## Lack of Viral Suppression  (Last updated December 24, 2019; last reviewed December 24, 2019)

| Panel's Recommendations |
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| • Because maternal antenatal viral load correlates with the risk of perinatal transmission of HIV, suppression of HIV RNA to undetectable levels should be achieved as rapidly as possible **(AII)**. |
| • For pregnant women who have not achieved viral suppression (after an adequate period of treatment): |
|     • Assess medication adherence, tolerability, dosing, potential problems with absorption, adherence to food requirements, and possible drug interactions. |
|     • If HIV RNA is >500 copies/mL, perform tests for resistance **(AII)**. |
|     • Consult an HIV treatment expert and consider possible antiretroviral regimen modification **(AIII)**. |
| • Intrapartum intravenous zidovudine prophylaxis and scheduled cesarean delivery at 38 weeks gestation are recommended for pregnant women living with HIV who have HIV RNA levels >1,000 copies/mL near the time of delivery **(AII)**. |
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| *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 HIV RNA level that is below the lower limits of detection of an ultrasensitive assay, and virologic failure is the inability to achieve or maintain an HIV RNA level <200 copies/mL. Baseline HIV RNA levels have been shown to affect the time to response in both pregnant and nonpregnant individuals, and no difference in time to viral response has been observed between pregnant and nonpregnant women.[1,2] In women living with HIV who participated in three prospective studies from seven African countries and who became pregnant after initiating antiretroviral therapy (ART), incident pregnancy did not affect time to viral suppression or time to virologic failure.[3]

HIV RNA levels should be assessed 2 to 4 weeks after an antiretroviral (ARV) drug regimen is initiated or changed to provide an initial assessment of the regimen's effectiveness.[4] Most patients with an adequate viral response at 24 weeks of treatment have had at least a 1 $\log_{10}$ decrease in HIV RNA within 1 week to 4 weeks after starting therapy.[4] Suppression of HIV RNA to undetectable levels should be achieved as rapidly as possible, because maternal antenatal HIV RNA level correlates with the risk of perinatal transmission of HIV. In addition, an analysis from the Women's Interagency HIV Study cohort found that higher viral loads were associated with an increased risk of pregnancy loss through miscarriage or stillbirth.[5] However, a recent report from the HIV Outpatient Study noted that among 119 pregnancies that were analyzed between 2005 and 2015, 33 women (27.7%) were not virally suppressed (HIV RNA >500 copies/mL) at the end of pregnancy. Failure to achieve virologic suppression remains a common problem for pregnant women in the United States.[6]

## *Causes of Detectable Viremia*

Poor adherence is frequently associated with lack of virologic suppression, and this issue should be addressed when the viral load does not decline as expected. 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.[7] Factors that can contribute to suboptimal adherence include unplanned pregnancy, a history of intimate partner violence, a lack of prior experience with taking ART, and a lack of knowledge about the role of ART in preventing perinatal transmission.[8,9] Evaluation of and support for adherence during pregnancy is critical to achieving and maintaining maximal viral suppression.

The lack of virologic suppression by late pregnancy may indicate virologic failure, but it may also represent inadequate time on ART. In a retrospective multicenter cohort of 378 pregnant women, 77.2% of women achieved HIV RNA <50 copies/mL by delivery; success in achieving viral suppression varied by baseline HIV RNA level. In women with baseline HIV RNA levels <10,000 copies/mL, the gestational age of their

infants at ART initiation did not affect the likelihood of achieving viral suppression up to 26.3 weeks gestation. In women with baseline HIV RNA levels >10,000 copies/mL, however, delaying ART initiation past 20.4 weeks in women with baseline HIV RNA levels >10,000 copies/mL significantly reduced the probability of achieving maximal suppression at delivery.[1] Among 1,070 treatment-naive pregnant women with HIV who participated in the prospective cohort study IMPAACT P1025, initiating ART at >32 weeks gestation was also associated with a significantly higher risk of having a viral load >400 copies/mL at delivery.[10] A report from the French Perinatal Cohort found no perinatal transmission among 2,651 infants born to women who received ART before conception, continued ART throughout pregnancy, and delivered with a plasma HIV RNA <50 copies/mL with an upper limit for the 95% confidence interval [CI] of 0.1%). In the entire cohort of 8,075 mother-infant pairs that were followed from 2000 through 2011, HIV RNA level and timing of ART initiation were independently associated with perinatal transmission in a logistic regression analysis.[11]

