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What Primary Care Providers Need to Know about Pre-Exposure Prophylaxis (PrEP) for HIV Prevention: Narrative Review

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Abstract

As HIV prevalence climbs globally, including more than 50,000 new infections per year in the United States, we need effective HIV prevention strategies. The use of antiretrovirals for pre-exposure prophylaxis (known as "PrEP") among high-risk HIV-uninfected persons is emerging as one such strategy. Randomized controlled trials have demonstrated that once daily oral PrEP decreased HIV incidence among at-risk MSM and African heterosexuals, including HIV serodiscordant couples. An additional randomized control trial of a pericoital topical application of antiretroviral microbicide gel reduced HIV incidence among at-risk heterosexual South African women. Two other studies in African women did not demonstrate the efficacy of oral or topical PrEP, raising concerns about adherence patterns and efficacy in this population. The FDA Antiretroviral Advisory Panel reviewed these studies and additional data in May 2012 and recommended the approval of oral tenofovir-emtricitabine for PrEP in high-risk populations. Patients may seek PrEP from their primary care providers and those on PrEP require monitoring. Thus, primary care providers should become familiar with PrEP. This review outlines the current state of knowledge about PrEP as it pertains to primary care including identification of individuals likely to benefit from PrEP, counseling to maximize adherence and minimize potential increases in risky behavior, and monitoring for potential drug toxicities, HIV acquisition, and antiretroviral drug resistance. Issues related to cost and insurance coverage are also discussed. Recent data suggest that PrEP, in conjunction with other prevention strategies, holds promise in helping to curtail the HIV epidemic.

Human immunodeficiency virus (HIV) continues to spread with an estimated 2.6 million new infections globally (1) and 50,000 new infections in the United States per year (2). Thus, there is an urgent need for more effective HIV prevention strategies. Administration of antiretroviral medications to uninfected persons at high risk to protect against HIV

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acquisition, known as pre-exposure prophylaxis or "PrEP," has recently emerged as a promising prevention strategy. Over the past 2 years, randomized controlled trials have demonstrated that PrEP can decrease HIV incidence in high-risk populations. While FDA approval of oral tenofovir-emtricitabine for PrEP in high-risk populations is pending as we write this (3), clinicians can implement PrEP with off label use of available oral antiretroviral medications. Thus, it is important that practicing physicians understand this new evidence and its implications.

What is the Evidence Base for PrEP?

In 2010, the Center for the AIDS Programme of Research in South Africa 004 (CAPRISA-004) trial demonstrated that pericoital use of tenofovir 1% vaginal gel was associated with a 39% reduction in the risk of HIV acquisition among at-risk South African women after 2.5 years, as compared to placebo (4). This study was the first demonstration that PrEP can protect against HIV acquisition in humans. Several months later, the multi-national Pre-Exposure Prophylaxis Initiative (iPrEx) trial showed that a once-daily oral tablet containing a fixed-dose combination of tenofovir disoproxil fumarate and emtricitabine (TDF-FTC) led to a 44% reduction in HIV incidence among MSM after a median follow-up of 1.2 years (5). More recently, the Partners PrEP Study showed that daily oral PrEP reduced the risk of HIV acquisition by the HIV-uninfected partner in HIV discordant, heterosexual African couples by 67% with tenofovir and 75% with TDF-FTC after a median follow-up of nearly 2 years (6). In the TDF-2 Study, daily oral TDF-FTC for at-risk heterosexual men and women in Botswana decreased HIV incidence by 63% after 2 years (7). Although it is not known if the efficacy of PrEP protection will persist after long-term use, these studies demonstrated no waning of protection over the duration of follow-up.

Notably, two other trials failed to demonstrate the efficacy of oral or topical PrEP for African women. The FEM-PrEP study randomized at-risk women in several African countries to oral TDF-FTC or placebo. An independent data safety monitoring board terminated the study early due to ineffectiveness of the intervention (8, 9). The Vaginal and Oral Interventions to Control the Epidemic (VOICE) study randomized 5000 at-risk African women to receive either a gel (tenofovir versus placebo) or a pill (tenofovir or TDF-FTC versus placebo) to be used once daily. The oral tenofovir and topical gel arms were terminated due to a lack of efficacy (10). Suboptimal adherence to study medications is one possible explanation of the conflicting results among PrEP trials. The proportion of participants with detectable levels of study drug was far lower in FEM-PrEP than in Partners PrEP, suggesting substantially poorer adherence in the study that failed to show efficacy (8, 11). It is also possible that the women in studies that failed to show efficacy had riskier behaviors than women in other studies. The oral TDF-FTC arm of VOICE is ongoing and another trial of pericoitally-administered tenofovir gel among South African women is underway (12). While awaiting results of ongoing studies (Table 1), the urgency of the HIV epidemic and positive findings from several PrEP studies justify consideration of implementing PrEP before these results are available.

