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Use of Antiretrovirals for HIV Prevention: What Do We Know and What Don't We Know?

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Abstract

Pre-exposure prophylaxis (PrEP), in which HIV uninfected persons with ongoing HIV risk use antiretroviral medications as chemoprophylaxis against sexual HIV acquisition, is a promising new HIV prevention strategy. Proof-of-concept that PrEP, as oral or vaginal topical tenofovir-based products, protects against sexual HIV acquisition has been demonstrated in clinical trials conducted among men who have sex with men and heterosexual men and women. The degree of HIV protection in these trials was strongly related to the level of adherence to PrEP. Many questions are yet unanswered – including how to motivate uptake of and sustain adherence to PrEP for HIV prevention, how much PrEP use is enough to achieve HIV protection, and the potential of "next-generation" PrEP agents to improve on this effective technology.

Keywords

antiretroviral medications; chemoprophylaxis; global epidemic; HIV/AIDS; HIV prevention; pre-exposure prophylaxis (PrEP); sexual HIV transmission

Introduction

Antiretroviral medications markedly increase the survival of HIV infected persons and have long been the cornerstone of strategies to prevent vertical HIV transmission. Recently, a growing scientific interest in and advocacy for antiretroviral-based strategies for prevention of sexual HIV transmission has developed, and antiretroviral-based HIV prevention interventions are now among the most promising strategies for dramatically reducing HIV spread (1; 2). Antiretrovirals can be used for HIV prevention as antiretroviral treatment (ART) to reduce the infectiousness of HIV infected persons (3; 4) and as oral or topical chemoprophylaxis after a recognized high-risk exposure (i.e., post-exposure prophylaxis (PEP)) or on an ongoing basis as pre-exposure prophylaxis (PrEP) for persons with repeated HIV exposures (5–7). The past two years have seen significant new advances in knowledge regarding antiretroviral-based PrEP, including definitive demonstration that PrEP works for the prevention of HIV infection, regulatory approval of combination oral emtricitabine/

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tenofovir disoproxil fumarate (FTC/TDF) as the first PrEP agent with a label indication for prevention of sexual HIV acquisition, and the development of normative guidance for delivery of PrEP in clinical settings. At the same time, as would be expected for any new HIV prevention strategy, many questions are yet unanswered – including how to motivate uptake of and sustain adherence to PrEP for HIV prevention, how much use is sufficient to achieve HIV protection, and the potential of "next-generation" PrEP agents to improve this effective technology. This review will focus on the rationale and evidence for oral and topical antiretrovirals as PrEP for HIV prevention (what we know) and areas of uncertainty in the available data and next steps for the field (what we don't know).

What we know: primary HIV prevention remains urgently needed

More than 2.5 million persons are infected with HIV each year, and more than 34 million persons are living with HIV infection (8). The majority of new HIV infections occur in low- and middle-income countries, particularly in sub-Saharan Africa, the region with the highest prevalence (9). In the generalized, HIV epidemics of sub-Saharan Africa, key populations for prioritizing novel HIV prevention interventions include young women, who face very high incidence particularly in southern Africa (10), heterosexual HIV serodiscordant couples (11; 12), and commercial sex workers. Men who have sex with men (MSM) carry a disproportionate burden of the epidemic worldwide, having 19.3 higher odds of HIV infection than the general population (13). Injection drug users have increased risk of acquiring HIV infection, although this risk is minimized if clean needles are accessible in pharmacies and clean needle exchange programs.

The past decade has seen marked scale-up of ART worldwide, with declines in HIV-related morbidity and mortality as a result (8). However, the number of new infections, both worldwide and even in highly-resourced settings such as the United States, has been stable. As a result, the total number of persons infected with HIV continues to increase each year, resulting in an ever-growing treatment and care burden. Thus, after >30 years of the HIV epidemic, novel, effective, primary HIV prevention strategies remain urgently needed.

What we know: the preclinical evidence base for PrEP for HIV prevention was strong

The rationale for PrEP grows out of successful HIV prevention in HIV exposed infants with use of antiretroviral prophylaxis during labor, the early post-partum period, and during breastfeeding (14–17) and from non-human primate studies showing that PrEP prior to mucosal simian HIV (SHIV) challenge can provide partial or full protection against infection (18).

