Common Drug Review
Clinical 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.
Listing 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.

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

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ABBREVIATIONS

AE	adverse event
ART	antiretroviral therapy
CDC	Centres for Disease Control and Prevention
CDR	CADTH Common Drug Review
CI	confidence interval
DB	double-blind
FDA	Food and Drug Administration
FDC	fixed-dose combination
FTC	emtricitabine
FTC/TDF	emtricitabine/tenofovir disoproxil fumarate
HIV-1	human immunodeficiency virus type 1
IQR	interquartile range
MSM	men who have sex with men
OL	open-label
OLE	open-label extension (study)
PC	placebo-controlled
RAI	receptive anal intercourse
RCT	randomized controlled trial
RNA	ribonucleic acid
SAE	serious adverse event
STI	sexually transmitted infection
TDF	tenofovir disoproxil fumarate
TFV	tenofovir
URAI	unprotected receptive anal intercourse
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Human immunodeficiency virus (HIV) attacks CD4+ T cells, components of the immune system necessary for defending the body against infection, and, if left untreated, may lead to acquired immunodeficiency syndrome (AIDS). Despite the wide availability and effectiveness of condoms in reducing sexual transmission, significant numbers of new HIV infections occur annually. The Public Health Agency of Canada estimates that 2,570 new infections (range: 1,940 to 3,200) occurred in Canada in 2014, with an estimated incidence rate of 7.2 per 100,000 population (range 5.5 to 9.0 per 100,000 population).[1] There were approximately 1,396 new infections in 2014 in men who have sex with men (MSM), representing 54.3% of all new infections.[2] Current HIV prevention strategies focus on behaviour change, and include education about sexual health and safer sex, reducing substance use or promoting safer substance use, and encouraging those at risk to get properly tested and diagnosed. Pre-exposure prophylaxis (PrEP) for HIV is the use of drug therapy by HIV-negative individuals to reduce their risk of acquiring HIV infection. Emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) 200 mg/300 mg is a fixed-dose combination (FDC) tablet containing emtricitabine, a nucleoside HIV type 1 (HIV-1) reverse transcriptase inhibitor, and tenofovir disoproxil fumarate, the prodrug of tenofovir, a nucleotide analogue reverse transcriptase inhibitor. FTC/TDF is the only antiretroviral therapy indicated for PrEP in adults at high risk of acquiring HIV-1 infection. FTC/TDF is also indicated for use in combination with other antiretroviral drugs for the treatment of HIV-1 infection in adults; however, this indication is not the focus of this review.

Indication under review
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.
Listing criteria requested by sponsor
As per indication.

The objective of this review is to perform a systematic review of the beneficial and harmful effects of FTC/TDF 200 mg/300 mg, once daily, in combination with safer sex practices for PrEP to reduce the risk of sexually acquired HIV-1 infection in adults at high risk.

Results and Interpretation

Included Studies

Three double-blind (DB), placebo-controlled, randomized controlled trials (RCTs) assessing the safety and efficacy of once-daily FTC/TDF 200 mg/300 mg as PrEP in combination with HIV prevention services for adults at high risk of acquiring HIV-1 infection met the inclusion criteria for this review. All studies randomized participants in a 1:1 ratio to FTC/TDF or placebo. The iPrEx study (N = 2,499) was an international study conducted in adult MSM that continued until at least 85 seroconversion events occurred. The Partners PrEP study (N = 4,758) was conducted in adult Kenyan and Ugandan sexually active, serodiscordant, heterosexual couples who were followed for two to three years. The Centres for Disease Control's (CDC's) TDF2 study (N = 1,219) was conducted in Botswanan heterosexual men and women between 18 and 39 years who were sexually active; the study duration was planned for four years. The CDC TDF2 study was concluded early due to the lower-than-expected rate of retention of participants. In all three studies, study visits were scheduled every four weeks and included drug

dispensing, rapid blood testing for HIV-1 antibodies, adherence counselling, risk-reduction counselling, condom promotion, and treatment of symptomatic sexually transmitted infections (STIs) for all patients regardless of treatment group. In all studies, the primary end point was the incidence of HIV-1 infections based on rapid testing at each monthly visit using pre-specified testing algorithms. Other end points evaluated included sexual behaviour, the incidence of STIs, adherence to study drug, and HIV-1 drug resistance in seroconversion participants.

One of the main limitations of the included studies was the generalizability of results, due to the enrolled population. The iPrEx study enrolled MSM who were at very high risk of acquiring HIV-1 infection; the Partners PrEP study included serodiscordant couples in which the HIV-1–positive partner was not to be taking antiretroviral therapy (ART); and the majority of enrolled participants were from Hispanic (iPrEx) or African countries (Partners PrEP and CDC TDF2). As such, the characteristics of the patients enrolled in these trials may not reflect the full spectrum of patients who would be seen in the Canadian setting. Measures of treatment adherence were based on pill count and patient self-report, and may therefore have been subject to bias. As no adjustments for multiple testing were performed for secondary end points, results need to be interpreted with caution due to the potential for type I error. Although quality of life was cited as an important outcome according to the patient groups who provided input for this submission, health-related quality of life was not measured in any of the included studies.

Efficacy

In the iPrEx study, participants had been followed for a median of 1.2 years (range 1 day to 2.8 years) at the time of the primary data analysis. In the Partners PrEP study, HIV-1–negative partners were followed for a median of 23 months (range: one to 36 months). In the CDC TDF2 study, participants were followed for a median of 1.1 years (maximum: 3.7 years) before the study was concluded.

The incidence of HIV-1 seroconversion was the primary efficacy end point in all studies. Paired rapid HIV tests were administered at each monthly visit, and discordant or positive results were retested or confirmed using rigorous testing algorithms. In the primary efficacy analysis, participants determined to be HIV-positive at baseline were excluded. In all studies, there was a statistically significant reduction in the incidence of HIV-1 seroconversion with FTC/TDF compared with placebo. In the iPrEx study, there was a relative risk reduction of 44% (95% confidence interval [CI], 15% to 63%; *P* = 0.005) in HIV-1 seroconversion with FTC/TDF versus placebo. [redacted]. In the Partners PrEP study, there was a relative risk reduction of 75% (95% CI, 55% to 87%; *P* < 0.001) in HIV-1 seroconversion with FTC/TDF versus placebo. [redacted]. In the CDC TDF2 study, there was a relative risk reduction of 62.2% (95% CI, 21.5% to 83.4%; *P* = 0.03) in HIV-1 seroconversion with FTC/TDF versus placebo.

In all studies, an analysis of drug level detection in all HIV-1 seroconversion cases and matched controls (participants who did not seroconvert) was performed. All studies examined plasma levels of the drug components, and the iPrEx study also looked at intracellular drug levels. In the iPrEx study, there was detectable plasma FTC and tenofovir (TFV) in 6% of HIV-1 seroconversion participants compared with [redacted] of control participants. In the Partners PrEP study, there was detectable plasma TFV (FTC levels were not evaluated) in [redacted] of HIV-1 seroconversion participants compared with [redacted] of control

participants. In the CDC TDF2 study, there was detectable plasma FTC and TFV in 50% of HIV-1 seroconversion participants compared with approximately 80% of control participants.

In the iPrEx study, the mean and median rate of self-reported pill use was similar between the FTC/TDF and placebo groups (mean: 88.7% versus [redacted]; median: [redacted] for both groups). In the Partners PrEP study, study drug adherence was assessed using pill counts from returned study bottles; more than 98% of dispensed study bottles were returned, and 94% of dispensed study tablets were taken across treatment groups. In the CDC TDF2 study, rates of adherence were estimated to be similar across treatment groups according to pill counts (FTC/TDF 84.1% versus placebo 83.7%), and self-reported adherence for the preceding three days (FTC/TDF 94.4% versus placebo 94.1%). In the Partners PrEP study, an adherence sub-study (N = 1,147) was conducted, in which unannounced, home-based pill counts were conducted monthly for the first six months and then quarterly. Results from this sub-study suggested that adherence was high in the Partners PrEP study across treatment groups (mean: 98%) and corroborated by the results from self-report and pill counts in the full study. No adherence sub-studies were conducted in the iPrEx and CDC TDF2 study.

In addition to daily FTC/TDF or placebo, participants were given risk-reduction counselling at each monthly visit and were connected with existing local prevention services when required in the studies. Overall, no differences in sexual behaviour were seen between the FTC/TDF and placebo groups across studies. In the iPrEx study, the number of receptive anal intercourse (RAI) partners in the past 12 weeks decreased during the study from a mean of approximately 12 partners to a mean of fewer than five partners, and the percentage of those partners who used a condom increased from 50% to more than 70%. In the Partners PrEP study at enrolment, 27% of HIV-1–negative participants reported having had sex without a condom during the previous month. This percentage decreased during the follow-up period to 13% and 9% at 12 and 24 months, respectively, and this was similar between treatment groups. In the CDC TDF2 study, the percentage of sexual episodes using condoms with the main or most recent sexual partner was 81.4% (range: 76.6% to 86.4%) in the FTC/TDF group and 79.2% (range: 71.6% to 87.6%) in the placebo group at baseline, and remained similar between groups and stable over 24 weeks. The number of sexual partners in the previous month was similar between treatment groups throughout the study and declined slightly over time ($P < 0.001$ for trend; $P = 0.95$ between treatment groups). Because sexual risk behaviour was self-reported, results may be biased by social desirability and the incidence of STIs may be a more objective measure of sexual behaviour. However, the proportion of participants with STIs over time was not reported in any of the included studies, although the incidence of STIs was similar between the FTC/TDF and placebo groups.

In the patient input group submission, participants expressed that FTC/TDF PrEP would alleviate their anxiety and fear of becoming HIV-positive after engaging in risky sexual behaviour, whether it be condomless sex or sex with HIV-1–positive partners. However, health-related quality of life was not assessed in any of the included studies.

Harms

Overall, the incidence of adverse events (AEs) was similar across the FTC/TDF and placebo groups in the iPrEx study (69% versus 70%), the Partners PrEP study (86% versus 85%), and the CDC TDF2 study (91% versus 88%). Common AEs among the three studies included upper respiratory tract infection, pharyngitis, diarrhea, and headache. In the CDC TDF2 study, common AEs also included abdominal pain, dizziness, nausea, vomiting, and weight loss. The incidence of AEs was similar across the FTC/TDF and placebo groups in the iPrEx study (5% for both groups), the Partners PrEP study (7% for both groups), and the CDC TDF2 study (7% for both groups). In the iPrEx study, 2% of patients withdrew due to an

adverse event in both treatment groups. In the iPrEx study, there was no pattern of AEs that led to discontinuation. In the Partners PrEP study, two participants in the FTC/TDF group and one participant in the placebo group withdrew due to an adverse event. In the Partners PrEP study, all discontinuations were due to an increase in blood creatinine level that was confirmed on repeat testing. In the CDC TDF2 study, no participants withdrew from the study due to an AE. In the iPrEx study, one patient in the FTC/TDF group and four patients in the placebo group died. In the Partners PrEP study, eight patients in the FTC/TDF group and nine patients in the placebo group died. In the CDC TDF2 study, two patients in the FTC/TDF group and four patients in the placebo group died.

Notable harms associated with FTC/TDF include renal AEs and bone AEs. In the included studies, the incidence of elevated creatinine levels (defined as 1.5 times baseline level) did not exceed 2% in any group across studies, and the incidence of bone -fracture AEs did not exceed 1% across studies, with the majority of bone fractures being trauma-related. The Health Canada product monograph recommends that FTC/TDF for PrEP should not be used in HIV-1–uninfected individuals with creatinine clearance below 60 mL/min, which corresponds to the participants enrolled in the iPrEx and Partners PrEP studies.

The Health Canada product monograph recommends that FTC/TDF for PrEP be used as part of a comprehensive prevention strategy that includes safer sex practices, patients' knowledge of their HIV-1 status and the status of their partner(s), and regular testing for STIs. In the included studies, follow-up visits were conducted monthly, and included HIV testing, risk-reduction counselling, adherence counselling, treatment of symptomatic STIs, and provision of condoms and contraceptives. According to the clinical expert consulted by the CADTH Common Drug Review (CDR) for this review, participants on PrEP therapy would not likely be seen as frequently in clinical practice, and follow-up visits would likely be conducted every three months. According to the Health Canada product monograph, the use of FTC/TDF 200 mg/300 mg for PrEP must be prescribed only to individuals confirmed to be HIV-negative immediately prior to initial use and periodically (at least every three months) during use.

Conclusions

Three DB, placebo-controlled RCTs assessing the safety and efficacy of once-daily FTC/TDF 200 mg/300 mg as PrEP in combination with HIV prevention services for individuals at high risk of acquiring HIV-1 infection were included in this review. The iPrEx study was conducted in adult MSM, the Partners PrEP study was conducted in adult Kenyan and Ugandan sexually active, serodiscordant, heterosexual couples, and the CDC TDF2 study was conducted in young Botswanan heterosexual men and women. Results from all studies suggested that there was a statistically significant reduction in the incidence of HIV-1 seroconversion with FTC/TDF compared with placebo. Treatment adherence based on pill count and self-report was high across studies, but may be subject to bias. Sexual behaviour and the incidence of STIs did not differ between the FTC/TDF and placebo groups and small improvements were seen over time, although the reliance on participant interviews may also be vulnerable to bias. Although quality of life was cited as an important outcome according to patient-group input, this was not evaluated in the included studies. Overall, the incidence of AEs was similar between FTC/TDF and placebo groups, and the incidence of renal and bone AEs were low across studies. None of the studies were conducted in Canada, and there may be generalizability issues, as the included studies were conducted mainly in Hispanic and African countries where health care services may not be as accessible as they are in the Canadian setting.

TABLE 1: SUMMARY OF RESULTS

	iPrEx		Partners PrEP		CDC TDF2	
	FTC/TDF	Placebo	FTC/TDF	Placebo	FTC/TDF	Placebo
HIV-1 seroconversion (mITT set)	**(n = 1,224)**	**(n = 1,217)**	**(n = 1,576)**	**(n = 1,578)**	**(n = 601)**	**(n = 599)**
Person-years of follow-up	[redacted]	[redacted]	2,616	2,607	1,563	
Participants with seroconversion events, n	36	64	13	52	9	24
Rate per 100 person-years	2.2	3.8	0.50	1.99	1.2	3.1
Hazard ratio (95% CI)	0.56 (0.37 to 0.85)		0.25 (0.13 to 0.45)		NR	
Relative risk reduction, % (95% CI)	44 (15 to 63)		75 (55 to 87)		62.2 (21.5 to 83.4)	
P value	0.005		< 0.001		0.03	
Absolute rate reduction, per 100 person-years (95% CI)[a]	[redacted]		[redacted]		NR	
Harms (safety set), n (%)	**(n = 1,251)**	**(n = 1,248)**	**(n = 1,579)**	**(n = 1,584)**	**(n = 611)**	**(n = 608)**
Participants with > 0 AEs	867 (69)	877 (70)	1,362 (86)	1,350 (85)	557 (91)	536 (88)
Participants with > 0 SAEs	60 (5)	67 (5)	115 (7)	118 (7)	115 (7)	118 (7)
Participants with > 0 WDAEs	25 (2)	27 (2)	2 (< 1)	1 (< 1)	0	0
Number of deaths	1 (< 1)	4 (< 1)	8 (< 1)	9 (< 1)	2 (< 1)	4 (< 1)
Notable harms (safety set), n (%)	**(n = 1,251)**	**(n = 1,248)**	**(n = 1,579)**	**(n = 1,584)**	**(n = 611)**	**(n = 608)**
Elevated creatinine[b]	25 (2)	14 (1)	20 (1)	13 (1)	1 (< 1)	0
Bone fracture	15 (1)	11 (1)	9 (< 1)	13 (1)	7 (1)	6 (1)

AE = adverse event; CI = confidence interval; FTC/TDF = emtricitabine/tenofovir disoproxil fumarate; HIV = human immunodeficiency virus; mITT = modified intent-to-treat; NR = not reported; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] Provided by the manufacturer.[3]

[b] Defined as an increase in serum creatinine of at least 1.5 times the baseline value.

Sources: iPrEx Clinical Study Report (CSR),[4] Grant et al., 2010,[5] Partners PrEP CSR,[6] Baeten et al., 2012,[7] Thigpen et al., 2012.[8]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Human immunodeficiency virus (HIV) attacks CD4+ T cells, components of the immune system necessary for defending the body against infection.[9] HIV progressively impairs immune response and, if left untreated, may lead to acquired immunodeficiency syndrome (AIDS), the final stage of HIV where a patient can no longer fight off infections and certain malignancies. HIV is transmitted through bodily fluids, and can be passed from an infected individual to a healthy individual through unprotected sex and the sharing of drug needles.[10] An infected mother can also pass the virus to her baby during pregnancy or birth (vertical transmission) or breastfeeding. HIV can be divided into two major types, HIV type 1 (HIV-1) and HIV type 2 (HIV-2); HIV-1 is the predominant virus worldwide.[11]

At the end of 2014, Health Canada estimated that 75,500 people were living with HIV infection in Canada.[2] In spite of the fact that the sexual transmission of HIV is significantly reduced by the use of condoms, significant numbers of new HIV infections occur annually.[12,13] The Public Health Agency of Canada estimates that 2,570 new infections (range: 1,940 to 3,200) occurred in Canada in 2014, with an estimated incidence rate of 7.2 per 100,000 population (range: 5.5 per 100,000 population to 9.0 per 100,000 population).[1] There were approximately 1,396 new infections in 2014 in men who have sex with men (MSM), representing 54.3% of all new infections.[2] This estimate is similar to the 2011 estimate of 1,416 new infections. According to 2011 national estimates, MSM have incidence rates 71 times higher than other men, people who inject drugs have incidence rates 46 times higher than people who do not inject drugs, and males have incidence rates 3.3 times higher than females.[2] In 2011, approximately 95% of reported HIV/AIDS cases were from Ontario (42.6%); Quebec had 21.5% of cases, British Columbia 13.4%, Alberta 9.7%, and Saskatchewan 7.7%.[14] Canadian estimates for the year 2011 demonstrated that the populations most affected by new HIV infections vary across provinces, with MSM being the most affected risk group in British Columbia, Ontario, Quebec, and the Atlantic provinces, heterosexual individuals being most affected risk group in Alberta and Manitoba, and injection drug users being the most affected risk group in Saskatchewan.[2] The rising rates of gonorrhea, chlamydia, and syphilis in Canada serve to emphasize the inconsistency of condom use among sexually active populations.[15]

1.2 Standards of Therapy

The current standard of care for HIV management is to treat with highly active antiretroviral therapy (ART), with the primary goal of achieving and maintaining maximal suppression of viral load, which leads to restoration and preservation of immunologic function, improvement of quality of life, and reduction of HIV-related morbidity and mortality.[16] HIV-infected patients require ART for life, resulting in a heavy economic burden and high health care utilization. Reducing the number of additional HIV infections is an important step to alleviating this burden.

Current HIV prevention strategies focus on, among others, behaviour change (including education about sexual health and safer sex), reducing substance use or promoting safer substance use, and encouraging those at risk to get properly tested and diagnosed.[17] Despite the wide availability of sexual health resources in Canada, the incidence of HIV is not declining.[2]

Pre-exposure prophylaxis (PrEP) for HIV is the use of drug therapy, typically antiretrovirals, by HIV-negative individuals to reduce their risk of acquiring HIV infection.[18] Currently, Truvada (emtricitabine/tenofovir disoproxil fumarate [FTC/TDF]) 200 mg/300 mg is the only drug approved for this indication. Truvada was first approved by the US Food and Drug Administration (FDA) in 2012 for

HIV PrEP, and received a Notice of Compliance from Health Canada on February 23, 2016. The Centres for Disease Control and Prevention (CDC) and the World Health Organization (WHO) recommend the daily use of Truvada as a prevention option for sexually active MSM, sexually active adult heterosexual men and women, and adult intravenous drug users at substantial risk of HIV acquisition, to be used within a comprehensive HIV prevention package.[19,20]

1.3 Drug

FTC/TDF is a fixed-dose combination (FDC) tablet containing emtricitabine, a nucleoside HIV-1 reverse transcriptase inhibitor, and tenofovir disoproxil fumarate, the prodrug of tenofovir, a nucleotide analogue reverse transcriptase inhibitor. FTC/TDF is available as FDC tablets containing 200 mg FTC and 300 mg TDF. The Health Canada–recommended dose is one tablet taken orally once daily.

FTC/TDF is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults. This indication has previously been reviewed by the CADTH Common Drug Review (CDR) and received a recommendation to "list with criteria" (see the Canadian Expert Drug Advisory Committee's [CEDAC's] final recommendation, December 17, 2008).[21]

FTC/TDF is also indicated in combination with safer sex practices for PrEP to reduce the risk of sexually acquired HIV-1 infection in adults at high risk. This indication will be the focus of this review.

Indication under review
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.
Listing criteria requested by sponsor
As per indication.

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects FTC/TDF 200 mg/300 mg in combination with safer sex practices for PrEP to reduce the risk of sexually acquired HIV-1 infection in adults at high risk.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase 3 studies were selected for inclusion based on the selection criteria presented in Table 2.

TABLE 2: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adults at high risk[a] of HIV-1 infection. Subgroups of interest: Sex (female or male)
Intervention	FTC/TDF 200 mg/300 mg (FDC) in combination with safer sex practices
Comparators	Placebo, in combination with safer sex practices
Outcomes	**Key efficacy outcomes:** • HIV-1 seroconversion[b] • Sexual behaviour[b] • Incidence of STIs (e.g., chlamydia, gonorrhea, syphilis, herpes) **Other efficacy outcomes:** • Adherence and persistence to study medication • Quality of life as measured by a validated scale[b] • HIV-1 drug resistance **Harms outcomes:** • AEs, SAEs, WDAEs, mortality • Notable harms: renal impairment, bone AEs
Study Design	Published and unpublished phase 3 RCTs

AE = adverse event; FDC = fixed-dose combination; FTC/TDF = emtricitabine/tenofovir disoproxil fumarate; HIV-1 = human immunodeficiency virus type 1; RCT = randomized controlled trial; SAE = serious adverse event; STI = sexually transmitted infection; WDAE = withdrawal due to adverse event.

