Common Drug Review
Pharmacoeconomic Review Report

August 2014

Drug	dolutegravir (Tivicay)
Indication	Indicated for the treatment of HIV in both treatment-naive and treatment-experienced adults and children 12 years of age and older and weighing at least 40 kg, in combination with other antiretrovirals
Listing request	As per indication
Manufacturer	ViiV Healthcare ULC

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ABBREVIATIONS

AE	adverse event
ARAMIS	AntiRetroviral Analysis by Monte Carlo Individual Simulation
ART	antiretroviral therapy
ATZ	atazanavir
ATZ/r	atazanavir plus ritonavir
CD4+	helper-inducer T-lymphocyte surface antigen
CEA	cost-effectiveness analysis
CEPAC	Cost-Effectiveness of Preventing AIDS Complications
CI	confidence interval
CV	cardiovascular
CVD	cardiovascular disease
DB	double blind
DRV/r	darunavir plus ritonavir
DTG	dolutegravir
FTC	emtricitabine
HUI	Health Utilities Index
HRQOL	health-related quality of life
ICUR	incremental cost-utility ratio
INI	integrase inhibitor
NNRTI	non-nucleoside reverse transcriptase inhibitors
NRTI	nucleoside analogue reverse transcriptase inhibitor
LPV/r	lopinavir plus ritonavir
OI	opportunistic infection
OBT	optimized background therapy
OR	odds ratio
QALY	quality-adjusted life-year
RAL	raltegravir
RAMQ	Régie de l'assurance maladie du Québec
RCT	randomized controlled trial
SA	sensitivity analysis
TDF	tenofovir
TE	treatment-experienced
WDAE	withdrawal due to adverse event

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Dolutegravir (Tivicay)
Study question	• To determine the cost-effectiveness of DTG relative to Atripla, RAL, DRV/r, Complera, Stribild, ATZ/r, and LPV/r in treatment-naive patients. • To determine the cost-effectiveness of DTG relative to RAL in integrase inhibitor (INI) in treatment-experienced patients.
Type of economic Evaluation	Cost-effectiveness analysis and cost-utility analysis
Target population	• Treatment-naive and treatment-experienced adults and children 12 years of age and older and weighing at least 40 kg • No information was provided for INI-resistant patients
Treatment	• TN analysis: DTG 50 mg once daily • TE analysis: DTG 50 mg once daily for INI-naive; 50 mg twice daily once INI resistant
Outcomes	• QALYs • Life-years
Comparators	• TN analysis (head-to-head trials): Atripla, RAL + 2 NRTIs, DRV/r + 2 NRTIs (NMA); Complera, Stribild, ATZ/r + 2 NRTIs, LPV/r + 2 NRTIs • Treatment-experienced: RAL. The optimized background therapy (OBT) was assumed to be composed of DRV/r and TDF based on the most frequent OBT reported in the SAILING trial.
Perspective	Canadian ministry of health
Time horizon	Lifetime
Manufacturer's results (base case)	DTG is the dominant strategy in both TN and TE patients.
Key limitations and CDR estimate(s)	• DTG is priced at $18.50 per 50 mg tablet. • The model is informed by surrogate outcomes; however, these are well-accepted, and relative efficacy is informed by RCTs or appropriately conducted NMA. • Only small differences in QALYs occur and there is uncertainty regarding true differences; however, DTG would remain dominant given lower net costs. CDR analysis, where viral suppression at 48 weeks was assumed equivalent, did not alter conclusions. • The primary driver of costs is ART costs. In addition to the cost of first-line therapy, ART cost savings also occur, as DTG is expected to lead to fewer treatment failures (and less need for more expensive second-line through sixth-line treatment). While the clinical expert indicated this is a plausible assumption given known relative efficacy, if it does not transpire these cost savings may not be realized. • If only ART costs of first-line therapy are considered, DTG is less costly than five to seven of the eight comparators considered, depending on NRTI backbone used.

ART = antiretroviral therapy; ATZ/r = atazanavir/ritonavir; CDR = CADTH Common Drug Review; DRV/r = darunavir/ritonavir; DTG = dolutegravir; ICER = incremental cost-effectiveness ratio; INI = integrase inhibitor; LPV/r = lopinavir/ritonavir; OBT = optimized background therapy; QALY = quality-adjusted life-year; NRTI = nucleoside analogue reverse transcriptase inhibitor; RAL = raltegravir; RCT = randomized controlled trial; NMA = network meta-analysis; TDF = tenofovir; TE = treatment-experienced; TN = treatment-naive.

EXECUTIVE SUMMARY OF THE PHARMACOECONOMIC SUBMISSION

Background

Dolutegravir (Tivicay) (DTG) is being reviewed as a treatment of HIV in both treatment-naive and treatment-experienced adults and children 12 years of age and older and weighing at least 40 kg, in combination with other antiretrovirals. The recommended oral dose of DTG is 50 mg daily at a daily cost of $18.50.[1]

Summary of Economic Analysis

Treatment-Naive

The manufacturer conducted a cost-utility analysis comparing DTG with commonly used regimens (Atripla, raltegravir [RAL], darunavir plus ritonavir [DRV/r], and atazanavir plus ritonavir [ATZ/r]) or alternative regimens (Complera, Stribild, lopinavir plus ritonavir [LPV/r]).[2] The comparators for the evaluation of DTG with efficacy derived from head-to-head trials are: Atripla (SINGLE study), RAL (SPRING-2), and DRV/r (FLAMINGO). Both SINGLE and SPRING-2 were phase III, randomized, double-blinded studies, while FLAMINGO was a phase IIIb, randomized, open-label study. The comparators with efficacy and safety derived from the network meta-analysis (NMA) are: Complera, Stribild, ATZ/r, and LPV/r. Primary efficacy outcome was less than 50 copies/mL of HIV ribonucleic acid (RNA) at week 48. Viral suppression rate, monthly CD4+ cell count and monthly rate of viral rebound (late-failure rate) from the trial were also used to establish efficacy. The time horizon for the reference case was lifetime with monthly cycle, and used the Canadian public-payer perspective.

A micro-simulation approach was used in the economic model where patients passed through the model one at a time. This allowed individual histories of accumulating events to influence the probability of disease progression, including factors such as CD4+ cell count, viral load, opportunistic infections (OI) prophylaxis status, age, gender, and Framingham score. Simulated patients transition through mutually exclusive health states defined in terms of HIV (with or without [OIs]), combined with cardiovascular disease (CVD) health state. As patients pass through the model, they experienced the natural progression of HIV infection. Up to six successive antiretroviral therapies (ARTs) were followed in the model and these depended on treatment history and resistance status. The rates of adverse events (AE) were derived from the SINGLE, SPRING-2, and FLAMINGO trials.[3-5] Patients could switch treatment after an acute AE, or when a treatment was failing. The development of resistance following virologic failure after initial treatment was also derived from SINGLE, SPRING-2, and FLAMINGO trials.

