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BACKGROUND

- Understanding the risk-benefit trade-off for pregnancy and infant outcomes in clinical trials of pregnant wom 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 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 >= 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 experience 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 fo gestational age (<10th percentile, SGA), 8) infant hospitalization, and 9) infant grade 3 or 4 adverse eve
- Non-protocol specified analyses weighted the ranke outcome according to the study team's belief of their severity based on a tipping point strategy
 - Questionnaire included a hypothetical 2-arm study which infant death rate was 2.5% higher in one arn
 - Study team members blinded to the ranked outcon were asked to provide endpoint rates that would result in the 2 arms having a similar profile (Table
- 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

Risk-benefit Trade-off for Pregnancy and Infant Outcomes: DTG, EFV, TAF, and TDF

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ne		rate ana
	• DTG+FTC/TA	F provid
S	risk-benefit ti	rade-off.
	 RESULTS 79/216 (37%), 93/213 (44%), an outcomes in the DTG+FTC/TAF, Standard ORs consistently favor 	DTG+FTC/TDF, a
10	 DTG+FTC/TAF arm over the DT Ordinal ORs resulted in a better EFV/FTC/TDF (OR=0.60, 95% of The study team questionnaire re (Table 2), e.g., infant death was 	G+FTC/TDF arm risk-benefit trad confidence interv sulted in higher se considered 18 time
	 In the severity-weighted analy 	
	relative to DTG+FTC/TDF (OR= 95%CI:0.21, 0.36); DTG+FTC/T EFV/FTC/TDF (OR=0.41, 95%C	=0.64, 95%CI:0.49 DF had a better r
3)	95%CI:0.21, 0.36); DTG+FTC/T	=0.64, 95%CI:0.49 DF had a better r SI:0.32, 0.53).
3)	95%CI:0.21, 0.36); DTG+FTC/T EFV/FTC/TDF (OR=0.41, 95%C	=0.64, 95%CI:0.49 DF had a better r 1:0.32, 0.53). parisons for the DTG+FTC/TAF - D
ced: 3)	95%CI:0.21, 0.36); DTG+FTC/T EFV/FTC/TDF (OR=0.41, 95%C FIGURE 1. By-Arm Odds Ratio Com	=0.64, 95%CI:0.49 DF had a better r I:0.32, 0.53).
3) for vent ked	95%CI:0.21, 0.36); DTG+FTC/T EFV/FTC/TDF (OR=0.41, 95%C	=0.64, 95%CI:0.49 DF had a better r 1:0.32, 0.53). parisons for the DTG+FTC/TAF - D
3) or vent	95%CI:0.21, 0.36); DTG+FTC/T EFV/FTC/TDF (OR=0.41, 95%C FIGURE 1. By-Arm Odds Ratio Com	=0.64, 95%CI:0.49 DF had a better r 1:0.32, 0.53). parisons for the DTG+FTC/TAF - D
3) for vent ked ir	95%CI:0.21, 0.36); DTG+FTC/T EFV/FTC/TDF (OR=0.41, 95%C FIGURE 1. By-Arm Odds Ratio Com Infant Death Spontaneous Abortion/Stillbirth or Worse	=0.64, 95%CI:0.49 DF had a better r 1:0.32, 0.53). parisons for the DTG+FTC/TAF - D
3) for vent ked ir y in	95%CI:0.21, 0.36); DTG+FTC/T EFV/FTC/TDF (OR=0.41, 95%C FIGURE 1. By-Arm Odds Ratio Com Infant Death Spontaneous Abortion/Stillbirth or Worse HIV-1 Infection or Worse Very Preterm Delivery (< 32 Weeks) or Worse Major Congenital Anomaly or Worse	=0.64, 95%CI:0.49 DF had a better r 1:0.32, 0.53). parisons for the DTG+FTC/TAF - D
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3) for vent ked ir y in m	95%CI:0.21, 0.36); DTG+FTC/T EFV/FTC/TDF (OR=0.41, 95%C FIGURE 1. By-Arm Odds Ratio Com Infant Death Spontaneous Abortion/Stillbirth or Worse HIV-1 Infection or Worse Very Preterm Delivery (< 32 Weeks) or Worse Major Congenital Anomaly or Worse	=0.64, 95%CI:0.49 DF had a better r 1:0.32, 0.53). parisons for the DTG+FTC/TAF - D
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Overall support for the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) was provided by the National Institute of Allergy and Infectious Diseases (NIAID) 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), all components of the National Institutes of Health (NIH), under Award Numbers UM1AI068632-15 (IMPAACT LOC), UM1AI068616-15 (IMPAACT SDMC) and UM1AI106716-09 (IMPAACT LC), and by NICHD contract number HHSN275201800001I. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

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led the best overall

MI pairs experienced at least one of the ranked and EFV/FTC/TDF arms, respectively s over the EFV/FTC/TDF arm, and the (Figure 1)

de-off for DTG+FTC/TAF compared to val(CI):0.42, 0.88)

severity-weights for more extreme outcomes nes more severe than a single hospitalization AF had and even better risk-benefit trade-off 19, 0.84) and EFV/FTC/TDF (OR=0.28, risk-benefit trade-off relative to

