DolPHIN-1: Randomised controlled trial of dolutegravir (DTG)-versus efavirenz (EFV)-based therapy in mothers initiating antiretroviral treatment in late pregnancy


**Research funding and drug donation for DolPHIN-1 was provided by ViiV Healthcare**
Background

- Around 1.5M HIV+ women become pregnant each year

- Effective and timely ART has averted 1.6M infant infections

- In S Africa, around a fifth of HIV+ pregnant women initiate ART late, in 3rd trimester (T3)

- Late initiation associated with 7-fold increased risk of MTCT, and doubling of infant mortality in first year

Hypothesis:
Faster VL declines with DTG may reduce MTCT at birth & during breastfeeding (BF) in HIV+ mothers initiating ART in T3

Meyers et al. PLoS ONE 2015;10(9): e0138104
DolPHIN-1: Dolutegravir in Pregnant HIV mothers and their Neonates
NCT022245022

- HIV+ pregnant mums initiating ART in T3 (28-36w gestation)
  ≥18y, no ARVs in preceding 6m (no previous INSTIs), no depression, Hb ≥ 8g/dL, eGFR ≥ 50, ALT ≤ 5xULN, no active HBV
- Randomised 1:1 to receive DTG vs EFV until 2w PP
  plus TDF/3TC (Uganda) or TDF/FTC (S Africa). DTG (50mg/d), EFV (600mg/d)
- Primary endpoint: maternal PK of DTG
- Secondary endpoints: plasma VL <50 copies (or undetectable) at PP visit (0-2w PP), safety and tolerability, PK in cord blood and BM
### DoPHIN-1 Enrolment & Baseline Demographics

- **60 HIV+ mothers enrolled:** DTG (29), EFV (31)
- Equally split across both study sites
- Median gestation 31w
- No difference in baseline VL, CD4, previous obstetric history, gestation, BMI
- High use of traditional medicines noted

#### Baseline Median (Range)

<table>
<thead>
<tr>
<th></th>
<th>DTG (n=29)</th>
<th>EFV (n=31)</th>
<th>Total (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>27 (19-42)</td>
<td>25 (19-35)</td>
<td>26 (19-42)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68 (45-103)</td>
<td>65 (48-119)</td>
<td>66 (45-119)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26 (19-40)</td>
<td>25 (21-46)</td>
<td>26 (19-46)</td>
</tr>
<tr>
<td>Est gestation (w)</td>
<td>31 (27-35)</td>
<td>30 (27-36)</td>
<td>31 (27-36)</td>
</tr>
<tr>
<td>HIV VL log₁₀ copies</td>
<td>4 (2-5)</td>
<td>4 (3-6)</td>
<td>4 (2-6)</td>
</tr>
<tr>
<td>CD4 (cells/mm³)</td>
<td>343 (41-712)</td>
<td>466 (32-932)</td>
<td>394 (32-932)</td>
</tr>
<tr>
<td>HBsAg +ve *</td>
<td>0</td>
<td>2 (6.5%)</td>
<td>2 (3.3%)</td>
</tr>
<tr>
<td>Herbal/traditional medicines</td>
<td>5 (17.2%)</td>
<td>8 (25.8%)</td>
<td>13 (21.7%)</td>
</tr>
</tbody>
</table>

* missing data DTG (2) EFV (1)
Results – Maternal Plasma PK (T3 versus PP)

<table>
<thead>
<tr>
<th>DTG ng/mL (range)</th>
<th>T3 * (n=28)</th>
<th>PP * (n=27)</th>
<th>GMR (90%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AUC</strong>&lt;sub&gt;0-24h&lt;/sub&gt; (ng*h/mL)</td>
<td>35,322 (19,196 – 67,922)</td>
<td>37,575 (14,933 – 59,633)</td>
<td>0.95 (0.74 – 1.23)</td>
</tr>
<tr>
<td><strong>C&lt;sub&gt;max&lt;/sub&gt;</strong> (ng/mL)</td>
<td>2,435 (1,462 – 3,986)</td>
<td>2,843 (1,398 – 4,224)</td>
<td>0.91 (0.82 – 1.01)</td>
</tr>
<tr>
<td><strong>C&lt;sub&gt;trough&lt;/sub&gt;</strong> (ng/mL)</td>
<td>642 (188 – 3,088)</td>
<td>696 (204 – 1,443)</td>
<td>0.93 (0.76 – 1.14)</td>
</tr>
<tr>
<td><strong>DTG ≤ MEC</strong> (324ng/mL)</td>
<td>9/28 (32%)</td>
<td>6/27 (22%)</td>
<td></td>
</tr>
</tbody>
</table>

