Common Drug Review
Pharmacoeconomic Review Report

August 2016

Drug	emtricitabine/tenofovir disoproxil fumarate (Truvada)
Indication	For use in combination with safer sex practices for pre-exposure prophylaxis to reduce the risk of sexually acquired HIV-1 infection in adults at high risk.
Reimbursement request	As per indication
Dosage form(s)	emtricitabine/tenofovir disoproxil fumarate 200 mg/300 mg tablets
NOC date	February 23, 2016
Manufacturer	Gilead Sciences Canada, Inc.

Emtricitabine/tenofovir disoproxil fumarate (Truvada) Common Drug Review Pharmacoeconomic Report was prepared using PharmaStat data from IMS Health Canada Inc. The analyses, conclusions, opinions and statements expressed are those of the Canadian Agency for Drugs and Technologies in Health and not those of IMS Health Canada Inc.

Redactions: Confidential information in this document has been redacted at the request of the manufacturer in accordance with the *CADTH Common Drug Review Confidentiality Guidelines.*

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

AIDS	acquired immune deficiency syndrome
ARV	antiretroviral
CDR	CADTH Common Drug Review
CEA	cost-effectiveness analysis
FTC	emtricitabine
HIV	human immunodeficiency virus
ICER	incremental cost-effectiveness ratio
IDU	intravenous drug user
MSM	men who have sex with men
PrEP	pre-exposure prophylaxis
STI	sexually transmitted infection
TDF	tenofovir disoproxil fumarate

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Truvada, FTC 200 mg (FTC)/TDF 300 mg (TDF)
Study Question	"To determine the cost-effectiveness of FTC/TDF for PrEP versus placebo, from a health care system perspective, in HIV-negative individuals at high risk of infection."
Type of Economic Evaluation	CEA
Target Population	Adult patients at high risk of sexually acquired HIV-1 infection
Treatment	FTC 200 mg/TDF 300 mg once daily, in addition to safer sex practices
Outcome(s)	• Cost per HIV infection prevented • Cost per life-years gained
Comparator(s)	Safer sex practices
Perspective	Canadian public payer
Time Horizon	Lifetime (approximately 35 years)
Results for Base Case	ICER at baseline infection rate of Serodiscordant heterosexual couples a) (2.0[a]) = $374,146 per HIV infection prevented, $287,804 per life-year gained b) (3.1) = $127,633 per HIV infection prevented, $98,179 per life-year gained MSM c) (4.3) = $2,553 per HIV infection prevented, $1,964 per life-year gained d) (6.9) and (9.0) = FTC/TDF is dominant
Key Limitations	CDR identified the following limitations with the submitted economic analysis: • The manufacturer's economic analysis did not capture important factors that can affect the cost-effectiveness of FTC/TDF as PrEP. The most critical one was that the analysis did not consider duration of prophylactic treatment with FTC/TDF, considering the cost of one year of treatment, which renders the presented results of limited applicability. The analysis does not account for the fact that a patient could be on prophylaxis treatment for a number of years (up to a lifetime) and/or interrupt and resume treatment over time. The model lacks the flexibility to test treatment duration and the associated effect, and compliance to treatment with time. Relevant population-level benefits that may occur from reducing the risk of HIV transmission were not considered. Also, the potential impact of behavioural disinhibition with the intervention (whereby individuals receiving FTC/TDF for PrEP increase their level of risk behaviour) was not captured. Finally, the results are reported in terms of cost per HIV infection prevented and cost per life-year gained, for which a willingness-to-pay threshold is uncertain. • The manufacturer's economic analysis was driven by the baseline rates of infection risk that were derived from the placebo groups at the completion of trials assessing FTC/TDF for PrEP. The reported baseline infection values may underestimate the actual values in practice, considering that patients in the trials' placebo arm were offered comprehensive HIV prevention services, which are not likely available for individuals outside PrEP follow-up. This assumption is conservative against FTC/TDF. • The submitted economic analysis utilized the rate of reduction in HIV for FTC/TDF based on trials in MSM patients (86%; PROUD and IPERGAY trials) and applied this rate to patient populations with high and low baseline rates of infections (i.e., serodiscordant heterosexual couple and MSM populations). Study design and patient selection, which may have led to overestimates of HIV incidence and baseline risk, raise uncertainty regarding the results. The manufacturer submitted

	two pivotal trials for FTC/TDF as PrEP (Partners PrEP and iPrEx trials) in serodiscordant heterosexual couples and MSM, respectively. Results from these studies were used for CDR analyses. However, limitations with these studies, especially related to their generalizability to the Canadian setting, raise uncertainty regarding their results.
CDR Estimates	CDR extended the analysis performed by the manufacturer, primarily to validate the point that the treatment is most likely to be cost-effective in populations of patients with a higher risk of HIV infection. As such, the reported efficacies (rate of reduction in HIV incidence infection) from the pivotal trials for serodiscordant heterosexual couples (75%) and MSM populations (44%) were used. These additional analyses confirmed that, as shown by the manufacturer, the results are dependent on the baseline infection rates. However, the numerical results reported by the manufacturer and resulting from the CDR analyses cannot be considered at face value, as the analytic approach taken by the manufacturer did not consider duration of prophylactic treatment. The only possible conclusion is that treating patients at higher risk of HIV infection is more likely to represent a cost-effectiveness usage of the treatment.

CDR = CADTH Common Drug Review; CEA = cost-effectiveness analysis; FTC = emtricitabine; FTC/TDF = emtricitabine/tenofovir disoproxil fumarate; HIV = human immunodeficiency virus; ICER = incremental cost-effectiveness ratio; MSM = men who have sex with men; PrEP = pre-exposure prophylaxis; TDF = tenofovir disoproxil fumarate.

[a] Baseline rates of infection are derived from the placebo group at the completion of trials assessing FTC/TDF for PrEP. These are expressed per 100 person-years, and represent the proportion of incidence of HIV infection for the trials' placebo arm, adjusted over a one-year period. For example, 2.0 denotes a lower risk group with baseline rates of infection of 2 per 100 person-years compared with 9.0 denoting a higher risk of 9 per 100 person-years.

