Intracellular Concentrations of Tenofovir Diphosphate (TFV-DP) during Pregnancy in the PROMISE study: Description and Relationship with Adverse Pregnancy Outcomes

Poster # 83

Jim K. Aizire[1], Kristina M. Brooks[2], Mark Mirochnick[3], Pat Flynn[4], Mae Cababasay[5], Jennifer J. Kiser[2], George Siberry[6], Terry Fenton[5], Kevin Butler[5], Mary Glenn Fowler[7] and the PROMISE Study Team

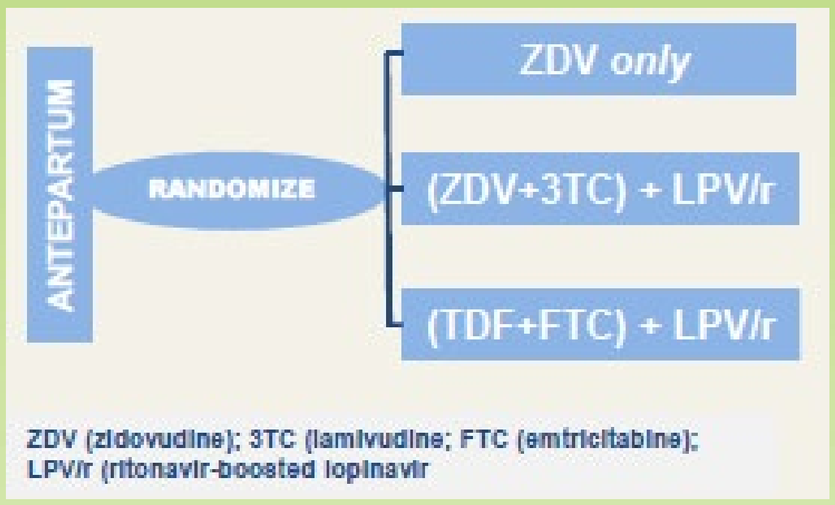
[1]Johns Hopkins Bloomberg School of Public Health, Department of Epidemiology, Baltimore, MD, USA
[2]University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences, Aurora, CO, USA
[3]Boston University School of Medicine, Boston, MA, USA
[4]St. Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis, USA
[5]Center for Biostatistics in AIDS Research, Harvard T. H. Chan School of Public Health, Boston, MA, USA
[6]Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland, USA
[7]Johns Hopkins School of Medicine, Department of Pathology, Baltimore, MD, USA

BACKGROUND

Higher risks of adverse pregnancy outcomes were reported among women on antiretroviral therapy (ART) containing tenofovir disoproxil fumarate (TDF) versus zidovudine (ZDV) based ART in the PROMISE (Promoting Maternal and Infant Survival Everywhere) trial:[1] *pre-term birth less than 34 weeks gestation (6.0% vs. 2.6%, P = 0.04); and early infant death (4.4% vs. 0.6%, P = 0.001), respectively.*

This sub-study examined the association between adverse pregnancy outcomes and concentrations of tenofovir diphosphate (TFV-DP) in dried blood spots (DBS), a measure of long-term drug exposure, in women receiving TDF-containing ART.

FIGURE 1. PROMISE study design (antepartum randomization)



METHODS

PROMISE study enrollment (2011-2013) across 14 sites in India, Malawi, South Africa, Tanzania, Uganda, Zambia, and Zimbabwe.

Sub-study inclusion criteria: Pregnant women randomized to receive TDF-FTC + LPV/r (14 weeks through delivery); who received at least one dose of TDF-FTC; and had a week-4 DBS sample drawn prior to delivery

Adverse pregnancy outcomes case definition:
a) Preterm delivery (PTD) prior to 34 weeks of gestation, OR
b) Stillbirth (SB) at or after 20 weeks gestation, OR
c) Early infant death (EID) prior to 14 days old.

Sub-study design and analyses:

- Case-control (matched) design: Cases were matched to controls (1:2 ratio) by site and gestational age at randomization.
- DBS samples collected at weeks 4 and 8 post-ART initiation were assayed for TFV-DP concentrations by liquid chromatography coupled with tandem mass (LC-MS/MS) methods. TFV-DP values below the lower limit of quantification (LLQ) were imputed as ½ LLQ, and in a separate sensitivity analysis imputed using 0 fmol/punch.
- Wilcoxon Signed Rank Test was used for case-control comparisons of TFV-DP concentrations, and conditional logistic regression was applied to examine TFV-DP concentrations as a predictor of individual and composite adverse pregnancy outcomes.
- Hypothesis testing used 0.05 alpha. Separate analyses were done at weeks 4 and 8.