In situations where there is ongoing and repeated exposure to HIV, PrEP offers both biologic and logistical advantages over PEP for HIV prevention. First, the efficacy of antiretroviral prophylaxis is theoretically greater if antiretroviral concentrations necessary for HIV protection are already achieved at the time of virus exposure. Second, while PEP requires recognition of HIV exposure and initiation of antiretroviral prophylaxis soon afterwards, PrEP would provide protection even if HIV exposures are unrecognized (e.g., sexual activity with a partner of unknown HIV status) or unacknowledged. Finally, repeated courses of PEP may be impractical for individuals with repeated and ongoing exposures. Thus, while PEP is an important and arguably underutilized HIV prevention intervention, for individuals with repeated HIV exposures, PrEP could provide more sustained HIV protection than PEP.

The nucleotide reverse transcriptase inhibitor tenofovir, as oral TDF, either alone or combination with the nucleoside reverse transcriptase inhibitor FTC, or as tenofovir topical gel, has been most intensively studied as PrEP. Tenofovir-based compounds had biologic qualities that made these agents attractive for PrEP: potent antiretroviral activity, including activity against all HIV subtypes; rapid onset of activity; early action in HIV's lifecycle, which could be important for blocking initial infection; long-intracellular half-life; and convenient dosing with few drug interactions. TDF and FTC/TDF are widely used as part of combination ART regimens for treatment of HIV infection, and a substantial and reassuring safety and tolerability profile had been established for these compounds prior to initiation of clinical trials of PrEP for HIV prevention – an important component for regulatory review given that PrEP was a new HIV prevention strategy. When used for HIV treatment, TDF is administered once-daily, at a dose of 300 mg (as branded Viread® in the United States), and FTC/TDF also includes 200 mg of FTC (co-formulated FTC/TDF is sold as branded Truvada® in the United States); these standard doses were chosen for studies of PrEP.

Non-human primate studies found that daily or intermittent PrEP using topical tenofovir gel, TDF, or FTC/TDF given prior to SIV/SHIV systemic and mucosal challenge provided high protection (70–100%), in a dose-dependent manner (18–22). There was some evidence of greater HIV protection using FTC/TDF compared to TDF alone, suggesting that combination PrEP could provide greater benefit than from a single agent. In humans, pharmacokinetics studies have found that topical dosing achieves considerably greater mucosal tissue tenofovir concentrations than oral dosing, that oral TDF results in higher colonic compared to vaginal tissue concentrations (although the reverse is true for FTC), and that vaginal dosing achieves detectable colonic levels (and vice versa) (23–26).

What we know: clinical trials demonstrate that oral TDF-containing PrEP is efficacious for HIV prevention

Eight randomized, double-blind, placebo-controlled clinical trials of oral and topical tenofovir-based PrEP for HIV prevention have been conducted (Table 1, listed in chronological order of reporting of their results). These trials were designed to rigorously evaluate the safety and efficacy of PrEP for HIV prevention. 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, such as referral for male circumcision, HIV counseling and testing of partners, referral or provision of ART to HIV-infected partners, and PEP. Clinical trial protocols included monthly study visits with HIV serologic testing (generally with point-of-care rapid tests), clinical evaluation (including quarterly laboratory safety monitoring), and individualized adherence counseling. Primary analyses from these studies followed intention-to-treat approaches, analyzing participants according to their randomized assignment to receive active PrEP or a placebo, regardless of adherence to study visits or the study medication regimen.

CAPRISA 004 enrolled 889 HIV-uninfected women, in urban and rural KwaZulu-Natal, South Africa, who were randomized to pericoital use of 1% tenofovir gel or placebo, dosed within 12 hours before sex and a second dose within 12 hours after sex, called the BAT24 strategy (for Before and After sex, not to exceed Two doses in 24 hours). The event-driven timing was developed to be somewhat analogous to the timing of dosing of peripartum nevirapine prophylaxis provided to HIV-infected women and their infants and CAPRISA 004 is the only completed PrEP trial that prescribed PrEP for use other than daily. In CAPRISA 004, tenofovir gel reduced the risk of HIV acquisition by 39% (HR 0.61; 95% CI 0.40–0.94 p=0.017) (27). The results of CAPRISA 004 were the first demonstration of HIV prevention using antiretrovirals as PrEP and the first example of efficacy for HIV prevention

for a topical vaginal microbicide (28). The HIV incidence rate was 9.1 per 100 women-years in the placebo arm of the trial, reflecting extraordinarily high background HIV risk in the study setting.

