (SD)	[redacted]		[redacted]	
Change from week 5, n	[redacted]		[redacted]	
Change from week 5, mean (SD)	[redacted]		[redacted]	
Sleep				
Week 5, n	[redacted]		[redacted]	
Mean (SD)	[redacted]		[redacted]	
Week 48, n	[redacted]		[redacted]	
Mean (SD)	[redacted]		[redacted]	
Change from week 5, n	[redacted]		[redacted]	
Change from week 5, mean (SD)	[redacted]		[redacted]	
Item 1: Anxiety before				
Week 5, n	[redacted]		[redacted]	
Mean (SD)	[redacted]		[redacted]	
Week 48, n	[redacted]		[redacted]	
Mean (SD)	[redacted]		[redacted]	
Change from week 5, n	[redacted]		[redacted]	
Change from week 5, mean (SD)	[redacted]		[redacted]	
Item 2: Pain				
Week 5, n	270		296	
Mean (SD)	1.9 (0.87)		1.8 (0.94)	
Week 48, n	278		303	
Mean (SD)	1.8 (0.76)		1.8 (0.77)	
Change from week 5, n	270		296	
Change from week 5, mean (SD)	–0.1 (0.90)		0.0 (1.06)	

Characteristic	FLAIR		ATLAS	
	CAB + RPV N = 283	CART N = 283	CAB + RPV N = 308	CART N = 308
Item 19: Satisfaction				
Week 5, n	270		296	
Mean (SD)	1.6 (0.72)		1.6 (0.74)	
Week 48, n	278		303	
Mean (SD)	1.5 (0.75)		1.5 (0.78)	
Change from week 5, n	270		296	
Change from week 5, mean (SD)	0.0 (0.85)		–0.1 (0.79)	
Item 20: Anxiety after				
Week 5, n	[redacted]		[redacted]	
Mean (SD)	[redacted]		[redacted]	
Week 48, n	[redacted]		[redacted]	
Mean (SD)	[redacted]		[redacted]	
Change from week 5, n	[redacted]		[redacted]	
Change from week 5, mean (SD)	[redacted]		[redacted]	
Item 21: Willingness				
Week 5, n	270		296	
Mean (SD)	1.4 (0.63)		1.4 (0.75)	
Week 48, n	278		303	
Mean (SD)	1.2 (0.58)		1.3 (0.70)	
Change from week 5, n	270		296	
Change from week 5, mean (SD)	–0.1 (0.69)		–0.1 (0.80)	

CAB + RPV = cabotegravir plus rilpivirine; CART = current antiretroviral therapy; CI = confidence interval; HIVTSQc = HIV Treatment Satisfaction Questionnaire change version; HIVTSQs = HIV Treatment Satisfaction Questionnaire status version; ISR = injection site reaction; ITT-E = intention-to-treat–exposed; LOCF = last observation carried forward; NA = not applicable; NR = not reported; PIN = Perception of Injection; SD = standard deviation.

Note: Summary of HIVTSQc total score at week 48 is presented as observed values and only for CAB +RPV group.

[a] Only applicable to CAB + RPV group since only this group received the injections.

[b] Baseline for PIN: first week that injections of CAB and RPV were administered.

Source: FLAIR Clinical Study Report,[7] ATLAS Clinical Study Report.[8]

Table 14: Summary of HAT-QoL, ACCEPT, SF-12, and NRS

Characteristic	FLAIR		ATLAS	
	CAB + RPV N = 283	CART N = 283	CAB + RPV N = 308	CART N = 308
HAT-QoL – Change from baseline in domain score in ITT-E population – (adjusted, LOCF)				
Life satisfaction score				
Baseline, n	[redacted]	[redacted]	[redacted]	[redacted]
Baseline score, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Week 48, n	[redacted]	[redacted]	[redacted]	[redacted]
Week 48, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, n	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

Characteristic	FLAIR		ATLAS	
	CAB + RPV N = 283	CART N = 283	CAB + RPV N = 308	CART N = 308
Adjusted change from baseline, n	[redacted]			
Adjusted mean (95% CI)	[redacted]			
Adjusted mean difference (95% CI)	[redacted]			
P value	[redacted]			
Disclosure worries score				
Baseline, n	[redacted]			
Baseline score, mean (SD)	[redacted]			
Week 48, n	[redacted]			
Week 48, mean (SD)	[redacted]			
Change from baseline, n	[redacted]			
Change from baseline, mean (SD)	[redacted]			
Adjusted change from baseline, n	[redacted]			
Adjusted mean (95% CI)	[redacted]			
Adjusted mean difference (95% CI)	[redacted]			
P value	[redacted]			
HIV medication score				
Baseline, n	[redacted]			
Baseline score, mean (SD)	[redacted]			
Week 48, n	[redacted]			
Week 48, mean (SD)	[redacted]			
Change from baseline, n	[redacted]			
Change from baseline, mean (SD)	[redacted]			
Adjusted change from baseline, n	[redacted]			
Adjusted mean (95% CI)	[redacted]			
Adjusted mean difference (95% CI)	[redacted]			
P value	[redacted]			
ACCEPT– Change from baseline in General Acceptance score in ITT-E population – (adjusted, LOCF)				
Baseline, n	258	267	303	300
Baseline score, mean (SD)	86.0 (21.27)	83.4 (23.68)	75.9 (26.53)	74.7 (26.06)
Week 48, n	280	280	307	305
Week 48, mean (SD)	87.9 (21.71)	83.8 (23.22)	89.2 (19.94)	78.3 (25.98)
Change from baseline at week 48, n	255	264	302	298
Change from baseline at week 48, mean (SD)	2.2 (25.03)	1.3 (27.56)	13.3 (32.22)	3.4 (29.37)
Week 48 adjusted, n	255	262	302	298
Adjusted mean (95% CI)	3.0 (0.4 to 5.6)	0.8 (–1.7 to 3.4)	13.7 (11.2 to 16.3)	3.0 (0.4 to 5.6)
Adjusted mean difference (95% CI)	2.2 (–1.4 to 5.8)		10.7 (7.1 to 14.4)	
P value	0.24		< 0.001	
SF-12 – Change from baseline in physical and mental component score in ITT-E population – (adjusted, LOCF)				
PCS				
Baseline, n	258	267	298	299

Characteristic	FLAIR		ATLAS	
	CAB + RPV N = 283	CART N = 283	CAB + RPV N = 308	CART N = 308
Baseline score, mean (SD)	55.85 (4.69)	55.69 (5.38)	55.24 (5.73)	54.61 (5.76)
Week 48, n	277	276	298	303
Week 48, mean (SD)	55.43 (5.00)	55.72 (5.69)	55.8 (5.51)	54.79 (6.23)
Change from baseline, n	252	260	272	288
Change from baseline, mean (SD)	–0.37 (5.49)	–0.06 (5.53)	0.81 (5.42)	0.11 (5.77)
Adjusted change from baseline, n	252	258	288	295
Adjusted change from baseline, mean (95% CI)	–0.29 (–0.88 to 0.29)	–0.13 (–0.71 to 0.45)	0.76 (0.18 to 1.33)	0.06 (–0.50 to 0.63)
Adjusted mean difference (95% CI)	–0.17 (–0.99 to 0.66)		0.7 (–0.11 to 1.50)	
P value	0.69		0.09	
MCS				
Baseline, n	258	267	301	297
Baseline score, mean (SD)	53.42 (8.51)	52.91 (8.65)	53.13 (8.19)	53.68 (7.33)
Week 48, n	277	276	298	303
Week 48, mean (SD)	53.41 (8.9)	51.59 (9.57)	53.54 (8.91)	53.37 (8.44)
Change from baseline, n	252	260	275	286
Change from baseline, mean (SD)	–0.09 (7.5)	–1.04 (9.28)	0.51 (8.86)	–0.45 (8.22)
Adjusted change from baseline, n	252	258	291	293
Adjusted change from baseline, mean (95% CI)	–0.01 (–0.97 to 0.95)	–1.12 (–2.06 to –0.17)	0.26 (–0.64 to 1.16)	–0.37 (–1.27 to 0.52)
Adjusted mean difference (95% CI)	1.10 (–0.25 to 2.45)		0.63 (–0.64 to 1.91)	
P value	0.11		0.33	
NRS[a] – Summary of NRS scores in ITT-E population – (LOCF)				
Week 4[b], n	[redacted]		[redacted]	
Mean (SD)	[redacted]		[redacted]	
Week 41, n	[redacted]		[redacted]	
Mean (SD)	[redacted]		[redacted]	
Change from week 4 scores, n	[redacted]		[redacted]	
Change from week 4 scores, mean (SD)	[redacted]		[redacted]	
Change from week 4, mean (SD)	[redacted]		[redacted]	

ACCEPT = Chronic Treatment Acceptance Questionnaire; CAB + RPV = cabotegravir plus rilpivirine; CART = current antiretroviral therapy; CI = confidence interval; HAT-QoL = HIV/AIDS-targeted quality of life; ITT-E = intention-to-treat–exposed; LOCF = last observation carried forward; MCS = Mental Component Score; NRS = Numeric Rating Scale; PCS = Physical Component Score; SD = standard deviation; SF-12 = Short Form (12) Health Survey.

[a] Only applicable to CAB + RPV group since only this group received the injections.

[b] Baseline for NRS.

Source: FLAIR Clinical Study Report,[7] ATLAS Clinical Study Report.[8]

Adherence

In both trials, 98% of the CAB + RPV injections were administered within seven days of the planned treatment window. No more than 2% of injection visits occurred between seven and 14 days of the planned injection visits. Across trials, oral bridging was used to deliver CAB + RPV at four of the missing injection visits. [redacted]

[redacted] No information on the adherence in the CART group was provided. Additionally, data pertaining specifically to adherence during the oral lead-in period was not available.

Resistance

The number of patients with CVF (defined as two consecutive HIV-1 RNAs ≥ 200 copies/mL after prior suppression to < 200 copies/m) by week 48 was low in both trials. In FLAIR, four and three patients in the CAB + RPV and CART groups, respectively, were categorized as CVF. In ATLAS, the numbers in the two groups were three and four, respectively (data not presented).

In FLAIR, one of the four patients with CVF in the CAB + RPV group never received an injection, therefore virology data were generated for the remaining three patients. All three of the remaining patients had treatment-emergent RPV-, INI-, and CAB-resistant mutations. Of these, a decrease in susceptibility was seen for all RPV and CAB-associated mutations. None of the three CVFs on CART had treatment-emergent resistance mutations (data not presented).

