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Risk Factors for Adverse Birth Outcomes in the PROMISE 1077BF/1077FF Trial

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Abstract

Background: In the multi-country PROMISE 1077BF trial, the risk of low birth weight (LBW; <2500g) and preterm delivery (PTD; <37 weeks) was higher among women initiating a protease inhibitor (PI)-based antiretroviral treatment (ART) regimen than in those receiving ZDV alone. Among those assigned to a PI regimen, tenofovir/emtricitibine was associated with the more severe outcomes of very LBW (VLBW; <1500g) and very PTD (VPTD; <34 weeks) compared to zidovudine/lamivudine.

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Conflict of Interest

The rest of the authors declared no conflict of interest.

Methods: We used multivariate logistic regression to further explore treatment findings, taking into account demographic baseline clinical and post-entry obstetrical factors. We evaluated individual adverse outcomes and composites that included stillbirth and early loss/spontaneous abortion.

Results: Among 3333 women delivering at least one live infant, median maternal age at enrollment was 26 years; 661 (20%) were primiparous, and 110 (3.3%) reported at least one prior PTD. Seventeen percent of newborns were LBW, 1% were VLBW, 17% had PTD, and 3% VPTD. Treatment allocation remained strongly associated with multiple adverse outcomes after controlling for other risk factors with both ART regimens exhibiting increased risk relative to ZDV alone. Other risk factors remaining significant in at least one of the multivariate models included: country, gestational age at entry, maternal age, maternal BMI, prior PTD, history of alcohol use, baseline HIV viral titer, multiple gestation and several obstetric risk factors.

Conclusion: ART effects on adverse pregnancy outcomes reported in the randomized PROMISE trial remained strongly significant even after controlling for demographic, baseline clinical and obstetrical risk factors, which were also associated with these outcomes.

Introduction

Among the many diverse elements of the global HIV/AIDS fight, few can compete with the remarkably successful efforts to prevent mother-to-child HIV transmission (PMTCT).[1] Current recommendations include universal HIV testing and counseling in antenatal care, followed by immediate, lifelong antiretroviral therapy (ART) for women found to be HIV seropositive. This approach, known as “Option B+”,[2, 3] can reduce the risk of vertical transmission to below 1%.[4] . However, exposure to ART in pregnancy may be associated with increased risk of adverse birth outcomes[5]. Studies from a variety of settings have linked antiretroviral drug exposure to a variety of adverse outcomes, including preterm birth, low birth weight, stillbirth, and neonatal death.[6–10]

The antenatal component of the Promoting Maternal and Infant Survival Everywhere (PROMISE) trial[11] compared the safety and efficacy of three PMTCT regimens. It found significantly lower rates of perinatal HIV transmission among women randomized to receive a three-drug ART combination than was seen in those receiving only zidovudine antenatally with intrapartum nevirapine; but also reported higher rates of adverse birth outcomes among those women receiving antepartum combination ART compared to those exposed to zidovudine alone . We sought to further explore these findings in a secondary analysis that considered demographic, baseline clinical, and post-entry obstetrical factors that may have mediated any adverse antiretroviral treatment effect or that may have independently increased the probability of adverse birth outcomes.

Methods

Study Setting and Population

PROMISE 1077BF/1077FF was a multi-component randomized trial conducted at fourteen sites in seven countries (six in Sub-Saharan Africa and one in India). The present analysis focused on the antepartum component of the trial, the design and findings of which have

been reported elsewhere[11]. This study enrolled HIV-infected pregnant women of at least 14 weeks gestation who did not meet clinical or $CD4^+$ T-lymphocyte (CD4) count requirements for treatment initiation based on country guidelines (usually 350 cells/ $mm^{3)}$. We excluded women with prior ART exposure, although prior receipt of one or two antiretroviral drugs to prevent perinatal HIV transmission in a prior pregnancy was permitted, as was thirty or fewer days of pre-randomization exposure during the current pregnancy. We excluded those with: entry hemoglobin concentration < 7.5 g/ dL , serious laboratory abnormalities based on DAIDS Toxicity Tables, 2004[12], active tuberculosis or recent TB treatment, hepatitis B (HBV) treatment, and pregnancies where fetus(es) had a serious malformation.

In the antepartum component of PROMISE, women were randomly assigned to one of three regimens/study arms: (A) zidovudine (ZDV) plus intrapartum single-dose nevirapine ("ZDV alone"); (B) zidovudine/lamivudine and lopinavir–ritonavir ("ZDV-based ART"); or (C) tenofovir (TDF), emtricitabine, and lopinavir–ritonavir ("TDF-based ART"). Under protocol versions 1.0 and 2.0, hereafter called **period 1**, women who tested negative for hepatitis B surface antigen (HBsAg) were eligible to be randomized into study arms A and B only, while those who tested HBsAg positive were eligible for any of the three arms. Under protocol version 3.0, hereafter referred to as **period 2**, which began in October 2012, participants were randomized with equal probability into any of the three study arms, irrespective of HBsAg status. This modification was made in response to evolving treatment guidelines regarding TDF safety for pregnant women.

Outcomes and Definitions

Maternal trial participants were evaluated at 2 and 4 weeks post enrollment and thereafter every 4 weeks until delivery. We used a modified Ballard newborn assessment [13, 14] as the primary approach to estimate gestational age at delivery. We defined preterm delivery (PTD) and very preterm (VPTD) delivery as <37 weeks and <34 weeks gestation at birth, respectively, and defined low birth weight (LBW) and very low birth weight (VLBW) as <2500g and <1500g, respectively. We also defined a *composite adverse pregnancy outcome* as any of the following: PTD, LBW, spontaneous abortion (<20 weeks gestation), or stillbirth (born dead without heart rate or respiratory effort on or after 20 weeks gestation). We further defined a *severe composite adverse pregnancy outcome* to include: VPTD, VLBW, spontaneous abortion, or stillbirth.

