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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Transmission and Mode of Delivery (Last updated December 7, 2018; last reviewed December 7, 2018)

Panel's Recommendations
• Scheduled cesarean delivery at 38 weeks gestation to minimize perinatal transmission of HIV is recommended for women with HIV RNA levels >1,000 copies/mL or unknown HIV levels near the time of delivery, irrespective of administration of antepartum antiretroviral therapy (ART) **(AII)**.
• Scheduled cesarean delivery performed solely for prevention of perinatal transmission in women receiving ART with HIV RNA ≤1,000 copies/mL **is not routinely recommended** given the low rate of perinatal transmission in this group **(AII)**.
• In women with HIV RNA levels ≤1,000 copies/mL, if scheduled cesarean delivery or induction is indicated, it should be performed at the standard time for obstetrical indications **(AII)**.
• In women with an HIV RNA >1,000 copies/mL or unknown HIV RNA level who present in spontaneous labor or with ruptured membranes, there is insufficient evidence to determine whether cesarean delivery reduces the risk of perinatal HIV transmission. Management of women originally scheduled for cesarean delivery because of HIV who present in labor must be individualized at the time of presentation **(BII)**. In these circumstances, consultation with an expert in perinatal HIV (e.g., telephone consultation with the National Perinatal HIV/AIDS Clinical Consultation Center at 888-448-8765) may be helpful in rapidly developing an individualized delivery plan.
• In women on ART with HIV RNA ≤1,000 copies/mL, duration of ruptured membranes is not associated with an increased risk of perinatal transmission, and vaginal delivery is recommended **(BII)**.
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*

Basis for Current Recommendations

Scheduled cesarean delivery, defined as cesarean delivery performed before the onset of labor and before rupture of membranes, is recommended for prevention of perinatal transmission of HIV in women with HIV RNA levels >1,000 copies/mL near delivery and for women with unknown HIV RNA levels.

This recommendation is based on findings from a multicenter, randomized clinical trial[1] and from a large individual patient data meta-analysis.[2] These two studies were conducted when the majority of women with HIV received no antiretroviral (ARV) drugs or zidovudine as a single drug and before the availability of viral load information. Study results have since been extrapolated to make current recommendations about the mode of delivery in an era when antiretroviral therapy (ART) during pregnancy is recommended and viral load information is readily available.

HIV RNA Level >1000 copies/mL as a Threshold for Recommendation of Scheduled Cesarean Delivery

The American Congress of Obstetricians and Gynecologists (ACOG) recommends that women with HIV RNA >1,000 copies/mL be counseled regarding the potential benefits of scheduled cesarean delivery.[3] Initially, the threshold of 1,000 copies/mL was based largely on data from the Women and Infants Transmission Study, a large prospective cohort study that reported no HIV transmission among 57 women with HIV RNA levels <1,000 copies/mL.[4] Studies reported since then have demonstrated that HIV transmission can occur in infants born to women with low viral loads. Most studies do not specify the exact time that the HIV RNA levels closest to delivery were measured. The Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission recommends viral load testing at approximately 34–36 weeks gestation to inform decisions about mode of delivery and to inform decisions about optimal treatment of the newborn. A Canadian retrospective analysis reported that 6% of women (n = 318) who had had an undetectable HIV RNA level at some point during pregnancy had detectable virus at delivery, thus demonstrating that viral rebound near delivery may occur even among women in care.[5]

In an analysis of 957 women with plasma viral loads ≤1,000 copies/mL, cesarean delivery (scheduled or urgent) reduced the risk of HIV transmission when adjusting for potential confounders including receipt of maternal ARV medications (adjusted odds ratio [AOR] 0.30; $P = 0.022$); however, zidovudine alone was the

regimen primarily used as prophylaxis.[6] Among infants born to 834 women with HIV RNA ≤1,000 copies/mL receiving ARV medications, 8 (1%) were born with HIV. In a report based on data from a comprehensive national surveillance system in the United Kingdom and Ireland, 3 (0.1%) of 2,309 and 12 (1.2%) of 1,023 infants born to women with HIV RNA levels <50 copies/mL and 50 to 999 copies/mL, respectively, were born with HIV, of which some infections appear to represent *in utero* transmission.[7]

Some studies demonstrate that transmission can occur even at very low HIV RNA levels. However, given the low rate of transmission among women with very low viral loads, it is unclear whether scheduled cesarean delivery confers any additional benefit in reducing transmission. Furthermore, there is evidence that complication rates for cesarean deliveries are higher in women with HIV than in women without HIV.[8] Therefore, decisions about mode of delivery for women receiving ART with HIV RNA levels ≤1,000 copies/mL should be individualized based on discussion between an obstetrician and a pregnant woman. Women should be informed that there is no evidence that a scheduled cesarean delivery performed solely for prevention of perinatal transmission is of any benefit in women receiving ART with HIV RNA ≤1,000 copies/mL and therefore **is not routinely recommended** for these women.

