Antiretroviral Drug Regimens and Pregnancy Outcomes

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Panel's Recommendations
• Clinicians should be aware of a possible increased risk of adverse neonatal outcomes (e.g., preterm birth [PTB]) in pregnant people who are receiving antiretroviral therapy (ART). However, given the clear benefits of ART for the health of the pregnant person and the prevention of perinatal transmission, HIV treatment should not be withheld due to concern for adverse pregnancy outcomes (AII). • Use of ART for the prevention of perinatal HIV transmission, especially preconception or in the first trimester, may be associated with an increased risk of PTB. However, the Panel does not recommend that people with HIV stop ART before conception or in early pregnancy for the purpose of preventing PTB (AII).
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*

In this section, the Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission (the Panel) provides a summary of recently published data on antiretroviral therapy (ART) and adverse pregnancy outcomes. Pregnant people with HIV, regardless of antiretroviral (ARV) drug use, may be at increased risk for adverse neonatal outcomes. These outcomes may include preterm birth (PTB) (delivery before 37 weeks of gestation), low birth weight (LBW) infants (those weighing <2,500 g), small-for-gestational-age (SGA) infants (those with a birth weight <10th percentile expected for gestational age and sex), and stillbirth (delivery of a nonviable infant after 20 weeks). The gestational age cutoff used to define stillbirth in the studies described varies by gestational age from ≥20 weeks to ≥28 weeks. Limited data suggest a potential association between HIV infection and complications of pregnancy, such as hypertensive disorders of pregnancy (HDP) (i.e., chronic hypertension, gestational hypertension, preeclampsia, and eclampsia). Some of the data described in this section involve historical ARV drugs that are no longer commonly prescribed. For additional historical data related to this topic, please refer to the archived versions of this section. For information related to ARV drug use and teratogenicity (i.e., their relation to birth defects), please refer to Teratogenicity and the individual drug sections in Appendix B: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy and Table 14. Antiretroviral Drug Use in Pregnant People with HIV: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy.

Interpretation of Adverse Pregnancy Outcomes Data

Multiple studies have evaluated the potential association between ARV drug use and PTB, LBW, SGA, and stillbirth with conflicting results. These adverse outcomes often occur without an identifiable cause, and it can be difficult to establish a causal link with medication exposure. Adverse pregnancy outcomes are relatively common, so a small increase in risk can have substantial public health impact.

Much of the conflicting data in earlier studies about ARV drugs and adverse pregnancy outcomes can be ascribed to the use of inappropriate comparison groups and failure to stratify the data by timing of ARV drug 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. People 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. Comparing pregnant people on ART to pregnant people without HIV is confounded by HIV status. Some evidence suggests that the risk of adverse outcomes varies by ARV drug, even within ARV drug classes. The risk of adverse outcomes also may depend on the timing of ART initiation. A suggested approach to evaluate ART and pregnancy outcomes is to use a comparative safety approach in which ARV drug regimens or ARV drug classes are compared with each other. Unfortunately, many studies continue to use comparison groups of women without HIV and women with HIV who are not taking ART or who are taking older regimens that are no longer recommended for treatment of HIV. Studies of the safety of newer ART, specifically integrase strand transfer inhibitors (INSTIs), on pregnancy outcomes are reassuring but limited.[1] More studies are needed to fully evaluate the association between the risk of adverse pregnancy outcomes and the use of specific ARV drugs, classes of ARV drugs, and ART.

Preterm Birth

Multiple meta-analyses and systematic reviews have evaluated the potential association of ARV drug use and PTB. Some large meta-analyses have not demonstrated a significant association between ARV drug use and PTB. The sample sizes pooled for these meta-analyses ranged from 13 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 drugs currently used.[2-6] A large meta-analysis of 61 observational studies (n = 409,781) compared the risk of PTB between HIV negative women and women with HIV who were either not on ART, prescribed zidovudine (ZDV) single-drug therapy, or prescribed ART. Although the risk of any PTB in women with HIV prescribed ART compared with women with HIV not on ART was not significantly different, women prescribed ART were less likely to experience spontaneous PTB than women not on ART (relative risk [RR] 0.46; 95% confidence interval [CI], 0.32–0.67).[5] Another meta-analysis compared pregnancy outcomes between women who received tenofovir disoproxil fumarate (TDF)–based regimens and women who received regimens that did not contain TDF. This study found no difference in the risk of PTB between these two groups.[2] A network meta-analysis of seven randomized controlled trials (RCTs) evaluated seven different ART regimens and their associations with PTB (including spontaneous PTB in three trials). When compared with women prescribed ZDV/lamivudine (3TC)/abacavir, women prescribed ZDV/3TC/lopinavir (LPV)/ritonavir (r) had an increased risk of spontaneous PTB (n = 991; RR 1.81; 95% CI, 1.21–2.71).[7] ART that contains LPV/r may be associated with a greater risk of PTB than other protease inhibitor (PI)–based regimens.