* 1 subject with undetectable levels throughout excluded

- Rich PK sampling in T3 and PP
- PP sampling (2-18d; median 8d) does not reflect return to normal physiology; exposures not significantly different from T3
- All but one [DTG] above 64 ng/mL (PA-IC<sub>90</sub>)
- In T3, 9/28 (32%) of [DTG] at or below 324 ng/mL (MEC)
- Cord:maternal blood ratio = 1.21 (0.51 – 2.11) [median (range)]

Min et al, AIDS 2011;25:1737
Results – PK in Breast Milk and Breastfeeding Infants

**Breast Milk**
- sampled at maternal plasma $C_{\text{max}}$ and $C_{\text{trough}}$
- Geometric mean $BM_{\text{max}}$ 70 (58 – 83) ng/mL; $BM_{\text{trough}}$ 24 (19 – 29) ng/mL
- $BM:MP$ at $C_{\text{max}}$ and $C_{\text{trough}}$ = 0.03 (3%)  

**Infant Plasma**
- sampled at maternal plasma $C_{\text{trough}}$; feed mandated at $C_{\text{max}}$ and infant sampling 1h later
- Geometric mean $IP_{\text{max}}$ 111 (50 – 172) ng/mL; $IP_{\text{trough}}$ 87 (47 – 127) ng/mL
- $IP:MP_{\text{max}}$ = 0.05 (0.02 – 0.07) ; $IP:MP_{\text{trough}}$ = 0.12 (0 – 0.26)
**Results: DTG Washout following Cessation**

**MP vs Breast Milk**
- Rapid washout following DTG cessation

**MP vs Infant Plasma**
- Slow washout of DTG in infants following cessation of DTG in mother
- Likely reflects accumulation from BF (+/- residual transplacental accumulation) due to decreased glucuronidation in the neonate
Results – Viral load at Post-partum Visit

- By ITT, significantly greater proportion of DTG subjects achieved virological suppression at PP (2w) visit
- Median time to HIV-1 RNA <50 copies was approximately halved with DTG compared to EFV
- 1 mother in the DTG arm had UD DTG concentrations, with no VL response; another with [DTG] < 64 ng/mL experienced virological rebound (3 class drug resistance from baseline sample)

<table>
<thead>
<tr>
<th>HIV-1 RNA level at PP visit</th>
<th>ITT (M=F)</th>
<th>DTG (N = 29)</th>
<th>EFV (N = 31)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50 copies/mL *</td>
<td>20 (69.0%)</td>
<td>12 (38.7%)</td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>≥50 copies/mL</td>
<td>9 (31%)</td>
<td>19 (61.3%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* <50 copies/mL or UD (Roche Ampliprep Cobas Taqman HIV-1 2.0)
** Pearson Chi-squared
Includes individuals missing or discontinued by visit

NRTI: M41L, L210W, T215Y, M184V
NNRTI: Y188L
PI: M46I, I84V, I54V, V32I, V82A, L33F, K43T
## Safety – Maternal outcomes

