Safety/Efficacy of DTG vs EFV, TDF vs TAF in Pregnancy/Postpartum: IMPAACT 2010

We conducted a Phase III, 3-arm, randomized, open-label trial to compare the safety and virologic efficacy of three regimens started during pregnancy by women living with HIV

- Dolutegravir + Emtricitabine/Tenofovir Alafenamide (DTG+FTC/TAF)
- Dolutegravir + Emtricitabine/Tenofovir Disoproxil Fumarate (DTG+FTC/TDF)
- Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate (EFV/FTC/TDF)

We previously reported the virologic efficacy of combined DTG-containing triple therapy arms vs. EFV arm and pairwise comparison of safety outcomes of the 3 study arms through delivery outcome

- DTG three-drug ART regimens had superior virologic efficacy to EFV/FTC/TDF; DTG+FTC/TAF had lowest rate of adverse pregnancy outcomes

We now present virologic efficacy and safety data from enrollment through 50 weeks postpartum
Arm 1: Maternal DTG+FTC/TAF During Pregnancy and Postpartum

Arm 2: Maternal DTG+FTC/TDF During Pregnancy and Postpartum

Arm 3: Maternal EFV/FTC/TDF During Pregnancy and Postpartum

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

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)
Objectives: Safety Outcomes

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

- **Maternal grade 3 or higher adverse events** through 50 weeks postpartum
- **Infant grade 3 or higher adverse events** through 50 weeks after birth
- **Infant mortality** through 50 weeks after birth
- **Infant HIV infection** through 50 weeks after birth
Whether proportions of mothers with HIV-1 RNA <200 copies/mL at 50 weeks postpartum differ when comparing a DTG-containing 3-drug regimen (DTG arms combined) initiated during pregnancy to EFV/FTC/TDF.
Enrollment and Retention

- Screened = 810
- Enrolled = 643 (79%)

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%)

- Live births = 617 (96%)
- Infants completed Week 50 = 566 (92%)

Maternal HIV-1 RNA available within original Week 50 window* = 573 (89.1%)

*Additional 30 women (4.7%) had HIV RNA within extended week 50 window permitted due to COVID-19
## 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/mm³)</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 (16%)</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>
</tr>
<tr>
<td><em><em>BMI</em> (kg/m²), median (Q1, Q3)</em>*</td>
<td>25.1 (22.5, 29.4)</td>
<td>24.5 (22.0, 28.1)</td>
<td>24.2 (21.5, 28.0)</td>
<td>24.7 (22.0, 28.4)</td>
</tr>
</tbody>
</table>

*Pre-pregnancy BMI was not available.

Median duration of antepartum follow-up: 17.4 weeks; *Pre-pregnancy BMI was not available
Results: Maternal and Infant Grade 3 or Higher Adverse Events by Arm Through 50 Weeks Postpartum

- Maternal Grade ≥3 AE
  - DTG+FTC/TAF: 25.1% (p=0.098)
  - DTG+FTC/TDF: 25.3% (p=0.25)
  - EFV/FTC/TDF: 27.9% (p=0.11)

- Infant Grade ≥3 AE
  - DTG+FTC/TAF: 30.8% (p=0.26)
  - DTG+FTC/TDF: 28.6% (p=0.26)
  - EFV/FTC/TDF: 30.9% (p=0.32)

- Infant Deaths
  - DTG+FTC/TAF: 1.0% (p=0.20)
  - DTG+FTC/TDF: 2.0% (p=0.91)
  - EFV/FTC/TDF: 6.9% (p=0.008)

- Stillbirth or Infant Deaths*
  - DTG+FTC/TAF: 4.6% (p=0.20)
  - DTG+FTC/TDF: 7.0% (p=0.008)
  - EFV/FTC/TDF: 8.5% (p<0.001)

*Post hoc analysis

Major congenital anomalies occurred among 4 infants:
- 2 in DTG+FTC/TAF arm:
  - Atrial septal defect
  - Talipes equinovarus in the right foot
- 2 in EFV/FTC/TDF arm:
  - Duodenal atresia/ileal stenosis
  - Subgaleal cyst
Results: Infant HIV Infection through Week 50 After Birth

4 infants had HIV infection
all were breastfed and received ARV prophylaxis

- 2 had first HIV positive test within 14 days after birth
  - 1 in DTG+FTC/TAF arm with maternal HIV RNA >9,000 copies/mL at all visits through delivery
  - 1 in DTG+FTC/TDF arm with highest maternal through delivery HIV RNA = 42 copies/mL
- 1 in DTG+FTC/TAF arm with first positive test at 6 weeks, with maternal HIV RNA <40 copies/mL from 8 weeks on study onward
- 1 in EFV/FTC/TDF arm with first positive test at 50 weeks after birth, with maternal HIV RNA >40 copies/mL through 26 weeks postpartum

Estimated prob. of infant HIV infection (n/N)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Estimated Probability</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG+FTC/TAF</td>
<td>0.98% (2/208)</td>
<td>0.28</td>
</tr>
<tr>
<td>DTG+FTC/TDF</td>
<td>0.50% (1/202)</td>
<td>0.31</td>
</tr>
<tr>
<td>EFV/FTC/TDF</td>
<td>0.55% (1/202)</td>
<td>0.47</td>
</tr>
</tbody>
</table>