For multiple births, if any of the infants met the criteria for an adverse or severe adverse outcome, the pregnancy was classified as having the corresponding outcome, either on the single outcomes evaluating prematurity or birth weight or on the composite outcomes.

Design of the present analysis

This study is a secondary analysis designed to investigate demographic, baseline clinical, and post-entry obstetrical risk factors associated with preterm delivery and low birth weight, along with the composite outcomes defined above. Note that the analyses for PTD, VPTD, LBW and VLBW were limited to pregnancies with at least one live birth (N=3333), while the analyses with the composite outcomes also included 90 singleton pregnancies whose only outcomes consisted of stillbirths or spontaneous abortions, yielding a total sample of

N=3423. These analyses assessed the independent effects of known and suspected risk factors on adverse pregnancy outcomes, and evaluated the extent to which they might have mediated the ART treatment effect on adverse birth outcomes.

Predictor variables included in this secondary analysis were as follows:

1. baseline maternal clinical and demographic factors: maternal age, maternal body mass index (BMI), gestational age, country, treatment group, CD4 count, HIV viral load, multiple gestation, history of prior preterm birth, history of cigarette smoking, history of alcohol use, and HBsAg status. All were assessed at entry except for maternal age, which was assessed at delivery.
2. maternal obstetrical risk factors identified post randomization and throughout the pregnancy: *abruptio* placentae, placenta previa, chronic hypertension, pregnancy induced hypertension, polyhydramnios, oligohydramnios, intrauterine growth restriction, preterm labor, premature rupture of membranes, vaginal bleeding, lower genital tract infection, and urinary tract infection (UTI).

Statistical Analysis

The overall strategy of the data analysis was to: 1) perform univariate logistic analyses to identify variables meeting a criterion of at least marginal association (p-value<0.15) with one or more of the pre-defined adverse pregnancy outcomes; 2) enter these variables into multivariate logistic models as predictors of pregnancy outcomes and examine their associations with these outcomes, controlling for one another (note: obstetrical risk factors with N<5 events were excluded from multivariate analyses); 3) utilize a backward elimination procedure to sequentially remove the least significant variable from the model, until only those with p-value<=0.10 remained; 4) enter the variables retained after the backward elimination procedure into models which restrict the data to participants accrued during period 2 of the trial where there was equal randomization to each of the three treatment arms. This allowed us to examine whether the effects of these predictors in the period 2 analyses were consistent with those found to be at least moderately associated with one of these outcomes in the full sample models covering period 1 and period 2 (p-value<0.10).

Results

Between April 2011 and October 2014, 3423 participants delivered. This included 1507 women randomized to ZDV alone (Arm A), 1497 women to ZDV-based ART (Arm B), and 419 to TDF-based ART (Arm C). The vast majority (97%) were black African. The median maternal age at enrollment was 26 years (interquartile range [IQR]: 22–30) and the median BMI at entry was 26.1 kg/m^2 (IQR: 23.5–29.7). Almost all maternal participants (97%) were WHO clinical stage 1 (asymptomatic) and 37% enrolled at 28 weeks of gestation or later. Only 197 (6%) of participants had received ARVs for prior PMTCT and 790 (23%) had used ARVs for PMTCT during the current pregnancy prior to study enrollment. A total of 681 women (20 %) were nulliparous, and 115 (3 %) reported at least one prior PTD. [See Digital Supplement Table S-1 for full baseline characteristics]

Every pregnancy with at least one live birth (n=3333) was included in the analyses for PTD, VPTD, LBW and VLBW outcomes. This included all of the 60 multiple gestation pregnancies. For each of the 3 treatment arms, the incidence of multiple gestation was 2% (data not shown). There were also 90 singleton pregnancies where the outcome was either stillbirth or spontaneous abortion; note that these were included in the composite and severe composite outcome definitions. Among the 3333 women delivering at least one live born infant, median birth weight was 2900g (IQR 2600–3200), with 558 infants weighing <2500 g. Median gestational age (GA) at birth was 39 weeks (IQR 38–40), and 557 infants were born prior to 37 weeks gestation. Among these pregnancies with at least one live birth, the percentages of PTD, VPTD, LBW and VLBW were 17%, 3%, 17% and 1% respectively. Among all pregnancies (n=3423), 27% had a composite and 6% had a severe composite adverse pregnancy outcome.

Predictor variables which did not meet the pre-established criteria to be included in the multivariate analyses (history of cigarette smoking, placenta *previa*, polyhydramnios, lower genital tract infection and hepatitis B status) are not included in Figure 1 or in any of the Tables. The clinical variables which met the p-value <0.15 criteria for inclusion in multivariate logistic analyses include: antiretroviral regimens, maternal age, maternal BMI at entry, HIV-RNA at baseline and CD4 at screening, history of alcohol use, country, gestational age at entry, multiple gestation, and prior preterm births. The following obstetrical complications also met the inclusion criteria: *abruptio* placentae, chronic hypertension, pregnancy-induced hypertension, oligohydramnios, intrauterine growth restriction, premature labor, premature rupture of membranes, urinary tract infection, and vaginal bleeding.

Complete results, which include all variables meeting the p-value<0.15 criteria for inclusion in the multivariate models, are presented in Digital Supplement Tables S-2 for PTD and VPTD and S-3 for LBW and VLBW. These models also include results restricted to data from period 2. Tables 1 and 2 present selected predictor variables, summarizing findings from these models. Digital Supplement Table S-4 presents results for the composite and severe composite outcomes.

