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Authors

Koss, Catherine A
Natureeba, Paul
Plenty, Albert
et al.

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Risk Factors for Preterm Birth among HIV-Infected Pregnant Ugandan Women Randomized to Lopinavir/ritonavir- or Efavirenz-based Antiretroviral Therapy

Catherine A. Koss, M.D.[1,2], **Paul Natureeba, M.B.Ch.B.**[2], **Albert Plenty, M.P.H.**[2,3], **Flavia Luwedde, M.B.Ch.B.**[2], **Julia Mwesigwa, M.B.Ch.B., M.Sc.**[2], **Veronica Ades, M.D.**[2,4], **Edwin D. Charlebois, M.P.H., Ph.D.**[2,3], **Tamara D. Clark, M.P.H.**[1,2], **Jane Achan, M.B.Ch.B., M.Med., Ph.D.**[2,5], **Theodore Ruel, M.D.**[2,6], **Bridget Nzarubara, M.B.Ch.B., M.Sc.**[2], **Moses R. Kamya, M.B.Ch.B., M.Med, M.P.H, Ph.D.**[2,7], **Diane V. Havlir, M.D.**[1,2], and **Deborah Cohan, M.D., M.P.H.**[2,8]

[1]HIV/AIDS Division, San Francisco General Hospital, University of California, San Francisco, San Francisco, CA, USA [2]Makerere University-University of California, San Francisco Research Collaboration, Kampala, Uganda [3]Center for AIDS Prevention Studies, University of California, San Francisco, San Francisco, CA, USA [4]Department of Obstetrics and Gynecology, New York University, New York, NY, USA [5]Department of Pediatrics, Makerere University College of Health Sciences, Kampala, Uganda [6]Division of Infectious Diseases, Department of Pediatrics, University of California, San Francisco, San Francisco, CA, USA [7]Department of Medicine, Makerere University College of Health Sciences, Kampala, Uganda [8]Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco, San Francisco, CA, USA

Abstract

Background—Protease inhibitor-based antiretroviral therapy (ART) has been associated with preterm birth in some studies. We examined risk factors for preterm birth among women randomized to lopinavir/ritonavir- or efavirenz-based ART.

Methods—This was a planned secondary analysis of the PROMOTE-Pregnant Women and Infants Study, an open-label, randomized controlled trial comparing the risk of placental malaria among HIV-infected, ART-naïve pregnant Ugandan women assigned to initiate lopinavir/ritonavir- or efavirenz-based ART at 12 to 28 weeks gestation. Gestational age was determined

Corresponding Author: Catherine A. Koss, M.D., HIV/AIDS Division, San Francisco General Hospital, University of California, San Francisco, Box 0874, San Francisco, CA 94110, catherine.koss@ucsf.edu, Tel +1 415 476 4082, ext. 441, Fax +1 415 502 2992.
Request for Reprints: Same as Catherine A. Koss, M.D., HIV/AIDS Division, San Francisco General Hospital, University of California, San Francisco, Box 0874, San Francisco, CA 94110, catherine.koss@ucsf.edu, Tel +1 415 476 4082, ext. 441, Fax +1 415 502 2992.

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Authorship:
D.C., D.V.H, E.D.C., and M.R.K. designed the study. P.N., F.L., J.M., V.A., B.N., and T.C. contributed significantly to the acquisition of data. C.A.K., A.P., E.D.C., M.R.K., D.V.H., and D.C. analyzed and interpreted the data. C.A.K. and D.V.H. authored the manuscript with input and important revisions from all authors, including P.N., A.P., F.L., J.M., V.A., E.D.C., T.D.C., J.A., T.R., B.N., M.R.K., and D.C.

based on last menstrual period and ultrasound biometry. All women received bednets and trimethoprim-sulfamethoxazole. Stillbirths, spontaneous abortions, and multiple gestations were excluded from the primary analysis. Potential risk factors for preterm birth (<37 weeks gestation) were evaluated by univariate and multivariate logistic regression.

Results—356 women were included in this analysis. At enrollment, median gestational age was 21 weeks, median CD4 cell count was 368 cells/mm^3. 14.7% of deliveries in the efavirenz arm and 16.2% in the lopinavir/ritonavir arm were preterm. Preterm birth was associated with gestational weight gain below 0.1 kg/week versus 0.1 kg/week or more (OR = 2.49, 95% CI: 1.38–4.47, p = 0.003). Neither ART regimen of lopinavir/ritonavir versus efavirenz (OR = 1.12, 95% CI: 0.63–2.00, p = 0.69) nor placental malaria (OR = 0.74, 95% CI: 0.38–1.44, p = 0.37) was associated with preterm birth.

Conclusions—Lopinavir/ritonavir was not associated with an increased risk of preterm birth compared to efavirenz. However, interventions are needed to address modifiable risk factors for preterm birth, such as nutritional status. (ClinicalTrials.gov, NCT00993031.)

Keywords

Antiretroviral therapy; highly active; HIV; nutrition during pregnancy; premature birth; prevention of mother-to-child transmission; protease inhibitors

INTRODUCTION

Combination antiretroviral therapy (ART) is now recommended for all HIV-infected pregnant and breastfeeding women, regardless of CD4 cell count, for the prevention of mother-to-child transmission (PMTCT) of HIV.[1] This strategy is also expected to improve women's health and reduce transmission to their partners, particularly if therapy is continued for life.[2] With the global scale-up of HIV treatment, large numbers of pregnant women will be starting ART in resource-limited settings. Several prior studies have shown a small, but significant, association between antiretroviral medications (ARVs),[3–11] particularly protease inhibitors (PIs),[12–16] and preterm birth, while others have not.[17–19] Preterm birth is the leading cause of neonatal deaths worldwide and is a major cause of developmental disability in surviving children.[20] The care of premature infants poses a significant challenge to the existing health care infrastructure in resource-limited settings. In Uganda, the preterm birth rate in the general population ranks 29th in the world at 13.6%, compared to the global preterm birth rate of 11.1%.[20,21] Additional studies are needed to evaluate possible risk factors for preterm birth, including ARVs.

