Antiretroviral Pharmacology for PrEP: Enhancing RCT Understanding with Small Intensive Studies

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PrEP Concentration-Response

 Equivalent Tenofovir ng/mL (median [IQR])
  10  100  1000  10000

 Relative Risk Reduction (mean [95% CI])
  0.0  0.2  0.4  0.6  0.8  1.0

- PP TDF po qd
- PP TDF/FTC po qd
- CDC TDF/FTC po qd
- iPrEX**TDF/FTC po qd
- CAPRISA 004*TFV gel BAT24
- (MTN-001 US TDF po qd)
- VOICE*TDF po qd
- VOICE*TDF gel qd

PrEP Concentration - Response

FEM-PrEP T/E po

Equivalent Tenofovir ng/mL (median [IQR])

Relative Risk Reduction (mean [95% CI])

0.0  0.2  0.4  0.6  0.8  1.0

10  100  1000  10000
Variables Influencing Infection

Regimen → Adherence → Pharmacokinetics (Distribution/clearance) → Pharmacodynamics

HIV Exposure & (Para)Sexual → Viral Kinetics (Distribution/clearance) → Viral Dynamics (Infectivity)

Behaviors set mass in motion
Particles (mass) move in Space & Time
Interactions of Drug, Host, Virus

HIV Infection → Toxicodynamics
Toxicity Off-target

Major → Major → Minor → Major?
Key Points

- Within study concentration-response
- Between study concentration-response
- Caution extrapolating MSM results to others
- Adherence (mostly) explains concentration $\sigma$
- Seroconverter adherence wanes with time
- Target concentration needs more work
- Drug concentration cannot explain all
- Daily regimen affords greatest protection
# Within Study 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>
<th>Adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPRISA 004</td>
<td>TFV gel BAT24</td>
<td>0.39 (0.04 – 0.60)</td>
<td></td>
<td>&gt;1,000 CVL&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.54 (0.20 – 0.96)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>VOICE</td>
<td>TFV gel qd&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.0 (-0.35 – 0.35)</td>
<td></td>
<td>In Analysis</td>
<td></td>
</tr>
<tr>
<td>iPrEX</td>
<td>TDF/FTC po qd</td>
<td>0.42 (0.15 – 0.63)</td>
<td></td>
<td>0.92 (0.40 – 0.99)&lt;sup&gt;c&lt;/sup&gt;; BLQ 10</td>
<td></td>
</tr>
<tr>
<td>Partners</td>
<td>TDF/FTC po qd</td>
<td>0.75 (0.55 – 0.87)</td>
<td></td>
<td>0.90 (0.58–0.98)&lt;sup&gt;c&lt;/sup&gt;; BLQ 0.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TDF po qd</td>
<td>0.67 (0.44 – 0.81)&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td>0.86 (0.67–0.94)&lt;sup&gt;c&lt;/sup&gt;; BLQ 0.3</td>
<td></td>
</tr>
<tr>
<td>CDC TDF2</td>
<td>TDF/FTC po qd</td>
<td>0.63 (0.22 – 0.83)</td>
<td></td>
<td>In Analysis</td>
<td>0.78 (0.41 – 0.94)&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td>TDF/FTC po qd</td>
<td>0.0 (-0.73 – 0.42)</td>
<td></td>
<td>No difference</td>
<td></td>
</tr>
<tr>
<td>VOICE</td>
<td>TDF po qd&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.0 (-0.35 – 0.35)</td>
<td></td>
<td>In Analysis</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>High adherence (>80% self-report); CVL>1,000 log-rank significant;<sup>b</sup>Detectable drug; <sup>c</sup>TDF v TDF/FTC NS; <sup>d</sup>Available supply of study drug
Among Study Concentration-Response

**VOICE** simulated by MTN-001 African sites
Rectal: Vaginal Tissue Comparison

Patterson, et al. Sci Trans Med 2011


<table>
<thead>
<tr>
<th>Day</th>
<th>RT:VT TFV 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>

TFV-DP RT:VT Gradient
- RT > 100x VT @ 24h
- Not sustained
- CD4 gradient smaller
Among Study Concentration-Response

Adherence v. PK Difference?

*Adjusted for 66x increased colon tissue concentration (→) and 20 times greater anal transmission risk (↔)

**VOICE simulated by MTN-001 African sites
Decay (PK) same after observed dose

Pre-dose concentration (adherence) 5x different

TFV catches up in 1 hr; TFV-DP in 8 hrs.
DOT: Benchmarks & Models

**STRAND**

<table>
<thead>
<tr>
<th>2/wk</th>
<th>4/wk</th>
<th>7/wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>n:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>21</td>
<td>22</td>
</tr>
</tbody>
</table>

TFV-DP (fmol/10^6 cells)

- % detected: 100% 100% 100%
- Median: 11 32 42

**HPTN 066**

- Serum TFV ng/mL
- 1 tab - weekly
- 1 tab - 2x weekly
- 2 tab - 2x weekly
- 1 tab - daily

