Combination Antiretroviral Drug Regimens and Maternal and Neonatal Outcomes

(Last updated November 14, 2017; last reviewed November 14, 2017)

Panel’s Recommendations

- Clinicians should be aware of a possible small increased risk of preterm delivery in pregnant women 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 taking antiretroviral therapy (ART) may be at increased risk for adverse pregnancy outcomes, including preterm birth or delivery (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, we provide a summary of the published data regarding ART and adverse neonatal outcomes. In addition, there are limited data suggesting a potential association between hypertensive disorders of pregnancy and maternal HIV. These data are summarized at the end of this section.

We have reviewed and summarized studies from 1986 to 2017 reporting on obstetric and neonatal outcomes in women with HIV. These studies are conducted in Europe (11), North America (9), sub-Saharan Africa (9), and Latin America (2). Study size and designs vary significantly; the total study participant numbers range from 183 to 10,592. The ART regimens evaluated in these studies differ and may include:

- No ART (8)
- Monotherapy: Single antiretroviral (ARV) drug (19)
- Dual therapy: Two ARV drugs (13), and
- Multi-ARVs: At least 3 ARV drugs; protease inhibitor (PI)-based (23) or non-PI-based (27).

Table 5. Results of Studies Assessing the Association Between Antiretroviral Regimens and Preterm Delivery lists the published, high-quality studies reporting potential effects of ART use on pregnancy outcomes. The studies’ conclusions regarding preterm birth or delivery, LBW, and SGA are provided. These data are weighted heavily regarding preterm birth or delivery (30), and fewer studies report outcomes of LBW (12), SGA (8), and stillbirth (11).

Pregnancy Outcomes

Preterm Delivery

All the studies reviewed in this section (33) have reported outcomes related to preterm delivery. Among the 19 studies that report an association between ART use and preterm delivery, the relative risks/odds ratios for preterm delivery range from 1.2 to 3.4.1-18 Conflicting findings regarding preterm delivery and ART use may be influenced by variability in the data available for analysis. For example, some studies have reported increased rates of preterm delivery when ART is initiated before or in early pregnancy compared to later in pregnancy. Maternal factors, such as HIV disease severity, may affect the timing of ART initiation during pregnancy. These variables may be associated with preterm delivery independent of ART use.19-21 In order to control for medical or obstetrical factors associated with preterm delivery, two studies have assessed spontaneous preterm delivery alone. One study included women initiating ART during pregnancy. Neither study reported an association between ART use and preterm delivery.22,23 In general, none of the studies reviewed in this section have comprehensively controlled for all potential factors that may be associated with...
Preterm Delivery and Antiretroviral Therapy Exposure Before Pregnancy

Seven of the 31 studies in Table 5 report an association between ART initiation prior to pregnancy and preterm delivery. The relative risks and odds ratios reported range from 1.20 to 2.05; the risk is attenuated in multivariate analysis. These studies were conducted in Europe (3), Latin America (1), and Africa (3) and included various ART regimens (including single-drug, two-drug, and multidayr regimens). A large meta-analysis of 11,224 women in 14 European and American studies did not demonstrate an increased rate of preterm delivery among women using ART during pregnancy.

Antiretroviral Therapy Regimens Associated with Preterm Delivery

PI-Based

Fifteen of the 31 studies in Table 5 investigate an associated risk between PI-based ART and preterm delivery. These studies include populations in Europe (4), North America (9), and Africa (3). The risk of preterm delivery ranges from 1.14 to 3.4. Five of these studies did not demonstrate a significant association between PI-based ART and preterm delivery.

The recent PROMISE trial study compared zidovudine-alone to lopinavir/ritonavir 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 preterm delivery were reported in women receiving zidovudine/lamivudine/lopinavir/ritonavir (P < 0.001) but not TDF/emtricitabine/lopinavir (P = 0.77). In contrast, extremely preterm delivery rates were higher among women receiving TDF/emtricitabine/lopinavir/ritonavir than women receiving zidovudine/lamivudine/lopinavir/ritonavir (P = 0.04). These rates of very preterm delivery were not significantly different compared to women receiving zidovudine-alone (P = 0.10).

