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Antiretrovirals and safer conception for HIV-serodiscordant couples

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Abstract

Purpose of review—Many men and women living with HIV and their uninfected partners attempt to conceive children. HIV-prevention science can be applied to reduce sexual transmission risk while respecting couples' reproductive goals. Here we discuss antiretrovirals as prevention in the context of safer conception for HIV-serodiscordant couples.

Recent findings—Antiretroviral therapy (ART) for the infected partner and pre-exposure prophylaxis (PrEP) for the uninfected partner reduce the risk of heterosexual HIV transmission. Several demonstration projects suggest the feasibility and acceptability of antiretroviral (ARV)s as periconception HIV-prevention for HIV-serodiscordant couples. The application of ARVs to periconception risk reduction may be limited by adherence.

Summary—For male-infected (M+F−) couples who cannot access sperm processing and female-infected (F+M−) couples unwilling to carry out insemination without intercourse, ART for the infected partner, PrEP for the uninfected partner, combined with treatment for sexually transmitted infections, sex limited to peak fertility, and medical male circumcision (for F+M couples) provide excellent, well tolerated options for reducing the risk of periconception HIV sexual transmission.

Keywords

antiretrovirals as prevention; conception; fertility; HIV prevention; HIV-serodiscordance; perinatal HIV transmission; sexual HIV transmission

INTRODUCTION

Studies in North America [1,2], Europe [3–5], and sub-Saharan Africa [6–10] report that 20–50% of HIV-infected men and women desire children. The contribution of intended

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conception to incident HIV infection is unknown, but likely represents a large proportion given high fertility rates and the importance of having children in most HIV endemic areas [11–13]. In most sub-Saharan African countries, up to half of those living with HIV report a serodiscordant partner and estimates suggest that up to 60% of new infections occur between stable, heterosexual, serodiscordant couples [14–16]. As men and women with HIV live longer, healthier lives, safer conception counseling for HIV-serodiscordant couples is a reproductive right [17–19] and should be included as a public health strategy to reduce HIV incidence among men, women, and their children in settings with generalized HIV epidemics [20,21▪▪,22▪]. Integrating effective HIV prevention strategies into comprehensive reproductive counseling is a rational step to protect uninfected partners and their children and to make progress towards eliminating HIV.

Several strategies allow HIV-serodiscordant couples to conceive with minimal transmission risk to the uninfected partner (Table 1) [23–33,34▪▪,35, 36,37▪▪,38▪▪,39▪▪,40–42]. For female-positive couples (F+M−), the safest option is vaginal insemination without intercourse (man ejaculates into a condom or cup and the contents are introduced via condom reversal or needle-less syringe) timed to peak fertility. This can be completed at home and confers zero risk to the male partner [43]. For male-positive serodiscordant couples (M+F−), laboratory techniques can isolate sperm (which do not harbor HIV) from seminal plasma and leukocytes [44]. ‘Washed’ or processed sperm can be introduced via intrauterine insemination or in-vitro fertilization with or without intracytoplasmic sperm injection [29,45,46]. Although there are no randomized, controlled trials (RCTs), sperm processing centers report 4638 M+F− inseminations, a 50% pregnancy rate, and no recorded HIV-transmissions [28–31]. These findings suggest the process is safe and effective, but it remains challenging for most people to access due to costs and limited availability [46–48].

For M+F− serodiscordant couples, who cannot access sperm processing, and F+M− couples unwilling to carry out insemination without intercourse, vaginal intercourse without condoms coupled with adjunct risk reduction strategies can reduce HIV transmission while allowing for conception [49–51]. Adjunct strategies include medical male circumcision (MMC) for F+M− couples [25–27], treatment for STIs [40,41], limiting unprotected sex to peak fertility, and the use of ARVs-as-prevention (Table 1). Recent data indicate that antiretroviral therapy (ART) for the infected partner and pre-exposure prophylaxis (PrEP) for the uninfected partner may offer benefits for HIV-serodiscordant couples who choose to conceive. The purpose of this article is to review how ARVs-as-prevention can be incorporated into comprehensive reproductive health counseling for serodiscordant couples.

