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Periconception pre-exposure prophylaxis to prevent HIV transmission: benefits, risks, and challenges to implementation

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Abstract

HIV-serodiscordant couples face complicated choices between fulfilling reproductive desire and risking HIV transmission to their partners and children. Sexual HIV transmission can be dramatically reduced through artificial insemination and sperm washing, however most couples cannot access these resources. We propose that periconception pre-exposure prophylaxis (PrEP) could offer an important, complementary therapy to harm reduction counseling programs that aim to decrease HIV transmission for couples who choose to conceive.

In this paper we describe the potential benefits of periconception PrEP and define critical points of clarification prior to implementation of PrEP as part of a reproductive health program. We consider sexual transmission risk, current risk reduction options, PrEP efficacy, cost, adherence, resistance, fetal toxicity, and impact of PrEP counseling on entry into health services. We address PrEP in the context of other periconception HIV prevention strategies, including antiretroviral treatment of the HIV-infected partner. We conclude that, should PrEP prove safe and efficacious in ongoing trials, periconception PrEP may offer a useful approach to minimize risk of HIV transmission for individuals of reproductive age in HIV-endemic countries.

Keywords

HIV; reproduction; fertility; serodiscordant couples; HIV prevention; HIV transmission; antiretroviral prophylaxis

In sub-Saharan Africa, the majority of new HIV infections occur in women of child-bearing age [1]. An extremely high risk of contracting HIV lies within stable sexual partnerships: seronegative partners within HIV-serodiscordant couples face a transmission risk that can exceed 10% per year. Population surveys and mathematical models estimate that transmission within stable heterosexual serodiscordant relationships may account for >60% of new HIV infections in Africa [2, 3]. HIV prevention programs focus on condom promotion as the primary method to prevent HIV transmission in sexually-active serodiscordant

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heterosexual couples. However, reliance on condoms does not acknowledge the strong psychological, social, and economic motives that underlie couples' desires to have children. New HIV-prevention strategies are needed to address the circumstances and reproductive goals of HIV-serodiscordant couples.

Matthews *et al.* recently proposed a patient-centered, harm reduction approach for counseling HIV-affected couples who want to have children [4]. This model offers behavioral strategies to minimize sexual and vertical HIV transmission risk while meeting individual fertility goals. Periconception pre-exposure prophylaxis (PrEP) could be a potential component of a comprehensive risk-reduction reproduction counseling program. With periconception PrEP, the seronegative partner would take antiretroviral drugs during periods of attempted conception. Results from ongoing clinical trials evaluating the safety and efficacy of PrEP for preventing HIV transmission are expected within 1–3 years.

In this paper we discuss the risks, benefits, and potential role of periconception PrEP for HIV-serodiscordant couples having unprotected sex with intent to conceive. We address PrEP in the context of other periconception HIV prevention strategies, including antiretroviral treatment of the HIV-infected partner.

Fertility desire supports a harm reduction approach to reproductive counseling

Couples in which one or both members are HIV infected face complicated choices between fulfilling reproductive desires and risking HIV transmission to their partners and children. Observational and cross-sectional studies in the US, Europe, and southern Africa report that 20–50% of HIV-positive individuals desire children. Improved availability of antiretroviral therapy (ART) may further increase fertility desires. [5–12]

Childbearing decisions are psychologically profound and are further influenced by social, cultural and economic factors particular to resource-limited settings. Infertility is a well-recognized cause of abandonment, abuse, and divorce, and in many communities women who do not have children are isolated and stigmatized [13–15]. The social, cultural, and economic value of child-bearing drives girls to strive for early pregnancy to demonstrate fertility and increase their marriage potential [16, 17]. In addition, lack of social programs to support older persons in resource-limited settings may influence desire for children[18, 19].

A harm reduction approach to reproductive counseling aims to lower the risk of infection for HIV-serodiscordant couples who want to pursue having children despite the risks [4]. Different strategies are available based on whether the man or the woman is infected (Table 1).

