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CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

BICTEGRAVIR/EMTRICITABINE/TENOFOVIR ALAFENAMIDE (B/FTC/TAF) (BIKTARVY)

(Gilead Sciences Canada, Inc.)

Indication: A complete regimen for the treatment of HIV-1 infection in adults with no known substitution associated with resistance the individual components of Biktarvy.

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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

3TC	lamivudine
ABC	abacavir
ARV	antiretroviral agent
B	bictegravir
B/FTC/TAF	bictegravir/emtricitabine/tenofovir alafenamide
CDR	CADTH Common Drug Review
DHHS	Department of Health and Human Services (US)
DTG	dolutegravir
E/C	elvitegravir/cobicistat
FTC	emtricitabine
HIV-1	HIV type 1
INSTI	integrase strand transfer inhibitor
NMA	network meta-analysis
NRTI	nucleoside/nucleotide reverse transcriptase inhibitors
QALY	quality-adjusted life-year
RAL	raltegravir
STR	single-tablet regimen
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Bictegravir/emtricitabine/tenofovir alafenamide (B/FTC/TAF, Biktarvy) (50 mg/200 mg/25 mg tablet)
Study Question	A cost-utility analysis was completed to evaluate the cost-effectiveness of B/FTC/TAF. The base case of the cost-utility analysis was conducted to evaluate the cost-effectiveness of B/FTC/TAF as a complete regimen for the treatment of HIV type 1 (HIV-1) infection in adults with no known substitutions associated with resistance to the individual components of B/FTC/TAF.
Type of Economic Evaluation	Cost-utility analysis
Target Population	All patients infected with HIV-1 — includes treatment-naive and treatment-experienced patients
Treatment	B/FTC/TAF (50 mg/200 mg/25 mg) once daily, with or without food
Outcome	Quality-adjusted life-years
Comparators	• ABC/DTG/3TC (Triumeq) • FTC/TAF (Descovy) + DTG (Tivicay) • E/C/F/TAF (Genvoya) • FTC/TAF (Descovy) + RAL (Isentress)
Perspective	Public payer (societal perspective included as scenario analysis)
Time Horizon	Lifetime (70 years)
Results for Base Case	B/FTC/TAF was dominant (i.e., less costly and more effective) over the comparator treatments.
Key Limitations	• Model may not reflect individualized nature of HIV treatment and overestimate B/FTC/TAF cost savings. • The model consisted of health states based on defined CD4 cell count ranges. The clinical expert indicated that CD4 cell counts provide much less prognostic value once a patient is on an ARV (i.e., this outcome is more important to patients not on any treatment) and viral load suppression has been achieved (i.e., number of copies of the virus < 50 copies/μL). The manufacturer's model may have overestimated the true efficacy of the included ARV treatments. • The relative efficacy for the comparators was based on an NMA that was conducted using studies in [redacted] despite the manufacturer's target population of both treatment-naive and treatment-experienced patients. The CDR Clinical Review team highlighted several limitations with the NMA, which led them conclude that the NMA does not provide compelling evidence that the safety and efficacy of B/FTC/TAF [redacted]. • The manufacturer's economic submission did not consider relevant comparators (e.g., FTC/RPV/TDF, Complera). The manufacturer did not provide justification as to why treatments such as FTC/RPV/TDF (or other NRTI-based regimens) were excluded, despite being included in the NMA.
CDR Estimate(s)	• Based on the uncertainty raised over the validity of using CD4 as a prognostic measure of ARV efficacy in HIV patients, which precluded modification of the model, CDR pharmacoeconomic reviewers considered the cost-effectiveness of B/FTC/TAF uncertain. • The CDR appraisal of the clinical RCT evidence found that B/FTC/TAF performed similarly to the comparator regimens in both treatment-naive and treatment-experienced patients. • At a daily cost of $39.22, B/FTC/TAF is less expensive than the publicly available prices of the comparator treatments identified by the manufacturer: ABC/DTG/3TC (Triumeq, $43.20), FTC/TAF + DTG (Descovy + Tivicay, $45.60), E/C/FTC/TAF (Genvoya, $46.39) and FTC/TAF + RAL (Descovy + Isentress, $54.16). B/FTC/TAF is more expensive than most TDF-based regimens (e.g., FTC/TDF + RAL [Truvada generic + Isentress, $35.36], FTC/TDF + DTG [Truvada generic + Tivicay, $26.80]), and several of the NTRI-boosted regimens.

3TC = lamivudine; ABC = abacavir; ARV = antiretroviral therapy; B = bictegravir; CDR = CADTH Common Drug Review; DTG = dolutegravir; E/C = elvitegravir/cobicistat; FTC = emtricitabine; HIV-1 = HIV type 1; NMA = network meta-analysis; NRTI = nucleoside/nucleotide reverse transcriptase inhibitor; QALY = quality-adjusted life-year; RAL = raltegravir; RCT = randomized controlled trial; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.

Drug	Bictegravir/emtricitabine/tenofovir alafenamide (B/FTC/TAF) (BIKTARVY)
Indication	A complete regimen for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults with no known substitution associated with resistance to the individual components of Biktarvy.
Reimbursement request	As per indication
Dosage form	Fixed-dose combination, single-tablet regimen of bictegravir 50 mg, emtricitabine 200 mg, and tenofovir alafenamide 25 mg.
NOC date	July 10, 2018
Manufacturer	Gilead Sciences Canada, Inc.

