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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Transmission and Mode of Delivery (Last updated October 26, 2016; last reviewed October 26, 2016)

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 due to the low rate of perinatal transmission in this group **(AII)**. In women with HIV RNA levels ≤1000 copies/mL, if scheduled cesarean delivery or induction is indicated, it should be performed at the standard time for obstetrical indications.
• 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 reduces the risk of perinatal HIV transmission. Management of women originally scheduled for cesarean delivery because of HIV infection 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 at a time when the majority of HIV-infected women 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.

In the randomized clinical trial, 1.8% of infants born to women randomized to undergo cesarean delivery were HIV-infected compared with 10.5% of infants born to women randomized to vaginal delivery ($P <$ .001). When adjusted for ARV use in pregnancy (zidovudine alone), scheduled cesarean delivery lowered risk of HIV transmission by 80%, although the results were no longer statistically significant (odds ratio [OR] 0.2; 95% CI, 0–1.7). The protective effect remained for scheduled delivery (adjusted OR [AOR] 0.3; 95% CI, 0.1–0.8) but not for emergency cesarean delivery (AOR 1.0; 95% CI, 0.3–3.7) when the data were analyzed by actual mode of delivery rather than by the group to which women were allocated.[1] Results from a large meta-analysis of individual patient data from 15 prospective cohort studies also demonstrated the benefit of scheduled cesarean delivery, with a 50% reduction in risk.[2]

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

The American College 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.

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 (AOR 0.30; $P = 0.022$); however, zidovudine alone was the regimen primarily used as prophylaxis.[5] Among infants born to 834 women with HIV RNA ≤1,000 copies/mL receiving ARV medications, 8 (1%) were HIV-infected. In a report 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 HIV infected, some of which appear to represent *in utero* transmission.[6]

The recent studies demonstrate that transmission can occur even at very low HIV RNA levels. However, given the low rate of transmission in this group, 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 HIV-infected women compared with HIV-uninfected women.[7] 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 the obstetrician and the mother. Women should be informed that there is no evidence of benefit for scheduled cesarean delivery performed solely for prevention of perinatal transmission in women receiving ART with HIV RNA ≤1,000 copies/mL and that it is not routinely recommended in this group.

Scheduled Cesarean Delivery in the Combination Antiretroviral Therapy Era

In surveillance data from the United Kingdom and Ireland, pregnant women receiving ART (i.e., at least 3 drugs) had transmission rates of about 1%, unadjusted for mode of delivery.[6] Given the low transmission rates achievable with use of maternal ART, the benefit of scheduled cesarean delivery is difficult to evaluate. Both the randomized clinical trial[1] and meta-analysis[2] documenting the benefits of cesarean delivery included mostly women who were receiving either no ARVs or zidovudine alone. However, other data partially address this issue.

In a report on births to HIV-infected women from the United Kingdom and Ireland between 2000 and 2011, perinatal transmission rates in women on ART with HIV RNA<1,000 copies/mL with planned cesarean delivery (13/3,814; 0.3%) were not significantly different than those in similar women with planned vaginal delivery (6/2,238; 0.3%).[8] 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. For preterm deliveries with HIV RNA <1,000 copies/mL, transmission rates were slightly higher among planned vaginal deliveries but the numbers were small and the differences were not statistically significant (1/9 [11.1%] vs. 1/17 [5.9%] for HIV RNA 400–1000 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).[9] Therefore, no evidence to date suggests any benefit from scheduled cesarean delivery in women who have been receiving ART for several weeks and who have achieved virologic suppression.

When the delivery method selected is scheduled cesarean delivery and the maternal viral load is >1000 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 levels increased significantly in women who received IV zidovudine for 3 to 6 hours compared with <3 hours before delivery (1.0 vs. 0.55, respectively).[10] This suggests that an interval of at least 3 hours may provide adequate time to reach equilibrium across the placenta, 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

HIV-infected women 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 if ART was begun immediately, reduction in plasma HIV RNA to undetectable levels usually takes several weeks, depending on the kinetics of viral decay for a particular drug regimen.[11-13] 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.

Timing of Scheduled Cesarean Delivery

For the general obstetric population, ACOG recommends that scheduled cesarean delivery not be performed before 39 weeks' gestation because of the risk of iatrogenic prematurity.[14,15] However, in cases of cesarean delivery performed to prevent transmission of HIV, ACOG recommends scheduling cesarean delivery at 38 weeks' gestation in order 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, 11.0% at 38 weeks, and 8.0% at 39 weeks.[15] 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 HIV-infected women and is rarely indicated before scheduled cesarean section for prevention of HIV transmission.

Among 1,194 infants born to HIV-infected mothers, 9 (1.6%) infants born vaginally had respiratory distress syndrome (RDS) compared with 18 (4.4%) infants born by scheduled cesarean delivery ($P < 0.001$). 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.[16] Although newborn complications may be increased in planned births <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 HIV-infected women 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 HIV-uninfected women.

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 HIV-infected women have increased rates of postoperative complications, mostly infectious, compared with HIV-uninfected women and that risk of complications is related to degree of immunosuppression and the receipt of suppressive ART.[17-22] Furthermore, a Cochrane review of six studies of HIV-infected women 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.[23] Complication rates in most studies[1,24-28] were within the range reported in populations of HIV-uninfected women with similar risk factors and not of sufficient frequency or severity to outweigh the potential benefit of reduced perinatal HIV transmission. A recent 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 HIV-infected women compared to HIV-uninfected women.[7] The rate of any complication associated with cesarean delivery was 117 per 1,000 deliveries among HIV-infected women compared with 67 per 1,000 deliveries among HIV-uninfected women. Therefore, HIV-infected women should be counseled regarding the specific risks associated with undergoing cesarean delivery in the setting of HIV infection.

Management of Women Who Present in Early Labor or with Ruptured Membranes

New data are available to address the question of whether performing cesarean delivery after the onset of labor or membrane rupture decreases risk of perinatal transmission of HIV. Most studies have shown a similar risk of 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).[6] A meta-analysis of HIV-infected women, most of whom were on zidovudine as a single drug or receiving no ARV medications, demonstrated a 2% increased transmission risk for every additional hour of ruptured membranes.[29] However, it is not clear how soon after the onset of labor or the rupture of membranes the benefit of cesarean delivery is lost.[30] A prospective study of 707 women in Ireland showed that among the 493 women on ART with HIV RNA levels <1,000, 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.[31] A prospective review of 2,398 HIV-infected women in the UK and Ireland most of whom were virally suppressed showed no association between duration of ruptured membranes and perinatal transmission in 2,116 term deliveries, regardless of viral load. Eighty-nine percent 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% 1000–9999 copies/mL, and 0.6% >10,000 copies/mL. Among mother-baby pairs with perinatal transmission and no evidence of in utero transmission, 2 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 30 minutes; 71 (3.4%) had rupture of membranes >24 hours and 24 (1.1%) had rupture of membranes >48 hours. The authors concluded that obstetric care of women on ART at term with ruptured membranes should be "normalized."[32,33] 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 with 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 ARV drug regimen should be continued and IV zidovudine initiated, if previously planned.

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

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