Prediction of Intracellular (IC) Tenofovir Diphosphate (TFV-DP) and Emtricitabine Triphosphate (FTC-TP) Concentrations Following Drug Intake Cessation

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Background

- Maintaining high level of adherence to antiretrovirals may be aided, in part, by introduction of fixed dose combination tablets
  - Tenofovir disoproxil fumarate (DF)/emtricitabine/efavirenz (Atripla®)
  - Tenofovir DF/emtricitabine/rilpivirine (Eviplera®, Complera®)
- Some patients may miss or delay doses due to specific circumstances e.g. busy lifestyle or personal issues
- Pharmacokinetic (PK) data describing prolonged time-course of antiretrovirals in plasma or peripheral blood mononuclear cells (PBMC) are lacking
- Important for understanding drug behaviour after treatment interruption and improving management of late and missed doses
- Assess appropriateness of compounds for pre-exposure prophylaxis (PrEP)
Background

Europe: No NNRTI, tenofovir or emtricitabine-associated resistance mutations
Viral load ≤100,000 copies/mL

US: Treatment-naïve patients with viral load ≤100,000 copies/mL
Switching virologically suppressed patients (<50 copies/mL)

1 Gilead Sciences Ltd. EVIPLERA® Summary of Product Characteristics 2014; 2 Gilead Sciences. COMPLERA® Prescribing Information 2014
Open-label, single-treatment arm, PK study at St Stephen’s Centre, Chelsea & Westminster Foundation Trust (London, UK)

Evaluate plasma PK of tenofovir (TFV), emtricitabine (FTC) and rilpivirine (RPV) and IC TFV-DP and FTC-TP PK in healthy, HIV negative volunteers over 9 days following drug intake cessation
Methods
**Study Design & PK Sampling**

**Inclusion:**
- HIV negative
- Healthy male & females
- 18-60 yr, BMI: 18-35 kg/m²
- Written informed consent

**Exclusion:**
- Significant illness e.g. HIV, HCV
- Abnormal laboratory parameters
- Medications 2 wks prior to study
- Use of hormonal birth control

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**SCREENING**

- TDF/FTC/RPV
  - (300/200/25 mg once daily)

**PK SAMPLING**

- (0, 2, 4, 8, 12, 24, 36, 48, 60, 72, 96, 120, 144, 168, 192, 216h)

**FOLLOW-UP**

- Final Dose
  - Up to 9 days after drug cessation

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**DY-14**

- Begin drug intake
  - (533kcal breakfast)

**DY1**

**DY14**

**DY23**

**DY30-36**

**PLASMA**

- TFV/FTC/RPV

**PBMC³**

- TFV-DP/FTV-TP

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³ Jackson et al., JAIDS 2013; 62 (3): 275-81; ⁴ Else et al., Bioanalysis 2014; 6 (14): 1907-21
Explore the use of nonlinear mixed effects modelling to predict IC TFV-DP and FTC-TP concentrations from plasma data and prior information.
PK Modelling

Prediction of IC TFV-DP and FTC-TP

Time matched plasma and IC data from previous healthy volunteer study (TDF/FTC/EFV, 300/200/600 mg once daily)\(^3\) used as prior information to establish link between plasma TFV and FTC and IC anabolites.

Data up to 156 h (6.5 days; EFV study) and 168 h (7 days; RPV study) included.

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**EFV study**\(^3\)

\[ n = 16 \text{ (5 female)} \]

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**TFV SAMPLES** (n/N)

- Plasma: 203/206
- IC: 183/207

**FTC SAMPLES** (n/N)

- Plasma: 206/206
- IC: 207/207

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**RPV study**

\[ n = 18 \text{ (11 female)} \]

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**TFV SAMPLES** (n/N)

- Plasma: 245/251
- IC: 250/251

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**Structural Model**

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**Covariate Model**

- Weight, BMI, sex, age, CrCL

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**Final Model**

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**Predictions**

- TFV-DP/FTC-TP
- 0-168 h (7 days)

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**Simulations**

- Visual Predictive Check

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\(^3\) Jackson et al., JAIDS 2013; 62 (3): 275-81
Individual, model predicted TFV-DP and FTC-TP concentrations used to calculate parameters (WinNonlin Phoenix v. 6.3)

