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 (Last updated July 31, 2012; last reviewed July 31, 2012)

Panel's Recommendation
• Clinicians should be aware of a possible small increased risk of preterm birth in pregnant women receiving protease inhibitor (PI)-based combination antiretroviral regimens; however, given the clear benefits of such regimens for both a woman's health and prevention of mother-to-child transmission, PIs 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*

Early data were conflicting as to whether receipt of combination antiretroviral (ARV) regimens during pregnancy is associated with adverse pregnancy outcomes and, in particular, preterm delivery. The European Collaborative Study and the Swiss Mother + Child HIV Cohort Study investigated the effects of combination ARV regimens in a population of 3,920 mother-child pairs. Adjusting for CD4 T-lymphocyte (CD4-cell) count and intravenous drug use, they found a roughly twofold increase in the odds of preterm delivery for infants exposed to combination regimens with or without protease inhibitors (PIs) compared with no drugs; women receiving combination regimens that had been initiated before pregnancy were twice as likely to deliver prematurely as those who started drugs during the third trimester.[1] However, PI-based combination regimens were received by only 108 (3%) of the women studied; confounding by severity or indication may have biased the results (that is, sicker women may have received PIs more often, but their advanced HIV infection may have actually caused the preterm births). Exposure to nucleoside reverse transcriptase inhibitor (NRTI) single-drug prophylaxis (primarily zidovudine) was not associated with prematurity.

An updated report from the European Collaborative Study, based on an adjusted analysis that included 2,279 mother-child pairs, found a 1.9-fold increased risk of delivery at less than 37 weeks with combination ARV regimens started during pregnancy and a 2.1-fold increased risk with combination ARV regimens started pre-pregnancy compared with mono- or dual-NRTI prophylaxis.[2] In this report, 767 women received combination ARV regimens during pregnancy, although the proportion receiving PIs was not specified. The risk of delivery before 34 weeks' gestation was increased by 2.5-fold for those starting combination ARV regimens during pregnancy and 4.4-fold for those entering pregnancy on combination ARV regimens.

In contrast, in an analysis of 7 prospective clinical studies that included 2,123 HIV-infected pregnant women who delivered infants between 1990 and 1998 and had received antenatal ARV regimens and 1,143 women who did not receive antenatal ARV drugs, the use of multiple ARV drugs compared with no drugs or treatment with 1 drug was not associated with increased rates of preterm birth, low birth weight, low Apgar scores, or stillbirth.[3] Nor were any significant associations between adverse pregnancy outcome and use of ARV drugs by class or by category (including combination ARV regimens) found in an analysis from the Women and Infants Transmission Study, including 2,543 HIV-infected women (some of whom were included in the previous meta-analysis).[4]

More recent data have continued to be conflicting as to whether preterm delivery is increased with combination ARV regimens. Table 7 reviews results from studies that have evaluated the association of ARV drug use during pregnancy and preterm delivery. Multiple studies have detected small but significant increases (odds ratio [OR] 1.2–1.8 in the largest studies) in preterm birth with PI- or non-PI-based combination ARV regimens

as well.[5-8] However, other recent studies that have controlled for maternal and pregnancy characteristics as well as factors related to HIV infection have shown no increase in adverse outcomes including preterm delivery and low birth weight in association with PI-containing drug regimens.[9-11] A meta-analysis of 14 European and American clinical studies found no increase in risk of preterm birth with either any ARV drug receipt compared with no drugs or combination ARV regimens including PIs compared with no drugs.[12] However, a significant but modest increased risk of preterm birth (OR 1.35; 95% confidence interval [CI], 1.08–1.70) was found in women who received combination regimens with PIs compared with combination regimens without PIs. Other reports have found increased rates of preterm birth when combination ARV regimens are compared with dual regimens[13] and when combination ARV regimens containing non-nucleoside reverse transcriptase inhibitors were compared with other combination ARV regimens.[14]

Other variables may confound these observational studies. Some studies have found increased rates of preterm birth if a combination ARV regimen is begun before conception or earlier in pregnancy compared with later during pregnancy, which itself may reflect confounding by severity or indication.[14, 15] Recent studies have assessed spontaneous preterm birth only, excluding delivery that was initiated at a preterm gestation because of medical or obstetrical reasons, and found no association between ARV and preterm birth.[16, 17] In an analysis of HIV-infected women enrolled in the ANRS French Perinatal Cohort from 1990 to 2009, preterm delivery rates were seen to increase over time, and preterm delivery was associated with combination ARV regimens versus either mono- or dual-ARV regimens and were highest in those who had initiated ARV before pregnancy.[18] A restricted analysis within this cohort of PI-based combination ARV regimens comparing boosted to unboosted PIs showed an association with induced preterm delivery for boosted PI regimens (adjusted odds ratio [AOR] 2.03; 95% CI, 2.06–3.89) that was not seen with spontaneous preterm birth. Boosted PI regimens were also associated with both medical and obstetrical complications, raising the possibility that the association with induced preterm delivery was mediated through these complications.

