

Safer Conception Strategies for HIV-Serodiscordant Couples: How Safe Is Safe Enough?

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(See the major article by Hoffman et al on pages 1534–43.)

With access to antiretroviral therapy (ART), human immunodeficiency virus (HIV)-infected men and women are living longer and healthier lives and have childbearing desires similar to those of HIV-unaffected individuals [1]. Many are in HIV-serodiscordant sexual partnerships (with an HIV-uninfected partner), and attempts at conception confer sexual HIV transmission risk [2]. HIV risk reduction strategies are available for HIV-serodiscordant couples, in which the male is infected, who want to conceive (Table 1), but there are limited data to inform which or how many concurrent methods a couple should adopt. ART for the HIV-infected male partner is recommended regardless of conception plans, to reduce HIV transmission risk to partners and improve the man's own health [11, 12]. Because adherence to ART is imperfect and genital shedding of HIV may occur even in the presence of suppressed

plasma viral load, couples may seek additional methods to reduce transmission risk. For an uninfected woman wishing to conceive with an infected male partner who is receiving ART, oral preexposure prophylaxis (PrEP) may be a valuable option, particularly if use of ART or ART adherence by the male partner is limited. Combining PrEP for the female partner (oral tenofovir/emtricitabine, or TDF/FTC) – with ART administration to the male partner for safer conception has been acceptable in observational studies [13–15]. Because PrEP trials were conducted without receipt of ART by the infected partner and ART trials were conducted without receipt of PrEP by the uninfected partner, there are no direct clinical data to estimate the benefit of using PrEP and ART together to decrease periconception HIV transmission risk, compared with either intervention alone.

In this issue of *The Journal of Infectious Diseases*, Hoffman et al use a thoughtfully designed simulation model to investigate the role of PrEP, ART, or both in male-infected, HIV-serodiscordant couples who are attempting to conceive. When clinical data are limited, simulation models can help to inform decision-making. If multiple studies provide partial information, a single model can integrate available data. When data are equivocal or missing, investigators make explicit assumptions about which values to use in a model and then vary these values in sensitivity analyses to identify the thresholds at which decisions would

change; this allows readers to understand whether more data are needed to accurately inform clinical choices [16]. Here, Hoffman et al combine transmission risks from separate PrEP trials, ART-as-prevention trials, and observational studies of age-stratified pregnancy rates, and conduct extensive sensitivity analyses on key model parameters. They focus this analysis on couples who maintain the high rates of ART-mediated viral suppression and PrEP adherence seen in the HPTN 052 and Partners PrEP trials [3, 5, 17, 18]. They also assume that both partners are aware of each others' HIV status, have been screened and treated for sexually transmitted infections (STIs), and have completed normal fertility evaluations. There are 3 primary messages from their analysis.

First, if couples limit condomless sex to the 2 days before and the day of ovulation, and if the male partner is receiving virally suppressive ART, PrEP for the female partner provides little additional benefit. The authors define a “successful” outcome as one in which the female partner remains uninfected and a full-term pregnancy occurs. With ART alone, the yearly chance of this successful outcome is 29.1%; with ART plus PrEP, this chance is 29.2%, which is essentially equivalent within the margin of error of the model results.

Second, if couples choose a single intervention, ART for the male partner is projected to be more effective in reducing transmission than PrEP for the female

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Table 1. Strategies for Minimizing Human Immunodeficiency Virus (HIV) Transmission Risk Among HIV-Serodiscordant Couples, in Which the Male Is Infected, That Are Attempting to Conceive

Method	Estimated Risk Reduction, %	Benefits	Limitations
Sex without condoms limited to peak fertility	Unknown	Reduces cumulative HIV exposure while permitting conception	Difficult for couples to determine time of peak fertility and/or negotiate condomless sex
ART for the infected partner	96% in clinical trial [3]; approximately 64% in non-trial setting [4]	Reduces morbidity and mortality for infected partner while reducing risk of transmission to uninfected partner	Detectable HIV may remain in semen despite suppressed plasma virus Treatment refusal and sub-optimal adherence are common
PrEP (oral, daily FTC/TDF) for the uninfected partner [5, 6]	63–75	Female controlled	Adherence challenges, risk of developing drug resistance if continued after HIV infection, some safety concerns regarding use during pregnancy
STI treatment [7, 8]	≤40	Reduces morbidity for the treated individuals and may reduce risk of HIV acquisition and transmission	Effective as an HIV risk reduction strategy in only 2 of 4 randomized controlled trials
Sperm processing [9, 10]	Approximately 100	Highly effective	Requires assisted reproductive technology (IUI, IVF, or ICSI), inaccessible to many couples

Abbreviations: ART, antiretroviral therapy; FTC, emtricitabine; ICSI, intracytoplasmic sperm injection; IUI, intrauterine insemination; IVF, in vitro fertilization; PrEP, preexposure prophylaxis; STI, sexually transmitted infection; TDF, tenofovir disoproxil fumarate.

partner. When neither ART nor PrEP are used, the yearly HIV transmission risk predicted by the model is 9.5%. Use of PrEP alone reduces this risk to 3.7%, but use of ART alone reduces the risk to 0.5%–0.6% (and provides other important health benefits of ART for the infected partner); ART plus PrEP confers minimal additional benefit (risk is reduced to 0.1%–0.2%).