[a] Factors that may identify individuals at high risk: "has partner(s) known to be HIV-1–infected, or engages in sexual activity within a high prevalence area or social network and one or more of the following: inconsistent or no condom use, diagnosis of STIs, exchange of sex for commodities (such as money, food, shelter, or drugs), use of illicit drugs or alcohol dependence, incarceration, partner(s) of unknown HIV-1 status with any of the factors listed above." (Source: Health Canada product monograph.[22])

[b] Outcomes identified by patients as important in patient-group submission.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Truvada (emtricitabine/tenofovir) and pre-exposure prophylaxis.

Methodological filters were applied to limit retrieval to randomized controlled trials. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on March 31, 2016. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on July 20, 2016. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (https://www.cadth.ca/grey-matters): Health Technology Assessment Agencies; Health Economics; Clinical Practice Guidelines; Drug and Device Regulatory Approvals; Advisories and Warnings; Drug Class Reviews; Databases (free). Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 3; excluded studies (with reasons) are presented in 0.

3. RESULTS

3.1 Findings From the Literature

A total of 230 studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 3, Table 4 and Table 5 and described in section 3.2 Included Studies. A list of excluded studies is presented in APPENDIX 3: EXCLUDED STUDIES.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

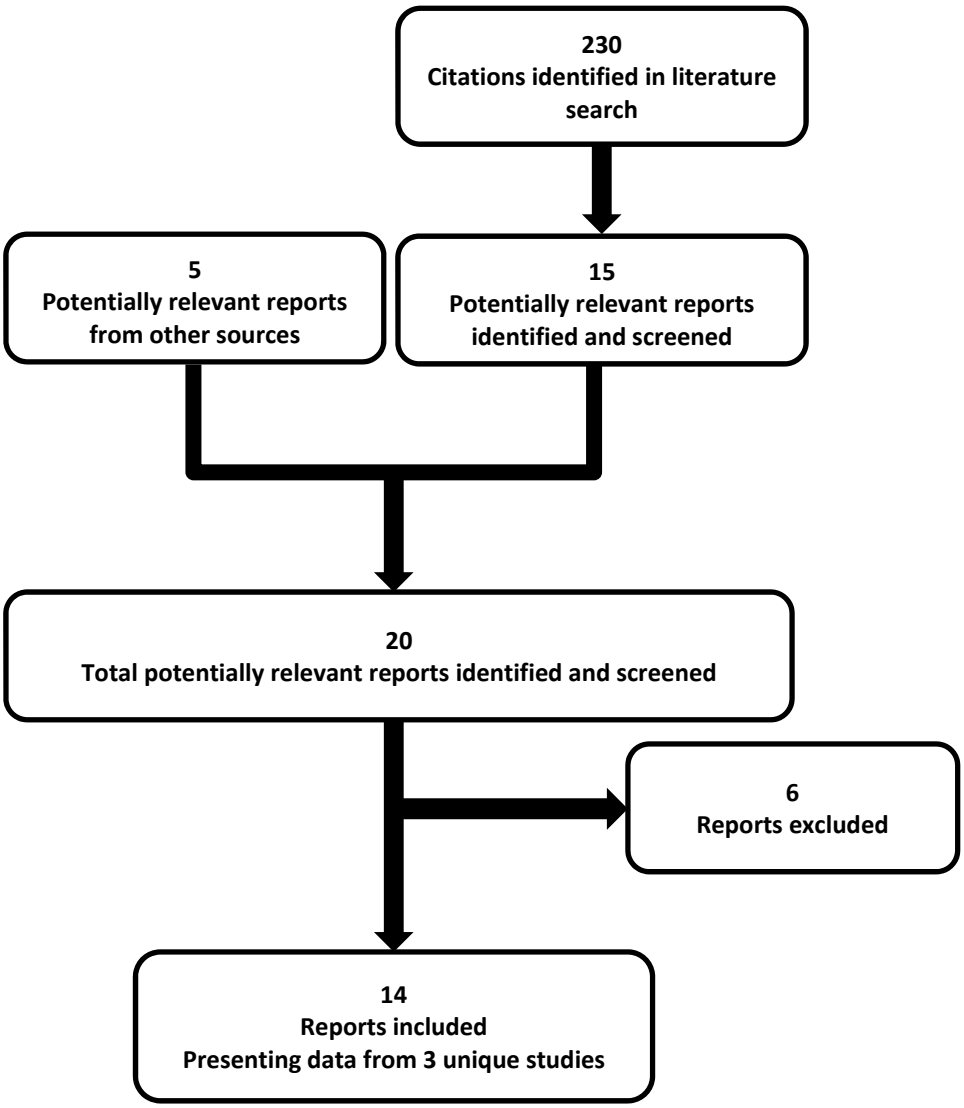

TABLE 3: DETAILS OF THE IPREX STUDY (MEN WHO HAVE SEX WITH MEN)

		iPrEx (CO-US-104-0288)
DESIGNS & POPULATIONS	**Study Design**	DB, PC, RCT
	Locations	11 centres in 6 countries: Brazil, Ecuador, Peru, South Africa, Thailand, US
	Randomized (N)	2,499
	Inclusion Criteria	– HIV-1–negative males ≥ 18 years with evidence of high risk for acquiring HIV-1 infection based on sexual encounters with males in the past 6 months and meeting one of the following criteria: no condom use during anal intercourse with an HIV-positive partner or partner of unknown HIV-1 status; anal intercourse with > 3 partners; exchanged money, gifts, shelter, or drugs for anal sex; had sex with partner and was diagnosed with an STI. – Adequate renal function (creatinine clearance ≥ 60 mL/min), hepatic function (ALT and AST ≤ 2 x ULN, bilirubin ≤ 1.5 mg/dL), and hematologic function (neutrophils ≥ 1,500/mm^3, platelets > 150,000/mm^3, hemoglobin ≥ 10 g/dL) within 28 days of enrolment.
	Exclusion Criteria	– Previously diagnosed active and serious infections (e.g., tuberculosis) – Acute hepatitis B infection – History of pathological bone fractures – Receiving or had received antiretroviral therapies – Active alcohol or drug use considered sufficient to hinder compliance
DRUGS	**Intervention**	FTC/TDF 200 mg/300 mg FDC taken orally once daily: – Given with a comprehensive package of infection prevention services (HIV testing, risk-reduction counselling, condoms, diagnosis and treatment for symptomatic STIs) – Participants were connected with local prevention and treatment services when required
	Comparator(s)	– Placebo given with a comprehensive package of infection prevention services
DURATION	**Duration**	Study continued until 85 seroconversion events were identified – Study visits scheduled every 4 weeks – High-risk behaviours assessed every 12 weeks – Evaluations for STIs performed every 24 weeks
OUTCOMES	**Primary End Point**	Incidence of HIV-1 seroconversion
	Other End Points	– HIV-1 drug resistance in seroconverted participants – Adherence (self-reported, clinic pill counts) – Sexual behaviour (number of partners in past 3 months, proportion of partners with whom condoms were used in past 3 months) – STIs
NOTES	**Publications**	Grant et al., 2010[5] Other publications: – Deutsch et al., 2015[23] – Marcus et al., 2013[24] – Solomon et al., 2014[25]

ALT = alanine aminotransferase; ART = antiretroviral therapy; AST = aspartate aminotransferase; DB = double-blind; FDC = fixed-dose combination; FTC/TDF = emtricitabine/tenofovir disoproxil fumarate; HIV-1 = human immunodeficiency virus type 1; PC = placebo-controlled; RCT = randomized controlled trial; RNA = ribonucleic acid; STI = sexually transmitted infection; ULN = upper limit of normal.

Note: Three additional reports were included (manufacturer's submission,[26] Health Canada's Reviewers Report,[27] and US Food and Drug Administration [FDA] Medical Review[28]).

Sources: iPrEx Clinical Study Report,[4] Grant et al., 2010.[5]

TABLE 4: DETAILS OF THE PARTNERS PREP STUDY (HETEROSEXUAL SERODISCORDANT COUPLES)

		Partners PrEP (CO-US-104-0380)
DESIGNS & POPULATIONS	**Study Design**	DB, PC, RCT
	Locations	9 centres in 2 countries: Kenya, Uganda
	Randomized (N)	4,758 couples
	Inclusion Criteria	Heterosexual HIV-1–serodiscordant couples who are sexually active (vaginal intercourse ≥ 6 times in previous 3 months) and planned to remain in the relationship for the duration of the study period. **HIV-1–negative partner** • Between 18 and 65 years old • Adequate renal function (creatinine clearance ≥ 60 mL/min), hepatic function (ALT and AST ≤ 2 x ULN, bilirubin ≤ 1.5 x ULN), and hematologic function (neutrophils ≥ 1,300/mm^3, platelets > 125,000/mm^3, hemoglobin ≥ 11 g/dL) within 56 days of enrolment. **HIV-1–positive partner** • HIV-1 infection based on positive enzyme immunoassay • CD4 cell count ≥ 250 cells/mm3 not meeting national guidelines for initiation of ART
	Exclusion Criteria	**HIV-1–negative partner** • Previously diagnosed active and serious infections (e.g., tuberculosis) • Acute hepatitis B infection • History of pathological bone fractures • Receiving or had received ART [redacted] • Current pregnancy or breastfeeding **HIV-1–positive partner** • Current use of ART
DRUGS	**Intervention**	**HIV-1–negative partner** • FTC/TDF 200 mg/300 mg FDC taken orally once daily **TDF 300 mg taken orally once daily** • to be given with HIV risk-reduction counselling
	Comparator(s)	Placebo • to be given with HIV risk-reduction counselling
DURATION	**Duration**	Participants were followed for 24 to 36 months to generate a sufficient accumulation of person-years to adequately evaluate study end points • Study visits scheduled every 4 weeks
OUTCOMES	**Primary End Point**	Incidence of HIV-1 seroconversion
	Other End Points	• HIV-1 drug resistance in seroconverted participants • Adherence (clinic pill counts) • Sexual behaviour (proportion of participants reporting having unprotected sex with HIV-1–positive partner in the past month) • STIs

		Partners PrEP (CO-US-104-0380)
NOTES	**Publications**	Baeten et al., 2012[7] Other publications: • Mugwanya et al., 2015[29] • Mujugira et al., 2011[30]

ALT = alanine amino transferase; ART = antiretroviral therapy; AST = aspartate aminotransferase; DB = double-blind; FDC = fixed-dose combination; FTC/TDF = emtricitabine/tenofovir disoproxil fumarate; HIV-1 = human immunodeficiency virus type 1; PC = placebo-controlled; MSM = men who have sex with men; RCT = randomized controlled trial; RNA = ribonucleic acid; STI = sexually transmitted infection; TDF = tenofovir disoproxil fumarate; ULN = upper limit of normal.
Note: Three additional reports were included (manufacturer's submission,[26] Health Canada Reviewers' Report,[27] and US Food and Drug Administration [FDA] Medical Review[28]).
Sources: Partners PrEP Clinical Study Report,[6] Baeten et al., 2012.[7]

TABLE 5: DETAILS OF THE CDC TDF2 STUDY (HETEROSEXUAL MEN AND WOMEN)

		CDC TDF2
DESIGNS & POPULATIONS	**Study Design**	DB, PC, RCT
	Locations	2 centres in Botswana
	Randomized (N)	1,219 men and women
	Inclusion Criteria	• HIV-1–negative heterosexual adults between 18 and 39 years old who are sexually active (≥ 1 partner in past 3 months) • Adequate renal function (creatinine clearance ≥ 60 mL/min), hepatic function (ALT and AST ≤ 2 x ULN, bilirubin ≤ 1.5 x ULN), and hematologic function (hemoglobin ≥ 8 g/dL) within 30 days of enrolment • Female participants willing to use effective contraception during study
	Exclusion Criteria	• Chronic illness requiring ongoing prescription medication • History of significant renal or bone disease • Current pregnancy or breastfeeding • Planning to move from trial community within 12 months
DRUGS	**Intervention**	FTC/TDF 200 mg/300 mg FDC taken orally once daily • to be given with HIV risk-reduction counselling
	Comparator(s)	Placebo • to be given with HIV risk-reduction counselling
DURATION	**Duration**	Planned 4 years of treatment, with HIV-1–uninfected participants remaining on assigned medication until the last enrolled participant has completed 12 months or closure of the study • Study visits scheduled every 4 weeks
OUTCOMES	**Primary End Point**	Incidence of HIV-1 seroconversion
	Other End Points	• Adherence (self-reported, clinic pill counts) • Sexual behaviour (number of sexual partners in previous month, percentage of sexual episodes using condoms with most recent sexual partner) • HIV-1 drug resistance in seroconverted participants
NOTES	**Publications**	Thigpen et al., 2012[8] Bone mineral density sub-study: Kasonde et al., 2014[8]

ALT = alanine amino transferase; ART = antiretroviral therapy; AST = aspartate aminotransferase; DB = double-blind; FDC = fixed-dose combination; FTC/TDF = emtricitabine/tenofovir disoproxil fumarate; HIV-1 = human immunodeficiency virus type 1; PC = placebo-controlled; RCT = randomized controlled trial; RNA = ribonucleic acid; STI = sexually transmitted infection; ULN = upper limit of normal.
Note: One additional report was included (manufacturer's submission[26]).
Source: Thigpen et al., 2012.[8]

3.2 Included Studies

3.2.1 Description of Studies

All three included studies were randomized controlled trials (RCTs), double-blind (DB), placebo-controlled studies that assessed the safety and efficacy of PrEP of oral FTC/TDF 200 mg/300 mg in combination with HIV prevention services. The manufacturer was responsible for providing the study drug, but was not involved in the design and conduct of the studies. Randomization was stratified by study site.

The Pre-exposure Prophylaxis Initiative study (iPrEx, N = 2,499) was an international study conducted in adult seronegative MSM who were at high risk of acquiring HIV-1 infection. Study duration was event driven, continuing until at least 85 seroconversion events occurred. The first participant was screened on July 10, 2007, and the last participant observation for the primary study analysis was performed on May 1, 2010. Cumulative safety and efficacy data from study visits through November 21, 2010 were also available. The primary sponsor for the iPrEx study was the US National Institutes of Health.

The Partners PrEP study (N = 4,758) was conducted in Kenyan and Ugandan adult heterosexual serodiscordant couples in which one partner had HIV type 1 (HIV-1) infection while the other partner did not, and in which the couple was sexually active with plans to remain in the relationship for the duration of the study period. In the Partners PrEP study, enrolled participants were planned to be followed for a minimum of 24 months up to a maximum of 36 months, and the follow-up schedule was designed to yield a sufficient accumulation of person-years to adequately evaluate the study end points. The first participant was screened on June 19, 2008, and the last participant observation occurred on July 10, 2011. The placebo group was discontinued after this date because predetermined stopping rules were met. The primary sponsor for the Partners PrEP study was the University of Washington.

The CDC TDF2 study (N = 1,219) was conducted in Botswanan heterosexual men and women who were sexually active. In the CDC TDF2 study, four years of treatment were planned, with HIV-1–uninfected participants to remain on assigned medication until the last enrolled participant had completed 12 months of treatment. The first participant was enrolled on March 22, 2007. A lower-than-expected rate of retention was observed during this study due to relocation of participants, and revised sample size calculations indicated that the study would need to expand enrolment. Due to the logistical challenges of doing so, the study was concluded early and all participants exited the study by May 31, 2010. The primary sponsor for the CDC TDF2 study was the US Centers for Disease Control and Prevention (CDC).

In all studies, study visits were scheduled every four weeks and included drug dispensing, rapid testing for HIV-1 antibodies, adherence counselling, risk-reduction counselling, condom promotion, and treatment of symptomatic sexually transmitted infections (STIs). HIV-1–uninfected women were also tested for pregnancy, and women who became pregnant stopped using the study drug.

3.2.2 Populations

a) Inclusion and exclusion criteria

Each of the three included studies focused on a different population at risk of acquiring HIV-1 infection, with inclusion criteria to reflect this. The iPrEx study included males at least 18 years of age with sexual encounters with men in the past six months meeting one of the following criteria: no condom use during anal intercourse, anal intercourse with more than three partners, diagnosis of an STI after a sexual encounter, or having transactional anal sex. The Partners PrEP study included heterosexual HIV-1–serodiscordant couples who were sexually active based on having had vaginal intercourse at least six times in the previous three months, with the HIV-1–negative partner being between 18 and 65 years of

age. The CDC TDF2 study included heterosexual males and females between 18 and 39 years of age who had had at least one sexual partner in the past three months. In all studies, participants were to have adequate renal, hepatic, and hematologic function. Exclusion criteria included a history of significant renal or bone disease, previous or current use of antiretroviral therapies, or issues that would hinder compliance or follow-up of the participant.

Participants who were not immune to hepatitis B virus were offered vaccination. Those who were not immune and who declined vaccination were tested for the virus annually and at the stop visit. Females who were pregnant or breastfeeding were excluded in the Partners PrEP and CDC TDF2 studies, and contraception was to be used upon enrolment. Women who became pregnant during the study were to be withdrawn from study drug. In the Partners PrEP study, women whose pregnancies did not go to term or that ended in stillbirth were permitted to resume the study drug after confirmation by a negative urine pregnancy test.

b) Baseline characteristics

Baseline characteristics were generally balanced across the FTC/TDF and placebo groups in all of the studies. In the iPrEx study, the mean age was 27 years, and 14% of the male-at-birth population identified themselves as transgender women. The largest proportion of patients (approximately 50%) was between 18 and 24 years of age, and more than 70% of the population was Hispanic. At screening, participants reported a mean of 18 sexual partners in the previous 12 weeks, with approximately 60% of participants having engaged in unprotected receptive anal intercourse (URAI) during that time. STIs were generally balanced across groups, with approximately one-third of participants testing positive for herpes simplex virus, gonorrhea, and chlamydia.

In the Partners PrEP study, the majority of HIV-1–negative partners were male (61% to 64%), and the mean age was approximately 33 years. Almost all of the enrolled couples were married (98%), and the mean number of years aware of the discordant status was 0.4 years. For the HIV-1–positive partners, the mean HIV-1 plasma ribonucleic acid (RNA) level was 3.9 $\log_{10}$ copies/mL and the mean CD4+ cell count was 498/mm^3. The proportion of participants with curable STIs was low, and ranged between 6% and 9% across groups.

In the CDC TDF2 study, approximately 54% of participants were male, and the majority of participants (87.5% to 90%) were between 21 and 29 years of age. More than 90% of participants were single, and 88% of participants had had at least one sexual partner in the previous month. The percentage of sexual episodes in which condoms had been used with the main or most recent partner was 80%, and 3.5% of participants had had sex with a known HIV-positive partner in the previous month. More than 30% of participants were seropositive for herpes simplex virus.

