Lack of Viral Suppression While on Antiretroviral Therapy in Pregnancy

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Panel's Recommendations
• Regular viral load monitoring is needed in pregnancy to quickly detect lack of viral suppression **(AII).** See Initial Evaluation and Continued Monitoring of HIV During Pregnancy. • To detect problems with viral suppression early, more frequent viral load monitoring (every 1–2 months) is recommended when regimens associated with lower drug levels in the third trimester or drugs with limited or no pharmacokinetic (PK) data about use in pregnancy are used **(AII).** See Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs During Pregnancy and When Trying to Conceive. • When lack of suppression is identified, a thoughtful evaluation of potential contributing factors is needed, including barriers to adherence, drug resistance, drug–drug and drug–food interactions, PK changes in pregnancy that affect drug levels, and combinations of these factors. Viral suppression management should address each of these factors, if relevant **(AII)** (see Antiretroviral Drug Resistance and Resistance Testing in Pregnancy and Virologic Failure in the Adult and Adolescent Antiretroviral Guidelines). After these factors are addressed, repeat viral load monitoring within 2 to 4 weeks **(AII).** • In general, adding a single antiretroviral drug to a virologically failing regimen **is not recommended** because this would rarely result in full virologic suppression and, therefore, may cause the development of resistance to one or more drugs in the regimen **(BII).** • Consider consulting with an HIV treatment specialist when modifying antiretroviral therapy (ART) due to inadequate viral suppression **(BIII).** Consultation is also available through the National Perinatal HIV/AIDS Hotline (1-888-448-8765). • Discontinuing or briefly interrupting ART may lead to a rapid increase in HIV RNA, a decrease in CD4 T lymphocyte cell count, the development of resistance mutations, and an increase in the risk of perinatal HIV transmission and clinical progression. Therefore, this strategy **is not recommended (AI).** Please see Intrapartum HIV Care for guidance about the use of intrapartum intravenous zidovudine prophylaxis and scheduled cesarean birth for pregnancy when viral suppression has not been achieved on ART.
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*

Virologic suppression to undetectable levels is defined as a confirmed plasma HIV RNA level that is below the lower limits of detection of an ultrasensitive assay. Suppression of HIV RNA to undetectable levels should be achieved as rapidly as possible in pregnancy because viral load affects the risk of perinatal transmission, with the lowest risk associated with viral load <50 copies/mL.[1,2] Baseline HIV RNA levels have been shown to affect the time to viral suppression both during pregnancy and in nonpregnant individuals, and no difference in time to viral response has been observed between pregnant and nonpregnant women.[3-5]

HIV RNA levels should be assessed regularly in pregnancy (see Initial Evaluation and Continued Monitoring of HIV During Pregnancy for guidance on timing and frequency). Physiologic changes that occur during pregnancy may result in lower levels of certain antiretrovirals (ARVs), resulting in loss of virologic control with the potential for perinatal transmission. To detect lack of viral suppression early, more frequent viral load monitoring (every 1–2 months) is recommended when

regimens associated with lower drug levels in the second or third trimester or drugs with limited or no pharmacokinetic (PK) data about use in pregnancy are used (see Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs During Pregnancy and When Trying to Conceive). **During pregnancy or breastfeeding, the definition of viral suppression (i.e., viral load <50 copies/mL) differs from thresholds used for nonpregnant individuals (**Adult and Adolescent Antiretroviral Guidelines**).**

For people initiating or changing antiretroviral therapy (ART), HIV RNA is expected to decline quickly, ideally achieving at least a tenfold (1 $\log_{10}$) drop within 4 weeks. With the use of integrase strand transfer inhibitors (INSTIs) as part of an ARV regimen, the decline may be even faster (e.g., a decrease of approximately 100-fold [2 $\log_{10}$] in HIV RNA levels can be expected by Week 2 of therapy).[6,7] In the United Kingdom, a multicenter, retrospective observational study of women initiating ART during pregnancy found that higher baseline viral load was the only independent factor associated with faster first-phase HIV RNA half-life decay, and that lower viral load on Day 14 after starting ART was associated with an increased likelihood of achieving an undetectable plasma viral load by 36 weeks of gestation or within 4 weeks of planned birth.[8]

