Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States

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Combination Antiretroviral Drug Regimens and Maternal and Neonatal Outcomes

Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States

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. However, given the clear benefits of such regimens for both a woman’s health and the prevention of perinatal transmission, HIV treatment should not be withheld for fear of altering 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

Women with HIV taking antiretroviral therapy (ART) may be at increased risk for adverse pregnancy outcomes, including preterm birth or delivery (PTD) (i.e., delivery before 37 weeks’ gestation), low birth weight (LBW) infants (<2,500 g), and small-for-gestational-age (SGA) infants (birth weight <10th percentile expected for gestational age). In this section, the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (the Panel) provides a summary of the published data regarding ART and adverse maternal and neonatal outcomes. There are limited data suggesting a potential association between hypertensive disorders of pregnancy (HDP) and maternal HIV.

We have reviewed and summarized studies from 1986 to 2018 that reported on maternal and neonatal outcomes in women with HIV. These studies were conducted in Europe, North America, sub-Saharan Africa, and Latin America. Study sizes and designs vary significantly; the number of participants in each study ranges from 183 to 10,592. The ART regimens evaluated in these studies differ, and may include:

- No ART
- Monotherapy, defined as the use of a single antiretroviral (ARV) drug
- Dual therapy, defined as the use of two ARV drugs
- Multidrug therapy, defined as the use of ≥3 ARV drugs: not specified (multi), nucleoside reverse transcriptase inhibitor-based regimens (multi-NRTI), non-nucleoside reverse transcriptase inhibitor-based regimens (multi-NNRTI), protease inhibitor (PI)-based regimens (multi-PI), non-PI-based regimens (multi-no PI), or specified ARVs

Table 5 lists the published, high-quality studies that reported potential effects of ART use on pregnancy outcomes. The studies’ conclusions regarding PTD, LBW, and SGA are provided. Most of the studies present data regarding PTD, and fewer studies report instances of LBW, SGA, and stillbirth.

Pregnancy Outcomes

Preterm Delivery

Most of the studies reviewed in this section have reported outcomes related to PTD. Among the studies that report an association between ART use and PTD, the relative risks (RRs)/odds ratios (ORs) for PTD range from 1.2 to 3.4.1-21 Conflicting findings regarding the association between PTD and ART use may be influenced by variability in the data available for analysis (e.g., for example, some studies have reported increased rates of PTD when ART is initiated before pregnancy or during early pregnancy compared to later in pregnancy). Maternal factors, such as HIV disease severity, may have affected the timing of ART initiation during pregnancy. These variables may be associated with PTD independent of ART use.22-24 In order to control for medical or obstetrical factors associated with PTD, two studies have assessed spontaneous PTD alone. One study included women who initiated ART during pregnancy. Neither study reported an association...
between ART use and PTD. Two large meta-analyses of 11,224 and 37,877 women which included 14 and 17 studies, respectively, did not report an increased rate of PTD among women using ART during pregnancy. In general, none of the studies reviewed in this section have comprehensively controlled for all potential factors that may be associated with PTD.

Preterm Delivery and Antiretroviral Therapy Exposure Before Pregnancy

Some studies report an association between ART initiation prior to pregnancy and PTD. The reported RRs and ORs range from 1.20 to 2.05; the risk is attenuated in multivariate analysis. These studies were conducted in Europe, Latin America, Africa, and North America and included various ART regimens (including no ART, single-drug, two-drug, and multidrug regimens). A retrospective cohort study that included >2,000 women on multidrug ART did not show an association between ART initiation before pregnancy and PTD.

Antiretroviral Therapy Regimens Associated with Preterm Delivery

PI-Based Regimens

An association between PI-based ART and PTD has been investigated. These studies include populations in Europe, North America, and Africa. The risk of PTD ranges from 1.14 to 3.4. Six studies did not demonstrate a significant association between PI-based ART and PTD. The recent Promoting Maternal and Infant Survival Everywhere (PROMISE) trial study compared zidovudine alone to lopinavir/ritonavir (LPV/r) ART combined with a dual-NRTI backbone of either zidovudine/lamivudine or tenofovir disoproxil fumarate (TDF)/emtricitabine. Compared to women receiving zidovudine alone, higher rates of extremely PTD (< 34 weeks) were reported in women receiving zidovudine/lamivudine/lopinavir/ritonavir (P < 0.001) but not TDF/emtricitabine/lopinavir/ritonavir (P = 0.77). In contrast, extremely PTD rates were higher among women receiving TDF/emtricitabine/lopinavir/ritonavir than among women receiving zidovudine/lamivudine/lopinavir/ritonavir (P = 0.04). These rates of extremely PTD were not significantly different than the rates among women receiving zidovudine alone (P = 0.10).

