Pharmacology Considerations for HIV Prevention

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Presented at the 13th Int. Workshop on Clin. Pharmacology of HIV Pharmacology – 2012, Barcelona Spain
Perspectives for next generation studies

- Event-driven, episodic, intermittent TFV-FTC dosing.

- Ultra-long acting medications (eg rilpivirine injection).

- New delivery systems (eg vaginal ring) and combinations (eg maraviroc, raltegravir).

Considerations unique to prevention

- Onset and duration of drug action.

- Dose-response, or concentration effect specific to HIV prevention.
Consideration 1

- Non-daily episodic regimens must provide an optimal onset and duration of drug action that covers the window of time that HIV needs to establish an infection.
Timing of mucosal transmission

Garcia-Lerma, et al. PMID:19963288.

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Initial infection - mucosa

- *Within* 24 hours of exposure, as early as 2 hours. – Initial replication in mucosal CD4 cells.

- Drug must be present in mucosa within 2-24 hours.

Initial infection – systemic?

- Virus infiltrates lymph nodes at 24 hours.
- Possible that systemic drug is needed to “mop up” viral exposure (?)..

Initial infection and HIV vulnerability

<table>
<thead>
<tr>
<th>Mode</th>
<th>Per Act Rate/1000</th>
<th>Single “founder” virus</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSX</td>
<td>1</td>
<td>80%</td>
</tr>
<tr>
<td>MSM</td>
<td>5</td>
<td>60%</td>
</tr>
</tbody>
</table>

“a substantial proportion of HSX and MSM patients acquire HIV-1 infection as a consequence of transmission and productive infection by literally one virion or one infected cell” – H. Li. PLoS Pathog. (PMID:20485520)

D. Smith, MMWR 2005;54(No. RR-2); M. Cohen NEJM (PMID. 21591946); E Russell. J Virol. (PMID 21593171)
The most important time to have therapeutic drug levels is at exposure when the virus is most vulnerable.

Drug levels clearly needed in mucosa (systemic?).

What about duration of drug action?
HIV clearance rates after exposure?

If no cell-associated HIV, ~3 days.
If replication occurred, 30 days.
Latency established - too late.

Timing of latency establishment (?)

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M. Cohen NEJM (PMID. 21591946)
Consideration 1

• Non-daily episodic regimens must provide an optimal onset and duration of drug action that covers the window of time that HIV needs to establish an infection.

What is well known:
- Drug should be present AT the time of exposure, or immediately thereafter.
- Mucosal drug penetration critical.

What is not well known:
- Are systemic drug concentrations required to “mop up” virus?
- Duration? ~ 3 days if no replication, 30 days if replication.
Consideration 2

• A target drug concentration (e.g., IC90 or EC90) that is specific to HIV prevention is required during the window of time that HIV needs to establish an infection.
Focus

- TFV, TDF ± FTC best studied compounds to date.

- Cell-dependent pharmacology, t-1/2 of active TFV-DP, 100 hours, that of FTC-TP, 50 hours.
PK-PD specific to HIV prevention has been elusive

- No PD surrogate for human PK-PD studies.
  - Rely on retrospective phase III trial data

- Likely a different dose response relationship for prevention vs Rx.

- Animal models needed to help guide PK-PD for prevention.

Barditch-Crovo. AAC. (PMID.11557462)

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Topical TFV gel delivers high mucosal levels

- 144 women received 1% TFV gel or oral TDF daily for 6 weeks.

- TFV-DP in vaginal homogenate was 100-fold higher than with oral dosing.

- Conversely, systemic levels were 50-fold higher with oral than gel dosing.

Hendrix. CROI 2011.
PK-PD link vaginal lymphocyte TFV-DP

- Pigtail macaques exposed to SHIV 3 day after 1% gel x 10 wks.
- TFV-DP in vaginal lymphocytes at 3 days was ~300 fmol/10^6 cells.
- Efficacy was 74%.
- Model consistent with 1000ng/ml identified in CAPRISA (74%).

In vitro cell model

![Graph showing PK-PD relationship](image)

IC/EC90 ~ 700 – 900 fmol/10^6 cells

Dobard C. (PMID. 22072766), Karim Lancet (PMID. 21763939)

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Can 700 – 900 fmol/10^6 vaginal lymphocytes be achieved with daily TDF oral dosing?

- Same study of 144 women found 72 fmol/10^6 cells cervical brush samples daily TDF and 1078 fmol/10^6 cells with gel.