Anderson, et al. CROI 2012

HPTN 066 Study Team (Donnell CROI 2012)
Population PK: Adherence & PK

- Combine data from HPTN 066 & MTN-001
- Build non-linear mixed effects model
- Estimate PK ($CL$, $V$, $Ka$) and adherence ($C_0$)

Observational Data

Adherence Measure ($C_0$)

Clearance ($CI$)

US White, US Black, Africa Black
Oral dosing (MTN-001)
iPrEx: [Drug] Falls in Seroconverters

Temporal pattern consistent with adherence change, but not PK change

Drug Detection* at Visit with First Evidence of HIV Infection for Case

- <50% drug detected in non-seroconverters
- HIV infection occurred during periods of low drug exposure

Partners: Transients in Non-seroconverters

Visit month

Drug concentration (ng/mL)

Below Detectable

0.3–40

≥ 40

≥ HPTN 066 Lower 95% CI

< HPTN 066 Lower 95% CI

< Lower limit of assay quantitation
# HPTN 066 Plasma TFV Comparisons

<table>
<thead>
<tr>
<th>Study</th>
<th>Daily</th>
<th>4x/week*</th>
<th>2x/week</th>
<th>Weekly</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DOT HPTN 066 Mean</strong></td>
<td>59</td>
<td>23.4</td>
<td>3.7</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>DOT HPTN 066 L95%CI</strong></td>
<td>40</td>
<td>15.9</td>
<td>2.5</td>
<td>0.2</td>
</tr>
<tr>
<td>MTN-001 US</td>
<td>~100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>~ 65 (67-75%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDC TDF2</td>
<td>~ 55 (62%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTN-001 Africa</td>
<td></td>
<td>~25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>iPrEX</td>
<td></td>
<td></td>
<td>~ 10 (42%)</td>
<td></td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td></td>
<td></td>
<td>&lt;10 (0%)</td>
<td></td>
</tr>
<tr>
<td>VOICE</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

Figures are mean/median TFV plasma concentration ng/mL (% relative risk reduction)  
*Model estimate
iPrEx vs STRAND Benchmarks

- Low % detection suggests < 2 doses/week.
- 0% cases, 18% controls in range of daily dosing.
- The majority of active arm dosing < daily, still the overall iPrEx trial efficacy was 42%.

Anderson CROI 2012

**iPrEx median, IQR of detectable levels in figure.
### iPrEx Risk Reduction & STRAND Dosing

<table>
<thead>
<tr>
<th>Adherence (STRAND)</th>
<th>iPrEx model estimate for HIV Relative Risk Reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 doses/wk</td>
<td>76% (56 to 96%)</td>
</tr>
<tr>
<td>4 doses/wk</td>
<td>96% (90 to &gt;99%)</td>
</tr>
<tr>
<td>7 doses/wk</td>
<td>99% (96 to &gt;99%)</td>
</tr>
</tbody>
</table>

90% effective TFV-DP ($EC_{90}$) = 16 (95% CI, 3 to 28) fmol/million viable PBMC. TFV-DP levels from STRAND analyzed with regression model from iPrEx. Anderson CROI 2012
Partners Seroconverters: More than [TFV]

Cases with consistently high levels of drug detected prior to seroconversion; consistent with daily dosing.
Relating Oral to Topical Dosing

MTN-001 Cross-Over
- TFV daily
- Oral, Vaginal, Dual
- Cross-over design
- 144 Women
- Africa, US
- Multi-site PK

- Relate Serum to tissue
- Vaginal tissue TFV-DP 100x higher with vaginal dosing
- Expect vaginal >> oral efficacy
Reconciling Oral & Topical Results

**Concentration-Response**

HIV replication inhibition

**PP TDF po**

**PP T/E po**

**CDC T/E po**

**iPrEX T/E po**

**CAPRISA T gel**

**MTN-001/3**

**FEM-PrEP T/E po**

**MTN-001/3**

**VOICE simulated by MTN-001 African sites**
Adherence (Oral) & HIV-Enabling? (Topical)

Concentration-Response

HIV replication inhibition

HIV enabling variable ("OTHER")

Seroconversion (HIV replication + HIV enabling effect)

(Concentration-response curves for both HIV inhibiting and enabling effects fitted to data by sigmoid $E_{max}$ model)
Key Clinical Pharmacology Points

- Clear within study concentration-response
- Clear between study concentration-response
- Caution extrapolating MSM results to others
- Adherence mostly explains concentration
- Seroconverter adherence wanes with time
- Critical concentration needs additional work
- Daily regimen affords greatest protection
Thank You

- Research Participants
- Pete Anderson, iPrEX
- Lut van Damme, FEM-PrEP
- Deborah Donnell, Partners PrEP Co-Is
- Mike Thigpen, Lynn Paxton, CDC TDF2 Co-Is
- Kris Patterson, Ken Mayers, HPTN 066 Co-Is
- MTN-001 Study Team
- Johns Hopkins Clinical Pharmacology