TABLE 6: SUMMARY OF BASELINE CHARACTERISTICS OF IPREX STUDY (MSM)

Characteristic	iPrEx	
	FTC/TDF (n = 1,251)	Placebo (n = 1,248)
Age, mean years	[redacted]	[redacted]
Transgender women, n (%)	339 (14)	
Age, n (%)		
18 to 24 years	591 (47)	662 (53)
25 to 29 years	274 (22)	241 (19)

Characteristic	iPrEx	
	FTC/TDF (n = 1,251)	Placebo (n = 1,248)
30 to 39 years	249 (20)	224 (18)
≥ 40 years	137 (11)	121 (10)
Race, n (%)		
Black/African-American	117 (9)	97 (8)
White	223 (18)	208 (17)
Mixed/Other	849 (68)	878 (70)
Asian	62 (5)	65 (5)
Hispanic	900 (72)	906 (73)
Education Level, n (%)		
Less than secondary	279 (22)	244 (20)
Completed secondary	430 (34)	453 (36)
Post-secondary	525 (42)	539 (43)
Number of alcoholic drinks on days when alcohol was consumed in the past month, n (%)		
0	206 (16)	184 (15)
1 to 4 per day	348 (28)	345 (28)
≥ 5 per day	666 (53)	687 (55)
Sexual risk factors at screening		
Mean (SD) number of partners in previous 12 weeks	18 (35)	18 (43)
URAI in previous 12 weeks, n (%)	732 (59)	753 (60)
URAI with HIV+ or unknown status partner in previous 6 months, n (%)	992 (79)	1,009 (81)
Transactional sex in previous 6 months, n (%)	517 (41)	510 (41)
Known HIV+ partner in previous 6 months, n (%)	23 (2)	32 (3)
STI diagnosed at screening		
Syphilis seroreactivity, n/n tested (%)	164/1240 (13)	162/1239 (13)
Serum HSV-2 infection, n/n tested (%)	458/1241 (37)	430/1243 (35)
Gonorrhea PCR positive, n/n tested (%)	7/20 (35)	5/22 (23)
Chlamydia PCR positive, n/n tested (%)	8/20 (40)	8/22 (36)
HBV status		
Susceptible	827 (66)	803 (64)
Immune due to natural infection	247 (20)	222 (18)
Immune due to prior vaccination	149 (12)	190 (15)
Current infection	7 (1)	6 (0)
Indeterminate	21 (2)	27 (2)

FTC/TDF = emtricitabine/tenofovir disoproxil fumarate; HBV = hepatitis B virus; HIV = human immunodeficiency virus; HSV = herpes simplex virus; MSM = men who have sex with men; PCR = polymerase chain reaction; SD = standard deviation; STI = sexually transmitted infection; URAI = unprotected receptive anal intercourse.
Sources: iPrEx Clinical Study Report,[4] Grant et al., 2010,[5] Deutsch et al., 2015,[23] and US Food and Drug Administration (FDA) Medical Review.[28]

TABLE 7: SUMMARY OF BASELINE CHARACTERISTICS OF PARTNERS PREP STUDY (SERODISCORDANT HETEROSEXUAL COUPLES)

Characteristic	Partners PrEP			
	FTC/TDF (n = 1,579)		Placebo (n = 1,584)	
	Seronegative partner	Seropositive partner	Seronegative partner	Seropositive partner
Age, median (IQR) years	[redacted]	[redacted]	[redacted]	[redacted]
Age, n (%)				
18 to 24 years	177 (11)	287 (18)	172 (11)	273 (17)
25 to 34 years	690 (44)	636 (40)	688 (43)	629 (40)
35 to 44 years	498 (32)	460 (29)	513 (32)	509 (32)
≥ 45 years	214 (14)	196 (12)	211 (13)	173 (11)
Male, n (%)	1,013 (64)	566 (36)	963 (61)	621 (39)
Female, n (%)	566 (36)	1,013 (64)	621 (39)	963 (61)
Education, median (IQR) years	7 (4 to 10)	7 (4 to 9)	7 (4 to 10)	7 (4 to 9)
Any monthly income, n (%)	1,236 (78)	1,052 (67)	1,259 (79)	1,079 (68)
Couple characteristics,[a] n (%) or median (IQR)				
Married	1,540 (98)		1,552 (98)	
Years living with partner	7.1 (3.0 to 14.0)		7.1 (3.0 to 14.0)	
Number of children	2 (1 to 4)		2 (1 to 4)	
No children	368 (23)		342 (22)	
Years aware of discordant status	0.4 (0.1 to 2.0)		0.4 (0.1 to 2.0)	
Clinical characteristics, n (%) or median (IQR)				
HIV-1 plasma RNA, $\log_{10}$ copies/mL	NA	3.9 (3.1 to 4.5)	NA	3.9 (3.2 to 4.5)
CD4+ cell count/mm^3	NA	497 (380 to 664)	NA	499 (375 to 663)
Fully circumcised (men only)	540 (53)	177 (31)	509 (53)	202 (33)
Using contraception (women only)	275 (49)	324 (32)	299 (48)	321 (33)
Pregnant (women only)	0	135 (13)	0	118 (12)
Curable STI[b]	93 (6)	122 (8)	126 (8)	137 (9)
HSV-2 seropositive	814 (54)	NA	875 (58)	NA

FTC/TDF = emtricitabine/tenofovir disoproxil fumarate; HIV = human immunodeficiency virus; HSV = herpes simplex virus; IQR = interquartile range; NA = not applicable; RNA = ribonucleic acid; STI = sexually transmitted infection.
[a] Couple characteristics were reported by the HIV-1-seronegative partner.
[b] *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, or *Trichomonas vaginalis*.
Sources: Clinical Study Report[6]; Baeten et al., 2012.[7]

TABLE 8: SUMMARY OF BASELINE CHARACTERISTICS OF CDC TDF2 STUDY (HETEROSEXUAL MEN AND WOMEN)

Characteristic	CDC TDF2	
	FTC/TDF (n = 611)	Placebo (n = 608)
Age, n (%)		
18 to 20 years	10 (1.6)	15 (2.5)
21 to 29 years	550 (90.0)	532 (87.5)
30 to 39 years	51 (8.3)	61 (10.0)

Characteristic	CDC TDF2	
	FTC/TDF (n = 611)	Placebo (n = 608)
Male, n (%)	331 (54.2)	331 (54.4)
Female, n (%)	280 (45.8)	277 (45.6)
Education level, n (%)		
Primary or less	20 (3.3)	20 (3.3)
Secondary	446 (73.0)	445 (73.2)
Post-secondary	145 (23.7)	143 (23.5)
Marital status, n (%)		
Married	32 (5.2)	38 (6.2)
Single	578 (94.6)	567 (93.3)
Divorced or widowed	1 (0.2)	3 (0.5)
Alcohol use in the past 3 months, n/n responses (%)	359/601 (59.7)	340/599 (56.8)
Sexual behaviours at screening, n (%)		
Number of sexual partners in previous month		
0	73 (11.9)	78 (12.8)
1	410 (67.1)	405 (66.6)
2	86 (14.1)	86 (14.1)
≥ 3	32 (5.2)	28 (4.6)
Percentage of sexual episodes in which condoms were used with main or most recent sexual partner, % (range)	81.4 (76.6 to 86.4)	79.2 (71.6 to 87.6)
Sex with known HIV-positive partner in previous month		
Yes	21 (3.4)	22 (3.6)
No	479 (78.4)	474 (78.0)
STI diagnosed at screening, n/n tested (%)		
HSV-2 seropositive	208/601 (34.6)	220/600 (36.7)
Neisseria gonorrhoeae	12/578 (2.1)	12/565 (2.1)
Chlamydia trachomatis	43/578 (7.4)	54/566 (9.5)
Treponema pallidum	5/599 (0.8)	9/597 (1.5)
Trichomonas vaginalis (women)	19/256 (7.4)	14/248 (5.6)

FTC/TDF = emtricitabine/tenofovir disoproxil fumarate; HBV = hepatitis B virus; HIV = human immunodeficiency virus; HSV = herpes simplex virus; STI = sexually transmitted infection.
Source: Thigpen et al., 2012.[8]

3.2.3 Interventions

In all studies, patients were randomized 1:1 to FTC/TDF 200 mg/300 mg FDC or placebo, administered orally once daily. For the Partners PrEP study, a TDF 300 mg arm was also included (randomized 1:1:1); however, the results from this arm are not presented in this review. In addition to FTC/TDF, patients were given HIV infection prevention services at every scheduled visit, which included HIV testing, risk-reduction counselling, condoms, and diagnosis and treatment of symptomatic STIs (Table 9). In addition, adherence counselling was provided to all participants at each visit. Adherence counselling included reminding participants to contact study staff with questions about product use, as well as reminders to not share the study agent with other individuals.

TABLE 9: ADDITIONAL INTERVENTIONS AT MONTHLY VISITS

iPrEx	Partners PrEP	CDC TDF2
• Dispense condoms • Risk-reduction counselling • Adherence counselling • HIV-1 pre- and post-test counselling	• Provision of condoms and contraceptives (if indicated) • Couples HIV-1 counselling • Risk-reduction counselling • Contraception counselling • Adherence counselling • HIV-1 pre- and post-test counselling	• Dispense condoms and contraceptives (if indicated) • Risk-reduction counselling • Adherence counselling • HIV-1 pre- and post-test counselling

HIV = human immunodeficiency virus.
Sources: Grant et al., 2010,[5] Baeten et al., 2012,[7] Thigpen et al., 2012.[8]

Prohibited medications included antiretroviral therapies, interferon or interleukin therapies, aminoglycoside antibiotics, amphotericin B, cidofovir, systemic chemotherapeutic drugs, other drugs with significant nephrotoxic potential, and other drugs that may inhibit or compete for elimination via active renal tubular secretion.

In all included studies, adherence to study medication was monitored by participant self-report and clinic-based pill counts at pill dispensing visits.

3.2.4 Outcomes

a) HIV-1 Seroconversion

In all included studies, the primary efficacy end point was the incidence of HIV-1 infections based on pre-specified testing algorithms. Paired HIV blood rapid tests were performed in parallel, and samples that elicited discordant results were retested. In the iPrEx study, discordant or positive results were retested or confirmed using Western blot, and if results were still unclear, a new specimen was taken from the participant. In the Partners PrEP study, discordant or positive results were retested or confirmed using two wells of an enzyme-linked immunosorbent assay (ELISA) immunoassay. In the CDC TDF2 study, a single oral test was initially used, and participants with positive results were tested with paired blood HIV tests. All samples were confirmed with ELISA and ribonucleic acid polymerase chain reaction (RNA PCR), and inconclusive results would elicit a new sample collection and repeat testing with ELISA and PCR. In the iPrEx and Partners PrEP studies, paired HIV rapid tests that were concordant negative were accepted to be a negative result. In the CDC TDF2 study, negative initial oral test results were accepted to be a negative result.

In the iPrEx study, an HIV Events Committee was established to review all events and adjudicate any events that could not be confirmed through the testing algorithm. In the Partners PrEP study, an "Endpoint Committee" assessed the final determination of seroconversion. It is unclear whether there was a separate committee to adjudicate seroconversion events in the CDC TDF2 study.

b) Sexual Behaviour

In the iPrEx study, a structured interview for sexual behaviour was conducted at screening and every 12 weeks during follow-up. The interview collected information about numbers of sexual partners, and numbers of receptive and insertive anal sexual partners with or without the use of condoms. In the Partners PrEP study, sexual behaviour information was collected at each monthly follow-up visit. In the CDC TDF2 study, information on sexual episodes associated with condom use and number of sexual partners in the previous month was collected at each study visit.

c) Sexually Transmitted Infections

In the iPrEx study, evaluations for STIs were performed at least every 24 weeks. In the Partners PrEP study, STI screening was performed every 12 months. In the CDC TDF2 study, participants were tested annually for syphilis and every six months for gonorrhea, chlamydia, trichomoniasis, and vaginosis. In all studies, symptomatic STIs were to be diagnosed and treated at every monthly visit.

d) Adherence to the Study Medication

In all studies, adherence to the study medication was measured by survey and clinic pill count.

e) Quality of Life

Quality of life was not assessed in any of the included studies.

f) HIV-1 Resistance

Participants who had HIV-1 seroconversion detected were tested for plasma RNA levels, CD4+ cell counts, and viral drug resistance.

In the Partners PrEP study, the HIV-1–positive partner was monitored for HIV-1 disease progression at quarterly follow-up visits, and was referred for ART if they met the national criteria for initiation due to CD4+ decline or clinical symptoms.

g) Harms

An adverse event (AE) was defined as any untoward medical occurrence in a clinical research participant who has been administered an investigational product and whose untoward medical occurrence does not necessarily have a causal relationship with the product. Clinical AEs were evaluated by a medical officer, and summaries of AE reports were reviewed with clinical medical staff and site investigators. A serious adverse event (SAE) was defined as any medical occurrence that resulted in death, that was considered life-threatening, or that resulted in disability or hospitalization. Expedited AEs were defined to include all SAEs criteria with the addition of fetal loss, grade 2 creatinine elevation, and all bone fractures. All SAEs and expedited AEs were to be reported to the safety monitor within 48 hours.

3.2.5 Statistical Analysis

a) Sample Size Calculation

In the iPrEx study, a sample size of 3,000 participants (1,500 per group) was planned to produce the minimum target of 85 seroconversion events to yield a power of 80% with a one-sided alpha of 0.05 to reject a null hypothesis of efficacy of 30% or less if the true efficacy were 60% or more. In the Partners PrEP study, a sample size of 3,900 HIV-1–uninfected participants (1,300 participants per group) was planned to produce 191 seroconversion events to yield a power of 80% with a one-sided alpha of 0.05 to reject a null hypothesis of 30% or less if the true efficacy were 60% or more, assuming a loss-to-follow-up rate of 18%. The planned sample size was increased after study initiation to 4,700 HIV-1–uninfected participants, based on the incidence rate from another HIV-1 prevention study (2.8 per 100 person-years) in serodiscordant couples.[31] In the CDC TDF2 study, a sample size of 1,200 participants was planned to provide 80% power with a one-sided alpha of 0.025 to detect a 65% reduction in HIV seroconversion, based on a background HIV incidence rate of 5%.

b) HIV-1 Seroconversion

HIV-1 infection as measured by seroconversion was assessed monthly, and was the primary end point for evaluating treatment effect. In the iPrEx and CDC TDF2 studies, the event time for HIV infection was the time of first site-detected positive HIV-1 RNA test with a dynamic range of at least 50 copies/mL. In

the Partners PrEP study, the event time for HIV infection was the time of the first site-detected positive HIV-1 antibody test.

In all studies, a Cox proportional hazards model stratified by study site using randomization group as a covariate was used for the primary analyses. In the iPrEx and Partners PrEP studies, two null hypotheses were tested: 1) zero efficacy with an alternative hypothesis of positive efficacy, using a one-sided significance level for rejection of 0.025 for the comparison of FTC/TDF versus placebo; 2) less than 30% efficacy with a one-sided Wald test versus an alternative hypothesis of more than 30% efficacy (corresponding with the premise for which the studies were powered). In the CDC TDF2 study, one null hypothesis was tested: less than 10% efficacy with an alternative hypothesis of more than 10% efficacy for the specific alternative of 65% efficacy (based on power calculation), using a one-sided significance level for rejection of 0.025 for the comparison of FTC/TDF versus placebo.

c) Sexual Behaviour

In the CDC TDF2 study, logistic and Poisson regression models were used to assess differences over time in the proportion of sexual episodes associated with condom use in the previous month and the number of sexual partners in the previous month, respectively.

d) Missing Data

Participants who dropped out of the study, who were terminated, who refused further testing prior to the completion of follow-up, or who died prior to completion of follow-up were uninformatively censored at their last HIV-1 test. [redacted].

e) Subgroup Analyses

Subgroup analysis based on sex

In the Partners PrEP and CDC TDF2 studies, subgroup analysis based on sex (female and male) was performed to investigate the uniformity of any treatment effects found in the overall analysis.

Subgroup analysis based on drug levels

In the iPrEx study, a pre-specified subgroup analysis was performed to investigate whether drug levels correlated with a protective effect. Participants with HIV infection were matched with two seronegative participants (one from each treatment group) according to study site, and the levels of emtricitabine and tenofovir were assessed in plasma and peripheral-blood mononuclear cells.

In the Partners PrEP study, a post-hoc analysis of drug level detection in plasma samples was performed by the manufacturer, using a case-cohort design in which tenofovir levels in HIV-1 seroconverters were tested in addition to 100 randomly selected HIV-1–negative participants from each treatment group (200 total). Emtricitabine levels were not evaluated.

In the CDC TDF2 study, drug levels were assayed in HIV-1 seroconverters using the samples collected most recently before the date of seroconversion. For each seroconverter, samples from three non-seroconverters were randomly chosen from the FTC/TDF group that had been collected closest to the corresponding seroconverter's sample, and the samples were matched by sex and study site.

f) Multiplicity

No adjustments for multiple statistical testing were performed in the included studies.

g) Analysis populations

In the included studies, the following data sets were defined:

Modified Intention-to-Treat (mITT) Set

[redacted] and had at least one on-study HIV assessment, excluding participants determined to be HIV-positive at the time of randomization. This data set was used for primary efficacy analyses.

Safety Analysis Set

In the iPrEx and Partners PrEP studies, this was defined as all randomized participants who were dispensed the study drug. In the CDC TDF2 study, this was defined as all randomized patients.

3.3 Patient Disposition

In the iPrEx study, 10 participants (two FTC/TDF, eight placebo) were found retrospectively to have HIV-1 infection at baseline, and approximately [redacted] of patients discontinued from the study. In the Partners PrEP study, nine participants (three FTC/TDF, six placebo) were found to have HIV-1 infection at baseline, and 1% of participants discontinued from the study. Retention of partner participants in each study group was at least 96% over the course of the study (Table 11). In the Partners PrEP study, the most common reason for not dispensing study medication was pregnancy (Table 12). Time off study medication due to pregnancy and breastfeeding accounted for 5.3% of the follow-up time among women (2.0% among all participants). In the CDC TDF2 study, 16 participants (nine FTC/TDF, seven placebo) did not receive any study drug, and three patients (one FTC/TDF, two placebo) were found to have HIV-1 infection at baseline. In the CDC TDF2 study, more than 30% of participants discontinued from the study; the most common reasons for discontinuations were participant withdrawal, relocation, or loss to follow-up. Overall, discontinuations were similar between treatment groups across the included studies.

TABLE 10: PATIENT DISPOSITION

	iPrEx		Partners PrEP		CDC TDF2	
	FTC/TDF	Placebo	FTC/TDF	Placebo	FTC/TDF	Placebo
Screened, N	4,905		7,856		2,533	
Randomized, N (%)	2,499		4,758[b]		1,219	
	1,251 (100)	1,248 (100)	1,579 (100)[b]	1,584 (100)[b]	611 (100)	608 (100)
Did not receive study drug, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	9 (1)	7 (1)
No follow-up visit,[a] n (%)	25 (2)	23 (2)	8 (< 1)	10 (< 1)	0	0
HIV-1–infected at baseline, n (%)	2 (< 1)	8 (< 1)	3 (< 1)	6 (< 1)	1 (< 1)	2 (< 1)
Followed for seroconversion, n (%)	1,224 (98)	1,217 (98)	1,568 (99)	1,568 (99)	601 (98)	599 (99)
Discontinuation, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	208 (34)	189 (31)
AE	25 (2)	28 (2)	[redacted]	[redacted]	0	0
Death	1 (< 1)	4 (< 1)	8 (1)	9 (1)	2 (< 1)	4 (< 1)
Lost contact with participant	[redacted]	[redacted]	[redacted]	[redacted]	52 (9)	63 (11)
Participant relocated	[redacted]	[redacted]	[redacted]	[redacted]	49 (8)	36 (6)
Withdrawn by investigator	[redacted]	[redacted]	[redacted]	[redacted]	10 (2)	6 (1)
Withdrawn by participant	[redacted]	[redacted]	[redacted]	[redacted]	90 (15)	74 (12)

	iPrEx		Partners PrEP		CDC TDF2	
	FTC/TDF	Placebo	FTC/TDF	Placebo	FTC/TDF	Placebo
Other reason	[redacted]	[redacted]	[redacted]	[redacted]	5 (1)	6 (1)
mITT, n (%)	1,224 (98)	1,217 (98)	1,568 (99)	1,568 (99)	601 (98)	599 (99)
Safety, n (%)	1,251 (100)	1,248 (100)	1,579 (100)	1,584 (100)	611 (100)	608 (100)

AE = adverse event; FTC/TDF = emtricitabine/tenofovir disoproxil fumarate; HIV-1 = human immunodeficiency virus type 1; mITT = modified intention-to-treat.
[a] Participants who did not have an on-study follow-up HIV test.
[b] Four participants in the FTC/TDF group and 2 participants in the placebo group were determined not to meet eligibility criteria for the study after randomization.
Sources: iPrEx Clinical Study Report (CSR),[4] Grant et al., 2010,[5] Partners PrEP CSR,[6] Baeten et al., 2012,[7] Thigpen et al., 2012,[8] US Food and Drug Administration (FDA) Medical Review.[28]

TABLE 11: RETENTION OF PARTICIPANTS OVER TIME IN THE PARTNERS PREP STUDY

	Partners PrEP	
	FTC/TDF	Placebo
Randomized, N (%)	1,579 (100)	1,584 (100)
Retained, actual/expected (%)		
6-month visit	1,553/1,578 (98)	1,559/1,579 (99)
12-month visit	1,379/1,414 (98)	1,378/1,406 (98)
18-month visit	1,070/1,106 (97)	1,083/1,111 (97)
24-month visit	753/784 (96)	760/783 (97)
30-month visit	296/309 (96)	301/308 (98)
36-month visit	16/16 (100)	18/18 (100)

FTC/TDF = emtricitabine/tenofovir disoproxil fumarate.
Sources: Partners PrEP Clinical Study Report,[6] Baeten et al., 2012.[7]

TABLE 12: PREGNANCIES IN THE PARTNERS PREP STUDY

	Partners PrEP	
	FTC/TDF	Placebo
Total female HIV-1–negative participants, n	566	621
Female participants reporting a pregnancy, n (%)	74 (13)	88 (14)
Number of pregnancies reported	80	96
Incidence (95% CI) per 100 participant-years	8.8 ([redacted])	10.0 ([redacted])

CI = confidence interval; HIV = human immunodeficiency virus; FTC/TDF = emtricitabine/tenofovir disoproxil fumarate.
Sources: Partners PrEP Clinical Study Report,[6] Baeten et al., 2012.[7]

3.4 Exposure to Study Treatments

In the iPrEx study, participants were followed for 3,324 person-years (median: 1.2 years; maximum: 2.8 years) at the time of the primary data cut-off, with [redacted] person-years of follow-up in the FTC/TDF group and [redacted] person-years of follow-up in the placebo group. In the Partners PrEP study, HIV-1–negative partner participants were followed for a total of 7,830 person-years (median: 23 months; range: 1 to 36 months), including the TDF 300 mg group, at the time of the primary data cut-off, with 2,616 person-years of follow-up in the FTC/TDF group and 2,607 person-years of follow-up in the placebo group. In

the CDC TDF2 study, participants were followed for 1,563 person-years (median: 1.1 years; maximum: 3.7 years) before the study was stopped.

The duration of exposure to the study drug was reported only for the iPrEx study. The mean (standard deviation) exposure was [redacted] weeks in the FTC/TDF group and [redacted] weeks in the placebo group. The median (range) exposure was [redacted] weeks in the FTC/TDF group and [redacted] weeks in the placebo group.

TABLE 13: DURATION OF EXPOSURE TO STUDY DRUG IN THE IPREX STUDY; SAFETY SET

	iPrEx	
	FTC/TDF (n = 1,251)	Placebo (n = 1,248)
Overall exposure (weeks)		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]

FTC/TDF = emtricitabine/tenofovir disoproxil fumarate; SD = standard deviation.
Sources: iPrEx Clinical Study Report,[4] Grant et al., 2010.[5]

3.5 Critical Appraisal

3.5.1 Internal Validity

Randomization was stratified by study site and for all studies, and in the CDC TDF2 study, randomization was also stratified by gender. Generally, baseline characteristics were balanced between FTC/TDF and placebo groups across studies.

There were discontinuations in approximately [redacted] of participants in the iPrEx study and in more than 30% of participants in the CDC TDF2 study. [redacted] and participants who discontinued early were censored at their last HIV-1 test. Discontinuations were similar between the FTC/TDF and placebo groups in both studies, as well as the reasons for discontinuations. However, as a larger-than-expected proportion of participants was lost to follow-up in the CDC TDF2 study, the study had not enrolled enough participants to meet the initial power calculations for the primary end point. Logistical challenges to recruitment precluded the expansion of the study, and the study was concluded early. Due to this limitation, results from the CDC TDF2 study need to be interpreted with caution.

No adjustments for multiple statistical testing were performed in the included studies. Therefore, results for secondary end points and secondary analyses to the primary end point need to be interpreted with caution due to the potential for type 1 error.

