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CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

DOLUTEGRAVIR/RILPIVIRINE (JULUCA)

(ViiV Healthcare ULC)

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

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

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Abbreviations

ABC	abacavir
ADE	AIDS-defining event
ART	antiretroviral therapy
ARV	antiretroviral
cAR	current antiretroviral regimen
DTG	dolutegravir
FDC	fixed-dose combination
FTC	emtricitabine
RNA	ribonucleic acid
RPV	rilpivirine
TAF	tenofovir alafenamide
QALY	quality-adjusted life-year

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	DTG/RPV (Juluca) 50 mg/25 mg tablet
Study Question	What is the cost-effectiveness of DTG/RPV compared with other HIV-1 treatment regimens used in Canada in the treatment of adults with virologically suppressed HIV-1 infection (HIV-1 RNA < 50 copies per mL)?
Type of Economic Evaluation	Cost-utility analysis
Target Population	Adult patients with virologically suppressed HIV-1 infection (HIV-1 RNA < 50 copies/mL)
Treatment	DTG/RPV FDC 50 mg/25 mg tablet once daily
Outcome	QALY
Comparators	Current ARV regimen representing current care in Canada, including: • DRV/c + TAF/FTC (Prezcobix + Descovy) • DTG/ABC/3TC (Triumeq) • DTG + TAF/FTC (Tivicay + Descovy) • EVG/c/TAF/FTC (Genvoya) • RPV/TAF/FTC (Odefsey)
Perspective	Canadian public health care payer
Time Horizon	Lifetime (approximately 120 years)
Results for Base Case	• DTG/RPV was less costly (savings of at least $42,469) and less effective (loss of 0.089 QALYs) than all other ARV regimens, based on the manufacturer's probabilistic base case. • DTG/RPV is a cost-effective option unless a decision-maker is willing to pay at least $477,574 for a gain of one QALY. • At willingness-to-pay thresholds for a QALY gain equal to or greater than $477,574, RPV/TAF/FTC is the optimal therapy; all other ARV regimens were dominated (associated with greater total costs and no additional QALYs).
Key Limitations	• Modelling may not reflect individualized nature of HIV treatment and may overestimate cost savings associated with DTG/RPV • Lack of model transparency and flexibility
CDR Estimate(s)	• DTG/RPV is associated with lower total costs and fewer QALYs (loss in health outcomes) compared with other ARV regimens. • The magnitude of cost savings associated with DTG/RPV is unclear given the individualized nature of therapy (e.g., which patients might switch to DTG/RPV, and why and when patients might switch from DTG/RPV) which would affect the time on DTG/RPV and the potential cost savings associated with DTG/RPV. However, the potential saving comes at the expense of reduced population health (a loss of 0.09 QALYs). • The cost of the components of Juluca (DTG + RPV, $34.39 daily) is less than the unit cost of the DTG/RPV co-formulated FDC tablet ($34.87 daily).

3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; CDR = CADTH Common Drug Review; DTG = dolutegravir; DRV = darunavir; DRV/c = darunavir/cobicistat; EVG/c = elvitegravir/cobicistat; FDC = fixed-dose combination; FTC = emtricitabine; ICER = incremental cost-effectiveness ratio; RNA = ribonucleic acid; RPV = rilpivirine; TAF = tenofovir alafenamide; QALY = quality-adjusted life-year.

Drug	Dolutegravir/rilpivirine (Juluca)
Indication	As a complete regimen to replace the current antiretroviral regimen for the treatment of HIV-1 infection in adults who are virologically stable and suppressed (HIV-1 RNA less than 50 copies per mL)
Reimbursement Request	As per indication
Dosage Form(s)	Dolutegravir 50 mg/ rilpivirine 25 mg fixed-dose combination
NOC Date	May 18, 2018
Manufacturer	ViiV Healthcare ULC

Executive Summary

Background

Dolutegravir/rilpivirine (DTG/RPV) (Juluca) is an oral single-tablet regimen indicated for the treatment of HIV-1 infection in adults who are virologically suppressed (HIV ribonucleic acid [RNA] < 50 copies/mL).[1] It contains: dolutegravir, an integrase stand transfer inhibitor (INSTI); and rilpivirine, a non-nucleoside reverse transcriptase inhibitor (NNRTI). DTG/RPV is available as a fixed-dose combination (50 mg/25 mg) tablet and is taken once daily.[1] At the manufacturer-submitted unit price of $34.87 per tablet, the annual cost of treatment is approximately $12,728 per patient.[2] The manufacturer is seeking reimbursement in accordance with the Health Canada indication.

The manufacturer submitted a cost-utility analysis based on a hybrid decision tree Markov health state–transition model which estimated the incremental costs and health outcomes associated with DTG/RPV compared with currently available treatments in adults with virologically suppressed HIV-1 infection in Canada.[2] In the model, patients transitioned between a total of six therapy lines (three antiretroviral [ARV] therapy lines and three salvage therapies); within each therapy line, Markov health states defined according to HIV-1 viral load and CD4+ cell count predicted within-therapy line transitions. The analysis was run over a lifetime time horizon (up to 80 years from model initiation) using a monthly cycle length and it was based on the perspective of the Canadian public health care system.

The manufacturer reported that DTG/RPV was less costly and led to worse outcomes (loss of quality-adjusted life-years [QALYs]) over a lifetime time horizon when compared with other ARV regimens for the treatment of HIV-1 infection in virologically suppressed adults; DTG/RPV also resulted in lower overall survival compared with other ARV therapies in the manufacturer's base case. Based on a sequential analysis of the manufacturer's base case, DTG/RPV was considered to be a cost-effective option unless a decision-maker is willing to pay at least $477,574 for a gain in one QALY. At willingness-to-pay thresholds for a QALY gain greater or equal to $477,574, rilpivirine/tenofovir alafenamide/emtricitabine (RPV/TAF/FTC) is the optimal therapy. All other ARV treatment regimens were associated with greater total costs with no additional QALY gain.