Executive Summary

Background

Bictegravir/emtricitabine/tenofovir alafenamide (B/FTC/TAF, BIKTARVY) is an oral single-tablet regimen (STR) with the indication for the treatment of HIV type 1 (HIV-1) infection in adults with no known substitution associated with resistance to the individual components of B/FTC/TAF.[1] It contains bictegravir (B), an unboosted integrase strand transfer inhibitor (INSTI), as well as emtricitabine (FTC) and tenofovir alafenamide (TAF), nucleoside reverse transcriptase inhibitors (NRTIs). B/FTC/TAF is available as a fixed-dose combination of 50 mg of B (equivalent to 52.5 mg of bictegravir sodium), 200 mg of FTC, and 25 mg of TAF (equivalent to 28 mg of tenofovir alafenamide fumarate) tablet, taken once daily.[1] At the manufacturer-submitted price of $39.22 per tablet, the annual cost of treatment is approximately $14,315 per patient.[2] The manufacturer is seeking reimbursement in accordance with the Health Canada indication.[2]

The manufacturer submitted a cost-utility analysis based on a Markov cohort model, which estimated the incremental costs and health outcomes associated with B/FTC/TAF compared with some of the treatments recommended by the US Department of Health and Human Services (DHHS) guidelines:

- Abacavir/dolutegravir/lamivudine (ABC/DTG/3TC) (Triumeq)
- Emtricitabine/tenofovir alafenamide (FTC/TAF) (Descovy) + dolutegravir (DTG) (Tivicay)
- Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/FTC/TAF) (Genvoya)
- Emtricitabine/tenofovir alafenamide (FTC/TAF) (Descovy) + raltegravir (RAL) (Isentress).

In the model, patients transitioned between a total of five core health states (and death), defined according to CD4 cell count ranges. The analysis was run over a lifetime time horizon (up to 70 years from model initiation), with a median patient age at entry of 48 years, using a 13-week cycle length for the first four cycles and then a 26-week cycle length for the remainder of the model. The flow of patients was described via calculated transition probabilities, in which patients either remained on the first-line treatment, continued to a subsequent treatment line when they experienced treatment failure, or transitioned to death from any health state. The analysis was based on the perspective of the Canadian public health care system.

The manufacturer reported that B/FTC/TAF was less costly and led to better outcomes (quality-adjusted life-year [QALY] gains) over a lifetime time horizon when compared with other treatments for adults with HIV-1 infection (treatment-naive or treatment-experienced). Based on a sequential analysis of the manufacturer's base case, B/FTC/TAF was considered to be a cost-effective option, as it dominated all other treatments included as comparators — all other treatments were associated with greater total costs with no additional QALY gain.[2]

Summary of Identified Limitations and Key Results

The manufacturer's economic model consisted of five core health states based on defined CD4 cell count ranges, a biologic outcome. The clinical expert consulted on this review questioned the use of CD4 cell count as a health state, as it provides limited prognostic value once a patient is on an antiretroviral (ARV) (i.e., this outcome is more important to patients not on any treatment) and viral load suppression has been achieved (i.e., number of copies of the virus < 50 copies/μL). For treatment-naive patients, viral load suppression is not met upon entry into the model. The clinical expert elaborated that changes in CD4 counts are associated with considerable variability and are therefore unreliable compared with viral counts. Thus, the model may be most applicable to the treatment-experienced population.

The manufacturer may have overestimated the true efficacy of the ARV treatments included by assuming greater incremental benefits in risk reduction with incremental rise in CD4 cell counts, despite evidence suggesting similar benefits at higher CD4 cell counts. Patients were reported to reach a higher CD4 cell count range at a faster rate and maintain it for a longer duration. Furthermore, feedback from the clinical expert consulted for this review indicated that, given the individualized nature of HIV treatment, the manufacturer's model may not reflect how patients may be treated in actual practice, which may impact the relative effects of treatment. This is particularly problematic when modelling beyond the first-line of therapy.

The relative efficacy for the comparators was based on a network meta-analysis (NMA) conducted using studies in [redacted] while the target population for the manufacturer's analysis are all patients with HIV (treatment-naive and treatment-experienced). The manufacturer acknowledged that, due to heterogeneity in study design and prior treatment regimens, an NMA was not feasible in the [redacted] thus, the data from [redacted] were extrapolated to the [redacted]. CADTH Common Drug Review (CDR) considered this assumption to be inappropriate; thus, the results may only reflect the [redacted]. The manufacturer's NMA suggested [redacted]. CDR clinical reviewers identified several limitations with the NMA, and concluded that the NMA does not provide compelling evidence that the safety and efficacy of B/FTC/TAF [redacted]. The relative efficacy of the comparators was then applied to weighted-average estimates from the B/FTC/TAF randomized controlled trials; this methodology is highly questionable.

Finally, the manufacturer's economic submission did not consider all relevant comparators. For example, emtricitabine (FTC)/rilpivirine (RPV)/tenofovir disoproxil fumarate (TDF) (Complera) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) + two NRTIs regimen, which is a relevant comparator, according to the clinical expert consulted on this

review. Additionally, several other TDF-based regimens or boosted-NRTI treatments may be relevant comparators for B/FTC/TAF in either a treatment-naive or treatment-experienced population and were presented by the manufacturer in its submitted NMA. B/FTC/TAF is more costly than several TDF and boosted-NRTI regimens.

Conclusions

Based on the uncertainty raised over the validity of using CD4, a biologic measure, as a prognostic measure of ARV efficacy in HIV patients, the actual cost-effectiveness of B/FTC/TAF is uncertain. Given the limitations with the structure of the submitted model, CDR did not undertake reanalyses based on an uncertain model structure. CDR clinical reviewers concluded that the NMA does not provide compelling evidence that the safety and efficacy of B/FTC/TAF [redacted], and that the RCTs indicated [redacted].

