

Update PROMISE 1077BF Safety Findings

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May 31, 2017



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Background

- PROMISE 1077 BF/1077FF was a large multi site IMPAACT trial conducted in 14 sites in 7 countries in East and Southern Africa and 1 site in India which ran from March 2011 through Sept 2016.
- The study was designed to address the relative safety and efficacy of several proven antiretroviral regimens for women with high CD4 counts who at the time of the trial did not meet treatment criteria.
- A number of Important safety findings have been identified through the PROMISE trial. Today we will provide updates on maternal safety findings from the PROMISE trial including
 - Factors Associated with LBW and PTD
 - Hepatotoxicity associated with EFV based ART
 - Changes in Maternal Bone Mineral Density post partum period



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IMPAACT Multi-site PROMISE Trial: Optimizing PMTCT and Mother/Infant Health Survival

Includes 14 NIH IMPAACT Clinical Research Sites in Eastern and Southern Africa and India where the option of formula feeding was also safe and available.

Sites in:

- *India** (1)
- *Malawi* (2)
- *South Africa** (5)
- *Tanzania* (1)
- *Uganda* (1)
- *Zambia* (1)
- *Zimbabwe* (3)



Antepartum Clinical and Obstetrical Factors Associated with Preterm Delivery (PTD) and Low Birth Weight (LBW)

- The Antepartum Component of PROMISE found that Maternal ART was more efficacious than ZDV in reducing the risk of early Mother to Child HIV Transmission (**0.5% vs 1.8%**) **but was also associated with significantly increased risk of PTD and LBW.** *NEJM Nov 2016, Fowler et al*
- Dr. Sebikari and colleagues have further explored the role of clinical and obstetrical factors in relation to these adverse pregnancy outcomes and whether they modulated the treatment effects found.



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Secondary Analyses Methods

- Univariate analyses assessed both clinical and obstetrical factors associated with LBW and/or PTD
- Multivariate analyses was used to adjust for these factors in relation to treatment randomization effect
- Key Clinical Factors Associated with LBW and/or PTD included:
 - Maternal BMI
 - Gestational Age
 - Multiple births
 - Abruptio placenta
 - Prior preterm birth
 - Chronic Hypertension
 - Oligohydramnios
 - In Utero Growth Restriction
 - Vaginal Bleeding
 - Premature Rupture of Membranes



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ART Remains a Significant Predictor of Predictor of LBW/PTD in Multivariate Analyses

Pregnancy Outcome	3TC-ZDV vs ZDV	FTC-TDF vs ZDV	FTC-TDF vs 3TC-ZDV
Preterm delivery (<37 weeks)	1.75 [1.42, 2.17]	1.69 [1.24, 2.31]	0.96 [0.71, 1.30]
Low Birth Weight (<2500 grams)	2.60 [2.07, 3.26]	2.09 [1.49, 2.94]	0.81 [0.59, 1.11]
Composite (stillbirth, spontaneous abortion, PTD, LBW)	2.20 [1.84, 2.63]	1.62 [1.23, 2.14]	0.74 [0.57, 0.96]
Very preterm delivery (< 34 weeks)	1.158 [0.73, 1.87]	2.91 [1.66, 5.10]	2.51 [1.45, 4.35]
Very low birth weight (<1500 grams)	1.748 [0.77, 3.95]	4.70 [1.82, 12.12]	2.69 [1.11, 6.50]

Conclusions

- A number of obstetrical and clinical risk factors were related to LBW and/or PTD 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).*
- Receipt of PI based ART *remained a significant Risk Factor for LBW and PTD in multivariate analyses*



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