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Risk Factors for Preterm Birth in Pregnant Women Randomized to Lopinavir- or Efavirenz-based ART

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Background

- Preterm birth is a major cause of perinatal morbidity and mortality.
- 2013 World Health Organization Consolidated Guidelines recommend combination antiretroviral therapy (ART) for all HIV-infected pregnant and breastfeeding women.[1]
- There are conflicting data on the association between ART, particularly protease inhibitors, and preterm birth.[2-4]
- One randomized trial showed an increased risk of preterm birth with lopinavir/ritonavir-based vs. triple NRTI ART.[5]
- As more HIV-infected pregnant women start ART in resource-limited settings, it will be critical to understand potential risk factors for preterm birth, including ART.

Methods

Objective

- To evaluate potential risk factors for preterm birth, including ART, among HIV-infected pregnant women

Study Design

- Planned secondary analysis of the PROMOTE-Pregnant Women and Infants Study (NCT00993031)
- Open-label, randomized controlled trial comparing the risk of placental malaria among HIV-infected, ART-naïve pregnant Ugandan women randomized to lopinavir/ritonavir (LPV/r) or efavirenz (EFV) based ART[6]

Study Population

- Recruited from Tororo District Hospital and antenatal and HIV clinics in Tororo in rural eastern Uganda
- *Inclusion Criteria:* Age ≥16 years, 12-28 weeks gestation, living ≤30 km from study site
- *Exclusion Criteria:* ARV exposure within 24 months or prior ART, toxicity to trimethoprim-sulfamethoxazole (TS), active TB, WHO stage 4 condition, hemoglobin <7.5 g/dL, ANC <750 cells/mm^3, platelet count <50,000 cells/mm^3, ALT >225 U/L, AST >225 U/L, total bilirubin ≥2.5x ULN, creatinine ≥1.8x ULN

Methods (cont'd)

ART Regimens

- Randomized to LPV/r/AZT/3TC or EFV/AZT/3TC
- LPV/r dose was increased from 400/100 mg BID to 600/150 mg BID from 30 weeks gestation until delivery

Study Procedures and Ultrasound Dating

- All women given daily TS and insecticide-treated bednets
- Gestational age at enrollment was calculated by last menstrual period (LMP) and ultrasound biometry
- Estimated date of delivery was based on:
  - *LMP* if ultrasound concordant within 7, 14, and 21 days in the first, second, and third trimester
  - *Ultrasound* if LMP and ultrasound did not concur
- Placental malaria was evaluated by histopathology

Outcomes

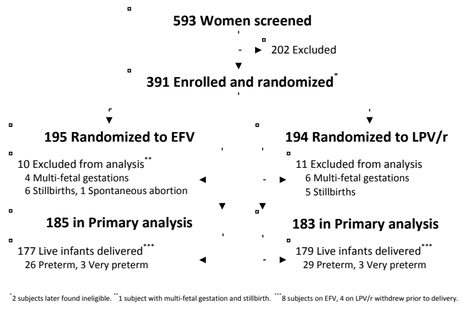
- Primary outcome:
  - *Preterm birth:* <37 weeks gestation
  - Stillbirths and spontaneous abortions excluded
- Secondary outcomes:
  - *Very preterm birth:* <32 weeks gestation
  - *Composite birth outcome:* Preterm birth, stillbirth, or spontaneous abortion
- Multiple gestations were excluded from all analyses

Statistical Analysis

- Univariate and multivariate Cox proportional-hazards modeling
- Censoring at study withdrawal or at 37 weeks for live births after 37 weeks gestation. Women contributed time until loss to follow-up or delivery up to 37 weeks.
- Multivariate analysis included ART regimen and potential risk factors unevenly distributed between study arms at baseline or with p<0.10 on univariate analysis.

Results

Screening, Randomization, and Follow-up



*2 subjects later found ineligible. **1 subject with multi-fetal gestation and stillbirth. ***8 subjects on EFV, 4 on LPV/r withdrew prior to delivery.

