The review of pre-exposure prophylaxis (PreP) for HIV prevention

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Abstract

Human Immunodeficiency Virus (HIV) epidemic continues to represent a major global health issue. Today, there are several tools available to prevent the spread of HIV infection. However, there are several constraints to the current prevention strategies including low condom use, low acceptance of testing, low awareness of vulnerability and more emphasis on treatment. Prevention strategy is redirected towards reducing acquisition of HIV. Pre-exposure prophylaxis or PrEP is the latest groundbreaking innovation in biomedical research in the prevention of HIV transmission.The purpose of this paper is to review preexposure prophylaxis for HIV prevention including the current guidelines in the use of PreP.

Keywords: *preexposure prophylaxis, tenofovir disoproxil fumarate (TDF), emtricitabine (FTC) (Source: DeCS).*

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Una revisión sobre la profilaxis pre-exposición (PrEP) para la prevención del VIH

Resumen

El virus de la Inmunodeficiencia Humana (VIH) continúa representando un importante problema de salud mundial. Hoy en día, existen varias herramientas disponibles para evitar la propagación de la infección por el VIH. Sin embargo, existen varias restricciones a las estrategias de prevención actuales, incluyendo el bajo uso del condón, baja aceptación de la prueba, la escasa conciencia de la vulnerabilidad y un mayor énfasis en el tratamiento. La estrategia de prevención se redirige hacia la reducción de la transmisión del VIH. La profilaxis pre-exposición o PrEP es la última innovación pionera en la investigación biomédica en la prevención de la transmisión del VIH. El propósito de este trabajo fue revisar la profilaxis de pre-exposición para la prevención del VIH, incluyendo las directrices actuales en el uso de PrEP.

Palabras clave: *VIH, profilaxis pre-exposición, tenofovirdisoproxilfumarate (TDF), emtricitabine (FTC) (Fuente MeSH).*

What does this paper contribute to the wider global clinical community?

- Human Immunodeficiency Virus (HIV) epidemic continues to represent a major global health issue**.**
- There are several constraints to the current prevention strategies for HIV prevention including low condom use, low acceptance of testing, low awareness of vulnerability and more emphasis on treatment.
- Pre-exposure prophylaxis or PrEP is the latest groundbreaking innovation in biomedical research in the prevention of HIV transmission.

The Statistics

In the 21st century, the Human Immunodeficiency Virus (HIV) epidemic continues to represent a major global health issue. This disease currently affects more than 35 million people worldwide (1). In the United States alone, 1.1 million Americans are living with the HIV and there is a predicted 50,000 new cases of HIV infections every year (2).

In 18 Latin American countries, excluding Mexico reported that 1.5M people are living with HIV/AIDS at the end of 2012. An estimated 86,000 new diagnosed cases and 52,000 AIDS-related deaths (Avert, 2014). The largest number of incidence in HIV includes Brazil (530,000-660,000), Mexico (170,000), Columbia (150,000), Venezuela (110,000), Argentina (98,000) and the most severe is Belize (1.4% of its population) (3).

The Latin-American, the burden of this disease is among specific groups, such as men who have sex with men (MSM), female sex workers, intravenous drug users, and migrants (2,3). In Latin-America, about 12,0% of MSM, 6.1% of female sex workers, and 2 million people who inject drugs are living with HIV. A new trend in HIV incidence is from international migration particularly between the US and Mexico. A new link has been made between the movement of people and spread of HIV/AID and factors include: gender norms, multiple sex partners, illegal migration and low socio-economic status (3). The "machismo" culture in Latin-American limits women in negotiating on safe sex practice such as condom use. Migrants who travel alone may visit female sex works during their travel, which increases transmission to their partner. Both illegal immigrants and those with low socio-economic status may have limited access to HIV care.

Similar burden is seen in the US, particularly among the gay, bisexual, the men who have sex with men, and blacks/African-Americans and Hispanic/Latinos. The men who have sex with men community represents an estimated 4,0 % of the total US population and accounts for 78,0% of new HIV infections in men and 63,0% of the overall new HIV infection (2). Most compelling is that the greatest number of HIV infection among the MSM occurs in youngest age group (aged 13-24).