Couples composed of an HIV-negative man and an HIV-positive woman can be taught home artificial insemination, timed to the woman's fertile period. While this is likely to reduce transmission to zero, the acceptability of this approach has not been studied, particularly in resource-limited settings. For couples composedof an HIV-positive man and an HIV-negative woman (or couples with an HIV-positive woman who are unwilling to practice artificial insemination), informed natural conception is the only option, with use of adjunctive biomedical strategies to minimize risk. These strategies include delaying conception attempts until the HIV-positive partner is on ART with an undetectable viral load, receiving treatment for sexually transmitted infections (STIs), and limiting unprotected sex to peak fertility. This strategy of managed conception in the setting of full viral suppression in the positive partner can minimize, but likely does not fully eliminate, HIV transmission risk [20–22]. In resource-limited settings, this strategy is constrained by

guidelines that limit use of ART to HIV-infected persons with CD4 counts below thresholds of 200 or 250 cells/mm^3 and by lack of viral load monitoring. More technologically-intensive options, including sperm washing (process whereby sperm are separated from seminal fluid in the laboratory then inserted into the vaginal canal) which has been shown to minimize male-to-female transmission of HIV[23], are neither geographically nor economically accessible in most areas of the world.

Pre-exposure prophylaxis to prevent HIV transmission (PrEP)

With PrEP, an HIV-negative individual takes antiretroviral medications to maintain blood and genital drug levels sufficient to prevent HIV acquisition, with a postulated mechanism of preventing initial viral replication. The recent introduction of potent antiretrovirals with low incidence of side-effects, long half-life, and excellent genital tract penetration has made PrEP a potentially feasible option for reducing HIV transmission. Tenofovir disoproxil fumarate (TDF or Viread®, introduced in 2001) and co-formulated emtricitabine/tenofovir disoproxil fumarate (FTC/TDF or Truvada®, approved in 2004), effectively prevented transmission in macaque SIV/SHIV mucosal challenge studies [24]. One phase II study, among high-risk women in West Africa, demonstrated safety of tenofovir for longer-term use in HIV-negative women [25].

Five efficacy trials of TDF or FTC/TDF as PrEP are underway, including two enrolling African women and one enrolling African HIV-serodiscordant heterosexual couples [26, 27]. If current studies demonstrate PrEP efficacy and safety, chemoprophylaxis could play an important role in preventing periconception HIV transmission among serodiscordant couples with an HIV-infected partner not yet eligible for, failing, or not taking antiretroviral therapy. PrEP could plausibly serve to further reduce periconception transmission risk when the HIV-positive partner has ART-mediated viral suppression. Potential benefits and risks of periconception PrEP use are summarized below.

Primary Benefits

Minimize horizontal transmission

Observational studies suggest that most new HIV infections in sub-Saharan Africa occur within stable sexual partnerships [3, 28]. While few studies have examined what proportion of transmission occurs in the context of intentional procreation, serodiscordant couples attempting to procreate comprise a particularly high-risk group for HIV transmission [2, 3,10]. PrEP may be a useful adjunct for serodiscordant couples when uptake and adherence to other periconception behavioral risk reduction strategies is incomplete.

A pilot study by Vernazza and colleagues supports the proof of concept for periconception PrEP. Among 21 Italian male-positive serodiscordant couples who practiced hormonally-timed, unprotected intercourse during pre-exposure tenofovir prophylaxis, the seronegative female partners achieved a 50% pregnancy rate with no seroconversions or adverse events among newborns [29, 30]. Notably, for all couples in this small series, the HIV-positive partner had plasma HIV suppression on ART.

Autonomy of administration

Women account for the majority, and a growing proportion, of incident HIV infections in endemic areas. Currently recommended sexual HIV prevention strategies for women include abstinence and condom use; both require the willingness of male partners and neither allows for conception. An HIV-negative woman may have difficulty requiring that her partner initiate ART and maintain a controlled viral load prior to conception, or in having direct knowledge of his ART adherence or viral load. Periconception PrEP may offer a female-

controlled protective option independent of her partner's initiation of, adherence to, and viral suppression with ART.

PrEP and anal sex

An ongoing trial will assess the efficacy of oral PrEP for prevention among men who have sex with men [31]. In addition, limited information on efficacy of oral PrEP and and anal sex will be obtained from the minority of African heterosexual women who report anal sex in three ongoing trials of heterosexual women and couples. We propose periconception PrEP in the context of intended pregnancy and would continue to recommend barrier protection in the setting of anal sex, as most efficacy data will be obtained about PrEP and risk of HIV infection from anal sex exposure from men who have sex with men.

PrEP for men in female-positive serodiscordant couples

The safest conception option for HIV-negative men partnered with HIV-positive women is artificial insemination, which eliminates the risk of transmission. However, this option may not be acceptable to all couples and may not be feasible in all settings. PrEP - coupled with male circumcision, timed conception, STI evaluation and treatment, and viral load suppression of the positive partner - offers an alternative means of mitigating transmission risk in unprotected vaginal intercourse.

