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CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

DOLUTEGRAVIR/LAMIVUDINE (DOVATO)

(ViiV Healthcare ULC)

Indication: As a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescents 12 years of age and older and weighing at least 40 kg.

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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.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

3TC	lamivudine
ABC	abacavir
ART	antiretroviral therapy
BIC	bictegravir
CD4+	cluster of differentiation 4 positive
CKD	chronic kidney disease
CVD	cardiovascular disease
DTG	dolutegravir
EVG/c	elvitegravir/cobicistat
FTC	emtricitabine
NMA	network meta-analysis
ODB	Ontario Drug Benefit
QALY	quality-adjusted life-year
RPV	rilpivirine
STR	single-tablet regimen
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Dolutegravir/lamivudine (DTG/3TC; Dovato)
Study Question	What is the cost-utility of dolutegravir/lamivudine versus guideline recommended first-line antiretroviral regimens for the treatment of HIV-1 infection in adults and adolescents aged 12 years and older weighing at least 40 kg.
Type of Economic Evaluation	Cost-utility analysis
Target Population	Adults and adolescents, aged 12 years and older, weighing at least 40 kg with HIV-1
Treatment	DTG/3TC 50 mg/300 mg once daily, followed by three subsequent lines of therapy
Outcome	QALY
Comparators	• Dolutegravir/abacavir/lamivudine (Triumeq) • Dolutegravir/tenofovir disoproxil fumarate/emtricitabine (Tivicay) + (Truvada) • Elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine (Genvoya) • Bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy)
Perspective	Canadian public health care payer
Time Horizon	Lifetime (up to 80 years)
Results for Base Case	Dolutegravir/lamivudine was less costly and more effective than all comparator ART regimens (dominant)
Key Limitations	• The NMA used to support the economic evaluation was associated with several limitations (i.e., sparsity of the evidence networks and the noninferiority design of the primary RCTs that precluded the establishment of precise estimates of differences between treatment regimens). This resulted in substantial uncertainty with the comparative treatment effect estimates used in the economic analysis. • The durability of response and potential for resistance mutations with DTG/3TC is unclear, making the long-term cost-effectiveness of DTG/3TC uncertain. • For first-line regimens containing TDF, the inclusion of a different CVD risk profile was considered inappropriate. The duration of the waning period in terms of the effects of treatment on fractures and CKD were also considered too long. • The manufacturer modelled disease progression using CD4+ T-cell counts, which was not considered to be the most appropriate prognostic marker when compared with viral load. • The time period for assessment of virologic failure (12 months) was too long.
CDR Estimate(s)	CADTH undertook a reanalysis to remove the differential impact of TDF on CVD risk, and reduced both the observation period for virologic suppression and the waning period of the impact of treatment on CKD and fractures. • DTG/3TC dominated all comparators evaluated (i.e., lower expected costs and higher expected QALYs). • CADTH was unable to address several key limitations, including uncertainties in the relative treatment effects in the manufacturer's NMA, uncertainties associated with the model structure, and concerns with the long-term durability of response with DTG/3TC. • The model results were primarily driven by drug acquisition costs. The magnitude of cost savings associated with DTG/3TC is unclear as not all first-line ART regimens were considered and the individualized nature of therapy that would affect the time patients are on DTG/3TC. The cost of DTG/3TC co-formulated FDC tablet ($30.44 daily) is more costly than the cost of the individual components of DTG + 3TC ($27.08 daily). • The economic findings of DTG/3TC are based on limited comparative clinical information to support the benefits over established three- and four-drug regimens.

3TC = lamivudine; ART = antiretroviral; CD4 = cluster of differentiation 4 positive; CKD = chronic kidney disease; CVD = cardiovascular disease; DTG = dolutegravir; FDC = fixed-dose combination; NMA = network meta-analysis; QALY = quality-adjusted life-year; RCT = randomized controlled trial; TDF = tenofovir disoproxil fumarate.

Drug	dolutegravir/lamivudine (Dovato)
Indication	As a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescents 12 years of age and older and weighing at least 40 kg
Reimbursement Request	As per indication
Dosage Form(s)	Fixed-dose combination oral tablet containing dolutegravir 50 mg/lamivudine 300 mg
NOC Date	August 22, 2019
Manufacturer	ViiV Healthcare ULC

Executive Summary

Background

Dolutegravir/lamivudine (DTG/3TC; Dovato) is a fixed-dose combination of two drugs indicated as a complete regimen for the treatment of adults and children 12 years of age and older who weigh at least 40 kg and have HIV-1 infection.[1] DTG/3TC consists of a single tablet containing 50 mg DTG, an integrase inhibitor, and 300 mg 3TC, a nucleoside reverse transcriptase inhibitor, to be taken once daily. At the manufacturer-submitted price of $30.44 per tablet, the annual cost of treatment is approximately $11,110.[2] The manufacturer's reimbursement request was in accordance with the Health Canada indication.[1]

The manufacturer submitted a cost-utility analysis based on a hybrid decision tree and Markov state transition model that assessed the costs and quality-adjusted life-years (QALYs) of treatment with DTG/3TC in comparison with current standard single-tablet regimens (STRs) (DTG/ abacavir [ABC]/3TC [Triumeq], elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine [FTC] [Genvoya], and bictegravir/FTC/tenofovir alafenamide [Biktarvy]) and multi-tablet drug regimens (DTG/tenofovir disoproxil fumarate [TDF]/FTC [Tivicay + Truvada]). Health states were defined based on viral load, CD4+ (cluster of differentiation 4 positive) T-cell count and treatment line with the model allowing patients to receive up to two additional lines of antiretroviral therapy (ART) before moving on to salvage therapy (on which they would remain until death). The Markov health states captured disease progression according to CD4+ cell count, as well as the occurrence of clinical events (i.e., adverse treatment events, AIDS-defining events, and long-term toxicities). The decision tree captured treatment discontinuation to stratify subsequent therapy lines. The manufacturer sponsored network meta-analysis (NMA) informed the relative efficacy inputs in terms of virologic (viral load) and immunological response (CD4+ T-cell count), as well as the safety inputs, for all first-line therapies. The analysis was conducted over a lifetime time horizon (up to 80 additional years), from the Canadian public health care payer perspective with costs and QALYs discounted at 1.5%.[1]

In the manufacturer's base case, DTG/3TC was associated with fewer costs and higher QALYs than all comparator regimens. As a result, it was dominant and, across all willingness-to-pay thresholds, it would be considered the most likely cost-effective strategy. The manufacturer stated the results were driven by the drug acquisition costs.

Summary of Identified Limitations and Key Results

CADTH identified several key limitations pertaining to the comparative clinical effectiveness and safety of modelled treatment strategies, the structure of the model in capturing disease progression and the individualized nature of HIV-1 treatment, and the time period for assessment of virologic failure.

The manufacturer's comparative clinical efficacy inputs were based on the results of a manufacturer's sponsored NMA. The CADTH clinical review found no evidence for a difference in efficacy or safety between DTG + 3TC and other first-line ART regimens that were included in the manufacturer's pharmacoeconomic submission. Further, data from the GEMINI trials that informed the economic model were from results reported at 48 weeks.[3] The durability of response and potential for resistance mutations over an extended period of use is uncertain. As a result of these two limitations, the clinical effectiveness and cost-effectiveness of DTG/3TC remains uncertain. Additional limitations with the clinical inputs related to the assessment for virologic failure and long-term toxicity. The clinical expert consulted by CADTH indicated that there was limited evidence of association between first-line treatment regimens containing TDF and an increased risk of cardiovascular disease when compared with other comparators, nor was the duration of the waning period for treatment effects on biomarkers appropriate. The manufacturer's model assumed that the waning period would be nine years for fractures and chronic kidney disease risks while the clinical expert expected that, in clinical practice, this would be 2.5 years and six months, respectively. These input values for long-term toxicities used in the manufacturer's base case likely biased costs and QALYs against DTG + TDF/FTC.

