Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States

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Lack of Viral Suppression  

Panel’s Recommendations

- Because maternal antenatal viral load correlates with risk of perinatal transmission of HIV, suppression of HIV RNA to undetectable levels should be achieved as rapidly as possible (AII).
- If an ultrasensitive HIV RNA assay indicates failure of viral suppression (after an adequate period of treatment):
  - Assess adherence and perform tests for resistance if HIV RNA level is > 500 copies/mL (AII).
  - Consult an HIV treatment expert and consider possible antiretroviral regimen modification (AIII).
- 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 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 non-pregnant individuals, with no difference in response between pregnant and non-pregnant women.\(^1,2\) 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.\(^3\) Most patients with an adequate viral response at 24 weeks of treatment have had at least a 1 log copies/mL HIV RNA decrease within 1 to 4 weeks after starting therapy.\(^3\) Suppression of HIV RNA to undetectable levels should be achieved as rapidly as possible, because maternal antenatal HIV RNA level correlates with 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).\(^4\)

Issues associated with adherence are frequently associated with lack of virologic suppression and should be assessed when viral load does not decline as expected. A systematic review and meta-analysis of adherence to antiretroviral therapy (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.\(^5\) Evaluation of and support for adherence during pregnancy is critical to achievement and maintenance of maximal viral suppression.

The lack of virologic suppression by late pregnancy may indicate virologic failure but 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. With baseline <10,000 copies/mL, gestational age at initiation did not affect success up to 26.3 weeks. 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 participating 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.\(^6\) 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 confidence interval [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.\(^7\)

The response to ART may also be affected by the presence of acute HIV-1 infection. In a prospective study of
serial measures of plasma HIV-RNA and CD4 lymphocyte (CD4) counts after ART initiation (non-nucleoside reverse transcriptase inhibitor-based) in 25 women with acute HIV infection and 30 women with chronic HIV infection in Kenya, mean baseline HIV viral load was similar but the rate of viral decline following ART initiation was significantly slower among women with acute HIV than those with chronic infection (after adjustment for baseline CD4 count). Strategies to accelerate viral decline may be considered in this situation, in consultation with HIV treatment experts (see Acute HIV Infection section).

A three-pronged approach is indicated for management of women on ART regimens who have suboptimal suppression of HIV RNA, taking into account time on treatment. The 3 steps should be:

- Assessment of adherence, tolerability, incorrect dosing, or potential problems with absorption (e.g., nausea/vomiting, 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.

The role of therapeutic drug monitoring (TDM) in reducing the risk of virologic failure is still undefined. In a cohort of pregnant women with HIV, 66 (39%) underwent TDM. Comparing women who had and did not have TDM, multivariate analysis found that it 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 in the care of ARV-experienced adults should be consulted, particularly if a change in drug regimen is necessary due to resistance or adverse effects. In certain situations, regimen simplification may be considered to promote better adherence. Other possible interventions include adherence education, treatment of comorbidities such as nausea or vomiting, and directly-observed drug administration in the home or hospital setting.

Among 662 pregnancies 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. These findings also highlight the importance, as much as possible, of avoiding changing effective ARV regimens 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. 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. However, the efficacy and safety of this approach in pregnancy have not been evaluated in clinical trials, and only case series and a retrospective cohort are available, primarily involving raltegravir. In the setting of a failing regimen related to non-adherence 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 with raltegravir. In addition, if the reason for viremia is poor adherence, it is unclear that adding a new drug to the existing regimen would improve adherence. There have been 2 reports of marked elevations in transaminase levels following introduction of a raltegravir-containing regimen in late pregnancy, with return to normal levels after raltegravir discontinuation. 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 in infants born to pregnant women receiving raltegravir-based ART found that, while raltegravir readily crossed the placenta, elimination was highly variable and extremely prolonged in some infants, raising potential infant safety concerns. At the current time, although this approach is increasingly being used in clinical practice, data are
insufficient to recommend routinely adding raltegravir alone to a regimen for women in whom ART is failing in late pregnancy.

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).

References


15. Grinsztejn B, Nguyen BY, Katlama C, et al. Safety and efficacy of the HIV-1 integrase inhibitor raltegravir (MK-


