Antiretroviral Drug Regimens and Maternal and Neonatal Outcomes

Updated: January 31, 2023
Reviewed: January 31, 2023

Panel's Recommendations
• Clinicians should be aware of a possible increased risk of adverse neonatal outcomes (e.g., preterm birth) in pregnant people who are receiving antiretroviral therapy (ART). However, given the clear benefits of ART for both maternal health and the prevention of perinatal transmission, HIV treatment should not be withheld due to concern for adverse pregnancy outcomes (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 maternal and neonatal 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), very preterm birth (vPTB) (delivery before 32 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 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 maternal complications of pregnancy, such as hypertensive disorders of pregnancy (HDP) (i.e., chronic hypertension, gestational hypertension, pre-eclampsia, and eclampsia). Some of the data described in this section include historical HIV treatment strategies—such as single-drug and two-drug ARV regimens—and older 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 use and teratogenicity (i.e., their relation to birth defects), please refer to Teratogenicity and the individual drug sections in Appendix B and Table 14.

Key Points

Maternal ARV use for the prevention of perinatal HIV transmission, especially preconception or in the first trimester, may be associated with an increase in PTB. The Panel does not recommend that people with HIV stop ART before conception or in early pregnancy for the purpose of preventing PTB.

ART that contains boosted protease inhibitors (PI) may increase the risk of PTB. When PI-based regimens are indicated, the Panel recommends the use of darunavir/ritonavir (DRV/r) or atazanavir/ritonavir (ATV/r) (see Recommendations for Use of Antiretroviral Drugs During Pregnancy: Overview and Table 7).

Infants exposed to ART before birth may be at increased risk of being LBW or SGA. Maternal ARV use during pregnancy may be an indication for enhanced antenatal surveillance—such as ultrasounds—to evaluate for poor fetal growth.

Stillbirth is a rare outcome in resource-rich settings, and data related to stillbirth and ARV use are limited. The Panel cannot make a specific recommendation regarding the prevention of stillbirth among pregnant people with HIV.

Limited data suggest an association between HDP and maternal HIV, but no known interventions effectively reduce this risk. Providers should not withhold or adjust ART for the purpose of preventing HDP.

Interpretation of Adverse Pregnancy Outcomes Data

The association between ARV use and PTB, fetal growth restriction, and stillbirth has been an area of research for many years, with multiple studies that include conflicting results. Because these outcomes often occur without an identifiable cause, it can be difficult to establish a causal link with a medication in a single case. These outcomes are relatively common, so even 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 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. Growing 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 regimens or ARV drug classes are compared with each other. Unfortunately, many available studies continue to use comparison groups of women without HIV and women with HIV who are not on ARVs or who are on a single-drug or two-drug ARV regimen, which are no longer recommended for treatment in pregnancy. 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 ARVs, and ART.

Preterm Birth

Multiple meta-analyses and systematic reviews are available to evaluate the potential association of ARV use and PTB. Some large meta-analyses have not demonstrated a significant association between ARV 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 ART or ARV drug classes currently used.[1-5] 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 not on ART, prescribed zidovudine (ZDV) single-drug therapy, or prescribed ART. Compared to women with HIV not on ART, women prescribed ZDV were less likely to experience PTB (relative risks [RR] 0.70; 95% confidence interval [CI], 0.62–0.79; I^2 index = 66%; 19 studies; n

= 24,222). Although the risk of any PTB in women prescribed ART compared to women not on ART was not significant, women prescribed ART were less likely to experience spontaneous PTB compared to women not on ART (RR 0.46; 95% CI, 0.32–0.67).[4] Another meta-analysis showed a modest but statistically significant increase in the risk for PTB in women who initiated 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% CI, 1.09–2.67). An additional 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. 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), LBW (six trials), and SGA (two trials).[6] In this network meta-analysis, the ART regimen ZDV/lamivudine (3TC)/lopinavir/ritonavir (LPV/r) was associated with an increase in PTB compared with ZDV single-drug therapy (n = 5,789; RR 1.43; 95% CI, 1.08–1.91). When compared with ZDV/3TC/abacavir (ABC), ZDV/3TC/LPV/r was associated with an increased risk of spontaneous PTB (sPTB) (n = 991; RR 1.81; 95% CI, 1.21–2.71). No differences were observed in vPTB between the regimens evaluated (4 trials; n = 1,819).[6]