Previous observational studies, mainly conducted in Europe and North America, have generated conflicting results regarding the potential association between ARVs and preterm birth. Several studies have shown an increased risk of preterm birth with ART use compared to no ARV exposure or ARV monotherapy or dual therapy,[3–11] with some studies showing an association specifically with PIs,[12–16] while other studies have not demonstrated this association.[17–19] Data from Africa are also conflicting. The Mma Bana study, a randomized controlled trial in Botswana, found an increased risk of preterm birth with lopinavir/ritonavir (LPV/r)-based ART compared to a triple NRTI ART regimen.[22,23] In contrast, the Kesho

Bora study, which randomized women in Burkina Faso, Kenya, and South Africa to LPV/r-based triple ARV prophylaxis versus zidovudine plus single-dose nevirapine (sdNVP), did not find a difference in rates of preterm birth.[24]

As more HIV-infected pregnant women initiate and continue ART in resource-limited settings, it will be critical to understand risk factors for preterm birth in this population. We sought to evaluate potential risk factors for preterm birth, including ART exposure, among HIV-infected pregnant women at any CD4 cell count who were randomized to receive LPV/r- or EFV-based ART.

METHODS

Study Design and Population

We conducted a planned secondary analysis of preterm birth in the PROMOTE-Pregnant Women and Infants Study (ClinicalTrials.gov, NCT00993031). This was an open-label, single-site, randomized trial comparing the risk of placental malaria among HIV-infected, ART-naïve pregnant Ugandan women who were randomized at study enrollment to start LPV/r- or EFV-based ART at 12 to 28 weeks gestation. Women were assigned to a treatment arm and started ART on the date of enrollment. Results of the primary study endpoint (placental malaria) have been described previously.[25]

The study was conducted at Tororo District Hospital (TDH) in rural eastern Uganda. Women were recruited from the TDH antenatal clinic and HIV testing service, the AIDS Support Organization (an HIV clinic in Tororo), and other health centers in the surrounding area. Eligible women were at least 16 years old, infected with HIV-1 with confirmation by two assays, and lived within 30 kilometers of the study site. Participants had either never received ART or had received sdNVP or other abbreviated monotherapy or dual therapy for PMTCT more than 24 months prior to enrollment. Women were eligible for enrollment at any CD4 cell count. Women were excluded if they had prior dose-limited toxicity to trimethoprim-sulfamethoxazole (TS) within 14 days, active tuberculosis or other WHO Stage 4 disease, cardiac disease, or abnormal laboratory values including hemoglobin <7.5 g/dL, absolute neutrophil count <750 cells/mm^3, platelet count <50,000 cells/mm^3, ALT >225 U/L, AST >225 U/L, total bilirubin ≥2.5 times the upper limit of the normal range (ULN), and creatinine ≥1.8 times ULN.

All participants provided written informed consent in their preferred language. The study protocol was approved by the Makerere University Faculty of Medicine's Research and Ethics Committee, the Ugandan National Council of Science and Technology, and the Committee on Human Research at the University of California, San Francisco.

Study Procedures

At enrollment, all women underwent a history and physical examination and collection of baseline laboratory studies. All women received daily TS and insecticide-treated bednets. Women were also given a basic care package including a safe water vessel, multivitamins, and condoms. Antepartum study visits occurred every 4 weeks until delivery and as needed for any adverse events or health conditions requiring evaluation. Women were encouraged

to deliver at Tororo District Hospital. Socioeconomic status was assessed by performing principal component analysis of questions regarding household possessions, as previously described.[26]

Gestational age at enrollment was determined based on last menstrual period (LMP) and ultrasound measurement of biparietal diameter, head circumference, abdominal circumference, and femur length. Estimated gestational age was based on LMP if the ultrasound was concordant within 7 days prior to 13 weeks gestation, 14 days at 13 to 24 weeks gestation, and 21 days at 25 or more weeks gestation, and was based on ultrasound if LMP and ultrasound did not concur.

Enrollment was stratified at study entry by gravidity (gravida 1 versus gravida 2 or higher) and gestational age at the time of enrollment (less than 24 weeks versus 24 or more weeks). Randomization was performed in permuted blocks of 2 or 4. Participants were randomized 1:1 to receive LPV/r plus lamivudine/zidovudine or EFV plus lamivudine/zidovudine. Women received two tablets of lopinavir/ritonavir 200 mg/50 mg twice daily; the dose was increased to three tablets twice daily from 30 weeks gestation until delivery, then reduced to two tablets twice daily. The dose of EFV was 600 mg daily. Women in both arms received lamivudine/zidovudine 150 mg/300 mg twice daily. AbbVie Pharmaceuticals (North Chicago, Illinois) provided LPV/r (Aluvia) for study participants.

Outcomes

The primary outcome of interest for this analysis was preterm birth, defined as less than 37 weeks gestation. Stillbirths and spontaneous abortions were excluded from the analysis of the primary outcome. Secondary outcomes included very preterm birth (less than 32 weeks gestation) and a composite outcome of preterm birth, stillbirth, and spontaneous abortion. Multiple gestations were excluded from all analyses.

Statistical Analysis

Baseline characteristics of enrolled patients were compared using the χ^2 or Fisher exact test for categorical variables or the Wilcoxon rank-sum test for continuous variables. We used univariate and multivariate logistic regression modeling to evaluate potential risk factors for preterm birth. The multivariate analysis included potential risk factors that were unevenly distributed between study arms at baseline ($p < 0.10$) or associated with preterm birth on univariate analysis ($p < 0.10$). Given prior studies suggesting an association between preterm birth with use of protease inhibitors, ART regimen was also included in the multivariate model.[12–16] Weekly gestational weight gain was defined as the change in weight from study enrollment until the last antenatal weight measurement prior to delivery, divided by the time from enrollment until that visit. In addition, weight gain within the first 28 days after enrollment was evaluated. This analysis excluded one woman with fewer than 28 days of follow-up prior to delivery. Statistical analysis was performed using Stata software, version 13 (College Station, Texas).

