Preexposure prophylaxis:

An emerging clinical approach to preventing HIV in high-risk adults

Abstract: The HIV antiretroviral drug emtricitabine/tenofovir disoproxil fumarate (Truvada) was recently approved as preexposure prophylaxis (PrEP) therapy for adults at high risk for sexually acquired HIV infection. This article reviews the data supporting the efficacy of PrEP, and provides other relevant data regarding the implementation of PrEP.

By Christopher W. Blackwell, PhD, ARNP, ANP-BC, CNE, AGACNP-BC

The FDA recently approved the HIV antiretroviral drug emtricitabine/tenofovir disoproxil fumarate (Truvada) as pre-exposure prophylaxis (PrEP) therapy for adults at high risk for sexually acquired HIV infection.[1] To support their approval, the FDA evaluated data from several studies that assessed the use of either tenofovir disoproxil fumarate (TDF) alone or in combination with emtricitabine (FTC) as a once-daily regimen to prevent HIV in individuals at high risk. The 2010 Preexposure Prophylaxis Initiative (iPrEx) study showed the combination regimen of FTC plus TDF was highly efficacious.[2] Data indicated that, in addition to a comprehensive preventive approach (providing condoms, monthly HIV testing, and risk reduction counseling), the

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once-daily regimen provided an additional 44% protection for the traditionally high-risk sample of men who have sex with men.[2] However, the data showed much higher levels of efficacy when adherence was considered. Those enrolled in the study that had detectable serum levels of the medication showed up to a 90% reduction in HIV transmission.[3] This emphasizes the significance of patients taking the medication every day.

The tenofovir disoproxil fumarate and emtricitabine study (TDF2) found the combination therapy was 62% effective at reducing the risk of acquiring HIV in uninfected, heterosexually active men and women.[3,4] Similar to the iPrEx study, data from the TDF2 study also indicated regimen adherence as significantly increasing its efficacy, with a 90% reduction of infection in participants with detectable serum medication levels. Another study, known as the Partners PrEP study, compared TDF with combination TDF and FTC. This trial found that among HIV serodiscordant couples (in which one partner is HIV infected and the other is not), the TDF and FTC combination reduced overall HIV transmission by 75%. This study also found efficacy to be equal in both men and women.[3,4] Again, a commonality among the studies was the finding that the efficacy of the regimen was highly related to its adherence.[3,4] The iPrEx study found a high level of efficacy variance depending on how well participants adhered to the regimen.[2] Similarly, in the TDF2 study, only half of the participants taking the TDF and FTC combination became infected with HIV, and these participants were found to have very low serum levels of the drug[3-6]; therefore, regimen adherence is essential.

Determining risk and evaluation for treatment

Risk evaluation is salient in the determination of patients' appropriateness for PrEP therapy. Clinicians must possess the skills necessary to obtain an appropriate sexual history from patients to assess their risk for sexually acquired HIV infection. Approaching the subject of sexuality can be sensitive. Clinicians should avoid any assumptions about their patients' sexual orientation and should use language that is neutral and nonjudgmental. Instead of asking "Are you married?" or "Do you have a girlfriend?" a more direct approach is preferred. Asking the patient to "Tell me about your sexual practices" or asking "Do you have sexual relationships with men, women, or both?" are both open-ended and nonjudgmental approaches that can yield a great detail about one's sexual history and facilitate the construction of an appropriate plan of care.[7] In addition, patients should be asked about their number of sex partners and the HIV status of their partner(s). Their frequency of condom usage during sexual encounters and determination of female patients' plans for pregnancy are also pertinent.[3]

Initiation of PrEP: Pretreatment evaluation[3,13]

Prior to initiation of therapy, perform the pretreatment evaluation to determine eligibility for therapy.

- Document HIV-negative antibody test:
  - Test for HIV if patient reports unsafe sex with an HIV-infected partner
  - Test for HIV if patient reports symptoms of acute HIV infection (symptoms include fever, chills, malaise, anorexia, nighttime diaphoresis, lymphadenopathy, dysphagia, nausea, emesis, diarrhea, and/or myalgia)
- In females, document a negative urine pregnancy test
- Provide education regarding possible risks of using PrEP during pregnancy
- Do not prescribe PrEP for female patients who are breastfeeding
- Confirm creatinine clearance of 60 mL/min or greater (use Cockgroft-Gault formula)
- Assess status of care in HIV-infected partners and provide referral as needed
- Screen for hepatitis B and initiate treatment when indicated
- Screen for and treat any sexually transmitted infections

PrEP therapy is indicated for patients considered high risk for sexually acquired HIV. Examples of such individuals might include a non-HIV-infected partner of an HIV-infected individual[4,8]; heterosexuals, homosexuals, or bisexuals with multiple sex partners; male and female sex workers; substance abusers; and those who inconsistently use condoms during sexual intercourse. The clinician must document an HIV-negative serostatus in the patient before initiating PrEP therapy.[3]

