Reproductive Options for HIV-Concordant and Serodiscordant Couples  

For Couples Who Want to Conceive

For Concordant (Both Partners are HIV-Infected) and Discordant Couples:
- Expert consultation is recommended so that approaches can be tailored to couples’ specific needs (AIII).
- Partners should be screened and treated for genital tract infections before attempting to conceive (AII).
- Both partners should attain maximum viral suppression before attempting conception (AIII).

For Discordant Couples:
- The couple should be counseled and only attempt conception after the HIV-infected partner has initiated antiretroviral therapy and have achieved sustained suppression of plasma viral load below the limits of detection (AI).
- Administration of antiretroviral pre-exposure prophylaxis 30 days before and 30 days after conception for HIV-uninfected partners may offer an additional tool to reduce the risk of sexual transmission, particularly if the HIV-infected partner’s plasma viral load is unknown or detectable (BII). It is not known whether pre-exposure prophylaxis for the uninfected partner confers additional benefit when the infected partner receiving antiretroviral therapy has demonstrated sustained viral suppression.

Discordant Couples with HIV-Infected Women:
- The safest conception option is assisted insemination at home or in a provider’s office with a partner’s semen during the peri-ovulatory period (AII).

Discordant Couples with HIV-Infected Men:
- The use of donor sperm from an HIV-uninfected man with artificial insemination is the safest option (AIII).
- When the use of donor sperm is unacceptable, the use of semen preparation techniques coupled with either intrauterine insemination or in vitro fertilization should be considered (BII).
- Semen analysis is recommended for HIV-infected men before conception is attempted to prevent unnecessary exposure to infectious genital fluid. Semen abnormalities appear to be more common among HIV-infected men than HIV-uninfected men (AII).

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

The objective of this section is to provide guidance for safe conception and pregnancy while maximizing efforts to prevent transmission to an HIV-uninfected partner and perinatal transmission of HIV.

For couples in which one or both partners are HIV-infected, optimal health should be attained before attempting conception; couples should be counseled to only attempt conception after HIV-infected partners have initiated antiretroviral therapy (ART) and have achieved sustained suppression of plasma viral load below the limits of detection. For concordant or serodiscordant couples who want to conceive, expert consultation is recommended so that approaches can be tailored to specific needs.

Before attempting to conceive, both partners should be screened for genital tract infections. Treatment of such infections is important because genital tract inflammation is associated with genital tract shedding of HIV.

Serodiscordant Couples

Before conception is attempted, the HIV-infected partner should be receiving ART and have achieved sustained suppression of plasma viral load below the limits of detection. HPTN 052 was a randomized clinical trial designed to evaluate whether immediate versus delayed initiation of ART by HIV-infected individuals with CD4 T lymphocyte (CD4) cell counts of 350 to 550 cells/mm³ could prevent sexual transmission of HIV among serodiscordant couples. Most of the participants were from Africa (54%), with 30% from Asia and 16% from North and South America. This study showed that earlier initiation of ART led to a 96% reduction in transmission of HIV to the uninfected partner. Of 28 cases of HIV infection...
documented to be genetically linked to the infected partner, 27 occurred in the 877 couples in which the HIV-infected partner delayed initiation of ART until the CD4 cell count fell below 250 cells/mm³, whereas only one case of HIV infection occurred in the 886 couples with an HIV-infected partner who began immediate ART; 17 of the 27 transmissions in the delayed-therapy group occurred in individuals with CD4 cell counts >350 cells/mm³. The majority of transmissions (82%) were observed in participants from Africa. Thus this randomized trial clearly demonstrated that provision of treatment to infected individuals can reduce the risk of transmission to their uninfected sexual partners.6

It is important to recognize that no single method (including treatment of the infected partner) is fully protective against transmission of HIV. Effective ART that decreases plasma viral load to undetectable levels is also associated with decreased concentration of virus in genital secretions. However, discordance between plasma and genital viral loads has been reported, and individuals with an undetectable plasma viral load may have detectable genital tract virus.7,9 In addition, antiretroviral (ARV) drugs vary in their ability to penetrate the genital tract.10 In a prospective study of 2,521 African HIV-infected serodiscordant couples, higher genital HIV RNA concentrations were associated with greater risk of heterosexual HIV-1 transmission and this effect was independent of plasma HIV concentrations.11 Each log₁₀ increase in genital HIV-1 RNA levels increased the risk of female-to-male or male-to-female HIV transmission by 1.7-fold.11 Hence, the use of ART reduces but does not completely eliminate the risk of HIV sexual transmission in couples who have decided to conceive through condomless intercourse.12

