Antiretroviral Drug Resistance and Resistance Testing in Pregnancy

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Panel's Recommendations
• HIV drug-resistance testing (genotypic and, if indicated, phenotypic) 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 (including those who have received pre-exposure prophylaxis) **(AIII)**, *or* • Modifying ARV regimens for women who are newly pregnant and receiving ARV drugs or who have suboptimal virologic response to the ARV drugs started during pregnancy **(AII).** • Phenotypic resistance testing is indicated for treatment-experienced persons on failing regimens who are thought to have multidrug resistance **(BIII)**. • ART should be initiated in pregnant women prior to receiving results of ARV-resistance testing; ART should be modified, if necessary, based on the results of resistance assays **(BIII)**. • If the use of an integrase strand transfer inhibitor (INSTI) is being considered 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 if: • A patient received prior treatment that included an INSTI, *or* • A patient has a history with a sexual partner on INSTI therapy. • Documented zidovudine (ZDV) resistance does not affect the indications for use of intrapartum intravenous ZDV (see Intrapartum Care for Women with HIV)**(BIII)**. • 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 HIV Infection) **(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 risk of developing 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 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 obtaining a comprehensive history of ARV drug use) is recommended for women 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 (including those who have received pre-exposure prophylaxis), *or*
- Modifying ARV regimens for women who are newly pregnant and receiving ARV drugs or who have suboptimal virologic response to ARV drugs that were initiated during pregnancy.

In most settings, the results of resistance testing guide the selection of the initial ARV regimen. However, ART

should be initiated in ARV-naive pregnant women or ARV-experienced women who are not presently on ART without waiting for the results of resistance testing, as earlier viral suppression is associated with lower risk of perinatal transmission. The regimen can be modified, if required, when test results return.

It is increasingly common for integrase strand transfer inhibitors (INSTIs) to be included in ARV regimens for pregnant women.[1] Resistance to INSTIs is generally uncommon among ARV-naive individuals in the United States.[2] INSTI resistance was detected in 2.4% of ART-naive persons and 9.6% of ART-experienced persons with HIV in North Carolina[3] and in 2.9% of ART-naive participants from an HIV clinic in Santa Clara County, California.[4] The prevalence of INSTI resistance increased slightly from 0.0% in 2004 to 1.4% in 2013 in Washington, DC.[5] A polymorphism or a substitution associated with INSTI resistance was found in 1.4% of INSTI-naive persons in 16 clinical trials.[6]

The development of INSTI resistance is infrequent among people who receive INSTI-based ART (only 1.48% to 3.80% of people develop resistance). A modeling study found that testing for INSTI resistance at ART initiation was not cost-effective and did not improve clinical outcomes.[7] Routine INSTI-resistance testing is generally not indicated in pregnant women. However, such testing can be considered when a patient received prior treatment that included an INSTI or when a patient has a history with a sexual partner on INSTI therapy.

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 and is recommended for treatment-experienced persons on failing regimens with suspected multidrug resistance (see Drug-Resistance Testing in the Adult and Adolescent Antiretroviral Guidelines). At some institutions, testing for INSTI resistance may have to be ordered separately.

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 with HIV. In addition, pre-existing resistance to a drug in an ARV regimen may diminish the regimen's efficacy in preventing perinatal transmission. Maternal drug resistance can be transmitted to the fetus, which can limit treatment options for the infant. Resistance to ARV drugs appears to be more common in women who acquired HIV perinatally than in other women with HIV.[8] The complexities of managing pregnant women with perinatally acquired HIV warrant consultation with an expert in HIV.[9] (see Prenatal Care, Antiretroviral Therapy, and HIV Management in Women with Perinatal HIV Infection for more information).

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, increasing the risk of developing resistance in women receiving ARV drugs. Pharmacokinetic changes during pregnancy (e.g., increased plasma volume and renal clearance) may lead to subtherapeutic drug levels, increasing the risk that resistance will develop.