What Must Clinicians Consider when Implementing Pre-Exposure Prophylaxis?

Translating the efficacy of PrEP observed in trials to public health effectiveness will require successful implementation in real-world clinical settings. Realization of the benefits of PrEP will require identifying individuals who are most likely to benefit from it, monitoring for adverse effects, addressing costs, and training providers to responsibly prescribe PrEP. HIV specialists who routinely prescribe antiretroviral medications and may identify at-risk persons who are sexual partners of their HIV-infected patients are likely to be among the

first clinicians involved in PrEP delivery. However, other types of settings such as sexually transmitted disease (STD) clinics and primary care practices are likely to be other venues for PrEP prescription. Since primary care physicians are likely to care for many at-risk individuals, the successful implementation of PrEP will also require their engagement.

Are Other Drugs Likely to be Useful for PrEP?

The only PrEP regimen that has demonstrated efficacy and is currently recommended and available for prescribing is TDF-FTC (5–7). Tenofovir, a nucleotide reverse transcriptase inhibitor, is rapidly absorbed and provides sustained drug concentrations in blood and genital tissues and secretions for many days (14). Its long intracellular half-life could allow for intermittent dosing strategies to minimize cost and side effects. The nucleoside analogs emtricitabine and lamivudine are also well-tolerated and concentrate well in genital tissues (14, 15), but have a propensity to quickly select for resistant mutants. Other agents under study for PrEP include oral agents from drug classes not commonly used for HIV treatment, (e.g., the chemokine receptor 5 antagonist maraviroc) and topical agents that can be delivered via gel or intravaginal rings (e.g., the non-nucleoside reverse transcriptase inhibitor dapivirine) (16). Agents that should be avoided as PrEP include nevirapine and abacavir given risks of severe hypersensitivity reactions (17, 18).

Oral and topical PrEP each have theoretical merits and drawbacks, but only oral TDF-FTC is currently available. Tenofovir gel is still being evaluated in the FACTS-001 trial, and these data will be an important part of submission for FDA approval of tenofovir gel for PrEP.

Daily ingestion of oral PrEP results in sustained systemic and genital antiretroviral concentrations, which provides a continuous antiretroviral barrier to establishment of HIV infection, by inhibiting HIV integration into host cell genomes. Continuous protection is desirable when potential exposure is frequent, as with HIV serodiscordant couples, MSM with multiple partners, or sex workers, particularly when exposure is largely through unplanned sexual encounters. In addition, HIV-uninfected individuals who are unable to negotiate the use of condoms during sexual contact due to power inequality between partners (19) or cultural and legal barriers (20) could use oral PrEP without notifying their partners. Potential challenges for implementing daily oral PrEP include cost (over $10,000 per person annually in the U.S. for the drugs alone), the need for ongoing clinical monitoring for drug toxicities, and suboptimal adherence with a daily regimen, especially if risky behavior is intermittent.

The benefits of pericoital topical PrEP include high local drug exposure with lower systemic drug levels (21), presumably leading to decreased likelihood of drug toxicity, and potentially improved adherence. Less frequent dosing may make PrEP more affordable, especially in resource-constrained environments. Yet, topical PrEP will be more difficult to employ without partner knowledge. It is also possible that unless the gel is used on a daily basis, even in the absence of sex, it may not provide sufficient protective drug exposure if intercourse is unplanned.

Is PrEP Safe?

Available data suggests that PrEP with TDF-FTC has no serious, short term safety or tolerability concerns. Yet, tenofovir use has been associated with renal toxicity and decreased bone mineral density when used as part of treatment regimens in HIV-infected persons (22, 23), so clinicians will need to be alert for similar toxicities in patients who use tenofovir-based PrEP.

