Preventing New Human Immunodeficiency Virus Infections With Pre-exposure Prophylaxis
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ABSTRACT
Human immunodeficiency virus (HIV) pre-exposure prophylaxis (PrEP) with emtricitabine/tenofovir (TDF/FTC) can reduce HIV infection risk by 92% in people at high risk for HIV. TDF/FTC was approved for HIV PrEP by the Food and Drug Administration in 2012. Primary care nurse practitioners (NPs) have not embraced this tool for the prevention of new HIV infection. A number of barriers exist that may prevent primary care NPs from prescribing HIV PrEP for patients in need. This article clarifies current recommendations for HIV PrEP and provides practical guidance for primary care NPs to incorporate this tool into their routine practice.

Keywords: harm reduction, human immunodeficiency virus prevention, injection drug users, pre-exposure prophylaxis, sexual/gender minority

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The Centers for Disease Control and Prevention (CDC) estimates that there were 37,600 new human immunodeficiency virus (HIV) infections in 2014. Pre-exposure prophylaxis (PrEP) is a highly effective tool for the prevention of new HIV infections that was approved by the Food and Drug Administration (FDA) in 2012. PrEP is largely underused by primary care providers. This clinical feature will address provider barriers that impede prescribing PrEP to high-risk patients and provide a straightforward approach for nurse practitioners (NPs) to offer PrEP in the primary care setting.

BACKGROUND
The CDC estimates that 1.1 million people are infected with HIV in the United States, with 1 in 7 people unaware of his or her HIV status. Of the new diagnoses of HIV in the US in 2015, 82% are men who have sex with men (MSM). Black people make up the majority (45%) of new HIV diagnoses followed by whites and Hispanics. Most troubling about new cases of HIV in the US is the fact that if current HIV incidence rates persist, 1 in 2 black MSM and 1 in 4 Latino MSM will be diagnosed with HIV during their lifetime. The overall lifetime risk of HIV diagnosis in the US among all MSM is now 1 in 99.

Among women with a new diagnosis of HIV, 61% are black, 19% are white, and 15% are Hispanic. Heterosexual black women represent the largest group of new HIV infections among women.

Thirty-five years after the HIV/AIDS epidemic was first identified, effective treatments have dramatically decreased the number of deaths from HIV/AIDS. More than 6,000 people still died from HIV-related illnesses in 2014. Although life expectancy and quality of life have increased markedly for people living with HIV (PLWH), the reality remains that, if not treated, HIV can lead to devastating health consequences and death. PLWH have the potential to transmit the infection to others through sexual contact and shared injection drug paraphernalia.

Antiretroviral therapies have improved the quality and quantity of life for PLWH. HIV is now viewed as...
a chronic disease in high-resource countries. Although the care of PLWH has shifted to primary care settings, services for the prevention of new HIV infections in these settings remain incomplete. The tool kit of many NPs for the prevention of new HIV infections remains the same—condoms, safer sex education, and clean needles. Lacking from this tool kit for many NPs are newer strategies that have been found to be most effective in preventing new HIV infections including universal HIV testing and linkage to care, HIV treatment and viral load suppression to reduce transmission, and PrEP for those at high risk of HIV acquisition.

PREVENTING NEW HIV INFECTIONS

The first combination drug for HIV PrEP was approved by the FDA in 2012. Emtricitabine/tenofovir (FTC/TDF) is a fixed-dose combination of 2 nucleoside reverse transcriptase inhibitors. Used for the treatment of HIV since 2004, FTC/TDF was shown to be effective as a daily treatment for the prevention of HIV infection. Although evidence of the safety and efficacy of FTC/TDF as HIV PrEP has been demonstrated in numerous trials, prescribers should be familiar with 2 large-scale clinical trials on which approval of the treatment was based. The first trial focused on serodiscordant heterosexual couples (Partners PrEP) and the other focused on MSM (Pre-Exposure Prophylaxis Initiative [iPrEx]).

In the Partners PrEP trial, serodiscordant heterosexual couples in 2 countries were randomized to receive tenofovir, FTC/TDF, or placebo. Treatment in the FTC/TDF arm of the trial was associated with a 75% reduction in HIV acquisition, but researchers observed a 90% reduction in those who had detectable drug levels in their system. The trial was originally intended to last up to 36 months but stopped 18 months early after an interim analysis showed statistically significant efficacy in the FTC/TDF group compared with the other 2 groups.

