# Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States



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## Lack of Viral Suppression (Last updated December 7, 2018; last reviewed December 7, 2018)

| 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)**.<br>• If an ultrasensitive HIV RNA assay indicates failure of viral suppression (after an adequate period of treatment):<br>  • If HIV RNA level is >500 copies/mL, assess medication adherence, adherence to food requirements, and possible drug interactions and perform tests for resistance **(AII)**.<br>  • Consult an HIV treatment expert and consider possible antiretroviral regimen modification **(AIII)**.<br>• Scheduled cesarean delivery at 38 weeks' gestation is recommended for pregnant women living with HIV who have HIV RNA levels >1,000 copies/mL near the time of delivery **(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* |

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, with no difference in time to response between pregnant and nonpregnant women.[1,2] In women living with HIV who participated in three prospective studies from seven African countries and became pregnant after antiretroviral therapy (ART) initiation, 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 effectiveness.[4] Most patients with an adequate viral response at 24 weeks of treatment have had at least a 1 log decrease in HIV RNA within 1 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 (miscarriage or stillbirth).[5]

Poor adherence is frequently associated with lack of virologic suppression, and this issue should be addressed when viral load does not decline as expected. A systematic review and meta-analysis of adherence to ART) 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.[6] 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% achieved HIV RNA <50 copies/mL by delivery, with success of viral suppression varying by baseline HIV RNA level. For women with baseline HIV RNA levels <10,000 copies/mL, the gestational age of their infants at ART initiation did not affect success of viral suppression up to 26.3 weeks. In women with baseline >10,000 copies/mL, however, delaying initiation past 20.4 weeks significantly reduced the ability to achieve maximal suppression at delivery.[1] Among 1,070 treatment-naive pregnant women with HIV who participated in IMPAACT P1025, a prospective cohort study, initiation of ART at >32 weeks' gestation was also associated with a significantly higher risk of having viral load >400 copies/mL at delivery.[7] A report from the French Perinatal Cohort found no perinatal transmission among 2,651 infants born to women who were receiving ART before conception, continued ART throughout pregnancy, and delivered with a plasma HIV RNA <50 copies/mL (upper limits of CI, 0.1%). In the entire cohort of 8,075 mother/infant pairs followed from 2000 through 2011, HIV RNA level and timing of ART initiation were independently associated with perinatal transmission in a logistic regression analysis.[8]

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 infection after adjustment for baseline CD4 count, but the rate of viral decline following ART initiation was significantly slower among women with acute HIV infection.[9] Strategies to accelerate viral decline may be considered in this situation, 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, perinatal HIV in the mother was a risk factor for detectable viral load near delivery, reflecting complex clinical, psychosocial, adherence, and resistance issues.[10] If needed, ART regimens should be optimized in consultation with HIV treatment experts and attention should be given to other possible contributing factors (see The Management of Prenatal Care and General Principles of Antiretroviral Therapy and HIV Management in Women with Perinatal HIV Infection).

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:

- Assessment of adherence, tolerability, correct dosing, or potential problems with absorption (e.g., nausea/vomiting, gastroesophageal reflux disease [GERD], lack of attention to food requirements);
- ARV drug resistance studies if plasma HIV RNA is above the threshold for resistance testing, generally >500 copies/mL; and
- Consideration of ART regimen modification (see Pregnant Women Living with HIV Who Are Currently Receiving Antiretroviral Therapy and Table 7).

The role of therapeutic drug monitoring (TDM) in reducing the risk of virologic failure is still undefined.[11] In a cohort of pregnant women with HIV, 66 (39%) had TDM.[12] Comparing women who did and did not have TDM, multivariate analysis found that TDM was associated with medication alterations during pregnancy but was not associated with any difference in viral breakthrough during pregnancy or detectable viral load at birth; there were no transmissions in either group.

Experts with experience in caring for ARV-experienced adults should be consulted, particularly if a change in drug regimen is necessary due to resistance or adverse effects. Regimen simplification may be considered to promote better adherence. Other possible interventions include adherence education, treatment of problems that may interfere with drug absorption such as vomiting, taking ART in accordance with food requirements, and directly-observed drug administration in the home or hospital setting (See Table 10).[13]

Among 662 pregnancies that were followed in Italy between 2001 and 2008, treatment modification during pregnancy was independently associated with an HIV-1 RNA level >400 copies/mL in late pregnancy (adjusted odds ratio, 1.66; 95% CI, 1.07–2.57; $P = 0.024$), highlighting the importance of using potent and well-tolerated regimens during pregnancy to maximize effectiveness and minimize the need to modify treatment.[14] These findings also highlight the importance of avoiding changing effective ARV regimens whenever possible in women who become pregnant on ART (see Pregnant Women Currently Receiving ART).

The integrase strand transfer inhibitor (INSTI) class of drugs has been associated with rapid viral load reduction. Raltegravir has been shown to reduce viral load by approximately 2 log copies/mL by week 2 of therapy in ART-naive patients.[15,16] Because of these data, the addition of raltegravir or another INSTI in late pregnancy has been suggested for women who have high viral loads and/or in whom multiple drug-resistant mutations have resulted in incomplete suppression of viremia.[17-19] However, the efficacy and safety of this approach during pregnancy have not been evaluated in clinical trials, and only case series and two retrospective cohorts are available, primarily involving raltegravir.[20-22] In a recent retrospective study from Argentina, 13 women had raltegravir added to a standard PI-based ART regimen after their initial regimen failed to achieve viral suppression. The mean gestational age at raltegravir initiation was 33 weeks

(range: 29–37 weeks) and median exposure was 25.5 days (range: 7–43 days); 70% of women achieved viral suppression (<50 copies/mL) prior to delivery, with a median viral decay of 1.48 log. In the same study, 15 women had raltegravir added to a standard PI-based regimen due to late presentation; the mean gestational age at raltegravir initiation was 34 weeks (range: 33–36 weeks), baseline viral load was 12,217 copies/mL (range: 3,881–40,310 copies/mL) and median exposure was 30 days (range: 7–30 days). Prior to delivery, 45.5% of women achieved viral suppression with a median viral decay of 2.15 log.[22]

Including raltegravir or dolutegravir as part of an ART regimen for women who have never been on ART and present late in pregnancy with high viral loads may be considered to more rapidly reduce viral load and decrease risk of perinatal transmission. (See Pregnant Women Living with HIV Who Have Never Received ARV Drugs, Table 6, and Table 7.) However, in the setting of a failing regimen related to nonadherence and/or resistance, there are concerns that the addition of a single agent may further increase risk of resistance and potential loss of future effectiveness. In addition, when poor adherence is the reason for viremia, 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.

There have been two reports of marked elevations in transaminase levels following introduction of a raltegravir-containing regimen in late pregnancy, with these levels returning to normal after discontinuation.[20,23] Furthermore, data in 19 mother-infant pairs enrolled in a multicenter trial to determine washout pharmacokinetics and safety of *in utero*/intrapartum exposure to raltegravir found that, while raltegravir readily crossed the placenta, elimination was highly variable and extremely prolonged in some infants, raising potential infant safety concerns.[24]

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 positive hepatitis C virus (HCV) RNA.[25] 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.

Scheduled cesarean delivery at 38 weeks' gestation is recommended for pregnant women living with HIV who have HIV RNA levels >1,000 copies/mL near the time of delivery (see Transmission and Mode of Delivery).[26,27]

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