The manufacturer's primary measure of disease progression was CD4+ T-cell counts, with costs, utilities, and certain clinical events dependent on CD4+ T-cell counts. The clinical expert consulted by CADTH confirmed that, while CD4+ T-cell counts are a valid biologic measure of the efficacy of ART in patients with HIV-1, they may not be the most relevant markers of disease progression. The published literature agrees with this assessment and indicates that viral load is a better predictor of patient prognosis, particularly after treatment.[4-7] Viral load was incorporated within the model, but only to determine whether patients would remain on their current therapy or switch to another. Further to this issue with the model structure, the treatment of HIV-1 is complex and highly individualized. The submitted model may not sufficiently capture the individualized nature of HIV therapy in this population, particularly the use of "pooled" efficacy profiles for all subsequent treatment lines. This is not representative of clinical practice as subsequent treatment after first-line therapy depends on previous therapy and a patient's individual preferences.

Additionally, the clinical expert consulted by CADTH indicated that, rather than the twelve months used by the manufacturer in its base case, three months would be a sufficient period of time in clinical practice to assess virologic failure and, if appropriate, switch to another line of therapy.

CADTH identified several other limitations: the manufacturer's model required a total runtime of more than 16 hours, impacting CADTH's ability to explore uncertainties, and the manufacturer did not consider all relevant comparators, rendering the results uncertain in their absence. Furthermore, there is limited data on the clinical effects of treatment on a younger population as the GEMINI trials were conducted on adult patients aged 18 years or older (mean age approximately 32 years of age) whereas the Health Canada indication is for patients 12 years of age or older. However, the expert consulted for this review did not

express concern regarding drug absorption, metabolism, or toxicity in patients younger than 18 years of age.

While not all limitations could be addressed, CADTH did undertake a reanalysis incorporating a shorter time of assessment for virologic failure (changed from 12 months to three months), removing the increased risk of cardiovascular disease with TDF, and applying more appropriate lengths for the waning period of TDF on fracture risk (changed from nine years to 2.5 years) and chronic kidney disease (changed from nine years to six months). The results remained consistent with the manufacturer's base case and DTG/3TC dominated all comparators (DTG/3TC was less costly and more effective). However, these results require careful consideration. The driver of the cost differences are largely driven by drug costs and, although the current most commonly prescribed first-line regimens were considered in the model, not all ART regimens were considered. Some have lower annual drug costs compared with DTG/3TC. Furthermore, CADTH noted that the combined price of the individual components of Triumeq (DTG + ABC/3TC) is substantially less costly than its STR.

Conclusions

Based on the CADTH reanalysis, DTG/3TC resulted in lower costs and greater QALYs than its comparators, thus dominating all first-line ART regimens evaluated. These results are subject to uncertainty given that CADTH could not address limitations related to the model structure, the manufacturer's submitted NMA that informed comparative clinical effectiveness estimates, and the long-term durability of treatment response with DTG/3TC. The magnitude of cost savings associated with DTG/3TC is unclear given the individualized nature of HIV treatment, particularly relating to the timing and reasons for treatment switching, as well as the limited data on the comparative clinical effectiveness of DTG/3TC with other three- and four-drug regimens.

The model results were primarily driven by drug acquisition costs. Although the current most commonly prescribed first-line regimens were considered in the model, not all ART regimens were considered (some of which have lower annual drug costs). Furthermore, in a scenario analysis where the price of the individual components of DTG/ABC/3TC was used (i.e., DTG + ABC/3TC), DTG/3TC was no longer dominant and the resulting incremental cost-utility ratio was $78,576 per QALY gained compared with DTG + ABC/3TC. It should further be noted that the STR of DTG/3TC at the submitted daily price of $30.44 is more costly (approximately $3.35 daily) than the sum of its individual components ($27.08; DTG, $19.83, and 3TC, $7.25, daily). This difference represents an additional cost of $101.90 monthly, or $1,223 annually, per person.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic submission

The manufacturer submitted a hybrid Markov state transition model and decision tree comparing DTG/3TC, a single-tablet fixed-dose combination, to current standard single-tablet regimens (STRs) (dolutegravir [DTG]/abacavir [ABC]/lamivudine [3TC] [Triumeq], elvitegravir/cobicistat [EVG/c]/tenofovir alafenamide [TAF]/emtricitabine [FTC] [Genvoya], and bictegravir [BIC]/FTC/TAF [Biktarvy]) and multi-tablet regimens (DTG/tenofovir disoproxil fumarate [TDF]/FTC [Tivicay + Truvada]), for the treatment of HIV-1 infection in adults and children older than 12 years of age who weigh at least 40 kg. The selected comparators reflected recommended first-line regimens by the US Department of Health and Human Services guidelines[8] and represented the regimens with the highest market shares in Canada. In addition to first-line therapy, the model permitted treatment switches to up to two antiretroviral (ART) treatment lines and an additional salvage therapy line. The analysis was conducted from the Canadian public health care payer perspective with monthly cycles over a lifetime time horizon (up to 80 additional years), with a discount rate of 1.5% applied to costs and quality-adjusted life-years (QALYs).[1] Baseline characteristics upon model entry were based primarily on data from the GEMINI trials, which included treatment-naive patients but did not include treatment-experienced patients within its trial program.[3]

The Markov state transition model was designed to reflect the natural history of disease and the effects of treatment, with health states defined based on viral load (50 copies/mL or less and more than 50 copies/mL), cluster of differentiation 4 positive (CD4+) T-cell count (100 cells/mm^3 or less, 100 cells/mm^3 to 199 cells/mm^3, 200 cells/mm^3 to 349 cells/mm^3, 350 cells/mm^3 to 499 cells/mm^3, and 500 cells/mm^3 or more) and treatment line (See Figure 1).[1] Disease progression was based on CD4+ T-cell count. During each cycle, patient's viral status and CD4+ T-cell count could improve, decline, or remain constant. Within these health states, patients could further experience clinical events (i.e., adverse events, AIDS-defining events, long-term toxicities [chronic kidney disease (CKD), cardiovascular disease (CVD), fracture]), or move to the absorbing mortality state. The incidence of death and AIDS-defining events were adjusted for the risk based on CD4+ T-cell count, whereas, for long-term toxicities, the incidence was time, exposure, or both to first-line treatment regimens containing TDF.[1] Viral load was only used to determine whether patients would remain on their current therapy or switch to another. Specifically, every twelve months, the decision tree assessed whether patients would discontinue treatment and, if treatment was discontinued, allocated patients to the appropriate treatment line based on the reason for discontinuation (See Figure 2). Patients who discontinued were stratified based on whether the reason for discontinuation was due to virologic (i.e., elevated viral load for 12 months or virologic rebound) or non-virologic (any other reason for discontinuation) reasons as this would impact the efficacy of subsequent lines of therapies.[1]

Data from the GEMINI clinical trials were used to populate transition probabilities between viral load and CD4+ T-cell count health states for DTG/3TC. The GEMINI clinical trial program evaluated the clinical efficacy and safety of DTG + 3TC given as individual tablets and it was assumed that this would be bioequivalent to the single-tablet fixed-dose combination of DTG/3TC.[3] A manufacturer-submitted network meta-analysis (NMA) was then used to inform the relative treatment effects for all first-line treatment comparators to DTG + 3TC. A published NMA informed the pooled efficacy and safety for subsequent

treatment lines,[9] while treatment efficacy for the salvage therapy treatment line was obtained from the literature.[10,11] Adverse event risks were obtained from the GEMINI trials, as well as the NMA, while clinical event risks were obtained from a combination of clinical trial data, published literature, and clinical expert opinion.[1] All-cause mortality was obtained from Statistics Canada life tables for 2014 to 2016,[12] adjusted by the relative risk of mortality based on CD4+ T-cell count categories and the presence of cardiovascular comorbidities.[13] A one-time increased risk of death was applied at the time of an AIDS-defining event.[14]

Health state utility values were obtained from the GEMINI trials using the EuroQol 5-Dimensions questionnaire and reported by CD4+ T-cell count category.[3] Additionally, disutilities were applied additively to each of the health states based on a patient's age and the occurrence of clinical events (CVD,[15] fracture [by type of fracture],[16,17] CKD [by stage],[18] adverse events,[3] and AIDS-defining event[19]). Health state costs and resource use by CD4+ T-cell count category, in the form of disease management costs (e.g., outpatient care, opportunistic infection prophylaxis, non-HIV medication) were obtained from published literature and the Ontario Drug Benefit (ODB) formulary.[1] The ODB formulary further informed comparator drug costs.[20]

Manufacturer's Base Case

In the manufacturer's base case, there were no major differences observed in life expectancy (approximately 29 years). DTG/3TC had fewer costs and higher QALYs than all comparators (See Table 2). As a result, it was dominant and was the most likely cost-effective strategy across all willingness-to-pay thresholds. A more detailed breakdown of the costs of the probabilistic analysis can be found in 3TC = lamivudine; ABC = abacavir; DTG = dolutegravir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; LY = life-year; QALY = quality-adjusted life-year;
TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.

