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BACKGROUND

- Women with HIV (WHIV) who conceive on antiretroviral treatment (ART) may have higher risk of adverse pregnancy outcomes including spontaneous abortion, stillbirth, preterm birth, low birth weight¹
- An increasing proportion of pregnant WHIV are now on ART from conception
- However, few studies have prospectively captured pregnancy outcomes among WHIV receiving ART during conception.

METHODS

- In IMPAACT 2010 (VESTED), 643 WHIV in 9 countries were randomized to start 1 of 3 ART regimens between 14-26 weeks gestation: dolutegravir (DTG) plus emtricitabine (FTC)/tenofovir alafenamide (TAF); DTG+FTC/tenofovir disoproxil fumarate (TDF); or efavirenz (EFV)/FTC/TDF
- Due to a protocol amendment based on recommendations at the time, to mitigate risks of neural tube defects in infants whose mothers conceived on DTG, women who did not wish to take effective contraception following delivery were switched from DTG to another antiretroviral (usually EFV) during the 50 weeks of postpartum follow-up
- We describe adverse pregnancy outcomes in women who became pregnant during postpartum follow-up (subsequent pregnancy): spontaneous abortion (<20 weeks), stillbirth (≥20 weeks), preterm delivery (<37 weeks) and small for gestational age (SGA; <10th centile)

TABLE 1. Composite pregnancy outcome in subsequent pregnancies by ART regimen at time of subsequent pregnancy

Outcome	ARV Treatment at Start of Pregnancy events/N (%)				
	DTG+FTC/TAF	DTG+FTC/TDF	EFV/FTC/TDF	Non-Study Treatment	Total
Stillbirth or Spontaneous Abortion*	1/2 (50%)	0/2 (0%)	5/12 (41.7%)	1/3 (33%)	7/19 (36.8%)
Preterm Delivery (<37 Weeks)	0/1 (0%)	0/2 (0%)	2/7 (28.6%)	1/2 (50%)	3/12 (25%)
Small for Gestational Age (<10 th Percentile)	0/0 (NA)	0/1 (0%)	1/4 (25%)	0/1 (100%)	1/6 (16.7%)
Composite Adverse Outcome	1/2 (50%)	0/2 (0%)	8/12 (66.7%)	2/3 (66.7%)	11/19 (57.9%)

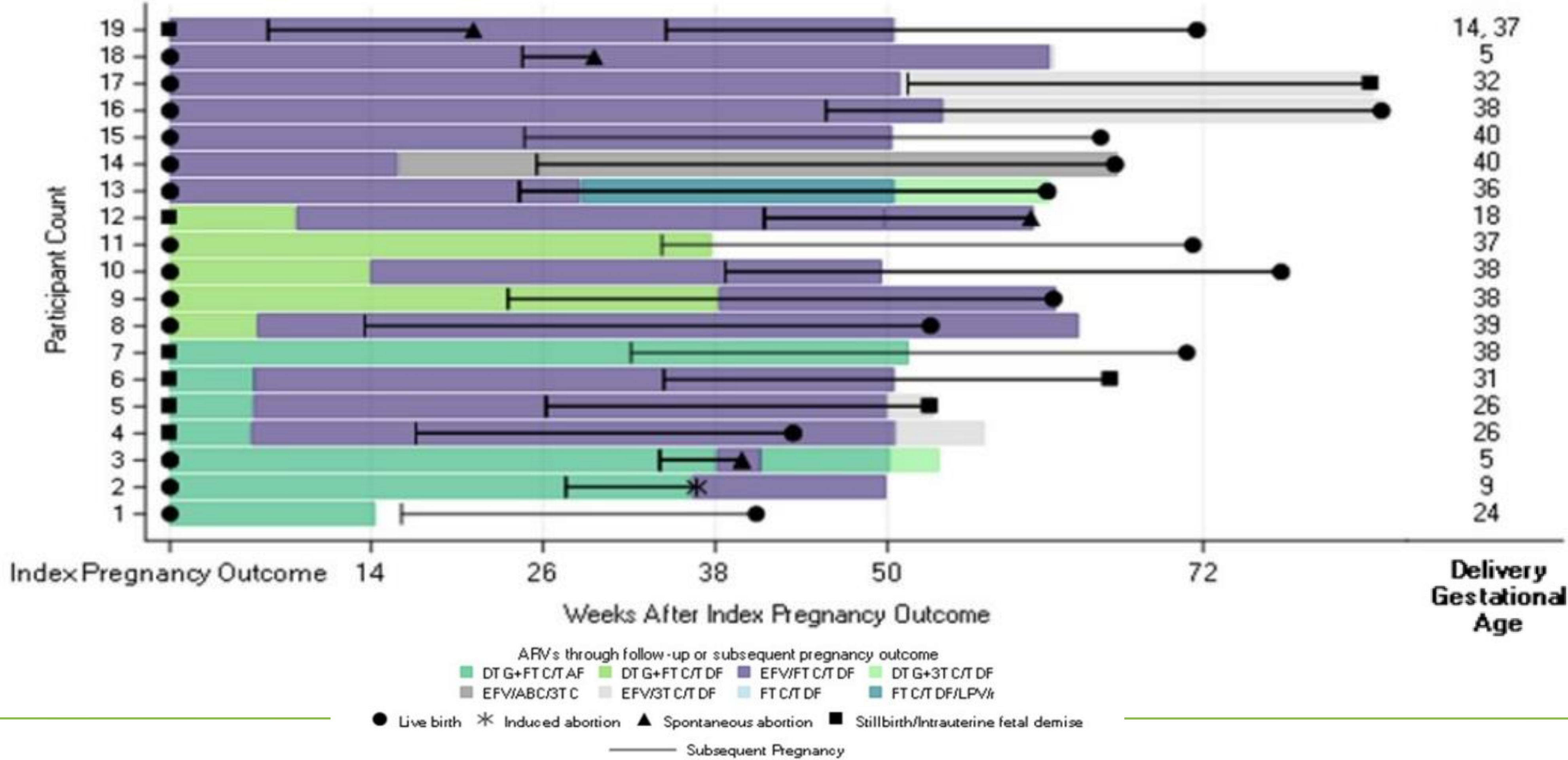
* One pregnancy resulting in induced abortion excluded from composite outcome analysis