HIV utilities were derived from a Canadian study that examined the relationship between HUI3-derived health preference score and HIV health status measured by CD4+ cell count.[6] Utility decrements associated with the CVD were derived from a US study.[7] The costs for ART and OI prophylaxis treatment were obtained from the RAMQ List of Medications. Health care resource utilization costs (costs of HIV, OI, CVD, and death) were based on Canadian studies.[8-11]

Treatment-Experienced

The manufacturer conducted a cost-utility analysis comparing DTG relative to RAL with optimized background therapy (OBT) in integrase inhibitor(INI)–naive TE patients.[2] Efficacy data were obtained from the SAILING clinical trial, which was a phase III, randomized, double-blinded, active-controlled, non-inferiority study.[12] DRV/r + tenofovir was assumed to be OBT based on the SAILING baseline population. Viral suppression rate, monthly CD4+ cell count, and monthly rate of viral rebound (late-failure rate) from

the trial were used to establish efficacy. The reference-case time horizon was lifetime with monthly cycle, and used the Canadian public-payer perspective.

The same micro-simulation approach was used in the economic model where patients passed through the model one at a time with individual characteristics and accumulating events, and same health states as the treatment-naive model. Up to four successive ART regimens were followed in the model and these depended on treatment history and INI-resistance status. Patients could switch treatment after an acute AE, or when a treatment was failing. AEs were considered only through treatment discontinuation due to AEs, as no difference was observed between RAL and DTG in the SAILING trial. The prevalence of resistance was based on data from the SAILING trial. NRTI and non-nucleoside reverse transcriptase inhibitors (NNRTI) plus NRTI resistance were considered at the beginning of the model, and the potential development of INI resistance was considered after failure on the first treatment.

HIV utilities were derived from the same Canadian study that examined the relationship between HUI3-derived health preference score and HIV health status measured by CD4+ cell count.[7] Utility decrements associated with CVD were derived from a US study.[13] The costs for ART and OI prophylaxis treatment were obtained from the RAMQ List of Medications. Health care resource utilization costs (costs of HIV, OI, CVD, and death) were based on Canadian studies.[8,14-16]

Results of Manufacturer's Analysis
Treatment-Naive
The manufacturer reported DTG being the dominant strategy (less cost and more effective) when compared with Atripla, RAL, DRV/r, and other indirect comparators (Complera, Stribild, ATZ/r, LPV/r).

Treatment-Experienced
The manufacturer reported DTG as the dominant strategy when compared with RAL.

Interpretations and Key Limitations
Use of Surrogate End Points
The model uses surrogate end points of viral suppression and CD4+ cell count to predict clinical outcomes, including OI, resistance, and mortality; however, these are well-accepted indicators of clinical outcomes and an accepted standard to adjudicate relative efficacy.

Magnitude of Benefit
The incremental QALYs with DTG compared with other relevant treatment strategies are small: an additional 15 to 48 days of perfect life for treatment-naive and an additional 81 days of perfect life for treatment-experienced; however, this does not alter conclusions, as DTG is less costly in most analyses.

Uncertainty in Relative Efficacy
While RCTs of some relevant comparators are available, the FLAMINGO trial is an open-label study, and there are no head-to-head trials for DTG versus Complera, Stribild, ATZ/r and LPV/r. An NMA was conducted in appropriate manner to estimate relative efficacy. In CDR reanalysis assuming no difference in viral suppression at 48 weeks between comparators did not alter overall conclusions. Even if no additional QALYs occur with DTG, it would still remain attractive given lower net costs.

Drug Cost
The cost of antiretroviral therapy is the key driver of costs (comprising approximately 87% of total costs). ART costs are lower for DTG, driven by either lower drug-acquisition costs of DTG (in some but

not all comparators), as well as lower likelihood of treatment failure or resistance (associated with use of second- through sixth-line therapies, which are more costly). The lower likelihood of progressing down the treatment algorithm has face validity (according to the clinical expert) based on clinical estimates of improved efficacy in most outcomes. DTG drug costs are greater compared with generic efavirenz (EFV) plus Truvada (instead of Atripla), leading to an ICUR of $44,604 for DTG; however, the clinical expert indicates that in the current era of therapy, the majority of patients would be receiving Atripla and not generic EFV + Truvada. If there is no difference in progression to second- through sixth-line therapies, DTG would remain less costly than five to seven of the eight comparators considered, depending on the NRTI backbone used.

Integrase Inhibitor–Resistant Patients

The recommended dose of DTG in patients who are INI resistant is 50 mg twice daily. No economic information was provided for this patient population.

Results of CDR Analysis

Treatment-Naive – Efficacy for Virologic Suppression

When equivalent virological suppression is assumed for DTG versus Complera, Stribild, ATZ/r, and LPV/r, DTG remains the dominant strategy (less costly and more effective).

Issues for Consideration

According to the clinical expert, the level of adherence is a major predictor of the effectiveness of treatment. As such, the once-daily DTG might have an advantage to improve adherence over other regimens with more frequent administration, which may have an impact on real-world effectiveness.

Conclusions

The manufacturer-submitted pharmacoeconomic model is based on well-established methods. While the model uses surrogate outcomes and links them to hard clinical outcomes, these surrogates are well-accepted markers of future clinical events and are used by prescribers to influence treatment decisions.

The manufacturer reports that DTG is dominant compared with commonly used comparators for both treatment-naive and treatment-experienced patients with HIV. Effectiveness estimates that are used to inform efficacy in the model include outcomes such as viral suppression at 48 weeks and are based on data from both randomized control trials as well as network meta-analyses. In general, DTG is more effective at viral suppression than many of the comparators, which leads to a very minor increase in incremental QALYs. Also, due to a reduced probability of requiring regimens further down the treatment algorithm (e.g., second- through sixth-line drugs which are more costly) due to treatment failure, net ART costs (the primary driver of costs in the model) are lower. Manufacturer-conducted sensitivity analysis and CDR reanalysis indicated the results were largely robust. When ART costs alone are considered, if more expensive drugs along the treatment algorithm are required, DTG remains less costly than most of the comparators considered (five or seven of the eight comparators, depending on the NRTI backbone used).

The economic attractiveness of DTG is driven by its pricing — it is priced lower than some (but not all) comparators, including the other INI (RAL) — and by its slightly greater effectiveness, which leads to reduced use of second- through sixth-line treatments (which are more costly), and very small differences in QALYs.