According to the clinical expert consulted by CDR, the HIV-1 testing algorithms used in each study were quite rigorous and would likely screen out false-positive results. Participants who had a positive test at a study visit had their samples from previous visits tested to determine the exact time point at which viral RNA was detectable.

3.5.2 External Validity

The Partners PrEP and CDC TDF2 studies were conducted solely in African participants. According to the clinical expert consulted for this review, there may be differences in the standard of care and services available in countries outside of the Western context that may limit the generalizability of study results. In addition, premarital sex is less culturally acceptable in Botswana than in Western countries, which

may have limited the recruitment of these participants in the CDC TDF2 study, and potentially affect the reporting of sexual behaviours during the study.

In the iPrEx study, no Canadian participants were enrolled, and the majority of participants were from Hispanic countries. The clinical expert noted that the generalizability issues associated with a lack of Canadian participants would be related to the health care system and the availability of services for participants at risk of HIV infection in these countries compared with Canada.

According to the clinical expert, the MSM population enrolled in the iPrEx study was a very high-risk population (average of 18 sexual partners in the past 12 weeks at baseline), which may be more extreme than what may be seen in Canadian clinical practice. In the Partners PrEP study, eligibility criteria were specified so that the HIV-1–infected partner could not be eligible for ARTs at baseline, which may not be entirely generalizable to the Canadian population, where HIV-1–infected individuals would be on ART with the goal of reducing viral load. However, not all HIV-1–infected individuals in a relationship are initially aware of their status, and results from this study may be generalizable to that demographic.

In the Partners PrEP and CDC TDF2 studies, a requirement for enrolment was that the participant would not relocate for the duration of the study. This could potentially exclude several participants, particularly in a young, mobile population such as the one in the CDC TDF2 study. The logistics of conducting a study with relocating participants is challenging, although this would likely be a characteristic of the at-risk population in Canada.

Patient groups reported that individuals at high-risk of HIV-1 experience anxiety and fear regarding the lack of control of their own sexual health, the possibility of HIV infection, and the stigma associated with a positive HIV status, and they have expectations that PrEP will be able to alleviate these concerns. However, quality of life outcomes were not assessed in any of the included studies, so the impact of FTC/TDF using PrEP on a patient's well-being is unknown.

Adherence according to pill counts and patient self-report was generally high in all studies; however, adherence according to self-report and pill count is subject to bias due to inaccurate reporting or potential disposal of pills prior to the study visit. Follow-up visits in all three studies were conducted monthly, at which participants were tested for HIV-1, provided with counselling, and treated for symptomatic STIs. According to the clinical expert, follow-up visits would likely occur less frequently in clinical practice (i.e., likely every three months) compared with the monthly visits that occurred in the included studies. Therefore, interventions such as adherence counselling and risk-reduction counselling would be provided less frequently in clinical practice, potentially limiting the generalizability of the studies.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (section 2.2, Table 2). See 0 for detailed efficacy data.

3.6.1 HIV-1 Seroconversion

In the iPrEx study, participants were followed for 1,659 person-years in the FTC/TDF group and for 1,669 person-years in the placebo group (median: 1.2 years; range: one day to 36 months) at the time of the primary data cut-off (May 1, 2010). During this time, HIV-1 seroconversion was observed in 110 participants, of which 10 had plasma HIV RNA subsequently detected from baseline specimens and were

excluded from the analyses (Table 14). Of the 100 participants with emergent HIV-1 infection, 36 participants were in the FTC/TDF group (2.2 per 100 person-years) and 64 participants were in the placebo group (3.8 per 100 person-years), corresponding to a relative risk reduction of 44% (95% confidence interval [CI], 15% to 63%; *P* = 0.005). Follow-up assessments of the primary end point included data through the end of DB treatment period (July 31, 2010 data cut-off) and the end of treatment plus eight weeks of follow-up (November 21, 2010 data cut-off) (Table 19). The relative risk reduction in HIV-1 seroconversion with FTC/TDF compared with placebo was similar to the primary analysis at the end of treatment (42%; 95% CI, 18% to 60%; *P* = 0.002) and at the end of treatment plus eight weeks of follow-up (39%; 95% CI, 14% to 57%; *P* = 0.004). Although the primary end point at the various cut-off dates were all statistically significant, the lower bound of the CIs was less than 30%, meaning the null hypothesis of efficacy of 30% or less could not be rejected. In the iPrEx study, for 100 participants on FTC/TDF for one year, a mean of 1.6 seroconversions (95% CI, 0.5 to 2.8) would be prevented compared with those on placebo.

In the Partners PrEP study, HIV-1–negative partners were followed for 2,616 person-years in the FTC/TDF group and for 2,607 person-years in the placebo group at the time of the primary data cut-off (median: 23 months; range: 1 to 36 months). During this time, HIV-1 seroconversions were observed in 96 participants, of which 14 had plasma HIV RNA subsequently detected from baseline specimens and were excluded from the analyses (Table 14). Of the 82 participants with emergent HIV-1 infection, 13 participants were in the FTC/TDF group (0.50 per 100 person-years) and 52 participants were in the placebo group (1.99 per 100 person-years), corresponding to a relative risk reduction of 75% (95% CI, 55% to 87%; *P* < 0.001). The lower bound of the CI exceeded 30%, ruling out the null hypothesis of efficacy of 30% or less. In the Partners PrEP study, for 100 participants on FTC/TDF for one year, a mean of 1.5 seroconversions (95% CI, 0.9 to 2.1) would be prevented compared with those on placebo.

In the CDC TDF2 study, participants were followed for 1,563 person-years (median: 1.1 years; maximum: 3.7 years). During this time, HIV-1 seroconversions were observed in 36 participants, of whom three had plasma HIV RNA subsequently detected from baseline specimens and were excluded from the analyses (Table 14). Of the 33 participants with emergent HIV-1 infection, nine were in the FTC/TDF group (1.2 per 100 person-years) and 24 were in the placebo group (3.1 per 100 person-years), corresponding to a relative risk reduction of 62.2% (95% CI, 21.5% to 83.4%; *P* = 0.03).

TABLE 14: HIV-1 SEROCONVERSION; MODIFIED INTENTION-TO-TREAT SET

	iPrEx		Partners PrEP		CDC TDF2	
	FTC/TDF (n = 1,224)	Placebo (n = 1,217)	FTC/TDF (n = 1,576)	Placebo (n = 1,578)	FTC/TDF (n = 601)	Placebo (n = 599)
HIV-1 seroconversion						
Person-years of follow-up	[redacted]	[redacted]	2,616	2,607	1,563	
Participants with seroconversion events, n	36	64	13	52	9	24
Rate per 100 person-years	[redacted]	[redacted]	0.50	1.99	1.2	3.1
Hazard ratio (95% CI)	0.56 (0.37 to 0.85)		0.25 (0.13 to 0.45)		NR	
Relative risk reduction, % (95% CI)	44 (15 to 63)		75 (55 to 87)		62.2 (21.5 to 83.4)	
P value	0.005		< 0.001		0.03	
Absolute rate reduction, per 100 person-years (95% CI)[a]	[redacted]		[redacted]		NR	

CI = confidence interval; FTC/TDF = emtricitabine/tenofovir disoproxil fumarate; HIV = human immunodeficiency virus; mITT = modified intention-to-treat; NR = not reported.
[a] Provided by the manufacturer.[3]
Source: iPrEx Clinical Study Report (CSR),[4] Grant et al., 2010,[5] Partners PrEP CSR,[6] Baeten et al., 2012,[7] Thigpen et al., 2012.[8]

In the iPrEx study, no HIV seroconversion event was reported during the DB treatment phase among any participant who initiated post-exposure prophylaxis (PEP) (Table 15). The US Food and Drug Administration (FDA) conducted sensitivity analyses of the iPrEx data assuming that all FTC/TDF participants who received PEP and did not seroconvert would have become HIV-infected on the day PEP began. The results of this analysis indicated that the use of PEP in the iPrEx study did not significantly affect the overall efficacy results.

TABLE 15: POST-EXPOSURE PROPHYLAXIS IN THE IPREX STUDY; MODIFIED INTENTION-TO-TREAT SET

	iPrEx	
	FTC/TDF (n = 1,224)	Placebo (n = 1,217)
Used PEP (Grant et al. values), n (%)	8 (< 1)	13 (1)
Used PEP (FDA values), n (%)	13 (1)	20 (2)

FDA = US Food and Drug Administration; FTC/TDF = emtricitabine/tenofovir disoproxil fumarate; PEP = post-exposure prophylaxis.
Sources: iPrEx Clinical Study Report,[4] Grant et al., 2010,[5] FDA.[28]

In the Partners PrEP study, approximately 30% of HIV-1–positive partner participants initiated ART post-randomization during the study (Table 16). Because the risk of HIV transmission to the HIV-1–negative partner participant is dependent on viral load, the FDA conducted sensitivity analyses to evaluate the effect of ART initiation on PrEP efficacy by censoring participants whose partner had initiated ART. The results of these analyses showed that the initiation of ART did not significantly affect the original conclusions.

TABLE 16: ANTIRETROVIRAL THERAPY USE BY HIV-1–INFECTED PARTICIPANTS IN THE PARTNERS PREP STUDY; SAFETY SET

	Partners PrEP	
	FTC/TDF (n = 1,579)	Placebo (n = 1,584)
Number of participants reporting ART use during study follow-up, n (%)	[redacted]	[redacted]
Number of participants ever eligible for ART by national guidelines, n (%)	[redacted]	[redacted]

ART = antiretroviral therapy; FTC/TDF = emtricitabine/tenofovir disoproxil fumarate; HIV = human immunodeficiency virus.
Source: Partners PrEP Clinical Study Report,[6] Baeten et al., 2012.[7]

a) Subgroup analysis based on sex

In the studies that looked at heterosexual male and female participants (Partners PrEP, CDC TDF2), subgroup analyses according to sex were performed on the primary efficacy end point (Table 20). In the Partners PrEP study, the relative risk reduction with FTC/TDF compared with placebo was 66% in females (95% CI, 29% to 84%) and 84% in males (95% CI, 54% to 94%). In the CDC TDF2 study, the relative risk reduction with FTC/TDF compared with placebo was 49% in females (95% CI, –22% to 81%) and 80% in males (95% CI, 25% to 97%).

b) Analysis based on FTC/TDF drug levels

In all studies, an analysis of drug level detection in HIV-1 seroconversion cases and controls was performed. All studies examined the plasma levels of drug components, and the iPrEx study also looked at intracellular drug levels. In the iPrEx study, there was detectable plasma FTC and tenofovir (TFV) in 6% of HIV-1 seroconversion participants compared with 48.6% of control participants. In the Partners PrEP study, there was detectable plasma TFV in 55.6% of HIV-1 seroconversion participants compared with 83.1% of control participants. In the CDC TDF2 study, there was detectable plasma FTC and TFV in 50% of HIV-1 seroconversion participants compared with approximately 80% of control participants.

TABLE 17: PLASMA EMTRICITABINE AND TENOFOVIR LEVELS BY HIV-1 INFECTION STATUS

	iPrEx		Partners PrEP		CDC TDF2	
Detectable drug	Case (+)	Control (–)	Case (+)	Control (–)	Case (+)	Control (–)
Plasma FTC, n/n total (%)	2/33 (6.1)	17/35 (48.6)	NR	NR	2/4 (50.0)	56/69 (81.2)
Plasma TFV, n/n total (%)	2/33 (6.1)	17/35 (48.6)	20/36 (55.6)	374/464 (80.6)	2/4 (50.0)	55/69 (79.7)
Intracellular FTC, n/n total (%)	3/34 (8.8)	22/42 (52.4)	-	-	-	-
Intracellular TFV, n/n total (%)	2/34 (5.9)	21/42 (50.0)	-	-	-	-

- = not assessed; FTC = emtricitabine; HIV = human immunodeficiency virus; NR = not reported; TFV = tenofovir.
Sources: iPrEx Clinical Study Report (CSR),[4] Grant et al., 2010,[5] Partners PrEP CSR,[6] Baeten et al., 2012,[7] Thigpen et al., 2012.[8]

3.6.2 Sexual Behaviour

In the iPrEx study, the number of receptive anal intercourse (RAI) partners in the previous 12 weeks and the proportion of partners with whom anal intercourse was performed using condoms was analyzed throughout the course of the study (Table 21). The number of sexual partners with whom respondents had had RAI decreased after study enrolment from a mean of approximately 12 partners to a mean of less than five partners in the previous 12 months, and the percentage of those partners who used a

condom increased from 50% to more than 70%. The results of the assessments of sexual behaviours were similar between the FTC/TDF and placebo groups at all time points ($P = 0.97$).

In the Partners PrEP study, the proportion of HIV-1–negative participants who reported having unprotected sex with their HIV-1–positive partner in the prior month was assessed throughout the maximum 36-month follow-up period of the study (Table 22). At enrolment, 27% of HIV-1–negative participants reported having had sex without a condom during the previous month. This percentage decreased during the follow-up period to 13% and 9% at 12 and 24 months, respectively, and this was similar between treatment groups. The proportion of patients reporting engaging in sexual intercourse with outside partners did not differ across study groups (FTC/TDF, 29.9% versus placebo 29.1%).

In the CDC TDF2 study, the number of sexual partners in the previous month and the percentage of sexual episodes using condoms with the main or most recent casual sexual partner in the previous month were analyzed over 24 months after randomization. The percentage of sexual episodes using condoms with the main or most recent sexual partner was 81.4% (range: 76.6% to 86.4%) in the FTC/TDF group and 79.2% (range: 71.6% to 87.6%) in the placebo group at baseline, and remained similar between groups and was stable over 24 months ($P = 0.87$ for trend; $P = 0.95$ between treatment groups). The number of sexual partners in the previous month were similar between treatment groups throughout the study and declined slightly over time ($P < 0.001$ for trend; $P = 0.95$ between treatment groups).

3.6.3 Sexually Transmitted Infections

In the iPrEx study, the incidence of STIs was analyzed by study visit as a separate outcome measure, with STI testing being performed every 24 weeks regardless of whether symptoms were reported (Table 23). There were no statistically significant between-group differences in the incidence of syphilis, gonorrhea, chlamydia, genital warts, or genital ulcers during follow-up.

In the Partners PrEP study, approximately 30% of participants reported having had sex with an outside partner (Table 24). The proportion of patients who reported any STI was similar between the FTC/TDF and placebo groups (4.8% versus 5.3%).

In the CDC TDF2 study, the incidence of STIs was reported as AE data (Table 25). The incidence of chlamydia and trichomoniasis (in women) were similar across treatment groups. There was a higher proportion of participants that reported having gonorrhea (4.6% versus 3.0% and sore genital ulcers (2.0% versus 1.0%) in the FTC/TDF group compared with the placebo group. A slightly higher proportion of patients reported having genital herpes in the placebo group compared with the FTC/TDF group (5.8% versus 4.6%).

3.6.4 Adherence

In the iPrEx study, the mean and median rate of self-reported pill use was similar between the FTC/TDF and placebo groups (mean: 88.7% versus [redacted] median: 95.4% for both groups) (Table 26).

In the Partners PrEP study, study drug adherence was assessed using pill counts from returned study bottles (Table 27). As there was an FTC/TDF and a TDF arm and similar pills were not available for both, participants took two tablets daily. More than 98% of dispensed study bottles were returned, and 94% of dispensed study tablets were taken. Self-reported adherence was also assessed at study visits. At [redacted] of total study visits where self-reported adherence information was taken, participants indicated that

they had missed at least one dose of the study drug during the previous month, and at [redacted] of study visits, participants reported having missed two or more consecutive doses.

In the CDC TDF2 study, rates of adherence were estimated to be similar across treatment groups according to pill counts (FTC/TDF, 84.1% versus placebo 83.7%) and self-reported adherence for the preceding three days (FTC/TDF, 94.4% versus placebo 94.1%).

3.6.5 Quality of Life

Quality of life was not assessed in any of the included studies.

3.6.6 HIV-1 Drug Resistance

In the iPrEx study, no FTC or TDF resistance mutations were detected among the 36 participants who had HIV-1 seroconversion during the study. Among the 10 participants who were subsequently found to have had plasma HIV-1 RNA at baseline (two FTC/TDF; eight placebo), two patients in the FTC/TDF group (M184V and M184I) and one patient in the placebo group (M184V, T215Y, and K103N) were found to have FTC-resistant virus.

In the Partners PrEP study, resistance testing was performed in 63 of the 65 participants who had HIV-1 seroconversion during the study in the FTC/TDF and placebo groups. One participant in the FTC/TDF group and one participant in the placebo group developed resistance mutations to non-nucleoside reverse transcriptase inhibitors (NNRTIs) (K103N or V106A). Of the three patients in the FTC/TDF group who were subsequently found to have plasma HIV-1 RNA at baseline, one participant developed FTC-resistant virus (M184V).

In the CDC TDF2 study, one participant in the placebo group developed a K65R mutation intermittently at low levels after seroconversion. The one participant in the FTC/TDF group who had had HIV-1 infection at baseline developed K65R, M184V, and A62V reverse transcriptase resistance mutations at high levels.

3.7 Harms

Only those harms identified in the review protocol are reported below (see 2.2.1, Protocol). See 0 for detailed harms data.

3.7.1 Adverse Events

Analyses of AEs by the iPrEx study team included all events reported through the May 1, 2010 cut-off date, regardless of whether study drug had been discontinued. The manufacturer's safety analyses included treatment-emergent AEs occurring on or after the first study drug dispense date and on or before 30 days after the last study drug dose date and numbers are presented in Table 28. Overall, the incidence of AEs was similar across the FTC/TDF and placebo groups in the iPrEx study (69% versus 70%), the Partners PrEP study (86% versus 85%), and the CDC TDF2 study (91% versus 88%) (Table 18). Common AEs included upper respiratory tract infections, pharyngitis, diarrhea, and headache. In the CDC TDF2 study, common AEs also included abdominal pain, dizziness, nausea, vomiting, and weight loss.

3.7.2 Serious Adverse Events

The incidence of SAEs was similar across the FTC/TDF and placebo groups in the iPrEx study (5% for both groups), the Partners PrEP study (7% for both groups), and the CDC TDF2 study (7% for both groups).

3.7.3 Withdrawals Due to Adverse Events

In the iPrEx study, 2% of patients withdrew due to an adverse event in both treatment groups. In the iPrEx study, there was no pattern of AEs that led to discontinuation. In the Partners PrEP study, two participants in the FTC/TDF group and one participant in the placebo group withdrew due to an adverse event. In the Partners PrEP study, all discontinuations were due to an increase in blood creatinine level that was confirmed on repeat testing. In the CDC TDF2 study, no participants withdrew from the study due to an adverse event.

3.7.4 Mortality

In the iPrEx study, one patient in the FTC/TDF group (motor vehicle accident) and four patients in the placebo group (one injury, one head injury, one gunshot wound, one unknown) died, with no deaths considered by the investigator to be related to study drug. In the Partners PrEP study, eight patients in the FTC/TDF group (one gunshot wound, one poisoning, one pulmonary tuberculosis, two road traffic accident, one gastroenteritis, one pulmonary embolism, one influenza-like illness) and nine patients in the placebo group (three road traffic accidents, one hematemesis, one febrile infection, one electrocution, one suicide, one hypotension, one diabetic complication) died. Two of the deaths in the FTC/TDF group (pulmonary embolism, influenza-like illness) were considered by the investigator to be possibly related to the study drug. In the CDC TDF2 study, two patients in the FTC/TDF group (one motor vehicle accident, one suicide) and four patients in the placebo group (two motor vehicle accident, one homicide, one cerebrovascular accident) died.

3.7.5 Notable Harms

The incidence of elevated creatinine AEs was low across treatment groups in all included studies (2% or less).

The incidence of bone fractures was 1% or less across treatment groups in all included studies. Bone fractures were generally reported to be traumatic rather than pathological, resulting from motor vehicle accidents, direct force, or altercations.

TABLE 18: HARMS; SAFETY SET

	iPrEx		Partners PrEP		CDC TDF2	
	FTC/TDF (n = 1,251)	Placebo (n = 1,248)	FTC/TDF (n = 1,579)	Placebo (n = 1,584)	FTC/TDF (n = 611)	Placebo (n = 608)
AEs						
Participants with > 0 AEs, n (%)	867 (69)	877 (70)	1,362 (86)	1,350 (85)	557 (91)	536 (88)
Common AEs						
Abdominal pain	24 (2)	15 (2)	3 (< 1)	2 (< 1)	155 (25)	156 (26)
Depression	43 (3)	62 (5)	1 (< 1)	0	NR	NR
Diarrhea	46 (4)	56 (4)	38 (2)	39 (2)	76 (12)	65 (11)
Dizziness	NR	NR	0	1 (< 1)	92 (15)	67 (11)
Dysmenorrhea	NA	NA	2 (< 1)	2 (< 1)	32 (5)	34 (6)
Headache	56 (4)	41 (3)	1 (< 1)	3 (< 1)	227 (37)	226 (37)
Nausea	20 (2)	9 (< 1)	1 (< 1)	0	113 (19)	43 (7)
Pelvic inflammatory disease	NA	NA	48 (3)	55 (3)	6 (1)	10 (2)
Pharyngitis	70 (6)	85 (7)	18 (1)	15 (1)	39 (6)	37 (6)

	iPrEx		Partners PrEP		CDC TDF2	
	FTC/TDF (n = 1,251)	Placebo (n = 1,248)	FTC/TDF (n = 1,579)	Placebo (n = 1,584)	FTC/TDF (n = 611)	Placebo (n = 608)
Rash	NR	NR	3 (< 1)	2 (< 1)	39 (6)	42 (7)
Urethritis	49 (4)	63 (5)	16 (1)	20 (1)	NR	NR
URTI	42 (3)	47 (4)	159 (10)	142 (9)	231 (38)	241 (40)
Vomiting	NR	NR	4 (< 1)	0	69 (11)	43 (7)
Weight loss	27 (2)	14 (1)	4 (< 1)	6 (< 1)	75 (12)	61 (10)
SAEs						
Participants with > 0 SAEs, n (%)	60 (5)	67 (5)	115 (7)	118 (7)	115 (7)	118 (7)
WDAEs						
Participants with > 0 WDAEs, n (%)	25 (2)	27 (2)	2 (< 1)	1 (< 1)	0	0
Deaths						
Number of deaths, n (%)	1 (< 1)	4 (< 1)	8 (< 1)	9 (< 1)	2 (< 1)	4 (< 1)
Notable harms, n (%)						
Renal AEs						
Elevated creatinine[a]	25 (2)	14 (1)	20 (1)	13 (1)	1 (< 1)	0
Bone AEs						
Bone fracture	15 (1)	11 (1)	9 (< 1)	13 (1)	7 (1)	6 (1)

AE = adverse event; FTC/TDF = emtricitabine/tenofovir disoproxil fumarate; SAE = serious adverse event; WDAE = withdrawal due to adverse event; URTI = upper respiratory tract infection.