EXECUTIVE SUMMARY

Background

Emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF) (200 mg/300 mg) (Truvada) is a fixed-dose combination (FDC) of two nucleoside reverse transcriptase inhibitors (NRTIs). FTC is converted in the cell into emtricitabine 5' triphosphate, and TDF is converted into tenofovir diphosphate. Both inhibit the activity of reverse transcriptase, which is used by human immunodeficiency virus type 1 (HIV-1) to replicate.[1] FTC/TDF is indicated for use in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired human immunodeficiency virus type 1 (HIV-1) infection in adults at high risk.[1] The manufacturer is requesting reimbursement as per the Health Canada–approved indication.[2]

Truvada is available as a 200 mg/300 mg tablet. The recommended dose is one tablet once daily.[1] The manufacturer submitted a confidential price of $29.08 per tablet ($29.08 daily).[2] Truvada (FTC/TDF) was previously reviewed for the treatment of HIV infection by the CADTH Canadian Drug Expert Committee (CDEC) and received a positive recommendation.[3]

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted a cost-effectiveness analysis (CEA) comparing FTC/TDF in combination with safer sex practices to safer sex practices alone. The analysis was conducted from the perspective of a Canadian public payer, over a lifetime time horizon (approximately 35 years). The CEA reported the results in terms of incremental cost per HIV infection prevented and incremental cost per life-year gained. In this analysis, the number of HIV infections prevented by treatment was determined by multiplying the baseline rate of infection by the efficacy (reduction of risk of infection) of FTC/TDF for PrEP. The cost of one year of FTC/TDF treatment was applied per patient. The number of HIV infections prevented was multiplied by the lifetime cost per infection, which was subtracted from the cost of FTC/TDF for PrEP therapy (one year of treatment). The resulting total cost was divided by the number of infections prevented to determine the cost per HIV infection prevented, and by the number of years of life saved (estimated based on the literature) for the cost per life-year gained.[2] The rate of reduction in HIV incidence seen in two pragmatic trials assessing men who have sex with men (MSM), 86%, was applied to the analysis.[2] Baseline rates of infection were derived from five trials, two in serodiscordant heterosexual couples and three in MSM. Baseline rates of infection were derived from the placebo groups at the completion of trials assessing FTC/TDF for PrEP. These are expressed per 100 person-years, and represent the proportion of the incidence of HIV infection for the trials' placebo arm, adjusted over a one-year period.

In the base-case analysis, FTC/TDF resulted in incremental cost-effectiveness ratios (ICERs) of $374,146 per HIV infection prevented and $127,633 per HIV infection prevented at the lowest baseline rates of infection of 2.0 per 100 person-years and 3.1 per 100 person-years, respectively (based on trials in serodiscordant heterosexual couples). In populations with higher baseline rates of infection (based on trials in MSM), FTC/TDF resulted in an ICER ranging from $2,553 per HIV infection prevented (rate of 4.3 per 100 person-years) to dominance (lower risk of HIV infection and less costly) over safer sex practices alone at the higher rates of 6.9 per 100 person-years and 9.0 per 100 person-years, respectively.

Summary of Identified Limitations and Key Results

The CADTH Common Drug Review (CDR) identified the following key limitations with the submitted economic analysis.

The main limitation was the choice of the approach for modelling, which was too simplistic and, more critically, did not consider the duration of prophylactic treatment with FTC/TDF (applying one year of treatment per patient), which renders the presented results of limited interest. Also, the model lacks the flexibility to vary parameters such as the treatment effect over the duration of treatment. Furthermore, it ignores the population-level benefits that may occur from reducing the risk of HIV transmission and the impact of therapy on the potential behavioural disinhibition with treatment, which may increase the level of risk of HIV infection. Such factors are likely to influence the cost-effectiveness of FTC/TDF as PrEP; however, this could not be tested by CDR because of the model's lack of flexibility. Other limitations identified were the uncertainty about the baseline rates of infection and the true efficacy and effectiveness of FTC/TDF for PrEP.

CDR reanalyses extended the assessment of the manufacturer to validate its conclusion that the higher the baseline rate of HIV infection, the more likely the intervention is to be cost-effective. CDR analyses showed that the ICER for FTC/TDF compared with safer sex practices alone ranged from $476,037 per HIV infection prevented to FTC/TDF dominating placebo (i.e., less costly and more effective), comparing a population at low risk of HIV infection with a population at high risk of HIV infection.

Conclusions

CDR's key limitation with the FTC/TDF economic submission is the approach used by the manufacturer to calculate the cost-effectiveness of FTC/TDF as PrEP. Many factors that may influence the likely cost-effectiveness of FTC/TDF as PrEP were not included, the critical one being that the model did not integrate duration of treatment as a factor. Patients can be on prophylaxis treatment for a number of years up to a lifetime, or may interrupt and resume treatment over time, which renders the presented results of limited interest and means they cannot be taken at face value. Alternative modelling using either individual-level or population-level transmission models, including variables about treatment duration, would have been necessary to appropriately inform the decision problem.

CDR analyses simply validated the conclusions from the manufacturer that the more high-risk the population for HIV infection, the most likely it is that the intervention will be cost-effective. The numerical results from both the manufacturer and CDR cannot be taken at face value and are of limited usage in the context of the decision problem.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-effectiveness analysis (CEA) comparing emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) in combination with safer sex practices to safer sex practices alone, to reduce the risk of sexually acquired human immunodeficiency virus (HIV) type 1 infections in adults at high risk. Patient populations assessed in the analysis were serodiscordant heterosexual couples and men who have sex with men (MSM). The analysis was conducted from the perspective of a Canadian public payer, from a lifetime time horizon. The CEA reported the cost per HIV infection prevented and the cost per life-year gained.

In the manufacturer's CEA, the number of HIV infections prevented by treatment was determined by multiplying the baseline rate of infection (infection rate per 100 person-years) by the efficacy of FTC/TDF for pre-exposure prophylaxis (PrEP). The number of HIV infections prevented was multiplied by the lifetime cost associated with one HIV infection; the resulting cost was subtracted from the cost of daily FTC/TDF treatment and monitoring for PrEP therapy over one year. This total cost was divided by the number of infections prevented to determine the cost per HIV infection prevented, and by the number of years of life gained to determine the cost per life-year gained.[2]

Multiple baseline rates of infection (infection rate per 100 person-years) were used for different scenario analyses. These were taken from the placebo groups of trials assessing FTC/TDF for PrEP. The infection rate was 2.0 per 100 person-years in Partners PrEP (serodiscordant heterosexual couples), while in iPrEx it was 4.3 per 100 person-years (MSM population).[4,5] Another trial in heterosexual men and women (CDC TDF2) had a placebo infection rate of 3.1 per 100 person-years. For two additional trials in MSM populations, IPERGAY and PROUD, the rates were respectively 6.9 per 100 person-years and 9.0 per 100 person-years, respectively.[6,7]

The efficacy for FTC/TDF was obtained from the IPERGAY and PROUD trials, which reported an 86% reduction in HIV infections with FTC/TDF for PrEP.[6,7] This value was used for all the scenarios assessed by the manufacturer's base case. The literature provided the estimate of the lifetime cost per HIV infection ($320,571)[8] as well as the years of life lost from one HIV infection (7.4 years).[9,10] A 5% discount rate was applied to these data. All costs were reported in 2016 Canadian dollars.

2. MANUFACTURER'S BASE CASE

The manufacturer's results for FTC/TDF were dependent on the baseline rate of infection risk for the underlying population (Table 2).

