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Oral Pre-Exposure Prophylaxis (PrEP) for Prevention of HIV in Serodiscordant Heterosexual Couples in the United States: Opportunities and Challenges

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Abstract

Oral HIV pre-exposure prophylaxis (PrEP) is a promising new biomedical prevention approach in which HIV-negative individuals are provided with daily oral antiretroviral medication for the primary prevention of HIV-1. Several clinical trials have demonstrated efficacy of oral PrEP for HIV prevention among groups at high risk for HIV, with adherence closely associated with level of risk reduction. In the United States (US), three groups have been prioritized for initial implementation of PrEP—injection drug users, men who have sex with men at substantial risk for HIV, and HIV-negative partners within serodiscordant heterosexual couples. Numerous demonstration projects involving PrEP implementation among MSM are underway, but relatively little research has been devoted to study PrEP implementation in HIV-serodiscordant heterosexual couples in the US. Such couples face a unique set of challenges to PrEP implementation at the individual, couple, and provider level with regard to PrEP uptake and maintenance, adherence, safety and toxicity, clinical monitoring, and sexual risk behavior. Oral PrEP also provides new opportunities for serodiscordant couples and healthcare providers for primary prevention and reproductive health. This article provides a review of the critical issues, challenges, and opportunities involved in the implementation of oral PrEP among HIV-serodiscordant heterosexual couples in the US.

Introduction

HIV pre-exposure prophylaxis (PrEP) provides a promising new approach for slowing the spread of HIV in the United States (US) and worldwide. Oral PrEP entails providing HIV-negative individuals with oral antiretroviral (ARV) medication for the prevention of HIV acquisition. Several phase 3 clinical trials have demonstrated the efficacy of PrEP for the primary prevention of HIV-1 among specific populations.[1–4] In July 2012, the US Food and Drug Administration (FDA) approved the use of daily oral emtricitabine [FTC]/tenofovir disoproxil fumarate [TDF] (Truvada™, Gilead Sciences) as the first PrEP agent for HIV prevention among adults at high risk. The US Centers for Disease Control and Prevention (CDC) recommended that Truvada use be part of a comprehensive package of prevention services that includes HIV counseling and testing, adherence to PrEP, condom promotion, and screening and treatment of sexually transmitted infections.[5] Three groups have been prioritized for initial implementation of PrEP by the CDC: injection drug users (IDUs), men who have sex with men (MSM) at substantial risk of HIV acquisition, and HIV-negative partners within serodiscordant heterosexual couples.[5]

Despite its promise, PrEP uptake in the US has been slow.[6] Implementation of PrEP among adults at risk for HIV

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infection in real-world settings presents a number of concerns and challenges that must be resolved before the public health benefits of this approach can be realized.[7–9] Several demonstration projects are already underway to study the implementation challenges of daily oral PrEP among MSM in US cities, but less attention has been paid to PrEP implementation challenges faced by HIV-serodiscordant heterosexual couples in the US. While some barriers and facilitators to PrEP use among same-sex and heterosexual couples likely are universal, the specific issues among heterosexual couples for PrEP use in the US remain understudied and are therefore the focus of this review.

Implementation challenges for US heterosexual couples span issues of access, behavior, safety, and public health. One concern regarding PrEP implementation is that uptake of the drug will not reach the highest priority users due to barriers operating at the system, provider, and client levels.[7] Among those who initiate PrEP, drug adherence has been closely linked to efficacy,[10] and concerns have been raised that suboptimal adherence could render PrEP ineffective. Two trials among women in Africa found a lack of efficacy related to non-adherence, raising concerns about PrEP use by women in particular; however, the generalizability of these findings to US women and couples is unclear.[11–13] The levels and determinants of PrEP adherence have not been studied among HIV-serodiscordant heterosexual couples in the US.

Although the safety profiles of FTC and TDF are well-studied and generally favorable in HIV-infected persons, tenofovir has been linked to renal impairment[14] and loss of bone mineral density (BMD).[15] The safety of FTC and TDF has also been studied in HIV-negative men who have sex with men.[16] However, the safety and toxicity of oral PrEP use by HIV-negative heterosexual women and men at elevated risk for HIV infection in the US is understudied. Moreover, initiation of PrEP in those with acute HIV-infection can select for ARV-resistant strains, potentially rendering FTC/TDF ineffective as part of an ART regimen.[17] CDC clinical practice guidelines therefore recommend quarterly HIV testing of PrEP users,[5,18] but it is unclear if this rate of testing is necessary or feasible for those on PrEP.[19,20] Empirical data are also lacking on whether PrEP initiation among US serodiscordant heterosexual couples will lead to decreased condom use and potentially higher risk of infection.[19]

