Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States

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Combination Antiretroviral Drug Regimens and Pregnancy Outcome

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Panel's Recommendations
• Clinicians should be aware of a possible small increased risk of preterm birth 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 outcome **(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 (PTD) (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 brief summary of the published data regarding ART and adverse pregnancy outcomes.

We have reviewed and summarized studies from 1986 to 2015 reporting on birth outcomes in HIV-infected women. These studies are conducted in Europe (11), North America (8), sub-Saharan Africa (6), and Latin America (2). Study size and designs vary significantly; the total study participant numbers range from 183 to 9,504. The ART regimens evaluated in these studies differ and may include no ART (8), monotherapy (single antiretroviral [ARV] drug) (19), dual therapy (2 ARV drugs) (13), and multi-ARV drugs (at least 3 ARV drugs) [protease inhibitor (PI)-based (22) or non-PI-based (26)]. 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 PTD, LBW, and SGA are provided. These data are weighted heavily regarding PTD (26), and fewer studies report outcomes of LBW (12), SGA (7), and stillbirth (10).

Preterm Delivery

All of the studies reviewed in this section (27) have reported outcomes related to PTD. Among the 16 studies that report an association between ART use and PTD, the relative risks/odds ratios for PTD range from 1.2 to 3.4.[1-16] Conflicting findings regarding PTD and ART use may be influenced by variability in the data available for analysis. For example, some studies have reported increased rates of PTD 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 PTD independent of ART use.[17,18] In order to control for medical or obstetrical factors associated with PTD, two studies have assessed spontaneous PTD alone. One study included women initiating ART during pregnancy. Neither study reported an association between ART use and PTD.[19,20] 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

Six of the 27 studies in Table 5 report an association between ART initiation prior to pregnancy and PTD.[1] The relative risks and odds ratios reported range from 1.20 to 2.05; the risk is attenuated in multivariate analysis.[14] These studies were conducted in Europe (3), Latin America (1), and Africa (2) and included various ART regimens (including single-drug, two-drug and multi-drug regimens). A large meta-analysis of 11,224 women in 14 European and American studies did not demonstrate an increased rate of PTD among women using ART during pregnancy.[4]

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Antiretroviral Therapy Regimens Associated with Preterm Delivery

PI-Based

Thirteen of the 27 studies in Table 5 investigate an associated risk between PI-based ART and PTD. These studies include populations in Europe (4), North America (7), and Africa (2). The risk of PTD ranges from 1.2 to 3.4.[1,3-6,8,15,19,21,22] Four of these studies did not demonstrate a significant association between PI-based ART and PTD.[15,19,21,22] The use of ritonavir to boost a PI-based regimen 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.[15]

Non-PI-Based

Exposure to nucleoside reverse transcriptase inhibitor single-drug prophylaxis (primarily zidovudine) was not associated with PTD.[1] Other reports have found increased rates of PTD when ART is compared with dual-ARV regimens[9] and when non-nucleoside reverse transcriptase inhibitor-based ART regimens were compared with other forms of ART.[18]

Mechanism for Preterm Delivery

The potential mechanism of action by which protease inhibitors (PIs) may increase a woman's risk of PTD is unknown. Papp et al demonstrated in cell culture, mouse models, and in HIV-infected pregnant women that exposure to PI, with the exception of darunavir, can decrease plasma progesterone levels. Low levels of plasma progesterone during pregnancy may potentially be associated with fetal loss, PTD, and LBW.[23] Papp et al subsequently demonstrated that HIV-infected pregnant women 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.[24]

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%.[8,14,16,21,22,25,26] Of the 13 studies that address effects of ART on birth weight, only 3 demonstrate a significant association between any ART use and LBW.[16,26,27] Five studies report the rates of SGA, which range from 7.3% to 31%.[11,14,16,28,29] 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]).[16] Two studies in Botswana report a positive association with ART use (both non-PI-based and PI-based) and SGA.[11,30] 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]).[11] Seven studies report rates of stillbirth ranging from 0.5% to 11.4%.[7,11,12,14,22,26] Only 1 study reported a positive 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]).[11]