[a] Defined as an increase in serum creatinine of at least 1.5 times the baseline value.

Sources: iPrEx Clinical Study Report (CSR),[4] Grant et al., 2010,[5] Partners PrEP CSR,[6] Baeten et al., 2012,[7] Thigpen et al., 2012.[8]

4. DISCUSSION

4.1 Summary of Available Evidence

Three DB, placebo-controlled RCTs assessing the safety and efficacy of once-daily FTC/TDF200 mg/300 mg as PrEP in combination with HIV prevention services for individuals at high risk of acquiring HIV-1 infection met the inclusion criteria for this review. The iPrEx study (N = 2,499) was an international study conducted in adult MSM that continued until at least 85 seroconversion events occurred. Participants who completed the iPrEx study had the option of enrolling in a 72-week open-label extension (OLE) study along with participants who had completed other MSM studies (see APPENDIX 5). The Partners PrEP study (N = 4,758) was conducted in adult Kenyan and Ugandan sexually active, serodiscordant, heterosexual couples, and followed participants for 24 to 36 months. The CDC TDF2 study (N = 1,219) was conducted in Botswanan heterosexual men and women between 18 and 39 years who were sexually active where participants were planned to be treated for four years. The CDC TDF2 study was concluded early due to the lower-than-expected rate of retention of participants. In all studies, study visits were scheduled every four weeks and included drug dispensing, rapid testing for HIV-1 antibodies, adherence counselling, risk-reduction counselling, condom promotion, and treatment of symptomatic STIs. In all studies, the primary end point was the incidence of HIV-1 infections based on rapid testing at each monthly visit using pre-specified testing algorithms. Other end points evaluated included sexual behaviour, the incidence of STIs, adherence to study drug, and HIV-1 drug resistance in seroconversion participants.

The main limitations of the included studies were the generalizability of results due to the enrolled population. The iPrEx study enrolled MSM that were at very high risk of acquiring HIV-1, the Partners PrEP study included serodiscordant couples in which the HIV-1–positive partner was not to be taking ART, and the majority of enrolled participants were from Hispanic (iPrEx) or African (Partners PrEP and CDC TDF2) countries. Measures of treatment adherence were based on pill count and patient self-report, and may therefore have been subject to bias. As no adjustments for multiple testing were performed for secondary end points, the results need to be interpreted with caution. Although quality of life was cited as an important outcome according to patient-group input, health-related quality of life was not measured in any of the studies.

An ongoing phase 4, two-year, randomized, open-label study (planned N = 5,000) conducted in the UK compared FTC/TDF PrEP administered immediately to FTC/TDF PrEP delayed for one year in adult MSM (see APPENDIX 6). A phase 3, DB RCT (N = 414) conducted in France and Canada assessed the safety and efficacy of TDF/FTC administered as on-demand PrEP in adult MSM (see APPENDIX 7.)

4.2 Interpretation of Results

4.2.1 Efficacy

The three studies included in this review were conducted in different populations, but inclusion and exclusion criteria for each study allowed for the enrolment of individuals at risk for acquiring HIV-1 infection who would likely be able to tolerate once-daily FTC/TDF FDC 200 mg/300 mg for PrEP. However, the iPrEx study and Partners PrEP studies excluded patients with active alcohol or drug use considered sufficient to hinder compliance, which may reduce the generalizability of results to the at-risk population in Canada. In addition, none of the studies were conducted in Canada, with the iPrEx study enrolling mainly Hispanic participants from South American countries, and the Partners PrEP and CDC TDF2 studies enrolling African participants from Kenya, Uganda, or Botswana. The clinical expert consulted by CDR noted that differences in metabolism or biological effects of FTC/TDF between races

are not known, but there may be differences in the health care systems and access to HIV prevention services in developing countries that may limit generalizability of the included studies to the Canadian context. In the iPrEx study, the adult MSM participants enrolled had characteristics that would be defined as a very high-risk population, with participants having had a mean of 18 partners in the previous 12 weeks at baseline. According to the clinical expert, this MSM population may be at higher risk than patients who would normally be seen in a Canadian clinic. In the Partners PrEP study, HIV-1–infected partner participants were not to be eligible for ART according to national guidelines, which limits the generalizability of results to serodiscordant couples in which the HIV-1–infected partner is currently being treated with ART. However, the goal of ART in HIV-1–infected patients is suppression of viral replication as indicated by a plasma HIV-1 viral load below 40 copies/mL, at which level the risk of transmission would be low and the efficacy of FTC/TDF as PrEP would be difficult to demonstrate.[32] The CDC TDF2 study enrolled a young heterosexual population between 18 and 39 years of age, which is relevant to the at-risk population in Canada. However, due to the mobile nature of this young population in Botswana, retention of participants in the CDC TDF2 study was difficult and the study was concluded early due to the logistical challenge of increasing recruitment to meet revised power calculations.

The incidence of HIV-1 seroconversion was the primary efficacy end point in all studies. Paired rapid HIV tests were administered at each monthly visit, and discordant or positive results were retested or confirmed using rigorous testing algorithms. In all studies, there was a statistically significantly reduced risk of HIV-1 seroconversion for patients receiving FTC/TDF compared with placebo. The relative risk reductions with FTC/TDF versus placebo ranged from 44% (95% CI, 15 to 63) in the iPrEx study to 75% (95% CI, 55 to 87) in the Partners PrEP study. The FDA evaluated the robustness of the results from the iPrEx and Partners PrEP studies by conducting sensitivity analyses of participants who initiated PEP therapy and HIV-1–positive partner participants who initiated ART, which did not significantly alter the primary analysis. The reason for the differences in relative risk reduction of HIV-1 seroconversion with FTC/TDF versus placebo across studies is unclear, but may be explained in part by adherence to therapy. Results from the analyses of plasma drug levels among HIV-1 seroconverters and non-seroconverters in the included studies suggest that a lower proportion of HIV-1 seroconverters had detectable drug levels than non-seroconverters. Subgroup analyses based on sex in the Partners PrEP and CDC TDF2 studies did not suggest a difference in the efficacy of FTC/TDF based on sex. However, a pharmacokinetic study (N = 15) demonstrated that a single dose of FTC/TDF results in tenofovir concentrations that were 100-fold higher in rectal tissue than in vaginal and cervical tissues, and detectable for 14 days after administration.[33]

Adherence based on pill counts and self-report was high across studies (> 80%), and adherence counselling was given at each monthly visit. Due to the subjective nature of these measures, there is the potential for misreporting by participants. In the Partners PrEP study, an adherence sub-study (N = 1,147) was conducted in which unannounced, home-based pill counts were conducted monthly for the first six months and then quarterly.[34] Results from this sub-study suggested that adherence was high in the Partners PrEP study and corroborated with the results from self-report and pill counts in the full study.[34] High adherence seen in the Partners PrEP study may also have been due to the enrolled population, in which the HIV-1–negative partner in a serodiscordant, monogamous relationship may receive support from their HIV-1–infected partner and be motivated to preserve the relationship.[34] No adherence sub-studies were conducted in iPrEx and CDC TDF2. Two DB, placebo-controlled RCTs (VOICE, phase 2b, N = 5,029; FEM-PrEP, phase 3, N = 2,120) evaluating the safety and efficacy of FTC/TDF for PrEP were conducted in sexually active African women at risk of acquiring HIV infection.[35,36] Both studies were terminated early due to a lack of efficacy, which was found to be due to poor adherence. In the

FEM-PrEP study, analysis of plasma and intracellular drug levels among a sub-cohort of the population demonstrated that 12% had achieved good adherence, 23% had rarely taken FTC/TDF, and 60% had had fluctuating adherence, despite self-reporting of high adherence during the trial.[37] Participants had difficulty accurately reporting their adherence in a clinical trial setting because they assumed that reporting poor adherence would result in negative consequences.[37]

On-demand PrEP is not a Health Canada–approved regimen for FTC/TDF 200 mg/300 mg; however, one study has been conducted to assess on-demand PrEP therapy with FTC/TDF due to the difficulty of adhering to a daily regimen.[38] The IPERGAY study was a DB, placebo-controlled RCT (N = 414) conducted in adult MSM in France and Canada to assess the safety and efficacy of on-demand PrEP with FTC/TDF (see APPENDIX 7).[38] In the IPERGAY study, participants were to take two pills 2 to 24 hours before sex, followed by a third pill 24 hours after the first drug intake and a fourth pill 24 hours later. For consecutive episodes of sexual intercourse, participants were to take one pill per day and two post-exposure pills after the last episode. Results from the IPERGAY study suggest that there is a reduction in the incidence of HIV-1 seroconversions in MSM with on-demand FTC/TDF compared with placebo (431.3 person-years follow-up; relative risk reduction 86%; 95% CI, 40 to 98), although results need to be interpreted with caution as the study was concluded early after stopping rules were met and continued as an open-label RCT. Adherence was suboptimal, with 43% of participants taking the drug correctly, 29% taking it at a suboptimal dose, and 28% of participants not taking any drug. A four-month, DB, placebo-controlled RCT (N = 72) was conducted in healthy African MSM and female sex workers to assess adherence to daily versus intermittent PrEP regimens; results from this small study suggested that adherence rates were better with daily dosing than with intermittent, coitally timed dosing.[39] As this was a small study, results need to be interpreted with caution.

In addition to daily FTC/TDF or placebo, participants were provided with risk reduction counselling at each monthly visit and connected to local prevention services when required in the studies. Overall, sexual behaviour was similar between the FTC/TDF and placebo groups across studies. In the iPrEx study, the number of RAI partners in the previous 12 weeks decreased during the study, and the percentage of partners who used a condom increased in both FTC/TDF and placebo groups. In the Partners PrEP study, the proportion of participants reporting having had sex without a condom in the previous month decreased during the study in both FTC/TDF and placebo groups. In the CDC TDF2 study, the percentage of sexual episodes using condoms with the most recent sexual partner remained constant during the study, and the number of sexual partners in the previous month declined slightly over time. Because sexual risk behaviour was self-reported, results may be biased by social desirability; the incidence of STIs may be a more objective measure of sexual behaviour. However, the proportion of participants with STIs over time was not reported in any of the included studies, although the incidence of STIs was similar between the FTC/TDF and placebo groups.

In the patient-group submission, participants expressed that FTC/TDF PrEP would alleviate their anxiety and fear of becoming HIV-positive after engaging in risky sexual behaviour, whether it be condomless sex or sex with HIV-1–positive partners (see APPENDIX 1). This highlights the potential issue of sexual risk compensation, or engaging in more risky sexual behaviours if receiving PrEP with FTC/TDF. Risky sexual behaviours decreased or stayed constant over time in both the FTC/TDF and placebo groups across studies. The interpretation of this result, however, is limited because of the DB nature of the studies' participants. A secondary analysis of the iPrEx study found that there was no evidence of sexual risk compensation in participants who believed they were receiving FTC/TDF.[24] The PROUD study is an ongoing, real-world, open-label RCT study evaluating the safety and efficacy of FTC/TDF as PrEP for MSM in the UK administered immediately compared with delaying PrEP for a year (see APPENDIX 6).[40]

A sample size of 5,000 has been planned, and results from the first 544 participants suggested that there were no statistically significant differences in bacterial STIs between the group that received immediate treatment and the delayed treatment group. When compared with the iPrEx study, PROUD demonstrated a larger relative risk reduction in HIV-1 seroconversion with FTC/TDF compared with no therapy (relative risk reduction 86%; 95% CI, 64 to 96). However, the population in the PROUD study was highly selective and was at substantially higher risk of acquiring HIV infection than the overall MSM population attending sexual health clinics in England (9.0 HIV-1 seroconversions per 100 patient-years in the delayed group; median 10 partners in past 90 days).[41]

4.2.2 Harms

Overall, the incidence of AEs was similar between the FTC/TDF and placebo groups across the included studies. Common AEs included pharyngitis, upper respiratory tract infection, diarrhea, and headache. The incidence of certain AEs was higher in the CDC TDF2 study, and also included abdominal pain, dizziness, nausea, vomiting, and weight loss. In the 72-week OLE study that included participants who completed MSM studies including iPrEx (N = 1,603; 95% from iPrEx study), the most common AEs that resulted in stopping FTC/TDF use were nausea and abdominal pain (see APPENDIX 5).

The safety profile of FTC/TDF has been well studied in HIV-1–infected patients and is comparable to that of TDF alone.[42] Notable harms associated with FTC/TDF include renal AEs and bone AEs. In the included studies, the incidence of elevated creatinine AEs did not exceed 2% in any group across studies, and the incidence of bone fractures did not exceed 1% across studies, with the majority of bone fractures being trauma-related. In the iPrEx and Partners PrEP studies, renal function was further analyzed by measuring creatinine clearance and estimated glomerular filtration rate (eGFR) over time. In both studies, FTC/TDF was associated with a decrease in creatinine clearance and decline in eGFR over time compared with placebo.[25,29,43] However, both creatinine clearance and eGFR decreases were reversible after discontinuation of treatment.[25,29,43] The Health Canada product monograph recommends that FTC/TDF for PrEP not be used in HIV-1–uninfected individuals with creatinine clearance below 60 mL/min, which is consistent with the characteristics of the participants enrolled in the iPrEx and Partners PrEP studies.[22]

In the iPrEx and CDC TDF2 studies, bone mineral density (BMD) sub-studies were conducted to evaluate the effect of FTC/TDF on bone loss.[44,45] In both the iPrEx BMD sub-study (N = 498) and the CDC TDF2 BMD sub-study (N = 220), small but statistically significant decreases in spine and hip BMD were observed with FTC/TDF compared with placebo.[44,45] The Health Canada product monograph recommends that an assessment of BMD should be considered in patients who have a history of pathologic bone fracture or who are at risk for osteopenia or osteoporosis.[22] Participants with these characteristics were not enrolled in the iPrEx, Partners PrEP, and CDC TDF2 studies, which limits the generalizability of these safety results to that population.

The Health Canada product monograph recommends that FTC/TDF for PrEP be used as part of a comprehensive prevention strategy that includes safer sex practices, knowledge of their HIV-1 status and that of their partner(s), and regular testing for STIs.[22] In the included studies, follow-up visits were conducted monthly and included HIV testing, risk reduction counselling, adherence counselling, treatment of symptomatic STIs, and provision of condoms and contraceptives. According to the clinical expert, participants on PrEP therapy would not likely be seen as frequently in clinical practice, and follow-up visits would likely be conducted every three months. According to the Health Canada product monograph, the use of FTC/TDF 200 mg/300 mg for PrEP must be prescribed only to individuals confirmed to be HIV-negative immediately prior to initial use and periodically (at least every three months) during use.[22]

4.3 Potential Place in Therapy

The information in this section is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

Sexual health services are available in most communities, and provide counselling, condoms, testing for HIV and other STIs, and treatment for STIs. In spite of the fact that the sexual transmission of HIV is significantly reduced by the use of condoms, significant numbers of new HIV infections occur annually.[12,13] Aside from barrier methods, other interventions to reduce the sexual transmission of HIV include male circumcision and through treatment of STIs.[46-49] PEP with antivirals after sexual exposure to HIV has not been studied in RCTs, but other evidence (animal transmission models,[50] perinatal clinical trials,[51] observational studies of health care workers receiving prophylaxis after occupational exposures,[52] and observational and case studies of PEP use after sexual exposure)[53-55] suggests its effectiveness. However, antivirals are not approved for this indication, and access may be limited by cost and timely access to providers.

There remains, therefore, the need for further interventions to help prevent HIV transmission, according to the clinical expert consulted for this review. The clinical trials for PrEP with Truvada demonstrate that Truvada reduces the risk of HIV acquisition and is well tolerated. Long-term kidney and bone toxicities are possible, but according to the clinical expert consulted, are uncommon and manageable. There are no data available as to the effectiveness of other antivirals to reduce HIV acquisition when used as PrEP, aside from tenofovir, which appears to be less effective than Truvada.[7]

PrEP, in conjunction with safe practices, would be considered for HIV-negative adults identified as being at high risk for HIV infection through sexual exposure. The clinical expert indicated that these patients would likely come to the attention of health care providers through self-referral, through referral from primary care physicians after the diagnosis of an STI or identification of an ongoing significant sexual risk, or after the provision of PEP after a potential sexual exposure to HIV. Although PrEP could be a prevention option for any heterosexual or homosexual person considered at high risk for HIV infection, experience from a US cohort of persons using PrEP found that 95.1% of users identified as homosexual men.[56] In Canada, there are an estimated 369,500 MSM, of whom an estimated 329,870 are not HIV-infected.[57]

Aside from reduced kidney function, there would be few barriers to the prescription of Truvada for PrEP. HIV seronegative status would be required for the initiation of treatment, and PrEP would likely be provided by specialist and family physicians by quarterly prescription, with ongoing counselling and testing for HIV and other STIs. The duration of treatment would be indefinite, presumably determined by the ongoing risk for HIV infection.

5. CONCLUSIONS

Three DB, placebo-controlled RCTs assessing the safety and efficacy of once-daily FTC/TDF 200 mg/300 mg as PrEP in combination with HIV prevention services for individuals at high risk of acquiring HIV-1 infection were included in this review. The iPrEx study was conducted in adult MSM, the Partners PrEP study was conducted in adult Kenyan and Ugandan sexually active, serodiscordant heterosexual couples, and the CDC TDF2 study was conducted in young Botswanan heterosexual men and women. Results from all studies suggest that there was a statistically significant reduction in the incidence of HIV-1 seroconversion with FTC/TDF compared with placebo. Treatment adherence based on pill count and self-report was high across studies, but may be subject to bias. Sexual behaviour and the incidence of STIs did not differ between FTC/TDF and placebo groups, and small improvements were seen over time, although the reliance on participant interviews may also have been vulnerable to bias. Although quality of life was cited as an important outcome according to patient-group input, this was not evaluated in the included studies. Overall, the incidence of AEs was similar between FTC/TDF and placebo groups, and the incidence of renal and bone AEs was low across studies. None of the studies were conducted in Canada, and there may be generalizability issues, as the included studies were conducted mainly in Hispanic and African countries where health care services may not be as accessible as in the Canadian setting.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input
Three patient groups provided input for this submission.

Toronto Sex Workers Action Project (Maggie's) is an organization run for and by local sex workers. Their mission is to assist sex workers to live and work in safety and dignity by fighting to control their own bodies, sexuality, and working lives. Maggie's has collaborated with the Sistering and Women's HIV/AIDS Initiative in order to collect data about the experiences of cis (born female and self-identified as female) and trans (born male and self-identified as female) women living in poverty and who face a high risk of human immunodeficiency virus (HIV) infection or who are HIV-positive. Maggie's declares no conflicts of interest in the preparation of this submission.

The Canadian Treatment Action Council (CTAC) is Canada's national non-governmental organization addressing access to treatment, care, and support for people living with HIV and hepatitis C. CTAC meaningfully engages community members, service providers, policy-makers, and other stakeholders to identify, develop, and implement policy and program solutions. In fiscal year 2015–2016, CTAC received unrestricted organizational and educational grants from Gilead Sciences, AbbVie, and ViiV Healthcare Canada. No other company or organization played a role in preparing CTAC's submission.

The AIDS Committee of Toronto (ACT) was founded to address the emerging and urgent challenges of HIV and acquired immune deficiency syndrome (AIDS), and has since grown into the largest HIV service organization. ACT offers a comprehensive slate of free and confidential capacity-building programs and support services for people living with HIV. They also work as community advocates and sexual health educators to reduce the rates of HIV transmission and prevent new infections from occurring. ACT is funded in part by Gilead Sciences Canada, along with several other pharmaceutical companies. Gilead's contributions are restricted to funding the Community Health Forums, and are not used for any other purpose. ACT declares no conflicts of interest in the preparation of this submission

2. Condition-Related Information
Maggie's gathered information through focus groups and one-on-one interviews recruited through open calls for participation and outreach to community partners. In total, 26 cis or trans women at high-risk of HIV infection or who were HIV-positive were used to inform this submission.

CTAC gathered information through anonymous online surveys following two public national consultation Webinars advertised on CTAC's website, social media and member or partner communications. In total, 20 completed surveys were used to inform this submission. Fifteen were male, two were female, and one was a transgender male. Seventeen participants reported gay, bisexual, or queer sexual orientation.

ACT gathered information through focus groups and one-on-one interviews recruited through ACT's existing social media, email lists from program staff, and recruitment posters advertised through community partners. A total of 23 gay, bisexual, or queer men at high-risk of HIV infection or who are HIV-positive participated and were used to inform this submission.

