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

Poster # 83

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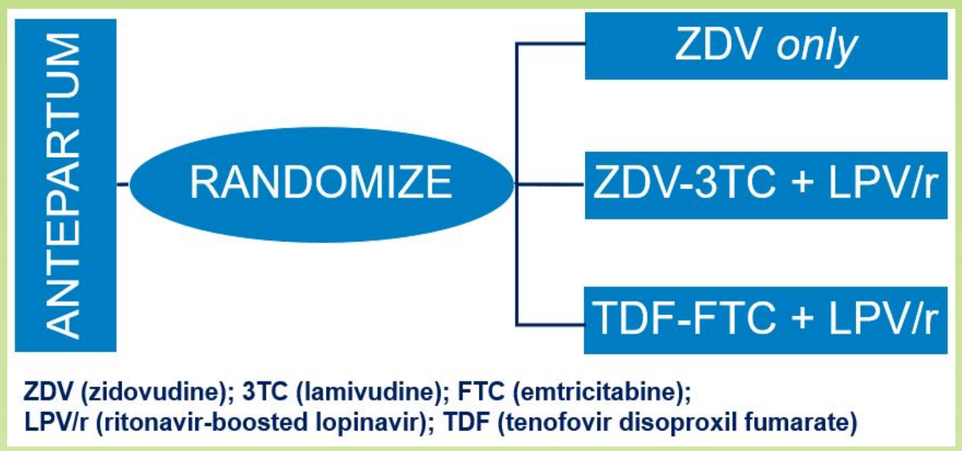
BACKGROUND

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)



ZDV (zidovudine); 3TC (lamivudine); FTC (emtricitabine); LPV/r (ritonavir-boosted lopinavir); TDF (tenofovir disoproxil fumarate)

METHODS

PROMISE study enrollment (2011-2014) across 14 sites in India, Malawi, South Africa, Tanzania, Uganda, Zambia, and Zimbabwe.

Sub-study inclusion criteria: Pregnant women randomized to the PROMISE antepartum component TDF-FTC+LPV/r (14 weeks through delivery); who received at least 4 weeks of TDF-FTC prior to delivery; and had a week 4 (or week 8) DBS sample drawn prior to delivery.

Definition of cases (women with adverse pregnancy outcomes)
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 used to examine the associations between TFV-DP concentrations and the composite adverse pregnancy outcome, and each of its components, respectively.
- Hypothesis testing used 0.05 alpha. Separate analyses were done at weeks 4 and 8.

RESULTS

- Overall, 33 mothers in the PROMISE antepartum component TDF-FTC + LPV/r arm had adverse pregnancy outcomes, and 23 received at least 4 weeks of TDF-FTC (Truvada) prior to delivery, of these 22 and 16 had weeks 4 and 8 TFV-DP concentrations data, respectively (table 1).
- Of the 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 significant difference between cases and controls in terms of median TFV-DP concentrations (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)

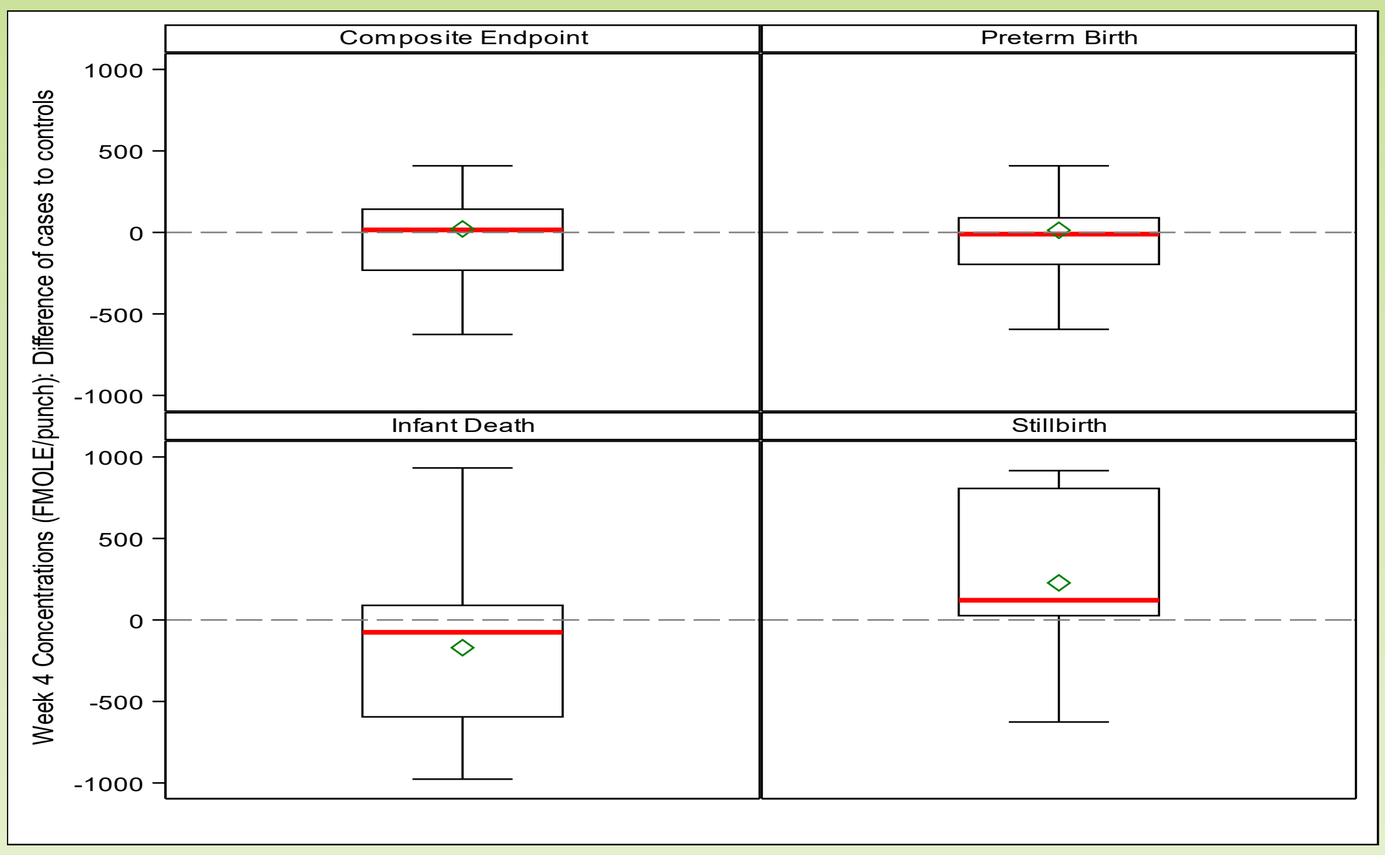


TABLE 1. Risk estimates of adverse pregnancy outcomes among cases versus controls – primary analysis[1]

	Week 4			Week 8		
Outcome	**Size (n)**	**Odds Ratio (95% CI)**	**P value**	**Size (n)**	**Odds Ratio (95% CI)**	**P value**
Composite	22	1.27 (0.74, 2.18)	0.389	16	1.74 (0.66, 4.60)	0.264
Pre-term birth	15	1.10 (0.47, 2.53)	0.841	9	0.96 (0.28, 3.30)	0.942
Early Infant Death	9	0.91 (0.44, 1.87)	0.800	6	1.47 (0.42, 5.11)	0.548
Still-birth	6	3.71 (0.36, 38.13)	0.271	6	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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