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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According to the March of Dimes, preterm birth or delivery (PTD) affects approximately 10% of live births in the United States, and approximately 8% of U.S. infants are low birth weight (LBW) infants. Women with HIV who are taking antiretroviral therapy (ART) may be at increased risk for adverse neonatal outcomes, including PTD (delivery before 37 weeks gestation), LBW infants (those weighing <2,500 g), and small for gestational age (SGA) infants (those with a birth weight <10th percentile expected for gestational age), especially when compared to women without HIV. There are limited data suggesting a potential association between hypertensive disorders of pregnancy (HDP) and maternal HIV. In this section, the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (the Panel) provides a summary of data published since 2015 regarding ART and adverse maternal and neonatal outcomes. For historical data related to this topic, please refer to the archived versions of this section. For information related to ART use and teratogenicity (birth defects), please refer to Teratogenicity and the individual drug sections in Appendix B and Table 8.

Adverse Pregnancy Outcomes

The association between the use of ART and preterm birth, fetal growth restriction, miscarriage, and stillbirth has been an area of research for many years with multiple studies that include conflicting results. These outcomes are common and often occur without an identifiable cause, so it can be difficult to establish a causal link with a medication in an individual case. However, because these outcomes are relatively common, even a small increase in risk can have a substantial public health impact.

Much of the conflicting data in earlier studies about antiretroviral (ARV) drugs and adverse pregnancy outcomes can be ascribed to the use of inappropriate control groups and failure to stratify the data by timing of ARV initiation (before or after conception). Potential associations between ART and adverse pregnancy outcomes are difficult to establish because of the challenge of finding appropriate comparator groups. Women with HIV who do not receive ART in pregnancy are not an appropriate comparator, because they have an increased risk of adverse outcomes due to their immunocompromised status. However, comparing women on ART to women without HIV is confounded by HIV status. The best way to evaluate ART and pregnancy outcomes is to use a comparative safety approach in which ART regimens are compared to each other. This approach is preferred because of growing evidence that the risk of adverse outcomes varies by ARV drug, and even within ARV drug classes. Risks of adverse outcomes may also depend on the timing of ART initiation, with an increased risk of adverse outcomes among women who are receiving ART before conception use. More studies are needed to fully evaluate the association between the use of specific ARV regimens and the risk of adverse pregnancy outcomes.

Preterm Delivery

Three large meta-analyses have failed to demonstrate a significant association between ART use and PTD. The sample sizes pooled for these meta-analyses ranged from 14 to 90 studies and included 11,224 to 37,877 women and/or infants. Most of the studies that were included in these meta-analyses were observational.
studies, and most were older studies that do not include some of the ARV regimens currently used. There was also significant heterogeneity in data collection. The meta-analysis by Kourtis et al. showed a modest but statistically significant increase in the risk for PTD in women who initiated combination ART before pregnancy or during the first trimester, compared with women who initiated ART during the second trimester or later (odds ratio [OR] 1.71, 95% confidence interval [CI], 1.09–2.67). The meta-analysis by Nachega et al. compared pregnancy outcomes between women who received tenofovir disoproxil fumarate (TDF)-based regimens and women who received regimens that did not contain tenofovir. This study found no difference in the risk of PTD between these two groups.

Among the studies that report an association between the use of ART and PTD, the relative risks (RRs)/ORs for PTD range from 1.2 to 3.4. Variability in the available data may be a factor in conflicting results, (e.g., some studies have reported increased rates of PTD when ART is initiated before pregnancy or during early pregnancy compared to later in pregnancy). Maternal factors, such as HIV disease severity, may have affected the timing of ART initiation during pregnancy and may be associated with PTD independent of ART use. In general, none of the studies reviewed in this section have comprehensively controlled for all factors that may be associated with PTD.

Preterm Delivery and Antiretroviral Therapy Exposure Before Pregnancy

Some studies report an association between initiating ART before pregnancy and PTD, reporting RRs and ORs that range from 1.20 to 2.05. These studies were conducted in Asia, Europe, Latin America, Africa, and North America and included various ARV regimens (including no ART and single-drug, two-drug, and multidrug regimens). The association between PTD and ART use prior to conception is attenuated in some multivariate analyses. A retrospective cohort study that included >2,000 women on multidrug ART did not show an association between ART initiation before pregnancy and PTD. Certain ARV regimens, such as those that contain lopinavir/ritonavir (LPV/r), may be more closely associated with PTD than others.