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

Baseline Rate of Infection (100 patient-years)	HIV Cases Prevented	Total Costs[b]	Cost per HIV Infection Prevented
Trials in Heterosexual Populations			
2.0	1.7	$643,530	$374,146
3.1	2.7	$340,270	$127,633
Trials in MSM			
4.3	3.7	$9,441	$2,553
6.9	5.9	($707,356)	Dominant[a]
9.0	7.7	($1,286,307)	Dominant[a]

FTC/TDF = emtricitabine/tenofovir disoproxil fumarate; HIV = human immunodeficiency virus; MSM = men who have sex with men.
Note: () denotes cost savings.
[a] A dominant option is associated with greater health gains and lower total costs.
[b] Lifetime savings for HIV infections prevented (discounted) + FTC/TDF treatment and monitoring cost per 100 person-year (not discounted).
Source: Adapted from manufacturer pharmacoeconomic submission, Table 11 (page 19) and Table 12 (page 20).[2]

3. SUMMARY OF MANUFACTURER'S SENSITIVITY ANALYSES

Sensitivity analyses were conducted by the manufacturer around the efficacy of FTC/TDF compared with placebo for both the discordant heterosexual couples and the MSM populations, using the results of adherent patients from the Partners PrEP (90% for the serodiscordant heterosexual couples population) and iPrEx trials (92% for the MSM population), respectively, and the intention-to-treat (ITT) data from Partners PrEP (75% for the serodiscordant heterosexual couples). Additional sensitivity analyses examined life-years gained and the lifetime cost of HIV infection based on alternative literature sources. FTC/TDF utilization was also varied from one pill daily to an alternate regimen that followed the IPERGAY study design: a loading dose of two pills two to 24 hours prior to sex, a third pill 24 hours after the loading dose, and a fourth pill 48 hours after the loading dose.[2]

Results of the manufacturer sensitivity analyses indicated that results were generally sensitive to variation in the parameters on efficacy, utilization, and lifetime costs of an HIV infection (Table 16).

4. LIMITATIONS OF MANUFACTURER'S SUBMISSION

- **Type of economic analysis:** The manufacturer's approach to assessing the cost-effectiveness of FTC/TDF for PrEP and to estimating the cost per HIV infection prevented represents an overly simplistic approach. The main issue was that the analysis did not consider the duration of prophylactic treatment with FTC/TDF, calculating the cost of treatment for only one year, which renders the presented results of limited interest. This is especially considering that a patient can be on prophylaxis treatment for a number of years up to a lifetime, or may interrupt and resume treatment over time. These variables were not integrated into the analysis. This represents an important limitation that cannot be assessed by CDR with the model provided by the manufacturer, and which render the numerical results presented of limited interest. Also, the approach does not provide population-level benefits that may occur from reducing the risk of HIV transmission by reducing the likelihood of infection among HIV-uninfected individuals. Next, the approach of the cost-effectiveness assessment lacks flexibility in assessing the effect of treatment across duration of treatment. Furthermore, the approach does not take into account potential individuals' behavioural

disinhibition with treatment, whereby individuals receiving FTC/TDF for PrEP increase their level of risky behaviour.

- **Baseline rates of infection:** One main driver of the manufacturer's economic analysis was the baseline rates of infection risk, taken from the clinical trials assessing FTC/TDF for PrEP (Partners PrEP, iPrEx, IPERGAY, PROUD, and TDF-2).[4-7,11] Although these rates were reported in the submitted economic report as reflecting the infection risk for the underlying (untreated) population under assessment, these infection rates were actually the clinical trials' incidence of HIV infection for the placebo groups at the trials' completion. The study design of these trials included all patients in the placebo groups to receive comprehensive HIV prevention services throughout the length of the trials, including testing, counselling, sexually transmitted infection (STI) treatment and free condoms. Therefore, these infection rate values may be an underestimation of the actual values in clinical practice, in which the untreated population is not likely to benefit from such HIV prevention services. This underestimation is in disfavour of FTC/TDF for PrEP.
- **Uncertainty over the effectiveness/efficacy of FTC/TDF as PrEP:** The submitted economic analysis utilized the rate of reduction in HIV infection by FTC/TDF based on the pragmatic trials in MSM patients (PROUD and IPERGAY), and applied the rate to patient populations with high and low baseline rates of infections (i.e., serodiscordant heterosexual couple population and MSM population). The CADTH Common Drug Review (CDR) Clinical Report for FTC/TDF in PrEP identified several limitations that raise uncertainty about the applicability of these studies' results in the submitted economic analysis, such as the generalizability of study results, study design, and the selection of patients that may have led to an overestimation of HIV incidence. (For detailed information, refer to the CDR Clinical Review Report.) Furthermore, as part of the clinical submission, the manufacturer submitted two pivotal trials for FTC/TDF as PrEP (Partners PrEP and iPrEx) in serodiscordant heterosexual couples and MSM, respectively. The reported efficacies for FTC/TDF from the two trials were not incorporated into the cost-effectiveness base-case analysis; only the efficacy in serodiscordant heterosexual couples was used in a sensitivity analysis. These two studies were used by CDR for conducting additional CEA. The CDR Clinical Review Report for FTC/TDF indicated that the limitations of the two studies were the generalizability of the results due to enrolled populations, and the unreliability of the reporting of adherence with the lack of correspondence to plasma drug levels. Therefore, the results of the Partners PrEP and iPrEx warrant cautious interpretation.

5. CADTH COMMON DRUG REVIEW REANALYSES

The manufacturer's analyses were developed to validate the manufacturer's conclusion, using alternative data, that the higher the risk of HIV infection for a given population, the more likely the intervention is to be cost-effective. The manufacturer applied the efficacy of FTC/TDF (86%) based on the IPERGAY and PROUD trials in MSM patients, and applied that rate to patient populations with high and low baseline rates of infections (i.e., serodiscordant heterosexual couples and MSM populations).[2] As part of the sensitivity analysis, the manufacturer tested the results from Partners PrEP (90% for adherent patients; 75% for the ITT population; for the serodiscordant heterosexual couples population) and from iPrEx (92% for adherent patients of the MSM population). CDR reanalyses were conducted that used the values from the ITT analyses of the two pivotal trials for FTC/TDF (Partners PrEx and iPrEx) in serodiscordant heterosexual couples (75%) and MSM populations (44%), respectively. The CDR analyses simply validated that the higher the risk of HIV infection is for a given population, the more likely the intervention is to be cost-effective. However, considering the limitations with the manufacturer's analytical approach, numerical results from both the manufacturer and CDR cannot be taken at face value.

Of note, the calculations proposed by the manufacturer used parameters that may lack transparency in some context. For this reason, using the same general approach and costs, CDR presented calculations of the results using n of patients for each individual trial as shown in **Error! Reference source not found.**APPENDIX 6.