According to CTAC, gay, and other men who have sex with men (MSM) have been disproportionately affected by the HIV epidemic in Canada since the 1980s, representing the majority of existing and new infections. CTAC submits that these men's experiences of physical, mental, and sexual health, and their intention and efforts to remain HIV-negative, must be appreciated in this context. HIV-negative individuals reported experiences of being in a situation in which they felt unable, or were unable, to control their sexual health, had a significant fear of HIV infection, and were experiencing the stigma associated with a positive HIV status. They described recurring anxiety associated with a range of sexual encounters with others whose HIV status is positive or uncertain. The people who provided input reported that the fear and anxiety associated with HIV status has a significant negative effect on sexual and mental health, as well as on personal and sexual relationships. "Before PrEP I was living in fear of 'when' I would become HIV+." Some reported that the anxiety of becoming HIV-positive is so debilitating that it affects their professional life. "*I didn't know what to do the first time the condom broke, in 2013. I was doing my Master's [at a university.] After I was going through a terrible time at university because I was thinking about it all of the time. For me it was very difficult to work on my thesis.*" Others reported that the anxiety is so great that they are unable to have any sort of relationship with those who are HIV-positive or with those whose HIV status is uncertain. "*Every time I get tested, and I get tested every three months, the week before I'm shaking and worried I'm going to test positive — I'm really, really anxious about it.*" "*It's hard to get intimately involved with someone when you're worried about them being HIV-positive and having not told you...*"

Caregivers were defined as either HIV-positive individuals in a relationship with HIV-negative individuals or counsellors or service providers working with HIV-negative individuals. HIV-positive caregivers reported anxiety and struggles over being responsible for managing the risk of HIV transmission and the barriers arising from using condoms during intercourse. They also reported their fear of HIV transmission as being a burden in forging meaningful relationships with HIV-negative partners.

One patient group (Maggie's) emphasized women's concerns associated with HIV transmission, particularly when the risk of violence is present: "... *having access to PrEP would mean I don't have to worry about not being able to protect myself if I'm a victim of sexual assault or if a condom breaks or if someone takes the condom off while having sex. This is a huge risk. And it is something my partner threatens me about.*"

3. Current Therapy-Related Information

Tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) is the first therapy approved for HIV pre-exposure prophylaxis (PrEP). In the absence of a therapeutic drug for HIV prevention, all patient groups reported that currently the most common method to prevent HIV infection is the use of condoms. However, most participants emphasized that condoms alone are not enough to quell their fear and anxiety of becoming infected with HIV. They expressed their distress with the lack of efficacy of condoms, actual and anticipated condom breakage, and the potential that penetrative sexual partners will remove condoms during intercourse. Some reported their dislike or hatred of condoms, for a variety of reasons. For some, condoms are a barrier to intimacy or trust between sexual and intimate partners, which negatively affects these relationships. "*I found myself engaging in condomless sex with casual partners, especially when drinking. This led to stress and anxiety about HIV. It also caused upset in my relationship with my partner, as it disrupted our sex life when we needed to use condoms with each other as a result of me engaging in high-risk sex with other people. I experienced guilt and shame around my sexual choices, because I did not want to put my partner at risk.*" Others reported a lack of pleasure or erectile problems when using condoms as a preventive measure. For these reasons, some participants noted that they are not using condoms during intercourse by choice, which they report is a

cause for shame as they are knowingly putting themselves at risk. "*I often don't like using condoms... and there's a lot of guilt and shame that comes with wanting that, as well. To know that in a situation I can be spontaneous and not worry about the stress or the post-coital shame — whatever comes after it — that just knowing that I can take preparation before I actually get put in that situation where you don't think clearly or rationally, that I can prepare myself to have a backup plan in that case... To have that safety net that if something does go wrong...*" Others reported an increasing prevalence of pressure to engage in, and expectation of, condomless anal intercourse in the sexual networks of gay and other MSM. HIV-positive caregivers highlighted that they often bear the responsibility of education associated with HIV, infection risk, and risk management strategies. They also expressed the struggle to balance the responsibility of HIV management and barriers to intimacy (i.e., condoms).

Sex workers were reported to be pressured into condomless intercourse due to financial incentives. "*There is more risk in the sex industry and the choice of not using protection because it is more money, you know, because people want to go bareback and they pay more money because you are taking that risk on."* (Note: Almost all participants in this focus group agreed with this).

4. Expectations About the Drug Being Reviewed

Generally, positive experiences and expectations were reported by patients both with and without experience with FTC/TDF. Patient groups highlighted, based on patient reports, that the stress, anxiety, and fear associated with becoming HIV-positive would lessen, and that the barriers to intimacy or relationships between HIV discordant individuals would diminish with the use of FTC/TDF. Those who had experience with the drug reported a better sex life, greater ease with sexuality and sexual expression, and improved relationships with their sexual or intimate partners. "*The feeling of protection that I get from PrEP has allowed me to enjoy sex more and more frequently, explore condomless sex safely with my primary partner, and eliminated my anxiety over illness as I no longer feel at significant risk of seroconversion. PrEP has changed my life.*" Some patients reported that the stigma associated with HIV-positive individuals has been completely eliminated with the use of FTC/TDF, opening the door to relationships otherwise unexplored. "*I'm looking to have a relationship and I've met a lot of great poz guys, but I could never go further with them. But if I was on PrEP I could go further.*" "*Since being on PrEP, my anxiety over sex has largely been eliminated and I personally have learned that the stigma toward HIV+ people can be eradicated— it has for me!*"

Some patients reported that the use of FTC/TDF is an added layer of protection along with safe sex practices (i.e., condoms). Other patients highlighted that they are looking for alternative options for safe sex practices that allow for more intimate relations. *"PrEP allows me to connect and be intimate with my sexual partner in a way that was not possible with condoms...*"

Some indicated that adherence to FTC/TDF is much easier and practical than using condoms. "*... it is much easier to be consistent about my PrEP use. I just take it with my vitamin every morning. I don't need to negotiate condom use in the heat of the moment. PrEP is much better in this way. Even if I missed a dose at some point, I'd still have very high levels of protection. But if I don't use a condom, I have zero risk reduction for that time*." Some patient suggested that they would rather temporarily take FTC/TDF instead of taking a lifetime of HIV treatment: "*I'd rather be on PrEP when I'm young because the alternative is me getting HIV and having to take those drugs anyway, and that's for my entire life. I could be on them for 30 or 40 years because I got HIV or I could be on them for 10 years, prevent it, and then go back off of them.*" Maggie's particularly highlights that with the use FTC/TDF there would be a reduced risk of violence when negotiating HIV prevention before intercourse.

Patients also reported their willingness to accept certain adverse events (AEs) associated with FTC/TDF, as they are eclipsed by the benefits of using this drug as an HIV prevention method. AEs such as nausea, vomiting, headache, renal impairment, and low bone density are reported by patient groups as being associated with the drug; however, patients who provided input noted that most of these AEs are common to HIV treatment given a positive HIV status, and that they are manageable.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	March 31, 2016
Alerts:	Bi-weekly search updates until July 20, 2016
Study Types:	randomized controlled trials
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.po	Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY		
Line #	**Search Strategy**	**Results**
1	"Emtricitabine, Tenofovir Disoproxil Fumarate Drug Combination"/	131
2	(Truvada* or Emzavir* or Recovir EM or Teno Em or Tenvor EM or Trenstad*).ti,ab,kf,ot,hw,rn,nm.	438
3	(731772-45-5 or "731772455").rn,nm.	0
4	1 or 2 or 3	529
5	(emtricitabin* or emtriva* or coviracil* or racivir* or Hui Er Ding* or Xin Luo Shu* or 524W91 or "BW 1592" or "BW 524 w 91" or "BW 524 W91" or "BW 524W" or BW524W or BW524W91 or "DRG 0208" or DRG0208 or "psi 5004" or psi5004 or "HSDB 7337" or HSDB7337 or G70B4ETF4S or dOTFC or FTC).ti,ab,ot,kw,hw,rn,nm.	15089
6	(143491-57-0 or "143491570").rn,nm.	5653
7	5 or 6	15090
8	(tenofovir* or GS 1278 or GS1278 or "GS 4331-05" or GS433105 or HSDB 7165 or HSDB7165 or PMPA or OTT9J7900I or TDF or viread* or Agifovir* or Glonovir* or Ricovir* or Tenof or Tenofir* or Tenohop* or Tenolam* or Tenozet* or Tenvir* or Tenvor* or Viraday*).ti,ab,ot,kf,hw,rn,nm.	24830
9	(379270-37-8 or 377091-31-1 or 147127-20-6).rn,nm.	10584
10	8 or 9	24830
11	7 and 10	10233
12	4 or 11	10279
13	12 use pmez	1627
14	*emtricitabine plus tenofovir disoproxil/	420
15	(Truvada* or Emzavir* or Recovir EM or Teno Em or Tenvor EM or Trenstad*).ti,ab,kw.	443
16	14 or 15	794
17	*emtricitabine/	644
18	(emtricitabin* or emtriva* or coviracil* or racivir* or Hui Er Ding* or Xin Luo Shu* or 524W91 or "BW 1592" or "BW 524 w 91" or "BW 524 W91" or "BW 524W" or BW524W or BW524W91 or "DRG 0208" or DRG0208 or "psi 5004" or psi5004 or "HSDB 7337" or HSDB7337 or G70B4ETF4S or dOTFC or FTC).ti,ab,kw.	8333
19	17 or 18	8505
20	*tenofovir disoproxil/	1013
21	(tenofovir* or GS 1278 or GS1278 or "GS 4331-05" or GS433105 or HSDB 7165 or HSDB7165 or PMPA or OTT9J7900I or TDF or viread or Agifovir or Glonovir or Ricovir or Tenof or Tenofir or Tenohop or Tenolam or Tenozet or Tenvir or Tenvor or Viraday).ti,ab,kw.	13807
22	20 or 21	13880
23	19 and 22	3982
24	16 or 23	4325
25	conference abstract.pt.	2186750
26	24 not 25	2998
27	26 use oemezd	1610
28	13 or 27	3237
29	Pre-exposure prophylaxis/	960
30	Primary prevention/	46916
31	pc.fs.	2130505
32	29 or 30 or 31	2149758

MULTI-DATABASE STRATEGY		
Line #	**Search Strategy**	**Results**
33	32 use pmez	1098532
34	pre-exposure prophylaxis/ or "prevention and control"/ or prevention/ or control/ or primary prevention/ or prophylaxis/ or protection/ or chemoprophylaxis/ or infection prevention/ or immunoprophylaxis/ or disease control/ or infection control/	558329
35	34 use oemezd	518058
36	(prevention or prevent or prevents or preventive or preventing or protecting or protect or protects or protection or protective or chemoprophyla* or immunoprophyla* or prophyla* or preexposure or preventative).ti,ab,kw,kf.	3419669
37	PrEP.ti,ab,kw,kf.	6721
38	((Pre or before or prior or advance) adj3 (expos* or risk or contact or intercourse or sex*)).ti,ab,kw,kf.	92801
39	33 or 35 or 36 or 37 or 38	4408285
40	28 and 39	998
41	Randomized Controlled Trial.pt.	411023
42	Pragmatic Clinical Trial.pt.	274
43	exp Randomized Controlled Trials as Topic/	196972
44	"Randomized Controlled Trial (topic)"/	93773
45	Randomized Controlled Trial/	809324
46	Randomization/	155706
47	Random Allocation/	148390
48	Double-Blind Method/	230781
49	Double Blind Procedure/	129520
50	Double-Blind Studies/	224804
51	Single-Blind Method/	41296
52	Single Blind Procedure/	21730
53	Single-Blind Studies/	43273
54	Placebos/	262260
55	Placebo/	284968
56	(random* or sham or placebo*).ti,ab,hw,kf,kw.	2601071
57	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	428966
58	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	1182
59	or/41-58	2650431
60	40 and 59	335
61	remove duplicates from 60	223

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	March 2016
Keywords:	Truvada, Pre-exposure prophylaxis
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for searching health-related grey literature" (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Marazzo et al., 2015[35]	Phase 2b study
Van Damme et al., 2012[36]	Outcome combined incidence of HIV-1 and HIV-2
Mutua et al., 2012[39]	Intermittent dosing
Baeten et al., 2016[58]	Not a comparison of interest
Buchbinder et al., 2014[59]	Not a subgroup of interest
Murnane et al., 2013[60]	

APPENDIX 4: DETAILED OUTCOME DATA

HIV-1 Seroconversion

TABLE 19: HIV-1 SEROCONVERSION IN THE IPREX STUDY AT DIFFERENT CUT-OFF DATES; MODIFIED INTENTION-TO-TREAT SET

	iPrEx	
	FTC/TDF (n = 1,224)	Placebo (n = 1,217)
May 1, 2010 data cut-off (primary analysis)		
Person-years of follow-up	[redacted]	[redacted]
Participants with seroconversion events, n (%)	36 (2.9)	64 (5.3)
Incidence per 100 person-years (95% CI)	2.2[a]	3.8[a]
Hazard ratio (95% CI)	0.56 (0.37 to 0.85)	
Relative risk reduction, % (95% CI)	44 (15 to 63)	
P value	0.005	
July 31, 2010 data cut-off (end of treatment)		
Person-years of follow-up	[redacted]	[redacted]
Participants with seroconversion events, n (%)	48 (3.9)	83 (6.8)
Incidence per 100 person-years (95% CI)	2.3[a]	3.9[a]
Hazard ratio (95% CI)	0.58 (0.40 to 0.84)	
Relative risk reduction, % (95% CI)	42 (18 to 60)	
P value	0.002	
November 21, 2010 data cut-off (end of treatment + 8 weeks)		
Person-years of follow-up	[redacted]	[redacted]
Participants with seroconversion events, n (%)	52 (4.2)	85 (7.0)
Incidence per 100 person-years (95% CI)	2.4[a]	4.0[a]
Hazard ratio (95% CI)	0.61 (0.43 to 0.86)	
Relative risk reduction, % (95% CI)	39 (14 to 57)	
P value	0.004	

CI = confidence interval; FTC/TDF = emtricitabine/tenofovir disoproxil fumarate; HIV = human immunodeficiency virus; NR = not reported.
[a] Calculated by the CADTH Common Drug Review.
Sources: iPrEx Clinical Study Report,[4] iPrEx addendum.[61]

TABLE 20: SUBGROUP ANALYSIS ACCORDING TO SEX OF PRIMARY EFFICACY END POINT; MODIFIED INTENTION-TO-TREAT SET

	Partners PrEP		CDC TDF2	
	FTC/TDF (n = 1,576)	Placebo (n = 1,578)	FTC/TDF (n = 601)	Placebo (n = 599)
Primary analysis				
Person-years of follow-up	2,616	2,607	1,563	
Participants with seroconversion events, n (%)	13 (0.8)	52 (3.3)	9	24
Incidence per 100 person-years (95% CI)	0.50 (0.27 to	1.99 (1.49	1.2	3.1

	Partners PrEP		CDC TDF2	
	FTC/TDF (n = 1,576)	Placebo (n = 1,578)	FTC/TDF (n = 601)	Placebo (n = 599)
	0.85)	to 2.62)		
Hazard ratio (95% CI)	0.25 (0.13 to 0.45)			
Relative risk reduction, % (95% CI)	75 (55 to 87)		62 (22 to 83)	
P value	< 0.001		0.03	
Sex				
Female				
Person-years of follow-up	[redacted]	[redacted]	NR	
Participants with seroconversion events, n/n total (%)	9/566 (1.6)	28/619 (4.5)	7/280 (2.5)	14/277 (5.1)
Incidence per 100 person-years (95% CI)	0.95 (0.44 to 1.81)	2.81 (1.87 to 4.06)	NR	NR
Hazard ratio (95% CI)	0.34 (0.16 to 0.72)		0.51 (0.19 to 1.78)[a]	
Relative risk reduction, % (95% CI)	66 (28 to 84)[a]		49 (–22 to 81)	
Male				
Person-years of follow-up	[redacted]	[redacted]	NR	
Participants with seroconversion events, n/n total (%)	4/1,010 (0.4)	24/959 (2.5)	2/331 (0.6)	10/331 (3.0)
Incidence per 100 person-years (95% CI)	0.24 (0.07 to 0.61)	1.49 (0.96 to 2.22)	NR	NR
Hazard ratio (95% CI)	0.16 (0.06 to 0.46)		0.20 (0.03 to 0.75)[a]	
Relative risk reduction, % (95% CI)	84 (54 to 94)[a]		80 (25 to 97)	

CI = confidence interval; FTC/TDF = emtricitabine/tenofovir disoproxil fumarate; NR = not reported.
[a] Calculated by the CADTH Common Drug Review.
Source: Partners PrEP Clinical Study Report,[6] Baeten et al., 2012,[7] Thigpen et al., 2012.[8]

Sexual Behaviour

TABLE 21: RECEPTIVE ANAL INTERCOURSE AND PROTECTED ANAL INTERCOURSE OVER TIME IN THE IPREX STUDY; SAFETY SET

	iPrEx					
Week	FTC/TDF			Placebo		
	N at Study Week	Mean (SE) RAI Partners	Protected Anal Intercourse (%)	N at Study Week	Mean (SE) RAI Partners	Protected Anal Intercourse (%)
0	1,251	12.2 (0.8)	51	1,248	11.2 (0.8)	50.4
12	1,118	7.2 (0.7)	74.5	1130	5.6 (0.5)	73
24	1,033	5.6 (0.5)	75.6	1,053	5.3 (0.5)	73
36	946	5.3 (0.5)	78.4	960	4.2 (0.3)	72.2
48	824	5.8 (0.7)	73.4	840	4.5 (0.5)	74.9
60	689	5 (0.5)	75.4	670	4.5 (0.5)	72.1
72	551	5 (0.8)	73.9	543	4.6 (0.7)	70.1
84	445	6.4 (1.1)	77.4	434	4.1 (0.5)	75.1
96	365	5.2 (0.7)	76.4	360	4.8 (0.9)	74

	iPrEx					
Week	FTC/TDF			Placebo		
108	269	5.1 (1)	78.2	271	3.9 (0.6)	76.3
120	157	5.7 (1.2)	75.6	147	4.6 (0.9)	83.3
132	72	3.5 (0.8)	74	63	5.7 (1.6)	83.6

FTC/TDF = emtricitabine/tenofovir disoproxil fumarate; RAI = receptive anal intercourse; SE = standard error.
Sources: iPrEx Clinical Study Report,[4] Grant et al., 2010.[5]

TABLE 22: PROPORTION OF PARTICIPANTS REPORTING ANY UNPROTECTED SEX AND OUTSIDE SEX PARTNERS IN THE PREVIOUS MONTH IN THE PARTNERS PREP STUDY; SAFETY SET

	Partners PrEP		
Month	**N at Study Week**	**Number (%) Reporting Unprotected Sex**	**Number (%) With Outside Partners**
0	4,758	1,271 (27)	407 (9)
3	4,565	789 (17)	414 (9)
6	4,492	640 (14)	444 (10)
12	3,950	511 (13)	485 (12)
18	3,090	356 (12)	379 (12)
24	2,168	204 (10)	292 (13)
30	867	56 (7)	111 (13)
35	118	11 (9)	NR

NR = not reported.
Source: US Food and Drug Administration Medical Review.[28]

Sexually Transmitted Infections

TABLE 23: PARTICIPANTS WITH SEXUALLY TRANSMITTED INFECTIONS BY VISIT IN THE IPREX STUDY

	iPrEx	
	FTC/TDF	Placebo
Syphilis, n		
Week 24	173	165
Week 48	159	145
Week 72	108	111
Week 96	87	70
Warts, n		
Week 24	44	35
Week 48	37	34
Week 72	26	22
Week 96	15	19
Genital ulcer, n		
Week 24	18	18
Week 48	11	14
Week 72	6	11
Week 96	2	2

	iPrEx	
	FTC/TDF	Placebo
Gonorrhea, n		
Week 24	8	8
Week 48	4	6
Week 72	1	2
Week 96	1	1
Chlamydia, n		
Week 24	9	8
Week 48	0	2
Week 72	1	3
Week 96	0	1

FTC/TDF = emtricitabine/tenofovir disoproxil fumarate.
Sources: iPrEx Clinical Study Report,[4] Grant et al., 2010.[5]

TABLE 24: OUTSIDE SEXUAL PARTNERS AND INCIDENCE OF SEXUALLY TRANSMITTED INFECTIONS IN THE PARTNERS PREP STUDY; SAFETY SET

	Partners PrEP	
	FTC/TDF (n = 1,579)	Placebo (n = 1,584)
Participants reporting outside sexual partner, n (%)	469 (29.7)	459 (28.9)
P value versus placebo[a]	0.67	
Participants reporting any STI, n (%)	76 (4.8)	85 (5.4)
P value versus placebo[b]	0.49	

FTC/TDF = emtricitabine/tenofovir disoproxil fumarate; STI = sexually transmitted infection.
[a] *P* value calculated by chi-squared test of proportions.
[b] *P* value calculated via generalized estimating equations, using logistic link and robust standard errors to adjust errors for correlation within responses from the same participant over time.
Sources: Partners PrEP Clinical Study Report,[6] Baeten et al., 2012.[7]

TABLE 25: SEXUALLY TRANSMITTED INFECTION ADVERSE EVENTS IN THE CDC TDF2 STUDY; SAFETY SET

	CDC TDF2	
	FTC/TDF (n = 611)	Placebo (n = 608)
STI AE, n (%)		
Neisseria gonorrhoeae	28 (4.6)	18 (3.0)
Chlamydia trachomatis	76 (12.4)	75 (12.3)
Trichomonas vaginalis	20 (3.3)	18 (3.0)
Genital herpes	28 (4.6)	35 (5.8)
Sore genital ulcer	12 (2.0)	6 (1.0)

AE = adverse event; FTC/TDF = emtricitabine/tenofovir disoproxil fumarate; STI = sexually transmitted infection.
Source: Thigpen et al., 2012.[8]

Adherence

TABLE 26: ADHERENCE TO STUDY DRUG IN THE IPREX STUDY; SAFETY SET

	iPrEx	
	FTC/TDF (n = 1,251)	Placebo (n = 1,248)
Self-reported pill use		
N	[redacted]	[redacted]
Mean (SD), %	88.7 (18.1)	[redacted]
Median (range), %	[redacted]	[redacted]

FTC/TDF = emtricitabine/tenofovir disoproxil fumarate; SD = standard deviation.
Sources: iPrEx Clinical Study Report,[4] Grant et al., 2010.[5]