The iPrEx study enrolled 2499 HIV seronegative men who have sex with men and transgender women from Brazil, Ecuador, Peru, South Africa, Thailand, and the United States, with the majority from the South American sites and 9% from the US (6). The trial demonstrated that those randomized to receive daily oral FTC/TDF, compared to those randomized to placebo, had 44% (95% CI 15–63%, p=0.005) reduced HIV acquisition risk, the first demonstration that oral PrEP was efficacious for HIV prevention.

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 (29). For 62% of couples, the HIV-uninfected partner was male. In July 2011, the study's independent Data Safety Monitoring Board recommended that the placebo arm be discontinued because the study crossed a pre-defined 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: 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. After July 2011, the trial continued based on additional recommendations from the independent Data Safety Monitoring Board: the active TDF and FTC/TDF arms were continued without pause and subjects in the placebo arm were re-randomized to TDF or FTC/TDF, in order to collection additional information on single- (TDF) versus dual-therapy (FTC/TDF) as PrEP. Results from this continuation phase of the study, evaluating TDF versus FTC/TDF as PrEP, are expected in 2013.

The TDF2 study enrolled 1200 heterosexual HIV uninfected men and women in Botswana (90% <30 years of age). The study demonstrated that FTC/TDF PrEP had 63% efficacy (95% CI 22–83%, p=0.01) for HIV protection compared to placebo (7). 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).

Thus, four clinical trials, involving men who have sex with men and heterosexual men and women, from a diversity of geographic settings, demonstrated that PrEP was efficacious for the prevention of HIV acquisition, with randomized comparisons against placebo demonstrating HIV protection efficacy of 39–75%, in intention-to-treat analysis. The results of these studies were an important step in the history of HIV prevention (30).

What we know: not all clinical trials of PrEP have demonstrated efficacy for HIV prevention

Although four clinical trials of PrEP demonstrated conclusive efficacy of this new HIV prevention strategy, two trials, both conducted among African women, did not demonstrate HIV protection. These disparate findings have been the source of considerable consternation for the field and hypotheses regarding the potential reasons for their results (31).

The FEM-PrEP study enrolled 2021 high-risk HIV uninfected women from Kenya, South Africa, and Tanzania. The study was stopped by its Independent Data Monitoring Committee in April 2011 because of demonstrated lack of efficacy for HIV protection

(efficacy estimate 6%, 95% CI −52–41%, p=0.8) (32). Subsequent analyses from the study (detailed below) have led the study team to conclude that study drug adherence was too low in FEM-PrEP to assess the efficacy of FTC/TDF PrEP for HIV prevention.

The VOICE trial was a 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 5021 HIV uninfected women from South Africa, Uganda, and Zimbabwe. The Data Safety Monitoring Board for the VOICE trial recommended discontinuation of the oral TDF arm in September 2011 (33) and the vaginal gel arms in December 2011 (34) due to lack of efficacy for these products for HIV prevention in the study population. The daily oral FTC/TDF and placebo arms were continued through mid-2012 and will report results in early 2013.

Three clinical trials of PrEP are ongoing. The Bangkok Tenofovir Study is testing daily oral TDF PrEP among 2413 HIV uninfected injection drug users in Thailand; results are expected in late 2012 or early 2013 (35). Because of the different route of HIV exposure, with high associated risk for HIV transmission, the results of the Bangkok Tenofovir Study will be important for determining whether PrEP should be a part of harm-reduction strategies for injection drug users. The FACTS 001 study is repeating the CAPRISA 004 trial in a larger and more diverse population of South African women; its results are eagerly anticipated, since a topical microbicide approach to PrEP, which would avoid substantial systemic exposure to PrEP agents and which could be used intermittently with sex, might be attractive for some women. Finally, the IPERGAY trial is testing peri-intercourse dosing of oral FTC/TDF in a recently-initiated study among MSM in France and Canada (36).