Characteristics of Pregnant Women at Enrollment

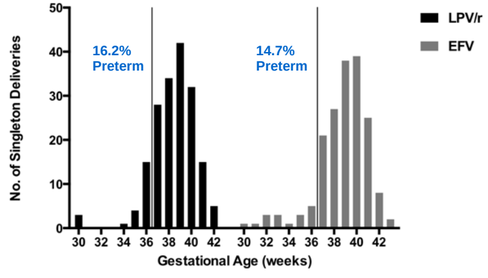
	EFV	LPV/r	p
Age years, median (IQR)	30 (26, 33)	29 (25, 33)	0.53
Gravidity median (IQR)	5 (3, 6)	5 (3, 6)	0.60
Prior preterm delivery no. (%)	11 (5.9)	12 (6.6)	0.81
Time since HIV diagnosis <3 years, no. (%) ≥3 years, no. (%)	 138 (74.6) 47 (25.4)	 114 (62.3) 69 (37.7)	 **0.01**
CD4 cell count cells/mm^3, median (IQR)	369 (269, 486)	375 (282, 510)	0.36
HIV-1 RNA $\log_{10}$ c/ml, median (IQR)	4.3 (3.5, 4.9)	4.1 (3.3, 4.8)	0.26
Taking TS prophylaxis prior to enrollment no. (%)	116 (62.7)	115 (62.8)	0.98
BMI, kg/m^2 <20, no. (%) 20<23, no. (%) ≥23, no. (%)	 54 (28.1) 81 (43.8) 48 (25.9)	 36 (19.7) 93 (50.8) 52 (28.4)	 0.10

Results (cont'd)

Univariate Analysis of Potential Risk Factors for Preterm Birth (N=368)

	Preterm n (%)	HR (95% CI)	p
ART regimen EFV LPV/r	 26 (14.7%) 29 (16.2%)	 ref 1.10 (0.65-1.88)	 0.70
Maternal gestational weight gain <0.1 kg/week ≥0.1 kg/week	 27 (24.5%) 28 (11.6%)	 **2.32 (1.37-3.94)** ref	 **0.002**
Gestational age at ART initiation 12-23 weeks 24-28 weeks	 30 (12.4%) 25 (21.7%)	 ref **1.85 (1.09-3.14)**	 **0.023**
CD4 cell count <200 cells/mm^3 ≥200 cells/mm^3	 11 (22.0%) 44 (14.4%)	 1.59 (0.82-3.07) ref	 0.19
Placental malaria No Yes	 36 (17.4%) 14 (13.5%)	 ref 0.75 (0.40-1.39)	 0.35

Distribution of Gestational Age at Delivery



Results (cont'd)

Multivariate Analysis

- After controlling for time since HIV diagnosis (unevenly distributed at baseline) and ART regimen:
  - Maternal gestational weight gain <0.1 kg/week vs. ≥0.1 kg/week remained significantly associated with preterm birth (aHR 2.21, 95% CI: 1.28-3.83, p = 0.005).
  - Trend toward increased risk of preterm birth with gestational age at ART initiation of 24-28 weeks vs. 12-23 weeks (aHR 1.69, 95% CI 0.97-2.87, p = 0.065).
  - LPV/r vs. EFV was not associated with preterm birth.

Secondary Outcomes

- 3 infants in each arm (1.7%) were born very preterm.
- 32/191 subjects (16.8%) on EFV vs. 34/188 (18.1%) on LPV/r experienced the composite birth outcome (p = 0.81).

Conclusions

- Lopinavir/ritonavir was not associated with an increased risk of preterm birth compared to efavirenz.
- Maternal gestational weight gain <0.1 kg/week vs. ≥0.1 kg/week was associated with preterm birth.
- Placental malaria was not associated with preterm birth.
- These findings support the use of lopinavir/ritonavir as an option for the treatment of HIV-infected pregnant women.
- 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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Acknowledgements

The authors thank the PROMOTE study participants, the study staff, and the practitioners at Tororo District Hospital. This work was supported by NIH/NICHD P01 HD059454 (D.H.) and NIH/NIAID T32 AI060530 (D.H./C.A.K.). AbbVie Pharmaceuticals donated lopinavir/ritonavir (Aluvia) for the parent trial.