A Semi-Mechanistic Population Pharmacokinetic-Pharmacodynamic Model for Tenofovir in Rectal Mucosal Mononuclear Cells of Healthy Volunteers

Priya Jayachandran¹, Maria Garcia-Cremades¹, Peter Anton³, Craig Hendrix², Rada Savic¹

¹Department of Bioengineering and Therapeutic Sciences, University of California San Francisco, San Francisco, CA, USA, ²Division of Clinical Pharmacology, Department of Medicine, Johns Hopkins University, Baltimore, MD, USA, ³University of California Los Angeles, Los Angeles, CA, USA

Priya Jayachandran, PharmD, MSE

NIH T32 Clinical Pharmacology Fellow

UCSF • Principle Investigator: Rada Savic, PhD

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HIV Pre-Exposure Prophylaxis: Topical Product Development

**AIM**
Define a tissue-specific prophylactic target tenofovir concentration above which HIV infection is suppressed using pharmacokinetic-pharmacodynamic modeling

**Problem**
10-20x higher risk of HIV infection unprotected anal (vs. vaginal) intercourse

**Population**
- msm
- high-risk females

**Solution**
tenofovir rectal microbicide

**Oral PrEP Formulation**
- emtricitabine (FTC) 200 mg
- tenofovir disoproxil fumarate (TDF) 300 mg

**Intracellular**
- Tenofovir (TFV)
- tenofovir diphosphate (TFVdp)
The RMP-02/MTN-006 Study\(^1\): Phase I Pharmacokinetic Study in HIV-1 Seronegative Adults

**Screen** | **Enroll** | **Randomize**
---|---|---

**VISIT**

**Single Oral**

- 300 mg TDF

**Single Rectal**

- 1% TFV gel

**Multiple Rectal**

- x 6
- x 1

### Plasma Matrices:
- Plasma TFV concentration
- PBMC TFVdp concentration

### Rectal Matrices:
- Tissue TFV concentration
- Tissue TFVdp concentration
- MMC TFVdp concentration

### HIV infectability study:
- p24 explant tissue assay

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**Dosing events: [x]**

\(TDF = \text{tenofovir disoproxil fumarate};\ TFV = \text{tenofovir};\ TFVdp = \text{tenofovir diphosphate}\)

Pharmacokinetic Profiles of TFV/TFVdp Drug in Each Matrix

Plasma Matrices

- Plasma TFV (0.3-387 ng/mL)

- PBMC TFVdp (LLOQ-62 fmol/million cells)

Rectal Matrices

- Tissue TFV (LLOQ-430 ng/mg)

- Tissue TFVdp (LLOQ-7,188 fmol/mg)

- MMC TFVdp (LLOQ-31,153 fmol/million cells)

LLOQ = lower limit of quantification; BLQ = below limit of quantification
Concentrations deemed BLQ not included
Pharmacodynamic Profiles of Cumulative p24 Antigen Expression Levels from \textit{ex vivo} Explant Assay

Cumulative p24 antigen expression decreases with increasing TFVdp drug concentration

\textit{Median (solid, black = baseline); individual (dotted); cumulative p24 antigen level = 500 pg/mL (dashed)}

Concentrations deemed BLQ (10 pg/mL) included
A Semi-mechanistic population PKPD model with a viral growth compartment and a delayed compartment for p24 antigen expression

2-compartment plasma popPK model with an effect compartment for each cellular (PBMC, MMC) and tissue (rectal tissue) matrix

TFV competitively inhibits HIV-1 reverse transcriptase
A significant linear PKPD relationship was observed between p24 antigen expression level and TFVdp concentration in MMCs.

The magnitude of the slope is biased without consideration for the rate of drug degradation.

Assumption: constant degradation rate\(^2\) \( (k_{\text{deg}} = 0.0018 \text{ h}^{-1}) \)

## Model Summary and Visual Predictive Checks

<table>
<thead>
<tr>
<th>Model Description/Parameter</th>
<th>Pharmacokinetic Driver</th>
<th>Inter-individual Variability, %CV (RSE, %)</th>
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<tbody>
<tr>
<td></td>
<td>OFV/Significance/Population Estimate</td>
<td>CD$_4^-$</td>
</tr>
<tr>
<td>No treatment effect</td>
<td></td>
<td>8201</td>
</tr>
<tr>
<td>Treatment effect</td>
<td></td>
<td>Not significant</td>
</tr>
<tr>
<td>PKPD effect</td>
<td></td>
<td>8168 (dOFV = -33)</td>
</tr>
<tr>
<td>Drug degradation effect</td>
<td></td>
<td>8161 (dOFV = -40)</td>
</tr>
<tr>
<td>Slope ([pg/mL]/(fmol/million cells))</td>
<td>4.20x10$^{-4}$ (9)</td>
<td>8.0x10$^{-5}$ (44)</td>
</tr>
<tr>
<td>Proportional error [%CV]</td>
<td></td>
<td>86.9 (5)</td>
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<tr>
<td>Additive error [pg/mL]</td>
<td></td>
<td>3.53 (10)</td>
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What target MMC TFVdp concentration will lead to full viral suppression in the *ex vivo* assay?

Cumulative p24 antigen level = 500 pg/mL (dashed)

**[MMC TFVdp] > 5500 fmol/million cells**
Conclusions

We have established a dose-concentration-response effect using explant tissue to describe the effect of single (oral and rectal) and multiple (rectal) dose administrations of tenofovir to suppress p24 antigen expression in healthy volunteers.

Population PK Model

- TFV and TFVdp PK in plasma and rectal matrices were successfully characterized using a multi-compartmental PK model.
- Accumulation of TFVdp in MMCs appears to be higher following rectal compared to oral administration.

Population PKPD Model

- The PKPD relationship appears to be independent of cell type.
- Drug degradation effect in the ex vivo assay must be considered to derive unbiased parameter estimates and to maximize the utility of the explant assay.

Tissue-Specific Prophylactic Target TFVdp Concentration

- MMC TFVdp concentrations $> 5500$ fmol/million cells are desired for full viral suppression (p24 antigen expression profile).