Antiretroviral Drug Regimens and Maternal and Neonatal Outcomes

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Panel's Recommendations
• Clinicians should be aware of a possible increased risk of adverse neonatal outcomes (e.g., preterm delivery) in pregnant women who are receiving antiretroviral therapy (ART). However, given the clear benefits of ART for both a woman's health and the prevention of perinatal transmission, HIV treatment should not be withheld due to concern for adverse pregnancy outcomes **(All)**.
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 Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (the Panel) provides a summary of data on antiretroviral therapy (ART) and adverse maternal and neonatal outcomes published since 2015.Women with HIV, regardless of antiretroviral (ARV) drug use, may be at increased risk for adverse neonatal outcomes. These outcomes may include preterm delivery (PTD) (delivery before 37 weeks gestation), very preterm delivery (vPTD) (delivery before 32 weeks 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 cut-off 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) (pregestational hypertension, gestational or pregnancy-induced 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 (birth defects), please refer to Teratogenicity and the individual drug sections in Appendix B and Table 10.

Key Points

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

ART that contains boosted lopinavir (LPV/r) may increase the risk of PTD compared with other boosted protease inhibitor (PI)-based regimens. For pregnant women who require PI-based regimens during pregnancy, the Panel recommends the use of darunavir/r (DRV/r) or atazanavir (ATV/r).

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 ultrasound, 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 women 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 preterm birth, fetal growth restriction, 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 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. 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. Comparing pregnant women on ART to women 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. Risks of adverse outcomes may also 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 Delivery

Several meta-analyses and systematic reviews are available to evaluate the potential association of ARV use and PTD. Three large meta-analyses did not demonstrate a significant association between ARV 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 ART or ARV drug classes currently used.[1–3] The meta-analysis by Kourtis et al. showed a modest, but statistically significant, increase in the risk for PTD 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% confidence interval [CI], 1.09–2.67).[1] 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 TDF. This study found no difference in the risk of PTD between these two groups. A recent network meta-analysis of seven randomized controlled trials evaluated seven different ART regimens and their associations with PTD (including spontaneous PTD in three trials), LBW (six trials), and SGA (two trials).[4] An overall increase in PTD was associated with ART regimen ZDV/3TC/LPV/r compared with ZDV single-drug regimen (n = 5,789, relative risk [RR] 1.43, 95% CI, 1.08–1.91), and, compared with ZDV/3TC/ABC, ZDV/3TC/LPV/r was associated with an increased risk of spontaneous PTD (sPTD) (n = 991, RR 1.81, 95% CI, 1.21–2.71). There were no differences in vPTD between the regimens evaluated (4 trials, n = 1,819).[4]

Among the observational studies that reported an association between the use of ARVs and PTD, the RRs/ORs for PTD ranged from 1.2 to 3.4.[1,5–27] Some studies have reported increased rates of PTD when ART is initiated before pregnancy or during early pregnancy compared to later in pregnancy. Variability in the available data may be a factor in conflicting results. 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 ARV use.[28–31] In general, none of the studies reviewed in this section have comprehensively controlled for all factors that may

be associated with PTD. A recent observational study that evaluated ARV use among women with HIV in British Columbia reduced confounding variables by excluding multigestation 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 PTD 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 sPTD (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/first-trimester ARV use nor PI-based ART was associated with PTD.[32]

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.[5,21–23,26,31,33–36] 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 PTD and ARV use prior to conception is attenuated in some multivariate analyses.[17,21,36–38] An observational study of >2,000 women on multidrug ART did not show an association between ART initiation before pregnancy and PTD.[34] Certain ART, such as regimens that contain 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.[1,4,5,7–9,11,16,18,20,21,23,35,36,39–42] 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.[43]

Not all the studies reviewed for this section have identified an association between PI use and an increased risk of PTD. Seven studies did not demonstrate a significant association between PI based ART and PTD.[18,32,39–41,44,45] For example, a retrospective Canadian study of women who were on regimens that included unboosted PIs did not report increased rates of PTD among these women.[18]