A secondary analyses of data collected during a randomized, controlled clinical trial conducted in Botswana in women with CD4 T-lymphocyte counts >200 cells/mm^3—267 randomized to receive lopinavir/ritonavir/zidovudine/lamivudine (PI group) and 263 randomized to receive abacavir/zidovudine/lamivudine (NRTI group) begun between 26 and 34 weeks' gestation for prevention of mother-to-child transmission and not for maternal health indications—did show an association between PI-containing ARV regimens and preterm delivery. In logistic regression analysis, use of combination PI-based ARV regimens was the most significant risk factor for preterm delivery (OR 2.03; 95% CI, 1.26–3.27).[19] Those receiving the latest initiation of ARV drugs had the highest preterm delivery rates. However the 20% background rate for preterm delivery in this population was not different from that seen in the PI group, and there was no difference between the 2 groups in neonatal morbidity and mortality. An observational study also from Botswana found that use of combination ARV regimens from before conception was not associated with very preterm delivery (AOR 0.78), which could not be assessed in the controlled clinical trial.[20]

Clinicians should be aware of a possible increased risk of preterm birth with use of combination ARV drug regimens; however, given the clear benefits for maternal health and reduction in perinatal transmission, these agents should not be withheld because of the possibility of increased risk of preterm delivery. Until more information is known, HIV-infected pregnant women who are receiving combination regimens for treatment of their HIV infection should continue their provider-recommended regimens. They should receive careful, regular monitoring for pregnancy complications and for potential toxicities.

Table 7. Results of Studies Assessing Association Between Antiretroviral Regimens and Preterm Delivery (page 1 of 3)

Study Location(s)/ Dates of Study/ Reference	Total Number of Pregnancies/ Total on ARV Drugs	Types of ARV Regimens Compared (Numbers)	Association Noted Between PI-Containing or Other Multi-ARV Regimens and PTD	Special Notes
European Collaborative + Swiss Mother and Child HIV Cohort Study 1986–2000[1]	3,920/896	Mono (573) Multi, no PI (215) PI-multi (108)	YES (compared with no ARV) Multi: 1.82 (1.13–2.92) PI-multi: 2.60 (1.43–4.7)	• Increase in PTD if ARV begun before pregnancy versus in third trimester
United States 1990–1998[3]	3,266/2,123	Mono (1,590) Multi (396) PI-multi (137)	NO (compared with mono) Multi: 0.95 (0.60–1.48) PI-multi: 1.45 (0.81–2.50)	• 7 prospective clinical studies
European Collaborative Study 1986–2004[2]	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 prepregnancy: 2.05 (1.43–2.95)	
United States 1990–2002[4]	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[21]	1,337/999	Mono (492) Multi (373) PI-multi (134)	YES (compared with other multi) PI-multi: 1.8 (1.1–3.03)	• PI-multi reserved for advanced disease, those who failed other multi-ARV regimens
Brazil, Argentina, Mexico, Bahamas 2002–2005[22]	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

Table 7. Results of Studies Assessing Association Between Antiretroviral Regimens and Preterm Delivery (page 2 of 3)

Study Location(s)/ Dates of Study/ Reference	Total Number of Pregnancies/ Total on ARV Drugs	Types of ARV Regimens Compared (Numbers)	Association Noted Between PI-Containing or Other Multi-ARV Regimens and PTD	Special Notes
Meta-analysis, Europe and United States 1986–2004[12]	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[7]	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
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 low birth weight decreased over time
United Kingdom, Ireland 1990–2005[5]	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)	
United States 2002–2007[16]	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

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Swiss Mother and Child HIV Cohort Study 1985–2007[13]	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 mono/dual with PTD compared with no ARV • No confounding by duration of ARV or maternal risk factors
Botswana 2006–2008[19]	530/530	Lopinavir/ritonavir +zidovudine +lamivudine (267) Abacavir +zidovudine +lamivudine (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 26–34 weeks for MTCT prevention • All CD4-cell counts >200 cells/mm^3
Botswana 2007–2010[20]	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 2000–2008[10]	803/739	Mono/dual (32) Multi-no PI (281) Multi-PI (426)	NO No association between ARV and PTD	• Greatest PTD risk if no antepartum ARV received
Spain 1986–2010[17]	519/371	Mono/dual NRTI (73) All multi (298) Multi-PI (178)	NO (compared with no ARV + mono/dual) • Spontaneous PTD not associated with multi-ARV or multi-PI before or during pregnancy	• Iatrogenic PTD associated with multi-ARV given in second half of pregnancy and prior PTD

Key to Abbreviations: ARV = antiretroviral, BMI = body mass index, dual = two ARV drugs, mono = single ARV drug, MTCT = mother-to-child transmission, multi = three or more ARV drugs, multi-PI = combination ARV with PI, NNRTI = non-nucleoside analogue reverse transcriptase inhibitor, NRTI = nucleoside analogue reverse transcriptase inhibitor, PI = protease inhibitor, PTD = preterm delivery

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