RESULTS

- Overall, mothers who met the case-definitions and were included in these analyses include 15 PTDs; 6 SBs; 23 EIDs; and 22/33 (66.7%) met the composite outcome definition.
- Of the 22 mothers included in the composite outcome analyses, TFV-DP concentrations were comparable: at week 4, overall median (inter-quartile range (IQR)) was 706 (375 – 1,023) fmol/punch and the median (IQR) for the difference between cases and controls TFV-DP concentrations was 15.45 (-232.00 – 142.50) fmol/punch (figure 2); and at week 8 were 806 (414 – 1,265) fmol/punch and 47.90 (-152.75 – 725.50) fmol/punch, respectively.
- There was no difference between cases and controls for the composite endpoint matching (p-value of 0.86 and 0.35 for weeks 4 and 8, respectively).
- For the primary analysis, the Odds Ratio (95% Confidence Interval) of composite adverse pregnancy outcomes was 1.27 (0.74, 2.18) at week 4, and 1.74 (0.66, 4.60) at week 8 (table 1).
- Similarly, non-significant differences were observed for individual adverse pregnancy outcomes. Study findings did not differ between LLQ imputation methods.

FIGURE 2. Boxplot of FV-DP differences between cases and controls at week 4 (Primary Analysis)

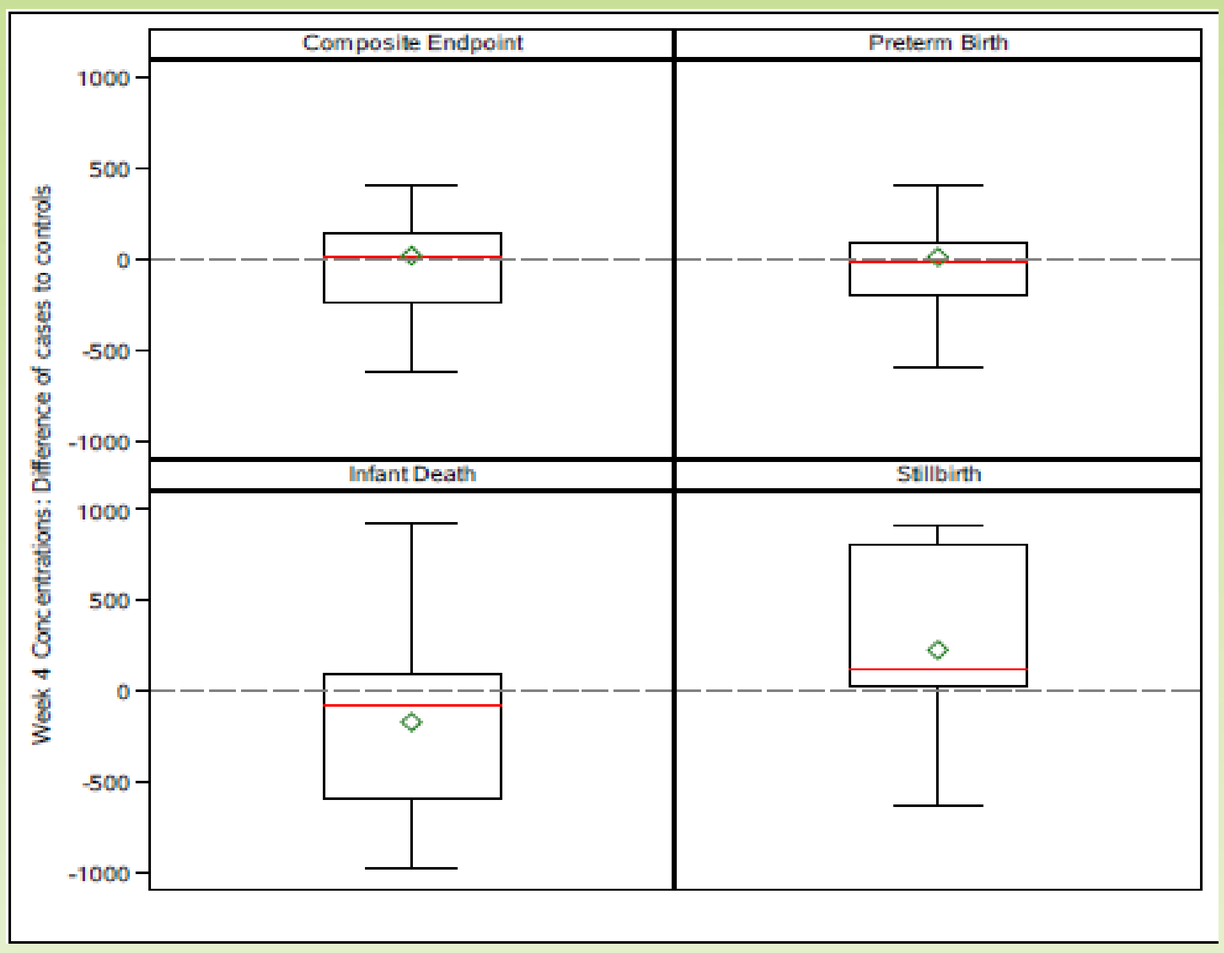


TABLE 1. Risk estimates of adverse pregnancy outcomes among cases versus controls – primary analysis[1]

	Week 4		Week 8	
Outcome	**Odds Ratio (95% CI)**	**P value**	**Odds Ratio (95% CI)**	**P value**
Composite, n= 22	1.27 (0.74, 2.18)	0.389	1.74 (0.66, 4.60)	0.264
Pre-term birth, n= 15	1.10 (0.47, 2.53)	0.841	0.96 (0.28, 3.30)	0.942
Early Infant Death, n= 9	0.91 (0.44, 1.87)	0.800	1.47 (0.42, 5.11)	0.548
Still-birth, n= 6	3.71 (0.36, 38.13)	0.271	2.21 (0.41, 11.90)	0.357

