Pharmacokinetics in Microbicide Development

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Objectives
How does PK inform microbicide development?

• Describe, Explain, Predict Concentration-Response
• Give examples through
  – Concentration-time-distance relationships (PK)
  – Concentration-response relationship (PK/PD)
  – Regimen selection
  – Clinical trial interpretation
  – Clinical trial simulation
• Identify optimized PK study design approaches to microbicide development
Sample Handling & Analyte Quantitation

- Development of assay begins with plasma
- Validation per FDA Bioassay Guidance
  - Precision & accuracy
  - Stability benchtop, e.g., maraviroc tissue
  - Stability freezer
  - Stability post-freezer, e.g., TFV-DP tissue
- All biological matrices require separate validation
- All collection devices require separate validation
What’s the goal of PK-PD Studies?

Relating Conc’n, Distance, Time, & Outcome

Survival Analysis
event v. time

Pharmacodynamics
event v. concentration

Pharmacokinetics
concentration v. time

\[ S(t) = S_0 + \left[ E_{SLOPE} (C_e) + \alpha \right] \cdot t \]

\[ E_{SLOPE} = \frac{E_{\text{max}} \cdot (k_e \cdot C_e/k_{1e})^\gamma}{EC_{50}^\gamma + (k_e \cdot C_e/k_{1e})^\gamma} \]

\[ C_e = \frac{D \cdot k_{1e}}{V_c \cdot (k_{e0} - k_e)} (e^{-k_{et}} - e^{-k_{e0}t}) \]
Luminal Distribution

Does rectal gel adequately cover “HIV”?

“Microbicide”($^{111}$In-DTPA) “HIV” ($^{99m}$Tc-SC) in Ejaculate

Rectal TFV gel (0h), simulated sex/ejaculation (1h), SPECT/CT (2h)

- PK-distance parameters indicate “HIV” surrogate within “microbicide” luminal distribution
- Voxel-by-voxel “HIV” covered by “microbicide” 86% (SD 0.19)
- Guides sampling sites for colon biopsies

CHARM 02 (Hiruy, et al. ARHR 2015)
**Luminal Distribution**

Which rectal formulation covers best?

<table>
<thead>
<tr>
<th>Study</th>
<th>CDC Imaging*</th>
<th>P5-Aim 2**</th>
<th>P5-Aim 2**</th>
<th>P5-Aim 1***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation</td>
<td>gel</td>
<td>gel</td>
<td>fluid</td>
<td>enema</td>
</tr>
<tr>
<td>Volume</td>
<td>10 mL</td>
<td>10 mL</td>
<td>10 mL</td>
<td>125 mL</td>
</tr>
<tr>
<td>Osmolality</td>
<td>hyper-osmolar</td>
<td>iso-osmolar</td>
<td>iso-osmolar</td>
<td>iso-osmolar</td>
</tr>
<tr>
<td>Post-dose</td>
<td>4h</td>
<td>4h</td>
<td>4h</td>
<td>4h</td>
</tr>
<tr>
<td>D_{max}</td>
<td>14.0 (9.0–63)</td>
<td>12.9 (11.6, 20)</td>
<td>23.1 (14.9, 25.1)</td>
<td>38.6 (23.8–41.7)</td>
</tr>
<tr>
<td>DC_{max}</td>
<td>6.0 (2.0–14)</td>
<td>5.1 (2.0, 8.3)</td>
<td>5.3 (3.3, 7.2)</td>
<td>17.5 (8.2–24.1)</td>
</tr>
<tr>
<td>D_{ave}</td>
<td>6.7 (3.2–29)</td>
<td>6.4 (4.7, 7.5)</td>
<td>6.8 (4.7, 10.2)</td>
<td>19.6 (9.8–23.6)</td>
</tr>
<tr>
<td>D_{min}</td>
<td>-</td>
<td>-2.6 (-3.5, 0.8)</td>
<td>-3.8 (-3.8, -3.5)</td>
<td>2.0 (-1.3–3.4)</td>
</tr>
</tbody>
</table>

Rectal HIV ~10-15 cm (relative to coccyx)

median and range for CDC Imaging (BJCP 2012), IQR for all others.

D_{max}, greatest proximal distance at which radiolabel is detected

DC_{max}, distance at which greatest radiolabel concentration is detected

D_{ave}, mean residence distance (similar to mean residence time)

D_{min}, most distal location of radiolabel

All distances are relative to coccyx

3-D Pharmacology
Where & when should PK sampling occur?

Pharmacokinetics (PK)
- Topical
  - Lumen 5
  - CD4+ Cells: TFV → TFVpp 6
- Oral
  - Tissue 3
  - CD4+ Cells: TFV → TFVpp 4
  - Blood 1

Pharmacodynamics (PD)
- [Drug Concentration]
- [Seroconversion]

Pharmacokinetic – Pharmacodynamic Link

Doesn’t have to be active drug @ site of action, it only has to be informative
Concentration-Response
What are target tissue concentrations?

