REVIEW

Oral antiretroviral chemoprophylaxis: current status

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Purpose of review
Preexposure prophylaxis (PrEP), in which HIV uninfected persons with ongoing HIV risk use oral antiretroviral medications as chemoprophylaxis against sexual HIV acquisition, is a promising new HIV prevention strategy.

Recent findings
During the past 2 years, proof-of-concept that PrEP protects against sexual HIV acquisition has been demonstrated in three clinical trials, conducted among MSM and heterosexual men and women. These trials used daily oral tenofovir disoproxil fumarate, alone or coformulated with emtricitabine. The degree of HIV protection in these trials was strongly related to the level of adherence to PrEP. Two additional clinical trials, both among heterosexual women, did not demonstrate HIV protection with PrEP, with low adherence to daily use of PrEP the leading hypothesis for lack of efficacy; adherence and biologic mechanisms for lack of efficacy in these trial populations are being evaluated.

Summary
Oral chemoprophylaxis, using tenofovir and combination emtricitabine–tenofovir, is effective for prevention of sexual HIV transmission. Next steps in the field include rigorous evaluation of uptake and adherence to PrEP in implementation settings.

Keywords
emtricitabine, HIV prevention, preexposure prophylaxis, sexual HIV-1 transmission, tenofovir

INTRODUCTION

Antiretroviral medications have the potential to be used for HIV prevention as treatment to reduce the infectiousness of HIV-infected persons [1▪▪] or, for HIV-uninfected persons, as chemoprophylaxis after a recognized high-risk exposure [i.e., post-exposure prophylaxis (PEP)] or on an ongoing basis as preexposure prophylaxis (PrEP) for persons with repeated HIV exposures [2]. Although many clinicians have experience prescribing antiretroviral treatment and PEP, antiretroviral PrEP is a new HIV prevention strategy. This review will focus on the rationale and evidence for oral antiretrovirals as PrEP for HIV prevention, hypotheses to explain areas of uncertainty in the available data and next steps for the field.

CHEMOPROPHYLAXIS FOR HIV PREVENTION: RATIONALE

The oral nucleotide reverse transcriptase inhibitor tenofovir disoproxil fumarate (TDF), either alone or combination with the nucleoside reverse transcriptase inhibitor emtricitabine (FTC), has been most intensively studied as PrEP. TDF and FTC–TDF have important biologic qualities that made these agents attractive as potential PrEP medications: potent antiretroviral activity, including activity against all HIV subtypes; rapid onset of activity after ingestion; early action in HIV's lifecycle, which could be important for blocking initial infection; and once-daily dosing with few drug interactions. TDF and FTC–TDF are widely used as part of combination antiretroviral therapy regimens for treatment of HIV infection, and a substantial and reassuring safety and tolerability profile has been established. TDF is administered once daily for HIV treatment, at a dose of 300 mg (as branded Viread), and FTC–TDF also includes 200 mg of FTC (coformulated FTC–TDF is sold branded Truvada); these standard doses were chosen for studies of PrEP.

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KEY POINTS

- Proof-of-concept has been demonstrated oral pre-exposure prophylaxis (PrEP), using daily oral tenofovir–emtricitabine, protects against sexual HIV acquisition in three clinical trials, conducted among MSM and heterosexual men and women.
- The degree of HIV protection in clinical trials of PrEP was strongly related to pill-taking adherence for lack of efficacy.
- Next steps in the field include rigorous evaluation of uptake and adherence to PrEP in implementation settings.

Animal model studies and evidence from studies of prevention of mother-to-child HIV transmission provided additional rationale for evaluating oral PrEP for HIV prevention. Nonhuman primate studies found that daily or intermittent PrEP using TDF and FTC/TDF given prior to simian immunodeficiency virus–simian–human immunodeficiency virus systemic and mucosal challenge provided high protection (70–100%), in a dose-dependent manner [3–7]. There was some evidence of greater HIV protection using FTC–TDF compared with TDF alone, suggesting that combination PrEP could provide greater benefit than from a single agent. Additional evidence that PrEP may be effective for HIV prevention comes from studies of infant prophylaxis using oral antiretrovirals to reduce HIV risk from ongoing HIV exposure through breast milk [8].