Multiple observational studies describe an association between the use of ARV drugs during pregnancy and an increased risk of PTB.[4,8-19] In general, the observational studies reviewed in this section have not controlled comprehensively for all factors that may be associated with PTB. A recent observational study that evaluated ARV drug use among women with HIV in British Columbia reduced confounding variables by excluding multiple gestation pregnancies and antiquated ARV drug regimens (i.e., single-drug therapy, two-drug therapy, and triple nucleoside reverse transcriptase inhibitor [NRTI] regimens). The authors concluded that women with HIV were twice as likely to experience PTB as the general population. Compared with women with HIV who were not

on ART during pregnancy, women who were on any ART were less likely to have spontaneous PTB (hazard ratio [HR] 0.54; 95% CI, 0.29–1.04), and the protective effect for each week of ART was cumulative (HR 0.98; 95% CI, 0.96–0.99). Neither preconception or first-trimester ARV drug use nor PI-based ART was associated with PTB.[20]

Antiretroviral Therapy and Preterm Birth

Protease Inhibitor–Based Regimens

The association between the use of PI-based ART and PTB has been investigated in multiple studies across Europe, North America, and Africa.[7,8,10,12,13,15,21-24] Not all the studies reviewed for this section have identified an association between PI use and an increased risk of PTB.[10,20,21,25,26]

A meta-analysis of 10 studies (eight prospective cohort studies, one RCT, and one surveillance study) demonstrated that the use of PI-based ART is associated with an increased risk of PTB, 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.[27] Another meta-analysis using data from 34 observational studies (n = 57,546) evaluated differences in infant outcomes between pregnant women with HIV prescribed PI-based and non-PI ART.[28] PI-based ART was not associated with an increased risk of PTB. In subanalyses, the authors compared individual PI ARV drugs and determined that women prescribed LPV/r were more likely to experience PTB than women prescribed nelfinavir (RR 1.33; 95% CI, 1.03–1.72; I^2=0%; four studies; n = 1,937 women). Compared with women prescribed nonboosted PI-based ART, women prescribed boosted PIs were more likely to experience PTB (RR 1.36; 95% CI, 1.12–1.65; I^2=0%; five studies; n = 3,333).[28] ART that includes PIs boosted with ritonavir may be associated with an increased risk of PTB compared with nonboosted PI regimens.[29] Despite this potential association between the use of PI-based ART and PTB, some pregnant people may require PI-based regimens. In these cases, the Panel recommends the use of darunavir/ritonavir (DRV/r) over LPV/r.[30]

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

A meta-analysis of 17 studies of women with HIV who were on ART (n = 37,877) compared those on TDF regimens with women who were on regimens that did not include TDF. TDF-based ART was associated with a modest reduction in the rate of PTB (RR 0.9; 95% CI, 0.81–0.99; I^2 = 59%).[2] Some observational studies have shown an association between the use of NRTI-based regimens and PTB. When compared with women without HIV, South African women with HIV who were taking nevirapine (NVP)/emtricitabine (FTC)/TDF had higher rates of PTB (aOR 1.2; 95% CI, 1.0–1.5).[14] When compared with women without HIV, women who were taking efavirenz (EFV)/FTC/TDF were at increased risk of PTB (aOR 1.98; 95% CI, 1.12–3.53).[17] Another study of South African women who received EFV/FTC/TDF did not show an increased risk of PTB when compared with women who were on NVP-based ART or other multidrug regimens.[31]

Integrase Strand Transfer Inhibitor–Based Regimens

INSTIs are a preferred class of ARV drug for HIV treatment in pregnancy. As INSTI use increases among people with HIV, INSTI exposure during pregnancy is observed more often.[20,23,32,33] In the VESTED International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) RCT

comparing pregnant participants receiving EFV/TDF/FTC (n = 207), dolutegravir (DTG)/TDF/FTC (n = 202), and DTG/tenofovir alafenamide (TAF)/FTC (n = 208), women taking ART with EFV were more likely to experience PTB than women taking ART with DTG/TAF/FTC (12% vs. 6%; 95% CI, -11.8% to -0.9%; *P* = 0.02). The percentage of PTB was similar between DTG ART groups.[34]