RESULTS

Study Participants

From December 2009 through September 2012, a total of 391 patients were enrolled and randomized to a study arm; two were later found to be ineligible for the study, leaving a total of 389 eligible patients who were enrolled (Figure 1). Analysis of the primary outcome included a total of 356 women who delivered live-born singleton infants; 177 women had been assigned to EFV and 179 women had been assigned to LPV/r. Baseline demographic and clinical characteristics were similar between the ART randomization arms (Table 1), with the exception of time since HIV diagnosis, with more women in the EFV arm than the LPV/r arm diagnosed with HIV in the 3 years prior to enrollment ($p = 0.011$). Although time since HIV diagnosis was correlated with previous use of TS, the proportion of women taking TS prior to enrollment was similar in each study arm (64.4% in the EFV arm and 62.6% in the LPV/r arm). Median maternal age was 30 years (IQR 26–33) in the EFV arm and 29 years (IQR 25–33) in the LPV/r arm. Median CD4 cell count was 369 cells/mm^3 (IQR 271–487) in the EFV arm and 368 cells/mm^3 (IQR 281–510) in the LPV/r arm.

All women underwent ultrasound confirmation of dating. Gestational age was determined by LMP for the one woman enrolled before 13 weeks gestation, for 152 of 268 (56.7%) women enrolled at 13 to 24 weeks, and for 55 of 87 (63.2%) women enrolled at 25 to 28 weeks. Median gestational age at enrollment was 21 weeks in each study arm. Fifty-seven women in the EFV arm and 58 women in the LPV/r arm enrolled between 24 and 28 weeks gestation.

Gestational Age at Delivery and Relationship of ART to Preterm Birth

Most women delivered between 36 and 41 weeks gestation, with a similar distribution among women taking EFV and LPV/r (Figure 2). Median gestational age at delivery was 39.1 weeks (IQR 37.9–40.4) in the EFV arm and 38.6 weeks (IQR 37.3–39.9) in the LPV/r arm. The prevalence of preterm birth was 15.4% among all live-born singleton infants. In the EFV arm, 26 (14.7%) women delivered preterm, while in the LPV/r arm, 29 (16.2%) women delivered preterm. In total, 19 infants were delivered by cesarean section. Five preterm deliveries (three in the EFV arm and two in the LPV/r arm) were cesarean deliveries; the remaining preterm deliveries were spontaneous.

Univariate Analysis of Potential Risk Factors for Preterm Birth

Women who gained less than 0.1 kilogram (kg) per week during the study period versus 0.1 kg or more per week had higher odds of preterm birth (OR = 2.49, 95% CI: 1.38–4.47, $p = 0.003$), (Table 2). The odds ratio for the association between weight gain within 28 days of enrollment and preterm birth was 0.84 (95% CI 0.74–1.00, $p = 0.055$). In addition, gestational age of 24 to 28 weeks at ART initiation was associated with higher odds of preterm birth than ART initiation at 12 to 23 weeks gestation (OR = 1.95, 95% CI: 1.09–3.51, $p = 0.03$). Neither ART regimen of LPV/r versus EFV (OR = 1.12, 95% CI: 0.63–2.00, $p = 0.69$) nor placental malaria by histopathology was associated with preterm birth (OR = 0.74, 95% CI: 0.38–1.44, $p = 0.37$). There was no association between preterm birth and

maternal age, socioeconomic status, gravidity, baseline CD4 cell count, baseline HIV-1 RNA, or anemia.

Multivariate Analysis of Potential Risk Factors for Preterm Birth

In multivariate analysis, maternal gestational weight gain remained significantly associated with preterm birth (aOR 2.37, 95% CI: 1.29–4.36, p = 0.006) after adjustment for time since HIV diagnosis (which was unevenly distributed between study arms at baseline) and ART regimen. A trend remained toward higher odds of preterm birth with gestational age at ART initiation of 24 to 28 weeks versus 12 to 23 weeks; however, this was no longer statistically significant in the multivariate model (aOR 1.76, 95% CI 0.96–3.23, p = 0.07).

Secondary Outcomes

Three infants in each arm (1.7%) were born very preterm. Among all singleton deliveries, 32 of 183 (17.5%) in the EFV arm and 34 of 184 (18.5%) in the LPV/r arm met the criteria for the composite outcome of preterm birth, stillbirth, or spontaneous abortion, with no significant difference between study arms (p = 0.81).

DISCUSSION

Our study found no difference in rates of preterm birth among HIV-infected pregnant women randomized to receive lopinavir/ritonavir- versus efavirenz-based ART. We did find an increased risk of preterm birth for women who experienced gestational weight gain of less than 0.1 kg per week during the study period. There was a trend toward an increased risk of preterm birth among women starting ART at 24 to 28 weeks gestation versus 12 to 23 weeks gestation. Placental malaria was not associated with preterm birth.

One of the important questions this study addresses is the risk of preterm birth among HIV-infected pregnant women initiating PI- versus NNRTI-based ART. A proposed mechanism for ART leading to an increased risk of preterm birth is that ART may alter Th1 and Th2 cytokine responses.[27] During pregnancy, as well as with progressive HIV infection, there is a decrease in Th1 and an increase in Th2 cytokine responses. Fiore and colleagues have hypothesized that ART reverses the normal Th1 to Th2 shift in cytokine response in pregnancy and thus may contribute to preterm delivery.