While the CDC recently announced support of PrEP as a national guideline in May 2014, roll-out of oral PrEP nationally still is at an early stage and health providers and other stakeholders are just beginning to face these implementation challenges. This early phase roll-out provides an historic opportunity to study the implementation process across clinical sites and identify factors at multiple levels (provider, couple, individual) associated with PrEP process outcomes—uptake/maintenance, adherence, safety, clinical monitoring, and risk behavior. At present, we have little or no knowledge to help identify and address the most pressing PrEP implementation challenges among US HIV-serodiscordant heterosexual couples. This population of men and women is very different from those included in prior PrEP trials in terms of physical and mental health, substance abuse, potential for risk compensation, relationship dynamics, conception desires, and other important factors. In this review, we examine critical opportunities and challenges involving PrEP implementation among HIV-serodiscordant heterosexual couples in the US. It is hoped that this review will help focus policy directives and guide research to provide a knowledge base to inform the development of effective PrEP interventions, evidence-based practice, and models of care delivery.

Effectiveness, Efficacy, and Potential Impact of Oral PrEP for HIV Prevention

Several pharmacological compounds and formulations have been considered for use as PrEP for HIV prevention. Daily oral combination emtricitabine/tenofovir disoproxil fumarate (FTC/TDF; Truvada™, Gilead Sciences, Inc.) and daily oral TDF have been the most widely studied and successful PrEP compounds to date. Both FTC and TDF are licensed for use in the treatment of HIV-infected patients and have favorable safety profiles for this indication.[21,22] In addition to their ease of administration, these ARV drugs are well-suited for PrEP because they act early in the HIV lifecycle, have high potency and high genital tract concentration.[23] Phase 3 clinical trials conducted primarily in Africa, and to a lesser extent in Latin America, have demonstrated various levels of overall effectiveness of daily oral FTC/TDF or TDF for the primary prevention of sexually acquired HIV-1 in high-risk populations, including MSM [iPrEx study, 44% protection (95% CI: 15, 63)[1]], sexually active heterosexual male and female young adults [TDF2 study, 62% (CI: 22, 83)[3]], and HIV-serodiscordant heterosexual couples [Partners PrEP study, 75% (CI: 55, 87)[2]]. Subsequently, a trial in Thailand showed that daily oral tenofovir reduced HIV incidence in people who inject drugs [Bangkok Tenofovir, 49% (CI: 9,72)[4]]. Two other Phase 3 trials of daily oral FTC/TDF involving mostly young, unmarried, women (FEM-PrEP study; VOICE FTC/TDF arm) showed no evidence of a risk reduction effect.[11,12]

Analyses of trial data indicate that the wide range of drug effectiveness estimates reported across studies might be due, in large part, to differences in adherence to therapy, with a clear link between adherence and protection against HIV infection. Measurable drug levels were detected in only 29% (VOICE) and 32% (FEM-PrEP) of women receiving FTC/TDF in the trials reporting little to no risk reduction effectiveness,[11,12] whereas 78% of samples in the FTC/TDF arm of the Partners PrEP trial had detectable drug levels.[24] Subgroup analyses comparing trial participants with detectable drug levels with those in the placebo control group showed high levels of protection (84–92%), indicating high efficacy with adherence.[10] Indeed, protection against HIV infection reached 94–100% among participants in the Partners PrEP trial who consistently had measureable drug levels across multiple assessments[10] or who maintained >80% adherence as measured by unannounced pill counts.[25] Given the high levels of efficacy observed across various risk groups, including MSM, heterosexual HIV-serodiscordant couples, and adult heterosexual men and women, there is little doubt that PrEP will also be efficacious in reducing HIV risk among heterosexual men and women in the US, *among those who adhere to the medication*; however, little is known regarding PrEP-related uptake, acceptability, factors supporting initial and sustained adherence, adverse effects, and behavioral risk compensation in this population.

The cost-effectiveness and potential impact of PrEP on HIV epidemics has been explored in numerous modeling studies.[26]

PrEP modeling studies have yielded inconsistent results due to differences in the complexity and underlying assumptions of the models.[26,27] A recent systematic review of these modeling studies found that PrEP implementation in South Africa could, under certain assumptions, substantially reduce HIV incidence and be cost-effective, especially if prioritized to high-risk groups. A study of HIV-serodiscordant heterosexual couples in South Africa suggested that administering PrEP to the HIV-uninfected partner could be more cost-effective than early ART of the infected partner, depending on ART coverage and other factors.[28] Abbas et al.[29] further showed that PrEP scale-up is associated with a lower prevalence of drug resistance than increased ART coverage. Modeling studies using US data suggest that PrEP could have a substantial impact on reducing HIV incidence among MSM,[30–33] but might only be cost-effective if targeted to high-risk subgroups.[32,33] No such modeling studies, however, have evaluated the potential impact of PrEP implementation in HIV-serodiscordant heterosexual couples on the US epidemic, and findings from modeling studies involving other populations and settings are not generalizable.