Among the observational studies that reported an association between the use of ARVs and PTB, the RRs/ORs for PTB ranged from 1.18 to 1.69.[3,7-21] In general, the 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 use among women with HIV in British Columbia reduced confounding variables by excluding multiple gestation pregnancies and antiquated ARV regimens (single- and two-drug therapy, and triple nucleoside reverse transcriptase inhibitor [NRTI] regimens). They determined that women with HIV were twice as likely to experience PTB as the general population. Compared with women who were not on ART during pregnancy, women who were on any ART were less likely to have sPTB (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 use nor PI-based ART was associated with PTB.[22]

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 to women initiating ART during pregnancy (RR 1.16; 95% CI, 1.03–1.31; $I^2 = 81\%$)).[5] Additional studies report an association between initiating ART before pregnancy and PTB, reporting RRs/ORs that range from 1.14 to 2.82.[15-17,20,23-27] 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). The association between PTB and ARV use prior to conception is attenuated in some multivariate analyses.[11,15,27-30] An observational study of >2,000 women on ART did not show an association between initiation before pregnancy and PTB.[24] A secondary analysis of 2,217 women with HIV enrolled in a RCT in Tanzania (99% were prescribed TDF/3TC/efavirenz [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).[31] Certain ART—such as regimens that contain LPV/r—may be more strongly associated with PTB than other regimens.

Antiretroviral Therapy Regimens That Are Associated With 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. The RRs/ORs of PTB reported in these studies range from 1.55–2.17.[6,10,12,14,15,17,25,27,32-34] A small 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.[35] A larger 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.[36] PI-based ART was not associated with an increased risk of PTB or vPTB. In subanalyses, the authors compared individual PI ARVs and determined that women prescribed LPV/r were more likely to experience PTB than women prescribed nelfinavir (NFV) (RR 1.33; 95% CI, 1.03–1.72; I^2=0%; 4 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%; 5 studies; n = 3,333].[36] Not all the studies reviewed for this section have identified an association between PI use and an increased risk of PTB. Other studies have not identified a significant association between PI-based ART and PTB.[12,22,32,33,37,38]

Regimens that include PIs boosted with ritonavir may be associated with an increased risk of PTB compared with nonboosted PI regimens. Although more prospective data are needed, ART that contains LPV/r may increase the risk of PTB compared to regimens that contain other ritonavir-boosted PIs. 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 DRV/r or ATV/r over LPV/r.

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%); however, no significant difference in the risk of vPTB was observed between these two groups.[1] Some observational studies have shown an association between the use of non-PI based regimens and PTB. When compared with women without HIV, South African women with HIV who were taking NVP/emtricitabine (FTC)/TDF had higher rates of PTB (aOR 1.2; 95% CI, 1.0–1.5).[16] 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).[19] Another study of South African women who received EFV/FTC/TDF did not show an increased risk of PTB, SGA infants, or LBW infants when these women were compared with women who were on NVP-based ART or other multidrug regimens.[24]

Integrase Strand Transfer Inhibitor–Based Regimens

Integrase strand transfer inhibitors (INSTIs) are preferred ARVs for HIV treatment. As INSTI use increases among people with HIV, INSTI exposure during pregnancy is observed more often.[22,27,39,40]

In the Tsepamo study, women who initiated EFV/FTC/TDF or dolutegravir (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.[18] Some of these historical controls were from a systematic review of six sources (two cohort studies, three databases, and one report). This systematic review was designed to evaluate pharmacokinetics of DTG during pregnancy and adverse pregnancy outcomes related to DTG exposure.[41]

In the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) 2010 trial comparing participants receiving EFV/TDF/FTC (n = 207), DTG/TDF/FTC (n = 202), and DTG/tenofovir alafenamide (TAF)/FTC (n = 208) in pregnancy, women on ART with EFV were more likely to experience PTB when compared to women on 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.[42] A large observational study of preconception ART regimens 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.[43] 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%).[44] Lastly, 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).[45]

Birth Weight

For the purpose of this section, abnormalities of birth weight related to ARV 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 reflect preterm birth or growth restriction; 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