The iPrEx study reported infrequent and comparable rates of serious adverse between daily oral TDF-FTC and placebo, although participants randomized to TDF-FTC experienced more nausea and minimal, but statistically significant, weight loss in the first few weeks of the study compared to the placebo arm (5). Counseling patients who initiate TFC-TDF about these potential symptoms might minimize self-discontinuation of drugs. In iPrEx, those assigned to TDF-FTC more often developed elevated serum creatinine (2%) compared to those in the placebo group (1%), but this difference was not statistically significant, and creatinine elevations normalized after discontinuation of study drug (5). Among 5 iPrEx participants who developed creatinine elevations, 4 did not experience a new elevation when TDF-FTC was restarted. Other PrEP trials have also been reassuring with no differences in adverse renal events being seen between men receiving daily oral tenofovir or placebo in a U.S. safety study (24) or among heterosexuals in 3 African PrEP studies (6–8). Long-term effects of tenofovir on bone demineralization will also need to be assessed given minor changes in bone density seen in the U.S. PrEP safety study and iPrEx (25, 26). However, in both of these studies, the level of demineralization was not clinically significant, and there was no evidence of increased fractures or other adverse clinical sequelae (25, 26). Although the safety findings in these first PrEP studies are reassuring, long term safety data are lacking and patients who initiate PrEP will need ongoing monitoring for adverse effects.

With regard to the safety of topical PrEP, serious adverse events were rare and similar among the women in CAPRISA-004 assigned to use tenofovir gel and those who used the placebo gel. However, women who used tenofovir gel reported a higher rate of diarrhea than placebo gel users. Investigators speculated that this could be due to local drug effect, but the mechanism remains unknown (4). A safety study of the vaginal gel applied rectally documented increased local discomfort compared to a placebo gel, probably because of glycerin being part of the vaginal gel (27). A glycerin-free rectal formulation of tenofovir gel was well-tolerated by men and women in a Phase 1 safety study (28), and Phase 2 studies are being planned for MSM. Yet, because of high levels of non-adherence in iPrEx and CAPRISA-004 and the longest duration of follow-up was 72 weeks in iPrEx (29), the “true” adverse event profile among those who routinely use PrEP remains uncertain.

What Counseling and Monitoring Should Accompany PrEP Prescription?

The Centers for Disease Control and Prevention (CDC) has published guidance for the prescription of daily oral TDF-FTC as PrEP to at-risk MSM (30). If the FDA accepts the advice of its Advisory Panel, the CDC will likely revise this guidance to extend to heterosexual discordant couples and other high-risk individuals.

The CDC recommends that providers document a negative HIV antibody test immediately before starting PrEP and test for acute HIV infection if symptoms consistent with this syndrome are present. The CDC also recommends regular, serial HIV testing during PrEP use. Individuals who acquire HIV infection during PrEP should immediately discontinue PrEP to reduce the risk of developing drug resistance and to enable initiation of a therapeutic antiretroviral regimen. Optimal frequency of HIV testing requires further study. Rapid HIV antibody testing was performed monthly in iPrEx, and no emergent drug resistance was detected in participants assigned to TDF-FTC who seroconverted (5), but monthly testing may be impractical in some clinical settings. Home HIV testing, which is currently under study, may enable patients to monitor themselves and be a useful adjunct to clinical testing. Currently, the CDC suggests HIV antibody testing every 2–3 months for MSM on daily TDF-FTC as PrEP (30).

The CDC also advises screening for sexually transmitted infections before initiating PrEP and then at least every 6 months in the absence of symptoms suggesting sexually transmitted

infections (30). Of course, patients should be tested if symptoms suggesting infection are present and treated if infection is diagnosed.

The CDC recommends baseline screening for hepatitis B infection (30). Both tenofovir and emtricitabine have activity against hepatitis B, and clinically significant hepatitis flares have occurred in HIV-infected persons with active hepatitis B during antiviral initiation or interruption (31, 32). Completed PrEP trials have shown no evidence of increased rates of hepatic inflammation in persons using tenofovir versus placebo, including trials conducted in regions where hepatitis B prevalence is high (4, 33). The CDC suggests that providers offer hepatitis B vaccination to seronegative MSM, which is sound clinical practice for sexually active persons. For MSM with active hepatitis B, providers are advised to consider using TDF-FTC for both treatment of active hepatitis B and as PrEP, to monitor liver function carefully, and to avoid sudden drug discontinuation (30).

The CDC guidance also recommends documenting that estimated creatinine clearance is greater than 60 mL/minute before initiating TDF-FTC and repeating renal function testing at 3 months after initiation and then yearly thereafter (30).