Scheduled Cesarean Delivery in the Antiretroviral Therapy Era

In surveillance data from the United Kingdom and Ireland published in 2008, pregnant women receiving ART (i.e., ≥3 drugs) had transmission rates of about 1%, unadjusted for mode of delivery.[7] Given the low transmission rates achievable with use of maternal ART, the benefit of scheduled cesarean delivery is difficult to evaluate. Most of the women included in both the randomized clinical trial[1] and meta-analysis[2] documenting the benefits of cesarean delivery were receiving either no ARV drugs or zidovudine alone. However, other data partially address this issue.

In a report on births to women with HIV from the United Kingdom and Ireland between 2000 and 2011, perinatal transmission rates in women on ART with HIV RNA <1,000 copies/mL who had a planned cesarean delivery (13/3,544; 0.3%) were not significantly different than those in women who had a planned vaginal delivery (6/2238; 0.3%).[9] Similarly, data from the French Perinatal Cohort showed no difference in transmission rates between vaginal delivery and planned cesarean delivery among women on ART with suppressed viral loads, 0.3% in both groups of women. For preterm deliveries in women with HIV RNA <1,000 copies/mL, transmission rates were slightly higher among planned vaginal deliveries than among planned cesarean deliveries, but the number of women with viral loads <400 copies/ml was low and the differences across viral load levels were not statistically significant (1/9 [11.1%] vs. 1/17 [5.9%] for HIV RNA 400–1,000 copies/mL; 1/39 [2.6%] vs. 1/56 [1.8%] for HIV RNA 50–400 copies/mL; 1/189 [0.5%] vs. 0/143 [0%] for HIV RNA <50 copies/mL, for planned vaginal deliveries and elective cesarean deliveries, respectively).[10] Among 290 deliveries in Finland from 1993 to 2013, 75.4% of women delivered vaginally, 12.5% by elective cesarean, and 12.5% by emergency cesarean; 80% had HIV RNA <50 copies/mL. There were no perinatal HIV transmissions across the delivery methods.[11] Therefore, no evidence to date suggests any benefit from scheduled cesarean delivery in women who have been receiving ART for several weeks and who and are virally suppressed at or near delivery.

When the delivery method selected is scheduled cesarean delivery and the maternal viral load is >1,000 copies/mL, a 1-hour loading dose followed by a continuous intravenous (IV) zidovudine infusion for 2 hours (3 hours total) before scheduled cesarean delivery should be administered. In a study of the pharmacokinetics of IV zidovudine in 28 pregnant women, the ratio of cord blood-to-maternal-zidovudine concentration was significantly greater in women who received IV zidovudine for 3 to 6 hours before delivery than in those who received the infusion for <3 hours before delivery (1.0 vs. 0.55, respectively).[12] This suggests that an interval of ≥3 hours may provide adequate time for ZDV to cross the placenta and equilibrate with maternal concentrations, although the relationship between specific cord blood zidovudine levels or cord blood-to-maternal-zidovudine levels and efficacy in preventing perinatal transmission of HIV is unknown.

Because unscheduled cesarean delivery is performed for both maternal and fetal indications, when an unscheduled cesarean delivery is indicated in a woman who has a viral load >1,000 copies/mL, consideration

can be given to shortening the interval between initiation of IV zidovudine administration and delivery. For example, some experts recommend administering the 1-hour loading dose of IV zidovudine and not waiting to complete additional administration before proceeding with delivery.

