CADTH

CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

Doravirine (Pifeltro)

(Merck Canada Inc.)

Indication: Doravirine (Pifeltro) is indicated, in combination with other antiretroviral medicinal products, for the treatment of adults infected with HIV-1 without past or present evidence of viral resistance to doravirine.

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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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Table of Contents

Tables

Figure

Abbreviations

3TC	lamivudine
ABC	abacavir
ARV	antiretroviral
CDR	CADTH Common Drug Review
CVD	cardiovascular
DOR	doravirine
DTG	dolutegravir
DRV/r	ritonavir-boosted darunavir
EFV	efavirenz
FTC	emtricitabine
ICUR	incremental cost-utility ratio
MTR	multiple-tablet regimen
NMA	network meta-analysis
NRTI	nucleoside reverse transcriptase inhibitor
QALY	quality-adjusted life-year
STR	single-tablet regimen
TAF	tenofovir a
TDF	tenofovir disoproxil fumarate
WTP	willingness-to-pay

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Doravirine (Pifeltro)
Study Question	To assess the cost-effectiveness of DOR, in combination with two NRTI backbones, for first-line treatment of HIV-1–infected adult patients in Canada, when compared with other current, major ARV therapies
Type of Economic Evaluation	Cost-utility analysis
Target Population	Treatment-naive, community-dwelling adult HIV patients in Canada
Treatment	DOR+ TDF/FTC (Truvada) followed by 3 subsequent lines of therapy
Outcomes	QALYs LYs
Comparators	Multiple-tablet regimens: EFV + TDF/FTC, DTG + TDF/FTC, DRV/r + TDF/FTC Single-tablet regimens: EFV/TDF/FTC (Atripla), DTG/ABC/3TC (Triumeq), DRV/r + TDF/FTC — followed by 3 subsequent lines of therapy
Perspective	Canadian publicly funded health care payer
Time Horizon	Lifetime (maximum 83 years, predicted average ~39 years)
Results for Base Case	**Multiple-tablet regimens:** • At a willingness-to-pay above $205,967 per QALY, DOR + TDF/FTC was the optimal treatment. • At a willingness-to-pay below $205,967 per QALY, EFV + TDF/FTC was the optimal treatment. **Single-tablet regimens:** • At a willingness-to-pay below $441,884 per QALY, DOR+TDF/FTC was the optimal treatment. • At a willingness-to-pay above $441,884 per QALY, DTG/ABC/3TC was the optimal treatment.
Key Limitations	• The modelled population reflects the patients included in three DOR studies in treatment-naive patients. The clinical effectiveness and cost-effectiveness of DOR in patients who have failed previous treatment are unknown. No economic information was presented for patients who switched treatment if they were adequately responding to an alternate ARV regimen despite the availability of these data. • The network meta-analysis used to support the economic evaluation was associated with several limitations and excluded several relevant comparators, resulting in substantial uncertainty with the findings. • The manufacturer modelled disease progression using CD4+ T-cell counts, which were not considered the most appropriate prognostic markers. • Additional limitations included: outdated cost of EFV/TDF/FTC, uncertain utility values, and uncertainty associated with modelling subsequent treatments.

CDR Estimates	
	• CADTH undertook a reanalysis to address the outdated price of EFV/TDF/FTC in the STR comparison. Once addressed, the results aligned more closely with the manufacturer's MTR analysis. DOR + TDF/FTC was not a cost-effective option if a decision-maker's willingness-to-pay was below $168,387 per QALY when compared with EFV/TDF/FTC. A price reduction of between 25% and 40% was required for DOR + TDF/FTC to be considered the optimal therapy at a willingness-to-pay of $50,000 per QALY. • Scenario analyses undertaken to address the impact of alternative utility values and HIV-care costs, focus on initial lines of therapy, and consider alternative DTG/ABC/3TC costs found that including subsequent lines of therapy had a large impact on the results. • CADTH was unable to address several key limitations, including uncertainty associated with the model structure, comparative effectiveness, and exclusion of relevant comparators. The cost-effectiveness of DOR + relevant backbone treatments compared with other relevant comparators therefore remains uncertain.

3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; DOR = doravirine; DRV/r = ritonavir-boosted darunavir; DTG = dolutegravir; EFV = efavirenz; FTC = emtricitabine; LY = life-year; MTR = multiple-tablet regimen; NMA = network meta-analysis; NTRI = nucleoside reverse transcriptase inhibitor; QALY = quality-adjusted life-year; STR = single-tablet regimen; TDF = tenofovir disoproxil fumarate.

Drug	Doravirine (Pifeltro)
Indication	Pifeltro (doravirine) is indicated, in combination with other antiretroviral medicinal products, for the treatment of adults infected with HIV-1 without past or present evidence of viral resistance to doravirine
Reimbursement Request	As per indication
Dosage Form	100 mg tablet
NOC Date	October 12, 2018
Manufacturer	Merck Canada Inc.

Executive Summary

Background

Doravirine (DOR; Pifeltro) is a non-nucleoside reverse transcriptase inhibitor developed as a single agent to be used with two nucleoside reverse transcriptase inhibitor backbones. DOR is indicated in Canada for the treatment of adults with HIV-1 infection in adults without past or present evidence of viral resistance to DOR in combination with other antiretroviral medicinal products.[1] DOR is available as a 100 mg oral tablet, and it is taken once daily with or without food.[1] At the manufacturer-submitted price of $16.65 per tablet,[2] the annual cost of treatment is approximately $6,077 per patient. The manufacturer's reimbursement request was in accordance with the Health Canada indication.[2]

The manufacturer submitted a cost-utility analysis that assessed the impact of DOR in addition to a tenofovir disoproxil fumarate/emtricitabine (TDF/FTC, Truvada) backbone compared with single-tablet regimens (STRs: dolutegravir/abacavir/lamivudine [DTG/ABC/3TC, Triumeq], efavirenz/TDF/FTC [EFV/TDF/FTC, Atripla], ritonavir-boosted darunavir + TDF/FTC) and multiple-tablet regimens (MTRs: DOR + TDF/FTC, DTG + TDF/FTC, EFV + TDF/FTC, and ritonavir-boosted darunavir + TDF/FTC).[3] The model allows patients to receive up to two additional lines of active therapy before they move on to a salvage therapy (including non-suppression and partial suppression), on which they would stay until death; these regimens are reported in Table 2. The analysis was undertaken over a lifetime time horizon (maximum of 83 years), from the perspective of the Canadian public health care payer.[3]

The model tracked adult HIV-1 patients who started first-line therapy at model entry. After 96 weeks of treatments (the longest follow-up period in DOR clinical trials), patients who were virologically suppressed continued with the initial treatment, whereas patients who were not virologically suppressed moved directly on to second-line therapy.[3]

Data from a pooled ad hoc analysis of Protocol 007 (for DOR, 100 mg arm only), Protocol 018, and Protocol 21, as well as a manufacturer-supplied network meta-analysis (NMA) were used to inform patient characteristics, clinical efficacy, and safety inputs.[3] Key health

outcomes and risks in the model were CD4+ T-cell counts, lipid profiles, risk of cardiovascular disease (CVD), and risk of diabetes.

In the manufacturer's base case, in comparison with STRs, strategies starting with DOR + TDF/FTC were associated with the lowest total costs. DTG/ABC/3TC was associated with greater total costs and more quality-adjusted life-years (QALYs) — as such the incremental cost-utility ratio (ICUR) for DTG/ABC/3TC was $441,884 per QALY when compared with DOR + TDF/FTC. When compared with MTRs, strategies starting with EFV, DOR, or DTG were the most efficient treatment options. Initial treatment with EFV was the optimal strategy up to a willingness-to-pay (WTP) of $205,967 per QALY gained. If a decision-maker's WTP was between $205,967 and $308,278 per QALY, DOR was the optimal strategy. If a decision-maker's WTP was more than $308,278 per QALY, DTG was the optimal strategy.[3] The results are driven by the cost of and time on initial treatment regimens — DTG/ABC/3TC is more costly than DOR + TDF/FTC and more patients remain on DTG/ABC/3TC longer than initial therapy given the effects on CD4+ T-cell count suggested by the manufacturer.

