CADTH

CADTH COMMON DRUG REVIEW

Pharmacoeconomic 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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Abbreviations

ADE	AIDS-defining events
AE	adverse event
ART	antiretroviral therapy
ARV	antiretroviral
CAB	cabotegravir
CAB + RPV	cabotegravir plus rilpivirine
CD4+	cluster of differentiation 4 positive
HIV-1	HIV type 1
IM	intramuscular
ICER	incremental cost-effectiveness ratio
QALY	quality-adjusted life-year
RNA	ribonucleic acid
RPV	rilpivirine
WTP	willingness to pay

Table 1: Summary of the Sponsor's Economic Submission

Drug product	Cabotegravir oral tablets (Vocabria) and cabotegravir plus rilpivirine extended release IM injections (Cabenuva)
Study question	From the perspective of a publicly funded health care payer, what is the cost utility of cabotegravir plus rilpivirine as a complete regimen versus combination oral ART for the treatment of HIV-1 infection in adults who are virologically stable and suppressed?
Type of economic evaluation	Cost-utility analysis
Target population	Adult patients with suppressed HIV-1 RNA viral load (< 50 copies per mL)
Treatment	1. Oral lead-in: cabotegravir 30 mg + rilpivirine 25 mg administered once daily for one month 2. IM initiation injection: single dose of cabotegravir 600 mg + rilpivirine 900 mg administered at month 1. 3. IM continuation injection: cabotegravir 400 mg + rilpivirine 600 mg administered monthly
Outcomes	QALYs
Comparator	Combination of oral ART, based on pooling of nine ARV regimens: • Dolutegravir/lamivudine (Dovato) • Bictegravir/emtricitabine/tenofovir (Biktarvy) • Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (Genvoya) • Dolutegravir/rilpivirine (Juluca) • Abacavir/dolutegravir/lamivudine (Triumeq) • Dolutegravir (Tivicay) + emtricitabine/tenofovir (generics) • Tenofovir alafenamide/emtricitabine/rilpivirine (Odefsey) • Darunavir/cobicistat (Prezcobix) + emtricitabine/tenofovir (generics) • Darunavir/cobicistat/emtricitabine/tenofovir alafenamide (Symtuza)
Perspective	Canadian public health care payer
Time horizon	Lifetime (60 years)
Results for base case	Incremental cost-effectiveness ratio = $6,815 per QALY gained[a] compared to combined oral ART
Key limitations	• The sponsor compared cabotegravir + rilpivirine to a single comparator consisting of a pooled combination of oral ARV regimens. Given the lack of comparative clinical evidence for cabotegravir + rilpivirine compared with individual regimens, the cost-effectiveness of cabotegravir + rilpivirine relative to individual ARV regimens is unknown. • The sponsor assumed reduced adherence in the oral ART arm only, and consequentially, assumed poor adherence would decrease viral load suppression and increase the probability of viral load rebound. A lack of clinical evidence exists to support these assumptions. • The sponsor modelled HIV-1–related disease progression using CD4+ T-cell count, which, when compared to viral load, was not considered to be an accurate prognostic marker. • The submitted economic model does not reflect the individualized nature of HIV-1 treatment and may overestimate the cost savings associated with cabotegravir + rilpivirine. • As the durability of response to cabotegravir + rilpivirine is unclear, the long-term cost-effectiveness of cabotegravir + rilpivirine is uncertain. • Potential administration costs for cabotegravir + rilpivirine were excluded, which may have underestimated the total cost of cabotegravir + rilpivirine.

CADTH estimate(s)	CADTH undertook a reanalysis that assumed no difference in adherence between cabotegravir + rilpivirine and oral ARTs. • Compared to oral ART, cabotegravir + rilpivirine was associated with lower costs and fewer QALYs. The incremental cost-effectiveness ratio for combined oral ART compared with cabotegravir + rilpivirine was $37,501 per additional QALY gained. If a decision-maker is willing to pay $50,000 per QALY, oral ARTs would be the optimal therapy. • The model results were primarily driven by drug acquisition costs. The potential cost savings associated with CAB + RPV is uncertain given the model was sensitive to potential costs associated with cabotegravir + rilpivirine administration and given the individualized nature of therapy (e.g., treatment switching which would affect the time patients are on cabotegravir + rilpivirine). • Potential cost savings come at the expense of reduced population health (a loss of 0.02 QALYs) although there is high uncertainty associated with these estimates.

ART = antiretroviral therapy; ARV = antiretroviral; CD4+ = cluster of differentiation 4 positive; HIV-1 = HIV type 1; IM = intramuscular; QALY = quality-adjusted life-year; RNA = ribonucleic acid.

[a] As the sponsor's model was not stable at 350 iterations (sponsor's base case), CADTH re-ran the sponsor's base case at 5,000 iterations.

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 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 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 injection 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 forms	Oral: cabotegravir tablets (30 mg) Intramuscular injections: cabotegravir (600 mg/3mL, 400 mg/2mL) and rilpivirine (900 mg/3mL, 600 mg/2mL) long-acting suspensions
NOC date	March 18, 2020
Sponsor	ViiV Healthcare ULC

Executive Summary

Background

Cabotegravir oral tablets (CAB; Vocabria), in combination with rilpivirine (RPV) oral tablets and cabotegravir plus rilpivirine (CAB + RPV; Cabenuva) extended release injections constitute a complete two-drug treatment regimen and are indicated for the treatment of HIV type 1 (HIV-1) infection in adults who are virologically stable and suppressed (HIV-1 ribonucleic acid [RNA] < 50 copies/mL).[1] 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 (30 mg) are taken in combination with RPV tablets (25 mg) once daily for at least 28 days. The final oral doses of CAB and RPV should be taken on the same day that the initiation intramuscular (IM) injections are started. Initiation of the IM injections consists of CAB (600 mg) and RPV (900 mg) in the first month followed by continuation of monthly IM injections of CAB (400 mg) and RPV (600 mg) during scheduled visits.[1] At the sponsor-submitted prices of $26.52 per CAB tablet (RPV is $15.50 per tablet according to the Ontario Drug Benefit Formulary),[2] $2,418.75 per initiation injection (600 mg/400 mg), and $1,209.38 per continuation injection (600 mg/900 mg), the first-year cost of CAB + RPV is $15,742 per patient; thereafter, the annual maintenance cost is $14,513 per patient.[3] The sponsor's reimbursement request was in accordance with its Health Canada indication.[3]

The sponsor submitted a cost-utility analysis based on a hybrid model of a decision tree, integrating a Markov cohort state transition model to capture disease progression, to evaluate the costs and quality-adjusted life-years (QALYs) of CAB + RPV relative to a pooled comparator of combination oral antiretroviral therapies (ARTs).[3] To construct a single representative oral ART comparator, the sponsor pooled together nine combinations: dolutegravir/lamivudine (Dovato), bictegravir/emtricitabine/tenofovir (Biktarvy), elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (Genvoya), dolutegravir/rilpivirine

(Juluca), abacavir/dolutegravir/lamivudine (Triumeq), dolutegravir (Tivicay) plus emtricitabine/tenofovir (generics), tenofovir alafenamide/emtricitabine/rilpivirine (Odefsey), darunavir/cobicistat (Prezcobix) plus emtricitabine/tenofovir (generics), and darunavir/cobicistat/emtricitabine/tenofovir alafenamide (Symtuza) to represent the most commonly used antiretroviral (ARV) regimens in Canada.[3] The Markov health states captured disease progression with health states defined by treatment line (first-line ART, two subsequent lines of ART, and salvage therapy), viral load, and CD4+ (cluster of differentiation 4 positive) T-cell count. While in these states, patients could develop clinical events (i.e., related adverse events [AEs], AIDS-defining events [ADEs], and cardiovascular disease). The decision tree captured switches to subsequent treatments according to the reason for discontinuation.[3] The model's efficacy inputs for first-line ART were based on the pooled data from the ATLAS and FLAIR trials.[4,5] The impact of treatment adherence was modelled in the oral ART strategy only and relied on assumptions to describe the relationship between adherence on viral load suppression and viral load rebound. The analysis was conducted based on the Canadian public health care payer's perspective over a lifetime time horizon (up to 60 years) with a discount rate of 1.5% applied to both costs and QALYs.[3]

The sponsor reported a base case (350 Monte Carlo simulations) where CAB + RPV was associated with fewer costs and more QALYs relative to the combination of oral ARTs.[3] Increasing the number of Monte Carlo simulations to 5,000 iterations, the incremental cost-effectiveness ratio (ICER) for CAB + RPV was found to be $6,815 per QALY gained compared to a combination of oral ARTs. At a willingness-to-pay (WTP) threshold of $50,000 per QALY, CAB + RPV had a 52% chance of being the most cost-effective strategy.[3]

Summary of Identified Limitations and Key Results

CADTH identified several key limitations with the sponsor's economic evaluation, pertaining to: the choice of comparator; the assumptions on differential adherence between the modelled strategies; the structure of the model that described disease progression based on CD4+ T-cell count; the individualized nature of HIV-1 treatment; the assumptions of the durability of CAB + RPV's efficacy over the model's time horizon; and the exclusion of potential resource use costs associated with CAB + RPV administration in clinical practice.