Multiple studies have demonstrated associations of *in utero* ARV exposure with LBW, although studies are heterogeneous in study population and design and comparison groups.[13,16,38,46-50] Reported rates of LBW among infants who were exposed to ART range from 8.9% to 23.8%.[2,11,13,15,16,18,25,28,32-34,47-49,51,52] In a meta-analysis of 12 studies (n = 40,495), women prescribed ZDV single-drug therapy were less likely than women with HIV not on ART to deliver LBW infants (RR 0.77; 95% CI, 0.67–0.88); *I*2= 68%). Women on ART were not more likely to deliver LBW infants compared to women with HIV not on ART.[4] In a systematic review of 13 studies (nine observational studies and four RCTs) that compared ZDV single-drug therapy with non-nucleoside reverse transcriptase inhibitor (NNRTI)- and PI-based regimens, the NNRTI- and PI-based regimens were associated with an increased risk of LBW infants.[3] In a network meta-analysis of six RCTs (n = 5,471), when compared to ZDV single-drug therapy, ZDV/3TC/LPV/r was associated with the highest risk of LBW (RR 1.87; 95% CI, 1.58–2.2).[6] 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 to 10% (DTG/TDF) and 6% (DTG/TAF) of infants exposed to DTG. These percentages

mirror those reported for PTB in the previous section.[42] 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).[15] 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).[30]

Small for Gestational Age

Among infants born to women with HIV, the reported rates of SGA infants range from 7.3% to 31%.[8,11,13,16-19,24,28,37,38,42,51,53,54]

In a meta-analysis of four studies (n = 4681), women prescribed ZDV single-drug therapy were not more likely to deliver SGA infants than ART-naive women with HIV. But 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 studies; n = 6,818].[4] Another meta-analysis (34 studies), reported that women with HIV prescribed PI-based ART are more likely to deliver SGA infants (RR 1.24; 95% CI, 1.08–1.43; I^2 = 67%; 11 studies; n = 25,893) and very SGA infants ((RR 1.40; 95% CI, 1.09–1.81; I^2 = 0; 3 studies; n = 6,765].[36] Two studies in Botswana reported a positive association between ARV use (for both PI-based and PI-sparing regimens) and SGA.[8,25,55] When compared with FTC/TDF/EFV, both NVP-based and LPV/r-based ART were associated with an increased incidence of SGA.[25] 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).[42] Among women prescribed TDF/3TC/EFV, those initiating therapy 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).[31] An observational cohort study of French women with HIV reported similar percentages of SGA infants born to women initiating ART containing raltegravir (RAL) before and during pregnancy (3.7% as first-line ART and 6.2% as second-line ART).[44]

In summary, the data are mixed regarding the effect of ARV use on birth weight. Given the potential for LBW or SGA infants, maternal use of ARV 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%.[8,9,11,18,23,25,26,33,41,47,49,51,56] 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%).[1] In a meta-analysis evaluating the difference in stillbirth between PI-based and non-PI ART, data from a single study (n = 6,952) showed that PI-based ART was not associated with an increased risk of stillbirth (RR 1.04; 95% CI, 0.06–1.79).[36] 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) compared to EFV-based ART (1.9%).[42] An observational study of Brazilian women with HIV reported similar percentages of stillborn infants in women prescribed ART with DTG compared to EFV (1% in both groups).[43] 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]

Some studies have evaluated the association between time of ART initiation and the risk of stillbirth. Reported associations with ART initiation before and during pregnancy and stillbirth are mixed. Among women with HIV who delivered in the United Kingdom and Ireland between 2007 and 2015 (n = 10,434), preconception ARV 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 compared with the general population (2.5%, n = 8,380).[58] Another 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).[25] 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 to 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.[30] Another study of Kenyan women (n = 724) reported 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). Most of these women were prescribed TDF+3TC/FTC+EFV.[57] 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, elvitegravir, 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).[44]

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

Maternal Outcomes

Hypertensive Disorders of Pregnancy

Limited data suggest that women with HIV may have an increased risk of HDP. No studies have evaluated the effect of specific ARV drugs on HDP. A meta-analysis did not reveal a clear association between maternal HIV and HDP.[59] 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 revealed that women with low CD4 counts (<200 cells/mm^3) on ART had an increased risk of maternal death from HDP compared with women 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).[23] 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 have increased risk of adverse pregnancy outcomes regardless of HIV status.[63] 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). They observed higher rates of HDP among women on INSTIs (25%, n = 23) and NNRTIs (24%, n = 7) compared with women on PI-based ART (10%, n = 55). Preconception ARV use was associated with an increased risk of HDP.[40]

Although these limited data may suggest an association between HDP and maternal HIV, no known interventions reduce this risk, and 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. Preventative Services Task Force recommendations.[64]

Summary

Clinicians should be aware of a possible increased risk of adverse maternal and neonatal outcomes with the use of ARV 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. Clinicians should monitor pregnant people with HIV for potential pregnancy complications, including PTB, LBW infants, and SGA infants.