Summary of Identified Limitations and Key Results

CADTH pharmacoeconomic reviewers identified several key limitations pertaining to: the generalizability of the population modelled to how DOR will be used in Canadian practice; uncertainty associated with the comparative effectiveness and safety information; and concerns related to the modelling of disease progression. These limitations could not be addressed by CADTH, and thus affect the confidence in any reanalyses based on other key limitations that could be undertaken.

The clinical trials submitted to Health Canada and included in the economic evaluation by the manufacturer recruited patients who were treatment-naive. This was the basis for the manufacturer's economic analysis (Protocol 007, Protocol 018, and Protocol 21). As such, the clinical effectiveness and cost-effectiveness of DOR in patients who had failed previous treatment are unknown. Not all relevant comparators were included in the manufacturer's economic evaluation. Based on feedback from the clinical expert consulted by CADTH for this review, DTG/ABC/3TC is likely to be the most appropriate comparator regimen in treatment-naive patients. Additionally, the manufacturer considered a backbone treatment for DOR (TDF/FTC) that is unlikely to be used in clinical practice (ABC/3TC or TAF-based regimens more likely to be used).

The manufacturer's comparative clinical effectiveness estimates for the economic model were based on the results of an NMA. The CADTH clinical review identified several limitations with the manufacturer-submitted NMA that reduced the ability of the reviewers to validate the results, resulting in significant uncertainty associated with the results of the NMA. The manufacturer's decision to model disease progression using CD4+ T-cell counts was considered to be inappropriate by the CADTH clinical expert. Viral load is considered a better prognostic marker by the expert, which is also supported by the literature. Further, the assumption of different utility values based on CD4+ T-cell counts is highly uncertain given the questionable validity of this outcome as a prognostic marker. As such, the validity of the model is highly questionable.

CADTH identified several other limitations with the model inputs: relevant adverse events (e.g., bone and renal outcomes) were not considered, mortality was overestimated given the incorporation of both HIV-related mortality and CVD-related mortality, which are unlikely to be mutually exclusive, and the incorporation of outdated costs ($22.66 compared with the

current public price for EFV/TDF/FTC of $11.33) or uncertain costs (for annual medical care for HIV-1). Additionally, CADTH noted the price of the individual components of Triumeq (DTG, ABC/3TC) is substantially less than the cost of the STR.

Given the key limitations identified with the manufacturer's model, CADTH was unable to undertake reanalyses that would reflect the cost-effectiveness of DOR + backbone compared with most appropriate comparators in the population in whom the drug is likely to be used in clinical practice (treatment-naive and -experienced patients).

CADTH did undertake a reanalysis to account for the outdated price for EFV/TDF/FTC STR, as well as scenarios assessing the impact of utility values, HIV-care costs, modelling multiple lines of therapy, and an alternative pricing scenario for DTG/ABC/3TC. Based on alternative pricing for EFV/TDF/FTC, DOR + TDF/FTC is no longer the least costly option in the STR analysis, and is associated with an ICUR of $168,387 per QALY compared with EFV/TDF/FTC. Incorporating lower health care costs, considering a single base-utility value across CD4+ T-cell ranges and excluding subsequent therapies (except salvage therapy) did not affect the results in most situations. When removing subsequent, non-salvage therapies in the MTR analysis, DOR + TDF/FTC was no longer an optimal treatment. If the price of DTG + ABC/3TC is included in the STR analysis, DOR + TDF/FTC is the optimal treatment only if a decision-maker is willing to pay more than $205,000 per QALY when compared with EFV/TDF/FTC.

However, the results for DOR + TDF/FTC compared with STRs require careful consideration. The main driver of the cost differences is drug costs and time on initial therapy (DTG/ABC/3TC was more effective; patients spent longer on treatment, but it is the most costly agent). As such, because the model considered treatment sequences, if patients remain on DTG/ABC/3TC longer (as they are responding to treatment), the results will be biased against treatment strategies in which patients spend longer on DTG/ABC/3TC. Furthermore, feedback from the clinical expert consulted by CADTH indicated that EFV-based regimens may not be the most appropriate comparator for DOR + TDF/FTC.

Conclusions

The comparative effectiveness and safety of DOR + backbone compared with relevant comparator treatments is uncertain given the limitations with the manufacturer-submitted NMA. Based on CADTH's review of the DOR clinical studies, the manufacturer's claim that DOR + backbone is noninferior to EFV- and darunavir-based regimens (i.e., older antiretroviral treatments) based on virologic response may be reasonable. Comparative clinical effectiveness and cost-effectiveness information for DOR- and [redacted]-based regimens are uncertain, given the limitations associated with the manufacturer's NMA.

The results of the manufacturer's economic evaluation are reflective of a treatment-naive population. The cost-effectiveness of DOR in a treatment-experienced population is unknown.

Based on the CADTH reanalysis, in a treatment-naive population, DOR + TDF/FTC was the optimal treatment compared with EFV/TDF/FTC only if the decision-maker is willing to pay more than $168,000 per QALY. A price reduction of more than 25% is required for DOR + TDF/FTC to be the optimal treatment if a decision-maker is willing to pay $50,000 per QALY. When compared with MTRs, a price reduction of more than 40% is required for DOR + TDF/FTC to become the optimal treatment if a decision-maker's WTP is $50,000 per QALY.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted a state-transition, discrete, stochastic, patient-level simulation that assessed the cost-effectiveness of doravirine (DOR), in combination with two nucleoside reverse transcriptase inhibitor (NRTI) backbones, for first-line treatment of HIV-1–infected adult patients in Canada, when compared with other current, major antiretroviral (ARV) therapies (Table 2). The selected population is in line with the clinical data submitted to Health Canada; as such, the target population is treatment-naive, community-dwelling adult HIV patients in Canada.[3] The choice of modelling approach was based on the following considerations:

- Key variables (CD4+ T-cell count and lipid profiles) are continuous, rather than categorical
- Some risks (such as cardiovascular disease [CVD]; see below) are dependent on individual patient characteristics and time on treatments

CD4+ T-cell counts (cells/uL) were stratified into ranges (< 100, 100 to 199, 200 to 349, 350 to 499, and ≥ 500) to inform mortality parameters, utility values, and cost inputs.

The manufacturer stated that although the comparators included (see Table 2) did not represent all alternative treatment pathways patients may encounter in real life, the comparators chosen were deemed reflective of the most probable and representative pathways for the average patient by HIV experts and based on IQVIA claims data.[3]

Table 2: Manufacturer's Comparator List

Strategies	First-Line Therapy	Second-Line Therapy	Third-Line Therapy	Salvage Therapy
S1	DOR+TDF/FTC	DTG/ABC/3TC	DRV/r + TDF/FTC	DTG + ETR + DRV/r
S2	EFV/TDF/FTC	DTG/ABC/3TC	DRV/r + TDF/FTC	DTG + ETR + DRV/r
S3	DTG/ABC/3TC	RAL + TDF/FTC	DRV/r + TDF/FTC	DTG + ETR + DRV/r
S4	DRV/r + TDF/FTC	DTG/ABC/3TC	RAL + TDF/FTC	DTG + ETR + DRV/r
M1	DOR+TDF/FTC	DTG + TDF/FTC	DRV/r + TDF/FTC	DTG + ETR + DRV/r
M2	EFV + TDF/FTC	DTG + TDF/FTC	DRV/r + TDF/FTC	DTG + ETR + DRV/r
M3	DTG + TDF/FTC	RAL + TDF/FTC	DRV/r + TDF/FTC	DTG + ETR + DRV/r
M4	DRV/r + TDF/FTC	DTG + TDF/FTC	RAL + TDF/FTC	DTG + ETR + DRV/r

DOR = doravirine; DTG = dolutegravir; DRV/r = ritonavir-boosted darunavir; EFV = efavirenz; ETR = etravirine; RAL = raltegravir; TDF/FTC = tenofovir disoproxil fumarate/emtricitabine.

Source: Manufacturer's pharmacoeconomic submission.[3]

The model tracks a set of adult HIV-1 patients with different initial characteristics who were starting their first-line therapy at model entry. After 96 weeks of treatments (the longest follow-up period in DOR clinical trials), those who were virologically suppressed continued the therapy, whereas those who were not virologically suppressed moved directly to second-line therapy. The model allowed patients to receive up to three lines of active therapy, before moving on to a salvage therapy (including non-suppression and partial suppression), on which they would stay until death.