The sponsor modelled, in their base case, a single comparator based on combined oral ARTs (i.e., pooling together nine oral regimens). Although the comparative efficacy and safety were based on the pooled estimates from the ATLAS and FLAIR trials,[4,5] four of the model's comparator regimens were not studied in the trial including dolutegravir/lamivudine (Dovato), bictegravir/emtricitabine/tenofovir (Biktarvy), dolutegravir/rilpivirine (Juluca), and darunavir/cobicistat/emtricitabine/tenofovir alafenamide (Symtuza). The sponsor's model included the option to conduct the analysis against individual comparators,[3] however, this was deemed inappropriate as no difference was assumed in the comparative efficacy estimates. Considering these issues, the cost-effectiveness of CAB + RPV compared to individual oral regimens remains unknown.

Adherence was identified by CADTH as a main driver of the differences observed in the estimated QALYs. The sponsor modelled decreased adherence in the oral ART strategy (reduction in adherence = 8.12% over the model's time horizon) but assumed no reduction in adherence in CAB + RPV users (i.e., 100% adherence). As a result of nonadherence, oral ART users were modelled to have a decreased risk of viral load suppression and an

increased risk of viral rebound.[3] The ATLAS and FLAIR trials did not report on adherence end points in the pooled ART arm[4,5] and the rationale for differential adherence is not well substantiated. While reasonable adherence on CAB + RPV is expected by the clinical expert consulted by CADTH, they also reported that the population most likely to be on CAB + RPV would be those who are highly motivated and in which adherence on oral ARTs is expected to be similarly high. While CAB + RPV may be used in less motivated populations with adherence issues, there is limited comparative evidence on the impact of adherence in this patient population. The impact of poor adherence on CAB + RPV may be more significant as it may result in delayed dosing or missing treatment for an entire month. An assumption of lower adherence in the comparator arm would underestimate the total QALYs associated with the comparator.

The sponsor modelled CD4+ T-cell count as the indicator of HIV-1–related disease progression. Furthermore, costs, utilities, mortality, and select clinical events were stratified by CD4+ T-cell count. According to CADTH's clinical expert, CD4+ T-cell count may not accurately capture disease progression in patients with HIV-1. Published studies of HIV-1–positive populations align with the expert's view, and have identified viral load as the more appropriate predictor of prognosis in patients who are ART treated.[6-9] The sponsor did, however, incorporate viral load to model whether patients would remain on their current therapy or switch to another. Additionally, the treatment of HIV-1 is complex and highly individualized. The submitted model does not sufficiently capture the individualized nature of HIV-1 therapy in this population, particularly the use of "pooled" efficacy profiles for subsequent treatment lines. This is not representative of clinical practice, as subsequent treatment would depend on previous therapy and a patient's individual preferences. Furthermore, the clinical efficacy inputs used were based on data from the ATLAS and FLAIR trials, with outcomes collected at 48 weeks.[4,5] In the absence of published data on CAB + RPV's effectiveness beyond 48 weeks, the durability of response to CAB + RPV over the patient's lifetime remains uncertain.

The sponsor excluded costs for CAB + RPV administration.[3] [redacted], a CADTH request for additional information did not provide further details on the program.[10] According to the clinical expert consulted by CADTH, patients are most likely to obtain CAB + RPV injections in three health care settings: an HIV clinic, a physician's office, or through home care. Given the uncertainties with the patient support program, there may be additional expenses to the health care system relating to the administration of CAB + RPV depending on the setting in which patients receive therapy.

Given the model structure and issues with the clinical data, there were limited reanalyses that could be conducted. CADTH's reanalysis removed the differential nonadherence rates. In addition, multiple scenario analyses were conducted including setting utilities to be identical across all CD4+ T-cell count health states; incorporating administration costs; and adopting a societal perspective.

Conclusions

Based on the CADTH reanalysis, CAB + RPV is associated with lower total costs and fewer total QALYs compared with combined oral ART. Given the individualized nature of HIV-1 treatment, particularly relating to the timing and reasons for treatment switching, savings relating to the use of CAB + RPV may have been overestimated by the sponsor. Cost savings may not be realized depending on the setting in which CAB + RPV is administered and whether these costs are borne by the public health care payer. Potential cost savings may come at an expense of reduced population health (a loss of 0.02 QALYs), although there is high uncertainty associated with these estimates as indicated by the distribution of results on the cost-effectiveness plane. This estimate was further found to be sensitive to assumptions on adherence.

Results from the model are associated with uncertainty as CADTH could not address limitations related to the model structure and the durability of CAB + RPV's efficacy over the model's time horizon. The cost-effectiveness of CAB + RPV compared to individual, commonly prescribed first-line regimens (oral ARV regimens) is unknown at this time, and some ARV regimens have lower annual drug costs than CAB + RPV.

Information on the Pharmacoeconomic Submission

Summary of the Sponsor's Pharmacoeconomic Submission

The sponsor submitted a hybrid model of Markov state transition and decision tree processes to assess the cost utility of CAB + RPV as a complete two-drug regimen (i.e., CAB oral tablets, in combination with RPV oral tablets, followed by CAB + RPV initiation and continuation injections) relative to oral ART for the treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA < 50 copies/mL).[3] The comparator represented a pooled arm of nine regimens that, according to the sponsor, were the most commonly used ARV regimens currently used by Canada. They included dolutegravir/lamivudine (Dovato), bictegravir/emtricitabine/tenofovir (Biktarvy), elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (Genvoya), dolutegravir/rilpivirine (Juluca), abacavir/dolutegravir/lamivudine (Triumeq), dolutegravir (Tivicay) plus emtricitabine/tenofovir (generics), tenofovir alafenamide/emtricitabine/rilpivirine (Odefsey), darunavir/cobicistat (Prezcobix) plus emtricitabine/tenofovir (generics), and darunavir/cobicistat/emtricitabine/tenofovir alafenamide (Symtuza). Patients began in the first modelled ART line but could subsequently switch to two other ART lines before salvage therapy. The sponsor performed the analysis from a Canadian public health care payer perspective over a lifetime horizon (up to 60 years) with monthly cycles. Costs and QALYs were both discounted at 1.5%.[3] Patient characteristics (e.g., mean age of 39 years) reflected the pooled ATLAS and FLAIR trial populations, which were comprised of patients who are treatment naive and treatment experienced, respectively.[4,5]

The sponsor modelled the clinical course of HIV-1 disease progression predominantly through CD4+ T-cell count, defined categorically by the following distinct health states: less than 50 cells/mm^3, 50 cells/mm^3 to 199 cells/mm^3, 200 cells/mm^3 to 349 cells/mm^3, 350 cells/mm^3 to 500 cells/mm^3, and greater than 500 cells/mm^3. Each month, the patients' CD4+ T-cell count could improve, remain the same, or worsen, depending on their current CD4+ T-cell count. In addition to CD4+ T-cell count, health states were defined by treatment lines (first-, second-, and third-line and salvage therapy) and HIV-1 RNA viral load (≤ 50 or > 50 copies/mL). Discontinuation of treatment due to virologic or non-virologic reasons was separately modelled as this would impact the efficacy of subsequent lines of therapy. Among those who developed virologic failure or virologic rebound, a decreased ability to maintain viral suppression on subsequent treatment lines was assumed. While in any health state, patients could develop ADEs such as acute viral, bacterial, fungal, or protozoal opportunistic infections based on their CD4+ T-cell count and time on treatment; AEs related to the first modelled ART line as observed on the ATLAS and FLAIR trials; or cardiovascular disease based on the Framingham risk score.[4,5,11] Patients could move from any health state to the absorbing death state. Mortality was informed by the Statistics Canada life tables[12] for 2014–2016 and was adjusted for a relative risk increase associated with CD4+ T-cell count, as well as with the incidence of ADE and cardiovascular disease.[4,5,13]