It is possible that patients on PrEP will feel that the protection of PrEP will compensate for very high risk behaviors and that such behavior could mitigate the benefits of PrEP. Thus, in addition to monitoring for medication-related adverse effects and HIV acquisition, providers should monitor PrEP users for high-risk behaviors. Such behavior has not been observed in studies of PrEP to date (4–6, 33). Levels of risk-taking actually decreased during iPrEx, with the total number of receptive anal sexual partners decreasing over time and the percentage of sexual partners using condoms increasing to a plateau over the first 6 months of trial participation (5). However, this could be attributable to the intensive behavioral counseling that accompanied PrEP provision as part of the informed consent process, as well as participant realization that they might be assigned to placebo. The CDC suggests behavioral counseling and condom provision at least every 2–3 months during PrEP use (30). Patients and providers must understand that PrEP does not provide complete protection against HIV acquisition. Further studies of how providers can deliver effective counseling against risk compensation during PrEP use in the context of routine clinical care will be essential.

Management of HIV Acquisition during PrEP

PrEP users who acquire HIV-infection require immediate testing for antiretroviral resistance. The use of 1–2 antiretrovirals during acute infection facilitates the development of resistance by selecting for transmitted or newly-evolved resistant strains. Early detection of resistance allows for therapeutic choices that minimize additional mutations that could compromise therapeutic options. Individuals who acquired HIV after being randomized to use PrEP in iPrEx and several other PrEP trials did not exhibit drug resistance, but it is possible that many acute infections occurred in non-adherent individuals, limiting the opportunities for resistance to evolve (4–6). Four of 33 women who acquired HIV after being randomized to receive daily TDF-FTC in FEM-PrEP exhibited resistance to emtricitabine, but it is not known whether these women were infected with drug-resistant virus or if resistance emerged after infection. None of these women had detectable resistance to tenofovir (8). A modeling study concluded that PrEP use is likely to have a detectable but relatively minor impact on the development of drug resistance (34). However, assessment of drug resistance among those who become infected while using PrEP will be important as PrEP use expands beyond the clinical trial environment.

Adherence Counseling

Clinicians will need to counsel persons who use PrEP about the importance of adherence. A case-control analysis in iPrEx showed that 9% of men who acquired HIV infection after being randomized to TDF-FTC had detectable levels of study drug compared to 51% of men who remained uninfected (5), underscoring that PrEP's effectiveness depends on adherence. Although self-reported rates of pill use in iPrEx were high (more than 89% average pill use), only 54% of those randomized to the TDF-FTC arm had detectable serum levels of study drug during random screenings, suggesting that actual adherence was lower (35).

It will be important to determine the least amount of medication that provides optimal protection and which patterns of non-daily use result in the best adherence, particularly for individuals whose risky behaviors are intermittent. Intermittent dosing could mitigate nonadherence and feasibility trials are currently underway (13, 36). However, event-driven dosing regimens may confront similar challenges to optimal adherence as regimens with more frequent schedules, as only approximately 40% of women in CAPRISA-004 reported using the gel at least 50% of the time (4).

Are At-Risk Persons interested in using PrEP…and will Clinicians Prescribe it?

Currently, awareness and utilization of PrEP are limited among at-risk persons, but interest in using PrEP exists. A national survey of U.S. MSM using a social networking website conducted 1 month after release of iPrEx results demonstrated that 19% of participants were aware of PrEP, <1% had used PrEP, and 79% expressed interest in PrEP use once they knew about it (37). Over 97% of women who participated in CAPRISA-004 found tenofovir 1% gel to be acceptable and expressed intent to use it if it was approved (4).

A survey of Massachusetts-based HIV specialists and generalist physicians suggested that many clinicians (73%) would be willing to prescribe PrEP to at-risk MSM based on the iPrEx results (38). Clearly, recommendations from public health authorities and the safety and efficacy data that emerge from clinical trials of PrEP will influence actual prescribing behavior (39).

Cost Considerations

Costs will be a substantial barrier to PrEP. A modeling study of PrEP use among MSM in the U.S. estimated that the cost to administer TDF-FTC once daily with associated monitoring and care would be $11,740 annually per person, with 91% due to drug costs (40). Models suggest that, in the absence of an increase in high risk behavior among people on PrEP, oral PrEP could be cost-effective among high-risk MSM in the U.S. (40, 41)and serodiscordant heterosexual couples (42) in South Africa. Topical PrEP is likely to be cost-effective among South African women (43). Availability of generic drugs could reduce costs for oral PrEP, but the patent for TDF-FTC (Truvada®, Gilead Sciences, Foster City, California) does not expire until 2021 (44).

