Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States

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Reproductive Options for HIV-Concordant and Serodiscordant Couples (Last updated July 31, 2012; last reviewed July 31, 2012)

Panel's Recommendations

- For serodiscordant couples who want to conceive, expert consultation is recommended so that approaches can be tailored to specific needs, which may vary from couple to couple **(AIII)**. It is important to recognize that treatment of the infected partner may not be fully protective against sexual transmission of HIV.
- Partners should be screened and treated for genital tract infections before attempting to conceive **(AII)**.
- For HIV-infected females with HIV-uninfected male partners, the safest conception option is artificial insemination, including the option of self-insemination with a partner's sperm during the peri-ovulatory period **(AIII)**.
- For HIV-infected men with HIV-uninfected female partners, the use of sperm preparation techniques coupled with either intrauterine insemination or *in vitro* fertilization should be considered if using donor sperm from an HIV-uninfected male is unacceptable **(AII)**.
- For serodiscordant couples who want to conceive, initiation of antiretroviral therapy (ART) for the HIV-infected partner is recommended (**AI** for CD4 T-lymphocyte (CD4-cell) count ≤550 cells/mm^3, **BIII** for CD4-cell count >550 cells/mm^3). If therapy is initiated, maximal viral suppression is recommended before conception is attempted **(AIII)**.
- Periconception administration of antiretroviral pre-exposure prophylaxis (PrEP) for HIV-uninfected partners may offer an additional tool to reduce the risk of sexual transmission **(CIII)**. The utility of PrEP of the uninfected partner when the infected partner is receiving ART has not been studied.

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*

For serodiscordant couples who want to conceive, expert consultation is recommended so that approaches can be tailored to specific needs, which may vary from couple to couple.

Before attempting to conceive, both partners should be screened for genital tract infections. If any such infections are identified, they should be treated because genital tract inflammation is associated with genital tract shedding of HIV.[1, 2] Semen analysis is recommended for HIV-infected males before conception is attempted because HIV, and possibly antiretroviral therapy (ART), may be associated with a higher prevalence of semen 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 getting pregnant naturally is low or even nonexistent.[3-6]

Observational studies have demonstrated a decreased rate of transmission of HIV in heterosexual serodiscordant couples among whom the index partners were on ART compared with those not on therapy.[7-9] HPTN 052 is 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/mm^3 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. Data from this study showed that earlier initiation of ART led to a significant 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/mm^3, whereas only 1 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/mm^3. The majority of transmissions (82%) were observed in participants from Africa. These are the first data from a randomized trial to demonstrate that provision of treatment to infected individuals can reduce the risk of transmission to their uninfected sexual partners.[10] Based on the results from HPTN 052, initiation of ART would be recommended for the infected partner in a serodiscordant couple who has a CD4-cell count of ≤550 cells/mm^3 if the couple wishes to conceive. Initiation of ART is also recommended for HIV-infected individuals with CD4-cell counts >550 cells/mm^3, although the benefit of ART in reducing sexual transmission from individuals with higher CD4-cell counts has not been determined. Before conception is attempted, maximal viral suppression is recommended for individuals who are on ART for their own health and those who do not require therapy but opt to start ART to prevent sexual transmission.

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. 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. Each $\log_{10}$ 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] Discordance between plasma and genital viral loads has been reported, and individuals with an undetectable plasma viral load may have detectable genital tract virus.[12-14] In addition, antiretroviral (ARV) drugs vary in their ability to penetrate the genital tract.[15] Thus, maximal plasma viral suppression may not completely eliminate risk of heterosexual transmission. Although use of ART may not eliminate all risk of sexual transmission, it may contribute to lowering risk in couples who have decided to conceive through unprotected intercourse despite known risks.

Reducing the risk of perinatal transmission is another potential rationale for starting ART before conception in HIV-infected women who do not yet need treatment for their own health. Data suggest that early and sustained control of HIV viral replication may be associated with decreasing residual risk of perinatal transmission,[16, 17] but that does not completely eliminate the risk of perinatal transmission.[17] In addition, reports are mixed on the possible effects of combination ARV drug regimens on prematurity and low birth weight, with some but not all data suggesting that such outcomes may be more frequent in women on ARV drugs at conception[18, 19] (see Special Considerations Regarding the Use of Antiretroviral Drugs by HIV-Infected Pregnant Women and Their Infants).