Secondary benefits

Increased HIV testing and linkage to care

Comprehensive reproductive counseling programs that offer risk reduction strategies, including PrEP if efficacious, may create an important entry point to draw individuals and couples into HIV testing, treatment and prevention opportunities. Voluntary HIV counseling and testing (VCT) uptake is a major bottleneck to expanded secondary prevention efforts and ART access, with only 12% of men and 10% of women in 132 high-prevalence countries knowing their HIV status [32]. Later diagnosis of HIV is associated with higher mortality. In addition, for HIV-serodiscordant couples who are unaware of their serostatus, couples VCT has been associated with behavioral risk reduction [33–40]. ART to prevent mother to child transmission (PMTCT) also remains underutilized [1]. A program that acknowledges couples' desire for children and offers novel prevention strategies may increase HIV testing, early linkage to PMTCT programs for HIV-positive women, and circumcision for HIV-negative men.

Risks

If PrEP is shown to be effective in preventing HIV acquisition, several important uncertainties and challenges to the provision of periconception PrEP will remain. These include knowledge of optimal dosing regimens for short-term use, large-scale data on teratogenicity, considerations of cost, and full understanding of adherence, viral resistance, and behavioral risk compensation outside of clinical trial settings. Data from ongoing trials will guide further research related to these issues. Offering limited prophylaxis at a focused, high-risk time, eg. periconception, has advantages with respect to these risks (less fetal exposure, less cost, potentially fewer adherence challenges) compared to long-term, daily PrEP.

Safety

PrEP teratogenicity is central to the risk-benefit analysis of periconception PrEP use. Animal models suggest that prolonged exposure to high-dose tenofovir can decrease bone density and lead to growth restriction in infant macaques [41]. However, studies of physiologic dosing

in macaques and rodent models have shown no evidence of fetal damage [42, 43]. The most recent report from the antiretroviral pregnancy registry showed no evidence of increased birth defects among 678 infants born to HIV-infected women who took tenofovir during their first trimester [44]. More detailed retrospective studies have also failed to show deleterious effects in infants or mothers [43–45]. Currently, tenofovir is an FDA category B drug (no evidence of risk in humans) and the World Health Organization recommends tenofovir–based therapy as an alternative to zidovudine (AZT) in pregnant women [46]. Ongoing clinical trials (of tenofovir-based PrEP and PMTCT strategies) and post-marketing data will further elucidate the potential risk of early fetal exposure. While additional data are pending, PrEP that is limited to periods of conception combined with pregnancy testing will ensure limited fetal exposure.

There is greater experience with the perigestational use of other antiretroviral agents, such as AZT or lamivudine (3TC), which are less costly and widely-used in resource-limited settings. Some argue for consideration of these agents in PrEP [47]. Challenges with these agents include a low barrier to resistance and a shorter half-life. Current PREP efficacy trials do not include these compounds, although most trials include a compound closely related to lamivudine—emtricitabine, in co-formulation with tenofovir. The efficacy of these agents in preventing HIV acquisition will remain speculative.

Adherence

Should PrEP prove efficacious, adherence to a prophylactic daily medication may be problematic. Whether high levels of adherence to ART as treatment will be replicated in HIV prevention is unclear [48–50]. While ART is associated with profound improvements in health status for HIV-positive persons, PrEP confers no clinical improvements in HIV-negative persons and may confer side effects. The net balance of PrEP adherence motivators, facilitators, and barriers may lead to lower levels of adherence for PrEP compared with ART. Indeed, in the phase II study of PrEP among high-risk women in West Africa, daily tenofovir adherence was estimated at only 60% [25]. Adherence is being studied in ongoing PrEP trials

However, periconception PrEP may provide fewer barriers to adherence compared with standing PrEP. Most importantly, this would be a shorter-term commitment offered within the context of a comprehensive reproductive health program. Eliminating the need for daily medication and linking pill-taking to a particular activity (and the goal of pregnancy) may improve adherence. Clinical trial data suggest problems with adherence to coitally-dependent methods, such as diaphragms and microbicides [51–53].

