Antepartum weight gain and adverse pregnancy outcomes in IMPAACT 2010

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Background and Rationale

- ART containing dolutegravir (DTG) and/or tenofovir alafenamide fumarate (TAF) is associated with greater weight gain in both non-pregnant and pregnant women\(^1,2\)

- Efavirenz (EFV) and tenofovir disoproxil fumarate (TDF) have been associated with low weight gain in pregnancy\(^2\)

- Both insufficient and excessive weight gain in pregnancy have been associated with adverse pregnancy outcomes\(^3\)

- IMPAACT 2010: pregnant women with HIV-1 randomized to start treatment with DTG+FTC/TAF, DTG+FTC/TDF, or EFV/FTC/TDF
  - Significantly lower rate of adverse pregnancy outcomes in women in DTG+FTC/TAF arm than other two arms\(^4\)

1-Venter WDF et al NEJM 2019; 2-Caniglia E et al, Eclinical Medicine 2020; 3-Ukah UV et al. PLOS Medicine 2019; 4-Primary outcomes presented at CROI 2020, Abstract 130
Objectives and Methods

- Estimated by-arm differences in average antepartum weekly weight gain using generalized estimating equations
- Evaluated associations between weight gain and adverse pregnancy outcomes using Cox-proportional hazards regression:
  - Composite outcome of stillbirth (≥20 wks GA), preterm delivery (<37 wks GA) and small for gestational age (SGA: <10th percentile)
  - Individual components of the composite outcome
  - Neonatal death
- Weight categories: low weight gain <0.18 kg/week and high weight gain >0.59 kg/week (Institute of Medicine Guidelines)

*Weight included as a time-varying covariate; analyses adjusted for gestational age at baseline
Key Eligibility Criteria

- Pregnant women 14-28 weeks gestation
- ART-naïve
Participants were enrolled at 22 sites in 9 countries (Botswana, Brazil, India, South Africa, Tanzania, Thailand, Uganda, US, Zimbabwe)

Screened = 810

Enrolled = 643 (79%) Jan 2018 – Feb 2019

Antepartum weight data available = 643 (100%)

Antepartum weight and pregnancy outcome data available = 632 (98.3%)
### 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>Enrollment weight, mean kg (SD)</strong></td>
<td>67.7 (15.1)</td>
<td>66.3 (16.8)</td>
<td>64.5 (13.3)</td>
<td>66.2 (15.2)</td>
</tr>
</tbody>
</table>

*Median duration of antepartum follow-up: 17.4 weeks*
Results: Average Weekly Maternal Weight Gain by Arm

- DTG+FTC/TAF: 0.378 kg/week
- DTG+FTC/TDF: 0.319 kg/week
- EFV/FTC/TDF: 0.291 kg/week

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

- p=0.011
- p<0.001
- p=0.19
Low, Normal, and High Antepartum Weight Gain by Arm

- Low Weight Gain: 32 (15.0%), 50 (23.6%), 62 (30.0%)
- Normal Weight Gain: 154 (72.3%), 141 (66.5%), 132 (63.8%)
- High Weight Gain: 27 (12.7%), 21 (9.9%), 13 (6.3%)
Low Antepartum Weight Gain and Adverse Pregnancy Outcomes

Composite outcome definition: stillbirth (≥20 wks), preterm delivery (<37 wks), and small for gestational age (<10th percentile)

Adjusted for gestational age stratum at baseline
High Antepartum Weight Gain and Adverse Pregnancy Outcomes

Over all treatment arms, significant association between higher average weekly weight gain and a lower risk of any adverse pregnancy outcome: HR 0.50 (95% CI 0.25-0.97, p= 0.04).

Composite outcome definition: stillbirth (≥20 wks), preterm delivery (<37 wks), and small for gestational age (<10th percentile)

Adjusted for gestational age stratum at baseline
Weight Gain and Composite Adverse Pregnancy Outcome*

by Arm

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Weight Gain</th>
<th>Proportion with Event</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-Value: Interaction of Weight and Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG+FTC/TAF</td>
<td>Normal</td>
<td>21%</td>
<td>Reference</td>
<td>Lower Risk</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>41%</td>
<td>2.7 (1.39, 5.21)</td>
<td>Higher Risk</td>
</tr>
<tr>
<td>DTG+FTC/TDF</td>
<td>Normal</td>
<td>33%</td>
<td>Reference</td>
<td>Lower Risk</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>32%</td>
<td>0.8 (0.45, 1.47)</td>
<td>Higher Risk</td>
</tr>
<tr>
<td>EFV/FTC/TDF</td>
<td>Normal</td>
<td>27%</td>
<td>Reference</td>
<td>Lower Risk</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>40%</td>
<td>1.4 (0.83, 2.37)</td>
<td>Higher Risk</td>
</tr>
<tr>
<td>Total</td>
<td>Normal</td>
<td>27%</td>
<td>Reference</td>
<td>Lower Risk</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>38%</td>
<td>1.4 (1.02, 1.96)</td>
<td>Higher Risk</td>
</tr>
</tbody>
</table>

Adjusted for gestational age stratum at baseline

*Composite outcome definition: stillbirth (≥20 wks), preterm delivery (<37 wks), and small for gestational age (<10th percentile)
Future Analyses and Limitations

- Further planned analyses
  - Weight gain and severe outcomes (very preterm <32 weeks; very small for gestational age (<3rd percentile), stillbirth, and neonatal death)
  - Weight gain and macrosomia
  - Weight gain and C-section
  - Detailed analysis of postpartum weight through 50 weeks

- Limitations: lack of pre-pregnancy weight/BMI; predominantly an African population, all women initiated ART in pregnancy
Conclusions

- Low weight gain during pregnancy was most common in women starting EFV/FTC/TDF and least common with DTG+FTC/TAF
- Low but not high weight gain associated with adverse pregnancy outcomes
- Weight gain on DTG+FTC/TAF approached average weight gain recommended in the 2\textsuperscript{nd}/3\textsuperscript{rd} trimester based on IOM standards
- The lower rate of adverse pregnancy outcomes observed in the DTG+FTC/TAF arm could be related to higher antepartum weight gain
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