Source: Manufacturer's pharmacoeconomic submission.[1]

Table 11, Appendix 4.

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

Therapy	Cost ($)	QALYs	Life-Years	ICUR (Incremental Cost/ QALY Gained)
DTG/3TC	852,023	24.910	28.648	Reference
DTG + TDF/FTC	874,859	24.748	28.671	Dominated by DTG/3TC
BIC + TAF/FTC	883,584	24.875	28.589	Dominated by DTG/3TC
DTG + ABC/3TC	895,832	24.892	28.609	Dominated by DTG/3TC
EVG/c + TAF/FTC	903,446	24.860	28.570	Dominated by DTG/3TC

3TC = lamivudine; ABC = abacavir; BIC = bictegravir; DTG = dolutegravir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life year; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.

Source: Manufacturer's pharmacoeconomic submission.[1]

Summary of Manufacturer's Sensitivity Analyses

The manufacturer reported that additional analyses were run by changing the discount rate to 0% and 3% per year (in separate analyses), altering the waning time frame of biomarkers that were used to model long-term toxicity, and applying GEMINI trial efficacy inputs for DTG + TDF/FTC. While the magnitude of the results differed, the results were robust with DTG/3TC remaining dominant. The manufacturer also conducted one-way sensitivity analyses and did not identify any parameters that significantly impacted the cost-effectiveness results.

Limitations of Manufacturer's Submission

- **The comparative clinical effectiveness of modelled treatment strategies is highly uncertain.** As noted in the CADTH clinical review report,[9] the sparsity of the evidence networks and the noninferiority design of the primary randomized controlled trials precluded the establishment of precise estimates of differences between treatment regimens. Although no evidence for a difference in efficacy or safety between DTG/3TC and comparators included in the manufacturer's pharmacoeconomic submission was identified, the comparative clinical efficacy remains uncertain. A scenario analysis assuming equal treatment efficacy was conducted to assess the impact of this limitation on the CADTH base case.
- **There was uncertainty in the durability of long-term response and the potential for resistance mutations with DTG/3TC.** The data used to inform the clinical effects for DTG/3TC in the economic evaluation were from the GEMINI trials (reported at 48 weeks). An assumption that treatment efficacy persists was assumed in extrapolating treatment effects beyond 48 weeks. As noted in the clinical review report, there is uncertainty in the durability of long-term response with DTG + 3TC given the limited time frame in which the data were collected. This is of concern given the potential for emergence of resistance to mutations with the two-drug regimen of DTG/3TC that may not be captured within the current time period for which there is clinical data. The clinical review report concludes that longer-term data are needed to assess the durability of response and potential for emergence of resistance mutations beyond 48 weeks. Although the manufacturer subsequently provided data up to 96 weeks suggesting that DTG + 3TC may remain noninferior to DTG + TDF/FTC, this conclusion is speculative due to the paucity of the methodological details available to assess the validity of the results. Should the assumption not hold that clinical effects persist beyond 48 weeks and DTG/3TC is inferior in terms of long-term efficacy, or lead to a greater incidence of resistance mutations, the clinical benefit of DTG/3TC would be overestimated as currently applied within the economic model. This limitation could not be addressed in the CADTH reanalyses and increases the uncertainty in the cost-effectiveness of DTG/3TC.
- **There was an overestimation of the long-term toxicity impacts of first-line treatment containing TDF**. The CADTH clinical review noted that differences in lipid, bone, or renal parameters were not considered clinically relevant in the currently available studies that have directly compared DTG + 3TC with DTG + TDF/FTC. The clinical expert consulted by CADTH further indicated the inclusion of a different cardiovascular toxicity profile for patients on ART regimens containing TDF, and also noted that the waning time frame of renal function and fracture risk biomarkers that were used to model long-term toxicity was inappropriate. Specifically, the clinical expert indicated there was no consistent evidence of an association between TDF and an increased risk of CVD. The waning period for treatment effects on biomarker inputs used to model the probability of fractures and CKD,

estimated to be nine years, was also longer than expected in clinical practice (2.5 years and six months, respectively). The long-term toxicity-related inputs as used in the manufacturer's base case likely biased costs and QALYs against DTG + TDF/FTC. This was addressed in the CADTH base case by applying the same CVD profile for all first-line regimens and by decreasing the mean duration of the treatment waning effect on bone mineral density fracture risk and estimated glomerular filtration rate to 2.5 years and six months, respectively, for the DTG + TDF/FTC comparator.

- **DTG/3TC is more costly than the sum of its individual components.** When the STR of DTG/3TC is compared with the multi-tablet regimens consisting of its individual components, at the submitted daily price of $30.44 per tablet, DTG/3TC is more costly (approximately $3.35 daily) than the sum of its individual components: DTG ($19.83 daily) and 3TC ($7.25 daily). This difference represents an additional monthly cost of $101.90, or $1,223 annually, for the DTG/3TC STR compared with the cost incurred by its individual components. Should the price of DTG or 3TC be lower in any jurisdiction than the list price that was sourced from the ODB formulary in this review — which does not account for existing Product Listing Agreements — the difference in cost between the STR product and its individual components may be even greater. Cost savings are therefore not realized by the use of the DTG/3TC STR when compared with the DTG + 3TC multi-tablet regimen.
- **The validity of CD4+ T-cell counts as a marker for burden of disease is uncertain.** The manufacturer incorporated different costs, utilities, and events based on CD4+ T-cell counts in its model. The clinical expert consulted by CADTH confirmed that while CD4+ T-cell counts are a valid biologic measure of the efficacy of ART in patients with HIV-1 and there have been some reports suggesting a rough association, there is a lot of variance with these estimates and they may not be the most relevant marker of disease progression. The published literature appears to align with the feedback from the CADTH clinical expert in that there is a wide range of viral load found in patients with HIV-1 within a given range of CD4+ T-cell count (e.g., HIV-1 patients with 200 CD4 cells/mm^3 to 300 CD4 cells/mm^3 had a plasma HIV ribonucleic acid range between 200 copies/mL and 234,000 copies/mL), and indicates that viral load, not CD4 cell count, is a better predictor of prognosis, especially after treatment.[4-7] Viral load was incorporated within the model, but only to determine whether patients would remain on their current therapy or switch to another.

  Further to this issue, inconsistencies were present within the manufacturer's health state utility values by CD4+ T-cell count category that were obtained directly from the GEMINI trials.[3] For example, patients with a CD4+ T-cell count of greater than 500 had a lower utility value (0.959) than patients with a CD4+ T-cell count between 350 and 500 (0.960). This does not meet face validity under the assumption that CD4+ T-cell counts are an appropriate measure of disease progression. This further supports the feedback from the clinical expert indicating that CD4+ T-cell counts may not appropriately capture disease progression. As such, the manufacturer's assumption that patients experience different quality of life based on changes in the range of CD4+ T-cell count health states is highly uncertain. 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.
- **The 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 Department of Health and Human Services guidelines for the use of ART 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 as subsequent treatment reflected a "pooled treatment." For second- and third-line ART, although treatment efficacy was dependent on the reason for discontinuation, it was assumed to be identical for all patients discontinuing for the same reason. Efficacy values were pooled to derive weighted mean efficacy values from studies in the literature for patients discontinuing due to virologic and non-virologic reasons, respectively.[21-23] Treatment costs were assumed to be identical for second- and third-line therapy and reflected an average of numerous ART regimens, including all comparators in the model except for DTG/3TC. This is not representative of clinical practice, as subsequent treatment after first-line therapy depends on previous therapy and a patient's individual preferences. This issue could not be addressed within CADTH reanalyses.

- **The time period for assessment of virologic failure was not representative of clinical practice.** The manufacturer assumed the time period for assessment of virologic failure would be 12 months. Based on feedback from the clinical expert consulted by CADTH, the typical time frame for determining virologic failure would be every three months in Canadian practice, and patients would be switched to an alternative line of therapy if virologic suppression is not achieved. The CADTH reanalysis updated this parameter input from 12 months to three months.

