# ICAP Journal Club

ICAP's Journal Club is designed to inform ICAP staff and colleagues of the latest scientific literature by providing a succinct summary and critical analysis of important studies, and by discussing the implications of the research on clinical work.

## Article

Lockman S, Brummel SS, Ziemba L, et al. **Efficacy and safety of dolutegravir with emtricitabine and tenofovir alafenamide fumarate or tenofovir disoproxil fumarate, and efavirenz, emtricitabine, and tenofovir disoproxil fumarate HIV antiretroviral therapy regimens started in pregnancy (IMPAACT 2010/VESTED): A multicentre, open-label, randomised, controlled, phase 3 trial**. *Lancet*. 2021;397(10281):1276-1292. https://doi.org/10.1016/S0140-6736(21)00314-7

## Study Summary

The International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) 2010/Virologic Efficacy and Safety of ART Combinations with TAF/TDF, EFV, and DTG (VESTED) study is a multi-center, open-label, randomized controlled, phase 3 trial that compared the virological efficacy and safety of two antiretroviral therapy (ART) regimens containing dolutegravir (DTG), with either tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide fumarate (TAF), and an efavirenz (EFV)-containing regimen, when started in pregnancy.

Study Setting

- Twenty-two clinical research sites in nine countries (Botswana, Brazil, India, South Africa, Tanzania, Thailand, Uganda, the USA, and Zimbabwe).

Methods

- Pregnant women aged ≥18 years, with confirmed HIV-1 infection and at 14–28 weeks' gestation, were eligible to participate.
- Eligible women had to be ART-naive with the following exceptions: on ART ≤14 days during the current pregnancy; previous TDF or TDF with emtricitabine (FTC) pre-exposure prophylaxis; or having been on ART during previous pregnancies with the last dose taken ≥6 months prior.
- Women were excluded if they were pregnant with a fetus that had a known anomaly or multiple fetuses; had a history of psychiatric illness; had an acute illness requiring systemic treatment in the preceding 14 days; had active tuberculosis; had alanine aminotransferase or aspartate aminotransferase ≥2.5 times the upper limit of normal; or had an estimated creatinine clearance (CrCl) of <60 mL/min.

- Eligible women were randomly assigned (1:1:1) to receive either once-daily oral DTG 50mg, and once-daily oral fixed-dose combination FTC 200mg and TAF 25mg (DTG/FTC/TAF group); once-daily oral DTG 50mg, and once-daily oral fixed-dose combination FTC 200mg and TDF 300mg (DTG/FTC/TDF group); or once-daily oral fixed-dose combination of EFV 600mg, FTC 200mg, and TDF 300mg (EFV/FTC/TDF group).
- Study drugs were open-label and randomization was stratified by gestational age (14–18, 19–23, and 24–28 weeks) and by country.
- Following randomization, prenatal study visits occurred every four weeks and at delivery.
- Maternal HIV-1 RNA, alanine aminotransferase, aspartate aminotransferase, and creatinine concentrations were measured before randomization and regularly throughout follow-up. At the birth visit, an HIV-1 test (nucleic acid, RNA, or DNA) was done in infants.
- In cases of virological failure (defined as two successive plasma viral load [VL] test results ≥200 copies/mL, with the first test occurring ≥24 weeks on study regimen) or drug toxicity, site investigators could prescribe alternative ART regimens.
- The primary efficacy outcome was the proportion of participants with viral suppression (defined as VL <200/mL) at or within 14 days of delivery.
- The primary safety outcome was a composite adverse pregnancy outcome, defined as the occurrence of spontaneous abortion (at <20 weeks' gestation), stillbirth (at ≥20 weeks' gestation), preterm delivery (at <37 weeks' gestation in live-born babies), or the infant being born small for gestational age (birthweight <10th percentile for gestational age, adjusted for sex).
- Other safety outcomes included the occurrence of maternal grade 3 or higher adverse events between enrollment and 14 days postpartum, and the occurrence of infant grade 3 or higher adverse events between birth and 28 days.
- Analyses were by intention-to-treat and –10% was set as the non-inferiority margin for virological efficacy of the combined DTG-containing groups versus the EFV/FTC/TDF group.