In addition to reducing the risk of HIV transmission between partners, starting ART before conception in HIV-infected women may also reduce the risk of perinatal transmission.13 Data suggest that early and sustained control of HIV viral replication may be associated with decreasing residual risk of perinatal transmission,14,15 but not complete elimination of the risk of perinatal transmission.15 In addition, reports are mixed on the possible effects of ART on prematurity and low birthweight, with some but not all data suggesting that such outcomes may be more frequent in women on ARV drugs at conception.16-18

The implications of initiating therapy before conception and the need for strict adherence to achieve plasma viral load below the limits of detection should be discussed with the couple. Consultation with an expert in HIV care is strongly recommended.

Periconception pre-exposure prophylaxis (PrEP) can be used to minimize risk of transmission of HIV within discordant couples. PrEP is the use of ARV medications by an HIV-uninfected individual to maintain blood and genital drug levels sufficient to prevent acquisition of HIV. Many studies have demonstrated that PrEP reduces the risk of HIV acquisition in both men and women, with minimal risk of incident ARV resistance. Other trials failed to demonstrate PrEP efficacy, likely related to suboptimal levels of adherence.6,19-24 Table 4 summarizes clinical trials of PrEP.25
### Table 4. Clinical Trials of Pre-Exposure Prophylaxis

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study Population</th>
<th>Location</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF2</td>
<td>1,219 sexually active adults; 55% male, 45% female; 94% unmarried; approximately 90% aged 21–29</td>
<td>Botswana</td>
<td>Daily oral TDF/FTC</td>
<td>63% protection</td>
<td>&gt;30% did not complete study; cannot draw definitive conclusions for women and men separately.</td>
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<tr>
<td>PIP</td>
<td>4,758 heterosexual serodiscordant couples; 38% HIV-negative female, 68% HIV-negative male partner; 98% married; median age 33</td>
<td>Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, Zambia</td>
<td>Daily oral TDF or TDF/FTC</td>
<td>67% protection with TDF alone; 75% protection with TDF/FTC</td>
<td>Discordant couples may be a distinct, unique population.</td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td>1,951 heterosexual women aged 18–35 at high risk of infection</td>
<td>Kenya, South Africa, Tanzania</td>
<td>Daily oral TDF/FTC</td>
<td>Trial discontinued for futility in April 2011.</td>
<td>Adherence assessment with monthly clinical samples to measure drug concentration is pending.</td>
</tr>
<tr>
<td>VOICE MTN-003</td>
<td>5,029 heterosexual women aged 18–45 in high-prevalence areas</td>
<td>Uganda, South Africa, Zimbabwe</td>
<td>Daily oral TDF or daily oral TDF/FTC or daily topical TFV gel</td>
<td>No study drug significantly reduced the risk of HIV acquisition. Estimates of effectiveness were less than 0 for TDF and TDF/FTC daily oral dosing (negative 48.8% and negative 4.2% TDF/FTC respectively), and reduced risk of HIV infection of 14.7% for TDF gel.</td>
<td>Adherence to study drugs was low; TFV was detected in 30% of the oral TDF arm, 29% in the oral TDF/FTC arm, and 25% in the TDF gel arm.</td>
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Key to Acronyms: TDF = tenofovir disoproxil fumarate; TFV = tenofovir; FTC = emtricitabine


PrEP may offer an additional strategy for safer conception. Couples should be advised to use condoms at all times except during the fertile period. Several studies evaluating the efficacy of PrEP in heterosexual discordant couples planning pregnancy are ongoing, but complete data are not yet available.

Only daily dosing of combination tenofovir disoproxil fumarate (TDF) and emtricitabine is currently Food and Drug Administration-approved for use as PrEP. Adherence is critical. The use of continued PrEP is recommended for anyone who is at ongoing risk of HIV acquisition.

Pregnancy and breastfeeding are not contraindications to PrEP. Currently, there is no reported increase in congenital anomalies among children born to women exposed to TDF (2.3%) or to emtricitabine (2.4%) during the first trimester. Data from studies of infants born to HIV-infected mothers and exposed to TDF through breast milk suggest limited drug exposure. Condom use should be encouraged in pregnancy because several studies have reported increased incidence of HIV acquisition during pregnancy, which may also lead to increased perinatal transmission.

