Pharmacy and Wellness Review

January 2013

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**Truvada® Recommended by FDA Committee for Pre-exposure Prophylaxis in High-Risk HIV-Negative Individuals**

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**Abstract**

Once-daily combination tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) has received Food and Drug Administration (FDA) approval for use in pre-exposure prophylaxis (PrEP) against Human Immunodeficiency Virus (HIV) infection in high-risk individuals. In clinical trials, FTC/TDF has been shown to reduce the risk of HIV acquisition by 62 percent in sexually active heterosexual men and women. Similarly, use of FTC/TDF demonstrated a 44 percent reduction in HIV infection within the men who have sex with men population. When used compliantly and in conjunction with safe sex practices, it appears that FTC/TDF can play an important role in reducing the impact and incidence of HIV infection.

**Introduction**

On July 16, 2012, the United States Food and Drug Administration approved Truvada®, a combination of tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC), as the first drug indicated for pre-exposure prophylaxis (PrEP) against Human Immunodeficiency Virus (HIV) infection in high-risk adults. Although neither drug component is new, once-daily combination FTC 200 mg/TDF 300 mg has been shown to decrease the chance of HIV infection by approximately 62 percent. When taken as directed and used as part of a comprehensive set of safe-sex practices, FTC/TDF appears to demonstrate significant potential in reducing the incidence of HIV transmission both within the United States and worldwide.

Typical HIV patients present with varying symptoms depending on the stage of infection. In the first few weeks, an HIV infected individual may appear asymptomatic, or experience flu-like symptoms including fever, headache, rash or sore throat. As the infection progresses, plasma CD4+ counts decrease, resulting in a loss of immune function, increasing vulnerability to opportunistic infections, and ultimately leading to acquired immunodeficiency syndrome (AIDS). FTC/TDF acts as a combination reverse transcriptase inhibitor (NRTI). Both FTC and TDF are pro-drugs that are converted to active nucleoside/nucleotide analogs in the body, which then compete for incorporation into HIV DNA. Incorporation of the active drug causes termination of HIV DNA chain growth and inhibits activity of viral reverse transcriptase, which prevents disease development by blocking both viral genome incorporation into host cell DNA and viral replication.

Those at the highest risk for HIV infection include men who have sex with men, African-Americans, and young individu-
provided a 62.2 percent reduction in HIV infection as compared to placebo (p=0.03). In the as-treated analysis, data was limited to participants who became infected within 30 days of their last self-reported dose of medication, yielding a total of four infections within the FTC/TDF group and a protective efficacy of 77.9 percent (p=0.01). However, within the treatment group, mean plasma drug levels were significantly lower in participants that became infected as compared to plasma levels of participants that did not become infected (0.3 ng/mL vs 30.6 ng/mL for TDF, p=0.007; and 0.5 ng/mL vs 103.3 ng/mL for FTC, p=0.009). Therefore, these results show that while FTC/TDF can provide a significant reduction in the risk of HIV infection, its efficacy in PrEP is largely dependent on adherence to the medication regimen.2

FTC/TDF has also shown desirable efficacy of HIV prophylaxis in the men who have sex with men population. In the iPrEx study, a randomized, placebo-controlled trial by Grant et al., 2,499 HIV-negative men or transgender women who have sex with men were randomly assigned to receive one daily FTC/TDF or placebo.7 Participants were then tested for HIV infection monthly and were followed for 3,324 person-years (median, 1.2 years; maximum, 2.8 years). During the follow-up period, a total of 100 participants became infected; 36 in the FTC/TDF group and 64 in the placebo group, resulting in a 44 percent reduction in HIV infection (p=0.005).7 Furthermore, within the treatment group, plasma levels of FTC/TDF were detected in 9 percent of infected subjects, whereas detectable levels were discovered in 51 percent of non-infected subjects. Similar to other studies, these results further demonstrate the importance of adherence, as there is a strong relationship between detectable plasma levels of FTC/TDF and its prophylactic effect.2,7

The Partners PrEP, TDF2, and iPrEx studies all shared a common limitation in that each study included participants with an acute HIV infection that was missed during the enrollment process.2,6,7 The Partners PrEP enrolled 14 participants with current HIV infection of which eight received either TDF or FTC/TDF.6 TDF2 study enrolled a total of three infected participants of which two were entered into the treatment group.2 In the iPrEx study, 10 participants were found to have plasma HIV RNA after enrollment of which five had symptoms of acute viral syndrome at enrollment.7 A major concern with initiating FTC/TDF therapy in an HIV positive patient is the risk of retroviral resistance. In the TDF2 study, one enrolled HIV-infected participant receiving FTC/TDF, developed reverse transcriptase resistance mutations at high levels of approximately 100 percent, thereby limiting use of reverse transcriptase medications as an HIV treatment therapy.6 Of the participants enrolled with HIV infection in the Partners PrEP study, two developed resistance.6 To avoid the issue of resistance, acute HIV infections can be screened for, not only overt symptoms but also testing for HIV antibodies if no symptoms are present, and additional testing for HIV RNA if possible when HIV antibodies results are negative.7

It is important to recognize that each of the three clinical trials performed included a comprehensive package of HIV prevention services in addition to the FTC/TDF therapy. These services included risk reduction (RR) counseling, screening and treatment of sexually transmitted infections (STIs) and free condoms.2,6,7 Participants in the Partners PrEP study also received condom counseling and referral for male circumcision.6 The TDF2 study performed individualized counseling on RR during quarterly visits and at any other visits upon request.2 When using FTC/TDF as PrEP HIV, prevention services are an integral part of the therapy and must be included in order to best prevent HIV infections.