Observational studies of INSTI use during pregnancy have not reported an association with an increased risk of PTB when compared with non-INSTI ART. Additionally, when compared with one another, individual INSTIs have not been associated with an increased risk of PTB. In the Tsepamo study, women who initiated EFV/FTC/TDF or DTG/FTC/TDF during pregnancy were at increased risk of PTB (aOR 1.2; 95% CI, 1.1–1.3) compared with women without HIV. However, when these regimens were compared with one another, there was no significant difference in the risk of PTB. A total of 845 women who received DTG/FTC/TDF were compared with 4,593 historical controls who received EFV/FTC/TDF, and there was no difference in the risk of PTB between these groups. Some of the historical controls were from a systematic review of six sources (two cohort studies, three databases, and one report).[16]

A large observational study of preconception ART containing DTG (n = 384) or EFV (n = 1,045) in Brazilian women did not demonstrate a difference in gestational ages at delivery; of note, 57 women in the DTG group included exposures to EFV.[35] A French case-control observational study comparing women with HIV prescribed INSTI ART (n = 246) and DRV/r ART matched by ARV backbone (n = 246) did not demonstrate any differences in PTB when ART was initiated before (16.8% vs. 16.1%) and during pregnancy (12.8% vs. 11.2%).[36] A retrospective cohort of 813 women with HIV during pregnancy did not find a significant difference in PTB between INSTI and non-INSTI groups (21% vs 16%, *P* = 0.3).[37] Another cohort study compared ART containing DTG (n = 120) to other INSTI-based regimens with either elvitegravir (EVG) (n = 159) or raltegravir (RAL) (n = 86), and the percentage of pregnant people with PTB was similar when comparing regimens (16.7% vs. 17.6% vs. 15.1%, respectively).[38] Very limited data suggest no association between the use of long-acting injectable cabotegravir in combination with rilpivirine during pregnancy and PTB.[39]

Preterm Birth and Antiretroviral Therapy Exposure Before Pregnancy

A meta-analysis of 24 observational studies (n = 38,293 pregnancies) in 15 countries reported that women initiating ART before pregnancy were at increased risk of PTB compared with women initiating ART during pregnancy (RR 1.16; 95% CI, 1.03–1.31; $I^2 = 81\%$).[6] Additional observational studies have described an association between initiating ART before pregnancy and an increased risk of PTB.[13-15,18,23,24,31,40,41] These studies were conducted in Asia, Europe, Latin America, Africa, and North America and included various ART (including no ART and single-drug, two-drug, and multidrug regimens). A secondary analysis of 2,217 women with HIV enrolled in a RCT in Tanzania (99% were prescribed TDF/3TC/EFV) reported that women initiating ART before 20 weeks of gestation were 30% more likely to experience PTB than women initiating ART after 20 weeks of gestation (adjusted risk ratio [aRR] 1.3; 95% CI, 1.03–1.67).[42] The association between PTB and ARV drug use prior to conception is attenuated in some multivariate analyses.[9,13,23,43-45] An observational study of >2,000 women on ART did not show an association between initiation before pregnancy and PTB.[31] ART should not be withheld prior to conception or in the first trimester for the prevention of PTB.

Birth Weight

For the purpose of this section, abnormalities of birth weight related to ARV drug use are commonly reported as LBW infants or SGA infants. LBW may reflect constitutionally small infants, growth restriction, and/or preterm birth; SGA may reflect 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

In a meta-analysis of 12 studies (n = 40,495), women with HIV on ART were not more likely to deliver LBW infants than women with HIV not on ART.[5] In a systematic review of 13 studies (nine observational studies and four RCTs) that compared ZDV single-drug therapy with other ART combinations, the non-nucleoside reverse transcriptase inhibitor (NNRTI)– and PI-based regimens were more likely to be associated with an increased risk of LBW infants than a regimen of ZDV alone.[4] In a single RCT of women prescribed DTG/TAF/FTC, DTG/TDF/FTC, or EFV/TDF/FTC, 12% of infants in the EFV group were LBW compared with 10% (DTG/TDF) and 6% (DTG/TAF) of infants exposed to DTG. These percentages mirror those reported for PTB in the previous section.[34] A secondary analysis of the MOTIVATE study (a behavioral intervention study in Kenya) reported that among 1,275 women with HIV prescribed ART (74% EFV/TDF/3TC and 4% a PI-based regimen), the percentage of LBW infants was similar between women starting ART before conception and after conception (3.3% and 4.4%, respectively).[45] An observational study that included 4,646 births reported an increased risk of LBW infants among women who received preconception FTC/TDF/LPV/r compared with those who received FTC/TDF/ATV/r (unadjusted risk ratio 1.97; 95% CI, 1.2–3.4).[13] Although multiple observational studies have reported associations between *in utero* ARV drug exposure and LBW, these studies are heterogeneous in population, design, and comparison groups.[3,9,11,13,14,16,21,22,24,26,43,46-51] Given this potential association between ARV drug use and LBW, providers may consider additional monitoring for fetal growth abnormalities during pregnancy.