Women of Color, HIV-Serodiscordant Couples, and Oral PrEP

Over the past 2 decades, women around the world have increasingly shouldered the burden of the HIV/AIDS pandemic. In recent decades, the female proportion of people living with HIV/AIDS globally has risen to 50%.[34] In the US, the proportion of women among new AIDS cases has increased dramatically since 1985, from 8% to 21%.[35] This trend is most evident among African American and Latina women, who make up 27% of the female population in the US, but account for 81% of women living with HIV/AIDS.[35] AIDS remains among the top five leading causes of death for African American women aged 25–54, and it is the tenth leading cause of death for Latina women aged 35–44.[36] About 88% of all incident HIV infections among minority women are sexually acquired,[35] primarily from minority men. Multiple physiological, epidemiological, and psychosocial factors converge to place African American and Latina women at high risk for HIV.[37,38] Gender-based social inequalities, in particular, have limited women's options with regard to self-protective sexual behavior, and there is an urgent need for HIV prevention methods that empower women, such as PrEP.[39] Oral PrEP represents one of the first commercially available forms of HIV prophylaxis that can be controlled by women.

Male-to-female HIV transmission

Evidence has further shown that most women who become HIV-infected acquire the virus from a husband or other primary male partner.[34,40–49] In research conducted with substance-using African American and Latina women in East Harlem, NY, HIV incidence was 2.54 infections per 100 person years among women with a steady male partner as compared to 1.06 infections among women with casual partners and 1.39 among women with commercial sex partners, a relative risk of 2.4 and 1.9, respectively.[47] These differences reflected the relative high rate of sex and low rate of condom use in primary relationships. Similarly, Kalichman et al.[50] estimated that HIV transmission rates were nearly double for women with a primary male partner compared to women with nonprimary partners. Among Latina women in California, Wilson et al.[51] reported that women's risk of acquiring HIV from a primary partner was more than 6 times greater than from a nonprimary partner. Not surprisingly, the relative risk of HIV transmission is higher in HIV-serodiscordant couples: a recent multisite cohort study (HPTN 064) involving over 2000 minority women found an HIV incidence rate of 0.32 per 100 person years, but noted that women with an HIV-positive partner had 8 times the risk of infection compared to women with partners of unknown status.[38]

Female-to-male HIV transmission

Although fewer data are available to estimate the relative risk of HIV acquisition for men from primary female partners, it is estimated that 40–60% of all HIV-serodiscordant heterosexual couples in the US are female-positive.[47,52–54] A population-based survey of HIV-infected persons receiving care in 1996 estimated that 70% of HIV-positive women and 58% of HIV-infected men had a steady primary partner, and that 75% of these partners were HIV-negative or serostatus unaware.[55] Given recent HIV prevalence estimates,[35,56] these data indicate that there are about 200,000 HIV-serodiscordant heterosexual couples in the US Evidence suggests that among these couples, consistent condom use is low to moderate (15–50%),[47,52,54,57,58] safe injection practices among injectors are low,[59] and the majority of infected partners do not achieve viral suppression (60–80%).[54,60–62] These data support recent recommendations by the FDA, CDC, WHO, and UNAID that HIV-serodiscordant heterosexual couples represent a high priority group for PrEP implementation both internationally and domestically.[63,64]

PrEP Implementation Challenges and Opportunities for US Serodiscordant Couples

HIV-serodiscordant couples face a number of unique PrEP-related challenges and opportunities.

Uptake/acceptability/maintenance

Oral PrEP uptake (i.e., prescription rate) primarily depends on the acceptability of oral PrEP by healthcare payers, providers, administrators, policy-makers, and PrEP users and their infected partners. In this context, we broadly define acceptability (as distinct from adherence) as the degree to which prescribers and end-users are willing to implement/prescribe or use oral PrEP based on perceived need, predisposing factors, and the balance of costs and rewards relative to alternatives, in the context of social exchanges.[65] Providers in several surveys identified individuals in HIV-serodiscordant couples as the most ideal candidates for PrEP, but also noted the lack of current treatment models for coordinated care.[66,67] An important opportunity unique to serodiscordant couples is that high-priority candidates for PrEP can be identified and recruited through HIV-positive partners already linked to services. Uninfected partners of HIV-positive patients should constitute an easy group to engage for potential PrEP uptake, but 34% of providers surveyed stated that PrEP was not relevant to their practice, largely because they only treat HIV-positive patients,[67] and many

uninfected individuals in discordant relationships may not have access to regular clinical care.[68]

