Assessing the safety and efficacy of dolutegravir in HIV-positive pregnant women in Sub-Saharan Africa: A meta-analysis

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Background

• The current recommended 1st line antiretroviral treatment for pregnant women consists of:

  TDF + 3TC (or FTC) + DTG


• Dolutegravir is part of the 1st line recommendation as it is well tolerated and causes a rapid reduction in the viral load

• With concerns regarding NNRTI drug resistance in Africa, dolutegravir is further favoured as it has a higher barrier to drug resistance

• Aim: to analyse results from recent trials that have studied pregnant women to compare DTG-based treatments against the previous standard-of-care treatment (TDF /3TC or FTC /EFV)
<table>
<thead>
<tr>
<th>Trial</th>
<th>Location</th>
<th>Treatment Arms</th>
<th>Sample Size (pregnant women)</th>
<th>Total Sample:</th>
</tr>
</thead>
<tbody>
<tr>
<td>DolPHIN-1</td>
<td>South Africa, Uganda</td>
<td>TDF/XTC+DTG vs TDF/XTC/EFV</td>
<td>DTG-Arm 29 EFV-Arm 31</td>
<td>1074 pregnant women</td>
</tr>
<tr>
<td>DolPHIN-2</td>
<td>South Africa, Uganda</td>
<td>TDF/XTC+DTG vs TDF/XTC/EFV</td>
<td>DTG-Arm 137 EFV-Arm 131</td>
<td></td>
</tr>
<tr>
<td>NAMSAL</td>
<td>Cameroon</td>
<td>TDF/3TC+DTG vs TDF/3TC/EFV</td>
<td>DTG-Arm 13 EFV-Arm 12</td>
<td></td>
</tr>
<tr>
<td>ADVANCE</td>
<td>South Africa</td>
<td>TAF/FTC+DTG vs TDF/FTC/EFV</td>
<td>DTG-Arm 26 EFV-Arm 30</td>
<td></td>
</tr>
<tr>
<td>IMPAACT 2010</td>
<td>Brazil, Botswana, India, Tanzania, Thailand, South Africa, USA, Zimbabwe</td>
<td>TAF/FTC+DTG vs TDF/FTC/EFV</td>
<td>DTG-Arm 216 EFV-Arm 211</td>
<td></td>
</tr>
</tbody>
</table>
Meta-Analysis Endpoints

Efficacy endpoints:
- Viral suppression rate
  (ADVANCE, DolPHIN-1, DolPHIN-2: <50 cp/mL, IMPAACT 2010: <200 cp/mL)
  (NAMSAL did not have viral suppression results for pregnant women)
- Mother-to-child-transmission cases (MTCTs)

Safety endpoints:
- Stillbirths
- Neonatal deaths
- Small-for-gestational-age infants (SFGA)
- Preterm births
- Mothers and infants experiencing ≥1 adverse event
  (DolPHIN-1, DolPHIN-2, IMPAACT 2010: ≥ Grade 3 Adverse Event, ADVANCE: Serious Adverse Event)
Viral Suppression

- **Viral load** was measured at delivery in each trial.
- DTG was associated with significantly higher levels of viral suppression compared to EFV - OR: 2.90, 95% CI: [1.54, 5.46], p=0.001.
- Treatment duration was considerably longer in ADVANCE compared to DolPHIN-1, DolPHIN-2 and IMPAACT 2010.
### Viral Suppression vs MTCT

#### Trial Data

<table>
<thead>
<tr>
<th>Trial</th>
<th>MTCT cases DTG-Arm (n/N)</th>
<th>MTCT cases EFV-Arm (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DolPHIN-1</td>
<td>0/29</td>
<td>0/31</td>
</tr>
<tr>
<td>DolPHIN-2</td>
<td>3/137</td>
<td>0/131</td>
</tr>
<tr>
<td>NAMSAL</td>
<td>0/13</td>
<td>0/12</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>0/51</td>
<td>0/30</td>
</tr>
<tr>
<td>IMPAACT 2010</td>
<td>2/429</td>
<td>0/211</td>
</tr>
<tr>
<td>Total</td>
<td>5/659</td>
<td>0/415</td>
</tr>
</tbody>
</table>

#### Endpoint Proportion

- **MTCT**: 1% (n/N = 5/659, 0/415)
- **Viral Suppression**: 90% (p = 0.001), 72% (p = 0.18)

**Note:**
- DTG-arm: Blue bar
- EFV-arm: Green bar
- p-values indicate statistical significance.
Stillbirths, Neonatal Deaths, MTCTs

- No statistically significant difference for neonatal deaths and MTCT cases
- Borderline statistically significant difference for stillbirths – with a higher proportion occurring in the DTG-arm
Adverse Events: DTG vs EFV

