Clinical Pharmacology of Antiretrovirals for HIV Prevention: Implications for PrEP Efficacy and Adherence

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Johns Hopkins University School of Medicine
Pre-Exposure Prophylaxis

- PrEP ï prophylaxis for HIV susceptible
- Prevention control to receptive partner
- PMTCT precedent supported by animal models
- 1996-2009, 6 RCT luminally active vaginal gels failed
- 2010-2012, 6 RCT oral (TFV±FTC) & topical (TFV)
  - Efficacy demonstrated, but highly variable results
- 2012 FDA market approval for TDF/FTC (Truvada)
  - Combination with safer sex practices
  - Adults (men & women) at high risk of HIV infection
  - Single oral daily dose
  - Label emphasizes importance of adherence
- RCTs alone leave many unanswered questions
Outline
Clinical pharmacology studies informé

- concentration-response relationship (target?)
- how many doses before protection?
- colon tissue advantage?
- topical dosing advantage?
- adherence source of study variability?
- limitation of adherence estimates?
- EMS and PK combination usefulness?
Concentration-response

- As drug concentration increases, efficacy increases
- Identify concentration target
- Informs dose & frequency
- Identify site of action (?)
- Poor concentration-response indicates additional variables
  - Clues to mechanism of action
  - Clues to management

Relative Risk Reduction

Ln(Drug Exposure at site of action)
# PrEP Concentration-Response

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>Relative Risk Reduction (95% CI)</th>
<th>All Subjects</th>
<th>Drug Detectible</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Partners</strong></td>
<td>TDF po qd</td>
<td>0.67 (0.44 i 0.81)</td>
<td>0.86 (0.57i 0.95); BLQ 0.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TDF/FTC po qd</td>
<td>0.75 (0.55 i 0.87)</td>
<td>0.90 (0.56i 0.98); BLQ 0.3</td>
<td></td>
</tr>
<tr>
<td><strong>CDC TDF2</strong></td>
<td>TDF/FTC po qd</td>
<td>0.62 (0.22 i 0.83)</td>
<td>50% SC, 80+% NSC; BLQ 0.3</td>
<td></td>
</tr>
<tr>
<td><strong>iPrEx</strong></td>
<td>TDF/FTC po qd</td>
<td>0.42 (0.15 i 0.63)</td>
<td>0.92 (0.40 i 0.99); BLQ 10</td>
<td></td>
</tr>
<tr>
<td><strong>FEM-PrEP</strong></td>
<td>TDF/FTC po qd</td>
<td>0.06 (-0.41 i 0.52)</td>
<td>No diff. 25% v 35%; BLQ 10</td>
<td></td>
</tr>
<tr>
<td><strong>VOICE</strong></td>
<td>TDF po qd</td>
<td>-0.49 (-1.30 – 0.035)</td>
<td>No difference; BLQ 0.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TDF/FTC po qd</td>
<td>-0.04 (-0.50 – 0.30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CAPRISA 004</strong></td>
<td>TFV gel BAT24</td>
<td>0.39 (0.04 i 0.60)</td>
<td>&gt;1,000 CVF increased RRR</td>
<td></td>
</tr>
<tr>
<td><strong>VOICE</strong></td>
<td>TFV gel qd°</td>
<td>0.15 (-0.20 – 0.40)</td>
<td>No difference; BLQ 0.3</td>
<td></td>
</tr>
</tbody>
</table>

Concentration-response among and within RCTs.
Plasma and CVF demonstrate concentration-response.
Why no consistent pattern in the data?
iPrEx-informed concentration target

EC$_{90}$ = 16 fmol/M (95% CI 3-28) viable cells (24-48 freshly lysed cells).

Can single oral dose achieve EC$_{90}$?

Å Method differences require rescaling EC$_{90}$ (16 viable = 24-48 freshly lysed)
Å Most subjects below iPrEx EC$_{90}$ with single dose (none sustained above)
Å Most subjects above iPrEx EC$_{90}$ at steady-state (3 weeks)

Does dosing route affect concentrations?

- 144 women daily oral, vaginal, & combination dosing, 6 weeks each

- Vaginal tissue TFV-DP Vaginal 130x > Oral (topical tissue advantage)
- Serum TFV Oral 56x > Vaginal (serum doesn’t reflect tissue)

Hendrix, et al. PLOS One 2013
Are iPrEx targets the same for women?