EFFICACY TRIALS OF DAILY ORAL PRE-EXPOSURE PROPHYLAXIS FOR HIV PREVENTION

Six randomized, double-blinded, placebo-controlled clinical trials of oral PrEP, prescribed for use once-daily, are completed or ongoing (Table 1 [9▪▪–12▪▪, 13–15], listed in chronological order of reporting of their results). These trials were designed to rigorously evaluate the safety and efficacy of oral PrEP for HIV prevention, and they mandated intensive clinical and counseling procedures, including monthly study visits with HIV serologic testing to identify breakthrough infections early and minimize exposure to PrEP during acute HIV infection (generally with point-of-care rapid tests) and clinical evaluation, regular laboratory safety testing and individualized medication adherence counseling. PrEP was delivered in a context of a package of HIV prevention services, including HIV and risk-reduction counseling, screening and treatment for sexually transmitted infections, free provision of condoms and other services.

The iPrEx (Pre-exposure Prophylaxis Initiative) study enrolled 2499 HIV seronegative MSM and transgender women from Brazil, Ecuador, Peru, South Africa and Thailand, with the majority from the South American sites and 9% from the USA [9▪▪]. The trial demonstrated that daily oral FTC–TDF reduced HIV acquisition risk by 44% [95% confidence interval (CI) 15–63%, $P = 0.005$]. Subgroup analyses indicated higher efficacy associated with higher adherence to the study medication – 73% among those with at least 90% adherence as measured by counts of unused pills. The relationship between detection of tenofovir or emtricitabine in blood samples (a biomarker of adherence) and HIV protection was assessed as well – only 8% of seroconverters had detectable study drug at the visit closest to seroconversion, compared with 54% of a matched subset of nonseroconverters. Having detectable drug was strongly associated with substantially lower HIV risk (relative risk reduction 92%, 95% CI 40–99%, $P < 0.001$).

The FEM-PrEP (Pre-exposure Prophylaxis Trial for HIV Prevention among African Women) study enrolled 2021 high-risk HIV-uninfected women from Kenya, South Africa, and Tanzania. The study was stopped due to futility by its Independent Data Monitoring Committee in April 2011 (efficacy estimate 6%, 95% CI −52 to 41%, $P = 0.8$) [10▪▪]. Like iPrEx, FEM-PrEP tested archived blood samples from the trial for the presence of the study medication, and this testing suggested that adherence to daily oral FTC–TDF was very low in FEM-PrEP: only 26% of nonseroconverting controls had consistent tenofovir levels detected in plasma (and only 15% of seroconverters as well). The study team concluded that study drug adherence was too low to assess the efficacy of FTC–TDF PrEP for HIV prevention in the study population.

The TDF2 study enrolled 1219 heterosexual HIV-uninfected men and women in Botswana (90% <30 years of age). The study demonstrated that FTC–TDF PrEP had 62% efficacy (95% CI 22–83%, $P = 0.01$) for HIV protection compared with placebo [11▪▪]. Among those known to be receiving study product at the time of seroconversion (i.e., censoring follow-up time for those who had been lost to follow-up or had study product held for other reasons), efficacy was 78% (95% CI 41–94, $P = 0.005$). FTC–TDF appeared to provide protection for both men (overall: 80%, $P = 0.03$; subgroup receiving medication: 82%, $P = 0.06$) and women (overall: 49%, $P = 0.1$; subgroup receiving medication: 76%, $P = 0.02$), although the relatively small size of the study limited statistical significance for these subgroup analyses.

Table 1. Current status of efficacy trials of daily oral preexposure prophylaxis for HIV prevention

