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CURRENT CONTROVERSIES (P KLEINPLATZ AND C MOSER, SECTION EDITORS)

Pre-exposure Prophylaxis for the Prevention of HIV Disease in Heterosexuals

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Abstract Pre-exposure prophylaxis (PrEP) for HIV infection is gaining increased use among MSM (men who have sex with men), but HIV infection among heterosexuals is also a significant problem. Currently, one medication is FDA approved for PrEP and others are in trials. The current review will focus on the specific issues among heterosexuals as well as review the use and effectiveness of PrEP in general.

Keywords Pre-exposure prophylaxis (PrEP) · Truvada (TVD) · Tenofovir (TDF) · Heterosexual sex · HIV infection · Antiretroviral therapy (ART) · Treatment as prevention (TasP)

Introduction

Despite dramatic biomedical advances, new HIV infections continue at unacceptably high rates worldwide. According to UNAIDS, worldwide HIV prevalence in 2012 was 34 million, 50 % of whom were women. There were 2.5 million new HIV infections and 1.7 million HIV-related deaths in that year [1]. In 2011, comparing other economically similar countries, an estimated 900,000 people were living with HIV in Western and Central Europe (http://www.avert.org/hiv-aids-western-central-europe.htm#sthash.waQOC6J6.dpuf).

In many countries, heterosexual transmission is the main route of infection. Although much of the focus in the USA has been on men who have sex with men (MSM), heterosexuals are also at risk of acquiring HIV through penile-vaginal, penile-anal sexual intercourse, and sexual contact involving blood. It has been estimated that condom use is only 80 % effective in preventing heterosexual HIV transmission (C) [2]. Transmission rates vary by the sex acts involved and source patient's viral load. The CDC (D) estimates overall HIV seroconversion per 10,000 exposures to be 138 for receptive anal intercourse, 11 for insertive anal intercourse, 8 for receptive penile-vaginal intercourse, and 4 for insertive penile-vaginal intercourse. The transmission risk from receptive or insertive oral sex was considered low, but no estimate was given.

In 2010, the Centers for Disease Control and Prevention (www.cdc.gov/hiv/statistics/surveillance/incidence/index.html) reported 47,500 new infections in the US, 63 % of which were among MSM. Among women, 84 % of infections were attributable to heterosexual contact. Subgroups disproportionally hit were Black Americans with a rate 7.9 times higher than White Americans while Hispanics had a 3 times higher rate. A large percentage of infections were in younger people (31 % of new infections in people age 25–34 and 26 % age 13–24). Of those infected with HIV, 38 % of the black men reported heterosexual contact as their major risk factor (www.cdc.gov/hiv/statistics/surveillance/incidence/index.html).

In July of 2012, the FDA approved Truvada (TVD, a fixed dose combination of emtricitabine and tenofovir) for the prevention of HIV transmission based on two large studies of clinical trials in a number of countries worldwide. Truvada was already approved from the treatment of chronic HIV infection in combination with other anti-HIV drug classes. In two large international studies, TVD has been shown to reduce the risk of HIV infection by 42 % in MSM and by 75 % in heterosexual couples, respectively. If we look closer at the data, HIV prevention rates increased to 92 and 90 % for

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persons who were actually found to have levels of tenofovir in their blood, indicating adherence with the medication.

In the IPrex study ("Iniciativa Profilaxis Pre-Exposición") [3••], 2499 HIV-negative high-risk men who have sex with men were randomized to receive either TVD once daily or placebo once daily. All study participants were given HIV testing, risk reduction counseling, testing for other sexually transmitted infections, and condoms. Only 3 of 34 HIV seroconverters (previously HIV-negative men who then tested HIV positive) in the TVD group had detectable levels of the drug in their blood at the time of HIV seroconversion. It is not known if they had been taking TVD regularly.

The so-called Partners Pre-exposure Prophylaxis (PrEP) Study [4••] was a study of 4758 heterosexual African couples in sero-discordant relationships (one partner in the couple was HIV positive but not eligible for antiviral therapy, the other was HIV negative). In Partners PrEP Study, TVD was compared to tenofovir alone or placebo in a randomized double-blind placebo-controlled efficacy and safety study. All participants received safer sex practice counseling, alone and as a couple, monthly HIV testing for the negative partner, free condoms, testing and treatment for sexually transmitted diseases, and monitoring of the HIV-positive partner. Only the HIV-negative partner in the couple received either placebo or active drug. The primary endpoint was HIV infection in the HIV-negative partner. Only 3 of 12 of the HIV seroconverters in the TVD group had detectible drug levels of the drug in their blood at the time of seroconversion.