Special Considerations

FTC/TDF is a renally cleared drug, and precautions must be taken with patients who are using FTC/TDF for PrEP and have impaired renal function. If the patient’s renal function is <60 mL/min, FTC/TDF use is not recommended.8 The patient’s creatinine clearance (CrCl) should be measured every three months initially, then every six months.9

Based on a lack of clinical studies, FTC/TDF is not recommended for pregnant or lactating women. In the TDF2 study, women could not continue with the study if they had a positive pregnancy test; however, of the 107 pregnancies, neither the rate of pregnancy nor the rate of fetal loss differed between the study groups (p=0.56, and p=1.00, respectively).2 The Partners PrEP trial also excluded women who became pregnant but were allowed to return after the pregnancy.5 Both FTC and TDF are currently used to prevent perinatal transmission from HIV-infected women to their newborns. Currently, there is no evidence of adverse effects on fetuses exposed to FTC and TDF; however, the data is not complete because the combination of FTC/TDF has not been clinically tested yet due to pregnant women being removed from clinical studies, so health care providers should use their best clinical judgment. Pregnancy tests should be done routinely every two to three months in women taking FTC/TDF for PrEP.9

Bone mineral density loss is another side effect that must be taken into consideration. Currently, long-term studies have not been performed to determine the exact effects of FTC/TDF when used as PrEP on bone mineral density. The TDF2 study did look at bone mineral density in a subset of the participants. The results showed a decline in bone mineral density in the forearm, hip, and lumbar spine in participants who received FTC/TDF versus placebo (p=0.004 at the forearm, p<0.001 at hip and lumbar spine).2 These results do not show long-term effects of FTC/TDF on bone mineral density, and more studies need to be done to determine these long-term effects. Therefore, patients taking FTC/TDF should receive regular bone mineral density tests.

Pharmacist Information

Use of FTC/TDF as PrEP is aimed at high risk individuals including those with HIV-positive partners or those who engage in sexual activity within a high prevalence area and have one or more of the following characteristics: inconsistent or no condom use, diagnosis of STI, exchange of sex commodities, use of illicit drugs or alcohol dependence, incarceration or partner of unknown HIV status and any of the above risks.8 FTC/TDF should not be used as PrEP for
HIV if the patient is already HIV-positive or if HIV status is unknown. An HIV test must be performed before taking FTC/TDF for PrEP as well as every three months during therapy to avoid the possibility of drug resistance. At each three month visit, clinicians should test patients for hepatitis B infection and STIs. No more than 90 pills should be dispensed at a time to ensure FTC/TDF PrEP is not being taken concurrently with an undiagnosed HIV infection.

A vital counseling point for the pharmacist to emphasize to the patient taking FTC/TDF for PrEP is the importance of compliance. Medication adherence counseling should be given every time the patient comes in for no more than a 90 day supply of FTC/TDF. The Partners PrEP study, TDF2 study, and iPrEx study all discovered that detectable amounts of FTC/TDF in the plasma led to a decrease in HIV risk. In addition, another trial looking at the use of FTC/TDF as PrEP for prevention of HIV had to stop entirely due to low levels of medication adherence. Help patients develop a routine to ensure their medication is being taken properly to ensure they do not acquire HIV.

An integral part of PrEP is combining the use of FTC/TDF with other standard prevention interventions including risk-reduction counseling, the use of condoms, medication adherence counseling and testing for STIs. When it comes to RR counseling, studies have been done to identify the optimum style that results in the greatest success in preventing the spread of HIV.

Project RESPECT, a multicenter randomized controlled trial, looked into three different RR counseling styles in order to determine the most efficacious approach. Participants received either enhanced counseling (four session interviews of 200 minutes total), brief counseling (two sessions of 40 minutes total), or didactic messages (two sessions without engagement of ten minutes total). Development of STIs was lower in the enhanced counseling as well as brief counseling arm (11.5 percent and 12 percent) compared to the didactic messages arm (relative risk 14.6 percent, 0.81; 95 percent confidence interval, 0.67-0.98). These results are clinically significant in that even spending as few as two 20-minute sessions with a patient, engaging him or her through a more conversational way of counseling can improve health outcomes. Based on these results, pharmacists should make an effort to create a dialogue between their patients, particularly those at risk, about the importance of condom use as well as avoiding risky behaviors such as multiple partners, using injectable drugs and engaging in anal intercourse.

Conclusion

There is currently no cure for HIV, therefore, all forms of prevention, including FTC/TDF should be implemented to avoid later health ramifications. Currently, trials have been conducted in three populations of high-risk individuals including men who have sex with men, heterosexual individuals and heterosexual couples with one seropositive partner, showing a significant protective effect of FTC/TDF against transmission of HIV. However, the benefit is only seen in combination with safe sex practices and strict compliance. Pharmacists have an important role in patient education of proper use of FTC/TDF. In this way, pharmacists can maximize the protective effects of FTC/TDF, thereby reducing the transmission of HIV and overall impact of the disease.

References