- Single dose TDF, 6 women (paired across all matrices)
- Weekly tissue sampling x 2 weeks
- RV:VT TFV-DP homogenate c/w Patterson (STM 2011)
- RT:VT ratio varies with drug moiety & sample type
- Initial 24h colon:vaginal gradients not sustained
  - colon homogenate and CD4 cell half-life < vaginal tissue
- Rectal advantage clearest with > weekly dosing

<table>
<thead>
<tr>
<th>Day</th>
<th>RT:VT TFV Plasma Median (IQR)</th>
<th>RT:VT TFV-DP Homogenate Median (IQR)</th>
<th>RT:VT TFV-DP CD4 Cells Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>33.8 (6.8, 37.8)</td>
<td>123.7 (8.4, 155.4)</td>
<td>19.20 (9.60, 28.8)</td>
</tr>
<tr>
<td>8</td>
<td>4.5 (0.9, 31.3)</td>
<td>1.7 (0.3, 2.8)</td>
<td>0.20 (0.17, 0.23)</td>
</tr>
<tr>
<td>15</td>
<td>0.3 (0.3, 0.3)</td>
<td>2.5 (2.5, 2.6)</td>
<td>0.15 (0.15, 0.15)</td>
</tr>
</tbody>
</table>

Louissaint, et al. ARHR 2013
Can tissue provide useful frame of reference?
[Tissue] reference informs conc\textsuperscript{-}response

Adherence or PK Differences?

- PP T/E po
- PP T po
- CDC T/E po
- iPrEX MSM T/E po
- CAPRISA 004 T gel
- VOICE T/E po
- VOICE T/Gel
- FEM-PrEP T/E po

Relative Risk Reduction for HIV Infection

Tissue Adjusted Plasma Tenofovir (ng/mL)
MTN-001

Variation in adherence or PK?

☐ Pre-dose concentration (adherence, PK) 5:1 ratio
☐ Decay (PK) same after observed dose
☐ Crude adjustment indicates similar PK across sites
☐ Formal Pop PK analysis confirms adherence>>PK variation
☐ Raised concern about potential for poor adherence at VOICE sites
Uses of Adherence Data

- Interpret
  - Clinical study outcomes

- Intervene
  - Targeted adherence counseling
  - Real-time clinical site evaluation

- Optimize
  - Clinical trial simulation
DOT Benchmarks

Expected Values as Reference

STRAND

2/wk 4/wk 7/wk
n: 21 21 22

100% 100% 100%

median: 11 32 42
IQR: 6-13 25-39 31-47


HPTN 066

Serum TFV ng/mL

Donnell, *et al.* CROI 2012
### HPTN 066 (DOT) Benchmark

<table>
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<th>Daily</th>
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<td>HPTN066 L95%CI</td>
<td>40</td>
<td>16</td>
<td>7</td>
<td>3</td>
<td>0.2</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>~65 (67-75%)</td>
<td></td>
<td></td>
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<td></td>
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<td>&lt;10 (0%)</td>
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<td></td>
<td></td>
<td>&lt;0.3(0%)</td>
</tr>
</tbody>
</table>

Figures are TFV plasma concentration ng/mL (% relative risk reduction)
*Model estimate
# Discordant Adherence Outcomes

<table>
<thead>
<tr>
<th>Adherence Measure</th>
<th>TDF Oral</th>
<th>FTC/TDF Oral</th>
<th>TFV Gel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product return</td>
<td>87%</td>
<td>92%</td>
<td>86%</td>
</tr>
<tr>
<td>Self report</td>
<td>90%</td>
<td>91%</td>
<td>90%</td>
</tr>
<tr>
<td>TFV ever detected (LLOQ 0.31 ng/mL)</td>
<td>42%</td>
<td>50%</td>
<td>45%</td>
</tr>
<tr>
<td>Samples with TFV &gt;LLOQ (mean)</td>
<td>30%</td>
<td>29%</td>
<td>25%</td>
</tr>
</tbody>
</table>
VOICE

Was topical adherence worse than oral?

