

CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

EMTRICITABINE/TENOFOVIR DISOPROXIL FUMARATE (Truvada — Gilead Sciences Canada, Inc.)

Indication: Pre-exposure Prophylaxis of HIV-1 Infection

Recommendation:

The CADTH Canadian Drug Expert Committee (CDEC) recommends that emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) be reimbursed for use as pre-exposure prophylaxis (PrEP) of human immunodeficiency virus type 1 (HIV-1) in combination with safer sex practices to reduce the risk of sexually acquired HIV-1 infection in adults at high risk for infection, if the following conditions are met:

Conditions:

1. Provided in the context of a sexual health program by a prescriber experienced in the treatment and prevention of HIV-1 infection.
2. Reduced price.

Reasons for the Recommendation:

1. Three double-blind, randomized, placebo-controlled trials (iPrEx [N = 2,499], Partners PrEP [N = 4,758], CDC TDF2 [N = 1,219]) showed a statistically significant reduction in the incidence of HIV-1 seroconversion with FTC/TDF compared with placebo in men who have sex with men (MSM), serodiscordant heterosexual couples, and heterosexual sexually active men and women, respectively.
2. While FTC/TDF may represent a cost-effective PrEP option in patients at high risk of infection, the cost-effectiveness is highly uncertain, especially for individuals at a lower risk of exposure to HIV-1 infection.

Of Note:

1. CDEC noted that the optimal provision of FTC/TDF is likely within a sexual health program managed in partnership with public health services.
2. Patients should receive adherence counselling.

Background:

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 of FTC and 300 mg of TDF. The Health Canada-recommended dose is one

tablet taken orally once daily. FTC/TDF is indicated in combination with other antiretroviral drugs for the treatment of HIV-1 infection in adults. 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, which is the indication for this submission.

Summary of CDEC Considerations:

CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of randomized controlled trials (RCTs) and pivotal studies of FTC/TDF for PrEP, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues that are important to individuals at risk of HIV-1 infection.

Patient Input Information:

The following is a summary of information provided by three patient groups (Maggie's: The Toronto Sex Workers Action Project; the Canadian Treatment Action Council; and the AIDS Committee of Toronto) that responded to the CDR call for patient input:

- MSM represent the majority of existing and new HIV-1 infections, and uninfected MSM experience fear of acquiring HIV-1, recurring anxiety associated with sexual encounters with HIV-1-positive partners or partners whose HIV status is unknown, and negative impacts on mental health.
- Female sex workers expressed concern about acquiring HIV-1 infection due to the risk of sexual assault, and pressure to accept condomless intercourse due to financial incentives.
- Condoms alone are not enough to alleviate the risks and fears of HIV-1 infection due to lack of efficacy, potential breakage, and the potential for partners to remove condoms during intercourse. Condoms are also cited as a barrier to sexual pleasure and intimacy with partners.
- The use of FTC/TDF is hoped to provide additional protection against HIV-1 infection while allowing for more intimate relations.

Clinical Trials

The CDR systematic review included three phase 3, double-blind, 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 adults at high risk of acquiring HIV-1 infection. 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 CDC TDF2 study (N = 1,219) was conducted in Botswanan heterosexual men and women aged between 18 and 39 years who were sexually active, and 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.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- HIV-1 seroconversion — The incidence of HIV-1 seroconversion was the primary efficacy end point in all studies. In all studies, pre-specified HIV-1 testing algorithms were used in which paired HIV blood rapid tests were performed in parallel, and samples eliciting discordant results were retested. Positive results were confirmed using Western blot or immunoassays. 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. In the Partners PrEP study, the event time for HIV infection was the time of the first site-detected positive HIV-1 antibody test.
- Sexual behaviour — In the iPrEx study, a structured interview for sexual behaviour was conducted at screening and every 12 weeks during follow-up. 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 on the number of sex partners in the last month was collected at each study visit.
- Adherence — In all studies, adherence was measured by patient self-report and clinic pill count.