The efficacy profiles for CAB + RPV and combined oral ART were informed by the pooled data of the ATLAS and FLAIR trials. Other published studies informed the remaining efficacy profiles for patients who switched treatment (i.e., second- and third-line therapy or salvage therapy). Adherence was defined as having one or more treatment interruptions. Based on observational data in the literature,[14,15] efficacy was further reduced in all oral ART to reflect the expected adherence while perfect adherence was assumed for CAB + RPV. The

sponsor assumed that nonadherence would lead to reductions in the probability of viral suppression, as well as increases in the probability of viral rebound based on a linear model.[14,15]

Baseline utility measures, stratified by CD4+ T-cell count, were obtained from a study using the Short Form (36) Health Survey-based preferences among patients who are treatment-naive and treatment-experienced HIV-1 positive.[16] Using an additive model, the sponsor combined baseline utility estimates with utility decrements associated with age and the incidence of clinical events. Cost estimates for health system resource utilization (for HIV-1 management, opportunistic infection prophylaxis, AEs, ADEs, cardiovascular disease, and end-of-life care) were based on estimates from the literature. The Ontario Drug Benefit Formulary informed drug acquisition costs, including oral rilpivirine. The cost of the combined oral ART comparator was the average weighted price of each of the included regimens.

Sponsor's Base Case

In the sponsor's reported results based on 350 iterations, CAB + RPV was found to be less costly and more effective than combined oral ART (i.e., CAB + RPV dominated combined oral ART). Results were driven by the costs of first-line therapy (CAB + RPV incurred $27,100 more than combined oral ART) which were offset by cost savings from salvage therapy (CAB + RPV incurred $30,003 less than combined oral ART).[3]

The sponsor's probabilistic base case was found to not be reproducible over multiple model runs at 350 iterations. Improved stability in the model results were noted by CADTH when the number of Monte Carlo iterations increased to 5,000. Unlike the sponsor's reported base case, the updated results at 5,000 iterations suggested that CAB + RPV was more costly ($626) and more effective (0.092 QALYs) than combined oral ART (Table 2). The ICER of CAB + RPV when compared to combined oral ARTs was $6,815 per QALY gained.

In CADTH's re-estimation of the sponsor's base case, the total expected cost of CAB + RPV was $647,491 while that of combined oral ARTs was $646,865 over a patient's lifetime. Both comparators generated a similar number of life-years (CAB + RPV = 24.33; combined oral ART = 24.21). The total QALYs of each comparator were 18.05 and 17.96, respectively. A detailed breakdown of the clinical outcomes and costs by categories from the sponsor's probabilistic analysis can be found in Table 11 and Table 12 of Appendix 4.

At a WTP threshold of $50,000 per QALY, there was a 52% chance that CAB + RPV represented the most cost-effective strategy.

Table 2: Summary of Results of the Sponsor's Base Case

	Total costs ($)	Incremental cost of CAB + RPV ($)	Total QALYs	Incremental QALYs of CAB + RPV ($)	ICER (incremental cost [$] per QALY)
PSA of 350 iterations (reported by the sponsor) [a]					
CAB + RPV	647,323	Reference	18.05	Reference	Reference
Oral ART	647,334	21	17.95	–0.10	Dominated
PSA of 5,000 iterations [b]					
Oral ART	646,865	Reference	17.959	Reference	Reference
CAB + RPV	647,491	626	18.051	0.092	6,815

ART = antiretroviral therapy; CAB + RPV = cabotegravir plus rilpivirine; ICER = incremental cost-effectiveness ratio; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year.

[a] Sponsor's pharmacoeconomic submission.[3]

[b] CADTH re-estimated the sponsor's base case results using 5,000 simulations.

Summary of Sponsor's Sensitivity Analyses

The sponsor conducted multiple sensitivity analyses.[3] Probabilistic scenario analyses included:

- a discount rate of 0%
- a definition of combined oral ART comparator exclusively comprised of integrase strand transfer inhibitor single-tablet regimens with subsequent lines of any integrase strand inhibitor-based regimen
- a three-month treatment duration without response prior to discontinuation to assess different assumptions surrounding when treatment switching occurs due to lack of response
- subsequent lines of ART only included ART protease-inhibitors
- subsequent lines of ART only included ART non-nucleoside reverse transcriptase inhibitors
- equal efficacy between comparators
- only first-line ART without subsequent lines of treatment were modelled
- omission of the effects of nonadherence on oral ART

The sponsor suggested that the assumptions underlying treatment adherence and the modelling of only first-line therapy had the greatest impacts on the relative value of CAB + RPV.[3]

Limitations of Sponsor's Submission

The following limitations were identified with the sponsor's pharmacoeconomic submission:

- **Inappropriate choice of comparator:** The sponsor submitted a comparison of CAB + RPV versus a pooled strategy of multiple combinations of oral ARTs. The latter represented a blended comparator consisting of nine ARV regimens. Despite the use of pooled efficacy and safety data from the ATLAS and FLAIR trials, the sponsor included four regimens in the mix of oral ART that the trial patients did not receive: dolutegravir/lamivudine (Dovato), bictegravir/emtricitabine/tenofovir (Biktarvy),

dolutegravir/rilpivirine (Juluca), and darunavir/cobicistat/emtricitabine/tenofovir alafenamide (Symtuza). Additionally, the clinical expert consulted by CADTH noted that physicians rarely prescribe Symtuza, limiting the comparability of the modelled oral ART strategy to existing Canadian practice.

Where multiple comparators are relevant to the funding decision, HIV-1 treatments should be considered on their own, and all comparators should be assessed in a sequential analysis. Several alternative ARV regimens are cheaper than the first-year cost of CAB + RPV based on its submitted price ($15,742) (e.g., $9,907 per year for dolutegravir [Tivicay] + emtricitabine/tenofovir disoproxil fumarate [generics]; see Appendix 1). While the submitted model had the functionality to compare CAB + RPV with each of the nine individual regimens, these analyses only incorporated differences in treatment costs and lacked regimen-specific comparative efficacy and safety parameters for individual ART. As such, the interpretation of the economic value of CAB + RPV was restricted to a comparison with the pooled comparator and the cost-effectiveness of CAB + RPV relative to individual treatments is unknown.

- **Alternate adherence-related assumptions between comparators were inappropriate:** The main driver of the differences in treatment effects between CAB + RPV and oral ARTs was adherence. The sponsor assumed CAB + RPV users were fully adherent to their treatment while adherence was reduced in oral ART users by 8.12%. Reduced adherence would result in a decreased probability of viral load suppression and an increased probability of viral load rebound. Adherence end points in the ATLAS and FLAIR trials (i.e., number of missed injections) were exclusively available in patients randomized on CAB + RPV while such data were not collected in the comparator arm (i.e., oral ARV regimens). CADTH's clinical expert asserted that the place in therapy for CAB + RPV would include those who are already highly motivated and, less frequently, those with proven or anticipated difficulties with adherence.

  In the first group, as patients are highly motivated, the clinical expert consulted by CADTH expected no differences in adherence between CAB + RPV versus combination oral ART. In the latter group, many issues were identified in how the relationship between adherence and its clinical impact was modelled. The sponsor defined nonadherence as having one or more treatment interruptions, based on published literature.[14,15] Concerns with the sponsor's approach to capture the impact of adherence on treatment efficacy included the fact that the proportion of patients not adherent in the model differed from its cited source, and this was then incorporated into an algorithm that had limited face validity according to the clinical expert consulted by CADTH on this review. The clinical expert noted that the impact of poor adherence with modern single-tablet regimens has not been sufficiently researched. The impact of poor adherence on CAB + RPV may be more significant as it may result in delayed dosing or missing treatment for an entire month.