The use of ritonavir to boost a PI-based regimen may be associated with preterm delivery compared to non-boosted PI regimens. In a small, retrospective Canadian study, women taking non-boosted PI regimens did not have increased rates of preterm delivery. A small meta-analysis of 10 studies (8 prospective cohort, 1 randomized controlled trial, and 1 surveillance study) demonstrated an increased risk of preterm birth associated with PI-based ART, aOR 1.32 (CI 1.04-1.6) with an I² = 47% (moderate heterogeneity). When evaluating the effects of initiating PI-based ART in the first and third trimesters of pregnancy, the pooled effect was non-significant.

Non-PI-Based

Exposure to NRTI single-drug prophylaxis (primarily zidovudine) was not associated with preterm delivery. Other reports have found increased rates of preterm delivery when ART is compared with dual-ARV regimens and when non-nucleoside reverse transcriptase inhibitor-based ART regimens were compared with other forms of ART.

Mechanism for Preterm Delivery

The potential mechanism of action by which PIs may increase a woman’s risk of preterm delivery is unknown. Papp et al. demonstrated in cell culture, 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, preterm delivery, and LBW. Papp et al. subsequently demonstrated that pregnant women with HIV exposed to PI-based ART with low serum progesterone have elevated levels of human placental 20-α-hydroxysteroid dehydrogenase levels, an enzyme that inactivates serum progesterone. These women were also noted to have lower prolactin levels in comparison to controls.

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

Fewer studies included in Table 5 have evaluated the effects of ART use on outcomes of LBW, SGA, and stillbirth. Reported rates of LBW range from 7.4% to 36%. Of the 15 studies that address
effects of ART on birth weight, five demonstrate an association between any ART use and LBW.\textsuperscript{16,31-34} Seven studies report the rates of SGA, which range from 7.3% to 31%.\textsuperscript{11,14,16,18,21,26,35,36} When comparing the initiation of monotherapy in pregnancy versus ART initiated before pregnancy and continued during pregnancy, ART was associated with SGA (1.34 [95% CI, 1.05–1.7]).\textsuperscript{16} Three studies in Botswana report a positive association with ART use (both non-PI-based and PI-based) and SGA.\textsuperscript{11,18,37} Continuation of ART initiated before pregnancy and initiation of ART during pregnancy may be associated with SGA (1.8 [95% CI, 1.6–2.1] and 1.5 [1.2–1.9]).\textsuperscript{11} When compared to emtricitabine/TDF/efavirenz ART, both nevirapine-based and lopinavir/ritonavir-based ART were associated with increased SGA.\textsuperscript{18} Ten studies report rates of stillbirth ranging from 0.5% to 11.4%.\textsuperscript{7,11,12,14,18,21,25,31,33} Two studies have evaluated the association between continuation of ART, both non-PI-based and PI-based, or starting ART during pregnancy and a risk of stillbirth (1.5 [95% CI, 1.2–1.8] and 2.5 [95% CI, 1.6–3.5])\textsuperscript{11} and (aRR 2.31 [95% CI, 1.64–3.26]).\textsuperscript{18} In the latter study, zidovudine/lamivudine/nevirapine was associated with a significantly increased rate of stillbirth compared to emtricitabine/TDF/efavirenz.

**Maternal Outcomes**

**Hypertensive Disorders of Pregnancy**

Limited data suggest as association of hypertensive disorders of pregnancy and maternal HIV. An earlier meta-analysis\textsuperscript{38} reported an increased association between maternal HIV and hypertensive disorders of pregnancy, but a more recent meta-analysis\textsuperscript{39} did not reveal a clear association of maternal HIV with pregnancy-induced hypertension, preeclampsia, or eclampsia. An Italian study demonstrated an increased risk for both early and late-onset preeclampsia (aOR=2.50, 95% CI, 1.51–4.15; aOR=2.64, 95% CI, 1.82–3.85) as well as pre-eclampsia with severe features (aOR=2.03, 95% CI, 1.26–3.28 respectively) when comparing pregnant women living with HIV versus without HIV.\textsuperscript{40}

Few studies have evaluated the effect of combination ART on 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 preeclampsia when compared to women who were not exposed to ART (aOR = 2.3, 95% CI, 1.1–4.9)\textsuperscript{41,42} A secondary analysis of South African data revealed that amongst women with low CD4 T lymphocyte counts (<200 cells/mm$^3$), there was an increased risk of maternal death from hypertensive disorders of pregnancy when comparing those on combination ART vs. those who received no ART during pregnancy (RR = 1.15, 95% CI, 1.02–1.29).\textsuperscript{41} It is unclear whether this finding 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 preterm delivery with use of ART. Given the clear benefits for maternal health and reduction in perinatal transmission, these agents should not be withheld due to concern for increased risk of preterm delivery. Until more information is available, pregnant women with HIV receiving ART should continue their provider-recommended regimens and receive regular monitoring for pregnancy complications, including preterm delivery.\textsuperscript{44}
### Table 5. Results of Studies Assessing the Association Between Antiretroviral Regimens and Preterm Delivery (page 1 of 5)