Small for Gestational Age

Infants exposed to HIV *in utero* may be at risk for SGA.[9,11,14-17,25,26,31,34,43,50,52,53] In a meta-analysis of five studies (n = 6,818), women prescribed ART were more likely to deliver SGA infants than women with HIV not on ART (RR 1.38; 95% CI, 1.09–1.75).[5] Another meta-analysis (34 studies), reported that women with HIV prescribed PI-based ART are more likely to deliver SGA infants than women with HIV prescribed non-PI ART (RR 1.24; 95% CI, 1.08–1.43; I^2 = 67%; 11 studies; n = 25,893).[28] In an RCT, the percentage of SGA infants was similar among women with HIV randomized to DTG-based ART (TAF or TDF/FTC) or EFV-based ART (16%, 23%, and 21%, respectively).[34]

In an observational study of birth outcomes in Botswana, Zash et al. reported a positive association between ARV drug use (for both PI-based and PI-sparing regimens) and SGA among women with HIV.[24] When compared with FTC/TDF/EFV, both NVP-based and LPV/r-based ART were associated with an increased incidence of SGA infants born to women with HIV.[24] In another observational study, women prescribed TDF/3TC/EFV before 20 weeks of gestation were less likely to deliver SGA infants than women initiating after 20 weeks of gestation (aRR 0.71; 95% CI, 0.55–0.3).[54] An observational cohort study of French women with HIV reported similar percentages

of SGA infants born to women initiating ART containing RAL before and during pregnancy (3.7% as first-line ART and 6.2% as second-line ART).[36]

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

Stillbirth

Stillbirth is a relatively rare outcome in resource-rich settings, and data related to stillbirth and ARV drug use are limited. Some studies have reported an association between HIV infection and stillbirth.[9,16,21,24,40,41,46,48,50,55,56] In a meta-analysis of 17 studies that included 37,877 women with HIV who were on ART, three studies included stillbirth outcomes. Women with HIV who were on TDF-based ART had a lower risk of stillbirth than those who were on other regimens (pooled RR 0.6; 95% CI, 0.43–0.84; I^2 = 72%).[2] In a meta-analysis evaluating the difference in stillbirth between PI-based and non-PI ART, data from a single study (n = 6,952) reported that PI-based ART was not associated with an increased risk of stillbirth (RR 1.04; 95% CI, 0.06–1.79).[28] In a single RCT, the percentage of stillborn infants was not significantly higher among pregnant women randomized to DTG-based ART (3.7% DTG/TAF and 5.2% DTG/TDF) than to EFV-based ART (1.9%).[34] An observational study of Brazilian women with HIV reported similar percentages of stillborn infants in women prescribed ART with DTG compared with EFV (1% in both groups).[35] A secondary analysis of data collected from Kenyan women with HIV enrolled in an RCT reported that 4.4% (34 of 774) experienced a stillbirth. Most women on ART (n = 723) were prescribed TDF+3TC/FTC+EFV (535 or 74%). The differences in the percentages of stillbirths were not statistically significant between TDF-based (2.3%) and ZDV-based (0%) ART nor between EFV-based (2.8%) and NVP-based (0%) ART.[57]