At a daily cost of $39.22, B/FTC/TAF is less expensive than the publicly available prices of the comparator treatments of identified by the manufacturer: ABC/DTG/ 3TC (Triumeq, $43.20), FTC/TAF + DTG (Descovy + Tivicay, $45.60), and E/C/FTC/TAF (Genvoya, $46.39) and FTC/TAF + RAL (Descovy + Isentress, $54.16), but is more expensive than most TDF-based regimens (e.g., FTC/TDF + RAL [Truvada generic + Isentress, $35.36], FTC/TDF + DTG [Truvada generic + Tivicay, $26.80]), and several of the NTRI-boosted regimens.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's PE Submission

The manufacturer submitted an economic model that captured health outcomes in terms of quality-adjusted life-years (QALY) gained. The model compared the cost-effectiveness of bictegravir/emtricitabine/tenofovir alafenamide (B/FTC/TAF) with available antiretroviral (ARV) regimens for the treatment of HIV type 1 (HIV-1) infection in adults with no known substitution associated with resistance to the individual components of B/FTC/TAF (i.e., the anticipated Health Canada indication).[1] The list of comparators included the recommended initial ARV regimens for initial therapy, per the US Department of Health and Human Services (DHHS) guidelines, that were aligned with market research claims data in Canada: abacavir/dolutegravir/lamivudine (ABC/DTG/3TC) (Triumeq), emtricitabine/tenofovir alafenamide (FTC/TAF) + DTG (Descovy + Tivicay), elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/FTC/TAF) (Genvoya), and FTC/TAF + raltegravir (RAL) (Descovy + Isentress).[2]

The target population was all patients infected with HIV-1 with an average age of 45 years; the model provided the options to select both subgroups of treatment-naive patients and of treatment-experienced patients with virologic suppression. Treatment-experienced patients will already have received one or more therapies when they begin the "first-line" treatment in the model. The initial distribution of patients across health states, determined by baseline CD4 cell count, is taken from expert clinician opinion of a typical representation of clinical practice in Canada.

The cycle length for the analysis was 13 weeks for the first four cycles and then 26 weeks for subsequent cycles for the remainder of the model over a lifetime time horizon (up to 70 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.[2]

The manufacturer submitted a Markov model consisting of six health states (five core health states and death), based on defined CD4 cell count ranges, as recorded in the B/FTC/TAF pivotal trials (Figure 1).[2] Patients enter the model in one of the CD4 cell count health states corresponding to first-line treatment.[2] At the end of each cycle, patients can remain in the same state, move to a higher or lower CD4 cell count state, move to the equivalent health state in the next line of treatment, or move to the death state.[2] Transition probabilities between different health states for B/FTC/TAF were derived from selected B/FTC/TAF studies; specifically, annual CD4 cell count changes were assumed to be normally distributed with the means and standard deviations calculated from the pivotal trials for B/FTC/TAF, and relative effects of other treatment regimens were derived from the results of a network meta-analysis (NMA). Utility values were derived from the literature. Each health state has an associated utility describing the quality of life of patients in that stage of disease progression, as well as non–treatment-related costs to account for the ongoing management and care of HIV patients. The submitted model includes the non–AIDS-related comorbidities and treatment-related adverse events that patients can experience from any health state. Patients can experience treatment failure leading to subsequent treatment lines from any health state and can die from any health state.[2]

Manufacturer's Base Case

The manufacturer reported that B/FTC/TAF was associated with a total cost of $541,445 and 19.03 QALYs over the model time horizon (Table 2). B/FTC/TAF was associated with lower total costs and better outcomes (more QALYs gained) when compared with other ARV regimens, thereby dominating them.

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

	Total Costs ($)	Incremental Cost Versus B/FTC/TAF ($)	Total QALYs	Incremental QALYs Versus B/FTC/TAF	ICUR ($/QALY) Versus B/FTC/TAF
Non-dominated options					
B/FTC/TAF	**541,445**	**–**	**19.03**	**–**	**–**
Dominated options					
ABC/DTG/3TC (Triumeq)	562,778	21,333	18.98	–0.05	Dominated
FTC/TAF + DTG (Descovy + Tivicay)	571,211	29,766	19.00	–0.03	Dominated
E/C/FTC/TAF (Genvoya)	578,120	36,675	19.00	–0.03	Dominated
FTC/TAF + RAL (Descovy + Isentress)	586,570	45,125	18.91	–0.12	Dominated

3TC = lamivudine; ABC = abacavir; DTG = dolutegravir; E/C = elvitegravir/cobicistat; FTC = emtricitabine; ICUR = incremental cost-utility ratio; RAL = raltegravir; TAF = tenofovir alafenamide; QALY = quality-adjusted life-year.

All costs are presented in 2018 Canadian dollars.