The implications of initiating therapy before conception solely for prevention of sexual and/or perinatal transmission should be discussed with patients. These issues include willingness and ability to commit to potential lifelong therapy, the potential risks versus benefits of stopping or continuing the regimen after conception in the male or postpartum in the female, and the need for strict adherence to achieve maximal viral suppression. Consultation with an expert in HIV care is strongly recommended.

For HIV-discordant couples in which the female is the HIV-infected partner, the safest form of conception is artificial insemination, including the option to self-inseminate with the partner's sperm during the peri-ovulatory period. Condom use should be advised at all times.

For HIV-discordant couples in which the male is the HIV-infected partner, the use of sperm preparation techniques coupled with either intrauterine insemination or *in vitro* fertilization has been reported to be effective in avoiding seroconversion in uninfected women and offspring in several studies.[20, 21] The National Perinatal HIV Hotline (1-888-448-8765) is a resource for a list of institutions offering reproductive services for HIV-serodiscordant couples. More data are needed to demonstrate the complete efficacy of these techniques, and couples should be cautioned about the potential risk of transmission of HIV to the uninfected partner and to their offspring.[21] Discordant couples who do not have access to assisted reproduction services

and who still want to try to conceive after comprehensive counseling should be advised that timed, peri-ovulatory unprotected intercourse after the infected partner has achieved maximal viral suppression (with use of condoms at all other times) may reduce but not completely eliminate the risk of sexual transmission.[21] 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).

Periconception pre-exposure prophylaxis (PrEP) may offer an additional option in the future to minimize risk of transmission of HIV within discordant couples. PrEP is use of ARV medications by an HIV-uninfected individual to maintain blood and genital drug levels sufficient to prevent acquisition of HIV. An experimental 1% tenofovir gel used intravaginally both before and after sex reduced the incidence of HIV infection in women by up to 54% in a randomized, placebo-controlled trial conducted in South Africa.[22] This product is not available commercially, and additional trials are needed to confirm these findings. Five efficacy trials of PrEP with oral ARV agents (primarily tenofovir alone) have been completed or are currently under way.[23] In one study of daily tenofovir/emtricitabine in HIV-seronegative men who have sex with men, there was a 44% reduction in the risk of acquisition of HIV compared with placebo.[24, 25] The TDF2 study, a placebo-controlled trial of PrEP to prevent sexual transmission in HIV-uninfected, heterosexual, sexually active, healthy adults aged 18 to 39 years in Botswana, found that daily oral PrEP with tenofovir/emtricitabine taken by the HIV-uninfected partner reduced the risk of acquisition of HIV by 63% (95% confidence interval [CI], 21.5–83.4; $P = .0133$) and was effective in both men and women.[26] The Partners PrEP Study, a placebo-controlled, three-arm trial, also found that daily PrEP with tenofovir or tenofovir/emtricitabine significantly reduced HIV transmission in discordant heterosexual couples in Kenya and Uganda. Those who received tenofovir had 62% fewer HIV infections (95% CI, 34–78; $P = .0003$) and those who received tenofovir/emtricitabine had 73% fewer HIV infections (95% CI, 49–85; $P = <.0001$) than those who received placebo, and these regimens were effective in both men and women.[27] However, the FEM-PrEP clinical trial, designed to study whether HIV-uninfected women at high risk of being exposed to HIV can safely use a daily dose of tenofovir/emtricitabine to prevent infection, was stopped early by its Data and Safety Monitoring Board (DSMB) because it was highly unlikely the study would be able to demonstrate the effectiveness of tenofovir/emtricitabine in preventing HIV infection in the study population. The approximate rate of new HIV infections among trial participants was 5% per year. A total of 56 new HIV infections had occurred, with an equal number of infections in participants assigned to tenofovir/emtricitabine and those assigned to a placebo.[28] The VOICE study is the first trial to evaluate both daily oral (tenofovir or tenofovir/emtricitabine) and topical (1% tenofovir microbicide gel) PrEP and has enrolled more than 5,000 HIV-uninfected heterosexual women in South Africa, Uganda, and Zimbabwe. The oral tenofovir and tenofovir gel arms of the study were stopped by its DSMB because it concluded that the study would be unable to show any difference between a daily dose of oral tenofovir or tenofovir gel and placebo in preventing HIV infection. The tenofovir/emtricitabine study arm is ongoing. Data on the FEM-PrEP, TDF2, Partners PrEP, and VOICE studies are preliminary.