To date, TVD is the only approved medication to prevent HIV infection from sexual exposure. Truvada as PrEP is not approved outside the USA by any local regulators and in most cases remains inaccessible outside of research studies. This review summarizes the key science to date as well as ongoing challenges for the use of PrEP among heterosexuals.

PrEP for Heterosexual Couples

Globally, strategies of other chemo-prophylaxis methods for PrEP have been used in heterosexual women with mixed results. The FEM-PrEP (the Pre-exposure Prophylaxis Trial for HIV Prevention among African Women) study was conducted among women in sub-Saharan Africa [5]. In this study, PrEP with oral TVD vs. placebo found TVD to be ineffective, and the trial was halted earlier than planned. Results were potentially attributed to low levels of adherence to the medication regimen, but other possibilities are that there are differences in levels of effective prevention in different populations, social groups, or geographical locations [5]. Similar recent results were seen in the recent VOICE trial, "Vaginal and Oral Interventions to Control the Epidemic," also known as MTN-003, conducted in three African countries This was a study assessing five treatment groups (oral tenofovir alone, oral tenofovir with emtricitabine, oral placebo, vaginal tenofovir gel, and vaginal placebo gel). A 36-month maximum follow-up was planned, but this study was also halted early by the safety monitoring board. On close inspection, only 30 % of study participants had detectable drug levels, again emphasizing the challenges of medication adherence in some high-risk persons [6•].

It is widely known that suppressed viral loads in the HIV-infected partner reduce the transmission risk to the uninfected partner, this is known as TasP (treatment as prevention) [7]. It is estimated that combining antiretroviral therapy and condom use will reduce HIV transmission by 99.2 % (D).

Recent data from the 22nd Conference on Retroviruses and Opportunistic Infections (CROI); February 23–26, 2015; Seattle, Washington, produced more optimistic data on the use of different forms of PrEP in heterosexuals [8•]. A demonstration project among African HIV sero-discordant (one partner HIV positive, one partner HIV negative) heterosexual partners assessed the effectiveness of open-label PrEP, offering Truvada for PrEP as a "bridge" to antiretroviral therapy (ART) for the HIV-infected partner in the relationship (until ART initiation by the HIV-infected partner and for the first 6 months after ART is started). In other words, prior to the HIV-infected partner's ability to acquire antivirals for the treatment of known HIV infection, and for the first 6 months after his or her initiation of ART, the HIV-negative partner has access to TVD PrEP. This PrEP access group was compared to historical controls from the Partners PrEP Study, placebo arm. Authors reported a near elimination of HIV transmission in the PrEP-treated group; 21.7 new HIV infections were predicted, but only 1 new infection was observed in 440 person-years of follow-up. That one HIV transmission was found to be in a couple with poor PrEP adherence, as measured by blood level of tenofovir, in the HIV-negative person and no active ART for the HIV-infected person [8•].

Tenofovir Gel

A hopeful candidate for PrEP for women, but not approved for use in any country at this time, is 1 % tenofovir gel for intravaginal insertion. Studies demonstrate that drug concentrations are 1000-fold higher in vaginal tissues with tenofovir gel than with oral TDF [9]. Tenofovir 1 % gel has been shown in prior phase IIB trials to prevent male-to-female penile-vaginal HIV transmission; however, additional data is necessary for licensure and no version of this medication is yet available outside of clinical trials. The Centre for the AIDS Programme of Research in South Africa (CAPRISA 004) study [10•] demonstrated TDF 1 % vaginal gel reduced HIV acquisition by 39 % overall and 54 % when used consistently, when compared to placebo. Unfortunately, multi-center double-blind randomized placebo-controlled trial of 1 % TDF gel

used vaginally before and after sex in 2029 HIV-negative women failed to demonstrate efficacy; again, the poor effectiveness was attributed to poor adherence [11]. At present, there is no pharmaceutical manufacturer of this product.

Other PrEP candidates include cabotegravir (E) [12], single-agent tenofovir, and injectable forms of rilpivirine and other new compounds now in phase 2 clinical trials.

Use of PrEP Among Women

Women considering PrEP and interested in sexual contact with men are concerned about interactions with hormonal birth control, use in pregnancy, use during lactation, and the effects of other sexually transmitted diseases. It is known from previous studies in sero-discordant heterosexual couples that for each 10-fold increase in genital HIV-1, RNA levels increase the risk of both male-to-female and female-to-male HIV transmission by 1.7-fold [13]. Transmission risk is assumed highest in those who do not know they are infected and subsequently may have higher HIV viral loads.

A meta-analysis [14] including more than 18 studies compared women using depot medroxyprogesterone acetate (DMPA) vs. other forms of hormonal contraception. Women treated with DMPA were at statistically significantly increased risk for HIV infection. Relative to no hormonal contraception use, the adjusted hazard ratio for HIV acquisition was 1.50 (95 % CI 1.24–1.83) for DMPA. Women using other forms of hormonal contraception (norethisterone enanthate or oral combination products) were less susceptible to HIV infection [14–16].