4 infants had HIV infection all were breastfed and received ARV prophylaxis
Results: Maternal Virologic Outcomes

Maternal HIV-1 RNA Suppression at week 50 postpartum
- Combined DTG Arms: 96.3%
- EFV/FTC/TDF: 96.4%

p = 0.97

Maternal Virologic Failure
2 successive HIV RNA ≥200 copies/mL at or after 24 weeks on study
- DTG+FTC/TAF: 4.1%
- DTG+FTC/TDF: 5.1%
- EFV/FTC/TDF: 10.4%

p = 0.63, 0.012, 0.040

Per ITT analysis
Post hoc statistical comparisons
Results: Maternal Weight

Average Weekly Maternal Weight Change
Enrollment through Week 50 Postpartum

Maternal Obesity at Week 50
(BMI ≥ 30 kg/m²)

-0.027
-0.050
-0.084

p=0.041
p<0.001
p=0.002

22.6%
18.4%
15.0%

p=0.31
p=0.056
p=0.37

DTG+FTC/TAF
DTG+FTC/TDF
EFV/FTC/TDF

Post hoc statistical comparisons
Conclusions

- Rates of maternal and infant grade ≥3 AEs were similar across arms from enrollment to Week 50 postpartum
  - Infant mortality was higher (though stillbirths somewhat less frequent) in the EFV arm
- The proportion of women with virologic suppression at week 50 postpartum was similarly high in the combined DTG 3-drug ART arms vs. the EFV arm
  - More women experienced virologic failure (and switched antiretrovirals due to virologic failure) in the EFV arm
- The rate of weight loss was significantly higher in the EFV arm and lowest in the DTG+FTC/TAF arm, which had the highest prevalence of obesity at week 50 postpartum
- Results from this study provide additional reassuring data for use of DTG and TAF during pregnancy and postpartum
Acknowledgements

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Questions and Discussion
Extra Slides
Maternal AEs ≥3 through 50 weeks postpartum

<table>
<thead>
<tr>
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<th>EFV/FTC/TDF (N = 211)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>5 (2.3%)</td>
<td>5 (2.3%)</td>
<td>9 (4.3%)</td>
</tr>
<tr>
<td>Laboratory abnormalities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low hemoglobin (most grade 3)</td>
<td>16 (7.3%)</td>
<td>33 (15.3%)</td>
<td>23 (10.9%)</td>
</tr>
<tr>
<td>Low estimated CrCl (all grade 3)</td>
<td>8</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>Elevated AST</td>
<td>4</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>5 (2.3%)</td>
<td>5 (2.3%)</td>
<td>7 (3.3%)</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>4 (1.8%)</td>
<td>2 (0.9%)</td>
<td>2 (0.9%)</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>0</td>
<td>1 (0.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Estimated delivery CrCl, week 50</td>
<td>124 (42)</td>
<td>118 (35)</td>
<td>131 (36)</td>
</tr>
</tbody>
</table>
**Infant AEs Grades ≥ 3 through 50 weeks after birth**

<table>
<thead>
<tr>
<th></th>
<th>DTG+FTC/TAF (N = 208)</th>
<th>DTG+FTC/TDF (N = 202)</th>
<th>EFV/FTC/TDF (N = 207)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major congenital anomaly</td>
<td>2 (1.0%)</td>
<td>0</td>
<td>2 (1.0%)</td>
</tr>
<tr>
<td>Any (Grade ≥ 2) reported congenital/genetic anomaly</td>
<td>6 (2.9%)</td>
<td>5 (2.5%)</td>
<td>4 (1.9%)</td>
</tr>
<tr>
<td>Laboratory abnormalities*</td>
<td>27 (12.9%)</td>
<td>25 (12.4%)</td>
<td>29 (14.0%)</td>
</tr>
<tr>
<td>Infections</td>
<td>10 (4.8%)</td>
<td>17 (8.4%)</td>
<td>19 (9.1%)</td>
</tr>
<tr>
<td>Respiratory disorders</td>
<td>11 (5.3%)</td>
<td>7 (3.5%)</td>
<td>13 (6.3%)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>4 (1.9%)</td>
<td>1 (0.5%)</td>
<td>7 (3.4%)</td>
</tr>
<tr>
<td>Stillbirths or infant deaths (combined)</td>
<td>10 (4.8%)</td>
<td>15 (7.4%)</td>
<td>18 (8.7%)</td>
</tr>
</tbody>
</table>

* Most frequent abnormalities: Neutrophil count decreased, Hemoglobin decreased, and increased blood creatinine level
<table>
<thead>
<tr>
<th>Reason</th>
<th>DTG+FTC/TAF N=208</th>
<th>DTG+FTC/TDF N=202</th>
<th>EFV/FTC/TDF N=207</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virologic failure or drug resistance</td>
<td>0</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>Adverse events</td>
<td>4</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Postpartum fertility choices</td>
<td>11</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Other reasons*</td>
<td>18</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>33</td>
<td>25</td>
<td>26</td>
</tr>
</tbody>
</table>

*Other; most frequent reasons were withdrew consent, relocated, noncompliance