A national survey also reported that among IV drug users without HIV infection, 34,0% shared syringes in the past year, 50,0% shared their injection equipment, 69,0% had unprotected vaginal sex and 23,0% had unprotected male-female anal sex. In women, new HIV infection is attributed to heterosexual contact (24,0%) and IV drug use (16,0%). Blacks/african-americans and hispanics/latinos accounts for about 44,0% and 21,0% of new HIV infections, respectively (2).

The HIV Basics

HIV is a condition that affects the immune system particularly the T cells and CD4 cells, which weakens the body's defense to fight infection. It is believed that HIV came from a chimpanzee in Western

Africa and humans became infected by it after ingesting the infected animal. The disease can be transmitted through sexual contact, sharing contaminated needles or equipment (works), after blood transfusion of infected blood, during pregnancy, childbirth and breastfeeding, occupational exposure and rarely after organ transplantation (4).

Today, there are several tools available to prevent the spread of HIV infection. These include limiting the number of sexual partners, using condoms correctly and consistently, never sharing needles and the newer biomedical approaches, preexposure and post-exposure prophylaxis. However, there are several constraints to the current prevention strategies including low condom use, low acceptance of testing, low awareness of vulnerability and more emphasis on treatment to name a few (5). Therefore, prevention strategy is redirected towards reducing acquisition of HIV. The purpose of this paper is to review preexposure prophylaxis for HIV prevention including the current guidelines in the use of PreP.

What is Pre-exposure prophylaxis?

Pre-exposure prophylaxis or PreP is the latest groundbreaking innovation in biomedical research in the prevention of HIV transmission (2). It is defined as experimental approach to HIV prevention, which include taking antiretroviral (ARV) drugs before potential HIV exposure in order to reduce the risk of HIV infection and continued during periods of risks (5).

In short, PreP is an approach in which uninfected individuals take an ARV drug in order to build up drug concentration in their bodies so that in the event that they become exposed to the virus the medicine may reduce their chance of acquiring HIV (5) This is different from post-exposure prophylaxis, in which individuals are given the ARV drug within 3 days after exposure to HIV (5).

The drugs

Two ARV are under the category of PreP, tenofovirdisoproxilfumarate (TDF) alone or combination emtricitabine (FTC) (6). Currently, Truvada® is the only drug approved by the US Food and Drug Administrations for daily use as PreP for individuals at very high-risk of getting HIV infection through sexual contact. Truvada, an oral antiviral chemotherapeutic drug, manufactured by Gilead, is a combination FTC and TDF medication is classified anucleoside-nucleotide reverse transcriptase inhibitor (NRTI) (6). Truvada works by blocking viral deoxyribonucleic acid (DNA) elongation chain of the HIV.

The termination of this viral DNA replication results in limiting new viral replicas (viral load) and limitation of infection of nearby healthy cells (6). The drug dosage is 200mg TDF and 300 mg FTC daily with or without food (5). Warning label for the drug include new onset or worsening renal impairment, severe exacerbation of hepatitis B, lactic acidosis, and severe hepatomegaly with steatosis including fatal cases. Hepatic function test, creatinine clearance and serum phosphorus should be monitored. The use of this drug is cautioned in someone with a creatinine clearance <30ml/min or those on hemodialysis (5).

Studies on PreP

Current evidences have shown that PreP provides a high level of protection if taken correctly and consistently. Table 1 presents a quick synopsis of the most recent evidence of the use of PreP (7-15). Although PrEP was first described in 2010 in a landmark international study, Iniciativa Profilaxis Pre-Exposición (iPrex), an earlier study of 936 African women was the one of the first studies that examined the effectiveness of the drug TDF-FTC on HIV negative women (7).