Efficacy

- 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. In the iPrEx study, for 100 participants treated with 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, 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. In the Partners PrEP study, for 100 participants treated with 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, 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 the iPrEx study, the number of receptive anal intercourse partners in the past 12 weeks decreased during the study from a mean of approximately 12 partners to a mean of less 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 sex without a condom during the prior 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).
- In the iPrEx study, the mean and median rates of self-reported pill use were similar between the FTC/TDF and placebo groups (mean: 88.7% versus 89.6%; median: 95.4% for both groups). In the Partners PrEP study, study drug adherence was assessed using pill counts from returned study bottles, and 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 (94.4% versus 94.1%).

Harms (Safety and Tolerability)

- 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 infections, pharyngitis, diarrhea, and headache. In the CDC TDF2 study, common AEs also included abdominal pain, dizziness, nausea, vomiting, and weight loss. The incidence of serious 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 AE in both treatment groups. In the Partners PrEP study, two participants in the FTC/TDF group and one participant in the placebo group withdrew due to an AE. 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.
- In the included studies, the incidence of elevated creatinine (defined as 1.5 times baseline level) levels 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.

Cost and Cost-Effectiveness

FTC/TDF (200 mg/300 mg; Truvada), was submitted by the manufacturer at a confidential price of \$29.08 per tablet. The recommended dose is one tablet daily.

The manufacturer submitted a cost-effectiveness analysis comparing FTC/TDF in combination with safer sex practices to safer sex practices alone to reduce the risk of sexually acquired HIV-1 infections in adults at high risk. Patient populations assessed in the analysis were serodiscordant heterosexual couples and MSM. The analysis was conducted from the perspective of a Canadian public payer, over a lifetime time horizon (35 years). The manufacturer reported the results in terms of incremental cost per HIV infection prevented, and incremental cost per life-year gained. In this analysis, the number of HIV infections prevented was determined using the baseline rate of infection and the reduction of rate of infection as reported by the clinical trials assessing FTC/TDF for PrEP. Total costs included the lifetime cost of treating HIV (or the cost avoided) and the cost of FTC/TDF for PrEP therapy for one year. The resulting total cost was divided by the number of infections prevented to determine the incremental cost per HIV infection prevented and by the number of years of life saved (estimated based on the literature) for the incremental cost per life-year gained.

CDR identified a number of limitations with the manufacturer's economic analysis, the major and driving issue being that the analysis did not take into account duration of prophylactic treatment with FTC/TDF. The analysis considered the cost of one year of prophylactic treatment. The possibility that a patient could be on prophylaxis treatment for a number of years (up to a lifetime), and/or interrupt and resume treatment over time was not considered. Given the paucity of clinical data on multiple or long-term prophylaxis use, CDR is unable to assess implications of likely use in actual practice.

CDR tested alternative data in terms of baseline rates of infection and of rates of reduction in HIV infection by FTC/TDF. Analyses resulted in FTC/TDF compared with safer sex practices alone ranging from \$476,037 per HIV infection prevented, to FTC/TDF dominating safer sex practices alone (i.e., less costly and more effective), from low to high population risk of HIV infection. However, the numerical results reported by the manufacturer and resulting from the CDR analyses should be interpreted with caution, as the analytic approach taken by the manufacturer did not consider duration of prophylactic treatment. The most likely conclusion is that treating people at high risk of HIV infection is likely to represent a cost-effective use of FTC/TDF prophylaxis.

Other Discussion Points:

CDEC noted the following:

- CDEC heard from the clinical expert involved in the review, and discussed the use of on-demand PrEP based on the IPERGAY study. Although the results of the IPERGAY study suggested that the use of FTC/TDF for on-demand PrEP was associated with a reduction in the incidence of HIV-1 seroconversion compared with placebo, this is not a Health Canada–approved indication.
- CDEC discussed the definition of “high risk,” noting that the risk of HIV-1 infection in adults is dependent on both individual factors and the prevalence of HIV-1 infection in a given setting.

CDEC Members:

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeyesundera.

July 20, 2016 Meeting

Regrets: None

Conflicts of Interest: None

About This Document:

CDEC provides formulary reimbursement recommendations or advice to CDR-participating drug plans.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information.

The CDEC recommendation or record of advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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