TABLE 27: ADHERENCE TO STUDY DRUG IN THE PARTNERS PREP STUDY; SAFETY SET

	Partners PrEP	
	FTC/TDF (n = 1,579)	Placebo (n = 1,584)
FTC/TDF or placebo FTC/TDF pill counts		
Number of participants assessed	1,565	1,570
% of expected bottles returned	98	98
% doses taken of dispensed	97	97
Bottles with ≥ 50% doses taken	99	99
Bottles with ≥ 75% doses taken	98	98
Bottles with ≥ 90% doses taken	93	92
Bottles with ≥ 95% doses taken	84	85
Self-reported adherence		
Number of participants assessed	[redacted]	[redacted]
Number of visits assessed	[redacted]	[redacted]
Missed dose (%)	[redacted]	[redacted]
Missed 2+ consecutive doses (%)	[redacted]	[redacted]

FTC/TDF = emtricitabine/tenofovir disoproxil fumarate.
Sources: Partners PrEP Clinical Study Report,[6] Baeten et al., 2012.[7]

Harms

TABLE 28: HARMS IN THE IPREX STUDY ACCORDING TO MANUFACTURER ANALYSIS; SAFETY SET

	iPrEx	
	FTC/TDF (n = 1,251)	Placebo (n = 1,248)
AEs		
Participants with > 0 AEs, n (%)	[redacted]	[redacted]
Common AEs		
Abdominal pain	[redacted]	[redacted]
Depression	[redacted]	[redacted]
Diarrhea	[redacted]	[redacted]

	iPrEx	
	FTC/TDF (n = 1,251)	Placebo (n = 1,248)
Dizziness	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Pharyngitis	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Respiratory tract infection	[redacted]	[redacted]
Urethritis	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
SAEs		
Participants with > 0 SAEs, n (%)	[redacted]	[redacted]
WDAEs		
Participants with > 0 WDAEs, n (%)	[redacted]	[redacted]

AE = adverse event; FTC/TDF = emtricitabine/tenofovir disoproxil fumarate; SAE = serious adverse event; WDAE = withdrawal due to adverse event; URTI = upper respiratory tract infection.
Source: iPrEx Clinical Study Report.[4]

APPENDIX 5: SUMMARY OF OPEN-LABEL EXTENSION STUDY WITH PARTICIPANTS FROM MSM PrEP STUDIES

Objective

To summarize the open-label extension (OLE) study recruiting participants from three studies (ATN 082, iPrEx, and the US Safety Study) that evaluated the efficacy and safety of emtricitabine/tenofovir disoproxil fumarate (TDF/FTC) as a once-daily pre-exposure prophylaxis (PrEP) for human immunodeficiency virus type 1 (HIV-1) in gay men or men who have sex with men (MSM).[5]

Findings

Study Design

The OLE study was a 72-week study that enrolled patients who had completed the ATN 082, iPrEx, or US Safety Study randomized controlled trials (RCTs) to investigate PrEP uptake, adherence, and sexual practices in a manner more akin to clinical practice. Generally, the trial designs and the inclusion and exclusion criteria of the previous RCTs were similar to those of the OLE; however, the ATN 082 study included only men between 18 and 22 years of age, and the intervention in the US Safety Study consisted only of TDF. All participants were offered daily oral PrEP with FTC/TDF 200 mg/300 mg FDC along with a comprehensive package of prevention services such as counselling and contraception, among others, if they were HIV negative and had no symptoms of acute HIV infection. PrEP was deferred or interrupted for participants with an acute viral syndrome or any positive HIV test throughout the study until HIV test results were negative. Outcomes experienced by study participation were reported regardless of whether participants chose to take PrEP. Study visits were conducted every four weeks up until week 12, and every 12 weeks thereafter up to week 72. Participants were able to start PrEP at any time within the first 48 weeks of the extension phase.

Participants were eligible to enrol in the OLE if they met the following criteria:

- Male at birth
- Reported having had anal intercourse with men
- Older than 18 years of age.

Efficacy was assessed by monitoring the incidence of HIV infection, HIV incidence as a function of dry blood spot TDF concentrations, HIV resistant strains, adherence, and sexual behaviour. Profile likelihood confidence intervals (CIs) were used because of the small number of infections in each dosing category. It was estimated that the concentration of drug associated with 90% protection had a relative risk of 0.10 compared with the group with no exposure to PrEP. Adjustments were made for non-condom receptive anal intercourse (RAI), age, number of partners, history of syphilis, and enrolment site. Predictors of drug concentrations were assessed, by dosing category, with an ordinal logistic regression model, adjusted for study site and time on study. Comparisons of HIV incidence between the previous RCTs (ATN 082, iPrEx, and US Safety Study) and the OLE were assessed.

Adherence was assessed using tenofovir (TFV) blood plasma concentrations and dry blood spot emtricitabine (TDF) concentrations. Sexual behaviour was assessed based on patient self-report, and data were analyzed using generalized estimating equations. Safety was assessed by monitoring treatment interruptions.

Results

A total of 1,678 (62%) of 2,680 eligible participants enrolled in the OLE study. The majority of the participants screened for inclusion were from the iPrEx trial (1,526; 90.9%). Seventy-five (4.5%) tested positive for HIV at enrolment, leaving a total of 1,603 (95.5%) eligible to receive PrEP in the OLE. A total of 1,128 (70.4%) started PrEP at enrolment, 97 (6.1%) started PrEP within 48 weeks of enrolment, and 378 (23.6%) never started PrEP. Of the 1,225 who received PrEP, 1,033 (84.3%) completed the study, 36 (2.9%) exited early, and one (< 0.1%) died. Patient disposition is detailed in Table 29.

TABLE 29: PATIENT DISPOSITION

	OLE Study
Eligible to enrol, N[a]	**2,680**
ANT082	68
iPrEx	2,336
US Safety Study	271
Screened, N	**1,678**
ANT082	46
iPrEx	1,526
US Safety Study[b]	106
HIV-1–infected at baseline, n	**75**
Followed for seroconversion, n (%)	**1,603 (100)**
Started PrEP at enrolment	1,128 (70)
Started PrEP after enrolment	97 (6)
Never started PrEP	378 (24)
Completed the study, n (%)	**1,345 (84)**
Started PrEP at enrolment	945 (59)
Started PrEP after enrolment	88 (5)
Never started PrEP	312 (19)
Discontinuation for those on PrEP, n (%)	
Death	1 (< 1)
Lost contact with participant	65 (5)
Participant relocated	75 (6)
Exited early	36 (3)
Incarcerated	2 (< 1)
Other reason	3 (< 1)

OLE = open-label extension; PrEP = pre-exposure prophylaxis.
[a] Enrolment numbers are people who were HIV-negative when they left the previous study.
[b] Participants enrolled in Boston and San Francisco.
Source: Grant et al.[5]

Of the 1,603 eligible to receive PrEP, 265 (17%) were white, 125 (8%) were black, 73 (5%) were Asian, and 1,094 (72%) were Latino. Those who enrolled in the OLE tended to be older (mean age 28 years versus 26 years, $P < 0.0001$), were more likely to report non-condom RAI (60% versus 55%, $P = 0.03$), and were more likely to have a history of syphilis (15% versus 10%, $P = 0.001$) or herpes (38% versus 30%, $P < 0.0001$) compared with those who did not enroll in the OLE. A similar number of participants from the placebo and the treatment groups from the previous studies participated in the OLE. Of the 446 participants who had been in the treatment group in the previous iPrEx trial, those who had detectable

drug were more likely to enroll in the OLE than those without detectable drug (69% versus 57%, *P* = 0.02). Patient baseline characteristics are detailed in Table 30.

TABLE 30: BASELINE CHARACTERISTICS

Characteristic	OLE Study
	FTC/TDF (n = 1,225)
Age, n (%)	
18 to 24 years	247 (20)
25 to 29 years	315 (26)
30 to 39 years	394 (32)
≥ 40 years	269 (22)
Race, n (%)	
White	265 (17)
Black	125 (8)
Asian	73 (5)
Latino	1,094 (72)
Country, n (%)	
USA	224 (18)
Brazil	192 (16)
Peru	562 (46)
Ecuador	153 (12)
South Africa	40 (3)
Thailand	54 (4)
Education Level, n (%)[a]	
Less than secondary	264 (22)
Completed secondary	387 (32)
Post-secondary	566 (46)
Alcohol use, n (%)	
< Once a month	103 (8)
1 to 4 on days when drinking	403 (33)
≥ 5 on days when drinking	250 (20)
Refused to answer or did not know	469 (38)
Methamphetamine use, n (%)[a]	
No	1,190 (97)
Yes	26 (2)
Cocaine use, n (%)[a]	
No	1,070 (87)
Yes	101 (8)
Reported non-condom receptive anal intercourse at OLE entry, n (%)	
No	809 (66)
Yes	416 (34)
Transgender, n (%)	
No	1,085 (89)

Characteristic	OLE Study
	FTC/TDF (n = 1,225)
Yes	140 (11)
Known HIV-positive partner, n (%)	
No	1,083 (88)
Yes	142 (12)
Syphilis rapid plasma regain at entry, n (%)	
No	1,028 (84)
Yes	197 (16)
Herpes simplex virus-2, n (%)	
No	613 (50)
Yes	612 (50)
Gonorrhea[a] by urine PCR, n (%)[a]	
No	1,186 (97)
Yes	25 (2)
Randomized experience[a]	
Placebo	550 (45)
Active, no drug at week 8	65 (5)
Active, drug at week 8	155 (13)

FTC/TDF = emtricitabine/tenofovir disoproxil fumarate; HIV = human immunodeficiency virus; OLE= open-label extension; PCR = polymerase chain reaction.
[a] Data missing for some participants.
Source: Grant et al.[5]

Efficacy

A total of 41 participants had HIV-1 seroconversion in the OLE study, of which 13 did not receive PrEP (2.6 infections per 100 person-years; 95% CI, 1.5 to 4.5), and 28 of those on FTC/TDF (1.8 infections per 100 person-years, 95% CI, 1.3 to 2.6). Of those receiving FTC/TDF, the HIV incidence was 49% (95% CI, –1 to 74) lower than among those who did not receive PrEP, when adjusted for the higher risk sexual behaviour at baseline among participants using PrEP, and 36% (95% CI, –24 to 67) lower if not adjusted. Considering only participants who participated in the iPrEx trial, there was a reduction of 53% (95% CI, 26 to 70) in HIV incidence when compared with the placebo group in the iPrEx trial (3.93 infections per 100 person-years), and a reduction of 51% (95% CI, 23 to 69) in HIV incidence when compared with the time between the previous randomized trial and the OLE (3.81 infections per 100 person-years).

The relationship between HIV incidence and dried blood spot TDF was assessed. The authors indicated that the results suggested a strong association between HIV incidence and TDF levels and reported no infections at visits where TDF concentrations were 700 fmol per punch or greater (associated with a regimen of four to seven tablets per week). The study also reports that a concentration of TDF from dry blood spots of 611 fmol per punch (95% CI, 216 to 1,006) (associated with a regimen of two to three tablets per week) achieved a 90% risk reduction of HIV acquisition. There was only one participant taking PrEP with a reported case of HIV resistance to emtricitabine in the OLE. The results detailing the association between HIV incidence and TDF levels are presented in Table 31.

TABLE 31: EFFECT OF TENOFOVIR DIPHOSPHATE IN DRIED BLOOD SPOT ON HIV INFECTION

	BLQ	LLOQ to < 350 fmol per punch	350 fmol to 699 fmol per punch	700 fmol to 1,249 fmol per punch	≥ 1,250 fmol per punch
Estimated dose (tablets per week)	None	< 2	2 to 3	4 to 6	7
Follow-up (% of visits)	25	26	12	21	12
HIV infections, n	18	9	1	0	0
Person-years per infection	384	399	179	316	181
HIV incidence (95% CI)	4.70 (2.99 to 7.76)	2.25 (1.19 to 4.79)	0.56 (0.00 to 2.50)	0.00 (0.00 to 0.61)	0.00 (0.00 to 1.06)
HR versus previous placebo (95% CI)[a]	1.55 (0.88 to 2.56)	0.69 (0.32 to 1.32)	0.19 (0.01 to 0.88)	0.00 (0.00 to 0.25)	0.00 (0.00 to 0.50)
HR versus concurrent off-PrEP (95% CI)[b]	1.25 (0.60 to 2.64)	0.56 (0.23 to 1.31)	0.16 (0.01 to 0.79)	0.00 (0.00 to 0.21)	0.00 (0.00 to 0.43)

BLQ = below limit of quantification; CI = confidence interval; HIV = human immunodeficiency virus; HR = hazard ratio; LLOQ = lower limit of quantification; PrEP= pre-exposure prophylaxis.
Note: Drug concentration measurements were not available for 5% of visits.
[a] Adjusted for study site.
[b] Adjusted for study site, age, number of sexual partners, non-condom receptive anal intercourse, and syphilis.
Source: Grant et al.[5]

Treatment adherence was assessed based on blood plasma tenofovir concentrations for 305 patients at week four, 851 patients at week eight, and 33 patients at week 12. Thirty-six participants were not assessed for treatment adherence. Tenofovir (TFV) was detected in 71% of participants, and detection varied by region, ranging from 62% of participants in Ecuador to 83% of participants in the US. The authors reported a similar proportion of patients with detectable TFV in blood plasma in the OLE compared with the first eight weeks of the previous iPrEx trial. Drug concentrations based on dried blood spots were higher among those who had more years of education; were older participants; had had non-condom receptive anal intercourse, more sexual partners, a history of syphilis or herpes, any HIV-positive sexual partner, or lower estimated creatinine clearance and was not associated with alcohol use, methamphetamine use, or cocaine use.

Participants receiving PrEP and participants not receiving PrEP reported similar decreases in sexual behaviours (i.e., total number of sexual partners, RAI and insertive anal intercourse) during the OLE study. The percentage of patients engaging in non-condom RAI decreased from 34% to 25% for those taking PrEP, and from 27% to 20% for those not taking PrEP. The incidence of syphilis was similar for those taking PrEP compared with those not taking PrEP, with a hazard ratio of 1.35 (95% CI, 0.83 to 2.19, 7.2 infections per 100 patient-years versus 5.4 infections per 100 patient-years).

Safety

Treatment was interrupted 380 times for 365 participants for reasons other than loss to follow-up, completion of the study, or HIV infection. Reasons for treatment interruption included participant preference (40%), adverse events (24%), effects of significant but unrelated comorbidities (10%), relocation of travel (14%) and other (14%), which included suspected acute HIV infection (2%) and sexual behaviour warranting a post-exposure prophylaxis (PEP) (4%). Gastrointestinal symptoms such as

nausea or abdominal pain were the most common symptoms requiring study drug interruption. In total, there were three cases of increased creatinine levels, all of which returned to normal after study drug interruptions and none of which returned upon treatment continuation.

Limitations

There are many limitations in the OLE study, the main being that it was an open-label (OL) trial and there was the lack of a consistent and appropriate comparator group against which to evaluate the outcomes of interest in the review. The OL trial design, in which both the investigators and the patients are unblinded to treatment allocation, may have had an impact on subjective outcomes such as sexual behaviour as it was assessed in this study. The comparator groups used in this study were variable depending on the outcome measures assessed, and the baseline characteristics of the participants in the comparator groups were not presented in the study. Consequently, the long-term comparative efficacy and safety of FTC/TDF as PrEP remains uncertain. In addition, given that the patients who received FTC/TDF as PrEP in this study were self-selected from the cohort of patients participating in the previous RCTs (for example, compared with the RCTs, a high proportion of participants were Latino, participants tended to engage in riskier sexual behaviour, and tended to be more adherent to treatment), the generalizability of the results of this study should be made with caution. Finally, it is uncertain how the decrease in the percentage of patients engaging in risky sexual behaviour during the study period may have impacted the incidence of HIV reported.

Summary

In general, OL trial designs such as the one presented here may be more reflective of clinical practice in terms of the level of treatment adherence and the sample population enrolled. The results from the OLE study suggest a reduction in the incidence of HIV seroconversion with the use of TDF/FTC and a dose-efficacy relationship between TDF levels and HIV incidence. Treatment with TDF/FTC as PrEP was generally well tolerated. Results suggest a similar decrease in the total number of sexual partners and in both non-condom RAI and insertive anal intercourse for those participating in the trial, regardless of exposure to TDF/FTC as PrEP. Caution is required when interpreting the results of the OLE study, given the key limitations.

APPENDIX 6: SUMMARY OF THE PILOT PHASE OF THE PROUD STUDY

Objective

To summarize the pilot phase of the ongoing PROUD study, which evaluated the effectiveness and safety of emtricitabine/tenofovir disoproxil fumarate (TDF/FTC) 200 mg/300 mg fixed-dose combination (FDC) as a once-daily pre-exposure prophylaxis (PrEP) for human immunodeficiency virus type 1 (HIV-1) in gay men or men who have sex with men (MSM).[40]

Findings

Study Design

PROUD is a phase 4, open-label (OL), randomized controlled trial (RCT) conducted in 13 sexual health clinics in the UK in which neither patients nor investigators were blinded to treatment allocation. All participants were offered a comprehensive package of prevention services such as counselling and contraception, among others. Patients were randomized 1:1 to either an immediate treatment arm (patients received FTC/TDF 200 mg/300 mg FDC once daily immediately at enrolment) or a deferred treatment arm (patients received FTC/TDF 200 mg/300 mg FDC once daily one year after enrolment). Randomization was done via Web-based access to a central computer-generated list with variable block sizes (four, six, and eight) and was stratified by study site. To better simulate a public health PrEP program, no screening visits took place, and data on sexually transmitted infections (STIs) that were documented at other clinics or non-study visits were also collected. Follow-up visits occurred quarterly for the duration of the two-year trial. PROUD was designed with a sample size of 5,000 participants, powered to detect a 50% reduction in HIV incidence from 2.5 to 1.25 infections per 100 person-years. For the pilot phase, participants were included based on the time to accrue and retain 10% of the planned sample size (n = 500). Data from the pilot phase analysis are summarized in this report.

Patients were eligible for inclusion if they met the following criteria:

- Previously attended the enrolling clinic
- Screened for HIV and other STIs
- Tested HIV-negative four weeks prior to or on the day of enrolment
- Male at birth
- Aged 18 years and older
- Had had anal intercourse without a condom in the previous 90 days and were likely to have anal intercourse without a condom in the next 90 days.

Patients were excluded from the study if they met the following criteria:

- Diagnosed with acute viral illness possibly due to HIV seroconversion
- Contraindication to TDF or FTC
- Treated for hepatitis B

The primary efficacy outcome was the time to accrual of 500 participants and retention. Secondary outcomes included the incidence of HIV infection during the deferral period, adherence, and risk compensation related to sexual practices. Adherence was measured by assessing overall prescriptions of the study drug, and risk compensation was measured using a questionnaire related to sexual behaviour at baseline and at one year. The number of different anal sex partners at one year was compared

between groups using a stratified trend with respect to baseline anal sex partners at enrolment. Safety was assessed by monitoring adverse events (AEs) and serious adverse events (SAEs).

All analyses included all participants according to their randomized allocation (intention-to-treat [ITT]) apart from the exclusion of individuals with a reactive HIV result at enrolment in the analysis of HIV incidence (modified intention-to-treat [mITT]). The authors also noted that a 90% confidence interval (CI) was reported instead of a 95% CI, as they were mainly interested in the lower confidence limit (i.e., the minimum effectiveness).

The authors noted that because the analysis was based on a pilot phase, it was unlikely to show the effectiveness of PrEP; therefore, the data were initially monitored by a single independent expert who was not masked to allocation.

Results

Of the enrolled 544 participants, 275 were randomized to the immediate treatment group and 269 were randomized to the deferred treatment group. Of the 275 patients in the immediate treatment group, two (0.7%) were HIV-positive at enrolment and five (1.8%) did not undertake an HIV test after enrolment. The remaining 268 participants contributed to the analysis of HIV-1 seroconversion, of which three (1.1%) withdrew, 17 (6.2%) were lost to follow-up, and one (0.4%) died. Of the 269 patients in the deferred treatment group, one (0.4%) was HIV-positive at enrolment and 13 (4.8%) did not undergo an HIV test after enrolment. The remaining 255 participants contributed to the analysis of HIV-1 seroconversion, of which four (1.5%) withdrew and 16 (5.9%) were lost to follow-up. Patient disposition is detailed in Table 32.

TABLE 32: PATIENT DISPOSITION

	PROUD	
	Immediate treatment group	**Deferred treatment group**
Enrolled, N[a]	544	
Randomized, N	275	269[b]
HIV-1–infected at enrolment, n (%)	2 (0.7)	1 (0.4)
Not tested for HIV at enrolment, n (%)	5 (1.8)	13 (4.8)
Followed for seroconversion, n (%)	268 (97)	255 (95)
Discontinuation, n (%)		
Death	1 (0.4)	0
Loss to follow-up[c]	17 (6.2)	16 (5.9)
Withdrew consent	3 (1.1)	4 (1.5)
HIV status assessed, n (%)[d]	247 (90)	235 (87)

HIV = human immunodeficiency virus.
[a] 19 pairs of partners were assigned to the same group (14 to the immediate treatment group and five to the deferred treatment group) including six pairs (all assigned to the immediate treatment group) that were not enrolled concurrently.
[b] One participant received immediate pre-exposure prophylaxis in error despite being allocated to the deferred treatment group and was included in the deferred treatment group for analyses.
[c] Reasons for loss to follow-up included unable to contact, moved away, and non-attendance as no longer at risk.
[d] HIV status ascertained after a confirmed HIV-positive or HIV-negative test (48 weeks or after October 13, 2014).
Source: McCormack et al., 2016.[40]

The included population was mostly white and was born outside the UK. The majority of participants disclosed no partners and had been diagnosed with a STI in the previous 12 months. Missing baseline

characteristic data were similar in the immediate treatment group compared with the deferred treatment group. The most common missing characteristics being chemsex use (seven versus eight), history of STI (13 versus 10), previous HIV tests (10 versus 10), and use of post-exposure prophylaxis (PEP) (15 versus 15) in the immediate treatment group versus the deferred treatment group, respectively. Patient baseline characteristics are detailed in Table 33 and were similar between treatment groups.