Regimens that include PIs boosted with ritonavir may be associated with an increased risk of PTD compared with unboosted PI regimens. The Promoting Maternal and Infant Survival Everywhere (PROMISE) trial study compared outcomes in women who received zidovudine (ZDV) alone with outcomes in women who received LPV/r-based ART with a two-drug 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/3TC/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%; $P = 0.77$).[46] Sebikari et al. published a follow-up study of the PROMISE trial. After controlling for other risk factors, receipt of either ZDV/3TC/ LPV/r or FTC/TDF/ LPV/r remained associated with PTD. The aOR of PTD for women who received ZDV/3TC/LPV/r compared to ZDV alone was 1.8 (95% CI, 1.5–2.3), and the aOR for women who received FTC/TDF/LPV/r compared to ZDV alone was also 1.8 (95% CI, 1.3–4.0). Comparing these two LPV/r-based regimens with each other found no significant difference in the risk of PTD (aOR 0.97; 95% CI, 0.72–1.31).[42]

An observational study of >6,000 women in the United Kingdom and Ireland demonstrated increased rates of PTD among women with HIV who were on 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/mm³ (aOR 1.99; 95% CI, 1.02–3.85).[23] An observational study combined data 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 FTC/TDF/LPV/r compared with women who received FTC/TDF/ATV/r. Among women who initiated ART before conception, the risk of PTD was higher for the LPV/r regimen.[21] In a follow-up study, these authors evaluated the impact of ART among women who had enrolled in SMARTT and experienced subsequent pregnancies. Notable limitations of this study were inclusion of iatrogenic PTDs, counting more than one subsequent delivery for some participants, and the potential for short interval pregnancy effect. In subsequent pregnancies, women starting PI-based ART in the first trimester experienced an increased risk of PTD (OR 1.97, 95% CI, 9.27–3.07). This effect was not seen with preconception PI-based ART or second-and third-trimester ART initiation.[36] 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 DRV/r or ATV/r over LPV/r.

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

Fewer studies have evaluated the risk of PTD among women on non-PI-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 PTD (RR 0.9; 95% CI, 0.81–0.99; I^2 = 59%); however, there was no significant difference in the risk of very PTD between these two groups.[2] Some observational studies have shown an association between the use of non-PI based regimens and PTD. When compared with women without HIV, South African women with HIV who were taking NPV/FTC/TDF had higher rates of PTD (aOR 1.2; 95% CI, 1.0–1.5).[22] When compared with women without HIV, women who were taking EFV/FTC/TDF 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. Another study of South African women who received EFV/FTC/TDF did not show an increased risk of PTD, SGA infants, or LBW infants when these women were compared with women who were on NVP-based ART or other multidrug regimens.[34]

Integrase Strand Transfer Inhibitor-Based Regimens

Integrase strand transfer inhibitors (INSTIs) are preferred ARVs for HIV treatment. As INSTI use increases among persons with HIV, INSTI exposure during pregnancy is observed more often.[32,36,47,48] Limited data from observational studies are available to assess the relationship between INSTI-based regimens and PTD. In the Tsepamo study, women who initiated EFV/FTC/TDF or DTG/FTC/TDF during pregnancy were at increased risk of PTD (aOR 1.2; 95% CI, 1.1–1.3) compared with women without HIV. However, when these regimens were compared with one another, no significant differences existed 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 related to DTG exposure. A total of 845 women who received DTG/FTC/TDF were compared with 4,593 historical controls who received EFV/FTC/TDF, and no clear difference existed in the risk of PTD between these groups.[49] Pooled data from the Antiretroviral Registry (APR) (n = 265) and the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) (n = 101) determined that rates of PTD among women on ART containing DTG were similar to or slightly higher than the general population (10.9% APR and 13.8% EPPICC).[50] Women in the Pediatric HIV/AIDS Cohort (PHACS) SMARTT study who initiated INSTIs during the first trimester had an increased risk of PTD in subsequent pregnancies (OR 2.39, 95% CI, 1.04–5.46). Limitations to this study are detailed in the previous section.[36] In an observational study of women with HIV in British Columbia, INSTI use was not associated with an increased

risk of PTD.[32] Additional studies are needed to determine potential impact of INSTI use in pregnancy outcomes.