Study (location)	Population	Design and PrEP Agent	Status	Relative reduction in HIV incidence due to PrEP	Reference
iPrEx (Brazil, Ecuador, Peru, South Africa, Thailand, US)	2499 MSM and transgender women	1 : 1 randomization to FTC/TDF or Placebo	Completed. FTC/TDF effective for HIV prevention	FTC/TDF: 44% (95% CI 15–63%, $P=0.005$)	[9▪▪]
FEM-PrEP (Kenya, South Africa, Tanzania)	2120 women	1 : 1 randomization to FTC/TDF or Placebo	Completed. Trial stopped early for lack of efficacy for HIV prevention	FTC/TDF: 6% (95% CI −52–41%, $P=0.8$)	[10▪▪]
TDF2 Study (Botswana)	1219 Heterosexual men and women	1 : 1 randomization to FTC/TDF or Placebo	Completed. FTC/TDF effective for HIV prevention	FTC/TDF: 63% (95% CI 22–83%, $P=0.01$)	[11▪▪]
Partners PrEP Study (Kenya, Uganda)	4758 heterosexual men and women with known HIV infected partners (HIV serodiscordant couples)	1 : 1:1 randomization to TDF, FTC/TDF, or Placebo	Ongoing. TDF and FTC/TDF effective for HIV prevention. Trial continued with blinded follow-up to compared TDF to FTC/TDF	TDF: 67% (95% CI 44–81%, $P<0.0001$); FTC/TDF: 75% (95% CI 55–87%, $P<0.0001$)	[12▪▪]
VOICE (South Africa, Uganda, Zimbabwe)	3021 women (additional women randomized to tenofovir gel topical PrEP or placebo)	1 : 1:1 randomization to TDF, FTC/TDF, or Placebo	Ongoing. Oral TDF arm stopped early for lack of efficacy for HIV prevention. FTC/TDF arm continued	TDF: No efficacy for HIV prevention. Efficacy estimate not yet available. FTC/TDF: Results expected early 2013	[13,14]
Bangkok Tenofovir Study (Thailand)	2413 injection drug users	1 : 1 randomization to TDF or placebo	Ongoing	TDF: Results expected late 2013	[15]

CI, confidence interval; FEM-PrEP, Pre-exposure Prophylaxis Trial for HIV Prevention among African Women; FTC, emtricitabine; iPrEx, Pre-exposure Prophylaxis Initiative; PrEP, preexposure prophylaxis; TDF, tenofovir disoproxil fumarate.

The Partners PrEP Study enrolled 4758 HIV-uninfected men and women from Kenya and Uganda who were at risk of HIV because of having a known HIV-infected partner who was not yet eligible for antiretroviral according to the national guidelines of those two countries [16]. In July 2011, the study's Data Safety Monitoring Board recommended that the placebo arm be discontinued because the study crossed a predefined stopping boundary for demonstrating PrEP efficacy for HIV protection. TDF efficacy was 67% (95% CI 44–81, $P<0.0001$) and FTC–TDF efficacy was 75% (95% CI 55–87, $P<0.0001$); the difference between TDF and FTC–TDF was not statistically significant ($P=0.23$). Both TDF and FTC–TDF significantly reduced HIV risk for both men and women [12▪▪]: for TDF 63% ($P=0.01$) for men and 71% ($P=0.002$) for women and for FTC–TDF 84% ($P<0.001$) for men and 66% ($P=0.005$) for women, and these degrees of HIV protection for women and men were statistically comparable. Adherence to study drug was measured by multiple means – pill counts of unused study medication, electronic pill cap monitoring and home visits for unannounced pill counts [17] – and was very high. Tenofovir was detected in 82% of blood samples from a randomly selected subpopulation of nonseroconverters (confirming high adherence); detection was less frequent (31%) in those who acquired HIV. Detection of tenofovir was associated with substantial HIV protection (86%, $P<0.001$ for the TDF arm and 90%, $P=0.002$ for the FTC–TDF arm) [18].

The VOICE (Vaginal and Oral Interventions to Control the Epidemic) trial is an ongoing five-arm study of daily oral or topical PrEP (i.e., oral TDF, oral FTC–TDF, oral placebo, vaginal tenofovir gel, vaginal placebo gel) among HIV-uninfected African women. The Data Safety Monitoring Board for the VOICE trial recommended discontinuation of the oral TDF arm in September 2011 [13] due to inability to demonstrate efficacy; the FTC–TDF and placebo arms are ongoing and will report results in early 2013. Lastly, the ongoing Bangkok Tenofovir Study is testing daily oral TDF PrEP among HIV-uninfected 2413 injection drug users in Thailand; results are expected in late 2012 [15].