In ATLAS, all three CVF cases in the CAB + RPV group had treatment-emergent RPV resistance mutations leading to decreased virus susceptibility to the drug. One CVF patient in the CAB + RPV group had INI resistance mutation with a prior history of raltegravir use, resulting in resistance to CAB, raltegravir, and elvitegravir, but the virus remained sensitive to DTG. Another CVF patient in the CAB + RPV group had mutations to the NNRTI, which could contribute to RPV resistance. In the CART group, two cases of NRTI- and NNRTI-associated mutations were found each, and one case of INI-associated mutations were found. One of the NRTI-associated mutations corresponded to a decrease in susceptibility to emtricitabine (data not presented).

Harms

Only those harms identified in the CADTH review protocol are reported as follows.

Adverse Events

Data for the oral lead-in period and maintenance phase are presented separately in Table 15 and Table 16. Unless otherwise specified, safety results presented are for the maintenance phase (including the oral lead-in and IM injection period for the safety population set).

During the maintenance phase in both trials, patients in the CAB + RPV group reported more AEs compared with the CART group (Table 16). More than 90% patients in the CAB + RPV group experienced at least one AE across trials, whereas the overall frequency of AEs in the CART group was 71% and 80%, in ATLAS and FLAIR, respectively. The majority of AEs were grade 1 or 2 in severity. The increased incidence of AEs in the CAB + RPV group was in part attributable to various ISRs resulting from the monthly IM injections (overall frequency 86% and 83% in FLAIR and ATLAS, respectively, details under Notable Harms). The incidence of non-ISR AEs occurred at a higher frequency in the CAB + RPV group (87% and 80% between CAB + RPV and CART in FLAIR, respectively; 86% and 71% between CAB + RPV and CART in ATLAS, respectively). The CAB + RPV group also reported more grade 3 to 4 AEs than placebo (11% and 4% in FLAIR; 11% and 7% in ATLAS). Overall, the most frequent AEs (incidence of ≥ 10% in any group) included (in no particular order) injection site pain, nasopharyngitis, injection site nodule, headache, upper

respiratory tract infection, injection site induration, and diarrhea. Across trials, the frequency of common AEs was comparable in the two treatment groups, with the exception of ISR events (pain, nodule, induration, swelling, and pruritus), headache, pyrexia, hemorrhoids, back pain, and dizziness, which were reported more frequently in the CAB + RPV group.

Serious Adverse Events

Overall, there were no fatal SAEs and the incidence of nonfatal SAEs was low across trials (range = 4% to 6%), with comparable SAE frequency observed between treatment groups. The individual SAEs occurred across a variety of system organ classes, and no particular pattern was observed. Hepatitis A and colitis were the only nonfatal SAEs that occurred in more than one patient in FLAIR and ATLAS, respectively.

Withdrawals Due to Adverse Events

During the maintenance phase, a small proportion of patients (≤ 4%) in each treatment group in both trials reported an AE leading to withdrawal or permanent discontinuation of the study. Patients in the CAB + RPV group had a numerically greater proportion of WDAEs compared with the CART group. However, it should be noted that three patients in each trial withdrew during the oral lead-in period and never received CAB + RPV IM injections. Aside from ISRs, the causes for withdrawal included acute viral hepatitis and a variety of AEs (e.g., disturbance in attention, dysarthria, amnesia, renal failure, fatigue, headache, depression suicidal, diarrhea, nausea, asthenia, myalgia, and anxiety).

Mortality

In FLAIR, no deaths were reported during the maintenance phase in either treatment group, although one death was reported in a patient in the CAB + RPV group during the induction phase (cause of death was possible homicide). In ATLAS, one death was reported in the CART treatment group due to methamphetamine overdose.

Notable Harms

Notable harms identified in the CADTH review protocol (Table 3) included the following: ISRs, depressive disorders, hepatotoxicity, skin reactions, hypersensitivity, bone-related AEs, and renal function. Data during the maintenance phase are summarized in Table 17.

Data pertaining to ISRs was only applicable to the CAB + RPV group since only these patients received an injectable therapy. During the maintenance phase, ISRs were the most frequently reported AEs in patients receiving CAB + RPV, with more than 80% reporting at least one ISR event. Of the different ISR events, injection site pain was the most commonly reported AE (> 75%), followed by injection site nodules (12% to 16%), induration (10% to 13%), nodules and swelling (7% to 8%), injection site pruritus (6%), and erythema (5%). Other ISRs reported at a lower frequency (< 5%) included warmth, bruising, hematoma, hemorrhage, discoloration, anesthesia, discomfort, granuloma, necrosis, cyst, and scar (data not presented). Most ISRs were grade 1 or 2 in severity, with grade 3 ISRs accounting for 1% or less of all ISRs. No ISRs were reported as SAEs, and six patients in the two trials withdrew from the study due to an ISR event (four in FLAIR and two in ATLAS). The majority of ISRs (88%) were resolved within seven days and the median duration for ISRs was three days in both trials. The AE profile for CAB or RPV injections were similar when considered separately and no substantial difference was noted between the characteristics of CAB or RPV ISRs (data not presented). In both trials, the incidence of ISRs decreased over time with a reduction in the number of patients reporting pain.

Approximately 70% patients reported having ISRs at the initial 3 mL loading injections, which was reduced to 11% to 20% at week 48 (data not presented).

The number of patients with psychiatric disorders ranged between 8% and 13% across trials (similar proportion between treatment groups); however, the frequency of depression was no more than 2% in either treatment group of either trial.

The proportion of patients who met liver stopping criteria during the maintenance phase did not exceed 2% in either trial. There were no reported cases of hepatotoxicity among these patients. The majority of these cases were found to have viral hepatitis. None of the liver stopping criteria in the CAB + RPV groups represented drug-induced liver injury, as adjudicated by an independent hepatic adjudication committee.

There were no confirmed drug hypersensitivity reactions to CAB + RPV in either FLAIR or ATLAS. A total of four patients in the two studies reported a hypersensitivity reaction during the maintenance phase, and this did not result in withdrawal.

Rash occurred in 1% to 4% of patients in the two treatment groups across trials. None were considered to be grade 3 to 4 or SAEs, and did not result in discontinuation.

A number of renal and bone biomarkers were assessed in FLAIR and ATLAS, of which the creatinine and estimated glomerular filtration rate (eGFR) are reported for renal function and alkaline phosphatase is reported for bone status. In both studies, creatinine and eGFR level remained relatively stable through the maintenance phase. In FLAIR, the mean change at week 48 from baseline in serum creatinine was –8.97 and 5.00 in the CAB + RPV and CART groups, respectively; the mean change from baseline in creatinine-adjusted eGFR was 9.5 and –0.7 in the two groups, respectively; and mean change from baseline in vitamin D level was –0.3 and –6.4 in the two groups, respectively. In ATLAS, the mean change at week 48 from baseline in serum creatinine was 1.59 and 0.82 in the CAB + RPV and CART groups, respectively; the mean change from baseline in creatinine-adjusted GFR was –2.5 and –1.9 in the two groups, respectively; and mean the change from baseline in vitamin D level was –4.8 and 1.5 in the two groups, respectively.

Table 15: Summary of Harms – Oral Lead-In Period (Safety Population)

Harms	FLAIR		ATLAS	
	CAB + RPV N = 283	CART N = 283	CAB + RPV N = 308	CART N = 308
AEs				
[redacted]	[redacted]		[redacted]	
Most common AEs by SOC, n (%)[a]				
[redacted]	[redacted]		[redacted]	
[redacted]	[redacted]		[redacted]	
[redacted]	[redacted]		[redacted]	
[redacted]	[redacted]		[redacted]	
SAEs				
[redacted]	[redacted]		[redacted]	
WDAEs[b]				
[redacted]	[redacted]		[redacted]	

AE = adverse event; CAB + RPV = cabotegravir plus rilpivirine; CART = current antiretroviral therapy; SAE = serious adverse event; SOC = system organ class; WDAE = withdrawal due to adverse event.

[a] Occurring in 5% or more of patients in either treatment group in either trial.

[b] WDAEs refer to withdrawal from the study due to an AE.

Source: FLAIR Clinical Study Report,[7] ATLAS Clinical Study Report.[8]

Table 16: Harms During the Maintenance Phase in the FLAIR and ATLAS Trials (Safety Population)

Harms	FLAIR		ATLAS	
	CAB + RPV N = 283	CART N = 283	CAB + RPV N = 308	CART N = 308
AEs				
Patients with > 0 AEs, n (%)	267 (94)	225 (80)	294(95)	220 (71)
Any grade 3 to 4 AEs, n (%)	31 (11)	11 (4)	35 (11)	23 (7)
Most common AEs, n (%)[a]				
Injection site pain	227 (80)	0	231 (75)	NA
Nasopharyngitis	56 (20)	48 (17)	52 (17)	42 (14)
Injection site nodule	44 (16)	0	37 (12)	NA
Headache	39 (14)	21 (7)	34 (11)	17 (6)
URTI	38 (13)	28 (10)	32 (10)	25 (8)
Injection site induration	38 (13)	0	30 (10)	NA
Diarrhea	32 (11)	25 (9)	22 (7)	15 (5)
Influenza	25 (9)	20 (7)	17 (6)	14 (5)
Cough	-	-	16 (5)	14 (5)
Vitamin D deficiency	23 (8)	13 (5)	-	-
Injection site swelling	23 (8)	0	23 (7)	NA
Back pain	22 (8)	13 (5)	21 (7)	10 (3)
Pyrexia	22 (8)	4 (1)	21 (7)	9 (3)

Harms	FLAIR		ATLAS	
	CAB + RPV N = 283	CART N = 283	CAB + RPV N = 308	CART N = 308
Hemorrhoids	16 (6)	3 (1)	-	-
Injection site pruritus	16 (6)	0	-	-
Nausea	16 (6)	11 (4)	-	-
Gastroenteritis	15 (5)	11 (4)	-	-
Pharyngitis	15 (5)	9 (3)	-	-
Dizziness	15 (5)	3 (1)	-	-
Fatigue	-	-	22 (7)	6 (2)
Respiratory tract infection, viral	-	-	11 (4)	17 (6)
SAEs				
Patients with > 0 SAEs, n (%)	18 (6)	12 (4)	13 (4)	14 (5)
Most common SAEs by SOC, n (%)[b]				
Infections and infestations	4 (1)	4 (1)	6 (2)	4 (1)
Gastrointestinal disorders	4 (1)	1 (< 1)	2 (< 1)	2 (< 1)
Hepatobiliary disorders			2 (< 1)	0
Neoplasms benign, malignant, and unspecified	2 (< 1)	3 (1)	1 (< 1)	2 (< 1)
Injury, poisoning, and procedural complications	1 (< 1)	2 (< 1)	0	3 (< 1)
Psychiatric disorders	0	2 (< 1)	-	-
WDAEs[b]				
Patients with > 0 WDAEs, n (%)	9 (3)	4 (1)	13 (4)	5 (2)
Most common WDAEs, n (%)[c]				
Acute hepatitis B	2 (< 1)	0	-	-
Hepatitis A	2 (< 1)	0	2 (< 1)	0
Injection site pain	2 (< 1)	0	4 (1)	0
Headache			2 (< 1)	0
Deaths				
Number of deaths, n (%)	0	0	0	1

AE = adverse event; CAB + RPV = cabotegravir plus rilpivirine; CART = current antiretroviral therapy; NA = not applicable; SAE = serious adverse event; SOC = system organ class; URTI = upper respiratory tract infection; WDAE = withdrawal due to adverse event.

