Poster #776

Antenatal antiretroviral therapy and adverse birth outcomes: the PROMISE trial

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BACKGROUND

Several observational studies have shown an association between antiretroviral therapy (ART) in pregnancy and adverse birth outcomes, including preterm birth.

The PROMISE 1077BF/1077FF trials found that three-drug combination ART reduced mother-to-child HIV transmission to less than 1%. However, these combination antiretroviral regimens, taken during the antenatal period, also increased the frequency of adverse birth outcomes compared to antenatal zidovudine alone (Fowler, *NEJM* 2016).

This finding is concerning as national programs seek to expand universal ART for HIV-infected pregnant and breastfeeding women (i.e., Option B+). It is possible that the reductions in pediatric HIV infections could be offset by morbidity and mortality associated with preterm delivery and other birth complications.

In this secondary analysis, we studied the association between antiretroviral regimen during pregnancy and adverse birth outcomes in the context of this large randomized trial.

METHODS

The PROMISE 1077BF/1077FF trials were multi-center studies conducted at 14 sites in seven countries: India, Malawi, South Africa, Tanzania, Uganda, Zambia, and Zimbabwe.

PROMISE enrolled HIV-infected women who had CD4 cell counts ≥350 cells/mm^3, were not eligible for HIV treatment based on local country guidelines, were pregnant at ≥14 weeks gestation, and not in labor. Women who agreed to participate were randomized to receive either: (1) **Arm A:** ZDV only, (2) **Arm B:** ZDV + 3TC + LPV/r , and (3) **Arm C:** TDF + FTC + LPV/r.

All women were screened for active hepatitis B infection. In early version of the study, women with a negative HBsAg test were randomized to Arms A and B only. Women who tested HBsAg+ could be randomized to any of the three arms.

Beginning in October 2012, in version 3.0 of the protocol, participants were randomized with equal probability to all three study arms. This modification was made in response to evolving treatment guidelines for pregnant women, including greater acceptability of TDF use during the antenatal period.

We studied the association between antiretroviral regimen and several adverse birth outcomes (Table 1). Gestational age at delivery was estimated by Ballard score when available; otherwise, it was determined via obstetrical history and assessment.

We evaluated the effects of study treatment on the adverse pregnancy outcomes in logistic models adjusting for baseline factors and obstetrical complications, in order to determine whether the treatment effect might change in models which controlled for these potentially mediating factors.

Table 1: Definitions of study outcomes

Outcome	Definition
Preterm delivery (PTD)	Delivery <37 weeks gestation
Low birthweight (LBW)	Infant birth weight <2500 g
Composite outcome	PTD, LBW, stillbirth (infant death ≥20 wks gestation), spontaneous abortion (infant demise <20 wks gestation)
Very preterm delivery (VPTD)	Delivery <34 weeks gestation
Very low birthweight (VLBW)	Infant birth weight <1500 g
Severe composite outcome	VPTD, VLBW, stillbirth, spontaneous abortions

The primary analyses presented here include data from all participants. Variables included in these models were restricted to those with at least marginal associations (p<0.15 in univariate analyses) with one or more of the pregnancy outcomes listed above.

Alongside antiretroviral regimens, factors meeting the criteria for inclusion in the logistic models included: maternal age, BMI, baseline HIV viral load and CD4, alcohol use, country, gestational age at entry, multiple gestation, and number of prior premature births.

The following obstetrical complications were also included: abruptio placenta, chronic hypertension, pregnancy-induced hypertension, oligohydramnios, intrauterine growth restriction, premature labor, premature rupture of membranes, urinary tract infection, and vaginal bleeding.

In sensitivity analyses, we restricted data to only those enrolled in version 3.0 of the protocol to ensure that results were consistent with those observed on the full sample. The same controlling variables met criteria for inclusion (see above), with the exception of maternal age, baseline CD4, abruptio placenta, chronic hypertension, intrauterine growth restriction, and vaginal bleeding.

In our models, we encountered instances where valid coefficients for variables with relatively few events could not be estimated; however, inclusion of these variables provided a valid control for their effects in mediating the associations between treatment and outcomes.

RESULTS

From April 2011 to September 2014, 3529 HIV-infected pregnant women were enrolled into the PROMISE trial. In November 2014, the study's DSMB recommended that all participating sites be notified of the efficacy and safety data through day 14 postpartum. At the time, 3423 (97%) participants had delivered and were included in this analysis.

Overall, these 3423 participants were allocated to Arm A (n=1507), Arm B (n=1497), and Arm C (n= 419). The characteristics of participants in each study arm are shown in Table 2.

Table 2: Comparison of patient characteristics between study arms

	ZDV only (Arm A)	ZDV+3TC+LPV/r (Arm B)	TDF+FTC+ LPV/r (Arm C)
Age, median (Q1, Q3)	26 (22,30)	26 (23, 30)	26 (22,30)
CD4 count, median (Q1, Q3)	531 (433, 676)	526 (439, 650)	532 (432, 680)
WHO stage 1, n (%)	1454 (97%)	1459 (98%)	409 (98%)
Gestational age (weeks) at enrollment, median (Q1, Q3)	26 (21, 30)	25 (21, 30)	26 (22, 32)
HBsAg+ at screening, n (%)	38 (3%)	47 (3%)	45 (11%)
BMI, median (Q1, Q3)	26.0 (23.5, 29.6)	26.3 (23.4, 29.8)	26.2 (23.5, 30.1)
Country			
India	46 (3%)	46 (3%)	0 (0%)
Malawi	471 (31%)	479 (32%)	146 (35%)
South Africa	500 (33%)	485 (32%)	69 (16%)
Tanzania	23 (2%)	24 (2%)	10 (2%)
Uganda	204 (14%)	198 (13%)	83 (20%)
Zambia	32 (2%)	31 (2%)	18 (4%)
Zimbabwe	231 (15%)	234 (16%)	93 (22%)