REVIEW OF THE PHARMACOECONOMIC SUBMISSION

1.   INTRODUCTION

1.1   Study Questions
"To determine the cost-effectiveness of dolutegravir (DTG) relative to Atripla/efavirenz (EFV), raltegravir (RAL), boosted darunavir (DRV/r), Complera/rilpivirine (RPV), Stribild/elvitegravir (EVG), boosted atazanavir (ATZ/r) and boosted lopinavir (LPV/r)."

(Manufacturer's submission: *Cost-Effectiveness Model for Dolutegravir (ARAMIS-DTG) in Treatment-Naive HIV Patients,* page 11.)

"To determine the cost-effectiveness of DTG relative to raltegravir (RAL) in integrase inhibitor (INI) naive TE patients."

(Manufacturer's submission: *Cost-Effectiveness Model for Dolutegravir (ARAMIS-DTG) in Treatment-Experienced HIV Patients,* page 9.)

1.2   Treatment
a)   Treatment-Naive
Treatment consisted of DTG (50 mg per day) plus NRTI backbone (according to RCT split: 60% Kivexa and 40% Truvada).

b)   Treatment-Experienced
Treatment consisted of DTG (50 mg per day) plus OBT (DRV/r + tenofovir [TDF]).

1.3   Comparators
a)   Treatment-Naive
Treatment consisted of Atripla, RAL plus 2 NRTIs, DRV/r plus 2 NRTIs, Complera, Stribild, ATZ/r plus 2 NRTIs, LPV/r + 2 NRTIs. The NRTI backbone (TDF plus emtricitabine [FTC] as part of the fixed-dose combination, or a blend of Truvada and Kivexa) differed according to the comparator but was considered to be equivalent in both treatment groups in the model in terms of both efficacy and safety.

b)   Treatment-Experienced
Treatment consisted of RAL (800 mg per day) plus OBT (DRV/r + TDF).

1.4   Type of Economic Evaluation
A cost-utility analysis was undertaken and is appropriate according to the CADTH guidelines. The perspective utilized in the two models is that of the Canadian public payer.

1.5   Population
a)   Treatment-Naive
Characteristics from patients in the DTG clinical trials (SPRING-2, SINGLE, and FLAMINGO) were used to inform transition probabilities for each simulated patient. Patients were assigned age, gender, CD4+ cell count, viral load, OI prophylaxis status, and Framingham score based on random probabilistic draws from the trial populations.

b) Treatment-Experienced

Characteristics from patients in the SAILING clinical trial were used to inform transition probabilities for each simulated patient. Patients were assigned age, gender, CD4+ cell count, viral load, OI prophylaxis status, Framingham score, and resistance status (NRTI resistance or NRTI + non-nucleoside reverse transcriptase inhibitors [NNRTI] resistance) based on random probabilistic draws from the baseline trial population.

2. METHODS

Models to assess treatment of HIV are mature. They are based on models developed independent of industry to inform reimbursement decisions and have been refined over time. The model used in this submission is based on well-accepted pharmacoeconomic models (Cost-Effectiveness of Preventing AIDS Complications [CEPAC]).

Please see Table 5 for a summary of the key limitations associated with the methodology used by the manufacturer.

2.1 Model Structure

a) Treatment-Naive

The cost-utility analysis was conducted using a micro-simulation model, where simulated patients pass through the model one at a time. This allows individual characteristics to be used, and the history of events can be incorporated and used to adjust the probability of disease progression (Figure 1). Patients may transition through 12 mutually exclusive Markov health states plus death: six HIV health states (one HIV health state without OIs and five with acute OI of varying types); two cardiovascular disease health states (with and without CVD); and death (Figure 2). The reference-case time horizon was lifetime with monthly cycle length and used the Canadian public-payer perspective. Individuals were assigned age, gender, CD4+ cell count, viral load, OI prophylaxis status, and Framingham score based on random probabilistic draws from the baseline characteristics of the population of the clinical trials at entry to the model. CD4+ cell count is adjusted for every model cycle using a tracker variable. The patient's CD4+ cell count impacts the transition to the HIV-related events, including OIs and mortality. Within each cycle, individuals are at risk of developing CVD based on a probability calculated using the Framingham equation, which is based on baseline characteristics as well as changes in lipid status (which may be influenced by treatment). The model allowed for treatment switches (Figure 3). Individuals could switch treatment after an acute AE, or when a treatment was failing. The model assumed a minimum time on treatment of three months, except in the case of late failures and when there was a switch due to an acute AE. Patients switching therapy were assumed to incur extra costs for an additional doctor visit.

The treatment for second and subsequent therapies was based on an algorithm developed by Canadian HIV clinicians for treatment pathways that would be used in Canada. Subsequent treatment choices were influenced by the reason for discontinuation (tolerability, resistance, specific resistance mutations).

FIGURE 1: THE INTERACTION BETWEEN TREATMENT, VIRAL LOAD AND CD4+ CELL COUNT
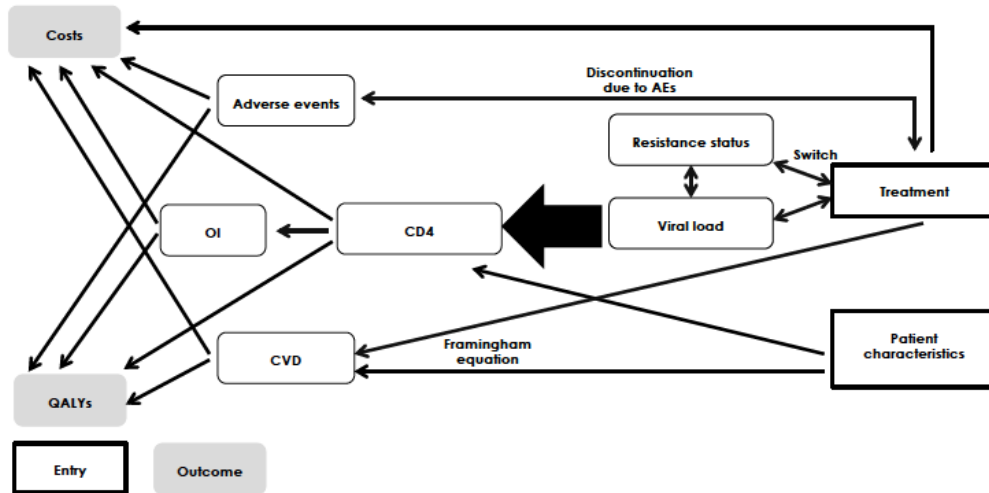
Source: Manufacturer's pharmacoeconomic submission.