ADDITIONAL OUTCOMES FROM PRE-EXPOSURE PROPHYLAXIS CLINICAL TRIALS: SAFETY, RESISTANCE, SEXUAL BEHAVIOR

Trials have found that oral TDF and FTC–TDF appear to be well tolerated among HIV-uninfected persons, with the rate of both serious and mild adverse events generally balanced between those

receiving PrEP and those receiving placebo. In both iPrEx and Partners PrEP, gastrointestinal side effects (e.g., nausea, diarrhea) occurred more commonly in those assigned active PrEP, although these symptoms were present only in a minority of individuals (~10% or less), were mild in severity and were generally limited to the first month after initiation of the medication. A modest (1%) reduction in bone mineral density was observed in the iPrEx study and in an earlier phase II study of TDF PrEP in MSM [19]; decline in bone mineral density is a known side effect of TDF when used for HIV treatment and has not been associated with increased risk of fracture. Oral TDF has been associated with renal complications in HIV-infected persons, particularly proximal tubular dysfunction with or without reduced glomerular filtration, but PrEP clinical trials have not found increased risk of renal complications in HIV uninfected persons. Finally, data from Partners PrEP [20] and from the Antiretroviral Pregnancy Registry [21] suggest that use of TDF and FTC–TDF in early pregnancy is not associated with increased rates of birth defects, although more data are needed to fully assess the safety of these medications through pregnancy.

Antiretroviral resistance has been rare in PrEP trials and limited to those with seronegative acute infection at the time of randomization: two of two individuals in iPrEx (both M184I/V mutations), two of eight individuals in Partners PrEP (one K65R and one M184 V mutation), and one of one individual in TDF2 (K65R and M184 V). Five cases of M184 V resistance were observed in FEM-PrEP, one in the placebo arm and three potentially transmitted and not acquired on PrEP. Adherence to PrEP, protection against HIV infection, and antiretroviral resistance appear to be tightly interwoven: low adherence provides little HIV protection but little risk of resistance if infection is acquired, whereas high adherence potentially blocks most transmissions. Whether there is a window of modest PrEP use that confers diminished HIV protection but sufficient drug pressure to select for resistance is unknown. Clearly, HIV testing must be done to minimize PrEP use by those already infected.

Finally, the question increased sexual risk-taking accompanying PrEP use has been explored in iPrEx and Partners PrEP, where self-reported condom use increased during the studies and sexually transmitted infection rates fell to an equivalent degree across both active PrEP and placebo arms. In iPrEx, one important correlate of detection of tenofovir in blood was unprotected anal receptive sex, suggesting that those at highest risk of HIV were more, and not less, likely to use the medication.

UNDERSTANDING THE DIVERGENT RESULTS OF EFFICACY TRIALS OF DAILY ORAL PREEXPOSURE PROPHYLAXIS

The iPrEx, TDF2, and Partners PrEP trials provide clear evidence that daily oral PrEP, using TDF and FTC–TDF, reduces the risk of sexual HIV acquisition. The lack of HIV protection in the FEM-PrEP (testing FTC–TDF) and VOICE (testing TDF) trials, as well as the wide range of efficacy estimates in iPrEx, TDF2 and Partners PrEP suggests that there are important factors that influence PrEP efficacy.

Biological hypotheses to explain divergent PrEP trial results have focused on trying to explain the lack of efficacy for PrEP in women at high-risk who were enrolled in FEM-PrEP and VOICE. Pharmacokinetics studies have found that oral dosing of TDF achieves higher concentrations (by a factor of 10-fold) in rectal tissue compared to cervicovaginal tissue [22,23], leading some to hypothesize that oral PrEP could be less effective in women, whose primary exposure is through vaginal sex, compared to MSM, whose primary risk is through receptive anal sex (of note, no studies of tenofovir concentrations in relevant mucosal tissue for heterosexual men have been done). Arguing against this hypothesis are gender-specific subgroup results from Partners PrEP and TDF2, which found that PrEP provides high protection against HIV for women, equivalent to that seen for heterosexual men. Others have hypothesized that important cofactors for HIV acquisition – including mucosal inflammation due to sexually transmitted infections or other conditions, contact with partners with acute HIV infection and intravaginal practices and use of hormonal contraception [24,25] – that likely were common in the FEM-PrEP and VOICE populations might interact with PrEP in some way as to influence HIV protection efficacy. Although this hypothesis is intriguing, there are no data at this time to explain how these factors would blunt or even completely override HIV protection provided by PrEP.