Prior observational studies have shown conflicting results with regard to the risk of preterm birth with ART, with some studies showing an increased risk with ART[3–11] or specifically PIs,[12–16] and other studies showing no increased risk.[17–19] A meta-analysis of European and American studies conducted prior to 2004 did not show an association between overall use of ART and preterm birth; however, there was a small, but significant, increased risk with PI use.[28] In a more recent multi-center US cohort, after adjusting for confounding by ART indication and controlling for baseline CD4 cell count, HIV-1 RNA, and stage of disease, there was no association between PIs and preterm birth.[29]

The randomized design of PROMOTE permitted us to address the question of the association between PIs and the risk of preterm birth without the bias that may occur in observational studies. To our knowledge, only two other randomized trials have been

published in which HIV-infected pregnant women were randomized to receive combination ART or triple ARV prophylaxis.[22–24] It is interesting that our results contrast with those of the Mma Bana study, which found an increased rate of preterm birth among women on LPV/r-based ART (21.4%) compared to triple NRTI ART (11.8%).[22] One notable distinction between the Mma Bana study and PROMOTE is the difference in gestational age at ART initiation. In PROMOTE, women started ART at a gestational age as early as 12 weeks and at a median of 21 weeks, while in the Mma Bana study, the gestational age at ART initiation was 26 to 34 weeks. In addition, the comparison treatment arms were different, with EFV-based ART used in PROMOTE and triple NRTI ART used in Mma Bana. The possibility cannot be excluded that both EFV and LPV/r increase the risk of preterm birth while triple NRTI ART does not, thus accounting for the lack of difference in PROMOTE and an increased risk with LPV/r in Mma Bana. In addition, HIV-infected pregnant women in PROMOTE received TS prophylaxis, which has been associated with a reduced risk of preterm delivery among HIV-infected pregnant women with CD4 cell counts <200 cells/mm^3.[30] Similar to our findings, and in contrast to Mma Bana, the Kesho Bora study did not show a difference in rates of preterm birth with LPV/r-based triple ARV prophylaxis (13%) versus zidovudine and sdNVP (11%); however, these findings may have been limited by the later timing of ARV initiation of 28 to 36 weeks gestation.[24] For the first 19 of 39 months of the Kesho Bora Study, women were randomized to initiate an ARV regimen at 34 weeks gestation; after a protocol change, women started ARVs as early as 28 weeks gestation.

In our study, maternal gestational weight gain of less than 0.1 kg per week was associated with an increased risk of preterm birth. This association remained significant with examination of gestational weight gain as a continuous variable and on multivariate analysis. In additional analyses, gestational weight gain was not associated with age, education level, socioeconomic status, CD4 cell count, viral load at enrollment, clinical malaria, placental malaria, opportunistic infections, or sexually transmitted infections. The poor gestational weight gain among many women in the study is striking. The median weekly weight gain during the study period was 0.19 kg, well below the 0.4 to 0.5 kg per week gestational weight gain recommended by the Institute of Medicine for women with normal pre-pregnancy BMI, although specific guidelines have not been developed for women in East Africa.[31] Furthermore, nearly one fifth of women gained no weight during the study period. These results expand on our prior finding that gestational weight gain was associated with low infant birth weight and adverse birth outcomes.[26] These findings are also consistent with those from a prior study of both HIV-infected and HIV-uninfected women in Malawi, in whom gestational weight gain was protective against preterm birth.[32] Of note, established measures of gestational weight gain may be subject to bias associated with duration of follow-up time.[33] We have attempted to mitigate this by evaluating weight gain within 4 weeks of study enrollment. However, this approach also may not fully reflect weight change over the duration of our study, in which nearly half of women who either lost weight or did not gain weight during pregnancy initially gained weight in the first month of the study. Our findings suggest that maternal nutritional status may be a modifiable risk factor for preterm birth in HIV-infected women, even those who are receiving ART.

Infection with *P. falciparum* during pregnancy has also been associated with adverse maternal and infant outcomes, including preterm birth, low birth weight, and infant mortality, with the highest risk of placental malaria occurring among primigravid women.[34] HIV-infected women have impaired immune responses to malaria, placing them and their children at increased risk of complications from malaria.[35,36] In contrast to prior studies, we did not detect an increased risk of preterm birth among women with placental malaria.[34,37] Rates of placental malaria detected by histology in our study may have been lower overall because all subjects received TS, which confers protection against malaria, and because of the high proportion of multigravid women (over 80% were gravida 3 or higher).[38] In addition, most women in our study (96%) had WHO stage 1 HIV disease and thus may have had relatively preserved immune responses to malaria compared to prior studies in patients with advanced HIV.

We also found a higher risk of preterm birth on univariate analysis among women starting ART later in pregnancy, at 24 to 28 weeks gestation versus 12 to 23 weeks gestation. After adjustment for weight gain and in examining gestational age at ART initiation as a continuous variable, this remained a trend but was no longer statistically significant. Prior studies have shown conflicting results with regard to the impact of the timing of ART initiation on preterm birth. Several observational studies have demonstrated an association between preterm birth and continuation of preconception ART or ART exposure in the first trimester compared to later in pregnancy, though timing of ART initiation was variable among studies.[11,28,39] In contrast, other studies found an increased risk of preterm birth among women starting ART during pregnancy compared to women continuing preconception ART.[7,40] One of the few studies examining this question in Africa, a surveillance study of six hospitals in Botswana, found no difference in preterm birth with initiation of ART before 32 weeks versus after 32 weeks gestation, with most women receiving nevirapine-based ART.[3] The authors did note an increased risk of preterm birth among women taking combination ART prior to conception compared to all other HIV-infected women, and among women initiating combination ART during pregnancy compared to those initiating zidovudine monotherapy.