Other minor limitations identified include:

- **The manufacturer did not consider all relevant comparator treatments.** Although the clinical expert consulted by CADTH indicated that the list of first-line regimens included in the economic evaluation submitted by the manufacturer was representative of clinical practice in most of Canada, it was noted that several relevant comparator treatments were not considered in the analysis (e.g., FTC/rilpivirine [RPV]/TDF [Complera], FTC/RPV/TAF [Odefsey], and raltegravir [Isentress] + FTC/TDF [Truvada]). As a result, the cost-effectiveness of DTG/3TC compared with all relevant comparators is uncertain.

- **The manufacturer's model required a long run time**. The manufacturer's model required a total run time of more than 16 hours to complete 500 simulations. Although results were stable at 500 replications, the lengthy run time significantly impacted CADTH's ability to run reanalyses and explore potential uncertainties.

- **The manufacturer only considered a subset of the indicated population approved by Health Canada.** The Health Canada indication is for adult patients and children who are at least 12 years of age. The available clinical data informing the clinical effects of DTG/3TC within the manufacturer's model stems from the two pivotal GEMINI trials. These trials were conducted in adult patients who were at least 18 years of age or greater. There remains limited data on the clinical effects of DTG/3TC on patients with HIV-1 infection who are younger than 18 years of age, and the cost-effectiveness of DTG/3TC in those younger than 18 years of age remains unknown. However, the expert consulted by CADTH did not express concern regarding drug absorption, metabolism, or toxicity in patients younger than 18 years of age.

  The Health Canada indication further does not restrict by prior ART exposure, while the submitted model only permits exploration of the cost-effectiveness of DTG/3TC as first-line therapy. Based on the CADTH clinical review, the GEMINI trials assessed DTG + 3TC in ART-naive adult patients with HIV-1 infection and screening HIV-1 ribonucleic acid of 1,000 copies/mL to 500,000 copies/mL or fewer. An additional trial, ASPIRE, was identified that assessed the impact of switching to DTG + 3TC in ART-experienced,

virologically suppressed patients, although findings from this study were not used to inform the economic model. Although the study concluded that DTG + 3TC was noninferior to DTG + TDF/FTC, the CADTH clinical review noted that an outdated noninferiority margin was used, leading to uncertainty with these results. Feedback from the clinical expert consulted by CADTH suggested that there would not be many treatment-naive patients initiating treatment in Canada, and that the potential role for DTG/3TC for the vast majority of patients would be for those adequately controlled on a recommended first-line regimen and seeking to switch to DTG/3TC due to patient preference. Given that DTG/3TC is a two-drug regimen and the pill size may be smaller than other STRs, patients and clinicians may prefer to switch to this treatment if its efficacy is similar to other three- and four-drug regimens. No information was presented to assess the cost-effectiveness of patients switching from a current regimen to DTG/3TC. The clinical effectiveness and cost-effectiveness of DTG/3TC in treatment-experienced patients remains unknown, though the clinical expert consulted by CADTH indicated that the data in treatment-naive patients for DTG/3TC were likely generalizable to treatment-experienced patients.

CADTH Common Drug Review Reanalyses

CADTH undertook a reanalysis that addressed the limitations with the model by doing the following:

1. reducing the time period for observation for virologic suppression from 12 months to three months
2. assuming no treatment differences in long-term toxicities related to CVD, and reducing the waning period for treatment impact on biomarkers to 2.5 years (range used: two to three years) for bone mineral density and six months (range used: six to 12 months) for estimated glomerular filtration rate.

Additionally, CADTH removed the 6% to 8% mark-up and dispensing fees associated with prescription medications. The results (presented in Table 3) remained similar to those reported in the manufacturer's base case, with DTG/3TC dominating all comparators assessed (DTG/3TC was the least costly and most effective intervention).

Table 3: Summary of Results of the CADTH Base Case

		Therapy	Cost ($)	QALYs	Life-Years	ICUR (Incremental Cost/ QALY Gained)
	Manufacturer base case	DTG/3TC	852,023	24.910	28.648	Reference
		DTG + TDF/FTC	874,859	24.748	28.671	Dominated by DTG/3TC
		BIC + TAF/FTC	883,584	24.875	28.589	Dominated by DTG/3TC
		DTG + ABC/3TC	895,832	24.892	28.609	Dominated by DTG/3TC
		EVG/c + TAF/FTC	903,446	24.860	28.570	Dominated by DTG/3TC
1.	Observation of virologic suppression at every 3 months	DTG/3TC	926,721	24.166	27.686	Reference
		DTG + TDF/FTC	951,845	24.019	27.714	Dominated by DTG/3TC
		BIC + TAF/FTC	949,110	24.118	27.610	Dominated by DTG/3TC
		DTG + ABC/3TC	954,871	24.132	27.636	Dominated by DTG/3TC
		EVG/c + TAF/FTC	960,610	24.096	27.589	Dominated by DTG/3TC
2.	No difference in CVD toxicity for TDF and	DTG/3TC	802,484	25.194	28.572	Reference
		DTG + TDF/FTC	805,990	25.101	28.540	Dominated by DTG/3TC

		Therapy	Cost ($)	QALYs	Life-Years	ICUR (Incremental Cost/ QALY Gained)
	reduction of the waning period for treatment effects on BMD and eGFR	BIC + TAF/FTC	839,286	25.112	28.466	Dominated by DTG/3TC
		DTG + ABC/3TC	851,545	25.126	28.483	Dominated by DTG/3TC
		EVG/c + TAF/FTC	859,092	25.092	28.442	Dominated by DTG/3TC
3.	Removal of mark-up or dispensing fees	DTG/3TC	833,887	25.029	28.681	Reference
		DTG + TDF/FTC	861,485	24.829	28.663	Dominated by DTG/3TC
		BIC + TAF/FTC	870,875	24.960	28.587	Dominated by DTG/3TC
		DTG + ABC/3TC	882,379	24.970	28.605	Dominated by DTG/3TC
		EVG/c + TAF/FTC	889,833	24.943	28.568	Dominated by DTG/3TC
	CADTH base case (1-3 combined)	DTG/3TC	882,221	24.297	27.631	Reference
		DTG + TDF/FTC	884,613	24.253	27.657	Dominated by DTG/3TC
		BIC + TAF/FTC	905,458	24.239	27.558	Dominated by DTG/3TC
		DTG + ABC/3TC	910,621	24.259	27.584	Dominated by DTG/3TC
		EVG/c + TAF/FTC	916,697	24.221	27.535	Dominated by DTG/3TC

3TC = lamivudine; ABC = abacavir; BIC = bictegravir; BMD = bone mineral density; CVD = cardiovascular disease; DTG = dolutegravir; eGFR = estimated glomerular filtration rate; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.

CADTH also undertook several scenario analyses to address the uncertainty around certain model parameters. These analyses included:

1. applying equal efficacy to all therapies within the model
2. using the prices of the individual components of DTG/ABC/3TC ($25.49) instead of its STR price ($43.20)
3. setting utilities to be identical across all CD4+ T-cell count health states
4. setting viral suppression assessment to every six months instead of three months.

Results of the scenario analyses are presented in Appendix 4, Table 12. The results remained robust across all scenario analyses, with DTG/3TC dominating all comparators, except for the scenario assessing the changing of the price of DTG/ABC/3TC to the price of the individual components. In this scenario, the expected treatment costs of DTG + ABC/3TC were reduced and it became the cheapest first-line ART strategy. The incremental cost-utility ratio for DTG/3TC compared with DTG + ABC/3TC was $78,576 per QALY gained.

Given that DTG/3TC dominated all comparators in both CADTH's and the manufacturer's base case, price reduction scenarios were not conducted.

Issues for Consideration

- The use of DTG/3TC is not currently recommended by Department of Health and Human Services guidelines as initial, first-line therapy in adult patients with HIV-1 infection, and the use of other two-drug regimens is only recommended in certain clinical situations.[8] The clinical expert consulted by CADTH noted that some clinicians have had concerns in the past with prescribing two-drug regimens due to lower efficacy.
- The manufacturer's cost-utility analysis is primarily based on publicly sourced list prices of relevant ART regimens; these list prices do not reflect confidential pricing negotiations such as any existing Product Listing Agreements. For example, price reductions were a

condition of reimbursement for recent ART reviews (e.g., BIC/FTC/TAF [Biktarvy], DTG/RPV [Juluca], and Doravirine/3TC/TDF [Delstrigo]).[24-26] CADTH is therefore unable to assess the impact of potentially lower prices for comparator ART regimens on the results of the current analysis owing to the confidential nature of negotiated pricing agreements.