Summary of Identified Limitations and Key Results

The manufacturer attempted to model multiple sequences of treatment over the lifetime of a patient. While this approach effectively considers the downstream treatment and health care costs of patients, there is significant uncertainty with respect to which patients might switch to DTG/RPV, why patients might switch from DTG/RPV and when, and subsequent treatment efficacy. Based on feedback from the clinical expert consulted for this review, the choice of therapy is based on individual criteria; as such, it is difficult to fully capture the reasons and timing of switching using a defined set of treatment algorithms. Given the individualized nature of HIV treatment, the manufacturer's model may not reflect how patients may be treated in actual practice. This is particularly problematic where modelling beyond the first line of therapy potentially overestimates the cost savings associated with DTG/RPV. The model was further complicated, given the manufacturer's desire to capture six lines of therapy; specifically, the model's functionality relied on the use of complex coding and a separate data repository file, which ultimately resulted in a lack of transparency and reduced model flexibility. It was therefore not possible to conduct reanalysis using the manufacturer's model.

Conclusions

DTG/RPV is associated with lower total costs and fewer total QALYs compared with other ARV regimens. Given the individualized nature of HIV treatment, particularly relating to the timing and reasons for treatment switching, savings relating to the use of DTG/RPV may have been overestimated by the manufacturer. The magnitude of cost savings associated with DTG/RPV is unclear and could not be verified by the CADTH Common Drug Review (CDR) owing to the complexity of the submitted model. Nonetheless, as reported by the manufacturer, potential cost savings come at the expense of reduced population health (a loss of 0.09 QALYs).

It should be noted that the unit cost of the DTG/RPV single-tablet regimen ($34.87 daily) is greater than the sum of its individual components (DTG plus RPV, $34.39 daily). Cost savings are therefore not realized by the use of the DTG/RPV co-formulated product when compared with the list price of its individual components (DTG plus RPV).

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted an economic model that captured health outcomes in terms of quality-adjusted life-years (QALYs) gained. The model compared the cost-effectiveness of dolutegravir/rilpivirine (DTG/RPV) with available current antiretroviral regimens (cAR) in the management of virologically suppressed HIV-1 infection; cAR comprised ARV regimens likely to occupy the greatest market share within Canada at the time of DTG/RPV listing and included: darunavir/cobicistat/tenofovir alafenamide/emtricitabine (DRV/c/TAF/FTC) (Prezcobix plus Descovy), dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) (Triumeq), dolutegravir/tenofovir alafenamide/emtricitabine (DTG/TAF/FTC) (Tivicay plus Descovy), elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine (EVG/c/TAF/FTC) (Genvoya), and rilpivirine/tenofovir alafenamide/emtricitabine (RPV/TAF/FTC) (Odefsey).[2] The target population was based on the population of patients within the SWORD-1 and SWORD-2 clinical trials, with an average age of 43 years; modelled patients were also assumed to be predominantly male (78%). The model was run using monthly cycles over a lifetime time horizon (up to 80 years from model initiation) in the base case. All costs and outcomes were discounted at an annual rate of 1.5% and the analysis was conducted from the perspective of the Canadian publicly funded health care system.

Model Structure

A hybrid decision tree Markov multi-state cohort model was developed in Microsoft Excel to simulate the course of HIV-1 infection in virologically suppressed adults living with HIV who received treatment with DTG/RPV and those receiving cAR therapies. The model was based on a maximum of six therapy lines, including an initial therapy line (antiretroviral therapy [ART] 1), two subsequent lines of therapy (ART 2 and ART 3), and up to three salvage treatments (Figure 1). Within each of the six modelled treatment lines, patients entered the Markov process (Figure 2) and transitioned through health states based on HIV-1 viral load (< 50 copies/mL, 50 copies/mL to 400 copies/mL, > 400 copies/mL) and CD4+ cell count (> 500 cells/mm^3, 350 cells/mm^3 to 500 cells/mm^3, 200 cells/mm^3 to 350 cells/mm^3, 50 cells/mm^3 to 200 cells/mm^3, < 50 cells/mm^3); death was included as an absorbing state. All patients entered the model with virologically suppressed disease in the maintenance treatment line (ART 1) and were assumed to receive treatment with DTG/RPV or any of the comparator regimens included in the model (cAR). During each monthly cycle, patients' viral status could improve, decline, or remain constant. Patients could transition from the initial maintenance therapy to a subsequent line of therapy (ART 2) based on treatment-specific discontinuation rate and associated reason for discontinuation (i.e., due to tolerability, virologic failure, or any other reason). Transition from the second therapy line to the subsequent line of therapy (ART 3) was assumed to occur due to virologic or any other reason for discontinuation; patients who discontinued therapy owing to tolerability reasons were assumed to follow the same treatment pathway as those who discontinued for any other reason. Modelled patients were assumed to transition to salvage therapy as a result of the development of resistance (i.e., discontinuation due to virologic reasons), with resistant patients receiving fewer lines of salvage therapy than non-resistant patients; patients receiving a third line of salvage therapy were assumed to have exhausted all available

treatment options and were therefore unable to discontinue treatment. At any point, patients could transition to death, as informed by general population mortality adjusted by the additional mortality risk in the HIV-1 population and the risk of experiencing an AIDS-defining event, with no direct treatment effect assumed.