FIGURE 2: MARKOV MODEL
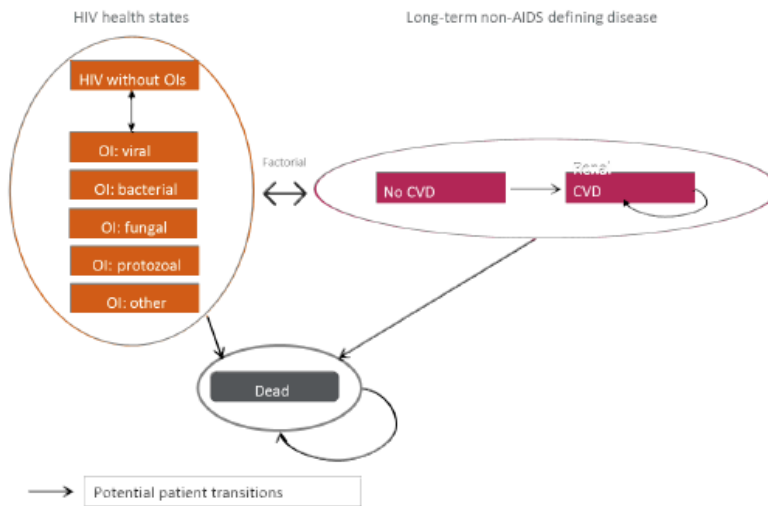
Source: Manufacturer's pharmacoeconomic submission.

FIGURE 3: TREATMENT-SWITCHING RULES
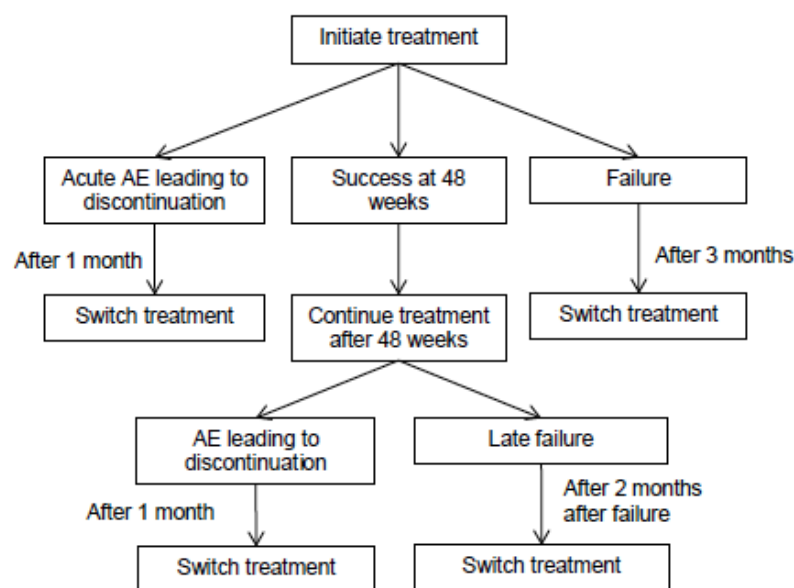
Source: Manufacturer's pharmacoeconomic submission.

b) Treatment-Experienced
The same model was also used for treatment-experienced patients.

2.2   Clinical Inputs
a) Efficacy
Treatment-Naive
Efficacy was defined using virological suppression at 48 weeks (from trials), CD4+ cell count (from trials and modelled), and late failure (modelled). The late-failure rate is treatment-specific and was estimated by examining viral load suppression by treatment at different times (48, 96, and 240 weeks). The sources of efficacy data comparing DTG to efavirenz (EFV) were the SINGLE trial[3] and the STARTMRK trials;[17] SPRING-2[4] and STARTMRK trials for DTG versus RAL, and FLAMINGO[5] and STARTMRK trials for DTG versus DRV/r. The efficacy for the other comparators was derived from the network meta-analysis (NMA). The development of resistance following virologic failure after initial treatment was derived from SINGLE, SPRING-2, and FLAMINGO clinical studies.

Treatment-Experienced
The sources of efficacy for first ART in the model for DTG and RAL were the SAILING[12] and BENCHMRK studies.[18] The rate of CD4+ cell count recovery was treatment-specific, while the late-failure rate was non–treatment-specific and was derived from BENCHMRK. The prevalence of resistance (NRTI resistance or NRTI plus NNRTI resistance) was based on data from the SAILING trial. The development of INI resistance following virologic failure was also derived from the SAILING trial. The development of resistance was not considered after failure of subsequent ARTs in the model.

b)   Harms
Treatment-Naive
Acute AEs (grade 2 to 4) led to a switch to the next treatment based on the discontinuation rate as reported in various clinical trials. The probabilities for DTG were derived from the SINGLE, SPRING-2, and FLAMINGO trials. Only AEs leading to discontinuation were considered in the model after first therapy.

Treatment-Experienced
AEs were considered only through discontinuation of treatment due to AEs, which led to a switch to the next treatment, as no difference was observed between RAL and DTG in SAILING regarding adverse events (AEs). Discontinuation rates due to AEs were based on clinical trials. The probabilities for DTG were derived from the SAILING trial.

c)   Disease Progression
Treatment-Naive
CD4+ cell count over time is dependent on treatment status. Successful treatment (based on virologic suppression) results in an increase in the CD4+ cell count over two years (based study data), although no increase is assumed to occur after five years (based on observational studies). If treatment fails, CD4+ count is assumed to be maintained as the patient changes therapy (first 12 months), and subsequent decline is dependent on the viral load with next-line therapy. The rate of decline is based on an equation derived from the Multicenter AIDS Cohort Study (MACS).[19] The risk of acute OIs is dependent on the disease history of the specific OI, the CD4+ cell count, and the time on and status of treatment based on the Antiretroviral Therapy Cohort Collaboration.[20] The risk of CVD was estimated from the Framingham equation for CHD supplemented with the Framingham equation for stroke. The equation was estimated every year, updating age and lipid parameters (from trials) during the first two years (Atripla and RAL) or the first year only (DVR/r). Beyond this period, the Framingham equation was updated to account for increasing age only.

Treatment-Experienced
Same methodology was used to calculate CD4+ decline rate and rate of acute OIs in the treatment-experienced patients. For the Framingham equation, age and lipid parameters (from SAILING) were updated during the first six months. Beyond this period, the equation was updated to account for increasing age only.

d)   Mortality
Treatment-Naive
Mortality was modelled using four main causes of death: 1) HIV; 2) acute OIs; 3) CVD; and 4) all-cause mortality (excluding HIV and CVD-related death). General HIV mortality and acute OI mortality rates were derived from MACS (1995) and corrected for highly active antiretroviral therapy exposure stratified by baseline CD4+ cell level.[21] The standard mortality ratio (SMR) was derived using the British Columbia Centre for Excellence in HIV/AIDS (BC-CfE) study. Baseline mortality and CVD mortality were obtained from Statistics Canada.