[a] Occurring in 5% or more of patients in either treatment group in either trial.

[b] WDAEs refer to withdrawal from the study due to an AE.

[c] Occurring in greater than one patient in either treatment group in either trial.

Source: FLAIR Clinical Study Report,[7] ATLAS Clinical Study Report.[8]

Table 17: Notable Harms – Maintenance Phase (Safety Population)

Harms	FLAIR		ATLAS	
	CAB + RPV N = 283	CART N = 283	CAB + RPV N = 308	CART N = 308
Injection site reaction AEs				
Number of subjects with injections	278 (98)		303 (98)	
Number of subjects with ISRs	239 (86)	NA	250 (83)	
Number of injections	7,704		6,978	
Number of ISRs	2,203		1,460	
Rash-related AEs				
Rash	6 (2)	8 (3)	11 (4)	4 (1)
Psychiatric events				
Any psychiatric disorders	38 (13)	27 (10)	32 (10)	24 (8)
Depression	6 (2)	4 (1)	3 (< 1)	6 (2)
Depressed mood	3 (1)	1 (< 1)	2 (< 1)	2 (< 1)
Suicidal ideation	1 (< 1)	1 (< 1)	1 (< 1)	2 (< 1)
Suicide attempt	0	1 (< 1)	0	1 (< 1)
Hepatotoxicity				
Liver stopping criteria	7 (2)	2(< 1)	4 (1)	1 (< 1)
Renal-related biomarkers				
Serum creatinine (µmol/L)				
Baseline, n	283	283	308	308
Baseline, mean (SD)	89.00 (16.06)	85.80 (15.66)	79.05 (16.38)	77.83 (16.5)
Week 48, n	247	262	265	292
Week 48, mean (SD)	79.95 (15.61)	90.88 (87.65)	80.77 (16.46)	78.65 (16.20)
Change from baseline at week 48, n	247	262	265	292
Change from baseline at week 48, mean (SD)	–8.97 (9.74)	5.00 (85.53)	1.59 (11.25)	0.82 (7.85)
Week 52, n			280	282
Week 52, mean (SD)			80.31 (16.5)	77.81 (16.29)
Change from baseline at week 52, n			280	282
Change from baseline at week 52, mean (SD)			0.86 (10.65)	0.08 (8.59)
GFR from creatinine adjusted using CKD-EPI (mL/min/1.73m^2)				
Baseline, n	283	283	308	308
Baseline, mean (SD)	94.3 (17.61)	97.9 (17.70)	100.5 (18.30)	101.1 (17.72)
Week 48, n	247	261	264	291
Week 48, mean (SD)	103.6 (16.34)	96.9 (18.21)	97.6 (16.97)	99.3 (17.09)
Change from baseline at week 48, n	247	261	264	291
Change from baseline at week 48, mean (SD)	9.5 (11.35)	–0.7 (10.86)	–2.5 (11.80)	–1.9 (8.50)
Week 52, n			280	282
Week 52, mean (SD)			98.4 (17.53)	100.3 (17.55)
Change from baseline at week 52, n			280	282

Harms	FLAIR		ATLAS	
	CAB + RPV N = 283	CART N = 283	CAB + RPV N = 308	CART N = 308
Change from baseline at week 52, mean (SD)			–1.7 (10.89)	–1.1 (9.25)
Bone biomarkers				
Vitamin D (nmol/L)				
Baseline, n	282	278	308	305
Baseline, mean (SD)	61.5 (25.23)	61.9 (23.79)	65.2 (30.73)	63.6 (31.78)
Week 48, n	261	263	282	293
Week 48, mean (SD)	60.8 (25.06)	55.6 (23.66)	59.3 (24.99)	65.4 (33.30)
Change from baseline at week 48, n	260	259	282	290
Change from baseline at week 48, mean (SD)	–0.3 (20.09)	–6.4 (20.07)	–4.8 (21.87)	1.5 (21.77)
Bone specific alkaline phosphatase (mcg/L)	n = 256	n = 259		
Model adjusted geometric mean for ratio to maintenance baseline (day 1) (95% CI)	0.95 (0.93 to 0.97)	0.96 (0.94 to 0.99)		
Model adjusted geometric mean for treatment ratio (95% CI)	0.99 (0.95 to1.02)			
P value	0.46			

AE = adverse event; CAB + RPV = cabotegravir plus rilpivirine; CART = current antiretroviral therapy; CI = confidence interval; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration equation; GFR = glomerular filtration rate; ISR = injection site reaction; NA = not applicable; SD = standard deviation.

Note: Baseline refers to the beginning of the maintenance phase in both trials.

Source: FLAIR Clinical Study Report,[7] ATLAS Clinical Study Report.[8]

Critical Appraisal

Internal Validity

The two studies included in this review, FLAIR and ATLAS, were generally conducted well with sound methodology. Both were RCTs that used acceptable methods to randomize patients to treatment groups. The treatment groups appeared to be generally balanced with respect to baseline characteristics between treatment arms in each study. The trials were OL in design, therefore no measures to ensure blinding and to conceal treatment allocation were implemented. It is unclear to what extent the trial results were biased due to the OL nature of the trials, although reporting and recall bias is unlikely to occur in many efficacy and safety outcomes that were measured in blood or plasma samples in an objective manner. Nonetheless, the possibility remains that ascertainment of treatment allocation influenced patient reporting of subjective outcomes (HRQoL) as well as patients' decisions on whether to remain in the trial, potentially biasing the primary efficacy outcome.

The maintenance phase of both studies included virologically suppressed HIV-1 patients who switched from a current ARV regimen to the CAB + RPV regimen. The primary efficacy end point was the proportion of patients with virologic failure (defined as HIV-1 RNA ≥ 50 copies/mL) between the treatment groups, which is consistent with the latest FDA–recommended primary end point for switch trials.[39] A number of additional virologic end points were measured, including the proportion of patients who achieved virologic

suppression (HIV-1 RNA < 50 copies/mL). The choice of virologic and immunologic end points was consistent with the standard set of outcomes measured in HIV-1 trials. The FDA–recommended noninferiority margin is 4% for HIV-1 RNA of 50 copies/mL or greater in switch trials. However, the trials had a 6% noninferiority margin in place for the primary efficacy end point, citing insufficiency in the sample size of the trials individually to assess the aforementioned outcome with adequate power. The clinical expert consulted for this review indicated the difference between a 4% and 6% noninferiority margin is negligible in the practical setting, and shared no concern over the results of the primary analysis regarding its validity. Additionally, the pooled analysis of the FLAIR and ATLAS studies (described in Appendix 3) assessed the noninferiority of CAB + RPV to CART with a 4% margin. Therefore, the use of a 6% noninferiority margin in the FLAIR and ATLAS trial is of minimal concern.

Both trials assessed a number of HRQoL outcomes, with a focus on HRQoL affected by an injectable regimen. However, most of the HRQoL measures had limited to no evidence of validity, responsiveness, or reliability, and were lacking an established MID, particularly in patients with HIV-1. Evidence of reliability was documented for ACCEPT, HAT-QoL, and HIVTSQ (both versions) but not for the other HRQoL instruments. The clinical expert indicated the limited usefulness and application of the HRQoL scales in the clinical setting, as informal assessment of HRQoL with the patient is used in clinical practice. There is also a potential for bias in the assessment of HRQoL outcomes, especially those administered exclusively to the CAB + RPV group that are focused on assessing the patient's experience with the CAB and RPV injections. This is because there is potential for patients to rate their answer to the HRQoL scales worse on the first exposure to injection due to relative unfamiliarity; scores on the HRQoL measure may become more positive as patients become more comfortable with the injections as treatment progresses. Additionally, the initiation injection may result in greater discomfort compared with continuation injections due to a higher volume for the former. This would result in worse HRQoL scores at baseline or for the first week of injection, which may increase the likelihood of detecting a benefit with continued treatment. This may explain in part the finding that the incidence of ISRs in patients receiving CAB + RPV was much higher during the first few injection visits, which followed a downward trend in subsequent weeks and closer to the end of the 48-week period. Overall, the changes in various HRQoL scores at week 44 or 48 compared to that at baseline were relatively small and were likely suffering from random error and/or missing data due to failure in providing responses to HRQoL questionnaires by up to 10% patients across trials. Moreover, the between-group differences were highly inconsistent across the two trials despite the similarity of trial design, duration, and identical outcome measures. This is particularly the case for the outcome measures of patients' satisfaction with the treatment, such as with the HIVTSQs, HIVTSQc, ACCEPT, and HAT-QoL instruments.

The statistical analyses plan, including handling of missing data (using the FDA Snapshot method with missing data = failure), deriving sample size or power, and adjusting for multiple comparisons was carried out appropriately and generally followed FDA guidance for HIV-1 trials. In both trials, subgroups of interest to this review were pre-planned; however, testing of the interaction between relevant subgroups was only done for sex at birth (both trials) and plasma HIV-1 RNA level prior to ARV regimen (FLAIR only). The subgroup analyses were considered exploratory and were likely underpowered. Further, an adjustment for multiplicity was not done for subgroup analyses. A wide 95% CI with an upper bound crossed the pre-set noninferiority margin of 6%, perhaps due to large random variation of small sample size in the subgroup. Overall, there is no strong signal of treatment effect difference (i.e., viral load) by subgroups.

Patients enrolled in FLAIR were initially ART-naive and underwent a 20-week induction phase of ARV treatment and only those who achieved virologic suppression continued in the trial and were randomized. Approximately 10% patients in FLAIR did not complete the induction phase, which was noticeably high according to the clinical expert. Following randomization, there was no notable imbalance between treatment groups in either studies with respect to dropouts or completion rate. Hence, there is minimal concern for biases introduced by differential dropouts.

External Validity

Both FLAIR and ATLAS were multinational trials, enrolling patients from a range of countries across North America, South America, Western Europe, and Asia. A total of 23 and 34 patients were randomized from Canadian sites in the two trials, respectively.