Manufacturer's Base Case

The manufacturer reported no major differences in life expectancy (approximately 39 years) or time living with cardiovascular disease (CVD) between arms (approximately four years, see Table 13).

DOR + tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) is less costly and less effective than dolutegravir (DTG) single-tablet regimen (STR), and DTG STR is associated with greater total costs, resulting in an incremental cost-utility ratio (ICUR) of more than $400,000 per quality-adjusted life-year (QALY) compared with DOR + TDF/FTC. This is largely driven by the cost of the DTG-based regimen and the time on therapy (the time on initial therapy is considerably longer with DTG compared with DOR). Efavirenz (EFV) STR and ritonavir-boosted darunavir (DRV/r) STRs were dominated by (more costly and less effective than) DOR + TDF/FTC (Table 3).[3]

Table 3: Summary of Results of the Manufacturer's Base Case: Single-Tablet Regimen

	Total QALYs	Total Costs ($)	Incremental Cost per QALY	
			Versus least costly alternative	Sequential ICUR
DOR → DTG.s → DRV/r	22.40	$568,721		
EFV.s → DTG.s → DRV/r	22.20	$578,922	Dominated	Dominated by DOR
DRV/r → DTG.s → RAL	22.32	$616,837	Dominated	Dominated by DOR
DTG.s → RAL → DRV/r	22.54	$631,695	$441,884	$441,884

DOR = doravirine; DTG = dolutegravir; DRV/r = ritonavir-boosted darunavir; EFV = efavirenz; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; RAL = raltegravir; s = single-tablet regimen.

Source: Derived from manufacturer's pharmacoeconomic submission.[3]

When comparing DOR with multiple-tablet regimens (MTRs), DOR + TDF/FTC is more costly and more effective than EFV + TDF/FTC, but is associated with a high ICUR ($206,000 per QALY). DTG + TDF/FTC may be the preferred strategy if decision-makers are willing to pay more than $308,000 per QALY. DRV/r + TDF/FTC was dominated by (more costly and less effective than) DOR + TDF/FTC (Table 4).[3]

Table 4: Summary of Results of the Manufacturer's Base Case: Multiple-Tablet Regimen

	Total QALYs	Total Costs ($)	Incremental Cost per QALY	
			Versus least costly alternative	Sequential ICUR
EFV.m → DTG.m → DRV/r	22.20	$460,896		
DOR → DTG.m → DRV/r	22.39	$501,287	$205,967	$205,967
DRV/r → DTG.m → RAL	22.31	$537,765	$672,023	Dominated by DOR
DTG.m → RAL → DRV/r	22.52	$539,267	$245,444	$308,278

DOR = doravirine; DTG = dolutegravir; DRV/r = ritonavir-boosted darunavir; EFV = efavirenz; ICUR = incremental cost-utility ratio; m = multiple-tablet regimen; QALY = quality-adjusted life-year; RAL = raltegravir.

Source: Derived from manufacturer's pharmacoeconomic submission.[3]

As can be seen in the supplemental tables in Appendix 4 (Table 15), the results are driven by the differences in the cost of the treatment regimens, which are substantially affected by the time on therapy. As DOR + TDF/FTC is less costly than dolutegravir/abacavir/lamivudine (DTG/ABC/3TC), and patients remained on their initial regimen of DTG/ABC/3TC for a

longer period of time than patients receiving DOR + TDF/FTC, this may drive the large difference in costs between the two treatments.

Summary of Manufacturer's Scenario Analyses

The manufacturer reported that additional analyses were run by changing both discount rates to 0% and 3% per year. While the magnitude of the results differed, the results were in the same direction and were generally similar to the base-case results.

Limitations of Manufacturer's Submission

CADTH identified the following key limitations with the manufacturer's pharmacoeconomic submission:

- **The manufacturer only considered a subset of the indicated population approved by Health Canada.** The Health Canada indication is for adult patients with HIV-1 and is not restricted by prior use, while the submitted model assumes use of DOR as first-line therapy only. Based on the CADTH clinical review, all the included trials assessed DOR in treatment-naive patients or in patients switching treatment who were stable on another HIV-1 regimen. Feedback from the clinical expert consulted by CADTH suggested that if a patient is controlled on a preferred regimen, they may not switch to DOR + backbone, although there are plausible situations when this would occur (particularly when patients are currently on EFV/TDF/FTC). No information was presented to assess the cost-effectiveness of patients switching from a current regimen to DOR + backbone. The clinical effectiveness and cost-effectiveness of DOR in treatment-experienced patients are unknown.
- **The manufacturer did not consider all relevant comparator treatments.** Feedback from the clinical expert consulted by CADTH was that several relevant comparator treatments were not considered (e.g., bictegravir/FTC/TAF, elvitegravir/cobicistat/FTC/TAF, FTC/rilpivirine/TAF), and some of the included comparator treatments were not as relevant (e.g., EFV/TDF/FTC is not a recommended first-line treatment, and DRV/r is used less frequently due to drug-drug interactions and increased adverse events). The most relevant comparison considered by the manufacturer was DOR + backbone vs. DTG/ABC/3TC.

  Additionally, Juluca (DTG + 3TC) presents a new paradigm in treatment, one that could see greater uptake in the future. While the clinical expert considered treatments such as raltegravir to be a reasonable treatment option, it is no longer commonly used in practice.
- **The comparative clinical effectiveness of modelled treatment strategies is highly uncertain.** The [redacted] suggested that DOR is [redacted] and shows [redacted] compared with [redacted]; DOR showed [redacted]. However, the CADTH clinical reviewers indicated that missing information, coupled with the small network size, failure to assess the network meta-analysis (NMA) assumptions, and differences in trial design and the definition used for protocol-defined virologic failure to determine virologic response, translate to a high degree of uncertainty in the presented efficacy and safety results.

- **The validity of CD4+ T-cell counts as a marker for disease progression is uncertain.** The manufacturer incorporated different costs, utilities, and effects based on CD4+ T-cell counts in their model. The manufacturer justified the use of CD4+ T-cell counts by stating that there is an association between CD4+ T-cell count and viral load, which has been reported as the most important prognostic factor. The clinical expert consulted by CADTH confirmed that, while CD4+ T-cell counts are a valid biologic measure of the efficacy of ARV therapy in patients with HIV and some reports have suggested a rough association, there is considerable variance with these estimates. The published literature appears to align with feedback from the CADTH clinical expert, in that there is a wide range of viral loads found in HIV-1 patients within a given range of CD4+ T-cell counts (e.g., HIV-1 patients with 200-300 CD4+ T-cells/mm^3 had a plasma HIV ribonucleic acid range between 200 and 234,000 copies/mL), and indicates that viral load, not CD4+ T-cell count, is a better predictor of prognosis, especially after treatment.[4-7] As such, CD4+ T-cell counts may not provide the most relevant marker of disease progression for patients with HIV-1.
- **The modelled backbone treatment for DOR may not be aligned with expected use in clinical practice.** The manufacturer modelled DOR + TDF/FTC, which appeared to be the most commonly used backbone in the clinical trials. Feedback from the clinical expert consulted by CADTH suggested that in clinical practice, DOR would most likely be used with a TAF-based regimen or 3TC/ABC (Kivexa), as the STR of DOR/TDF/3TC provides a TDF option.
- **Relevant adverse events were not considered in the model.** Feedback from the clinical expert consulted by CADTH indicated that bone and renal outcomes would be important to consider given that the backbone used by the manufacturer for DOR was TDF/FTC, while most relevant comparators use TAF (bictegravir/FTC/TAF, elvitegravir/cobicistat/FTC/TAF, FTC/rilpivirine/TAF). Studies have reported a difference between TDF and TAF in terms of bone and renal outcomes,[8-10] and these events were not considered in the submitted model.
- **Mortality is overestimated in the model.** The manufacturer acknowledged in its submission the risk of double-counting by modelling HIV-related mortality and CVD-related mortality separately. As the risk of CVD is higher in patients with HIV-1, this component could be incorporated into HIV-related mortality. As such, there is the potential for double-counting, which may overestimate mortality in the model. This is likely to apply to all treatment arms, but may favour DOR given the lipid profile applied by the manufacturer in the model. However, the impact on the results is likely to be minimal.
- **Validity of utility value assumptions is highly uncertain.** As previously indicated, CADTH identified the model structure as a source of uncertainty, as well as the validity of CD4+ T-cell counts as relevant markers of health states. As such, the manufacturer's assumption that patients experience different quality of life based on changes in the range of CD4+ T-cell counts in health states is highly uncertain.
- **The cost of HIV-1 care is unlikely to be appropriate.** The information used to derive the annual costs of HIV-1 care (exclusive of ARV therapy) was not provided in sufficient detail to verify the estimates. Feedback from the clinical expert consulted by CADTH suggested that the values appear to be overestimated if patients are receiving ARV treatment, although they may appropriately represent the costs of patients who were not treated with ARVs.

