Safety and Efficacy of DTG vs EFV and TDF vs TAF in Pregnancy: IMPAAACT 2010 TRIAL

L Chinula, SS Brummel, L Ziemba, L Stranix-Chibanda, A Coletti, C Krotje, P Jean-Philippe, L Fairlie, T Vhembo, D Wabwire, RM Hoffman, PE Sax, JS Stringer, JS Currier, S Lockman, on behalf of the IMPAAACT 2010 Study Team
Background and Rationale

• WHO now recommends dolutegravir (DTG)-based antiretroviral treatment (ART) globally, given favorable efficacy, toxicity, resistance, and cost profiles
• Countries are transitioning from efavirenz (EFV)- to DTG-based first-line ART
  – Tenofovir alafenamide fumarate (TAF) is a recommended first-line agent for adults in the US
• *It is essential to obtain pregnancy safety and efficacy data for agents that are expected to be widely used by women during pregnancy, such as DTG and TAF*
• We designed a Phase III, three-arm randomized open-label trial to compare the safety and virologic efficacy of three regimens started by women living with HIV (WLHIV) during pregnancy
Enrollment at 14-28 weeks gestation

Delivery

Completion of follow-up at 50 weeks postpartum

Weeks on Study Antepartum  Weeks on Study Postpartum

Arm 1: Maternal DTG+FTC/TAF During Pregnancy and Postpartum
- Maternal follow-up for ~12-26 weeks prior to delivery
- Maternal and infant follow-up for 50 weeks after delivery (infant receives local standard prophylaxis)

Arm 2: Maternal DTG+FTC/TDF During Pregnancy and Postpartum
- Maternal follow-up for ~12-26 weeks prior to delivery
- Maternal and infant follow-up for 50 weeks after delivery (infant receives local standard prophylaxis)

Arm 3: Maternal EFV/FTC/TDF During Pregnancy and Postpartum
- Maternal follow-up for ~12-26 weeks prior to delivery
- Maternal and infant follow-up for 50 weeks after delivery (infant receives local standard prophylaxis)

Key Eligibility Criteria
- Pregnant WLHIV 14-28 weeks gestation
- ART-naïve (up to 14 days ART in current pregnancy allowed)

Participants were enrolled at 22 sites in 9 countries
Study Objectives: Virologic Efficacy

Whether treatment initiated during pregnancy with a DTG-containing regimen (DTG arms combined) is non-inferior to EFV/FTC/TDF with regard to HIV-1 RNA <200 copies/mL at delivery (primary)

• -10% non-inferiority margin in favor of EFV for virologic efficacy
• Assessed superiority after establishing non-inferiority
Study Objectives: Safety

Whether rates of the following outcomes differ for any pairwise regimen comparison:

• **Adverse pregnancy composite outcome** (primary): occurrence of preterm delivery (PTD) <37 weeks, small for gestational age (SGA) <10th centile, stillbirth (SB) ≥20 weeks, or spontaneous abortion (SAB) <20 weeks

• **Maternal grade 3 or higher adverse events** through 50 weeks postpartum (*this analysis includes follow-up through 14 days postpartum*)

• **Infant grade 3 or higher adverse events** through 50 weeks postpartum (*this analysis includes follow-up through 28 days after birth*)

• **Infant neonatal death** (≤28 days) (*post-hoc*)
Screened = 810

Screening failure = 167 (20.6%)
  • Gestational age outside of 14-28 weeks = 66 (40%)
  • Paused study enrollment = 15 (9%)
  • Maternal history of suicidal ideation = 13 (8%)
  • Did not return to clinic = 11 (7%)
  • Mother was not ART-naive = 9 (5%)
  • Multiple gestation or fetal anomaly = 8 (5%)

Enrolled = 643 (79%)

Pregnancy outcome available = 640 (99.5%)

Delivery HIV-1 RNA available = 605 (94%)