The response to ART may also be affected by other factors. A prospective study recorded serial measures of plasma HIV RNA and CD4 T lymphocyte (CD4) counts after non-nucleoside reverse transcriptase inhibitor-based ART was initiated in 25 women with acute HIV infection and 30 women with chronic HIV infection in Kenya. The mean baseline HIV viral load was similar among women with acute HIV and women with chronic HIV after adjusting for baseline CD4 count, but the rate of viral decline following ART initiation was significantly slower among women with acute HIV.[12] Strategies to accelerate viral decline may be considered in women with acute HIV, though these strategies should be discussed with HIV treatment experts (see Acute HIV Infection). In a population-based surveillance study in the United Kingdom and Ireland that compared 70 pregnancies in 45 women with perinatally acquired HIV and 184 pregnancies in 118 women with horizontally-acquired HIV, perinatally acquired HIV in the mother was a risk factor for detectable viral load near delivery; this finding reflects complex clinical, psychosocial, adherence, and resistance issues.[13] Among 2,123 births that occurred between 2007 and 2015 and were reported in the Surveillance Monitoring of ART Toxicities Study as part of the Pediatric HIV/AIDS Cohort Study, women with perinatally acquired HIV had a higher perinatal transmission rate (1.1%; 95% CI, 0.3% to 4.3% vs. 0.4%; 95% CI, 0.2% to 1.0%) and higher likelihood of having HIV RNA >1,000 copies/mL close to delivery than women with non-perinatally acquired HIV.[14] If needed, ART 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 Women with Perinatal HIV Infection).

## *Managing Suboptimal Viral Suppression*

A three-pronged approach is indicated for managing women on ART regimens who have suboptimal suppression of HIV RNA, taking time on treatment into account. The three steps are:

- Assessing adherence, tolerability, correct dosing, or potential problems with absorption (e.g., nausea/vomiting, gastroesophageal reflux disease [GERD], lack of attention to food requirements);

- Ordering ARV drug resistance tests if plasma HIV RNA is above the threshold for resistance testing (generally >500 copies/mL); *and*

- Considering modifying the ART regimen (see Pregnant Women Living with HIV Who Are Currently Receiving Antiretroviral Therapy and Table 5).

The role of therapeutic drug monitoring (TDM) in reducing the risk of virologic failure is still undefined.[15] In a cohort of pregnant women with HIV, 66 (39%) received TDM.[16] Multivariate analysis found that receiving TDM was associated with medication alterations during pregnancy. However, the incidences of viral breakthrough during pregnancy or detectable viral load at birth were similar between women who received TDM and those who did not, and no instances of perinatal transmission were reported in either group. However, this analysis was limited by the retrospective observational nature of this study, the presence of significant baseline differences in adherence between those who received TDM and those who did not, and

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Before modifying an ARV regimen, consult an expert in clinical care for ARV-experienced adults. 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. 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, and directly observing drug administration in the home or hospital setting (see Table 8).[17]

Among 662 pregnancies that were followed in Italy between 2001 and 2008, treatment modification during pregnancy was independently associated with an HIV RNA level >400 copies/mL in late pregnancy (adjusted odds ratio 1.66; 95% CI, 1.07–2.57; $P = 0.024$). This highlights the importance of using potent and well-tolerated regimens during pregnancy to maximize effectiveness and minimize the need to modify treatment.[18] These findings also highlight the importance of avoiding changing effective ARV regimens whenever possible in women who become pregnant while taking ART (see Pregnant Women Living with HIV Who Are Currently Receiving Antiretroviral Therapy).