PI-based regimens boosted with ritonavir may be associated with PTD compared to non-boosted PI regimens. In a small, retrospective Canadian study, women taking non-boosted PI regimens did not have increased rates of PTD. A study of >6,000 women in the UK and Ireland demonstrated increased rates of PTD among women with HIV who were taking PI-based ART before pregnancy, especially 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). A retrospective cohort study combining observations from the Surveillance Monitoring for ART Toxicities (SMARTT) study and International Maternal and Pediatric Adolescent AIDS Clinical Trials (IMPAACT) for a total of 4,646 live birth outcomes reported that rates of PTD and LBW were 19% among women taking PI-based regimens. A small meta-analysis of 10 studies (eight prospective cohort studies, one randomized controlled trial, and one surveillance study) demonstrated an increased risk of PTD associated with the use of PI-based ART, with an adjusted odds ratio (aOR) of 1.32 (95% CI, 1.04–1.6) and I² = 47% (moderate heterogeneity). When evaluating the effects of initiating PI-based ART during the first and third trimesters of pregnancy, the pooled effect was nonsignificant.

Non-PI-Based Regimens

Exposure to single NRTI ART (primarily zidovudine) was not associated with PTD. South African women with HIV who were taking emtricitabine/TDF plus nevirapine had higher rates of PTD than women without HIV (aOR = 1.2; 95% CI, 1.0–1.5). Other reports have found increased rates of PTD when multidrug ART is compared with dual-ARV regimens and when NNRTI-based ART regimens are compared with other forms of ART. A retrospective cohort study of South African women on efavirenz/emtricitabine/TDF did not show an increased risk of PTD, SGA, or LBW when these women were compared to women taking nevirapine-based ART or other multidrug regimens. In a meta-analysis of 17 studies in which women with HIV (n = 37,877) who were taking ART that included TDF were compared to women who were taking ARV...
regimens that did not contain tenofovir, TDF-based ART was associated with lower rates of PTD (RR = 0.9; 95% CI, 0.81–0.99, I² = 59%).

**Mechanism for Preterm Delivery**

The potential mechanism of action by which PIs may increase a woman’s risk of PTD is unknown. Papp et al. demonstrated in cell culture, in mouse models, and in pregnant women with HIV that exposure to PIs (except for darunavir) can decrease plasma progesterone levels. Low levels of plasma progesterone during pregnancy may potentially be associated with fetal loss, PTD, and LBW. Papp et al. subsequently demonstrated that pregnant women with HIV who have low serum progesterone experience elevated levels of human placental 20-α-hydroxysteroid dehydrogenase, an enzyme that inactivates serum progesterone, after being exposed to PI-based ART. These women were also noted to have lower prolactin levels when compared to controls.

**Other Pregnancy Outcomes: Low Birth Weight, Small-for-Gestational-Age, and Stillbirth**

In addition to evaluating the effect of ART use on PTD, some studies have assessed other pregnancy outcomes including LBW, SGA, and stillbirth. Reported rates of LBW range from 7.4% to 36%. Six studies have demonstrated an association between any ART use and LBW infants.

Some studies have demonstrated an association between ART use and SGA. The reported rates of SGA range from 7.3% to 31%. In a study that compared the effects of initiating monotherapy during pregnancy to the effects of initiating multidrug ART before pregnancy and continuing ART during pregnancy, ART was associated with severe SGA (RR = 1.34; 95% CI, 0.98-1.84). Three studies in Botswana reported a positive association between ART use (both non-PI-based and PI-based regimens) and SGA. Continuation of ART that was initiated before pregnancy and initiation of ART during pregnancy may be associated with SGA (aOR = 1.8; 95% CI, 1.6–2.1 and aOR = 1.5; 95% CI, 1.2–1.9). When compared to emtricitabine/TDF/efavirenz ART, both nevirapine-based and LPV/r-based ART were associated with increased incidence of SGA. In contrast, a retrospective cohort of women with HIV who were taking TDF/emtricitabine/efavirenz, nevirapine-based ART, or other multidrug regimens before pregnancy did not show any association between these regimens and SGA. Women in the Netherlands who were taking PI-based ART before pregnancy had a higher risk of SGA (OR = 1.35; 95% CI, 1.03–1.77) than women taking NNRTI-based ART.

