Pharmacology Lessons from Chemoprophylaxis Studies

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St Stephen’s AIDS Trust
Chelsea and Westminster Hospital
London, UK
**Pre tenofovir generation 1996-2009**
**PK did not inform trials**

<table>
<thead>
<tr>
<th>Study Drug</th>
<th>Mechanism of Action</th>
<th>Sample Size</th>
<th>Seroconversions</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonoxynol 9</td>
<td>Surfactant</td>
<td>892</td>
<td>59, 45</td>
<td>1.5 (1.0–2.2)</td>
</tr>
<tr>
<td>Savvy (C31G)</td>
<td>Surfactant</td>
<td>2,153</td>
<td>21, 12</td>
<td>1.7 (0.9–3.5)</td>
</tr>
<tr>
<td>Cellulose Sulfate</td>
<td>Polyanion</td>
<td>1,333</td>
<td>23, 11</td>
<td>0.8 (0.3–1.8)</td>
</tr>
<tr>
<td>Carraguard</td>
<td>Polyanion</td>
<td>6,202</td>
<td>134, 151</td>
<td>0.9 (0.7–1.1)</td>
</tr>
<tr>
<td>Pro2000</td>
<td>Polyanion</td>
<td>*3,099</td>
<td>36, 51</td>
<td>0.7 (0.5–1.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.6 (on Rx, p=0.04)</td>
</tr>
<tr>
<td>Pro2000 (MRC)</td>
<td>Polyanion</td>
<td>9,385</td>
<td>145, 143</td>
<td>1.00 (0.79–1.26)</td>
</tr>
</tbody>
</table>

In parallel with RCT, in vitro studies demonstrate toxicity for 3 of these products
*4-arm study, 1,550 enrolled in Pro2000 and placebo gel arms

Hendrix 2012
## Tenofovir generation 2010-2012
PK informed interpretation, not design

<table>
<thead>
<tr>
<th>STUDY</th>
<th>REGIMEN</th>
<th>RELATIVE RISK REDUCTION (95% CI)</th>
<th>DRUG DETECTABLE</th>
<th>ADHERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEM-PrEP</td>
<td>TDF/FTC po QD</td>
<td>0.0 (-0.73-0.42)</td>
<td>SC 15%, NSC 26%, NS, LLOQ 10</td>
<td></td>
</tr>
<tr>
<td>VOICE</td>
<td>TDF po QD</td>
<td>0.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>iPrEX</td>
<td>TDF/FTC po QD</td>
<td>0.42 (0.15-0.63)</td>
<td>0.92 (0.44-0.99), LLQ 10</td>
<td></td>
</tr>
<tr>
<td>CDC TDF2</td>
<td>TDF/FTC po QD</td>
<td>0.63 (0.2200.83)</td>
<td>SC 50%, NSC 80%, LLOQ 0.3</td>
<td>0.78 (0.41-0.94)</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), LLOQ 0.3</td>
<td></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)</td>
<td></td>
</tr>
<tr>
<td>CAPRISA</td>
<td>TFV gel BAT24</td>
<td>0.39 (0.04-0.60)</td>
<td>&gt; 1000 CVF</td>
<td>0.54 (0.20-0.96)*</td>
</tr>
<tr>
<td>VOICE</td>
<td>TFV get QD</td>
<td>0.0</td>
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Hendrix 2012
IDEALLY

Large RCTs should contain sparse PK assessment

Linked to smaller formal/intensive PK studies

• Importance of understanding concentration-response
• Factors affecting dose selection
• Future trial design
The optimal PrEp agent

- Safe
- Penetrates target tissues
- Protect against HIV in tissue
- Demonstrates long-lasting activity with convenient dosing
- Unique drug resistance profile / high genetic barrier to resistance
- No significant drug-drug interactions
- Not part of current HIV treatment combinations
- Affordable and easy to use/implement
TFV and FTC are the only ARVs proven efficacious in prospective randomised clinical PrEP trials

HIV acquisition is the primary outcome used / large sample size CTs

Lack of surrogate marker for PrEP

Important role of CLINICAL PHARMACOLOGY to explain the variable drug responses
Proviral DNA
Viral RNA

TFV

PROVIRAL DNA
VIRAL RNA

TFV

FTC

CONTROLLING THE HIV EPIDEMIC WITH ANTIRETROVIRALS
From Consensus to Implementation
Tenofovir, emtricitabine intracellular and plasma, and efavirenz plasma concentration decay following drug intake cessation: implications for HIV treatment and prevention.

Terminal TFV-DP $t_{1/2} = 164$ h

Jackson et al. JAIDS2013
Tenofovir, emtricitabine intracellular and plasma, and efavirenz plasma concentration decay following drug intake cessation: implications for HIV treatment and prevention.