Model Inputs

The movement of patients between different viral load and CD4+ cell count states within the model's Markov process was determined by transition matrices relating to each modelled line of therapy. Specifically, seven transition matrices were generated by adjusting published summary statistics of the change in CD4+ cell count (natural history) by monthly viral suppression probabilities, which were derived from 48-week suppression probability estimates sourced from the SWORD trials for the DTG/RPV and cAR efficacy profiles, or the published literature for all other efficacy profiles (i.e., treatment-experienced [TE]-stable switch, TE-failing switch, Salvage 1, Salvage 2, and Salvage 3 efficacy profiles).[2] The probability of mortality was based on adjusting all-cause mortality data for the Canadian general population[3] by the additional mortality risk in the HIV-1 population (stratified by CD4+ cell count) derived from a study by Lewden at al.[4] All-cause mortality rates were also adjusted for patients experiencing AIDS-defining events (ADEs) by applying ADE-specific mortality multipliers sourced from the Multicenter AIDS Cohort Study.[5] No added increase due to cardiovascular disease (CVD) was included in the model.

Health state utilities in the model were sourced from a study by Kauf et al. and applied in the model to each of the CD4+ cell count health states.[6] Disutility due to adverse events was also sourced from this study and applied to modelled patients upon occurrence for the duration of the cycle of incidence. A utility decrement associated with an initial CVD event and a chronic utility decrement applied to each cycle after the initial event was also included in the model; disutility due to CVD was sourced form an unpublished study by Ara and Brazier.[7] Disutility associated with ADEs was also applied upon occurrence in the cycle of incidence and derived from a study by Paltiel et al.[8]

Costs included were those for disease management (stratified by CD4+ cell count), drug-acquisition costs (excluding dispensing fees or mark-ups), as well as costs for the treatment of grade 3 or 4 adverse events, CVD, ADEs, and end-of-life care costs. All costs were reported in 2017 Canadian dollars.

Manufacturer's Base Case

The manufacturer reported that DTG/RPV was associated with a total cost of $510,614 and 15.392 QALYs over the model time horizon (Table 2). DTG/RPV was associated with lower total costs and worse outcomes (lower QALYs gained) when compared with other ARV regimens; treatment with DTG/RPV also resulted in lower overall survival compared with cAR therapies (incremental loss of approximately 0.12 life-years over a lifetime analytic horizon).

Based on a sequential incremental cost-utility ratio (ICUR) analysis of the manufacturer's base case, DTG/RPV is a cost-effective option unless a decision-maker is willing to pay at least $477,574 for a gain of one QALY; however, cost savings associated with DTG/RPV may be realized only at the expense of population health (a loss of 0.09 QALYs). If a decision-maker's willingness to pay for a QALY gain is equal to or greater than $477,574, RPV/TAF/FTC is the optimal therapy. All other treatment regimens are dominated based on the manufacturer's probabilistic base case.

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

	Total Costs ($)	Incr. Cost Vs. DTG/RPV ($)	Total LYs	Incr. LYs Vs. DTG/RPV	Total QALYs	Incr. QALYs Vs. DTG/RPV	ICUR ($/QALY) Vs. DTG/RPV	Sequential ICER ($/QALY)
Non-dominated options								
DTG/RPV	**510,614**	–	**21.145**	–	**15.392**	–	–	–
RPV/TAF/FTC	553,183	42,569	21.263	0.118	15.481	0.0891	477,574	477,574
Dominated options								
EVG/c/TAF/FTC	573,482	62,868	21.263	0.118	15.481	0.0891	705,307	Dominated by RPV/TAF/FTC
DTG/ABC/3TC	573,915	63,301	21.263	0.118	15.481	0.0891	710,165	Dominated by RPV/TAF/FTC
DTG/TAF/FTC	594,654	84,039	21.263	0.118	15.481	0.0891	942,828	Dominated by RPV/TAF/FTC
DRV/c/TAF/FTC	611,408	100,793	21.263	0.118	15.481	0.0891	1,130,788	Dominated by RPV/TAF/FTC

3TC = lamivudine; ABC = abacavir; DRV = darunavir; DVR/c = darunavir/cobicistat; DTG = dolutegravir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; Incr. = incremental; LY = life-year; QALY = quality-adjusted life-year; RPV = rilpivirine; TAF = tenofovir alafenamide; vs. = versus.

Note: All costs are presented in 2017 Canadian dollars.

Source: Adapted from the manufacturer's submission.[2] Total costs and QALYs are discounted probabilistic values.

Summary of Manufacturer's Sensitivity Analyses

The manufacturer conducted a range of probabilistic scenario analyses; these analyses considered alternative assumptions relating to time horizon (one year and 15 years), discount rate (0% and 3% per annum), cost of disease management for HIV-1 (outpatient care disease-management costs from Krentz and Gill[9]), rate of ADE (set to zero), mortality related to ADE (set to zero), HIV-1 mortality (set to zero), first modelled line efficacy (set efficacy equal for DTG/RPV and comparators in the model), and end-of-life costs (set to value from Fassbender et al.[10])

All analyses led to the same conclusion, with DTG/RPV being less costly and less effective than cAR therapies; where the efficacy of DTG/RPV and cAR in the first modelled line was assumed to be equal, DTG/RPV remained the least costly treatment option. The incremental cost per QALY gained for RPV/TAF/FTC (the next most costly treatment) compared with DTG/RPV ranged from $426,742 to $4,577,133 (Table 9).

Limitations of Manufacturer's Submission

The CADTH Common Drug Review (CDR) identified the following limitations with the manufacturer's submission:

DTG/RPV is more costly than the sum of its individual components: At the submitted daily price of $34.87 per tablet, DTG/RPV is more costly (approximately $0.48 more daily) than the sum of its individual components: DTG ($19.25 daily) and RPV ($15.14 daily). This difference represents an additional monthly cost of $14.70, or $176.51 annually, for the DTG/RPV co-formulated fixed-dose combination (FDC) product compared with the cost incurred by the sum of its individual components. Should the price of DTG or RPV be lower

in any jurisdiction than the list price sourced from the Ontario Drug Benefit Formulary used in this review — which does not account for existing Product Listing Agreements — the difference in cost between the co-formulated FDC product and its individual components may be even greater. Cost savings are therefore not realized by the use of the DTG/RPV single-tablet regimen when compared with the list price of its individual components.