Incorporating risk reduction methods into a couple’s sexual practice requires mutual HIV testing and disclosure, understanding HIV transmission risks, knowledge of and access to risk-reduction strategies, a relationship in which sexual practices and reproductive decisions are considered, discussed, negotiated, and practiced, and ability to adhere to risk-reduction strategies [52▪]. Mutually disclosed serodiscordant couples, who carry out equitable discussions about sex, conception, and family planning are likely a rare population [53–55]. We apply the data to the context of mutually disclosed serodiscordant couples while acknowledging that prior to offering safer conception strategies, mutual HIV-testing, disclosure, and communication must be supported as an essential first step in any reproductive counseling program [21▪▪,52▪].

Antiretrovirals for prevention

We present data supporting the use of ART for the infected partner and antiretroviral PrEP for the un-infected partner as HIV prevention for heterosexual discordant couples, demonstration projects which apply these strategies to periconception risk, and make

recommendations for the use of ARVs for prevention for serodiscordant couples who choose to conceive.

Data supporting antiretroviral therapy for the infected partner as prevention— Observational data first published over a decade ago show that low plasma HIV RNA is associated with decreased sexual HIV transmission [36,56,57]. ART for the infected partner was associated with a 92% reduction in HIV-acquisition risk among uninfected partners in a secondary analysis of the Partners in Prevention Trial [35] and ecologic data show an association between lowering community-level viral load (through increased testing and treatment) and decreased HIV incidence [58,59].

In the HIV Prevention Trials Network Study 052, 1763 mutually disclosed HIV-serodiscordant couples in which the infected partner had a CD4 cell count between 350 and 550 cells/mm^3 were randomized to ART at enrolment or upon decline in CD4 to 250 or fewer cells per μl or onset of AIDS-defining illness. Early therapy was associated with a 96% reduced risk of genetically linked transmissions [34▪▪]. For couples who attempt natural conception, delaying sex without condoms until the infected partner is on ART with a suppressed plasma viral load can dramatically reduce HIV transmission.

Data supporting oral or topical pre-exposure prophylaxis for the uninfected partner—With PrEP, an HIV-uninfected individual uses antiretroviral medications continuously or before and after exposure to minimize HIV acquisition. In CAPRISA-004, high-risk HIV-uninfected heterosexual women randomized to pericoital 1% tenofovir vaginal gel versus placebo had a 39% reduction in HIV acquisition [60▪▪]. Conversely, the Microbicide Network VOICE trial arm of tenofovir gel was halted due to lack of efficacy; details are not yet available. An additional efficacy study of pericoital tenofovir gel is enrolling and alternative topical antiretrovirals are under investigation (http://www.avac.org).

In the first completed placebo-controlled trial of oral, daily emtricitabine/TDF(FTC/TDF) as PrEP, HIV acquisition was reduced by 44% among HIV-seronegative men or transgender women having sex with men [61]. In the Partners PrEP trial, HIV acquisition was reduced by 67% and 75% among HIV-serodiscordant couples taking oral TDF or FTC/TDF, respectively, without significant differences by sex [37▪▪]. Having detectable drug levels was associated with 86% risk reduction for TDF and 90% risk reduction for those in the FTC/TDF arm. In the CDC TDF2 trial, HIV acquisition was reduced by 63% among men and women taking daily FTC/ TDF [38▪▪]. In contrast, the FEM-PrEP trial of daily FTC/ TDF and the VOICE trial arm of oral TDF for heterosexual women were halted for futility [39▪▪,62,63]. These divergent findings may relate to adherence [39▪▪,64] and qualitative data from partners PrEP participants, who had high adherence, suggest stable serodiscordant couples were motivated to adhere to PrEP in order to preserve the relationship [65▪▪]. These data support the application of daily, oral PrEP to minimize periconception HIV transmission among uninfected men and women with an HIV-infected partner not eligible for, failing, or not taking ART. PrEP may further reduce periconception transmission when the infected partner has viral suppression on ART. These data informed the recent US Food and Drug Administration approval of FTC/TDF as PrEP for at-risk HIV-uninfected men and women [66].