Source: Adapted from the manufacturer's submission.[2]

Summary of Manufacturer's Sensitivity Analyses

The manufacturer conducted several probabilistic and one-way deterministic sensitivity analyses in which the inputs were varied within the associated 95% credible or confidence intervals, where applicable, or through using a 20% variation of the mean value. One-way sensitivity analyses were conducted versus the primary single-tablet regimen (STR) comparator, ABC/DTG/3TC (Triumeq), as a proxy versus all additional DHHS-recommended therapies. The main drivers of the deterministic results included the cost of individual therapies and the variability in accrual of outcomes or costs associated with non–AIDS-related morbidities. Another main driver of the cost-effectiveness results was the relative risk of improving or worsening CD4 cell count obtained from the NMA; the model is highly sensitive to changes in these parameters, given the similarity in treatment effects among comparators, as small changes in the probability of improving will drive changes in the incremental QALYs. The model was not sensitive to the discount rate, the probabilities of adverse events, the baseline CD4 cell count, and the multiplier input value for additional mortality attributable to poor CD4 cell count.[2]

The results of the manufacturer's multivariate probabilistic sensitivity analyses were robust and aligned with the manufacturer's base-case results (i.e., B/FTC/TAF dominated other ARV regimens).[2]

Limitations of Manufacturer's Submission

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

- **Validity of CD4 counts to stratify health states:** The manufacturer's economic model consisted of five core health states based on defined CD4 cell count ranges.
  - The clinical expert consulted on this review confirmed that, while CD4 cells are a valid biologic measure to the efficacy of ARV in patients with HIV, they provide limited prognostic value once a patient is on an ARV and viral load suppression has been achieved (i.e., number of copies of the virus < 50 copies/μL). For treatment-naive patients entering the model, the requirement of viral load suppression is not met; therefore, the reliability of CD4 cell counts as modelled in the manufacturer's economic evaluation is questionable.
  - Once the viral load is suppressed, reduced risk of a new AIDS event or death follows a CD4 cell count gradient; patients with the highest CD4 cell counts have the lowest risk of a new AIDS-defining event or death, while patients with CD4 cell counts < 200 cells/μL have higher risk. Based on the clinical expert feedback and an available published study, the benefits associated with a higher CD4 cell count appear to be similar for patients with a CD4 cell count either between 200 and 350 cells/μL and those with a CD4 cell count between 350 and 500 cells/μL, with the study indicating that patients with a CD4 cell count above 500 cells/μL may exhibit only slight incremental benefits.[3,4] The similarity in benefits between 200 and 350 cells/μL or between 350 and 500 cells/μL was not considered in the manufacturer's model, in which incremental benefits in risk reduction were accrued with an incremental rise in CD4 cell counts, thereby possibly overestimating the true efficacy of ARVs included in the model.
- **Modelling structure may not accurately reflect 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 DHHS guidelines for the use of ARV agents in adults and adolescents living with HIV-1 and emphasized by the clinical expert consulted by CADTH for this review. The submitted model may not sufficiently capture the individualized nature of HIV therapy in this specialized population, particularly for efficacy profiles beyond the first line of therapy. Therefore, the value of assessing the cost-effectiveness of B/FTC/TAF 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 B/FTC/TAF is used potentially overestimates the cost savings associated with this treatment.
- **NMA populations and application:** The manufacturer's base-case analysis was modelled in all patient populations (treatment-naive and treatment-experienced), and relative treatment effects of comparator treatments were obtained from a manufacturer-funded NMA. However, based on the manufacturer's NMA report, the NMA was conducted using studies in [redacted], and that, due to heterogeneity in study design and prior treatment regimens, the NMA was not feasible in the [redacted]. The expected cost-effectiveness for B/FTC/TAF compared with other ARVs in treatment-experienced HIV patients is not clear. Furthermore, the manufacturer based the B/FTC/TAF efficacy inputs in the model on a weighted average of the B/FTC/TAF studies, not all of which were included by the

manufacturer in the NMA. The relative risks for treatment effects for the comparators were then applied, which is methodologically inappropriate.

- **Technical uncertainty with the submitted model:** The results of the manufacturer's economic evaluation were based on a deterministic base-case analysis. When CDR attempted to calculate and check the robustness of the results of the probabilistic base-case analysis, CDR noted that the submitted model demonstrated significant concerns when processing more than 500 iterations, thereby raising uncertainty concerning the model's robustness, the probabilistic analysis' utilized ranges, distributions, and mean point estimates.
- **Exclusion of relevant comparators:** The manufacturer's economic submission did not consider several relevant comparators: NNRTI + two NRTI regimens such as FTC/RPV/TDF (Complera) and efavirenz/FTC/TDF (Atripla), boosted-NRTI regimens such as atazanavir (Reyataz) with ritonavir (Norvir) + abacavir/lamivudine (generics), and TDF-based INSTI + two NRTI regimens such as FTC/TDF + RAL (Truvada + Isentress) and FTC/TDF + DTG (Truvada + Tivicay). The manufacturer did not provide adequate justification as to why these comparators were excluded, particularly as several additional comparators included in the NMA were not considered in the manufacturer's analysis.

CADTH Common Drug Review Reanalyses

Based on the limitations identified by CDR, the model was deemed inappropriate to assess the cost-effectiveness of B/FTC/TAF compared with relevant comparator treatments in both the treatment-naive and treatment-experienced populations. The CDR clinical review found that B/FTC/TAF was similar to the comparator treatments considered in the treatment-naive population (based on the NMA and clinical studies) and in the treatment-experienced population (based on clinical studies). Therefore, CDR considered the comparative costs of B/FTC/TAF with other DHHS-recommended treatments (Table 3).

Issues for Consideration

- **Confidential pricing of comparator ARV regimens:** The manufacturer's cost-effectiveness analysis is based on publicly sourced list prices of 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.
- **Availability of bictegravir as a single drug:** Bictegravir is not available as a single drug, like other integrase inhibitors in Canada such as DTG (Tivicay) and RAL (Isentress), which makes it challenging for CDR to assess whether the combination product B/FTC/TAF is more or less costly than the sum of the individual components, which could affect any potential cost savings with the use of this combination product.

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. Input was gathered at a workshop in Toronto, Canada, and through survey data collected for the patient submission on DTG and RPV (Juluca). No survey respondents had experience with the single-dose, combination drug B/FTC/TAF.