Treatment Effects on Adverse Pregnancy Outcomes Remain Significant after Controlling for Demographic/Baseline Clinical and Obstetric Factors:

In multivariate analyses, for the PTD and LBW outcomes, the adjusted odds ratios of both ART regimens compared to the ZDV alone regimen remained significantly greater than 1.0, indicating increased risk, and for the composite outcomes, they showed similar patterns that were at least marginally significant. However, for VPTD and VLBW, the ZDV-based ART regimen did not differ significantly from ZDV alone, while the TDF-based ART regimen exhibited significantly greater odds ratios than ZDV alone, indicating increased risk of delivery at <34 weeks gestation, as well as increased risk of birth weight <1500g. When comparing the two ART regimens, the TDF-based ART regimen demonstrated significantly higher risk of VLBW and VPTD compared to ZDV-based ART. These patterns held true for: the univariate analyses of treatment effects, the multivariate models prior to backward elimination, the multivariate models subsequent to backward elimination and multivariate

models restricted to those accrued during period 2 (Figure 1 and Digital Supplement Tables S-2, S-3, S-4).

Other Significant Predictors of Adverse Pregnancy Outcomes (Digital Supplement Tables S-2 and S-3):

In addition to the treatment effects, other factors significantly associated with preterm delivery and/or low birth weight that remained in multivariate models after backward elimination, included: maternal BMI at entry, HIV-RNA at baseline, gestational age at entry, prior preterm births, country, *abruptio* placentae, multiple gestation, hypertension, maternal age at delivery, oligohydramnios, intra uterine growth restriction, premature labor, preterm rupture of membranes and vaginal bleeding.

Discussion

The association of ART with adverse pregnancy outcomes remains strong after controlling for other well-known demographic, clinical and obstetrical risk factors.

In these analyses of data from HIV positive women in the PROMISE multi-country trial conducted in East and Southern Africa and India, maternal ART effect remained a significant risk factor for LBW/VLBW and PTD/VPTD adverse pregnancy outcomes compared to antenatal ZDV alone, even after adjustment for a number of key demographic/clinical and obstetrical risk factors. These multivariate analyses reinforce the initial antepartum component findings from PROMISE, which found that use of antepartum PI based ART was associated with increased risk of adverse birth outcomes compared to ZDV alone.[11]

Both ART regimens (TDF/FTC/LPV/r and ZDV/3TC/LPV/r) were associated with an elevated risk for moderate outcomes of PTD <37 weeks and LBW <2500g, and the composite outcome (including stillbirths and spontaneous abortions) when compared to antenatal ZDV alone. The TDF-based, but not the ZDV-based, ART regimen had a significantly higher risk for severe outcomes, relative to the ZDV alone arm. Moreover, relative to the TDF-based ART regimen, the ZDV-based regimen was associated with significantly lower risk of the severe outcomes (VPTD and VLBW) but not the moderate outcomes (PTD and LBW). These strong treatment effects, which were evident even after adjustment for various risk factors, could potentially be explained by treatment- associated changes in progesterone levels: several studies report that PI regimens were associated with lowered progesterone levels, which can increase the risk of preterm delivery.[15–18] Given that PIs have poor transplacental transfer, it unlikely that there is a direct effect on the fetus. Other potential mechanisms may include an independent effect of TDF-FTC, or a TDF-FTC/LPV/r interaction, on hormonal levels as well as possible chronic residual immune activation which is known to occur in patients who are stable and on ART. [19] In addition, specific ART regimens may increase the risk of placental insufficiency, potentially related to placental endothelial damage, which could likewise affect fetal growth and risk of preterm delivery[20}.The fact that the antiretroviral treatment effects remained significant, while controlling for multiple clinical and obstetrical risk factors, suggests that these background risk factors were not the primary biological factors mediating the ARV treatment effects.

The results from this analysis are comparable with findings from some, but not all, prior research studies that showed an association between adverse pregnancy outcomes including PTD/LBW and PI based regimens[21,]]. These include studies performed in Botswana, where HIV positive women who were on a PI based ART regimen had significantly increased risk of preterm births, still births and small for gestational age infants compared to those on an antenatal NRTI regimen[22]. More recent Botswana surveillance findings reported by Zash et al [23] found a higher risk of adverse pregnancy outcomes for women on ZDV/3TC/LPV/r ART compared to TDF/FTC/EFV or TDF FTC/LPV/r ART.

Additional Risk Factors for Adverse Pregnancy outcomes in PROMISE are consistent with findings in general populations of pregnant women.

These analyses also found that a number of obstetrical, demographic and clinical risk factors were related to adverse pregnancy outcomes among PROMISE HIV-infected women; this is consistent with findings from observational studies in non-HIV-infected populations.[24–26] In PROMISE, the demographic/clinical factors associated with LBW and/or PTD included: maternal BMI at entry, HIV-RNA at baseline, history of prior PTD outcomes and study treatment regimen. Obstetric risk factors included several common complications of pregnancy (i.e., multiple pregnancy, pregnancy induced hypertension, chronic hypertension, intrauterine growth restriction, *abruptio* placentae, oligohydramnios, premature labor, premature rupture of membranes, vaginal bleeding and gestational age at entry).