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 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 ARV use and LBW infants.[19,22,45,46,51–55] Reported rates of LBW among infants who were exposed to ART range from 7.4 percent to 36 percent.[3,11,17,19,21,22,24,30,35,37,39,41,42,46,52,53,56,57] In a systematic review of 13 studies (nine observational studies and four randomized controlled trials) that compared ZDV single-drug therapy with NNRTI- and PI-based regimens, the NNRTI- and PI-based regimens were associated with LBW infants.[27] In a network meta-analysis of six RCTs (n = 5,471), when compared to ZDV alone, ZDV/3TC/LPV/r was associated with the highest risk of LBW (RR 1.87, 95% CI, 1.58–2.2).[4] In a Chinese cohort of 748 infants exposed to either NVP, EFV, or LPV/r with a two-drug NRTI backbone, any preconception ARV use was associated with an increased risk of LBW infants (aOR 1.92; 95% CI, 1.1–3.4).[26] 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).[21] Women enrolled in the PROMISE trial who were randomized to ART following their first delivery or after breast feeding had increased risk of having LBW infants in subsequent pregnancies (OR 2.65, 95% CI, 1.2–5.81 and 2.94, 95% CI, 1.24–6.98, respectively).[57]

Small for Gestational Age

Among infants born to women with HIV, the reported rates of SGA infants range from 7.3 percent to 31 percent.[14,17,19,22–25,30,34,37,44,45,58,59] A South African prospective observational study reported that women with HIV were more likely to have SGA infants than women without HIV (14% vs. 8%).[25] Three studies in Botswana reported a positive association between ARV use (for both PI-based and PI-sparing regimens) and SGA.[14,35,60] In a study that compared the effects of initiating single-drug therapy during pregnancy with 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 not statistically significant (RR 1.34; 95% CI, 0.98–1.84).[19] When compared with FTC/TDF/EFV, both NVP-based and LPV/r-based ART were associated with an increased incidence of SGA.[35] When compared with women on non-nucleoside reverse transcriptase inhibitor–based ART, women in the Netherlands on PI-based ART before pregnancy had a higher risk of SGA (OR 1.35; 95% CI, 1.03–1.77).[45] Brazilian women on LPV/r-based ART had an increased risk of delivering SGA infants compared with women taking NFV-based ART.[37] In contrast, an observational study of women with HIV who were on FTC/TDF/EFV, NPV-based ART, or other multidrug regimens before pregnancy did not show an association between these regimens and SGA.[34]

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 percent to 11.4 percent.[10,14,15,17,24,30,31,33,35,41,49,52,53,61] 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]

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 PI-sparing regimens. 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).[14] Zash et al. 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).[35] 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.[61] Women with HIV who delivered in Malawi from 2012 to 2015, 71 percent of whom were on ART preconception or in the first trimester, did not experience higher rates of stillbirth compared with the general population (2.5%, n = 8,380).[62]

When evaluating the association between the use of ARV 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 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.[63] An observational Italian study comparing women with HIV with women without HIV 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).[64] 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).[65] Among these women, those on ART before pregnancy and those who were not on ART before pregnancy had similar rates of HPD (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).[33] A small U.S. observational study demonstrated that women with HIV (n = 85) were not more likely to experience HPD 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.[48]

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.

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. 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