Terminal FTC-TP $t_{1/2} = 39$ h

Jackson et al. JAIDS2013
Predicted TFV-DP accumulation to steady-state in humans with 3 different dosing strategies

STRAND: Directly observed dosing showed TFV-DP concentrations that corresponded with HIV risk reduction of 76% for 2 doses per week, 96% for 4 doses per week, 99% for 7 doses per week

Anderson et al. JAC 2010; Anderson et al. STM 2012
## Within study concentration-response comparison

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*INCREASED RR REDUCTION WITH DETECTABLE DRUG IN PLASMA

*INCREASED RR REDUCTION WITH >80% ADH and [CVF]>1000ng/mL

Hendrix 2012
Sources of PHARMACODYNAMIC variability

- Virological factors
- Immunological factors
- Host biology/genetics
- Adherence
- PK
- Drug interactions
- Tissue penetration
- Cell type
- Toxicity
- ETC…

DRUG CONCENTRATION vs. DRUG EFFECT
Gaps?

• Fundamental HIV transmission biology incompletely understood
  • What is the site of action to target?
  • What is the required duration of action?
• Validation of animal models and *ex vivo* HIV challenge
• Clinical proof-of-concept design needed
What are the drug distribution targets?
Lack of data on concentration-effect relationship

Drug concentration

Steady state

Maximum protection

Protection against HIV

Drug dose

Time

How high should the dose be to achieve 100% HIV protection?

Ideally months...

When should the following dose be administered to maintain protection?

Are ex vivo challenge experiments adequate to assess PrEP PDs?

Would “maximum” be 100%?

Thanks to Alan Winston and UK PrEP Pharmacology Group
A pharmacokinetic evaluation of the exposure and distribution of TMC278LA for use as pre-exposure prophylaxis, in plasma and genital tract / rectal compartments, following a single intramuscular dose at different doses in HIV negative healthy volunteers.

- HIV negative volunteers (60 female, 6 male)
- Aged 18 – 50 years
- Low behavioural risk for infection
- Female: > 50% of enrolled; self-identified African or African-Caribbean ancestry
- Administered 300 (n = 20), 600 (n = 20), 1200 (n = 20) mg RPV-LA (G001 formulation) intramuscularly (gluteus maximus)
- Sampling:
  - plasma PK
  - cervicovaginal fluid (CVF; females) & rectal fluid (RF; males) PK
  - tissue biopsies: vaginal (VT; females) & rectal (RT; males) PK
  - cervicovaginal lavage (CVL; females) PK & PD

<table>
<thead>
<tr>
<th>Day</th>
<th>Plasma PK</th>
<th>Genital/rectal fluid PK</th>
<th>Tissue Biopsy (vaginal/rectal)PK</th>
<th>CVL for PK and PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>🟥</td>
<td>🌿</td>
<td>🆕</td>
<td>🌿</td>
</tr>
<tr>
<td>0 (4 h)</td>
<td>🟥</td>
<td>🌿</td>
<td>🆕</td>
<td>🌿</td>
</tr>
<tr>
<td>0 (8h)</td>
<td>🟥</td>
<td>🌿</td>
<td>🆕</td>
<td>🌿</td>
</tr>
<tr>
<td>1</td>
<td>🟥</td>
<td>🌿</td>
<td>🆕</td>
<td>🌿</td>
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<tr>
<td>3</td>
<td>🟥</td>
<td>🌿</td>
<td>🆕</td>
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<tr>
<td>7</td>
<td>🟥</td>
<td>🌿</td>
<td>🆕</td>
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<tr>
<td>11</td>
<td>🟥</td>
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<tr>
<td>14</td>
<td>🟥</td>
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<tr>
<td>21</td>
<td>🟥</td>
<td>🌿</td>
<td>🆕</td>
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<tr>
<td>28</td>
<td>🟥</td>
<td>🌿</td>
<td>🆕</td>
<td>🌿</td>
</tr>
<tr>
<td>42</td>
<td>🟥</td>
<td>🌿</td>
<td>🆕</td>
<td>🌿</td>
</tr>
<tr>
<td>56</td>
<td>🟥</td>
<td>🌿</td>
<td>🆕</td>
<td>🌿</td>
</tr>
<tr>
<td>84</td>
<td>🟥</td>
<td>🌿</td>
<td>🆕</td>
<td>🌿</td>
</tr>
</tbody>
</table>
PLASMA 300, 600 & 1200 mg doses:

Dose proportionality: geometric mean (90% CI)