Modelling structure may not accurately reflect the individualized nature of HIV-1 treatment: Treatment of HIV-1 infection in adult patients is complex and highly individualized; this is reflected by the updated US Department of Health and Human Services (DHHS) guidelines for the use of ARV drugs in adults and adolescents living with HIV[11] and emphasized by the clinical expert consulted by CADTH for this review. While the submitted model may be comprehensive in its attempt to characterize the disease course of virologically suppressed adults with HIV-1 infection through the use of a number of treatment algorithms, this model may not sufficiently capture the individualized nature of HIV therapy in this specialized population, particularly for efficacy profiles beyond the first line of therapy. Therefore, the value of assessing the cost-effectiveness of DTG/RPV beyond the first modelled line may be limited if the modelled treatment algorithms do no not accurately align with real-world clinical practice. More importantly, modelling beyond the first line of therapy in which DTG/RPV is used potentially overestimates the cost savings associated with this treatment.

Lack of transparency and flexibility relating to the manufacturer's model: The submitted model had several issues that made validation and evaluation challenging. In particular, the coding used in modelling and the reliance on a separate data repository Excel sheet to ensure the model's functionality resulted in longer than necessary model run time and led to decreased transparency. Thus, validation, as well as simple reanalyses adopting alternative assumptions (e.g., restricting analysis to first modelled line only), were challenging to conduct and verify. Given the complexity of the model, a breakdown of costs by different cost components (i.e., drug costs, cost of opportunistic infection prophylaxis, outpatient visit costs, etc.) — rather than costs stratified by CD4+ count states — would have made validation easier to conduct and improved the model's flexibility.

CADTH Common Drug Review Reanalyses

Based on the appraisal of the clinical data submitted by the manufacturer (see CDR Clinical Review), it was not possible to conclude whether noninferiority was demonstrated statistically in the SWORD clinical trials. This conclusion was made on the basis of the manufacturer's reliance on potentially outdated criteria for establishing noninferiority and the availability of updated guidance relating to the noninferiority margin in "switch" noninferiority trials. The manufacturer appropriately accounted for this in its economic model, accepting that DTG/RPV resulted in worse health outcomes (fewer life-years [LYs] and fewer QALYs gained) than the comparator ARV regimens. While the manufacturer's approach to modelling treatment efficacy is appropriate, it is complicated by the uncertainty in modelling multiple treatment algorithms that may not fully reflect the individualized nature of HIV treatment and treatment sequencing, which relies on the assumption that the development of treatment resistance (due to treatment failure) is based on the same efficacy profile for patients receiving second- or third-line therapies, irrespective of the treatment received in the first therapy line. Modelling the cost-effectiveness of DTG/RPV beyond the first treatment line has the potential to overestimate the cost saving associated with this treatment. Given the complexity of the submitted model and associated lack of transparency and flexibility, CDR was unable to verify the extent of cost savings that may be generated by

switching to DTG/RPV. Price-reduction analyses were not conducted, given that DTG/RPV was less costly and less effective (fewer QALYs) than other ARV regimens.

Issues for Consideration

- **Confidential pricing of comparator ARV regimens:** The manufacturer's cost-effectiveness analysis is based on publicly sourced list prices for relevant ARV regimens; these list prices do not reflect confidential pricing negotiations, such as any existing Product Listing Agreements. CDR is therefore unable to assess the impact of potentially lower prices for comparator ARV regimens on the results of the current analysis, owing to the confidential nature of negotiated pricing agreements.
- **Use of DTG/RPV as an initial therapy in HIV-infected adults:** The use of DTG/RPV as an initial, first-line therapy in adult patients with HIV-1 infection is not currently recommended by the DHHS guidelines for the use of ARV drugs in adults and adolescents living with HIV. This product is considered in terms of regimen switching and suggested as an option for the management of TE patients in the setting of virologic suppression. The potential for DTG/RPV to supplant the use of more commonly available three-drug single-tablet regimens is therefore unclear.

Patient Input

Patient input was received from the Canadian Treatment Action Council (CTAC), an organization whose aim is to address access to treatment, care, and support for people living with HIV and hepatitis C. Patients noted that a number of negative mental health outcomes are associated with their HIV diagnosis, particularly resulting from treatment-related side effects, coping with stigma, discrimination, and related stress. Patients also noted that their HIV treatment was effective at suppressing their viral load, and that ARV therapy generally led to improvement in their quality of life and ability to engage in daily activities. Viral load suppression and aspects of quality of life (through the use of progressively higher utility values with improved immunologic response, i.e., increased CD4+ cell count) were captured by the manufacturer in its model, and reflected the perspectives provided by the patient input submission (i.e., suppression of viral load with minimal side effects and quality-of-life improvement by all ARV treatments).

Based on the received input, HIV infection also exerts a significant impact on caregivers of patients living with HIV, particularly relating to challenges in providing support surrounding disclosure of HIV status and the ability to acquire a social safety net. Information relating to the potential impact of this condition on caregivers was not discussed as part of the manufacturer's submission.

Conclusions

The cost of the components of Juluca (DTG plus RPV, $34.39 daily) is less than the unit cost of the DTG/RPV co-formulated FDC tablet ($34.87); therefore, cost savings are not realized by the use of the co-formulated product compared with the individual components.

Based on the manufacturer's economic evaluation, DTG/RPV generates lower total costs, and fewer LYs and QALYs compared with other ARV regimens. However, savings associated with switching to DTG/RPV may have been overestimated, owing to issues relating to the structure of the manufacturer's model and the individualized nature of HIV

treatment (e.g., for whom switching is appropriate, and the time and reasons for switching). Given the lack of transparency and flexibility with the submitted model, CDR could not verify the extent of cost savings that may result from switching to DTG/RPV. However, based on the clinical data submitted by the manufacturer, the cost savings may be realized at the expense of population health (a loss of 0.09 QALYs).

