In Silico Pharmacokinetic/Pharmacodynamic Simulation Of Long Acting Tenofovir Injectable Formulation For Pre-exposure Prophylaxis Strategies

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Introduction

• PrEP offers a promising strategy to reduction of HIV acquisition

• 18 studies investigating PrEP in various high risk populations
  – >70% efficacy (vs placebo) with no increase in adverse events*

• iPRESX study demonstrated 44% efficacy**
  – When accounting for detectable drug, >90% efficacy

*Fonner et al 2016, **Anderson et al 2012,
Physiologically Based Pharmacokinetic Modelling to Inform Development of Intramuscular Long-Acting Nanoformulations for HIV

Table 3  Prediction of the dose and release rate of a single intramuscular injection of antiretrovirals

<table>
<thead>
<tr>
<th>Drug</th>
<th>Intramuscular dose (mg)</th>
<th>Release rate (h^{-1})</th>
<th>Weekly/ monthly</th>
<th>AUC (µg x h/mL)^{a}</th>
<th>C_{max} (ng/mL)^{a}</th>
<th>C_{trough} (ng/mL)^{a}</th>
<th>Cut-off limit (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir</td>
<td>1,300</td>
<td>0.002</td>
<td>Monthly</td>
<td>52.2 ± 15.4</td>
<td>99.2 ± 28.6</td>
<td>43.8 ± 17.2</td>
<td>18 [2] (IC_{90})</td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>0.008</td>
<td>Weekly</td>
<td>16.6 ± 7.1</td>
<td>155.6 ± 58.5</td>
<td>49.1 ± 23.0</td>
<td></td>
</tr>
</tbody>
</table>

Table 4  Validation and prediction of the intracellular concentration of emtricitabine triphosphate and tenofovir diphosphate

<table>
<thead>
<tr>
<th>Active drug</th>
<th>Intracellular C_{ss,avg} (fmol/10^6 cells)</th>
<th>Weekly/ monthly</th>
<th>Intramuscular prediction (fmol/10^6 cells)</th>
<th>Intracellular C_{trough} (fmol/10^6 cells)</th>
<th>Intracellular C_{max} (fmol/10^6 cells)</th>
<th>In vitro IC_{50} (fmol/10^6 cells)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>Simulated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir diphosphate</td>
<td>150.7 ± 92.9 [22]</td>
<td>156.5 ± 59.5</td>
<td>Monthly</td>
<td>154.2 ± 46.5</td>
<td>164.6 ± 49.3</td>
<td>150 [24]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Weekly</td>
<td>163.0 ± 59.0</td>
<td>174.9 ± 62.8</td>
<td></td>
</tr>
</tbody>
</table>

C_{max} maximum concentration, C_{ss,avg} mean steady-state concentration, C_{trough} trough concentration at the end of the duration, IC_{50} 50% inhibitory concentration
• Predicted relationship between intracellular TFV-DP and extent of protection from HIV acquisition

- 50% - 3 fmol/10^6 cells (95% CI, <1-7)
- 90% - 16 fmol/10^6 cells (95% CI, 3-28)
- 99% - 33 fmol/10^6 cells (95% CI, 6-60)

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Anderson et al 2012
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90% - 16 fmol/10^6 cells (95% CI, 3-28)
99% - 33 fmol/10^6 cells (95% CI, 6-60)

• Aims
  – To assess the feasibility of long acting injectables of TFV
  – Identify dose and release rates for PrEP
Methods

\[ TFV_{\text{plasma}} \quad V_{\text{max}} \quad K_{\text{in}} \quad K_{\text{m}} \quad K_{\text{out}} \]

Duwal et al. 2012
• PBPK Model
  – PK simulated in Matlab (R2013b)
  – Age, BMI and weight were used to allometrically scale organ weights and cardiac output
  – Physicochemical properties, in vitro apparent permeability, in vitro intrinsic clearance and cytochrome P450 induction were obtained from the literature.