- The clinical expert consulted by CADTH noted that much of the emphasis on ART is focused on improving patient compliance as best as possible given that patients may be taking these medications for more than 40 years. As a result, even incremental changes in pill size or pill number may be worth switching for, which is notable given that the pill size of DTG/3TC is smaller than its STR comparators.

Patient Input

Input for this review was received by one patient group, the Canadian Treatment Action Council. The feedback received from this group noted the impact of existing treatments in improving quality of life, as well as the ease of use of STRs. Patients noted that, while they may have relative stability on their current ART, some are willing to change to newer regimens that promise greater ease of use as long as viral suppression is maintained. Much of the input also related to societal factors (e.g., loss of productivity, caregiver burden) which could have been incorporated in a scenario analysis from the societal perspective, but was not presented by the manufacturer in its submission. Patients also noted the importance of tailoring treatment to individual needs, which is a sentiment echoed by the clinical expert consulted by CADTH. These elements were not addressed in the existing economic evaluation.

Conclusions

Based on the CADTH reanalysis, DTG/3TC resulted in lower costs and greater QALYs than its comparators, thus dominating all of the evaluated first-line ART regimens. These results are subject to uncertainty given that CADTH could not address limitations related to the model structure, the manufacturer's submitted NMA that informed comparative clinical effectiveness estimates, and the long-term durability of treatment response with DTG/3TC. The magnitude of the cost savings associated with DTG/3TC is unclear given the individualized nature of HIV treatment, particularly relating to the timing and reasons for treatment switching, as well as the limited data on the comparative clinical effectiveness of DTG/3TC with other three- and four-drug regimens.

The model results were primarily driven by drug acquisition costs. Although the current most commonly prescribed first-line regimens were considered in the model, not all ART regimens were considered (some of which have lower annual drug costs). Furthermore, in a scenario analysis where the price of the individual components of DTG/ABC/3TC was used (i.e., DTG + ABC/3TC), DTG/3TC was no longer dominant and the resulting incremental cost-utility ratio was $78,576 per QALY gained compared with DTG + ABC/3TC. It should be further noted that the STR of DTG/3TC at the submitted daily price of $30.44 is more costly (approximately $3.35 daily) than the sum of its individual components ($27.08: DTG, $19.83, and 3TC, $7.25, daily). This difference represents an additional cost of $101.90 monthly, or $1,223 annually, per person.

Appendix 1: Cost Comparison

The comparators presented in the following tables represent recommended antiretroviral regimens for initial therapy of individuals infected by HIV-1 by the US Department of Health and Human Services guidelines,[8] including Department of Health and Human Services–recommended initial regimens in certain clinical situations (updated October 2018). Costs of comparator products were sourced from the Ontario Drug Benefit Formulary (accessed May 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 4: CADTH Common Drug Review Cost Comparison Table of Department of Health and Human Services–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								
Dolutegravir/lamivudine (Dovato)	50 mg/300 mg	Tablet	30.4400[a,b]	1 tablet daily	30.44	1	1	11,110
DHHS-Recommended Initial Antiretroviral Regimens								
INSTI + 2 NRTIs								
Dolutegravir/abacavir/ lamivudine (Triumeq)	50 mg/600 mg/300 mg	Tablet	44.1827[c]	1 tablet daily	44.18	1	1	16,127
Dolutegravir (Tivicay) + emtricitabine/tenofovir disoproxil fumarate (Truvada)	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[d]	1 tablet daily	39.22	1	1	14,316
Raltegravir (Isentress) + emtricitabine/tenofovir disoproxil fumarate (Truvada)	400 mg 200 mg/300 mg	Tablet	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 mg/25 mg	Tablet	14.0301 26.1020[d]	400 mg twice daily 1 tablet daily	54.16	2	3	19,769

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 Regimens for Switch Therapy								
INSTI + NNRTI								
Dolutegravir/rilpivirine (Juluca)	50 mg/25 mg	Tablet	34.8677	1 tablet daily	34.87	1	1	12,727

DHHS = Department of Health and Human Services; INSTI = integrase strand transfer inhibitor; 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] Manufacturer-submitted price.

[b] CADTH noted that the price of the individual components (DTG + 3TC) was less than the price of the single-tablet regimen ($27.09). The annual cost of these two treatments used in combination is $9,889.

[c] CADTH noted that the price of the individual components (DTG + ABC/3TC) was less than the price of the single-tablet regimen ($25.83). The annual cost of these two treatments used in combination is $9,303.

[d] IQVIA Delta PA, wholesale acquisition price (accessed May 2019).

Table 5: CADTH Common Drug Review 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								
Boosted PI + 2 NRTIs								
Darunavir/cobicistat/emtricitabine/tenofovir alafenamide (Symtuza)	800 mg/150 mg/ 200 mg/10 mg	Tablet	52.2670[a]	1 tablet daily	52.27	1	1	19,077
Darunavir (Prezista) with ritonavir (Norvir) + emtricitabine/tenofovir disoproxil fumarate (Truvada)	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[a]	800 mg daily 100 mg daily 1 tablet daily	50.35	1	3	18,378
Darunavir/cobicistat (Prezcobix) + emtricitabine/tenofovir disoproxil fumarate (Truvada)	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[a]	1 tablet daily 1 tablet daily	50.53	1	2	18,444
Atazanavir (generics) with ritonavir (Norvir) + emtricitabine/tenofovir disoproxil fumarate (Truvada)	300mg 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[a]	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)	300 mg 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 (Truvada)	100 mg 200 mg/300 mg	Tablet	16.6500[a] 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[a] 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[a] 5.9875	1 tablet daily 1 tablet daily	22.64	1	2	8,263
Doravirine/lamivudine/ tenofovir disoproxil fumarate (Delstrigo)	100 mg/300 mg/300 mg	Tablet	28.7900[b]	One tablet daily	28.79	1	1	10,508

Drug/Comparator Regimen	Strength	Dosage Form	Price ($)	Recommended Use	Daily Cost ($)	Frequency of Use (per Day)	Number of Pills (per Day)	Annual Drug Cost ($)
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	3.8031 26.1020[c]	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
INSTI + 2 NRTIs								
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
Raltegravir (Isentress) + Abacavir/lamivudine (generics)	400 mg 600 mg/300 mg	Tablet	14.0301 5.9875	400 mg twice daily 1 tablet daily	34.04	2	3	12,427

DHHS = Department of Health and Human Services; INSTI = integrase strand transfer inhibitor; 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] Manufacturer-submitted price.[27]

[b] Manufacturer-submitted price.[24]

[c] IQVIA Delta PA, wholesale acquisition price (accessed May 2019).

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 the CADTH Common Drug Review

☐ 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	

CADTH

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

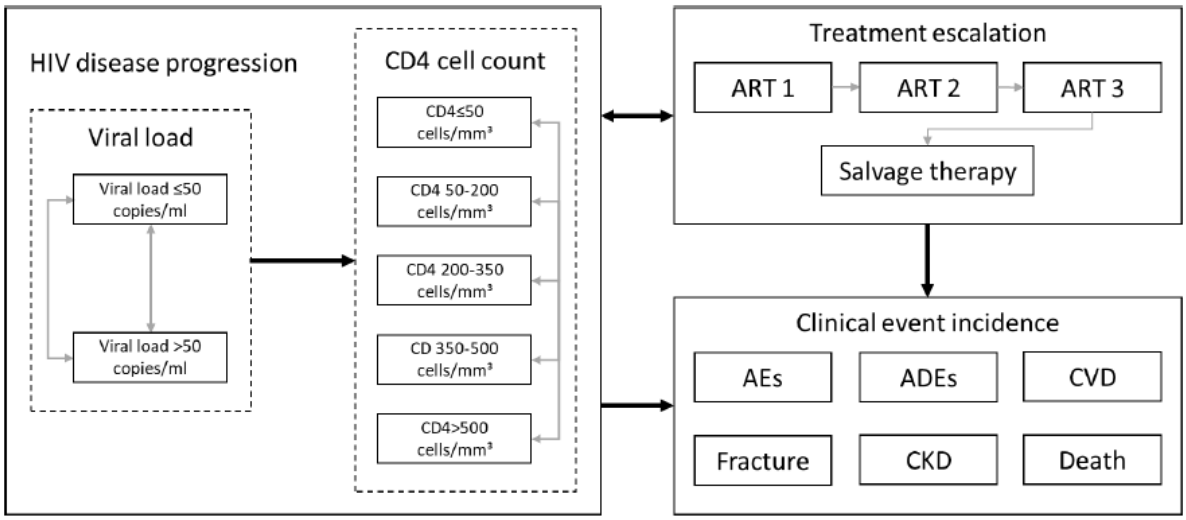
No other health technology assessment agencies have reviewed dolutegravir/lamivudine for the requested CADTH Common Drug Review indication.