Women Presenting Late in Pregnancy

Women with HIV who present late in pregnancy and are not receiving ARV drugs may not have HIV RNA results available before delivery. Without current therapy, HIV RNA levels are unlikely to be ≤1,000 copies/mL at baseline. Even when ART is initiated immediately, reduction in plasma HIV RNA to undetectable levels may take several weeks, depending on the baseline viral load and kinetics of viral decay for a particular drug regimen.[13-15] In this instance, scheduled cesarean delivery is likely to provide additional benefit in reducing the risk of perinatal transmission of HIV for women, unless viral suppression can be documented before 38 weeks gestation. Although some experts would recommend a cesarean delivery in a woman who has virologic suppression for a brief period (e.g., <2 weeks), given this scenario, many others would support a vaginal delivery as long as the woman's plasma HIV RNA level was <1000 copies/mL by the day of delivery.

Timing of Vaginal Delivery

A comparison of 613 women (with HIV RNA level <1,000 copies/mL) who delivered vaginally at 38 to 40 weeks gestation and 303 women who delivered vaginally at ≥40 weeks gestation demonstrated no difference (0.3 vs. 0.5%) in perinatal HIV transmission by estimated gestational age at delivery, which suggests that women without an indication for scheduled cesarean delivery for prevention of perinatal HIV transmission should be delivered according to standard obstetrical indications.[16]

Timing of Scheduled Cesarean Delivery

For the general obstetric population, ACOG recommends that a scheduled cesarean delivery not be performed before 39 weeks gestation because of the risk of iatrogenic prematurity.[17,18] However, when cesarean delivery is indicated to prevent transmission of HIV, ACOG recommends scheduling cesarean delivery at 38 weeks gestation to decrease the likelihood of onset of labor or rupture of membranes before delivery.[3] In all women undergoing repeat cesarean delivery, the risk of any neonatal adverse event—including neonatal death, respiratory complications, hypoglycemia, newborn sepsis, or admission to the neonatal intensive care unit—is 15.3% at 37 weeks gestation, 11.0% at 38 weeks gestation, and 8.0% at 39 weeks gestation.[18] Gestational age should be determined by best obstetrical dating criteria, including last menstrual period and early ultrasound for dating purposes. Amniocentesis to document lung maturity should be avoided when possible in women with HIV and is rarely indicated before a scheduled cesarean section for prevention of HIV transmission.

Among 1,194 infants born to mothers with HIV, nine (1.6%) born vaginally and 18 (4.4%) delivered by scheduled cesarean had respiratory distress syndrome (RDS) ($P < 0.001$). There was no statistically significant association between mode of delivery and infant RDS in an adjusted model that included infant gestational age and birth weight.[19] Although newborn complications may be increased in planned cesarean delivery <39 weeks gestation, the benefits of planned cesarean delivery at 38 weeks are generally thought to outweigh the risks if the procedure is performed for prevention of HIV transmission. When scheduled cesarean delivery is performed in women with HIV with an HIV RNA ≤1,000 copies/mL for an indication other than decreasing HIV transmission, cesarean delivery should be scheduled based on ACOG guidelines for women without HIV.

Risk of Maternal Complications

Administration of perioperative antimicrobial prophylaxis is recommended for all women to decrease maternal infectious morbidity associated with cesarean delivery. Most studies have demonstrated that women with HIV have higher rates of postoperative complications, mostly infectious, than women without HIV and that their risk of complications is related to degree of immunosuppression and the receipt of suppressive ART.[20-25] Furthermore, a Cochrane review of six studies in women with HIV concluded that urgent cesarean delivery was associated with the highest risk of postpartum morbidity, scheduled cesarean delivery was intermediate in risk, and vaginal delivery had the lowest risk of morbidity.[26,27] Complication rates in women with HIV in most studies[1,28-32] were

within the range reported in populations of women without HIV with similar risk factors and not of sufficient frequency or severity to outweigh the potential benefit of reduced perinatal HIV transmission. A U.S. study of nationally representative data from a large administrative database demonstrated that—even in the era of ART—infectious complications, surgical trauma, prolonged hospitalization, and in-hospital deaths remain higher among women with HIV than among women without HIV.[8] The rate of any complication associated with cesarean delivery was 117 per 1,000 deliveries among women with HIV and 67 per 1,000 deliveries among women without HIV. A meta-analysis of primarily observational studies in women with HIV also reported higher morbidity with elective cesarean delivery than with vaginal delivery (OR 3.12) and no reduction in perinatal HIV transmission among the mothers on ART.[33] Therefore, women with HIV should be counseled regarding the specific risks associated with undergoing cesarean delivery in the setting of HIV infection.