<table>
<thead>
<tr>
<th>Study Location(s); Dates of Study</th>
<th>Total Number of Pregnancies/Total 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<sup>1</sup> | 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 preterm delivery if ARV begun before pregnancy versus in third trimester |
| United States; 1990–1998<sup>24</sup> | 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<sup>45</sup> | 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 |
| United States; 1990–2002<sup>24</sup> | 2,543/Not given | Early (<25 Weeks):  
• Mono (621)  
• Multi, ≥2 without PI or NNRTI, (198)  
• Multi, with PI or NNRTI (357)  
Late (≥32 Weeks):  
• Mono (932)  
• Multi, ≥2 without PI or NNRTI (258)  
• Multi, with PI or NNRTI (588) | • NO (compared with mono)  
• No association between any ARV and preterm delivery | • Preterm delivery decreased with ARV compared with no ARV. |
| United States; 1990–2002<sup>2</sup> | 1,337/999 | • Mono (492)  
• Multi (373)  
• Multi-PI (134) | • YES (compared with other multi)  
• Multi-PI: 1.8 (1.1–3.03) | • Multi-PI reserved for advanced disease, those who failed other multi-ARV regimens. |
| Brazil, Argentina, Mexico, Bahamas; 2002–2005<sup>30</sup> | 681/681 | • Mono/dual NRTI (94)  
• Multi-NNRTI (257)  
• Multi-PI (330) | • NO (compared with mono/dual NRTI)  
• No association between any ARV regimen and preterm delivery | • All on ARV for at least 28 days during pregnancy  
• Preeclampsia/eclampsia, cesarean delivery, diabetes, low BMI associated with preterm delivery |
| Meta-Analysis, Europe and United States; 1986–2004<sup>4</sup> | 11,224/Not given | • Multi-no PI (including dual) or multi-PI (2,556) | • YES (only comparing PI with multi)  
• PI versus multi-no PI: 1.35 (1.08–1.70) | • 14 studies, 5 in preterm-delivery-ARV comparison  
• No overall increase in preterm delivery with antepartum ARV  
• Preterm delivery increased in those on ARV pre-pregnancy and in first trimester compared with later use. |
### Table 5. Results of Studies Assessing the Association Between Antiretroviral Regimens and Preterm Delivery (page 2 of 5)