Low maternal BMI at entry (<18.5) was a significant risk factor for PTD, with 9 of 24 low BMI mothers delivering prior to 37 weeks, where odds ratios were greater than 1.0 for the multivariate analyses, but were only statistically significant with the data restricted to participants enrolled in period 2. Univariate analyses revealed a significant association between low BMI and LBW, but this relationship was not statistically significant in multivariate analyses. None of the low BMI mothers delivered prior to 34 weeks or had infants with birth weight <1500g; thus, valid odds ratios could not be estimated. In contrast, high BMI was protective against risk of PTD, VPTD, LBW and VLBW, where the univariate odds ratios were <1.0; but not statistically significant (except for PTD), while the adjusted odds ratios in the multivariate analyses on the full sample were all <1.0 with p-values close to 0.02. The association between low maternal BMI and PTD and LBW could potentially be explained by nutritionally deficient diet, strenuous daily life or medical illness.[27–28]

Maternal baseline HIV-RNA >20,000 copies was not associated with LBW or VLBW, but was associated with significantly greater risk for PTD and VPTD in univariate analyses. In multivariate analyses, the odds ratios remained above 1.0 with the p-values only remaining marginally statistically significant for PTD, but not for VPTD. This is consistent with a Kenyan study where maternal plasma and cervical HIV-RNA levels were associated with higher chances of preterm births.[29]

Gestational age at study entry was included in the models to adjust for the fact that mothers could be enrolled from 14 weeks gestation through delivery. Results indicate that those enrolling earlier in gestation were more likely to deliver prematurely and consequently, to have infants with lower birth weight than those enrolling later. However, although this could

be the result of longer exposure to study drugs, it could also be a trivial result, indicating that those enrolling early simply had a longer time period during which a delivery could be premature, while those enrolling late had either little or no time for this to happen. Thus, the effects of gestational age at entry should be interpreted with caution, but it is important to control for this variable in the multivariate analyses, since gestational age at entry may have implications for the effects of the other variables in the models.

In line with prior obstetrical research, multiple gestation was a very strong risk factor for PTD, VPTD, LBW and VLBW, which remained highly significant across the multivariate analyses, including those with data restricted to participants enrolled during period 2. In the data on the full sample, history of prior preterm births was also a significant risk factor for PTD and LBW, but not for VPTD or VLBW; however, this effect was not present with data restricted to those accrued under period 2. In the general obstetric literature, both of these factors, multiple gestation and prior preterm births, are well known risk factors for the outcomes of interest.[24]

The effects of country (as seen in Digital Supplemental Table S-2 and S-3) appear to be significant and complex. South Africa was chosen as the reference country for the calculation of odds ratios, because of its relatively advanced level of medical care. Univariate analyses revealed that, with the exception of Tanzania, all other countries differed significantly from South Africa with respect to PTD, with Malawi, Zambia and India showing greater risk, while Uganda and Zimbabwe appeared to be protective. Further study may be needed to understand these results.

In PROMISE, the youngest maternal age category at delivery (18-<21yrs) was a significant risk factor for PTD in univariate, but not multivariate analyses. Other studies, [29–30] have shown that teenage pregnancy, which is often associated with limited access to prenatal and antenatal care, poor nutrition and risky behaviors such as smoking and alcohol consumption, is associated with LBW, as well as PTD.

Various obstetric risk factors known to be related to adverse pregnancy outcomes were also included in these analyses. Pregnancy induced hypertension was significantly associated with PTD, VPTD, LBW and VLBW in univariate and multivariate analyses that included all data; it remained significant for PTD and LBW, but was only marginally significant for VPTD and not significant for VLBW in data restricted to period 2. Chronic hypertension had more complex effects, exhibiting a significant association with VPTD and VLBW, but not PTD and LBW, in univariate analyses, and remaining significant for VPTD and VLBW in multivariate analyses after backward selection. Oligohydramnios was strongly associated with PTD, VPTD, LBW, and VLBW in both univariate and multivariate models. Intrauterine growth restriction was significantly associated with PTD, LBW, and VLBW in both univariate and multivariate analyses, while it was significantly associated with VPTD only in univariate analyses. Premature labor and premature rupture of membranes were each significantly associated with PTD, VPTD, LBW and VLBW, with these effects persisting in multivariate analyses and in period 2 data. In the data on the full sample, vaginal bleeding was a significant risk factor for LBW in univariate and multivariate analyses but was not significant for the other outcomes. *Abruptio placenta* which was a relatively rare event, was

a risk factor for PTD, VPTD, LBW and VLBW where relatively high odds ratios persisted throughout univariate and multivariate analyses. These findings are consistent with literature from general obstetrical observational studies concerning general risk factors associated with low birth weight and preterm delivery. [24–26]

Strength and Limitations.

These analyses had certain limitations. Some potential obstetrical risk factors were too rare events for inclusion in the multivariate analysis. Moreover, the only triple ART regimens were PI-based. Due to limited availability of ultrasound and potential inaccuracies in estimation of last menstrual period, the estimation of gestational age depended on Ballard assessment. This may have resulted in some misclassification of gestational age determination at birth. [31]

However, major strengths of the PROMISE trial were that it was a randomized study which reduced the risk of potential bias, that it had a large sample size and that it was performed at multiple international sites, hence enhancing its validity and generalizability. In addition, the PROMISE study had strong data quality, given the high degree of quality control, quarterly site visits to monitor the trial data, ongoing internal data review and presentations to the external data safety monitoring board (DSMB).