  By overestimating the rate of nonadherence in the oral ART arm and describing its impacts based on an unvalidated mathematical algorithm, the sponsor potentially underestimated the expected QALYs associated with combined oral ARTs. Given the paucity of evidence, CADTH set adherence to be identical between CAB + RPV and oral ARTs.

- **Validity of CD4+ T-cell count as a marker for burden of disease is uncertain:** The sponsor modelled CD4+ count-specific costs, utilities, and mortality incidence. CADTH's clinical expert noted that, while CD4+ T-cell count is a valid biologic measure of ART's efficacy in patients with HIV-1 infection, it provides only an approximate indication of the patient's disease progression. In published studies, patients who were HIV-1 positive who had CD4+ T-cell counts within a certain range had a wide range of viral loads (e.g.,

patients with HIV-1 with 200 CD4+ cells/mm^3 to 300 CD4+ cells/mm^3 had plasma HIV-1 RNA ranges between 200 copies/mL and 234,000 copies/mL).[7-9,17] Such data suggests that viral load, not CD4+ cell count, may be a better predictor of the clinical course of disease progression. The sponsor's approach likely introduced uncertainty in the model's estimation of total costs and QALYs for each comparator. The impact of this assumption was assessed in a scenario analysis where the same utility value was applied to all CD4+ T-cell count states.

- **Model structure may not accurately reflect individualized nature of HIV-1 treatment:** The sponsor captured some sources of heterogeneity while modelling the efficacy of ART (e.g., variation in efficacy associated with first-, second-, and third-line ART and salvage therapy), but not all. While the sponsor modelled treatment efficacy in patients who switched to second- and third-line ART as a function of the reason for discontinuation (i.e., virologic versus non-virologic), the sponsor modelled an identical efficacy profile for all patients discontinuing for the same reason. The omission of such sources of heterogeneity is a noteworthy limitation since the treatment of HIV-1 infection in adult patients is complex and highly individualized. The updated US Department of Health and Human Services guidelines for the use of ART in adults living with HIV-1 indicate a variety of patient-specific issues that should be accounted for (e.g., individual preferences and psychiatric illness) and that may impact the overall cost-effectiveness of CAB + RPV.[18] The value of assessing the cost-effectiveness of CAB + RPV beyond the first modelled line may therefore be limited as the modelled treatment algorithms do not align accurately with real-world practice.
- **Uncertainty in the durability of long-term response of CAB + RPV:** The model's efficacy data were based on observations from the ATLAS and FLAIR trials.[4,5] The trials were only 48 weeks in length. As the sponsor modelled cost-effectiveness outcomes over a lifetime horizon, the trials' efficacy measures (i.e., the proportion who maintained virologic suppression at 48 weeks) were extrapolated based on an assumption that the estimates persisted lifelong. If treatment response to CAB + RPV were to reduce over time, this would lower total QALY estimated by the model. However, the clinical expert consulted by CADTH reported that, among adherent patients, virologic failure is uncommon after the first year. In the absence of long-term efficacy or effectiveness data to verify this approach, long-term estimates of the costs and effects are uncertain.
- **CAB + RPV administration costs:** The sponsor omitted resource use and health system costs for CAB + RPV's administration on the basis that such costs would be funded through their patient support program.[3] In response to CADTH's request for additional information about the program, the sponsor noted that the details of this program would not be finalized until the product's receipt of a Notice of Compliance.[10] As such, CADTH did not have sufficient information to assess whether additional administration costs to the health care system would exist with CAB + RPV. Uncertainties remain with the program's patient eligibility criteria including when it would come into effect, the duration of the sponsor-funded program, and the extent to which administration costs would be covered. Depending on the finalized details of the patient support program, additional administration costs may still exist for a public health care payer. CADTH's clinical expert was consulted to propose anticipated resource use that may be required to administer CAB + RPV. It was noted that CAB + RPV would likely be offered under three potential health care settings: an HIV clinic, a physician's office, or through home care. Differences in resource utilization may be expected under each setting. No additional costs would be expected if CAB + RPV was to be administered in an HIV clinic although additional costs would be expected in the other settings. Given uncertainties as to how CAB + RPV will be

implemented in a Canadian setting, scenario analyses were conducted to assess how the economic value of CAB + RPV may differ if provided in alternative settings (i.e., in a physician's office or a home care setting) and are not covered by the sponsor as part of its patient support program.

- **Probabilistic analysis was not stable and, to improve stability by increasing the number of simulations, required long run times:** As noted, the sponsor conducted a probabilistic analysis with only 350 simulations and in which the results could not be reproduced. In assessing model convergence by increasing the number of simulations (i.e., 500, 1000, and 5,000 simulations), stability was achieved at 5,000 simulations. Substantial differences in the mean outputs across simulations were observed between the sponsor's base case and an analysis based on 5,000 simulations (i.e., CAB + RPV switched from being dominant to becoming more costly and more effective than oral ART) indicating that random error was not inconsequential. This may be partly due to the fact that the sponsor incorporated standard error estimates for some parameters based on an arbitrary assumption that it would be a percentage of the mean estimates (e.g., 10%). Of note, by increasing the number of simulations from 350 to 5,000, the sponsor's model required a runtime of more than 54 hours per analysis.

CADTH Common Drug Review Reanalyses

CADTH could not fully address limitations associated with the following: the choice of comparator; the structure of the model in capturing HIV-1–related disease progression; the individualized nature of HIV-1 treatment; and the durability of CAB + RPV's efficacy over the model's time horizon.

Based on the appraisal of the clinical data submitted by the sponsor (see CADTH Clinical Review), it was not possible to conclude whether differences exist in adherence between CAB + RPV and oral ARTs. CADTH conducted a reanalysis, based on 5,000 Monte Carlo simulations, that assumed no difference in adherence between CAB + RPV and oral ARTs. Additionally, CADTH removed the mark-up and dispensing fees associated with prescription medications. The CADTH base-case reanalysis assumed that there would be no additional administration costs associated with CAB + RPV (i.e., would be reflective of administration in an HIV clinic setting).

Compared with the sponsor's results, the CADTH reanalysis found that CAB + RPV was associated with lower total costs and less total QALYs. As such, the ICER calculated was instead for combined oral ART in which the ICER was $37,501 per additional QALY gained when compared to CAB + RPV (Table 13). CAB + RPV was the optimal strategy at WTP thresholds below $37,501 per QALY, otherwise combined oral ART was the optimal strategy. The cost-effectiveness plane illustrates that significant parameter uncertainty exists with the analysis as the estimated ICERs were located in all four quadrants. For example, 33% of the simulations were located in the northwest quadrant (CAB + RPV was dominated, i.e., CAB + RPV was more costly and less effective than oral ART) and 31% of the simulations were located in southeast quadrant (CAB + RPV was dominant i.e., CAB + RPV was less costly and more effective than oral ART). Further information is described in Figure 3 in Appendix 4.

Table 3: CADTH Reanalysis of Limitations

Description	Sponsor's base case value	CADTH value	Results are relative to oral ART		
			Incremental cost ($)	Incremental QALYs	ICER ($/QALY)
Sponsor's base case	**Reference** [a]		626	0.092	6,815
Sponsor's base case (including removal of mark-up and dispensing)	Included mark-up (6% to 8%) and dispensing fees ($8.83)	Removal of mark-up and dispensing fees	–1,081	0.094	CAB + RPV dominates
CADTH base case (including removal of mark-up and dispensing)	Different percentages of adherence between CAB + RPV and oral ARTs	Same percentages of adherence between CAB + RPV and oral ARTs	–693	–0.018	37,501[b]

ART = antiretroviral therapy; CAB + RPV = cabotegravir plus rilpivirine; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

[a] CADTH re-estimated the sponsor's base case results using 5,000 simulations.

[b] Results are based on CAB + RPV as a reference since the ICER is calculated against the less costly strategy (CAB + RPV) compared with the next most costly strategy (oral ART).

CADTH also undertook several scenario analyses to address the uncertainty around certain model parameters. The results are summarized in Table 14. These analyses included:

1. setting utilities to be identical across all CD4+ T-cell count health states (utility value = 0.74)
2. assuming CAB + RPV injections occurred in a home care setting and were administered by a nurse ($71.00 per appointment)
3. assuming a physician administered CAB + RPV injections within their clinical practice ($6.75 for first injection, $3.89 for subsequent injections, and $15.00 for a minor assessment)
4. adopting a societal perspective (included age- and gender-specific monthly wages and proportions who were employed).