The strongest hypothesis to explain divergent results across PrEP trials is differences in adherence to daily oral PrEP. Adherence to antiretroviral therapy is the key to its efficacy for HIV treatment, and, thus, it is reasonable to expect that adherence would be critical to the efficacy of antiretroviral PrEP. Moreover, of course, for individuals who did not take PrEP at all, no protection would be expected. Most individuals in FEM-PrEP (70%) perceived themselves to have little or no chance of acquiring HIV, which could explain low PrEP use in that trial. Missed doses and missed visits to collect PrEP study medication undoubtedly diminished efficacy in PrEP trials, and there appears to be a strong dose–response relationship between

Table 2. Dose–response relationship between adherence and efficacy for HIV prevention in trials of daily oral FTC/tenofovir disoproxil fumarate preexposure prophylaxis

Study	Population	HIV protection estimate (randomized comparison versus placebo)	Frequency of detection of study medication in blood samples of nonseroconverters	HIV protection estimate (as related to high adherence)
Partners PrEP Study	Heterosexual men and women with known HIV-infected partners (HIV serodiscordant couples)	75%	81%	90% in individuals with detectable tenofovir levels
TDF2	Young heterosexual men and women	63%	79%	78% excluding follow-up periods when individuals had no PrEP refills for >30 days
iPrEx	MSM and transgender women	44%	51%	92% in individuals with detectable tenofovir levels
FEM-PrEP	Women	6%	35–38% at a single visit, 26% at two consecutive visits	Investigators concluded that use of PrEP was too low to evaluate efficacy
VOICE	Women	Trial still ongoing	Not yet available	Not yet available

FEM, emtricitabine; iPrEx, Pre-exposure Prophylaxis Initiative; PrEP, preexposure prophylaxis; VOICE, Vaginal and Oral Interventions to Control the Epidemic.

PrEP use and HIV protection in PrEP trials (Table 2). Thus, efficacy estimates from the clinical trials are underestimates of the true biologic efficacy of PrEP for preventing HIV infection, and the protection estimates when tenofovir was present in blood from the iPrEx and Partners PrEP trials may, thus, more closely reflect the true biologic efficacy. Additional analyses in the FEM-PrEP and VOICE studies will be necessary to understand PrEP use, predictors of use and HIV protection for African women at high risk of infection.

NEXT STEPS FOR PREEXPOSURE PROPHYLAXIS

In May 2012, the Antiviral Drugs Advisory Committee to the US Food and Drug Administration recommended that a formal label indication for HIV prevention be made for branded FTC–TDF (Truvada), a landmark for HIV prevention. Guidelines from WHO and CDC are in development and will help guide use of PrEP in clinical settings.

The critical next step question for PrEP will be whether implementation outside of rigorous clinical trials can be feasibly done. Several PrEP trials have provided active PrEP to their study participants (iPrEx, Partners PrEP, TDF2), to fulfill promises of access to effective products for placebo-arm participants and to understand adherence and sexual behavior in the absence of placebo. In addition, demonstration projects of PrEP are planned in diverse populations and geographic settings. A follow-on study to Partners PrEP will evaluate staged use of PrEP and antiretroviral therapy in Kenyan and Ugandan HIV serodiscordant couples [26▪], an important next step to bring together the benefits of treatment and PrEP for HIV prevention. Most demonstration projects are planning less frequent and less-intensive visits than were done in the clinical trials. Operations research needs to be done to understand delivery of PrEP to those at highest risk [26▪–28▪], evaluate delivery models of PrEP and motivate and monitor PrEP adherence.

The potential for less-than-daily dosing of oral FTC–TDF is being evaluated in pharmacokinetic studies [29] and in a recently initiated trial among MSM in France and Canada (IPERGAY) [30]. For most persons, PrEP should be envisioned as a time-limited prevention strategy, for periods (months to a few years) of highest behavioral risk, for example during periods when attempting to conceive [31]. In this way, time-limited PrEP is an important contrast to use of antiretrovirals as treatment, which is necessarily life long.

CONCLUSION

Daily oral TDF and FTC–TDF PrEP are effective strategies for HIV prevention. Analyses from ongoing and completed PrEP trials will provide a more complete understanding of effectiveness in different populations and reasons for divergent efficacy estimates. Successful HIV prevention on a population scale will need to incorporate multiple, evidence-based biologic and behavioral strategies to achieve maximal benefits, including behavior change, HIV testing, male circumcision, antiretroviral treatment for HIV-infected persons and PrEP.

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Conflicts of interest

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There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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