Table 1. Summary of the recent studies on the use PreP in HIV prevention

Clinical trial	Participants	Drug allocation		Setting	Primary endpoint	Data analysis	Results
FHI-West Africa Study (Peterson, et al., 2007) (7)	HIV negative women (N=936)	TDF (N=469)	Placebo (N=467)	Ghana, Camaroon, Nigeria	Safety and preliminary effectiveness of TDF vs placebo	Intent-to-treat	No difference in clinical and laboratory safety outcomes between the groups. The efficacy analysis showed 2 new HIV infection in the TDF group and 6 in the placebo group. Study power was not achieved because of premature closure of two sites.
iPrEx (Grant et al (2010) (8)	HIV seronegative men or transgender women who have sex with men (N=2499)	TDF/FTC (1251)	Placebo -(1248)	Peru, South Africa, US, Brazil, Thailand, Ecuador	Safety and efficacy of the TDF/FTC versus placebo	Modified intention-to-treat	43,8% reduction in the incidence of HIV (p=0,005)
Partners PreP (Baeten et al. 2011) (9)	HIV-1 serodiscordant couples (N=4758)	TDF (N=1584) / TDF/FTC (N=1579)	Placebo (N=1584)	9 sites in Kenya and Uganda	Seropositivity in partners of previously seronegative for HIV 1	Modified intention-to-treat	82 HIV-1 infections occurred in seronegative participants (17 with TDF; 13 with TDF/FTC; 52 in placebo group.
Mutua et al., 2012 (10)	African men who have sex with men and female sex workers (N=72)	Daily FTC/TDF vs placebo (N=24/12)	Intermittent FTC/TDF vs placebo (N=24/12)	2 Centers Kenya	Safety, adherence, acceptability, HIV behavior change	Safety and adherence to intermittent PreP regimen	Safety was similar in either the daily or intermittent groups. Adherence more difficult with intermittent and post-coital dosing compared to daily dosing.
TDF2 (Thigpen, 2012) (11)	Heterosexually active men and women (N=1219)	TDF/FTC (N=611)	Placebo (N=608)	Botswana	Difference in HIV infection rates	Modified intention-to-treat	33 participants became infected (9 in TDF and 24 in the placebo group).
Fem-PreP (Van Damme et al, 2012) (12)	Heterosexually active women (N=2120)	TDF/FTC (N=1024)	Placebo (N=1032)	Kenya, South Africa, Tanzania	Safety and effectiveness of TDF/FTC in preventing HIV acquisition	Effectiveness and safety analysis	88 women became infected with HIV (33 in the TDF/FTC group and 35 in the placebo group).
VOICE (MTN, 2013) (13)	Heterosexually active women (N=5029)	Oral TDF / TDF/FTC	TDF vaginal gel	Uganda, South Africa, Zimbabwe	Safety and effectiveness in preventing sexual transmission of HIV in women	Safety and effectiveness	All three products were not effective to the women enrolled in the study.
Bangkok tenofovir study (Choopanya, et al., 2013) (14)	IV drug users (N=2413)	TDF (N=1204)	Placebo (1209)	17 treatment centers in Bangkok, Thailand	HIV infection	Modified intention-to-treat	48,9% reduction in HIV incidence (p=0·01)
Project PrePare (Hosek et al., 2013) (15)	Young MSM (N=68)	FTC/TDF (N=20) / No pill (N=19)	Placebo (N=19)	2 clinical sites in Chicago, US	To evaluate specific components of a PerP delivery protocol	Accetability, Feasibility, Acceptance and Risk Compensation	PreP is safety and well tolerated, low medication adherence (62,0%), high acceptability, and decreased risk behavior over time.

Indication

At present, PreP is only indicated for adults without symptoms of acute infection or established HIV infection in select individuals who are at very high risk for HIV infection (16). Routine assessment of sexual history is the first step towards identifying high-risk sexual behaviors for HIV acquisition (16). Table 2 presents some brief questions that health care professionals can ask to identify high risksexual practices in the past six months among high-risk individuals (16).High-risk individuals include those MSM, IV drug users, heterosexual adults and heterosexual HIV discordant couples (16). In addition, in the MSM community, PreP is indicated on any of their male partners in the past six months, who are not in a monogamous partnership but recently tested to be HIV negative.