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 PTD 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 PTD. Until more information is available, HIV-infected pregnant women receiving ART should continue their provider-recommended regimens and receive regular monitoring for pregnancy complications, including PTD.[31]

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Table 5. Results of Studies Assessing the Association Between Antiretroviral Regimens and Preterm Delivery (page 1 of 4)

Study Location(s); Dates of Study	Total Number of Pregnancies/ Total on ARV Drugs	Types of ARV Regimens Compared (Numbers)	Association Noted Between ARV Regimens and PTD	Notes
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 begun before pregnancy versus in third trimester
United States; 1990–1998[21]	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[32]	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[27]	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 PTD	• PTD decreased with ARV compared with no ARV.
United States; 1990–2002[3]	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[25]	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 PTD	• All on ARV for at least 28 days during pregnancy • Preeclampsia/eclampsia, cesarean delivery, diabetes, low BMI associated with PTD
Meta-Analysis, Europe and United States; 1986–2004[4]	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 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.
Italy; 2001–2006[5]	419/366	• Multi-PI second trimester (97) • Multi-PI third trimester (146)	• YES • Multi-PI second trimester: 2.24 (1.22–4.12) • Multi-PI third trimester: 2.81 (1.46–5.39)	• Multivariate association also with hepatitis C

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Table 5. Results of Studies Assessing the Association Between Antiretroviral Regimens and Preterm Delivery (page 2 of 4)

Study Location(s); Dates of Study	Total Number of Pregnancies/ Total on ARV Drugs	Types of ARV Regimens Compared (Numbers)	Association Noted Between ARV Regimens and PTD	Notes
United States; 1989–2004[6]	8,793/6,228	• Mono (2,621) • Dual (1,044) • Multi-no PI (1,781) • Multi-PI (782)	• YES (compared with dual) • Multi-PI associated with PTD: 1.21 (1.04–1.40)	• Lack of antepartum ARV also associated with PTD • PTD and LBW decreased over time.
United Kingdom, Ireland; 1990–2005[7]	5,009/4,445	• Mono/dual (1,061) • Multi-NNRTI or multi-PI (3,384)	• YES (compared with mono/dual) • Multi: 1.51 (1.19–1.93)	• Similar increased risk with PI or no-PI multi • No association with duration of use
Germany, Austria; 1995–2001[8]	183/183	• Mono (77) • Dual (31) • Multi-PI (21) • Multi-NNRTI (54)	• YES (compared with mono) • Multi-PI: 3.40 (1.13–10.2)	N/A
United States; 2002–2007[19]	777/777	• Mono (6) • Dual (11) • Multi-no PI (202) • Multi-PI (558)	• NO (compared PI with all non-PI) • Multi-PI: 1.22 (0.70–2.12)	• All started ARV during pregnancy. • Analyzed only spontaneous PTD
Swiss Mother and Child HIV Cohort Study; 1985–2007[9]	1,180/941	• Mono (94) • Dual (53) • Multi (PI or no PI) (409) • Multi-PI (385)	• YES (compared with no ARV) • Multi: 2.5 (1.4–4.3)	• No association of mono/dual with PTD compared with no ARV • No confounding by duration of ARV or maternal risk factors
Botswana; 2006–2008[10]	530/530	• LPV/r plus ZDV plus 3TC (267) • ABC plus ZDV plus 3TC (263)	• YES • Multi-PI versus multi-NRTI: 2.03 (1.26–3.27)	• 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 >200 cells/ mm^3
Botswana; 2007–2010[30]	4,347/3,659	• ARV, regimen unspecified (70) • Mono (2,473) • Multi, 91% NNRTI (1,116)	• NO • No association between multi-ART and very PTD (<32 weeks' gestation)	• Observational; multi-ART before conception associated with very-small-for-gestational-age and maternal hypertension during pregnancy
Spain; 1986–2010[20]	519/371	• Mono/dual NRTI (73) • All multi (298) • Multi-PI (178)	• NO (compared with no ARV plus mono/dual) • Spontaneous PTD not associated with multi-ARV or multi-PI before or during pregnancy	• PTD associated with multi-ARV given in second half of pregnancy and with prior PTD
Botswana; 2009–2011[11]	9,504/7,915	• Mono (4,625) • All multi (3,290) • Multi-PI (312)	• YES (multi-ARV before and during pregnancy compared to mono) 1.2 (1.1–1.4) and 1.4 (1.2–1.8) • YES (multi-PI compared to multi-no PI before pregnancy 2.0 (1.1–3.6)	• ART group classified by initiation before and during pregnancy

