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## BACKGROUND

- Understanding the risk-benefit trade-off for pregnancy and infant outcomes in clinical trials of pregnant women is complex due to multiple outcomes of interest
- Clinical trials often summarize risks and benefits in separate analyses, which can be misleading
- Alternatively, risk and benefit can be compared using a **desirability of outcome ranking (DOOR) with weights to account for the severity of the outcome**
- We employed this strategy using data from the IMPAACT 2010 (VESTED) trial

## METHODS

- 643 pregnant women living with HIV** in 9 countries were randomized in 2018-2019 to one of three antiretroviral treatment arms: **dolutegravir (DTG)+emtricitabine (FTC)/tenofovir alafenamide (TAF)**; **DTG+FTC/tenofovir disoproxil fumarate (TDF)**; or **efavirenz (EFV)/FTC/TDF**
- Key inclusion criteria included  $\geq 18$  years of age, confirmed HIV-1 infection, ART-naïve at screening, no evidence of multiple gestation or fetal anomaly, gestational age of 14-28 weeks
- Mother-infant (MI) pair adverse **outcomes were grouped in a pre-specified secondary outcome according to the most severe outcome experienced**: 1) infant death, 2) spontaneous abortion or stillbirth, 3) infant HIV infection (benefit via reduction), 4) very preterm delivery (<32 weeks), 5) major congenital anomaly, 6) preterm delivery (<37 weeks), 7) small for gestational age (<10th percentile, SGA), 8) infant hospitalization, and 9) infant grade 3 or 4 adverse event
- Non-protocol specified **analyses weighted the ranked outcome** according to the study team's belief of their severity based on a tipping point strategy
  - Questionnaire included a hypothetical 2-arm study in which infant death rate was 2.5% higher in one arm
  - Study team members blinded to the ranked outcome were asked to provide endpoint rates that would result in the 2 arms having a similar profile (Table 1)
- Odds ratios (ORs) were computed for the composite outcomes at each level of the ranked outcome plus more severe events
- Weighted and unweighted ordinal ORs were computed to provide a summary OR across all event types**

- The risk-benefit trade-off was clearer with the weighted ranked outcome that includes many outcomes, compared to previously reported separate analyses.**
- DTG+FTC/TAF provided the best overall risk-benefit trade-off.**

## RESULTS

- 79/216 (37%), 93/213 (44%), and 101/211 (48%) MI pairs experienced at least one of the ranked outcomes in the DTG+FTC/TAF, DTG+FTC/TDF, and EFV/FTC/TDF arms, respectively
- Standard ORs consistently favored the DTG arms over the EFV/FTC/TDF arm, and the DTG+FTC/TAF arm over the DTG+FTC/TDF arm (Figure 1)
- Ordinal ORs resulted in a **better risk-benefit trade-off for DTG+FTC/TAF compared to EFV/FTC/TDF (OR=0.60, 95% confidence interval(CI):0.42, 0.88)**
- The study team questionnaire resulted in higher severity-weights for more extreme outcomes (Table 2), e.g., infant death was considered 18 times more severe than a single hospitalization
- In the severity-weighted analysis, DTG+FTC/TAF had an even better risk-benefit trade-off relative to DTG+FTC/TDF (OR=0.64, 95%CI:0.49, 0.84) and EFV/FTC/TDF (OR=0.28, 95%CI:0.21, 0.36); DTG+FTC/TDF had a better risk-benefit trade-off relative to EFV/FTC/TDF (OR=0.41, 95%CI:0.32, 0.53).**

FIGURE 1. By-Arm Odds Ratio Comparisons for the Composite and Ordinal Outcome Measures

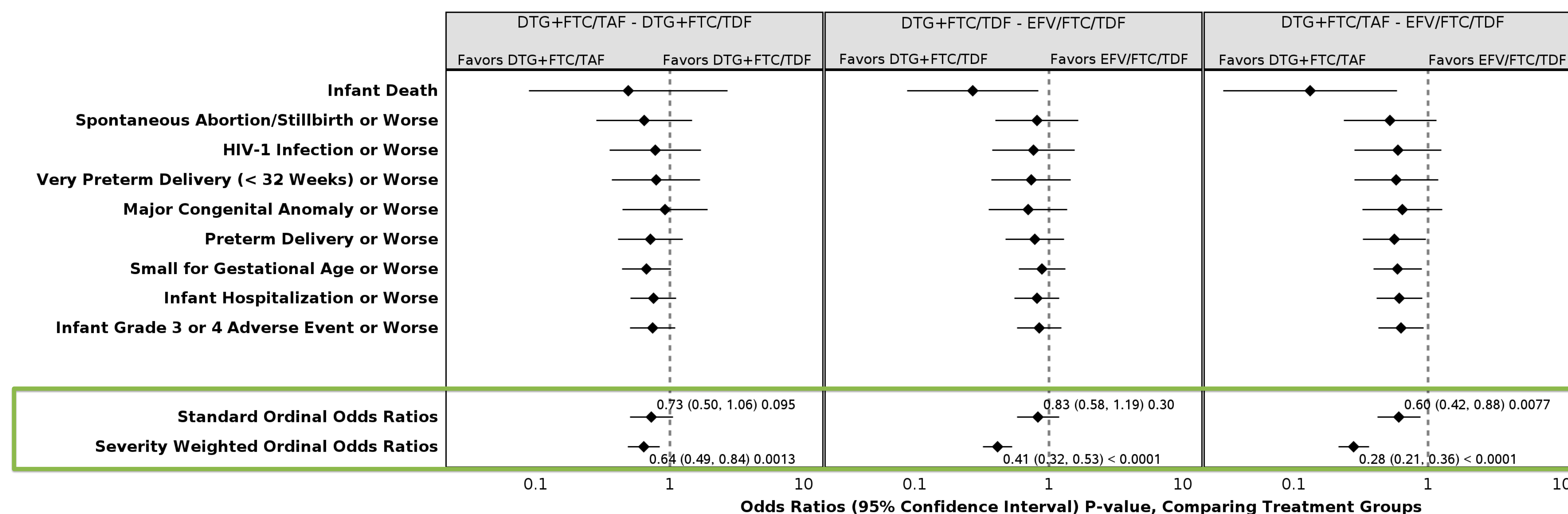


TABLE 1. Hypothetical Study Results Used to Derive Severity Weights

	Arm A	Arm B
Infant Death through 1 Year of Life	2.5%	5%
Infant HIV Infection	?	2.5%

TABLE 2. Severity Weights From Tipping Point Analysis

Ranked Outcome	Severity Weight
Infant Death through 1 Year of Life	18
Spontaneous abortion or stillbirth	4.9
Infant HIV-1 Infection	5.7
Very Preterm Delivery (<32 weeks)	4.0
Major Congenital Anomaly	2.4
Preterm Delivery (<37 weeks)	1.6
Small for Gestational Age (< 10 <sup>th</sup> percentile)	1.5
Infant Hospitalization	1.0
Infant Grade 3 or 4 Adverse Event	1.0
None of the Above	1.0

## CONCLUSIONS

- The risk-benefit trade-off was clearer with these ranked outcome analyses, compared to the many separate previously reported analyses which favored different arms for outcomes of different severity in IMPAACT 2010**
- When more severe outcomes were given more weight, DTG+FTC/TAF provided the overall best and clearest risk-benefit trade-off. Similarly, DTG+FTC/TDF had a better risk-benefit profile than EFV/FTC/TDF

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