The main strengths of our study include its randomized design and ultrasound dating. Use of ultrasound improves the accuracy of measurements of gestational age, thereby reducing misclassification of preterm versus term deliveries and preterm infants versus those who are small for gestational age. In addition, we enrolled women as early as 12 weeks gestation and at any CD4 cell count, improving generalizability. One of the ART regimens included efavirenz, which is considered first-line for all HIV-infected adults, including pregnant women, per 2013 WHO Consolidated Guidelines.[1] Limitations of our study include that it was a planned secondary analysis and may not have detected a small increase in the risk of preterm birth. We also did not have information for many of the patients on substance abuse, a known risk factor for preterm birth, though based on interviews with a number of our study subjects, we believe that the prevalence of substance abuse was low.

Our study adds to the limited but growing body of literature on randomized trials of ART use in HIV-infected pregnant women. In contrast to prior studies, we did not find an increased risk of preterm birth with lopinavir/ritonavir-based ART. These findings support

the use of lopinavir/ritonavir as an option for the treatment of HIV-infected pregnant women. However, preterm birth remains a significant public health problem and interventions are needed to address modifiable risk factors for preterm birth, such as nutritional status, among HIV-infected pregnant women, including those on ART.

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REFERENCES

1. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva, Switzerland: World Health Organization; 2013.
2. Schouten EJ, Jahn A, Midiani D, et al. Prevention of mother-to-child transmission of HIV and the health-related Millennium Development Goals: time for a public health approach. Lancet. 2011; 378:282–284. [PubMed: 21763940]
3. Chen JY, Ribaudo HJ, Souda S, et al. Highly active antiretroviral therapy and adverse birth outcomes among HIV-infected women in Botswana. J Infect Dis. 2012; 206:1695–1705. [PubMed: 23066160]
4. Lopez M, Figueras F, Hernandez S, et al. Association of HIV infection with spontaneous and iatrogenic preterm delivery: effect of HAART. AIDS. 2012; 26:37–43. [PubMed: 22008651]
5. Lorenzi P, Spicher VM, Laubereau B, et al. Antiretroviral therapies in pregnancy: maternal, fetal and neonatal effects. Swiss HIV Cohort Study, the Swiss Collaborative HIV and Pregnancy Study, and the Swiss Neonatal HIV Study. AIDS. 1998; 12:F241–F247. [PubMed: 9875571]
6. Rudin C, Spaenhauer A, Keiser O, et al. Antiretroviral therapy during pregnancy and premature birth: analysis of Swiss data. HIV Med. 2011; 12:228–235. [PubMed: 20726902]
7. Short CE, Douglas M, Smith J, Taylor G. Preterm delivery risk in women initiating antiretroviral therapy to prevent HIV mother-to-child transmission. HIV Med. 2014; 15:233–238. [PubMed: 24025074]
8. Sibiude J, Warszawski J, Tubiana R, et al. Premature delivery in HIV-infected women starting protease inhibitor therapy during pregnancy: role of the ritonavir boost? Clin Infect Dis. 2012; 54:1348–1360. [PubMed: 22460969]
9. Thorne C, Patel D, Newell ML. Increased risk of adverse pregnancy outcomes in HIV-infected women treated with highly active antiretroviral therapy in Europe. AIDS. 2004; 18:2337–2339. [PubMed: 15577551]
10. Townsend CL, Cortina-Borja M, Peckham CS, Tookey PA. Antiretroviral therapy and premature delivery in diagnosed HIV-infected women in the United Kingdom and Ireland. AIDS. 2007; 21:1019–1026. [PubMed: 17457096]
11. Watts DH, Williams PL, Kacanek D, et al. Combination antiretroviral use and preterm birth. Journal of Infectious Diseases. 2013; 207:612–621. [PubMed: 23204173]
12. Cotter AM, Garcia AG, Duthely ML, Luke B, O'Sullivan MJ. Is antiretroviral therapy during pregnancy associated with an increased risk of preterm delivery, low birth weight, or stillbirth? J Infect Dis. 2006; 193:1195–1201. [PubMed: 16586354]
13. European Collaborative Study. Swiss Mother + Child HIV Cohort Study. Combination antiretroviral therapy and duration of pregnancy. AIDS. 2000; 14:2913–2920. [PubMed: 11398741]

