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L|E|C|O|M Point

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Special Topics: Truvada Approved for HIV Prevention

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Current epidemiological studies show the number of new HIV infections in the US since the mid 1990s has remained approximately 50,000 per year[1]. As part of the ongoing fight to prevent the spread of HIV, *Truvada* was approved in 2004 by the U.S. Food and Drug Administration (FDA). It is a combination drug consisting of emtricitabine (FTC) 200mg and tenofovir disoproxil fumarate (TDF) 300mg[2]. As part of a comprehensive treatment approach known as Highly Active Anti-Retroviral Therapy (HAART), *Truvada* is commonly used in combination with other anti-retrovirals to treat HIV patients.

On July 16, 2012, the FDA approved the use of *Truvada* as pre-exposure prophylaxis (PrEP) in HIV-negative patients at high risk of becoming infected. High-risk includes: (1) partnerships where one partner is HIV positive (serodiscordant) and condom use is inconsistent, (2) intercourse with more than three partners in the previous six months, (3) exchanging money, gifts, shelter, or drugs for sex with a partner in the previous six months, (4) intercourse with a partner diagnosed with a sexually transmitted infection (STI) in the last six months, or (5) intercourse with a partner of unknown HIV status in the last six months[1]. Two pivotal studies support *Truvada's* use as PrEP.

iPrEx Study:

The iPrEx study was sponsored by the NIH. It was designed to evaluate the safety and efficacy of once-daily oral FTC/TDF for HIV prevention among men and transgender women who have sex with men[3]. The study was conducted in 2499 HIV-seronegative subjects. Patients received a combination of two oral antiretroviral drugs, FTC/TDF, or placebo once daily. Subjects were followed for a maximum of 2.8 years. All subjects received HIV testing, risk-reduction counseling, condoms, and management of sexually transmitted infections including diagnosis and treatment when warranted.

The study showed a 44% risk reduction in the treatment group. However, in patients with an adherence rate of 90% or more, the risk reduction increased to 73% and 92% in patients with detectable blood levels of the study drug[3]. Detectable drug concentration was considered to be an indicator of drug efficacy. A limitation of the iPrEx study was a clear definition of a minimum protective drug concentration. In the FTC/TDF group, the study drug was detected in 51% of seronegative subjects and 9% of those patients who became infected with HIV.

Nausea (2%), headache (4%), depression (3%), and weight loss (2%) were the most common side effects. One of *Truvada's* components, tenofovir disoproxil fumarate, has been known to decrease renal function and elevate serum creatinine, primarily in those with pre-existing renal impairment.

The Partners Study

The Partners Study was sponsored by the University of Washington and compared daily oral TDF to FTC/TDF. Both drugs were considered potential pre-exposure prophylaxis agents among East African heterosexual men and women in HIV-serodiscordant partnerships[4]. In this study, 4747 HIV-serodiscordant heterosexual couples were randomly assigned to one of three study groups: once-daily TDF, FTC/TDF, or matching placebo. They were followed for 36 months. The primary endpoint was seropositivity in partners previously seronegative for HIV (Partner PrEP).

Results showed a relative risk reduction of 67% in the tenofovir group and 75% in the *Truvada* group[4]. The study drugs were provided in conjunction with other HIV prevention initiatives such as HIV testing, risk reduction counseling, diagnosis and treatment for any STIs and education on proper condom use (as with the iPrEx Study). A side effect profile similar to that seen in the iPrEx study was noted.

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Safety:

Truvada has been known to have an adverse effect on bone mineral density (BMD). The iPrEx study showed no difference in BMD between the FTC/TDF group (1%) and the placebo group (<1%) (p =0.41). Effects seen were reversible upon discontinuation of the drug[5]. Patients with a known history of bone pathologies should not start *Truvada*. *Truvada* carries a black box warning for lactic acidosis and severe hepatomegaly with steatosis (fatty liver). As a result, caution should be used in patients with a history of liver disease[2]. Baseline creatinine clearance should be assessed in patients at risk for renal failure before starting the drug. Subsequently, serum phosphate levels should also be assessed in patients at risk for Fanconi syndrome due to the risk of hypophosphatemia[6].

Risk Evaluation and Mitigation Strategies (REMS) are established to guide healthcare professionals to provide the necessary education to uninfected patients. The REMS emphasizes consistent daily dosing, HIV testing every 3 months if possible, and HIV prevention strategies such as proper condom use, counseling and testing. Prescribers will be required to provide a medication guide and safety brochure for prospective *Truvada* users. In conjunction, pharmacists will be required to provide a medication guide with every filled prescription. The cost of *Truvada* is currently $1149.01 for a 30-day supply[7].

Truvada's approval marks a major stepping stone in the fight to decrease the spread of HIV. The new indication for *Truvada* as pre-exposure prophylaxis in HIV negative patients gives high-risk patients a chance to avoid infection.