The proportion of patients who were screening failures ranged from 12% in ATLAS to 22% in FLAIR. The primary reason for screening failure was not meeting eligibility criteria. While it is standard practice to exclude patients based on baseline resistance to the study drug(s), and to include those who are otherwise healthy, do not have significant comorbidities or interfering medication history, and are expected to be adherent to study protocol, having restrictive exclusion criteria may lead to the enrolment of a highly selected patient population which may affect the generalizability of the findings. The clinical expert consulted for this review indicated the eligibility criteria in the two trials were reasonable and shared no concern with regard to the generalizability of the findings.

According to the clinical expert consulted by CADTH, the baseline demographic and clinical characteristics in FLAIR and ATLAS were generally reflective of treatment-experienced, virologically suppressed patients in a Canadian setting. However, it was noted that the proportion of injectable drug users constituted no more than 5% of the trial population. Since this is a high-risk group due to their susceptibility to HIV-1 transmission through needle use, the clinical expert projected a higher proportion of injectable drug users in the real world. Other notable eligibility criteria included not having serious liver, cardiovascular, or kidney impairments (i.e., not having exclusionary laboratory values), active infection, or acute hepatitis. The results may therefore not be generalizable to patients with these conditions. The trial sponsor indicated that the FLAIR and ATLAS trials recruited 22% to 34% of female patients, respectively, a group of patients generally underrepresented in HIV-1 clinical trials. It should be noted that patients in ATLAS are likely to be treatment adherent and fairly homogeneous, whereas FLAIR likely included a broad selection of patients with unknown adherence records prior to the trial.

The primary analysis period in both trials spanned 48 weeks, a standard time frame used in HIV-1 trials, and consistent with the FDA–recommended minimum analysis duration for the virologic end points. The trials are ongoing, with a planned duration of 120 to 148 weeks. Even though data for a few weeks in the extension phase are available, a longer follow-up with complete data will likely be more conclusive of the durability of the IM CAB + RPV regimen.

The CAB + RPV intervention regimen implemented in both trials was aligned with the dosing and administration recommended by Health Canada, with a four-week oral lead-in period with daily administered tablets, followed by a single initiation injection, and once-monthly injection continued thereafter. The comparators used in the trials included many of the recent ARV regimens commonly prescribed in clinical practice. Patients in the comparator arm in FLAIR primarily received ABC/DTG/3TC through the maintenance

phase. Although information on comparators used in the CART group in ATLAS was not provided, their ARV regimen prior to the start of the trial included contemporary and commonly prescribed ARV regimens. Notably, the ATLAS trial compared the CAB + RPV regimen against a combination of oral ARTs; therefore, the comparative efficacy and safety of individual ARTs are unknown. However, this is unlikely to affect the generalizability of the trial as patients had exposure to a wide variety of oral ARTs. Further, the primary efficacy analysis did not show any difference between the three major drug classes (PI, INI, and NNRTI) (data not presented).

Indirect Evidence

No indirect evidence was submitted by the sponsor; an independent search for indirect evidence conducted by CADTH did not find any published indirect evidence that met the inclusion criteria of the CDR review protocol.

Other Relevant Studies

No long-term extension studies or additional studies considered to address important gaps in the evidence included in the systematic review were submitted by the sponsor.

Discussion

Summary of Available Evidence

The evidence base for this review comprised of two phase III trials, FLAIR (N = 566) and ATLAS (N = 618), with a similar design and methodology. Both studies were randomized, active-controlled, OL, noninferiority studies designed to evaluate the safety and efficacy of the two-drug regimen of CAB + RPV for the treatment of HIV-1 infection in virologically suppressed adult patients (HIV-1 RNA < 50 copies/mL) who switched from a three-drug oral ART regimen. FLAIR included ART-naive patients, who underwent a 20-week induction phase with ARV treatment; those who achieved viral suppression entered the maintenance phase. ATLAS included virologically suppressed patients who were on a stable ARV regimen (containing two NRTIs plus an INI, NNRTI, or a PI) and did not have an induction phase; eligible patients directly entered the maintenance phase. The treatment period relevant for this review was the maintenance phase, during which patients were randomized (1:1) to continue their baseline oral ARV regimen or switch to receive CAB + RPV. The CAB + RPV regimen was administered in three stages: oral lead-in period, in which patients received individual oral CAB + RPV (30 mg + 25 mg) once daily for at least four weeks; followed by separate IM initiation injections of CAB + RPV (600 mg + 900 mg), and separate continuation doses of CAB + RPV (400 mg + 600 mg) every four weeks thereafter. The primary efficacy outcome in both trials was virologic failure defined as the proportion of patients with HIV-1 RNA of 50 copies/mL or greater at week 48 (calculated using the FDA Snapshot algorithm). A 6% noninferiority margin was applied to the primary analysis in both studies. The following secondary efficacy outcomes were measured: the proportion of patients that achieved virologic suppression (HIV-1 RNA < 50 copies/mL) as per the snapshot algorithm; and CD4+ cell count over time. HRQoL was assessed using a number of measures including the HIVTSQs and HIVTSQc, PIN, ACCEPT, HAT-QoL, SF-12, and NRS.

Key evidence gaps include the OL study design, uncertainty associated with HRQoL results, and the lack of long-term data. The data available from the FLAIR and ATLAS trials were limited to 48 weeks of treatment. Both trials are ongoing, with limited data available for some patients post-week 48. In the absence of more compelling long-term data, the durability of the treatment effect and potential for emergence of resistance beyond 48 weeks remain uncertain.

Interpretation of Results

Efficacy

In both trials, the two-drug CAB + RPV regimen was shown be noninferior to daily oral three-drug ARV regimen with respect to the primary efficacy outcome of virologic failure. In both trials, the proportion of patients with virologic failure (defined as HIV-1 RNA ≥ 50 copies/mL) in the CAB + RPV and CART groups was similar at week 48. Both trials employed a noninferiority margin of 6% for the primary analysis. Although this noninferiority margin was less restrictive than the FDA–recommended 4% margin for switch trials, the clinical expert indicated that the practical difference is minimal. The CAB + RPV regimen was also shown to be noninferior to oral ARV regimen in achieving virologic suppression; more than 90% patients in both trials achieved virologic suppression by week 48 (based on the 10% noninferiority margin for this outcome in both trials). The rates of CVF were low (<

1.5%) in both treatment groups through week 48. The high response rate and low CVF rate among these patients was expected because they achieved virologic suppression on an ART prior to the start of the treatment. In both trials, the discontinuation rates were low and similar between treatment groups.

Patients in both trials sustained a satisfactory immunologic response throughout the trial duration, as noted by a progressive increase in CD4+ cell count from baseline through week 48. The clinical expert indicated that CD4+ cell count as a marker for HIV-1 management is relatively less important in clinical setting compared to virologic end points. Nonetheless, the improvement in CD4+ cell count over time provides supportive evidence for the clinical benefits of CAB + RPV. However, as the analysis for immunologic end points was not controlled for multiplicity, the results should be interpreted with considerations of potential for inflated type I error.

HRQoL was identified as an important outcome to patients, and both trials included multiple assessments of patients' HRQoL through the measurement of the following patient-reported outcomes: HIVTSQ, PIN, ACCEPT, HAT-QoL, NRS, and SF-12. These instruments are designed to assess various aspects of HRQoL, including acceptance of an injectable regimen and complications resulting from it. Of the HRQoL measures, the difference in HIVTSQs total score between treatment groups and change from baseline in the acceptability of ISR domain of the PIN questionnaire were tested statistically with control for multiplicity. Results of the HIVTSQs and PIN were statistically significant in favour of the CAB + RPV group in ATLAS; but statistical significance was not reached in FLAIR (after adjusting for multiplicity). The remaining measures showed a numerical benefit in patients' HRQoL in favour of CAB + RPV.

Although the results may suggest a small benefit of CAB + RPV in HRQoL, a number of limitations present challenges in interpreting these outcomes. Overall, the changes in various scores at week 44 or 48 compared to that at baseline were relatively small, and were likely suffering from either random error or missing data due to a large proportion of missing data (up to 10%) for various reasons at week 44 or 48. Moreover, the between-group differences were highly inconsistent across the two trials despite the similarity of trial design, duration, and identical outcome measures. This is particularly the case for outcome measures of patients' satisfaction to the treatment, such as HIVTSQs and HIVTSQc, ACCEPT**,** and HAT-QoL instruments. With the exception of the HIVTSQs total score and PIN, none of the remaining HRQoL analyses were adjusted for multiplicity, therefore, results of these analyses should be interpreted with caution. Evidence for the validity, reliability, and MID of the instruments were scarce in the literature, especially in patients with HIV-1, therefore, the appropriateness of using these measures and any associated biases are unclear. In addition, the improvement observed in HRQoL may be a function of a more negative experience at the first exposure to CAB and RPV IM injections. This may be due to relative unfamiliarity with the regimen or increased discomfort due to the larger volume of the initiation injections; scores on the HRQoL measure may become more positive as patients become more comfortable with the injections as treatment progresses. However, according to the clinical expert, the severity of AEs associated with injections tend to normalize over time, resulting in a greater acceptance of the IM mode of administration, resulting in an improvement in HRQoL at later timepoints. Finally, the clinical expert indicated limited use of a formal HRQoL instrument in the clinical setting, instead an informal discussion about patients' HRQoL and desire or reason to switch treatment is generally adequate.

Among other efficacy end points identified in the CADTH review protocol, resistance to the study medications occurred infrequently. Adherence to the planned treatment schedule for CAB + RPV administration was high in both trials, with few injections administered outside of the allowable treatment window and only one injection was missed without supplementation by the oral bridging strategy. Both of these observations can, in part, be explained by the selection of patients in the two trials. The high adherence rate is expected in patients who were on a stable ARV regimen (ATLAS) or selected to be compliant with study protocol and successfully achieved suppression of viral load through ARV pre-treatment (FLAIR), both of which may result from a high degree of adherence. Similar to the previous end points, adherence with a longer duration of CAB + RPV treatment is unknown. Nonetheless, the clinical expert speculated that a once-monthly regimen would improve adherence and avoid high pill burden associated with current standard of care.

The comparators used in FLAIR and ATLAS are considered relevant ARTs for virologically suppressed patients and represent ARV regimens commonly prescribed in clinical practice. The ARV regimen used in the induction regimen of FLAIR (ABC/DTG/3TC) was an appropriate first-line ART according to the DHHS guidelines.[5] Although information on comparators used in the CART group in ATLAS was not provided, their ARV regimen prior to the start of the trial included contemporary and commonly prescribed ARV regimens. Notably, the ATLAS trial compared the CAB + RPV regimen against a combination of oral ARTs; therefore, the comparative efficacy and safety of individual ARTs are unknown. However, this is unlikely to affect the generalizability of the trial as patients had exposure to a wide variety of oral ARTs.