Several studies evaluating the efficacy of PrEP in heterosexual discordant couples planning pregnancy are ongoing but complete data are not yet available. 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 tenofovir 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.[29]

The use of daily oral PrEP during pregnancy and lactation for HIV-uninfected women with HIV-infected partners has had limited study. PrEP may offer an additional strategy for safer conception. However, it will be important to have outcome studies that examine adverse events, including risk of congenital abnormalities. Additionally, the utility of daily oral PrEP when the HIV-infected partner is receiving ART has

not been studied. 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. Only combination tenofovir/emtricitabine is being evaluated in current heterosexual PrEP trials. Laboratory testing for HIV infection, baseline renal function, and hepatitis B virus (HBV) infection should be performed before initiating PrEP. Screening for sexually transmitted diseases also is recommended. Individuals receiving PrEP should be monitored for potential side effects such as renal dysfunction and clinical toxicities. They 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. Should HIV infection be documented, the ARV agents should be discontinued to minimize selection of drug-resistant virus, and measures should be instituted to prevent perinatal transmission if pregnancy occurs. Individuals with chronic HBV should be monitored for possible hepatitis flares when PrEP is stopped.[30] Clinicians are strongly encouraged to register uninfected women who become pregnant while receiving PrEP with the Antiretroviral Pregnancy Registry.

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

Clinicians may increasingly be seeing HIV-uninfected women who present during pregnancy and indicate that their partners are HIV infected. They, 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. These women also should receive a second HIV test during the third trimester, preferably before 36 weeks of gestation, as is recommended for high-risk women. Furthermore, pregnant women who present in labor without results of third-trimester testing should be screened with a rapid HIV test on the labor and delivery unit. If at any time during pregnancy a clinician suspects that a pregnant woman may be in the "window" period of seroconversion (that is, she has signs or symptoms consistent with acute HIV infection), then a plasma HIV RNA test should be used in conjunction with an HIV antibody test. If the plasma HIV RNA is negative, it should be repeated in 2 weeks. All 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 (that is, fever, pharyngitis, rash, myalgia, arthralgia, diarrhea, headache) and the importance of seeking medical care and testing if they experience such symptoms.

Women who test positive on either conventional or rapid HIV tests should receive appropriate evaluation and interventions to reduce perinatal transmission of HIV, including immediate initiation of appropriate ARV prophylaxis 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 negative 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.[31, 32]

References

1. Mitchell C, Hitti J, Paul K, et al. Cervicovaginal shedding of HIV type 1 is related to genital tract inflammation independent of changes in vaginal microbiota. *AIDS Res Hum Retroviruses*. Jan 2011;27(1):35-39. Available at http://www.ncbi.nlm.nih.gov/pubmed/20929397.
2. Johnson LF, Lewis DA. The effect of genital tract infections on HIV-1 shedding in the genital tract: a systematic review and meta-analysis. *Sex Transm Dis*. Nov 2008;35(11):946-959. Available at

http://www.ncbi.nlm.nih.gov/pubmed/18685546.

