Effectiveness of oral pre-exposure prophylaxis (PrEP) for HIV

Questions

- What is the efficacy of oral tenofovir disoproxil fumarate with or without emtricitabine as pre-exposure prophylaxis (PrEP) for HIV in the context of clinical trials?
- Has this efficacy been realized in real-world implementation?
- What are the key factors implicated in its efficacy and what is the frequency of breakthrough infections?

Key Take-Home Messages

- Oral PrEP (tenofovir disoproxil fumarate with emtricitabine) is highly protective against HIV acquisition across various populations and across different dosing schedules (1, 2).
- Open label and demonstration projects in both high- and low-income country settings have shown that oral tenofovir disoproxil fumarate with or without emtricitabine as PrEP can be delivered feasibly within existing health systems (2).
- The protective efficacy of oral PrEP (tenofovir disoproxil fumarate with or without emtricitabine) for HIV prevention is highly dependent on adherence to the prescribed regimen (1–7).
- Extremely rare cases of HIV infection with optimal adherence have been reported when transmission of drug-resistant mutations or atypical patterns of seroconversion have occurred (8–15).

The Issue and Why It's Important

New HIV infections continue to occur every year in Canada (16), and HIV infection continues to disproportionately affect vulnerable populations (16, 17). For example, in 2016, men who have sex with men represented over 44% of all reported cases of adults (16). Black individuals represented over 41% of all HIV infections through heterosexual contact, and Indigenous individuals represented

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over 59% of infection through injection drug use (16). Researchers have suggested that combining emerging biomedical prevention interventions with current prevention strategies offers the best hope of reducing new HIV infections (17).

One of these biomedical prevention strategies is pre-exposure prophylaxis (PrEP), which relies on self-administration of antiretroviral medication *before* anticipated exposure to HIV (17). At the time of writing, the only regimens of PrEP approved by national and international guidelines are an oral dosage containing a formulation of tenofovir disoproxil fumarate and emtricitabine (TDF/FTC) (18–22), or tenofovir disoproxil fumarate (TDF) alone (19, 22). Current guidelines in Canada (18), the U.S. (19), Europe (20), and Australia (21) all recommend 300mg of TDF and 200mg of FTC among populations at high risk of contracting HIV. The World Health Organization (WHO) recommends PrEP containing TDF alone or in combination with FTC as part of combination HIV prevention (22).

While most guidelines currently recommend a one pill daily dosing schedule, studies have explored the efficacy of intermittent (also referred to as on-demand, time-driven, or event-driven) dosing schedules (23), where tablets are taken less than once per day. Canadian guidelines offer a weak recommendation for an intermittent regimen (defined as two pills 2 to 24 hours before sexual exposure, followed by one pill daily until 48 hours after last sexual activity), as an alternative for men who have sex men (18). Furthermore, Canadian guidelines do not recommend TDF alone (18). The U.S. guidelines do not recommend 'on demand' use; however, TDF alone as an alternative regimen is recommended among heterosexually active adults and people who inject drugs only (19). No guideline specifically recommends PrEP for adolescents.

Although the implementation of oral PrEP is in its infancy in Canada – TDF/FTC was approved in 2016 – there is now an opportunity for widespread scale-up of this prevention method (17). Expanding knowledge on PrEP will contribute to the current efforts to eliminate new HIV infections (17).

This review explores the efficacy of TDF with or without FTC in clinical trials and in real-world implementation, and the key factors implicated in its efficacy.

What We Found

The efficacy of PrEP in clinical trials

Our search yielded a substantial number of systematic reviews exploring various aspects of PrEP (e.g. efficacy, adherence, safety) across a variety of populations (1–7, 24, 25). Additionally, we identified one overview of systematic reviews that explored effectiveness of

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PrEP in preventing HIV infection in men who have sex with men (26).