Harms

Overall, patients in the CAB + RPV group in both trials experienced more AEs compared with those in the CART group. The higher incidence of AEs was, in part, due to the various ISRs that were exclusively associated with CAB + RPV injection. However, the incidence of non-ISR AEs was also higher in the CAB + RPV group in both trials. This can be explained by the selection of the patients in both trials, where patients receiving CART had been on a stable ARV regimen for more than six months (ATLAS) or may have developed tolerance through CART induction treatment (FLAIR). Aside from ISRs, the most common AEs in both treatment groups included AEs related to infection, gastrointestinal disorders, and general disorders (headache, nausea, or vomiting). Given the parenteral route of administration, a long-acting injectable regimen eliminates dosing restrictions with regard to food, and may therefore have fewer drug-drug interactions at the level of the gastrointestinal tract. This may result in fewer gastrointestinal AEs compared with oral regimens. The incidence of SAEs and WDAEs were low through 48 weeks of IM injection. The oral lead-in period for CAB + RPV was also well tolerated with no patterns observed for clinical AEs or laboratory abnormalities, and few patient withdrawals. One death occurred during the treatment period in ATLAS, and one death occurred during the induction phase of FLAIR.

Notable harms relevant for this review included ISRs, depressive disorders, hepatotoxicity, skin reactions, hypersensitivity, bone-related AEs, and renal function. Of the different ISR events, injection site pain was the most commonly reported AE (> 75%) in both trials, followed by injection site nodules (range 12% to 16%) and induration (range 10% to 13%). No ISRs were reported as SAEs and the incidence of grade 3 ISRs and withdrawal due to ISRs was low. The majority of ISRs were resolved within a week, and the incidence decreased over time resulting from a reduction in the number of patients reporting ISRs.

These patterns were consistent with the clinical expert's expectation for CAB + RPV injection. The remaining notable safety end points occurred in a small number of patients, or were absent in either group. Laboratory biomarkers remained stable and showed no signs of abnormal patterns over time.

Conclusions

Results from two OL RCTs (FLAIR and ATLAS) in HIV-1 infected virologically suppressed patients demonstrated that once-monthly injection of CAB + RPV is noninferior to oral CART with respect to virologic failure (HIV-1 RNA ≥ 50 copies/mL) and virologic suppression (HIV-1 RNA < 50 copies/mL) at week 48. CAB + RPV may be associated with small benefits of HRQoL over CART, including patient's satisfaction and acceptance of treatment; however, the HRQoL results are inconclusive and associated with many uncertainties. The safety profile of CAB + RPV did not show any additional signs of concern. While patients in the CAB + RPV group reported more AEs, the majority were a result of ISRs, which were mostly resolved within a week, and not of concern according to the clinical expert.

Long-term trials of the CAB + RPV regimen are ongoing, with a planned duration of 120 to 148 weeks. Results of these trials will provide more conclusive evidence of the durability of the IM CAB + RPV regimen. Overall, CAB + RPV is an effective regimen with no major safety concerns and could be a new treatment option in virologically suppressed patients.

Appendix 1: Literature Search Strategy

Clinical Literature Search

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946–present) Embase (1974–present) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	September 19, 2019
Alerts:	Bi-weekly search updates until project completion
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.dq	Candidate term word
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.rn,nm	CAS registry number (MEDLINE)
.ot	Original title
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

MULTI-DATABASE STRATEGY

Line #	Search Strategy
1	(vacabria* or cabenuva*).ti,ab,kf,ot,hw.
2	(cabotegravir* or 744-LA or 744LA or CAB or GSK-1265744* or GSK1265744* or GSK 1265744* or GSK-744 or GSK744 or GSK744LA or GSK744LAP or S-265744* or S265744* or HMH0132Z1Q or 3L12PT535M).ti,ab,kf,ot,hw,rn,nm.
3	rilpivirine/
4	(rilpivirin* or edurant* or endurant* or HSDB-8153 or HSDB8153 or R-278474 or R278474 or TMC-278 or TMC278 or FI96A8X663 or 212WAX8KDD).ti,ab,kf,ot,hw,rn,nm.
5	3 or 4
6	2 and 5
7	1 or 6
8	7 use medall
9	(vacabria* or cabenuva*).ti,ab,kw,dq.
10	*cabotegravir/
11	(cabotegravir* or 744-LA or 744LA or CAB or GSK-1265744* or GSK1265744* or GSK 1265744* or GSK-744 or GSK744 or GSK744LA or GSK744LAP or S-265744* or S265744*).ti,ab,kw,dq.
12	10 or 11
13	*rilpivirine/
14	(rilpivirin* or edurant* or endurant* or HSDB-8153 or HSDB8153 or R-278474 or R278474 or TMC-278 or TMC278 or FI96A8X663 or 212WAX8KDD).ti,ab,kw,dq.
15	13 or 14
16	12 and 15
17	9 or 16
18	17 use oemezd
19	(conference abstract or conference review).pt.
20	18 not 19
21	8 or 20
22	remove duplicates from 21

CLINICAL TRIAL REGISTRIES

ClinicalTrials.gov	Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials. Search terms: (cabotegravir* AND rilpivirine*) AND HIV-1
WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials. Search terms: (cabotegravir* AND rilpivirine*) AND HIV-1

OTHER DATABASE

PubMed	Searched to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.

Grey Literature

Dates for Search:	September 12–13, 2019
Keywords:	Cabotegravir, 744LA, GSK744, GSK1265744, rilpivirine, TMC278, HIV-1
Limits:	No limits

Relevant websites from the following sections of the CADTH grey literature checklist Grey Matters: A Practical Tool For Searching Health-Related Grey Literature (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug And Device Regulatory Approvals
- Advisories And Warnings
- Drug Class Reviews
- Clinical Trial Registries
- Databases (Free)
- Internet Search
- Open Access Journals.

Appendix 2: Excluded Studies

Table 18: Excluded Studies

Reference	Reason for exclusion
Margolis DA, Gonzalez-Garcia J, Stellbrink HJ et al. Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomized, open-label, phase IIb, noninferiority trial. Lancet. 2017 Sep 23;390(10101):1499-1510.[40]	Phase II study

Appendix 3: Pooled Analysis

Objective

The sponsor conducted a pre-planned pooled analysis of the FLAIR and ATLAS trials, and the data informed the economic analysis in the pharmacoeconomic report. Therefore, a brief summary and appraisal of the pooled analysis is provided in this appendix.

Methods

The population characteristics and intervention schedule in the pooled dataset remained unchanged compared to the individual trials. Similar to the individual trials, the primary efficacy outcome for the pooled analyses was to evaluate the noninferiority of pooled CAB + RPV compared with CART in a proportion of subjects with plasma HIV-1 RNA of 50 copies/mL or greater as per the FDA's Snapshot algorithm at week 48.

The statistical analysis plan for the pooled analysis followed the same methodology as the individual trials described previously. For the primary efficacy analysis, adjusted estimates of the difference in the proportion of patients with virologic failure between the two pooled treatment groups were presented along with two-sided 95% CI based on a stratified analysis using Cochran–Mantel–Haenszel weights. A 4% noninferiority margin was used for the primary comparison. Noninferiority was concluded if the upper bound of the two-sided 95% CI for the primary adjusted difference between the two treatment groups was less than 4%. In total, the primary analysis was adjusted for 10 strata formed by the combination of randomized stratification factors within each study (four strata from FLAIR and six strata from ATLAS). A second adjusted difference was done as a sensitivity analysis, adjusted to study (FLAIR and ATLAS) and biological sex (male, female) factors, which stratified the pooled data into four strata. The weighted least squares chi-square statistic was used to test for homogeneity of treatment effect across the analysis strata. Tests of homogeneity were assessed at the one-sided 10% level of significance. The overall between-treatment difference was further summarized by baseline characteristics and demographic factors. No adjustment was done for subgroup analyses.

In addition to the primary efficacy analysis, the following secondary efficacy analyses were performed: proportion of patients with plasma HIV-1 RNA concentration of less than 50 copies/mL at week 48 overall, which was further summarized by baseline characteristics or demographic factors. The proportion of patients with virologic or tolerability failure was estimated using the Kaplan–Meier nonparametric method based on the time to failure for each reason.

No multiplicity adjustment was made for the efficacy analyses. A post hoc Bonferroni procedure was done for the HRQoL outcomes to control type I error at the 5% significance level. Since there were seven statistical tests performed for the three HRQoL end points (two for HIVTSQs and PIN each, three for ACCEPT), the Bonferroni adjusted significance level alpha was 0.0071 (0.05/7). The P values of HRQoL analyses can therefore be judged against this Bonferroni adjusted alpha level.

All patients from the FLAIR and ATLAS studies were included in the pooled analysis. Data up to week 48 during the maintenance visit were pooled and extension data were not included. The ITT-E and safety populations as applied per the individual trials were used in the pooled efficacy and safety analysis, respectively. In addition, the PP population was used for a subset of the efficacy analysis.

Results

Baseline Characteristics

Demographic and baseline characteristics in the pooled analysis were similar across treatment groups (Table 19). At the baseline of the maintenance phase, the mean age of the patients was approximately 39 years, the majority of the patients were male, White, with HIV-1 stage 1, and a CD4+ cell count of approximately 670 cells/μL. Since the FLAIR and ATLAS trial recruited patients who were naive to and experienced with ARV regimens, respectively, their baseline level of plasma HIV-1 RNA and medication history prior to and during the trial were different. Therefore, baseline data for these variables were not pooled.

Table 19: Summary of Demographic Characteristics – Pooled Data (ITT-E Population)

Characteristic	Pooled (FLAIR and ATLAS)	
	CAB + RPV N = 591	CART N = 591
Age (years), n (%)		
Mean (SD)	38.9 (10.46)	39.8 (11.28)
≤ 35	223 (38)	225 (38)
35 to < 50	269 (46)	241 (41)
≥ 50	99 (17)	125 (21)
Sex, n (%)		
Female	162 (27)	168 (28)
Male	429 (73)	423 (72)
Race, n (%)		
White	423 (72)	403 (68)
Black	109 (18)	133 (23)
Maintenance baseline CD4+ count (cells/μL)		
Mean (SD)	672.7 (264.26)	670.2 (273.20)
CDC category, n (%)		
HIV infection stage 1	429 (73)	420 (71)
HIV infection stage 2	156 (26)	165 (28)
HIV infection stage 3	6 (1)	6 (1)

CAB + RPV = cabotegravir plus rilpivirine; CART = current antiretroviral treatment; CD4+ = cluster of differentiation 4 positive; CDC = Centers for Disease Control and Prevention; ITT-E = intention-to-treat–exposed; SD = standard deviation.