The acceptability and uptake of oral PrEP among HIV-negative partners within serodiscordant couples in the US is mostly unknown. In a review of research on the acceptability of ART for HIV prevention, Young and McDaid[69] found no published studies exploring PrEP acceptability and use among HIV-serodiscordant couples in the US. Studies conducted in Africa and China with serodiscordant couples found a high degree of acceptability and willingness to use daily oral PrEP if shown to be safe and effective.[70–73] In studies of US heterosexuals, African American men and women expressed substantial interest in oral PrEP, but also voiced concerns about potential side-effects, costs, partial effectiveness, stigma, low personal susceptibility to HIV, and the burden of taking daily medication.[74] PrEP acceptability was highest among African American and White women reporting the highest risk behaviors.[75,76] For HIV-serodiscordant couples, acceptability may be further shaped by partner and relationship factors such as relationship power imbalances, the desire to conceive or to protect the uninfected partner from infection, or to maintain intimacy.[55] Intimate partner violence predicted higher acceptability of oral PrEP among African American and White women in a recent telephone survey.[77]

Oral PrEP adherence

Adherence, as measured by drug levels, to daily FTC/TDF regimen in Phase 3 blinded trials ranged from nearly 80% in the Partners PrEP trial [24] to 29% in the one arm of the VOICE study,[12] with a clear dose–response relationship between PrEP adherence and efficacy across and within trials.[78–80] Clearly, sustained adherence is essential for the successful implementation and impact of PrEP. Knowledge regarding the levels and determinants of PrEP adherence among HIV-serodiscordant couples in the US is scarce.[81] In a recent survey of US women, about 80% said they could remember to take a pill to prevent HIV every day for 2 months.[77] Studies in Africa suggest that younger, unmarried, sexually active women have difficulty maintaining PrEP adherence despite concerted efforts by providers, but those in HIV-serodiscordant relationships are able to maintain much higher adherence levels. Ware et al.[73] credit the high adherence rates observed in the Partners PrEP study to the social exchange dynamics within sexual relationships: HIV discordance causes a ''discordance dilemma'' (i.e., the cost of potentially acquiring HIV against the reward of preserving the relationship) and PrEP is viewed by both partners as a solution to the dilemma—a means of safeguarding health while preserving intimacy in the relationship. HIV-positive partners were thus motivated to support PrEP adherence, which was viewed as an important enabling factor. Further analysis of ancillary data from the Partners PrEP study found that lower PrEP adherence in HIV-serodiscordant African couples was associated with younger age, heavy alcohol use, and sex with an outside partner.[25] It is not clear, however, whether these findings will generalize to US HIV-serodiscordant couples.

In general, HIV-negative partners within serodiscordant couples perceive themselves to be at heightened risk for HIV acquisition, and perceived risk has been linked to increased PrEP adherence.[10] Yet, prior studies of condom use in the US have demonstrated that a substantial proportion of discordant couples do not use condoms for protection despite their awareness of high HIV risk—so-called informed exposure.[82] Currently, we do not know whether this behavior can be attributed to condom aversion alone, or if other factors, such as fatalism, relationship commitment, or power inequity, are at play that might also reduce PrEP adherence.[83]

Dual ART/PrEP use and adherence

The role of PrEP in serodiscordant couples in which the HIV-infected partner is virally suppressed has not been adequately explored. Studies of treatment-as-prevention provide overwhelming evidence that high adherence to ART in HIV-infected individuals reduces the risk of sexual transmission to partners by as much as 96%;[84,85] achieving viral suppression in the infected partner is therefore a highly effective prevention approach for HIV-serodiscordant couples.[86] Lack of perceived utility of PrEP in the context of a virally suppressed HIV-positive partner has been expressed by some providers.[8] Yet, a 2013 survey of infectious disease physicians in the US and Canada reported that 63% would prescribe PrEP to persons with an infected partner receiving ART (compared to 90% willingness to prescribe PrEP if the infected partner was not on ART).[67] Moreover, only one in three providers would discontinue PrEP if the infected partner became virologically suppressed.