Unlike CADTH's base case, oral ART was found to dominate CAB + RPV (oral ART was less costly and more effective than CAB + RPV) in the scenarios that included CAB + RPV's administration costs and a societal perspective.

Given that CADTH's base-case reanalysis found that CAB + RPV resulted in a lower than expected cost and QALYs in comparison to combined oral ART, additional analyses that explored price reductions were not necessary.

Issues for Consideration

- The product monograph states that it is important to carefully select patients who agree to the required monthly injection dosing schedule.[1] CADTH's clinical expert envisioned the greatest uptake of CAB + RPV among those already taking ART and who are selected or self-selected to switch therapy due to high motivation. However, the expert noted feasibility-related challenges in the administration of CAB + RPV. Health care providers will need to resolve how to efficiently accommodate monthly injections for all patients within their existing medical practice. The process may initially lead to missed injection appointments, potentially hindering adherence, and may exacerbate access issues in the

long-term (e.g., perceived HIV-related stigma or low socioeconomic status)[19] among those who already have limited access to health services.

- 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. The clinical expert consulted by CADTH further noted challenges in when and how to switch treatment upon discontinuation. The product monograph notes that, in order to minimize the risk of developing viral resistance, it is essential that an alternative, fully suppressive antiretroviral regimen is adopted no later than one month after the final injection doses of CAB + RPV.[1] In the model, patients discontinued therapy for virologic (failure or rebound) or non-virologic reasons and it was assumed that patients would switch to a subsequent line of oral therapy immediately upon CAB + RPV discontinuation.
- CADTH was unable to assess the impact of potentially lower prices of comparators on the economic results. Thus, it is unknown if the reduced effective price of comparators, arising from confidential pricing negotiations such as product listing agreements, would lead to differing conclusions than the current analysis that is based on the list prices of the branded drugs list prices.

Patient Input

Five patient groups from the Canadian Treatment Action Council contributed to this review. The groups included Realize, AIDS Committee of Toronto (ACO), MAX, Edmonton Men's Health Collective, the Community-Based Research Centre, and the Alliance for South Asian AIDS Prevention (ASAAP). Each of the patient groups, except for ASAAP and ACO, reported that they received funding from ViiV Healthcare ULC.

One of the overarching goals of ART that the groups expressed desire for was the potential reduction in HIV-related stigma. Patients suggested that regimens which required a lower frequency of drug consumption might enhance their privacy and discretion around living with HIV. In their feedback, some patients explained that HIV-related stigma exacerbates adherence to a daily pill regimen although it is unclear whether the reduction in adherence in the model was directly attributed to differences in stigma between ART. While some patients noted that currently available treatments have fewer side effects than older regimens, they would be willing to switch to newer regimens that offer additional protection against unwarranted disclosure and HIV-related stigma.

Much of the input was also related to societal factors (e.g., out-of-pocket costs, transportation costs, and caregiver burden), which were not incorporated in the sponsor's submitted scenario analysis of a societal perspective. Patients also noted the importance of tailoring treatment to individual needs, which aligned with feedback from CADTH's clinical expert. Such elements were not addressed in the submitted economic evaluation and were noted to be a key limitation to the submitted economic evaluation.

Conclusions

Based on the CADTH reanalysis, CAB + RPV is associated with lower total costs and fewer total QALYs compared with combined oral ART. Given the individualized nature of HIV-1 treatment, particularly relating to the timing and reasons for treatment switching, savings relating to the use of CAB + RPV may have been overestimated by the sponsor. Cost savings may not be realized depending on the setting in which CAB + RPV is administered and whether these costs are borne by the public health care payer. Potential cost savings may come at an expense of reduced population health (a loss of 0.02 QALYs) although there is high uncertainty associated with these estimates as indicated by the distribution of results on the cost-effectiveness plane. This estimate was further found to be sensitive to assumptions on adherence.

Results from the model are associated with uncertainty as CADTH could not address limitations related to the model structure and the durability of CAB + RPV's efficacy over the model's time horizon. The cost-effectiveness of CAB + RPV compared to individual commonly prescribed first-line regimens (oral ARV regimens) is unknown at this time, some of which have lower annual drug costs than CAB + RPV.

Appendix 1: Cost Comparison

The comparators presented in Table 4 represent recommended antiretroviral regimens for initial therapy of HIV-1 infected individuals by the US Department of Health and Human Services, including their recommended initial regimens in certain clinical situations (updated July 2019).[18] Costs of comparator products were sourced from the Ontario Drug Benefit Formulary (accessed September 2019), unless otherwise specified. Existing product listing agreements are not reflected in Table 4; therefore, these prices may not represent the actual costs to public drug plans.

Table 4: CADTH Cost Comparison Table of DHHS–Recommended Initial Regimens

Drug/comparator regimen	Strength	Dosage form	Price ($)	Recommended use	Daily cost ($)	Frequency of use (per day)	Number of pills (per day)	Annual drug cost ($)
Submitted drug								
Cabotegravir sodium (Vocabria) + rilpivirine (Edurant)	30 mg 25 mg	Tablet	26.5155[a] 15.5000	1 oral tablet daily for 28 days[b], then 1 600 mg/400 mg IM injection for the next month, followed by monthly 400 mg/600 mg IM injection	26.52 15.50	1	2	First year: 15,742[c] Subsequent year: 14,513
Cabotegravir + rilpivirine (Cabenuva)	600 mg/900 mg 400 mg/600mg	Single-dose vials	2,418.7500[a] 1,209.3750[a]		80.63 40.31	NA	NA	
DHHS–recommended initial antiretroviral regimens								
INSTI + 2 NRTIs								
Dolutegravir/abacavir/ lamivudine (Triumeq)	50 mg/600 mg/300 mg	Tablet	44.1827[d]	1 tablet daily	44.18	1	1	16,127
Dolutegravir (Tivicay) + emtricitabine/tenofovir disoproxil fumarate (generics)	50 mg 200 mg/300 mg	Tablet	19.8397 7.3035	50 mg daily 1 tablet daily	27.14	1	2	9,907
Dolutegravir (Tivicay) + emtricitabine/tenofovir alafenamide (Descovy)	50 mg 200 mg/25 mg	Tablet	19.8397 26.1020[d]	50 mg daily 1 tablet daily	45.94	1	2	16,769
Bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy)	50 mg/200 mg/25 mg	Tablet	39.2227[e]	1 tablet daily	39.22	1	1	14,316
Raltegravir (Isentress) + emtricitabine/tenofovir disoproxil fumarate (generics)	400 mg 200 mg/300 mg	Tablet	14.0301 7.3035	400 mg twice daily 1 tablet daily	35.36	2	3	12,908

Drug/comparator regimen	Strength	Dosage form	Price ($)	Recommendeduse	Daily cost ($)	Frequency of use (per day)	Number of pills (per day)	Annual drug cost ($)
Raltegravir (Isentress) + emtricitabine/tenofovir alafenamide (Descovy)	400 mg 200 mg/25 mg	Tablet	14.0301 26.1020[d]	400 mg twice daily 1 tablet daily	54.16	2	3	19,769
DHHS–recommended regimens for switch therapy								
INSTI + NNRTI								
Dolutegravir/rilpivirine (Juluca)	50 mg/25 mg	Tablet	34.8678	1 tablet daily	34.87	1	1	12,727

DHHS = Department of Health and Human Services; freq. = frequency; INSTI = integrase strand transfer inhibitor; IM = intramuscular; NA = not applicable; no. = number; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed September 2019), unless otherwise indicated, and do not include dispensing fees.

Note: Annual cost is based on 365 days of treatment. The publicly available prices of treatments vary between provinces.

[a] Sponsor-submitted price for the smallest dispensable unit is 30 tablets.

[b] Sponsor recommended that patient take oral lead-in daily for one month or for 28 days or more.

[c] Calculation in the oral lead-in phase assumes patients are dispensed a bottle containing 30 tablets for cabotegravir (i.e., wastage of two tablets is assumed).

[d] Sponsor-submitted price.[20]

[e] IQVIA Delta PA, wholesale acquisition price (accessed October 2019).