The iPrEx trial was a randomized, double-blind, placebo-controlled study in 6 countries, enrolling 2,499 individuals. In this trial, MSM and transgender women were randomized to receive daily FTC/TDF or placebo. The study showed a 44% reduction in HIV acquisition within the TDF/FTC treatment arm, despite low adherence to the study drug (51% as evaluated by serum drug levels). None of the participants who had a new diagnosis of HIV had serum therapeutic levels of FTC/TDF, suggesting treatment nonadherence as opposed to treatment failure was the cause of HIV acquisition.

There is compelling evidence to support PrEP as an effective tool to reduce HIV infections. NPs should begin incorporating this strategy into their overall approach to preventing new HIV infections. Primary care NPs are ideally situated to be at the forefront of the movement to eliminate new HIV infections in this generation.

NP’ BARRIERS TO PrEP PRESCRIBING

Health care providers report a number of barriers to incorporating PrEP in their practice. Patient-level barriers include concerns that patients receiving PrEP will engage in higher-risk behaviors and/or not adhere to treatment. Additionally, NPs may be concerned about drug toxicity of PrEP. System-level barriers include concerns about an NP’s ability to appropriately prescribe PrEP and the overall cost of treatment.

Patient Risk Behaviors

A common concern that NPs have regarding PrEP is the perception that a PrEP prescription will increase risk-taking behavior and/or reduce safer sex practices. On the contrary, the clinical literature does not support this concern. Data from the iPrEx trial confirm that participants were, in fact, more likely to engage in sexual risk reduction behaviors while receiving PrEP. Additionally, PrEP is a component of a larger risk reduction program, which requires regularly scheduled provider follow-up. These follow-up encounters are opportunities to further engage patients in an overall program of risk reduction.

It may be helpful to consider HIV PrEP in the context of other strategies for PrEP. For a patient traveling to a malaria-endemic part of the world, the NP will prescribe appropriate antimalarial medication, in addition to teaching strategies to avoid being bitten by mosquitoes. For the patient who is unwilling or unable to use insect repellent, the NP would not withhold antimalarials because doing so would cause harm. Similarly, withholding PrEP from a patient at...
high risk for HIV increases the patient's risk for HIV acquisition.\textsuperscript{9,12} Just as the patient in this scenario will eventually leave the malaria risk zone, most individuals receiving PrEP will transition into a part of life when there is no longer a need for this tool.

**Patient Adherence**

NPs may be concerned that some of the behaviors that lead a person to require PrEP (eg, injection drug use and high-risk sexual behaviors) are themselves markers of circumstances that would impede drug adherence. Data support that patients who are prescribed PrEP overwhelmingly adhere to the regimen.\textsuperscript{13} Patients who seek PrEP or respond to an NP's offer of PrEP are highly motivated to avoid HIV infection. NPs can capitalize on this motivation to engage patients in numerous strategies to reduce HIV risk.

**Drug Toxicity**

Although all drug therapies carry inherent risks of toxicity, the NP caring for people at high risk for HIV must consider the alternative of drug side effects—new HIV infection. FTC/TDF is generally considered a safe and well-tolerated medication.\textsuperscript{14} NP adherence to monitoring guidelines and careful history taking are the best tools to mitigate the infrequent risks associated with FTC/TDF-based PrEP.

**Patient Selection**

A lack of confidence in an NP’s ability to select appropriate patients to whom to offer PrEP can be a barrier to integrating PrEP into one’s practice.\textsuperscript{7} Any person at increased risk for HIV is a candidate for PrEP. When considering whether a patient is a candidate for PrEP, it is important to consider behavior and risk factors as opposed to sexual orientation, the gender of sexual partners, or gender identity. Any person with an HIV-infected partner, a recent sexually transmitted infection (STI), a high number of sexual partners, or who inconsistently uses condoms should be offered PrEP to prevent HIV infection.\textsuperscript{8} Additionally, any person who has had sex without a condom with an individual whose HIV status is unknown is a candidate for PrEP.\textsuperscript{8} People who are commercial sex workers (eg, prostitutes, escorts, and adult film performers) as well as anyone who injects drugs using shared equipment should be offered PrEP.\textsuperscript{8}