Eleven studies reported rates of stillbirth ranging from 0.5% to 11.4%. 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 non-PI-based and PI-based regimens. A greater risk of stillbirth was observed among women who continued ART during pregnancy (aOR = 1.5; 95% CI, 1.2–1.8) and among women who started ART during pregnancy (aOR = 2.5; 95% CI, 1.6–3.5) in one of those studies and (aOR = 0.99; 95% CI, 0.69-1.42). In the latter study, use of zidovudine/lamivudine/nevirapine was associated with a significantly increased rate of stillbirth compared to use of emtricitabine/TDF/efavirenz. The risk of perinatal mortality, which includes stillbirths and neonatal deaths, was noted to be higher among children born to South African women with HIV who were taking ART before pregnancy when compared to the children of women who started ART during pregnancy (OR = 3.25; 95% CI, 1.38–8.04). In a meta-analysis of 17 studies that included 37,877 women with HIV who were taking ART, three studies included stillbirth outcomes. Women with HIV who were taking TDF-based ART had a lower risk of stillbirth than those who were taking ART that did not include TDF (pooled RR = 0.6; 95% CI, 0.43–0.84, I² = 72%).

**Maternal Outcomes**

**Hypertensive Disorders of Pregnancy**

Limited data suggest and association between **HDP** and maternal HIV. An earlier meta-analysis reported an association between maternal HIV and **HDP**, but a more recent meta-analysis did not reveal a clear association between maternal HIV and pregnancy-induced hypertension, preeclampsia, or eclampsia. An Italian study demonstrated an increased risk for both early-onset and late-onset preeclampsia (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) when comparing pregnant women with HIV to pregnant women without HIV.47

Few studies have evaluated whether the use of combination ART is associated with a higher risk of pre-eclampsia. No studies have evaluated the effect of specific ARV drugs on maternal hypertension. In the NISDI cohort, women exposed to ART in the first trimester had an increased risk of pre-eclampsia when compared to women who were not exposed to ART (aOR = 2.3; 95% CI, 1.1–4.9)48,49 A secondary analysis of South African data revealed that amongst women with low CD4 cell counts (<200 cells/mm³), there was an increased risk of maternal death from hypertensive disorders of pregnancy when comparing women who were taking combination ART to women who received no ART during pregnancy (RR = 1.15; 95% CI, 1.02–1.29).50 A more recently published retrospective study on South African women with HIV demonstrated that those who were on ART before pregnancy and those who were not on ART before pregnancy had similar rates of HPD (15.7% and 14.9%, respectively). Women with HIV were less likely to have HDP than women without HIV (OR = 0.67; 95% CI, 0.48–0.93).28 It is unclear whether the potential association between HIV and HDP reflects the fact that immune reconstitution associated with ART initiation plays a role in increasing inflammatory responses associated with preeclampsia/eclampsia or whether there is a direct effect of ART on this outcome.

**Unknown Effects of Newer Antiretroviral Drugs on Pregnancy Outcomes**

Data are insufficient regarding the effects of newer ARV drug classes on adverse pregnancy outcomes. Therefore, potential adverse pregnancy outcomes associated with these drug classes, which include integrase inhibitors, fusion inhibitors, and CCR5 antagonists, are not addressed in this section.

**Summary**

Clinicians should be aware of a possible increased risk of adverse maternal and neonatal outcomes with the use of ART for prevention of perinatal HIV infection. Given that ART has clear benefits for maternal health and reduces the risk of perinatal transmission, these agents should not be withheld due to concern for increased risk of adverse neonatal outcomes. Until more information is available, pregnant women with HIV who are receiving ART should continue their provider-recommended regimens. Additional monitoring for pregnancy complications, including PTD, should be considered.51

**Table 5. Results of Studies Assessing the Association Between Antiretroviral Regimens and Preterm Delivery** (page 1 of 8)