- Furthermore, the manufacturer's cost for EFV/TDF/FTC in the model was outdated, which artificially increased the costs in that treatment arm. CADTH noted that the price of the individual components of DTG/ABC/3TC was substantially less than the cost of the STR.
- **Model structure may not accurately reflect the individualized nature of HIV-1 treatment.** Treatment of HIV-1 infection in adult patients is complex and highly individualized; this is reflected by the updated US Department of Health and Human Services guidelines for the use of ARV agents in adults living with HIV-1 and emphasized by the clinical expert consulted by CADTH for this review. The submitted model may not sufficiently capture the individualized nature of HIV therapy in this population, particularly for efficacy profiles beyond the first line of therapy. Therefore, the value of assessing the cost-effectiveness of DOR + backbone beyond the first modelled line may be limited if the modelled treatment algorithms do not accurately align with real-world clinical practice. More importantly, modelling beyond the first line of therapy in which DOR + backbone is used potentially overestimates the cost savings associated with this treatment.

CADTH Common Drug Review Reanalyses

CADTH undertook a reanalysis that corrected the cost of EFV/TDF/FTC in the STR analysis. The results suggest general alignment with the MTR results (Table 5).

Table 5: CADTH Reanalysis Versus Single-Tablet Regimens, Updated Cost of EFV/TDF/FTC

	Total QALYs	Total Costs ($)	Incremental Cost per QALY	
			Versus least costly alternative	Sequential ICUR
EFV.s → DTG.s → DRV/r	22.20	$535,856	-	-
DOR → DTG.s → DRV/r	22.40	$568,721	$168,387	$168,387
DRV/r → DTG.s → RAL	22.32	$616,837	$708,989	Dominated by DOR
DTG.s → RAL → DRV/r	22.54	$631,695	$283,809	$441,884

DOR = doravirine; DTG = dolutegravir; DRV/r = ritonavir-boosted darunavir; EFV = efavirenz; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; RAL = raltegravir; s = single-tablet regimen.

When considering the results of the analyses comparing DOR + TDF/FTC with STRs, it is important to consider that the results are driven by the medication costs. As DTG/ABC/3TC is the most costly regimen, patients remain on this treatment as initial line therapy for longer than the comparator treatments, and fewer patients will receive DTG/ABC/3TC (due to death and discontinuation), this will affect the total medication costs for that arm more than other treatment arms.

CADTH undertook additional exploratory analyses on the manufacturer's MTR analysis and CADTH's reanalysis of the STR comparison, assessing reduced HIV-1 health care costs, a single utility value for patients regardless of CD4+ T-cell count, assuming all patients move on to salvage therapy (as defined by the manufacturer) beyond the initial treatment, and an alternative cost for DTG/ABC/3TC (STR analysis only). In six of the seven exploratory analyses, the direction of the results did not change, but there were some small implications based on the willingness-to-pay (WTP) for additional QALYs (Table 16, Table 17). However, when CADTH modelled only first-line treatment then moved patients onto salvage therapy in the MTR analysis, DTG was the optimal therapy if a decision-maker's WTP was $71,688 per QALY or greater. If a decision-maker's WTP was less than $71,688 per QALY, EFV was the

optimal therapy. DOR was subject to extended dominance through EFV and DTG (Table 17).

CADTH developed a series of price-reduction scenarios based on the CADTH reanalysis of DOR compared with STRs, and the manufacturer's analysis of DOR compared with MTRs (Table 6).

The results indicated that a price reduction of more than 25% is required for DOR + TDF/FTC to become the optimal therapy compared with a scenario in which a decision-maker's WTP is $100,000 per QALY. A price reduction of more than 40% is required for DOR + TDF/FTC to become the optimal therapy compared with a scenario in which the WTP is $50,000 per QALY.

Table 6: CADTH Reanalysis Price-Reduction Scenarios

ICURs of Submitted Drug Versus Comparator		
Price	**Comparison of DOR vs. STRs (CADTH reanalysis)**	**Comparison of DOR vs. MTRs**
Submitted	If λ < $168,387, EFV/TDF/FTC is optimal therapy If $168,387 < λ < $441,884, DOR + TDF/FTC is optimal therapy If λ > $441,884 DTG/ABC/3TC is optimal therapy	If λ < $205,967, EFV + TDF/FTC is optimal therapy If $205,967 < λ < $308,278, DOR + TDF/FTC is optimal therapy If λ > $308,278 DTG + TDF/FTC is optimal therapy
25% reduction	If λ < $72,499, EFV/TDF/FTC is optimal therapy If $72,499 < λ < $573,205, DOR + TDF/FTC is optimal therapy If λ > $573,205 DTG/ABC/3TC is optimal therapy	If λ < $110,533, EFV + TDF/FTC is optimal therapy If $110,533 < λ < $460,182, DOR + TDF/FTC is optimal therapy If λ > $460,182 DTG + TDF/FTC is optimal therapy
40% reduction	If λ < $14,967 EFV/TDF/FTC is optimal therapy If $14,967 < λ < $651,997, DOR + TDF/FTC is optimal therapy If λ > $651,997 DTG/ABC/3TC is optimal therapy	If λ < $53,272, EFV + TDF/FTC is optimal therapy If $53,272 < λ < $551,324, DOR + TDF/FTC is optimal therapy If λ > $551,324 DTG + TDF/FTC is optimal therapy
50% reduction	If λ < $704,525 DOR + TDF/FTC is optimal therapy If λ > $704,525 DTG/ABC/3TC is optimal therapy	If λ < $15,098, EFV + TDF/FTC is optimal therapy If $15,098 < λ < $612,085, DOR + TDF/FTC is optimal therapy If λ > $612,085 DTG + TDF/FTC is optimal therapy

λ = willingness to pay; 3TC = lamivudine ; DOR = doravirine; DTG = dolutegravir; DRV/r = ritonavir-boosted darunavir; EFV = efavirenz; FTC = emtricitabine; ICUR = incremental cost-utility ratio; MTR = multiple-tablet regimen; STR = single-tablet regimen; TDF = tenofovir disoproxil fumarate.

CADTH noted that the manufacturer used set random numbers to allow reproducibility of the results. CADTH noted that the results are relatively stable over multiple model runs with alternate random-number generation.

Issues for Consideration

- CADTH is currently reviewing a combination product of DOR that includes TDF/3TC (i.e., DOR/TDF/3TC). CADTH noted that the manufacturer did not consider this combination when assessing the individual DOR tablet as an add-on treatment to two NRTIs.
- Feedback from the clinical expert consulted by CADTH indicated that DOR is likely to be given with a TAF-based backbone or ABC/3TC, given the bone and renal issues with TDF-based regimens, as opposed to being used as part of a fixed-dose combination that includes TDF.
- The clinical expert indicated that pill burden would be an important consideration when recommending starting patients on DOR + backbone when compared with available STRs, and when switching patients from STRs.

Patient Input

One patient group, the Canadian Treatment Action Council, provided input for this review and identified several societal factors that currently affect patients with HIV-1, including family support, social determinants of health, stigma, funding or services for addictions, mental health, housing, and food security. A scenario analysis from the societal perspective, which could have incorporated these aspects, was not presented by the manufacturer. The patient group indicated that patients surveyed reported that newer treatments seem to suppress viral load well, but expressed concern with adverse events associated with older HIV treatments, and that comorbidities that patients with HIV-1 may experience may be due to their antiretroviral therapy.

The patient group noted that the new chemical composition may provide another treatment option if resistance to other treatments is a problem, and that differences in drug-drug interactions or adverse events would be considered important to patients. Given the paucity of information at this time, reassessment should be considered as evidence becomes available.

