



**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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### Panel's Recommendations

- Artificial rupture of membranes (ROM) can be performed for standard obstetric indications in virologically suppressed women with HIV who are on antiretroviral therapy (ART) (BII).
- The following procedures should generally be avoided because of a potential increased risk of HIV perinatal 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)
- 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 P450 (CYP) 3A4 enzyme inhibitor (e.g., a protease inhibitor, integrase inhibitor, cobicistat), 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 at 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 between the duration of rupture of membranes (ROM) and perinatal transmission of HIV in the era of effective antiretroviral therapy (ART) are reassuring. A prospective cohort study of 707 pregnant women on ART included 493 women with delivery HIV RNA <1,000 copies/mL with no cases of perinatal transmission for up to 25 hours of membrane rupture; logistic regression found that a viral load >10,000 copies/mL was the only independent risk factor for transmission.<sup>1</sup> A large, prospective, population-based surveillance study in the United Kingdom and Ireland evaluated data collected from 2007 through 2012 on 2,116 pregnancies; this data included information on the duration of ROM. The infants in this study were delivered at term vaginally or by emergency cesarean delivery to women with HIV who were on ART. 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 durations of ROM (0.64% with a duration of ROM ≥4 hours compared with 0.34% for a duration of ROM <4 hours; odds ratio [OR] 1.90, 95% CI, 0.45–7.97). In women with viral loads <50 copies/mL, there was no difference between the perinatal transmission rate for a duration of ROM ≥4 hours and the rate for a duration of ROM <4 hours (0.14% for ≥4 hours vs. 0.12% for <4 hours; OR 1.14, 95% CI, 0.07–18.27). Among infants born preterm, no transmissions occurred during 163 deliveries where the maternal viral load was <50 copies/mL.<sup>2</sup> If spontaneous ROM occurs before labor or early in labor, interventions to decrease the interval to delivery (e.g., administration of oxytocin) can be considered based on obstetric considerations in virologically suppressed women with HIV. Women with detectable viral loads should not undergo artificial ROM unless there is a clear obstetric indication.

Obstetric procedures that increase the risk of fetal exposure to maternal blood, such as invasive fetal monitoring, have been associated with an increased risk of perinatal transmission rates in some studies, primarily those performed in the pre-ART era.<sup>3–6</sup> Data are limited on the use of fetal scalp electrodes during labor in women who are receiving suppressive ART and 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 regarding the potential risk of perinatal transmission of HIV associated with operative vaginal delivery using forceps or the vacuum extractor and/or the use of episiotomy;<sup>4,6</sup> existing data

are mostly from the pre-ART era. A prospective, population-based surveillance study in the United Kingdom and Ireland reported 251 operative deliveries (using forceps or vacuum) from January 2008 through March 2016. One infant who was delivered operatively is known to have acquired HIV, although there were other significant risk factors that may have contributed to this transmission.<sup>7</sup> Although information on HIV RNA levels was not included in this report, during this time period 80% to 90% of pregnant women living with HIV in the United Kingdom achieved viral suppression by the time of delivery.<sup>7,8</sup> Operative deliveries should be performed only if there are clear obstetric indications. There are no data from the ART era regarding the risk of perinatal HIV transmission associated with episiotomy or with vaginal or perineal tears, specifically in the absence of maternal viremia; indications for episiotomy should be the same as they are for women without HIV (e.g., a need for expedited vaginal delivery, a need for operative vaginal delivery, shoulder dystocia).

Delayed cord clamping has been associated with improved iron stores in both term and preterm infants as well as a lower incidence of necrotizing enterocolitis and intraventricular hemorrhage in preterm infants born to mothers without HIV. The American College of Obstetricians and Gynecologists now recommends this practice in vigorous term and preterm infants, with clamping delayed for  $\geq 30$  to 60 seconds after birth.<sup>9-11</sup> In the setting of HIV infection, a recent study of 64 mother-infant pairs in which 32 infants had early cord clamping (i.e., performed 30 seconds after birth) and 32 infants had delayed cord clamping (i.e., performed 120 seconds after birth) found that mean hemoglobin levels at 24 hours of life were significantly higher in the delayed cord clamping group ( $P = 0.05$ ). This difference persisted at 1 month of age ( $P < 0.05$ ), despite differential prescribing of iron supplementation to infants with anemia. All mothers were on stable antiretroviral (ARV) regimens. During 18 months of follow-up, there were no HIV transmissions and no increased risk of jaundice or polycythemia with delayed cord clamping.<sup>12</sup>

### ***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 a possible increased risk of respiratory depression, particularly with patient-controlled analgesia during labor, in women receiving ritonavir-containing regimens. However, a 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 the plasma fentanyl concentrations associated with a decrease in minute ventilation.<sup>13</sup> 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 caused by uterine atony. However, methergine should not be coadministered with drugs that are potent CYP3A4 enzyme inhibitors, including protease inhibitors (PIs). Concomitant use of ergotamines with PIs and/or cobicistat has been associated with exaggerated vasoconstrictive responses.<sup>14</sup> When uterine atony results in excessive postpartum bleeding in women who are receiving PIs or cobicistat, methergine should be used only if alternative treatments such as prostaglandin F<sub>2</sub>-alpha, misoprostol, or oxytocin are unavailable or are contraindicated. If no alternative medications are available and the need for pharmacologic treatment outweighs the risks, methergine should be used at the lowest effective dose for the shortest possible duration. In contrast, additional uterotonic agents may be needed when using other ARV drugs that are CYP3A4 inducers (e.g., nevirapine, efavirenz, etravirine) because of the potential for decreased methergine levels and inadequate treatment effect.

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