However, many respondents expressed interest in this combination for benefits in terms of smaller pill size and ability to take the medication with or without food. Patients noted that a number of negative mental health outcomes are associated with their HIV diagnosis, particularly resulting from treatment-related side effects as well as 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, such as 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 with 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 acquiring 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

Based on the uncertainty raised over the validity of using CD4, a biologic measure, as a prognostic measure of ARV efficacy in HIV patients, the actual cost-effectiveness of B/FTC/TAF is uncertain. Given the limitations with the structure of the submitted model, CDR did not undertake reanalyses based on an uncertain model structure. CDR clinical reviewers concluded that the NMA does not provide compelling evidence that [redacted], and that the randomized controlled trials indicated [redacted].

At a daily cost of $39.22, B/FTC/TAF is less expensive than the publicly available prices of the comparator treatments of identified by the manufacturer — ABC/DTG/ 3TC (Triumeq, $43.20), FTC/TAF + DTG (Descovy + Tivicay, $45.60), E/C/FTC/TAF (Genvoya, $46.39) and FTC/TAF + RAL (Descovy + Isentress, $54.16) but is more expensive than most TDF-based regimens (e.g., FTC/TDF + RAL [Truvada generics + Isentress, $35.36], FTC/TDF + DTG [Truvada generics + Tivicay, $26.80]) and several of the NTRI-boosted regimens.

Appendix 1: Cost Comparison

The comparators presented in Table 3 represent recommended antiretroviral regimens for initial therapy for patients with HIV-1 infection, according to the US Department of Health and Human Services (DHHS) guidelines, including DHHS-recommended initial regimens in certain clinical situations (updated October 2017).[5] Costs of comparator products were sourced from the Ontario Drug Benefit Formulary (accessed June 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 Agents for Adults With HIV-1 Infection

Drug/ Comparator Regimen	Strength	Dosage Form	Price ($)	Recommended Use	Daily Cost ($)	Freq. of Use (Per Day)	Number of Pills (Per Day)	Annual Drug Cost ($)
Bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy)	**50 mg/ 200 mg/ 25 mg**	**Tab**	**39.2227[a]**	**1 tablet daily**	**39.22**	**1**	**1**	**14,315**
DHHS-Recommended Initial Antiretroviral Regimens								
INSTI + 2 NRTIs								
Dolutegravir/abacavir/ lamivudine (Triumeq)	50 mg/ 600 mg/ 300 mg	Tab	43.2020	1 tablet daily	43.20	1	1	15,768
Dolutegravir (Tivicay) + Emtricitabine/tenofovir disoproxil fumarate (Truvada, generics)	50 mg 200 mg/ 300 mg	Tab	19.4993 7.3035	50 mg daily 1 tablet daily	26.80	1	2	9,782
Dolutegravir (Tivicay) + Emtricitabine/tenofovir alafenamide (Descovy)	50 mg 200 mg/ 25 mg	Tab	19.4993 26.1020[bc]	50 mg daily 1 tablet daily	45.60	1	2	16,644
Elvitegravir/cobicistat/ emtricitabine/tenofovir disoproxil fumarate (Stribild)	150 mg/ 150 mg/ 200 mg/ 300 mg	Tab	48.0177	1 tablet daily	48.01	1	1	17,526
Elvitegravir/cobicistat/ emtricitabine/tenofovir alafenamide (Genvoya)	150 mg/ 150 mg/ 200 mg/ 10 mg	Tab	46.3894[b]	1 tablet daily	46.39	1	1	16,932
Raltegravir (Isentress) + Emtricitabine/tenofovir disoproxil fumarate (Truvada, generics)	400 mg 200 mg/ 300 mg	Tab	14.0301 7.3035	400 mg twice daily 1 tablet daily	35.36	2	3	12,906
Raltegravir (Isentress) + Emtricitabine/tenofovir alafenamide (Descovy)	400 mg 200 mg/ 25 mg	Tab	14.0301 26.1020[bc]	400 mg twice daily 1 tablet daily	54.16	2	3	19,768
DHHS-Recommended Regimens for Switch Therapy								
INSTI + NNRTI								
Dolutegravir/rilpivirine (Juluca)[b]	50 mg/ 25 mg	Tab	34.8667[d]	1 tablet daily	34.87	1	1	12,728