<table>
<thead>
<tr>
<th>Study Location(s); Dates of Study</th>
<th>Total Number of Pregnancies/Total Number on ARV Drugs</th>
<th>Types of ARV Regimens Compared (Numbers)</th>
<th>Association Noted Between ARV Regimens and Preterm Delivery</th>
<th>Notes</th>
</tr>
</thead>
</table>
| European Collaborative Study and Swiss Mother and Child HIV Cohort Study; 1986–2000\(^1\) | 3,920/896 | • Mono (573)  
• Multi-no PI (215)  
• Multi-PI (108) | • YES (compared with no ARV)  
• Multi: 1.82 (1.13–2.92)  
• Multi-PI: 2.60 (1.43–4.7) | • Increase in PTD if ARV was initiated before pregnancy versus in third trimester. |
| United States; 1990–1998\(^{30}\) | 3,266/2,123 | • Mono (1,590)  
• Multi (396)  
• Multi-PI (137) | • NO (compared with mono)  
• Multi: 0.95 (0.60–1.48)  
• Multi-PI: 1.45 (0.81–2.50) | • 7 prospective clinical studies. |
| European Collaborative Study; 1986–2004\(^{52}\) | 4,372/2,033 | • Mono (704)  
• Dual (254)  
• Multi (1,075) | • YES (compared with mono/dual)  
• Multi in pregnancy: 1.88 (1.34–2.65)  
• Multi pre-pregnancy: 2.05 (1.43–2.95) | • N/A |
Table 5. Results of Studies Assessing the Association Between Antiretroviral Regimens and Preterm Delivery (page 2 of 8)