Conclusions

The comparative effectiveness and safety of DOR + backbone compared with relevant comparator treatments is uncertain given the limitations of the manufacturer-submitted NMA. Based on CADTH's review of the DOR clinical studies, the manufacturer's claim that DOR + backbone is noninferior to EFV- and DRV-based regimens (i.e., older ARV treatments) based on virologic response may be reasonable. Comparative clinical effectiveness and cost-effectiveness information for DOR- and [redacted]-based regimens are uncertain, given the limitations associated with the manufacturer's NMA.

The results of the manufacturer's economic evaluation are reflective of a treatment-naive population. The cost-effectiveness of DOR in a treatment-experienced population is unknown.

Based on the CADTH reanalysis, in a treatment-naive population, DOR + TDF/FTC is the optimal treatment compared with EFV/TDF/FTC only if the decision-maker is willing to pay more than $168,000 per QALY. A price reduction of more than 25% is required for DOR + TDF/FTC to be the optimal treatment if the decision-maker is willing to pay $50,000 per QALY. When compared with MTRs, a price reduction of more than 40% is required for DOR + TDF/FTC to become the optimal treatment if the decision-maker's WTP is $50,000 per QALY.

Appendix 1: Cost Comparison

The comparators presented in Table 7 represent recommended antiretroviral regimens for initial therapy of HIV-1 infected individuals by the US Department of Health and Human Services guidelines, including recommended initial regimens in certain clinical situations (updated October 2018).[11] Costs of comparator products were sourced from the Ontario Drug Benefit Formulary (accessed January 2019), unless otherwise specified. Existing product listing agreements are not reflected in the table; therefore, these prices may not represent the actual costs to public drug plans.

Table 7: CDR Cost Comparisons of Antiretroviral Agents for Adults with HIV-1 Infection in Certain Clinical Situations

Drug/Comparator Regimen	Strength	Dosage Form	Price ($)	Recommended Use	Daily Cost ($)	Freq. of Use (Per Day)	Number of Pills (Per Day)	Annual Drug Cost ($)
Submitted drug								
Doravirine (Pifeltro)	**100 mg**	**Tab**	**16.6500[a]**	**1 tablet daily**	**16.65**	**1**	**1**	**6,077**
Drug regimens with submitted drug								
Doravirine (Pifeltro) + Emtricitabine/tenofovir alafenamide (Descovy)	100 mg 200/25 mg	Tab	16.6500[a] 26.1020[b]	1 tablet daily 1 tablet daily	42.75	1	2	15,604
Doravirine (Pifeltro) + abacavir/lamivudine (generics)	100 mg 600/300 mg	Tab	16.6500[a] 5.9875	1 tablet daily 1 tablet daily	22.64	1	2	8,263
Doravirine (Pifeltro) + emtricitabine/tenofovir disoproxil fumarate (Truvada)	100 mg 200/300 mg	Tab	16.6500[a] 7.3035	1 tablet daily 1 tablet daily	23.95	1	2	8,743
DHHS-recommended initial regimens in certain clinical situations								
Boosted PI + 2 NRTIs								
Darunavir/cobicistat/emtricitabine/ tenofovir alafenamide (Symtuza)	800/150/ 200/10	Tab	52.2670[b]	1 tablet daily	52.27	1	1	19,077
Darunavir (Prezista) with ritonavir (Norvir) + emtricitabine/tenofovir disoproxil fumarate (Truvada)	800 mg 100 mg 200/300 mg	Tab	22.1720 1.4671 7.3035	800 mg daily 100 mg daily 1 tablet daily	30.74	1	3	11,294
Darunavir (Prezista) with ritonavir (Norvir) + emtricitabine/tenofovir alafenamide (Descovy)	800 mg 100 mg 200/25 mg	Tab	22.1720 1.4671 26.1020[b]	800 mg daily 100 mg daily 1 tablet daily	49.74	1	3	18,156
Darunavir/cobicistat (Prezcobix) + emtricitabine/tenofovir disoproxil fumarate (Truvada)	800/150 mg 200/300 mg	Tab	23.8672 7.3035	1 tablet daily 1 tablet daily	31.17	1	2	11,377
Darunavir/cobicistat (Prezcobix) + emtricitabine/tenofovir alafenamide (Descovy)	800/150 mg 200/25 mg	Tab	23.8672 26.1020[b]	1 tablet daily 1 tablet daily	49.97	1	2	18,239
Atazanavir (generics) with ritonavir (Norvir) + emtricitabine/tenofovir disoproxil fumarate (Truvada)	300mg 100 mg 200/300 mg	Cap	19.0681 1.4671 7.3035[d]	300 mg daily 100 mg daily 1 tablet daily	27.84	1	3	10,161

Drug/Comparator Regimen	Strength	Dosage Form	Price ($)	Recommended Use	Daily Cost ($)	Freq. of Use (Per Day)	Number of Pills (Per Day)	Annual Drug Cost ($)
Atazanavir (generics) with ritonavir (Norvir) + emtricitabine/tenofovir alafenamide (Descovy)	300mg 100 mg 200/25 mg	Cap	19.0681 1.4671 26.1020	300 mg daily 100 mg daily 1 tablet daily	46.64	1	3	17,022
Darunavir/cobicistat (Prezcobix) + abacavir/lamivudine (generics)	800/150 mg 600/300 mg	Tab	23.8672 5.9875	1 tablet daily 1 tablet daily	29.85	1	2	10,897
Darunavir (Prezista) with ritonavir (Norvir) + abacavir/lamivudine (generics)	800 mg 100 mg 600/300 mg	Tab	22.1720 1.4671 5.9875	800 mg daily 100 mg daily 1 tablet daily	29.63	1	3	10,814
Atazanavir (generics) with ritonavir (Norvir) + abacavir/lamivudine (generics)	300mg 100 mg 600/300 mg		19.0681 1.4671 5.9875	300 mg daily 100 mg daily 1 tablet daily	26.52	1	3	9,681
NNRTI + 2 NRTIs								
Efavirenz/tenofovir disoproxil fumarate/emtricitabine (Atripla)	600/300/200 mg	Tab	11.3300	1 tablet daily	11.33	1	1	4,135
Efavirenz (generics) + emtricitabine/tenofovir alafenamide (Descovy)	600 mg 200/25 mg	Tab	3.8031 26.1020[b]	600 mg daily 1 tablet daily	29.91	1	2	10,915
Emtricitabine/rilpivirine/ tenofovir disoproxil fumarate (Complera)	200/25/300 mg	Tab	44.8643	1 tablet daily	44.86	1	1	16,375
Emtricitabine/rilpivirine/ tenofovir alafenamide (Odefsey)	200/25/25 mg	Tab	42.3670[b]	1 tablet daily	42.37	1	1	15,464
InSTI + 2 NRTIs								
Elvitegravir/cobicistat/ emtricitabine/tenofovir disoproxil fumarate (Stribild)	150/150/ 200/300 mg	Tab	48.0177	1 tablet daily	48.02	1	1	17,526
Elvitegravir/cobicistat/ emtricitabine/tenofovir alafenamide (Genvoya)	150/150/ 200/10 mg	Tab	45.1440	1 tablet daily	45.14	1	1	16,478
Raltegravir (Isentress) + abacavir/lamivudine (generics)	400 mg 600/300 mg	Tab	14.0301 5.9875	400 mg twice daily 1 tablet daily	20.02	2	3	7,306

CDR = CADTH Common Drug Review; DHHS = US Department of Health and Human Services; freq. = frequency; InSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor.

Notes: All prices are from the Ontario Drug Benefit Formulary (accessed January 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. CADTH is currently reviewing a fixed-dose combination of doravirine/lamivudine/tenofovir disoproxil fumarate.

[a] Manufacturer-submitted price.

[b] IQVIA Delta PA, wholesale acquisition price (accessed January 2019).