In addition, caution should be exercised in proceeding with a cesarean delivery in circumstances where there is no clear evidence of benefit, especially in younger women who are likely to have additional pregnancies and perhaps multiple cesarean deliveries. Increased risk of abnormal placentation (e.g., placenta previa, placenta accrete, placenta increta, placenta percreta) and intrapartum hemorrhage are associated with increasing numbers of cesarean deliveries. These risks should be considered and discussed with the woman before proceeding with a cesarean delivery.[34,35]

Managing Women Who Present in Early Labor or with Ruptured Membranes

Most studies have shown a similar risk of HIV transmission for cesarean delivery performed for obstetric indications after labor and membrane rupture as for vaginal delivery. In one study, the HIV transmission rate was similar in women undergoing emergency cesarean delivery and those delivering vaginally (1.6% vs. 1.9%, respectively).[7] A meta-analysis of studies in women with HIV, most of whom were receiving no ARV drugs or only zidovudine, demonstrated a 2% increased transmission risk for every additional hour of ruptured membranes.[36] However, it is not clear how soon after the onset of labor or the rupture of membranes the benefit of cesarean delivery is lost.[37] A prospective study of 707 women in Ireland showed that among the 493 women on ART with HIV RNA levels <1,000 copies/mL, no cases of perinatal transmission occurred with membranes ruptured for up to 25 hours. Only a viral load of >10,000 copies/mL was an independent risk factor for perinatal transmission.[38] A prospective review of 2,398 women with HIV in the UK and Ireland, most of whom were virally suppressed, showed no association between duration of ruptured membranes and perinatal HIV transmission in 2,116 term deliveries, regardless of maternal viral load. Eighty-nine percent of the women had HIV RNA levels <50 copies/mL; among the remaining 11%, 9% had HIV RNA levels 50–399 copies/mL, 1% 400–999 copies/mL, 0.4% 1,000–9,999 copies/mL, and 0.6% >10,000 copies/mL. Among mother-baby pairs with perinatal transmission and no evidence of *in utero* transmission, 2 mothers had undetectable HIV RNA levels (<50 copies/mL), one had an HIV RNA level of 50–399 copies/mL, and 2 had levels >10,000 copies/mL. Among term deliveries, median duration of rupture of membranes was 3 hours and 30 minutes; 71 (3.4%) had rupture of membranes >24 hours, and 24 (1.1%) had rupture of membranes >48 hours. The study authors concluded that obstetric care of women on ART at term with ruptured membranes should be "normalized."[39,40] Because it is not clear whether cesarean delivery after onset of labor reduces the risk of perinatal HIV transmission, management of women originally scheduled for cesarean delivery who present in labor must be individualized at the time of presentation. In these circumstances, consultation with an expert in perinatal HIV may be helpful. Because the delivery plan in the setting of labor must be made quickly, telephone consultation via a 24-hour, 7-day-a-week hotline (e.g., the National Perinatal HIV/AIDS Clinical Consultation Center [888-448-8765] may be helpful in rapidly developing an individualized plan).

The woman's oral ARV drug regimen should be continued, and IV zidovudine initiated (if previously planned) regardless of the mode of delivery.

When membrane rupture occurs before 37 weeks gestation, decisions about timing of delivery should be based on best obstetrical practices, considering risks to the infant of prematurity and of HIV transmission. Steroids should be given, when appropriate, to accelerate fetal lung maturity because no data exist to suggest that these recommendations need to be altered for women with HIV. When the decision is made to deliver, route of delivery should be according to obstetrical indications.

Operative Vaginal Delivery

In the past, before data from the era of ART was available, HIV was considered a relative contraindication to operative vaginal delivery with forceps or vacuum, but data from the era of ART had been lacking. Peters et al. reviewed the deliveries of 9,072 women living with HIV in the United Kingdom between 2008 and 2016. The percentage of women with viral suppression was 80% for the deliveries from 2007 through 2011 and 90% for those from 2012 through 2014. Among the 3,023/3,663 vaginal deliveries with data as to whether forceps or vacuum device were used, 249 (8.2%) involved operative delivery (5.6% using forceps, 2.4% using vacuum device, 0.1% using both forceps and vacuum device, and 0.2% device type unknown). Among the 222 infants with known HIV status at 18 months of age, there was 1 case of HIV transmission with multiple possible causes and not enough evidence to confirm intrapartum transmission. The study authors concluded that operative delivery is a safe option for women who are virally suppressed.[41]

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