3. Garrido N, Meseguer M, Remohi J, Simon C, Pellicer A. Semen characteristics in human immunodeficiency virus (HIV)- and hepatitis C (HCV)-seropositive males: predictors of the success of viral removal after sperm washing. *Hum Reprod*. Apr 2005;20(4):1028-1034. Available at http://www.ncbi.nlm.nih.gov/pubmed/15608027.
4. Dulioust E, Du AL, Costagliola D, et al. Semen alterations in HIV-1 infected men. *Hum Reprod*. Aug 2002;17(8):2112-2118. Available at http://www.ncbi.nlm.nih.gov/pubmed/12151446.
5. Cardona-Maya W, Velilla P, Montoya CJ, Cadavid A, Rugeles MT. Presence of HIV-1 DNA in spermatozoa from HIV-positive patients: changes in the semen parameters. *Curr HIV Res*. Jul 2009;7(4):418-424. Available at http://www.ncbi.nlm.nih.gov/pubmed/19601777.
6. Bujan L, Sergerie M, Moinard N, et al. Decreased semen volume and spermatozoa motility in HIV-1-infected patients under antiretroviral treatment. *J Androl*. May-Jun 2007;28(3):444-452. Available at http://www.ncbi.nlm.nih.gov/pubmed/17215546.
7. Donnell D, Baeten JM, Kiarie J, et al. Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. *Lancet*. Jun 12 2010;375(9731):2092-2098. Available at http://www.ncbi.nlm.nih.gov/pubmed/20537376.
8. Del Romero J, Castilla J, Hernando V, Rodriguez C, Garcia S. Combined antiretroviral treatment and heterosexual transmission of HIV-1: cross sectional and prospective cohort study. *BMJ*. 2010;340:c2205. Available at http://www.ncbi.nlm.nih.gov/pubmed/20472675.
9. Lu W, Zeng G, Luo J, et al. HIV transmission risk among serodiscordant couples: a retrospective study of former plasma donors in Henan, China. *J Acquir Immune Defic Syndr*. Oct 1 2010;55(2):232-238. Available at http://www.ncbi.nlm.nih.gov/pubmed/21423851.
10. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med*. Aug 11 2011;365(6):493-505. Available at http://www.ncbi.nlm.nih.gov/pubmed/21767103.
11. Baeten JM, Kahle E, Lingappa JR, et al. Genital HIV-1 RNA predicts risk of heterosexual HIV-1 transmission. *Sci Transl Med*. Apr 6 2011;3(77):77ra29. Available at http://www.ncbi.nlm.nih.gov/pubmed/21471433.
12. Cu-Uvin S, DeLong AK, Venkatesh KK, et al. Genital tract HIV-1 RNA shedding among women with below detectable plasma viral load. *AIDS*. Oct 23 2010;24(16):2489-2497. Available at http://www.ncbi.nlm.nih.gov/pubmed/20736815.
13. Sheth PM, Kovacs C, Kemal KS, et al. Persistent HIV RNA shedding in semen despite effective antiretroviral therapy. *AIDS*. Sep 24 2009;23(15):2050-2054. Available at http://www.ncbi.nlm.nih.gov/pubmed/19710596.
14. Politch JA, Mayer KH, Welles SL, et al. Highly active antiretroviral therapy does not completely suppress HIV in semen of sexually active HIV-infected men who have sex with men. *AIDS*. Mar 23 2012. Available at http://www.ncbi.nlm.nih.gov/pubmed/22441253.
15. Taylor S, Davies S. Antiretroviral drug concentrations in the male and female genital tract: implications for the sexual transmission of HIV. *Curr Opin HIV AIDS*. Jul 2010;5(4):335-343. Available at http://www.ncbi.nlm.nih.gov/pubmed/20543610.
16. Townsend CL, Cortina-Borja M, Peckham CS, de Ruiter A, Lyall H, Tookey PA. Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000-2006. *AIDS*. May 11 2008;22(8):973-981. Available at http://www.ncbi.nlm.nih.gov/pubmed/18453857.
17. Tubiana R, Le Chenadec J, Rouzioux C, et al. Factors associated with mother-to-child transmission of HIV-1 despite a maternal viral load <500 copies/ml at delivery: a case-control study nested in the French perinatal cohort (EPF-ANRS CO1). *Clin Infect Dis*. Feb 15 2010;50(4):585-596. Available at http://www.ncbi.nlm.nih.gov/pubmed/20070234.
18. Kourtis AP, Schmid CH, Jamieson DJ, Lau J. Use of antiretroviral therapy in pregnant HIV-infected women and the risk of premature delivery: a meta-analysis. *AIDS*. Mar 12 2007;21(5):607-615. Available at http://www.ncbi.nlm.nih.gov/pubmed/17314523.