Drug/ Comparator Regimen	Strength	Dosage Form	Price ($)	Recommended Use	Daily Cost ($)	Freq. of Use (Per Day)	Number of Pills (Per Day)	Annual Drug Cost ($)
DHHS-Recommended Initial Regimens in Certain Clinical Situations								
Boosted PI + 2 NRTIs								
Darunavir/cobicistat/emtricitabine/tenofovir alafenamide (Symtuza)	800 mg/ 150 mg/ 200 mg/ 10 mg	Tab	52.2670[bc]	1 tablet daily	52.27	1	1	19,079
Darunavir (Prezista) with ritonavir (Norvir) + Emtricitabine/tenofovir disoproxil fumarate (Truvada, generics)	800 mg 100 mg 200 mg/ 300 mg	Tab	22.1720 1.5487 7.3035	800 mg daily 100 mg daily 1 tablet daily	31.02	1	3	11,322
Darunavir (Prezista) with ritonavir (Norvir) + Emtricitabine/tenofovir alafenamide (Descovy)	800 mg 100 mg 200 mg/ 25 mg	Tab	22.1720 1.5487 26.1020[bc]	800 mg daily 100 mg daily 1 tablet daily	49.82	1	3	18,184
Darunavir/cobicistat (Prezcobix) + Emtricitabine/tenofovir disoproxil fumarate (Truvada, generics)	800 mg/ 150 mg 200 mg/ 300 mg	Tab	23.8672 7.3035	1 tablet daily 1 tablet daily	31.17	1	2	11,377
Darunavir/cobicistat (Prezcobix) + Emtricitabine/tenofovir alafenamide (Descovy)	800 mg/ 150 mg 200 mg/ 25 mg	Tab	23.8672 26.1020[bc]	1 tablet daily 1 tablet daily	49.97	1	2	18,239
Atazanavir (Reyataz) with ritonavir (Norvir) + Emtricitabine/tenofovir disoproxil fumarate (Truvada, generics)	300mg 100 mg 200 mg/ 300 mg	Cap	11.2165 1.5487 7.3035	300 mg daily 100 mg daily 1 tablet daily	20.07	1	3	7,326
Atazanavir (Reyataz) with ritonavir (Norvir) + Emtricitabine/tenofovir alafenamide (Descovy)	300mg 100 mg 200 mg/ 25 mg	Cap	11.2165[e] 1.5487 26.1020[bc]	300 mg daily 100 mg daily 1 tablet daily	38.87	1	3	14,188
Darunavir/cobicistat (Prezcobix) + Abacavir/lamivudine (generics)	800 mg/ 150 mg 600 mg/ 300 mg	Tab	23.8672 5.9875	1 tablet daily 1 tablet daily	29.86	1	2	10,899
Darunavir (Prezista) with ritonavir (Norvir) + Abacavir/lamivudine (generics)	800 mg 100 mg 600 mg/ 300 mg	Tab	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 mg/ 300 mg		11.2165[e] 1.5487 5.9875	300 mg daily 100 mg daily 1 tablet daily	18.75	1	3	6,844

Drug/ Comparator Regimen	Strength	Dosage Form	Price ($)	Recommended Use	Daily Cost ($)	Freq. of Use (Per Day)	Number of Pills (Per Day)	Annual Drug Cost ($)
NNRTI + 2 NRTIs								
Efavirenz/tenofovir disoproxil fumarate/emtricitabine (Atripla, generics)	600 mg/ 300 mg/ 200 mg	Tab	22.6600	1 tablet daily	22.66	1	1	8,271
Efavirenz (generics) + Emtricitabine/tenofovir alafenamide (Descovy)	600 mg 200 mg/ 25 mg	Tab	3.8030 26.1020[bc]	600 mg daily 1 tablet daily	32.37	1	2	11,815
Emtricitabine/rilpivirine/ tenofovir disoproxil fumarate (Complera)	200 mg/ 25 mg/ 300 mg	Tab	44.8643	1 tablet daily	44.86	1	1	16,374
Emtricitabine/rilpivirine/ tenofovir alafenamide (Odefsey)	200 mg/ 25 mg/ 25 mg	Tab	42.3670[bc]	1 tablet daily	42.37	1	1	15,465
INSTI + 2 NRTIs								
Raltegravir (Isentress) + Abacavir/lamivudine (generics)	400 mg 600 mg/ 300 mg	Tab	14.0301 5.9875	400 mg twice daily 1 tablet daily	34.05	2	3	12,428

CDR = CADTH Common Drug Review; DHHS = Department of Health and Human Services; HIV-1 = HIV type 1; 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 June 2018),[6] unless otherwise indicated, and do not include dispensing fees.

[a] Manufacturer-submitted price.[2]

[b] Delta PA, wholesale acquisition price (accessed June 2018).[7]

[c] Not available on any public drug plans.

[d] Dolutegravir/rilpivirine is not currently listed as a recommended initial regimen in the DHHS guidelines (accessed June 2018); DHHS guidelines note that persons with HIV who have sustained viral suppression with no drug resistance may be maintained on regimens including only two active drugs, including dolutegravir/rilpivirine.[5]

[e] Saskatchewan Drug Benefit Formulary (accessed April 2018).[8]

Appendix 2: Additional Information

Table 4: 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 5: 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		