A topic that deserves more focus is the use of TVD for PrEP when conception is desired by HIV sero-discordant heterosexual couples. While expert consultation is advised, the clinical guidelines suggest that when maximal suppression with ART can be achieved in the infected partner, TVD for PrEP can be considered for the uninfected partner (http://aidsinfo.nih.gov/guidelines/html/3/perinatal-guidelines/153/reproductive-options-for-hiv-concordant-and-serodiscordant-couples). It is important to reiterate that studies showing TVD may offer an additional level of protection to the HIV uninfected partner; however, guidelines stress that the utility and safety of PrEP in pregnancy outcomes have not been well validated. The complete antiretroviral suppression alone in the HIV-infected partner (TasP), the use of TVD in the uninfected partner, or the combination of TasP and PrEP has not been adequately studied or shown to be fully protective against HIV transmission to the uninfected partner [17].

TVD is classified by the FDA as a category B drug, fetal harm possible but unlikely. Nevertheless, it is considered unsafe for lactation and cessation of breastfeeding is recommended, though these concerns are primarily based on the use of the drug by HIV+ mothers (A).

Many authors have examined the role of genital ulcer disease and other sexually transmitted infections on the increased risk of HIV transmission [18]. All comprehensive PrEP guidelines (see [19] for an example) emphasize the role of testing and treating all sexually transmitted infections to help reduce HIV transmission to an uninfected partner.

Guidelines

The US Public Health Service/CDC, in addition to other international organizations (IAS, International AIDS Society), released the first federal PrEP guidelines in May 2014. PrEP, in the form of oral TVD, is recommended as a prevention option for sero-negative adults at high risk for HIV acquisition. For self-identified heterosexuals, they suggest high risk for (1) a man who has sex with both women and men (behaviorally bisexual), (2) those who infrequently use condoms during sex with one or more partners of unknown HIV status, (3) whom partners are known to be at substantial risk of HIV infection (IDU or bisexual male partner), or (4) an ongoing sexual relationship with an HIV-positive partner [20].

TVD is a known, but not FDA-approved, treatment for chronic hepatitis B virus (HBV) infection. It is unknown whether TVD would protect against HBV infection in susceptible individuals, and no claims are made by the manufacturer. Individuals with chronic HBV should be closely monitored for possible hepatitis flares when TVD is discontinued for any reason.

On July 12, 2013, the CDC updated its recommendations for prevention of HIV transmission among injection drug users, some of whom are heterosexual. The recommendation was based on the Bangkok Tenofovir Study [21], which demonstrated a decreased risk of HIV infection of 49 % overall and a 74 % reduction for those taking at least 71 % of study medication doses [21].

All guidelines underscore the importance of patient counseling about medication adherence and concomitant HIV risk reduction practices, which include encouraging condom use. Toxicities in certain populations need to be taken into account by PrEP prescribers. HIV-negative persons with a creatinine clearance of <60 ml/min should not be started on Truvada, owing to potential renal complications in patients with compromised renal function. There were no episodes of renal failure in the TVD Partners PrEP or IPrex drug trials [3••, 4••]. Early studies in HIV-positive patients receiving medications in the same class that includes the components of TVD reported episodes of lactic acidosis and liver toxicities. Neither of these complications have been seen in the TVD for PrEP trials, but vigilance is suggested. Placebo and TVD arms of the IPrex and Partners PrEP trials showed similar rates of clinical side effects, which include headache, diarrhea, depression, and sexually transmitted infection acquisition, among others. Prescribers are advised to educate themselves on potential complications and perform follow-up

labs for monitoring as suggested in the Truvada label (see http://www.truvada.com/truvada-side-effects). Psychotherapists and educators who may see these patients are also advised to be aware of these guidelines to urge potential PrEP participants to inquire about starting PrEP, to assure the PrEP participants are following up with their health-care provider in a timely manner, and to understand the limitations of PrEP. The general practice has been to test baseline hepatitis sero-status and perform serum creatinine (a marker for kidney function), HIV serology, syphilis serology, and offer other sexually transmitted infection testing every 3 months while on TVD.

Although the use of oral PrEP has been increasing in MSM populations in the USA, there is very little awareness of its benefits in other high-risk groups. Men and women who have multiple partners or are partnered with individuals who have multiple partners may use PrEP as an added layer of protection. It may help prevent HIV transmission when the condom breaks or when individuals are not sure of their partners' drug or sexual behavior. Having a discrete daily one pill option that does not need to be disclosed to a partner may empower people who exchange sex for commodities or who may not feel empowered or capable of denying sex requests.