Conclusion

In conclusion, these analyses demonstrate that, even after adjustment for a number of well-established clinical, demographic and obstetrical risk factors, maternal PI based ART regimens given for PMTCT among HIV-infected pregnant women remained an important risk factor for PTD/VPTD and LBW/VLBW outcomes, compared to antenatal ZDV alone. Moreover, TDF-based ART was significantly associated with greater numbers of severe adverse pregnancy outcomes than was ZDV-based ART. With the current rollout of lifetime ART according to “test and treat” recommendations by WHO and being implemented by the Ministries of Health, these results which corroborate potential negative effects of maternal ART on pregnancy outcomes, need to be considered in the management of HIV positive pregnant women so as to reduce the risk of low birth weight and preterm delivery outcomes, as well as composite adverse pregnancy outcomes, that are associated with high rates of infant morbidity and mortality, particularly in resource limited settings. Further research is needed to elucidate the biologic mechanisms underlying these adverse pregnancy outcomes, in order to optimize maternal treatment/PMTCT regimens. In addition, more studies are required to investigate whether this effect occurs with other PI’s or more recent ARV’s such as some integrase inhibitors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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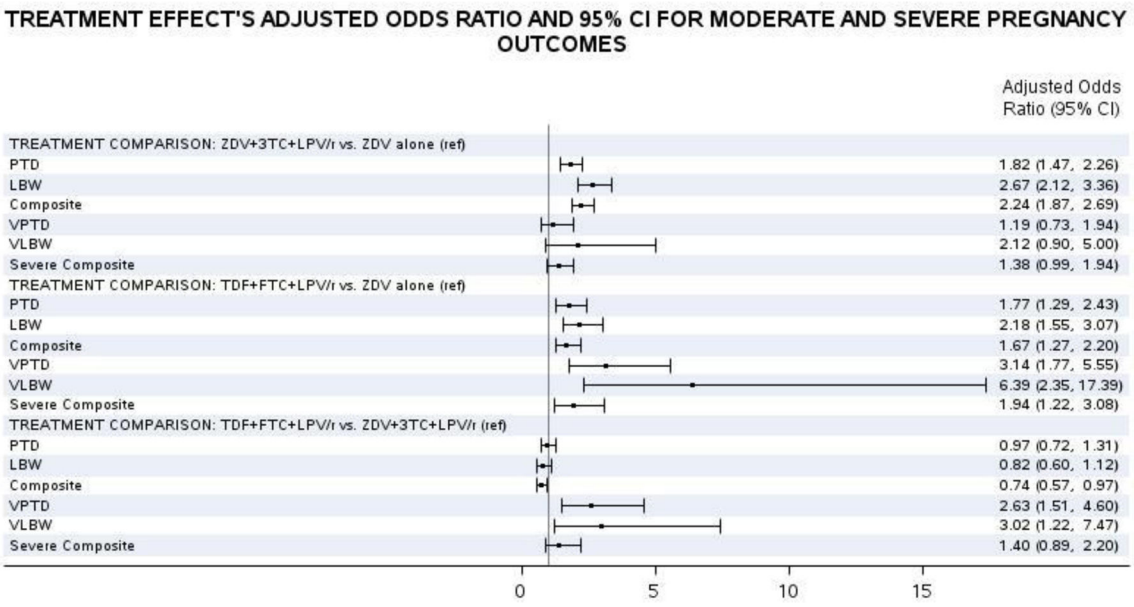

Figure 1: Maternal Treatment Effects on Adverse Pregnancy Outcomes after Controlling for Demographic/Baseline Clinical and Obstetric Factors

Definition of pregnancy outcomes:

PTD = Preterm delivery (<37 Wks), LBW = Low birth weight (<2500 g), Composite = Preterm delivery, low birth weight, spontaneous abortion or stillbirth, VPTD = Very preterm delivery (<34 Wks), VLBW = Very low birth weight (<1500 g), Service Composite = Very preterm delivery, very low birth weight, spontaneous abortion or stillbirth.

Table 1:

Analysis results for M-I pairs with preterm delivery (PTD: <37 weeks) and very preterm delivery (VPTD: <34 weeks) outcomes

			Counts		Univariate Analysis		Multivariate Analysis Backward Selection		Ver3.0 Counts		Ver3.0 Multivariate Analysis*	
Risk Factor		**Pregnancy Outcome**	**Y**	**N**	**Odds Ratio**	**95% CI**	**Adjusted Odds Ratio**	**95% CI**	**Y**	**N**	**Adjusted Odds Ratio**	**95% CI**
Treatment	ZDV+sdVNP+TRV tail	PTD	190	1277	.	.	.	.	52	345	.	.
	Triple ARV (3TC-ZDV/LPV-RTV)	PTD	289	1165	1.667	1.37–2.04	1.822	1.47–2.26	70	324	1.809	1.17–2.80
	Triple ARV (FTC-TDF/LPV-RTV)	PTD	78	334	1.570	1.18–2.10	1.769	1.29–2.43	69	312	1.614	1.04–2.51
	ZDV+sdVNP+TRV tail	VPTD	37	1430	.	.	.	.	11	386	.	.
	Triple ARV (3TC-ZDV/LPV-RTV)	VPTD	43	1411	1.178	0.75–1.84	1.191	0.73–1.94	9	385	1.241	0.45–3.44
	Triple ARV (FTC-TDF/LPV-RTV)	VPTD	25	387	2.498	1.49–4.20	3.138	1.77–5.55	23	358	3.055	1.30–7.16
Maternal BMI at entry	< 18.5	PTD	9	15	2.816	1.23–6.48	2.015	0.78–5.19	4	2	9.100	1.42–58.52
	18.5 - <30	PTD	444	2084	.	.	.	.	159	752	.	.
	≥ 30	PTD	99	670	0.694	0.55–0.88	0.677	0.52–0.89	25	220	0.482	0.28–0.82
	< 18.5	VPTD	0	24	†	†	†	†	0	6	†	†
	18.5 - <30	VPTD	84	2444	.	.	.	.	38	873	.	.
	≥ 30	VPTD	19	750	0.737	0.45–1.22	0.467	0.25–0.87	4	241	0.122	0.03–0.61
HIV-RNA at baseline	< 1000	PTD	94	553	.	.	.	.	35	188	.	.
	1000 - < 10000	PTD	186	1060	1.032	0.79–1.35	1.036	0.77–1.39	67	371	0.988	0.59–1.65
	10000- < 20000	PTD	82	369	1.307	0.95–1.81	1.280	0.90–1.83	26	132	1.066	0.56–2.04
	≥ 20000	PTD	194	788	1.448	1.11–1.90	1.345	1.00–1.82	63	288	1.362	0.80–2.31
	< 1000	VPTD	16	631	.	.	.	.	7	216	.	.
	1000 - < 10000	VPTD	30	1216	0.973	0.53–1.80	0.841	0.43–1.65	15	423	0.789	0.27–2.29
	10000- < 20000	VPTD	16	435	1.451	0.72–2.93	1.404	0.65–3.02	7	151	1.486	0.43–5.17
	≥ 20000	VPTD	43	939	1.806	1.01–3.23	1.649	0.86–3.17	14	337	1.525	0.52–4.48
Gestational age at entry		PTD	.	.	0.972	0.96–0.99	.	.	.	.	.	.
		VPTD	.	.	0.938	0.91–0.97	0.951	0.92–0.99	.	.	0.950	0.89–1.01