Source: Pooled Clinical Study Report.[33]

Patient Disposition

In the pooled analysis, a total of 591 patients underwent randomization in the maintenance phase and received treatment with the CAB + RPV regimen or CART. The proportion of patients who withdrew from the trials were similar across treatment groups; 9% versus 7% in the CAB + RPV and CART groups, respectively. The most common reasons for withdrawal were AEs and consent withdrawal (Table 20).

Table 20: Summary of Patient Disposition in Pooled Analysis – Maintenance Phase

	Pooled (FLAIR and ATLAS)	
	CAB + RPV N = 591	CART N = 591
Completion status, n (%)		
Ongoing at time of analysis	259 (44)	261 (44)
Completed	281 (48)	290 (49)
Withdrawn	51 (9)	40 (7)
Reason for discontinuation, n (%)		
Adverse events	22 (4)	9 (2)
Lack of efficacy (CVF)	8 (1)	7 (1)
Protocol deviation	5 (< 1)	4 (< 1)
Protocol-specified stopping criterion met	1 (< 1)	0
Lost to follow-up	3 (< 1)	3 (< 1)
Physician decision	4 (< 1)	5 (< 1)
Withdrew consent	8 (1)	12 (2)
Outcomes of AEs resulting in study withdrawal	22 (4)	9 (1)

AE = adverse event; CAB + RPV = cabotegravir plus rilpivirine; CART = current antiretroviral treatment; CVF = confirmed virologic failure.

Source: Pooled Clinical Study Report.[33]

Exposure to Study Treatments

[redacted]

Table 21: Summary of Extent of Exposure in Pooled Analysis – Maintenance Phase

Exposure	Pooled (FLAIR and ATLAS)	
	CAB + RPV N = 591	CART N = 591
Overall exposure, days mean (SD)	[redacted]	[redacted]
Weeks, n (%) [redacted]	[redacted]	[redacted]

Exposure	Pooled (FLAIR and ATLAS)	
	CAB + RPV N = 591	CART N = 591
[redacted]	[redacted]	[redacted]

CAB + RPV = cabotegravir plus rilpivirine; CART = current antiretroviral treatment; SD = standard deviation.

Source: Pooled Clinical Study Report.[33]

Efficacy

As noted previously, the pooled analysis used a 4% noninferiority margin for the primary outcome of virologic failure (HIV-1 RNA ≥ 50 copies/mL) per FDA Snapshot algorithm. The adjusted mean difference between the treatment groups was 0.2 (95% CI, –1.4 to 1.7), meeting the noninferiority criterion, as the upper bound of 95% CI for the adjusted treatment was below 4%. Analysis using the PP population supported the results. Both groups had similar response to virologic suppression, with a between-treatment difference of –1.4 (95% CI, –4.1 to 1.4), meeting the noninferiority margin of –10%. Few patients met the CVF criteria through week 48; CVF incidence in each pooled group was 1.2%.

The treatment effect for the primary end point was consistent across the stratification factors such as study and sex at birth (P ≥ 0.10 for pre-specified tests of treatment-by-strata interaction) and across the 10 randomization factors combined from each study (P ≥ 0.10 from post hoc test) (data not presented).

The proportion of patients without efficacy-related discontinuation (CVF or discontinuation due to lack of efficacy) by week 48 were 98.6% for CAB + RPV and 98.8% for CART and the between-treatment difference was –0.2% (95% CI, –1.5% to 1.1%).

Table 22: Virologic Outcomes in Pooled Analyses – Maintenance Phase

Virologic efficacy outcomes	Pooled (FLAIR and ATLAS)	
	CAB + RPV N = 591	CART N = 591
Virologic failure		
ITT-E population at week 48		
HIV-1 RNA ≥ 50 copies/mL at week 48, n/N (%)	11/591 (1.9)	10/591 (1.7)
Difference in proportion[a], % (95% CI)	0.2 (–1.3 to 1.7)	
Adj. difference in proportion[b], % (95% CI)	0.2 (–1.4 to 1.7)	
PP population at week 48		
HIV-1 RNA ≥ 50 copies/mL at week 48, n/N (%)	10/572 (1.7)	10/574 (1.7)
Difference in proportion[a], % (95% CI)	0.0 (–1.5 to 1.5)	
Adj. difference in proportion[b], % (95% CI)	0.0 (–1.5 to 1.5)	
Reasons for virologic failure, n (%)		
Data in window not below threshold	3 (0.5)	3 (0.5)
Discontinued for lack of efficacy	7 (1.2)	5 (0.8)
Discontinued for other reason while not below threshold	1 (0.2)	2 (0.3)
Change in background therapy	0	0
No virologic data	30 (5.1)	23 (3.9)

Virologic efficacy outcomes	Pooled (FLAIR and ATLAS)	
	CAB + RPV N = 591	CART N = 591
Discontinued study due to AE or death	19 (3.2)	7 (1.2)
Discontinued study for other reasons	11 (1.9)	16 (2.7)
On study but missing data in window	0	0
Virologic suppression		
ITT-E population at week 48		
HIV-1 RNA < 50 copies/mL at week 48, n/N (%)	550/591 (93)	558/591 (94)
Difference in proportion[a], % (95% CI)	–1.4 (–4.1 to 1.4)	
Adj. difference in proportion[b], % (95% CI)	–1.4 (–4.1 to 1.4)	
Confirmed virologic failure		
Confirmed virologic failure, n (%)	7 (1.2)	7 (1.2)

Adj = adjusted; AE = adverse event; ART = antiretroviral therapy; CAB + RPV = cabotegravir plus rilpivirine; CART = current antiretroviral treatment; CI = confidence interval; CMH = Cochran–Mantel–Haenszel; HIV-1 = HIV type 1; IM = intramuscular; ITT-E = intention-to-treat–exposed population; PP = per-protocol population; q.4.w. = every 4 weeks; RNA = ribonucleic acid.

[a] Difference is the proportion on CAB + RPV (q.4.w. IM) minus the proportion on CART (unadjusted).

[b] Based on CMH-stratified analyses adjusting to baseline viral load and sex at birth for Study 201584, adjusting to the third ART class and sex at birth for Study 201585 and adjusting to 10 strata for pooled analysis.

Source: Pooled Clinical Study Report.[33]

Pooled analyses of the HRQoL measures showed a statistically significantly greater benefit in the CAB + RPV group compared with CART (HIVTSQs and ACCEPT), and at week 48 from baseline in the CAB + RPV group exclusively (PIN) (Table 23).

Table 23: Summary of HIVTSQ, PIN, and ACCEPT Questionnaire in Pooled Analysis – Maintenance Phase

Characteristic	Pooled (FLAIR and ATLAS)	
	CAB + RPV N = 591	CART N = 591
HIVTSQs – Change from baseline in total treatment satisfaction score in ITT-E population – (adjusted, LOCF)		
Week 44, n	557	552
Adjusted mean (95% CI)[a]	3.9 (3.2 to 4.5)	0.5 (–0.1 to 1.2)
Adjusted mean difference (95% CI)	3.4 (2.5 to 4.3)	
P value[b]	< 0.001	
PIN – acceptance domain PIN scores – (adjusted, LOCF)		
Week 5, n	567	ND
Week 5, mean (SD)	2.10 (1.04)	
Week 48, n	582	
Week 48, mean (SD)	1.62 (0.80)	
P value[c]	< 0.001	
ACCEPT – Change from baseline in General Acceptance domain score in ITT-E population – (adjusted, LOCF)		
Week 48, n	557	562
Week 48, adjusted mean (95% CI)[a]	8.8 (7.0 to 10.6)	2.0 (0.2 to 3.8)

Characteristic	Pooled (FLAIR and ATLAS)	
	CAB + RPV N = 591	CART N = 591
Adjusted mean difference (95% CI)	6.8 (4.2 to 9.4)	
P value[b]	< 0.001	

ACCEPT = Chronic Treatment Acceptance Questionnaire; ANCOVA = analysis of covariance; CAB + RPV = cabotegravir plus rilpivirine; CART = current antiretroviral therapy; CI = confidence interval; HIVTSQs = HIV Treatment Satisfaction Questionnaire Status Version ; INSTI = integrase strand transfer inhibitor; ITT-E = intention-to-treat–exposed; LOCF = last observation carried forward; ND = not done; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PIN = Perception of Injection; SD = standard deviation.

[a] Adjusted mean is the estimated mean change from baseline score by visit in each treatment calculated from a ANCOVA model including the covariates of baseline score, sex at birth, age (< 50 or ≥ 50), and race (White or non-White) for pooled analysis; additional covariates included were a third agent class (INSTI, PI, or NNRTI) for ATLAS and an induction baseline at week –20 of HIV-1 RNA (< 100,000 or ≥ 100,000 copies/mL) for FLAIR.

[b] Statistical significance can be claimed if the P value is less than the Bonferroni adjusted alpha of 0.0071.

[c] Week 41 or 48 was compared with the first visit (week 5) based on Wilcoxon signed rank test, respectively; Bonferroni alpha = 0.0071; P values are derived for "acceptance" only; and a Bonferroni procedure adjusts for multiple testing.

Source: Pooled Clinical Study Report.[33]

Harms

Overall, the safety pattern seen in the individual trials continued in the pooled analysis. There was an imbalance between the treatment groups in the incidence of AEs during the 48 weeks of the maintenance phase. Similar to the individual trials, the disproportionate incidence was largely driven by the occurrence of ISRs in the CAB + RPV group. The majority of the AEs were grade 1 or 2 in intensity. The most commonly reported non-ISR AEs in either treatment group were similar, with the exception of hemorrhoids, pyrexia, dizziness, fatigue, headache, nausea, and back pain, which occurred at higher rates in the CAB + RPV group. The incidence of SAEs and WDAEs were low (≤ 5%). Among notable harms, most of the patients in the CAB + RPV group experienced ISRs related to pain (77%); other ISRs included nodule (14%), induration (12%), swelling (8%), erythema (4%), and pruritus (4%). The incidence and severity of ISRs decreased over time, with approximately 70% of patients reporting an ISR at first injection to approximately 16% of subjects reporting an ISR at week 48. Most ISRs were grade 1 (75%) and 2 (36%) in severity, and resolved in a median of three days. Cases of hepatoxicity, hypersensitivity, rash, depression, and abnormalities in renal and bone biomarkers were absent or minimal (data not presented).