Appendix 4: Reviewer Worksheets

Manufacturer's Model Structure

The manufacturer's model structure consisted of a hybrid Markov state transition model and decision tree process. Three antiretroviral therapy lines and an additional salvage therapy line were modelled to reflect the risk of treatment failure. Within each treatment line, several health states (Markov state transition model) were defined based on viral load and cluster of differentiation 4 positive (CD4+) T-cell count (see Figure 1). During each cycle (one month in length) a patient's viral status and CD4+ T-cell count could improve, decline, or remain constant. Within these health states, patients could experience clinical events (i.e., AIDS-defining events, chronic kidney disease, cardiovascular disease, fracture), or move to the absorbing death state.

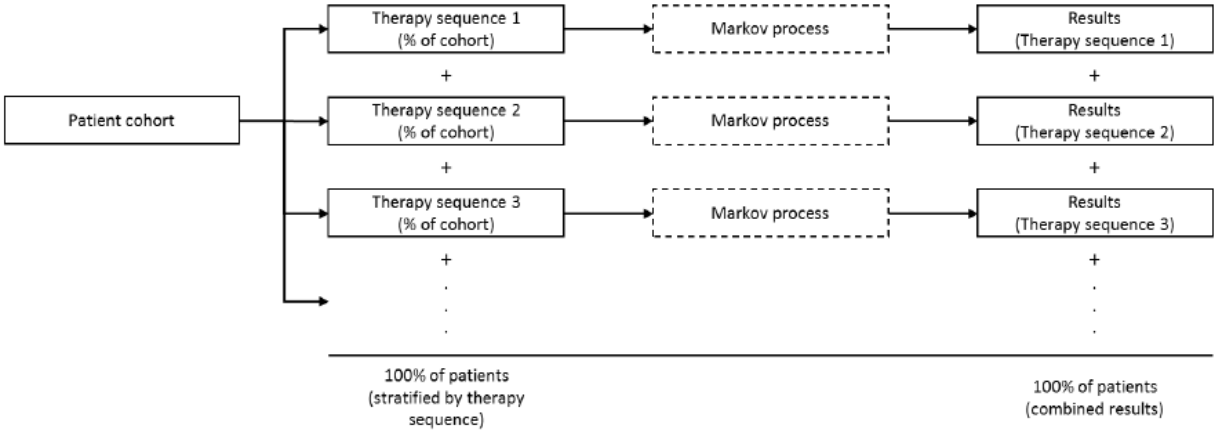
Figure 1: Model Schematic — Cohort-Level Markov State Transition Model



Source: Manufacturer's pharmacoeconomic submission.[1]

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

Figure 2: Model Schematic — Decision Tree



Source: Manufacturer's pharmacoeconomic submission.[1]

Table 8: Data Sources

Data Input	Description of Data Source	Comment
Baseline characteristics	Combination of the GEMINI trials,[3] published literature, and assumptions.[28]	Appropriate.
Efficacy and adverse events	Efficacy and safety of DTG/3TC were based on the GEMINI trials.[3] Comparative efficacy and safety parameters for the first line of therapy were obtained from a NMA.[9] Subsequent treatment line data were obtained from the published literature.[10,11,21-23]	As noted in the CADTH clinical review, the manufacturer-submitted NMA[9] identified no evidence for a difference in efficacy and safety between DTG + 3TC and the comparators included in the manufacturer's pharmacoeconomic submission. Additionally, the sparsity of the evidence networks and the noninferiority design of the primary RCTs precluded the establishment of precise estimates of differences between treatment regimens.
Natural history	Data for the following clinical events were included: • AIDS-defining event[29] • cardiovascular disease, based on lipid profiles[3] • fracture risk based on a risk equation from the literature[30] and BMD estimates from the literature[31] • renal function (based on estimated glomerular filtration rate).[3,32]	Separate profiles for biomarkers related to CVD, fractures, and CKD were applied for first-line drugs with TDF. The clinical expert consulted by CADTH indicated this was appropriate for fractures and CKD, but that there was no association between regimens with TDF and CVD. Additionally, the clinical expert noted the waning period for treatment impact on biomarkers related to fractures and CKD (nine years in length) were too long.
Utilities	Data for health state utility values observed from the GEMINI trials using the EQ-5D and reported by CD4+ T-cell count category.[3] The following disutilities were applied: • age-dependent decrement • cardiovascular disease[15] • fracture (type of fracture)[16,17] • chronic kidney disease (by stage) [18]	Health state utilities by CD4+ T-cell count may not appropriately capture disease progression and accompanying quality of life impact. This is supported by the fact that patients with a CD4+ T-cell count of 300 to 500 had a higher health state utility in the submitted model than patients with a CD4+ T-cell count greater than 500. This does not meet face validity when basing disease progression on CD4+ T-cell count.

Data Input	Description of Data Source	Comment
	• adverse events • AIDS-defining event.[19]	
Mortality	All-cause mortality obtained from Statistics Canada life tables for 2014 to 2016,[12] adjusted by the relative risk of mortality based on CD4+ T-cell count states,[13] CVD risk, and AIDS-defining event mortality.[14]	Appropriate.
Resource Use and Costs		
Drug	Cost of DTG/3TC from manufacturer,[2] cost of comparators from ODB formulary.[20]	The manufacturer included mark-up and dispensing fees. These are not considered as part of CADTH analyses and such costs were excluded from the CADTH base case and all scenario analyses.
Event	The following event costs were captured: • CVD (initial event and subsequent costs)[33] • fracture costs (by type of fracture)[17] • CKD costs (by CKD stage)[34] • end-of-life care in last three months • several different AIDS-defining events.[35]	Appropriate.
AEs	AE costs obtained from a combination of ODB e-formulary for medications, expert opinion, and published literature.[28,36]	Unclear from the manufacturer's report what these costs encompass. Unlikely to have a large impact on analysis results.
Health state	Disease management costs (e.g., outpatient care, opportunistic infection prophylaxis, non-HIV medication) by CD4+ T-cell count category obtained from published literature and ODB formulary.[20]	Appropriate.

3TC = lamivudine; AE = adverse event; BMD = bone mineral density; CD4+ = cluster of differentiation 4 positive; CKD = chronic kidney disease; CVD = cardiovascular disease; DTG = dolutegravir; EQ-5D = EuroQol 5-Dimensions questionnaire; NMA = network meta-analyses; ODB = Ontario Drug Benefit; RCT = randomized controlled trial; TDF = tenofovir disoproxil fumarate.