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<tbody>
<tr>
<td>United States; 1990–2002&lt;sup&gt;41&lt;/sup&gt;</td>
<td>2,543/Not given</td>
<td>Early (≤25 Weeks):  • Mono (621)  • ≥2 ARVs without PI or NNRTI (198)  • Multi-NNRTI or Multi-PI (357) Late (≥32 Weeks):  • Mono (932)  • ≥2 ARVs without PI or NNRTI (258)  • Multi-NNRTI or Multi-PI (588)</td>
<td>• NO (compared with mono)  • No association between any ARV and preterm delivery</td>
<td>PTD decreased with receipt of any ARV, ART that contained ZDV, and other ARV regimens compared with no ARV.</td>
</tr>
<tr>
<td>United States; 1990–2002&lt;sup&gt;3&lt;/sup&gt;</td>
<td>1,337/999</td>
<td>Mono (492)  • Multi-no PI (373)  • Multi-PI (134)</td>
<td>YES (compared with Mono and Multi-no PI)  Multi-PI: 1.8 (1.1–3.03)</td>
<td>Multi-PI reserved for those with advanced disease and those who experienced virologic failure while on other multi-ARV regimens.</td>
</tr>
<tr>
<td>Brazil, Argentina, Mexico, Bahamas; 2002–2005&lt;sup&gt;38&lt;/sup&gt;</td>
<td>681/681</td>
<td>Mono/Dual NRTI (94)  • Multi-NNRTI (257)  • Multi-PI (330)</td>
<td>NO (compared with Mono/Dual-NRTI)  No association between any ARV regimen and PTD</td>
<td>All patients were on ARV for ≥28 days during pregnancy.  Pre-eclampsia/eclampsia, cesarean delivery, diabetes, and low BMI were associated with PTD.</td>
</tr>
<tr>
<td>Meta-Analysis, Europe and United States; 1986–2004&lt;sup&gt;4&lt;/sup&gt;</td>
<td>11,224/Not given</td>
<td>Multi-no PI (including Dual) or Multi-PI (2,556)</td>
<td>YES (only comparing Multi-PI with Multi-no PI)  PI vs. Multi-no PI: 1.35 (1.08–1.70)</td>
<td>14 studies, 5 in PTD ARV comparison.  No overall increase in PTD with antepartum ARV.  PTD increased in those on ARV pre-pregnancy and in first trimester compared with later use.</td>
</tr>
<tr>
<td>United States; 1989–2004&lt;sup&gt;6&lt;/sup&gt;</td>
<td>8,793/6,228</td>
<td>Mono (2,621)  • Dual (1,044)  • Multi-no PI (1,781)  • Multi-PI (782)</td>
<td>YES (compared with Dual)  Multi-PI: 1.21 (1.04–1.40)</td>
<td>Lack of antepartum ARV also associated with PTD.  PTD and LBW decreased over time.</td>
</tr>
</tbody>
</table>
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<tr>
<td>United Kingdom, Ireland; 1990–2005</td>
<td>5,009/4,445</td>
<td>• Mono/Dual (1,061) • Multi-NRTI or Multi-PI (3,384)</td>
<td>• YES (compared with Mono/Dual) • Multi-PI or Multi-NRTI: 1.51 (1.19–1.93)</td>
<td>Similar increased risk with Multi-PI or Multi-no PI. No association with duration of ARV use.</td>
</tr>
<tr>
<td>Germany, Austria; 1995–2001</td>
<td>183/183</td>
<td>• Mono (77) • Dual (31) • Multi-NRTI (54) • Multi-PI (21)</td>
<td>YES (compared with Mono) Multi-PI: 3.40 (1.13–10.2)</td>
<td>N/A</td>
</tr>
<tr>
<td>United States; 2002–2007</td>
<td>777/777</td>
<td>• Mono (6) • Dual (11) • Multi-no PI (202) • Multi-PI (558)</td>
<td>NO (compared PI with all non-PI) Multi-PI: 1.22 (0.70–2.12)</td>
<td>All patients started ARV during pregnancy. Study analyzed only spontaneous PTD.</td>
</tr>
<tr>
<td>Swiss Mother and Child HIV Cohort Study; 1985–2007</td>
<td>1,180/941</td>
<td>• Mono (94) • Dual (53) • Multi-PI or Multi-no PI (409) • Multi-PI (385)</td>
<td>YES (compared with no ARV) Multi: 2.5 (1.4–4.3)</td>
<td>No association of Mono/Dual with PTD compared with no ARV. No confounding by duration of ARV or maternal risk factors.</td>
</tr>
<tr>
<td>Botswana; 2006–2008</td>
<td>530/530</td>
<td>• Multi-NRTI, ABC plus ZDV plus 3TC (263) • Multi-PI, LPV/r plus ZDV plus 3TC (267)</td>
<td>YES Multi-PI vs. Multi-NRTI: 2.03 (1.26–3.27)</td>
<td>Secondary analysis of data from randomized, controlled clinical trial of ARV begun at 26–34 weeks for prevention of perinatal transmission. All CD4 cell counts &gt;200 cells/mm³</td>
</tr>
<tr>
<td>Botswana; 2007–2010</td>
<td>4,347/3,659</td>
<td>• ARV, regimen unspecified (70) • Mono (2,473) • Multi (1,116), 91% Multi-NRTI</td>
<td>NO No association between multi-ART and very PTD (&lt;32 weeks’ gestation)</td>
<td>Observational; multi-ART before conception associated with very SGA and maternal hypertension during pregnancy.</td>
</tr>
<tr>
<td>Spain; 1986–2010</td>
<td>519/371</td>
<td>• Mono/Dual NRTI (73) • All Multi (298) • Multi-PI (178)</td>
<td>NO (compared with No ARV plus Mono/Dual) Spontaneous PTD not associated with Multi ARV or Multi-PI before or during pregnancy</td>
<td>PTD associated with Multi-ARV given in second half of pregnancy and with prior PTD.</td>
</tr>
<tr>
<td>Botswana; 2009–2011</td>
<td>9,504/7,915</td>
<td>• Mono (4,625) • All Multi (3,290) • Multi-PI (312)</td>
<td>YES (Multi-ARV before and during pregnancy compared with Mono): 1.2 (1.1–1.4) and 1.4 (1.2–1.8) YES (Multi-PI compared with Multi-no PI before pregnancy): 2.0 (1.1–3.6)</td>
<td>ART group classified by initiation before and during pregnancy.</td>
</tr>
<tr>
<td>France, ANRS French Perinatal Cohort; 1990–2009</td>
<td>8,696/8,491</td>
<td>• Mono (950) • Dual (590) • Multi-PI (2,414)</td>
<td>YES (Multi compared to Mono): 1.69 (1.38–2.07) YES (before conception compared to during pregnancy): 1.31 (1.11–1.55)</td>
<td>Patients on ART before and during pregnancy had increased rates of PTD.</td>
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<tr>
<td>United States; 2000–2011&lt;sup&gt;43&lt;/sup&gt;</td>
<td>183/183</td>
<td>• Multi-PI (183)</td>
<td>• NO (no control group without ART)  &lt;br&gt;  • Rate of PTD: 18.6%</td>
<td>• SGA rate: 31.2%  &lt;br&gt;  • Patients on NNRTI-based ART less likely to have SGA: 0.28 (0.1–0.75).</td>
</tr>
<tr>
<td>United States; 2007–2010&lt;sup&gt;13&lt;/sup&gt;</td>
<td>1,869/1,810</td>
<td>• Mono/Dual (138)  &lt;br&gt;  • Multi-NRTI (193)  &lt;br&gt;  • Multi-NNRTI (160)  &lt;br&gt;  • Multi-PI (1,319)</td>