In addition, women should have a documented negative pregnancy test.[3] Clinicians should explain to women who are pregnant or planning to become pregnant that although there are no documented adverse reactions in infants exposed to FTC/TDF, data are not complete for children born to HIV-negative women who become pregnant while undergoing PrEP therapy.[4] PrEP therapy should not be prescribed for women who are breastfeeding.[3] If the patient's partner is HIV-positive, the current level of care that partner is receiving should be evaluated, and resources offered if necessary. Finally, confirm that the patient's creatinine clearance is 60 mL/min or greater using the Cockcroft-Gault formula.[3] Additional recommendations include screening/vaccination initiation for hepatitis B and screening/treatment for sexually transmitted infections (STIs). (See *Initiation of PrEP: Pretreatment evaluation.*)

PrEP treatment regimen

The PrEP dosage is one Truvada tablet (emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg).[3,8] The drug is taken orally with or without food and should be prescribed with a frequency of once daily.[3,8] In addition to the medication, which should be prescribed in no more than a 90-day supply, the patient should be educated about risk reduction strategies, particularly consistent use of condoms during every sexual encounter.[3]

Monitoring

The patient should have a repeat HIV antibody test performed every 2 to 3 months.[3] It is also essential that regimen adherence is reviewed at each follow-up visit (or more often if adherence is inconsistent). Safer sex education should be reinforced every 2 to 3 months, and the patient should be screened for bacterial STIs every 6 months, even if the patient is asymptomatic.[3] Finally, a negative pregnancy test should be documented at each follow-up visit.[3] If the female patient becomes pregnant during the course of therapy, she should be counseled that comprehensive data do not exist assessing long-term risk of exposure to FTC/TDF in the infant; the clinician should assist the patient in making a decision to either continue or discontinue PrEP therapy. The drug manufacturer Gilead is continuing to monitor the fetal effects of pregnant women exposed to Truvada. Therefore, clinicians are encouraged to register pregnant patients who have been exposed to the drug by calling 1-800-258-4263.[8] Three months after treatment initiation, the patient's creatinine clearance should be assessed and should be reassessed every 6 months while the patient remains on PrEP.[3] (See *Treatment monitoring recommendations*.)

Adverse events

Abdominal pain, headache, and weight loss were the most common adverse events associated with FTC/TDF uncovered in PrEP clinical trials.[8] Diarrhea also occurred, but the incidence of diarrhea was actually higher in those receiving placebo compared to treatment (7% versus 8%, respectively).[8] Serious adverse events that have been associated with the drug include renal damage, osteopenia, alteration in the distribution of body fat, and triggering of latent inflammation from prior infections (also known as immune reconstitution syndrome).[8] Life-threatening adverse events (which rarely occur) include lactic acidosis and hepatoxicty.[8,9] Because efficacy is heavily dependent on adherence, it is essential to assess patients for the presence of adverse events closely and manage any symptoms that arise.[2-5,8,10] The boxed warnings for FTC/TDF include assurance of a negative HIV antibody test in patients prior to treatment initiation (due to risk of resistance in individuals who are already infected with HIV), monitoring for lactic acidosis and severe hepatomegaly with steatosis, and careful screening and monitoring of liver function in patients with hepatitis B infection.[8] Finally, Gilead has developed resources that can be accessed by clinicians as part of the FDA's Risk Evaluation and Mitigation Strategy designed to track adverse events and ensure drug benefits outweigh their risks.[9]

Treatment monitoring recommendations[3]

- Document HIV-negative antibody test every 2 to 3 months
- Review adherence and provide safer sex counseling at each follow-up visit
- Screen for bacterial STIs, even if asymptomatic, every 6 months
- In females, document a negative urine pregnancy test and counsel pregnant patient regarding possible risks if PrEP is continued
- Assess creatinine clearance 3 months after treatment initiation and then every 6 months while on PrEP

Cost considerations

The financing of antiretrovirals for PrEP is emerging as an important healthcare policy issue.[11] A 2011 cost-effectiveness model by the CDC estimated the daily cost of PrEP at $22, which equals $8,030 per year.[11,12] Additional monitoring and screening costs per person were estimated to be $1,300 per year.[11] Unfortunately, most private insurance companies do not currently cover PrEP. The Patient Protection and Affordable Care Act requires insurers to cover preventive services with an A or B rating from the United States Preventive Services Task Force (USPSTF).[11] Therefore, a significant step toward private insurance coverage for PrEP in the United States is to nominate it for review by the USPSTF.[11] However, approval of chemoprophylaxis by the USPSTF has been challenging, as the panel has only approved 2 out of 45 proposals.[11] Consequently, cost could continue to be a significant impedance to the implementation of PrEP in those who may need it most.

Moving forward

PrEP therapy with the use of FTC/TDF is a newly approved approach to preventing HIV in individuals at high risk for sexually acquired infection. The once-daily regimen has been shown as significantly effective at preventing HIV in both men and women including heterosexual and bisexual persons. Evaluating patient appropriateness for PrEP, performing pretreatment evaluations prior to initiation of treatment, and close monitoring of therapy

are all responsibilities NPs will assume as this treatment becomes more widespread in the U.S. healthcare system. Cost of the therapy is also a major blockade to its implementation, and this will continue to be a prevalent issue in the foreseeable future.

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Christopher W. Blackwell is an associate professor and coordinator of Nurse Practitioner Programs at University of Central Florida, College of Nursing, Orlando, Fla.

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