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>F 300 mg</th>
<th>F 600 mg</th>
<th>F 1200 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; ng/mL</td>
<td>33.7 (27.8-39.6)</td>
<td>81.9 (68.7-95.1)</td>
<td>160.2 (137.5-182.9)</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; day</td>
<td>7.9 (4.2-11.5)</td>
<td>6.0 (3.4-8.6)</td>
<td>6.2 (4.3-8.1)</td>
</tr>
<tr>
<td>t½ day</td>
<td>42.6 (27.8-57.8)</td>
<td>39.1 (33.4-44.9)</td>
<td>38.2 (29.8-46.6)</td>
</tr>
<tr>
<td>C&lt;sub&gt;28&lt;/sub&gt; ng/mL</td>
<td>19.3 (16.0-22.6)</td>
<td>44.2 (33.6-54.7)</td>
<td>82.9 (66.6-99.1)</td>
</tr>
<tr>
<td>C&lt;sub&gt;50&lt;/sub&gt; ng/mL</td>
<td>9.1 (7.7-10.6)</td>
<td>22.6 (19.1-26.1)</td>
<td>45.3 (35.8-54.9)</td>
</tr>
<tr>
<td>C&lt;sub&gt;84&lt;/sub&gt; ng/mL</td>
<td>6.4 (5.5-7.3)</td>
<td>16.2 (13.0-19.3)</td>
<td>30.2 (23.7-36.6)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;84&lt;/sub&gt; ng.day/mL</td>
<td>1231.0 (1053.9-1408.1)</td>
<td>2934 (2568.5-3300.4)</td>
<td>5981.6 (5155.9-6807.4)</td>
</tr>
</tbody>
</table>

TARGET?
CVF 300, 600 & 1200 mg doses:
Dose proportionality: geometric mean (90% CI)

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>F 300 mg</th>
<th>F 600 mg</th>
<th>F 1200 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ ng/mL</td>
<td>67.4 (41.5-93.3)</td>
<td>99.3 (66.5-132.1)</td>
<td>199.9 (154.7-245.1)</td>
</tr>
<tr>
<td>$T_{\text{max}}$ day</td>
<td>5.3 (2.5-8.2)</td>
<td>7.2 (3.1-11.3)</td>
<td>8.5 (5.06-11.9)</td>
</tr>
<tr>
<td>$t_{1/2}$ day</td>
<td>33.6 (22.7-44.5)</td>
<td>31.1 (25.3-36.8)</td>
<td>43.7 (31.1-56.4)</td>
</tr>
<tr>
<td>$C_{28}$ ng/mL</td>
<td>24.8 (13.7-35.9)</td>
<td>39.4 (17.7-61.1)</td>
<td>84.8 (63.7-106.1)</td>
</tr>
<tr>
<td>$C_{56}$ ng/mL</td>
<td>12.4 (6.4-18.5)</td>
<td>18.3 (11.5-25.1)</td>
<td>35.9 (27.8-44.1)</td>
</tr>
<tr>
<td>$C_{84}$ ng/mL</td>
<td>11.7 (6.9-16.6)</td>
<td>14.9 (7.3-22.4)</td>
<td>35.9 (25.5-46.3)</td>
</tr>
<tr>
<td>$\text{AUC}_{84}$ ng.day/mL</td>
<td>2027.1 (1409.2-2645.1)</td>
<td>3207.3 (2262.4-4152.1)</td>
<td>6499.5 (5264.2-7734.7)</td>
</tr>
</tbody>
</table>

TARGET?
VT 300, 600 & 1200 mg doses:
Dose proportionality: geometric mean (90% CI)

<table>
<thead>
<tr>
<th>[RPV] in VT</th>
<th>F 300 mg</th>
<th>F 600 mg</th>
<th>F 1200 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 7 ng/mL (n=5)</td>
<td>16.3 (14.5-18.2)</td>
<td>39.4 (31.2-47.6)</td>
<td>-</td>
</tr>
<tr>
<td>Day 14 ng/mL (n=10)</td>
<td>13.9 (8.1-19.8)</td>
<td>41.4 (29.1-53.7)</td>
<td>53.9 (28.6-79.3)</td>
</tr>
<tr>
<td>Day 28 ng/mL (n=15)</td>
<td>31.8 (9.08-54.5)</td>
<td>33.8 (20.3-47.3)</td>
<td>66.6 (38.8-94.4)</td>
</tr>
<tr>
<td>Day 56 ng/mL (n=10)</td>
<td>31.9 (27.4-36.4)</td>
<td>-</td>
<td>94.9 (33.3-156.6)</td>
</tr>
</tbody>
</table>
A subject tested positive for HIV antibodies on study day 84

HIV viral load on study day 56 = 370 copies/mL
HIV viral load on study day 84 = 175060 copies/mL

Received the lowest studied dose of 300 mg IM

Plasma [RPV] = 24.3 ng/mL on day 28
10.5 ng/mL on day 42 (presumed exposure to HIV)
6.8 ng/mL on day 56
7.5 ng/mL on day 84

