



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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Antiretroviral Drug Resistance and Resistance Testing in Pregnancy (Updated September 14, 2011)

Indications for Antiretroviral Drug-Resistance Testing in HIV-Infected Pregnant Women

Panel's Recommendations

- HIV drug-resistance testing is recommended for:
 - All pregnant women with HIV RNA levels above the threshold for resistance testing (e.g., >500–1,000 copies/mL) not currently receiving antiretroviral (ARV) drugs, before starting treatment or prophylaxis **(AIII)**.
 - All pregnant women receiving antenatal ARV drugs who have suboptimal viral suppression or persistent viral rebound to detectable levels after prior viral suppression on an ARV regimen **(AII)**.
- Empiric initiation of ARV drugs before results of resistance testing are available may be warranted, with adjustment as needed after the test results are available, for optimal prevention of perinatal transmission **(BIII)**.

Resistance testing is recommended for all ARV-naive pregnant women with HIV RNA levels above the threshold for resistance testing (e.g., >500–1,000 copies/mL) before initiating treatment or prophylaxis if prior resistance testing has not been done. For details regarding genotypic and phenotypic resistance testing see [Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents](#). Ideally, resistance testing would have been done at a preconception visit to allow receipt of results and to select an appropriate ARV drug regimen during pregnancy or before pregnancy if maternal therapy was indicated.

Resistance testing should also be performed before initiation of therapy or prophylaxis in pregnant women with HIV RNA levels above the threshold for resistance testing (e.g., >500–1,000 copies/mL) who received prophylaxis in previous pregnancies and are now restarting ARV drugs for prevention of perinatal transmission. No data currently are available to address the utility of resistance testing during pregnancy in women who do not require treatment for their own health or in women with multiple pregnancies who **have received corresponding courses** of ARV prophylaxis for prevention of mother-to-child transmission. The identification of baseline resistance mutations may allow selection of more effective and durable ARV regimens for women who need treatment and help ensure a wider range of future treatment options for women receiving ARV drugs solely for perinatal prophylaxis. There is no evidence, however, that baseline resistance testing in pregnancy is associated with a reduction in rates of perinatal transmission.

Resistance testing should also be performed following initiation of an ARV regimen during pregnancy or in HIV-infected pregnant women who are receiving antiretroviral therapy (ART) when they present for obstetrical care if there is suboptimal viral suppression or persistent viral load rebound to detectable levels after prior viral suppression on the ARV regimen.

In most settings, the results of resistance testing guide selection of the initial ARV regimen. In some situations in pregnant women, however, the clinician may choose to initiate empiric ARV drug regimen before resistance-testing results are available to optimize prevention of perinatal transmission of HIV. Once resistance test results are obtained, the ARV drug regimen can be modified as needed. **Most experts believe that for women in the third trimester, the benefits of immediate initiation of ARV drugs for prevention of mother-to-child transmission, pending results of resistance testing, outweigh the possible risk of short-term use of a regimen that could be suboptimal because of pre-existing resistance.**

Significance of Antiretroviral Drug Resistance in Pregnancy

The development of ARV drug resistance is one of the major factors leading to therapeutic failure in HIV-infected individuals. In pregnancy, it is associated with specific concerns that differ from those seen in the nonpregnant population. Pre-existing resistance to a drug in an ARV prophylaxis regimen may diminish the regimen's efficacy in preventing perinatal transmission. The development of resistance to drugs used during pregnancy for prophylaxis of perinatal transmission may limit future maternal treatment options or decrease the effectiveness of prophylactic regimens in the current pregnancy or during future pregnancies. Infant treatment options also may be limited if maternal resistance is present or develops and resistant virus is transmitted to the fetus.

Several factors unique to pregnancy may increase the risk of development of resistance. If drugs with significant differences in half-life (such as nevirapine or efavirenz combined with two nucleoside analogue drugs) are included in the ARV regimen, simultaneous postpartum discontinuation of all regimen components may result in persistent subtherapeutic drug levels and increase the risk of development of non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance (see [Stopping Antiretroviral Therapy during Pregnancy](#)). Problems such as nausea and vomiting in early pregnancy may compromise adherence and increase the risk of resistance in women receiving ARV drugs. Pharmacokinetic (PK) changes during pregnancy, such as increased plasma volume and renal clearance, may lead to subtherapeutic drug levels, increasing the risk that resistance will develop.

Incidence of Antiretroviral Resistance Emerging from the Use of Perinatal Prophylactic Regimens

The presence of mutations conferring resistance to nucleoside analogue drugs appears to be correlated with more advanced maternal disease and longer duration of prior or current exposure to these drugs¹⁻⁴. The development of zidovudine drug resistance when zidovudine is used alone appears uncommon in women with higher CD4 cell counts and lower viral loads⁵⁻⁶ but is more of a concern in women with advanced disease and lower CD4 cell counts².