Treatment-Experienced
Same mortality rates were used in the treatment-experienced model.

e)   Quality of Life
Treatment-Naive
Although EQ-5D (EuroQol 5-dimensions questionnaire) scores were an outcome in the clinical trials, HIV utilities were derived from a Canadian study examining the relationship between HUI3-derived health

preference score and CD4+ cell count.[6] Utility decrements associated with CVD were derived from a US study.[7] Utilities associated with OIs or AEs were not considered in the base-case analysis but were included in the sensitivity analysis.

Treatment-Experienced
The same utilities mentioned earlier were also applied in the treatment-experienced model.

More details on how the utility scores were assigned are listed in the next section.

f) Costs
Resource use was considered from the perspective of the public payer.

g) Drug Costs
Treatment-Naive
The cost of DTG ($18.50 per tablet) was obtained from the manufacturer. The costs for ART were obtained from the RAMQ List of Medications. Each first regimen used a blended backbone (60% Kivexa and 40% Truvada) based on the clinical trials for DTG. The cost for salvage therapy was defined based on data from IMS Brogan ██████.

Treatment-Experienced
The costs for ART were obtained from the RAMQ List of Medications. The cost for salvage therapy was defined based on data from IMS Brogan ██████.

h) Event Treatment Costs
Treatment-Naive
Costs associated with HIV were obtained from Canadian sources. Outpatient care costs (HIV clinic visit, HIV-related specialist visits, non-HIV physicians, lab tests) were obtained from a Canadian study using a Southern Alberta cohort.[8] Costs for OI (in-patient only) were derived from a cost-effectiveness study in BC.[9] The cost of death was calculated from a study in Alberta.[10] The costs for OI prophylaxis treatment (trimethoprim-sulfamethoxazole and azithromycin) were sourced from the Ontario Drug Benefit Formulary. The costs of acute AEs were determined based on medication costs, physician visits, and model assumptions were based on current Canadian sources. Costs of CVD were derived from a study on Canadian outpatients with coronary heart disease, cerebrovascular disease, or peripheral artery disease.[11]

Treatment-Experienced
The event treatment costs used in the treatment-experienced model were the same as that used in the treatment-naive model, except for the costs of acute AE, as no difference was observed between RAL and DTG in the clinical trial.

i) Utilities
Treatment-Naive
HIV utilities were derived from the Isogai et al. study. In that study, a regression model that included CD4+ cell count (plus squared term), age (plus squared term), and sex, was used to calculate utility for each simulated patient.[6] Utility decrements associated with CVD (0.0977) were derived from the Franks et al. study.[7]

Treatment-Experienced
The same utility allocation was used for treatment-experienced patients.

j) Time Horizon
Both models used lifetime time horizon and was appropriate according to the CADTH guideline.

k) Discounting
Costs and consequences occurring after 12 months were discounted at an annual rate of 5%, as per CADTH guidelines. The results were presented in 2013 Canadian dollars.

l) Validation
Formal information on model validation was not provided in the submission; however, the current model was based on previous models on HIV drugs (ARAMIS model, based on the original CEPAC model) which have been validated, and discussion on comparison of overall life expectancy and incremental QALYs with external estimates was provided.

3. RESULTS

3.1 Manufacturer's Base Case

a) Treatment-Naive
In the reference case, the manufacturer reported the total cost for DTG was $315,086, a cost saving of $7,753 compared with Atripla. Treatment with DTG resulted in 10.62 total QALYs, an additional 0.132 QALY compared with Atripla. Hence, DTG was the dominant strategy. DTG was also the dominant strategy when compared with RAL, DRV/r, Complera, Stribild, ATZ/r, and LPV/r in the manufacturer's base case. Details on the costs and QALYs are listed in Table 2.

The incremental QALYs with DTG range from 0.041 to 0.132 over a lifetime horizon (or an additional 15 to 48 days of life with perfect health). The bulk of costs (87%) are from ART treatment. In all base-case scenarios, ART costs are lower for DTG, which is influenced by drug-acquisition cost (in analyses where comparators have greater drug-acquisition costs), as well as a lower likelihood of progressing to second-, third-, and fourth- to sixth-line therapy (greater drug costs occur with moving down to subsequent treatments regimens).

b) Treatment-Experienced
In the reference case, the manufacturer reported that the total cost for DTG was $353,957, a cost saving of $3,745 compared with RAL. Treatment with DTG resulted in 8.255 total QALYs, an additional 0.222 QALY (81 additional days of life with perfect health) compared with RAL. Hence, DTG was the dominant strategy.

The bulk of costs (87%) are from ART treatment driven primarily by lower drug-acquisition costs for DTG versus RAL.

TABLE 2: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASE

	Total Costs ($)	Incremental Cost of DTG ($)	Total QALYs	Incremental QALYs of DTG	Incremental Cost per QALY
Treatment-Naive					
DTG	315,086	−7,735	10.620	0.132	Dominant
Atripla	322,821		10.487		
DTG	312,943	−28,572	10.593	0.041	Dominant
RAL	341,516		10.552		
DTG	312,128	−19,093	10.607	0.070	Dominant
DRV/r	331,221		10.537		
DTG	315,086	−2,688	10.620	0.126	Dominant
Complera	317,774		10.494		
DTG	312,943	−11,084	10.593	0.074	Dominant
Stribild	324,027		10.519		
DTG	312,128	−22,175	10.607	0.098	Dominant
ATZ/r	334,303		10.510		
DTG	312,128	−18,895	10.607	0.118	Dominant
LPV/r	331,022		10.489		
Treatment-Experienced					
DTG	353,957	−3,745	8.255	0.222	Dominant
RAL	357,702		8.033		

ATZ/r = atazanavir/ritonavir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; LPV/r = lopinavir/ritonavir; RAL = raltegravir.
Source: Manufacturer's pharmacoeconomic submission.

3.2   Summary of the Manufacturer's Sensitivity Analyses

As the model was a complex micro-simulation model, and running time was high, no probabilistic sensitivity analyses were carried out. Uncertainty was addressed using one-way deterministic sensitivity analyses (which varied model parameters by using alternative values) and scenario analyses.

a)   One-way Sensitivity Analyses
Treatment-Naive
A series of one-way sensitivity analyses (95% confidence interval (CI) of the parameter, unless specified) were conducted by the manufacturer for DTG versus Atripla, RAL, and DRV/r where efficacy and safety data from head-to-head trials were available, including: difference in viral suppression at week 48; difference in late-failure rate between week 48 and week 96; cost of subsequent treatment (± 10%); and efficacy of subsequent treatment (± 5%).

The scenario analyses included: cost of EFV (generic versus Atripla); cost of RAL; cost of DTG plus backbone; cost of salvage (± 25%); the removal of treatment-specific effect on resistance; alternative sets of utilities (Kauf 2008); addition of disutilities due to AEs; addition of utilities related to OIs; discounting (0%, 3%); use of cohort based on an observational study in BC.