Risk Factor		Pregnancy Outcome	Counts Y	Counts N	Univariate Analysis Odds Ratio	Univariate Analysis 95% CI	Multivariate Analysis Backward Selection Adjusted Odds Ratio	Multivariate Analysis Backward Selection 95% CI	Ver3.0 Counts Y	Ver3.0 Counts N	Ver3.0 Multivariate Analysis* Adjusted Odds Ratio	Ver3.0 Multivariate Analysis* 95% CI
Multiple gestation	Singleton	PTD	522	2751	.	.	.	.	175	971	.	.
	Twins/triplets	PTD	35	25	7.378	4.38–12.43	6.280	3.56–11.09	16	10	10.417	4.30–25.23
	Singleton	VPTD	90	3183	.	.	.	.	36	1110	.	.
	Twins/triplets	VPTD	15	45	11.791	6.34–21.93	9.464	4.67–19.17	7	19	16.912	5.47–52.27
Prior preterm births	Nulliparous	PTD	125	536	1.243	1.00–1.55	1.150	0.88–1.51	43	191	1.363	0.85–2.19
	Parous, no prior preterm	PTD	404	2153	.	.	.	.	144	764	.	.
	Parous, at least one preterm	PTD	28	82	1.820	1.17–2.83	1.704	1.04–2.79	4	25	1.176	0.36–3.82
	Nulliparous	VPTD	20	641	0.979	0.60–1.61	.	.	10	224	.	.
	Parous, no prior preterm	VPTD	79	2478	.	.	.	.	32	876	.	.
	Parous, at least one preterm	VPTD	6	104	1.810	0.77–4.25	.	.	1	28	.	.
Abruptio Placenta	Yes	PTD	5	3	8.372	2.00–35.14	15.473	3.36–71.33	2	1	33.347	2.80–396.70
	No	PTD	552	2773	.	.	.	.	189	980	.	.
	Yes	VPTD	3	5	18.959	4.47–80.41	32.463	6.26–168.31	1	2	36.238	2.18–602.63
	No	VPTD	102	3223	.	.	.	.	42	1127	.	.
Chronic Hypertension	Yes	PTD	6	21	1.429	0.57–3.56	.	.	1	2	.	.
	No	PTD	551	2755	.	.	.	.	190	979	.	.
	Yes	VPTD	4	23	5.519	1.87–16.25	4.944	1.32–18.59	1	2	9.623	0.25–370.10
	No	VPTD	101	3205	.	.	.	.	42	1127	.	.
Pregnancy Induced Hypertension	Yes	PTD	42	80	2.748	1.87–4.04	3.836	2.46–5.99	7	25	2.753	1.00–7.54
	No	PTD	515	2696	.	.	.	.	184	956	.	.
	Yes	VPTD	15	107	4.861	2.72–8.68	5.832	2.87–11.86	3	29	4.228	0.93–19.23
	No	VPTD	90	3121	.	.	.	.	40	1100	.	.
Oligohydramnios	Yes	PTD	12	17	3.575	1.70–7.53	3.046	1.27–7.30	2	4	2.150	0.18–25.17
	No	PTD	545	2759	.	.	.	.	189	977	.	.
	Yes	VPTD	5	24	6.675	2.50–17.85	17.509	5.19–59.03	0	6	†	†
	No	VPTD	100	3204	.	.	.	.	43	1123	.	.