TABLE 33: BASELINE CHARACTERISTICS

	PROUD	
	Immediate treatment group	**Deferred treatment group**
Age, median (IQR)	35 (30 to 43)	35 (29 to 42)
Ethnicity, n (%)		
White	220 (81)	219 (83)
Black	14 (5)	15 (6)
Asian	11 (4)	10 (4)
Other	28 (10)	21 (8)
University degree, n (%)	161 (59)	166 (62)
Unemployed, n (%)	24 (9)	20 (8)
Born outside the UK, n (%)	110 (40)	107 (40)
Relationship status, n (%)		
Partner, living together	87 (32)	73 (27)
Partner, living separately	40 (15)	46 (17)
No partner	146 (53)	147 (55)
Circumcised, n (%)	77 (28)	79 (30)
Chemsex in the previous 90 days,[a] n (%)	115 (43)	116 (45)
STI diagnosed in previous 12 months, n (%)		
Any	164 (63)	167 (65)
Bacterial[b]	150 (58)	155 (60)
Rectal gonorrhea or chlamydia	89 (34)	83 (32)
Number of HIV tests in previous 12 months, median (IQR)	3 (2 to 4)	3 (2 to 4)
Used PEP in previous 12 months, n (%)	91 (35)	93 (37)

HIV = human immunodeficiency virus; IQR = interquartile range; PEP = post-exposure prophylaxis; STI = sexually transmitted infection.
[a] Use of either gamma-hydroxybutyrate, 4-methylmethcathinone, or methamphetamine to facilitate or enhance sex.
[b] Gonorrhea, chlamydia, or syphilis.
Source: McCormack et al., 2016.[40]

Efficacy

Three HIV infections occurred in the immediate treatment group compared with 20 in the deferred treatment group. The authors noted that the three infections that occurred in the immediate treatment group were attributable to the lack of adherence to the study drug. HIV incidence was reported to be 1.2 cases per 100 patient-years (90% CI, 0.4 to 2.9) in the immediate treatment group compared with 9.0 cases per 100 patient-years (90% CI, 6.1 to 12.8) in the deferred treatment group. The difference in the incidence of HIV-1 between the two groups suggested a relative rate reduction of 86% (90% CI, 64 to 96; *P* = 0.0001) and a relative rate difference of 7.8 cases per 100 patient-years (90% CI, 4.3 to 11.3) in favour of the immediate treatment group. The authors suggested that, based on the results from this

trial, 13 men (90% CI, 9 to 23) in this study would have needed to receive PrEP for one year to avert one HIV infection.

All five participants (including the two individuals who had HIV at enrolment) in the immediate treatment group who had HIV infection were tested for resistance. Two of the three participants with a reactive test at enrolment or the four-week visit developed mutations thought to be due to exposure to FTC. No resistance was detected in the two other participants with later infections. The authors noted that the absence of resistance was not surprising given their apparent non-adherence to PrEP. No participants had mutations associated with TDF treatment.

A total of 271 (99%) participants in the immediate treatment group and 263 (98%) in the deferred treatment group completed questionnaires related to sexual behaviour in the previous 90 days at baseline. Two hundred and twelve (77%) participants in the immediate treatment group and 194 (74%) in the deferred treatment group completed questionnaires at one year. The total number of different anal sex partners varied widely from baseline to one year; however, the authors reported no significant difference between groups. A larger proportion of participants in the immediate treatment group reported receptive anal sex with 10 or more partners without a condom compared with the deferred treatment group (21% versus 12%; *P* = 0.03).

One hundred and fifty-two (57%) of participants in the immediate treatment group compared with 124 (50%) in the deferred treatment group were diagnosed with at least one bacterial STI. The most common STIs were gonorrhea and chlamydia. After adjusting for the number of STI screening tests, the authors reported no statistically significant difference in the incidence of any individual bacterial STIs (odds ratio: 1.07; 90% CI, 0.78 to 1.46; *P* = 0.74) between the immediate and deferred treatment groups. Bacterial STIs are detailed in Table 34.

TABLE 34: BACTERIAL SEXUALLY TRANSMITTED INFECTIONS

	PROUD				
	Immediate Treatment Group	**Deferred Treatment Group**	**Unadjusted Odds Ratio**	**Adjusted Odds Ratio (90% CI)[a]**	***P* Value**
Any STI	152/265	124/247	1.33	1.07 (0.78 to 1.46)	0.74
Gonorrhea[b]	103/261	89/242	1.12	0.86 (0.62 to 1.20)	0.46
Chlamydia[b]	77/261	54/242	1.46	1.27 (0.89 to 1.80)	0.27
Syphilis	30/263	22/247	1.32	1.29 (0.79 to 2.10)	0.39
Rectal gonorrhea or chlamydia	93/258	77/238	1.18	1.00 (0.72 to 1.38)	0.99

CI = confidence interval; STI = sexually transmitted infection.
Note: Infections diagnosed during deferral phase of follow-up; analysis based on participants with at least one screen.
[a] Adjusted for the number of screens for specific infection.
[b] Detected in throat, urethra, or rectum.
Source: McCormack et al., 2016.[40]

Safety

AEs were assessed only in the immediate treatment group during the deferral phase. A total of 21 (8%) of the 275 participants in the immediate treatment group experienced an interruption or missed doses due to AEs, of which 20 restarted treatment with the study drug. Three of the 21 participants experienced elevated creatinine concentration leading to treatment interruption, of which two had

comorbidities and were taking concomitant prescription drugs and one was thought to be due to recreational drug use. The most common AEs were nausea, headache, and arthralgia. A total of 29 SAEs (including one death) were reported in 27 participants; however, none were deemed attributable to the study drug.

Limitations

There are many limitations related to the PROUD study. The first is that the results presented are based on the pilot phase of the study with an arbitrary cut-off of 10% of the planned sample size. Although a statistically significant difference was found in some outcomes including HIV incidence, the study may not have been adequately powered to detect a difference between the two treatment groups for other outcomes of interest such as safety. Further, the early termination of the study may have increased the probability of experiencing a type I error. The trial consisted of an open-label (OL) design, whereby both the investigators and the patients were unblinded to treatment allocation; this may have an impact on subjective outcomes such as adherence and risk compensation. The absence of adherence data and the lack of sexual behaviour data are other important limitations, as they limit the assessment of risk compensation behaviour associated with adherence and the use of PrEP. The higher-than-expected incidence of HIV for the included sample in this trial may not be representative of the general population. Finally, the study was conducted in the UK, where standard clinical practice may differ from that which is seen in Canada.

Summary

In general, OL trial designs such as the one presented here may be more reflective of clinical practice in terms of the level of treatment adherence and the sample population enrolled. The results of the pilot phase of the ongoing PROUD study suggest that immediate treatment with FTC/TDF as PrEP was associated with a reduction in the incidence of HIV infection compared with deferred treatment. There were no significant differences in number of sexual partners or STIs for those taking FTC/TDF as PrEP compared with those not receiving PrEP; however, a larger proportion of participants reported receptive anal sex with 10 or more partners without a condom in the immediate treatment group compared with the deferred treatment group. Overall, treatment with FTC/TDF as PrEP was generally well tolerated. The results of this study should be interpreted with caution given the high-risk nature of the sample of participants enrolled and given that the results are based on data derived from the pilot phase of the study, which may not have adequate power to detect differences between groups for some outcomes of interest.

APPENDIX 7: SUMMARY OF THE DOUBLE-BLIND PHASE OF THE IPERGAY STUDY

Objective

To summarize the double-blind (DB) phase of the ongoing IPERGAY study, which evaluated the efficacy and safety of FTC/TDF for on-demand, pre-exposure prophylaxis (PrEP) for human immunodeficiency virus (HIV) type 1 in gay men or men who have sex with men (MSM).[38]

Findings

Study Design

IPERGAY was a phase 3, multi-centre, DB, placebo-controlled, randomized controlled trial (RCT) conducted in six centres in France and one centre in Canada. Participants were randomized 1:1 to either an active treatment group or a placebo group. All participants were offered a comprehensive package of prevention services such as counselling and contraception, among others. Patients in the active treatment group received tenofovir disoproxil fumarate (TDF) (300 mg) and emtricitabine (FTC) (200 mg) fixed-dose combination (FDC) on-demand therapy, in which patients took a loading dose of two pills with food two to 24 hours before sex, followed by a third pill 24 hours after the loading dose and a fourth pill 48 hours after the loading dose. Randomization was done via a fixed-size block of four and was stratified by country. Follow-up visits were scheduled at weeks four and eight after enrolment and every eight weeks thereafter for the duration of the four-year trial. The authors reported that 64 HIV seroconversion events would provide 80% power to detect a 50% relative reduction in the incidence of HIV-1 infection at a two-sided alpha level of 0.05. Therefore, a sample size of 1,900 participants with a 12- to 36-month follow-up would be required to achieve the target number of events, given that the expected HIV incidence in the placebo group was three cases per 100 patient-years and considering a loss to follow-up of 15 participants per 100 patient-years. As per request from the data and safety monitoring board, an unblinded interim analysis was conducted; consequently, the placebo group was discontinued and all the study participants were offered on-demand PrEP. The study was ongoing as an OL study at the time of this review; data from the DB phase of the study were summarized for this report.

Patients were eligible to participate in the DB phase if they met the following criteria:

- HIV-negative
- Aged 18 years and older
- MSM or transgender females who have sex with men
- At high risk for HIV infection (defined as unprotected anal intercourse with at least two partners in the previous six months)

Patients were excluded from participating in IPERGAY if they met the following criteria:

- Tested positive for hepatitis B antigen
- Chronic hepatitis C infection
- Creatinine clearance < 60 mL/minute
- Alanine aminotransferase level > 2.5 times the upper limit of the normal range
- Glycosuria or proteinuria > 1+ on urine dipstick testing

The primary efficacy end point was assessed by monitoring the incidence of HIV-1 infection. Genotypic testing was also performed at the time of diagnosis to assess resistant HIV strains. Adherence to the study drug was assessed by pill counts at every visit, by plasma drug concentrations for the first 113 participants enrolled in the study, and at the most recent sexual intercourse by means of computer-assisted interviews. Safety was assessed by monitoring adverse events (AEs).

All participants who received at least one dose of the study drug were included in the safety analyses. AEs were recorded at each visit regardless of their association with the treatment. All participants who were randomized were included in the intention-to-treat (ITT) analysis. A modified intention-to-treat (mITT) analysis approach was used for the HIV-1 seroconversion end point, in which participants were excluded if they had been HIV-positive before receiving any study drug, if they were lost to follow-up or withdrew consent between randomization and enrolment, and did not receive any study drug. The Kaplan–Meier method was used to estimate the cumulative probability of HIV-1 infection per group, and used the log-rank test to perform between-group comparisons. Probit and binomial mixed models were used to assess sexual behaviour in the two study groups.

Results

Of the 445 participants enrolled, 206 were randomized to the treatment group and 208 were randomized to the placebo group. Of the 206 participants in the treatment group, 199 (96.6%) received intervention, four (1.9%) withdrew consent, two (1%) were lost to follow-up, and one (0.5%) acquired HIV before receiving the study drug. Of the 208 patients in the placebo group, 201 (96.6%) received intervention, two (1%) withdrew consent, three (1.4%) were lost to follow-up, and two (1%) acquired HIV before receiving placebo. A total of 49 (12%) participants discontinued follow-up during the trial, of whom 23 (12%) were in the treatment group and 26 (13%) were in the placebo group, resulting in a total of 431.3 person-years of follow-up. The median duration of follow-up was 9.3 months (interquartile range [IQR] 4.9 to 20.6). Patient disposition is detailed in Table 35.

TABLE 35: PATIENT DISPOSITION

	IPERGAY	
	TDF/FTC	Placebo
Enrolled, N	445	
Randomized, N	414	
Allocation, N	206	208
Received intervention, N	199	201
Did not receive intervention, n (%)	7 (4)	7 (3)
Withdrew consent	4 (2)	2 (1)
Lost to follow-up	2 (1)	3 (1)
Acquired HIV-1 infection	1 (1)	2 (1)
Discontinuation, n (%)	23 (12)	26 (13)
Loss to follow-up	6 (3)	6 (3)
Withdrew consent	14 (7)	17 (8)
Other	3 (2)	3 (1)

TDF/FTC = tenofovir disoproxil fumarate/emtricitabine; HIV = human immunodeficiency virus.
Source: Molina et al.[38]

Baseline characteristics of participants are detailed in Table 36 and were similar between treatment groups. All participants were male (100%), with a median age of 35 years in the treatment group and 34 in the placebo group. The majority of participants (72% in the treatment group and 74% in the placebo group) declared their relationship status as "not in a couple." The median number of sexual partners in the previous two months (eight partners) and the median number of episodes of sexual intercourse in the previous four weeks (10 episodes) was the same in both groups. The proportion of participants reporting consumption of more than five alcoholic drinks per day in the previous month and recreational drug use were 25% and 43%, respectively, in the treatment group and 21% and 46%, respectively, in the corresponding placebo group.

TABLE 36: BASELINE CHARACTERISTICS

Characteristics	IPERGAY	
	TDF/FTC (N = 199)	Placebo (N = 201)
Male, n (%)	199 (100)	201 (100)
Age in years, median (IQR)	35 (29 to 43)	34 (29 to 42)
Age group in years, n (%)		
18 to 24	31 (16)	27 (13)
25 to 29	26 (13)	30 (15)
30 to 39	72 (36)	73 (36)
40 to 49	50 (25)	55 (27)
≥ 50	20 (10)	16 (8)
White race, n (%)[a]	188 (94)	178 (89)
Relationship, n (%)		
Not in a couple	144 (72)	149 (74)
In a couple with HIV-1–positive partner	19 (10)	13 (6)
Other	36 (18)	39 (19)
Post-secondary education, n (%)	146 (73)	141 (70)
> 5 alcoholic drinks per day in previous month, n (%)	49 (25)	42 (21)
Use of recreational drugs, n (%)[b] **Site of enrolment, n (%)**	85 (43)	92 (46)
France		
Paris	96 (48)	105 (52)
Lyon	47 (24)	36 (18)
Nice	13 (7)	18 (9)
Tourcoing	13 (7)	14 (7)
Nantes	9 (5)	6 (3)
Montreal	21 (11)	22 (11)
Sexual risk factors at screening, median (IQR)		
Median number of partners in previous two months	8 (5 to 17)	8 (5 to 16)
Median number of episodes of sexual intercourse in previous four weeks	10 (6 to 18)	10 (5 to 15)
Circumcised, n (%)	38 (19)	41 (20)

Characteristics	IPERGAY	
	TDF/FTC (N = 199)	Placebo (N = 201)
STI diagnosed at screening, n (%)[c]	49 (25)	62 (31)
HBV, n (%)		
Susceptible	46 (23)	38 (19)
Immune from natural infection	18 (9)	31 (15)
Immune from vaccination	135 (68)	132 (66)

HBV = hepatitis B virus; HIV = human immunodeficiency virus; IQR = interquartile range; STI = sexually transmitted infection; TDF/FTC = tenofovir disoproxil fumarate/emtricitabine.
[a] Race was reported by investigators.
[b] Recreational drugs that were reported in the previous 12 months included ecstasy, crack cocaine, cocaine, crystal, speed, and gamma-hydroxybutyric acid or gamma-butyrolactone.
[c] Infections included syphilis, gonorrhea, and chlamydia.
Source: Molina et al.[38]

Efficacy

Based on the mITT population, 16 HIV-1 seroconversions occurred during the study, two of which occurred in the treatment group and 14 of which occurred in the placebo group. The incidence was 0.91 per 100 person-years in the treatment group and 6.60 per 100 person-years in the placebo group, resulting in a relative reduction of 86% (95% confidence interval [CI], 40 to 98; *P* = 0.002) in favour of the treatment group. Of the two HIV-1 seroconversion events in the FTC/TDF group, the authors reported that the patients had not been adherent to the intervention based on pill counts and on plasma drug concentrations. The authors also noted that none of the 16 HIV-1 seroconversions that occurred during the study were drug-resistant strains.

Treatment adherence measured by pill counts suggested that participants took a median of 15 pills (IQR, 11 to 21) per month in the treatment group compared with a median of 15 pills (IQR, 9 to 21) in the placebo group. Treatment adherence as measured by tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) plasma levels in a subset of patients found that participants in the treatment group had an 86% and 82% rate of detection of TDF and FTC, respectively. Finally, according to self-report measures of treatment adherence, 28% of participants had not taken treatment or placebo, 29% had taken a suboptimal regimen, and 43% had taken the dose correctly. Adherence to the intervention using patient self-report based on the last sexual intercourse is detailed in Table 37.

Sexual behaviour was reported as unchanged throughout the study period when compared with baseline. There were no statistically significant differences between the treatment group and placebo group in the total number of episodes of sexual intercourse in the four weeks before visits, the proportion of episodes of receptive anal intercourse without condoms, and in the proportion of episodes of anal sex without condoms during the most recent sexual intercourse. There was a small but statistically significant difference in the number of sexual partners in the previous two months in the placebo group compared with the treatment group (7.5 versus 8, respectively; *P* = 0.001). The number of new sexually transmitted infections (STIs) in the treatment group was 41% compared with 33% in the placebo group (*P* = 0.10). Thirty-nine per cent of the STIs were associated with rectal infections. Overall, 81 participants (20%) acquired chlamydia infections during follow-up, 88 (22%) acquired gonorrhea, 39 (10%) syphilis, and 5 (1%) hepatitis C virus infection. No participant acquired hepatitis B virus infection.

TABLE 37: ADHERENCE TO INTERVENTION BASED ON PATIENT SELF-REPORT FOR THE LAST SEXUAL INTERCOURSE

% PrEP Use (Min to Max)	TDF/FTC n = 649 Acts	Placebo n = 563 Acts	Total n = 1,212 Acts[a]
Correct use[b]	45 (36 to 57)	40 (22 to 49)	43 (35 to 51)
Suboptimal use	27 (14 to 35)	31 (18 to 44)	29 (20 to 38)
No PrEP	27 (15 to 37)	29 (24 to 44)	28 (20 to 38)

TDF/FTC = tenofovir disoproxil fumarate/emtricitabine; max= maximum; min = minimum; PrEP = pre-exposure prophylaxis.
[a] 1,212 episodes of sexual intercourse were assessed in 319 participants.
[b] Defined as at least one pill 24 hours before sex and one pill 24 hours after sex.
Source: Molina et al.[38]

Safety

A total of 186 (93%) participants in the treatment group and 181 (90%) in the placebo group reported any AE. Overall AEs were similar between groups; however, drug-related gastrointestinal AEs were more common in the treatment group compared with the placebo group (14% versus 5%; *P* = 0.002), the most common being nausea, vomiting, diarrhea, abdominal pain, and other gastrointestinal disorders. In addition, elevations in serum creatinine levels were more common in the treatment group compared with the placebo group (18% versus 10%; *P* = 0.03). However, all but one of these events was grade 1, and none led to study drug discontinuation. Two participants (1%) in the treatment group had a decrease in creatinine clearance below 60 mL per minute. There were no significant differences in SAEs between treatment groups, and no deaths were reported. Detailed data outlining AEs are presented in Table 38.

TABLE 38: ADVERSE EVENTS

Adverse Events[a]	IPERGAY	
	TDF/FTC (N = 199)	Placebo (N = 201)
Any AEs, n (%)	186 (93)	181 (90)
Any SAEs, n (%)	20 (10)	17 (8)
Death, n (%)	0	0
Any grade 3 or 4 event, n (%)	19 (10)	15 (7)
Treatment discontinuation due to AEs, n (%)	1 (1)	0
Gastrointestinal AEs, n (%)	28 (14)	10 (5)
Nausea	16 (8)	2 (1)
Vomiting	3 (2)	0
Abdominal pain	13 (7)	3 (1)
Diarrhea	8 (4)	6 (3)
Other gastrointestinal disorder	1 (1)	2 (1)
Bone fracture, n (%)	3 (2)	6 (3)
Confirmed laboratory event, n (%)		
Elevated plasma creatinine		
Any grade	35 (18)	20 (10)
Grade 1	35 (18)	19 (9)
Grade 2	0	1 (< 1)
Proteinuria ≥ 2+	11 (6)	9 (4)
Glycosuria ≥ 2+	1 (1)	0
Elevated alanine aminotransferase		

Adverse Events[a]	IPERGAY	
	TDF/FTC (N = 199)	Placebo (N = 201)
Any grade	33 (17)	26 (13)
Grade 1	24 (12)	17 (8)
Grade 2	8 (4)	5 (2)
Grade 3	0	1 (< 1)
Grade 4	1 (1)	3 (1)

AE = adverse event; TDF/FTC = tenofovir disoproxil fumarate/emtricitabine.
[a] Adverse events reported for participants during the double-blind phase of the study.
Source: Molina et al.[38]

Limitations

The intervention in the IPERGAY trial consisted of on-demand use of FTC/TDF for PrEP, which is not a dosing regimen approved by Health Canada. In addition, the median number of pills of FTC/TDF taken during the IPERGAY trial does not correspond with the dosing regimen specified in the product monograph. Given the nature of the non-daily dosing regimen of FTC/TDF in this trial, the dose of FTC/TDF using on-demand therapy depends on incidence of sexual practice. In this study, the median number of pills taken was 15 per month, so it remains unclear whether FTC/TDF as PrEP would be efficacious for individuals who have sexual intercourse less frequently. Also, IPERGAY was designed as a DB RCT; however, as per request from the data and safety monitoring board, an unblinded interim analysis was conducted; consequently, the placebo group was discontinued and all the study participants were to be offered on-demand PrEP. The median follow-up was 9.3 months (IQR, 4.9 to 20.6), so the long-term efficacy and safety of on-demand FTC/TDF as PrEP is uncertain.

Summary

The results of the IPERGAY study suggest that the use of TDF/FTC for on-demand PrEP was associated with a reduction in the incidence of HIV-1 seroconversion compared with placebo. Sexual behaviour appeared to remain constant over the course of the study period for patients in both groups, and treatment with TDF/FTC for on-demand PrEP was generally well tolerated. Given the short-term nature of the study and the use of an intermittent dosing regimen, caution is required when interpreting the results of this study.

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