References

1. Nachega JB, Uthman OA, Mofenson LM, et al. Safety of tenofovir disoproxil fumarate-based antiretroviral therapy regimens in pregnancy for HIV-infected women and their infants: a systematic review and meta-analysis. *J Acquir Immune Defic Syndr*. 2017;76(1):1-12. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28291053.

2. Veroniki AA, Antony J, Straus SE, et al. Comparative safety and effectiveness of perinatal antiretroviral therapies for HIV-infected women and their children: systematic review and network meta-analysis including different study designs. *PLoS One*. 2018;13(6):e0198447. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29912896.

3. Saleska JL, Turner AN, Maierhofer C, Clark J, Kwiek JJ. Use of antiretroviral therapy during pregnancy and adverse birth outcomes among women living with HIV-1 in low- and middle-income countries: a systematic review. *J Acquir Immune Defic Syndr*. 2018;79(1):1-9. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29847475.

4. Portwood C, Murray C, Sexton H, et al. Adverse perinatal outcomes associated with HAART and monotherapy. *AIDS*. 2022;36(10):1409-1427. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35608111.

5. Sexton H, Kumarendran M, Brandon Z, Shi C, Kirtley S, Hemelaar J. Adverse perinatal outcomes associated with timing of initiation of antiretroviral therapy: systematic review and meta-analysis. *HIV Med*. 2022. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35665582.

6. Tshivuila-Matala COO, Honeyman S, Nesbitt C, Kirtley S, Kennedy SH, Hemelaar J. Adverse perinatal outcomes associated with antiretroviral therapy regimens: systematic review and network meta-analysis. *AIDS*. 2020;34(11):1643-1656. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32701581.

7. Rudin C, Spaenhauer A, Keiser O, et al. Antiretroviral therapy during pregnancy and premature birth: analysis of Swiss data. *HIV Med*. 2011;12(4):228-235. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20726902.

8. Chen JY, Ribaudo HJ, Souda S, et al. Highly active antiretroviral therapy and adverse birth outcomes among HIV-infected women in Botswana. *J Infect Dis*. 2012;206(11):1695-1705. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23066160.

9. Sibiude J, Warszawski J, Tubiana R, et al. Premature delivery in HIV-infected women starting protease inhibitor therapy during pregnancy: role of the ritonavir boost? *Clin Infect Dis*. 2012;54(9):1348-1360. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22460969.

10. Watts DH, Williams PL, Kacanek D, et al. Combination antiretroviral use and preterm birth. *J Infect Dis*. 2013;207(4):612-621. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23204173.

11. Kreitchmann R, Li SX, Melo VH, et al. Predictors of adverse pregnancy outcomes in women infected with HIV in Latin America and the Caribbean: a cohort study. *BJOG*. 2014;121(12):1501-1508. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24602102.

12. Kakkar F, Boucoiran I, Lamarre V, et al. Risk factors for pre-term birth in a Canadian cohort of HIV-positive women: role of ritonavir boosting? *J Int AIDS Soc*. 2015;18:19933. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26051165.

13. Li N, Sando MM, Spiegelman D, et al. Antiretroviral therapy in relation to birth outcomes among HIV-infected women: a cohort study. *J Infect Dis*. 2015;213(7):1057-1064. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26265780.

14. Van Dyke RB, Chadwick EG, Hazra R, Williams PL, Seage GR, 3rd. The PHACS SMARTT study: assessment of the safety of In utero exposure to antiretroviral drugs. *Front Immunol*. 2016;7:199. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27242802.

15. Rough K, Seage GR, 3rd, Williams PL, et al. Birth outcomes for pregnant women with HIV using tenofovir-emtricitabine. *N Engl J Med*. 2018;378(17):1593-1603. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29694825.