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Risk Factor		Pregnancy Outcome	Counts Y	Counts N	Univariate Analysis Odds Ratio	Univariate Analysis 95% CI	Multivariate Analysis Backward Selection Adjusted Odds Ratio	Multivariate Analysis Backward Selection 95% CI	Ver3.0 Counts Y	Ver3.0 Counts N	Ver3.0 Multivariate Analysis* Adjusted Odds Ratio	Ver3.0 Multivariate Analysis* 95% CI
Intrauterine Growth Restriction	Yes	PTD	7	4	8.820	2.57–30.23	7.898	2.00–31.13	3	2	3.814	0.45–32.36
	No	PTD	550	2772	.	.	.	.	188	979	.	.
	Yes	VPTD	2	9	6.951	1.48–32.56	.	.	0	5	.	.
	No	VPTD	103	3219	.	.	.	.	43	1124	.	.
Premature Labor	Yes	PTD	27	21	6.683	3.75–11.91	6.122	3.23–11.61	11	4	21.248	6.01–75.09
	No	PTD	530	2755	.	.	.	.	180	977	.	.
	Yes	VPTD	8	40	6.573	3.00–14.42	6.108	2.35–15.86	6	9	22.735	5.87–88.11
	No	VPTD	97	3188	.	.	.	.	37	1120	.	.
Premature Rupture of Membranes	Yes	PTD	23	17	6.990	3.71–13.17	10.113	5.13–19.95	5	2	26.120	4.73–144.13
	No	PTD	534	2759	.	.	.	.	186	979	.	.
	Yes	VPTD	9	31	9.669	4.48–20.87	18.201	7.23–45.80	2	5	46.838	3.58–612.20
	No	VPTD	96	3197	.	.	.	.	41	1124	.	.
Vaginal Bleeding	Yes	PTD	2	16	0.623	0.14–2.71	.	.	0	0	.	.
	No	PTD	555	2760	.	.	.	.	191	981	.	.
	Yes	VPTD	1	17	1.816	0.24–13.78	.	.	0	0	.	.
	No	VPTD	104	3211	.	.	.	.	43	1129	.	.
UTI	Yes	PTD	35	226	0.757	0.52–1.09	.	.	15	97	.	.
	No	PTD	522	2550	.	.	.	.	176	884	.	.
	Yes	VPTD	9	252	1.107	0.55–2.22	.	.	2	110	.	.
	No	VPTD	96	2976	.	.	.	.	41	1019	.	.

*Only the covariates that remained in the All Data multivariate model after backward selection were included in the multivariate model for Version 3.0 Data.

†In the models for the VPTD pregnancy outcome, we encountered instances where valid coefficients for categorical variables having no events in specific categories could not be estimated. For example, the <18.5 category of maternal BMI had no events for VPTD. However, inclusion of these variables provided a valid means of controlling for their effects in estimating the associations between the other variables in the models and the outcomes.

Table 2:

Analysis results for M-I pairs with low birth weight (LBW: <2500 g) and very low birth weight (VLBW: <1500 g) outcomes

			Counts		Univariate Analysis		Multivariate Analysis Backward Selection		Ver3.0 Counts		Ver3.0 Multivariate Analysis*	
Risk Factor		Pregnancy Outcome	Y	N	Odds Ratio	95% CI	Adjusted Odds Ratio	95% CI	Y	N	Adjusted Odds Ratio	95% CI
Treatment	ZDV+sdVNP+TRV tail	LBW	170	1250	.	.	.	.	33	340	.	.
	Triple ARV (3TC-ZDV/LPV-RTV)	LBW	320	1081	2.177	1.78–2.67	2.669	2.12–3.36	73	299	3.699	2.21–6.18
	Triple ARV (FTC-TDF/LPV-RTV)	LBW	68	319	1.567	1.15–2.13	2.183	1.55–3.07	62	294	2.800	1.66–4.72
	ZDV+sdVNP+TRV tail	VLBW	12	1408	.	.	.	.	1	372	.	.
	Triple ARV (3TC-ZDV/LPV-RTV)	VLBW	18	1383	1.527	0.73–3.18	2.118	0.90–5.00	2	370	7.410	0.43–128.55
	Triple ARV (FTC-TDF/LPV-RTV)	VLBW	10	377	3.112	1.33–7.26	6.390	2.35–17.39	9	347	28.236	2.34–340.30
Maternal BMI at entry	< 18.5	LBW	12	11	5.060	2.22–11.54	1.871	0.68–5.16	1	4	0.344	0.01–13.41
	18.5 - <30	LBW	432	2004	.	.	.	.	133	723	.	.
	≥ 30	LBW	110	630	0.810	0.65–1.02	0.731	0.56–0.95	30	202	0.739	0.45–1.22
	< 18.5	VLBW	0	23	†	†	†	†	0	5	†	†
	18.5 - <30	VLBW	32	2404	.	.	.	.	11	845	.	.
	≥ 30	VLBW	8	732	0.821	0.38–1.79	0.328	0.12–0.89	1	231	0.055	0.00–0.97
HIV-RNA at baseline	< 1000	LBW	105	521	.	.	.	.	39	172	.	.
	1000 - < 10000	LBW	204	997	1.015	0.78–1.31	.	.	65	345	.	.
	10000- < 20000	LBW	74	351	1.046	0.75–1.45	.	.	12	132	.	.
	≥ 20000	LBW	173	776	1.106	0.85–1.44	.	.	51	283	.	.
	< 1000	VLBW	9	617	.	.	.	.	3	208	.	.
	1000 - < 10000	VLBW	11	1190	0.634	0.26–1.54	.	.	4	406	.	.
	10000- < 20000	VLBW	4	421	0.651	0.20–2.13	.	.	1	143	.	.
	≥ 20000	VLBW	16	933	1.176	0.52–2.68	.	.	4	330	.	.
Gestational age at entry		LBW	.	.	0.964	0.95–0.98	0.971	0.95–0.99	.	.	0.986	0.95–1.02
		VLBW	.	.	0.886	0.84–0.94	0.881	0.82–0.94	.	.	0.828	0.72–0.95
Multiple gestation	Singleton	LBW	516	2638	.	.	.	.	149	929	.	.