TABLE 3: CADTH COMMON DRUG REVIEW ANALYSES RESULTS — EFFICACY RATE OF FTC/TDF FOR PREP

		Manufacturers' Base Case (Efficacy Rate of 86%)	CDR Reanalysis (Efficacy Rate of 75% in Heterosexuals, and 44% in MSM)
	Baseline Rate of Infection (per 100 Person-Years)	**Cost per HIV Infection Prevented**	**Cost per HIV Infection Prevented**
Trials in Heterosexual Populations	2.0	$374,146	$476,037
	3.1	$127,633	$193,370
Trials in MSM	4.3	$2,553	$310,990
	6.9	Dominant[a]	$73,010
	9.0	Dominant[a]	Dominant[a]

CDR = CADTH Common Drug Review; FTC/TDF = emtricitabine/tenofovir disoproxil fumarate; HIV = human immunodeficiency virus; MSM = men who have sex with men; PrEP = pre-exposure prophylaxis.
[a] A dominant option is associated with greater health gains and lower total costs.
Source: Manufacturer's base case results adapted from manufacturer pharmacoeconomic submission, Table 11 (page 19) and Table 12 (page 20).[2]

6. ISSUES FOR CONSIDERATION

The determination of high-risk patients may not be confirmed by validated clinical tools, but may instead be based on subjective observations by the examining physician, as noted by the clinical expert consulted by CDR. Such subjective observations may not always lead the physician to conduct further clinical or diagnostic exploration into the risk status of the patient. Using this informal approach to determining patients as high risk may lead to increased utilization of FTC/TDF.

7. PATIENT INPUT

The patient input information for FTC/TDF as PrEP was provided by three patient groups: Maggie's (Toronto Sex Workers Action Project), the Canadian Treatment Action Council (CTAC), and the AIDS Committee of Toronto (ACT). Patient groups highlighted improvements in quality of life in terms of reduced stress, anxiety, and fear associated with becoming HIV-positive and diminished barriers to intimacy or relationships between HIV serodiscordant individuals with the use of FTC/TDF. The manufacturer's economic analysis of FTC/TDF in PrEP did not incorporate improvements in quality of life. As for adherence to FTC/TDF as PrEP, some patients reported the use of FTC/TDF to be in addition to safe sex practices (i.e., condoms), while others regarded FTC/TDF as an alternative option to condoms, which may question the true efficacy and cost-effectiveness of the intervention in real-life settings.

8. CONCLUSIONS

The CDR's key limitation with the FTC/TDF economic submission is the approach used by the manufacturer to calculate the cost-effectiveness of FTC/TDF as PrEP. Many factors that may influence the likely cost-effectiveness of FTC/TDF as PrEP were not included, the critical one being that the model did not integrate duration of treatment as a factor. A patient can be on prophylaxis treatment for a number of years up to a lifetime, or may interrupt and resume treatment over time, which renders the presented results of limited interest, and they cannot be taken at face value. Alternative modelling using either individual-level or population-level transmission models, including variables about treatment duration, would have been necessary to appropriately inform the decision problem.

CDR analyses simply validated the conclusions from the manufacturer that the higher a population is at risk of HIV infection, the more likely the intervention is to be cost-effective. The numerical results from both the manufacturer and CDR cannot be taken at face value and are of limited usage in the context of the decision problem.

APPENDIX 1: COST COMPARISON

The treatment options presented in Table 4 have been deemed to be appropriate by clinical experts. Treatment options may be recommended (appropriate) practice versus actual practice. Costs are manufacturer list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table and as such may not represent the actual costs to public drug plans. Refer to APPENDIX 5 for the list of other antiretroviral (ARV) drugs for treatment-naive adult patients.

TABLE 4: COST COMPARISON TABLE FOR HIV ARV DRUGS IN PRE-EXPOSURE PROPHYLAXIS

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Use	Daily Cost ($)	Freq. of Use (Per Day)	No. Pills (Per Day)
Emtricitabine/tenofovir disoproxil fumarate (Truvada)	200 mg/ 300 mg	Tab	29.0800[a]	1 tablet daily	29.08	1	1
Tenofovir disoproxil (Viread)[b]	300 mg	Tab	19.1264	1 tablet daily	19.13	1	1

ARV = antiretroviral therapy; freq = frequency.
Note: All prices are from the Ontario Drug Benefit Formulary (accessed April 2016), unless otherwise indicated.[12]
[a] Manufacturer's submitted confidential price.[2]
[b] Based on the US Department of Health and Human Services guidelines on pre-exposure prophylaxis for the prevention of HIV infection in the United States (2014 update).[13]

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 5: WHEN CONSIDERING ONLY COSTS, OUTCOMES AND QUALITY OF LIFE, HOW ATTRACTIVE IS FTC/TDF RELATIVE TO PLACEBO?

FTC/TDF (Truvada) Versus Placebo	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	At baseline infection rate of I. (2.0) = $374,146 per HIV infection prevented II. (3.1) = $127,633 per HIV infection prevented III. (4.3) = $2,553 per HIV infection prevented IV. (6.9) and (9.0) = FTC/TDF is dominant					

CE = cost-effectiveness; FTC/TDF = emtricitabine/tenofovir disoproxil fumarate; HIV = human immunodeficiency virus; NA = not available.
Note: Based on manufacturer base-case results.[2]

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 6: 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 7: AUTHORS INFORMATION

Authors of the Pharmacoeconomic Evaluation Submitted to the CADTH Common Drug Review			
☐ Adaptation of Global model/Canadian model done by the manufacturer			
☐ Adaptation of Global model/Canadian model done by a private consultant contracted by the manufacturer			
☐ Adaptation of Global model/Canadian model done by an academic consultant contracted by the manufacturer			
☒ Other (please specify): Analysis was designed and conducted by a private consultant			
	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		

APPENDIX 4: REVIEWER WORKSHEETS

Manufacturer's Model Structure

In the manufacturer's cost-effectiveness analysis (CEA), the number of human immunodeficiency virus (HIV) infections prevented by treatment was determined by multiplying the baseline rate of infection by the efficacy of emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) for PrEP. The number of HIV infections prevented was multiplied by the cost per infection, and subtracted from the cost of FTC/TDF for PrEP therapy for 100 person-years, to yield the total cost. The total cost per 100 person-years was divided by the number of infections prevented to determine the cost per HIV infection prevented, and by the number of years of life preserved from HIV infection avoided for results in cost per life-year gained.[2]

TABLE 8: DATA SOURCES

Data Input	Description of Data Source	Comment
Baseline rate of infection	• Infection rates for placebo subjects were of 2.0 per 100 person-years in Partners PrEP, while in iPrEx it was 4.3 per 100 person-years. ○ Subgroups within each trial had varying levels of baseline risk, depending on their sexual practices (such as RAI) and use of prevention strategies (such as condom use).[14,15] • The only other relevant trial in a heterosexual population had a placebo infection rate of 3.1 per 100 person-years (CDC TDF2).[11] • Much higher baseline infection rates were seen in high-risk Western MSM populations: 6.9 per 100 person-years and 9.0 per 100 person-years in IPERGAY and PROUD, respectively.[6,7]	Uncertain. Reported values may not be reflective of actual baseline infection rates of the target patient population for this indication for FTC/TDF.
Efficacy	Reduction in seroconversions was based on published studies: • Partners PrEP[4] • A phase 3, randomized, DB study conducted in 4,758 serodiscordant couples in Kenya and Uganda. There were three comparator arms: daily FTC/TDF, daily TDF, and placebo. • iPrEx[5] • A phase 3, randomized, DB study conducted in 2,499 HIV-negative MSM from 11 sites in 6 countries (Peru, Ecuador, Brazil, US, Thailand, and South Africa). There were two comparator arms: daily oral FTC/TDF and placebo. • All patients/couples in both studies received comprehensive HIV prevention services throughout the trial, including testing, counselling, STI treatment, and free condoms.	Uncertainty over the generalizability of the results and reliability of adherence to medication reporting require results to be interpreted with caution.
Effectiveness	• IPERGAY[7] • A randomized, DB study conducted in 400 HIV-negative men who were having unprotected anal sex with men, conducted in France and Canada. There	• The manufacturer applied reduction rates from the pragmatic trials IPERGAY and PROUD.