<table>
<thead>
<tr>
<th>Study Location(s); Dates of Study</th>
<th>Total Number of Pregnancies/Total 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>
<tbody>
<tr>
<td>Italy; 2001–2006³</td>
<td>419/366</td>
<td>• Multi-PI second trimester (97)</td>
<td>• YES</td>
<td>• Multivariate association also with hepatitis C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Multi-PI third trimester (146)</td>
<td>• Multi-PI second trimester: 2.24 (1.22–4.12)</td>
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<td></td>
<td></td>
<td></td>
<td>• Multi-PI third trimester: 2.81 (1.46–5.39)</td>
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<tr>
<td>United States; 1989–2004⁶</td>
<td>8,793/6,228</td>
<td>• Mono (2,621)</td>
<td>• YES (compared with dual)</td>
<td>• Lack of antepartum ARV also associated with preterm delivery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Dual (1,044)</td>
<td>• Multi-PI associated with preterm delivery: 1.21 (1.04–1.40)</td>
<td>• Preterm delivery and LBW decreased over time.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Multi-no-PI (1,781)</td>
<td>• Multi: 1.51 (1.19–1.93)</td>
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<tr>
<td></td>
<td></td>
<td>• Multi-PI (782)</td>
<td>• Similar increased risk with PI or no-PI multi</td>
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<tr>
<td>United Kingdom, Ireland; 1990–2005⁷</td>
<td>5,009/4,445</td>
<td>• Mono/dual (1,061)</td>
<td>• YES (compared with mono/dual)</td>
<td>• No association with duration of use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Multi-NNRTI or multi-PI (3,384)</td>
<td>• Multi: 3.40 (1.13–10.2)</td>
<td></td>
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<tr>
<td>Germany, Austria; 1995–2001⁸</td>
<td>183/183</td>
<td>• Mono (77)</td>
<td>• YES (compared with mono)</td>
<td>N/A</td>
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<tr>
<td></td>
<td></td>
<td>• Dual (31)</td>
<td>• Multi-PI: 3.40 (1.13–10.2)</td>
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<td></td>
<td></td>
<td>• Multi-PI (21)</td>
<td>• All started ARV during pregnancy.</td>
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<td></td>
<td></td>
<td>• Multi-NNRTI (54)</td>
<td>• Analyzed only spontaneous preterm delivery</td>
<td></td>
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<tr>
<td>United States; 2002–2007²²</td>
<td>777/777</td>
<td>• Mono (6)</td>
<td>• NO (compared PI with all non-PI)</td>
<td>• No association of mono/dual with preterm delivery compared with no ARV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Dual (11)</td>
<td>• Multi-Pl: 1.22 (0.70–2.12)</td>
<td>• No confounding by duration of ARV or maternal risk factors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Multi-no-PI (202)</td>
<td>• All started ARV during pregnancy.</td>
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<tr>
<td></td>
<td></td>
<td>• Multi-PI (588)</td>
<td>• Analyzed only spontaneous preterm delivery</td>
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<tr>
<td>Swiss Mother and Child HIV Cohort Study; 1985–2007⁹</td>
<td>1,180/941</td>
<td>• Mono (94)</td>
<td>• YES (compared with no ARV)</td>
<td>• Secondary analysis of data from randomized, controlled clinical trial of ARV begun at 26–34 weeks for prevention of perinatal transmission</td>
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<tr>
<td></td>
<td></td>
<td>• Dual (53)</td>
<td>• Multi: 2.5 (1.4–4.3)</td>
<td>• All CD4 cell counts &gt;200 cells/mm³</td>
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<tr>
<td></td>
<td></td>
<td>• Multi, PI or no PI, (409)</td>
<td>• No association of mono/dual with preterm delivery compared with no ARV</td>
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<tr>
<td></td>
<td></td>
<td>• Multi-PI (385)</td>
<td>• No confounding by duration of ARV or maternal risk factors</td>
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</tr>
<tr>
<td>Botswana; 2006–2008¹⁰</td>
<td>530/530</td>
<td>• LPV/r plus ZDV plus 3TC (267)</td>
<td>• YES</td>
<td>• Secondary analysis of data from randomized, controlled clinical trial of ARV begun at 26–34 weeks for prevention of perinatal transmission</td>
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<tr>
<td></td>
<td></td>
<td>• ABC plus ZDV plus 3TC (263)</td>
<td>• Multi-PI versus multi-NRTI: 2.03 (1.26–3.27)</td>
<td>• All CD4 cell counts &gt;200 cells/mm³</td>
</tr>
<tr>
<td>Botswana; 2007–2010¹⁷</td>
<td>4,347/3,659</td>
<td>• ARV, regimen unspecified (70)</td>
<td>• NO</td>
<td>• Observational: multi-ART before conception associated with very-small-for-gestational-age and maternal hypertension during pregnancy</td>
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<td></td>
<td></td>
<td>• Mono (2,473)</td>
<td>• No association between multi-ART and very preterm delivery (&lt;32 weeks’ gestation)</td>
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<tr>
<td></td>
<td></td>
<td>• Multi, 91% NNRTI (1,116)</td>
<td>• No association between multi-ART and very preterm delivery (&lt;32 weeks’ gestation)</td>
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<tr>
<td></td>
<td></td>
<td>• NO (compared with no ARV plus mono/dual)</td>
<td>• Preterm delivery associated with multi-ART given in second half of pregnancy and with prior preterm delivery</td>
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<tr>
<td></td>
<td></td>
<td>• Multi (178)</td>
<td>• Spontaneous preterm delivery not associated with multi-ARV or multi-PI before or during pregnancy</td>
<td></td>
</tr>
<tr>
<td>Spain; 1986–2010²³</td>
<td>519/371</td>
<td>• Mono/dual NRTI (73)</td>
<td>• NO (compared with no ARV plus mono/dual)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• All multi (298)</td>
<td>• Spontaneous preterm delivery not associated with multi-ARV or multi-PI before or during pregnancy</td>
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<tr>
<td></td>
<td></td>
<td>• Multi-PI (178)</td>
<td>• Preterm delivery associated with multi-ARV given in second half of pregnancy and with prior preterm delivery</td>
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</tbody>
</table>
| Botswana; 2009–2011<sup>11</sup> | 9,504/7,915                                   | • Mono (4,625)                           | • 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)  
• ART group classified by initiation before and during pregnancy |       |
| France; ANRS French Perinatal Cohort 1990–2009<sup>12</sup> | 8,696/8,491                                   | • Mono (950)                           | • YES (multi-ARV compared to mono): 1.69 (1.38–2.07)  
• YES (before conception compared to during pregnancy): 1.31 (1.11–1.55)  
• Patients on ART before and during pregnancy had increased rates of preterm delivery |       |
| United States; 2000–2011<sup>36</sup> | 183/183                                        | • Multi-PI (183)                         | • NO (no control group without ART)  
• Rate of preterm delivery: 18.6%  
• SGA rate: 31.2%  
• NNRTI-based ART less likely to have SGA: 0.28 (0.1–0.75) |       |
| United States; 2007–2010<sup>13</sup> | 1,869/1,810                                   | • Mono/dual (138)                       | • YES (compared with no ARV in first trimester)  
• Multi-PI in first trimester vs. none in first trimester  
• Preterm delivery 1.55 (1.16–2.07); spontaneous preterm delivery 1.59 (1.10–2.30)  
N/A |       |
| Latin America; 2002–2012<sup>14</sup> | 1,512/1,446                                   | • Multi-PI (907)                         | • YES (when on ARVs at conception); preterm delivery 1.53 (1.11–2.09)  
• ART for treatment rather than prophylaxis associated with increased rates of LBW (<2,500 g) infants: LBW 1.8 (1.26–2.56)  
• Multi-non-PI associated with decreased risk of LBW (0.33 [0.14–0.74]) and stillbirth (0.11 [0.04-0.34])  
• Multi-PI associated with decreased risk of stillbirth: 0.14 (0.05–0.34) |       |
| Uganda; 2009–2012<sup>46</sup>  | 356/356                                        | • Multi-PI, LPV/r (179)                 | • NO (no control group without ART)  
• Trend in increased preterm delivery among women starting ART 24–28 week GA was NS: aOR 1.76 (0.96–3.23) |       |
| Italy; 1997–2013<sup>47</sup>   | 158/158                                        | • Mono/dual (27)                        | • NO (no control group without ART)  
• Preterm delivery rate was 17% for this cohort, trend towards association with longer duration of ART: 2.82 (0.35–8.09) |       |
| Canada; 1988–2011<sup>15</sup>  | 589/530                                        | • Multi-non-boosted PI (220)            | • YES (compared to multi-non-boosted PI): 2.01 (1.02–3.97)  
• NO (non-PI compared to non-boosted PI): 0.81 (0.4–1.66)  
• Highest risk of preterm delivery among women not taking ART compared to non-boosted PI group: 2.7 (1.2–6.09) |       |
Table 5. Results of Studies Assessing the Association Between Antiretroviral Regimens and Preterm Delivery (page 4 of 5)