Live births = 617 (96%) singletons
## Maternal Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>DTG+FTC/TAF (N = 217)</th>
<th>DTG+FTC/TDF (N = 215)</th>
<th>EFV/FTC/TDF (N = 211)</th>
<th>Total (N = 643)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (median years)</strong></td>
<td>26.8</td>
<td>26.0</td>
<td>26.6</td>
<td>26.6</td>
</tr>
<tr>
<td><strong>Enrolled in Africa</strong></td>
<td>187 (86%)</td>
<td>189 (88%)</td>
<td>188 (89%)</td>
<td>564 (88%)</td>
</tr>
<tr>
<td><strong>Gestational age (median weeks)</strong></td>
<td>22.1</td>
<td>21.3</td>
<td>22.1</td>
<td>21.9</td>
</tr>
<tr>
<td><strong>CD4 count (median cells/mm(^3))</strong></td>
<td>467</td>
<td>481</td>
<td>439</td>
<td>466</td>
</tr>
<tr>
<td><strong>HIV-1 RNA (median copies/mL)</strong></td>
<td>781</td>
<td>715</td>
<td>1357</td>
<td>903</td>
</tr>
<tr>
<td><strong>HIV-1 RNA &lt;50</strong></td>
<td>36 (17%)</td>
<td>37 (17%)</td>
<td>27 (13%)</td>
<td>100 (16%)</td>
</tr>
<tr>
<td><strong>ART in pregnancy prior to entry</strong></td>
<td>176 (81%)</td>
<td>180 (84%)</td>
<td>176 (83%)</td>
<td>532 (83%)</td>
</tr>
<tr>
<td><strong>Median days on ART</strong></td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
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</tbody>
</table>

Median duration of antepartum follow-up: 17.4 weeks
Virologic Suppression at Delivery was Significantly Higher in the DTG Arms Compared with EFV Arm

Proportion of women with HIV-1 RNA <200 copies/mL at delivery visit:

Combined DTG-ART arms vs EFV/FTC/TDF arm

Risk difference 6.5% (2.0%, 10.7%) p=0.005

Risk difference 6.0% (1.6%, 10.3%) p=0.008

DTG arms had shorter time to viral suppression: log-rank p-value <0.001
Adverse Pregnancy Outcomes by Arm

Notes: stillbirth was post-hoc analysis; and no spontaneous abortions occurred
Maternal and Infant
Grade 3 or Higher Adverse Events by Arm

- Maternal grade ≥3 AE
  - DTG+FTC/TAF: 20.7%
  - DTG+FTC/TDF: 26.0%
  - EFV/FTC/TDF: 22.3%
  - p=0.27
  - p=0.58

- Infant grade ≥3 AE
  - DTG+FTC/TAF: 13.9%
  - DTG+FTC/TDF: 16.3%
  - EFV/FTC/TDF: 20.8%
  - p=0.51
  - p=0.069

- Neonatal death
  - DTG+FTC/TAF: 1.0%
  - DTG+FTC/TDF: 1.5%
  - EFV/FTC/TDF: 4.8%
  - p=0.63
  - p=0.019
  - p=0.053
Maternal and Infant Grade 3 or Higher Adverse Events by Arm

- Maternal grade ≥3 AE: 20.7%, 26.0%, 22.3%
- Infant grade ≥3 AE: 13.9%, 16.3%, 20.8%
- Neonatal death: 1.0%, 1.5%, 4.8%

Legend:
- DTG+FTC/TAF
- DTG+FTC/TDF
- EFV/FTC/TDF
Average Weekly Maternal Weight Gain by Arm

Recommended IOM weight gain 2nd/3rd trimesters (0.42 kg/week)

- DTG+FTC/TAF: 0.378 kg/week, p=0.011
- DTG+FTC/TDF: 0.319 kg/week
- EFV/FTC/TDF: 0.291 kg/week, p=0.19

p<0.001

Not statistically significant
Conclusions

• All three study regimens showed high efficacy, and safety that was similar to or better than that observed in other studies of ART in pregnancy
• DTG-containing ART had superior virologic efficacy at delivery compared to EFV/FTC/TDF
• DTG+FTC/TAF was associated with significantly fewer adverse pregnancy outcomes (driven by lower preterm and SGA rates) and fewer neonatal deaths than EFV/FTC/TDF
• Results affirm the WHO recommendation to use DTG in all populations, including during pregnancy, and showed that TAF may be preferable to TDF in pregnancy
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Operations Center: Anne Coletti and Katie McCarthy
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Site Investigators of Record:
Botswana: Gaborone and Molepolole: Gaerolwe Masheto
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