Resistance

PrEP is unlikely to prove 100% effective. Hence, individuals may acquire HIV while taking PrEP, and those who continue PrEP with tenofovir monotherapy or tenofovir/emtricitabine dual therapy during unrecognized acute infection, may not achieve viral suppression in the setting of a high viral load and may select for resistance mutations. Emtricitabine commonly selects for the M184V mutation which confers high resistance to emtricitabine and lamivudine. This selection occurs rapidly, on the order of weeks [54]. Tenofovir most frequently selects for the K65R mutation, resulting in intermediate intra-class NRTI resistance; this mutation develops on the order of months [55]. However, both the M184V and K65R mutations are associated with a significant decrease in HIV replication capacity and hypersusceptibility to zidovudine. While awaiting data from ongoing PrEP trials on the prevalence and clinical significance of resistant mutations, it is clear that identifying seroconversion early will be crucial and highlights the need to administer PrEP in settings

where frequent testing will be available to identify incident HIV infections and stop PrEP promptly.

Pill-sharing also risks development of resistant virus among infected partners and increases the probability of the uninfected partner being exposed to resistant virus. Modeling studies suggest that existing resistance in circulating HIV-1 strains in sub-Saharan Africa should not affect PrEP efficacy [56].

Cost

Cost will pose a major barrier to deployment of chronic PrEP for HIV prevention. Ongoing trials study the effects of newer drugs, principally TDF and FTC/TDF. A recent cost-effectiveness study of daily PrEP with FTC/TDF for a men-who-have-sex-with-men population in the US predicted a cost of $298,000 per year of life gained [57]. This was driven by non-generic FTC/TDF (Truvada) cost at $724 per month and could be attenuated substantially if discounted drug pricing were available or generic formulations used [58]. More detailed evaluation suggests that if drug costs diminish or if the population were at higher risk the intervention could prove cost-effective. Time-limited periconception PrEP for serodiscordant couples in HIV-endemic settings, may be a more cost-effective approach for use of PrEP to prevent HIV transmission.

Regardless of drug price, programmatic costs of drug administration, HIV testing, and safety lab monitoring in HIV-negative individuals will be high. Mathematical models suggest that PrEP is likely to be cost-effective in resource-limited settings, but the costs and barriers for rolling out PrEP will be substantial [59]. The anticipated secondary benefits of enhanced HIV testing and increased uptake of other HIV prevention and treatment services may improve cost-effectiveness.

Behavioral Risk Compensation

Risk compensation occurs when individuals modify behavior in response to an altered perception of the probability of harm [60]. Mathematical modeling suggests that if PrEP (or any preventive intervention) results in increased risk behavior, benefit will be tempered [59, 61]. While users of biomedical prevention strategies, such as PrEP, may be prone to risk compensation, participants in vaccine, microbicide and post-exposure prophylaxis trials have not shown increased risk behavior to date [51, 62–64]. Ghanaian women in the tenofovir phase II PrEP trial did not increase self-reported sexual risk behavior [65]. Male circumcision trials have shown more variable changes in risk in the context of significant counseling and follow-up [60]. However, behavior in trials does not necessarily mimic normal life patterns. Behavioral counseling to minimize risk compensation will be an essential component to any biomedical prevention strategy. Periconception PrEP may offer a novel strategy to recruit at-risk, seronegative individuals into risk reduction counseling.

Treatment-as-prevention: the role of suppressive ART

Suppressive ART for the HIV-infected partner appears to be highly effective) strategy for reducing transmission in the setting of unprotected heterosexual sex, based on observational studies. A recent meta-analysis showed no recorded transmissions between couples with viral load suppression below 400 copies/ml.

Based on this data, mathematical models predict one transmission event per 79 person-years among serodiscordant couples on ART with viral load suppression [21].

For HIV-infected partners who meet clinical or immunologic criteria, ART should be initiated for their health, as well as for minimization of sexual transmission [66]. Recent

observational data suggest that those who initiate ART at CD4 counts between 351–500 cells/uL may have reduced mortality compared to deferred treatment [67]. It may be reasonable to consider such "early" ART initiation for those who want to have a child with a seronegative partner. An international, multi-site trial is currently studying the risk of horizontal transmission within serodiscordant couples in which the HIV-infected partner is started on treatment at CD4 counts between 350–550 versus at CD4 counts 200–250 or AIDS-defining illness [68]. In some resource-rich settings public health departments encourage treatment initiation at diagnosis [69].