The reference-case result for DTG compared with Atripla, RAL, and DRV/r was DTG being the dominant strategy (less costly and more effective). None of the sensitivity analyses change this conclusion, except when the cost of generic EFV plus Truvada was used instead of Atripla, where the ICUR was $44,604 per QALY.

Treatment-Experienced

A series of one-way sensitivity analyses (95% CI of the parameter, unless specified) was conducted by the manufacturer including: difference in viral suppression at week 48; cost of subsequent treatment (± 10%); and efficacy of subsequent treatment (± 5%); cost of salvage (± 25%); drug-acquisition cost of RAL; removal of treatment-specific effect on resistance; alternative sets of utilities (Kauf 2008); addition of disutilities due to AEs; addition of utilities related to OIs; and discounting (0%, 3%).

The reference-case result for DTG compared with RAL found DTG to be the dominant strategy. The conclusion remained the same with all sensitivity analyses, except when a 0% discount rate was used. The ICUR was $11,787 per QALY.

b) Probabilistic Sensitivity Analysis

No probabilistic sensitivity analyses were carried out due to model complexity.

3.3 CADTH Common Drug Review Analyses

CDR has performed reanalyses based on different assumptions as listed subsequently. Due to model complexity, the CDR analysis used 10,000 simulations instead of the manufacturer's default setting of 500,000, and this might result variability.

The QALYs gained between strategies is small (the largest incremental QALY from DTG versus RAL in the treatment-naive analyses was less than two months of perfect health [0.132]). Because of this, and given the lower number of simulations and that small incremental QALYs may lead to instability in the ICURs, it may be more meaningful to focus on incremental costs and QALYs, rather than the ICURs.

a) Treatment-Naive

Efficacy of Virologic Suppression

Since there is no head-to-head trial comparing DTG to Complera, Stribild, ATZ/r, or LPV/r, an NMA was used to inform the efficacy parameters in the model. While the NMA was appropriately conducted, uncertainty remains regarding true relative efficacy. Since the 95% CI of the OR for virological suppression at 48 weeks for Stribild and Complera cross unity, the same virological suppression is assumed (with an increase in CD4+ cell count when successful). DTG remains the dominant strategy (less costly and more effective) when the same efficacy is assumed. As the 95% CI of OR for virological suppression at 48 weeks for RAL in the NMA also crossed unity (but did not in the head-to-head trial), an analysis assuming virological suppression equivalent to as RAL was conducted. In this case, DTG remained less costly (–$28,113) but also less effective (–0.018 QALY), resulting in an ICUR of $1,586,792 for RAL per QALY due to the small incremental QALY (versus DTG).

Cardiovascular Mortality

In the current era of treatment of HIV, incremental differences in CV mortality may be less important than in the past. An exploratory analysis was performed, where CV mortality was assumed to be zero for Atripla, RAL, and DRV/r was performed. DTG remained the dominant strategy (less costly and more effective) when CV mortality is set to zero.

Death Costs

The cost of death was calculated from a Canadian study that included mostly cancer patients, which might not necessarily reflect the cost for HIV patients.[10] When death costs are excluded for Atripla, RAL, and DRV/r, DTG remains the dominant strategy.

b) Treatment-Experienced
Cardiovascular Mortality
When CV mortality is assumed to be zero for RAL, DTG remains the dominant strategy (less costly and more effective) in treatment-experienced patients.

Death Costs
When death costs are excluded for RAL, DTG remains the dominant strategy.

TABLE 3: CDR REANALYSIS OF ICURS FOR DTG IN TREATMENT-NAIVE AND TREATMENT-EXPERIENCED PATIENTS

	Incremental Cost ($)	Incremental Effectiveness (QALY)	ICUR ($ per QALY) Based on Manufacturer's Analysis
Treatment-Naive (Based **on 10,000 Simulations Except Base Case**			
DTG vs. Atripla			
Manufacturer's base case	−7,735	0.132	Dominant
Base case 10,000	−8,827	0.110	Dominant
No CV mortality	−9,500	0.062	Dominant
No death costs	−8,752	0.110	Dominant
DTG vs. RAL			
Manufacturer's base case	−28,572	0.041	Dominant
Base case 10,000	−26,807	0.075	Dominant
No CV mortality	−27,868	0.053	Dominant
No death costs	−26,807	0.075	Dominant
Same efficacy	−28,113	−0.018	DTG less costly and less effective; the ICUR for RAL vs. DTG is $1,586,792
DTG vs. DRV/r			
Manufacturer's base case	−19,093	0.070	Dominant
Base case 10,000	−18,503	0.086	Dominant
No CV mortality	−17,283	0.111	Dominant
No death costs	−18,436	0.086	Dominant
DTG vs. Complera			
Manufacturer's base case	−2,688	0.126	Dominant
Base case 10,000	−6,629	0.068	Dominant
Same efficacy	−2,842	0.023	Dominant
DTG vs. Stribild			
Manufacturer's base case	−11,084	0.074	Dominant
Base case 10,000	−11,609	0.072	Dominant
Same efficacy	−6,239	0.119	Dominant
DTG vs. ATZ/r			
Manufacturer's base case	−22,175	0.098	Dominant
Base case 10,000	−22,360	0.107	Dominant
Same efficacy	−18,512	0.001	Dominant
DTG vs. LPV/r			
Manufacturer's base case	−18,895	0.118	Dominant
Base case 10,000	−20,078	0.104	Dominant
Same efficacy	−12,246	0.026	Dominant
Treatment-Experienced (Based **on 10,000 Simulations Except Base Case**			
DTG vs. RAL			
Manufacturer's base case	−3,745	0.222	Dominant
Base case 10,000	−6,889	0.137	Dominant

	Incremental Cost ($)	Incremental Effectiveness (QALY)	ICUR ($ per QALY) Based on Manufacturer's Analysis
No CV mortality	−2,992	0.230	Dominant
No death costs	−6,752	0.137	Dominant

ATZ/r = atazanavir/ritonavir; CV = cardiovascular; DRV/r = darunavir/ritonavir; DTG = dolutegravir; LPV/r = lopinavir/ritonavir; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; RAL = raltegravir.
Source: Manufacturer's pharmacoeconomic submission.

Drug-Acquisition Costs
ART costs are the primary driver of total costs, although ART costs are driven by both ART acquisition costs and the probability of moving from first-line to second- through sixth-line therapy (which are more costly). While efficacy estimates support the base-case assumption that DTG is likely to lead to a lower probability of requiring second- through sixth-line therapy, this is not definitively established. Further, the predicted incremental QALY differences are small. As such, it may be informative to simply examine drug-acquisition costs of first-line therapy.

Table 4 provides incremental daily and annual costs, including the range of costs depending on the NRTI backbone used (where appropriate, as some pills include triple therapy). Further information on ART costs is provided in APPENDIX 1: COST-COMPARISON TABLE FOR HIV.