It is unknown whether insurers will cover PrEP. Without insurance, out-of-pocket expenses are likely to be prohibitive for many high-risk persons. Moreover, given that nearly 3,000 Americans are on waiting lists to receive funds for treatment (45), and globally less than 1/2 of persons who need treatment are receiving it (1), issues of how best to use limited resources must be considered. Increased funding for both treatment and prevention will be crucial to minimize discord (44). Given limited resources, clinicians and policymakers will need to think carefully about which individuals are most likely to benefit from PrEP.

Who Should Clinicians Offer PrEP?

Identifying individuals who are most likely to benefit from PrEP requires an understanding of local transmission dynamics. Generalized heterosexual epidemics predominate in some nations (e.g. South Africa), whereas concentrated epidemics, including injection drug users, sex workers, and MSM, exist in others (e.g. Thailand (46)). In the U.S., MSM are associated with the largest number of new infections (61%) (2), and the epidemic disproportionately affects African-Americans in urban areas and in smaller cities in the South (47).

The incorporation of HIV risk assessment into primary care has remained challenging since the beginning of the HIV epidemic, but will be essential to implement PrEP on a wide scale (48–50). Individual risk behaviors change over time, so serial risk assessment is necessary (51). Stigma associated with homosexuality in many cultures and criminalization of sexual practices in some nations (52) may limit the willingness of providers to ask, and patients to disclose, risky practices. Computer-assisted self-interviews may enable disclosure of risky behaviors (53). Strategies to develop provider comfort and skills around risk assessment will be important to optimize PrEP use.

HIV Serodiscordant Couples: Treating HIV-infected Partners, PrEP, or Both?

A recent study of 1763 HIV serodiscordant heterosexual couples demonstrated that early administration of ART to the HIV-infected partner (who had to have a CD4 count between 350 and 550 cells/mm^3) reduced the risk of HIV transmission to the uninfected partner by 96%, as compared to those whose ART initiation was delayed, during a median follow-up of 1.7 years (54). These results suggest that early administration of ART to HIV-infected persons offers an additional strategy for using antiretrovirals to decrease HIV transmission. Clinical events (primarily extrapulmonary tuberculosis) were less frequent among those who initiated ART sooner, suggesting that earlier treatment benefited the index participants as well as their partners. However, genotypic testing demonstrated that 11 of 39 participants who were initially uninfected acquired HIV from persons other than their primary partner during the course of the study, highlighting that treating infected partners does not completely protect their partners if they have other sexual contacts.

The efficacy of administering PrEP to the uninfected partner of a serodiscordant couple that is monogamous, in which the HIV-positive partner is on antiretroviral medications, is unknown. PrEP could potentially offer protection in this context during periods when the HIV-infected partner is viremic, such as early after initiating ART (i.e., before virologic suppression), when adherence is suboptimal, or after virologic failure. Clinicians caring for serodiscordant couples will need to discuss the relative merits of early ART for the infected partner plus or minus PrEP for the uninfected partner to determine the optimal strategies. For high-risk individuals without a single defined partner, PrEP may be the best option.

Conclusion

Primary care providers can play an important role in identifying persons who are at high-risk for HIV acquisition and helping them to make informed decisions about PrEP in combination with other prevention strategies. The efficacy of PrEP for MSM (44%), serodiscordant couples (67–75%), and heterosexual men and women in Africa (63%) is favorable when compared to other prophylactic measures, including voluntary medical male circumcision for African males (38–66%) (55) and early ART in HIV-infected members of serodiscordant couples (96%) (54, 56). Antiretrovirals can also decrease rates of mother-to-child transmission to 1–2% (57) and offer protection when administered as post-exposure

prophylaxis (58). Similar to other prevention strategies, PrEP does not provide complete protection against HIV acquisition. Available evidence suggests that PrEP would be most effective as part of a multifaceted "prevention package." Clinicians and policymakers must tailor prevention interventions to address local epidemic dynamics (59) and individual patient preferences.

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Table 1

Completed and Ongoing Efficacy Trials of HIV Antiretroviral Pre-Exposure Prophylaxis (PrEP).