CVF [RPV] = 32.9 ng/mL on day 28
18.3 ng/mL on day 42 (presumed exposure to HIV)
11.2 ng/mL on day 56
14.0 ng/mL on day 84

May suggest that higher exposures of RPV are needed to protect against HIV infection
SSAT040: PD data

- CVL samples collected by aspiration of 10 mL normal saline (after cervical lavage) at baseline, 28 and 56 days post-dose
- N = 10 on 300mg and N = 10 on 1200mg
- Antiviral activity determined against HIV-1BaL challenge of TZM-bl cells
- PK/PD correlation established using all data points from both doses

<table>
<thead>
<tr>
<th>PK/PD correlation</th>
<th>TMC-278 (ng/ml)</th>
<th>HIV-1 inhibition (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>0.4773</td>
<td>0</td>
</tr>
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</table>

Thanks to Betsy Harold and Pedro Mesquita, Albert Einstein College of Medicine.
SSAT040: PD data

![Graphs showing HIV-1 inhibition over time post-treatment for different drug doses.](image)

Thanks to Betsy Harold and Pedro Mesquita, Albert Einstein College of Medicine.
Simulation of drug concentration profiles following multiple dosing of immediate release vs. extended release: higher versus lower dose?

- NNRTI at 600 mg po every 24 hours
- NNRTI at 100 mg sc every 10 days

Target
- Plasma or IC?
- IC\textsubscript{50}, MEC?

How high can the C\textsubscript{max} be and for how long? Or if lower, would it limit the AEs?
Safety and Efficacy of Ibalizumab + OBR in Treatment-Experienced Patients

- Humanized monoclonal antibody to non-HIV binding epitope of CD4
- Blocks HIV-1 entry into cell
- TMB-202: randomized, double-blind phase IIb study in heavily treatment-experienced patients
  - 800 mg IV q2w + OBR (n = 59)
  - 2000 mg IV q4w + OBR (n = 54)

  OBR contained ≥ 1 active agent

- HIV-1 RNA < 50 at wk 24
  - 44% in 800 mg q2w arm
  - 28% in 2000 mg q4w arm

- No d/c due to study drug
- Phase I trial ongoing assessing s.c. administration

Khanlou et al, ICAAC 2011. Thank you to CCO.
Mean Plasma S/GSK1265744 Concentration-Time Profiles Following Single Dose LAP Formulation Administration
Human PK data PLUS macaque efficacy data suggest real promise for GSK744 as an agent for PrEP

IWCPHT-2013
• Administered as IM injection to healthy volunteers in a long-acting nanosuspension formulation
• $t_{1/2} = 21 - 50$ days
• 400 mg IM either a single IM injection or split into 2 x 200 mg IM injections
• Median ratio of GSK744 concentrations in cervicovaginal tissue to plasma ranged from 16% to 28%
• Median ratio of rectal tissue to plasma (obtained only from male participants) was ≤ 8%
• Association between higher tissue concentrations with higher plasma concentrations suggests low tissue concentrations may be improved with higher doses

CROI-2013
• Efficacy of GSK744 for PrEP in 8 macaques that received IM doses of GSK744 at two time points 4 weeks apart
• 8 macaques receiving placebo became infected with SHIV
• None of the 8 treated macaques had detectable virus 3 weeks after the final viral challenge

Collectively, human PK data PLUS macaque efficacy data suggest real promise for GSK744 as an agent for PrEP
First study of repeat dose co-administration of GSK1265744 and TMC278 long-acting parenteral nanosuspensions: pharmacokinetics, safety, and tolerability in healthy adults

Spreen et al. IAS 2013

PrEP = SINGLE AGENT?

• GSK744 LAP and TMC278 LA formulations were generally safe and well tolerated - with mild-moderate ISR in majority subjects
• GSK744 LAP PK indicated that q 4 wks or less frequent injections will maintain plasma concentrations > 4x PA-IC$_{90}$
• TMC278 LA PK suggested q 4 wks injections give plasma concentrations comparable to oral RPV 25 mg OD
New Approaches to Antiretroviral Drug Delivery: Challenges and Opportunities

Marta Boffito¹; Akil Jackson¹; Andrew Owen²; Stephen Becker³

¹St. Stephen’s Centre, Chelsea and Westminster Hospital, London, UK; ²University of Liverpool, Liverpool, UK; ³Bill and Melinda Gates Foundation, Seattle, WA, USA.

In press
Conclusions

Small clinical pharmacology studies inform:

- concentration-response in PrEP RCTs
- adherence
- concentrations in anatomic site of HIV acquisition
- how to achieve “target” concentrations

Early planning and completion of clinical pharmacology studies is improving the drug development process for the next generation of PrEP agents.