Pregnant People Who Have Not Achieved Viral Suppression on Antiretroviral Therapy

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Panel's Recommendations
• Regular viral load monitoring is needed in pregnancy to quickly detect lack of viral suppression (AII). • When lack of suppression is identified, a thoughtful evaluation of potential contributing factors is needed, including barriers to adherence, drug resistance, pharmacokinetic (PK) changes in pregnancy leading to insufficient drug levels, and combinations of these factors. Management of lack of viral suppression should address each of these factors if relevant (AII). • If changes to a current antiretroviral therapy (ART) regimen are needed, data are insufficient to recommend for or against adding an integrase strand transfer inhibitor to a current nonsuppressive regimen (AIII). • To detect problems with viral suppression early, more frequent viral load monitoring (every 1–2 months) is recommended when individuals are receiving regimens associated with lower drug levels in the third trimester or drugs with limited or no PK data about use in pregnancy (AII). • Consider consulting with an HIV treatment specialist when modifying ART due to inadequate viral suppression (BIII). Please see Intrapartum Care for People With HIV for guidance about use of intrapartum intravenous zidovudine prophylaxis and scheduled cesarean delivery for pregnant people who have not achieved viral suppression 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 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 maternal 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 in both pregnant and 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-Related Assessments 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 problems with viral suppression early, more frequent viral load monitoring (every 1–2 months) is recommended when individuals are receiving regimens associated with lower drug levels in the third trimester or drugs with limited or no pharmacokinetic (PK) data about use in pregnancy.

For patients initiating or changing antiretroviral therapy (ART), HIV RNA is expected to decline fairly quickly, ideally achieving at least a 10-fold (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 $\log_{10}$ drop] in HIV RNA levels can be expected by week 2 of therapy).[6,7] Failure to achieve virologic suppression remains a common problem for

pregnant people 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.[8]

Virologic failure is defined as the inability to achieve or maintain an HIV RNA level of <200 copies/mL (see Virologic Failure in the Adult and Adolescent Antiretroviral Guidelines).[6] If virologic suppression has not been achieved, even if virologic failure has not yet occurred (e.g., VL between the lower limit of assay detection and 200 copies/mL), causes of detectable viremia should be evaluated and addressed before considering a change in an ARV regimen.

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 gestation.[9]

Evaluating Factors Contributing to Detectable Viremia

Lack of virologic suppression is frequently associated with inadequate adherence. 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.[10] Factors that can contribute to suboptimal adherence 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.[11-13] Other factors that have been associated with lack of viral suppression in pregnancy, and likely associated with 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.[14-16]

Other potential causes of detectable viremia include drug-drug interactions and lack of attention to food requirements with some ARV agents (e.g., rilpivirine (RPV), darunavir) that affect adequate drug absorption; concomitant administration or inadequate spacing of vitamins or foods containing calcium or iron (e.g., dolutegravir [DTG], raltegravir [RAL], elvitegravir; see Appendix B: Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy); and overall poor tolerability, particularly with the usual nausea and vomiting or hyperemesis gravidarum in pregnancy.

A retrospective study of 318 pregnant women addressed the risk of viral rebound in pregnancy among women who received ART for ≥4 weeks and who had had ≥1 prior undetectable viral load. Nineteen women (6%) had viral rebound (HIV RNA >50 copies/mL) within 1 month before delivery; 6 of these 19 women had viral loads above 1,000 copies/mL. Significant predictors of viral rebound included cocaine use and testing positive for hepatitis C virus RNA.[17] Viral load testing is currently recommended at 34 to 36 weeks gestation for delivery planning; providers may consider repeat testing subsequently in selected patients who are at increased risk for viral rebound. Risk for viral rebound may be greater in people receiving regimens with PK concerns for lower drug levels in late

pregnancy (e.g., cobicistat-boosted regimens and RPV) (see Table 7. Situation-Specific Recommendations for Use of Antiretroviral Drugs and People Taking Antiretrovirals When They Become Pregnant).

The lack of virologic suppression by late pregnancy may indicate virologic failure, but it may also represent inadequate time on ART for people who initiated ART in 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 ART at >32 weeks gestation also was associated with a significantly higher risk of having a viral load >400 copies/mL at delivery.[18] 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.[19] In the French Perinatal Cohort of 14,630 women living with HIV and delivering from 2000 to 2017, both HIV RNA level at delivery and timing of ART initiation were independently associated with risk of perinatal transmission of HIV.[1]

Pregnant people with acute HIV generally have high viral loads. Strategies to accelerate viral decline, such as addition of INSTIs to existing regimens or as new regimens, may be considered in collaboration with HIV treatment experts (see Early [Recent and Acute] HIV Infection).