- No statistically significant difference for mothers experiencing ≥1 adverse event

- Borderline statistically significant difference for infants experiencing ≥1 adverse event—with a higher proportion in the EFV-arm
### Preterm births

#### Relative risk of preterm births with EFV

**4% higher absolute risk of preterm births with EFV**

<table>
<thead>
<tr>
<th>Trial</th>
<th>DTG-Arm (n/N)</th>
<th>EFV-Arm (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DolPHIN-1</td>
<td>0/29 (0%)</td>
<td>2/31 (6%)</td>
</tr>
<tr>
<td>DolPHIN-2</td>
<td>21/124 (17%)</td>
<td>19/120 (16%)</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>0/51 (0%)</td>
<td>1/30 (3%)</td>
</tr>
<tr>
<td>IMPAACT 2010</td>
<td>31/429 (7%)</td>
<td>25/211 (12%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>52/633 (8%)</strong></td>
<td><strong>47/392 (12%)</strong></td>
</tr>
</tbody>
</table>
SFGA Infants

<table>
<thead>
<tr>
<th>Trial</th>
<th>DTG-Arm (n/N)</th>
<th>EFV-Arm (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DolPHIN-1</td>
<td>0/28 (0%)</td>
<td>1/31 (3%)</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>2/29 (7%)</td>
<td>3/13 (23%)</td>
</tr>
<tr>
<td>IMPAACT 2010</td>
<td>78/410 (19%)</td>
<td>41/207 (20%)</td>
</tr>
<tr>
<td>Total</td>
<td>80/467 (17%)</td>
<td>45/251 (18%)</td>
</tr>
</tbody>
</table>

*p=0.38  p=0.82  p=0.47  p=0.20

*N-number of live infants
Adverse Events: TAF/FTC/\]+DTG vs TDF/FTC+DTG

- ADVANCE and IMPAACT 2010 had two DTG-based treatment arms:
  TAF/FTC+DTG
  TDF/FTC+DTG

- No statistically significant difference for mothers and infants experiencing ≥1 adverse event

<table>
<thead>
<tr>
<th>Participants</th>
<th>Proportion of participants</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mothers</td>
<td>TAF/FTC/DTG 21% (51/243, 58/240)</td>
<td>p=0.77</td>
</tr>
<tr>
<td>Infants</td>
<td>TDF/FTC/DTG 24% (33/221, 36/218)</td>
<td>p=0.62</td>
</tr>
<tr>
<td>Total</td>
<td>TAF/FTC/DTG 15% (84/464, 94/458)</td>
<td>p=0.80</td>
</tr>
<tr>
<td></td>
<td>TDF/FTC/DTG 17% (84/464, 94/458)</td>
<td></td>
</tr>
</tbody>
</table>
Adverse Events: TAF/FTC/DTG vs TDF/FTC/DTG

- Trend of more mothers and infants with ≥1 adverse with TDF/FTC+DTG in IMPAACT 2010

- Trend of more mothers and infants with ≥1 adverse with TAF/FTC+DTG in ADVANCE

- Overall no significant difference between the treatments
ADVANCE Trial: Mean change in weight (kg) to Week 96: Women

- TAF/FTC+DTG: +8.2 kg
- TDF/FTC+DTG: +4.6 kg
- TDF/FTC/EFV: +3.2 kg
- TAF/FTC+DTG: +12.3 kg
Implications + Limitations

• The safety profile of dolutegravir and efavirenz are similar in the results of this meta-analysis

• However, these results only illustrate the short-term effects of dolutegravir and TAF/FTC

• Pregnant women in these trials received antiretroviral treatment for a short duration with a limited long-term follow-up

• In reality, most women are likely to become pregnant after receiving antiretroviral treatment for years

• Future assessment is needed (studies, observational cohorts) on the long-term safety profile of dolutegravir due to its association with weight gain – being noticeably higher in black females

• There are concerns regarding the dolutegravir-associated weight gain possibly increasing the risk of obesity-associated adverse birth outcomes in its users
Conclusion

Efficacy:
• Dolutegravir was associated with greater virologic suppression than efavirenz
• As dolutegravir had significantly superior viral efficacy, it was unexpected to find five MTCT cases with dolutegravir versus none with efavirenz

Safety
• There were marginal differences between the treatment safety of dolutegravir and efavirenz
• The number of mothers and infants experiencing ≥1 adverse event was similar
• There was a trend for more stillbirths with dolutegravir but more preterm births with efavirenz
• There was no significant difference between the safety of TAF/FTC/DTG and TDF/FTC/DTG
Thanks to:

Study participants in each of the trials
Andrew Hill and his team