Data Input	Description of Data Source	Comment
	were two comparator arms: coitally-timed FTC/TDF, and placebo. The FTC/TDF for PrEP regimen was a loading dose of two pills 2 to 24 hours before sex, a third pill 24 hours after the loading dose, and a fourth pill 48 hours after the loading dose. • PROUD[6] • A randomized, open-label study conducted in 544 HIV-negative men who were having unprotected anal sex with men, conducted in the United Kingdom. There were two comparator arms of daily oral FTC/TDF as PrEP: either immediate initiation, or deferred by one year. • All participants in IPERGAY and PROUD received comprehensive HIV prevention services throughout the trial, including testing, counselling, STI treatment, and free condoms.	• IPERGAY used an FTC/TDF regimen other than that indicated, but was assumed by the manufacturer to have achieved an efficacy rate equivalent to daily therapy at half the dose.
Life expectancy	• Canadian epidemiological data from three publications were used to estimate life expectancy for HIV-positive individuals starting ART at age 20.[9,10,16] • There are variations in life expectancy based on patient characteristics such as gender, IDU status, and race including Aboriginal ancestry.	
Costs		
Drug	• Ontario Drug Benefit Formulary[12] • Markup (8%) and dispensing fee ($8.83) every 90 days were included in the analysis.[2]	
Event	The Canadian lifetime cost of an HIV infection was based on a 2015 Canadian economic evaluation of dolutegravir that assumed initiation of ART at age 36.5 years, using the least costly strategy (initiation with dolutegravir + backbone) and a 5% discount rate ($312,128).[8]	Considered less than the lifetime costs estimated in the only other recent Canadian ART economic evaluations (up to $562,651 in 2014 Canadian dollars).[17] The manufacturer assumed it was in line with a CEA of community HIV interventions (lifetime cost of $296,965 in 2011 Canadian dollars).[18]

ART = antiretroviral therapy; DB = double-blind; CEA = cost-effectiveness analysis; FTC/TDF = emtricitabine/tenofovir disoproxil fumarate; HIV = human immunodeficiency virus; IDU = injection drug use; MSM = men who have sex with men; PrEP = pre-exposure prophylaxis; RAI = receptive anal intercourse; STI = sexually transmitted infection.

TABLE 9: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
The incidence of infection was assumed to be that observed in the various trials (ranging from 2.0 infections/100 person-years of exposure to 9.0 infections/100 person-years of exposure).	Uncertain. The baseline infection rates from the included studies were reported from the placebo groups of the respective trials at the end of the study period. The placebo groups in the included trials were provided with HIV prevention services throughout the trial, including testing, counselling, STI

Assumption	Comment
	treatment, and free condoms. Therefore, the reported baseline infection values may underestimate the values of actual patients in clinical practice, who may not have been offered the HIV prevention services.
It was assumed that individuals at lower risk would not be prescribed therapy nor be motivated to adhere to the therapy.	Appropriate
A 7.4-year loss in life expectancy for each case of HIV infection was assumed.	Uncertain
FTC/TDF could be initiated at either a sexual health clinic or in a GP office. It was assumed that all follow-up maintenance occurred within a GP office.	Appropriate as confirmed by the clinical expert consulted by CDR.
IPERGAY study used a FTC/TDF dosing regimen other than indicated. However, the manufacturer deemed that it had achieved an efficacy rate equivalent to daily therapy at half the dose.	Uncertain. The limitations identified with the IPERGAY study (i.e., underpowered to detect outcome measure, overestimation of HIV incidence, and generalizability of results) warrant cautious interpretation of study results.

CDR = CADTH Common Drug Review; FTC/TDF = emtricitabine/tenofovir disoproxil fumarate; GP = general practice; HIV = human immunodeficiency virus; STI = sexually transmitted infection.

Manufacturer's Results

The results of the manufacturer's base-case analyses varied depending on the baseline rates of infection attributed to serodiscordant heterosexual couples and MSM populations as observed in the trials (Partners PrEP, iPrEx, IPERGAY, PROUD, and TDF2).[4-7,11] In heterosexual populations, FTC/TDF resulted in an ICER ranging from $127,633 to $374,146 per each HIV infection prevented compared with placebo, while in the MSM patient population, FTC/TDF resulted in an ICER of $29,553 per HIV infection prevented compared with placebo at a baseline infection rate of 4.3 per 100 person-years; however, it dominated placebo (i.e., was less costly and more effective) at higher baseline infection rates (Table 10).

TABLE 10: MANUFACTURER BASE-CASE RESULTS — COST PER HIV INFECTION PREVENTED

Infection Rate per 100 Person-Years			Costs per 100 Person-Years			Cost per HIV Infection Prevented
Baseline	FTC/TDF for PrEP	Difference	HIV Cases Prevented	FTC/TDF for PrEP	Total Cost	
Trials in Heterosexual Populations						
2.0	0.3	–1.7	–$551,382	$1,194,913	$643,530	$374,146
3.1	0.4	–2.7	–$854,642	$1,194,913	$340,270	$127,633
Trials in MSM						
4.3	0.6	–3.7	–$1,185,472	$1,194,913	$9,441	$2,553
6.9	1.0	–5.9	–$1,902,268	$1,194,913	–$707,356	Dominant[a]
9.0	1.3	–7.7	–$2,481,220	$1,194,913	–$1,286,307	Dominant[a]

FTC/TDF = emtricitabine/tenofovir disoproxil fumarate; HIV = human immunodeficiency virus; MSM = men who have sex with men; PrEP = pre-exposure prophylaxis.

[a] A dominant option is associated with greater health gains and lower total costs.

Source: Manufacturer pharmacoeconomic submission, Table 11, page 19.[2]

The results of FTC/TDF in terms of cost per life-year gained were also dependent on the baseline rate of infection, with FTC/TDF resulting in ICERs ranging from $98,179 to $287,804 per year of life gained compared with placebo in serodiscordant heterosexual couples while resulting in an incremental cost-effectiveness ratio (ICER) ranging from $1,964 per life-year gained to FTC/TDF being dominant in MSM patients (Table 11).

