Antiretroviral Drug Resistance and Resistance Testing in Pregnancy

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Panel's Recommendations
• Drug-resistance testing should be performed for people with virologic failure and HIV RNA levels >200 copies/mL (AI for >1,000 copies/mL, AIII for 501–1,000 copies/mL, CIII for confirmed HIV RNA 201–500 copies/mL). For people with confirmed HIV RNA levels >200 copies/mL but <500 copies/mL, drug-resistance testing may be unsuccessful but should still be considered. Perform resistance testing before— o Initiating antiretroviral therapy (ART) in antiretroviral (ARV)-naive pregnant persons who have not been previously tested for ARV resistance (AII), o Initiating ART in ARV-experienced pregnant persons (including those who have received pre-exposure prophylaxis) (AIII), *or* o Modifying ARV regimens for those who are newly pregnant and receiving ARV drugs or who have suboptimal virologic response to the ARV drugs started during pregnancy (AII). • ART should be initiated in pregnant persons before receiving results of ARV-resistance testing; ART should be modified, if necessary, based on the results of resistance assays (AII). • Phenotypic resistance testing is indicated for treatment-experienced persons on failing regimens who are thought to have multidrug resistance (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 (AIII). INSTI resistance may be a concern if— o A patient received prior treatment or pre-exposure prophylaxis that included an INSTI, *or* o A patient has had a sexual partner on INSTI therapy who was not virologically suppressed or with unknown viral load. • Documented zidovudine (ZDV) resistance does not affect the indications for use of intrapartum intravenous ZDV (see Intrapartum Care for People with HIV) (BIII). • Choice of ARV regimen for an infant born to a person 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) (BIII). • Pregnant persons 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 individuals 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 Persons with HIV

Identification of baseline resistance mutations allows for the selection of more effective and durable antiretroviral (ARV) regimens. Drug-resistance testing should be performed for people with virologic failure and HIV RNA levels >200 copies/mL. For people with confirmed HIV RNA levels >200 copies/mL but <500 copies/mL, drug-resistance testing may be unsuccessful but should still be considered. Perform resistance testing before—

- Initiating antiretroviral therapy (ART) in ARV-naive pregnant patients who have not been previously tested for ARV resistance,
- Initiating ART in ARV-experienced pregnant patients (including those who have received pre-exposure prophylaxis [PrEP]), *or*
- Modifying ARV regimens for those who are newly pregnant and receiving ARV drugs or who have suboptimal virologic response to ARV drugs that were initiated during pregnancy.

It is also important to obtain a comprehensive history of ARV drug use, including ARVs used for HIV PrEP. 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 persons or ARV-experienced individuals who are not presently on ART without waiting for the results of resistance testing because earlier viral suppression is associated with lower risk of perinatal transmission. The regimen can be modified, if required, when test results return.

Integrase strand transfer inhibitors (INSTIs) are used increasingly in ART regimens for pregnant people,[1] and the INSTI cabotegravir (Apretude) has been approved for PrEP. Resistance to INSTIs is generally uncommon among ARV-naive individuals in the United States.[2] In studies of INSTI resistance in North Carolina, resistance was detected in 2.4% (95% confidence interval [CI], 1.5% to 3.6%) of ART-naive persons and 9.6% (95% CI, 8.3% to 11.0%) of ART-experienced persons with HIV[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% ($P = 0.04$) in 2013 in Washington, D.C.[5] During 2014 to 2018, among 50,747 persons, Centers for Disease Control and Prevention surveillance within 3 months of HIV diagnosis identified 0.8% with INSTI resistance. A systematic review of 103 studies identified "surveillance" drug-resistance mutations in 0.5% of INSTI-naive individuals.[6,7] A polymorphism or a substitution associated with INSTI resistance was found in 1.4% of INSTI-naive persons in 16 clinical trials.[8]

The development of INSTI resistance is infrequent among people who receive INSTI-based ART (only 1.5% to 3.8% of people develop resistance).[9-11] A modeling study found that testing for INSTI resistance at ART initiation was not cost effective and did not improve clinical outcomes.[12] Genotype testing for INSTI resistance also is not considered cost effective in the United States when initiating ART.[13] Routine INSTI-resistance testing generally is not indicated in pregnant persons. However, such testing can be considered when a patient received prior treatment or PrEP that included an INSTI or when a patient has had a sexual partner on INSTI therapy who was not virologically suppressed or with unknown viral load.

HIV drug-resistance genotype testing detects mutations that confer resistance to protease inhibitors, nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors, and INSTIs. Phenotypic resistance testing is reserved generally 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.

There are currently no commercially available resistance tests for the CD4 T lymphocyte post-attachment inhibitor ibalizumab, gp120 attachment inhibitor fostemsavir, or capsid inhibitor lenacapavir.

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.[14] The complexities of managing pregnant people with perinatally acquired HIV warrant consultation with an expert in HIV.[15] See Prenatal Care, Antiretroviral Therapy, and HIV Management in People with Perinatal-Acquired 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 those 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.

Managing Antiretroviral Resistance During Pregnancy

The most effective way to prevent the development of ARV drug resistance in pregnancy is to follow recommendations for resistance testing and viral load monitoring and to support adherence to an effective ARV regimen that achieves maximal viral suppression (see Monitoring During Pregnancy). Management of pregnant people who have received ART or ARV prophylaxis previously, including resistance testing, is discussed in Pregnant People with HIV Who Have Previously Received Antiretroviral Medication But Are Not Currently on Antiretroviral Medications. Inadequate adherence and viral resistance should be considered when there is a suboptimal virologic response or viral rebound to an ARV regimen (see Pregnant People Who Have Not Achieved Viral Suppression on Antiretroviral Therapy). Because studies have shown that adherence to ART may worsen during the postpartum period,[16-19] arrangements should be made during pregnancy for appropriate postpartum follow-up and adherence support to prevent loss of virologic control and the development of resistance (see Postpartum Follow-Up of People with HIV).

The optimal prophylactic regimen for newborns of persons with drug-resistant HIV is unknown. Therefore, ARV prophylaxis for infants born to persons with known or suspected drug-resistant HIV 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). No evidence exists that neonatal prophylaxis regimens that have been customized to address maternal drug resistance are more effective than standard neonatal prophylaxis regimens.

Zidovudine Resistance During Pregnancy

Those who have documented zidovudine (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 patients with HIV RNA >1,000 copies/mL or unknown HIV viral load near delivery (see Intrapartum Care for People with HIV). A patient's ARV regimen should be continued orally during labor to the extent possible. The rationale for including ZDV intrapartum when a patient is known to have HIV with ZDV resistance is based on several factors. First, 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[20]; drug-resistance mutations may diminish viral fitness and possibly decrease transmissibility.[21] Second, the efficacy of ZDV prophylaxis appears to be based not only on a reduction in maternal HIV viral load, but also on the on its role as both PrEP and post-exposure prophylaxis in the infant.[22-24] 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,[25] which may provide additional protection against transmission. Third, ZDV penetrates the central nervous system better than other recommended nucleoside analogues; this may help eliminate a potential reservoir for transmitted HIV in the infant.[26] 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.

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