<table>
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<tr>
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<th>Notes</th>
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</table>
| United Kingdom; 2007–2012<sup>25</sup> | 493/493                                       | • Multi-PI, LPV/r  
• Multi-PI, ATV/r | • NO (comparing two PI-based regimens): aOR 1.87 (0.93–3.75) | Rate of preterm delivery 13% among women who conceived on ART and 14% among women who started ART during pregnancy.  
In multivariate analysis, a history of preterm delivery was associated with recurrent preterm delivery: aOR 5.23 (1.91–14.34) |
| Republic of the Congo; 2007–2012<sup>21</sup> | 188/188                                       | • Multi-non-PI, EFV-based (31)  
• Multi-non-PI, NVP-based (146) | • NO (comparing EFV 13% vs NVP 10%) | Rate of preterm delivery 11%, no difference between study groups  
LBW increased in EFV group (33% vs 16%, P = 0.04).  
Stillbirth rate 4% (8/188) |
| Tanzania; 2004–2011<sup>16</sup> | 3,314/2,862                                    | • Multi (1,094)  
• Mono (1,768)  
• No ART (452-excluded) | • YES (Multi before pregnancy vs Mono): 1.24 (1.05–1.47)  
• Very preterm delivery, 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) | Rate of preterm delivery 29%; women who conceived on ART more likely to have preterm delivery compared to women on ZDV monotherapy.  
Pregnancy-induced hypertension associated with preterm delivery: 1.25 (1.03–1.51) |
| 67 Countries and US Territories; APR 1989-2013<sup>33</sup> | 14,684/12,780 (ZDV), 1,904 (non-ZDV) | • Multi<sup>a</sup>  
• ARV with ZDV  
• ARV without ZDV | • NO (any ZDV-ARV vs non-ZDV-ARV exposure): 1.0 (0.9–1.2) | Preterm delivery rate 12%  
LBW rate 16%, RR of LBW with ZDV-ART vs non-ZDV ART RR: 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>26</sup> | 1,004/792                                      | • Multi, PI ART (597); non-PI ART (230)  
• No ART (177) | • NO (non-PI ART vs PI-ART): 0.9 (0.5–1.5) | Rate of preterm delivery: 13% to 21%  
Rate of SGA: 19% to 23%, OR 1.3 (0.8–1.9) |
| India, Malawi, South Africa, Tanzania, Uganda, Zambia, Zimbabwe, PROMISE Trial; 2011–2014<sup>32</sup> | 3,490/3,096                                    | • Mono (1,386)  
• All Multi (2,710)  
• ZDV-based (1385)  
• TDF-based (325) | • YES (Multi after 14 weeks vs mono) | Rate of preterm delivery: 21% on ZDV-based ART compared to ZDV-mono (P < 0.001).  
Rate very preterm delivery: 6% in TDF-based ART and 3% in ZDV-based ART (P = 0.04)  
LBW was more common in ZDV-based ART (23% vs. 12%) in ZDV-alone (P < 0.001) and TDF-based ART (17% vs 9%) in ZDV-alone, (P = 0.004) |
Table 5. Results of Studies Assessing the Association Between Antiretroviral Regimens and Preterm Delivery (page 5 of 5)