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

Perinatal Transmission

There is little evidence that the presence of resistance mutations increases the risk of perinatal transmission when pregnant women with HIV are on suppressive ART. Some studies have suggested that drug-resistance mutations may diminish viral fitness,[10] possibly leading to a decrease in transmissibility. A nested case-control study that was conducted as part of the NICHD/HPTN 040 (P1043) study found that pre-existing drug-resistance mutations in pregnant women who did not receive antepartum ARV drugs were not associated with an increased risk of perinatal HIV transmission.[11] Another nested case-control study, which was part of a larger study in Cape Town, South Africa, examined elevated viral loads in pregnant and postpartum women. The study found that at a matched postpartum time point, <10% of the elevated viral loads could be attributed to ARV resistance.[12]

In a study of 84 children with perinatal HIV infection in France that collected data between 2006 and 2017, transmitted drug resistance was found in 8.3% of participants. No participants had triple-class resistance; 5% had INSTI-related mutations (an E157Q mutation that primarily affects susceptibility to raltegravir and elvitegravir but not dolutegravir).[13]

Maternal Response to Subsequent Treatment Regimens

A study that used data collected from pregnant women enrolled in the French Perinatal Cohort between 2005 and 2009 evaluated the association between exposure to ARV drugs to prevent perinatal transmission during a previous pregnancy and the presence of a detectable viral load after exposure to ARV drugs during the current pregnancy.[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. Forty-eight percent of these women had previously used a PI-based regimen for ARV prophylaxis, 4% had used a regimen that did not include a PI, 19% had used a dual-NRTI regimen, and 29% had used zidovudine (ZDV) alone. A PI-based ARV 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 who had previously taken ARV drugs to prevent perinatal transmission. These women had stopped taking ARV drugs at least 24 weeks before study entry and had initiated a regimen of efavirenz, tenofovir disoproxil fumarate, and emtricitabine for treatment during the study.[15] Previous drug-resistance tests had not documented resistance in any of the women, and standard bulk genotyping did not detect resistance in any of the women at screening. Viral suppression was observed in 81% of women after 24 weeks of follow-up. Neither the number of prior ARV drug exposures to prevent perinatal transmission nor the drug class of prior exposure was associated with a failure to achieve viral suppression. Recent clinical series have confirmed this observation.[16,17]

Management of Antiretroviral Drug Resistance During Pregnancy

Women who have documented ZDV resistance and who did not receive ZDV as part of their antepartum regimen should still receive intravenous (IV) ZDV during labor when indicated (IV ZDV is indicated for women with HIV RNA >1,000 copies/mL near delivery; see Intrapartum Care for Women with HIV). A patient's normal ARV regimen should be continued orally during labor to the extent possible. The rationale for including ZDV intrapartum when a woman is known to harbor virus with ZDV 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 ZDV resistance.[18] Other studies have suggested that drug-resistance mutations may diminish viral fitness and possibly decrease transmissibility.[10] The efficacy of ZDV prophylaxis appears to be based not only on a reduction in maternal HIV viral load but also on the use of pre-exposure and post-exposure prophylaxis in the infant.[19-21] ZDV crosses the placenta readily and has a high cord-to-maternal-blood ratio. In addition, ZDV is metabolized to the active triphosphate within the placenta,[22] which may provide additional protection against transmission. ZDV penetrates the central nervous system (CNS) better than other recommended nucleoside analogues; this may help eliminate a potential reservoir for transmitted HIV in the infant.[23] ZDV's unique characteristics and its proven record in reducing perinatal transmission support the recommendation to administer intrapartum IV ZDV when indicated, even in the presence of known ZDV resistance.

The optimal prophylactic regimen for newborns of women with 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 HIV Infection). There is no evidence that neonatal prophylaxis regimens that have been customized to address maternal drug resistance are more effective than standard

neonatal prophylaxis regimens.

Prevention of Antiretroviral Drug Resistance

The most effective way for a patient to prevent the development of ARV drug resistance in pregnancy is to adhere to an effective ARV regimen that achieves maximal viral suppression. However, several studies have demonstrated that women's adherence to ART may worsen during the postpartum period.[24-29]

Previous versions of the Perinatal Guidelines have provided guidance for clinicians in cases where women stop their ARV regimen postpartum. However, the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission 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 Antiretroviral Guidelines).

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