Appendix 1: Cost Comparison

The comparators presented in Table 3 represent recommended antiretroviral regimens for initial therapy of HIV-1 infected individuals by the US Department of Health and Human Services (DHHS) guidelines, including DHHS-recommended initial regimens in certain clinical situations (updated October 2017).[11] Costs of comparator products were sourced from the Ontario Drug Benefit Formulary (accessed January 2018), 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 3: CDR Cost Comparison Table of Antiretroviral Drugs for Adults With HIV-1 Infection

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Use	Daily Cost ($)	Freq. of Use (per Day)	No. of Pills (per Day)	Annual Drug Cost ($)
Dolutegravir/rilpivirine (Juluca)[a]	**50/25 mg**	**Tablet**	**34.8700[b]**	**1 tablet daily**	**34.87**	**1**	**1**	**12,728**
DHHS-Recommended Initial Regimens for Most People With HIV								
INSTI + 2 NRTIs								
Dolutegravir/abacavir/ lamivudine (Triumeq)	50/600/300 mg	Tablet	43.2020	1 tablet daily	43.20	1	1	15,464
Dolutegravir (Tivicay) + Emtricitabine/tenofovir disoproxil fumarate (Truvada)	50 mg 200/300 mg	Tablet	19.2494 29.2140	50 mg daily 1 tablet daily	48.46	1	2	17,689
Dolutegravir (Tivicay) + Emtricitabine/tenofovir alafenamide (Descovy)	50 mg 200/25 mg	Tablet	19.2494 28.5700[c,d]	50 mg daily 1 tablet daily	47.82	1	2	14,454
Elvitegravir/cobicistat/ emtricitabine/tenofovir disoproxil fumarate (Stribild)	150/150/ 200/300 mg	Tablet	48.0177	1 tablet daily	48.01	1	1	17,526
Elvitegravir/cobicistat/ emtricitabine/tenofovir alafenamide (Genvoya)	150/150/200/ 10 mg	Tablet	46.3893 [c,d]	1 tablet daily	46.39	1	1	16,932
Raltegravir (Isentress) + Emtricitabine/tenofovir disoproxil fumarate (Truvada)	400 mg 200/300 mg	Tablet	14.0301 29.2140	400 mg twice daily 1 tablet daily	56.89	2	3	20,905
Raltegravir (Isentress) + Emtricitabine/tenofovir alafenamine (Descovy)	400 mg 200/25 mg	Tablet	14.0301 28.5700 [c,d]	400 mg twice daily 1 tablet daily	56.63	2	3	20,670

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Use	Daily Cost ($)	Freq. of Use (per Day)	No. of Pills (per Day)	Annual Drug Cost ($)
DHHS-Recommended Initial Regimens in Certain Clinical Situations								
Boosted PI + 2 NRTIs								
Darunavir (Prezista) with ritonavir (Norvir) + Emtricitabine/tenofovir disoproxil fumarate (Truvada)	800 mg 100 mg 200/300 mg	Tablet	22.1720 1.5183 29.2140	800 mg daily 100 mg daily 1 tablet daily	52.90	1	3	19,310
Darunavir (Prezista) with ritonavir (Norvir) + Emtricitabine/tenofovir alafenamide (Descovy)	800 mg 100 mg 200/10 mg	Tablet	22.1720 1.5487 28.5700[c,d]	800 mg daily 100 mg daily 1 tablet daily	52.29	1	3	19,086
Darunavir/cobicistat (Prezcobix) + Emtricitabine/tenofovir disoproxil fumarate (Truvada)	800/150 mg 200/300 mg	Tablet	23.8672 29.2140	1 tablet daily 1 tablet daily	53.08	1	2	19,375
Darunavir/cobicistat (Prezcobix) + Emtricitabine/tenofovir alafenamide (Descovy)	800/150 mg 200/10 mg	Tablet	23.8672 28.5710[c,d]	1 tablet daily 1 tablet daily	52.44	1	2	19,140
Atazanavir (Reyataz) with ritonavir (Norvir) + Emtricitabine/tenofovir disoproxil fumarate (Truvada)	300 mg 100 mg 200/300 mg	Cap	23.1034 1.5487 29.2140	300 mg daily 100 mg daily 1 tablet daily	53.87	1	3	19,661
Atazanavir (Reyataz) with ritonavir (Norvir) + Emtricitabine/tenofovir alafenamide (Descovy)	300 mg 100 mg 200/10 mg	Cap	23.1034[e] 1.5487 28.5700[c,d]	300 mg daily 100 mg daily 1 tablet daily	53.22	1	3	19,426
Darunavir/cobicistat (Prezcobix) + Abacavir/lamivudine (generics)	800/150 mg 600/300 mg	Tablet	23.8672 5.9875	1 tablet daily 1 tablet daily	29.86	1	2	10,897
Darunavir (Prezista) with ritonavir (Norvir) + Abacavir/lamivudine (generics)	800 mg 100 mg 600/300 mg	Tablet	22.1720 1.5487 5.9875	800 mg daily 100 mg daily 1 tablet daily	29.71	1	3	10,844
Atazanavir (Reyataz) with ritonavir (Norvir) + Abacavir/lamivudine (generics)	300 mg 100 mg 600/300 mg		23.1034[e] 1.5487 5.9875	300 mg daily 100 mg daily 1 tablet daily	30.64	1	3	11,183