Development of resistance associated with short-term use of ARV agents for prevention of mother-to-child transmission is most common with nevirapine, particularly single-dose nevirapine. Nevirapine has a low genetic barrier to resistance, with a single point mutation conferring resistance to nevirapine and to other first-generation NNRTI drugs. Furthermore, its long half-life, with blood levels detectable up to 21 days after a single dose in labor, increases selection pressure and the risk of resistance⁷. Factors associated with an increased risk of resistance following single-dose nevirapine exposure include high baseline viral load, low baseline CD4 cell count, viral subtype, and the number of maternal doses. The rate of genotypic resistance after exposure to single-dose nevirapine has varied in studies, ranging from 15% to 75%⁸⁻¹⁸. Studies using more sensitive real-time polymerase chain reaction (PCR) techniques suggest that up to one-half of resistance that develops is not detected by conventional sequence analysis^{16, 18-20}. The prevalence of resistance declines rapidly over time and the proportion of resistant virus in those with detectable virus 12 months after exposure is low. In a study of virus from 67 South African women, using a sensitive allele-specific resistance assay, the K103N mutation was seen in 87% of women at 6 weeks but in only 11% at 12 months after single-dose nevirapine exposure, with a median frequency of the mutation of 0.7% (range 0.5%–5.4%) in women with detectable resistance at 12 months²⁰.

In the PACTG 316 trial, the addition of single-dose nevirapine following antepartum administration of other ARV regimens (primarily combination regimens because 77% of women received antenatal combination ARV regimens still resulted in nevirapine resistance in 14 of 95 (15%; 95% confidence interval [CI], 8%–23%) women with detectable virus postpartum⁸. In this study, adding single-dose nevirapine

did not provide any additional efficacy in prevention of mother-to-child transmission but was associated with development of nevirapine resistance. Therefore, this approach is not recommended.

A recent study examined the presence of resistant mutations in HIV-1-infected women receiving combination ARV drug regimens that were stopped postpartum. All women evaluated received zidovudine and lamivudine, with 76% receiving nelfinavir and 8% receiving nevirapine. Rates of M184V/I mutations postpartum were 65% and 29% in women receiving dual or triple prophylaxis, respectively. NNRTI resistance was identified postpartum among 38% of nevirapine recipients, whereas only 1% of protease inhibitor (PI) recipients developed PI resistance²¹.

The Impact of Resistance on Pregnancy and the Risk of Perinatal Transmission of HIV

Perinatal Transmission

Perinatal transmission of resistant virus has been reported, but it appears to be unusual and there is little evidence that the presence of resistance mutations increases the risk of transmission when current recommendations for ARV management in pregnancy are followed. A substudy of the Women and Infants Transmission Study (WITS) followed pregnant women receiving zidovudine alone for treatment of HIV disease in the early 1990s. In this study, the detection of zidovudine resistance conferred an increased risk of transmission when analysis was adjusted for duration of membrane rupture and total lymphocyte count²; however, women in this cohort had characteristics that would indicate a need for ART under the current Department of Health and Human Services (HHS) recommendations for maternal health and for prevention of perinatal transmission. When transmitting mothers had mixed viral populations of wild-type and virus with low-level zidovudine resistance, only wild-type virus was detected in the infant²², and other studies have suggested that drug-resistance mutations may diminish viral fitness²³, possibly leading to a decrease in transmissibility. In another study, prevalence of ARV drug resistance among HIV-infected newborns in New York State was examined. Eleven (12.1%) of 91 infants born between 1989 and 1999 and 8 (19%) of 42 infants born between 2001 and 2002 had mutations associated with decreased drug susceptibility. However, perinatal exposure to ARVs was not found to be a significant risk factor for the presence of resistance during either time period²⁴⁻²⁵. Neither resistance to nevirapine that develops as a result of exposure to single-dose nevirapine nor exposure to single-dose nevirapine in a prior pregnancy has been shown to affect perinatal transmission rates²⁶⁻²⁷.

Maternal Response to Subsequent Treatment Regimens

Because nevirapine resistance mutations can be detected postpartum in a significant proportion of women receiving single-dose intrapartum nevirapine prophylaxis, the response to subsequent NNRTI-based combination therapy given for maternal health has been a concern^{12, 20, 26-29}. A study performed in Zambia, Kenya, and Thailand found that prior exposure to single-dose nevirapine was associated with an increased risk of treatment failure in pregnant women receiving NNRTI-based ART, with the greatest risk being in women receiving ART within 12 months of previous nevirapine exposure³⁰. The Optimal Combination Therapy After Nevirapine Exposure (OCTANE)/A5208 trial conducted in Africa compared nevirapine with lopinavir/ritonavir-based therapy in women requiring therapy who had prior exposure to single-dose nevirapine prophylaxis. The results suggest that prior exposure to single-dose nevirapine within 24 months of initiating therapy may be associated with a higher risk of viral failure with nevirapine-based therapy compared with lopinavir/ritonavir-based therapy. In this study, significantly more women in the nevirapine arm (29, 24%) failed to achieve a subsequent undetectable viral load (25) or died (4) compared with women in the lopinavir/ritonavir arm (8, 7%; 7 virologic failures and 1 death; $P < 0.0005$). Five of 13 (38%) women with documented nevirapine resistance at the start of therapy either had detectable virus or

died. This study demonstrates that women with documented nevirapine resistance are most likely to benefit from combination therapy that does not contain nevirapine (and because of cross resistance, efavirenz)²⁹.

Few data evaluate response to subsequent therapy in women who receive current combination drug regimens for prophylaxis and discontinue the drugs postpartum. In theory, however, resistance should not occur if the regimen that was discontinued had fully suppressed viral replication. Issues relating to the discontinuation of nevirapine-based combination therapy are discussed in [Prevention of Antiretroviral Drug Resistance](#).

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