The development of models of dual ART/PrEP delivery for HIV prevention among serodiscordant couples is at an early stage. The added protective benefit of PrEP in discordant couples in which the infected partner is virally suppressed is unknown. A demonstration project currently underway in Kenya and Uganda is exploring optimized delivery of ART/PrEP for prevention using a ''bridging strategy'' in which PrEP is offered to HIV-negative partners as a ''bridge'' during the first 6 months of ART in the HIV-positive partner.[87] In the US, ART is recommended for all HIV-infected persons regardless of clinical status,[88,89] and such an approach might be employed in the first months of treatment until viral suppression is achieved in the infected partner. Yet, nationally, HIV viral suppression is achieved only by 20–40% of HIV-infected persons.[52,61,62,90] PrEP can thus offer additional protection where ART fails or viral suppression cannot be sustained.[91] Initiation of PrEP in couples in which the HIV-infected partner is on ART might affect PrEP and ART adherence in complex ways; for example, by shifting the burden of protection to the uninfected partner (therein decreasing the infected partner's motivation to take ART), improving adherence to PrEP and ART in both partners through mutually reinforcing health promoting behaviors, or leading to shared ART and PrEP medicines, which could compromise the effectiveness of these regimens.[92] In addition, some have argued that different regimens should be prescribed to the infected (ART) and uninfected (PrEP) members of discordant couples to minimize the transmission of TDF- and FTC-resistant strains.[93]

These dynamics underline the need for coordinated clinical care and dual ART/PrEP adherence interventions tailored to the needs and profile of each couple.[94] Couple-based ART adherence interventions have been shown to improve adherence in the HIV-infected partner within discordant couples by leveraging support from the uninfected partner.[95]

This support dynamic might also extend to PrEP adherence interventions involving discordant couples. Moreover, injection drug use or sexual activity outside of the primary relationship by the uninfected partner might influence PrEP retention and adherence independently of ART use by the infected partner. One study of serodiscordant heterosexual couples found that 16% reported concurrent secondary sexual partners.[96] Thus, providers need to be attentive to external risks before discontinuing PrEP in response to viral suppression in the positive partner.

Safety and toxicity

Another concern is the long-term safety of daily oral FTC/TDF use by HIV-uninfected individuals.[97] Immediate adverse effects of FTC/TDF in PrEP safety trials included nausea, vomiting, diarrhea, and headaches, but these symptoms occurred in a minority of subjects (< 10%), usually in the first month, were relatively mild in most cases, and did not lead to discontinuation.[1–3 98,99] Tenofovir has been linked to renal impairment[14] and loss of bone mineral density (BMD)[100–102] when used for HIV treatment. Tenofovir use among HIV-negative persons in some but not all PrEP trials has been associated with a small yet statistically significant decrease in creatinine clearance (an indicator of renal function), which was reversible upon discontinuation.[103,104] Having increased risk factors for renal disease (e.g., older age, diabetes) or taking additional nephrotoxic drugs (e.g., cardiovascular agents, illicit drugs) might increase the likelihood of adverse events at lower tenofovir exposures while on PrEP.[103,105,106] Several safety trials conducted in healthy HIV-negative MSM[107,108] and heterosexual adults[3,109] found small ($\sim$1%) but statistically significant declines in BMD among those taking oral PrEP compared to controls, predominantly within the first year. Although these declines were not linked to any adverse clinical events, such as bone fractures,[16] studies were of relatively short duration and sample sizes were small, affording limited power. With the aging HIV demographic in the US, more uninfected partners within serodiscordant relationships could be at increased risk for renal toxicity and adverse sequelae of bone loss from a combination of sustained PrEP use and age-related risk factors, requiring close monitoring.

The safety of PrEP use during pregnancy or breastfeeding has not been fully examined. Antiretroviral Pregnancy Registry data indicate no increase in the prevalence of birth defects due to first trimester exposure to either FTC or TDF among HIV-infected pregnant women.[110] In utero tenofovir exposure with ART during pregnancy was also found to have no effect on infant growth (i.e., congenital, renal, or growth abnormalities) or infant mortality in a study of 226 live-births involving HIV-positive women in Uganda and Zimbabwe.[111] However, in a recent study, maternal tenofovir use for at least 8 weeks in the third trimester in HIV-positive women was associated with a 12% reduction in neonatal bone mineral content at 0–4 weeks postpartum; the clinical significance of this finding is not yet known.[112]

HIV testing and clinical monitoring

CDC clinical practice guidelines for PrEP provision recommend initial screening for HIV, Hepatitis B virus, and renal function, in addition to clinical monitoring at least every 3 months for HIV, symptoms of sexually transmitted infections (STIs), side-effects, adherence, and pregnancy, and at 3 months and every 6 months thereafter for STIs and renal function.[5] CDC guidelines are also provided for discontinuation of PrEP.[5] It is not clear, however, whether this frequency of HIV testing and clinical monitoring is optimal or necessary and whether it will be sustained by providers and acceptable to those on PrEP.[19] In a qualitative study of provider attitudes towards PrEP implementation, provider opinions regarding the appropriate frequency of HIV testing and clinical monitoring of PrEP varied from monthly to every 6 months.[113]