→ Expected 24 hour post-dose plasma TFV concentration with single dose
Requires adjustment to compare distributions of oral and vaginal dosing
Marazzo, et al., CROI 2013
Dosing Route-adjusted TFV Concentrations

Oral TDF

Vaginal 1% TFV Gel

Oral v. vaginal dosing adjustment suggests similar oral and topical adherence.
VOICE: Temporal Adherence

HIV seronegatives

percent (%) of women with detectable TFV

FTC/TDF
TDF
Tenofovir 1% Gel

quarterly visits

124 114 105 113 93 59
136 113 77 55 27 15
160 151 105 81 52 30
Drug detected in <50% non-seroconverters
LLOQ higher (10 ng/mL) compared to VOICE (0.31 ng/mL)
HIV infection occurred during periods of low drug exposure

## Partners PrEP: Temporal Adherence

<table>
<thead>
<tr>
<th></th>
<th>Cases (TDF = 17, FTC/TDF = 12)</th>
<th>Cohort (N = 198)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Visits prior to seroconversion</td>
<td>Seroconversion visits</td>
</tr>
<tr>
<td>TDF arm</td>
<td>35/63, 56%</td>
<td>6/17, 31%</td>
</tr>
<tr>
<td>FTC/TDF arm</td>
<td>20/36, 56%</td>
<td>3/12, 25%</td>
</tr>
</tbody>
</table>

- 25-31% of seroconverters had detectable levels of drug at seroconversion visit
- Assay LLOQ limited explanatory capacity for outcomes
- 56% had detectable tenofovir earlier
- All 3 studies showed adherence erosion

Donnell, et al. CROI 2012
Partners PrEP
Beyond LLOQ adherence thresholds

Adherent >40 ng/mL based on HPTN 066 lower 05% CI daily dosing
LLOQ 0.31 ng/mL
Donnell, et al. CROI 2011
### PK or PD based adherence threshold?

<table>
<thead>
<tr>
<th>Week</th>
<th>PK Threshold</th>
<th>PD Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt; Lower LOQ (0.25 ng/mL)</td>
<td>&gt;1,000 ng/mL</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adherence assessments using CVF PK (0.25) or PD (1,000) thresholds*
Variable Patterns of Adherence

- 90% Adherence takes many forms

- All PK matrices are insensitive to holidays vs. regular pattern

Electronic Event Monitoring Systems

MEMSCAP (micro-electromechanical systems)

Wisepill (SMS)

Proteus (SMS, swallowing, physiological)
Understanding Concentration-Response Optimal: Combining EMS & PK\textsubscript{IND}

- Adherence patterns vary
- Drug exposure varies widely
- Some patterns more permissive than others
- “On average” adherence analyses may mislead regarding targets
- Need event monitoring for both drug and sexual exposure ($Y_c$).
- EMS+Sparse PK\textsubscript{IND} sampling enables simulation of concentration for entire study
  - Powerful for understanding concentration-response (inform regimen)
  - Enables clinical trial simulation to optimize future RCT study designs

Summary

Clinical pharmacology studies informed

- concentration-response relationship (target)
- multiple oral doses before protection
- colon tissue advantage falls with dose frequency
- topical dosing tissue advantage dose per dose
- adherence greatest source of study variability
- RCT adherence rates non average miss holidays
- EMS and PK combination needed
Thank You
PK-based adherence intervention

- Study X: 3 product, 8 week per product, cross-over study
- 4 & 8 week plasma "real time" for drug concentration
- How do I select Yes/No PK result to inform adherence counseling?

<table>
<thead>
<tr>
<th>Route</th>
<th>Source</th>
<th>Sample Time</th>
<th>[TFV] Plasma X Days post dose (Dose Day = Day 0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>$^{14}$C-TDF SD</td>
<td>$C_{\text{max}}$ Median</td>
<td>175.0, 69.4, 27.6, 10.9, 4.3, 1.7, 0.7, 0.3, 0.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$C_{\text{max}}$ L25%</td>
<td>136.0, 54.0, 21.4, 8.5, 3.4, 1.3, 0.5, 0.2, 0.1</td>
</tr>
<tr>
<td>Vaginal</td>
<td>MTN-001 SS</td>
<td>$C_{\text{max}}$ Median</td>
<td>3.9, 1.5, 0.6, 0.2, 0.1, 0.0, 0.0, 0.0, 0.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$C_{\text{max}}$ L25%</td>
<td>2.2, 0.9, 0.3, 0.1, 0.1, 0.0, 0.0, 0.0, 0.0</td>
</tr>
<tr>
<td>Rectal</td>
<td>MTN-006 SD</td>
<td>$C_{\text{max}}$ Median</td>
<td>6.6, 2.6, 1.0, 0.4, 0.2, 0.1, 0.0, 0.0, 0.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$C_{\text{max}}$ L25%</td>
<td>4.6, 1.8, 0.7, 0.3, 0.1, 0.0, 0.0, 0.0, 0.0</td>
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</table>

