Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States

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Antiretroviral Drug Resistance and Resistance Testing in Pregnancy

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Panel's Recommendations

- HIV drug-resistance **genotype** studies should be performed in women living with HIV whose HIV RNA levels are above the threshold for resistance testing (i.e., >500 to 1,000 copies/mL) before:
  - Initiating antiretroviral therapy (ART) in antiretroviral (ARV)-naive pregnant women who have not been previously tested for ARV resistance (AII),
  - Initiating ART in ARV-experienced pregnant women (AIII), or
  - Modifying ART regimens for women who are entering pregnancy while receiving ARV drugs or who have suboptimal virologic response to ARV drugs started during pregnancy (AII).

- ART should be initiated in pregnant women prior to receiving results of ARV-resistance studies; ART should be modified, if necessary, based on the results of the resistance assay (BIII). If an integrase strand transfer inhibitor (INSTI) is being considered for an ART-naive patient and INSTI resistance is a concern, providers should supplement standard resistance testing with a specific INSTI genotypic resistance assay (BIII). INSTI resistance may be a concern because:
  - A patient received prior treatment that included an INSTI,
  - A patient has a history with a sexual partner on INSTI therapy, or
  - A patient is starting or changing ART regimen late in pregnancy, in which case an INSTI might be selected because of its ability to rapidly decrease viral load.

- Documented zidovudine resistance does not affect the indications for use of intrapartum zidovudine (BII).

- Choice of ARV regimen for an infant born to a woman with known or suspected drug resistance should be determined in consultation with a pediatric HIV specialist, preferably before delivery (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV (AIII)).

- Pregnant women living with HIV should be given ART to maximally suppress viral replication, which is the most effective strategy for preventing development of resistance and minimizing risk of perinatal transmission (AII).

- All pregnant and postpartum women should be counseled about the importance of adherence to prescribed ARV medications to reduce the potential for development of resistance (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

**Indications for Antiretroviral Drug-Resistance Testing in Pregnant Women Living with HIV**

Identification of baseline resistance mutations allows for the selection of more effective and durable antiretroviral (ARV) regimens. Genotypic resistance testing (in addition to a comprehensive history of ARV drug use) is recommended for women living with HIV who have HIV RNA levels above the threshold for resistance testing (i.e., >500 to 1,000 copies/mL) before:

- Initiating antiretroviral therapy (ART) in ARV-naive pregnant women who have not been previously tested for ARV resistance,

- Initiating ART in ARV-experienced pregnant women, or

- Modifying ART regimens for women who are entering pregnancy while receiving ARV drugs or who have suboptimal virologic response to ARV drugs started during pregnancy.

In most settings, the results of resistance testing guide the selection of the initial ART regimen. However, given the association between earlier viral suppression and lower risk of perinatal transmission, in ARV-naive pregnant women or ARV-experienced women not presently on ART, ART should be initiated without waiting for the results of resistance testing. The regimen can be modified, if required, when test results return.
Use of integrase strand transfer inhibitors (INSTIs) as part of the ART regimen for pregnant women is becoming increasingly common. Resistance to INSTIs is generally uncommon among ARV-naive individuals in the United States. INSTI resistance was detected in 2.4% of ART-naive persons and 9.6% of ART-experienced persons with HIV in North Carolina. The prevalence of INSTI resistance increased slightly from 0.0% in 2004 to 1.4% in 2013 in Washington, DC. A polymorphism or a substitution associated with INSTI resistance was found in 1.4% of INSTI-naive persons in 16 clinical trials.

Among people who receive INSTI-based ART, the development of INSTI resistance is infrequent (1.48% to 3.80%). A modeling study of INSTI resistance testing at ART initiation found increased costs without improved clinical outcomes. Routine INSTI resistance testing is generally not indicated in pregnant women. However, such testing can be considered in the following circumstances:

- A patient received prior treatment that included an INSTI,
- A patient has a history with a sexual partner on INSTI therapy, or
- A patient is starting or changing her ART regimen late in pregnancy, in which case an INSTI might be selected because of its ability to rapidly decrease viral load.

HIV drug resistance genotype testing detects mutations that confer resistance to protease inhibitors (PIs), nucleoside reverse transcriptase inhibitors (NRTIs), and non-nucleoside reverse transcriptase inhibitors (NNRTIs). Phenotypic resistance testing is generally reserved for cases of complex NRTI resistance patterns in patients with limited treatment options (see Drug-Resistance Testing in the Adult and Adolescent Guidelines). At some institutions, testing for INSTI resistance may require a separate order.

**Incidence and Significance of Antiretroviral Drug Resistance in Pregnancy**

The development of ARV drug resistance is one of the major factors leading to therapeutic failure in individuals living with HIV. In addition, pre-existing resistance to a drug in an ART regimen may diminish the regimen’s efficacy in preventing perinatal transmission. Infant treatment options also may be limited if maternal drug resistance is present (or develops) and resistant virus is transmitted to the fetus. Resistance to ARV drugs appears to be more common in women who acquired HIV perinatally than in other women with HIV. The complexities of managing pregnant women with perinatally acquired HIV warrant consultation with an expert in HIV.

Several factors that are unique to pregnancy may increase the risk of developing resistance. Problems such as nausea and vomiting in early pregnancy may compromise adherence and increase the risk of developing resistance in women receiving ARV drugs. Pharmacokinetic changes during pregnancy, such as increased plasma volume and renal clearance, may lead to sub-therapeutic drug levels, increasing the risk that resistance will develop.