People with perinatally acquired HIV may also face additional barriers to adherence and virologic suppression. Several studies from the United States and Europe have demonstrated that among pregnant people, perinatally acquired HIV is a risk factor for detectable viral load near the time of delivery and a higher perinatal transmission rate than non-perinatally acquired HIV.[20,21] 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 in People with Perinatal-Acquired HIV Infection).

Managing Lack of Viral Suppression

A three-pronged approach is indicated for evaluating and managing pregnant people on ART who have lack of suppression of HIV RNA, taking time on treatment into account. The three approaches are—

- 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,[22,23] lack of attention to food requirements);
- Ordering ARV drug resistance tests if plasma HIV RNA is above the threshold for resistance testing (usually HIV RNA >500 to 1,000 copies/mL but may be possible for HIV RNA >200 to <500 copies/mL in some laboratories); *and*
- Considering modifying the ARV regimen (see People With HIV Who Are Taking Antiretroviral Therapy When They Become Pregnant, Table 7, and Virologic Failure in the Adult and Adolescent Antiretroviral Guidelines).

Evaluation of and support for adherence during pregnancy are critical to achieving and maintaining maximal viral suppression. Access to and promotion of pre-pregnancy counseling and family planning services to reduce unintended pregnancy and help those with HIV achieve their childbearing aspirations, as well as early attention to the special need for adherence support among

immigrant communities affected by HIV and others with adverse neighborhood exposures, are critical to achieving and maintaining maximal viral suppression. In a retrospective cohort study at a Texas community center, group prenatal care for pregnant women living with HIV as compared to individual care showed promise in achieving viral suppression by the time of delivery (adjusted odds ratio = 2.29; 95% confidence interval [CI], 0.94–5.55; $P = 0.068$).[24] 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 Pregnant People with HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy), and directly observing drug administration in the home or hospital setting.[25]

Resistance testing should be performed when considering altering an ARV regimen in a pregnant person who has not achieved viral suppression (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 to <1,000 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 patients with current or prior INSTI exposure, INSTI resistance testing in addition to standard genotype testing should be obtained.

Adding an INSTI to a three-drug ARV regimen that does not already include an INSTI also has been suggested in the setting of lack of viral suppression due to known or suspected drug-resistant mutations or nonadherence.[26] However, the efficacy and safety of this approach during pregnancy have not been evaluated in clinical trials. The available data come from case series and two retrospective cohorts, and most of these data focus on the use of RAL;[7,27,28] data are not available for DTG. A prospective cohort study from Thailand enrolled 154 pregnant women with HIV. These women had either started ART at ≥32 weeks gestation (73% of women) or were receiving non-INSTI-based ART and had plasma HIV RNA levels >1,000 copies/mL at 32 to 38 weeks gestation (27% of women). These women received a standard, three-drug efavirenz- or lopinavir/ritonavir-based ARV regimen plus RAL intensification until delivery. The median gestational age at entry was 34 weeks (interquartile range [IQR] 33–36 weeks), and median duration of treatment was 21 days (IQR 8–34 days). The proportion of women with HIV RNA levels of <50 copies/mL and <1,000 copies/mL at delivery was 45% and 76%, respectively; 83% of those who were ART-naive had HIV RNA <1,000 copies/mL at delivery compared with 60% of those who were already on ART but who had not achieved virologic suppression. The overall perinatal transmission rate in this high-risk group of women was 3.9% (95% CI, 1.4% to 8.2%). Six instances of perinatal transmission occurred in this group; three of those instances occurred *in utero*.[29]

In cases where treatment failure is attributed to nonadherence and/or drug resistance, concerns exist that the addition of a single agent may further increase the risk of resistance and lead to the potential loss of future effectiveness of this agent. In addition, when poor adherence is the reason that the patient has not achieved or maintained virologic suppression, it is unclear that adding a new drug to the existing regimen will improve adherence. Currently, data are insufficient to recommend adding an INSTI to a failing ARV regimen for people in late pregnancy.

Before modifying an ARV regimen, consultation with a specialist in clinical care for ARV-experienced adults is recommended (The National Perinatal HIV hotline;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.

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