- "Non-Adherence" (below limit quantitation - pink) varies with route
- Equivalent adherence - oral 10 ng/mL c/w topical 0.3 ng/mL
- PBMC, hair, DBS insensitive +/- Tss too long with 8 week/product
Individual data from MTN-001 shown in single data points overlayed on population estimates from single dose (underestimates, but directly observed) reference cohorts: JHU (ICTR, $^{14}$C-TFV), MTN-006, CONRAD Gel Study (Jill Schwartz)
PK_{IND} Plus Event Monitoring

- Collect sparse PK data
  - to estimate PK_{IND}
- Collect drug taking events (MEMS)
- Estimate complete conc_{IND} v. time curve
- Evaluate sensitivity of seroconversion to various patterns of drug exposure
- Provides
  - Explanatory value
  - Predictive value
- HIV exposure monitoring elusive

Influence of Matrix Half-Life

- ↑HL drug, more doses influence each observation
- ↓HL drug, more influence of most recent dose
- None sensitive to drug holidays unless recent (↓HL)
Future Directions

- **PK/PD**
  - Multi-compartment modeling (MTN-001) to bridge RCTs
  - Pooling RCTs to assess PK-PD (PP, TDF2, VOICE)

- **Adherence**
  - Other matrices (PBMC, DBS, hair)
  - VOICE, Partners, HPTN 067, IAVI
  - MEMS informed Markov modeling (Partners PrEP)
  - Real-time adherence assessment (MTN-020, -017)

- **Clinical trial simulation**
  - Optimize design of next generation PrEP RCTs
  - Sensitivity to varying patterns of adherence
Questions
RCT Cart before the PK/PD Horse

Next Generation

- Expansion of formulation types to enhance adherence (PK differs)
- Different MOA (PK/PD may differ)
- Need more PK → PK/PD → RCT progression
Added Variability of Non-Daily Dosing

- PD Threshold: 1,000 ng/mL CVF
  - 3-8 days post-last dose
  - So, 3–8 days plus self-reported time since dosing

- Lower limit of quantitation
  - 3+–7+ weeks post-last dose
  - So, 3+–7+ wks plus self-reported time since dosing

- Added uncertainty of self-report for dosing
- Added uncertainty of self-report for exposure
HPTN 066 (CROI 2012)

## HPTN 066 (DOT) Benchmark

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Figures are TFV plasma concentration ng/mL (% relative risk reduction)

*Model estimate
PD Effect: *Ex vivo* Explant Challenge

- UC781 (IP/CP-HTM)
- TFV (MTN-006)
- Rectal Vehicle (IP/CP-HTM)

**Note:** 3 examples of statistically significant changes in p24 ag in explant model (up and down)
PK_{IND} Plus Event Monitoring

- Collect sparse PK data to estimate PK_{IND}
- Collect drug taking events (MEMS)
- Estimate complete concentration v. time curve
- Evaluate sensitivity of seroconversion to various patterns of drug exposure
- Provides
  - Explanatory value
  - Predictive value

Variable Patterns of Adherence

- 90% Adherence takes many forms

Electronic Event Monitoring

MEMSCAP (micro-electromechanical systems)

Wisepill

- Wisepill Dispenser
- Patient Cellphone
- Caregiver Cellphone
- SMS Reminders
- Prescription Times
- Reports

Wisepill Client

Wisepill Server
Electronic Event Monitoring

- Body Weight (from Wireless Scale)
- Blood Pressure (from Wireless sphygmomanometer)
- Medication Adherence & Physiologic Data (from Wearable Health Monitor)