Overall, the systematic reviews concluded that daily or on-demand oral TDF/FTC PrEP reduces HIV incidence among high-risk population groups, including men who have sex with men (1, 2, 5-7, 24, 25), people who inject drugs (1, 2, 6, 25), heterosexual men and women (1, 2, 5, 6, 24, 25), and women alone (1, 2, 4). One meta-analysis specifically explored how the efficacy of oral PrEP among different subgroups is affected by medication-taking compliance, concluding that protective efficacy of oral PrEP is increased with adherence (3). The overview of systematic reviews (26), containing systematic reviews published between 2012 and 2016, concluded that the use of oral TDF/FTC as PrEP reduces the probability of HIV infection in men who have sex with men with few or no adverse effects (26).

The systematic reviews included various combinations of 11 trials that were published between 2007 and 2015 examining efficacy of oral TDF (300mg) PrEP or TDF/FTC (300mg/200mg) (23, 27-37). Only one systematic review conducted by Fonner et al. in 2016 (1), and a later study by Desai et al. (2) that extended the Fonner et al. review to include articles published between April 2015 and September 2016 (2), included all of the 11 aforementioned trials. This meta-analysis showed a 51% pooled reduction in risk of HIV infection across trials, and a 70% pooled risk reduction in the studies that showed high adherence to TDF or TDF/FTC PrEP (1). Both reviews concluded that TDF/FTC is protective against HIV acquisition across all populations, and across different dosing schedules (i.e. daily and intermittent dosing), and that this does not differ by sex, route of transmission, or age (1, 2). Results also suggested that TDF alone was as effective as TDF/FTC (1).

These 11 trials on the efficacy of oral TDF/FTC or TDF alone are summarized below by population.

Men who have sex with men

The results of three randomized double-blind, placebo-controlled trials demonstrated the efficacy of oral TDF/FTC PrEP in men who have sex with men (23, 27, 28). The iPrex study enrolled 2,499 men and transgender women who have sex with men from Peru, Ecuador, South Africa, Brazil, Thailand, and the U.S. (27). Participants were randomized to receive either daily TDF/FTC or placebo. Results demonstrated a 44% risk reduction of HIV infection relative to placebo (27). The IPERGAY study randomized 400 men who have sex with men and transgender women from France and Canada to receive an 'on-demand' regimen of TDF/FTC (two pills 2–24 hours before sex, continuing with a daily pill during periods of sexual risk, followed by postexposure pills 24 and 48 hours after last sexual exposure) (28). An 86% relative risk reduction in HIV incidence

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was demonstrated among those randomized to the on-demand regimen (28). Lastly, the IAVI Kenya study randomized 67 men who have sex with men and five female sex workers to either daily TDF/FTC, intermittent TDF/FTC (two pills per week plus one pill 2 hours after sex), or placebo (23). No seroconversions were reported in either of the treatment arms (23).

One randomized double-blind, placebo-controlled trial, the U.S. MSM Safety study, evaluated the safety of daily TDF alone among 400 men who have sex with men from sites in San Francisco, Atlanta, and Boston (29). Participants were randomized to receive immediate or delayed study drug, or placebo. No seroconversions occurred among those taking TDF (29).

A systematic review and meta-analysis exploring the efficacy of oral TDF-based PrEP among men who have sex with men, specifically, concluded that it is an effective intervention to prevent against HIV infection in this population (7). All trials described in this section were included in the meta-analysis, as well data from some demonstration projects described later in this report (7).

Adolescent men who have sex with men

One small pilot study conducted in Chicago, Project PrEPare, reported no seroconversions among 58 men who have sex with men aged 18–22 receiving a behavioural intervention alone, the behavioural intervention and oral TDF/FTC, or the intervention with placebo (30).

Transgender women

Though no randomized trials examining the efficacy of oral TDF or TDF/FTC specifically among transgender individuals were found, a sub-analysis of the iPrex study examined results among the study's 339 transgender women participants (38). With 11 HIV infections in the active arm and 10 in the placebo arm, the efficacy of daily oral TDF/FTC was not demonstrated among this subgroup. However, none of the participants who seroconverted had detectable plasma drug levels at the time of infection (38).

People who inject drugs

Only one randomized, double-blind, placebo-controlled trial was conducted on the efficacy of oral TDF alone among people who inject drugs (31). The Bangkok Tenofovir study enrolled 2,413 participants from 17 drug-treatment clinics in Thailand to receive either a daily TDF regimen or placebo. A 48.9% reduction in HIV incidence was demonstrated (31).