14. Grosch-Woerner I, Puch K, Maier RF, et al. Increased rate of prematurity associated with antenatal antiretroviral therapy in a German/Austrian cohort of HIV-1-infected women. HIV Med. 2008; 9:6–13. [PubMed: 18199167]
15. Ravizza M, Martinelli P, Bucceri A, et al. Treatment with protease inhibitors and coinfection with hepatitis C virus are independent predictors of preterm delivery in HIV-infected pregnant women. J Infect Dis. 2007; 195:913–914. author reply 916–917. [PubMed: 17299723]
16. Schulte J, Dominguez K, Sukalac T, Bohannon B, Fowler MG. Declines in low birth weight and preterm birth among infants who were born to HIV-infected women during an era of increased use of maternal antiretroviral drugs: Pediatric Spectrum of HIV Disease, 1989–2004. Pediatrics. 2007; 119:e900–e906. [PubMed: 17353299]
17. Szyld EG, Warley EM, Freimanis L, et al. Maternal antiretroviral drugs during pregnancy and infant low birth weight and preterm birth. AIDS. 2006; 20:2345–2353. [PubMed: 17117021]
18. Tuomala RE, Shapiro DE, Mofenson LM, et al. Antiretroviral therapy during pregnancy and the risk of an adverse outcome. N Engl J Med. 2002; 346:1863–1870. [PubMed: 12063370]
19. Tuomala RE, Watts DH, Li D, et al. Improved obstetric outcomes and few maternal toxicities are associated with antiretroviral therapy, including highly active antiretroviral therapy during pregnancy. J Acquir Immune Defic Syndr. 2005; 38:449–473. [PubMed: 15764963]
20. World Health Organization. Born too soon: the global action report on preterm birth. Geneva: World Health Organization; 2012.
21. Blencowe H, Cousens S, Oestergaard MZ, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet. 2012; 379:2162–2172. [PubMed: 22682464]
22. Powis KM, Kitch D, Ogwu A, et al. Increased risk of preterm delivery among HIV-infected women randomized to protease versus nucleoside reverse transcriptase inhibitor-based HAART during pregnancy. J Infect Dis. 2011; 204:506–514. [PubMed: 21791651]
23. Shapiro RL, Hughes MD, Ogwu A, et al. Antiretroviral regimens in pregnancy and breast-feeding in Botswana. N Engl J Med. 2010; 362:2282–2294. [PubMed: 20554983]
24. Kesho Bora Study Group. de Vincenzi I. Triple antiretroviral compared with zidovudine and single-dose nevirapine prophylaxis during pregnancy and breastfeeding for prevention of mother-to-child transmission of HIV-1 (Kesho Bora study): a randomised controlled trial. Lancet Infect Dis. 2011; 11:171–180. [PubMed: 21237718]
25. Natureeba, P. Protease inhibitors and placental malaria in HIV-infected pregnant women in rural Uganda. Washington, D.C.: American Society of Tropical Medicine and Hygiene; 2013.
26. Young S, Murray K, Mwesigwa J, et al. Maternal nutritional status predicts adverse birth outcomes among HIV-infected rural Ugandan women receiving combination antiretroviral therapy. PLoS One. 2012; 7:e41934. [PubMed: 22879899]
27. Fiore S, Newell ML, Trabattoni D, et al. Antiretroviral therapy-associated modulation of Th1 and Th2 immune responses in HIV-infected pregnant women. J Reprod Immunol. 2006; 70:143–150. [PubMed: 16423410]
28. Kourtis AP, Schmid CH, Jamieson DJ, Lau J. Use of antiretroviral therapy in pregnant HIV-infected women and the risk of premature delivery: a meta-analysis. AIDS. 2007; 21:607–615. [PubMed: 17314523]
29. Patel K, Shapiro DE, Brogly SB, et al. Prenatal protease inhibitor use and risk of preterm birth among HIV-infected women initiating antiretroviral drugs during pregnancy. J Infect Dis. 2010; 201:1035–1044. [PubMed: 20196654]
30. Walter J, Mwiya M, Scott N, et al. Reduction in preterm delivery and neonatal mortality after the introduction of antenatal cotrimoxazole prophylaxis among HIV-infected women with low CD4 cell counts. J Infect Dis. 2006; 194:1510–1518. [PubMed: 17083035]
31. Weight gain during pregnancy: reexamining the guidelines. Washington, DC: Institute of Medicine and National Research Council; 2009.
32. van den Broek NR, Jean-Baptiste R, Neilson JP. Factors associated with preterm, early preterm and late preterm birth in Malawi. PLoS One. 2014; 9:e90128. [PubMed: 24595186]

33. Hutcheon JA, Bodnar LM, Joseph KS, Abrams B, Simhan HN, Platt RW. The bias in current measures of gestational weight gain. Paediatr Perinat Epidemiol. 2012; 26:109–116. [PubMed: 22324496]

34. Desai M, ter Kuile FO, Nosten F, et al. Epidemiology and burden of malaria in pregnancy. Lancet Infect Dis. 2007; 7:93–104. [PubMed: 17251080]

35. Dembo EG, Mwapasa V, Montgomery J, et al. Impact of human immunodeficiency virus infection in pregnant women on variant-specific immunity to malaria. Clin Vaccine Immunol. 2008; 15:617–621. [PubMed: 18199738]

36. Mount AM, Mwapasa V, Elliott SR, et al. Impairment of humoral immunity to Plasmodium falciparum malaria in pregnancy by HIV infection. Lancet. 2004; 363:1860–1867. [PubMed: 15183624]

37. Steketee RW, Nahlen BL, Parise ME, Menendez C. The burden of malaria in pregnancy in malaria-endemic areas. Am J Trop Med Hyg. 2001; 64:28–35. [PubMed: 11425175]

38. Newman PM, Wanzira H, Tumwine G, et al. Placental malaria among HIV-infected and uninfected women receiving anti-folates in a high transmission area of Uganda. Malar J. 2009; 8:254. [PubMed: 19912657]

39. Boer K, Nellen JF, Patel D, et al. The AmRo study: pregnancy outcome in HIV-1-infected women under effective highly active antiretroviral therapy and a policy of vaginal delivery. BJOG. 2007; 114:148–155. [PubMed: 17305888]

40. Martin F, Taylor GP. Increased rates of preterm delivery are associated with the initiation of highly active antiretrovial therapy during pregnancy: a single-center cohort study. J Infect Dis. 2007; 196:558–561. [PubMed: 17624841]