**Cost**

As of 2017, there is only 1 FDA-approved PrEP regimen, FTC/TDF. Despite the cost of the medication, it has been found to be cost-effective in comparison with treating new HIV infections.\textsuperscript{15} As new agents become available for PrEP, the cost (currently $1,300-$1,600\textsuperscript{16} per month) is expected to decline. The financial landscape of PrEP has changed over time. As of November 2017, most insurance companies and many state Medicaid programs provide coverage for PrEP, and the manufacturer has a medication assistance program.\textsuperscript{17} Although the current formulation of FTC/TDF is only available as a brand name product, the FDA granted the first license for a generic formulation of FTC/TDF in June 2017,\textsuperscript{18} although it may be months or years until this generic formulation becomes commercially available. The CDC provides resources that guide clinicians in reducing the financial barriers to PrEP.\textsuperscript{17}

**OFFERING PrEP TO PATIENTS**

It is important for the NP to view PrEP as not simply a prescription but rather an overall program of HIV risk reduction. In addition to prescription medication, PrEP includes routine office visits for risk reduction counseling, STI screening, linkage with behavioral health services if needed, and provision of condoms.

**The Unique Role of the NP in Reducing HIV Risk**

Core to the nursing role is the principle of patient advocacy. The American Nurses Association Code of Ethics says “The nurse promotes, advocates for, and protects the rights, health, and safety of the patient.”\textsuperscript{19} This duty to promote and advocate for the health of our patients is coupled with the NP-independent practice core competencies of health promotion and disease prevention.\textsuperscript{20} Together, the ethical orientation and practice preparation of NPs simultaneously prepare and compel us to offer all the tools at our disposal to prevent new HIV infections in patients at risk.

**Identifying Patients at Risk**

Most NPs are well versed in collecting a sexual history and risk assessment. This element of the patient history often begins with a transitional statement such as, “Now I am going to ask you some questions
about your sexual health.” General principles for collecting a sexual history include avoidance of the use of heteronormative language (eg, presuming a male patient has sex with females), body language that communicates comfort and confidence in addressing sensitive topics (eg, sit at the patient’s eye level and avoid note taking during the interview), and reflective listening coupled with clarifying questions. A valuable tool for the NP in interviewing patients and stratifying overall HIV risk is the CDC Sexual Risk Assessment Tool.8,21

The CDC identifies MSM as a priority group to receive PrEP. It is important for the NP to consider that not all men who are sexually active with other men identify as gay, so when describing behavior rather than identity, MSM is the more appropriate term.22 But, not all MSM are high risk. Many MSM are in committed, monogamous relationships and do not require HIV prevention. Therefore, a careful sexual history is always required.

The CDC does not provide specific guidance for PrEP in transgender people. In this population, NPs should be aware that transgender women (ie, male-to-female transgender people, a person whose assigned biological sex is male but who has a female gender identity) are at very high risk for HIV infection.23 This is because of a multitude of factors that include stigma, discrimination, and lack of employment opportunities that lead to a higher rate of transactional sex, higher rates of receptive anal sex without a condom, and higher numbers of partners.24 Transgender men (ie, female-to-male transgender people, a person whose assigned biological sex is female but who has a male gender identity) constitute a smaller proportion of new HIV diagnoses nationally. However, transgender men who have sex with cisgender (gender identity same as biological sex) men are likely at increased risk of HIV acquisition.25

In any serodiscordant couple, the HIV-negative partner is a candidate for PrEP. This is particularly true for an HIV-negative female whose partner is an HIV-positive male, especially if the female partner desires pregnancy. PrEP is FDA approved (category B) for use throughout pregnancy.14 It is essential that the NP have a risk-benefit discussion with any patient who may become pregnant and chooses to use PrEP.