Table 2. Risk behavior questionnaire for select high-risk individuals. Adapted from: USPHS (2014). Preexposure prophylaxis for the prevention of HIV infection in the US – 2014: A clinical practice guidelines. Accessioned on May 17, 2014

Risk assessment for MSM	Risk assessment for hetero-sexual	Risk assessment for IDU
• Have you had sex with men, women or both?	• Have you had sex with men, women or both?	• Have you ever injected drugs that were not prescribed to you by a health care provider?
• How many men have you had sex with?	• How many men and women have you had sex with?	• When did you last inject any non-prescribed drugs?
• How many times did you have receptive anal sex, in which you were the bottom with a man who was not wearing a condom?	• How many times did you have vaginal or anal sex when neither you nor your partner wore a condom?	• In the past 6 months, have you injected by using needles, syringes, or other drug paraphernalia that had already been used by another person?
• How many of your male sex partners were HIV-positive?	• How many of your sex partners were HIV-positive?	• In the past 6 months, have you been on a methadone treatment or other drug-based treatment program?
• With these HIV-positive male partners, how many times did you have insertive anal sex, in which you were the top without you wearing a condom?	• With these HIV-positive partners, how many times did you have vaginal or anal sex without a condom?	

Current CDC guidelines on the use of PreP

The CDC (2014) had issued guidelines for health providers to use when electing to prescribe PreP for HIV prevention in following select very high-risk population-the MSM, IV drug users, men and women in heterosexual HIV-discordant couple, and heterosexual adults. Each recommendation in the guidelines were given classifications based on its strength. Class I was based on randomized clinical trials with clinical outcomes or validated laboratory endpoints or both; Class II was from nonrandomized or observational cohort studies and Class III was based on expert opinions. Strengths of recommendations ranged from A considered strong to C, which were optimal (16). Table 3 presented the latest CDC guidelines with the classifications.

Table 3. Latest guidelines recommendation on the use of PreP for HIV prevention. Adapted from: USPHS (2014). Preexposure prophylaxis for the prevention of HIV infection in the US – 2014: A clinical practice guidelines. Accessioned on May 17, 2014

Classifications	Recommendations
Class IA	PreP is recommended as one prevention option for sexually-active adult MSM at substantial risk for HIV acquisition. (IA)
	PreP is recommended as one prevention option for adult heterosexually active men and women who are at substantial risk for HIV acquisition. (IA)
	PreP is recommended as one prevention option for adult injection drug users (IDU) at substantial risk for HIV acquisition. (IA)
	Active and chronic HIV infection must be excluded by symptom history and HIV testing immediately before PreP is administered. (IA)
	The only medication regimen approved by the FDA and recommended for PreP with all populations specified in their guideline is daily TDF 300mg co-formulated with FTC 200 mg (Truvada) (IA)
	HIV infection should be assessed for every 3 months while patients are taking PreP so that those with incident infection do not continue taking it causing resistance to either or both drugs (IA)
	TDF alone has shown substantial efficacy and safety in trials with IDUs and heterosexually active adults and can be considered as an alternative regimen for these populations, but the efficacy of TDF alone has not been studied among MSM. (IC)
Class II	PreP should be discussed to heterosexually active women or men whose partners are known to have HIV as one of the strategies to protect their uninfected partner during conception or pregnancy, in order for them to make an informed about the benefits and risks of PreP for mother and the fetus. (IIB)
Class III	The use of other antiretroviral medications for PrEP, either in place of or in addition to TDF/FTC (or TDF) is not recommended. (IIIA)
	The prescription of oral PrEP for coitally-timed or other noncontinuous daily use is not recommended.
	Renal function should be assessed at baseline and monitored at least every 6 months while patients are taking PrEP, and those in whom renal failure is developing do not continue to take it. (IIIA)
	When PrEP is prescribed, clinicians should provide access, directly or by facilitated referral, to proven effective risk-reduction services. Because high medication adherence is critical to PrEP efficacy, patients should be encouraged and enabled to use PrEP in combination with other effective prevention methods. (IIIA)
	Currently the data on the efficacy and safety of PrEP for adolescents are insufficient. Therefore, the risks and benefits of PrEP for adolescents should be weighed carefully in the context of local laws and regulations about autonomy in health care decision-making by minors. (IIIB)