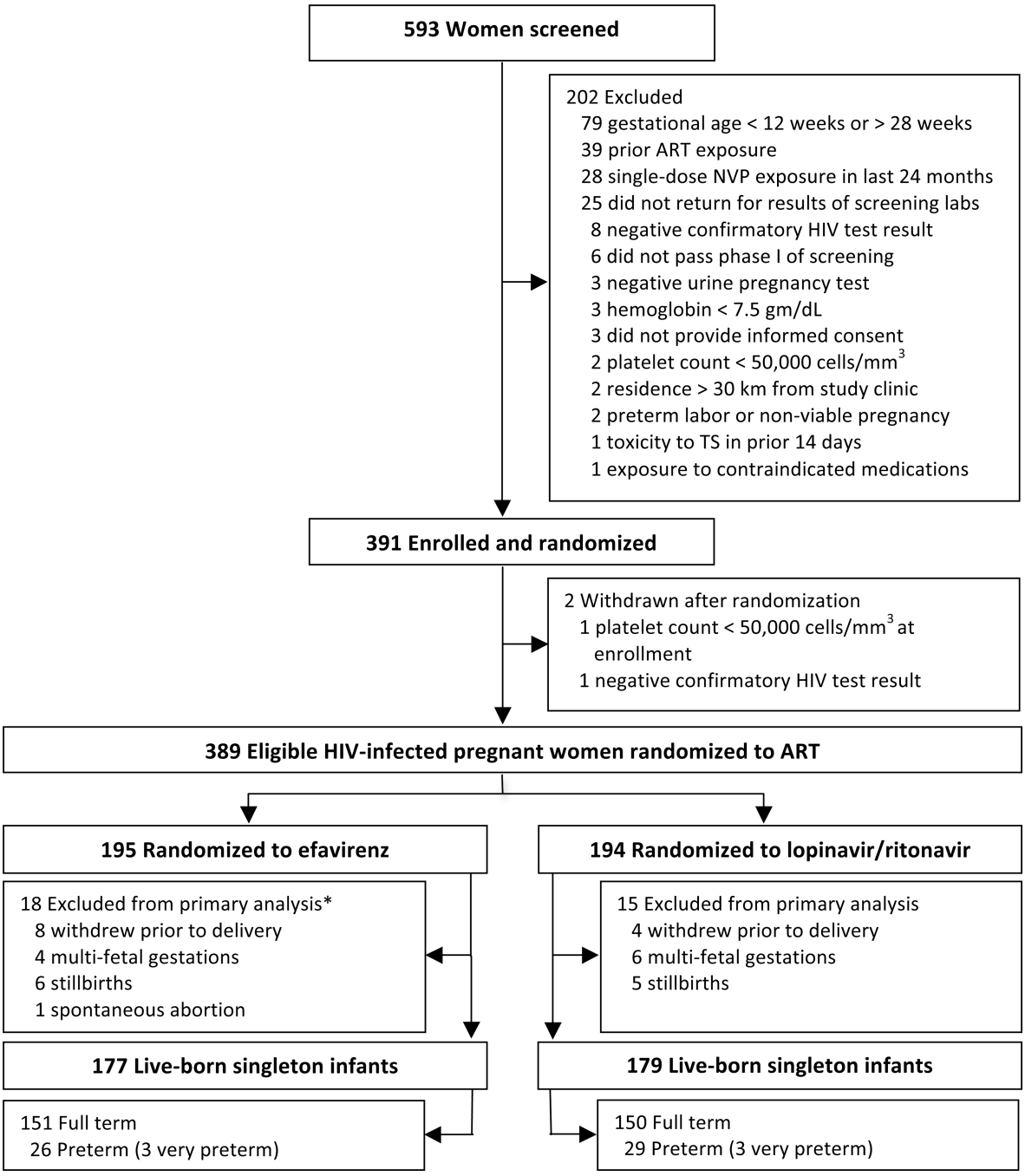

Figure 1. Screening, randomization, and follow-up of study patients

* One subject with multi-fetal gestation and stillbirth.

ART, antiretroviral therapy; NVP, nevirapine; TS, trimethoprim-sulfamethoxazole.

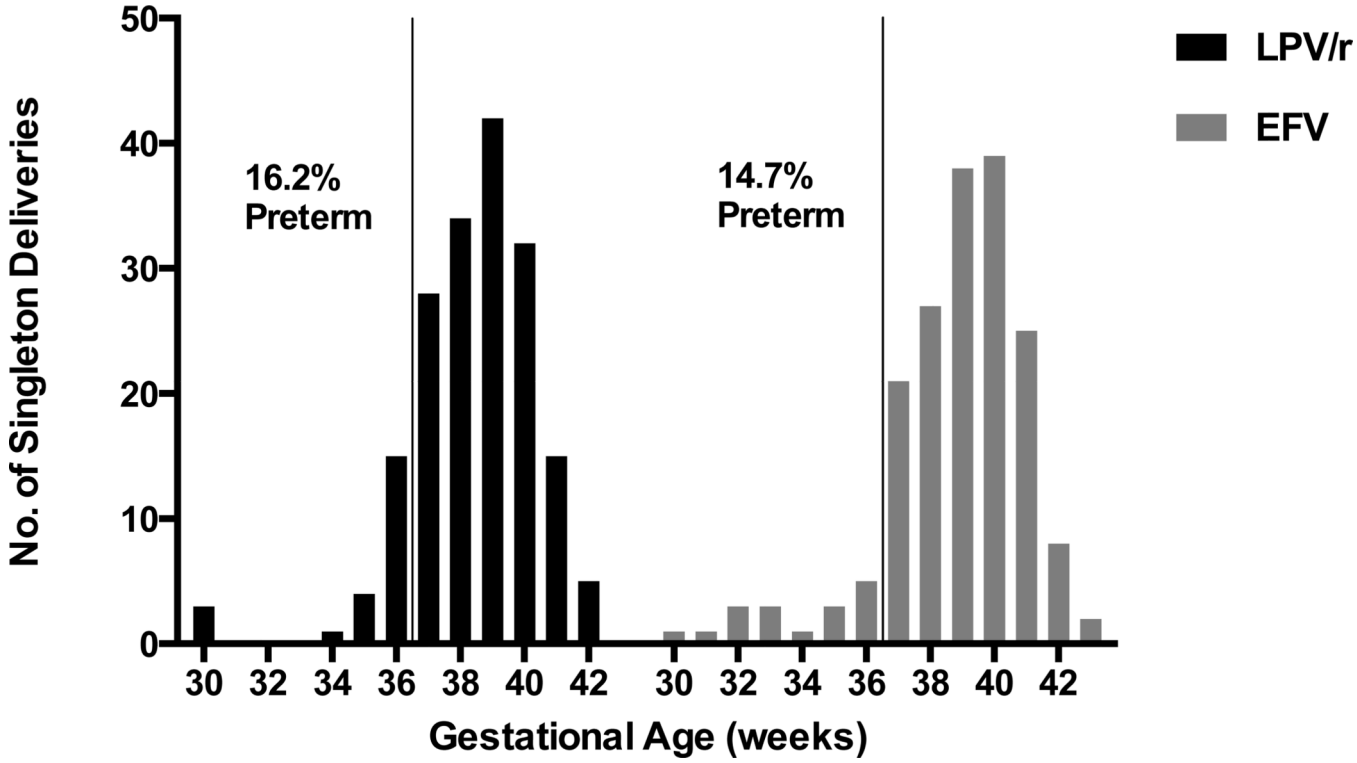

Figure 2. Distribution of gestational age at delivery

The vertical lines separate preterm and full term deliveries in each study arm.

