Background

- A **mega-model** utilizes multiple sources of raw data. Without the need for new clinical studies, mega-models can address novel research questions and add power for covariate detection. A challenge is accounting for variability and factors caused by the differences between the data sources.

- **Nevirapine** (NVP) is currently the most commonly used antiretroviral drug. Despite the availability of adequate PK data, important questions, including drug-drug interactions and genetic polymorphisms, still require further investigation.

Objective

To develop a mega-model of NVP PK in a population of HIV-infected South African adults on anti-retroviral therapy (ART) and investigate modelling strategies to jointly analyse data from different sources.

Methods

**Data:** PK data from three different sources (Table 1) were analyzed. The patients were recruited from public ART programs in Western Cape, South Africa, on an ART regimen including 200 mg NVP BID and sampled at steady state. The data included rich and sparse sampling schedules, day and night samples, fed and fasted doses, presence and absence of concomitant rifampicin-based antitubercular therapy. All samples were analyzed by the same laboratory. In total 115 individuals and 1107 samples were included.

**Modeling:** A non-linear mixed effects model was implemented in NONMEM. A stepwise development approach was used:

- exploratory analysis to identify study-specific features
- combining rich data (from Study 1 and 3)
- stepwise addition of sparse data (Study 1 and 3, then Study 2)

Each dose was regarded as a separate occasion. Model development was guided by goodness of fit metrics and VPCs.

**Missing data:** Since height was not recorded for some subjects (study 2), a regression model describing the relationship between gender, body weight (BW) and fat free mass (FFM, height required for calculations) was developed and used to impute FFM.

**Results**

**Table 2.** Final parameter estimates (variability as CV, precision as RSE%) and bootstrap results (n=200, stratified on study, precision as RSE%).

<table>
<thead>
<tr>
<th>Parameter estimates (RSE%)</th>
<th>Bootstrap (RSE%)</th>
</tr>
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<tbody>
<tr>
<td>CL/F pop. 1 [L/h•(kg FFM/42 kg)^0.75]</td>
<td>3.12 (5.1)</td>
</tr>
<tr>
<td>CL/F pop. 2 [L/h•(kg FFM/42 kg)^0.75]</td>
<td>1.45 (14.7)</td>
</tr>
<tr>
<td>Probability [%] to belong to pop. 2</td>
<td>17.3 (45.3)</td>
</tr>
<tr>
<td>V/F [L/(kg BW/70 kg)]</td>
<td>105 (4.9)</td>
</tr>
<tr>
<td>MTT [h] fed</td>
<td>2.46 (7.5)</td>
</tr>
<tr>
<td>MTT [h] fasted</td>
<td>0.596 (8.7)</td>
</tr>
<tr>
<td>F [%] when on TB-treatment</td>
<td>61.3 (8.7)</td>
</tr>
<tr>
<td>Prop error [%]</td>
<td>8.41 (5.4)</td>
</tr>
<tr>
<td>BSV CL/F [%]</td>
<td>29.4 (13.9)</td>
</tr>
<tr>
<td>BSV F when on TB-treatment [%]</td>
<td>34.1 (27.0)</td>
</tr>
<tr>
<td>BSV MTT [%]</td>
<td>64.0 (9.1)</td>
</tr>
</tbody>
</table>

**Conclusions**

- A model of oral NVP PK data from three different sources was developed and resulted in low residual variability and good precision in parameter estimates, indicating the feasibility of mega-models.

- Further data from diverse sources (including different ethnicities) are needed to create a true mega-model.

- A mixture model could be used to describe large differences in clearance between patients. This effect can probably be explained by genetic polymorphisms and a mixture model is an option when genotyping data is unavailable. Our estimated probability (17.3%) of belonging to the low clearance population agreed well with the earlier reported prevalence of T/T homozygotes for the CYP2B6 516G>T polymorphism in the South African population.

- Concomitant rifampicin-based antitubercular therapy and fed/fasted dosing conditions significantly impact NVP PK.

**References:**