Demonstrations of antiretrovirals-as-prevention for safer conception—Barreiro *et al.* [49] studied serodiscordant couples (40 M+F− and 22 F+M−) who attempted timed, natural conception while the infected partner was on ART (for at least 6 months), resulting in 76 pregnancies, 68 live births, 0 sexual transmissions, and 1 case of perinatal HIV transmission. Vernazza *et al.* [67▪▪] followed 37 M+F− couples through 170 cycles of

periovulatory unprotected intercourse while the infected partner was on ART and the uninfected partner was taking tenofovir or FTC/TDF as PrEP: ‘women achieved a 75% pregnancy rate with no documented seroconversions or adverse events’. Women were counseled to take tenofovir or FTC/TDF on the morning of the urine-measured luteinizing hormone (LH) peak, repeated 24 h later, and followed by intercourse about 36 h after the LH peak.

These series suggest the feasibility of ARV-based safer conception. While the numbers are too small to draw conclusions about safety, safer conception packages including ART, PrEP, timed conception, STI treatment, and MMC (for F+M− couples) are likely to confer nearly zero risk of HIV transmission when adherence is high. Given the risks, couples currently assume to attempt conception, the risk reduction may be considerable [22▪].

Recommendations—Based on the current data, we recommend the following approach for couples, who choose to attempt conception through intercourse (see Table 2).

- ART: Conception attempts should be delayed until the infected partner is on ART with a suppressed viral load [21▪▪,68▪], or for at least 6 months [69–72]. ART should be continued for life [73,74].
- PrEP initiation: The uninfected partner should take daily oral FTC/TDF PrEP starting before anticipated peak fertility. Although protection may be conferred within 24 h of the first dose, starting PrEP at the onset of menses will help to ensure maximal protection (based on pharmacokinetics and human behavior) during peak fertility [75–77]. Additional antiretroviral agents, formulations, and dosing schedules may be appropriate in the future pending additional data.
- PrEP discontinuation: Couples should be encouraged to resume condom use and discontinue PrEP once pregnancy is confirmed; as early as 21 days postconception with urine pregnancy testing, or 14 days postconception based on the first day of a missed period [78]. Concerns about fetal ARV exposure for M+F− couples, cost, toxicities, animal data, and the simpler protocol motivate the recommendation to stop PrEP when pregnancy is achieved. Post-exposure prophylaxis for 28-days prevents simian HIV acquisition among macaques [79,80], however there are no human data to suggest whether post-exposure prophylaxis is required on top of PrEP and partner viral load suppression. Animal studies do not support a long period of post-exposure prophylaxis after PrEP [81,82]. Oral PrEP trials administered continuous prophylaxis, but women with pregnancies discontinued PrEP; data regarding this subgroup will inform future practice [83▪▪].

  Couples who achieve pregnancy are at particular risk for transmitting and acquiring HIV [84–86] and condom use once pregnancy is achieved must be emphasized. For F+M− couples with insurmountable obstacles to condom use, continuing PrEP for the uninfected male through pregnancy should be considered. Given limited PrEP data in pregnant women (although many HIV-infected women take TDF and FTC/TDF with few reported problems [87]), we cannot currently formally recommend PrEP continuation for M+F− couples during pregnancy. However, for many women the risk reduction benefits of PrEP will outweigh the possible toxicities.
- PrEP without ART: For M+F− couples in which the infected partner does not meet local criteria for or want to take ART, or who are not willing to delay conception attempts, PrEP coupled with timed sex and STI treatment is an optional risk reduction strategy. For F+M− couples, we hesitate to recommend PrEP for the man without ART for the infected woman. In most cases, a woman should start ART for her own health regardless of pregnancy, and treatment may reduce the risk of

pregnancy-associated mortality for HIV-infected women [88,89]. In addition, for women with pregnancy, ART initiation is often recommended soon after pregnancy to prevent vertical transmission [72,90–92]; more time on ART and viral load suppression at conception are associated with reduced risk of perinatal transmission [93,94]. For women who do not need – or meet local criteria – to initiate ART for their own health and wish to avoid ART during early embryogenesis, periconception PrEP for the uninfected male with ARV initiation for the woman during pregnancy may be reasonable.