Diagram:
- Data Collection
- Upload
- Integration
- Feedback & Sharing

Providers

Family & Caregivers
Modeling Adherence for CTS

Markov Mixed Effect Regression

Table II. Estimates of $p(n)$ for ZDV data

<table>
<thead>
<tr>
<th>Meaning</th>
<th>Parameter*</th>
<th>Estimate</th>
<th>95% CI of estimate</th>
<th>Interindividual variability (-2SD, +2SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Model\ for\ p(n_j = 0</td>
<td>n_{j-1})$</td>
<td>( \theta^*_0 )</td>
<td>-2.45</td>
<td>-3.15, -1.74</td>
</tr>
<tr>
<td>Intercept</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$n_{j-1} = 0$</td>
<td>( \exp(\beta_{00}) )</td>
<td>1.55</td>
<td>0.85, 2.82</td>
<td>0.23, 10.27</td>
</tr>
<tr>
<td>$n_{j-1} = 2$</td>
<td>( \exp(\beta_{20}) )</td>
<td>2.03</td>
<td>1.49, 2.73</td>
<td></td>
</tr>
<tr>
<td>Weekend</td>
<td>( \exp(\theta^*_1) )</td>
<td>1.45</td>
<td>1.11, 1.89</td>
<td>0.65, 3.24</td>
</tr>
<tr>
<td>Midday</td>
<td>( \exp(\theta^*_2) )</td>
<td>3.24</td>
<td>2.19, 5.34</td>
<td>0.77, 15.2</td>
</tr>
<tr>
<td>Evening</td>
<td>( \exp(\theta^*_3) )</td>
<td>2.08</td>
<td>1.27, 3.39</td>
<td>0.37, 11.8</td>
</tr>
<tr>
<td>Age = 62</td>
<td>( \exp(\theta^*_4) )</td>
<td>0.31</td>
<td>0.08, 1.14</td>
<td></td>
</tr>
<tr>
<td>Age = 22</td>
<td>( \exp(-\theta^*_4) )</td>
<td>3.25</td>
<td>0.87, 12.1</td>
<td></td>
</tr>
<tr>
<td>$Model\ =\ p(n_j = 2</td>
<td>n_{j-1})$</td>
<td>( \theta^*_3 )</td>
<td>-4.19</td>
<td>-5.32, -3.06</td>
</tr>
<tr>
<td>Intercept</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$n_{j-1} = 0$</td>
<td>( \exp(\beta_{02}) )</td>
<td>3.67</td>
<td>1.02, 13.2</td>
<td>0.13, 106.32</td>
</tr>
</tbody>
</table>

* Exponentiated parameters are odds ratios

† Based on estimates of \( \Theta^* \) and \( \Omega^* \) only

CLINICAL TRIAL SIMULATION
Clinical Trial Simulation

Drug Regimen $\rightarrow$ Adherence $\rightarrow$ $PK_{IND}$ $\rightarrow$ [Drug] $\rightarrow$ Pharmacodynamics $\rightarrow$ HIV Infection

HIV Exposure & (Para)Sexual $\rightarrow$ Viral Kinetics Distribution/clearance $\rightarrow$ Viral Dynamics Infectivity $\rightarrow$ Toxicodynamics $\rightarrow$ Toxicity Off-target

Behaviors set mass in motion $\rightarrow$ Particles (mass) move in Space & Time $\rightarrow$ Interactions of Drug, Host, Virus
Why 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
Key Points

- + Within study concentration-response
- + Between study concentration-response
- Caution extrapolating MSM results to others
- Adherence (mostly) explains concentration \( \sigma \)
- Target concentration needs more work
- Drug concentration cannot explain all
Pop PK Model: Adherence & PK

- MTN-001 non-linear mixed effects model
- Estimate PK ($Cl$, $V$, $Ka$) and adherence ($C_0$)
- No PK differences; sign. Adherence difference

PK Model

Adherence Measure ($C_0$)

Clearance ($Cl$)


PrEP RCT PK-PD į Informed by PK

Adherence v. PK Difference?

Relative Risk Reduction for HIV Infection

Adjusted Plasma Tenofovir (ng/mL)
PK informed interpretation, not design

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>Relative Risk Reduction (95% CI) All Subjects</th>
<th>Drug Detectible</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partners</td>
<td>TDF po qd</td>
<td>0.67 (0.44 ‒ 0.81)</td>
<td>0.86 (0.57 ‒ 0.95); BLQ 0.3</td>
</tr>
<tr>
<td></td>
<td>TDF/FTC po qd</td>
<td>0.75 (0.55 ‒ 0.87)</td>
<td>0.90 (0.56 ‒ 0.98); BLQ 0.3</td>
</tr>
<tr>
<td>CDC TDF2</td>
<td>TDF/FTC po qd</td>
<td>0.62 (0.22 ‒ 0.83)</td>
<td>50% SC, 80+% NSC; BLQ 0.3</td>
</tr>
<tr>
<td>iPrEX</td>
<td>TDF/FTC po qd</td>
<td>0.42 (0.15 ‒ 0.63)</td>
<td>0.92 (0.40 ‒ 0.99); BLQ 10</td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td>TDF/FTC po qd</td>
<td>0.06 (-0.41 ‒ 0.52)</td>
<td>No diff. 25% v 35%;BLQ 10</td>
</tr>
<tr>
<td>VOICE</td>
<td>TDF po qd</td>
<td>-0.49 (-1.30 ‒ 0.035)</td>
<td>No difference; BLQ .0.3</td>
</tr>
<tr>
<td></td>
<td>TDF/FTC po qd</td>
<td>-0.04 (-0.50 ‒ 0.30)</td>
<td></td>
</tr>
<tr>
<td>CAPRISA 004</td>
<td>TFV gel BAT24</td>
<td>0.39 (0.04 ‒ 0.60)</td>
<td>&gt;1,000 CVF increased RRR</td>
</tr>
<tr>
<td>VOICE</td>
<td>TFV gel qd</td>
<td>0.15 (-0.20 ‒ 0.40)</td>
<td>No difference; BLQ 0.3</td>
</tr>
</tbody>
</table>
VOICE: Adjusted TFV Concentrations

