TENOFOVIR POPULATION PHARMACOKINETICS IN CHILDREN AND ADULTS

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BACKGROUND

- TDF is only FDA-approved in patients 12 years and older at a dose of 300 mg once daily

- There are very few published data on TFV PK in children, especially <12 years old

- Current investigational dose of TDF in children aged 2–8 years is 8 mg per kg of body weight once daily; children aged >8 years, median dose of 210 mg per m$^2$ of body surface area once daily, maximum dose of 300 mg once daily
BACKGROUND

• 18 children enrolled in single-dose and steady state PK study
• Ages 6.2 to 16.5 years
• Target dose 175 mg/m² once daily; actual median dose 208 mg/m² (7.1 mg/kg)

<table>
<thead>
<tr>
<th></th>
<th>Pediatric</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 AUC (ng*h/mL)</td>
<td>2150</td>
<td>3265</td>
</tr>
<tr>
<td>SS AUC (ng*h/mL)</td>
<td>2920</td>
<td>3371</td>
</tr>
</tbody>
</table>

BACKGROUND

• 32 mother-newborn pairs enrolled in PK study, with infant washout from maternal dosing
• Based on unified population model, the authors concluded that “a dose of 5–6 mg/kg TFV (i.e., 11–13 mg/kg of TDF) 1 h after birth would thus allow the neonate to obtain same exposure as adults.”
  • based on key assumption that newborn Vd (L/kg) same as mother

BACKGROUND

- 36 mother-newborn pairs
- Maternal TDF dosing 900 mg x 1 in labor
- Infants received TDF 6 mg/kg PO at 0, 72, 120 hours
- Inadequate infant concentrations (Cmin > 50 ng/mL)
- Daily infant 6 mg/kg dose under study

BACKGROUND

- 52 patients enrolled in intensive PK study
- Median age was 14 years, range 8-17
- Population modeling with NONMEM, allometric scaling
- Typical clearance similar to adults (96.2 vs. 90.9 L/h).
  - My conclusion: dosing in this age range likely to be similar to adults

OBJECTIVES

• To develop a unified pediatric and adult population model of TFV PK

• To estimate the starting doses of TDF for children of all ages that reproduce adult AUCs
METHODS

• CCTG 584 was a prospective study to measure the PK and PD interaction between ABV and TFV in adults. Sampling pre-dose, 0.5, 1, 2, 3, 6, and 24 h post-dose

• Pediatric data were obtained from a longitudinal PK study of children on ARVs. Sampling pre-dose, 0.5, 1, 2, 4, 8, 12 h post-dose

METHODS

• All TFV samples were analyzed using validated LC-MS assays

• Non-parametric population PK modeling as implemented in MM-USCPACK software (www.lapk.org)

• Assay error polynomial: $0.01 + 0.1[C]$

• For simulations, we log-transformed model parameters and used the full covariance matrix to generate 1000 TFV time concentration curves. TDF dosing was based on simulated AGE and WT.
## COVARIATE SIMULATION

<table>
<thead>
<tr>
<th></th>
<th>AGE &lt;18</th>
<th>AGE ≥ 18</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WT</strong></td>
<td>Sex-averaged, AGE-specific median from CDC growth curves, adjusted randomly by +/- 25%</td>
<td>Random variable with a uniform distribution between measured adult study population ranges</td>
</tr>
<tr>
<td><strong>CRCL</strong></td>
<td>(\frac{(2.6 \times WT^{0.662} \times \exp(-0.0822 \times AGE\times12) + 8.14 \times WT^{0.662} \times (1 - \exp(-0.0822 \times AGE\times12)))}{(BSA/1.73)})</td>
<td>Random variable with a uniform distribution between measured adult study population ranges</td>
</tr>
<tr>
<td><strong>BSA</strong></td>
<td>Dubois formula from sex-averaged, AGE-specific median HT from CDC growth curves, adjusted randomly by +/- 25% and WT</td>
<td>ND</td>
</tr>
</tbody>
</table>

Simulated Age Distribution
COVARIATE SIMULATION

![Graph showing the relationship between age (y) and CRCL (ml/min/1.73m²).](image)
## RESULTS

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>Age</strong></td>
<td>34.0 (8.8 – 58) years; 3 &lt; 12 years</td>
</tr>
<tr>
<td><strong>CRCL</strong></td>
<td>109.6 (70.6 – 337) ml/min/1.73m²</td>
</tr>
<tr>
<td><strong>WT</strong></td>
<td>69.1 (28.1 – 123.6) kg</td>
</tr>
<tr>
<td><strong>TDF dose</strong></td>
<td>300 mg (150 mg in those &lt;12) daily</td>
</tr>
</tbody>
</table>
RAW DATA

TFV (ng/mL) vs Time after dose (h) for different age groups:
- Child ≤ 12 years
- Adolescent > 12 to ≤ 18 years
- Adult > 18 years
### MODEL

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Weighed GM (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tlag (h)</td>
<td>0.15 (0.000046, 1.64)</td>
</tr>
<tr>
<td>Ka (h(^{-1}))</td>
<td>0.64 (0.084, 16.86)</td>
</tr>
<tr>
<td>(V1 (L))</td>
<td>(V1 = Vs \times WT)</td>
</tr>
<tr>
<td>Vs (L/kg)</td>
<td>3.20 (0.44, 19.10)</td>
</tr>
<tr>
<td>KCP (h(^{-1}))</td>
<td>0.96 (0.018, 2.70)</td>
</tr>
<tr>
<td>KPC (h(^{-1}))</td>
<td>0.13 (0.018, 2.70)</td>
</tr>
<tr>
<td>(KEL (h^{-1}))</td>
<td>(KELs \times CRCL/(WT/70)^{0.25})</td>
</tr>
<tr>
<td>KELs (h*mL/min/1.73m(^2))(^{-1})</td>
<td>0.0037 (0.00091, 0.015)</td>
</tr>
</tbody>
</table>
MODEL
RESULTS

Population

Posterior

Child
Adol
Adult

Observed

Predicted

Predicted

0 200 400 600 800 1000

0 200 400 600 800 1000

Wednesday, April 20, 2011
<table>
<thead>
<tr>
<th>Age Group</th>
<th>Cmax (mcg/mL)</th>
<th>AUC (mcg*h/mL)</th>
<th>CL (L/kg/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 2 years: 6 mg/kg</td>
<td>0.33</td>
<td>3.1</td>
<td>2.0</td>
</tr>
<tr>
<td>&gt;2 to 8 years: 8 mg/kg</td>
<td>0.44</td>
<td>2.8</td>
<td>2.7</td>
</tr>
<tr>
<td>&gt;8 to 12 years: 8 mg/kg</td>
<td>0.43</td>
<td>3.1</td>
<td>2.6</td>
</tr>
<tr>
<td>&gt;12 to 18 years: 300 mg</td>
<td>0.36 (0.38†)</td>
<td>3.1 (3.4†)</td>
<td>1.9</td>
</tr>
<tr>
<td>&gt;18 years: 300 mg</td>
<td>0.28 (0.30†)</td>
<td>2.2 (2.3†)</td>
<td>1.7</td>
</tr>
</tbody>
</table>

†Viread® package insert
CONCLUSIONS

• More data are needed to effectively and safely dose children <12 years of age with TDF

• Simulation suggests that a dose of 6 mg/kg in those <2 years of age would provide similar exposures to adults and supports current investigational dosing of 8 mg/kg from 2-12 years of age
ACKNOWLEDGEMENTS

• The study participants

• Mark Mirochnick for fruitful discussions

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