Situations in which viral suppression is not achieved (i.e., viral load ≥ 50 copies/mL) remain a common problem during pregnancies in the United States and globally. For example, a report from the HIV Outpatient Study noted that among 119 pregnancies between 2005 and 2015, 33 women (27.7%) were not virally suppressed (HIV RNA >500 copies/mL) at the end of pregnancy.[9] Additionally, in a single-site cohort study conducted in the United States that included 230 pregnancies from 2009 to 2019, rates of optimal virologic control at birth did not significantly differ among mothers receiving dolutegravir (DTG, 93.1%), rilpivirine (RPV, 92.1%), boosted darunavir (DRV, 82.6%), or efavirenz (76.9%) but were significantly lower among mothers receiving atazanavir (49.0%) or lopinavir (40.9%). Overall, 73.5% of the cohort had an undetectable viral load at birth.[10]

Evaluating Factors Contributing to Detectable Viremia

Lack of virologic suppression is frequently associated with inadequate adherence. Other potential causes of detectable viremia include drug–drug interactions, lack of attention to food requirements with some ARV agents (e.g., RPV, DRV) that affect adequate drug absorption, concomitant administration or inadequate spacing of vitamins or foods containing calcium or iron (e.g., DTG, bictegravir, raltegravir, elvitegravir; see Appendix B: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy), and overall poor tolerability of the ARV drug—exacerbated by nausea and vomiting associated with pregnancy or hyperemesis gravidarum.

Barriers to adherence should be addressed when the viral load does not decline as expected (see Adherence to the Continuum of Care in the Adult and Adolescent Antiretroviral Guidelines). A systematic review and meta-analysis of ART adherence during and after pregnancy in low-, middle-, and high-income countries (27% of studies were from the United States) found that only 73.5% of pregnant women achieved adequate (>80%) ART adherence.[11] Factors that can contribute to suboptimal adherence to ART or suboptimal retention across the HIV treatment continuum in pregnancy include depression and other mental health disorders, barriers to HIV seropositive status disclosure, adverse drug reactions, a history of intimate partner violence, substance use, a lack of prior experience with taking ART, and a lack of knowledge about the role of ART in preventing perinatal transmission.[12-17] Other factors that have been associated with lack of viral suppression in pregnancy and are likely related to difficulties with adherence include unintended pregnancy and social and economic vulnerabilities (e.g., living in the United States for less than 5 years with no family/friends' support, neighborhood exposures to crime), as well as poor engagement in prenatal care.[18-20]

A retrospective study of 318 pregnant women addressed the risk of viral rebound (to HIV RNA >50 copies/mL) in pregnancy among women who received ART for ≥4 weeks and who had one or more prior undetectable viral load test results. Nineteen women (6%) had a viral rebound within 1 month before birth; 6 of these 19 women had a viral load >1,000 copies/mL. Significant predictors of viral rebound included cocaine use and testing positive for hepatitis C virus RNA.[21] Viral load testing is currently recommended at 36 weeks of gestation, or within 4 weeks of planned delivery, to inform decisions about mode of delivery; providers may consider repeat testing subsequently in selected instances when there is increased risk for viral rebound. Risk for viral rebound may be greater when regimens with PK concerns for lower drug levels in late pregnancy are used (e.g., cobicistat-boosted regimens and RPV) (see Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs During Pregnancy and When Trying to Conceive and When Antiretroviral Therapy is Being Taken When Pregnancy Occurs).

A lack of virologic suppression by late pregnancy may indicate virologic failure, but it may also represent inadequate time on ART when initiation occurred during pregnancy. Among 1,070 ART-naive pregnant women with HIV who participated in the prospective cohort study International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) P1025, initiating three-drug ART at >32 weeks of gestation (with a protease inhibitor– or non-nucleoside reverse transcriptase inhibitor–based regimen or a nucleoside reverse transcriptase inhibitor–only regimen) also was associated with a significantly higher risk of having a viral load >400 copies/mL at birth.[22] A recent cross-sectional analysis of 10,052 pregnant women with HIV receiving antenatal care in public facilities in South Africa reported that failure to achieve viral suppression (HIV RNA ≤50 copies/mL) was associated primarily with late registration for antenatal care and late initiation of ART.[23] In the French Perinatal Cohort of 14,630 women with HIV who gave birth from 2000 to 2017, both HIV RNA level at birth and timing of ART initiation were independently associated with risk of perinatal transmission of HIV.[1,24] An observational study of 763 pregnancies in South Africa (2021–2023), describing treatment with tenofovir/lamivudine/DTG initiated before 18 weeks of gestation, identified younger age and viremia at enrollment as predictors of viremic episodes at delivery and postpartum.[24]

For pregnancies after perinatally acquired HIV, there may be additional barriers to adherence and virologic suppression. Several studies from the United States and Europe have demonstrated that during pregnancy, perinatally acquired HIV is a risk factor for detectable viral load near the time of birth, increased resistance mutations, and a higher perinatal transmission rate than non–perinatally acquired HIV.[25,26] If needed, ARV regimens should be optimized in consultation with HIV treatment experts, and other possible contributing factors should be considered (see Prenatal Care, Antiretroviral Therapy, and HIV Management When HIV Was Perinatally Acquired).