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Use	Daily Cost ($)	Freq. of Use (per Day)	No. of Pills (per Day)	Annual Drug Cost ($)
NNRTI + 2 NRTIs								
Efavirenz/tenofovir disoproxil fumarate/emtricitabine (Atripla)	600/300/200 mg	Tablet	45.3200	1 tablet daily	45.32	1	1	16,542
Efavirenz (generics) + Emtricitabine/tenofovir alafenamide (Descovy)	600 mg 200/25 mg	Tablet	3.8030 28.5700[c,d]	600 mg daily 1 tablet daily	32.37	1	2	11,816
Emtricitabine/rilpivirine/ tenofovir disoproxil fumarate (Complera)	200/25/300 mg	Tablet	44.8643	1 tablet daily	44.86	1	1	16,375
Emtricitabine/rilpivirine/ tenofovir alafenamide (Odefsey)	200/25/25 mg	Tablet	42.3670[d,f]	1 tablet daily	42.37	1	1	15,464
INSTI + 2 NRTIs								
Raltegravir (Isentress) + abacavir/lamivudine (generics)	400 mg 600/300 mg	Tablet	14.0301 5.9875	400 mg twice daily 1 tablet daily	20.02	2	3	7,306

CDR = CADTH Common Drug Review; DHHS = US Department of Health and Human Services; INSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor.
All prices are from the Ontario Drug Benefit Formulary (accessed April 2018),[12] unless otherwise indicated, and do not include dispensing fees.
[a] Dolutegravir/rilpivirine is not currently listed as a recommended initial regimen in the DHHS guidelines (accessed January 2018); DHHS guidelines note that individuals with HIV who have sustained viral suppression with no drug resistance may be maintained on regimens that include only two active drugs, including dolutegravir/rilpivirine.[11]
[b] Manufacturer-submitted price.
[c] Delta PA, wholesale acquisition price (accessed April 2018).
[d] Not available on any public drug plans.
[e] Saskatchewan Drug Benefit Formulary (accessed April 2018).[13]
[f] Manufacturer-submitted price.[14]

Appendix 2: Summary of Key Outcomes

Table 4: When Considering Only Costs, Outcomes and Quality of Life, How Attractive is Dolutegravir/Rilpivirine Relative to the Current Antiretroviral Regimen?

DTG/RPV Versus cAR	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)	X					
Drug treatment costs alone	X					
Clinical outcomes				X		
Quality of life				X		
Incremental CE ratio or net benefit calculation	DTG/RPV is less costly and less effective (fewer QALYs gained) than cAR					

cAR = current antiretroviral regimen; CE = cost-effectiveness; DTG = dolutegravir; NA = not applicable; RPV = rilpivirine.

Note: Current antiretroviral regimen (cAR) includes all comparator products included in the manufacturer's analysis (DRV/c + TAF/FTC (Prezcobix + Descovy), DTG/ABC/3TC (Triumeq), DTG/TAF/FTC (Tivicay + Descovy), EVG/c/TAF/FTC (Genvoya), and RPV/TAF/FTC (Odefsey).

Appendix 3: Additional Information

Table 5: 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 6: Authors Information

Authors of the Pharmacoeconomic Evaluation Submitted to CDR

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

☒ Adaptation of global model/Canadian model done by a private consultant contracted by the manufacturer

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

☐ Other (please specify)

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

CDR = CADTH Common Drug Review.

CADTH

Appendix 4: Summary of Other Health Technology Assessment Reviews of Drug

Note there were no reviews for dolutegravir/rilpivirine conducted by health technology assessment organizations available at the time of this review. Dolutegravir/rilpivirine is currently undergoing review at the Institut national d'excellence en santé et en services sociaux (INESSS) in Quebec.

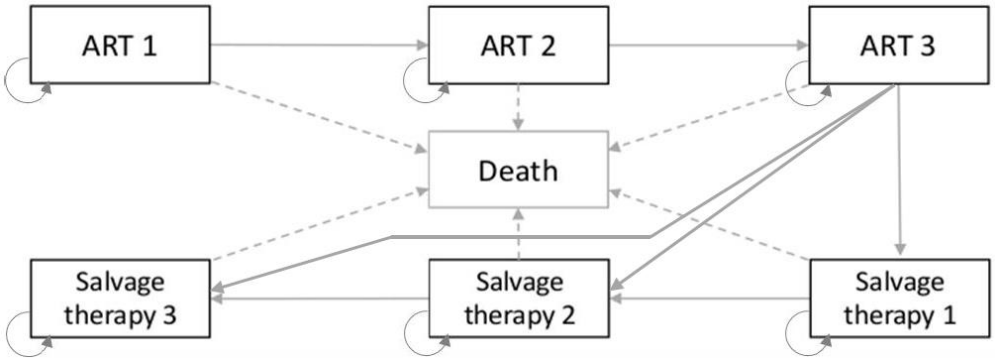
Appendix 5: Reviewer Worksheets

Manufacturer's Model Structure

The manufacturer submitted a hybrid decision tree Markov health state–transition model that estimates the incremental costs and health outcomes associated with dolutegravir/rilpivirine compared with currently available treatments in adults with virologically suppressed HIV-1 infection. The model assumes a maximum of six therapy lines; within each line of therapy, modelled patients enter a Markov process and transition though health states defined by HIV-1 viral load and CD4+ cell count.