The primary justification for frequent HIV testing is concern over the emergence of ARV resistance. Initiation of FCT/TDF for PrEP in those with acute HIV infections (or those who acquire HIV after initiating PrEP) can select for ARV-resistant HIV strains, rendering these drugs ineffective for use in treatment. However, in the PrEP clinical trials, among 105 participants in the active arms who acquired HIV after baseline, only 4 were found to have mutations associated with FTC or TDF resistance. Resistance was much more common among participants who were acutely infected with HIV at baseline; resistance developed in 6 of 11 such participants. Ruling out acute HIV infection at the time of PrEP initiation is important, but the optimal testing strategy for this is unclear. A modeling analysis found that HIV testing frequency among PrEP users would have no significant effect on the emergence of ARV-resistant variants in MSM.[20] In addition, findings from clinical trials suggest that high PrEP adherence yielded few seroconversions, low or no adherence was associated with the highest seroconversion rate but few occurrences of resistance, whereas moderate or suboptimal adherence led to an intermediate seroconversion rate and a higher risk of resistance.[10,114]

Qualitative research conducted with young heterosexual African American men and women in Atlanta found that most did not perceive repeated HIV testing as a barrier to taking PrEP.[74] Still, it is evident that many persons at highest risk for HIV, including those in discordant relationships, and who are therefore the best candidates for PrEP, also have the greatest difficulty keeping medical appointments due to impediments such as poverty, homelessness, and mental health and substance use disorders.[115] It is not clear whether relationship dynamics or factors such as the care of children will affect compliance with clinical monitoring in discordant couples.

Behavioral risk compensation

Concerns have been raised that PrEP initiation could lead to increased HIV transmission rates among some serodiscordant couples who reduced or eliminate condom use because they believe that barrier protection is no longer necessary.[116,117] Some, but not all, studies modeling the impact of PrEP on South African heterosexuals[118] and US MSM [20,30] suggest that risk compensation could negate any population benefits afforded by PrEP implementation, unless PrEP has high efficacy and optimal adherence is attained.[119] This concern hinges on several assumptions that merit reconsideration in light of current evidence.

The first assumption is that behavioral risk compensation will occur subsequent to PrEP implementation. This has been

explored in several trials, and oral PrEP use has not been associated with increased sexual risk behavior or STIs in the majority of these studies.[1–3,120–125] An analysis of longitudinal data from the Partners PrEP study found that among HIV-serodiscordant couples in the active PrEP arm, frequency of condom use and STIs did not change substantially after the effectiveness of oral PrEP was revealed to participants in July 2011.[125] Yet, assessments of risk compensation within clinical trials, including open-label extension studies, must be viewed with caution.[126] Historically, outside of clinical trials, sexual risk behaviors have been shown to increase at the population level following HIV biomedical breakthroughs.[127,128] For example, a meta-analysis found evidence of more frequent condomless sex among those who believed that taking ART provides protection against transmitting HIV.[129] A recent literature review of both quantitative and qualitative studies found an association between ARV treatment-related optimism and sexual risk behavior.[130] Qualitative studies revealed that optimistic beliefs about treatment as prevention were often adopted to justify condomless sex in HIV-serodiscordant couples[131]—a way to minimize the impact of HIV on the relationship and resolve the discordance dilemma noted above. Recent surveys suggest that similar trends might follow from PrEP implementation. HIV-negative MSM surveyed in the US viewed biomedical prevention as an alternative to using condoms, with 35–60% reporting that they would likely decrease condom use if they were to go on PrEP.[132,133] A qualitative sub-study of the Partners PrEP trial revealed that reducing reliance on condoms was a key factor predisposing heterosexual discordant couples to PrEP acceptability and adherence.[73] In a study involving STD clinic attendees in South Carolina, nearly half of those surveyed reported that it would be ''very difficult'' to both use condoms and take daily pills to prevent HIV infection.[134] No empirical studies have thus far examined the levels or correlates of behavioral risk compensation in US heterosexual couples subsequent to PrEP initiation.

A second assumption underlying the concern over PrEP-related risk compensation is that condom use is common within serodiscordant couples, and therefore the potential for reduction in condom use is substantial. While this may be the case for HIV-serodiscordant couples in Africa, with whom efficacy trials were conducted, it may be less of a concern for US discordant couples. Although evidence regarding condom use behavior in US HIV-serodiscordant couples is scarce, available evidence indicates that about 25% report never using condoms during intercourse, more than half use condoms inconsistently, and only 10–30% report consistent condom use.[47,52,54,57] Research has shown that negative attitudes toward condoms are particularly common in the context of close sexual partnerships due to the desire for intimacy and pregnancy intentions.[135,136] If condom reduction occurs among PrEP-using couples, changes in HIV transmission rates will largely depend on the balance between the degree of condom use reduction and PrEP adherence.