Table 5: CADTH Cost Comparison Table of Antiretroviral Agents for Adults With HIV-1 Infection in Certain Clinical Situations

Drug/comparator regimen	Strength	Dosage form	Price ($)	Recommended use	Daily cost ($)	Frequency of use (per day)	Number of pills (per day)	Annual drug cost ($)
DHHS–recommended initial regimens in certain clinical situations								
INSTI + 1 NRTIs								
Dolutegravir/lamivudine (Dovato)	50 mg/300 mg	Tablet	30.4400 [a]	1 tablet daily	30.44	1	1	11,110
INSTI + 2 NRTIs								
Raltegravir (Isentress) + abacavir/lamivudine (generics)	400 mg 600 mg/300 mg	Tablet	14.0301 5.9875	400 mg twice daily 1 tablet daily	34.05	2	3	12,427
Elvitegravir/cobicistat/ emtricitabine/tenofovir disoproxil fumarate (Stribild)	150 mg/150 mg/ 200 mg/300 mg	Tablet	48.0177	1 tablet daily	48.02	1	1	17,526
Elvitegravir/cobicistat/ emtricitabine/tenofovir alafenamide (Genvoya)	150 mg/150 mg/200 mg/10 mg	Tablet	45.1440	1 tablet daily	45.14	1	1	16,478
Boosted PI + 2 NRTIs								
Darunavir/cobicistat/emtricitabine/tenofovir alafenamide (Symtuza)	800 mg/150 mg/ 200 m/10 mg	Tablet	52.2670 [b]	1 tablet daily	52.27	1	1	19,077
Darunavir (Prezista) with ritonavir (Norvir) + emtricitabine/tenofovir disoproxil fumarate (generics)	800 mg 100 mg 200 mg/300 mg	Tablet	22.7000 1.5487 7.3035	800 mg daily 100 mg daily 1 tablet daily	31.55	1	3	11,517
Darunavir (Prezista) with ritonavir (Norvir) + emtricitabine/tenofovir alafenamide (Descovy)	800 mg 100 mg 200 mg/25 mg	Tablet	22.7000 1.5487 26.1020 [b]	800 mg daily 100 mg daily 1 tablet daily	50.35	1	3	18,378
Darunavir/cobicistat (Prezcobix) + emtricitabine/tenofovir disoproxil fumarate (generics)	800 mg/150 mg 200 mg/300 mg	Tablet	24.4300 7.3035	1 tablet daily 1 tablet daily	31.73	1	2	11,583

Drug/comparator regimen	Strength	Dosage form	Price ($)	Recommended use	Daily cost ($)	Frequency of use (per day)	Number of pills (per day)	Annual drug cost ($)
Darunavir/cobicistat (Prezcobix) + emtricitabine/tenofovir alafenamide (Descovy)	800 mg/150 mg 200 mg/25 mg	Tablet	24.4300 26.1020 [b]	1 tablet daily 1 tablet daily	50.53	1	2	18,444
Atazanavir (generics) with ritonavir (Norvir) + emtricitabine/tenofovir disoproxil fumarate (generics)	300 mg 100 mg 200 mg/300 mg	Capsule	19.0681 1.5487 7.3035	300 mg daily 100 mg daily 1 tablet daily	27.92	1	3	10,191
Atazanavir (generics) with ritonavir (Norvir) + emtricitabine/tenofovir alafenamide (Descovy)	300mg 100 mg 200 mg/25 mg	Capsule	19.0681 1.5487 26.1020 [b]	300 mg daily 100 mg daily 1 tablet daily	46.72	1	3	17,052
Darunavir/cobicistat (Prezcobix) + abacavir/lamivudine (generics)	800 mg/150 mg 600 mg/300 mg	Tablet	24.4300 5.9875	1 tablet daily 1 tablet daily	30.42	1	2	11,102
Darunavir (Prezista) with ritonavir (Norvir) + abacavir/lamivudine (generics)	800 mg 100 mg 600 mg/300 mg	Tablet	22.7000 1.5487 5.9875	800 mg daily 100 mg daily 1 tablet daily	30.24	1	3	11,036
Atazanavir (generics) with ritonavir (Norvir) + abacavir/lamivudine (generics)	300mg 100 mg 600 mg/300 mg	Capsule	19.0681 1.5487 5.9875	300 mg daily 100 mg daily 1 tablet daily	26.60	1	3	9,711
NNRTI + 2 NRTIs								
Doravirine (Pifeltro) + emtricitabine/tenofovir disoproxil fumarate (generics)	100 mg 200 mg/300 mg	Tablet	16.6500 [b] 7.3035	1 tablet daily 1 tablet daily	23.95	1	2	8,743
Doravirine (Pifeltro) + emtricitabine/tenofovir alafenamide (Descovy)	100 mg 200 mg/25 mg	Tablet	16.6500 [b] 26.1020 [b]	1 tablet daily 1 tablet daily	42.75	1	2	15,604
Doravirine (Pifeltro) + abacavir/lamivudine (generics)	100 mg 600 mg/300 mg	Tablet	16.6500 [b] 5.9875	1 tablet daily 1 tablet daily	22.64	1	2	8,263

Drug/comparator regimen	Strength	Dosage form	Price ($)	Recommended use	Daily cost ($)	Frequency of use (per day)	Number of pills (per day)	Annual drug cost ($)
Doravirine/lamivudine/ tenofovir disoproxil fumarate (Delstrigo)	100 mg/300 mg/300 mg	Tablet	28.7900 [c]	1 tablet daily	28.79	1	1	10,508
Efavirenz/tenofovir disoproxil fumarate/emtricitabine (Atripla)	600 mg/300 mg/200 mg	Tablet	11.3300	1 tablet daily	11.33	1	1	4,135
Efavirenz (generics) + emtricitabine/tenofovir alafenamide (Descovy)	600 mg 200 mg/25 mg	Tablet	3.8030 26.1020 [b]	600 mg daily 1 tablet daily	29.91	1	2	10,915
Emtricitabine/rilpivirine/ tenofovir disoproxil fumarate (Complera)	200 mg/25 mg/300 mg	Tablet	44.8643	1 tablet daily	44.86	1	1	16,375
Emtricitabine/rilpivirine/ tenofovir alafenamide (Odefsey)	200 mg/25 mg/25 mg	Tablet	42.3670	1 tablet daily	42.37	1	1	15,464

DHHS = Department of Health and Human Services; freq. = frequency; HIV-1 = HIV type 1; INSTI = integrase strand transfer inhibitor; no. = number; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed May 2019), unless otherwise indicated, and do not include dispensing fees.

Annual cost is based on 365 days of treatment. The publicly available prices of treatments vary between provinces.

[a] Sponsor-submitted price.[21]

[b] Sponsor-submitted price.[20]

[c] Sponsor-submitted price.[9]

Appendix 2: Additional Information

Table 6: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?	X		
Comments Reviewer to provide comments if checking "no"	None		
Was the material included (content) sufficient?	X		
Comments Reviewer to provide comments if checking "poor"	None		
Was the submission well organized and was information easy to locate?	X		
Comments Reviewer to provide comments if checking "poor"	None		

Table 7: Authors' information

Authors of the pharmacoeconomic evaluation submitted to CADTH

☐ Adaptation of global model/Canadian model done by the sponsor

☐ Adaptation of global model/Canadian model done by a private consultant contracted by the sponsor

☐ Adaptation of global model/Canadian model done by an academic consultant contracted by the sponsor

☒ Other (please specify) sponsor's consulting agency developed the model and report

	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document	X		
Authors had independent control over the methods and right to publish analysis	X		

