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 Previously Received Antiretroviral Treatment or Prophylaxis but Are Not Currently Receiving Any Antiretroviral Medications (Last updated July 31, 2012; last reviewed July 31, 2012)

Panel's Recommendations
• Obtain an accurate history of all prior antiretroviral (ARV) regimens used for treatment of HIV disease or prevention of transmission, including virologic efficacy, tolerance to the medications, results of prior resistance testing, and any adherence issues **(AIII)**. • If HIV RNA is above the threshold for resistance testing (that is, >500–1,000 copies/mL), ARV drug-resistance studies should be performed before starting an ARV drug regimen (see Antiretroviral Drug Resistance and Resistance Testing in Pregnancy) **(AIII)**. In women who present late in pregnancy, therapy or prophylaxis should be initiated promptly without waiting for the results of resistance testing **(BIII)**. • Choose and initiate a combination ARV drug regimen based on results of resistance testing and prior history of antiretroviral therapy while avoiding drugs with teratogenic potential or with known adverse potential for the mother **(AII)**. • Consult specialists in treatment of HIV infection about the choice of a combination ARV regimen in women who previously received ARV drugs for their own health **(AIII)**. • Perform repeat ARV drug-resistance testing **(AI)**, assess adherence, and consult with an HIV treatment specialist to guide changes in ARV drugs in women who do not achieve virologic suppression on their ARV regimens (see Monitoring of the Woman and Fetus During Pregnancy). ***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*

During a previous pregnancy, HIV-infected women may have received antiretroviral (ARV) drugs solely for prevention of perinatal transmission. At any time in the past, they also may have discontinued ARV drugs given to them for treatment of their own disease. A small number of clinical trials or observational studies have generated information about how effective antiretroviral therapy (ART) is in individuals who previously received ARV prophylaxis. The data are limited to outcomes with therapy containing nevirapine initiated after the use of peripartum single-dose nevirapine.[1-5]

Initial reports suggested a diminished virologic and clinical response to nevirapine-based ART if therapy was initiated within 6 months of intrapartum single-dose nevirapine exposure.[1-3] Subsequent reports have confirmed that a shorter interval between intrapartum single-dose nevirapine exposure and initiation of therapy with ART regimens containing nevirapine is associated with decreased efficacy of therapy and suggested that the diminished response may persist 12 to 24 months after exposure.[4, 5] In addition, the subsequent failure of non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ART after single-dose nevirapine has been associated with lower CD4 T-lymphocyte (CD4-cell) count and higher HIV-RNA plasma concentration at the time of single-dose nevirapine exposure and genotypic resistance to nevirapine. However, in a retrospective analysis of virologic suppression rates after initiation of an efavirenz-based ART regimen within 24 months of receipt of intrapartum single-dose nevirapine for prevention of perinatal transmission, no difference was seen between cases and controls who had never received single-dose nevirapine. Efficacy was similar when therapy was initiatied within and after 6 months of single-dose nevirapine.[6] Adding other ARV drugs to single-dose nevirapine (such as use of an ARV "tail") decreases rates of nevirapine resistance[7, 8] (see Antiretroviral Drug Resistance and Resistance Testing in Pregnancy), but the

effect on clinical response of subsequent initiation of NNRTI-based ART is unknown.

There is concern that time-limited use of ARV drugs during pregnancy for prophylaxis of perinatal transmission may lead to genotypic resistance and, thus, reduced efficacy of these ARV drugs when used either for indicated HIV therapy in a woman or during a subsequent pregnancy for prevention of perinatal transmission. Rates of resistance appear to be low, based on standard genotyping, after prophylaxis for prevention of perinatal transmission with combination ARVs consisting of zidovudine, lamivudine, and nevirapine.[9, 10] However, minority populations of virus with resistance to nevirapine or lamivudine have been detected using sensitive allele-specific polymerase chain reaction (PCR) techniques, particularly in women whose virus was inadequately suppressed during prophylaxis.[10-12] Only limited data are available on the impact of these resistance-conferring minority variants on prediction of virologic or clinical failure of subsequent ART, and the PCR-based assays are not widely available. Both standard and sensitive genotyping techniques appear to show a low rate of resistance to protease inhibitors (PIs) after pregnancy-limited use of PI-based combination ARV regimens for prophylaxis, but these results reflect assessments in only small numbers of women.[12, 13]