Risk Factor		Pregnancy Outcome	Counts Y	Counts N	Univariate Analysis Odds Ratio	Univariate Analysis 95% CI	Multivariate Analysis Backward Selection Adjusted Odds Ratio	Multivariate Analysis Backward Selection 95% CI	Ver3.0 Counts Y	Ver3.0 Counts N	Ver3.0 Multivariate Analysis* Adjusted Odds Ratio	Ver3.0 Multivariate Analysis* 95% CI
	Twins/triplets	LBW	42	12	17.893	9.36–34.22	22.492	11.26–44.94	19	4	51.460	16.00–165.46
	Singleton	VLBW	29	3125	.	.	.	.	8	1070	.	.
	Twins/triplets	VLBW	11	43	27.566	12.94–58.74	30.777	12.19–77.74	4	19	129.074	19.47–855.89
Prior preterm births	Nulliparous	LBW	137	495	1.484	1.19–1.85	1.246	0.97–1.61	38	177	1.387	0.87–2.20
	Parous, no prior preterm	LBW	388	2080	.	.	.	.	126	734	.	.
	Parous, at least one preterm	LBW	33	70	2.527	1.65–3.88	2.272	1.40–3.69	4	21	1.454	0.44–4.81
	Nulliparous	VLBW	8	624	1.042	0.48–2.28	.	.	2	213	.	.
	Parous, no prior preterm	VLBW	30	2438	.	.	.	.	9	851	.	.
	Parous, at least one preterm	VLBW	2	101	1.609	0.38–6.83	.	.	1	24	.	.
Abruptio Placenta	Yes	LBW	4	4	4.776	1.19–19.16	7.586	1.54–37.29	1	2	5.537	0.48–63.58
	No	LBW	554	2646	.	.	.	.	167	931	.	.
	Yes	VLBW	2	6	27.737	5.42–141.84	49.560	7.30–336.63	0	3	†	†
	No	VLBW	38	3162	.	.	.	.	12	1086	.	.
Chronic Hypertension	Yes	LBW	7	19	1.759	0.74–4.21	.	.	1	2	.	.
	No	LBW	551	2631	.	.	.	.	167	931	.	.
	Yes	VLBW	3	23	11.088	3.19–38.54	7.728	1.48–40.31	0	3	†	†
	No	VLBW	37	3145	.	.	.	.	12	1086	.	.
Pregnancy Induced Hypertension	Yes	LBW	47	69	3.440	2.35–5.04	3.434	2.18–5.41	8	19	4.289	1.65–11.18
	No	LBW	511	2581	.	.	.	.	160	914	.	.
	Yes	VLBW	11	105	11.065	5.38–22.75	12.983	5.24–32.17	1	26	10.456	0.47–234.41
	No	VLBW	29	3063	.	.	.	.	11	1063	.	.
Oligohydramnios	Yes	LBW	19	9	10.342	4.65–22.98	8.639	3.02–24.76	3	3	7.628	0.96–60.66
	No	LBW	539	2641	.	.	.	.	165	930	.	.
	Yes	VLBW	3	25	10.194	2.95–35.25	13.200	2.87–60.75	0	6	†	†
	No	VLBW	37	3143	.	.	.	.	12	1083	.	.
Intrauterine Growth Restriction	Yes	LBW	10	1	48.333	6.18–378.30	55.296	6.42–476.58	4	1	15.612	1.15–212.46

Risk Factor		Pregnancy Outcome	Counts Y	Counts N	Univariate Analysis Odds Ratio	Univariate Analysis 95% CI	Multivariate Analysis Backward Selection Adjusted Odds Ratio	Multivariate Analysis Backward Selection 95% CI	Ver3.0 Counts Y	Ver3.0 Counts N	Ver3.0 Multivariate Analysis* Adjusted Odds Ratio	Ver3.0 Multivariate Analysis* 95% CI
	No	LBW	548	2649	.	.	.	.	164	932	.	.
	Yes	VLBW	3	8	32.027	8.17–125.52	11.379	1.45–89.28	1	4	1.979	0.04–89.57
	No	VLBW	37	3160	.	.	.	.	11	1085	.	.
Premature Labor	Yes	LBW	27	18	7.435	4.07–13.60	5.735	2.86–11.51	8	4	17.127	4.63–63.41
	No	LBW	531	2632	.	.	.	.	160	929	.	.
	Yes	VLBW	4	41	8.478	2.89–24.91	5.067	1.31–19.64	2	10	27.353	3.58–209.13
	No	VLBW	36	3127	.	.	.	.	10	1079	.	.
Premature Rupture of Membranes	Yes	LBW	22	18	5.998	3.20–11.26	10.209	5.08–20.54	4	3	12.839	2.58–63.88
	No	LBW	536	2632	.	.	.	.	164	930	.	.
	Yes	VLBW	4	36	9.667	3.27–28.58	16.296	4.62–57.43	1	6	84.725	3.61->999.99
	No	VLBW	36	3132	.	.	.	.	11	1083	.	.
Vaginal Bleeding	Yes	LBW	7	11	3.048	1.18–7.90	2.972	1.00–8.87	0	0	.	.
	No	LBW	551	2639	.	.	.	.	168	933	.	.
	Yes	VLBW	1	17	4.755	0.62–36.60	.	.	0	0	.	.
	No	VLBW	39	3151	.	.	.	.	12	1089	.	.
UTI	Yes	LBW	40	216	0.870	0.61–1.24	.	.	15	94	.	.
	No	LBW	518	2434	.	.	.	.	153	839	.	.
	Yes	VLBW	5	251	1.660	0.65–4.28	.	.	0	109	.	.
	No	VLBW	35	2917	.	.	.	.	12	980	.	.

*Only the covariates that remained in the All Data multivariate model after backward selection were included in the multivariate model for Version 3.0 Data.

†In the models for the VLBW pregnancy outcome, we encountered instances where valid coefficients for categorical variables having no events in specific categories could not be estimated. For example, the <18.5 category of maternal BMI had no events for VLBW. However, inclusion of these variables provided a valid means of controlling for their effects in estimating the associations between the other variables in the models and the outcomes.