TABLE 4: ART COSTS OF FIRST-LINE THERAPY

Treatment-Naive	Daily Cost With 100% Kivexa ($)	Daily Cost With 100% Truvada ($)	Incremental Daily Cost ($) DTG vs. Comparator	Incremental Annual Cost ($) DTG vs. Comparator
DTG	42.12	45.93	—	—
Atripla[a]	42.64	42.64	−0.52 to 3.29	−190 to 1,201
RAL	50.62	54.43	−8.50	−3,103
DRV/r (400 mg)	47.11	50.92	−4.99	−1,822
DRV/r (600 mg)	57.88	61.69	−15.76	−5,753
Complera[a]	41.65	41.65	0.47 to 4.28	172 to 1,562
Stribild[a]	45.52	45.52	−3.40 to 0.41	−1,241 to 150
ATZ/r	48.12	51.93	−6.00	−2,189
LPV/r	45.54	49.35	−3.42	−1,248

ATZ/r = atazanavir/ritonavir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; LPV/r = lopinavir/ritonavir; RAL = raltegravir.
[a] Does not require blended backbone.

Price-reduction scenarios were not performed, as DTG was the dominant strategy (less costly and more effective).

4.   DISCUSSION

The economic model that this submission uses is based on previous iterations of models that were originally developed by non-industry experts to inform reimbursement of treatment for HIV by publicly funded bodies. As such, this model is relatively robust with respect to incorporating health states and outcomes, and the transitions between them. As it is a first-order Monte Carlo simulation, accounts for a variety of inputs, and considers a large number of (appropriate) comparators, this does lead to considerable model complexity; however, no major oversights in model structure or function were identified.

The key efficacy outcomes used to inform the model, and subsequent clinical outcomes, are surrogates, including viral load at 48 weeks, CD4+ cell count, etc. While existing randomized trials comparing DTG with relevant comparators are not long or large enough to evaluate hard clinical outcomes, these surrogate markers are well-accepted, and correlate well with clinical outcomes.

The relative efficacy of DTG is informed by both randomized control trials as well as a NMA. Both direct and indirect comparisons suggest that DTG is at least as effective, or more effective, than many of the comparators. While this leads to slightly improved clinical outcomes and QALYs, another impact is the subsequent reduction in the need to move to second- through sixth-line therapy (fourth line for treatment-experienced patients), due to lower failure of treatment. As subsequent therapies further down the treatment algorithm are associated with greater costs, this also contributes to lower net costs for DTG. According to the clinical expert, given the relative efficacy estimates, the reduced need for more costly therapy is a very plausible scenario. However, if this does not occur, drug costs may be higher for some of the comparators. Table 1 suggests that DTG is less costly than many comparators, but may be more costly for some.

The CDR reanalysis assessed the relative efficacy of virological suppression at 48 weeks (as there may be uncertainty regarding how a NMA is conducted, and some of the estimates crossed unity). When this efficacy parameter was set to unity, this did not change the overall conclusions of the model. Further, for the most part, neither the additional sensitivity analysis conducted by the manufacturer nor the CDR reanalysis changed the overall conclusions.

It should be noted that some of the incremental QALYs in the CDR reanalysis could be interpreted as counterintuitive, but this is likely because incremental QALYs are quite small. When a first-order Monte Carlo simulation is used, there can be a large amount of variability in the outcomes, particularly when a small number of simulations are run (which was necessary in this case given the very long time it took the model to run). The CDR reanalyses used a much smaller number of simulations than those in the manufacturer's submission.

TABLE 5: KEY LIMITATIONS OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Parameter/Assumption	Issue	Impact
Surrogate end points (viral suppression, CD4+ count, resistance) predict clinical outcomes in HIV	Large trials over a long time period to detect clinical end points have not been conducted using comparators of interest.	Minimal. These surrogates are well-accepted predictors of clinical outcomes. SA exploring relative efficacy in end points does not change conclusions.
High degree of model complexity	Complex model integrating HIV treatment, multiple comparators, various subsequent treatment algorithms, and using first-order Monte Carlo simulation.	While complex, the model is based on well-accepted and mature models to assess the cost-effectiveness of treatment of HIV.

SA = sensitivity analysis.

Issues for Consideration

According to the clinical expert, the level of adherence is a major predictor of the effectiveness of treatment. As such, the once-daily DTG might have an advantage to improve adherence over other regimens with more frequent administration, which may have an impact on real-world effectiveness.

It is possible that a triple-therapy product that includes DTG will subsequently be brought to market. The incremental cost and cost-effectiveness may be altered if priced higher. The manufacturer states that, "The Patented Medicine Prices Review Board (PMPRB) mandates that combination product cannot cost more than the price of the individual components."

Because there is limited clinical information for patients aged 12 to 18 years, the results of the economic evaluation cannot be generalized to this population.

Patient Input

Viral suppression, quality of life, and reduced side effects are important outcomes to HIV patients that were included by the manufacturer in the economic submission.

5. CONCLUSIONS

The manufacturer-submitted pharmacoeconomic model is based on well-established methods. While the model uses surrogate outcomes and links them to hard clinical outcomes, these surrogates are well-accepted markers of future clinical events and are used by prescribers to influence treatment decisions.

The manufacturer reports that dolutegravir is dominant compared with commonly used comparators for both treatment-naive and treatment-experienced patients with HIV. Effectiveness estimates that are used to inform efficacy in the model include outcomes such as viral suppression at 48 weeks and are based on data from both randomized control trials as well as network meta-analyses. In general, dolutegravir is more effective at viral suppression than many of the comparators, which leads to a very minor increase in incremental QALYs. Also, due to a reduced probability of requiring regimens further down the treatment algorithm (e.g., second- through sixth-line drugs, which are more costly) due to treatment failure, net ART costs (the primary driver of costs in the model) are lower. The manufacturer-conducted sensitivity analysis and CDR reanalysis indicated the results were largely robust. When ART costs alone are considered, if more expensive drugs along the treatment algorithm are required, dolutegravir remains less costly than most of the comparators considered (five or seven of the eight comparators, depending on the NRTI backbone used).

The economic attractiveness of dolutegravir is driven by its pricing — it is priced lower than some (but not all) comparators, including the other INI (raltegravir) — and by its slightly greater effectiveness, which leads to reduced use of second through sixth-line treatments (which are more costly), and very small differences in QALYs.

APPENDIX 1: COST-COMPARISON TABLE FOR HIV

Clinical experts have deemed the comparators presented in Table 6 to be appropriate. These comparators may be recommended (appropriate) practice, versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified.

