Risk Factors for Low Birth Weight and Preterm Delivery in the PROMISE Trial

POSTER #777

Dorothy Sebikari, Min Qin, Maxensia Owor, Jeffrey Stringer, Mona Farhad, Nahida Chakhtoura, Benjamin Chi, Karin Klingman , Gerhard Theron, Mary Glenn Fowler for the PROMISE Team

IMPAACT International Maternal Pediatric Adolescent AIDS Clinical Trials Network

PROMISE IMPAACT 1077

Promoting Maternal and Infant Survival Everywhere

ABSTRACT

Background: Although antiretroviral therapy (ART) in pregnancy can reduce vertical HIV transmission to <1%, it may also increase the risk of low birth weight (< 2500g, LBW) and preterm delivery (<37 weeks, PTD), conditions that confer significant morbidity and mortality to newborns in resource limited settings. In the multi-site PROMISE trial, we previously reported an increased risk of LBW and PTD among women initiating protease inhibitor (PI)-based ART during pregnancy, when compared to ZDV alone. We further describe obstetrical and clinical risk factors for LBW and PTD among study participants.

Methods and Materials: Within the antepartum component of PROMISE, we assessed baseline clinical and obstetrical risk factors associated with LBW and PTD. Risk factors with p-value <0.15 in univariate logistic regression were included in multivariate backward logistic regression models. We also adjusted for treatment arm, gestational age (GA) at entry, and country.

Results: Birth outcomes were available for 3423 HIV-infected women delivering between 4/2011-11/2014 across 14 sites in Africa and Asia. Among the 3333 women delivering at least one live born infant, median maternal age at enrollment was 26 years (IQR 22–30); 661 (20%) were primiparous, and 110 (3.3%) reported at least one prior PTD. Median birth weight was 2900g (IQR 2600–3200); and 558 (17%) infants weighed <2500 g. Median GA at birth was 39 weeks (IQR 38–40); 557 (17%, 95%CI: 16.1%-18.9%) were born prior to 37 weeks**.** In univariate analyses, clinical factors including maternal age 18-<21 year and entry RNA ≥20,000 copies were significant for PTD but not LBW; however, maternal age 18-<21 dropped out in the backward logistic model. In the final multivariate models, adjusted for country and GA at entry, obstetrical risk factors for LBW and/or PTD included BMI, multiple gestation, prior PTD, pregnancy or chronic hypertension, IUGR, placental abruption, preterm labor, oligohydramnios, PROM, and antenatal ART were significant risk factors.

Conclusion: Besides receipt of antenatal PI-based ART, a number of obstetrical risk factors contributed to LBW and PTD for HIV-infected pregnant women in PROMISE. Along with optimization of ART regimens, public health interventions are needed to address modifiable obstetrical risk factors, including education of pregnant women and clinicians on early warning signs and management of pregnancy-associated complications.

BACKGROUND

- PMTCT (Prevention of Mother to Child Transmission of HIV) is a major component in the global struggle against HIV /AIDS with ARV prophylaxis being one of the major components.
- The effectiveness and efficacy of maternal antiretroviral therapy (ART) given for PMTCT has been shown in several studies; and can reduce transmission to <1%.
- Maternal ART may also increase the risk of *low birth weight (< 2500g, LBW) and preterm delivery (<37 weeks, PTD)*, conditions that confer significant morbidity and mortality to newborns.
- Several studies done in developed and developing countries showed evidence of adverse outcomes in HIV + pregnant women on ART including PTD, LBW, still births and associated neonatal death.
- We previously reported an increased risk of LBW and PTD among women initiating protease inhibitor (PI)-based ART during pregnancy, when compared to ZDV alone in the PROMISE trial

METHODS

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

Pregnant women enrolled into the antepartum component of PROMISE were randomized to receive one of the three regimens:

- **Arm A:** ZDV + NVP at delivery + tenofovir (TDF)/emtricitabine
- **Arm B:** ZDV-lamivudine (3TC) + lopinavir/ritonavir (LPV-r)
- **Arm C:** TDF/FTC + LPV-r

This secondary analyses study the potential risk factors for LBW (<2500g) and PTD (<37wks gestation). Women with these outcomes were compared with those who had term infants and those who had infants with normal birth weight.

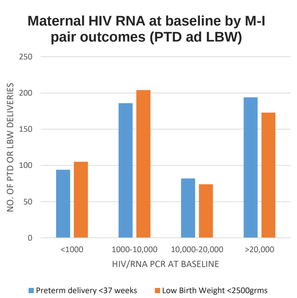
Potential risk factors consisted of baseline clinical and demographic factors, along with maternal obstetrical risk factors identified throughout the pregnancy. Treatment was also included as a predictor in the analyses. Risk factors with p-value <0.15 in univariate logistic regression were entered into multivariate logistic regression analyses with backward selection.