### The Initial PrEP Visit

Once the NP has identified a patient at increased risk for HIV and offered PrEP to the patient, the NP will optimally complete the appropriate teaching and laboratory work at this time to expedite PrEP initiation. A critical component of the initial PrEP visit is patient teaching. This teaching includes the importance of daily medication adherence and helping patients understand that PrEP is only 1 of the many tools they can use to reduce HIV risk. At this visit and all subsequent visits, the NP must empower patients to use all of the tools at their disposal to reduce their risk of HIV. These tools include mindful selection of sexual partners, use of condoms, strategies to reduce the risk of impaired decision making (eg, alcohol moderation), linkage with programs that provide safe drug injection resources, and linkage with behavioral health services if needed.

Baseline laboratory work is collected at this initial visit, including a comprehensive metabolic panel, serum testing for syphilis, hepatitis B (hepatitis B surface antigen and surface antibody), hepatitis C, and a fourth-generation HIV test. An HIV viral load should be drawn on anyone who has had sex without a condom in the past 30 days or has symptoms of acute HIV infection. This test will detect early HIV infection sooner than a fourth-generation HIV test. Gonorrhea and chlamydia nucleic acid amplification test specimens should be collected from all sites at which the patient may have been exposed (the pharynx, genital, and anal sites). A pregnancy test should be collected in cisgender women and transgender men who are at risk of being pregnant. Because FTC/TDF can reduce bone mineral density, the NP should make a clinical judgment about the patient’s osteoporosis risk, which may include ordering a dual-energy X-ray absorptiometry scan if the NP feels the patient is at high risk for osteoporosis.

Based on laboratory results, the NP can determine if PrEP is clinically appropriate. The only absolute contraindication to the initiation of PrEP is being HIV positive. PrEP can be used in a person with chronic active hepatitis B (HBV) infection, but the ongoing management of PrEP in people with chronic HBV should be in collaboration with a specialist because stopping PrEP can lead to an HBV flare.8 If a person has no active HBV infection but is
not HBV immune, vaccination should begin immediately. PrEP can be offered to patients with mildly impaired renal function but should be withheld if the creatinine clearance is less than 60 mL/min. PrEP can be used in pregnant cisgender female and transgender male patients. Osteopenia and osteoporosis do not disqualify a patient from receiving PrEP but must be closely monitored because nucleoside reverse transcriptase inhibitors reduce bone density.

Once laboratory results have been received and the patient is determined to be a candidate for PrEP, the NP should not delay in issuing a prescription for PrEP. This is typically done after a phone call to the patient to review the results. The initial PrEP prescription is for 30 tablets of once-daily FTC/TDF 200 mg/300 mg. FTC/TDF can be taken with or without food. The NP should advise the patient to initiate the prescription immediately. If the patient is unable to start the prescription within 7 days of the negative HIV test, the HIV test must be repeated before initiation. Additionally, the NP should advise the patient to avoid all high-risk sexual activity until protective levels of FTC/TDF are achieved. The time to protection after initiating PrEP depends on the site of exposure (ie, 7 days for anal and 21 days for cervical).

Side effects of FTC/TDF occur in a minority of patients, and they are most acute in the first 2 months of treatment. Side effects in this time frame may include abdominal bloating, nausea, and weight loss and, less frequently, headache, dizziness, and back pain. More severe and rare adverse effects include lactic acidosis, hepatomegaly with steatosis, new or worsening renal failure, decreased serum phosphorus, and bone loss without fracture.

The 30-day PrEP Follow-up Visit

After 4 weeks of treatment, the patient should return to the clinic for a follow-up visit. The focus of this visit continues to be overall risk reduction as well as assessment of medication adherence and tolerance. By this visit, most of the common FTC/TDF side effects have resolved (nausea, headache, and diarrhea). If the patient is tolerating PrEP and desires to continue treatment, the NP can then issue a 60-day supply of once-daily FTC/TDF 200 mg/300 mg and schedule an appointment for 2 months later.