TABLE 11: MANUFACTURER BASE-CASE RESULTS — COST PER LIFE-YEAR GAINED

Baseline Rate of Infection (per 100 Person-Years)	HIV Cases Prevented	Total Cost	Life-years Gained	Cost per Year of Life Gained
Trials in Heterosexual Populations				
2.0	–1.7	$643,530	2.24	$287,804
3.1	–2.7	$340,270	3.47	$98,179
Trials in MSM				
4.3	–3.7	$9,441	4.81	$1,964
6.9	–5.9	–$707,356	7.71	Dominant[a]
9.0	–7.7	–$1,286,307	10.06	Dominant[a]

HIV = human immunodeficiency virus; MSM = men who have sex with men.
[a] A dominant option is associated with greater health gains and lower total costs.
Source: Manufacturer pharmacoeconomic submission, Table 12, page 20.[2]

Manufacturer's Sensitivity Analyses

The manufacturer conducted several one-way sensitivity analyses that varied the following parameters of the model:

- FTC/TDF effectiveness: the efficacy of FTC/TDF for PrEP was varied from 86% to 90% (for heterosexuals) and to 92% (for MSM) based on the adherent patients from Partners PrEP and iPrEx, respectively.

TABLE 12: MANUFACTURER SENSITIVITY ANALYSIS RESULTS — HIGHER EFFICACY RATE OF FTC/TDF FOR PREP

Infection Rate per 100 Person-Years			Costs per 100 Person-Years			Cost per HIV Infection Prevented
Baseline	FTC/TDF for PrEP	Difference	HIV Cases Prevented	FTC/TDF for PrEP	Total Cost	
Trials in Heterosexual Populations						
2.0	0.3	–1.8	–$577,028	$1,194,913	$617,885	$343,269
3.1	0.4	–2.8	–$894,393	$1,194,913	$300,520	$107,713
Trials in MSM						
4.3	0.6	–4.0	–$1,268,179	$1,194,913	–$73,266	Dominant[a]
6.9	1.0	–6.3	–$2,034,985	$1,194,913	–$840,072	Dominant[a]
9.0	1.3	–8.3	–$2,654,328	$1,194,913	–$1,459,415	Dominant[a]

FTC/TDF = emtricitabine/tenofovir disoproxil fumarate; HIV = human immunodeficiency virus; MSM = men having sex with men; PrEP = pre-exposure prophylaxis.
[a] A dominant option is associated with greater health gains and lower total costs.
Source: Manufacturer pharmacoeconomic submission, Table 13, page 20.[2]

- In another sensitivity analysis, the efficacy of FTC/TDF for PrEP was reduced to 75% for heterosexuals only, based on results from the ITT analysis of the Partners PrEP study[4] (Table 13).

TABLE 13: MANUFACTURER SENSITIVITY ANALYSIS RESULTS — LOWER EFFICACY OF FTC/TDF FOR PREP (75% RATE REDUCTION, HETEROSEXUALS ONLY)

Infection Rate per 100 Person-Years			Costs per 100 Person-Years			Cost per HIV Infection Prevented
Baseline	FTC/TDF for PrEP	Difference	HIV Cases Prevented	FTC/TDF for PrEP	Total Cost	
Trials in Heterosexual Populations						
2.0	0.5	–1.5	–$480,857	$1,194,913	$714,056	$476,037
3.1	0.8	–2.3	–$745,328	$1,194,913	$449,585	$193,370

FTC/TDF = emtricitabine/tenofovir disoproxil fumarate; HIV = human immunodeficiency virus; PrEP = pre-exposure prophylaxis.
Source: Manufacturer pharmacoeconomic submission, Table 14, page 21.[2]

- Cost of lifetime HIV: the manufacturer conducted a sensitivity analysis that increased the lifetime costs of an HIV infection from $320,571 to $574,471 per patient based on another Canadian published trial that estimated the lifetime costs (Table 14).[17]

TABLE 14: MANUFACTURER SENSITIVITY ANALYSIS RESULTS — HIGHER LIFETIME COST PER HIV INFECTION

Infection Rate per 100 Person-Years			Costs per 100 Person-Years			Cost per HIV Infection Prevented
Baseline	FTC/TDF for PrEP	Difference	HIV Cases Prevented	FTC/TDF for PrEP	Total Cost	
Trials in Heterosexual Populations						
2.0	0.3	–1.7	–$988,091	$1,194,913	$206,822	$120,245
3.1	0.4	–2.7	–$1,531,541	$1,194,913	–$336,628	Dominant[a]
Trials in MSM						
4.3	0.6	–3.7	–$2,124,395	$1,194,913	–$929,483	Dominant[a]
6.9	1.0	–5.9	–$3,408,913	$1,194,913	–$2,214,001	Dominant[a]
9.0	1.3	–7.7	–$4,446,409	$1,194,913	–$3,251,496	Dominant[a]

FTC/TDF = emtricitabine/tenofovir disoproxil fumarate; HIV = human immunodeficiency virus; MSM = men who have sex with men; PrEP = pre-exposure prophylaxis.
[a] A dominant option is associated with greater health gains and lower total costs.
Source: Manufacturer's pharmacoeconomic submission, Table 15, page 21.[2]

- FTC/TDF utilization: based on the treatment regimen reported in the IPERGAY study (a loading dose of two pills two to 24 hours before sex, a third pill 24 hours after the loading dose, and a fourth pill 48 hours after the loading dose), the manufacturer conducted a sensitivity analysis that reduced the utilization from one pill daily to align with the IPERGAY regimen; this resulted in the annual utilization of FTC/TDF falling from 365 tablets to 180 tablets (Table 15).[2,7] Reducing the annual drug costs for FTC/TDF significantly affected the resulting ICER for FTC/TDF in heterosexual patients.

TABLE 15: MANUFACTURER SENSITIVITY ANALYSIS RESULTS — REDUCED DOSAGE OF FTC/TDF FOR PREP

Infection Rate per 100 Person-Years			Costs per 100 Person-Years			Cost per HIV Infection Prevented
Baseline	FTC/TDF for PrEP	Difference	HIV Cases Prevented	FTC/TDF for PrEP	Total Cost	
Trials in Heterosexual Populations						
2.0	0.3	–1.7	–$551,382	$612,079	$60,697	$35,289
3.1	0.4	–2.7	–$854,642	$612,079	–$242,563	Dominant[a]
Trials in MSM						
4.3	0.6	–3.7	–$1,185,472	$612,079	–$573,392	Dominant[a]
6.9	1.0	–5.9	–$1,902,268	$612,079	–$1,290,189	Dominant[a]
9.0	1.3	–7.7	–$2,481,220	$612,079	–$1,869,141	Dominant[a]

FTC/TDF = emtricitabine/tenofovir disoproxil fumarate; HIV = human immunodeficiency virus; MSM = men having sex with men; PrEP = pre-exposure prophylaxis.
[a] A dominant option is associated with greater health gains and lower total costs.
Source: Manufacturer's pharmacoeconomic submission, Table 16, page 22.[2]