16. Ramokolo V, Goga AE, Lombard C, Doherty T, Jackson DJ, Engebretsen IM. In utero ART exposure and birth and early growth outcomes among HIV-exposed uninfected infants attending immunization services: results from national PMTCT surveillance, South Africa. *Open Forum Infect Dis*. 2017;4(4):ofx187. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29062860.

17. Favarato G, Townsend CL, Bailey H, et al. Protease inhibitors and preterm delivery: another piece in the puzzle. *AIDS*. 2018;32(2):243-252. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29135577.

18. Zash R, Jacobson DL, Diseko M, et al. Comparative safety of dolutegravir-based or efavirenz-based antiretroviral treatment started during pregnancy in Botswana: an observational study. *Lancet Glob Health*. 2018;6(7):e804-e810. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29880310.

19. Malaba TR, Newell ML, Madlala H, Perez A, Gray C, Myer L. Methods of gestational age assessment influence the observed association between antiretroviral therapy exposure, preterm delivery, and small-for-gestational age infants: a prospective study in Cape Town, South Africa. *Ann Epidemiol*. 2018;28(12):893-900. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30293920.

20. Wang L, Zhao H, Cai W, et al. Risk factors associated with preterm delivery and low delivery weight among HIV-exposed neonates in China. *Int J Gynaecol Obstet*. 2018;142(3):300-307. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29772068.

21. Venkatesh KK, Morrison L, Tuomala RE, et al. Profile of chronic comorbid conditions and obstetrical complications among pregnant women with human immunodeficiency virus and receiving antiretroviral therapy in the United States. *Clin Infect Dis*. 2021;73(6):969-978. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33768226.

22. Albert AYK, Elwood C, Wagner EC, et al. Investigation of factors associated with spontaneous preterm birth in pregnant women living with HIV. *AIDS*. 2020;34(5):719-727. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31895145.

23. Sebitloane HM, Moodley J. Maternal and obstetric complications among HIV-infected women treated with highly active antiretroviral treatment at a regional hospital in Durban, South Africa. *Niger J Clin Pract*. 2017;20(11):1360-1367. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29303121.

24. Chetty T, Thorne C, Coutsoudis A. Preterm delivery and small-for-gestation outcomes in HIV-infected pregnant women on antiretroviral therapy in rural South Africa: results from a cohort study, 2010-2015. *PLoS One*. 2018;13(2):e0192805. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29470508.

25. Zash R, Jacobson DL, Diseko M, et al. Comparative safety of antiretroviral treatment regimens in pregnancy. *JAMA Pediatr*. 2017;171(10):e172222. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28783807.

26. Stringer EM, Kendall MA, Lockman S, et al. Pregnancy outcomes among HIV-infected women who conceived on antiretroviral therapy. *PLoS One*. 2018;13(7):e0199555. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30020964.

27. O'Brien BE, Williams PL, Huo Y, et al. Repeat pregnancies among US women living with HIV in the SMARTT study: temporal changes in HIV disease status and predictors of preterm birth. *J Acquir Immune Defic Syndr*. 2020;85(3):346-354. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32701825.

28. Delicio AM, Lajos GJ, Amaral E, Cavichiolli F, Polydoro M, Milanez H. Adverse effects in children exposed to maternal HIV and antiretroviral therapy during pregnancy in Brazil: a cohort study. *Reprod Health*. 2018;15(1):76. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29747664.

29. Uthman OA, Nachega JB, Anderson J, et al. Timing of initiation of antiretroviral therapy and adverse pregnancy outcomes: a systematic review and meta-analysis. *Lancet HIV*. 2017;4(1):e21-e30. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27864000.

30. Onono M, Odwar T, Wahome S, et al. Behavioral interventions can mitigate adverse pregnancy outcomes among women conceiving on ART and those initiated on ART during pregnancy: findings from the MOTIVATE trial in Southwestern Kenya. *J Acquir Immune Defic Syndr*. 2021;86(1):46-55. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33306563.

31. Quinn MK, Williams PL, Muhihi A, et al. Timing of antiretroviral therapy. *J Infect Dis*. 2022;226(4):687-695. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35678698.

32. Tuomala RE, Shapiro DE, Mofenson LM, et al. Antiretroviral therapy during pregnancy and the risk of an adverse outcome. *N Engl J Med*. 2002;346(24):1863-1870. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12063370.