TABLE 6: COST-COMPARISON TABLE FOR HIV

Drug/Comparator	Strength	Dosage Form	Price ($)	Average Daily Use	Average Daily Cost ($)	Frequency Of Use (Per Day)	Number Of Pills (Per Day)
Integrase Inhibitors							
Dolutegravir (Tivicay)	**50 mg**	**Tab**	**18.5000[a]**	**50 mg daily (50 mg twice daily for integrase-inhibitor experienced)**	**18.50** **(37.00)**	**1** **(2)**	**1** **(2)**
Raltegravir (Isentress)	400 mg	Tab	13.5000	400 mg twice daily	27.00	2	2
Nucleoside Analogue Reverse Transcriptase Inhibitors (NRTIs)							
Abacavir sulphate (Ziagen)	300 mg	Tab	6.8693	300 mg twice daily or 600 mg daily	13.74	2	2
Abacavir/lamivudine (Kivexa)	600 mg/300 mg	Tab	23.6191	1 tablet daily	23.62	1	1
Abacavir/lamivudine/ zidovudine (Trizivir)	300 mg/150 mg/ 300 mg	Tab	17.9388	1 tablet twice daily	35.88	2	2
Cobicistat/elvitegravir/ emtricitabine/tenofovir (Stribild)	150 mg/150 mg/ 200 mg/300 mg	Tab	45.5200	1 tablet daily	45.52	1	1
Didanosine EC (Videx EC)	125 mg 200 mg 250 mg 400 mg	EC cap	3.7433 5.9897 7.4193 12.0027	400 mg daily 250 mg daily for patients less than 60 kg	12.00 7.42	1	1
Efavirenz/tenofovir/ emtricitabine (Atripla)	600 mg/300 mg/ 200 mg	Tab	42.6443	1 tablet daily	42.64	1	1
Emtricitabine/rilpivirine/ tenofovir (Complera)	200 mg/25 mg/ 300 mg	Tab	41.6500	1 tablet daily	41.65	1	1
Emtricitabine/tenofovir (Truvada)	200 mg/300 mg	Tab	27.4320	1 tablet daily	27.43	1	1
Lamivudine (generic)	150 mg 300 mg	Tab	3.6269 7.2538	300 mg daily	7.25	1	1
Lamivudine/zidovudine (generic)	150 mg/300 mg	Tab	2.6103	1 tablet twice daily	5.22	2	2
Stavudine (Zerit)	15 mg 20 mg 30 mg 40 mg	Cap	4.5637 4.7453 4.9498 5.1315	Under 60 kg: 30 mg twice daily 60 kg or more: 40 mg twice daily	4.95 5.13	2	2

Drug/Comparator	Strength	Dosage Form	Price ($)	Average Daily Use	Average Daily Cost ($)	Frequency Of Use (Per Day)	Number Of Pills (Per Day)
Tenofovir (Viread)	300 mg	Tab	18.3639	1 tablet daily	18.36	1	1
Zidovudine (generic)	100 mg	Cap	1.3977[b]	200 mg three times daily or 300 mg twice daily	8.39	2 or 3	6
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)							
Delavirdine mesylate (Rescriptor)	100 mg	Tab	0.7285	400 mg three times daily	8.61	3	12
Efavirenz (Sustiva, generics)	50 mg 200 mg 600 mg	Cap Cap Tab	1.2680 5.0708 8.4984	600 mg daily	8.4984	1	1
Etravirine (Intelence)	100 mg 200 mg	Tab	5.8055 11.3730	200 mg twice daily	22.75	2	2
Nevirapine (generic)	200 mg	Tab	1.2346	200 mg twice daily	2.47	2	2
Nevirapine ER (Viramune XR)	400 mg	ER tab	2.4692	400 mg daily	2.47	1	1
Rilpivirine (Edurant)	25 mg	Tab	14.4950	25 mg daily	14.50	1	1
Chemokine Receptor Type 5 (CCR5) Inhibitor							
Maraviroc (Celsentri)	150 mg 300 mg	Tab	16.5000[a]	300 mg twice daily	33.00	2	2
Fusion Inhibitor							
Enfuvirtide (Fuzeon)	108 mg	Vial	39.7600[b]	90 mg SC twice daily	79.52	2	2 inj
Protease Inhibitors							
Atazanavir (Reyataz) with or without ritonavir	150 mg 200 mg 300 mg	Cap	11.3542 11.4207 22.4330[b]	400 mg daily or 300 mg daily with 100 mg ritonavir	22.84 22.43 + 1.47 = 23.90	1 to 2	1 to 3
Darunavir (Prezista) with ritonavir	75 mg 150 mg 400 mg 600 mg 800 mg	Tab	1.8930 3.7860 10.8580 15.4390 21.7160	800 mg daily with 100 mg ritonavir 600 mg twice daily with 100 mg ritonavir twice daily	21.72 + 1.47 = 23.18 30.88 + 2.93 = 33.81		
Fosamprenavir (Telzir) with ritonavir	700 mg	Tab	8.2076	1,400 mg with 200 mg ritonavir in one or two doses	16.42 + 2.93 = 19.35	2	4
Indinavir (Crixivan)	200 mg 400 mg	Cap	1.3467 2.6933	800 mg every 8 hours	16.16	3	6
Lopinavir/ritonavir (Kaletra)	100/25 mg 200/50 mg	Tab	2.7598 5.5197	400/100 mg twice daily	10.77	2	4
Nelfinavir (Viracept)	250 mg 625 mg	Tab	1.8473 4.6183	1,250 mg twice daily or 750 mg three times daily	18.47 16.63	2 3	4 9
Ritonavir (Norvir)	100 mg	Cap	1.4671	600 mg twice daily	17.61	2	12
Saquinavir mesylate (Invirase) with	200 mg 500 mg	Cap Tab	1.8851 4.3503	1,000 mg twice daily with	17.40 + 2.93 = 20.33	2	6

Drug/Comparator	Strength	Dosage Form	Price ($)	Average Daily Use	Average Daily Cost ($)	Frequency Of Use (Per Day)	Number Of Pills (Per Day)
ritonavir				100 mg ritonavir twice daily			
Tipranavir (Aptivus) with ritonavir	250 mg	Cap	8.2500[b]	500 mg twice daily with 200 mg ritonavir twice daily	16.50 + 2.93 = 19.43	2	8

cap = capsule; EC = enterically coated; ER = extended release; inj = injection; SC = subcutaneous; tab = tablet.

All prices are from the Ontario Drug Benefit Formulary (March 2014) unless otherwise indicated.

[a] Manufacturer's submitted price.

[b] Saskatchewan Formulary (March 2014).

APPENDIX 2: ADDITIONAL INFORMATION

TABLE 7: 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 8: AUTHOR INFORMATION

Authors	Affiliations		
Nicolas Despiegel, Delphine Anger, Dan Paech	OptumInsight		
	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		

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