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FDA Grants Approval for HIV Combination Pill

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The Food and Drug Administration (FDA) announced approval for Stribild on Monday August 27, 2012. Stribild is a once daily anti-HIV treatment developed by Gilead Sciences. Stribild is indicated and approved to treat HIV-1 infections in treatment naïve adults. Stribild is a combination product that contains emtricitabine (FTC) (200mg), tenofovir disoproxil fumarate (TDF) (300mg), elvitegravir (EVG) (150mg) and cobicistat (COBI) (150mg). FTC and TDF have prior FDA approval and are sold in combination under the brand name Truvada (FTC/TDF).

FTC and TDF are nucleoside reverse transcriptase inhibitors that interfere with the HIV viral RNA dependent DNA polymerase inhibiting viral replication. EVG inhibits the catalytic activity of HIV-integrase, thus preventing the proviral gene from integrating into human DNA. COBI inhibits enzymes of the CYP3A subfamily and enhances systemic exposure to EVG.

Stribild (EVG/COBI/FTC/TDF) was approved based on the results of two randomized, double blind, phase three non-inferiority clinical trials. 707 patients were randomly assigned to Stribild or to Atripla (efavirenz (EFV)/FTC/TDF)) once daily in the first trial and 715 patients were randomly assigned to Stribild or Truvada plus atazanavir (ATV) and ritonavir (RTV) once daily in the second trial. The studies measured the percentage of patients who had an undetectable level of HIV RNA in their blood at 48 weeks. In both trials Stribild was found to be non-inferior to the comparators. Common side effects include nausea and diarrhea. Stribild does carry the same Boxed Warning as Truvada, for lactic acidosis and hepatomegaly with steatosis.

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Letter to the Editor

Jacqueline Jourjy, PharmD, BCPS

With the recent FDA approval of Truvada for pre-exposure prophylaxis (PrEP) of HIV infection, there comes renewed hope for better control of the AIDS epidemic. Although unlikely that this pharmacologic approach to prevention will eliminate the epidemic altogether, with the limited tools and resources available to prevent and manage HIV/AIDS, this prophylactic option has gained favor in the eyes of many.

Taking Truvada once a day is only one aspect of intensive HIV prevention. Other modalities include safe sex practices, consistent condom use, comprehensive counseling, frequent HIV testing, and effective management of other sexually transmitted infections. Complete adherence to the one pill, once a day regimen is extremely important to prevent development of resistance and minimize the potential of contracting the virus.

There are several concerns regarding this new pharmacologic approach to HIV prevention. Some consider the use of Truvada for PrEP to be reckless and unjustified as this combination of antiretroviral medications is not without side effects. Others argue that by promoting the use of Truvada, individuals at risk of HIV infection will begin to neglect the use of condoms and other safe sex practices thereby sabotaging the effectiveness of this initiative entirely.

In addition to approving Truvada for PrEP, the FDA also approved a Risk Evaluation and Mitigation Strategy (REMS). One of the major concerns of using Truvada for the PrEP indication is the risk of developing drug resistance in a person who continues to take Truvada for PrEP after becoming infected with HIV. This concern is addressed under the educational goals of the REMS and is being achieved through provider training and the distribution of a medication guide. The REMS assessment plan will include surveys, monitoring the number of prescribers who complete the training and education program, and drug use data for Truvada for the PrEP indication.

LECOM School of Pharmacy
Center for Drug Information and Research (CDIR)

Hershey S. Bell, MD, MS, FAAFP
Professor, Vice President for
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The LECOM School of Pharmacy's vision is to be the innovative leader in graduating pharmacists who serve as highly skilled clinicians achieving optimal therapeutic outcomes in all aspects of pharmaceutical care. Our Strategic Plan has been written to reflect this vision. An objective for LECOM is to establish the School of Pharmacy as a leader in community education on health care topics and increase the visibility of the LECOM Center for Drug Information and Research (CDIR).

The LECOM CDIR seeks to provide unbiased pharmaceutical information and support to the entire LECOM family including healthcare practitioners, residents, students and patients. One important way in which we achieve our objective is by publishing our monthly newsletter, *LECOM Point*. Published by the team of pharmacy faculty you will meet below, The Point contains reports on new drugs and reviews on older ones using timely, independent evidence with accompanying analysis and commentary. As the LECOM CDIR expands, it is expected to become a major regional clinical resource for practitioners and patients.

MEET THE CDIR TEAM

"It is a pleasure and privilege to introduce the LECOM Center for Drug Information and Research (CDIR) team of health-science professionals and educators. Each of these faculty members serves their communities as drug information specialists. It is their expertise, collaborative efforts, and commitment to the LECOM School of Pharmacy's vision that allows the CDIR to provide drug literature education, communication and support services in an effort to ensure the safe and effective use of medications. We encourage you to visit our website and to utilize our service by submitting drug information inquiries to cdir@lecom.edu"

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