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Table 5. Results of Studies Assessing the Association Between Antiretroviral Regimens and Preterm Delivery (page 3 of 4)

Study Location(s); Dates of Study	Total Number of Pregnancies/ Total on ARV Drugs	Types of ARV Regimens Compared (Numbers)	Association Noted Between ARV Regimens and PTD	Notes
France; ANRS French Perinatal Cohort 1990–2009[12]	8,696/8,491	• Mono (950) • Dual (590) • Multi-PI (2,414)	• 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 PTD
United States; 2000–2011[29]	183/183	• Multi-PI (183)	• NO (no control group without ART) • Rate of PTD 18.6%	• SGA rate 31.2% • NNRTI-based ART less likely to have SGA 0.28 (0.1–0.75)
United States; 2007–2010[13]	1,869/1,810	• Mono/dual (138) • Multi-NRTI (193) • Multi-NNRTI (160) • Multi-PI (1,319)	• YES (compared with no ARV in first trimester) • Multi-PI in first trimester vs. none in first trimester • PTD 1.55 (1.16–2.07); spontaneous PTD 1.59 (1.10–2.30)	N/A
Latin America; 2002–2012[14]	1,512/1,446	• Multi-PI (907) • Multi-non-PI (409) • Mono/dual (130) • No ART or ART <28 days (66)	• YES (when on ARVs at conception), PTD 1.53 (1.11–2.09)	• ART for treatment rather than prophylaxis associated with increased rates of LBW (<2,500 gm) 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[33]	356/356	• Multi-PI (LPV/r) (179) • Multi-non-PI (EFV) (177)	• NO (no control group without ART)	• Trend in increased PTD among women starting ART 24–28 week GA was NS, aOR 1.76 (0.96–3.23)
Italy; 1997–2013[34]	158/158	• Mono/dual (27) • Multi-PI (114) • Multi-non-PI (17)	• NO (no control group without ART)	• PTD rate was 17% for this cohort, trend towards association with longer duration of ART 2.82 (0.35–8.09)
Canada; 1988–2011[15]	589/530	• Multi-non-boosted PI (220) • Multi-boosted PI with ritonavir (144) • Multi-non-PI (166) • Mono (77) • No ART (59)	• 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 PTD among women not taking ART compared to non-boosted PI group, 2.7 (1.2–6.09)

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Table 5. Results of Studies Assessing the Association Between Antiretroviral Regimens and Preterm Delivery (page 4 of 4)

Study Location(s); Dates of Study	Total Number of Pregnancies/ Total on ARV Drugs	Types of ARV Regimens Compared (Numbers)	Association Noted Between ARV Regimens and PTD	Notes
United Kingdom; 2007–2012[22]	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 PTD 13% among women who conceived on ART and 14% among women who started ART during pregnancy. • In multivariate analysis, a history of PTD was associated with recurrent PTD, aOR 5.23 (1.91–14.34)
Republic of the Congo; 2007–2012[26]	188/188	• Multi-non-PI, EFV-based (31) • Multi-non-PI, NVP-based (146)	• NO (comparing EFV 13% vs NPV 10%)	• Rate of PTD 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[16]	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)) • VPTD, 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 PTD 29%; women who conceived on ART more likely to have PTD compared to women on AZT monotherapy. • Pregnancy-induced hypertension associated with PTD, 1.25 (1.03–1.51)

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; BMI = body mass index; dual = two ARV drugs; LBW = low birth weight; mono = single ARV drug; multi = three or more ARV drugs; multi-PI = combination ARV with PI; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PTD = preterm delivery; VPTD= very preterm delivery

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