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Heterosexual men and women

Two double-blinded randomized placebo-controlled trials have demonstrated the efficacy of oral TDF or TDF/FTC in serodiscordant heterosexual couples. The Partners-PREP study (32) included 4,747 serodiscordant heterosexual couples in Kenya and Uganda. The non-HIV-infected partner of each couple was randomized to receive TDF alone, TDF/FTC, or placebo. Overall, the protective effects of TDF and TDF/FTC were comparable, with a 67% reduction in HIV due to TDF and 75% due to TDF/FTC, relative to placebo. The protective effects were not significantly different between seronegative men and seronegative women with untreated HIV-infected partners. The efficacy of TDF was 63% for seronegative men, and 71% for seronegative women. The efficacy of TDF/FTC was 84% for seronegative men and 66% for seronegative women (32). The IAVI Uganda Study randomized 72 HIV-uninfected partners in serodiscordant heterosexual couples to either daily or intermittent (two pills per week and one pill within 2 hours after sex) regimens of oral TDF/FTC (34). HIV-infected partners did not receive treatment. No HIV infections were reported (34).

A third randomized double-blind, placebo-controlled trial, The TDF-2 study (33), randomly assigned 1,219 heterosexual men and women to once daily TDF/FTC or placebo. The efficacy of daily oral TDF/FTC was 62.2% relative to the placebo group. Though this study was not powered to evaluate whether the efficacy of the drug differed by sex, the protection rate reached 80.1% among men, and 49.4% among women (33).

The Bangkok Tenofovir study, described in the previous section, was also not powered to assess whether the efficacy of TDF differed by sex. The reported incidence of HIV was 0.39 per 100 person-years in men and 0.20 per 100 person-years in women (31).

Women

While randomized trials that have recruited women described in the previous sections have shown the efficacy of oral TDF or TDF/FTC in both daily and intermittent regimens (23, 32–34), three randomized, double-blind placebo-controlled trials that recruited only women were unable to show that oral TDF or TDF/FTC reduced rates of HIV infection.

The West-African study enrolled 936 women from Ghana, Cameroon, and Nigeria to receive daily TDF or placebo (35). During the study two seroconversions occurred among women in the TDF group, and six occurred among the placebo group. However, the researchers were unable to conclusively evaluate the efficacy of daily TDF due to the early closure of the Cameroon and Nigeria study sites, affecting study power (35). The VOICE study randomized 5,029 women from South Africa, Uganda, and Zimbabwe to receive

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either oral TDF alone, oral TDF/FTC, vaginal gel PrEP with 1% TDF, or placebo (36). For the oral medications specifically, a modified intention-to-treat analysis showed that the effectiveness was –49.0% with TDF, and –4.4% with TDF/FTC (36). The Fem-PREP study was conducted in sub-Saharan Africa and randomized 2,120 heterosexual women at high risk of HIV to daily oral TDF/FTC or placebo (37). No difference in infection rates was observed between a daily TDF/FTC and placebo groups, showing an estimated hazard ratio of 0.94 (37).

Despite the results from the VOICE study and Fem-PREP study, a recent meta-analysis of all the included trials that recruited women participants found that oral TDF/FTC is estimated to be effective at preventing HIV infection in women, provided that adherence to PrEP is high (4).

The efficacy of PrEP in demonstration projects

Demonstration projects of PrEP, including open-label extensions of randomized placebo-controlled trials, show the feasibility of achieving effectiveness and high adherence among key populations in settings that more closely resemble the real world than clinical trials (17). Our search found articles describing 19 open-label or demonstration projects with published results of the effectiveness of oral TDF with or without FTC (12, 39–56). No systematic reviews or meta-analyses that specifically reviewed the effectiveness of PrEP in demonstration projects were found; however, results from some of these projects were included in systematic reviews described previously (1–3, 6, 7). Results of these studies are described in the sections below.