33. Perry M, Taylor GP, Sabin CA, et al. Lopinavir and atazanavir in pregnancy: comparable infant outcomes, virological efficacies and preterm delivery rates. *HIV Med*. 2015;17(1):28-35. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26200570.

34. Sebikari D, Farhad M, Fenton T, et al. Risk factors for adverse birth outcomes in the PROMISE 1077BF/1077FF trial. *J Acquir Immune Defic Syndr*. 2019;81(5):521-532. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31295174.

35. Mesfin YM, Kibret KT, Taye A. Is protease inhibitors based antiretroviral therapy during pregnancy associated with an increased risk of preterm birth? Systematic review and a meta-analysis. *Reprod Health*. 2016;13:30. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27048501.

36. Cowdell I, Beck K, Portwood C, et al. Adverse perinatal outcomes associated with protease inhibitor-based antiretroviral therapy in pregnant women living with HIV: a systematic review and meta-analysis. *EClinicalMedicine*. 2022;46:101368. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35521067.

37. Duryea E, Nicholson F, Cooper S, et al. The use of protease inhibitors in pregnancy: maternal and fetal considerations. *Infect Dis Obstet Gynecol*. 2015;2015:563727. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26617456.

38. Snijdewind IJM, Smit C, Godfried MH, et al. Preconception use of cART by HIV-positive pregnant women increases the risk of infants being born small for gestational age. *PLoS One*. 2018;13(1):e0191389. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29351561.

39. Floridia M, Dalzero S, Giacomet V, et al. Pregnancy and neonatal outcomes in women with HIV-1 exposed to integrase inhibitors, protease inhibitors and non-nucleoside reverse transcriptase inhibitors: an observational study. *Infection*. 2020;48(2):249-258. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31893354.

40. Saums MK, King CC, Adams JC, et al. Combination antiretroviral therapy and hypertensive disorders of pregnancy. *Obstet Gynecol*. 2019;134(6):1205-1214. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31764730.

41. Hill A, Clayden P, Thorne C, Christie R, Zash R. Safety and pharmacokinetics of dolutegravir in HIV-positive pregnant women: a systematic review. *J Virus Erad*. 2018;4(2):66-71. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29682297.

42. Lockman S, Brummel SS, Ziemba L, et al. Efficacy and safety of dolutegravir with emtricitabine and tenofovir alafenamide fumarate or tenofovir disoproxil fumarate, and efavirenz, emtricitabine, and tenofovir disoproxil fumarate HIV antiretroviral therapy regimens started in pregnancy (IMPAACT 2010/VESTED): a multicentre, open-label, randomised, controlled, phase 3 trial. *Lancet*. 2021;397(10281):1276-1292. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33812487.

43. Pereira GFM, Kim A, Jalil EM, et al. Dolutegravir and pregnancy outcomes in women on antiretroviral therapy in Brazil: a retrospective national cohort study. *Lancet HIV*. 2021;8(1):e33-e41. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33387477.

44. Sibiude J, Le Chenadec J, Mandelbrot L, et al. Risk of birth defects and perinatal outcomes in HIV-infected women exposed to integrase strand inhibitors during pregnancy. *AIDS*. 2021;35(2):219-226. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33048878.

45. Latham AH, Nissim OA, Spitznagel MC, Kirk SE, Tarleton JL, Lazenby GB. Impact of Integrase Strand Transfer Inhibitor Use During Pregnancy on Viral Suppression at Delivery and Infant Outcomes: A Statewide Retrospective Cohort Study. *J Acquir Immune Defic Syndr*. 2022;89(4):448-453. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35202051.

46. Tuomala RE, Watts DH, Li D, et al. Improved obstetric outcomes and few maternal toxicities are associated with antiretroviral therapy, including highly active antiretroviral therapy during pregnancy. *J Acquir Immune Defic Syndr*. 2005;38(4):449-473. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15764963.

47. Bisio F, Nicco E, Calzi A, et al. Pregnancy outcomes following exposure to efavirenz-based antiretroviral therapy in the Republic of Congo. *New Microbiol*. 2015;38(2):185-192. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25938743.

48. Fowler MG, Qin M, Fiscus SA, et al. Benefits and risks of antiretroviral therapy for perinatal HIV prevention. *N Engl J Med*. 2016;375(18):1726-1737. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27806243.