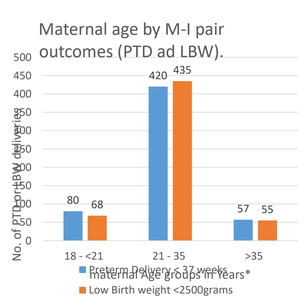
PROMISE 1077BF and 1077FF SITES

14 Sites in:
*India**
Malawi
*South Africa**
Tanzania
Uganda
Zambia
Zimbabwe
* Also FF sites

RESULTS

Birth outcomes were available for 3423 HIV-infected women delivering between 4/2011-11/2014 across 14 sites in Africa and Asia. 90 women had either stillbirths or spontaneous abortions and not included in the analyses presented below. Among the 3333 women delivering at least one live born infant, median maternal age at enrollment was 26 years (IQR 22–30).





Risk factors significant in the univariate analysis

- Maternal clinical, baseline and demographic factors including:
  Study treatment, country, age, BMI, baseline RNA and CD4, multiple gestation, # of prior premature births, history of alcohol use, chronic hypertension
- Obstetrical factors, including:
  Gestational age at study entry, UTI, pregnancy induced hypertension, oligohydramnios, intrauterine growth restriction, abruptio placenta, premature labor, premature rupture of membranes, vaginal bleeding
- **The following univariate results were specific to one outcome:**
  Maternal age and baseline RNA were significant risk factors for PTD, but not LBW
  Oligohydramnios and vaginal bleeding were significant risk factors for LBW, but not PTD Baseline
  CD4 and UTI were marginally significant risk factors for PTD, but not LBW

Table 1: Multivariate Analyses Results for Obstetrical Complications and Clinical Factors Associated with Preterm Delivery (<37 weeks)*Reference category

Risk Factor		# with Preterm Delivery (% with PTD for each row of each Risk Factor)	Adjusted Odds Ratio [95% CI]
Maternal age at delivery	18 - <21 years of age	80 (20.7%)	1.25 [0.91, 1.71]
	21 - <35 years of age*	420 (15.8%)	.
	≥ 35 years of age	57 (19.5%)	1.31 [0.93, 1.85]
Maternal BMI at entry	< 18.5	10 (40%)	2.05 [0.83, 5.04]
	18.5 - <30*	443 (17.5%)	.
	≥ 30	99 (12.9%)	0.65 [0.49, 0.85]
RNA at baseline	< 1000*	94 (14.5%)	.
	1000 - < 10000	186 (14.9%)	1.00 [0.75, 1.34]
	10000- < 20000	82 (18.2%)	1.23 [0.87, 1.76]
	≥ 20000	194 (19.8%)	1.35 [1.00, 1.82]
Multiple Gestation	Singleton*	522 (15.9%)	.
	Twins/triplets	35 (58.3%)	6.47 [3.69, 11.33]
# of premature births prior to current pregnancy	Nulliparous	125 (18.9%)	1.13 [0.86, 1.48]
	Parous, no prior preterm*	404 (15.8%)	.
	Parous, at least one preterm	28 (25.5%)	1.77 [1.09, 2.88]
Abruptio Placenta	Yes	5 (71.4%)	20.33 [3.60, 114.81]
	No*	552 (16.6%)	.
Chronic Hypertension	Yes	6 (22.2%)	2.63 [0.98, 7.04]
	No*	551 (16.7%)	.
Pregnancy Induced Hypertension	Yes	32 (31.4%)	3.54 [2.18, 5.76]
	No*	525 (16.2%)	.
Oligohyramnios	Yes	5 (27.8%)	2.62 [0.87, 7.90]
	No*	552 (16.7%)	.
Intrauterine Growth Restriction	Yes	3 (42.9%)	5.61 [1.20, 26.18]
	No*	554 (16.7%)	.
Premature Labor	Yes	18 (51.4%)	5.84 [2.84, 12.00]
	No*	539 (16.3%)	.
Premature Rupture of Membranes	Yes	16 (57.1%)	10.80 [4.90, 23.80]
	No*	541 (16.4%)	.
Treatment	ZDV+sdVNP+TRV tail*	190 (13%)	.
	Triple ARV (3TC-ZDV/LPV-RTV)	289 (19.9%)	1.76 [1.42, 2.18]
	Triple ARV (FTC-TDF/LPV-RTV)	78 (18.9%)	1.70 [1.24, 2.33]
Country	South Africa*	172 (16.9%)	.
	Malawi	230 (21.6%)	1.40 [1.09, 1.81]
	Zambia	29 (35.8%)	3.20 [1.90, 5.39]
	Uganda	52 (11%)	0.56 [0.39, 0.81]
	Zimbabwe	33 (6%)	0.30 [0.20, 0.45]
	Tanzania	14 (24.6%)	1.73 [0.90, 3.32]
	India	27 (30.7%)	1.75 [1.02, 3.01]

Table 2: Multivariate Analyses Results for Obstetrical Complications and Clinical Factors Associated with Low Birth Weight (<2500 gram)*Reference category

