The effect of systemic exposure to efavirenz, sex and age on the risk of virological non-suppression in HIV-infected African children.

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Objectives

- To describe the **effect of** systemic efavirenz (EFV) **exposure on viral suppression**.

- To identify other **factors influencing risk of viremia** (>100 copies/mL) in children from CHAPAS-3 study.

- To derive the minimum EFV **exposure predictive of a reduced risk of viremia** in African children.
Introduction - CHAPAS-3

Aged 1 month – 13 years¹ (N=470)

Strata 1: not previously treated (other than pMTCT), about to start ART with 2NRTIs + NNRTI (N=235)
Strata 2: aged 5 years or more, stable (undetectable viral load) on first-line d4T based regimen BD and received d4T for at least 2 years (N=235)

RANDOMISE²

Arm d4T
BD d4T+3TC+NNRTI³ (N=156)

Arm ZDV
BD ZDV+3TC+NNRTI³ (N=157)

Arm ABC
BD⁴ ABC+3TC+NNRTI³ (N=157)

PK SUBSTUDY 1 (week 6)
Full PK curves for:
• ZDV+3TC BD (n=48)
• NVP (any 3<6kg)
• EFV OD (n=32)

Follow-up: weeks 2, 6 then 6 weekly for first 24 weeks; then at least 12 weekly until 96 weeks after the last child is randomised
Primary endpoint: grade 2/3/4 clinical adverse events or 3(confirmed)/4(any) laboratory adverse events
Secondary endpoints: adherence/acceptability, skinfold thicknesses, cardiac function, cost, CD4%, viral load
<table>
<thead>
<tr>
<th></th>
<th>Naïve</th>
<th>Experienced</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>109</td>
<td>14</td>
<td>123</td>
</tr>
<tr>
<td>Age (years)*</td>
<td>4.04 (1.74 - 13.57)</td>
<td>7.59 (5.24 - 11.79)</td>
<td>4.29 (1.74 - 13.57)</td>
</tr>
<tr>
<td>Weight (kg) *</td>
<td>14.0 (6.2 -26.6)</td>
<td>20.3 (13.2 -29.0)</td>
<td>14.5 (6.2 - 29.0)</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>51/58</td>
<td>9/5</td>
<td>60/63</td>
</tr>
<tr>
<td>Viral Load (c/ml)*</td>
<td>171,650 (245 – 50 million)</td>
<td>&lt; 100</td>
<td>----</td>
</tr>
<tr>
<td>CD4%, median</td>
<td>19%</td>
<td>36%</td>
<td>20%</td>
</tr>
</tbody>
</table>

*(median, min-max)/baseline data
• **1482 EFV samples** (combination of sparse and intensive sampling) corresponding to **572** dosing intervals.

• **789 VL samples** - number of samples per patient varied.

• **POP-PK model*** was used to estimate mid-dose concentrations (C12h) for each dosing interval.

*See Poster P35*
Exploratory Analysis

Change in Viral Load over Time in Treatment Naive Patients

- Multiple Escapes
- Never suppressed
- Suppressed
- One Escape

Time (weeks)
Exploratory Analysis

- Differences in average values of PK parameters between suppression groups
- No statistical differences between the 5 suppression groups overall.
- Pairwise comparison - median systemic exposures in patients who achieved and sustained viral suppression were significantly higher than patients who never suppressed.
Main Analysis

• Conducted using Cox Proportional Hazards Regression Model.

• Method estimates relative risk of an event (VL >100 c/mL) in form of Hazard Ratio accounting for multiple events per patient.

• Restricted to matched PK - VL samples (measured on the same day).

• Excluded baseline and samples during the initial first suppression phase (up to week 48).

• On naïve patients only.
Main Analysis

• Exploratory analysis using splines.

• Hazard of non-suppression changed in non-linear manner with concentration.

Wide distribution of concentrations and skewedness of data.

Analysis repeated on log-transformed values.
Analysis Results

• Log2 concentrations as predictor.

• Trend corrected, more linear.

• Change expressed in relative (not absolute scale).

• Risk of viral non-suppression decreased by 40% for every two fold increase in mid-dose concentrations (95% CI: 24% - 51%, p<0.0001).

• The risk reached a plateau around values of 8mg/L (log2(C12h)=3).
The multivariate analysis identified male sex and older age as other independent risk factors for non-suppression.

<table>
<thead>
<tr>
<th>Group</th>
<th>Relative Hazard</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Girls &lt; 8y</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys &lt; 8y</td>
<td>5.55</td>
<td>1.97-15.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Girls &gt; 8y</td>
<td>12.72</td>
<td>4.89-33.07</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Boys &gt; 8y</td>
<td>11.23</td>
<td>2.64-47.76</td>
<td>0.001</td>
</tr>
</tbody>
</table>
The most predictive lower limit in C12h was established through likelihood profiling:

- The Cox Proportional Hazards Regression Model was run over a range of dichotomised concentration cut-offs.

- Explored range: from 0.5 and 5 mg/L, increments of 0.005 mg/L.

- The best cut-off was chosen with the lowest value of Akaike Information Criterion (AIC).
The lowest value of AIC was for concentrations between 1.12 and 1.16 mg/L (AIC=311.88) but for practical reasons we decided to choose the value of 1.2 mg/L (AIC = 312.83).
To explore the effect of a measurement error and variability in the response we conducted a bootstrap by re-simulating the data set 99 times each time modifying the PK parameters by a random number drawn from a normal distribution equalling +/- 5% of their original values.

Series of Cox proportional hazard regression models in the increments of C12h of 0.01 mg/L confirms selection of lower cut-off limit of 1.2 mg/L.
Conclusions

- The results of the Cox Proportional Hazards Model confirmed that **suboptimal EFV exposures increase risk of viremia**.

- **Hazard** of viremia changes in a **non-linear manner with concentrations**.

- **Relative** and not absolute changes in concentration are **more predictive** of the risk of non-suppression.

- **Hazard ratio decreases with increasing concentrations up to plateau level** and it can be speculated that further increases beyond that level would have no effect on change in hazard of non-suppression.
Conclusions

• Our analysis presented a robust approach to establishing the most predictive lower exposure cut-off values related to increased risk of viral viremia.

• Based on the results we suggest mid-dose interval concentrations of 1.2 mg/L should be utilised as new paediatric target minimum concentrations.
Conclusions

• Multivariate analysis showed that boys had a higher risk of non-suppression than girls for children < 8 years.

• The effect of male sex was modified by older age, where both sex groups had an increased risk of a detectable viral load compared to younger children.

• Further studies are warranted to evaluate the association on of treatment adherence with EFV exposure, sex and age.
Thank you!
We would like to acknowledge all CHAPAS-3 investigators, patients and parents without whom this study would not be possible.