The 90-day PrEP Follow-up Visit

Three months after the start of PrEP, the NP again works with the patient to empower him or her to engage in overall HIV risk reduction behavior. Additionally, the NP repeats a fourth-generation HIV test to confirm that there is no active HIV infection. The CDC recommends repeat bacterial STI testing at least every 6 months. Our practice is to repeat this testing every 90 days. Data suggest that screening less frequently misses a substantial number of STIs. If the initial HBV serology indicated the patient was not immune to HBV and the patient has not completed vaccination, the NP may repeat HBV testing (hepatitis B surface antigen and surface antibody). At the conclusion of this visit, the NP will issue a 90-day prescription for once-daily FTC/TDF 200 mg/300 mg and schedule an appointment for 3 months later.

After the 90-day visit, the patient returns every 3 months for ongoing risk reduction counseling, linkage with community resources for HIV risk reduction, and laboratory work. The HIV test is repeated every 3 months. Bacterial STI testing is optimally repeated every 3 months but no less frequently than every 6 months. Current CDC PrEP guidelines do not require annual screening for hepatitis C. However, consistent with CDC hepatitis C screening guidelines, we recommend screening for hepatitis C not less than annually in people who use injection drugs. Renal function testing is repeated every 6 months or more often if indicated by comorbidities, such as hypertension or diabetes.

For cisgender women or transgender men who may become pregnant, pregnancy testing should be performed every 3 months. Pregnancy is not a contraindication to PrEP, but the NP and the patient should engage in shared decision making regarding the continuation of PrEP because there are limited data on the effect of FTC/TDF on the developing fetus.

Stopping PrEP

At each visit, the NP and patient should engage in shared decision making regarding the continuation of PrEP. Social circumstances that may lead to the
discontinuation of PrEP include establishment of a stable, low-risk intimate relationship; discontinuation of injection drug use; management of substance use that previously had led to higher risk behavior; or dissolution of a serodiscordant relationship. Clinical indications that may lead to the discontinuation of PrEP include chronic nonadherence, seroconversion to HIV positive status, creatinine clearance less than 60 mL/min, medication intolerance, or alterations in bone health such as pathological fractures.

If discontinuation is because of renal disease, the medication should be stopped immediately. If the discontinuation of PrEP is because of new HIV infection, the regimen needs to be intensified and should be modified in collaboration with a health care provider experienced in HIV care. If discontinuation is because of a reduction in risk status or patient preference, the patient should be advised to stop 7 days after the last high-risk activity. Any person who wishes to resume PrEP medications after having stopped should undergo all the same preprescription evaluations as a person being newly prescribed PrEP.

Special Considerations

Pediatric Patients. At present, FTC/TDF does not carry an FDA-approved indication for HIV prevention in people under the age of 18. Studies are under way to evaluate the safety and efficacy of PrEP in at-risk adolescent populations. If a prescriber uses PrEP in an adolescent at high risk for HIV infection, it is essential to consider that presently such use is off-label, and regulations governing adolescent assent for treatment vary based on jurisdiction.

Breastfeeding. The World Health Organization and the CDC state that PrEP can be used during breastfeeding. These guidelines are in conflict with the manufacturer’s recommendation against breastfeeding during FTC/TDF treatment. The NP should share current recommendations and potential risks should a patient desire to breastfeed while using PrEP.

Emerging Evidence

On-demand Dosing. The recently concluded Action to Prevent Risk Exposure By and For Gay Men (Intervention Préventive de l’Exposition aux Risques avec et pour les Gays – IPERGAY) trial demonstrated the safety and efficacy of on-demand PrEP. This intermittent dosing regimen is not FDA approved and not in the current CDC guidelines. However, this approach may emerge over time as an alternative for people at high risk for HIV whose life circumstances make intermittent dosing a reasonable option.

New Agents. NPs familiar with PrEP often use the term interchangeably with FTC/TDF. However, there are numerous antiviral agents that may be useful as part of a PrEP regimen. Trials are under way of agents including long-acting injectable antivirals, topical microbicides, monoclonal antibodies, integrase inhibitors, and entry inhibitors. It is likely that new options for HIV PrEP will be available to patients in the coming years.

CONCLUSION

FTC/TDF-based PrEP is the most effective tool currently available to prevent new HIV infections in those at high risk for HIV. NPs that provide care to patients at high risk for HIV must have a knowledge of and ability to prescribe PrEP to fully meet these patients’ health care needs. Primary care NPs are positioned to lead the practice change that dramatically reduces new HIV infections in the coming decade.

References


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