What we know: consistent PrEP use is required for efficacy for HIV prevention

The lack of HIV protection in FEM-PrEP (testing FTC/TDF) and VOICE (testing TDF and tenfovir vaginal gel, with FTC/TDF results still pending), as well as the wide range of efficacy estimates across CAPRISA 004, iPrEx, Partners PrEP, and TDF2 suggests that there are important factors that influence PrEP efficacy. The strongest hypothesis to explain divergent results across PrEP trials is differences in use of PrEP. Consistent use of antiretroviral therapy is key to its HIV treatment benefits, and thus it is reasonable to expect that use would be critical to the efficacy of antiretroviral PrEP.

In CAPRISA 004, subgroup analyses demonstrated 54% efficacy in women who reported >80% use of the recommended doses with sex acts in the prior month (p=0.025), with lower efficacy in those reporting less than <80% adherence. In a case-control analysis of cervicovaginal tenofovir levels among HIV seroconverters and non-seroconverters, women with levels >1000 ng/mL had a 74% lower risk of HIV infection than those with <1000 ng/mL (26), potentially providing further evidence of an adherence-efficacy relationship. Studies aiming to determine systemic and tissue concentrations of PrEP medications required for HIV protection are valuable and more study is needed, including the effect of route of PrEP delivery (oral versus topical) and other factors (such as genital inflammation) on PrEP efficacy.

In iPrEx, the relationship between HIV protection and detection of tenofovir or emtricitabine in blood samples, as a biomarker of adherence, was assessed: only 9% of seroconverters had detectable study drug at the visit closest to seroconversion, compared with 54% of a matched subset of non-seroconverters. Having any detectable drug in the blood was strongly associated with substantially lower HIV risk (relative risk reduction 92%, 95% CI 40–99%, p<0.001) (6). In subsequent analyses, HIV risk was estimated to be reduced by 76% (95% CI 56–96%) among those with drug concentrations commensurate with use of 2 tablets per

week, 96% (95% CI 90–>99%) if drug concentrations indicated 4 tablets per week, and 99% (95% CI 96–>99%) if drug concentrations indicated use of 7 tablets per week (37).

In the Partners PrEP Study, where HIV protection efficacy in intention-to-treat analysis was the greatest across completed PrEP trials, adherence to study drug high when measured by multiple means – including pill counts of unused study medication, electronic pill cap monitoring, and home visits for unannounced pill counts (38). Tenofovir was detected in 82% of blood samples from a randomly-selected subpopulation of non-seroconverters (confirming high adherence); detection was less frequent (31%) in those who acquired HIV. Like in iPrEx, detection of tenofovir in blood was associated with substantial HIV protection (86%, $p<0.001$ for the TDF arm of Partners PrEP and 90%, $p=0.002$ for the FTC/TDF arm) (39).

In the TDF2 study, geometric mean blood tenofovir concentrations were significantly lower among the participants who acquired HIV compared to those who did not: 0.3 (95% CI 0.01–8.02) versus 30.6 ng/mL (95% CI 16.3–57.5, $p=0.007$) (7). 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, $p=0.005$).

In contrast, in FEM-PrEP, only 26% of non-seroconverting controls had consistent tenofovir levels detected in plasma (and only 15% of seroconverters as well), suggesting very low overall use of PrEP. Most subjects in FEM-PrEP (70%) perceived themselves to have little or no chance of acquiring HIV, which could explain low PrEP use in that trial.

In addition to non-use of dispensed pills, missed visits to collect PrEP study medication in part explain diminished efficacy in PrEP trials. Returning to pick up study medication is a key component of adherence for an intervention like PrEP that requires a supply of study medication to be on hand, and learning about how to maximize both product use and visit compliance is critical to next HIV prevention trials.

Thus, in summary, there appears to be a strong dose-response relationship between PrEP use and HIV protection in PrEP trials. Arguably, the protection estimates when tenofovir was present, such as in blood in the iPrEx and Partners PrEP trials and in cervicovaginal fluid in CAPRISA 004, may most closely reflect the true biologic efficacy of PrEP for HIV prevention.