This balance relates to a third assumption, which is that use of male latex condoms provides superior protection from HIV infection than does daily oral PrEP. However, when adherence is high and sustained, daily oral PrEP (FTC/TDF) has been shown to be 90–100% efficacious at preventing HIV transmission in serodiscordant African couples.[10,24,25] This level of protection is equal or superior to male latex condoms, which have been shown to be 85–95% effective at preventing HIV transmission.[137,138] PrEP does not, however, protect against other STIs, which could weaken its effectiveness, given that STIs are known co-factors for HIV.[139–141] A study involving 535 HIV-serodiscordant African American couples found that 14% self-reported having a STI in the past year.[54] Clinicians will need to closely monitor and implement strategies to promote condom use, test for HIV and STIs, and attain optimal levels of PrEP adherence in HIV-serodiscordant couples.

Conception and contraception

PrEP conveys both opportunities and challenges for heterosexual HIV-serodiscordant couples wishing to conceive without transmitting the virus. About one-third of HIV-serodiscordant heterosexual couples in the US desire to have children.[142] Even among discordant couples able to maintain consistent condom use, natural conception involves planned unprotected intercourse. In lieu of sperm washing and other advanced techniques, a harm-reduction approach to reproductive counseling is designed to reduce the risk of HIV transmission during conception for HIV-serodiscordant couples.[143] Methods include home artificial insemination (for female-positive couples), virally suppressive ART for the infected partner, condomless sex only during peak fertility, and screening and treatment for STIs. Use of PrEP periconception and during pregnancy by the uninfected partner provides an additional option for reducing the risk of HIV transmission.[55,144] Although TDF and FTC/TDF exposure in early pregnancy has not been linked to increased rates of birth defects when used either for ART or PrEP,[145,146] evidence is limited on the safety of PrEP for infants exposed during breastfeeding.[147]

On the flip side, more than half of HIV-serodiscordant heterosexual couples in the US want to avoid pregnancy. Condoms can help prevent both unintended pregnancy and HIV transmission in serodiscordant couples, but, as noted, the use of condoms has been limited in this group. Among alternative reversible contraceptive methods, hormonal contraception (HC) is the most widely used worldwide.[148] Although the prevalence of HC use among women of reproductive age in HIV-serodiscordant relationships is unknown, about 37% of married or cohabitating contracepting women in the US use HC.[149] One concern in the literature is that HC use might increase the risk of HIV transmission;[150,151] although observational studies addressing this question have yielded conflicting results,[152] the majority of pharmacokinetic studies have found no link between HC use and viral load in HIV-infected women.[150] Another concern is that the long-term combined use of tenofovir-containing PrEP and some progesterone-based hormonal contraceptives, such as depot medroxyprogesterone acetate, which has been linked to reductions in BMD,[153] might exacerbate the risk of bone loss and fractures in women.

Drug costs

The annual cost of daily oral Truvada/PrEP is estimated at $17,000 USD per patient in resource-rich settings.[154] Given that the majority of those at highest risk for HIV are also among the most economically disadvantaged, the cost of

PrEP will need to be covered by private and public payers. With few exceptions, state AIDS Drug Assistance Programs (ADAPs) have not provided funds for oral PrEP given their mandate to serve HIV-infected individuals.[155] Gilead Sciences, the maker of Truvada, has a Medication Assistance Program to help qualified individuals access the drug, but its utilization has been minimal. Many private health insurers are covering Truvada for PrEP[156] and Truvada has been added to a growing number of state Medicaid formularies, but it is not clear if ancillary procedures or counseling services will also be covered. Gilead recently announced an agreement with the Medicines Patent Pool to allow companies to make less expensive generic forms of the drug in return for a small royalty.[157] These trends suggest that current cost barriers will dissipate over the next few years, making PrEP more affordable and accessible to those at highest risk for HIV. Notably, there is some evidence to suggest that in the US, marriage is a significant predictor of having health insurance, especially for women.[158–160] El-Bassel et al.[54] reported that 75% of individuals within HIV-serodiscordant African American couples had some form of health insurance coverage.

Research Gaps

Although the efficacy of daily oral PrEP for HIV prevention in serodiscordant couples has been established, implementation research examining uptake, adherence, long-term safety, clinical monitoring and risk compensation among US HIV-serodiscordant heterosexual couples is lacking. Successful provision of PrEP in this group will require an understanding of factors operating concurrently at multiple levels that facilitate or impede implementation. Provider-level factors such as provider attitudes, PrEP policies, programs, and resources, and clinical site characteristics will influence PrEP outcomes. In addition, attitudes and characteristics of PrEP candidates and users, and their HIV-positive partners, as well as the dynamics of their relationship, will have an effect on PrEP implementation. Fundamentally, we know little about US HIV-serodiscordant couples' knowledge and attitudes toward PrEP.[55] Little is also known about community norms regarding PrEP provision within discordant relationships, which will likely play a role in successful implementation.