• Area under the curve 0-24 h (AUC\textsubscript{0-24})
• Area under the curve 0-168 h (AUC\textsubscript{0-168})
• Maximum concentration (C\textsubscript{max})
• Concentration 24 h post-dose (C\textsubscript{24})

Terminal elimination half-lives of TFV-DP and FTC-TP were calculated from the model derived parameter, k\textsubscript{40}
• Ln2/k\textsubscript{40}

Post-hoc Analysis: comparison with HIV prevention targets

90% risk reduction associated with

• TFV-DP: 16 fmol/10\textsuperscript{6} viable PBMCs\textsuperscript{5}
• FTC-TP: 3.7 pmol/10\textsuperscript{6} viable PBMCs\textsuperscript{5}
• Determine proportions below target values 24, 36, 48 and 72 h after stopping drug
• Representing a 12h delay in drug intake and 1-2 missed doses

\textsuperscript{5} Anderson et al., Sci Trans Med 2012; 4 (151): 151ra125
Results
## Demographics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>RPV study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Female [n (%)]</strong></td>
<td>Median (range) *</td>
</tr>
<tr>
<td>Age (years)</td>
<td>31 (19-47)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75 (60-105)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24 (21-31)</td>
</tr>
<tr>
<td>Serum creatinine (µmol/L)</td>
<td>73 (57-104)</td>
</tr>
<tr>
<td>Creatinine clearance (CrCL; ml/min/1.73m²)†</td>
<td>103 (78-146)</td>
</tr>
<tr>
<td>Ethnicity [n (%)]</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>10 (55.6)</td>
</tr>
<tr>
<td>Black-Caribbean</td>
<td>2 (11.1)</td>
</tr>
<tr>
<td>Black-African</td>
<td>2 (11.1)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (5.6)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1 (5.6)</td>
</tr>
<tr>
<td>Mixed ethnicity</td>
<td>2 (11.1)</td>
</tr>
</tbody>
</table>

* Unless stated otherwise  
† calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula

Study drug was well tolerated – no grade 3 or 4 adverse events were reported

3 Jackson et al., JAIDS 2013; 62 (3): 275-81; 6 Levey et al., Ann Inter Med 2009; 150 (9): 604-12
### PK Model

#### FTC Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate (RSE%)</th>
<th>IIV (%) (RSE%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL/F (L/h)</td>
<td>19.6 (5.9)</td>
<td>19.1 (29.4)</td>
</tr>
<tr>
<td>Vc/F (L)</td>
<td>69.5 (11.0)</td>
<td>45.2 (65.7)</td>
</tr>
<tr>
<td>Q/F (L/h)</td>
<td>3.70 (9.1)</td>
<td></td>
</tr>
<tr>
<td>Vp/F (L)</td>
<td>128 (9.5)</td>
<td>18.8 (22.3)</td>
</tr>
<tr>
<td>ka (h⁻¹)</td>
<td>0.53 fix</td>
<td></td>
</tr>
<tr>
<td>k₂₄ (h⁻¹)</td>
<td>0.15 (21.8)</td>
<td>60.8 (22.9)</td>
</tr>
<tr>
<td>k₄₀ (h⁻¹)</td>
<td>0.019 (6.1)</td>
<td></td>
</tr>
</tbody>
</table>

**Covariates**

- θ<sub>CrCL</sub> CL/F 0.0077 (30.9)

**Residual error**

- Proportional plasma (%) 36.1 (12.9)
- Proportional IC (%) 55.8 (13.3)

#### FTC Parameters

- 2 compartment, 1<sup>st</sup> order absorption; k<sub>a</sub> fixed to 1.05 h⁻¹ (TFV)\(^7\), 0.53 h⁻¹ (FTC)\(^8\)
- Effect compartment linked to plasma described IC data
- Significant covariates:
  - **Weight** on FTC CL/F
  - **CrCL** on TFV CL/F
  - **Food** effect on F1 (relative increase in F1 of 33% for RPV study vs. EFV study)

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\(^7\) Baheti et al., AAC 2011; 55 (11): 5294-9;
\(^8\) Valade et al., AAC 2014; 58 (4): 2256-61
PK Model

Visual Predictive Check

- Observed TFV; n=448
- Observed FTC; n=456
- Observed TFV-DP; n=183
- Observed FTC-TP; n=207