Within Study: iPrEx

Among Studies

Parameter | Estimate | CV% |
--- | --- | --- |
$E_{\text{max}}$ | 0.94 | 44 |
$EC_{50}$ | 43 | 44 |
$EC_{90}$ | 107 | 44 |
Gamma | 2.4 | 56 |

Controlling for covariates
IC$_{90}$ 16 fmol/10$^6$ PBMC


Hendrix, Cell 2013
Concentration-Response
What are target tissue concentrations?

Within Study: iPrEx

- EC\textsubscript{90} PBMC TFV-DP 16 fmol/10\textsuperscript{6} cells =>
- 4 doses per week adherence =>
- Css TFV-DP PBMC/MMC 4.4 oral 300mg TDF =>
- **Target** 83 fmol/10\textsuperscript{6} Colon MMC

MTN-001 (Hendrix, et al. PLOS One 2013)

Among Studies

- EC\textsubscript{90} Plasma TFV 107 ng/mL =>
- Daily adherence =>
- Css TFV 1% vaginal dose =>
- **Target** 2,000 fmol/mg tissue homogenate

HPTN 066 (Hendrix, et al., ARHR 2015)
How soon does protection occur?

Rectal Tissue Cell TFV-DP (fmol/M cells)

C30min

C24h

Single Oral  Single Rectal  Multiple Rectal

Single Oral  Single Rectal
### 14C-TDF Single Dose Study

<table>
<thead>
<tr>
<th>Location</th>
<th>Moiety</th>
<th>Half-life*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>TFV</td>
<td>69 (55, 77)</td>
</tr>
<tr>
<td>PBMC</td>
<td>TFV-DP</td>
<td>48 (38, 76)</td>
</tr>
<tr>
<td>Blood CD4+ Cells</td>
<td>TFV-DP</td>
<td>112 (100, 118)</td>
</tr>
<tr>
<td>VT</td>
<td>TFV</td>
<td>47 (38, 53)</td>
</tr>
<tr>
<td>VT</td>
<td>TFV-DP</td>
<td>53 (45, 68)</td>
</tr>
<tr>
<td>VT Total Cells</td>
<td>TFV-DP</td>
<td>66 (43, 202)</td>
</tr>
<tr>
<td>VT CD4+ Cells</td>
<td>TFV-DP</td>
<td>139 (121, 167)</td>
</tr>
<tr>
<td>CVL**</td>
<td>TFV</td>
<td>40 (38, 43)</td>
</tr>
<tr>
<td>CVL Cells</td>
<td>TFV-DP</td>
<td>-</td>
</tr>
<tr>
<td>CT</td>
<td>TFV</td>
<td>31 (24, 36)</td>
</tr>
<tr>
<td>CT</td>
<td>TFV-DP</td>
<td>34 (21, 40)</td>
</tr>
<tr>
<td>CT Total Cells</td>
<td>TFV-DP</td>
<td>82 (43, 89)</td>
</tr>
<tr>
<td>CT CD4+ Cells</td>
<td>TFV-DP</td>
<td>60 (52, 72)</td>
</tr>
<tr>
<td>Colon Brush</td>
<td>TFV</td>
<td>20 (20, 21)</td>
</tr>
</tbody>
</table>

Louissaint, et al. ARHR 2013

### MTN-013 Dapivirine Vaginal Ring Study

**Graphs showing Dapivirine levels in plasma, cervix, and cervicitis fluid.**

Chen, et al. JAIDS 2015
Sampling Frequency Impact

How to sample to estimate PK parameters?

<table>
<thead>
<tr>
<th>PK</th>
<th>Units</th>
<th>RF TFV (CH02)</th>
<th>RGVF TFV (CH02)</th>
<th>VF TFV (CH02)</th>
<th>VF TFV (CH01)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$</td>
<td>ng/ml</td>
<td>4 (1, 5)</td>
<td>6 (5, 8)</td>
<td>23 (13, 31)</td>
<td>5 (3, 6)</td>
</tr>
<tr>
<td>AUC</td>
<td>ng*hr/ml</td>
<td>30 (15, 55)</td>
<td>39 (19, 57)</td>
<td>82 (49, 137)</td>
<td>36 (23, 57)</td>
</tr>
</tbody>
</table>
Sampling for PK-PD
How to select sample times for PK-PD?

FAME 02b Single Dose DPV Gel v. Film Comparison

Plasma DPV (pg/mL)  CVF DPV (ng/mg)

Plasma $C_{max}$ relevant?  CVF & CT peak?  CVF & CT half-life?

MTN-013 DPV+MVC 28 day Vaginal Ring

Plasma & CVF inform tissue
Estimating Unknowns
How to estimate [drug] without sampling?