Specific recommendation

In addition, there are specific information that health professionals need to know when prescribing PreP.

Before initiating PreP

Before initiating PreP, it is necessary to determine patient's eligibility to receive PreP. This includes confirming that the patient is at substantial and ongoing high-risk for acquiring HIV infection. If any of the sexual partners are known HIV-infected, inquire if they are receiving antiretroviral medications and assist in linkage to care as necessary.

Test the patient for acute infection if he/she presents with symptoms consistent with an acute HIV infection(16).The patient's creatinine clearance must be calculated using the recommended Cockcroft-Gault formula to confirm that it is ≥60 ml/min. Additional recommendations prior to initiation include screening for hepatitis B infection, and immunizing if susceptible or treating if active infection exists; as well as screening and treating for sexual transmitted infection (STI). More importantly, HIV testing must be and a performed and a negative HIV antibody test immediately before starting the PreP must be documented. The preferred testing to determine HIV status is to use of fourth generation HIV antibody/antigen or HIV antibody immunoassay testing (16).

At the same time, individuals must not have had any at risk activity within the past 11-14 days (16).For heterosexual women, in addition to the above recommendations, it is imperative to discuss whether they are plan to become pregnant, are currently pregnant, or plan to breastfeed. It is necessary to disclose that the safety for infants exposed to the drug during pregnancy has not been fully assessed however, present evidence have not reported harm to the infant. PreP is currently not recommended to women who are breastfeeding (16).

Starting regimen

Truvada (200mg TDF and 300mg FTC) is prescribed as one tablet daily with or without food and the patient is given only 90-day supply. Subsequent refills are given only after HIV testing confirms that the patient remains uninfected with HIV. Women must have a negative pregnancy or if pregnant the women is informed about using the drug during pregnancy. At the same time, risk reduction, counseling on PreP medication adherence and condom use are provided with each visit (16).

Follow-up

Follow-up visit is scheduled at every 2-3 months, in which an HIV testing must be performed and a negative result documented, and medication adherence is assessed. Risk behaviors are assessed and risk reduction counseling including condom use are provided. At the same time, bacterial STIs are tested at every six even if asymptomatic and treated as needed (16).Women at each follow-up must have pregnancy test performed, and if pregnant, continued use of PreP must be discussed with both the patient and her prenatal care provider. Creatinine clearance is also checked at three months after starting PreP and every six months thereafter (16).

Discontinuing PreP

There are three occasions that PreP can be discontinued: at the patient's request, for safety concerns, and if patient acquires HIV infection. Healthcare professionals must confirm HIV acquisition by performing HIV tests and establish

linkage to HIV care. If a woman taking PreP becomes pregnant, the prenatal care provider is informed of TDF/FTC use in early pregnancy and coordinate care to maintain HIV prevention during pregnancy and while breastfeeding. If active hepatitis is diagnosed at the start of PreP, consider appropriate medications for treatment of hepatitis B infection (16).

Conclusion/Implications to practice

For over 30 years, HIV/AIDS infection has become a global epidemic. Despite compelling global efforts to break the spread the disease remains a burden to all countries affected. The paradigm has shifted to making prevention is the treatment in the spread of HIV infection. PreP is the latest biomedical approach in treatment of HIV, in addition to behavioral risk reduction. This article will impart the latest evidence in HIV care. Healthcare professionals, including advanced practice nurses are involved in the care of individuals not only with known HIV infection but with those who may be at high-risk to HIV transmission.

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