The PROMISE 1077B/1077F 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/mm³, 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 positive were randomized to any of the three arms.

In beginning 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 antepartum 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.

In the current report, we focused on the association between antiretroviral therapy and adverse birth outcomes, including preterm birth, stillbirth, and VPTD. We evaluated adverse birth outcomes in the participants enrolled in the PROMISE trial and evaluated several different regimens. We also evaluated whether there were any differences in the outcomes of women who were enrolled in the PROMISE trial versus those who were not.

The primary analyses presented here include data from all participants. Variables included in these models were restricted to those with at least marginal presence (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 assigned to Arm A (n=1507), Arm B (n=1492), and Arm C (n=419). The characteristics of participants in each study arm are shown in Table 2.

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 a higher risk of adverse birth outcomes compared to ZDV alone (Arm A).

When the analysis was restricted to severe outcomes (i.e., VPTD, LBW, stillbirth), 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 antiretroviral 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 LBW (AOR 3.37, 95% CI: 1.53-7.33).

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: 1.88-4.0) and LBW (AOR 7.95, 95% CI: 1.18-56.3).

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

CONCLUSION

The use of LPV-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.

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

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 Pediatr. Adolescent AIDS Clinical Trials (IMPaACT) Network was provided by the National Institute of Allergy and Infectious Diseases (NIAID) AIDS/avian influenza cooperative agreement U01 AI 68552 and NIAID, Office of the Director 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 author and does not necessarily represent the official views of the NIH.