Primary care, family planning, and STD clinics treating HIV-positive patients are ideal settings for the provision of ART/PrEP to discordant couples, because they can coordinate treatment of both members of the couple. Clinics specializing in HIV care are also potential sites of delivery, but generally do not treat HIV-negative persons and may increase the likelihood of HIV-associated stigma among potential PrEP clients. A major challenge will be to identify and engage potential PrEP candidates with HIV-positive partners who are either undiagnosed or not linked to care. Thus, research is needed on optimal methods for providers in different settings to identify, engage, communicate with, and provide care for potential PrEP users and their HIV-infected partners.[7,55] Such couple-based counseling and provision of care, while not uncommon in sub-Saharan African countries, is a relatively untapped approach in the US. Research devoted to ethical and confidentiality issues surrounding couple-based PrEP therapy is also paramount. Relatedly, we do not currently have sufficient data to formulate a model of care delivery for HIV-serodiscordant couples that strikes an optimal balance between provider/consumer burden and individual and public health. For example, evidence is needed on the severity and frequency of adverse events, levels of adherence, and occurrence of PrEP-related resistance in discordant couples to evaluate whether current clinical monitoring guidelines should be modified.[23]

Of particular importance, data on levels of PrEP adherence, optimal strategies for monitoring adherence, and the factors that influence adherence, including timing of dosing, among HIV-serodiscordant couples are also lacking. We do not know whether the high levels of PrEP adherence observed in the Partners PrEP trial will manifest in US couples in clinical settings. There is also a need for the formulation of theories to guide the development and testing of adherence counseling interventions for PrEP and dual ART/PrEP use in discordant couples.[79,161] Research exploring the introduction of innovative methods for measurement and intervention with adherence, such as the use of mobile technology, in a manner that leverages couple relationship dynamics is also needed. Although the safety profile of FTC/TDF for ART is well-defined, less is known about the long-term safety of daily oral PrEP in HIV-negative heterosexual adults in the US, including women taking hormonal contraceptives, and adults on nephrotoxic drugs, or who have chronic diseases, mental health or substance use disorders, or who experience food scarcity, fatigue or chronic stress.[79,106] More research is also needed on how PrEP-related side-effects and health risks will be perceived by and influence the behavior of HIV-uninfected partners in exchanges with providers and infected partners. It is essential to obtain additional data on the safety of tenofovir-containing PrEP to infants exposed during pregnancy and breastfeeding, so that providers can inform couples of the benefits and risks of PrEP use for conception.[55] In addition, no data currently exist on whether PrEP use within HIV-serodiscordant heterosexual couples in the US will lead to changes in sexual or drug-related risk behavior, or on the structural, dyadic, and individual level factors that might predict such changes, or whether different gender-related factors may be at play in male-positive compared to female-positive serodiscordant couples.[73] Finally, modeling studies are needed to evaluate the potential impact and cost-effectiveness of PrEP provision to serodiscordant couples on the HIV epidemic in the US, at the local and national levels.

Conclusions

Daily oral PrEP is an efficacious method for the primary prevention of HIV transmission to uninfected partners of HIV-positive individuals; as such, it represents a paradigm shift in HIV prevention science that has specific relevance and consequences for women and serodiscordant heterosexual couples. In addition to the opportunities afforded by PrEP for safer conception and the prevention of HIV through sexual and drug-related transmission, a number of challenges and critical questions remain involving PrEP implementation in US HIV-serodiscordant couples. These include the development and evaluation of optimal strategies for PrEP-related outreach, uptake, clinical monitoring, and adherence, as well as evidence regarding long-term safety, effects on risk behavior, and ethical concerns. Successful integration of PrEP into comprehensive prevention programs for HIV-serodiscordant couples

will require innovative models of care delivery that address couple dynamics and involve couple-based counseling and coordinated ART/PrEP provision. Fundamental to benefiting from the opportunities and addressing the challenges of PrEP implementation in US serodiscordant couples are the important roles played by partners, relationship dynamics, and gender issues on PrEP-related perspectives, behaviors, and outcomes, which have received little attention to date. Demonstration projects involving PrEP implementation among HIV-serodiscordant heterosexual couples in the US are urgently needed to address these research gaps.

Novel conceptual frameworks formulated to guide PrEP research involving US serodiscordant heterosexual couples are also needed. Such models must incorporate critical determinants of PrEP outcomes at multiple levels—provider, dyads, PrEP user, and HIV-positive partner. Identification of potentially modifiable factors at multiple levels that enable or impede PrEP implementation will help inform the development of effective and efficient interventions and programs to maximize the benefits of PrEP for HIV-serodiscordant heterosexual couples in the US.

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