Table 24: Overview of all Adverse Events During the Maintenance Phase, Pooled Phase III Studies

Harms	Pooled (FLAIR and ATLAS)	
	CAB + RPV N = 591	CART N = 591
AEs		
Patients with > 0 AEs, n (%)	561 (95)	445 (75)
Any grade 3/4/5 AE, n (%)	66 (11)	35 (6)
Number of subjects with injection	581 (98)	
Number of subjects with ISR event	489 (84)	
Most common AEs (≥ 5% incidence)		
Injection site pain	458 (77)	0
Nasopharyngitis	108 (18)	90 (15)
Upper respiratory tract infection	70 (12)	53 (9)

Harms	Pooled (FLAIR and ATLAS)	
	CAB + RPV N = 591	CART N = 591
Headache	73 (12)	38 (6)
Diarrhea	54 (9)	40 (7)
Injection site nodule	81 (14)	0
Influenza	42 (7)	34 (6)
Injection site induration	68 (12)	0
Back pain	43 (7)	23 (4)
Pyrexia	43 (7)	13 (2)
Vitamin D deficiency	31 (5)	25 (4)
Respiratory tract infection, viral	24 (4)	29 (5)
Cough	26 (4)	26 (4)
Injection site swelling	46 (8)	0
Nausea	30 (5)	16 (3)
Pharyngitis	23 (4)	21 (4)
Fatigue	29 (5)	14 (2)
Gastroenteritis	20 (3)	21 (4)
Dizziness	24 (4)	8 (1)
Hemorrhoids	20 (3)	5 (< 1)
Injection site pruritus	23 (4)	0
SAEs		
Patients with > 0 SAEs, n (%)	31 (5)	26 (4)
Fatal SAEs, n (%)	0	1 (< 1)
WDAEs		
Patients with > 0 WDAEs, n (%)	22 (4)	9 (2)

AE = adverse event; CAB + RPV = cabotegravir plus rilpivirine; CART = current antiretroviral therapy; ISR = injection site reaction; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

Source: Pooled Clinical Study Report.[33]

Summary

The sponsor conducted a pre-planned pooled analysis of the FLAIR and ATLAS trials, and the data informed the economic analysis in the CADTH pharmacoeconomic report. The individual FLAIR and ATLAS trials were not sufficiently powered for a 4% noninferiority margin as recommended by the FDA for switch trials in HIV-1; the recommended noninferiority margin of 4% was applied to the pooled analysis.

Overall, the study design was largely similar in FLAIR and ATLAS; both trials were OL, with mostly similar eligibility criteria, and treatment schedules. Likewise, demographic and baseline characteristics and patient disposition showed a similar pattern within and across studies before pooling the trial data. Finally, results of the efficacy and safety analysis were consistent across the two trials. Taken together, these indicate the rationale of pooling results were reasonable.

Notwithstanding the similarities between the trials, a number of differences are noteworthy. Patients included in the two trials were generally similar, with the major exception being the duration of ARV regimen exposure. In both trials, treatment with CAB + RPV was initiated following viral suppression (HIV-1 RNA < 50 copies/mL); however, patients in FLAIR had 20 weeks of ARV exposure whereas ATLAS included patients on stable (> 6 months) ARV

regimens. The clinical expert consulted for this CDR review indicated 20 weeks of ARV exposure is insufficient to ascertain viral suppression, and suggested patients in FLAIR closely resemble patients who are ARV naive. Other notable differences between the studies included a difference in the length of the maintenance phase, follow-up duration, presence of an induction phase in FLAIR, and the comparators used in the two trials. A formal statistical test to assess between-study homogeneity (e.g., I^2 or Cochrane's Q) was not conducted, therefore quantitative variability between the trials could not assessed. Despite these uncertainties, the similarities in trial design and conduct, as well as consistent findings in the pooled analysis and the individual trials, lend credibility to the findings of the pooled analysis.

Appendix 4: Description and Appraisal of Outcome Measures

Aim

To describe the following outcome measures and review their measurement properties (validity, reliability, responsiveness to change, and MID):

- ACCEPT Questionnaire
- HAT-QoL Instrument
- HIVTSQ
- NRS - Pain
- PIN Questionnaire
- SF-12.

Findings

Table 25: Summary of Outcome Measures and Their Measurement Properties

Outcome measure	Type	Conclusions about measurement properties	Minimal important difference
ACCEPT questionnaire	Generic, patient-reported measure of medication acceptance 25 items within 7 domains 3-point Likert-type scale, higher score indicates greater acceptance	Reliability of the overall acceptance score based on Cronbach's alpha = 0.85[41] Evidence of validity (convergent and divergent) for the overall acceptance score; however, the methodology is unclear[41] Responsiveness was not evaluated in the literature identified	Not identified
HAT-QoL instrument	HIV-specific, patient-reported assessment of HRQoL based on 4-week recall period 42-items, grouped into 9 dimensions; note: an adapted 14-item/3-dimension version was used in the FLAIR and ATLAS studies 5-point Likert scale from 1 to 5, dimension scores are converted from 0 to 100; higher scores indicate better function and well-being	Evidence of acceptable construct validity and reliability (internal consistency and test-retest) were demonstrated for the 42-item version[36,37] Responsiveness was not evaluated in the literature identified Evidence of a psychometric assessment was not identified for the 14-item version	Not identified
HIVTSQ	Patient-reported questionnaire that assesses treatment satisfaction, specific to patients with HIV-1	Using the 10-item version, there was weak (r = 0.18) to moderate (r = 0.32) evidence of construct validity[34] Reliability (internal consistency) was demonstrated in both the static and	Not identified

Outcome measure	Type	Conclusions about measurement properties	Minimal important difference
	10 or 12 items rated using a 7-point Likert scale. The static version ranges from 0 (very dissatisfied) to 6 (very satisfied). The change version ranges from –3 (much less satisfied) to 3 (much more satisfied)	change version of the 10-item HIVTSQ[42] Evidence of responsiveness and assessment of the 12-item version were not identified in the literature	
NRS - Pain	Patient-reported scale that measures post-injection site pain One-item scale answered on an 11-point from 0 (no pain) to 10 (extreme pain)	Although widely used and validated in other diseases and clinical situations, evidence of validity, reliability, and responsiveness in patients living with HIV-1 was not identified	Not identified
PIN questionnaire	Patient-reported measure of a patient's PIN 21-item questionnaire scored from 1 (most favourable perception) to 5 (least favourable)	Evidence of validity, reliability, and responsiveness was not identified	Not identified
SF-12	Patient-reported measure of HRQoL based on a 4-week recall period 12-item version of the Short Form Health Survey, composed of eight concepts belonging to either the PCS or MCS The PCS and MCS range from 0 to 100, where a higher score indicates better HRQoL	Evidence of discriminant validity for the PCS, but not the MCS, in patients living with HIV-1[38] Evidence of reliability and responsiveness was not identified for patients with HIV-1	Not identified

ACCEPT = Chronic Treatment Acceptance Questionnaire; HAT-QoL = HIV/AIDS-targeted quality of life; HIV-1 = HIV type 1; HIVTSQ = HIV Treatment Satisfaction Questionnaire; HRQoL = health-related quality of life; MCS = Mental Component Score; NRS = Numeric Rating Scale; PCS = Physical Component Score; PIN = Perception of Injection; SF-12 = Short Form (12) Health Survey.

Source: Arnould et al. (2013),[41] Holmes and Shea (1998),[36] Holmes and Ruocco (2008),[37] Woodcock and Bradley (2001),[34] Woodcock and Bradley (2006),[42] Delate et al. (2000).[38]

ACCEPT Questionnaire

The ACCEptance by the Patients of their Treatment (ACCEPT) questionnaire is a generic patient-reported measure of medication acceptance that was developed to determine how patients weigh the advantages and disadvantages of chronic treatment (medications taken chronically).[43] The questionnaire is composed of 25 items that fall within seven independent dimensions, which include General Acceptance, and six treatment-specific dimensions: medication inconvenience, long-term treatment, regimen constraints, numerous medications, side effects, and effectiveness.

The "General" domain is composed of three items relating to the advantages and disadvantages of a treatment, acceptability, and whether the treatment is worth taking chronically.[43] Patients rate each item using a Likert-like scale of three response choices:

"Yes and I don't find this easy to accept," "Yes and I find this easy to accept," and "No". This was the only domain assessed in the CAB + RPV trials.

The "Medication Inconvenience" domain consists of five items, evaluating preparation, mode of administration, form, storage conditions for journeys, and discreet uptake of medication. The "Long-term Treatment" domain includes three items relating to past and future duration of treatment and routine. The "Regimen Constraints" domain is made up of five items regarding: remembering to take the treatment, time to collect it from the pharmacy, remembering to bring treatment with oneself, always having it on oneself, and the frequency of administration. One item regarding having several medications makes up the "Numerous Medications" domain. Five items contribute to the "Side Effects" domain, which address the presence of side effects, side effects that are unpleasant and/or disabling, the need for supplementary drugs due to side effects, and the risk of serious side effects. The "Effectiveness" domain is composed of three items regarding the efficacy, preventive effect, and time to efficacy of a treatment. The treatment-attribute specific items are also answered by selecting one of the following three response choices: "Yes and I don't find this easy to accept," "Yes and I find this easy to accept," and "No" indicating the item was not an issue.[43] Categorical or ordinal data linearly transformed to a range from zero to 100 where a higher score is associated with greater acceptance.[43]

A study by Arnould et al.[41] assessed the ACCEPT questionnaire in a group of 182 patients recruited by pharmacists who were prescribed a drug indicated for various chronic diseases, including asthma, diabetes, cardiovascular disease, retroviral infections, and osteoporosis. The number of patients treated for a "retroviral infection" was not reported. Nevertheless, patients completed the ACCEPT questionnaire and the 4-item Morisky Medication Adherence Scale (MMAS-4) questionnaire one, three, and six months following consent to participation. Cronbach's alpha was used to assess the internal consistency reliability. Briefly, the overall acceptance score demonstrated reliability based on a threshold of 0.70[35] or greater (alpha = 0.85), as well as some of the domain-specific scores (alpha ranged from 0.67 to 0.87); however, the scores were only available as a range and not by domain. The study also reported the overall acceptance score as demonstrating convergent and divergent validity at 100%, and the convergent and divergent validity of the domain-specific scores ranging from 63% to 100% and 33% to 100%, respectively. Details about the methodology used was not provided.