Table 8: CDR Cost Comparisons of DHHS-Recommended Initial Regimens

Drug/Comparator Regimen	Strength	Dosage Form	Price ($)	Recommended Use	Daily Cost ($)	Freq. of Use (Per Day)	Number of Pills (Per Day)	Annual Drug Cost ($)
DHHS-recommended initial antiretroviral regimens								
InSTI + 2 NRTIs								
Dolutegravir/abacavir/lamivudine (Triumeq)	50/600/300 mg	Tab	43.2020[a]	1 tablet daily	43.20	1	1	15,769
Dolutegravir (Tivicay) + emtricitabine/tenofovir disoproxil fumarate (Truvada)	50 mg 200/300 mg	Tab	19.4993 7.3035	50 mg daily 1 tablet daily	26.80	1	2	9,783
Dolutegravir (Tivicay) + emtricitabine/tenofovir alafenamide (Descovy)	50 mg 200/25 mg	Tab	19.4993 26.1020[b]	50 mg daily 1 tablet daily	45.60	1	2	16,644
Bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy)	50/200/25 mg	Tab	39.2227[b]	1 tablet daily	39.22	1	1	14,316
Raltegravir (Isentress) + emtricitabine/tenofovir disoproxil fumarate (Truvada)	400 mg 200/300 mg	Tab	14.0301 7.3035	400 mg twice daily 1 tablet daily	35.36	2	3	12,908
Raltegravir (Isentress) + emtricitabine/tenofovir alafenamide (Descovy)	400 mg 200/25 mg	Tab	14.0301 26.1020[b]	400 mg twice daily 1 tablet daily	40.13	2	3	14,648
DHHS-recommended regimens for switch therapy								
InSTI + NNRTI								
Dolutegravir/rilpivirine (Juluca)[b]	50/25 mg	Tab	34.8677[a]	1 tablet daily	34.87	1	1	12,727

CDR = CADTH Common Drug Review; DHHS = US Department of Health and Human Services; freq. = frequency; InSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor.

Notes: All prices are from the Ontario Drug Benefit Formulary (accessed January 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] CADTH noted that the price of the individual components (dolutegravir + abacavir/lamivudine) was less than the price of the single-tablet regimen ($25.49). The annual cost of these two treatments used in combination was $9,303.

[b] IQVIA Delta PA, wholesale acquisition price (accessed January 2019).

Appendix 2: Additional Information

Table 9: Submission Quality

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

Table 10: Author Information

Authors of the Pharmacoeconomic Evaluation Submitted to CDR

☒ Adaptation of Global model/Canadian model done by the manufacturer
☐ Adaptation of Global model/Canadian model done by a private consultant contracted by the manufacturer
☐ Adaptation of Global model/Canadian model done by an academic consultant contracted by the manufacturer
☐ Other (please specify)

	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

CDR = CADTH Common Drug Review.

CADTH

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

At the time of the review, DOR had not been reviewed by other Health Technology Assessment bodies. The UK's National Institute for Health and Care Excellence is currently scoping a review of doravirine DOR for HIV-1 in adults.[12]

Appendix 4: Reviewer Worksheets

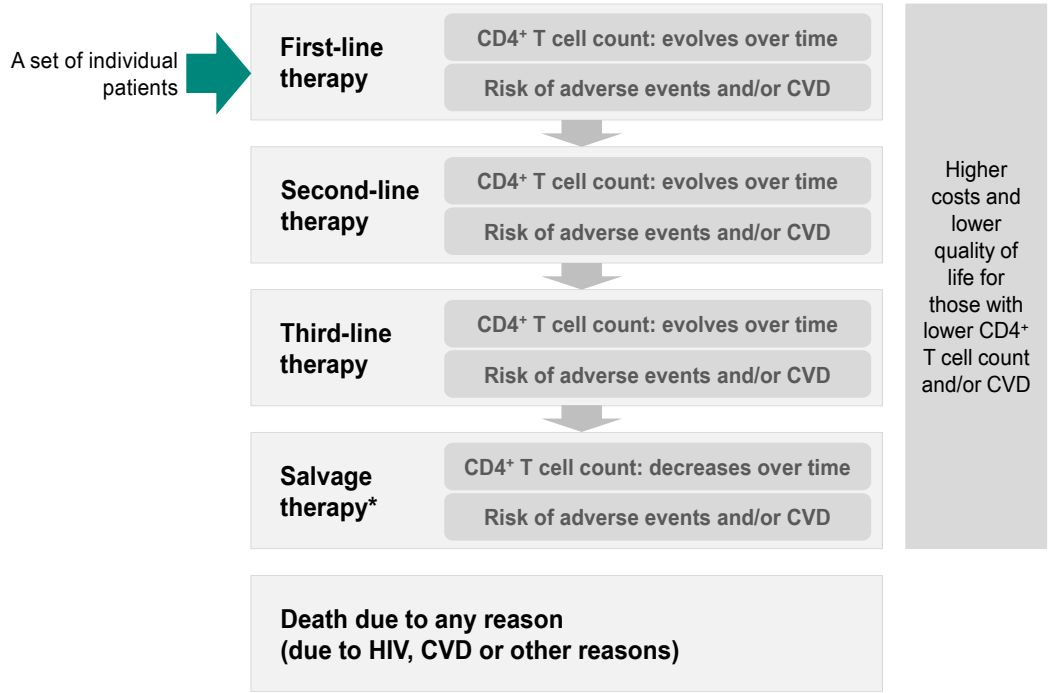
Manufacturer's Model Structure

The cost-effectiveness model is a state-transition, discrete, stochastic, patient-level simulation. The choice of modelling approach was based on the following considerations:

- Key variables (CD4+ T-cell count, lipid profiles; see Figure 1) are continuous, rather than categorical
- Some risks (such as cardiovascular disease; see Figure 1) are dependent on individual patient characteristics and time on treatments.

The cohort approach, if otherwise utilized, would create a high level of complexity as it would require many patient strata to be created. The model structure is provided in Figure 2.[3]

Figure 2: Model schematic



* Including non-suppression and partial suppression.

CVD = cardiovascular disease.

In the model, the following patient characteristics were updated every cycle (one year), as data were limited for the others:[3]

- Age: increased along with time in the model
- CD4+ T-cell count: depended on treatment in the first 96 weeks, and then followed the natural history
- Total cholesterol, and high-density lipoprotein: depending on treatment in the first 96 weeks
- Previous exposure to protease inhibitors
- Nucleoside reverse transcriptase inhibitors: depending on treatment received and duration of the treatment
- Diabetes.

Table 11: Data Sources

Data Input	Description of Data Source	Comment
Baseline characteristics	Pooled ad hoc analysis of Protocol 007 (for doravirine, 100 mg arm only), Protocol 018, and Protocol 21.[3] D:A:D study.[13]	Manufacturer excluded baseline characteristics of patients (phase II trial) who received a dose of DOR, which is not licensed in Canada. Impact on model is uncertain.
Efficacy	The majority of comparative efficacy and safety parameters were obtained from a simplistic network meta-analysis (NMA).[14]	Acceptable. However, CADTH clinical reviewers identified limitations with the submitted NMA, which may result in uncertainty.
Natural history	Baseline characteristics were expected to change over time. Data were available for (based on the pooled DOR trials): • Age • CD4+ T-cell count • Total cholesterol, and HDL • Previous exposure to PIs and NRTIs • Diabetes (PHAC and Stats Canada).[3]	Manufacturer excluded baseline characteristics of patients (phase II trial) who received a dose of DOR, which is not licensed in Canada. Impact on model is uncertain.
Health state utilities	Health state utilities: Kauf et al. (2008)[15] analyzed data from 5 trials of modern HAART. HRQoL, measured by Short-Form 6-Dimensions Health Survey, were reported by CD4+ T-cell count stratum.	Several other sources available with alternative (higher) values. Some uncertainty with the values, given the raw data indicate responses did not exhibit a consistent trend between health states.
Utility decrements	CVD-associated impacts were sourced from Ara and Brazier (2011);[16] review of EQ-5D data and health survey data in England from 2003 and 2006. Impact of AEs sourced from Kauf et al. (2008).[15]	Acceptable, though there is uncertainty with the application of the values.
AEs	Data were based on Protocol 007 (100 mg arm only), Protocol 018, and Protocol 21.[3]	Manufacturer excluded data from patients (phase II trial) who received a dose of DOR which is not licensed in Canada. Likely appropriate.
Population mortality	2014/2016 life tables (latest) published by Statistics Canada	Appropriate