Data regarding the timing of ART initiation and stillbirth are mixed, but timing of ART initiation is likely not a factor associated with an increased risk of stillbirth. Among women with HIV who delivered in the United Kingdom and Ireland between 2007 and 2015 (n = 10,434), preconception ARV drug use was not associated with an increased risk of stillbirth.[56] Women with HIV who delivered in Malawi from 2012 to 2015, 71% of whom were on ART preconception or during the first trimester, did not experience higher rates of stillbirth than the general population (2.5%, n = 8,380).[58] An observational study of 1,275 pregnant women with HIV in Kenya (2015–2019) demonstrated that women taking ART before conception had a similar incidence of stillbirth (2.7%) when compared with women taking ART after conception (2%). Most women in this cohort were prescribed TDF/3TC/EFV (71%), and only 4% were prescribed PI-based ART.[45] Another study of Kenyan women (n = 724), most of whom were prescribed TDF+3TC/FTC+EFV, reported that preconception ART use was not associated with an increased risk of stillbirth (1.3%, n = 425) compared with women starting ART after conception (2.9%, n = 346).[57] In contrast, an observational study reported that preconception use of ZDV/3TC/NVP was associated with a significantly increased rate of stillbirth compared with the use of FTC/TDF/EFV (adjusted relative risk 2.3; 95% CI, 1.6–3.3).[24] In a case-control study of a longitudinal cohort of French women with HIV (n = 808), the incidence of stillbirth was not significantly different between pregnant women receiving INSTI-based ART with RAL, EVG, or DTG and those receiving DRV-based ART. In women receiving a RAL-based regimen, stillbirths did not differ based on timing of ART exposure (2.3% at conception vs. 1.1% during pregnancy).[36]

Outcomes During Pregnancy

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 HIV and HDP.[59] Observational data evaluating differences in HDP among people with and without HIV are conflicting. An observational Italian study reported that women with HIV were more likely than women without HIV to be diagnosed with early-onset (before 34 weeks of gestation) and late-onset (after 34 weeks of gestation) preeclampsia (aOR 2.50; 95% CI, 1.51–4.15 and aOR 2.64; 95% CI, 1.82–3.85, respectively), as well as preeclampsia with severe features (aOR 2.03; 95% CI, 1.26–3.28).[60] A secondary analysis of observational data from South Africa reported that women with HIV with low CD4 counts (<200 cells/mm^3) on ART had an increased risk of maternal death from HDP compared with women with HIV and low CD4 counts who were not on ART during pregnancy (RR 1.15; 95% CI, 1.02–1.29).[61] Among these women, those on ART before pregnancy and those who were not on ART before pregnancy had similar rates of HDP (15.7% and 14.9%, respectively). These authors also described that women with HIV were less likely to have HDP than women without HIV (OR 0.67; 95% CI, 0.48–0.93).[40] In a South African observational cohort study (2013–2015) of women with and without HIV (n = 1,116), women with HIV were more likely to have hypertension at the first antenatal visit (adjusted relative risk 2.37; 95% CI, 1.29–4.35). Nearly half of all women in this cohort were obese (44% without HIV and 36% with HIV).[62] Most women with HIV initiated ART at the first antenatal visit (73%), and the ART prescribed was TDF/3TC/EFV or TDF/FTC/EFV. Hypertension at the initial antenatal visit did not indicate increased risk of adverse pregnancy outcomes, regardless of HIV status.[63] A subsequent large South African cohort (2018–2019) compared people without HIV (n = 146,575) and with HIV (n = 33,978), as well as those with HIV taking ART (n = 30,151) and not taking ART (n = 3,827). ART use initiated before or during pregnancy was not associated with an increased risk of HDP.[64] A small U.S. observational study demonstrated that women with HIV (n = 85) were not more likely to experience HDP than women without HIV (n = 3,556). The authors observed higher rates of HDP among women on INSTIs (25%, n = 23) and NNRTIs (24%, n = 7) than among women on PI-based ART (10%, n = 55). Preconception ARV drug use was associated with an increased risk of HDP.[33] In another retrospective study from the same academic center, INSTI use during pregnancy was associated with an increased risk of HDP compared with non-INSTI regimens (INSTI/TAF, 21%, n = 38; INSTI/TDF, 20%, n = 39; non-INSTI regimens, 7%, n = 214; TDF-exposed, 11%, n = 149).[65]

Although these limited data may suggest an association between HDP and HIV, and data varies regarding the association between ART and HDP, no known interventions reduce this risk. Providers should not withhold ART in the setting of HDP. Some pregnant people may benefit from low-dose aspirin to prevent or delay the onset of preeclampsia. For more information, please refer to U.S. Preventive Services Task Force recommendations.[66,67]

Summary

Clinicians should be aware of a possible increased risk of adverse outcomes for the birthing parent and neonate with the use of ARV drugs during pregnancy for prevention of perinatal HIV infection. Given that ART has clear benefits for the health of pregnant people and reduces the risk of perinatal HIV transmission, these agents should not be withheld because of concern for increased risk of adverse neonatal outcomes. Clinicians should monitor pregnant people with HIV for potential pregnancy complications, including PTB, LBW infants, and SGA infants.

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