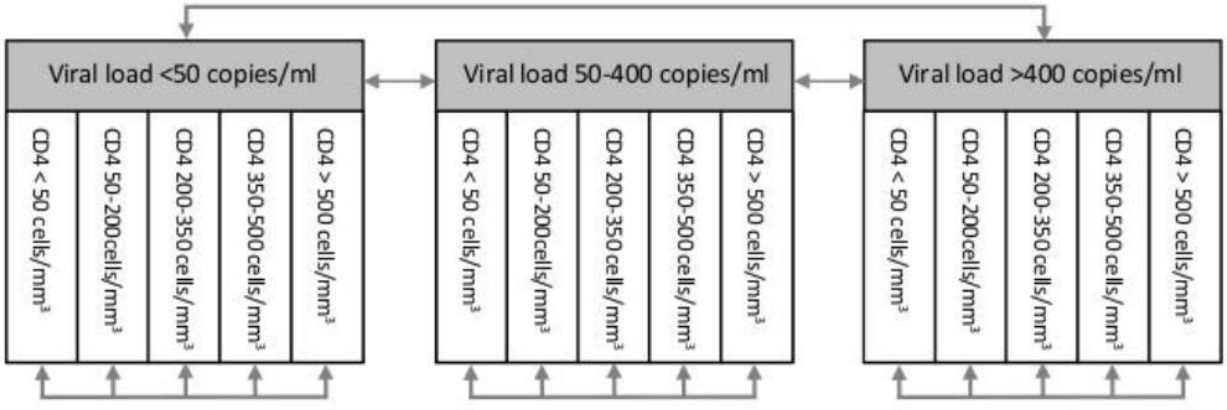
All patients begin in the maintenance treatment line (ART 1) and are treated with DTG/RPV or five comparator regimens included in the model. Transition from the initial maintenance therapy to a subsequent line of therapy is determined based on the treatment-specific rate of discontinuation and the reason for discontinuation (i.e., due to tolerability, virologic failure, or any other reason).

Figure 1: Manufacturer's Model Structure — Treatment Pathways



ART = antiretroviral therapy.
Source: Manufacturer's pharmacoeconomic submission.[14]

Figure 2: Manufacturer's Model Structure — Within-Therapy Line Markov Health States



Source: Manufacturer's pharmacoeconomic submission.[14]

Table 7: Data Sources

Data Input	Description of Data Source	Comment
Efficacy, safety, and withdrawals		
Efficacy • Virologic response (viral suppression) • Immunologic response	• Two randomized, phase III, multi-centre, open-label, active-controlled, parallel-group trials (SWORD-1 and SWORD-2). • Inputs for efficacy profiles relating to treatment switches (stable switch or failing switch after first modelled line) and the three salvage therapies were estimated based on published literature sources.	See CDR Clinical Review. Efficacy was measured in terms of virologic suppression at 48 weeks (as measured by viral load), and immunological response (as measured by the average increase in CD4+ cell count at 48 weeks).
AEs	• AEs included in the model were grade 3 or 4 AEs identified from the SWORD trials, including: diarrhea, nausea, vomiting, rash, nightmares / abnormal dreams, dizziness, depression, and insomnia. • The probability of experiencing AEs was sourced from the SWORD trials and other published literature, according to the various efficacy profiles. • The model also included five categories of AIDS-defining events (ADEs): acute viral OI, acute bacterial OI, acute fungal OI, acute protozoan OI, and other OI. ADE probabilities were sourced from a prospective cohort study by d'Arminio et al.[15]	Appropriate
Treatment discontinuation	The probability of discontinuation was based on efficacy profile and sourced from either the SWORD trials (first modelled line of therapy) or other published sources (second- and third-modelled ART lines and salvage therapy); 48-week probabilities were converted to monthly probabilities for inclusion in the model.	Appropriate.
Natural history		
Transition probabilities	• Transition matrices relating to seven efficacy profiles were used in the model to control patient movement between different viral load and CD4+ cell count states. Due to lack of access to individual patient data, transition matrices were generated by using published summary statistics of the change in CD4+ cell count with viral suppression probabilities to simulate cohorts described in the literature. • The probability of moving between viral load states was determined by adjusting the 48-week suppression probability to a one-month cycle length and was combined with the CD4+ health state transition matrix to produce the final state transition matrix.	The source of natural history data (i.e., published summary statistics of the change in CD4+ cell count) was not reported by the manufacturer. It was therefore not possible to validate these values. It is also unclear whether the data relating to simulated transition between CD4+ cell count states were sourced from a population of HIV-1 infected individuals in the absence of treatment.
Mortality • All-cause HIV-1 mortality • CVD mortality • ADE-related mortality	• All-cause mortality was informed using age- and gender-specific mortality rates derived from the 2011–2013 Canada-specific life tables,[3] adjusted by the additional mortality risk in the HIV-1 population (stratified by CD4+ cell count) as informed by relative risks from Lewden et al.[4] • All-cause mortality rates were further adjusted for patients experiencing ADEs by applying ADE-specific mortality probabilities sourced from the Multicenter AIDS Cohort Study (MACS).[5] • The increased risk of mortality relating to CVD was assumed to be accounted for in the adjusted all-cause mortality due to HIV-1 infection; no added increase in mortality due to CVD was therefore included in the model.	Appropriate.

Data Input	Description of Data Source	Comment
Utilities		
Health state utilities	• Utility values were applied in the model to each of the CD4+ cell count health states and sourced from a study by Kauf et al., which elicited utilities from patients receiving ART in five open-label trials using the SF-36 instrument.[6] • An age-related utility decrement was applied after the first year of treatment; baseline utilities specified by age were sourced from Canadian, gender-specific utility values.	Appropriate
Disutility Due to: • CVD • AEs • ADEs	• A utility decrement associated with an initial CVD event (applied to first cycle of event) and a chronic utility decrement (applied each subsequent cycle after event) were obtained from an unpublished study by Ara and Brazier.[7] • Disutilities due to AEs were applied upon occurrence for one cycle in the model and sourced from a study by Kauf et al.[6] and Simpson et al.[16] • Utility decrements associated with ADEs were also applied upon occurrence for one cycle and derived from a study by Paltiel et al.[8]	Appropriate
Resource use and costs		
Drug	• Drug-acquisition costs associated with most ARV regimens were sourced from the Ontario Drug Benefit Formulary,[12] with the exception of Odefsey and Descovy unit costs, which were obtained from their CDR submission documents.[14,17] • The monthly cost of salvage therapy was sourced from Despiegel et al.[18] and inflated to 2017 Canadian dollars using the Statistics Canada Consumer Price Index.	Existing price reductions for comparator ARV regimens are unknown.
Disease management (non–drug-related direct health care costs)	• Resource use and costs associated with all-cause health encounters among HIV-1 infected patients were included in the model according to CD4+ cell count health states and across various resource categories including: OI prophylaxis, outpatient visits to HIV-1 primary care provider, non-HIV medication, emergency department visits, and in-patient days. • Costs of OI prophylaxis treatment were sourced from the Ontario Drug Benefit Formulary. • Outpatient care and non-HIV medication monthly costs were sourced from a Canadian HIV-1 costing analysis by Mauskopf et al.; the appropriate source of costing data was missing. Outpatient care costs included mean monthly CD4+ health state costs of HIV-1 clinic visits, HIV-related specialist visits, non-HIV physician visits, and all laboratory testing (CD4+ cell count, viral load, HIV-1 genotypic resistance testing, serological tests, hematology, and routine chemistry testing). • Costs associated with in-patient care and emergency department visits were set to zero, as these costs were assumed to be captured in other disease-management categories. The costs associated with testing of CD4+ cell count, viral load, and HIV-1 genotypic resistance were excluded to avoid double counting, as these costs were already included in the composite cost of outpatient care.	The source of outpatient costs could not be verified, as it appears to be linked to a methodological review of economic evaluations in HIV.
AEs	The costs for treatment of the eight grade 3 or 4 AEs that were included in the model. Cost information was sourced from micro-costing estimates by Despiegel et al.[18] and updated to reflect the most recent Ontario fee schedules.	Appropriate.