Data Input	Description of Data Source	Comment
HIV-related mortality	Derived from a French study by Lewden et al. (2007).[17]	Generalizability is uncertain. See "Assumptions" Table for additional considerations.
CVD mortality	Based on one publication reporting SMR following MI by year after MI (Norgaard et al. 2010) in Denmark.[18]	Manufacturer indicated the estimates chosen were lower than other published values. However, generalizability to the Canadian setting is unknown. See "Assumptions" Table for additional considerations.
Resource use and costs		
Drug	Cost of DOR from manufacturer.[2] Costs of comparators from Ontario Drug Benefit Formulary (July 31, 2018 version).[3]	Appropriate sources, although the cost for EFV/TDF/FTC was outdated.
HIV management by CD4+ T-cell count	Nosyk et al. (2015) viewed 7 administrative databases and registries in BC (n = 11,836). Costs (excluding ARV therapies).[19]	The derivation of the values incorporated in the manufacturer's analysis were not well described, which made it difficult for CADTH to validate. Furthermore, the data appears to be for a population that is untreated, which would not be applicable in this case. Feedback from the clinical expert consulted by CADTH indicated the costs appeared to be an overestimate.
Management of CVD in HIV patients	Smolderen et al. (2010)[20] analyzed data from a registry which enrolled 1964 Canadian outpatients with CAD, CVD or PAD, or three or more CV risk factors	Not an HIV-1 patient population. Generalizability uncertain.
AEs	Costs of AE management from Despiégel et al. (2014), a cost-effectiveness analysis of DTG in Canadian settings. Mean duration of AEs reported in Simpson et al. (2014), a US study that investigated the cost of adverse events in HIV patients, was used.	Generalizability of duration information uncertain. AEs not captured in the Despiégel paper for alternate ARVs unknown.
Other	Costs were inflated using CPI of health care published by Statistics Canada.	Appropriate.

AE = adverse event; ARV = antiretroviral; CAD = coronary artery disease; CPI = consumer price index; CV = cardiovascular; CVD = cardiovascular disease; DOR = doravirine; EFV/TDF/FCT = efavirenz/tenofovir/emtricitabine; HAART = highly active antiretroviral therapy; HDL = high-density lipoprotein cholesterol; MI = myocardial infarction; NMA = network meta-analysis; PAD = peripheral arterial disease; PI = protease inhibitor; SMR = standardized mortality ratio.

Table 12: Manufacturer's Key Assumptions

Assumption	Comment
The manufacturer chose backbones and lines of therapies reportedly based on consultation with Canadian clinical HIV experts, and noted the list does not represent all alternative treatment pathways that patients may encounter in real life, but reflects the most probable and representative pathways for the average patient by HIV experts.	Feedback from the clinical expert consulted by CADTH suggested that several relevant comparators were excluded, based on the manufacturer's indication, and where the drug is likely to be used in clinical practice. Additionally, the incorporation of different later-line therapies between treatments may dilute the impact of the treatments assessed as first-line therapies in the model.
Model tracked patients to 100 years of age; the maximum time horizon included in the model is therefore 83 years, based on the lowest starting age of 18.	Appropriate.
Previous exposure to PIs and NRTIs was set to zero as the target population is treatment-naive.	May not be appropriate, as the indication is for patients without past or present evidence of viral resistance to doravirine; in practice it could be used in patients who have received prior treatment. One of the manufacturer-submitted trials was in patients switching from their current regimen if they were well maintained on their original regimen. Data for patients who have not responded to prior therapy were not identified as part of the CADTH clinical review, and thus have not been assessed.
Change CD4+ T-cell count is the main marker of disease progression.	Although the model was stated to be a discrete event simulation, the model incorporated different costs, utilities, and effects based on CD4+ T-cell count. The clinical expert consulted by CADTH indicated that CD4+ T-cell counts provide much less prognostic value than viral load. This feedback is aligned with published literature.[4-7]
Use of background patient characteristics as effect modifiers (e.g., inclusion of diabetes, family history of CVD, etc. in the model).	Baseline patient characteristics used in the model would not be expected to be treatment-effect modifiers, although some factors may be important when selecting ARV regimens (e.g., avoid PIs in patients with elevated cholesterol levels or diabetes).
In the NMA, "anchor" agents were pooled based on the assumption that the effect of the backbone agents were the same.	Feedback from the clinical expert consulted by CADTH suggested that this is a reasonable statement in terms of efficacy and safety.
NMA was appropriately conducted.	Feedback from the CADTH clinical reviewers suggested there were substantial issues with the submitted NMA, and that there is a high degree of uncertainty in the presented efficacy and safety results.
It was appropriate to incorporate a standardized mortality ratio (SMR vs. the general population) following MI, which was applied to the background mortality to estimate the probability of death due to CVD. It is acknowledged that this approach overestimated the mortality due to CVD, as it had been considered in the HIV-associated SMR. Nevertheless, it was not possible to identify a source that reports the SMR in HIV patients without CVD.	As noted by the manufacturer, this likely overestimated the mortality risk of CVD in HIV-1 patients, and may bias the results in favour of treatments with a better lipid profile, which the manufacturer appears to be claiming for DOR. CADTH notes that this is unlikely to have a large impact on the model results.
The manufacturer considered the following types of AEs appropriate to include in the model: gastrointestinal (diarrhea, nausea), neurological (dizziness, headache), psychological (abnormal dreams, depression), and rash.	Feedback from the clinical expert suggested that the choice of AEs was dependent on the comparators included. The clinical expert suggested that bone and renal outcomes would have been important, as all treatments included in the comparison used an older form of

Assumption	Comment
	tenofovir (TDF as opposed to tenofovir alafenamide fumarate; TAF). TAF is expected to reduce the risk of bone and renal AEs.[8-10]

AE = adverse event; ARV = antiretroviral; CVD = cardiovascular disease; DOR = doravirine; NMA = network meta-analysis; MI = myocardial infarction; NRTI = nucleoside reverse transcriptase inhibitors; PI = protease inhibitors; SMR = standardize mortality rate; TDF tenofovir disoproxil fumarate.

Manufacturer's Results

The manufacturer's model was based on a cohort of 2,500 patients, with 5,000 iterations to account for heterogeneity, and stochastic and parametric uncertainties. Patients were tracked until death or 100 years of age, whichever happened first.[3] Table 13 and Table 14 present the results of specific modelled outcomes, while Table 15 provides a breakdown of the cost information.

Table 13: Manufacturer's Results: Patient Time Spent on Treatment and Events in Years (Standard Deviation)

	On First-Line Therapy	On Second-Line Therapy	On Third-Line Therapy	On Salvage Therapy	Life Expectancy	With CVD
Single-tablet regimens						
DOR → DTG.s → DRV/r	14.79 (0.94)	15.86 (2.28)	4.32 (1.00)	4.19 (1.34)	39.16 (1.25)	3.72 (0.37)
EFV.s → DTG.s → DRV/r	12.19 (1.30)	17.23 (2.62)	4.76 (1.11)	4.72 (1.50)	38.90 (1.25)	3.95 (0.38)
DTG.s → RAL → DRV/r	19.40 (3.08)	11.79 (2.41)	4.11 (1.03)	4.09 (1.31)	39.39 (1.29)	3.66 (0.39)
DRV/r → DTG.s → RAL	10.37 (1.14)	18.18 (2.79)	7.03 (1.89)	3.55 (1.33)	39.13 (1.23)	3.97 (0.39)
Multiple-tablet regimens						
DOR → DTG.m → DRV/r	14.79 (0.94)	15.86 (2.28)	4.32 (1.00)	4.19 (1.34)	39.16 (1.25)	3.79 (0.38)
EFV.m → DTG.m → DRV/r	12.19 (1.30)	17.23 (2.62)	4.76 (1.11)	4.73 (1.50)	38.90 (1.24)	4.02 (0.38)
DTG.m → RAL → DRV/r	19.39 (3.08)	11.79 (2.41)	4.11 (1.03)	4.09 (1.31)	39.38 (1.29)	3.87 (0.40)
DRV/r → DTG.m → RAL	10.37 (1.14)	18.18 (2.79)	7.03 (1.89)	3.55 (1.33)	39.13 (1.23)	4.05 (0.39)

DOR = doravirine; DTG = dolutegravir; DRV/r = ritonavir-boosted darunavir; EFV = efavirenz; RAL = raltegravir; m = multiple-tablet regimen; s = single-tablet regimen.