Table 9: Manufacturer's Key Assumptions

Assumption	Comment
DTG/3TC fixed-dose combination is bioequivalent to its individual components (i.e., DTG + 3TC).	Health Canada's product monograph noted higher rates of AUC_T for DTG and C_{max} for 3TC, although this was not expected to significantly affect patient safety or antiviral efficacy based on historical clinical efficacy and safety data.[2]
GEMINI trial data used for DTG + 3TC was applicable to entire indicated population.	Although clinical data for treatment-experienced patients switching to DTG + 3TC was available, this did not inform the economic model. The clinical expert consulted by CADTH noted that they believed the data from the GEMINI trials for the treatment-naive population is likely to be generalizable to treatment-experienced patients. Additionally, there is limited data on the clinical effects of treatment on a younger population as the GEMINI trials were conducted on adult patients aged 18 years or older (mean age approximately 32 years of age) whereas the Health Canada indication is for patients 12 years of age or older. However, the expert consulted by CADTH for this review did not express concern regarding drug absorption, metabolism, or toxicity in patients younger than 18 years of age.
Treatment progression is appropriately captured by CD4+ T-cell count categories.	Not appropriate. The clinical expert consulted by CADTH noted that CD4+ T-cell counts are far less important in clinical practice than a suppressed viral load, and that increases in CD4+ T-cells in practice are meaningless with regards to patient progression when assuming a suppressed viral load.
All first-line comparator regimens have a long-term toxicity profile similar to dolutegravir/lamivudine, except for DTG + TDF/FTC.	This assumption was appropriate for chronic kidney disease and fractures, but was not appropriate for cardiovascular disease. The clinical expert consulted by CADTH indicated there is no consistent evidence of an association between TDF-containing regimens and cardiovascular disease.
Treatment impact on long-term toxicity waned between five and 12 years.	Not appropriate for fractures and chronic kidney disease. The clinical expert consulted by CADTH noted the treatment impact on long-term toxicity waned at around 2.5 years and six months for these toxicities, respectively.
Patients discontinuing treatment due to virologic reasons have all developed treatment resistance. Resistance does not impact the selection of future regimens.	Not appropriate. The clinical expert consulted by CADTH indicated that the selection of subsequent treatment in clinical practice is dependent on resistance in order to identify the appropriate subsequent therapy.
Different treatment efficacy applies for patients who discontinue for virologic reasons.	Appropriate.
Two additional lines of therapy and a salvage line of therapy are representative of clinical practice.	Simplification but considered appropriate.
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 a patient's individual preferences. This would then impact overall treatment efficacy and associated costs.

3TC = lamivudine; AUC_T = area under the curve, time; CD4+ = cluster of differentiation 4 positive; C_{max} = maximum serum concentration; DTG = dolutegravir; FTC = emtricitabine; TDF = tenofovir disoproxil fumarate.

Manufacturer's Results

The total quality-adjusted life-years, life-years, and costs from the manufacturer's base-case analysis are presented in Table 10; disaggregated costs are presented in
3TC = lamivudine; ABC = abacavir; DTG = dolutegravir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; LY = life-year; QALY = quality-adjusted life-year; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.

Source: Manufacturer's pharmacoeconomic submission.[1]

Table 11.

Table 10: Manufacturer's Results — Outcomes

Outcomes	DTG/3TC	DTG + TDF/FTC	BIC + TAF/FTC	DTG + ABC/3TC	EVG/c + TAF/FTC
Total QALYs	24.910	24.748	24.875	24.892	24.860
Total LYs	28.648	28.671	28.589	28.609	28.570
Total costs	$852,023	$874,859	$883,584	$895,832	$903,446

3TC = lamivudine; ABC = abacavir; DTG = dolutegravir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; LY = life-year; QALY = quality-adjusted life-year; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.

Source: Manufacturer's pharmacoeconomic submission.[1]

Table 11: Manufacturer's Results — Disaggregated Costs

Disaggregate Costs	DTG/3TC	DTG + TDF/FTC	BIC + TAF/FTC	DTG + ABC/3TC	EVG/c + TAF/FTC
Health state costs	$83,670	$83,657	$83,551	$83,566	$83,536
First-line therapy costs	$109,234	$96,508	$129,770	$145,070	$147,744
Subsequent line costs	$92,884	$95,050	$94,736	$94,789	$94,646
Salvage therapy costs	$396,373	$394,462	$406,730	$403,186	$408,940
Adverse event	$217	$303	$186	$352	$196.82
AIDS-defining event	$631	$628	$630	$629	$631.95
Cardiovascular disease	$126,325	$139,032	$125,507	$125,716	$125,319
Renal impairment	$28,006	$50,391	$27,784	$27,838	$27,737
Fractures	$2,361	$2,516	$2,345	$2,349	$2,341
End-of-life costs	$12,336	$12,326	$12,359	$12,351	$12,365

3TC = lamivudine; ABC = abacavir; BIC = bictegravir; DTG = dolutegravir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.

Source: Manufacturer's pharmacoeconomic submission.[1]

The results of the manufacturer's sequential analysis of the base case are presented in Table 2.

CADTH Common Drug Review Reanalyses

CADTH undertook several scenario analyses to address the uncertainty around certain model parameters. These analyses included applying equal efficacy to all first-line therapies within the model, using the prices of the individual components of dolutegravir [DTG]/abacavir [ABC]/lamivudine [3TC] ($25.49) instead of its single-tablet regimen price ($43.20), setting utilities to be identical across all CD4+ T-cell count health states, and setting viral suppression assessment to every six months instead of three months. The results remained robust across all scenario analyses, with DTG/3TC dominating all comparators, except for

the scenario assessing the individual component price of DTG/ABC/3TC (see Table 12). In this scenario, the expected treatment costs of DTG + ABC/3TC were reduced and it became the cheapest first-line antiretroviral therapy strategy. The incremental cost-utility ratio for DTG/3TC compared with DTG + ABC/3TC was $78,576 per quality-adjusted life-year gained.

Table 12: CADTH Common Drug Review Scenario Analyses

	Therapy	Cost ($)	QALYs	Life-Years	ICUR (Incremental Cost/QALY gained)
Equal treatment efficacy	DTG/3TC	886,829	24.416	27.760	Reference
	DTG + TDF/FTC	890,257	24.355	27.766	Dominated by DTG/3TC
	BIC + TAF/FTC	903,798	24.416	27.760	Dominated by DTG/3TC
	DTG + ABC/3TC	911,494	24.416	27.760	Dominated by DTG/3TC
	EVG/c + TAF/FTC	915,247	24.416	27.760	Dominated by DTG/3TC
Price of individual components for DTG + ABC/3TC	DTG + ABC/3TC	873,126	24.265	27.586	Reference
	DTG/3TC	876,622	24.310	27.637	$78,575.66
	DTG + TDF/FTC	878,199	24.262	27.662	Dominated by DTG/3TC
	BIC + TAF/FTC	899,495	24.246	27.562	Dominated by DTG/3TC
	EVG/c + TAF/FTC	910,896	24.228	27.538	Dominated by DTG/3TC
Utilities identical across CD4+ T-cell count health states	DTG/3TC	882,542	22.604	27.652	Reference
	DTG + TDF/FTC	885,211	22.548	27.670	Dominated by DTG/3TC
	BIC + TAF/FTC	905,876	22.544	27.572	Dominated by DTG/3TC
	DTG + ABC/3TC	910,948	22.562	27.599	Dominated by DTG/3TC
	EVG/c + TAF/FTC	917,067	22.527	27.548	Dominated by DTG/3TC
Observation period for viral suppression at every 6 months	DTG/3TC	828,433	24.849	28.254	Reference
	DTG + TDF/FTC	829,745	24.788	28.261	Dominated by DTG/3TC
	BIC + TAF/FTC	860,119	24.778	28.162	Dominated by DTG/3TC
	DTG + ABC/3TC	868,936	24.800	28.187	Dominated by DTG/3TC
	EVG/c + TAF/FTC	876,423	24.759	28.137	Dominated by DTG/3TC

3TC = lamivudine; ABC = abacavir; BIC = bictegravir; CD4+ = cluster of differentiation 4 positive; DTG = dolutegravir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life year; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.