There is concern that individuals on PrEP will eschew condoms and other risk reduction techniques, leading to an increase in other sexually transmitted infections. While little or no condom use may be an undesirable outcome for some PrEP users, it is not a reason to withhold medication from high-risk populations. It is encouraging however that rates of condom use over time were actually seen to increase for men in both the IPrex and Partners PrEP trials [3••, 4••].

Access Issues

Significant challenges to PrEP access exist. Providers who are utilizing PrEP for their patients in the USA are more likely to care for greater than 50 HIV-positive patients in their practices, be male or be self-identified as a gay-lesbian-bisexual-transgender (GLBT) person. Only 26 % of practitioners who care for HIV sero-discordant couples report prescribing PrEP ever. Of prescriptions written in 2013, 74 % were for MSM, 30 % were for women who have sex with men, 23 % were for men who have sex with women, 23 % were for HIV sero-discordant couples, and 1 % were for IVDUs [22].

Barriers to adherence may include challenges in uninfected patients who may or may not identify themselves as being at risk for HIV. The difficulty of strict adherence to daily dosing and the stigma associated with taking a medication known as part of a treatment for HIV infection are also concerns for anyone considering TVD PrEP. Privacy issues for young people who may still live at home, belief in efficacy of treatment, interest of study patients to please investigators with reports of compliance, monetary or access to health-care gains from study participation, and fear of adverse events associated with medications are other challenges to successful PrEP-HIV transmission risk reduction. In the VOICE trial [6•], despite extensive education and support from study staff, higher blood levels of active drug were associated with a higher trust in clinic staff and a belief of the efficacy of study medications. Participants with lower or no detectable drug levels had more distrust of clinic staff and feared more medication-related toxicities.

Cost of medication in the USA should not be a barrier to distribution of TVD for PrEP. Support is available on federally funded formularies, Medicare and Medicaid, as well as through most private insurances. Gilead Sciences also has a generous patient assistance program and provides no cost medication to patients with incomes up to five times the national poverty income level (https://start.truvada.com) [19]. Prescribers of TVD PrEP should educate themselves and feel comfortable with the responsibility of adequate patient follow-up. An excellent provider resource outlining all guidelines and follow-up care is available from Gilead Sciences: http://www.truvadaPrEPrems.com. This website provides materials to help health-care providers counsel and manage people safely and responsibly in the use of TVD for PrEP.

Conclusions

We now have data on the precise effectiveness of PrEP. PrEP effectively prevents the sexual transmission of HIV disease if administered and adhered to properly. Unfortunately, TVD for PrEP is only available in the USA at the time of publication of this review, and other forms of PrEP are not yet approved anywhere. Barriers to the distribution of widespread TVD for PrEP include prescriber comfort with TVD PrEP guidelines, patient follow-up considerations and testing requirements, adherence concerns, potential toxicities, and hormonal contraception considerations. The lack of PrEP studies done on heterosexual transmission in the developed world likely speaks to the high rate of MSM transmission in these countries (78 % of new HIV cases in 2010 were among MSM according to the CDC). Information gained from trials of a variety of forms of PrEP for use in heterosexual patients may lack expected efficacy as a result of social and cultural barriers in those countries.

It will be a challenge to create a support network to educate health-care providers, other professionals, and prospective patients about PrEP. Identifying providers who are comfortable discussing sexual issues and who are expert at prescribing TVD PrEP to referral sources may be necessary as well.

More study is needed into the potential effects of progesterone on HIV infectivity in the vaginal (and anal) canal and its implications. Studies with TVD PrEP in pregnancy have not been conducted and are needed. The potential to lower risks of HIV transmission for couples wanting to conceive needs to be studied further.

Future directions being studied for novel PrEP formulations include injectable formulations of antivirals, co-formulations of PrEP and hormone forms of contraception in vaginal rings, on-demand use of approved TVD PrEP formulations, and new biochemical candidates.

Successful HIV prevention with any chemo-prophylaxis requires a comprehensive approach. HIV prevention is more than identifying routes of transmission, the most appropriate drugs and formulations, and adherence support. A comprehensive understanding of barriers to HIV testing, belief systems around HIV infection in each community, and access to connection to successful HIV care is also crucial. The discussion of PrEP for prevention of HIV sexual exposure has energized the HIV/AIDS community, creating a new hope that we can transcend the difficulties associated with strict condom use as prevention. With adequate access and community support, the use of PrEP agents brings us much closer to stemming the pandemic of HIV disease and visualizing a world free of HIV and AIDS.

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Compliance with Ethics Guidelines

Conflict of Interest F. Lisa Sterman consults, speaks for, and is a stockholder of Gilead Sciences and also consults and speaks for Merck, Jansen, and ViiV Healthcare.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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