Appendix 3: Summary of Other Health Technology Assessment Reviews of Drug

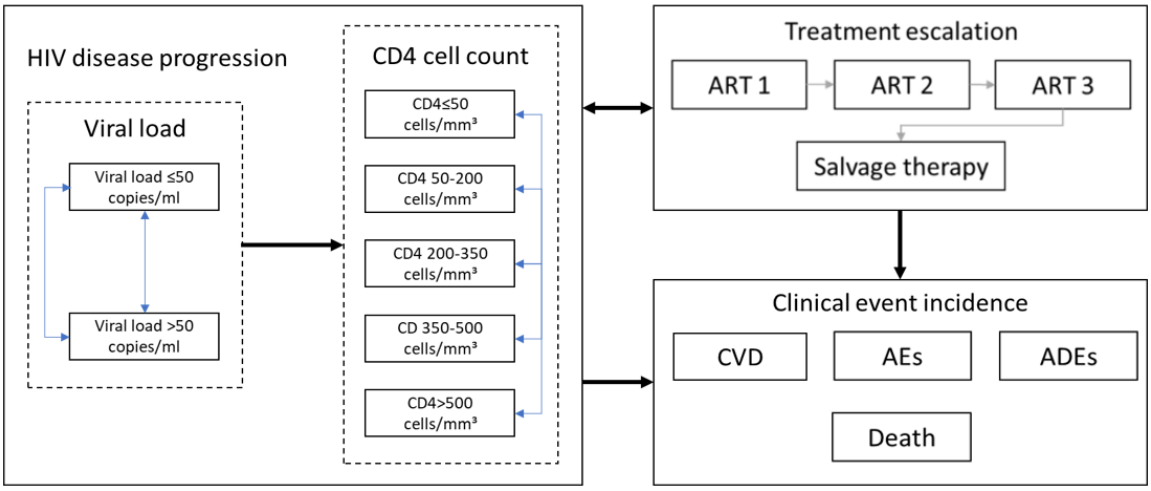
No other health technology assessment agencies have reviewed CAB + RPV for the requested CADTH Common Drug Review indication.

Appendix 4: Reviewer Worksheets

Sponsor's Model Structure

The sponsor built a hybrid model of a cohort Markov state transition model and a decision tree process. The sponsor modelled three ART lines, as well as a salvage therapy line, to reflect the risk of treatment failure and/or discontinuation. In the model, the cohort transitioned through health states that the sponsor defined by treatment line, viral load, and CD4+ T-cell count (Figure 1). While in these health states, patients could develop ADEs, treatment-related AEs, or cardiovascular disease. During each monthly cycle, transitions between health states depended on the cohort's viral status and CD4+ T-cell count and patients could move to the absorbing death state at any modelled cycle.

Figure 1: Model Schematic – Cohort-Level Markov State Transition Model

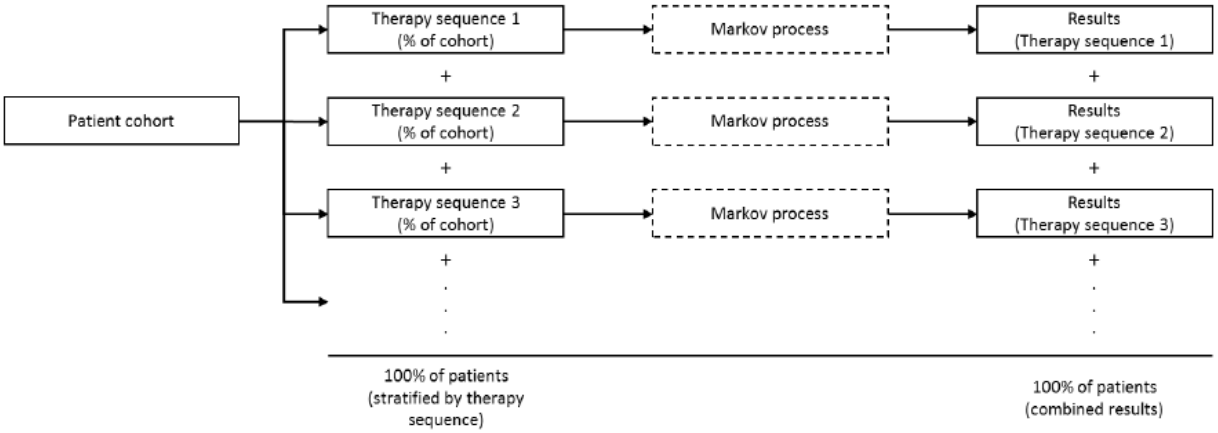


ADE = AIDS-defining event; AE = adverse event; ART = antiretroviral therapy; CD4 = cluster of differentiation 4; CVD = cardiovascular disease.

Source: Sponsor's pharmacoeconomic submission.[3]

The decision tree was used to allocate patients to the appropriate treatment line based on the reason for discontinuation (Figure 2).

Figure 2: Model Schematic – Decision Tree



Source: Sponsor's pharmacoeconomic submission.[3]

Table 8: Data Sources

Data input	Description of data source	Comment
Baseline characteristics	Combination of the ATLAS and FLAIR trials[4,5,22]	Appropriate.
Efficacy and adverse events	Efficacy and safety data of CAB + RPV and the oral ART comparator were based on the sponsor's pooled analysis of data from the ATLAS and FLAIR trials[22] Subsequent treatment line data were from published literature[23-26]	CADTH's clinical review could not assess the quantitative variability between the trials as the sponsor did not conduct any formal statistical test to assess between-study homogeneity. Since the trials' design and populations were largely similar, CADTH's clinical review concluded that the rationale for pooling the results was reasonable.
Natural history	Data for the following clinical events were included: • AIDS-defining event[11] • cardiovascular disease, based on lipid profiles[4,5,13]	Appropriate.
Utilities	Health state utility values were SF-6D measurements, by CD4+ T-cell count, from published literature.[16] Disutilities from published literature include: • age-dependent decrement based on HUI3 estimates[27] • cardiovascular disease based on EQ-5D estimates[28] • adverse events based on SF-36 estimates and assumptions[16] • AIDS-defining event MOS-HIV estimates[29]	Age-related disutilities were based on the HUI3, while the utility impacts of ADEs, treatment-related AEs, and cardiovascular disease were estimates from the MOS-HIV, SF-36, and EQ-5D surveys, respectively. The use of utility estimates from different multi-attribute utility scales does not align with CADTH's economic evaluation guidelines for modelling QALYs.[30] Although all index scores are interpreted on a 0 to 1 scale, the estimates are scaled differently across classification systems and can produce varying results. For example, comparative studies of the SF-6D and EQ-5D scores have identified evidence of floor effects in the SF-6D measures and ceiling effects in the EQ-5D measures, which stem from differences in health state classifications and the methods used to value them.[31-35]

Data input	Description of data source	Comment
Mortality	All-cause mortality obtained from Statistics Canada life tables for 2014–2016,[12] adjusted by the relative risk of mortality based on CD4+ T-cell count states[36] and AIDS-defining events.[37] The relative risk of mortality associated with cardiovascular disease, however, is based on the sponsor's assumption.[3]	Appropriate.
Resource use and costs		
Drug	Cost of CAB + RPV from sponsor,[3] cost of comparators from ODB Formulary.[38]	The sponsor included mark-up and dispensing fees. Such costs were excluded from the CADTH base case and all scenario analyses.
Event	The following event costs were captured: • cardiovascular disease (initial event and subsequent costs) [39] • end-of-life care in last 3 months • several different AIDS-defining events[40]	Appropriate.
AEs	Medications costs for AEs were from the Ontario's Schedule of Benefits[41] and Walmart's website[42]; resource use was based on expert opinion.	Appropriate.
Health state	Disease management costs (e.g., outpatient care, opportunistic infection prophylaxis, and non-HIV medication) by CD4+ T-cell count category were from published literature and ODB Formulary.[38]	Appropriate.

AE = adverse event; ART = antiretroviral therapy; CAB + RPV = cabotegravir plus rilpivirine; CD4+ = cluster of differentiation 4 positive; EQ-5D = EuroQol 5-Dimensions; HUI3 = Health Utilities Index Mark 3; MOS-HIV = Medical Outcomes Study HIV Health Survey; ODB = Ontario Drug Benefit; QALY = quality-adjusted life-year; SF-36 = Short Form (36) Health Survey; SF6D = Short Form 6-Dimension.

