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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HIV-Infected Pregnant Women Who Have Never Received Antiretroviral Drugs (Antiretroviral Naive) (Last updated July 31, 2012; last reviewed July 31, 2012)

Panel's Recommendations

- All HIV-infected pregnant women should receive a potent combination antiretroviral (ARV) regimen to reduce the risk of perinatal transmission of HIV **(AI)**. The choice of regimen should take into account current adult treatment guidelines, what is known about the use of specific drugs in pregnancy, and the risk of teratogenicity (Table 5).
- The decision as to whether to start the regimen in the first trimester or delay until 12 weeks' gestation will depend on CD4 T-lymphocyte (CD4-cell) count, HIV RNA levels, and maternal conditions such as nausea and vomiting **(AIII)**. Earlier initiation of a combination ARV regimen may be more effective in reducing transmission, but benefits must be weighed against potential fetal effects of first-trimester drug exposure.
- Combination ARV regimens should include a dual nucleoside reverse transcriptase inhibitor (NRTI) backbone that includes one or more NRTIs with high levels of transplacental passage (zidovudine, lamivudine, emtricitabine, tenofovir, or abacavir) **(AIII)**.
- ARV drug-resistance studies should be performed before starting the ARV regimen if HIV RNA is above the threshold for resistance testing (that is, >500–1,000 copies/mL) (see Antiretroviral Drug Resistance and Resistance Testing in Pregnancy) **(AI)**. If HIV is diagnosed later in pregnancy the ARV regimen should be initiated promptly without waiting for the results of resistance testing **(BIII)**.
- Nevirapine can be used as a component of the ARV regimen in pregnant women with CD4 cell counts ≤250 cells/mm^3. In pregnant women with CD4 cell counts >250 cells/mm^3, however, nevirapine should be used only if the benefit clearly outweighs the risk because the drug is associated with an increased risk of hepatic toxicity **(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*

Pregnant women with HIV infection should receive standard clinical, immunologic, and virologic evaluation.

They should be counseled about and offered combination antiretroviral (ARV) regimens containing at least 3 drugs for prevention of perinatal transmission of HIV. Use of an ARV regimen that successfully reduces plasma HIV RNA to undetectable levels substantially lowers the risk of perinatal transmission of HIV, lessens the need for consideration of elective cesarean delivery as an intervention to reduce risk of transmission, and reduces risk of ARV drug resistance in the mother. In an analysis of perinatal transmission in 5,151 HIV-infected women between 2000 and 2006 in the United Kingdom and Ireland, the overall mother-to-child transmission rate was 1.2%. A transmission rate of 0.8% was seen in women on ARV drugs for at least the last 14 days of pregnancy, regardless of the type of ARV regimen or mode of delivery.[1] After adjustment for viral load, mode of delivery, and sex of the infant, longer duration of use of ARV drugs was associated with reduced transmission rates.

The ARV regimen used in pregnancy generally should consist of two nucleoside reverse transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor (PI), consistent with the principles of treatment for non-pregnant adults but taking into account what is known about use of the drugs in pregnancy and risks of teratogenicity (see General Principles Regarding Use of Antiretroviral Drugs during Pregnancy).[2] The regimen initiated during pregnancy can be modified after delivery to include simplified regimens that were not used in pregnancy because there were insufficient pregnancy safety data or drugs may be stopped in women who do not feel prepared to continue lifelong

therapy at that point. Decisions regarding ARV use after pregnancy should be made by women in consultation with their HIV care providers, taking into account current recommendations and life circumstances (see General Principles Regarding Use of Antiretroviral Drugs during Pregnancy).

Fetuses are most susceptible to the potential teratogenic effects of drugs during the first trimester and the risks of ARV drug exposure during that period are not fully known. Therefore, women in the first trimester who do not require immediate initiation of therapy for symptomatic HIV disease can consider delaying initiation of ARV drugs until after 12 weeks' gestation. This decision should be carefully considered by health care providers and the women. The discussion should include an assessment of a woman's health status and the benefits and risks to her health of delaying initiation of ARV drugs for several weeks.

Although most perinatal transmission of HIV events occur late in pregnancy or during delivery, recent analyses suggest that early control of viral replication may be important in preventing transmission. In a recent French study, lack of early and sustained control of maternal viral load appeared strongly associated with residual perinatal transmission of HIV.[3] That study evaluated risk factors for perinatal transmission in women with HIV RNA <500 copies/mL at the time of delivery; overall HIV transmission was 0.5%. Women who transmitted were less likely to have received ARV drugs at the time of conception than were nontransmitters and were less likely to have HIV RNA <500 copies/mL at 14, 28, and 32 weeks' gestation. By multivariate analysis, plasma viral load at 30 weeks' gestation was significantly associated with transmission. Among women starting ARV drugs during pregnancy, the gestational age at initiation of therapy did not differ between groups (30 weeks), but viral load decreased earlier in the nontransmitters. The number of patients initiating therapy during pregnancy was too small to assess whether initiation of ARV drugs in the first trimester was associated with lower rates of transmission; although not statistically significant, viral load in naive women appeared to also decrease earlier in the nontransmitters. These data suggest that early and sustained control of HIV viral replication is associated with decreasing residual risk of transmission and favor initiating ARV drugs sufficiently early in naive women to suppress viral replication by the third trimester; however, this potential benefit must be balanced against the unknown long-term outcome of first-trimester drug exposure.