- Non-ARV prevention: ARV use should be combined with sex without condoms limited to peak fertility and STI treatment. For F+M− couples, MMC should be pursued.

No data exist to assess whether PrEP is a necessary adjunct for serodiscordant couples wherein the infected partner is on effective ART, however the highest level of protection is likely achieved by combining ART and PrEP. A public health approach may select one of these strategies: ART for the infected partner provides the highest-level of protection, but uninfected-partner PrEP is an effective risk reduction option when the infected partner is not reliably taking ART. Time-limited, periconception PrEP limits many potential drawbacks to continuous PrEP, including cost, adherence, toxicity, and behavioral risk compensation; additionally, it provides an opportunity to engage high-risk, uninfected individuals in prevention [48,95].

Limitations of antiretrovirals-as-prevention for safer conception—Differential HIV suppression in the genital tract and blood plasma may limit effectiveness of infected-partner ART as a safer conception strategy. Three to forty percentage of men and women with suppressed plasma viral load have detectable virus in the genital tract [96▪,97–100] and genital viral load correlates (independent of plasma load) with HIV transmission risk [96▪]. Studies of how genital shedding affects transmission, and which anti-retrovirals best suppress replication in genital compartments will further define strategies [76,101–104].

Concerns about tenofovir teratogenicity (FDA Class B) may limit deployment of periconception PrEP for women. Trials including systemic or topical tenofovir as PrEP excluded women with plans for pregnancy, although many women in these trials became pregnant [39▪▪,83▪▪] and reports on pregnancy outcomes are expected. The International Antiretroviral Pregnancy Registry reports outcomes for 1219 babies with first trimester exposure to tenofovir: 27 had birth defects, a prevalence of 2.2% (95% confidence interval 1.5, 3.2%), within the range observed in the general population [87] and WHO. and US Perinatal Guidelines recommend tenofovir in regimens initiated during pregnancy [90–92]. Fetal safety should be considered in future PrEP development. If topical preparations prove effective and nonspermicidal, these may provide protection with limited systemic effects.

HIV-exposed uninfected children born to women taking ARVs may have worse health outcomes than unexposed infants [105–108]. Teasing out the effects of exposure to ARVs versus HIV is ongoing. Guidelines recommend including ARV exposure in the child's medical history and having a low threshold to evaluate these children for mitochondrial toxicity [92]. Periconception PrEP as we propose results in minimal ARV exposure during embryogenesis.

ART-mediated viral load suppression and PrEP efficacy are highly dependent on adherence [39▪▪,60▪▪,61,109–111,112▪▪]. Stable serodiscordant partners may be motivated to adhere to ARVs for prevention [65▪▪] and several studies suggest that individuals may modify risk behavior in order to prevent their child from acquiring HIV [22▪,113–115]. Stable

serodiscordant couples who choose to conceive may be able to adhere to ARV prevention strategies and represent a priority group to consider for application of ARVs-as-prevention.

Additional considerations for serodiscordant couples who attempt conception

Financing of ARVs-as-prevention will depend on additional efficacy and effectiveness data, costs, and recommendations from governmental and international bodies. ARVs-as-prevention will be most cost-effective for high-risk populations with excellent adherence to effective strategies [116▪, 117,118]. Oral PrEP for HIV-serodiscordant couples attempting conception is predicted to avert 1–10% of new infections, with a cost of US$2000–8000 per infection prevented [116▪]. The model assumes high risk outside of these interventions and does not account for a decreased risk of perinatal transmission or expected benefits of engaging uninfected partners in prevention.

Periconception risk-reduction interventions that include ARVs will require healthcare worker involvement. Cross-sectional studies show that people living with HIV welcome safer conception advice from providers, but providers are not routinely discussing fertility desires or plans [13,22▪,119,120▪▪,121,122]. With improved prevention opportunities, work to help clinicians increase assessments of fertility plans and provide risk reduction counseling and interventions will be needed.