90% 92% 92% 94%
**Predicted PK Profiles & Parameters**

**TFV-DP**

- **n=18 volunteers; n=252 predicted TFV-DP concentrations**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Geometric mean TFV-DP (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;0-24&lt;/sub&gt; (fmol.h/10&lt;sup&gt;6&lt;/sup&gt; cells)</td>
<td>1456 (1302-2193)</td>
</tr>
<tr>
<td>CV%</td>
<td>66</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-168&lt;/sub&gt; (fmol.h/10&lt;sup&gt;6&lt;/sup&gt; cells)</td>
<td>7495 (6792-11486)</td>
</tr>
<tr>
<td>CV%</td>
<td>66</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (fmol/10&lt;sup&gt;6&lt;/sup&gt; cells)</td>
<td>92.2 (83.8-135)</td>
</tr>
<tr>
<td>CV%</td>
<td>60</td>
</tr>
<tr>
<td>C&lt;sub&gt;24&lt;/sub&gt; (fmol/10&lt;sup&gt;6&lt;/sup&gt; cells)</td>
<td>54.0 (48.2-87.9)</td>
</tr>
<tr>
<td>CV%</td>
<td>75</td>
</tr>
</tbody>
</table>

Predicted half-life = 116 h
Predicted PK Profiles & Parameters

FTC-TP

- Geometric mean

Predicted half-life = 37 h

$n=18$ volunteers; $n=252$ predicted FTC-TP concentrations

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Geometric mean FTC-TP (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$AUC_{0-24}$ (pmol.h/10^6 cells)</td>
<td>87.8 (79.2-150)</td>
</tr>
<tr>
<td>CV%</td>
<td>80</td>
</tr>
<tr>
<td>$AUC_{0-168}$ (pmol.h/10^6 cells)</td>
<td>273 (252-440)</td>
</tr>
<tr>
<td>CV%</td>
<td>70</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (pmol/10^6 cells)</td>
<td>6.15 (5.73-10.5)</td>
</tr>
<tr>
<td>CV%</td>
<td>75</td>
</tr>
<tr>
<td>$C_{24}$ (pmol/10^6 cells)</td>
<td>3.07 (2.88-5.63)</td>
</tr>
<tr>
<td>CV%</td>
<td>83</td>
</tr>
</tbody>
</table>
Comparison with HIV Prevention Targets

- Predicted concentrations at 24, 36, 48 and 72 h after stopping drug compared to HIV prevention targets (derived from iPrEx study data; TFV-DP: $16 \text{ fmol} / 10^6 \text{ cells}$, FTC-TP: $3.7 \text{ pmol} / 10^6 \text{ cells}$)\textsuperscript{5}

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>TFV-DP</th>
<th>FTC-TP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>%</td>
</tr>
<tr>
<td>24</td>
<td>1/18</td>
<td>6</td>
</tr>
<tr>
<td>36</td>
<td>0/18</td>
<td>0</td>
</tr>
<tr>
<td>48</td>
<td>1/18</td>
<td>6</td>
</tr>
<tr>
<td>72</td>
<td>4/18</td>
<td>22</td>
</tr>
</tbody>
</table>

- Majority of predicted TFV-DP concentrations \textbf{above} its threshold up to 3 days after final dose

- Most of predicted FTC-TP \textbf{below} its target between 24-72 h after stopping drug

\textsuperscript{5} Anderson \textit{et al.}, \textit{Sci Trans Med} 2012; 4 (151): 151ra125
Conclusions

• Prediction of TFV-DP and FTC-TP from plasma data was achieved through inclusion of prior information from a previous healthy volunteer study.

• The models, although relatively simplistic, described the data well, but also allows for refinement if further data become available.

• TFV plasma concentrations were higher in the RPV study (SSAT048) compared to the EFV study.

• Predicted TDF-DP and FTC-TP concentrations were generally in agreement with literature values\(^5,9-10\)

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Limitations

**Assumptions:**

- RPV and EFV have no or impact on TFV-DP and FTC-TP disposition
- Increased relative bioavailability assumed to be due to food intake but could be a result of inhibition of renal transporters by RPV or a combination of both

**Limitations:**

- An independent, external validation dataset required to evaluate the model, particularly to confirm TFV-DP and FTC-TP predictions
- IC rate constants ($k_{24}, k_{40}$) rely solely on prior data and are a simplification of the ongoing processes they describe
Acknowledgements

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