References

1. Pharmacoeconomic evaluation. In: CDR submission: Dovato (dolutegravir (DTG)/lamivudine (3TC)), 50 mg/300 mg, tablet [**CONFIDENTIAL** manufacturer's submission]. Laval (QC): ViiV Healthcare; 2019 Feb 21.
2. CDR submission: Dovato (dolutegravir (DTG)/lamivudine (3TC)), 50 mg/300 mg, tablet [**CONFIDENTIAL** manufacturer's submission]. Laval (QC): ViiV Healthcare; 2019 Feb 21.
3. Cahn P, Madero JS, Arribas JR, et al. Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naive adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, non-inferiority, phase 3 trials. *Lancet Infect Dis.* 2019;393(10167):143-155.
4. Govender S, Otwombe K, Essien T, et al. CD4 counts and viral loads of newly diagnosed HIV-infected individuals: implications for treatment as prevention. *PLoS One.* 2014;9(3):e90754.
5. Hughes MD, Johnson VA, Hirsch MS, et al. Monitoring plasma HIV-1 RNA levels in addition to CD4+ lymphocyte count improves assessment of antiretroviral therapeutic response. *Ann Intern Med.* 1997;126(12):929-938.
6. Kumar M, Kumar R, Mahdi AA, Dhole TN. Study of viral load and CD4 count in diagnosis of HIV-1 positive patients. *J Fam Med.* 2017;4(4):1117.
7. Mellors JW, Rinaldo CR Jr, Gupta P, White RM, Todd JA, Kingsley LA. Prognosis in HIV-1 infection predicted by the quantity of virus in plasma. *Science.* 1996;272(5265):1167-1170.
8. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. Rockville (MD): U.S Department of Health and Human Services; 2018 Oct 25: https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf. Accessed 2019 Jan 25.
9. Pharmacoeconomic evaluation. In: CDR submission: Onpattro (patisiran), solution for infusion 2 mg/mL [**CONFIDENTIAL** manufacturer's submission]. Amsterdam (NL): Alnylam Netherlands BV; 2019 Jan 24.
10. Cooper DA, Steigbigel RT, Gatell JM, et al. Subgroup and resistance analyses of raltegravir for resistant HIV-1 infection. *N Engl J Med.* 2008;359(4):355-365.
11. Steigbigel RT, Cooper DA, Kumar PN, et al. Raltegravir with optimized background therapy for resistant HIV-1 infection. *N Engl J Med.* 2008;359(4):339-354.
12. Statistics Canada. Life tables, Canada, provinces and territories, 1980/1982 to 2014/2016. 2018; https://www150.statcan.gc.ca/n1/pub/84-537-x/84-537-x2018002-eng.htm. Accessed 2019 May 13.
13. Lewden C, Morlat P, Raffi F, Dupon M, Dellamonica P, et al. HIV-infected adults with a CD4 cell count greater than 500 cells/mm3 on long-term combination antiretroviral therapy reach same mortality rates as the general population. *J Acquir Immune Defic Syndr Hum Retrovirol.* 2007;46(1):72-77.
14. Rydzak CE, Cotich KL, Sax PE, et al. Assessing the performance of a computer-based policy model of HIV and AIDS. *PLoS One.* 2010;5(9).
15. Ara R, Brazier J. Health related quality of life by age, gender and history of cardiovascular disease: results from the Health Survey for England. *(HEDS discussion paper 09/12)*. Sheffield (UK): ScHARR, The University of Sheffield; 2009: https://www.sheffield.ac.uk/polopoly_fs/1.292457!/file/9.12.pdf. Accessed 2019 May 13.
16. Szende A, Janssen B, Cabases J. Self-reported population health: an international perspective based on EQ-5D. Dordrecht (NL): Springer; 2014: https://www.ncbi.nlm.nih.gov/books/NBK500356/. Accessed 2019 May 14.
17. Nshimyumukiza L, Durand A, Gagnon M, et al. An economic evaluation: simulation of the cost-effectiveness and cost-utility of universal prevention strategies against osteoporosis-related fractures. *J Bone Miner Res.* 2013;28(2):383-394.
18. Gorodetskaya I, Zenios S, McCulloch CE, et al. Health-related quality of life and estimates of utility in chronic kidney disease. *Kidney Int.* 2005;68(6):2801-2808.
19. Paltiel AD, Scharfstein JA, Seage GR, 3rd, et al. A Monte Carlo simulation of advanced HIV disease: application to prevention of CMV infection. *Med Decis Making.* 1998;18(2 Suppl):S93-105.
20. Ontario Ministry of Health Long-Term Care. Ontario drug benefit formulary/comparative drug index. 2018; https://www.formulary.health.gov.on.ca/formulary/. Accessed 2018 Feb 15.
21. Antinori A, Lazzarin A, Uglietti A, Palma M, Mancusi D, Termini R. Efficacy and safety of boosted darunavir-based antiretroviral therapy in HIV-1-positive patients: results from a meta-analysis of clinical trials. *Sci Rep.* 2018;8(1):5288.
22. Baril JG, Angel JB, Gill MJ, et al. Dual therapy treatment strategies for the management of patients infected with HIV: a systematic review of current evidence in ARV-naive or ARV-experienced, virologically suppressed patients. *PLoS One.* 2016;11(2):e0148231.
23. Kanters S, Socias ME, Paton NI, et al. Comparative efficacy and safety of second-line antiretroviral therapy for treatment of HIV/AIDS: a systematic review and network meta-analysis. *Lancet HIV.* 2017;4(10):e433-e441.
24. CADTH Canadian Drug Expert Committee (CDEC) final recommendation: doravirine/lamivudine/tenofovir disoproxil fumarate (Delstrigo — Merck Canada Inc.). Ottawa (ON): CADTH; 2019 May 16: https://cadth.ca/sites/default/files/cdr/complete/SR0581%20Delstrigo%20-%20CDEC%20Final%20Recommendation%20May%2016%2C%202019%20for%20posting.pdf. Accessed 2019 May 22.

25. CADTH Canadian Drug Expert Committee (CDEC) final recommendation: bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy - Gilead Sciences Canada, Inc.). Ottawa (ON): CADTH; 2018 Oct 25: https://cadth.ca/sites/default/files/cdr/complete/SR0567%20Biktarvy%20-%20CDEC%20Final%20Recommendation%20October%2029%2C%202018.pdf. Accessed 2019 May 22.

26. CADTH Canadian Drug Expert Committee (CDEC) final recommendation: dolutegravir/rilpivirine (Juluca — ViiV Healthcare). Ottawa, ON: CADTH; 2018 Jun 20: https://cadth.ca/sites/default/files/cdr/complete/SR0551_cdr_complete_Juluca_June_22_18.pdf. Accessed 2019 May 22.

27. CADTH Canadian Drug Expert Committee (CDEC) final recommendation: doravirine (Pifeltro - Merck Canada Inc.). Ottawa (ON): CADTH; 2019 May 16: https://cadth.ca/sites/default/files/cdr/complete/SR0582%20Pifeltro%20-%20CDEC%20Final%20Recommendation%20May%2016%2C%202019%20for%20posting.pdf. Accessed 2019 May 22.

28. Despiegel N, Anger D, Martin M, et al. Cost-effectiveness of dolutegravir in HIV-1 treatment-naive and treatment-experienced patients in Canada. *Infect Dis Ther.* 2015;4(3):337-353.

29. d'Arminio Monforte A, Sabin CA, Phillips A, et al. The changing incidence of AIDS events in patients receiving highly active antiretroviral therapy. *Arch Intern Med.* 2005;165(4):416-423.

30. Kanis JA, Johnell O, Oden A, Dawson A, De Laet C, Jonsson B. Ten year probabilities of osteoporotic fractures according to BMD and diagnostic thresholds. *Osteoporos Int.* 2001;12(12):989-995.

31. Zhou W, Langsetmo L, Berger C, et al. Normative bone mineral density z-scores for Canadians aged 16 to 24 years: the Canadian Multicenter Osteoporosis Study. *J Clin Densitom.* 2010;13(3):267-276.

32. Gianotti N, Galli L, Poli A, et al. Estimated glomerular filtration rate trajectories in HIV-infected subjects treated with different ritonavir-boosted protease inhibitors and tenofovir disoproxil fumarate or abacavir. *Medicine (Baltimore).* 2016;95(22):e3780.

33. Akerborg O, Nilsson J, Bascle S, Lindgren P, Reynolds M. Cost-effectiveness of dronedarone in atrial fibrillation: results for Canada, Italy, Sweden, and Switzerland. *Clin Ther.* 2012;34(8):1788-1802.

34. Manns B, Hemmelgarn B, Tonelli M, et al. Population based screening for chronic kidney disease: cost effectiveness study. *BMJ.* 2010;341:c5869.

35. Anis AH, Guh D, Hogg RS, et al. The cost effectiveness of antiretroviral regimens for the treatment of HIV/AIDS. *PharmacoEcon.* 2000;18(4):393-404.

36. Vasiliadis HM, Dionne PA, Preville M, Gentil L, Berbiche D, Latimer E. The excess healthcare costs associated with depression and anxiety in elderly living in the community. *Am J Geriatr Psychiatry.* 2013;21(6):536-548.