What we know: additional outcomes from PrEP clinical trials: safety, resistance, sexual behavior

Trials have found that PrEP appears 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. The most prominent side effects were gastrointestinal (e.g., nausea, abdominal cramping) and these symptoms were present only in a minority of subjects (~10% or less), were mild in severity, and were generally limited to the first month after initiation of the medication. A modest (average 1%) reduction in bone mineral density was observed in the iPrEx study and in an earlier phase II study of TDF PrEP in men who have sex with men (40); 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 (41) and from the Antiretroviral Pregnancy

Registry (42) 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: 2/2 subjects in iPrEx (both M184I/V mutations), 2/8 subjects in Partners PrEP (one K65R and one M184V mutation), and 1/1 subject in TDF2 (K65R and M184V). Five cases of M184V resistance were observed in FEM-PrEP, one in the placebo arm and three were potentially transmitted and not acquired on PrEP. The absence of PrEP-selected drug resistance among persons with emergent infection indicates the strong correlation between PrEP use and protection: low use of PrEP provides little HIV protection but no discernable risk of resistance if infection is acquired, whereas high adherence blocks most transmissions. Blocking HIV transmission entirely is the only definitive way to prevent drug resistance.

Finally, the question of 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 during the course of the study, potentially suggesting that PrEP works synergistically with other components of the HIV prevention package provided to trial participants.

What we don’t know: how much is enough

Drug concentrations are promising surrogate markers of PrEP efficacy, with concentrations expected to differ depending on the route of PrEP dosing (e.g., topical or oral). Furthermore, the concentrations necessary for HIV protection are potentially related to the route of viral exposure (e.g., penile, vaginal, parenteral, rectal) and the drug (TDF, FTC/TDF, or other agents). As detailed above, in CAPRISA 004 a cervicovaginal fluid tenofovir concentration of >1000 ng/mL was associated with a 74% lower risk of HIV infection (26). In the iPrEx study, the intracellular tenofovir diphosphate concentrations required to reduce HIV incidence by 90% was estimated to be 16 fmol per million viable peripheral blood mononuclear cells (95% CI 3–28) (37). Using known relationships between blood and rectal compartments, the target protective concentration in rectal tissue was estimated to be 700 fmol per million rectal cells (95% CI 350–1400). Open-label studies are expected to provide more information about drug concentrations that are required for protection. Once estimates of target drug concentrations are further refined (i.e., have more narrow confidence intervals), they will become good candidates to serve as the primary outcome of the next generation of PrEP demonstration projects, which will aim to find better ways to inform choices among prevention options, including PrEP, and to foster effective use of chosen strategies.

One question is whether the degree of PrEP adherence needs to be higher for sexual transmission to women than to men who have sex with men, given pharmacokinetics studies that have found that oral dosing of TDF achieves higher concentrations (by a factor of 10-fold) in rectal tissue compared to cervicovaginal tissue (25; 43). 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 and higher, in the context of higher adherence. Vaginal tenofovir gel achieves very high concentrations in vaginal tissues, which likely explains the efficacy of topical dosing in spite of low systemic absorption.

What we don't know: how to predict or enhance effective use of PrEP

Identification of factors associated with effective use of PrEP would help guide implementation. In iPrEx, receptive anal intercourse without a condom reported at baseline was associated with higher HIV infection incidence, and higher PrEP efficacy, suggesting that utilization of PrEP was higher in persons with recognized risk factors for HIV acquisition (6). PrEP efficacy was very high in the Partners PrEP Study that enrolled HIV serodiscordant couples, whose perception of HIV transmission risk is clear. Other factors that may prove to be associated with more effective PrEP use could be older age, more informed choice of PrEP as a strategy, less substance use, and greater comfort when raising concerns with health care providers.

Identifying ways to promote effective use of prevention strategies is needed. Novel and brief counseling sessions that are client-centered and motivational were associated with increased adherence in the CAPRISA 004 trial and were utilized in the iPrEx trial (44). Approaches based on cognitive behavioral therapy and daily or weekly electronic reminders are being evaluated. Other approaches based on funding incentives, peer educators, home visits, and group therapy might be tried.

What we don't know: optimal PrEP dosing frequency, when to start, when to stop

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 (45), around the time of sexual debut, during struggles with sexual orientation, and when previously-safe relationship patterns are disrupted. In this way, time-limited PrEP is an important contrast to use of antiretrovirals as treatment, which is necessarily life-long.