'At-risk' Populations

Five studies examined the effectiveness of TDF-based PrEP in unspecified 'at-risk' populations (12, 39–42). In one study, data were collected from PrEP clinical care programmes in three U.S. cities (39). The majority of patients were men who have sex with men. Three seroconversions occurred after being prescribed PrEP (1.1%); however, one had suspected HIV infection when prescribed PrEP, one had confirmed poor adherence, and one became infected just prior to initiation of PrEP (39). One open-label demonstration study prescribed daily TDF/FTC for 30 months to people at risk of HIV in four clinics in Melbourne, Australia (40). No seroconversions were observed in participants who had commenced PrEP before HIV exposure (40). A study evaluating PrEP administration at the Walter Reed National Military Medical Centre, reviewing medical records for the 159 patients who received daily oral TDF/FTC between November 2013 and March 2016 also observed no cases of HIV seroconversions (41). A cohort study, conducted from July 2012 to June 2015 also assessed adherence and HIV incidence among Kaiser Permanente Northern California members initiating

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35. Peterson L, Taylor D, Roddy R, Belai G, Phillips P, Nanda K, et al. Tenofovir disoproxil fumarate for prevention of HIV infection in women: A phase 2, double-blind, randomized, placebo-controlled trial. PLoS Clin Trials. 2007;2(5):e27.

daily oral TDF/FTC PrEP (42). No seroconversions occurred during PrEP use, however two occurred among participants who had to discontinue PrEP due to lack of insurance coverage (42). Finally, a study of clinical data from the first 50 patients enrolled in a clinical PrEP program in Rhode Island, U.S. had one patient seroconvert while on PrEP with TDF levels consistent with high adherence, one of the first cases to demonstrate this in clinical practice (12). Authors state that, as the patient had several mutations associated with drug resistance (including medications other than TDF and FTC), the most likely cause was transmitted drug-resistance, which may decrease the efficacy of PrEP for preventing HIV acquisition (12).

Men who have sex with men and transgender women

Eight open label or demonstration projects recruited men who have sex with men and/or transgender women. In the open-label extension (OLE) of the iPrex study, men who have sex with men and transgender women who were previous enrolled in PrEP trials were given oral TDF/FTC for 72 weeks (43). Among those receiving PrEP, HIV incidence was 1.8/100 person-years, which was 53% lower than in the placebo arm of the prior randomized phase (3.9/100 person-years). Drug concentrations in dried blood spots were also strongly associated with HIV incidence among those receiving PrEP. HIV incidence was 4.7/100 person-years if drug was not detected, 2.3/100 person-years if drug levels were consistent with taking 2 tablets per week, 0.6/100 person-years for 2 to 3 tablets per week, and 0/100 person-years for 4 or more tablets per week (43). During the IPERGAY OLE, men who have sex with men and transgender women previously enrolled in the IPERGAY study were given on-demand TDF/FTC to be taken before and after sexual intercourse. One HIV seroconversion occurred in a participant who had discontinued PrEP, indicating a risk reduction in HIV incidence of 97% with on-demand PrEP (44).

The PROUD study was an open-label randomized controlled trial, where 544 British men who have sex with men were placed in either a group treated immediately with daily TDF/FTC, or a group deferred from treatment for a period of one year. There was a proportionate reduction in HIV acquisition among TDF/FTC participants of 86% when compared to the deferred group. It was concluded that no breakthrough infections occurred among participants who were on PrEP (45).

The PrEP Brasil study was a 48-week open-label demonstration study that assessed feasibility of daily oral TDF/FTC (46). PrEP was provided at no cost to men who have sex with men and transgender women in three HIV referral centres in Brazil. Two individuals seroconverted during follow-up (HIV incidence 0.51 per 100 person-years) however both of these patients had undetectable TDF concentrations at seroconversion (46).

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The PATH-PrEP study was an open-label single arm interventional cohort study conducted at two community-based clinical sites in Los Angeles. Men who have sex with men and transgender women received either a postexposure prophylaxis or PrEP-based HIV prevention package for at least 48 weeks. Plasma TDF levels collected during follow-up visits that were deemed low were given an adherence support intervention. One seroconversion occurred in a participant who had discontinued PrEP, indicating an HIV incidence rate of 0.4 per 100 person years (47).