Source: Sponsor's pharmacoeconomic submission.[3]

Table 9: Sponsor's Key Assumptions

Assumption	Comment
Clinical course of HIV-1–related disease progression was modelled based on CD4+ T-cell count categories.	Not appropriate. According to CADTH's clinical expert, CD4+ T-cell count is notably less useful in clinical practice than suppressed HIV-1 RNA viremia. In the expert's opinion, in patients who have suppressed viral load, increases in CD4+ T-cell count are meaningless with regards to patient's HIV-1–related disease progression. See "Limitations of Sponsor's Submission" for more details.
ATLAS and FLAIR trial data end points, reported at 48 weeks, were extrapolated to parameterize efficacy end points over a lifetime horizon.	Uncertain. In the absence of published data and limited extension studies of CAB + RPV's efficacy or effectiveness, the degree to which these end points vary with time is unclear. See "Limitations of Sponsor's Submission" for more details.
Pooled efficacy and safety end points for the combined oral ART as the comparator.	Not appropriate. In clinical practice patients use a variety of oral ARTs. Each regimen is associated with its own effectiveness, safety, and cost profiles. See "Limitations of Sponsor's Submission" for more details.
Pooling of efficacy and costs for subsequent treatment lines.	Not representative of clinical practice as subsequent treatment after first-line therapy depends on previous therapy and the patient's individual preferences. Such decisions would affect overall treatment efficacy and associated costs. See "Limitations of Sponsor's Submission" for more details.

Assumption	Comment
Nonadherence resulted in a decreased probability of viral load suppression and increased probability of viral rebound.	Not appropriate. Although the clinical expert consulted by CADTH agreed with the clinical outcomes that the sponsor modelled as consequences of nonadherence (both are precursors of viral resistance), the expert described viral suppression as a binary outcome associated with maintaining an HIV-1 RNA count below a minimum threshold (i.e., 50 copies/mL) rather than a continuous linear relationship as was assumed by the sponsor. The sponsor did not incorporate the potential impact from missed CAB + RPV injections or of the oral treatments during the lead-in phase.[5,6]
Two additional lines of ART and a salvage line of therapy were representative of clinical practice.	Simplification but considered appropriate.
Patients who discontinued current ART due to virologic failure developed ART resistance and experienced lower viral load suppression rate in subsequent ART than those who discontinued for non-virologic reasons.	Appropriate.

ART = antiretroviral therapy; CAB + RPV = cabotegravir plus rilpivirine; CD4+ = cluster of differentiation 4 positive; HIV-1 = HIV type 1; RNA = ribonucleic acid.

Sponsor's Results

The total QALYs, life-years, and costs from CADTH's analysis of the sponsor's base case, using a probabilistic sensitivity analysis with 5,000 simulations, are presented in Table 10. Disaggregated outcomes and costs are delineated in Table 11 and Table 12.

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Table 10: Sponsor's Probabilistic Results – Outcomes

	Total costs ($)	Total LYs	Total QALYs	Inc. cost ($)	Inc. LYs	Inc. QALYs	Inc. cost per LY ($)	ICER ($/QALY)
Oral ART	646,865	24.209	17.959	Reference				
CAB + RPV	647,491	24.327	18.051	626	0.118	0.092	5,290	6,815

ART = antiretroviral therapy; CAB + RPV = cabotegravir plus rilpivirine; ICER = incremental cost-effectiveness ratio; inc. = incremental; LY = life-year; QALY = quality-adjusted life-year.

Note: CADTH re-estimated the sponsor's base case results using 5,000 simulations.

Table 11: Sponsor's Probabilistic Results – Disaggregated Outcomes

QALYs gained by CD4+ health states	CAB + RPV	Oral ART
CD4+ T-cell count ≤ 50	0.081	0.081
CD4+ T-cell count 50 to 200	0.441	0.465
CD4+ T-cell count 200 to 350	1.721	1.847
CD4+ T-cell count 350 to 500	4.113	4.318
CD4+ T-cell count > 500	12.085	11.637

ART = antiretroviral therapy; CAB + RPV = cabotegravir plus rilpivirine; CD4+ = cluster of differentiation 4 positive; QALY = quality-adjusted life-year.

Note: CADTH re-estimated the sponsor's base case results using 5,000 simulations.

Table 12: Sponsor's Probabilistic Results – Disaggregated Costs

Costs categories	CAB + RPV	Oral ART
Health state costs	$73,200.40	$73,100.25
First-line therapy costs	$180,125.98	$154,427.45
Subsequent line costs	$36,330.15	$32,776.00
Salvage therapy costs	$291,979.84	$321,012.97
Adverse events	$125.43	$0.00
AIDS-defining events	$653.81	$659.60
Cardiovascular disease	$51,196.14	$50,970.90
End-of-life costs	$13,879.33	$13,917.89

ART = antiretroviral therapy; CAB + RPV = cabotegravir plus rilpivirine.

Note: CADTH re-estimated the sponsor's base case results using 5,000 simulations.

CADTH Common Drug Review Reanalyses

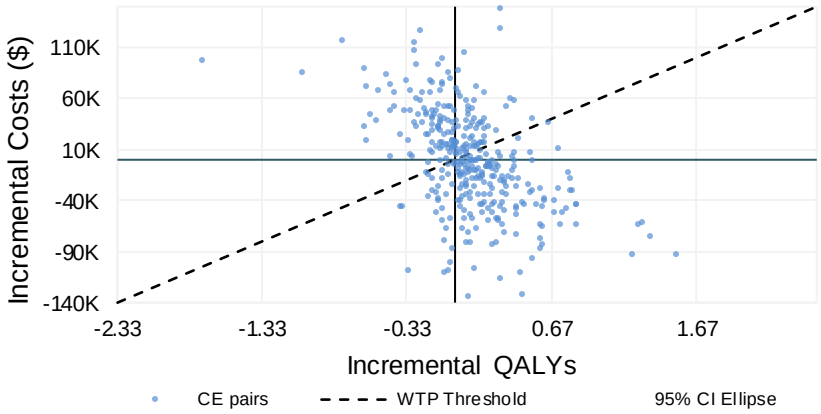
Table 13: CADTH Common Drug Review Reanalysis

	Total costs ($)	Total LYs	Total QALYs	Inc. cost ($)	Inc. LYs	Inc. QALYs	Inc. cost per LY ($)	ICER ($/QALY)
CAB + RPV	653,652	24.537	18.207	-	-	-	-	-
Oral ART	654,345	24.558	18.225	693	0.021	0.018	33,533	37,501

ART = antiretroviral therapy; CAB + RPV = cabotegravir plus rilpivirine; ICER = incremental cost-effectiveness ratio; inc. = incremental; LY = life-year; QALY = quality-adjusted life-year.

Note: CADTH's base case results using 5,000 simulations.

Figure 3: A Scatterplot of the CADTH Common Drug Review's Probabilistic Base Case



CE = cost-effectiveness; CI = confidence interval; QALY = quality-adjusted life-year; WTP = willingness to pay.

The scatterplot of CADTH's probabilistic base case (Figure 3) illustrates significant parameter uncertainty in the estimated ICERs that compare CAB + RPV's value relative to combined oral ART.

The results of four scenario analyses are presented in Table 14. In scenario four, CADTH adopted a societal perspective to address patients' interest in CAB + RPV's potential to reduce out-of-pocket costs and transportation costs. As the model's societal perspective only included age- and gender-specific monthly wages and proportions who were employed, CAB + RPV became more costly ($11,068) than oral ART due to the greater loss of productivity associated with CD4+ levels. Of note, additional productivity loss due to monthly health care visits for CAB + RPV administration was not considered in the analysis.

Table 14: CADTH Common Drug Review Scenario Analyses

	Scenario	Treatments	Cost ($)	QALYs	ICER ($ per QALY)
	CADTH base-case reanalysis[a]	CAB + RPV	653,652	18.207	37,501
		Oral ART	654,345	18.225	
1	**CADTH base case, including identical utility estimate across all CD4+ count categories**	CAB + RPV	653,720	16.967	74,525
		Oral ART	654,721	16.981	
2	**CADTH base case, including CAB + RPV's administration cost in a physician's office**	CAB + RPV	656,061	18.197	oral ART dominates
		Oral ART	654,371	18.214	
3	**CADTH base case, including CAB + RPV's administration cost in a home care drug administration site**	CAB + RPV	663,700	18.204	oral ART dominates
		Oral ART	654,832	18.223	
4	**CADTH base case from a societal perspective, based on loss of wages**	CAB + RPV	992,276	18.188	oral ART dominates
		Oral ART	981,208	18.207	

ART = antiretroviral therapy; CAB + RPV = cabotegravir plus rilpivirine; CD4+ = cluster of differentiation 4 positive; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

[a] CADTH's base case results using 5,000 simulations.

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