PrEP dosing frequency and timing relative to intercourse has not been optimized. Surveys of sexual intercourse suggest that both MSM and heterosexuals have intercourse approximately one time per week (on average); there are phases when intercourse is much more or less frequent. Guidance regarding when to start and stop PrEP is needed. TDF has a long intracellular half-life such that drug concentrations accumulate for approximately 21 days with daily dosing, so the most conservative guidance would be start PrEP 21 days before anticipated exposure. However, in MSM, the protective concentrations are reached after 4 doses in most men and after 7 doses for all men, suggesting a 7-day lead-in period may be sufficient. Stopping PrEP should primarily be driven by whether alternative ways for protection have been implemented: such alternatives may include negotiating safety with partners, consistent condom use, and use of non-penetrative sexual practices. In any case, continuing PrEP for 28 days after the last risky intercourse is reasonable as it allows some time to assess whether the safer behavioral strategy will be adopted in a durable manner, and provides the equivalent of PEP.

The potential for less-than-daily dosing of oral FTC/TDF is being evaluated in a number of studies. A small study in East Africa evaluated the behavioral feasibility of daily or non-daily regimens, finding that adherence was lower to the non-daily regimen (46). The HPTN ADAPT trial is evaluating the acceptability and feasibility of 3 dosing regimens of oral FTC/TDF in women and MSM: daily, twice a week and post-intercourse, and pre- and post-intercourse dosing (47). The IPERGAY trial is evaluating pre- and post-intercourse dosing in MSM (36). These studies have met multiple challenges related to how placebos interfere with adherence (as participants are unsure which pill they are taking), and how to measure sexual activity and pill use on a day-to-day basis, and whether use of a placebo is still

ethically acceptable since PrEP has been proven to reduce HIV acquisition rates. As with antiretroviral therapy, optimization of dosing will be driven by combining information from pharmacology, virology, and clinical trials.

What we don't know: optimal drugs for PrEP

Drugs other than tenofovir gel, TDF, and FTC are being evaluated for prophylactic use. Maraviroc blocks CCR5-mediated viral entry, which is an important step in transmission, and this potential PrEP agent is being evaluated in phase 2 studies, both as an oral medication and as a topical vaginal ring. Dapivirine and rilpivirine are non-nucleoside reverse transcriptase inhibitors that have high potency and long-half lives, making them potentially well-suited for PrEP. Dapivirine is being evaluated as a vaginal ring formulation in two phase 3 studies and rilpivirine is being assessed in earlier-phase work as a potential periodic injection. Integrase inhibitors have outstanding safety profiles and act very early in the viral life cycle, and are being considered for PEP and PrEP as well.

What we don't know: how best to implement PrEP for HIV prevention

In July 2012, the US Food and Drug Administration approved a formal label indication for HIV prevention be made for branded FTC/TDF (Truvada®) – the first medication approved for prevention of sexual HIV transmission (48). Guidance from WHO and CDC have been released recommending next clinical and research steps for the field (49–51).

The critical next step question for PrEP will be whether implementation outside of clinical trials can be feasibly done. The four PrEP trials that demonstrated efficacy for HIV prevention (CAPRISA 004, iPrEx, Partners PrEP, TDF2) have provided active PrEP to their study participants, to fulfill promises of access to effective products for placebo-arm participants and to understand adherence and sexual behavior in the absence of placebo. Data from those open-label extensions will be available beginning in 2013.

Starting in 2012, demonstration projects of PrEP have initiated, in diverse populations and geographic settings. Demonstration projects are planning less intensive visits than were done in the clinical trials, with implementation science research components to understand delivery of PrEP to those most in need (52–54), evaluate delivery models of PrEP, and motivate and monitor PrEP adherence. Provision of PrEP is particularly novel in settings where HIV treatment has been separated from facilities for HIV testing, general medical care, and sexually transmitted infection management, as is common in the United States. More integrated approaches to health services are warranted to foster use of prevention services and improve access to treatment programs.

Stigma leads to social exclusion of groups of people based on a single characteristic, such as HIV infection, sexual orientation, race or ethnic group. Stigma expands based on guilt-by-association, such that AIDS, antiretroviral drugs, and the people who use them can end up being regarded negatively. How PrEP will disturb or reinforce stigma remains to be seen: PrEP may be framed as a responsible and proactive approach to staying free of HIV, or as a sign of hazardous behavior. Framed positively, antiretroviral drugs and the people who use them for prevention and treatment may come into more generally positive regard, which would foster demand, adherence, and retention in care. Alternatively, PrEP may become regarded as an approach of last resort, relevant only for the desperate, which would minimize demand and reinforce the stigmatizing process that currently underlies limited use of antiretroviral therapy. In this way, PrEP is an opportunity for social science research into stigma, the social process that sustains it, and its impact on health-related behavior.