[1]Primary analysis (TFV-DP values below the Lower Limit of Quantification (LLQ) were set to ½ the LLQ or 12.5 fmol/punch; and PK concentrations were natural log transformed); Sensitivity analyses (TFV-DP values below the LLQ were set to ln1 = 0; and PK concentrations were natural log transformed) revealed similar results

CONCLUSIONS

TFV-DP levels in DBS samples were not significantly different between cases and controls at 4 and 8 weeks post-ART initiation, respectively, and were not associated with individual or composite adverse pregnancy outcomes.

These findings, based on data from a limited sample size, suggest that in-utero exposure to TDF-DP concentrations, as measured in DBS, was not significantly associated with the adverse pregnancy outcomes/ early infant deaths in the PROMISE trial that were seen at a higher rate among women on ART than those exposed to antepartum ZDV only.

REFERENCE

1. Fowler MG, Qin M, Fiscus SA, et al. Benefits and Risks of Antiretroviral Therapy for Perinatal HIV Prevention. *N Engl J Med*. 2016;375(18):1726-1737. doi:10.1056/NEJMoa1511691.

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Operations Center: M Allen, A Coletti, K George, M Valentine, K McCarthy, V Hardy
Statistical and Data Management Center: D Shapiro, T Fenton, K Butler, M Qin, C Marr, C Tierney, S Brummel, K Angelidou, M Basar, L Marillo, A Manzella, A Zadzilka
Laboratory Center: S Fiscus, A Loftis
CMC: J McIntyre, L Stranix, D Bhattacharya, R Hoffman, A Gupta, G Theron, B Chi, P Flynn, M Owor, J Currier

Site PROMISE Principal Investigators:
India: *BJMC,* Pune: R Bhosale, P Sambarey
Malawi: *Blantyre*: B Makanani, M Mallewa, T Taha; *UNC-Lilongwe*: F Martinson
South Africa: *CAPRISA Umlazi*, *Durban*: D Moodley; *Durban Paeds*, *Durban*: R Bobat, S Pillay; *FAM-CRU*, *Stellenbosch:* G Theron; *PHRU*, *Soweto*: A Violari; *Shandukani, Johannesburg*: L Fairlie, A Coovadia
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