Adverse pregnancy outcomes including spontaneous abortion, stillbirth and preterm delivery occurred in 11/20 (58%) of subsequent pregnancies in WHIV conceiving on ART in the IMPAACT 2010/VESTED study

RESULTS

- 19 (3%) of 643 women had 20 subsequent pregnancies on-study and were taking the following ART at conception: DTG+FTC/TAF (3), DTG+FTC/TDF (2), EFV/FTC/TDF (11, 1 woman with 2 pregnancies), non-study ART (lopinavir/ritonavir-based ART and non-study EFV-based ART) (2) and no ART (1)
- 4/20 (20%) spontaneous abortions, 3/20 (15%) stillbirths, and 1/20 (5%) induced abortions occurred. Three (25%) liveborn infants were preterm (24-, 26- and 36-weeks' gestation)
- Thus, only 12/20 (60%) subsequent pregnancies resulted in live birth and at least 1 adverse pregnancy outcome occurred in 11/20 (58%) subsequent pregnancies, more frequently with EFV/FTC/TDF at conception (8 [67%] of 12 pregnancies) than with DTG-ART at conception (1/4 women) [Figure 1]
- Of the 7 women who experienced spontaneous abortion or stillbirth in the subsequent pregnancy, 4 had experienced a stillbirth and 1 a neonatal death as outcomes of the earlier index pregnancy (the pregnancy at enrolment to the VESTED trial)
- No congenital anomalies were reported in subsequent pregnancies

FIGURE 1. Birth Outcomes for the 19 Subsequent Pregnancies in the VESTED Trial, by Week from Index Pregnancy



CONCLUSIONS

- **Adverse pregnancy outcomes were very common** in this cohort of WHIV who conceived on ART- **35% of pregnancies** ended in **stillbirth** or **spontaneous abortion**
- Most women with spontaneous abortion/stillbirth had experienced a **recent prior pregnancy loss** (potentially at higher risk for repeat adverse pregnancy outcome)
 - This finding should be considered in analyses of incident pregnancies occurring in trial participants
- Our **sample size** was too **small** to test differences in outcomes of subsequent pregnancies by regimen.
- **Data from larger cohorts of WHIV conceiving on ART** compared to HIV-negative and those not conceiving on ART are needed to elucidate factors associated with adverse pregnancy outcomes

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REFERENCES

1. Theron G, Brummel S, Fairlie L, et al. Pregnancy Outcomes of Women Conceiving on Antiretroviral Therapy (ART) Compared to Those Commenced on ART During Pregnancy. Clin Infect Dis. 2021 Jul 15;73(2):e312-e320. doi: 10.1093/cid/ciaa805.PMID: 32564058