Risk Factor		# with Low Birth Weight (% with LBW for each row of each Risk Factor)	Adjusted Odds Ratio [95% CI]
Maternal BMI at entry	< 18.5	13 (54.2%)	1.97 [0.74, 5.22]
	18.5 - <30*	431 (17.7%)	.
	≥ 30	110 (14.8%)	0.70 [0.53, 0.91]
Multiple Gestation	Singleton*	516 (16.4%)	.
	Twins/triplets	42 (77.8%)	21.96 [11.05, 43.64]
# of premature births prior to current pregnancy	Nulliparous	137 (21.7%)	1.22 [0.95, 1.58]
	Parous, no prior preterm*	388 (15.7%)	.
	Parous, at least one preterm	33 (32%)	2.40 [1.49, 3.86]
Abruptio Placenta	Yes	4 (57.1%)	9.19 [1.68, 50.06]
	No*	554 (17.3%)	.
Chronic Hypertension	Yes	7 (26.9%)	2.31 [0.89, 5.96]
	No*	551 (17.3%)	.
Pregnancy Induced Hypertension	Yes	37 (37.8%)	3.38 [2.08, 5.50]
	No*	521 (16.8%)	.
Oligohyramnios	Yes	10 (58.8%)	11.04 [3.49, 34.90]
	No*	548 (17.2%)	.
Intrauterine Growth Restriction	Yes	6 (85.7%)	49.09 [5.66, 425.66]
	No*	552 (17.2%)	.
Premature Labor	Yes	18 (56.3%)	6.76 [3.11, 14.68]
	No*	540 (17%)	.
Premature Rupture of Membranes	Yes	17 (60.7%)	12.79 [5.69, 28.77]
	No*	541 (17%)	.
Vaginal Bleeding	Yes	6 (42.9%)	4.45 [1.37, 14.42]
	No*	552 (17.3%)	.
Treatment	ZDV+sdVNP+TRV tail*	170 (12%)	.
	Triple ARV (3TC-ZDV/LPV-RTV)	320 (22.8%)	2.60 [2.07, 3.26]
	Triple ARV (FTC-TDF/LPV-RTV)	68 (17.6%)	2.10 [1.49, 2.94]
Country	South Africa*	198 (20.1%)	.
	Malawi	163 (16.1%)	0.89 [0.68, 1.16]
	Zambia	18 (24.3%)	1.77 [0.97, 3.24]
	Uganda	42 (9.1%)	0.45 [0.30, 0.67]
	Zimbabwe	76 (14.2%)	0.92 [0.66, 1.29]
	Tanzania	9 (16.7%)	0.90 [0.42, 1.96]
	India	52 (59.1%)	6.99 [4.12, 11.85]
Gestational age at entry		.	0.97 [0.95, 0.99]

Risk factors in the final models for both PTD and LBW

- Maternal *BMI, Multiple gestation, Prior PTD, pregnancy induced hypertension, Chronic hypertension, Intrauterine growth restriction, Abruptio placenta, Oligohydramnios, Premature labor,Premature rupture of membranes, Country, ART study regimen*

Variables meeting criteria for only PTD model

- Maternal age, Baseline RNA,

Variables meeting criteria for only LBW model

- Vaginal bleeding, Gestational age at entry

Variables not meeting criteria to be retained in either PTD or LBW model

- Baseline CD4, History of alcohol use, Urinary tract infection

CONCLUSION

We identified a variety of obstetrical and clinical risk factors related to LBW and/or PTD among PROMISE HIV+ women in the multivariable analyses, including :

- Several common complications of pregnancy: *Pregnancy induced hypertension, chronic hypertension, intrauterine growth restriction, abruptio placenta, oligohydramnios, premature labor, premature rupture of membranes and vaginal bleeding (LBW only).*
- Other clinical risk factors: *Maternal BMI at entry, multiple gestation, # of previous premature births, maternal age (PTD only) and baseline RNA (PTD only).*

Maternal age and baseline RNA were significant risk factors for PTD, but not LBW from the univariate analysis.
ART (Triple Antiretroviral regimens) was also associated with elevated risk for LBW and PTD, compared to antenatal zidovudine alone.
Potential obstetrical risk factors should be carefully evaluated as part of comprehensive antenatal care for HIV-infected women.
Pregnant clients need education about early warning signs of adverse pregnancy so they can seek immediate medical care.

DISCUSSION

Strengths

Data from randomized clinical trial.
Large sample size representing multiple international sites.

Limitations

Some potential obstetrical risk factors were too rare for inclusion in the multivariate analysis.
Our findings on risk factors for LBW and PTD may or may not be generalizable to settings other than those included in PROMISE study.

ACKNOWLEDGEMENT

- *Study participants for volunteering and committing to be part of the PROMISE study along with their infants*
- The members of the IRBs and the Community Advisory Board for their support of the study
- *Study staff and scientists at all the sites that took part in the study*
- Support from IMPAACT leadership: "PROMISE 1077BF/1077FF is funded by the US National Institutes of Health (NIH). Overall support for the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network was provided by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) under Award Numbers UM1AI068632 (IMPAACT LOC), UM1AI068616 (IMPAACT SDMC) and UM1AI106716 (IMPAACT LC), with co-funding from 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.
- The study products were provided free of charge by AbbVie, Gilead Sciences, Boehringer Ingelheim, and GlaxoSmithKline."