HIV/AIDS-Targeted Quality of Life

The HIV/AIDS-Targeted Quality of Life (HAT-QoL) instrument was created to assess HRQoL in patients living with HIV.[36] The HAT-QoL is composed of 42 items grouped into nine dimensions that assess overall function and well-being, which include: overall function (seven items); sexual function (three items); disclosure worries (five items); health worries (five items); financial worries (four items); HIV mastery (three items); life satisfaction (eight items); medication concerns (four items); and provider trust (three items).[36] The questionnaire is based on a four-week recall period and the items are answered using a 5-point Likert scale from 1 ("all of the time") to 5 ("none of the time").[7,8] Scores for the dimensions are computed by summing the corresponding item responses and converting the sums to a scale from 0 to 100, where a higher score indicates better function and well-being.[36]

The reliability and validity of the HAT-QoL was assessed in a convenient sample of 201 patients living with HIV who were recruited from an urban HIV specialty clinic, a medium-sized rural hospital's outpatient clinic, an AIDS Clinical Trials Unit, and an urban, hospital-

affiliated outpatient medical clinic.[36] Construct validity was assessed using self-reported HIV disease severity markers and sociodemographic variables, which were dichotomized and used to demonstrate statistically significant (P ≤ 0.05) relationships with the relevant dimensions. Internal consistency reliability was evaluated using Cronbach's alpha for each dimension. Excluding HIV mastery and medication concerns, which demonstrated moderate reliability (alpha = 0.57 and 0.54, respectively), the dimensions demonstrated acceptable (alpha ≥ 0.70) reliability, with a value of Cronbach's alpha ranging from 0.70 to 0.90.[36]

Test-retest reliability was also assessed in a study by Holmes and Ruocco (2008) that included 153 patients from HIV specialty and general medical clinics.[37] Patients were asked to the complete the HAT-QoL, then a subsample of 60 participants were asked to repeat the questionnaire approximately two weeks later. Test-retest reliability was evaluated using the intraclass correlation coefficient (ICC) for each of the dimensions, where a score of greater than 0.75 was considered highly correlated, 0.51 to 0.75 was moderately correlated, 0.26 to 0.50 was somewhat correlated, and 0.25 or less was minimally correlated.[37] Using this classification, most of the dimensions of the HAT-QoL were highly correlated (ICC ranged from 0.76 to 0.84). The overall function, financial worries, and provider trust dimensions were moderately correlated (ICCs of 0.73, 0.64, and 0.64, respectively).[37]

A shorter, 14-item adapted version of the HAT-QoL was used in the ATLAS and FLAIR trials. The 14 items were grouped into three dimensions, including "life satisfaction", "disclosure worries", and "HIV medication". Some of the areas addressed in each of the dimensions are described in Table 26.

Table 26: Description of the Dimensions Included in the 14-Item HAT-QoL

Dimension	Topics addressed by items
Life satisfaction	Enjoy living, will to live, content with life, food about myself, pleased with how healthy I've been, and so forth.
Disclosure worries	Limited what they tell others about themselves, afraid to disclose HIV status, worried about family finding out, worried about employer/colleagues finding out, and so forth.
HIV medication	Hard to live a normal life, medicine made them feel better, made them more sick, feel as though they're fighting HIV.

HAT-QoL = HIV/AIDs-targeted quality of life.

Source: ATLAS Clinical Study Report,[8] FLAIR Clinical Study Report.[7]

The 42-item version of the HAT-QoL is limited by the ceiling effects (44%) associated with the provider trust dimension,[44] but overall, the HAT-QoL demonstrates acceptable reliability and validity. A MID was not identified, nor was information regarding the responsiveness of the outcome measure. With regards to the use of the HAT-QoL in the ATLAS and FLAIR trials, a modified version of the HAT-QoL that was not validated based on what was available in the literature was used, which is also a limitation of the use of this outcome measure.

HIV Treatment Satisfaction Questionnaire

The HIV Treatment Satisfaction Questionnaire (HIVTSQ) is based on the commonly used Diabetes Treatment Satisfaction Questionnaire for patients with diabetes, and was designed to evaluate satisfaction with HIV medication for patients living with HIV. The original version of the HIVTSQ was composed of 10 items, including: "current treatment," "control," "side effects," "demands," "convenience," "flexibility," "understanding," "lifestyle,"

"recommend to others," and "continue."[42] Two items ("easy/difficult" and "pain/discomfort") were added to the original 10-item version of the HIVTSQ in 2016 to include an assessment of long-acting injectable treatment for HIV-1. The revised version includes 12 items overall, which can be reported individually or as a total score that includes 11 items, with the "pain/discomfort" item reported separately. The items have been summarized in Table 27.

Table 27: Items Included in the 12-Item HIVTSQ

Item number	Item label	Item wording
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

HIVTSQ = HIV Treatment Satisfaction Questionnaire.

Source: Woodcock et al. (2006),[42] ATLAS Clinical Study Report.[8]

Patients respond to the HIVTSQ items using a Likert scale ranging from 0 to 6, where 0 represents the least favourable option ("very dissatisfied") and 6 represents the most favourable option ("very satisfied"). The HIVTSQ "status version" (HIVTSQs) is one of two versions of the HIVTSQ, that measures patient satisfaction with their current treatment. The total score ranges from 0 to 66, where higher scores indicate a greater level of satisfaction with their HIV-1 treatment. There is also a HIVTSQ "change version" (HIVTSQc) that was designed to assess the change in treatment satisfaction between a patient's previous and current treatment. The individual items are scored from –3 ("much less satisfied now") to 3 ("much more satisfied now"). The total score for the HIVTSQc ranges from –33 to 33, where higher scores indicate a greater improvement in treatment satisfaction with the new treatment, and lower scores indicate lower treatment satisfaction with the new treatment, and a score of zero represents no change in satisfaction.

The construct validity of the original 10-item version of the HIVTSQ was assessed in a group of 150 patients living with HIV-1 infection (157 were asked to complete the questionnaire) who were participating in clinical trials for an oral PI, conducted in the US and Canada.[34] The HIVTSQ scores were correlated with viral load (copies of HIV-1 RNA/mL [$\log_{10}$]). Viral load was moderately correlated with the "control" item (Spearman's $r = 0.35$ at 8 weeks and $r = 0.32$ at 16 weeks; $P < 0.01$ for both). Adverse event scores (graded for severity) were assessed for correlation with the "side effects" item; however, the reported correlation was poor ($r = 0.18$; $P = 0.03$).[34]

A second study by Woodcock et al. assessed both the static and change version of the HIVTSQ using patients participating in a clinical trial for treatment of HIV-1.[42] At baseline, 126 of 152 (82.9%) of patients completed the HIVTSQs fully and 100 patients completed it at week 48. The internal consistency reliability of the HIVTSQs divided into subscales was evaluated using Cronbach's alpha. The "general satisfaction/clinical" subscale included items 1, 2, 3, 9, and 10; the "lifestyle/ease" subscale included items 4 to 8, and the "treatment satisfaction" scale included all 10 items. All three subscales demonstrated reliability based on a threshold of 0.70[35] with an alpha ranging from 0.821 to 0.890. The same method was applied to the HIVTSQc subscales, which also demonstrated reliability as the alpha for all three subscales were also greater than 0.80 (range from 0.882 to 0.916).

Overall, the 10-item version of the HIVTSQ has demonstrated weak (r = 0.18) to moderate (r = 0.32) evidence[45] in support of construct validity, and both the static and change version demonstrated acceptable internal consistency reliability (alpha ≥ 0.821) for each of the three subscales. Evidence of responsiveness and an MID were not identified, which is a limitation for the use of this outcome. In addition, psychometric analyses of the 12-item version of the HIVTSQ were not identified; however, the sponsor reported that datasets from the LATTE-2 trial support the use of the 12-item version without a reduction in validity.[7,8]

Numeric Rating Scale – Pain

A NRS is a segmented numeric version of the Visual Analogue Scale. The NRS was used to measure post-injection pain using one item in the FLAIR and ATLAS trials.[7,8] Patients respond by selecting a whole number from zero to 10, where zero corresponds to "no pain" and 10 corresponds to "extreme pain" regarding the intensity of their post-injection pain. The design of this outcome is easy to use and understand, but is highly subjective and subject to floor and ceiling effects. Although widely used and validated in other diseases and clinical situations, evidence of validity, reliability, and responsiveness and an MID for patients living with HIV-1 was not identified.

Perception of Injection Questionnaire

The Perception of Injection (PIN) questionnaire is based on the Vaccines' Perception of Injection Questionnaire (VAPI), which was developed to assess patient perception and acceptance of influenza vaccination and ISRs and validated for use in clinical trials.[46] The VAPI demonstrated evidence of construct validity and internal consistency reliability.[46] The PIN questionnaire was adapted for the CAB + RPV trials for use in patients living with HIV-1.[7,8] The questionnaire is composed of 21 items that measure injection site pain, local site reactions, the impact of an injection on functioning, anxiety before and after receiving an injection, the patient's willingness to pursue injectable treatment outside of a clinical trial, their satisfaction with the mode of treatment administration, and perceptions of individuals associated with receiving injections. Evidence of peer review of the PIN questionnaire was not identified, which is a limitation of this outcome. In addition, evidence of validity and an MID for the PIN was not identified in the literature.

12-Item Short Form Health Survey

The SF-12 is a generic measure of HRQoL based on the 36-item version of the survey (SF-36). Each item falls into one of eight health concepts, including:

- physical functioning, two items
- role physical two items
- bodily pain, one item
- general health, one item
- vitality, one item
- social functioning, one item
- role emotional, two items
- and mental health, two items.[7,8]

The “general health” concept measures the patient’s perception of their overall health, “vitality” assesses fatigue and energy levels, “bodily pain” measures the frequency of pain and how much pain interferes with normal functioning, “social functioning” measures how much a patient’s illness affects social functioning, “physical functioning” assesses the extent to which daily life is affected, “role physical” measures limitations in roles due to problems with physical health, “role emotional” assesses role limitations due to emotional issues, and “mental health” assesses psychological distress.[47]

Each concept falls under either the PCS or MCS, which correspond to the physical and psychological burden of disease, respectively. Each component score is reported on a range from 0 (lowest level of health) to 100 (highest level of health), with higher scores indicating better HRQoL.[7,8]

The discriminative ability of the SF-12 was evaluated in persons living with HIV-1 using the known-groups approach based on indicators of health such as laboratory values (CD4 cell count and HIV-1 RNA copies/mL) and clinician assessments.[38] A convenient sample of 475 patients from two HIV specialty clinics were included in this study. Patients were 18 years of age or older and had clinically documented HIV-1 infection. Receiver operating characteristic (ROC) area under the curves (AUCs) were used to assess the discriminative ability of the PCS and MCS. In summary, the PCS was able to discriminate between groups defined by CD4 cell count (ROC AUC = 0.631; 99% CI, 0.557 to 0.705) or HIV-1 RNA copies/mL (ROC AUC = 0.604; 99% CI, 0.510 to 0.697);[38] however, the MCS was not based on a predefined ROC AUC threshold of 0.50 where less than 0.50 indicates a model without discriminative ability. The authors noted that the baseline characteristics for patients were collected three months prior to the collection of survey results, which were based on a four-week recall period. This may have an impact on the results, although it is not expected to be significant.[38]

Test-retest reliability of the SF-12 has been demonstrated in the general US population, as well as discriminate validity using groups known to differ in physical and mental conditions.[47] However, evidence regarding the reliability and responsiveness or a MID for the SF-12 were not identified for patients living with HIV-1 and thus limits our ability to interpret the HRQoL data collected within this specific patient population.

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