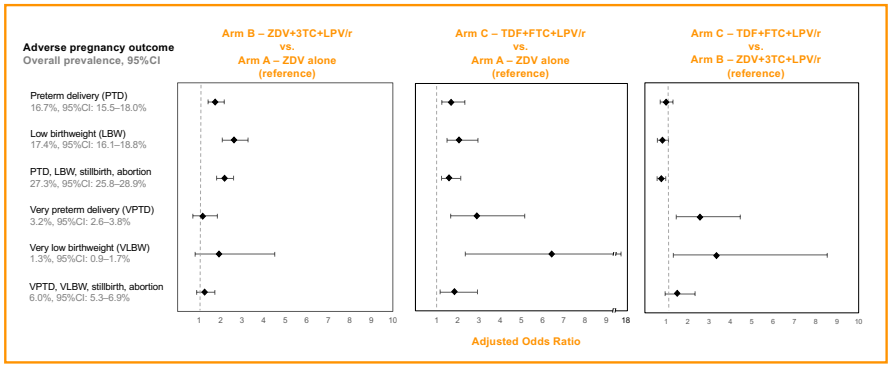

Figure 1: Adjusted odds ratios for different adverse pregnancy outcomes according to study arm

Table 3: Adjusted odds ratios (95% confidence intervals) in primary and sensitivity analyses according to study arm

	All Participants			Protocol Version 3.0 Only		
	ZDV+3TC+LPV/r vs. ZDV alone	TDF+FTC+LPV/r vs. ZDV alone	TDF+FTC+LPV/r vs. ZDV+3TC+LPV/r	ZDV+3TC+LPV/r vs. ZDV alone	TDF+FTC+LPV/r vs. ZDV alone	TDF+FTC+LPV/r vs. ZDV+3TC+LPV/r
Preterm delivery (PTD)	1.75 (1.42, 2.17)	1.70 (1.24, 2.33)	0.97 (0.72, 1.32)	1.74 (1.13, 2.67)	1.65 (1.07, 2.56)	0.95 (0.63, 1.43)
Low birthweight (LBW)	2.61 (2.08, 3.27)	2.10 (1.49, 2.95)	0.80 (0.58, 1.11)	3.70 (2.21, 6.20)	2.93 (1.73, 4.94)	0.79 (0.52, 1.20)
PTD, LBW, stillbirth, spontaneous abortion	2.17 (1.81, 2.60)	1.62 (1.23, 2.14)	0.75 (0.57, 0.98)	2.31 (1.59, 3.37)	1.76 (1.20, 2.59)	0.76 (0.54, 1.08)
Very preterm birth (VPTD)	1.14 (0.71, 1.85)	2.93 (1.66, 5.16)	2.56 (1.47, 4.46)	1.16 (0.42, 3.18)	3.26 (1.40, 7.55)	2.82 (1.18, 6.70)
Very low birthweight (VLBW)	1.92 (0.82, 4.51)	6.46 (2.35, 17.76)	3.37 (1.33, 8.53)	*	*	7.95 (1.18, 53.69)
VPTD, LBW, stillbirth, spontaneous abortion	1.24 (0.89, 1.73)	1.85 (1.16, 2.03)	1.49 (0.95, 2.35)	0.96 (0.45, 2.08)	2.20 (1.15, 4.23)	2.29 (1.13, 4.62)

* Too few outcome events to estimate 95% confidence interval

The prevalence of specific adverse birth outcomes in PROMISE is shown in Figure 1. When we considered outcomes with PTD and/or LBW, women on ZDV+3TC+LPV/r (Arm B) and TDF+FTC+LPV/r (Arm C) each had higher risk for adverse birth outcomes compared to ZDV alone (Arm A).

When the analysis was restricted to severe outcomes (i.e., VPTD, VLBW), the risk associated with Arm C remained elevated compared to Arm A; however, the risk seen with Arm B was no longer statistically significant.

In head-to-head comparisons between the two combination ART regimens, Arm C appeared to have a higher risk of severe adverse birth outcomes: VPTD (adjusted odds ratio [AOR] 2.56, 95%CI:1.47-4.46) and VLBW (AOR: 3.37, 95%CI:1.33-8.53).

The same comparisons yielded consistent findings in sensitivity analyses that restricted the data to those enrolled in protocol version 3.0 only: VPTD (AOR: 2.82, 95%CI:1.18-6.70) and VLBW (AOR: 7.95, 95%CI:1.18-53.69). Our previous work had revealed an association between these severe outcomes and infant death rates (Fowler, *NEJM* 2016).

CONCLUSION

The use of LPV/r-containing antiretroviral regimens (TDF+FTC+LPV/r, ZDV+3TC+LPV/r) was associated with an elevated risk for PTD and LBW, when compared to antenatal ZDV alone.

ZDV+3TC+LPV/r had a somewhat higher risk for severe outcomes, relative to the ZDV alone arm, but this was not statistically significant. However, the TDF+FTC+LPV/r arm had a significantly higher risk than either of the other arms.

This secondary analysis builds upon past work, by considering numerous adverse birth outcomes and adjusting for multiple clinical and obstetrical factors.

Further study is needed to determine potential mechanisms underlying these findings. These may include an independent effect of TDF-FTC, a result of drug-drug interactions with LPV/r, or other biological factors.

Support for the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network was provided by the National Institute of Allergy and Infectious Diseases (NIAID) via awards UM1AI068632, UM1AI068616, and UM1AI106716. Co-funding was provided by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.