TABLE 16: SUMMARY OF RESULTS OF THE MANUFACTURER'S SENSITIVITY ANALYSES

	Cost per HIV Infection Prevented					Cost per Year of Life Gained	
Baseline Rate of Infection (100 person-years)	Base-Case Results	Higher Efficacy for FTC/TDF (90% for Heterosexuals, 92% for MSM)	Lower Efficacy for FTC/TDF (75% for Heterosexuals Only)	Higher Lifetime Costs per HIV Infection	Reduced Dosage of FTC/TDF for PrEP	Base-Case Result	Alternate Years of Life Gained (From 1.3 to 1.6)
Trials in Heterosexual Populations							
2.0	$374,146	$343,269	$476,037	$120,245	$35,289	$287,804	$233,841
3.1	$127,633	$107,713	$193,370	Dominant[a]	Dominant[a]	$98,179	$79,771
Trials in MSM							
4.3	$2,553	Dominant[a]	N/A	Dominant[a]	Dominant[a]	$1,964	$1,596
6.9	Dominant[a]	Dominant[a]	N/A	Dominant[a]	Dominant[a]	Dominant[a]	Dominant[a]
9.0	Dominant[a]	Dominant[a]	N/A	Dominant[a]	Dominant[a]	Dominant[a]	Dominant[a]

FTC/TDF = emtricitabine/tenofovir disoproxil fumarate; HIV = human immunodeficiency virus; MSM = men having sex with men; PrEP = pre-exposure prophylaxis.
[a] A dominant option is associated with greater health gains and lower total costs.
Source: Adapted from manufacturer's pharmacoeconomic submission, Tables 13 to 17 (pages 20 to 22).[2]

APPENDIX 5: OTHER ANTIRETROVIRAL DRUGS FOR TREATMENT-NAIVE ADULT PATIENTS

The treatment options presented in Table 13 are from the recommended and alternative regimens options for treatment-naive patients in the US Department of Health and Human Services guidelines for the use of antiretroviral (ARV) drugs in HIV-1-infected adults (2015).[13]

TABLE 17: COST COMPARISON TABLE FOR HIV ANTIRETROVIRAL DRUGS IN TREATMENT-NAIVE ADULT PATIENTS

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Use	Daily Cost ($)	Freq. of Use (Per Day)	No. Pills (Per Day)
Recommended Antiretroviral Regimen Options							
INSTI-based							
Dolutegravir/abacavir/ Lamivudine (Triumeq)	50 mg/ 600 mg / 300 mg	Tab	41.3834	1 tablet daily	41.38	1	1
Dolutegravir (Tivicay) + Emtricitabine/tenofovir (Truvada)	50 mg 200 mg/ 300 mg	Tab	18.6665 28.5710	50 mg daily 1 tablet daily	47.24	1	2
Elvitegravir/cobicistat/ tenofovir alafenamide /emtricitabine (Genvoya)	150 mg/ 150 mg/ 10 mg/ 300 mg	Tab	46.3894[b]	1 tablet daily	46.39	1	1
Elvitegravir/cobicistat/ tenofovir disoproxil/ emtricitabine (Stribild)	150 mg/ 150 mg/ 200 mg/ 300 mg	Tab	46.3894	1 tablet daily	46.39	1	1
Raltegravir (Isentress) + Emtricitabine/tenofovir (Truvada)	400 mg 200 mg/ 300 mg	Tab	13.9050 28.5710	400 mg twice daily 1 tablet daily	56.38	2	3
PI-Based							
Darunavir (Prezista) with ritonavir (Norvir) + Emtricitabine/tenofovir (Truvada)	800 mg 100 mg 200 mg/ 300 mg	Tab	21.7160 1.5183 28.5710	800 mg daily 100 mg daily 1 tablet daily	51.81	1	3
Alternative Antiretroviral Regimen Options							
NNRTI-based							
Efavirenz/tenofovir disoproxil/Emtricitabine (Atripla)	600 mg/ 300 mg/ 200 mg	Tab	43.7833	1 tablet daily	43.78	1	1
Rilpivirine/tenofovir disoproxil/Emtricitabine (Complera)	25 mg/ 300 mg/ 200 mg	Tab	43.3428	1 tablet daily	43.34	1	1
PI-based							
Atazanavir (Reyataz) with ritonavir(Norvir) +	300 mg 100 mg	Cap	21.6003 1.5183	150 mg to 300 mg daily 100 mg daily	52.47	1	3

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Use	Daily Cost ($)	Freq. of Use (Per Day)	No. Pills (Per Day)
Emtricitabine/tenofovir (Truvada)	200 mg/ 300 mg		28.5710	1 tablet daily			
Atazanavir/cobicistat (Evotaz) + Emtricitabine/tenofovir (Truvada)	300 mg/ 150 mg 200 mg/ 300 mg	Tab	23.0500[b] 28.5710	1 tablet daily 1 tablet daily	51.62	1	2
Darunavir/cobicistat (Prezcobix) + Abacavir/lamivudine (Kivexa)	800 mg/ 150 mg 600 mg/ 300 mg	Tab	21.6240[b] 23.9498	1 tablet daily 1 tablet daily	47.12	1	2
Darunavir (Prezista) with ritonavir (Norvir) + Abacavir/lamivudine (Kivexa)	800 mg 100 mg 600 mg/ 300 mg	Tab	21.7160 1.5183 23.9498	800 mg daily 100 mg daily 1 tablet daily	47.18	1	3
Darunavir/cobicistat (Prezcobix) + Emtricitabine/tenofovir (Truvada)	800 mg/ 150 mg 200 mg/ 300 mg	Tab	21.6240[b] 28.5710	1 tablet daily 1 tablet daily	50.20	1	2

freq = frequency; INSTI = integrase strand transfer inhibitors; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor.

Notes:

- Based on the US Department of Health and Human Services guidelines for the use of antiretroviral drugs in adults infected with the human immunodeficiency virus (HIV) type 1 (2015 update).[13]
- All prices are from the Ontario Drug Benefit Formulary (accessed October 2015), unless otherwise indicated.[12]

[a] Quebec Drug Benefit Formulary (accessed April 2016).[19]

[b] Delta PA IMS Brogan.[20]

APPENDIX 6: CALCULATIONS OF THE RESULTS USING THE NUMBER OF PATIENTS FOR EACH INDIVIDUAL TRIAL

	iPrEx[5]		Partner's PrEP[4]		CDC TDF2[11]		IPERGAY[7]		PROUD[6]	
	FTC/TDF	**Placebo**	**FTC/TDF**	**Placebo**	**FTC/TDF**	**Placebo**	**FTC/TDF**	**Placebo**	**FTC/TDF Immediate**	**FTC/TDF Deferred**
HIV-1 seroconversion (mITT set), n	**1,224**	**1,217**	**1,576**	**1,578**	**601**	**599**	**199**	**201**	**268**	**255**
Person-years of follow-up	1,659	1,669	2,616	2,607	1,563	1,563	431	431	259	245
Participants with seroconversion events, n	36	64	13	52	9	24	2	14	3	20
Rate per 100 person-years	2.2	3.8	0.5	1.99	1.2	3.1	0.91	6.6	1.2	9
Cost FTC/TDF prophylaxis (annual) *(cost of FTC/TDF multiplied by n from HIV-1 seroconversion mITT set)*	$14,625,731	$0	$18,831,823	$0	$7,181,425	$0	$2,377,876	$0	$3,202,366	$0
Cost HIV infection (lifetime) *(cost of HIV infection multiplied by number of participants with seroconversions)*	$11,540,557	$20,516,545	$4,167,423	$16,669,693	$2,885,139	$7,693,705	$641,142	$4,487,994	$961,713	$6,411,420
Total cost	$26,166,288	$20,516,545	$22,999,247	$16,669,693	$10,066,564	$7,693,705	$3,019,018	$4,487,994	$4,164,079	$6,411,420
Incremental cost (for FTC/TDF)[a]	$5,649,742		$6,329,554		$2,372,860		–$1,468,976		–$2,247,341	

FTC/TDF = emtricitabine/tenofovir disoproxil fumarate; HIV = human immunodeficiency virus; mITT = modified intention-to-treat; PrEP = pre-exposure prophylaxis.