Data Input	Description of Data Source	Comment
CVD	CVD costs were sourced from a clinical trial of cardiovascular outcomes in high-risk patients with atrial fibrillation or atrial flutter (the ATHENA trial), transformed to monthly costs and inflated to 2017 Canadian dollars.[19]	Appropriate
End of life	Costs for end-of-life care were sourced from a study by CIHI that examined the health care resource use in the final month of life for Canadian patients with a terminal illness.[20]	Appropriate
ADE	The ADE-related costs (or costs associated with OIs) that were sourced from a study by Anis et al.[21] ADE-related costs were applied in the model as per event costs in the cycle of incidence, and all costs were inflated to 2017 Canadian dollars.	Appropriate.

ADE= AIDS-defining event; AE = adverse event; AIDS = acquired immune deficiency syndrome; ART = antiretroviral therapy; ARV = antiretroviral; CDR = CADTH Common Drug Review; CIHI = Canadian Institute for Health Information; CVD = cardiovascular disease; OI = opportunistic infection; SF-36 = Short Form (36) Health Survey.

Table 8: Manufacturer's Key Assumptions

Assumption	Comment
All patients are assumed to start in the viral load < 50 copies/mL health state, as all patients are required to be virologically suppressed to be eligible for DTG/RPV.	Appropriate.
Comparator regimens in the first modelled line all assumed to have the same efficacy profile based on the comparator arm of the SWORD trials.	This is appropriate according to the clinical expert consulted by CADTH.
All comparator regimens across all modelled lines have the same efficacy profile.	Simplifying assumption was deemed appropriate by the clinical expert consulted by CADTH.
Efficacy of treatment regimens received in the second- and third-modelled lines was independent of treatment and related to the reason for discontinuing therapy, i.e., patients were assumed to discontinue therapy and transition to subsequent therapy for virologic reasons (including virologic failure, and viral rebound), tolerability reasons, or any other reason.	Acceptable.
Patient who discontinue due to virologic reasons were assumed to develop resistance and, as such, have poorer suppression rates in subsequent lines of therapy.	Uncertain whether applying the same efficacy profile (TE-failing switch) is appropriate for both second- and third-line therapy as it does not account for differences in previous ARV exposure.
Patients receiving final salvage therapy were assumed to have exhausted available treatment options and unable to discontinue therapy.	Acceptable.
Virologic discontinuation and discontinuation for any other reason in years 2+ for the DTG/RPV and comparator arms in the first modelled line were assumed to be the mean of both arms from 48-week SWORD data.	Uncertain due to lack of long-term data to support this assumption.
Patients discontinuing treatment for virologic reasons were assumed to develop resistance, which determines their eligibility for future salvage therapies.	Acceptable.
Discontinuation due to AEs was assumed to be independent of viral load and CD4+ cell count, i.e., equal proportions of patients were assumed to discontinue from each health state.	Appropriate.

AE = adverse event; DTG = dolutegravir; TE = treatment-experienced; RPV = rilpivirine.

Manufacturer's Results

Table 9: Summary of Results of the Manufacturer's Scenario Analyses: RPV/TAF/FTC Compared With DTG/RPV

Model Parameter	Scenario Analysis Value	Incremental Cost Versus DTG/RPV ($)	Incremental QALY Versus DTG/RPV	ICUR ($/QALY) Versus DTG/RPV	Percentage Change From Reference Case
Reference Case				**477,574**	
Discounting	0%	51,864	0.121	**427,747**	−10%
	3%	35,818	0.071	**502,816**	5%
Time horizon	1 years	2,543	0.0007	**3,715,770**	678%
	15 years	28,226	0.026	**1,072,944**	125%
Cost of disease management for HIV-1	Krentz and Gill[9]	42,439	0.082	**515,348**	8%
Rate of ADE	0	42,938	0.089	**481,578**	0.8%
Mortality related to ADE	0	42,927	0.100	**428,993**	−10%
HIV-1 mortality	1.0	48,166	0.011	**4,577,113**	858%
First modelled line: equal efficacy	SWORD	–		**Dominated**	
End-of-life costs	$24,919	42,858	0.100	**426,742**	−11%

ADE = AIDS-defining event; DTG = dolutegravir; FTC = emtricitabine; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; RPV = rilpivirine; TAF = tenofovir alafenamide.

All costs are presented in 2017 Canadian dollars.

Source: Manufacturer's submission.[2] Costs and QALYs are discounted probabilistic values.

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