<table>
<thead>
<tr>
<th></th>
<th>DTG (N = 29)</th>
<th>EFV (N = 31)</th>
<th>Total (N = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Given birth</td>
<td>29 (100.0%)</td>
<td>31 (100.0%)</td>
<td>60 (100.0%)</td>
</tr>
<tr>
<td>Mode of delivery, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>25 (86.2%)</td>
<td>21 (67.7%)</td>
<td>46 (76.7%)</td>
</tr>
<tr>
<td>C-section</td>
<td>4 (13.8%)</td>
<td>10 (32.3%)</td>
<td>14 (23.3%)</td>
</tr>
<tr>
<td>Experiencing at least 1 adverse event Grade ≥ 3</td>
<td>2 (6.9%)</td>
<td>0</td>
<td>2 (3.3%)</td>
</tr>
</tbody>
</table>
| Experiencing at least 1 serious adverse event | 2 (6.9%)
|                                      | 1 (3.2%)*    |              | 3 (5.0%)      |

Maternal AEs and SAEs since starting ART (i.e. includes initial EFV-based ART in mothers subsequently randomised to DTG)

§ 1 case of Haemoglobin decreased (not related);  
1 case with Malaria + Urinary tract infection (possibly related), Stillbirth (not related), and ALT+ bilirubin increased + Hypokalaemia + Hyponatraemia (possibly related)  
* 1 case of Hypertension + Pre-eclampsia (unlikely related)
## Safety – Infant outcomes

<table>
<thead>
<tr>
<th></th>
<th>DTG (N = 29)</th>
<th>EFV (N = 31)</th>
<th>Total (N = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome of delivery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal healthy baby</td>
<td>28 (96.6%)</td>
<td>29 (93.5%)</td>
<td>57 (95.0%)</td>
</tr>
<tr>
<td>Stillbirth§</td>
<td>1 (3.4%)</td>
<td>-</td>
<td>1 (1.7%)</td>
</tr>
<tr>
<td>Congenital malformation</td>
<td>-</td>
<td>2 (6.5%)</td>
<td>2 (3.3%)</td>
</tr>
<tr>
<td><strong>of which syndactyly</strong>§</td>
<td>-</td>
<td>1 (3.2%)</td>
<td>1 (1.7%)</td>
</tr>
<tr>
<td>Multiple *</td>
<td>-</td>
<td>1 (3.2%)</td>
<td>1 (1.7%)</td>
</tr>
<tr>
<td><strong>Gestation age at birth, weeks</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>median (range)</td>
<td>39 (35-43)</td>
<td>38 (34-42)</td>
<td>38 (34-43)</td>
</tr>
<tr>
<td><strong>Length of baby, cm</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>median (range)</td>
<td>51 (44-58)</td>
<td>50 (33-55)</td>
<td>50 (33-58)</td>
</tr>
<tr>
<td><strong>Weight of baby, kg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>median (range)</td>
<td>3 (2-4)</td>
<td>3 (2-4)</td>
<td>3 (2-4)</td>
</tr>
<tr>
<td><strong>Experiencing at least 1 serious adverse event</strong></td>
<td>-</td>
<td>3 (9.7%)†</td>
<td>3 (5.0%)</td>
</tr>
</tbody>
</table>

§ Not related

* Not related.

**Multiple skeletal and limb defects** (talipes, multiplex arthrogryposis, developmental hip dysplasia, limb hyperextension)

**Cardiac defects** (Atrial septal defect, Persistent left superior vena cava) + cleft palate, hyporeflexia (? Larsen or TARP syndrome)

Note: The infant was also pre-term/small for gestational age, and had congenital syphilis.

† 2 cases with congenital malformations and 1 case of neonatal sepsis (not related)
In this pilot study, a significantly greater proportion of mothers initiating ART late in pregnancy achieved HIV-1 RNA <50 copies/mL with DTG- compared to EFV- based regimens.

DTG exposures in T3 were relatively low. In-utero accumulation of DTG was high (121%).

Breast milk accumulation of DTG was 3% with higher exposures in breastfed infants, likely due to reduced drug clearance.

Upon cessation, DTG was rapidly eliminated from breast milk; however infant washout was prolonged.

Safety of DTG and EFV was comparable; however evaluation is limited by small sample size, relatively short follow-up and by prior EFV use in all DTG mothers initiating ART.

DolPHIN-2 (NCT03249181) is a randomised comparison of DTG vs EFV initiation in third trimester (28w – labour; N = 250).
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