Antiretroviral Therapy Regimens That Are Associated with Preterm Delivery

Protease Inhibitor-Based Regimens

The association between the use of protease inhibitor (PI)-based ART and PTD has been investigated in multiple studies. These studies include populations in Europe, North America, and Africa. The RRs/ORs of PTD reported in these studies range from 1.14 to 3.4. However, a small meta-analysis of 10 studies (eight prospective cohort studies, one randomized controlled trial, and one surveillance study) demonstrated that the use of PI-based ART is associated with an increased risk of PTD, with an adjusted odds ratio (aOR) of 1.32 (95% CI, 1.04–1.6) and \( I^2 = 47\% \) (moderate heterogeneity). When evaluating the effects of initiating PI-based ART during the first and third trimesters of pregnancy, the pooled effect was not significant.

Not all of the studies reviewed for this section have identified an association between PI use and an increased risk of PTD. Six studies did not demonstrate a significant association between PI-based ART and PTD. For example, a retrospective Canadian study of women who were taking regimens that included unboosted PIs did not report increased rates of PTD among these women.

Regimens that include PIs boosted with ritonavir may be associated with an increased risk of PTD compared to unboosted PI regimens. The Promoting Maternal and Infant Survival Everywhere (PROMISE) trial study compared outcomes in women who received zidovudine (ZDV) alone to women who received LPV/r-based ART with a dual-nucleoside reverse transcriptase inhibitor (NRTI) backbone of either ZDV plus lamivudine (3TC) or emtricitabine (FTC) plus TDF initiated during pregnancy. Compared to women who received ZDV alone, women who received ZDV plus 3TC plus LPV/r had higher rates of PTD (13% vs. 20.5%; \( P < 0.001 \)). PTD rates among women who received TDF-based ART and those who received ZDV-based ART were not statistically different (19% vs. 18%; \( P = 0.77 \)). Sebikari et al. published a follow-up study of the PROMISE trial. After controlling for other risk factors, receipt of either ZDV plus 3TC plus LPV/r or FTC plus TDF...
plus LPV/r remained associated with PTD. The aOR of PTD for women who received LPV/r plus ZDV plus 3TC compared to ZDV alone was 1.8 (95% CI, 1.5–2.3), and the aOR for women who received LPV/r plus FTC plus TDF compared to ZDV alone was also 1.8 (95% CI, 1.3–4.0). When comparing the two ART regimens, there was no significant difference in the risk of PTD among women who received FTC plus TDF plus LPV/r and those who received ZDV plus 3TC plus LPV/r (aOR 0.97; 95% CI, 0.72–1.31).44

Another study of >6,000 women in the United Kingdom and Ireland demonstrated increased rates of PTD among women with HIV who were taking PI-based ART before pregnancy, especially regimens that contained LPV/r. This effect was increased when the women had CD4 T lymphocyte (CD4) cell counts <350 cells/mm² (aOR 1.99; 95% CI, 1.02–3.85).23 A retrospective cohort study combined observations from the Surveillance Monitoring for ART Toxicities (SMARTT) study and the International Maternal and Pediatric Adolescent AIDS Clinical Trials (IMPAACT) for a total of 4,646 live birth outcomes. Risk of PTD was similar or slightly higher in women who received LPV/r in combination with FTC and TDF than in women who received atazanavir/ritonavir (ATV/r) plus FTC and TDF; however, among women who initiated ART before conception, the risk of PTD was higher for the LPV/r regimen.21 Although more prospective data are needed, ART that contains LPV/r may increase the risk of PTD compared to regimens that contain other ritonavir-boosted PIs.

Despite this potential association between the use of PI-based ART and PTD, some pregnant women may require PI-based regimens. In these cases, the Panel recommends the use of darunavir/ritonavir or ATV/r over LPV/r.