Pharmacokinetics (PK)
- Lumen
  - CD4+ Cells: TFV → TFVpp
    - 6
- Tissue
  - CD4+ Cells: TFV → TFVpp
    - 4
- Blood
  - CD4+ Cells: TFV → TFVpp
    - 2

Pharmacodynamics (PD)

Doesn't have to be active drug @ site of action, it only has to be informative.
**MTN-001 PK Compartments**

Describe or Predict?

- Tenofovir daily
- Oral, Vaginal, Dual
- Cross-over design
- 144 Women
- Africa, US
- 6-compartment PK

- **If tissue relevant:** Expect vaginal $>$ oral efficacy
- **If systemic relevant:** Expect oral $>$ vaginal efficacy
- Vaginal tissue TFV-DP **Vaginal $130x$ > Oral** (topical tissue advantage)
- Serum TFV **Oral $56x$ > Vaginal** (serum doesn’t reflect tissue)
- Rectal gel dosing shows similar trends  
  
  Hendrix, et al. PLOS One 2013
Sparse Sampling PK
PK Estimates w/o intensive sampling?

- Traditional Intensive PK Sampling
  - Few Subjects, Many Times

- Sparse Sampling (Population PK)
  - Many Subjects, Few Times
PK Model Building (MTN-001)
Maximizing data from mixed site capacity?

Initial estimates from HPTN 050
Population PK Modeling
How to describe individual PK within a pop’n?

- Sparsely sampling each subject
- Model PK parameters (CL, V_c, KA)
- Adjust for adherence
- Covariate effect on PK parameters
- Inter-subject & residual variability
- Enables clinical trial simulation

Burns, et al., J Clin Pharmacol 2015
Modelling v. Simulation

- Modelling objective & process
  - Estimating where you don’t observe
  - Estimate parameters of explanatory or predictive value to your study question
  - Data to parameters, e.g., $C, t \rightarrow CL, V, HL$

- Simulation objective & process
  - Dosing regimens you didn’t study
  - Begin with parameters and generate data based on variety of experimental designs
  - Parameters to data, e.g., $CL, V, HL \rightarrow C, t$
Adjusting for Adherence
Simulation concurs with DOT

Population PK Simulation

Mechanistic Model Simulation

Burns, et al., J Clin Pharmacol 2015
Madrasi, et al., CPT Pharmacometrics Sys Pharmacol 2014
Applying PK Models to Simulate
How to optimize rectal formulations?

Single dose enhanced tenofovir enema for HIV prevention

TFV enema PK Enhancements
- Bioavailability (F)
  - TFV analogs
  - Hypotonic vehicle
- Sustained release (S)
  - Nanoparticle
  - Gelling agent

Reference Targets
- Colon CD4+ cell TFV-DP
- Bridging RCT-PK studies
Why perform Clinical Trial Simulation?

- Forces identification of knowledge on hand and what is missing and uncertain
- Identify uncertainty impact on trial outcomes
- May result in cheaper, cost effective studies
- May result in trials with fewer adverse events
- Allows trial “test drive” on a computer
- Ask “What if?” questions
Designing Microbicide RCT
What data are needed for PrEP CTS?

- Adherence
  - $PK_{IND} - PGx_{CL, V, k_a}$
  - [Drug]

- Pharmacodynamics
  - Toxicodynamics
    - Toxicity
      - Off-target

- HIV Infection
  - HIV Exposure & (Para)Sexual
    - Behaviors set mass in motion
  - Viral Kinetics
    - Distribution/clearance
    - Particles (mass) move in Space & Time
  - Viral Dynamics
    - Infectivity
    - Interactions of Drug, Host, Virus

- Drug Regimen
- Study Population

PKIND - PGx
CL, V, ka

Drug Regimen
Study Population
Refining RCT Design
Clinical Trial Simulation

- **Pharmacokinetic Model**
  \[
  C_e = \frac{D \cdot k_{1e}}{V_c \cdot (k_{e0} - k_e)} \left( e^{-k_e t} - e^{-k_{e0} t} \right)
  \]

- **Pharmacodynamic Model**
  \[
  E_{\text{SLOPE}} = \frac{E_{\text{max}} \cdot (k_{e0} \cdot C_e/k_{1e})^\gamma}{EC_{50}^\gamma + (k_{e0} \cdot C_e/k_{1e})^\gamma}
  \]

- **Infection Prevention Model**
  \[
  S(t) = S_0 + [E_{\text{SLOPE}}\left(C_e\right) + \alpha] \cdot t
  \]
Summary

What are PK design principles?

...sample throughout the dosing interval
...sample when PK parameter of interest is most influenced
...escalating doses to assess dose-proportionality
...sample to inform prescribing (how soon? how long?)
...single dose & steady-state
...multiple adjacent compartments simultaneously
...sparsely in many better than intensively in a few
...PK & PD simultaneously, range of concentrations & varied regimens (concentration-, time-dependent PK-PD)
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