<u>Study Population and Follow-up</u>

- Between January 2018 and February 2019, 810 pregnant women were screened for eligibility. Of these, 643 pregnant women were enrolled and randomly assigned to the DTG/FTC/TAF group (n=217), the DTG/FTC/TDF group (n=215), or the EFV/FTC/TDF group (n=211).
- Baseline characteristics of participants at enrollment were similar across the three groups, with a median age of 26.6 years (interquartile range [IQR] 22.5-31.6), median gestational age of 21.9 weeks (IQR 18.3-25.3) and 91% of participants were Black.
- Most participants (83%) took ART during their current pregnancy before enrollment, primarily EFV-based regimens, with a median duration on ART of 6 days (IQR 4–9).
- At enrollment, participants had a median VL of 902.5 copies/mL (IQR 152.0–5182.5), and 28% of participants had VL <200 copies/mL.

- The median duration between randomization and the pregnancy outcome was 17.4 weeks (IQR 14.3–21.1), during which time <1% of participants withdrew from the study and 97% did not miss any study visits.
- The assigned ART regimen was modified in 4% of participants before delivery, 3% in the DTG/FTC/TAF group, 2% in the DTG /FTC/TDF group, and 7% in the EFV/FTC/TDF group.
- VL at the delivery visit was available for 605 (94%) participants and 640 (>99%) had a recorded pregnancy outcome.

Efficacy Outcomes

- Of those with VL results available at delivery, 95% had viral suppression: 98% of participants in the combined DTG-containing groups vs. 91% of participants in the EFV/FTC/TDF group (estimated difference 6.5%, 95% confidence interval [CI] 2.0–10.7; p=0.0052), which met the pre-specified criteria for virological superiority.
- Participants in a DTG-containing groups also had a significantly shorter time to viral suppression than those in the EFV/FTC/TDF group (p<0.0001).
- At delivery, 95% of participants in the combined DTG-containing groups had VL<50 copies/mL, compared with 80% of participants in the EFV/FTC/TDF group (estimated difference 15.5%, 95% CI 9.5–21.4; p<0.0001).

Pregnancy Safety Outcomes

- Among those with recorded pregnancy outcomes, 4% had a stillbirth and of the livebirths, 9% were preterm, and 20% were small for gestational age.
- The composite adverse pregnancy outcome was reported in 30% of mother–infant pairs, and was significantly less frequent in the DTG/FTC/TAF group (24%) compared to the DTG/FTC/TDF group (33%; estimated difference –8.8%, 95% CI –17.3 to –0.3; p=0.043) or the EFV/FTC/TDF group (33%; estimated difference –8.6%, 95% CI –17.1 to –0.1; p=0.047).
- A higher proportion of participants in the DTG-containing groups had stillbirths (4% in the DTG/FTC/TAF group and 5% in the DTG /FTC/TDF) than in the EFV/FTC/TDF group (2%), although this difference was not statistically significant.
- In the DTG/FTC/TAF group, preterm delivery was significantly less frequent than in the EFV/FTC/TDF group (6% vs. 12%; p=0.023), and less frequent compared to the DTG/FTC/TDF group, but this difference was not statistically significant (6% vs. 9%; p=0.16).
- Infant mortality between birth and 28 days was higher in the EFV/FTC/TDF group (5%) than in the DTG/FTC/TAF group (1%; p=0.019) or DTG /FTC/TDF group (2%; p=0.050), with no significant difference between the two DTG-containing groups (p=0.65).
- Of the 617 live-born infants, 91% had at least one HIV nucleic acid test result available; two (<1%) of whom had at least one positive result. One infant was in the DTG/FTC/TAF group and the other was in the DTG /FTC/TDF group.
- Overall, 17% of live-born infants had at least one grade 3 or higher adverse event between birth and 28 days, with no significant differences between groups.