**Nucleoside Reverse Transcriptase Inhibitor-Based Regimens and Non-Nucleoside Reverse Transcriptase Inhibitor-Based Regimens**

Fewer studies have evaluated non-PI based ART regimens and PTD. In a meta-analysis of 17 studies in which women with HIV (n = 37,877) who were taking ART that included TDF were compared to women who were taking ARV regimens that did not include TDF, TDF-based ART was associated with a modest reduction in the rate of PTD (RR 0.9; 95% CI, 0.81–0.99; I² = 59%); however, there was no significant difference in the risk of very PTD between these two groups.2 Some cohort studies have shown an association between the use of non-PI based regimens and PTD. South African women with HIV who were taking FTC plus TDF plus nevirapine (NVP) had higher rates of PTD than women without HIV (aOR 1.2; 95% CI, 1.0–1.5).22 When compared to women without HIV, women who were taking FTC plus TDF plus efavirenz (EFV) were at increased risk of PTD.25 As stated in the introduction, using women without HIV as a control group may be an inappropriate study design choice. A retrospective cohort study of South African women who received FTC plus TDF plus EFV did not show an increased risk of PTD, SGA infants, or LBW infants when these women were compared to women who were taking NVP-based ART or other multidrug regimens.33

**Integrase Strand Transfer Inhibitor-Based Regimens**

Limited data from observational cohort studies are available to assess the relationship between integrase strand transfer inhibitor-based regimens (PI-sparing regimens) and PTD. Women who initiated FTC plus TDF plus EFV or FTC plus TDF plus dolutegravir (DTG) during pregnancy were at increased risk of PTD (aOR 1.2; 95% CI, 1.1–1.3) compared to women without HIV, but there was no significant difference in the risk of PTD between these two ART regimens. However, when these ART regimens were compared to one another, there were no significant differences in the risk of PTD.24 This study was included in a systematic review of six sources (two cohort studies, three databases, and one report) that was designed to evaluate adverse pregnancy outcomes that were related to DTG exposure. A total of 845 women who received FTC plus TDF plus DTG were compared to 4,593 historical controls who received FTC plus TDF plus EFV, and there was no clear difference in the risk of PTD between these groups.45

**Birth Weight**

For the purpose of this section, abnormalities of birth weight related to ART use are commonly reported as LBW infants (those weighing <2,500 g) or SGA infants (those with a birth weight <10th percentile expected for gestational age). LBW may be a reflection of preterm birth or growth restriction; SGA may be a reflection...
of growth restriction or constitutionally small infants. Given that LBW and SGA may be caused by different mechanisms, this section discusses studies that have reported LBW and SGA separately.

**Low Birth Weight**

Multiple studies have demonstrated an association between any ART use and LBW infants.\[^{18,22,42,46-50}\] Reported rates of LBW among infants who were exposed to ART range from 7.4% to 36%.\[^{3,10,16,18,20-22,30,39,43,47,48,51}\] In a systematic review of 13 studies (nine observational studies and four randomized controlled trials) that compared ZDV monotherapy to NNRTI- and PI-based regimens, the NNRTI- and PI-based regimens were associated with LBW infants.\[^{27}\]

In a Chinese cohort of 748 infants exposed to either NVP, EFV, or LPV/r with a dual-NRTI backbone, preconception ART use was associated with an increased risk of LBW infants (aOR 1.92, 95% CI, 1.1–3.4).\[^{26}\] A cohort study that included 4,646 births reported an increased risk of LBW infants among women who received preconception FTC plus TDF plus LPV/r compared to those who received FTC plus TDF plus ATV/r (unadjusted risk ratio 1.97, 95% CI, 1.2–3.4).\[^{21}\]

**Small for Gestational Age**

Among infants born to women with HIV, the reported rates of SGA infants range from 7.3% to 31%.\[^{13,16,18,20,22,23,25,30,33,35,41,42,52,53}\] A South African prospective study reported that women with HIV were more likely to have SGA infants than women without HIV (14% vs. 8%).\[^{33}\] Three studies in Botswana reported a positive association between ART use (for both PI-based regimens and regimens that did not contain PIs) and SGA.\[^{13,20,54}\] In a study that compared the effects of initiating monotherapy during pregnancy to the effects of initiating ART before pregnancy and continuing ART during pregnancy, SGA occurred more frequently in women who continued ART that was initiated before conception, but this finding was statistically nonsignificant (RR 1.34, 95% CI, 0.98–1.84).\[^{18}\] When compared to FTC plus TDF plus EFV, both NVP-based and LPV/r-based ART were associated with increased incidence of SGA.\[^{20}\]