1. Kourtis AP, Schmid CH, Jamieson DJ, Lau J. Use of antiretroviral therapy in pregnant HIV-infected women and the risk of premature delivery: a meta-analysis. *AIDS*. 2007;21(5):607-615. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17314523.
2. 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.
3. 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.
4. 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.
5. European Collaborative Study, Swiss Mother Child HIV Cohort Study. Combination antiretroviral therapy and duration of pregnancy. *AIDS*. 2000;14(18):2913-2920. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11398741.
6. European Collaborative Study. Levels and patterns of neutrophil cell counts over the first 8 years of life in children of HIV-1-infected mothers. *AIDS*. 2004;18(15):2009-2017. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15577622.
7. Cotter AM, Garcia AG, Duthely ML, Luke B, O'Sullivan MJ. Is antiretroviral therapy during pregnancy associated with an increased risk of preterm delivery, low birth weight, or stillbirth? *J Infect Dis*. 2006;193(9):1195-1201. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16586354.
8. Ravizza M, Martinelli P, Bucceri A, et al. Treatment with protease inhibitors and coinfection with hepatitis C virus are independent predictors of preterm delivery in HIV-infected pregnant women. *J Infect Dis*. 2007;195(6):913-914; author reply 916-917. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17299723.
9. Schulte J, Dominguez K, Sukalac T, Bohannon B, Fowler MG, Pediatric Spectrum of HIV Disease Consortium. Declines in low birth weight and preterm birth among infants who were born to HIV-infected women during an era of increased use of maternal antiretroviral drugs: Pediatric Spectrum of HIV Disease, 1989–2004. *Pediatrics*. 2007;119(4):e900-906. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17353299.
10. Townsend CL, Cortina-Borja M, Peckham CS, Tookey PA. Antiretroviral therapy and premature delivery in diagnosed HIV-infected women in the United Kingdom and Ireland. *AIDS*. 2007;21(8):1019-1026. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17457096.
11. Grosch-Woerner I, Puch K, Maier RF, et al. Increased rate of prematurity associated with antenatal antiretroviral therapy in a German/Austrian cohort of HIV-1-infected women. *HIV Med*. 2008;9(1):6-13. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18199167.
12. 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.
13. Powis KM, Kitch D, Ogwu A, et al. Increased risk of preterm delivery among HIV-infected women randomized to protease versus nucleoside reverse transcriptase inhibitor-based HAART during pregnancy. *J Infect Dis*. 2011;204(4):506-514. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21791651.

14. 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.

15. 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.

16. 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.

17. 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.

18. 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.

19. 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.

20. 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.

21. 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.

22. 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.

23. 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.

24. 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.

25. 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.

26. 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.

27. 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.

28. Machado ES, Hofer CB, Costa TT, et al. Pregnancy outcome in women infected with HIV-1 receiving combination antiretroviral therapy before versus after conception. *Sex Transm Infect*. 2009;85(2):82-87. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18987014.

29. van der Merwe K, Hoffman R, Black V, Chersich M, Coovadia A, Rees H. Birth outcomes in South African women receiving highly active antiretroviral therapy: a retrospective observational study. *J Int AIDS Soc.* 2011;14:42. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21843356.

30. 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.

31. 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.

32. 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.

33. 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.

34. 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.

35. 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.

36. O'Brien BE, Williams PL, Huo Y, et al. Repeat pregnancies among U.S. 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.

37. 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.

38. 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.

39. 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.

40. Patel K, Shapiro DE, Brogly SB, et al. Prenatal protease inhibitor use and risk of preterm birth among HIV-infected women initiating antiretroviral drugs during pregnancy. *J Infect Dis.* 2010;201(7):1035-1044. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20196654.

41. 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.

42. 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.

43. 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.

44. 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.

45. 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.

46. 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.

47. 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.

48. 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.

49. 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.

50. Vannappagari V, Thorne C, for APR and Eppicc. Pregnancy and neonatal outcomes following prenatal exposure to dolutegravir. *J Acquir Immune Defic Syndr.* 2019;81(4):371-378. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30939532.

51. 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.

52. 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.

53. 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.

54. 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.

55. Ekouevi DK, Coffie PA, Becquet R, et al. Antiretroviral therapy in pregnant women with advanced HIV disease and pregnancy outcomes in Abidjan, Cote d'Ivoire. *AIDS*. 2008;22(14):1815-1820. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18753864.

56. Szyld EG, Warley EM, Freimanis L, et al. Maternal antiretroviral drugs during pregnancy and infant low birth weight and preterm birth. *AIDS*. 2006;20(18):2345-2353. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17117021.

57. 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.

58. 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.

59. Aaron E, Bonacquisti A, Mathew L, Alleyne G, Bamford LP and 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.

60. 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.

61. 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.

62. 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.

63. 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.

64. 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.

65. 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.