Source: Adapted from the manufacturer's pharmacoeconomic submission.[3]

Table 14: Manufacturer's Results: Disease Outcomes in Number of Patients (Standard Deviation) (N = 2,500)

	Developed CVD	Died (Due to Other Reasons)	Died (Due to HIV)	Died (Due to CVD)
Single-tablet regimen				
DOR → DTG.s → DRV/r	726 (65)	822 (119)	1,558 (142)	120 (26)
EFV.s → DTG.s → DRV/r	773 (67)	801 (116)	1,577 (139)	123 (27)
DTG.s → RAL → DRV/r	726 (69)	836 (124)	1,543 (150)	121 (29)
DRV/r → DTG.s → RAL	770 (69)	818 (118)	1,556 (144)	126 (29)
Multiple-tablet regimen				
DOR → DTG.m → DRV/r	730 (66)	822 (119)	1,558 (142)	120 (26)
EFV.m → DTG.m → DRV/r	778 (67)	800 (115)	1,576 (139)	123 (27)
DTG.m → RAL → DRV/r	741 (68)	835 (124)	1,541 (149)	123 (29)
DRV/r → DTG.m → RAL	775 (70)	818 (118)	1,556 (144)	126 (29)

CVD = cardiovascular; DOR = doravirine; DTG = dolutegravir; DRV/r = ritonavir-boosted darunavir; EFV = efavirenz; RAL = raltegravir; m = multiple-tablet regimen; s = single-tablet regimen.

Source: Adapted from the manufacturer's pharmacoeconomic submission.[3]

Table 15: Manufacturer's Results: Cost Breakdown of Total Costs (Standard Deviation)

	Medications	Adverse Events	HIV Management	CVD Management	Total Costs
Single-tablet regimen					
DOR → DTG.s → DRV/r	$369,226 ($11,215)	$6,526 ($1,238)	$183,196 ($9,339)	$9,773 ($1,737)	$568,721 ($17,437)
EFV.s → DTG.s → DRV/r	$375,743 ($12,428)	$8,120 ($1,594)	$184,648 ($9,454)	$10,412 ($1,834)	$578,922 ($18,121)
DTG.s → RAL → DRV/r	$433,944 ($11,757)	$7,646 ($1,609)	$180,595 ($9,666)	$9,511 ($1,718)	$631,695 ($18,085)
DRV/r → DTG.s → RAL	$413,226 ($11,217)	$7,376 ($1,525)	$185,814 ($9,472)	$10,420 ($1,846)	$616,837 ($17,376)
Multiple-tablet regimen					
DOR → DTG.s → DRV/r	$301,595 ($11,389)	$6,526 ($1,238)	$183,190 ($9,336)	$9,976 ($1,770)	$501,287 ($17,579)
EFV.s → DTG.s → DRV/r	$257,504 ($14,177)	$8,120 ($1,594)	$184,640 ($9,450)	$10,633 ($1,870)	$460,896 ($19,535)
DTG.s → RAL → DRV/r	$340,904 ($12,507)	$7,644 ($1,608)	$180,550 ($9,663)	$10,169 ($1,824)	$539,267 ($18,665)
DRV/r → DTG.s → RAL	$333,918 ($12,038)	$7,376 ($1,525)	$185,811 ($9,468)	$10,660 ($1,888)	$537,765 ($17,983)

CVD = cardiovascular disease; DOR = doravirine; DTG = dolutegravir; DRV/r = ritonavir-boosted darunavir; EFV = efavirenz; RAL = raltegravir; s = single-tablet regimen.

Source: Adapted from the manufacturer's pharmacoeconomic submission.[3]

Manufacturer Scenario Analyses

The manufacturer undertook four scenario analyses, using an upper and lower estimate around the discount rate for the single-tablet regimen (STR) and multiple-tablet regimen (MTR) comparator analyses.[3]

In the STR analyses, efavirenz/tenofovir/emtricitabine (EFV/TDF/FTC) and ritonavir-boosted darunavir (DRV/r) + TDF/FTC are dominated by doravirine (DOR) + backbone regardless of whether the discount rate is set at 0% or 3%. The incremental cost-utility ratio for dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) relative to DOR + backbone ranged from $296,998 per quality-adjusted life-year (QALY) to $624,507 per QALY at the 0% and 3% discount rates, respectively.

In the MTR analyses, DRV/r + TDF/FTC is dominated by DOR + backbone regardless of whether the discount rate is set at 0% or 3%. EFV + TDF/FTC is the least costly option in both analyses. The ICUR for DOR + backbone compared with EFV + TDF/FTC ranged from $143,009 per QALY to $279,836 per QALY at the 0% and 3% discount rates respectively. The incremental cost-utility ratio for DTG + TDF/FTC compared with DOR + backbone ranged from $236,200 per QALY to $394,881 per QALY at the 0% and 3% discount rates, respectively.

CADTH Additional Reanalyses

Table 16: CADTH Reanalysis Versus STRs, Exploratory Analyses (Based on CADTH Base Case)

	Total QALYs	Total Costs ($)	Incremental Cost per QALY	
			Versus least costly alternative	Sequential ICUR
Lower HIV-care costs (assumed half of manufacturer values)				
EFV.s → DTG.s → DRV/r	22.20	$340,713	-	-
DOR → DTG.s → DRV/r	22.40	$381,560	$172,235	$209,283
DRV/r → DTG.s → RAL	22.32	$415,573	$655,396	Dominated by DOR
DTG.s → RAL → DRV/r	22.54	$418,291	$229,732	$257,738
Same utility values across CD4+ T-cell count states				
EFV.s → DTG.s → DRV/r	20.91	$455,575	-	-
DOR → DTG.s → DRV/r	21.07	$495,671	$240,832	$240,832
DRV/r → DTG.s → RAL	21.03	$531,168	$610,093	Dominated by DOR
DTG.s → RAL → DRV/r	21.16	$531,278	$293,084	$387,837
First-line + salvage (DRV/r +)				
EFV.s → DRV/r	21.71	$494,886	-	-
DTG.s → DRV/r	22.30	$526,062	$53,348	$53,348
DOR → DRV/r	21.97	$531,369	$140,600	Dominated by DTG
DRV/r → DRV/r	21.57	$572,934	Dominated by EFV	Dominated by DTG
Cost of individual components of DTG/ABC/3TC (DTG + ABC/3TC)				
EFV.s → DTG.s → DRV/r	22.20	$455,575	-	-
DOR → DTG.s → DRV/r	22.40	$495,671	$205,435	$205,435

	Total QALYs	Total Costs ($)	Incremental Cost per QALY	
			Versus least costly alternative	Sequential ICUR
DRV/r → DTG.s → RAL	22.32	$531,168	$661,805	Dominated by DOR
DTG.s → RAL → DRV/r	22.54	$531,278	$224,180	$249,852

DOR = doravirine; DTG = dolutegravir; DRV/r = ritonavir-boosted darunavir; EFV = efavirenz; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; RAL = raltegravir; s = single-tablet regimen.

Table 17: CADTH Reanalysis Versus MTRs, Exploratory Analyses (Based on Manufacturer Analysis)

	Total QALYs	Total Costs ($)	Incremental Cost per QALY	
			Versus least costly alternative	Sequential ICUR
Lower HIV-care costs (assumed half of manufacturer values)				
EFV.m → DTG.s → DRV/r	22.20	$346,039	-	-
DOR → DTG.s → DRV/r	22.39	$387,179	$209,389	$209,790
DRV/r → DTG.s → RAL	22.31	$422,173	$665,596	Dominated by DOR
DTG.m → RAL → DRV/r	22.52	$426,309	$251,389	$317,602
Same utility values across CD4+ T-cell count states				
EFV.m → DTG.s → DRV/r	20.90	$460,896	-	-
DOR → DTG.s → DRV/r	21.07	$501,287	$241,311	$241,311
DRV/r → DTG.s → RAL	21.02	$537,765	$619,853	Dominated by DOR
DTG.m → RAL → DRV/r	21.14	$539,267	$326,220	$521,279
First-line + salvage (DRV/r +)				
EFV.m → DRV/r	21.71	$494,036	-	-
DOR → DRV/r	21.97	$531,369	$143,874	Subject to extended dominance through EFV and DTG
DTG.m → DRV/r	22.27	$534,056	$71,688	$71,688
DRV/r → DRV/r	21.57	$572,934	Dominated by EFV	Dominated by EFV, DOR, DTG

DOR = doravirine; DTG = dolutegravir; DRV/r = ritonavir-boosted darunavir; EFV = efavirenz; ICUR = incremental cost-utility ratio; m = multiple-tablet regimen; QALY = quality-adjusted life-year; RAL = raltegravir.

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