The DEMO project was conducted from October 2012 to February 2015 among men who have sex with men and transgender women in two STI clinics in San Francisco and Miami, as well as a community health centre in Washington, DC. Daily, oral TDF/FTC was provided free of charge for 48 weeks. Two individuals became HIV-infected during follow-up (HIV incidence 0.43%) however both had TDF levels consistent with less than 2 doses per week at seroconversion (48).

Interim results published in a poster, presented at the 2016 Conference on Retroviruses and Opportunistic Infections, were found for the HPTN 073 trial, evaluating PrEP in a population of black men who have sex with men from Washington DC, Los Angeles, and Chapel Hill, North Carolina. Participants were offered daily oral TDF/FTC combined with a theory-based, culturally tailored care coordination program and followed for 12 months. Among the 178 men who took PrEP during the study, five seroconversions occurred –an HIV incidence of 2.9, compared to an incidence of 7.7 in men who never accepted PrEP. Of the five seroconverters who accepted PrEP, two reported discontinuing PrEP prior to seroconversion (49).

Adolescent and young adult men who have sex with men and transgender women

Two open-label demonstration projects of Project PrEPare have been conducted, providing young men who have sex with men with daily TDF/FTC for 48 weeks. In the first (50), 200 participants between 18 and 22 years of age were enrolled. Four HIV seroconversions occurred on study (3.29/100 person-years). None of the participants who seroconverted had detectable levels of tenofovir in the sample that was drawn closest to the seroconversion date (50). In the second study, 78 participants between the ages of 15 and 17 years old were enrolled. Three participants acquired an HIV infection during study follow-up, for an HIV incidence of 6.4 per 100 person years. TDF levels for seroconverters were all consistent with taking fewer than two doses per week at the likely time of seroconversion (51).

One 48-week prospective observational study conducted in a community health centre in Philadelphia administered oral TDF/FTC PrEP to 50 young men who have sex with men and

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transgender women of colour between the ages of 18 and 30 using weekly, biweekly, and/or monthly dispensation schedules. No seroconversions were reported (52).

Heterosexual serodiscordant couples

Two studies recruited heterosexual serodiscordant couples to examine the effectiveness of TDF/FTC (53, 54). The PrEP-C study used a timed regimen (before and after timed-ovulatory intercourse) among male HIV-positive/female HIV-negative couples wishing to conceive (53). All HIV-positive partners were also on ART. No seroconversions were observed during the study. During the open label extension of the Partners PrEP study, oral TDF/FTC was given to HIV-negative partners prior to and during the first 6 months after the partner living with HIV initiated ART. Results showed a 95% reduction in HIV incidence with daily TDF/FTC, and it was effective in all subgroups, including women (93%), HIV-negative partners under 25 (94%) and among couples with HIV partners with high viral loads (95%). Detectable drug levels were not found in any participant who seroconverted (54).

Women

One open label phase 2 randomized trial, the ADAPT Cape Town Trial, observed the effectiveness of different regimens of oral TDF/FTC among women in South Africa (55). Participants first received directly observed dosing once a week for five weeks, and then were randomly assigned to one of three unblinded regimens over 24 weeks: daily, time driven (twice weekly with post-intercourse 'boost'), or event-driven (before and after intercourse) (55). A later report, describing the characteristics of HIV seroconversions that occurred during this trial, reported two seroconversions in the one-weekly phase, and six seroconversions in the self-administered phase (two in each regimen). Seven of these eight participants who acquired HIV had infrequent PrEP dosing or suboptimal adherence. One woman in the time-driven arm had high-adherence through most follow-up visits, but was infected during a 7-day period with no dosing (57).

People who inject drugs

Only one conference abstract, describing the preliminary follow-up data from an open-label extension of the Bangkok TDF study, was also found that evaluated the effectiveness of oral TDF in people who inject drugs (56). Following the clinical trial, participants were offered one year of oral TDF, free of charge, at 17 drug treatment clinics in Bangkok. One participant became HIV-infected after starting PrEP, indicating an HIV incidence of 3.3 per 1000 person-years, while HIV incidence among placebo recipients from the original trial was 6.8 per 1000 person-years, and 3.5 per 1000 person-years for TDF recipients (56).