To date, treatment failure has not been demonstrated with reinitiation of combination ARV regimens following prophylactic use in pregnancy for prevention of transmission. In ACTG 5227, 52 women who had previously received combination ARV regimens for prevention of perinatal transmission, had no evidence of HIV drug resistance, and had an indication for restarting ART were prescribed a fixed-dose combination of efavirenz plus tenofovir/emtricitabine once daily. After 6 months of therapy, 81% achieved plasma viral loads below the limit of detection; the virologic suppression rate was similar regardless of the drug class of the prior combination ARV regimen and whether women had received such ARV regimens in 1 or more than 1 previous pregnancy.[14] Data from the French Perinatal Cohort assessed virologic suppression with a PI-based combination ARV regimen administered for prevention of perinatal transmission to women who had received ARV prophylaxis during a previous pregnancy. No differences in rates of undetectable viral load at delivery were noted among ARV-naive women when compared with those with previous prophylaxis or according to type of previous prophylaxis regimens received.[15] In addition, the United Kingdom and Ireland-based National Study of HIV in Pregnancy and Childhood found no increased risk of perinatal transmission in sequential pregnancies compared with 1 pregnancy at a time when most women received interventions for prevention of perinatal HIV transmission.[16] However, sufficiently large, prospective, observational studies and clinical trials are lacking to show that pregnancy-limited ARV prophylaxis has no effect on virologic outcome of subsequent ART.

Given the lack of substantive data, it is reasonable to use results of initial resistance testing, if available, to make preliminary decisions about ARV regimens in women whose only previous exposure to ARV drugs was during pregnancy for prophylaxis of perinatal transmission. However, interpretation of resistance testing after discontinuation of ARV drugs can be complex because drug-resistance testing is most accurate if performed while an individual is taking the ARV regimen or within 4 weeks of treatment discontinuation. In the absence of selective drug pressure, resistant virus may revert to wild-type virus, and although detection of drug-resistance mutations is informative for choosing a regimen, a negative finding does not rule out the presence of archived drug-resistant virus that could re-emerge once drugs are reinitiated. Therefore, when selecting a new regimen for use during the current pregnancy, all information from the previous pregnancy—including regimens received, viral response, laboratory testing (including HLA-B*5701 results), and any tolerance or adherence issues—and the results of resistance testing should be taken into consideration. In women who present late in pregnancy, therapy or prophylaxis should be initiated pending results of resistance testing. Careful monitoring of virologic response to the chosen ARV regimen is important.

If the chosen regimen produces an insufficient viral response, decisions about switching regimens should be guided by repeat resistance testing and assessment of medication adherence. These measures should be undertaken in consultation with an HIV treatment specialist.

Some women who receive ART for their own health choose to discontinue the drugs for a variety of reasons, and the length of time between treatment termination and pregnancy may vary. In these cases, careful clinical and laboratory assessments are necessary before therapy is reinitiated during pregnancy. The evaluations should include a review of a woman's prior history of virologic response and medication toxicity and her adherence to therapy. The appropriate choice of ARV regimen to be initiated during pregnancy will vary according to a woman's history of ART; the indication for stopping therapy; the effect of prior therapy on clinical, virologic, and immunologic status; and the results of past and current testing for resistance and for HLA-B*5701. It may be possible, for example, to restart the same regimen in women with a history of prior ART associated with successful suppression of viral load who then stopped all drugs simultaneously (or staggered discontinuation, if therapy was NNRTI based) and who have no evidence of resistance. On the other hand, the selection of an appropriate ARV regimen may be challenging even for health care providers experienced in HIV care in women with advanced HIV disease, a history of extensive prior ART, or previous significant toxicity or nonadherence to ARV drugs. In such cases, restarting the prior regimen for a week or two before performing a resistance assay may yield more accurate results. In addition to obtaining genotypic resistance testing, it is strongly recommended that specialists in the treatment of HIV infection be consulted early during the pregnancy about the choice of a suitable combination ARV regimen.

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