<table>
<thead>
<tr>
<th>Study Location(s); Dates of Study</th>
<th>Total Number of Pregnancies/Total 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>
<tbody>
<tr>
<td>United States and Puerto Rico; SMARTT 2007–2016</td>
<td>1,864/1,491</td>
<td>• Multi (1,491)</td>
<td>• YES: 1.59 (1.2–2.1)</td>
<td>• PI-based ART exposure in 1st trimester was associated with increased risk of spontaneous preterm delivery compared with no first-trimester ART</td>
</tr>
<tr>
<td>South Africa; 2011–2014</td>
<td>3,723/3,547</td>
<td>• Dual (974) • Multi (2,573)</td>
<td>• NO • Dual: 0.2 (0.08–0.5) • Multi: 0.3 (0.1–0.9)</td>
<td>• Preterm delivery 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)</td>
</tr>
<tr>
<td>Botswana; 2012–2014</td>
<td>11,932/10,592</td>
<td>• Multi, PI-based (398) • Multi, NNRTI-based (4,597)</td>
<td>• YES • Multi PI-based: 1.36 (1.06–1.75) • Multi NNRTI-based: 1.14 (1.01–1.29)</td>
<td>• SGA rates were significantly higher in multi PI-based ART (27.7% and 20.4%) and NVP-based ART (24.9% and 28.2%) compared to EFV-based ART (19.9%). • Stillbirth rates were higher in nevirapine-based ART: 2.31 (1.64–3.26).</td>
</tr>
<tr>
<td>19 Countries, 5 Continents; 2002–2013</td>
<td>23,490 (meta-analysis 10 studies)</td>
<td>• Multi, PI-based • Multi, PI-sparing</td>
<td>• YES • Multi-PI based ART: 1.3 (1.04–1.6), I² =47%</td>
<td>• 6 of 10 studies demonstrated increased risk of preterm delivery: aOR (1.2–4.14)</td>
</tr>
</tbody>
</table>

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; BMI = body mass index; CD4 = CD4 T lymphocyte; dual = two ARV drugs; EFV = efavirenz; GA = gestational age; LBW = low birth weight; mono = single ARV drug; multi = three or more ARV drugs; multi-PI = combination ARV with PI; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NS = non-significant; OR = odds ratio; PI = protease inhibitor; RR = relative risk; SGA = small for gestational age; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine


17. Van Dyke RB, Chadwick EG, Hazra R, Williams PL, Seage GR 3rd. The PHACS SMARTT Study: assessment of the...