Periconception administration of ARV pre-exposure prophylaxis for HIV-uninfected partners whose HIV-infected partner’s plasma viral load is unknown or detectable may offer an additional tool to reduce the risk of sexual transmission. The additional benefit of daily oral PrEP when the HIV-infected partner is receiving ART is unknown. Several modeling studies have analyzed the utility of PrEP under different conditions. Hoffman’s analysis shows that PrEP provides little added benefit when the HIV-infected male partner is on ART with suppressed viral load, condomless sex is limited to the ovulation window, and other modifiable...
transmission risks are optimized.35 In another modeling study by Mabileau et al to assess the residual risk of HIV transmission, cost and cost-effectiveness of various options for discordant couples where the male partner is HIV-infected and is on suppressive therapy with viral load below detectable:

- Treatment as prevention (TaP)
- Treatment as prevention limited to fertile days;
- Treatment as prevention with pre-exposure prophylaxis;
- Treatment as prevention and pre-exposure prophylaxis limited to fertile days; or
- Medically assisted procreation (MAP).

In the modeling studies HIV transmission was highest with TaP and lowest with MAP. Targeting fertility days with TaP was more effective than pre-exposure prophylaxis and TaP and cost less. The risk of HIV transmission was lower with TaP and pre-exposure prophylaxis limited to fertile days and MAP but cost more.36

**Pre-exposure Prophylaxis Use and Monitoring in HIV-Serodiscordant Couples**

If clinicians elect to use PrEP for HIV-uninfected women or men in serodiscordant couples, the couples should be educated about the potential risks and benefits and all available alternatives for safer conception. The Centers for Disease Control and Prevention (CDC) recommends that an HIV-uninfected partner planning pregnancy with an HIV-infected partner start daily oral TDF plus emtricitabine beginning 1 month before conception is attempted and continued for 1 month after conception is attempted.37 Recommended laboratory testing should include HIV diagnostic testing at baseline then every 3 months, renal function testing at baseline and then every 6 months, and pregnancy testing at baseline and every 3 months. Testing for hepatitis B virus (HBV) infection should be performed when initiating PrEP. HBV-uninfected individuals should be vaccinated if they have not received HBV vaccination or they lack immunity to HBV. Individuals receiving PrEP should be educated about symptoms associated with acute HIV infection and advised to contact their providers immediately for further evaluation, should symptoms occur. HIV-uninfected partners should undergo frequent HIV testing to detect HIV infection quickly. If HIV infection is documented, the PrEP ARV agents should be discontinued to minimize selection of drug-resistant virus, measures should be instituted to prevent perinatal transmission if pregnancy has occurred and attempts at conception stopped if pregnancy has not occurred, and the patient should be referred to an HIV specialist immediately. Individuals with chronic HBV should be monitored for possible hepatitis flares when PrEP is stopped.38 Clinicians are strongly encouraged to register HIV-uninfected women who become pregnant while receiving PrEP with the Antiretroviral Pregnancy Registry.

One study evaluated timed intercourse with PrEP in 46 heterosexual HIV-discordant couples with an HIV-uninfected female partner. The male HIV-infected partners were receiving ART and had undetectable plasma HIV RNA levels. One dose of oral TDF disoprol ifumarate (TDF) was taken by the women at luteinizing hormone peak and a second oral dose was taken 24 hours later. None of the women became HIV infected and pregnancy rates were high, reaching a plateau of 75% after 12 attempts.39 Another study from England reported the use of TDF with or without emtricitabine for PrEP by the HIV uninfected female partner with timed intercourse in 13 serodiscordant couples; PrEP was well tolerated and no HIV transmissions occurred.40

**Additional Options for Safer Conception**

For HIV-discordant couples in which the woman is the HIV-infected partner, the safest form of conception is assisted insemination, including the option to self-inseminate with the partner’s semen during the fertile period. Condom use should be advised at all times.

