Antiretroviral Drug Resistance and Resistance Testing in Pregnancy

Updated: March 31, 2026
Reviewed: March 31, 2026

Panel's Recommendations
• Drug-resistance testing should be performed in the presence of virologic failure and with 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). When HIV RNA levels are >200 copies/mL but <500 copies/mL, drug-resistance testing may be unsuccessful but should still be considered. • Antiretroviral therapy (ART) should be initiated during pregnancy before receiving results of ARV-resistance testing; ART should be modified, if necessary, based on the results of resistance assays **(AII).** • All prior and current drug-resistance test results, when available, should be reviewed and considered when considering a new regimen **(AIII).** • Perform HIV drug-resistance testing when— o Initiating ART during pregnancy when there is no history of prior antiretroviral (ARV) use or prior ARV-resistance testing results **(AII),** o Initiating ART during pregnancy with prior exposure to ARVs, including pre-exposure prophylaxis **(AIII),** *or* o Modifying ARV regimens during a new pregnancy or in the presence of virologic failure **(AII).** • In most cases, perform genotypic rather than phenotypic testing when there is no history of prior ART use **(AIII).** o Genotypic testing is preferred over phenotypic resistance testing to guide therapy in instances of suboptimal virologic response or virologic failure while on first- or second-line regimens and when resistance mutation patterns are known or not expected to be complex **(AII).** o The addition of phenotypic to genotypic resistance testing is recommended in the context of known or suspected complex drug-resistance mutation patterns **(BIII).** • In most cases, perform standard genotype testing (for reverse transcriptase and protease mutations rather than integrase strand transfer inhibitor [INSTI] mutations). Important exceptions include when— o Transmitted INSTI resistance is suspected (e.g., a prior sexual partner was on INSTI therapy and not virologically suppressed or with unknown viral load) **(AII).** o There was previous use of long-acting cabotegravir (CAB-LA) as pre-exposure prophylaxis, or o There was previous use of an INSTI-based regimen for post-exposure prophylaxis **(AIII)** or for treatment of HIV without sustained viral suppression **(AIII).** • The optimal time to perform drug-resistance testing depends on the clinical scenario: o When a non–long-acting ARV regimen is being taken, drug-resistance testing in the setting of virologic failure should be performed while the ARV regimen is still being taken, or, if that is not possible, within 4 weeks after discontinuation of the ARV regimen **(AII).** If more than 4 weeks have elapsed since the non–long-acting agents have been discontinued, resistance testing may still provide useful information to guide therapy; however, it is important to recognize that previously selected resistance mutations can be missed because of lack of drug-selective pressure **(CIII).** o In the context of previous CAB-LA–based ART use (e.g., cabotegravir with rilpivirine or lenacapavir) and virologic failure, resistance testing (including INSTI genotypic testing) should be performed regardless of the time since the last dose of long-acting ARV **(AIII).**

- Documented zidovudine (ZDV) resistance does not affect the indications for use of intrapartum intravenous ZDV (see Intrapartum HIV Care) **(BIII).**
- Choice of ARV regimen for an infant perinatally exposed to known or suspected drug-resistant HIV should be determined in consultation with a pediatric HIV specialist, preferably before delivery (see Antiretroviral Management of Infants With *In Utero,* Intrapartum, or Breastfeeding Exposure to HIV) **(BIII).**

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 During Pregnancy 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) during pregnancy when there is no history of prior ARV use or prior ARV-resistance testing results,
- Initiating ART during pregnancy with prior exposure to ARVs, including pre-exposure prophylaxis (PrEP), *or*
- Modifying ARV regimens during a new pregnancy or in the presence of virologic failure.

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 as soon as possible during pregnancy, regardless of prior ARV exposure or the availability of resistance testing results, 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 during pregnancy,[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 people and 9.6% (95% CI, 8.3% to 11.0%) of ART-experienced people 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] From 2014 to 2018, among 50,747 people, 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 people 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 during pregnancy. However, such

testing should be considered when a person is receiving an INSTI-based regimen, when a person 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.

Currently, 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 people on failing regimens with suspected multidrug resistance (see Drug-Resistance Testing in the Adult and Adolescent Antiretroviral Guidelines). INSTI-resistance testing is particularly important in people who experience virologic failure while taking an INSTI-containing regimen or in those with prior use of injectable long-acting cabotegravir (either for treatment of HIV or as PrEP). At many institutions, testing for INSTI resistance may have to be ordered separately.

Testing for fusion inhibitor resistance can be ordered separately when needed. 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, preexisting 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 perinatally acquired HIV during pregnancy warrant consultation with an expert in HIV.[15] See Prenatal Care, Antiretroviral Therapy, and HIV Management When HIV Was Perinatally Acquired 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 Initial Evaluation and Continued Monitoring of HIV During Pregnancy). Management of HIV during pregnancy with prior ART or ARV prophylaxis use, including resistance testing, is discussed in Previous Experience With Antiretroviral Medications but Not Currently on Antiretroviral Therapy During Current Pregnancy. Inadequate adherence and viral resistance should be considered when there is a suboptimal virologic response or viral rebound to an ARV regimen (see Lack of Viral Suppression While on Antiretroviral Therapy in Pregnancy). 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 HIV Management and Follow-Up).

The optimal prophylactic regimen for newborns perinatally exposed to drug-resistant HIV is unknown. Therefore, ARV prophylaxis for infants perinatally exposed to known or suspected drug-resistant HIV should be determined with the help of a pediatric HIV specialist, preferably before delivery (see Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV). 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

In the United States, zidovudine (ZDV) is rarely used for HIV treatment. In those who have documented ZDV resistance and who did not receive ZDV as part of their antepartum regimen, intravenous (IV) ZDV should be given 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 HIV Care). 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 its role as both PrEP and post-exposure prophylaxis in the infant.[22-24] ZDV crosses the placenta readily and has a high cord blood–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 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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