[a] A negative incremental cost denotes cost savings with FTC/TDF.

REFERENCES

1. PrTruvada® (Emtricitabine/Tenofovir Disoproxil Fumarate) Tablets (200 mg/300 mg) Antiretroviral Agent [product monograph]. Mississauga (ON): Gilead Sciences Canada Inc.; 2016 Mar 24.
2. Pharmacoeconomic evaluation. In: CDR submission: TRUVADA® (emtricitabine / tenofovir disoproxil fumarate) Company: Gilead Sciences Canada Inc. [**CONFIDENTIAL** manufacturer's submission]. Mississauga (ON): Gilead Sciences Canada Inc.; 2016 Mar 9.
3. Common Drug Review. CEDAC final recommendation and reasons for recommendation. Tenofovir/emtricitabine request for advice (Truvada® - Gilead Sciences Canada, Inc.) [Internet]. Ottawa: CADTH; 2008. [cited 2016 May 3]. Available from: https://www.cadth.ca/sites/default/files/cdr/complete/cdr_truvada_rfa_complete-dec17-08.pdf
4. Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med [Internet]. 2012 Aug 2 [cited 2016 Apr 1];367(5):399-410. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3770474/pdf/nihms493581.pdf
5. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med [Internet]. 2010 Dec 30 [cited 2016 Apr 1];363(27):2587-99. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3079639/pdf/nihms264954.pdf
6. McCormack S, Dunn DT, Desai M, Dolling DI, Gafos M, Gilson R, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. Lancet [Internet]. 2016 Jan 2 [cited 2016 Apr 1];387(10013):53-60. Available from: http://www.sciencedirect.com/science/article/pii/S0140673615000562
7. Molina JM, Capitant C, Spire B, Pialoux G, Cotte L, Charreau I, et al. On-demand preexposure prophylaxis in men at high risk for HIV-1 infection. N Engl J Med. 2015 Dec 3;373(23):2237-46.
8. Despiegel N, Anger D, Martin M, Monga N, Cui Q, Rocchi A, et al. Cost-effectiveness of dolutegravir in HIV-1 treatment-naive and treatment-experienced patients in Canada. Infect Dis Ther [Internet]. 2015 Sep [cited 2016 May 18];4(3):337-53. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4575289
9. Patterson S, Cescon A, Samji H, Chan K, Zhang W, Raboud J, et al. Life expectancy of HIV-positive individuals on combination antiretroviral therapy in Canada. BMC Infect Dis [Internet]. 2015 [cited 2016 May 18];15:274. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4504463
10. Samji H, Cescon A, Hogg RS, Modur SP, Althoff KN, Buchacz K, et al. Closing the gap: increases in life expectancy among treated HIV-positive individuals in the United States and Canada. PLoS ONE [Internet]. 2013 [cited 2016 May 18];8(12):e81355. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3867319
11. Thigpen MC, Kebaabetswe PM, Paxton LA, Smith DK, Rose CE, Segolodi TM, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. N Engl J Med [Internet]. 2012 Aug 2 [cited 2016 Apr 1];367(5):423-34. Available from: http://www.nejm.org/doi/pdf/10.1056/NEJMoa1110711
12. Ontario drug benefit formulary/comparative drug index: electronic version [Internet]. 2.2. Toronto: Ministry of Health and Long-Term Care; 2007 - [cited 2016 May 18; modified 2011 Jan 4]. Available from: https://www.healthinfo.moh.gov.on.ca/formulary/index.jsp

13. U.S. Public Health Service. Preexposure prophylaxis for the prevention of HIV infection in the United States - 2014: a clinical practice guideline [Internet]. Atlanta (GA): Centers for Disease Control and Prevention; 2014. 67 p. [cited 2016 May 19]. Available from: http://www.cdc.gov/hiv/pdf/prepguidelines2014.pdf

14. Buchbinder SP, Glidden DV, Liu AY, McMahan V, Guanira JV, Mayer KH, et al. HIV pre-exposure prophylaxis in men who have sex with men and transgender women: a secondary analysis of a phase 3 randomised controlled efficacy trial. Lancet Infect Dis [Internet]. 2014 Jun [cited 2016 Apr 1];14(6):468-75. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4133171/pdf/nihms600835.pdf

15. Murnane PM, Celum C, Mugo N, Campbell JD, Donnell D, Bukusi E, et al. Efficacy of preexposure prophylaxis for HIV-1 prevention among high-risk heterosexuals: subgroup analyses from a randomized trial. AIDS [Internet]. 2013 Aug 24 [cited 2016 Apr 1];27(13):2155-60. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3882910/pdf/nihms505879.pdf

16. Lima VD, Eyawo O, Ma H, Lourenco L, Chau W, Hogg RS, et al. The impact of scaling-up combination antiretroviral therapy on patterns of mortality among HIV-positive persons in British Columbia, Canada. J Int AIDS Soc [Internet]. 2015 [cited 2016 May 18];18:20261. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4598331

17. Brogan AJ, Smets E, Mauskopf JA, Manuel SA, Adriaenssen I. Cost effectiveness of darunavir/ritonavir combination antiretroviral therapy for treatment-naive adults with HIV-1 infection in Canada. PharmacoEconomics. 2014 Sep;32(9):903-17.

18. Choi SK, Holtgrave DR, Bacon J, Kennedy R, Lush J, McGee F, et al. Economic evaluation of community-based HIV prevention programs in Ontario: evidence of effectiveness in reducing HIV infections and health care costs. AIDS Behav. 2016 Jun;20(6):1143-56.

19. Régie de l'assurance maladie Québec [Internet]. Quebec (QC): Gouvernement du Québec; 2016. Liste des médicaments; 2016 [cited 2016 Apr 22]. Available from: http://www.ramq.gouv.qc.ca/fr/regie/publications-legales/Pages/liste-medicaments.aspx#

20. DeltaPA [database on the Internet]. Ottawa: IMS Brogan; 2016. [cited 2016 Apr 22]. Available from: http://www.imsbrogancapabilities.com/en/market-insights/delta-pa.html Subscription required.