Weights

Infant Dea Infant HIV

Ranked O Infant Deat Spontaneo Infant HIV-Very Preter Major Cong Preterm De Small for G Infant Hosp Infant Grad None of the

CONCLUSIONS

Composite and Ordinal Outcome Measures

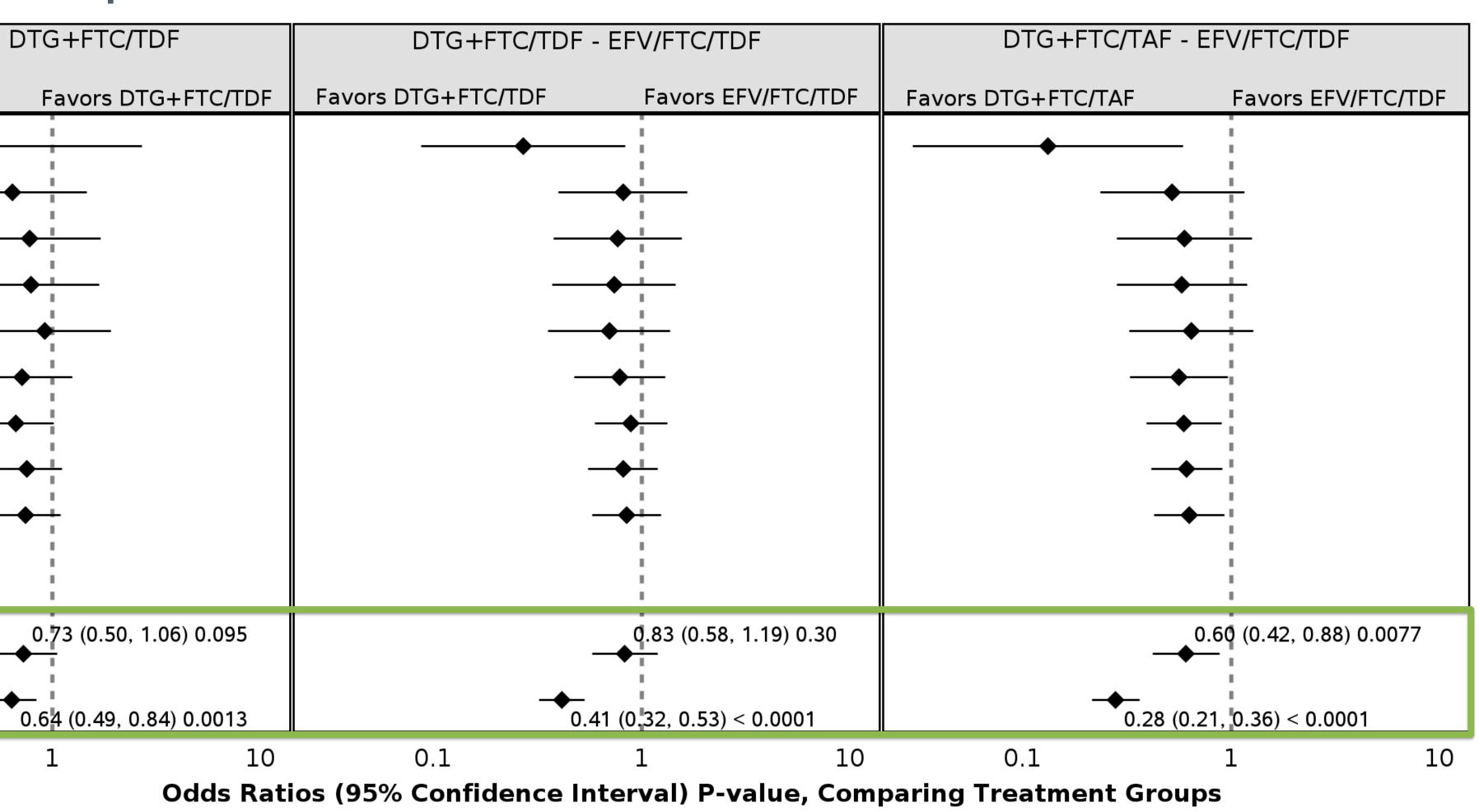


TABLE 1. Hypothetical Study Results Used to Derive Severity

	Arm A	Arm B
ath through 1 Year of Life	2.5%	5%
Infection	?	2.5%

TABLE 2. Severity Weights From Tipping Point Analysis

utcome	Severity Weight
th through 1 Year of Life	18
ous abortion or stillbirth	4.9
1 Infection	5.7
rm Delivery (<32 weeks)	4.0
genital Anomaly	2.4
elivery (<37 weeks)	1.6
Sestational Age (< 10 th percentile)	1.5
pitalization	1.0
de 3 or 4 Adverse Event	1.0
e Above	1.0

• 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 riskbenefit trade-off. Similarly, DTG+FTC/TDF had a better riskbenefit profile than EFV/FTC/TDF

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