



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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Panel's Recommendations

- Artificial rupture of membranes (ROM) performed in the setting of antiretroviral therapy and virologic suppression is not associated with increased risk of perinatal transmission and can be performed for standard obstetric indications (**BII**)
- The following should generally be avoided because of a potential increased risk of transmission, unless there are clear obstetric indications:
 - Artificial ROM in the setting of viremia (**BIII**)
 - Routine use of fetal scalp electrodes for fetal monitoring (**BIII**)
 - Operative delivery with forceps or a vacuum extractor (**BIII**)
 - Episiotomy (**BIII**)
- The ART regimen a woman is receiving should be taken into consideration when treating excessive postpartum bleeding resulting from uterine atony:
 - In women who are receiving a cytochrome P (CYP) 450 3A4 enzyme inhibitor (e.g., a protease inhibitor), methergine should be used only if no alternative treatments for postpartum hemorrhage are available and the need for pharmacologic treatment outweighs the risks. If methergine is used, it should be administered in the lowest effective dose for the shortest possible duration (**BIII**).
 - In women who are receiving a CYP3A4 enzyme inducer such as nevirapine, efavirenz, or etravirine, additional uterotonic agents may be needed because of the potential for decreased methergine levels and inadequate treatment effect (**BIII**).

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

Data on the association of duration of rupture of membranes (ROM) and perinatal transmission in the era of effective antiretroviral therapy (ART) are reassuring. A prospective cohort study of 707 HIV-infected pregnant women on ART included 493 women with delivery HIV-RNA <1,000 copies/mL with no cases of perinatal transmission with up to 25 hours of membrane rupture; logistic regression found that HIV viral load >10,000 copies/mL was the only independent risk factor for transmission.¹ A large prospective population-based surveillance study in the UK and Ireland included 2,116 pregnancies delivered at term vaginally or by emergency Cesarean delivery in women on ART during the period 2007-2012 with information on duration of ROM. The median duration of ROM was 3 hours 30 minutes (interquartile range, IQR 1-8 hours) and the overall perinatal transmission rate was not significantly different with longer duration of ROM (0.64% with duration of ROM ≥4 hours compared with 0.34% for ROM <4 hours, [OR 1.90, 95% CI 0.45-7.97]). In those women with a viral load <50 copies/mL, there was no difference in perinatal transmission rates with duration of ROM ≥4 hours, compared with <4 hours (0.14% for ≥4 hours versus 0.12% for <4 hour; OR 1.14, 95% CI 0.07–18.27). Among infants born preterm, there were no transmissions in 163 deliveries where the maternal viral load was <50 copies/mL.² If spontaneous ROM occurs before or early during the course of labor, interventions to decrease the interval to delivery (e.g., administration of oxytocin) can be considered based on obstetric considerations in HIV-infected women with viral suppression. Artificial ROM should be avoided unless there is a clear obstetric indication in women with detectable viral loads.

Obstetric procedures that increase the risk of fetal exposure to maternal blood, such as invasive fetal monitoring, have been implicated in increasing vertical transmission rates by some, but not all, investigators, primarily in studies performed in the pre-ART era.³⁻⁶ Data are limited on use of fetal scalp electrodes in labor in women receiving suppressive ART who have undetectable viral loads; routine use of fetal scalp electrodes for fetal monitoring should generally be avoided in the setting of maternal HIV infection.

Similarly, data are limited to those obtained in the pre-ART era regarding the potential risk of perinatal transmission of HIV associated with operative vaginal delivery with forceps or the vacuum extractor and/or use of episiotomy.^{4,6} These procedures should be performed only if there are clear obstetric indications. Delayed cord clamping has been associated with improved iron status in preterm infants and benefits such

as decreased risk of intraventricular hemorrhage in preterm births to HIV-uninfected mothers.^{7,8} Even though HIV-specific data on the practice are lacking, there is no reason to modify it in HIV-infected mothers.

Intrapartum Epidural Use and Pharmacologic Interactions with Antiretroviral Drugs

Ritonavir inhibition of cytochrome P450 (CYP) 3A4 decreases the elimination of fentanyl by 67%, raising concerns about possible increased risk of respiratory depression, particularly with patient-controlled analgesia during labor, in women receiving ritonavir-containing regimens. However, a recent pharmacokinetic simulation study suggests that even with maximal clinical dosing regimens of epidural fentanyl over 24 hours, ritonavir-induced CYP3A4 inhibition is unlikely to produce plasma fentanyl concentrations associated with a decrease in minute ventilation.⁹ This suggests that epidural anesthesia can be used safely regardless of ART regimen.

Postpartum Hemorrhage, Antiretroviral Drugs, and Methergine Use

Oral or parenteral methergine or other ergot alkaloids are often used as first-line treatment for postpartum hemorrhage resulting from uterine atony. However, methergine should not be coadministered with drugs that are potent CYP3A4 enzyme inhibitors, including protease inhibitors (PIs). Concomitant use of ergotamines and PIs has been associated with exaggerated vasoconstrictive responses. When uterine atony results in excessive postpartum bleeding in women receiving PIs, methergine should be used only if alternative treatments such as prostaglandin F₂-alpha, misoprostol, or oxytocin are unavailable. If no alternative medications are available and the need for pharmacologic treatment outweighs the risks, methergine should be used in as low a dose and for as short a period as possible. In contrast, additional uterotonic agents may be needed when other antiretroviral drugs that are CYP3A4 inducers (e.g., nevirapine, efavirenz, etravirine) are used because of the potential for decreased methergine levels and inadequate treatment effect.

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