Maternal Safety Outcomes

- Between enrollment and 14 days postpartum, 23% of participants had at least one grade 3 or higher adverse event, with no significant differences between groups.
- Participants in the DTG/FTC/TAF group had a significantly greater average weekly weight gain (0.378 kg/week) compared with those in the DTG/FTC/TDF group (0.319 kg/week; p=0.011) and the EFV/FTC/TDF group (0.291 kg/week; p=0.0002). There was no significant difference in weekly weight gain between participants in the DTG/FTC/TDF group and those in the EFV/FTC/TDF group.
- Estimated CrCl at delivery was significantly lower in the DTG/FTC/TDF group (134.9 mL/min) than in the DTG/FTC/TAF group (148.5 mL/min; p=0.0051) or the EFV/FTC/TDF group (155.5 mL/min; p<0.0001).

## Critical Analysis

This multi-center, open-label randomized controlled trial found that DTG-containing regimens, started at 14–28 weeks of pregnancy, had a significantly higher rate of viral suppression at delivery and a significantly shorter time to viral suppression than an EFV-containing regimen. Of the three regimens studied, DTG/FTC/TAF had the most favorable safety profile, with significantly fewer participants in this group reporting a composite adverse pregnancy outcome, and fewer neonatal deaths were seen in the DTG-containing groups. No significant differences were observed in the occurrence of maternal or infant grade 3 or higher adverse events among the three groups.

The following points should be considered when interpreting the study findings:

- The threshold for viral suppression was set at <200 copies/mL as this was considered more reliable and less variable than detection at lower thresholds, especially in diverse settings. In sensitivity analyses using VL thresholds of <400 copies/mL and <1000 copies/mL, participants in the DTG-containing groups still had a significantly shorter time to viral suppression compared to those in the EFV/FTC/TDF group.
- The study used an EFV dose of 600mg, which could have more side effects than the recommended EFV 400mg dose, and this may have contributed to the more frequent regimen changes seen in this group.
- The majority of participants had started ART before enrollment, and one in four had a suppressed VL at enrollment, which could have contributed to the high rates of viral suppression at delivery. However, analyses restricted to women with VL ≥200 copies/mL at enrollment showed similar results to the primary results.
- The study started women on DTG-containing regimens after 14 weeks' gestation, and therefore does not provide any additional information on the safety of DTG during

conception and the first trimester period, which is when there are concerns over neural tube defects developing in exposed infants. Only three major congenital anomalies were reported, none of which were neural tube defects.

- Pregnant women with multiple gestations, known fetal anomalies, or other medical conditions were excluded, which could have led to a lower overall incidence of adverse pregnancy outcomes than would be seen in real-world settings.
- While there was significantly more weight gain associated with the DTG/FTC/TAF regimen, mean weight gain in all three groups was still lower than the recommended weight gain in pregnancy of 0.42 kg/week. Furthermore, only one participant was diagnosed with gestational diabetes (in the DTG/FTC/TDF group), suggesting that there was not clinically significant weight gain during the study period.
- Similarly, renal adverse events were rare, with only four participants reporting grade 3 or higher CrCl, suggesting that differences observed between the groups in CrCl were not clinically significant.
- Although women in the EFV/FTC/TDF group had lower rates of viral suppression at birth, there were no documented perinatal transmissions in this group. It is important to note, however, that the study was not powered to detect differences in perinatal transmission between the groups.

## Implications

The IMPAACT 2010/VESTED study is a multi-center, open-label, randomized controlled trial that found DTG-based ART started in pregnancy had superior virological efficacy at delivery compared with an EFV-based regimen. Additionally, the DTG-based regimen with TAF was found to have a better safety profile, with fewer composite adverse pregnancy outcomes reported. The results of this trial support the World Health Organization's recommendation to use DTG-based regimens in all populations, including in women starting ART during pregnancy,[1] and suggest that a DTG-based regimen with TAF should be considered in this population.

*This article synopsis was written by Cassia Wells. Share your thoughts on this article or suggest an article for Journal Club by emailing her at caw2208@columbia.edu.*

## References

1) World Health Organization. Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV: supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: World Health Organization, 2018.