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Key factors implicated in the efficacy of PrEP

The efficacy of PrEP and adherence

Measures of adherence to PrEP varied among studies, and included self-report, pill count and drug concentrations in urine, plasma, or dried blood spots. In some cases, measures of drug levels may have been used in combination with other measures of adherence (i.e. pill count) (6). However, drug levels are thought to provide the most objective method for assessing adherence (6). The degree of adherence needed for TDF to be detected in blood is dependent on the test used, however most require two or more tablets per week for detection (2).

Suboptimal adherence to study drugs has been attributed as the primary reason for many HIV infections occurring in people receiving PrEP during clinical trials (2, 6). In fact, seven of the included systematic reviews and meta-analyses concluded that the efficacy of TDF or TDF/FTC is highly dependent on adherence to prescribed PrEP regimens (1–7). Fonner et al.'s 2016 meta-analysis found that among the 11 included randomized trials, those with adherence rates greater than 70% demonstrated the highest PrEP effectiveness and those with low adherence did not show any significant protective effect (1). Another 2018 meta-analysis (that analysed ten of the 11 included trials) specifically explored the association between medicine-taking compliance and PrEP efficacy. Authors found that HIV infection risk increased as compliance decreased with HIV incidence risk ratio being 0.28, 0.42, and 0.75 with good, moderate, and poor compliance, respectively (3). A 2018 meta-analysis on the efficacy of TDF based PrEP among men who have sex with men also found that high levels of blood-based adherence was more effective in reducing HIV incidence when compared to moderate levels (with incidence rates of 0.4% and 2.9%, respectively) (7).

Given that the VOICE and FEM-PrEP studies had the lowest adherence rates among trials that recruited women (4), researchers have speculated that the variability in efficacy of TDF or TDF/FTC among trials that recruited only women is likely due to adherence (58). Furthermore, pharmacokinetic differences between levels of TDF in vaginal and rectal tissues are such that a minimum of 6 doses of TDF/FTC per week is required to protect vaginal tissue from HIV, versus a minimum of 2 doses per week in colorectal tissue (59). This would suggest that the level of protection achieved by a PrEP regimen (i.e. daily or intermittent) may be affected by the site of HIV exposure (60). Furthermore, this suggests that high adherence to daily TDF-based PrEP may be especially important for women exposed to HIV through vaginal sex (60).

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HIV infections occurring in cases of high PrEP adherence

Worldwide, there have been eight apparent or confirmed cases of HIV infection despite long-term adherence to TDF/FTC (confirmed through drug-level testing) (8–15). An additional two cases of HIV infection have also been reported in individuals taking TDF alone for treatment of hepatitis B infection (61, 62). However, the influence that hepatitis B may have on HIV infection, and protective levels of TDF, is not known (61).

The efficacy of PrEP may be compromised when one is exposed to strains of HIV that are resistant to TDF and/or FTC (8), though this is extremely rare (9). Mutations that are resistant to TDF and/or FTC can also be driven to occur in undiagnosed HIV infection at the time of initiating PrEP, particularly when drug adherence is poor (2).

Upon diagnosis, seven of these cases were shown to have a multi-drug resistant virus. Three of these cases, occurring in New York (8), Seattle (9), and North Carolina (10), presented with strains that were resistant to both TDF and FTC, as well as other antiretroviral drugs that were not being administered. The other four cases, occurring in Toronto (11), Rhode Island (12), Thailand (13), and San Francisco (14), also had resistance to FTC and other antiretroviral drugs, but no resistance to TDF. In the New York, Toronto and San Francisco cases, researchers concluded that a multidrug-resistant virus was *transmitted* during PrEP use, rather than drug resistance *acquired* because of PrEP use (8, 11, 14), as the other antiretroviral drug resistance mutations would not have evolved by using TDF/FTC alone (8).