Trial name	High-Risk Population	Location	Drug and Means of Administration	N	Results
iPrEx (5)	MSM and transgender females	Brazil; Ecuador; Peru; South Africa; Thailand; U.S.	Daily oral TDF-FTC	2,499	PrEP reduced HIV incidence by 44% compared to placebo. Open label extension ongoing.
CAPRISA-004 (4)	Heterosexual women	South Africa	Pericoitally-administered topical vaginal TFV	1085	PrEP decreased HIV incidence by 39% compared to placebo
FEM-PrEP (8)	Heterosexual women	Kenya; South Africa; Tanzania	Daily oral TDF-FTC	2000	Stopped at interim analyses: unable to demonstrate efficacy of PrEP
TDF-2 (7)	Heterosexual men and women	Botswana	Daily oral TDF-FTC	1200	PrEP decreased HIV incidence by 63% compared to placebo
Partners PrEP (6)	Serodiscordant heterosexual couples	Kenya; Uganda	Daily oral tenofovir or TDF-FTC	4700	PrEP decreased HIV incidence by 67% (tenofovir) and 75% (TDF-FTC) compared to placebo
Bangkok Tenofovir Study (13)	Injection drug users	Thailand	Daily oral tenofovir	2400	Enrollment completed 2010; results expected in 2012
VOICE (10)	Heterosexual women	South Africa; Uganda; Zambia; Zimbabwe	Daily oral tenofovir, TDF-FTC, or topical vaginal TFV	5000	Oral tenofovir and topical TFV arms stopped at interim analyses: unable to demonstrate efficacy. Oral TDF-FTC arm ongoing.
FACTS-001 (12)	Heterosexual women	South Africa	Pericoitally-administered topical vaginal	2200	Enrolling

PrEP = pre-exposure prophylaxis; iPrEx = Pre-Exposure Prophylaxis Initiative; MSM = men who have sex with men; TDF-FTC = Fixed-dose combination of emtricitabine and tenofovir disoproxil fumarate. CAPRISA-004 = Center for the AIDS Programme of Research in South Africa 004 trial; TFV = Tenofovir 1% gel; VOICE = Vaginal and Oral Interventions to Control the Epidemic; FACTS-001 = Follow-on African Consortium for Tenofovir Studies 001 trial.

Table 2

Baseline and Follow-up Assessment, Testing, and Counseling that Clinicians should Provide when Prescribing HIV Antiretroviral Pre-Exposure Prophylaxis (PrEP).*

Before prescribing PrEP	Follow-Up Assessments	Frequency
Document negative HIV antibody test. Test for HIV RNA if signs/symptoms suggesting acute HIV infection are present.	Serial HIV antibody testing.	At least every 2–3 months. If HIV-infected, discontinue PrEP, obtain HIV resistance testing and link to HIV care.
Screen and treat for STDs: serologic testing for syphilis and NAATs for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* from appropriate mucosal sites.	Rescreening and treatment for STDs.	With any signs/symptoms of STD; at least every 6 months if asymptomatic.
Screen for hepatitis B infection. Vaccinate against hepatitis B if susceptible. If active hepatitis B exists, document baseline aminotransferase levels and consider using TDF-FTC for hepatitis B treatment and PrEP.	Monitor for signs/symptoms of hepatic inflammation and increases in aminotransferase levels. Avoid sudden discontinuation of TDF-FTC.	At least every 2–3 months. If discontinuing TDF-FTC, consider continuing treatment of hepatitis B with appropriate regimen.
Document calculated creatinine clearance ≥ 60 mL/minute.	Repeat renal function testing.	Three months after initiation, then yearly.
Behavioral risk assessment to confirm individual is at ongoing high risk for HIV acquisition. Provide risk reduction counseling and condoms.	Repeat risk assessment, counseling and provision of condoms.	Every visit; at least every 2–3 months.
Adherence counseling	Adherence assessment. Provide counseling and support as needed.	Every visit; at least every 2–3 months.

PrEP = pre-exposure prophylaxis. RNA = ribonucleic acid. STD = Sexually transmitted disease. NAAT = Nucleic acid amplification test. TDF-FTC = Fixed-dose combination of emtricitabine and tenofovir disoproxil fumarate.

* Bone mineral density as assessed by dual energy x-ray absorptiometry was decreased in TDF-FTC users in iPrEx. Further studies are underway to determine if ongoing assessments of bone mineral density for PrEP users in community settings are warranted.