ARV drug-resistance testing should be performed before starting an ARV regimen if HIV RNA is above the threshold for resistance testing (that is, >500–1,000 copies/mL). For details regarding genotypic and phenotypic resistance testing, see *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. Given the association of earlier viral suppression with lower risk of transmission as discussed above, if HIV is diagnosed in the second half of pregnancy the ARV regimen should be initiated promptly without waiting for the results of resistance testing. Because clinically significant resistance to PIs is less common than resistance to NNRTIs in ARV-naive individuals, a PI-based ARV drug regimen generally should be considered in this situation.

ARV prophylaxis is recommended for all pregnant women with HIV infection, regardless of viral load. Although rates of perinatal transmission are low in women with undetectable or low HIV RNA levels, there is no threshold below which lack of transmission can be ensured.[4-6] The mechanism by which ARV drugs reduce perinatal transmission of HIV is multifactorial. Although lowering maternal antenatal viral load is an important component of prevention in women with higher viral load, ARV prophylaxis is effective even in women with low viral load.[7-11] Additional mechanisms of protection include pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis of the infant. With PrEP, passage of the ARV drug across the placenta results in presence of drug levels sufficient for inhibition of viral replication in the fetus, particularly during the birth process when there is intensive viral exposure. Therefore, whenever possible, combination ARV drug regimens initiated during pregnancy should include zidovudine or another NRTI with high transplacental passage, such as lamivudine, emtricitabine, tenofovir, or abacavir (see Table 5).[12-15] With post-exposure prophylaxis, ARV drugs are administered to the infant after birth.

Use of nevirapine in pregnancy requires special consideration. A review of a large database of nevirapine studies indicated that women with CD4 cell counts >250 cells/mm^3 have an increased risk of developing symptomatic, often rash-associated, nevirapine-related hepatotoxicity that can be severe, life threatening, and in some cases fatal.[16, 17] A more recent study involving 820 women in Kenya, Zambia, and Thailand, however, did not find an association between CD4 cell count and development of hepatotoxicity.[18] Increased risk of rash and liver toxicity were associated with elevated baseline liver transaminases but not with CD4 cell count; all deaths from hepatic toxicity occurred in women with CD4 cell counts <100 cells/mm^3 at baseline on concomitant anti-tuberculosis therapy. In women with CD4 cell counts >250 cells/mm^3, nevirapine should be used as a component of a combination ARV regimen only when the benefit clearly outweighs the risk. If nevirapine is used, baseline and frequent monitoring of transaminase levels is required, particularly during the first 18 weeks of treatment (see Nevirapine and Hepatic/Rash Toxicity). Transaminase levels should be checked before starting nevirapine and again in women who develop a rash. Nevirapine should be stopped immediately in women who develop signs or symptoms of hepatitis.

The use of raltegravir in late pregnancy for women who have high viral loads has been suggested because of its ability to rapidly suppress viral load (approximately 2-log copies/mL decrease by Week 2 of therapy).[19-22] However, the efficacy and safety of this approach have not been evaluated and only anecdotal reports are available. Until more data become available on the safety of raltegravir use in pregnancy, this approach cannot be recommended for therapy-naive women.

Some women may wish to restrict fetal exposure to ARV drugs while reducing the risk of HIV transmission to their infants. Use of zidovudine alone during pregnancy for prophylaxis of perinatal transmission is not optimal, but it could be an option for women with low viral loads (that is, <1,000 copies/mL) on no ARV drugs. In the U.K. study discussed above, transmission rates were 0.7% for women receiving a triple-ARV drug regimen combined with planned cesarean delivery or with planned vaginal delivery and 0.5% in 464 women with HIV RNA levels below 10,000 copies/mL who received single-drug prophylaxis with zidovudine combined with planned cesarean delivery, not significantly different between groups. Zidovudine single-drug prophylaxis is recommended in the British HIV Association guidelines for women with HIV RNA levels <10,000 copies/mL and wild-type virus who do not require treatment for their own health.[23] Time-limited administration of zidovudine during the second and third trimesters is less likely to induce development of resistance in women with low viral loads than in those with higher viral loads. This lower rate of resistance is likely because of the low level of viral replication and the short duration of exposure.[24, 25] Women's choices after counseling to use or not use ARV drugs during pregnancy should be respected.

After delivery, considerations regarding continuation of the ARV regimen for treatment in mothers are the same as in other non-pregnant adults (see General Principles Regarding Use of Antiretroviral Drugs during Pregnancy).

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