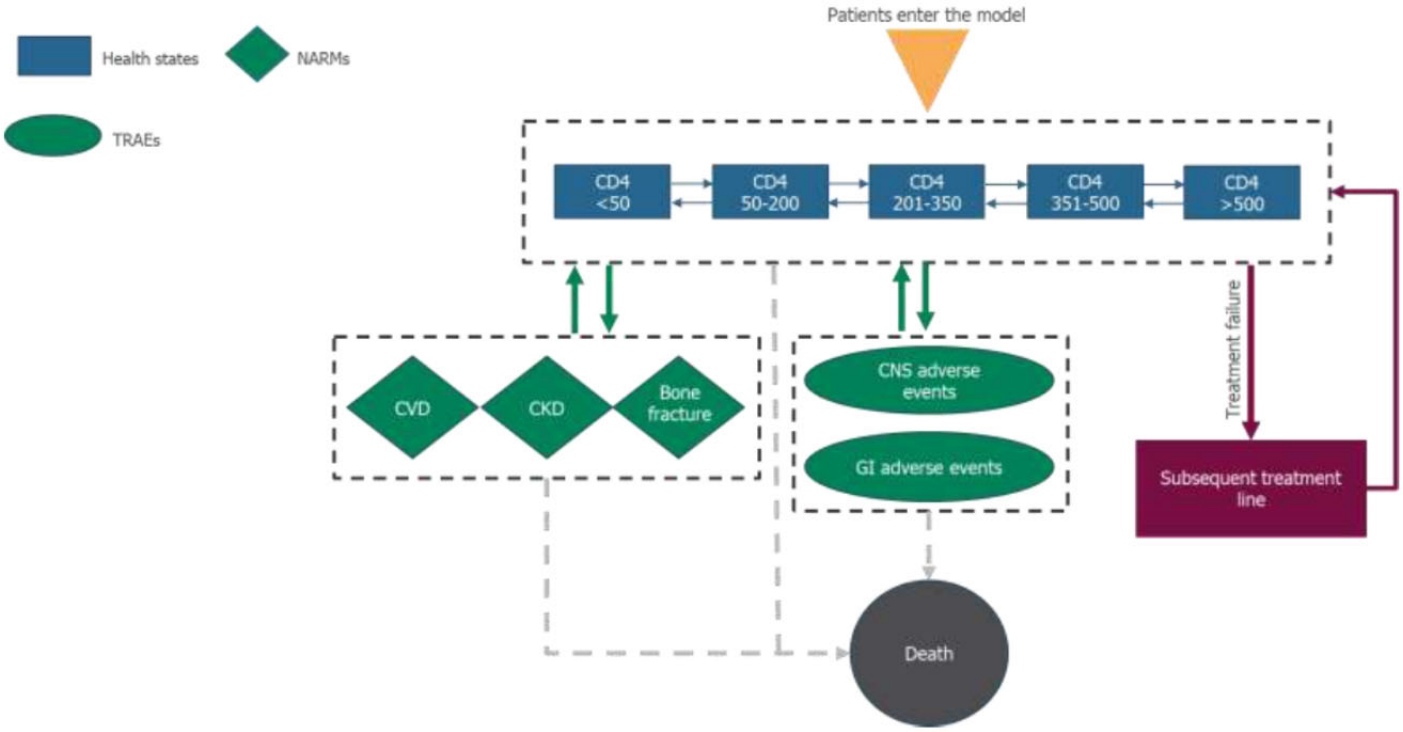
CDR = CADTH Common Drug Review.

Appendix 3: Reviewer Worksheets

Manufacturer's Model Structure

The manufacturer submitted a Markov model consisting of six health states (five core health states and death), based on defined CD4 cell count ranges as recorded in the B/FTC/TAF pivotal trials. Each health state has an associated utility describing the quality of life of patients in that stage of disease progression, as well as non–treatment-related costs to account for the ongoing management and care of HIV patients. Separate utility values for each health state are available from the literature and are incorporated into the model.[2]

Figure 1: Manufacturer's Model Structure — Treatment Pathways



CKD = chronic kidney disease; CNS = central nervous system; CVD = cardiovascular disease; GI = gastrointestinal; NARM = non–AIDS-related comorbidity; TRAE = treatment-related adverse event.

Source: Manufacturer pharmacoeconomic submission.[2]

Patients enter the model in one of the CD4 cell count health states corresponding to first-line treatment. At the end of each cycle, patients can remain in the same state, move to a higher or lower CD4 cell count state, move to the equivalent health state in the next line of treatment, or move to the death state. This flow of patients is described via calculated transition probabilities. The submitted model includes the non–AIDS-related comorbidities and treatment-related adverse events that patients can experience from any health state. Patients can experience treatment failure leading to a subsequent treatment line from any health state and can die from any health state.

Table 6: Data Sources

Data Input	Description of Data Source	Comment
Efficacy (B/FTC/TAF)	• Two randomized, double-blind, active-controlled, non-inferiority phase III studies were conducted to evaluate the efficacy and safety of B/FTC/TAF in treatment-naive subjects (Studies 1489 and 1490).[9,10] • Two randomized, active-controlled phase III studies evaluated the safety and efficacy of switching subjects with virologically suppressed HIV infection on a single- or multi-tablet regimen of ABC, 3TC, and DTG (double-blind) or a regimen of two NRTIs + boosted DRV or ATV (open-label) to B/FTC/TAF (Studies 1844 and 1878).[11,12] • A third switch study in women with virologically suppressed HIV infection was also conducted, in which patients switched from boosted ATV + FTC/TDF, E/C/FTC/TDF, or E/C/FTC/TAF to B/FTC/TAF (Study 1961).[13]	Appropriate sources; although application of the data (i.e., using a weighted average rather than meta-analysis techniques) is highly questionable.
Efficacy (Comparators)	A manufacturer-funded NMA that included [redacted].[2]	NMAs were conducted using [redacted]. For the treatment-experienced population, the feasibility assessment included the 12 trials identified in the SLR, and a further two B/FTC/TAF studies that were not yet published when the database searches were run. However, due to heterogeneity in study design and prior treatment regimens, NMA was not feasible in the [redacted].
Natural History	Transition probabilities were calculated according to the method used. [14]Annual CD4 cell count changes were assumed to be normally distributed, with the means and standard deviations calculated from the pivotal trials for B/FTC/TAF and relative effect of other treatment regimens based on results of the NMA.	According to clinical expert opinion, CD4 cell count ranges have minimal value as a prognostic measure of a treatment's efficacy compared with viral counts.
Utilities	Utility values for each of the primary health states (i.e., CD4 cell count ranges) were taken from a published study that estimated values using responses to the EuroQol 5-Dimensions (EQ-5D) quality-of-life instrument from 21,000 participants in HIV-1 clinical trials, including participants in Canada.[15]	Acceptable
Adverse Events	Disutilities are applied to the baseline CD4 cell count utilities for patients who experience non–AIDS-related morbidities (NARMs) and treatment-related adverse events (TRAEs) were based on published studies.[16]	Acceptable
Mortality	Background mortality is based on the age- and gender-adjusted general population mortality rate. All-cause mortality is taken from interim life tables for Canada and is based on the cohort's mean age.[2]	Appropriate
Resource use and Costs	Resources utilization incorporated in the B/FTC/TAF model was derived from the literature and a survey administered to Canadian clinical experts in the treatment of patients with HIV.	Acceptable