EFV, efavirenz; LPV/r, lopinavir/ritonavir.

Table 1

Maternal characteristics at enrollment by ART treatment arm

Characteristic	Efavirenz (N = 177)	Lopinavir/ritonavir (N = 179)
Maternal age, years, median (IQR)	30 (26, 33)	29 (25, 33)
Education level, no. (%)		
None	24 (13.6)	24 (13.4)
Primary school	111 (62.7)	123 (68.7)
Secondary school or more	42 (23.7)	31 (17.3)
Socioeconomic status, no. (%)		
Low	79 (44.6)	93 (52.0)
Middle	46 (26.0)	41 (22.9)
High	38 (21.5)	37 (20.7)
Gravidity, median (IQR)	5 (3, 6)	5 (3, 6)
Prior preterm delivery, no. (%)	8 (4.5)	12 (6.7)
Gestational age, weeks, median (IQR)	21 (18, 24)	21 (17, 25)
Time since HIV diagnosis, no. (%) *		
<3 years	131 (74.0)	110 (61.5)
≥3 years	46 (26.0)	69 (38.6)
HIV diagnosis during index pregnancy, no. (%)	78 (44.1)	67 (37.4)
CD4 cell count, cells/mm^3, median (IQR)	369 (271, 487)	368 (281, 510)
HIV-1 RNA, $\log_{10}$ copies/ml, median (IQR)	4.31 (3.46, 4.86)	4.15 (3.38, 4.77)
Taking TS prophylaxis prior to enrollment, no. (%)	114 (64.4)	112 (62.6)
BMI, kg/m^2, no. (%)		
<20	52 (29.4)	36 (20.1)
20<23	78 (44.1)	89 (49.7)
≥23	45 (25.4)	52 (29.1)
Systolic blood pressure, mm Hg, median (IQR)	104 (100, 111)	107 (100, 112)
Anemia (Hb <11 g/dL), no. (%)	86 (48.6)	82 (45.8)

NOTE.

* p = 0.011. ART, antiretroviral therapy; IQR, interquartile range; TS, trimethoprim-sulfamethoxazole; BMI, body mass index; Hb, hemoglobin

Table 2

Univariate analysis of potential risk factors for preterm birth

Potential risk factor	Full term births n	Preterm births n (%)	OR (95% CI)	p
	301	55 (15.4)		
Maternal age				
<20 years	10	2 (16.6)	1.12 (0.21–5.89)	0.62
20–24 years	56	10 (15.2)	ref	
25–29 years	89	16 (15.2)	1.01 (0.43–2.37)	
30–34 years	90	21 (18.9)	1.31 (0.57–2.98)	
≥35 years	55	6 (9.8)	0.61 (0.21–1.80)	
Socioeconomic status				
Low	146	26 (15.1)	ref	0.41
Middle	70	17 (19.5)	1.36 (0.69–2.68)	
High	66	9 (12.0)	0.77 (0.34–1.72)	
Gravidity				
1	20	1 (5.0)	0.26 (0.03–2.11)	0.39
2 or 3	79	15 (16.0)	ref	
4 or 5	100	17 (14.5)	0.90 (0.42–1.90)	
≥6	102	22 (17.7)	1.14 (0.55–2.33)	
Prior preterm delivery				
No	284	52 (15.5)	ref	0.95
Yes	17	3 (15.0)	0.96 (0.27–3.41)	
Gestational age at ART initiation				
12–23 weeks	211	30 (12.4)	ref	0.03
24–28 weeks	90	25 (21.7)	1.95 (1.09–3.51)	
Time since HIV diagnosis				
<3 years	200	41 (17.0)	ref	0.23
≥3 years	101	14 (12.2)	0.68 (0.35–1.30)	
CD4 cell count at enrollment, cells/mm^3				
CD4 <200	39	11 (22.0)	1.68 (0.80–3.53)	0.19
CD4 ≥200	256	43 (14.4)	ref	
HIV-1 RNA at enrollment, copies/ml				
<1,000	46	8 (14.8)	ref	0.12
1,000<10,000	82	13 (13.7)	0.91 (0.35–2.36)	
10,000<100,000	110	28 (20.3)	1.46 (0.62–3.45)	
≥100,000	58	5 (7.9)	0.50 (0.15–1.62)	
ART regimen				
Efavirenz	151	26 (14.7)	ref	0.69
Lopinavir/ritonavir	150	29 (16.2)	1.12 (0.63–2.00)	
Maternal gestational weight gain				
<0.1 kg/week	83	27 (24.5)	2.49 (1.38–4.47)	0.003

Potential risk factor	Full term births n	Preterm births n (%)	OR (95% CI)	p
≥0.1 kg/week	214	28 (11.6)	ref	
Anemia (Hb <11 g/dL) at any antenatal visit				
No	176	32 (15.4)	ref	0.52
Yes	121	18 (12.9)	0.82 (0.44–1.52)	
Placental malaria by histopathology				
No	171	36 (17.4)	ref	0.37
Yes	90	14 (13.5)	0.74 (0.38–1.44)	

NOTE. OR, odds ratio; CI, confidence interval; ART, antiretroviral therapy; Hb, hemoglobin.