Conclusions

PrEP is effective for HIV prevention. As with all prevention strategies, PrEP is only effective if used, and use starts with making a prevention choice. There have never been so many different options for HIV prevention: condoms, frequent HIV testing and early treatment of partners, PrEP, negotiating agreements for safety with partners, strategic positioning, seroadaptive sexual practices, clean needle exchange, and male circumcision are highly effective when used appropriately. Fostering a vibrant and attractive forum for HIV prevention is critical for those innovations to spread as widely as HIV.

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Table 1

Current status of efficacy trials oral and topical PrEP for HIV prevention

Study (location)	Population	Design	Status	Relative reduction in HIV incidence due to PrEP in intention-to-treat analysis	HIV protection as related to objective measures of PrEP use	Ref
CAPRISA 004 (South Africa)	889 women	1:1 randomization to tenofovir vaginal gel or placebo gel (coitally-associated use)	Completed. Tenofovir vaginal gel, used coitally, effective for HIV prevention.	Tenofovir gel: 39% (95% CI 6–60%, p=0.017)	Detection of high concentrations of tenofovir (>1000 ng/mL) in cervicovaginal fluid associated with 74% reduced HIV risk.	(27; 55)
iPrEx (Brazil, Ecuador, Peru, South Africa, Thailand, US)	2499 men who have sex with men and transgender women	1:1 randomization to daily oral FTC/TDF or placebo	Completed. FTC/TDF effective for HIV prevention.	FTC/TDF: 44% (95% CI 15–63%, p=0.005)	Tenofovir detected in blood samples from ~50% of a subset of HIV-uninfected subjects, versus 9% of those who acquired HIV. Detection of tenofovir associated with 92% HIV protection.	(6)
FEM-PrEP (Kenya, South Africa, Tanzania)	2120 women	1:1 randomization to daily oral 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)	Tenofovir consistently detected in blood samples from <30% of a subset of HIV-uninfected subjects.	(32)
Partners PrEP Study (Kenya, Uganda)	4758 heterosexual men and women with known HIV infected partners (HIV serodiscordant couples)	1:1:1 randomization to daily oral TDF, FTC/TDF, or placebo	Completed. 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) TDF vs. FTC/TDF: not statistically significant in primary analysis. Further data expected mid-2013.	Tenofovir detected in blood samples from 82% of a subset of HIV-uninfected subjects, versus 31% of those who acquired HIV. Detection of tenofovir in blood associated with 86–90% HIV protection.	(5)
TDF2 Study (Botswana)	1219 heterosexual men and women	1:1 randomization to daily oral FTC/TDF or placebo	Completed. FTC/TDF effective for HIV prevention.	FTC/TDF: 63% (95% CI 22–83%, p=0.01)	Significantly greater tenofovir blood concentrations in those who remained HIV uninfected compared with those who acquired HIV.	(7)
VOICE (South Africa, Uganda, Zimbabwe)	5021 women	1:1:1:1: randomization to daily oral TDF, FTC/TDF, or placebo or daily vaginal tenofovir gel or placebo gel	Completed. Analyses ongoing.	TDF and tenofovir gel: Discontinued early due to demonstrated lack of efficacy for HIV protection. FTC/TDF: Results expected early 2013.	Data not yet available.	(33; 34)
Bangkok Tenofovir Study (Thailand)	2413 injection drug users	1:1 randomization to daily oral TDF or Placebo	Completed. Analyses ongoing.	TDF: Results expected early 2013.	Data not yet available.	(35)

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Study (location)	Population	Design	Status	Relative reduction in HIV incidence due to PrEP in intention-to-treat analysis	HIV protection as related to objective measures of PrEP use	Ref
FACTS 001 (South Africa)	2600 women	1:1 randomization to tenofovir vaginal gel or placebo gel (coitally-associated use)	Trial ongoing.	Tenofovir gel: Results expected 2015.	Data not yet available.	(56)
IPERGAY (France, Canada)	1900 men who have sex with men	1:1 randomization to FTC/TDF or placebo, to be used “on demand”	Trial ongoing	FTC/TDF (intercourse-associated use): Results expected 2016.	Data not yet available.	(36)