Data Input	Description of Data Source	Comment
Drug	Treatment costs for B/FTC/TAF (anticipated marketed price) were provided by the manufacturer, with costs for comparator treatment regimens taken from the Ontario Drug Benefit (ODB) formulary. If not available from the ODB formulary, costs were provided by the manufacturer.	Existing price reductions for comparator ARV regimens are unknown.
AEs	• Costs associated with TRAEs were based on expert opinion and costed according to publicly available payment schedules.[2] • Risks of experiencing NARMs were based on published literature and had one-off costs associated with them in the model.[2]	Acceptable
Health State	Derived from the literature and a survey conducted by the manufacturer and administered to Canadian clinical experts in the treatment of patients with HIV.[2]	Acceptable

3TC = lamivudine; ABC = abacavir; ATV = atazanavir; B/FTC/TAF = bictegravir/emtricitabine/tenofovir alafenamide; DRV = darunavir; DTG = dolutegravir; E/C = elvitegravir/cobicistat; FTC/TAF = emtricitabine/tenofovir alafenamide; FTC/TDF = emtricitabine/tenofovir disoproxil fumarate; NARM = non–AIDS-related morbidities; NMA = network meta-analysis; NRTI = nucleoside/nucleotide reverse transcriptase inhibitors; ODB = Ontario Drug Benefit; SLR = systematic literature review; TRAE = treatment-related adverse event.

Table 7: Manufacturer's Key Assumptions

Assumption	Comment
The standard error for mean CD4 cell count change from baseline used to calculate transition probabilities for each treatment is assumed to be a fixed proportion of the mean CD4 cell count change from baseline, calculated from the average reported values in the B/FTC/TAF trial data.	Uncertain. According to clinical expert opinion, CD4 cell counts have minimal value as a prognostic measure in HIV patients on ARV treatment. Viral load counts were considered be more appropriate.
The proportion of patients starting second-/third-line treatment at any point in time is estimated by calculating the difference between those on first-/ second-line treatment in the current and previous cycles (in the same health state) and correcting for mortality.	Appropriate
If a patient moves off a treatment that has an associated cumulative risk (e.g., PI risk for CVD), the risk is assumed to immediately return to the baseline value.	Uncertain due to lack of data to support this assumption
For treatment regimens associated with a cumulative risk, this is applied from the start of the model if the relevant treatment is being taken at first-line in the model, and from the average time of switch to second-line treatment if the relevant treatment is being taken at second or subsequent lines.	Appropriate
The cumulative risk of CVD and CKD in any cycle is calculated by taking the proportion of patients alive, minus those already estimated to have the long-term NARM (i.e., the cumulative prevalence in the previous cycle multiplied by the probability of still being alive) and then multiplied by the probability of developing the NARM.	Appropriate
Where NMA results were not available for relative efficacy and TRAE rates, or where there were insufficient data from the NMA for certain treatment regimens, assumptions were made that they were equivalent to other similar regimens.	Uncertain

Assumption	Comment
The mortality probability above the age of 100 is assumed to be 1, in line with the lifetime time horizon assumption and based on the lack of data for mortality rates above this age. The maximum time horizon included in the model is therefore 70 years, based on the lowest starting age of 31 (in the treatment-naive population subgroup).	Appropriate

ARV = antiretroviral therapy; B/FTC/TAF = bictegravir/emtricitabine/tenofovir alafenamide; CKD = chronic kidney disease; CVD = cardiovascular disease; NARM = non–AIDS-related morbidities; NMA = network meta-analysis; PI = protease inhibitor; TRAE = treatment-related adverse event.

Manufacturer's Results

In addition to the reported probabilistic base-case analysis, the manufacturer included the results of a deterministic base-case analysis (Table 8).

Table 8: Summary of Results of the Manufacturer's Deterministic Base Case

Treatment Strategy	Total Costs ($)	Incremental Cost Versus Reference ($)	Total QALYs	Incremental QALYs Versus Reference	ICUR ($/QALY) Versus B/FTC/TAF
B/FTC/TAF	541,444.76		19.03		
FTC/TAF + RAL (Descovy + Isentress)	586,570.50	45,125.74	18.97	–0.06	Dominated
ABC/DTG/3TC (Triumeq)	562,777.69	21,332.93	18.98	–0.05	Dominated
E/C/FTC/TAF (Genvoya)	578,119.77	36,675.01	19.00	–0.04	Dominated
FTC/TAF + DTG (Descovy + Tivicay)	571,211.05	29,766.30	19.00	–0.03	Dominated

3TC = lamivudine; ABC = abacavir; B = bictegravir; DTG = dolutegravir; E/C = elvitegravir/cobicistat; FTC = emtricitabine; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life year; RAL = raltegravir; TAF = tenofovir alafenamide.

Source: Manufacturer's pharmacoeconomic submission.[2]

The manufacturer conducted several one-way sensitivity analyses using the deterministic base case versus the primary single-tablet regimen comparator, ABC/DTG/3TC (Triumeq), as a proxy versus all additional therapies recommended by the US Department of Health and Human Services. The main drivers of the cost-effectiveness results included the cost of individual therapies and the variability in accrual of outcomes or costs associated with non–AIDS-related morbidities, and the relative risk of improving or worsening CD4 cell count obtained from the network meta-analysis. The deterministic model was not sensitive to the discount rate, the probabilities of adverse events, the baseline CD4 cell count, and the multiplier input value for additional mortality attributable to poor CD4 cell count.[2]

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