TDF

- **Density**

\[ \log(1+\text{TFV concentration}) \]

- **Tenofovir 1% Gel**

- **Density**

\[ \log(1+\text{TFV concentration} \times 130) \]
PrEP RCT PK-PD: No Little Studies
How does clinical pharmacology inform?

- Concentration-response
  - Target concentration?
  - Target location?
  - Rational dosing
- Explain variable response among populations?
- Adherence assessment
  - *Post hoc* Interpretation of RCT outcomes?
  - Real-time study intervention?
At the site of action oral and topical dosing achieves the same effective concentration (best PK/PD model fit).

Distant Compartment Assessment

Oral

CD4+ Cells

TFV\rightarrow\text{TFVpp}\n
Lumen

5

Tissue

3

Blood

1

CD4+ Cells

TFV\rightarrow\text{TFVpp}\n
4

CD4+ Cells

TFV\rightarrow\text{TFVpp}\n
2

CD4+ Cells

TFV\rightarrow\text{TFVpp}\n
6

Pharmacokinetic \& Pharmacodynamic Link

VOICE Seroconversion

[CD4+ TFV-Diphosphate]
Distant Compartment Assessment

Oral

-Lumen 5
-CD4+ Cells TFV→TFVpp 6

-Tissue 3
-CD4+ Cells TFV→TFVpp 4

-Blood 1
-CD4+ Cells TFV→TFVpp 2

Pharmacokinetic İ Pharmacodynamic Link

Likelihood of Seroconversion

[CD4+ TFV-Diphosphate]
Distant Compartment PK Informative

Pharmacokinetics (PK)

Oral, Rectal, Vaginal Daily, Weekly, Coitally

Pharmacodynamics (PD)

Does dosing route affect concentrations?

- 144 Women
- Africa, US
- Tenofovir daily
- Oral, Vaginal, Dual
- Cross-over design
- 6 weeks each regimen
- 6-compartment PK
  - Plasma TFV, PBMC TFV-DP 8 hours (US intense, Africa sparse)
  - Vaginal tissue homogenate TFV, TFV-DP
  - Cervicovaginal lavage TFV
  - Endocervical cytobrush TFV-DP
**iPrEx: Contrasts women's cohorts**

Detection of drug relative reduction in HIV risk of 92% (95% CI 40-99)

Only ½ had measurable drug, far lower than oral women's studies (medians indicated are not medians)
iPrEx (MSM) target similar for women?

- Single dose TDF
- 6 men; 6 women (unpaired)
- Semi-weekly tissue sampling x 2 weeks

TFV 24h RT:VT $2.5 \log_{10}$

TFV-DP 24h RT:VT $2.2 \log_{10}$

Patterson, et al. Sci Trans Med 2011
VOICE Adherence Assessments

- Product return (pill/vaginal applicator)
- Self-report using ACASI

PK-related

- Quarterly blood sampling planned for exposure-response analysis

Case-cohort design:

- Random active arm subset (non-seroconverter + all seroconverters, N = 773)
- All samples from each participant, N = 3,298
- Median number of samples 4; range 1 - 12
- Small sample from placebo arms for blinding
Population PK: PK & Adherence

- **Estimate PK** \((CL, V, k_a)\), adherence \((C_0)\)
  - \(C_0\) represents the concentration present in the system at the time of the most recent dose
  - \(C = [SDF + C_0^{-b}t]\)
  - \(SDF = Dose \times (A \times e^{-a \times t} + B \times e^{-b \times t} - (A + B) \times e^{-ka \times t})\)

PK Model

- **Adherence Measure** \((C_0)\)

Gupta, *et al.* J PK PD 2008

- **Clearance** \((CL)\)

Chaturvedula, *et al.* 2012