Long-acting injectable formulations for children and adolescents using PBPK modelling

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• Current antiretroviral (ARV) formulations necessitate lifelong, daily dosing

• Suboptimal adherence in the clinical setting leads to high risk of treatment failure and ranges from 50 to 70 %

• Additional care and monitoring is necessary in special populations such as paediatric patients

• Injectable long-acting nano-formulations could represent a pharmacological option

• NIH funding call has been recently published to highlight the relevance of long-acting formulations in infants, children, young adults and pregnant women
Conventional vs Nanoformulation

Existing ARVs

Conventional tablets

Long-acting Nanoformulations
Paediatric patients

- Current paediatric doses are scaled down based on weight from adult dose
- Development of anatomy and physiology is not linear with age
**Aims**

- Design and validate a paediatric physiologically based pharmacokinetic (PBPK) model
- Identify the optimal doses for existing long-acting formulations of antiretrovirals according to weight categories of paediatric population
PBPK model

• Physiologically based pharmacokinetic (PBPK) modelling was used to inform the optimal dose of ARVs in children and adolescents
  ➢ Mathematical description of absorption, distribution, metabolism and elimination processes defining pharmacokinetics
  ➢ PBPK modelling integrates *in vitro* data to simulate drug distribution in virtual population
Parameter correlation

- % of body fat
  \[ (1.51 \times \text{BMI} - 0.7 \times \text{Age} - 3.6 + 1.4) \times \text{Weight} / 100 \] (7-18 years, male)

- Cardiac output
  \[ 3.107 \times (0.012 \times \text{Weight}^{1.369}) \times 60 \] (5-18 years)

- Regional blood flows

- Organ volume

- BMI

- Gender

- Weight

- Height

- Age

- Ethnicity

- Liver size
  \[ (271.58 + 0.163 \times \text{Age} \times 365) / 1000 \] (3-18 years, male & female)

- Plasma protein

- Cytochrome P450 expression

- Renal functions

- Transporter expression

- Parameter correlation
  \[ 3.107 \times (0.012 \times \text{Weight}^{1.369}) \times 60 \] (5-18 years)
Population variability

Essential PBPK Parameters

Variability

Virtual population
Intramuscular release rate

Metabolic clearance

Volume of distribution

\[ V_{ss} = (\Sigma V_t P_{tp} + (V_t^E + P) + V_p \]

\[ P_{tp, nonadipose} = \frac{P_{ow} \times (V_{nit} + 0.3 \times V_{phl})}{P_{ow} \times (V_{nil} + 0.3 \times V_{phl})} + 1 \times (V_{wt} + 0.7 \times V_{phl}) \]

\[ \times \frac{\dot{f}_{U_p}}{\dot{f}_{U_t}} \]
Physiologically Based Pharmacokinetic Modelling to Inform Development of Intramuscular Long-Acting Nanoformulations for HIV

Rajith K. R. Rajoli · David J. Back · Steve Rannard · Caren L. Freel Meyers · Charles Flexner · Andrew Owen · Marco Siccardi
Study design

Validation
- Weights and blood flow rates of children/adolescents at different ages
- Existing available IM formulations of cabotegravir and rilpivirine in adults

Prediction
- Release rates were kept similar to clinical formulations
- Pharmacokinetics in children and adolescents according to WHO weight categories

Optimization
- Identify theoretical target dose for once monthly/quarterly administration such that the drug plasma concentrations are above the protein binding adjusted IC\textsubscript{95} (PAIC\textsubscript{95}) or MEC values
Validation against clinical formulations

Intramuscularly administered cabotegravir (800 mg)

Concentration (µg/ml) vs. Time (Days)

- Mean
- Mean ± SD
- Clinical

- AUC: 4,467 vs. 5,257 µg.h/ml
- $C_{\text{max}}$: 3.3 vs. 3.54 µg/ml
- $C_{\text{trough}}$: 1.1 vs. 1.2 µg/ml
- Release rate: 0.00454 h$^{-1}$

$4^* \text{PAIC}_{95} = 0.664 \mu g/ml$

Validation against clinical formulations

Intramuscularly administered rilpivirine (900 mg)

- AUC - 74,420 vs. 91,087 ng.h/ml
- $C_{\text{max}}$ - 168 vs. 168.7 ng/ml
- $C_{\text{trough}}$ - 79.1 vs. 78.3 ng/ml
- Release rate – 0.0009 h$^{-1}$

## Prediction - Summary

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Rilpivirine (1\textsuperscript{st} and 2\textsuperscript{nd} dose in mg)</th>
<th>Cabotegravir (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 - 19.9</td>
<td>240, 180</td>
<td>960, 720</td>
</tr>
<tr>
<td>20 - 24.9</td>
<td>250, 190</td>
<td>960, 720</td>
</tr>
<tr>
<td>25 - 29.9</td>
<td>250, 190</td>
<td>970, 730</td>
</tr>
<tr>
<td>30 - 34.9</td>
<td>270, 200</td>
<td>980, 740</td>
</tr>
<tr>
<td>35 - 39.9</td>
<td>270, 200</td>
<td>1025, 770</td>
</tr>
<tr>
<td><strong>40 - 44.9</strong></td>
<td><strong>280, 210</strong></td>
<td><strong>1050, 790</strong></td>
</tr>
<tr>
<td>45 - 49.9</td>
<td>290, 220</td>
<td>1075, 810</td>
</tr>
<tr>
<td>50 - 54.9</td>
<td>300, 230</td>
<td>1100, 830</td>
</tr>
<tr>
<td>55 - 59.9</td>
<td>310, 230</td>
<td>1125, 840</td>
</tr>
<tr>
<td>60 - 64.9</td>
<td>310, 230</td>
<td>1150, 860</td>
</tr>
<tr>
<td>65 - 69.9</td>
<td>320, 240</td>
<td>1175, 880</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td><strong>4 weeks</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Cut-off limit (ng/ml)</strong></td>
<td><strong>20.3 (PAIC\textsubscript{95})</strong></td>
<td><strong>80 (MEC)</strong></td>
</tr>
</tbody>
</table>
Limitations

• The ontogeny and activity of transporters can affect distribution and elimination patterns

• Drugs with high lipophilicity tend to diffuse through the lymphatic circulation rather than through blood

• Physiological and metabolic variation of muscle composition in children compared to adults was not accounted

Conclusion

• This data could assist in dose optimisation of long-acting intramuscular antiretrovirals for paediatric patients improving adherence to therapy

• PBPK modelling represents a predictive tool to improve dosing strategies for use in selective population thus potentially simplifying antiretroviral therapy
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