Preconception counseling for HIV-serodiscordant couples should include couples-based HIV testing, counseling, supported disclosure, and education about serodiscordance [21▪▪, 54]. When couples understand their HIV status and transmission risks, we recommend a discussion of the options for having children. For those who choose to have children, we recommend a baseline fertility assessment to limit HIV exposure among those unlikely to conceive. Additional fertility evaluations should be pursued if initial assessments predict conception challenges or if pregnancy is not achieved after 6 months of conception attempts. We recommend the following baseline preconception evaluation for men and women living with HIV and their partners:

1. For individuals and couples living with HIV and their partners
    - **a.** Couples-based HIV testing, counseling, supported disclosure.
    - **b.** Education about serodiscordance, HIV transmission risk.
    - **c.** Assess plans for having children.
2. For those considering reproduction
    - **a.** Education about HIV transmission risks and periconception risk reduction strategies. (Table 1)
    - **b.** Fertility evaluation
        - **i.** Woman’s age, menstrual cycles
        - **ii.** Both partners’ fertility history
        - **iii.** Semen analysis when possible (especially if male partner infected).
        - **iv.** Additional fertility workup dictated by history (e.g. abnormal menses, advanced maternal age).
        - **v.** Full fertility workup (based on local standard) if no pregnancy after 6 months of conception attempts.
3. For those who choose to attempt conception

a. Standard of care preconception screening (STI screen, serologies for rubella, hepatitis B virus, cervical cancer screening) and immunizations (Tdap, MMR, HBV as appropriate).

b. Education re. timing peak fertility.

c. Referral to MMC (for F+M− couples).

d. ART: standard evaluation prior to initiation of ART, adherence counseling, supported disclosure to other supports.

e. PrEP (if indicated) evaluation: serum Cr, HBV, adherence counselling.

SUMMARY

Advances in ARV-based prevention dramatically increase safer conception options for HIV-serodiscordant couples. The standard of care in resource-rich settings has become sperm processing and assisted reproduction for M+F− couples, yet costs and limited access make this a difficult option for most. Given discordant genital and plasma viral loads, it is appropriate to recommend sperm processing for M+F− couples, who can access it, but for those who cannot or prefer other options, ARVs-as-prevention are an excellent alternative.

To further develop safer conception options for serodiscordant couples, additional research into effectiveness of ARVs-as-prevention, efficacy of topical PrEP agents, impacts of topical and systemic PrEP on pregnancy and pregnancy outcomes, how providers advise serodiscordant couples about safer conception practices, and how couples consider, negotiate and implement these practices in diverse settings is needed. Safer conception guidelines and policies are needed to facilitate and promote safer conception practices for HIV-serodiscordant couples who choose to conceive.

CONCLUSION

In order to minimize periconception HIV-transmission among serodiscordant couples, conception attempts should be delayed until the infected partner is on ART. For M+F− couples, ART for the infected partner may be combined with sperm processing or intercourse timed to peak fertility, PrEP for the uninfected partner, and STI treatment. For F+M− couples not willing to carry out non-intercourse insemination, we recommend infected-partner ART, MMC, sex without condoms timed to peak fertility, PrEP for the uninfected partner, and STI treatment. We recommend daily dosing of PrEP starting at menses and continuing until pregnancy is achieved. In cases where the infected partner does not want, meet criteria, or cannot adhere to ART, we recommend PrEP for the uninfected partner. Healthcare workers should be educated about these options to facilitate deployment.

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- ▪ of special interest
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KEY POINTS

- Antiretrovirals as HIV prevention can be applied to safer conception for serodiscordant couples to help couples meet reproductive goals while minimizing HIV transmission to uninfected partners.
- Antiretroviral (ARV)-based risk reduction strategies include delaying conception attempts until the infected partner is on ART, daily oral FTC/tenofovir disoproxilfumarate (TDF) PrEP for the uninfected partner until pregnancy is achieved, sex without condoms limited to peak fertility, and pretreating both partners for sexually transmitted infections (STIs). Medical male circumcision for female-positive couples should also be offered.
- Adherence to ART and PrEP will be critical to the effectiveness of these interventions. Stable serodiscordant couples attempting to conceive may have particular motivation to adhere to ART and periconception PrEP.