- Study of 10 women taking daily TDF-FTC for 30 days found 194 fmol/10^6 cells cervical brush samples at steady state.

No, it is not likely these levels can be reached with daily oral dosing.

Evidence that oral dosing is effective in women

- Partners in Prevention, n=4758, ♂♀, daily TDF or TDF-FTC versus placebo.

- TDF 67% (44 to 81%) effective and TDF-FTC 75% (55 to 87%) effective. Both significantly effective in women.

- A TFV level of 40 ng/mL was identified as protective.
Potential interpretation

• The target drug level requirement in vaginal mucosa may be higher when delivered topically (700-900 fmol/10^6 cells) than systemically (~72-194 fmol/10^6 cells) suggesting systemic drug may provide effect.
Oral TDF delivers high rectal mucosal levels

- 15 men and women received one TDF-FTC dose, rectal/female genital tract tissue sampled for 14 days.
  - TFV-DP in rectal tissue was 100-fold above the levels in female genital tract tissue.

- 19 men and women received 30 days of TDF-FTC with PBMC/rectal sampling.
  - TFV-DP levels were 20-fold higher in rectal mononuclear cells versus PBMC.

Patterson Sci Trans Med. (PMID 22158861) Anderson CROI 2012

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Suggests that oral TDF (±FTC) for MSM provides dual high exposure mucosally and systemically.
iPrEx study of MSM

- The iPrEx trial randomized 2499 MSM to daily FTC/TDF vs placebo.
  - Efficacy was 42% (95%CI 18% to 60%)\(^1\).

- Any drug detection was ~50% in the FTC-TDF arm and only 8% of those who contracted HIV.

- Drug levels in the active arm were further analyzed for relationship with HIV prevention efficacy.

Estimated HIV incidence by TFV-DP in IPREX

- Regression analysis of full iPrEx cohort, HIV incidence vs TFV-DP in active arm.

- 90% effective TFV-DP (EC90) = 16 (95%CI, 3 to 28) fmol/M viable PBMC*. 

Anderson. CROI 2012.
What does “16 fmol/10^6 viable cells” mean?

- These were viable PBMC stored in DMSO. Drug recovery was 48%. This translates to 40 fmol/10^6 cells with fresh lysed cells.

- Daily dosing is about 100 fmol/10^6 cells.

- Model predicts that high PrEP efficacy is well within the range of daily dosing for MSM.
Potential implication

• A different dose-response may exist for oral dosing in MSM versus women due to differing drug levels achieved in mucosa.

Consideration 3

- Long half-life drugs such as TFV-DP (100 hours) provide long duration of action, but also exhibit slow accumulation, which should be considered for onset of action with episodic dosing.
“Cell-PrEP”

HIV-negative

• Characterize TFV-DP/FTC-TP accumulation and elimination.

• Completed N=19 HIV-negative volunteers.
Accumulation of TFV-DP

- Long t-1/2 (100 hours), thus long accumulation.
- EC90 (40 fmol/10⁶ cells) in MSM is achieved on 3rd dose.
- The EC90 may be higher in women, requiring even more doses.

Anderson. CROI 2012.
Example 2 dose load followed by single dose

- Onset: 14 hours, duration 32 hours.
- Regimens should be optimized for onset and duration.
- Loading dose/period warranted?
Summary

- Episodic dosing requires drug at the time of exposure, so pre-dosing or immediate-acting. The duration of action required is unclear.

- Dose response may be unique for HSX versus MSM due to different mucosal drug levels.

- Long-half life drugs such as TFV-DP accumulate slowly, and may be suited for loading doses or periods.
Implications: Next generation studies

- Event-driven, episodic, intermittent dosing.
  - Fast onset of action is critical. Short and long acting drugs warranted.
  - TDF (±FTC) loading doses or loading dose period?
  - Combinations of locally and systemically acting drugs?

Variables in need of future study

Higher risk
- AIDS (7-fold)
- STI (5-fold)
- Acute HIV (9-fold)

Lower risk
- HIV + on ARV (25-fold)
- Condom (20-fold)
- Circumcision (2-fold)

References:
Varghese. Sex Transm Dism (PMID. 11773877); Boily. Lancet Infect Dis (PMID 19179227); Cohen. NEJM. (PMID. 21767103 )
THANK YOU

- Study participants; NIH/NIAID, study drug from Gilead Sciences