<td>• YES (compared with no ARV in first trimester)  &lt;br&gt;  • Multi-PI in first trimester vs. none in first trimester  &lt;br&gt;  • PTD 1.55 (1.16–2.07); spontaneous PTD 1.59 (1.10–2.30)</td>
<td>N/A</td>
</tr>
<tr>
<td>Latin America; 2002–2012&lt;sup&gt;14&lt;/sup&gt;</td>
<td>1,512/1,446</td>
<td>• No ART or ART &lt;28 days (66)  &lt;br&gt;  • Mono/Dual (130)  &lt;br&gt;  • Multi-no PI (409)  &lt;br&gt;  • Multi-PI (907)</td>
<td>• YES (when on ARVs at conception): PTD 1.53 (1.11–2.09)</td>
<td>• ART for treatment rather than prophylaxis was associated with increased rates of LBW (&lt;2,500 g) infants: 1.8 (1.26–2.56).  &lt;br&gt;  • Multi-no PI associated with decreased risk of LBW (0.33 [0.14–0.74]) and stillbirth (0.11 [0.04–0.34]).  &lt;br&gt;  • Multi-PI associated with decreased risk of stillbirth: 0.14 (0.05–0.34).</td>
</tr>
<tr>
<td>Uganda; 2009–2012&lt;sup&gt;23&lt;/sup&gt;</td>
<td>356/356</td>
<td>• Multi-NNRTI, EFV (177)  &lt;br&gt;  • Multi-PI, LPV/r (179)</td>
<td>• NO (no control group without ART)</td>
<td>• Trend in increased incidence of PTD among women starting ART 24–26-week GA was NS: aOR = 1.76 (0.96–3.23).</td>
</tr>
<tr>
<td>Italy; 1997–2013&lt;sup&gt;34&lt;/sup&gt;</td>
<td>158/158</td>
<td>• Mono/Dual (27)  &lt;br&gt;  • Multi-no PI (17)  &lt;br&gt;  • Multi-PI (114)</td>
<td>• NO (no control group without ART)</td>
<td>• PTD rate was 17% for this cohort.  &lt;br&gt;  • Trend towards association of PTD with longer duration of ART: 2.82 (0.35–8.09).</td>
</tr>
<tr>
<td>Canada; 1988–2011&lt;sup&gt;15&lt;/sup&gt;</td>
<td>589/530</td>
<td>• No ART (59)  &lt;br&gt;  • Mono (77)  &lt;br&gt;  • Multi-no PI (166)  &lt;br&gt;  • Multi-PI (166)  &lt;br&gt;  • Multi-boosted PI with RTV (144)</td>
<td>• YES (Multi-boosted PI compared to Multi-non-boosted PI): 2.01 (1.02–3.97)  &lt;br&gt;  • NO (non-PI regimens compared to Multi-non-boosted PI): 0.81 (0.4–1.66)</td>
<td>• Highest risk of PTD was among women not taking ART compared to non-boosted PI group: 2.7 (1.2–6.09).</td>
</tr>
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| United Kingdom; 2007–2012<sup>31</sup> | 493/493 | • Multi-PI, LPV/r (306)  
• Multi-PI, ATV/r (187) | • NO (comparing 2 PI-based regimens):  
aOR = 1.87 (0.93–3.75) | • Rate of PTD was 13% among women who conceived on ART and  
14% among women who started ART during pregnancy.  
• In a multivariate analysis, a history of PTD was associated with recurrent  
PTD: aOR = 5.23 (1.91–14.34).  
• Rate of PTD was 11%, with no difference between study groups.  
• LBW increased in EFV group (33% vs. 16%, P = 0.04).  
• Stillbirth rate was 4% (8/188). |
| Republic of the Congo; 2007–2012<sup>39</sup> | 188/188 | • Multi-no PI, EFV (31)  
• Multi-no PI, NVP (146) | • NO (comparing EFV 13% vs. NVP 10%) | • Rate of PTD was 29%; women who conceived on ART were more likely to have PTD compared to women on ZDV monotherapy.  
• Pregnancy-induced hypertension associated with PTD: 1.25 (1.03–1.51). |
| Tanzania; 2004–2011<sup>16</sup> | 3,314/2,862 | • No ART (452-excluded)  
• Mono (1,768)  
• Multi (1,094) | • YES (Multi before pregnancy vs. Mono): 1.24 (1.05–1.47)  
• Very PTD, YES (Multi before pregnancy vs. Mono): 1.42 (1.02–1.99)  
• NO (Multi during pregnancy compared to Mono): 0.85 (0.7–1.02) | • LBW rate was 16%; RR of LBW with ZDV ART vs. non-ZDV ART = 1.2 (1.0–1.3), P = 0.02.  
• Stillbirth rate: 1.5%, RR = 0.8 (0.5–1.1). |
| 67 Countries and US Territories, APR; 1989–2013<sup>40</sup> | 14,684/14,684 | • ARV with ZDV (12,780)  
• ARV without ZDV (1,904) | • NO (any ZDV-ARV vs. non-ZDV ARV exposure): 1.0 (0.9–1.2) | • PTD rate was 12%.  
• LBW rate was 16%; RR of LBW with ZDV ART vs. non-ZDV ART = 1.2 (1.0–1.3), P = 0.02.  
• Stillbirth rate: 1.5%, RR = 0.8 (0.5–1.1). |
| Texas, United States; 1984–2014<sup>32</sup> | 1,004/792 | • No ART (177)  
• Mono, Dual, or Multi-no PI (230)  
• Multi-PI (597) | • NO (no-PI ART vs. PI ART): 0.9 (0.5–1.5) | • Rate of PTD: 13% to 21%.  
• Rate of SGA: 19% to 23%, OR = 1.3 (0.8–1.9). |
<table>
<thead>
<tr>
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</table>
| India, Malawi, South Africa, Tanzania, Uganda, Zambia, Zimbabwe, PROMISE Trial; 2011–2014[^4] | 3,490/3,096 | • Mono (1,386)  
• All Multi (2,710)  
• Multi-PI with ZDV (1,385)  
• Multi-PI with TDF (325) | • YES (Multi ≥14 weeks vs. Mono) | • Rate of PTD: 21% on Multi-PI with ZDV ART compared to ZDV-Mono (P < 0.001).  
• Rate of very PTD: 6% in Multi-PI with TDF ART and 3% in Multi-PI with ZDV ART (P = 0.04).  
• LBW was more common in Multi-PI with ZDV ART compared to ZDV Mono (23% vs. 12%, P < 0.001) and in Multi-PI with TDF compared to ZDV Mono (17% vs. 9%, P = 0.004). |
| United States and Puerto Rico, SMARTT; 2007–2016[^17] | 1,864/1,658 | • Multi (1,658) | • YES: (Multi-PI vs. No ART): 1.59 (1.1–2.3) | • PI-based ART exposure in first trimester was associated with increased risk of spontaneous PTD compared with no first-trimester ART. |
• Multi (2,573) | • NO  
• Dual: 0.2 (0.08–0.5)  
• Multi: 0.3 (0.1–0.9) | • PTD rate regardless of ART: 22% to 23%.  
• LBW rate on ART: 9% to 15%. Risk of LBW: Dual 0.06 (0.02–0.2) and Multi 0.12 (0.04–0.4).  
• SGA rate on ART: 7% to 9%. Risk of SGA: Dual 0.37 (0.1 to 1.5) and Multi 0.3 (0.07 to 0.9).  
• Stillbirth rate on Dual (1.2%) and Multi (2.2%). Risk of stillbirth: Dual 0.08 (0.04–0.2) and Multi 0.2 (0.1–0.3). |
| Botswana; 2012–2014[^16] | 11,932/10,592 | • Multi-PI (398)  
• Multi-NNRTI (4,597) | • YES  
• Multi-PI: 1.36 (1.06–1.75)  
• Multi-NNRTI: 1.14 (1.01–1.29) | • SGA rates were significantly higher in Multi PI ART (27.7% and 20.4%) and NVP-based ART (24.9% and 28.2%) compared to EFV-based ART (16.9%).  
• Stillbirth rates were higher in NVP-based ART: 2.31 (1.64–3.26). |
Table 5. Results of Studies Assessing the Association Between Antiretroviral Regimens and Preterm Delivery (page 7 of 8)