**Impact of Resistance on the Risk of Perinatal Transmission of HIV and Maternal Response to Subsequent Therapy**

**Perinatal Transmission**

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 sub-study of the Women and Infants Transmission Study followed pregnant women receiving zidovudine alone for treatment of HIV in the early 1990s. In this study, detection of zidovudine resistance conferred an increased risk of transmission when analysis was adjusted for duration of membrane rupture and total lymphocyte count; however, women in this cohort had characteristics that would indicate a need for ART under current recommendations from the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (the Panel). When transmitting mothers had mixed viral populations of wild-type virus and virus with low-level zidovudine resistance, only wild-type virus was detected in their infants with HIV. Other studies have suggested that drug-resistance mutations may diminish viral fitness, possibly leading to a decrease in transmissibility.
Neither resistance to NNRTI drugs 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 rates.\textsuperscript{11}

Although perinatal exposure to ARVs has not been found to be associated with a significant risk for the presence of resistance, the prevalence of ARV drug resistance among newborns diagnosed with HIV in New York State was 11 of 91 infants (12.1\%) born between 1989 and 1999 and 8 of 42 (19\%) infants born between 2001 and 2002.\textsuperscript{12,13} Thus, for infants with HIV, there is a high risk of ARV drug resistance.

**Maternal Response to Subsequent Treatment Regimens**

The French Perinatal Cohort evaluated the association between exposure to ARV drugs to prevent perinatal transmission during a previous pregnancy and presence of a detectable viral load with exposure to ARV drugs during the current pregnancy in women followed between 2005 and 2009.\textsuperscript{14} Among 1,166 women who were not receiving ARV drugs at the time of conception, 869 were ARV-naive and 247 had received ARV drugs to prevent perinatal transmission during a previous pregnancy. Previous ARV prophylaxis was PI-based in 48\% of these women, non-PI-based in 4\%, NRTI dual ARV drugs in 19\%, and zidovudine as a single ARV drug in 29\%. A PI-based ART regimen was initiated in 90\% of the women during the current pregnancy; in multivariate analysis, ARV exposure during a prior pregnancy was not associated with detectable viral load in the current pregnancy. A separate study (ACTG A5227) evaluated viral suppression in 52 women with prior combination ARV exposure to prevent perinatal transmission who had stopped ARV drugs at least 24 weeks before study entry and were now initiating ART (efavirenz, tenofovir disoproxil fumarate, and emtricitabine) for treatment.\textsuperscript{15} None of the women had prior or recent resistance detected on standard bulk genotyping. Viral suppression was observed in 81\% of women after 24 weeks of follow-up, with no difference in response by number of prior ARV drug exposures to prevent perinatal transmission or the drug class of prior exposure. Recent clinical series have confirmed this observation.\textsuperscript{16,17}

**Management of Antiretroviral Drug Resistance during Pregnancy**

For women who have documented zidovudine resistance and whose antepartum regimen does not include zidovudine, intravenous (IV) zidovudine still should be given during labor when indicated (for HIV RNA >1,000 copies/mL near delivery; see Intrapartum Antiretroviral Therapy/Prophylaxis). Other ARVs should be continued orally during labor to the extent possible. The rationale for including zidovudine intrapartum when a woman is known to harbor virus with zidovudine resistance is based on several factors. Only wild-type virus appears to be transmitted to infants by mothers who have mixed populations of wild-type virus and virus with low-level zidovudine resistance.\textsuperscript{9} Other studies have suggested that drug-resistance mutations may diminish viral fitness and possibly decrease transmissibility.\textsuperscript{10} The efficacy of the zidovudine prophylaxis appears to be based not only on a reduction in maternal HIV viral load but also on the use of pre- and post-exposure prophylaxis in the infant.\textsuperscript{18-20} Zidovudine crosses the placenta readily and has a high cord-to-maternal-blood ratio. In addition, zidovudine is metabolized to the active triphosphate within the placenta,\textsuperscript{21,22} which may provide additional protection against transmission. Zidovudine penetrates the central nervous system (CNS) better than other nucleoside analogues except stavudine, which has similar CNS penetration; this may help eliminate a potential reservoir for transmitted HIV in the infant.\textsuperscript{23,24} Thus, intrapartum IV administration of zidovudine, when indicated, is recommended even in the presence of known zidovudine resistance, due to the drug’s unique characteristics and its proven record in reducing perinatal transmission.

The optimal prophylactic regimen for newborns of women with ARV drug-resistant virus is unknown. Therefore, ARV prophylaxis for infants born to women with known or suspected drug-resistant virus should be determined with the help of a pediatric HIV specialist, preferably before delivery (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV). There is no evidence that neonatal prophylaxis regimens that have been customized based on the presence of maternal drug resistance are more effective than standard neonatal prophylaxis regimens.
Prevention of Antiretroviral Drug Resistance

The most effective way to prevent development of ARV drug resistance in pregnancy is to adhere to an effective ARV regimen that achieves maximal viral suppression.

Several studies have demonstrated that women’s adherence to ART may worsen during the postpartum period.25-30

Previous versions of the Perinatal Guidelines have provided guidance for clinicians in cases where women stop their ART regimen postpartum. However, the Panel strongly recommends that ART, once initiated, not be discontinued. If a woman desires to discontinue ART after delivery, a consultation with an HIV specialist is strongly recommended (see Discontinuation or Interruption of Antiretroviral Therapy in the Adult and Adolescent Guidelines).

References