Managing Lack of Viral Suppression

Before modifying an ARV regimen, consultation with a specialist in clinical care for ARV-experienced adults is recommended (e.g., the National Perinatal HIV Hotline at 1-888-448-8765). This is particularly important in cases where a drug regimen must be modified due to resistance or adverse effects. Regimen simplification may be considered to promote better adherence. A three-pronged approach is indicated for evaluating and managing pregnancy when ART is being used and viral suppression has not been achieved, taking time on treatment into account. The approaches include the following:

- Assessing adherence, tolerability, correct dosing, or potential problems with absorption (e.g., nausea/vomiting, use of gastroesophageal reflux disease medications, coadministration of prenatal vitamins and iron with INSTIs,[27,28] lack of attention to food requirements); ARV drug-resistance testing should be considered before changing regimens if plasma HIV RNA levels are

>200 copies/mL while on the current regimen. For instances of confirmed HIV with RNA levels >200 copies/mL but <500 copies/mL, drug-resistance testing may be unsuccessful but should still be considered; *and*

- Considering modifying the ARV regimen (see When Antiretroviral Therapy is Being Taken When Pregnancy Occurs, Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs During Pregnancy and When Trying to Conceive, and Virologic Failure in the Adult and Adolescent Antiretroviral Guidelines); *and*
- Repeating viral load monitoring within 2 to 4 weeks after relevant factors contributing to detectable viral load are addressed.

Evaluation of and support for adherence during pregnancy are critical to achieving and maintaining maximal viral suppression. Prepregnancy counseling and family planning services should be promoted and accessible to reduce unintended pregnancy, help those with HIV achieve their childbearing aspirations, and provide an important opportunity to support ART adherence. Early attention to the special need for adherence support among immigrant communities affected by HIV and other communities with adverse neighborhood exposures is also critical to achieving and maintaining maximal viral suppression.[19] In a retrospective cohort study at a Texas community center, group prenatal care for pregnant women with HIV, as compared to individual care, showed promise in achieving viral suppression by the time of birth (adjusted odds ratio 2.29; 95% confidence interval, 0.94–5.55; $P = 0.068$).[29] Other possible interventions include adherence education, treating problems that may interfere with drug absorption (e.g., vomiting), ensuring that a patient is taking ART in accordance with food requirements (see Table 14. Antiretroviral Drug Use in Pregnancy: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy), and directly observing drug administration in the home or hospital setting.[30]

When considering altering an ARV regimen because viral suppression targets have not been reached, resistance testing should be performed during pregnancy while the current regimen is still being used (see Antiretroviral Drug Resistance and Resistance Testing in Pregnancy). Resistance testing generally can be performed when HIV RNA levels are ≥500 copies/mL. For HIV RNA >200 copies/mL to <500 copies/mL, drug-resistance testing may be unsuccessful but should still be considered. The results can be used to select a new ARV regimen with a greater likelihood of suppressing viral replication to undetectable levels. For instances of current or prior INSTI exposure, INSTI-resistance testing in addition to standard genotype testing should be obtained.

The Adult and Adolescent Antiretroviral Guidelines offer specific regimen modifications for situations in which viral suppression has not been achieved or viral load has rebounded (see Virologic Failure).

In addition, when poor adherence is the reason that the patient has not achieved or maintained viral suppression, it is unclear whether adding a new drug to the existing regimen will improve adherence. In general, adding a single ARV drug to a virologically failing regimen **is not recommended** because this would rarely result in full virologic suppression and, therefore, may risk the development of resistance to one or more drugs in the regimen.

Finally, discontinuing or briefly interrupting ART may lead to a rapid increase in HIV RNA, a decrease in CD4 T lymphocyte cell count, and an increase in the risk of perinatal transmission and clinical progression.[31-33] Therefore, this strategy **is not recommended** in the setting of virologic failure.

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