Women in the Netherlands who were taking PI-based ART before pregnancy had a higher risk of SGA (OR 1.35, 95% CI, 1.03–1.77) than women who were taking non-nucleoside reverse transcriptase inhibitor-based ART.\[^{32}\] In a Brazilian cohort of 787 infants, women who received LPV/r had an increased risk of delivering SGA infants compared to women who received NFV (P = 0.0004).\[^{33}\] In contrast, a retrospective cohort study of women with HIV who were taking FTC plus TDF plus EFV, NVP-based ART, or other multidrug regimens before pregnancy did not show any association between these regimens and SGA.\[^{33}\]

In summary, the data are mixed regarding the effect of ART use on birth weight. Given the potential for LBW or SGA infants, maternal use of ART during pregnancy may be an indication for enhanced antenatal surveillance of fetal growth, especially in cases where ART was initiated preconception.

**Stillbirth**

Reported rates of stillbirth among women with HIV range from 0.5% to 11.4%.\[^{9,13,14,16,20,30-32,39,45,47,48}\] In a meta-analysis of 17 studies that included 37,877 women with HIV who were taking ART, three studies included stillbirth outcomes. Women with HIV who were taking TDF-based ART had a lower risk of stillbirth than those who were taking ART that did not include TDF (pooled RR 0.6; 95% CI, 0.43–0.84; I^2 = 72%).\[^{2}\] Two studies have evaluated the association between continuing ART during pregnancy or starting ART during pregnancy and the risk of stillbirth, with data that include both PI-based regimens and regimens that do not contain a PI. In one study, a greater risk of stillbirth was observed among women who continued preconception ART during pregnancy than women who initiated ART during pregnancy (aOR 1.5; 95% CI, 1.2–1.8).\[^{13}\] In another study, Zash et al. reported that preconception use of ZDV plus 3TC plus NVP was associated with a significantly increased rate of stillbirth compared to the use of FTC plus TDF plus EFV (adjusted relative risk 2.3, 95% CI 1.6–3.3).\[^{20}\]

When evaluating the association between the use of ART and adverse pregnancy outcomes, more studies have examined PTD, LBW infants, and SGA infants than stillbirth. Given that stillbirth is a relatively rare outcome in resource-rich settings, data related to stillbirth and ART use are limited.

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Maternal Outcomes

Hypertensive Disorders of Pregnancy

Limited data suggest that women with HIV may have an increased risk of HDP. A meta-analysis did not reveal a clear association between maternal HIV and pregnancy-induced hypertension, preeclampsia, or eclampsia. An Italian study demonstrated an increased risk for both early-onset and late-onset pre-eclampsia (aOR 2.50; 95% CI, 1.51–4.15 and aOR 2.64; 95% CI, 1.82–3.85, respectively) as well as pre-eclampsia with severe features (aOR 2.03; 95% CI, 1.26–3.28) among women with HIV compared to women without HIV. A later study found that women with HIV were less likely to have HDP than women without HIV (OR 0.67; 95% CI, 0.48–0.93).

Few studies have evaluated whether the use of ART is associated with a higher risk of pre-eclampsia. No studies have evaluated the effect of specific ARV drugs on maternal hypertension. A secondary analysis of South African data revealed that among women with low CD4 counts (<200 cells/mm$^3$), there was an increased risk of maternal death from HDP when comparing women who were taking ART to women who received no ART during pregnancy (RR 1.15; 95% CI, 1.02–1.29). A retrospective study on South African women with HIV demonstrated that those who were on ART before pregnancy and those who were not on ART before pregnancy had similar rates of HPD (15.7% and 14.9%, respectively). Although these limited data may suggest an association between HDP and maternal HIV, there are no known interventions to reduce this risk, and providers should not withhold ART in the setting of HDP.

Summary

Clinicians should be aware of a possible increased risk of adverse maternal and neonatal outcomes with the use of ART for prevention of perinatal HIV infection. Given that ART has clear benefits for maternal health and reduces the risk of perinatal transmission, these agents should not be withheld due to concern for increased risk of adverse neonatal outcomes. Until more information is available, pregnant women with HIV who are receiving ART should continue using their provider-recommended regimens. Clinicians should monitor pregnant women with HIV for potential pregnancy complications, including PTD, LBW infants, and SGA infants. Monitoring may require additional prenatal visits and fetal ultrasounds; see Monitoring of the Woman and Fetus During Pregnancy for more information.

References