• TFV Validation (Oral TDF)
  – 500 patients (18-60 years)
  – Simulation of oral 300mg OD
  – 30 Days
Methods

• TDF LA Simulations
  – Screen of 100 patients (18-60 years)
  – Simulation of single injection covering 1 and 3 month
  – Doses 500, 750, 1000 and 1250mg
  – Release rates ranged from 0.0005 to 0.002 (h\(^{-1}\))

• Candidate Simulation
  – 500 patients (18-60 years)
  – Monthly injection of 750mg, 0.002h\(^{-1}\)
  – Quarterly injection of 1000mg, 0.001h\(^{-1}\)
**Results**

- PK Model Validation using results from orally administered TDF
  - 300mg once daily
  - 100 patients
  - 30 days

<table>
<thead>
<tr>
<th></th>
<th>$C_{\text{max}}$ (ng/mL)</th>
<th>$C_{\text{min}}$ (ng/mL)</th>
<th>$AUC_{24}$ (ngxh/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Clinical</td>
<td>326 (36.6%)</td>
<td>64.4 (39.4%)</td>
<td>3324 (41.2%)</td>
</tr>
<tr>
<td>Simulated</td>
<td>418 (21.1%)</td>
<td>52.2 (44.7%)</td>
<td>4637 (21.6 %)</td>
</tr>
</tbody>
</table>

*VIREAD. Gilead Sciences; 2014*
Results

- **Monthly Injection**
  - 750mg, 0.002h⁻¹

<table>
<thead>
<tr>
<th></th>
<th>Plasma Cmax (ng/ml)</th>
<th>Plasma Cmin (ng/ml)</th>
<th>Plasma AUC (µg x h/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>128.3 (56.37)</td>
<td>34.7 (18.08)</td>
<td>49.0 (24.67)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Intracellular Cmax (fmol/10⁶ cells)</th>
<th>Intracellular Cmin (fmol/10⁶ cells, 2 Days)</th>
<th>Intracellular Cmin (fmol/10⁶ cells, 30 Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>163.9 (65.09)</td>
<td>45.9 (16.00)</td>
<td>144.9 (58.74)</td>
</tr>
</tbody>
</table>
Results

• Monthly Injection
  – 750mg, 0.002h⁻¹

<table>
<thead>
<tr>
<th>1 month</th>
<th>Intracelluar Cmin (2 Days)</th>
<th>Intracelluar Cmin (30 Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50% Reduction (HIV-1)</td>
<td>&gt;99</td>
<td>100</td>
</tr>
<tr>
<td>90% Reduction (HIV-1)</td>
<td>97.2</td>
<td>&gt;99</td>
</tr>
<tr>
<td>99% Reduction (HIV-1)</td>
<td>78.8</td>
<td>98.6</td>
</tr>
</tbody>
</table>
Results

- Quarterly Injection
  - 1000mg, 0.001h⁻¹

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Standard Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma Cmax (ng/ml)</td>
<td>88.8 (40.11)</td>
<td></td>
</tr>
<tr>
<td>Plasma Cmin (ng/ml)</td>
<td>10.5 (4.08)</td>
<td></td>
</tr>
<tr>
<td>Plasma AUC (µg x h/mL)</td>
<td>83.1 (40.41)</td>
<td></td>
</tr>
<tr>
<td>Intracellular Cmax (fmol/10⁶ cells)</td>
<td>157.9 (65.08)</td>
<td></td>
</tr>
<tr>
<td>Intracellular Cmin (fmol/10⁶ cells, 2 Days)</td>
<td>40.7 (14.48)</td>
<td></td>
</tr>
<tr>
<td>Intracellular Cmin (fmol/10⁶ cells, 90 Days)</td>
<td>68.5 (27.15)</td>
<td></td>
</tr>
</tbody>
</table>
Results

- Quarterly Injection
  - 1000mg, 0.001h\(^{-1}\)

<table>
<thead>
<tr>
<th>3 months</th>
<th>Intracellular Cmin (2 Days)</th>
<th>Intracellular Cmin (90 Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50% Reduction (HIV-1)</td>
<td>&gt;99</td>
<td>100</td>
</tr>
<tr>
<td>90% Reduction (HIV-1)</td>
<td>95.8</td>
<td>98.8</td>
</tr>
<tr>
<td>99% Reduction (HIV-1)</td>
<td>69.6</td>
<td>91.6</td>
</tr>
</tbody>
</table>
Limitations

- The simulation of PreP PD assumed that the TFV distribution into key tissues and mucosa is comparable between the traditional oral formulations and intramuscular injections.

- Formulation specific factors not accounted for.

- Concentration cut-offs used were those generated in combination with emtricitabine and are likely to be different for monotherapy.
Discussion

• The pharmacokinetics of TFV following intramuscular injection were predicted using a validated *in silico* modelling approach.

• Simulations indicate sustained concentrations of TFV following monthly and quarterly injections.

• TFV may be a suitable candidate for LA-PrEP, assuming challenges in formulation of LA-TDF can be met.

• These data may be useful to inform development of TDF LA PrEP.
Discussion

Formulation → In Vitro → Pre-clinical In Vivo → Clinical Translation

PBPK
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