## The Role of Integrase Strand Transfer Inhibitors in Women with Detectable HIV RNA Levels During Pregnancy

The integrase strand transfer inhibitor (INSTI) class of drugs has been associated with rapid viral load reduction. Raltegravir (RAL) has been shown to reduce viral load by approximately 2 $\log_{10}$ copies/mL by Week 2 of therapy in ART-naive patients.[19,20] Because of this, the use of INSTIs have been suggested in three distinct scenarios in pregnancy:

• As part of a regimen for women who are not on ART and who present to care late in pregnancy;

• As the fourth ARV drug in a regimen for women with high viral loads; *or*

• As part of a new regimen for a woman who is experiencing virologic failure while on ART.

Including RAL or dolutegravir (DTG) as part of an ART regimen for women who have never been on ART and who present late in pregnancy with high viral loads is the preferred method to rapidly reduce viral load and decrease the risk of perinatal transmission (see Pregnant Women Living with HIV Who Have Never Received Antiretroviral Drugs, Table 4, and Table 5).[21,22] Two studies in pregnant women who presented for treatment late in pregnancy demonstrated more rapid viral decline in those who received INSTI-based regimens than in those who received efavirenz (EFV)-based ART. In the DolPHIN-2 study, 268 ART-naive women in Uganda and South Africa were randomized to receive DTG plus two nucleoside reverse transcriptase inhibitors (NRTIs) or EFV plus two NRTIs at a median gestational age of 31 weeks. At delivery, women in the DTG arm were significantly more likely than women in the EFV arm to achieve viral loads of <50 copies/mL (73.8% vs. 42.6%; adjusted risk ratio 1.66 [1.2–2.1], $P < 0.0001$).[23] Similarly, IMPAACT 1081 randomized 408 ART-naive women in South America, Africa, Thailand, and the United States who presented late in pregnancy to receive RAL plus two NRTIs or EFV plus two NRTIs. The median time to achieve a viral load of <200 copies/mL was 8 days for women who received RAL-based ART and 15 days for women who received EFV-based ART. The decline in viral load was greater in the women who received RAL than in those who received EFV at 2, 4, and 6 weeks after initiation.[24] The use of RAL or DTG (after the first trimester) as a fourth ARV drug can be considered in ART-naive women with high viral loads; however, there is limited evidence of benefit in this situation.

Adding RAL or another INSTI to a three-drug ARV regimen has also been suggested in the setting of incomplete viral suppression due to known or suspected drug-resistant mutations or nonadherence.[25] However, the efficacy and safety of this approach during pregnancy have not been evaluated in clinical trials. The available data comes from case series and two retrospective cohorts, and most of this data focuses on the use of RAL.[26-28] A recent 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 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 ART 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 overall was 45% and 76%, respectively; 83% of those who were ART-naive had HIV RNA <1,000 copies/mL at delivery as compared to 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 resistance, there are concerns 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, there are insufficient data to recommend adding an INSTI to a failing ART regimen for women in late pregnancy. However, after reviewing a woman's full treatment history and drug resistance results, a clinician may consider using an INSTI as part of a new regimen for pregnant women who are experiencing virologic failure on a non-INSTI ART regimen.

## Viral Rebound in Late Pregnancy

A recent 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; six 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.[30] Viral load testing is currently recommended at 34 to 36 weeks gestation for delivery planning; providers may consider repeat testing subsequently in selected women who are at increased risk for viral rebound.

## Intrapartum Management of Women with a Lack of Viral Suppression

Scheduled cesarean delivery at 38 weeks gestation and intrapartum intravenous zidovudine prophylaxis are recommended for pregnant women with HIV who have HIV RNA levels >1,000 copies/mL near the time of delivery (see Intrapartum Antiretroviral Therapy/Prophylaxis and Transmission and Mode of Delivery).[31,32]

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