Suppressive ART for the purpose of safer conception could be considered for asymptomatic partners who do not meet immunologic or clinical criteria to start treatment. However, the benefits of long-term ART for those with CD4 counts above 500 are unknown. Long-term ART at higher CD4 counts may lead to higher prevalence of drug resistance and cumulative drug toxicity, thus increasing the need for second-line agents in settings with a limited range of antiretroviral therapies. Short-course ART for the infected partner while the couple attempts conception is an alternative strategy analogous to time-limited ART for PMTCT in pregnant HIV-infected women who have high CD4 counts. Challenges of short-term ART would include adherence and the risk of resistance in the setting of little apparent clinical benefit to the positive partner. In addition, this strategy would require multiple interactions with the healthcare system: confirmation of HIV RNA suppression which is not available in many settings; delay of conception pending HIV RNA suppression; and careful tapering of medication upon treatment discontinuation to account for the longer half life of non-nucleoside reverse transcriptase inhibitors compared with other antiretroviral agents.

While the existing data for suppressive ART are compelling, managed conception in the setting of full viral suppression in the HIV-positive partner may not eliminate transmission risk [20, 22, 66]. PrEP may offer additional protection to suppressive ART.

Alternative chemoprophylactic strategies

Local administration of vaginal tenofovir has been effective in animal models and is currently under investigation in two trials enrolling HIV-negative women in sub-Saharan Africa [31]. Should this prove effective, safe, and acceptable, a non-spermicidal preparation could provide an alternative to systemic PrEP for mitigation of male-to-female transmission [70–72].

Post-exposure prophylaxis (PEP) for 28 days is currently used for occupational and non-occupational HIV exposure [73]. Studies in Kenya and in the US have demonstrated poor adherence [74–76]. Adherence requirements for periconception PEP would be even more demanding as monthly attempts at conception would require near-continuous use, thus approximating daily PrEP. Moreover, standard PEP regimens use three antiretroviral agents, with associated increased costs and potential for greater toxicity.

Summary

Despite significant advances in HIV treatment worldwide, new HIV infections continue at rates that surpass capacity for ART initiation [77, 78]. Enhanced prevention efforts should address reproductive decisions made by individuals in HIV-endemic areas. A range of options and evidence of their protective efficacy (table 1) should be discussed and considered as part of reproductive planning. Protective measures including circumcision, evaluation and treatment for STIs, and intercourse limited to peak fertility may contribute to harm reduction. Treatment-as-prevention would likely provide substantial additional protection. For HIV-infected partners who do not qualify for, are failing, or are unwilling to take ART, periconception PrEP for their partners may minimize sexual HIV transmission

risk. Periconception PrEP limits exposure, side effects, toxicity, and need for longer-term adherence. A comprehensive, patient-centered reproductive health program would create opportunities to link HIV-positive and HIV-negative at-risk individuals into prevention and care programs.

The critical first question is whether TDF and/or FTC/TDF demonstrate high efficacy in ongoing clinical trials. If PrEP should prove efficacious, global implementation will be complex. Carefully designed outcome studies will be necessary to answer questions regarding feasibility, acceptability, adherence, resistance, role of less expensive drugs, and behavioral change to guide implementation. Monitoring women and infants exposed to PrEP during conception and in early pregnancy for adverse events, including congenital abnormalities, is essential. If PrEP is efficacious and safe, chemoprophylaxis may be an important component of counseling programs that respect couples' fertility goals while minimizing HIV transmission.

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Table 1

Approaches to reduce sexual transmission risk for HIV-serodiscordant couples who want to conceive children in resource-limited settings

Infected partner	Strategy	Level of evidence† (protection)†
Male	---	---
Female	• Home artificial insemination • Circumcision	• 5 (complete) • 1A (partial) [79–81]
Either	• Delay conception until infected partner on treatment and VL suppressed • Suppressive ART for the infected partner, started at CD4 counts higher than currently recommended for HIV treatment • Limited unprotected sexual encounters timed to peak fertility • Screening + pre-treatment for STI's • Pre-exposure prophylaxis for the uninfected partner	• 2A (partial) [20, 21, 82] • 5 [68] • 2C (partial) [83] • 1Bδ(partial) [84–90] • 5

*STI: sexually transmitted infection

δPartial protection in one of six trials

†Oxford Centre for Evidence-based Medicine, Levels of Evidence (1A: RCT's with homogeneous support; 1B: individual RCT; 2A: cohort studies with homogeneity; 2C: ecological studies; 5: expert opinion without explicit supporting research)[91].