The Seattle, Rhode Island, Thailand and North Carolina cases are also suspected to have been due to transmission of multi-drug resistant strains, however this cannot be confirmed (9, 10, 12, 13). In the Rhode Island and Thailand cases, HIV acquisition *before* starting PrEP could not be ruled out (12, 13). In the North Carolina case, inadequate prescribing and follow-up make it difficult to determine whether TDF and FTC resistance was transmitted, or whether this resistance developed as a result of being on PrEP while infected with HIV (10).

The eighth case report, occurring in Amsterdam, did not detect any drug-resistant mutations; the underlying cause for this infection remains unclear (15). Authors hypothesise infection with a "wild-type" HIV virus, and that frequent condomless anal sex, potential repeated exposure to HIV, repeated diagnosis of sexually transmitted infections, and the pharmacokinetics of TDF/FTC in rectal mucosa may have contributed to seroconversion (15).

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Practical considerations

While daily oral TDF (with or without FTC) is protective against HIV infection, this is highly dependent on adherence (1–7). Researchers have recommended that support for adherence begin at the time PrEP is administered, be actively monitored, and be tailored to the individual patient (18). These interventions should emphasize that PrEP is effective with adherence (22).

As extremely rare cases of HIV infection with optimal adherence have been reported (8–15), researchers emphasize the importance of confirming an HIV-negative status before every prescription of PrEP is provided (18) and regular HIV-testing while on PrEP to minimize the risk of drug-resistant mutations (14, 15, 22). Others further recommend continued surveillance of mutations that may affect PrEP's efficacy (2, 8, 11). Promotion of awareness of atypical patterns of seroconversion (15), and potential risk of HIV infection while on PrEP (8) is also recommended.

Lastly, research on implementation is greatly needed to understand how best to deliver PrEP to at-risk populations as part of a comprehensive strategy for preventing HIV infection (18).

Factors That May Impact Local Applicability

Although evidence shows that TDF/FTC is effective across populations and settings (1), only one of the included trials was performed in Canada (28). Efforts should be made to tailor PrEP interventions to individual contexts (18, 22) and PrEP should be provided in combination with other HIV prevention options, including harm-reduction materials (18, 22).

The safety of TDF/FTC, including its effects on kidney function, bone mineral density, sexually transmitted infections, and pregnancy outcomes, are explored extensively in the included studies (1) and guidelines provide recommendations for prescribing PrEP based on this evidence (18, 19), however discussion of these topics was outside the scope of this review.

As current PrEP guidelines are for oral TDF or TDF/FTC only, this review does not explore alternative and emerging prophylactic drugs and delivery modalities that include long-acting injectable preparations (cabotegravir), vaginal rings and gels (dapivirine), broadly neutralizing monoclonal antibodies (bnAbs), and different oral drugs such as tenofovir alafenamide (TAF) with emtricitabine. Investigation of these alternatives in trials and demonstration projects are planned or ongoing (2).

What We Did

We searched Medline (including Epub Ahead of Print, In-Process & Other Non-Indexed Citations) using a combination of text term HIV and (text terms PrEP or pre-exposure prophylaxis or preexposure prophylaxis or [emtricitabine and tenofovir]) and text terms (effective* or efficac*). Reference lists of identified literature reviews and systematic reviews were also searched. All searches were conducted on August 27, 2018 and results limited to English articles published from 2008 to present. The search yielded 1,582 references from which 62 studies were included. Sample sizes of primary studies ranged from 13 to 5,029.

Rapid Response: Evidence into Action

The OHTN Rapid Response Service offers quick access to research evidence to help inform decision making, service delivery and advocacy. In response to a question from the field, the Rapid Response Team reviews the scientific and grey literature, consults with experts, and prepares a brief fact sheet summarizing the current evidence and its implications for policy and practice.

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Prepared by
Michelle Camilleri

Program Leads / Editors
David Gogolishvili

Contact
rapidresponse@ohtn.on.ca

For more information visit
www.ohtn.on.ca/rapid-response-service

THE ONTARIO HIV TREATMENT NETWORK

The Ontario HIV Treatment Network
1300 Yonge Street, Suite 600
Toronto ON M4T 1X3

www.ohtn.on.ca