19. Rudin C, Spaenhauer A, Keiser O, et al. Antiretroviral therapy during pregnancy and premature birth: analysis of Swiss data. *HIV Med*. Apr 2011;12(4):228-235. Available at http://www.ncbi.nlm.nih.gov/pubmed/20726902.

20. Aberg JA, Kaplan JE, Libman H, et al. Primary care guidelines for the management of persons infected with human immunodeficiency virus: 2009 update by the HIV medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis*. Sep 1 2009;49(5):651-681. Available at http://www.ncbi.nlm.nih.gov/pubmed/19640227.

21. Ethics Committee of the American Society for Reproductive M. Human immunodeficiency virus and infertility treatment. *Fertil Steril*. Jun 2010;94(1):11-15. Available at http://www.ncbi.nlm.nih.gov/pubmed/20236636.

22. Abdool Karim Q, Abdool Karim SS, Frohlich JA, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science*. Sep 3 2010;329(5996):1168-1174. Available at http://www.ncbi.nlm.nih.gov/pubmed/20643915.

23. Okwundu CI, Okoromah CA. Antiretroviral pre-exposure prophylaxis (PrEP) for preventing HIV in high-risk individuals. *Cochrane Database Syst Rev*. 2009(1):CD007189. Available at http://www.ncbi.nlm.nih.gov/pubmed/19160329.

24. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med*. Dec 30 2010;363(27):2587-2599. Available at http://www.ncbi.nlm.nih.gov/pubmed/21091279.

25. Michael NL. Oral preexposure prophylaxis for HIV--another arrow in the quiver? *N Engl J Med*. Dec 30 2010;363(27):2663-2665. Available at http://www.ncbi.nlm.nih.gov/pubmed/21091280.

26. Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral Preexposure Prophylaxis for Heterosexual HIV Transmission in Botswana. *N Engl J Med*. Jul 11 2012. Available at http://www.ncbi.nlm.nih.gov/pubmed/22784038.

27. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral Prophylaxis for HIV Prevention in Heterosexual Men and Women. *N Engl J Med*. Jul 11 2012. Available at http://www.ncbi.nlm.nih.gov/pubmed/22784037.

28. Van Damme L, Corneli A, Ahmed K, et al. Preexposure Prophylaxis for HIV Infection among African Women. *N Engl J Med*. Jul 11 2012. Available at http://www.ncbi.nlm.nih.gov/pubmed/22784040.

29. Vernazza PL, Graf I, Sonnenberg-Schwan U, Geit M, Meurer A. Preexposure prophylaxis and timed intercourse for HIV-discordant couples willing to conceive a child. *AIDS*. Oct 23 2011;25(16):2005-2008. Available at http://www.ncbi.nlm.nih.gov/pubmed/21716070.

30. Lampe MA, Smith DK, Anderson GJ, Edwards AE, Nesheim SR. Achieving safe conception in HIV-discordant couples: the potential role of oral preexposure prophylaxis (PrEP) in the United States. *Am J Obstet Gynecol*. Jun 2011;204(6):488 e481-488. Available at http://www.ncbi.nlm.nih.gov/pubmed/21457911.

31. Marinda ET, Moulton LH, Humphrey JH, et al. In utero and intra-partum HIV-1 transmission and acute HIV-1 infection during pregnancy: using the BED capture enzyme-immunoassay as a surrogate marker for acute infection. *Int J Epidemiol*. Aug 2011;40(4):945-954. Available at http://www.ncbi.nlm.nih.gov/pubmed/21471020.

32. Humphrey JH, Marinda E, Mutasa K, et al. Mother to child transmission of HIV among Zimbabwean women who seroconverted postnatally: prospective cohort study. *BMJ*. 2010;341:c6580. Available at http://www.ncbi.nlm.nih.gov/pubmed/21177735.