For HIV-discordant couples in which the man is the HIV-infected partner, the use of donor sperm from an HIV-uninfected man with artificial insemination is the safest option. When the use of donor sperm is unacceptable, the use of sperm preparation techniques coupled with either intrauterine insemination or in vitro fertilization with intracytoplasmic sperm injection has been reported to be effective in avoiding seroconversion in uninfected women and offspring in several studies.41-43
These sperm preparation techniques were largely developed prior to the studies demonstrating the efficacy of PrEP and ART in decreasing transmission to HIV-uninfected sexual partners. Therefore, the appropriate role of semen preparation techniques in the current context is unclear, particularly given their expense and technical requirements. Semen preparation should utilize optimal methods that can detect the presence of HIV. Couples should also consider the cost and other possible complications of in vitro fertilization. More data are needed to demonstrate the complete efficacy of these techniques, and couples should be cautioned that there may be a small risk of transmission of HIV to the uninfected partner and to their offspring. Semen analysis is recommended for HIV-infected men before conception is attempted because HIV, and possibly ART, may be associated with a higher prevalence of sperm abnormalities such as low sperm count, low motility, higher rate of abnormal forms, and low semen volume. If such abnormalities are present, the uninfected female partner may be exposed unnecessarily and for prolonged periods to her partner’s infectious genital fluids when the likelihood of conceiving naturally is low or nonexistent.

Discordant couples who do not have access to these reproduction services (i.e., artificial insemination, sperm preparation, in vitro fertilization) and who still want to try to conceive after comprehensive counseling should be advised that timed, periovulatory unprotected intercourse after the infected partner has achieved a plasma viral load below the limits of detection (with use of condoms at all other times) may reduce but not completely eliminate the risk of sexual transmission. HIV-uninfected women who become pregnant should be regularly counseled regarding consistent condom use to decrease their risk of sexual transmission of HIV and the possible risk of perinatal transmission (see Monitoring of HIV Uninfected Pregnant Women with a Partner Known to be HIV Infected).

**Concordant Couples**

Both partners should be on ART with maximum viral suppression before attempting conception. Periovulatory unprotected intercourse (with use of condoms at all other times) is a reasonable option. The risk of HIV superinfection or infection with a resistant virus is negligible when both partners are on ART and have fully suppressed plasma viral loads.

The National Perinatal HIV Hotline (1-888-448-8765) is a resource for a list of institutions offering reproductive services for HIV concordant/serodiscordant couples.

The CDC has issued guidelines for the use of PrEP in sexually active heterosexual adults.37

**Monitoring of HIV-Uninfected Pregnant Women with Partners Known to Be HIV-Infected**

HIV-uninfected women who present during pregnancy and indicate that their partners are HIV-infected, like all pregnant women, should be notified that HIV screening is recommended and they will receive an HIV test as part of the routine panel of prenatal tests unless they decline. HIV-uninfected pregnant women should also be counseled to always use condoms to reduce the risk of HIV acquisition and their HIV-infected partners should be virologically suppressed on ART. These women also should receive a second HIV test during the third trimester, preferably before 36 weeks’ gestation, as is recommended by CDC. Furthermore, pregnant women who present in labor without results of third-trimester testing should be screened on the labor and delivery unit with an expedited serum HIV test, preferably a fourth-generation antigen/antibody expedited HIV test. If at any time during pregnancy a clinician suspects that a pregnant woman may be in the “window” period of seroconversion (i.e., she has signs or symptoms consistent with acute HIV infection), then a plasma HIV RNA test should be used in conjunction with an HIV antigen/antibody fourth-generation test. If the plasma HIV RNA is negative, it should be repeated in 2 weeks. HIV-uninfected pregnant women with HIV-infected partners should always use condoms during sexual intercourse to prevent acquisition of HIV. Women should be counseled regarding the symptoms of acute retroviral syndrome (i.e., fever, pharyngitis, rash, myalgia, arthralgia, diarrhea, and headache) and the importance of seeking medical care and testing if they experience such symptoms.

Pregnancy and breastfeeding are not contraindications to PrEP, and PrEP should be considered in HIV-seronegative pregnant women who are at ongoing risk of HIV acquisition. However, the use of daily oral PrEP...
during pregnancy and lactation has not been well studied (see section on Serodiscordant Couples).

Women who test HIV seropositive on either conventional or rapid HIV tests should receive appropriate evaluation and interventions to reduce perinatal transmission of HIV, including immediate initiation of appropriate ART and consideration of elective cesarean delivery according to established guidelines (see Transmission and Mode of Delivery). In cases where confirmatory test results are not readily available, such as with rapid testing during labor, it is still appropriate to initiate interventions to reduce perinatal transmission (see Infant Antiretroviral Prophylaxis).

Women with HIV-infected partners who test HIV seronegative should continue to be regularly counseled regarding consistent condom use to decrease their risk of sexual transmission of HIV. Women with primary HIV infection during pregnancy or lactation are at high risk of transmitting HIV to their infants. 49,50

References


34. Mirochnick M, Best BM, Clarke DF. Antiretroviral pharmacology: special issues regarding pregnant women and...