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<tbody>
<tr>
<td>19 Countries, 5 Continents; 2002–201325</td>
<td>23,490 (meta-analysis of 10 studies)</td>
<td>• Mono, Dual, or Multi-no PI • Multi-PI</td>
<td>• YES</td>
<td>• Multi-PI: 1.3 (1.04–1.6), I² = 47%</td>
</tr>
<tr>
<td>South Africa; 2011–201426</td>
<td>1,461/1,159</td>
<td>• Dual (424) • Multi (735)</td>
<td>• YES</td>
<td>• Multi: 1.65 (1.17-2.33) • ART before pregnancy: 1.72 (1.33-3.01)</td>
</tr>
<tr>
<td>Netherlands; 1997–201521</td>
<td>2,184/1,392</td>
<td>•Multi (1,392) • PI-based and non-PI based ART</td>
<td>• NO</td>
<td>• 1.39 (0.99–1.94); comparing women on ART before pregnancy to those who started ART during pregnancy</td>
</tr>
<tr>
<td>South Africa, SAPMTCTE; 2012–201320</td>
<td>2,599/2,269</td>
<td>• Dual (873) • Multi (1,396)</td>
<td>• YES</td>
<td>• 1.2 (1.0–1.5) compared to infants who were not exposed to HIV • 1.7 (1.1–2.5) in infants exposed to ART from conception</td>
</tr>
<tr>
<td>Multiple Countries; 1993–201427</td>
<td>37,877 (meta-analysis of 17 studies)</td>
<td>• Multi with TDF • Other ART without TDF</td>
<td>• NO</td>
<td>• RR = 0.9 (0.81–0.99), I² = 59%; women on Multi with TDF had lower rates of PTD compared to women on other ART without TDF</td>
</tr>
</tbody>
</table>
Table 5. Results of Studies Assessing the Association Between Antiretroviral Regimens and Preterm Delivery (page 8 of 8)