Table 1

Strategies to reduce periconception risk of HIV transmission for serodiscordant couples

Couple	Method	Estimated risk reduction	Level of evidence[a](data)
F+M− (goal: ↓female to male transmission)	Nonintercourse insemination[b]	100%	2A; [23,24]
	Medical male circumcision	66%	1A; [25–28]
M+F− (goal: ↓male to female transmission)	Sperm washing +IUI or IVF (± ICSI)	~100%	2A; [28–31]
Either partner infected, pursuing natural conception +adjunct risk reduction strategies (goal: ↓sexual transmission)	Sex without condoms limited to peak fertility[c]	Unknown	1A; [23,24,32,33]
	ART for the infected partner	96%	1B; [34▪▪,35,36]
	PrEP (oral, daily FTC/TDF) for the uninfected partner	63–75%	1A[d]; [37▪▪–39▪▪]
	Treatment of STI's	≤40%	1B[e]; [40,41]

ART, antiretroviral treatment; FTC/TDF, emtricitabine/tenofovir disoproxil fumarate; ICSI, intracytoplasmic sperm injection; IUI, intrauterine insemination; IVF, in vitro fertilization; PrEP, pre-exposure prophylaxis.

[a]Oxford Centre for Evidence-based Medicine, Levels of Evidence (1A: RCTs with homogeneous support; 1B: individual RCT; 2A: cohort studies with homogeneity; 2C: ecological studies; 5: expert opinion without explicit supporting research) [42].

[b]Man ejaculates into a condom or cup and the contents are introduced via condom reversal or needle-less syringe at home, or through IUI with a healthcare professional – timed to the woman's peak fertility.

[c]Limiting sex without condoms to times of peak fertility reduces exposure, but does not affect HIV-1 transmission risk per coital act.

[d]Effective for heterosexual men in two of two RCTs and for women in two of four RCTs.

[e]Effective in one of six RCTs.

Table 2

Recommendations for mutually disclosed serodiscordant couples who choose to attempt conception through intercourse and have completed baseline fertility and preconception evaluation(s)

Risk reduction approaches	**Laboratory follow-up**	
M+F− serodiscordant couples	**Infected partner**	**Uninfected partner**
1 Infected partner on ART with suppressed viral load **2** Sperm washing +assisted reproduction	• Standard VL, CD4, safety lab monitoring while on ART	• Monthly HIV Ab test (VL based on symptoms and availability) • Monthly pregnancy test
1 Infected partner on ART with suppressed viral load (or on effective regimen for ≥6 months) **2** Daily oral PrEP with FTC/TDF for the uninfected partner until pregnancy achieved **3** Sex without condoms limited to peak fertility		• Monthly HIV Ab test (VL based on symptoms and availability) • Monthly pregnancy test • Baseline and monthly renal function while on PrEP • Ovulation monitoring (home LH kits, basal body temperature, cervical mucus monitoring)
F+M− serodiscordant couples	Infected partner	Uninfected partner
1 Vaginal insemination with collected semen (home or clinic) at peak fertility	• Routine VL, CD4, safety lab monitoring for infected individual on ART • Monthly pregnancy test • Ovulation monitoring (home LH kits, basal body temperature, cervical mucus monitoring)	• Monthly HIV Ab test (VL based on symptoms and availability)
1 Infected partner on ART with suppressed viral load (or on effective regimen for ≥6 months) **2** MMC **3** Daily oral PrEP with FTC/TDF for the uninfected partner until pregnancy achieved **4** Sex without condoms limited to peak fertility.		• Monthly HIV Ab test (VL based on symptoms and availability) • Baseline and monthly renal function while on PrEP

Ab, antibody; ART, antiretroviral treatment; F+M−, female-infected couple; FTC/TDF, emtricitabine/tenofovir disoproxil fumarate; LH, luteinizing hormone; M+F−, male-infected couple; MMC, male medical circumcision; PrEP, pre-exposure prophylaxis; VL, HIV viral load.