49. Vannappagari V, Koram N, Albano J, Tilson H, Gee C. Association between in utero zidovudine exposure and nondefect adverse birth outcomes: analysis of prospectively collected data from the Antiretroviral Pregnancy Registry. *BJOG*. 2016;123(6):910-916. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26269220.

50. Njom Nlend AE, Nga Motaze A, Moyo Tetang S, Zeudja C, Ngantcha M, Tejiokem M. Preterm birth and low birth weight after In utero exposure to antiretrovirals initiated during pregnancy in Yaounde, Cameroon. *PLoS One*. 2016;11(3):e0150565. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26999744.

51. Moodley T, Moodley D, Sebitloane M, Maharaj N, Sartorius B. Improved pregnancy outcomes with increasing antiretroviral coverage in South Africa. *BMC Pregnancy Childbirth*. 2016;16:35. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26867536.

52. Theron G, Brummel S, Fairlie L, et al. Pregnancy outcomes of women conceiving on antiretroviral therapy (ART) compared to those commenced on ART during pregnancy. *Clin Infect Dis*. 2020;ciaa805. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32564058.

53. Watts DH, Brown ER, Maldonado Y, et al. HIV disease progression in the first year after delivery among African women followed in the HPTN 046 clinical trial. *J Acquir Immune Defic Syndr*. 2013;64(3):299-306. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23846568.

54. Aaron E, Bonacquisti A, Mathew L, Alleyne G, Bamford LP, Culhane JF. Small-for-gestational-age births in pregnant women with HIV, due to severity of HIV disease, not

antiretroviral therapy. *Infect Dis Obstet Gynecol*. 2012;2012:135030. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22778533.

55. Parekh N, Ribaudo H, Souda S, et al. Risk factors for very preterm delivery and delivery of very-small-for-gestational-age infants among HIV-exposed and HIV-unexposed infants in Botswana. *Int J Gynaecol Obstet*. 2011;115(1):20-25. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21767835.

56. Favarato G, Townsend CL, Peters H, et al. Stillbirth in Women Living With HIV Delivering in the United Kingdom and Ireland: 2007-2015. *J Acquir Immune Defic Syndr*. 2019;82(1):9-16. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31149953.

57. Jiang W, Ronen K, Osborn L, et al. Predictors of adverse pregnancy outcomes among Kenyan women with HIV on antiretroviral treatment in pregnancy. *AIDS*. 2022;36(7):1007-1019. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35652673.

58. Msukwa MT, Keiser O, Jahn A, et al. Timing of combination antiretroviral therapy (cART) initiation is not associated with stillbirth among HIV-infected pregnant women in Malawi. *Trop Med Int Health*. 2019;24(6):727-735. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30891866.

59. Browne JL, Schrier VJ, Grobbee DE, Peters SA, Klipstein-Grobusch K. HIV, antiretroviral therapy, and hypertensive disorders in pregnancy: a systematic review and meta-analysis. *J Acquir Immune Defic Syndr*. 2015;70(1):91-98. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26322669.

60. Sansone M, Sarno L, Saccone G, et al. Risk of preeclampsia in human immunodeficiency virus-infected pregnant women. *Obstet Gynecol*. 2016;127(6):1027-1032. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27159742.

61. Sebitloane HM, Moodley J, Sartorius B. Associations between HIV, highly active anti-retroviral therapy, and hypertensive disorders of pregnancy among maternal deaths in South Africa 2011-2013. *Int J Gynaecol Obstet*. 2017;136(2):195-199. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28099739.

62. Bengtson AM, Phillips TK, le Roux SM, et al. Does HIV infection modify the relationship between pre-pregnancy body mass index and adverse birth outcomes? *Paediatr Perinat Epidemiol*. 2020;34(6):713-723. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32490582.

63. Bengtson AM, Phillips TK, le Roux SM, et al. High blood pressure at entry into antenatal care and birth outcomes among a cohort of HIV-uninfected women and women living with HIV initiating antiretroviral therapy in South Africa. *Pregnancy Hypertens*. 2021;23:79-86. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33285444.

64. Davidson KW, Barry MJ, Mangione CM, et al. Aspirin Use to Prevent Preeclampsia and Related Morbidity and Mortality: United States Preventive Services Task Force Recommendation Statement. *JAMA*. 2021;326(12):1186-1191. Available at: https://pubmed.ncbi.nlm.nih.gov/34581729/.