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| United Kingdom/Ireland; 2007–2015<sup>56</sup> | 6,073/6,073 | • Multi-PI (4,184)  
• Multi-NNRTI (1,889) | • YES  
• Multi-PI associated with PTD: 1.56 (1.19-2.04)  
• Multi-PI before conception with CD4 count <350 cells/mm<sup>3</sup>, 1.99 (1.02-3.85) and 1.9 (1.01–3.57) and with CD4 count >350 cells/mm<sup>3</sup>, 1.61 (1.07–2.43) | • PTD rate was 10.4%.  
• SGA rate was 20.4%. |
| South Africa; 2010–2015<sup>53</sup> | 4,435/2,549 | • Multi-NNRTI, EFV plus TDF plus FTC/3TC (1,481)  
• Multi-NNRTI, other EFV-based ART (187)  
• Multi-NNRTI, NVP-based ART (343)  
• ZDV (528) | • NO  
• NVP-based ART aOR = 0.66 (0.27–1.63) (NS) and other EFV-based ART (aOR 0.72; 95% CI, 0.24±2.12) vs. EFV plus TDF plus FTC/3TC. | • PTD rate was 10.4%.  
• SGA rate was 10.4%.  
• LBW rate was 9.6%. |
| North America; 2007–2013<sup>18</sup> | 4,646/1,621 | • Multi-PI, TDF plus FTC plus LPV/r, TDF plus FTC plus ATV/r, ZDV plus 3TC plus LPV/r (1,621) | • YES  
• TDF plus FTC plus ATV/r vs. ZDV, plus 3TC plus LPV/r: aOR = 0.69 (0.51–0.94) | • PTD rate was 19%.  
• LBW rate was 19.6%. |

Note: The data presented in the column Association Noted between ARV Regimens and Preterm Delivery represent the published results of the study in the corresponding row. Depending on the study designs, these are adjusted and unadjusted odds ratios and relative risks.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; aOR = adjusted odds ratio; ART = antiretroviral therapy; ARV = antiretroviral; ATV/r = atazanavir/ritonavir; BMI = body mass index; CD4 = CD4 T lymphocyte; dual = 2 ARV drugs; EFV = efavirenz; FTC = emtricitabine; GA = gestational age; HCV = hepatitis C virus; low birth weight; mono = single ARV drug; multi = 3 or more ARV drugs; multi-PI = combination ART with PI; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NS = nonsignificant; NVP = nevirapine; OR = odds ratio; PI = protease inhibitor; PROMISE = Promoting Maternal and Infant Survival Everywhere; PTD = preterm delivery; RR = relative risk; RTV = ritonavir; SAPMTCTE = South African Prevention of Mother-to-Child Transmission Evaluation; SGA = small for gestational age; SMARTT = Surveillance Monitoring for ART Toxicities; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

References