Third, the authors identify key factors that influence HIV transmission and pregnancy risks. The most influential parameter is the degree to which couples limit condomless sex to peak fertility, which can be difficult to identify [19]. When couples pursue condomless sex throughout each month, the model-projected chance of the successful outcome (healthy pregnancy without HIV transmission) is lower, at 17.8%/year with no intervention, because of increased HIV transmission without improved pregnancy chance. While both interventions still provide benefit (yearly chance of successful outcome when PrEP alone is used, 23.1%; yearly chance when ART alone is used, 26.8%), adding female PrEP to male ART again adds very little (yearly chance, 27.3%). Other critical factors include the degree to which ART

reduces HIV transmission, the rate of STIs and their impact on HIV transmission, and age of the female partner. The authors are developing an online tool, which they call a clinical dashboard, that will allow patients and providers to project HIV risk and pregnancy chance for individual scenarios of age, ART use, STI treatment, and timing of condomless sex.

There are challenges to implementing safer conception that are beyond the scope of this modeling analysis but are important in clinical practice. Hoffman et al assume normal male and female fertility. Low sperm count and motility are more common in HIV-infected men, and female subfertility is higher in HIV-prevalent settings; these will reduce pregnancy chance for any of the modeled interventions [20–22]. The authors also simulate monthly HIV testing for the female partner. Delayed testing and ART initiation would impair safer conception efforts: if a woman becomes both pregnant and infected with HIV, untreated acute infection will markedly increase perinatal transmission risk; if HIV infection occurs and PrEP is not stopped, drug-resistant HIV may emerge [23, 24]. Additionally, male-partner ART adherence

and viral suppression may be imperfect or unknown to female partners. Treatment refusal is common, and 5%–25% of patients receiving ART have detectable virus in plasma, perhaps with higher rates among patients without clinical symptoms of AIDS [25–29]. Uncertainty about the partner’s ART use may be an important motivation for periconception PrEP. Finally, many people in serodiscordant relationships do not know the HIV status of their partners. Disclosure strategies, including couples-based HIV counseling and testing, are needed to support at-risk men and women to know whether partners are infected—an essential first step before individuals or couples can identify the need for safer conception approaches [30].

In addition to these implementation challenges, current clinical data leave several key questions about periconception PrEP unanswered. First, to estimate the combined impact of both interventions, Hoffman et al use per-sexual-act data from separate PrEP and ART trials; this is a strength of their model-based approach in the face of limited data [3, 5]. They assume an additive effect of ART and PrEP on HIV transmission risk reduction, but it

is biologically plausible that once transmission risks are lowered with PrEP or ART, a second intervention will have less impact than when offered alone. If so, adding PrEP to ART would confer less benefit than projected in this analysis.

Another important data gap focuses on the clinical risks of TDF when used for periconception PrEP. TDF is part of recommended ART regimens for HIV-infected pregnant women and women of childbearing age [11, 12]. Toxicities among children and adults receiving TDF to treat HIV infection include loss of bone density and renal tubular dysfunction [31, 32]. Although increased risks of congenital anomalies and renal disease have not been observed in >2500 infants exposed to TDF in utero as part of long-term treatment of their HIV-infected mothers, data on bone development and growth are equivocal [33–37]. Compared with TDF exposure throughout pregnancy, it is likely that risks are even lower when exposure is limited to periconception. Significant risks of miscarriage, fetal anomalies, or growth impairment were not seen in Partners PrEP participants who became pregnant and stopped PrEP at an average of 5 weeks gestation [38]. Even a small risk of toxicity, however, would reduce the rationale for using TDF-based PrEP as a backup to ART use by the male partner if the additive risk-reduction benefit is small.

A third data gap centers around adherence to periconception PrEP. The VOICE and FEM-PrEP trials showed significant nonadherence among women, who reported trial-related barriers (ie, the use of an experimental drug and the possibility of random assignment to the placebo group), as well as pill fatigue and self-perceived low risk for HIV infection [39–42]. When used for a limited period to safely conceive, PrEP adherence could theoretically be higher, leading to greater PrEP efficacy [17].

What should patients and providers conclude from the work by Hoffman et al? Attempts at condomless sex to conceive should ideally begin by ensuring that the HIV-infected male partner is

adherent to ART with a suppressed viral load, that both partners have normal fertility and are treated for STIs, and that couples identify and limit condomless sex to the time of ovulation. If these conditions are met, there is likely no benefit to adding PrEP for an HIV-uninfected female partner. In many situations, however, these criteria will not be realistic or feasible. PrEP may be a valuable tool when an HIV-infected male partner declines to receive ART, when an HIV-uninfected woman is unsure of her partner's adherence to ART or viral suppression status, or as a so-called bridge to suppression immediately after her partner initiates ART [43].

The debate about periconception PrEP began with observational data, expert opinion, and patient demand for strategies to facilitate safer conception without assisted reproductive technology. One might think that ideal information would come from randomized trial of ART, PrEP, and ART plus PrEP, with long-term follow-up of acceptability, adherence, HIV transmission, and pregnancy outcomes. Such a trial may not be feasible, because it would require large numbers of patients and long follow-up times; even if conducted, the findings of the trial might be obsolete if newer and more-effective PrEP regimens are introduced before trial completion. As more data become available from demonstration studies of both PrEP and ART as prevention, modeling studies like the work by Hoffman et al will help patients and providers make important, individualized decisions now about the role of both ART and PrEP in safer conception.

Notes

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