Modelling the impact of different patterns of adherence to PrEP on the observed efficacy in clinical trials

DOBROMIR DIMITROV, PHD
Introduction

- Four randomized trials have indicated that pre-exposure prophylaxis (PrEP) products based on tenofovir significantly reduced HIV acquisition ... and two other trials were not able to demonstrate PrEP efficacy.

- One key conclusion: The success of future PrEP interventions at population level will strongly depend on the individual adherence. How optimistic we should be?

<table>
<thead>
<tr>
<th>Adherence</th>
<th>iPrEX</th>
<th>Partners PrEP</th>
<th>VOICE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self reported</td>
<td>89-95%</td>
<td>92%</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Drug detection</td>
<td>51% of HIV-9% of HIV+</td>
<td>82% of HIV-31% of HIV+</td>
<td>29-30%</td>
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</tbody>
</table>
Protection provided by PrEP

• 38%-75% efficacy in the clinical trials which found PrEP effective

• How exactly is PrEP protection affected by adherence?
  • **iPrEx** - 73% efficacy when PrEP is used 90% of the days or more
  • **Partners PrEP** – detectable drug was associated with 86% (TDF) and 90% (TDF-FTC) reduction in relative risk of acquiring HIV
  • **iPrEx** team estimated that PrEP retains 96% protection if taken every other day and 76% if taken 2 days per week

• Related questions …
  • How long PrEP should be taken to start providing protection?
  • What happens with PrEP protection when few doses are skipped?
Motivation

- PrEP is prescribed to be taken daily. We assume 70% efficacy when taken consistently.
- Different protection functions are possible.
- Different patterns of skipping doses are possible.
- All of the above may affect the effectiveness of PrEP.

20% overall adherence.
Main Questions

How important are these factors (protection waning and adherence patterns) to the results of PrEP clinical trials?

• Do they enhance or dilute observed efficacy and by how much?

What is the impact of these factors on the population-level effectiveness of PrEP?

• How to optimize the public-health impact of PrEP use in the community?

• Potential effects on the risk of drug-resistance emergence if infected while using PrEP
Methods

• Stochastic individual-based mathematical model simulates placebo-controlled randomized clinical trial in a female population.

• Trial participants are enrolled over 1 year period using inclusion criteria of VOICE. Assigned to an active (PrEP) or control (placebo) arms with 1:1 allocation ratio.

• Event-driven trial is simulated, i.e., the trial concludes when a specific number of infections have been reached.

• Sexual activity of participants is simulated for the duration of the trial. Rates of initiation and dissolution of partnerships, frequency, type, and protection of sexual acts are calibrated for South Africa.

• Scenarios with different PrEP protection functions, overall level and pattern of adherence are investigated.
Scenarios explored

Overall adherence to PrEP

- Uniform adherence for all participants (20%, 50%, 80% explored)
- Mixed population – half with 20% adherence and half with 80%
- Risk-driven adherence – 80% probability to take PrEP in days when sex is expected, 20% otherwise

Adherence patterns

- Randomly skipped doses
- Doses skipped (taken) at regular intervals
- Block adherence

Waning of PrEP protection

- Fast (protects only the days taken)
- Intermediate-retains 60% (day 2) and 20% (day 3)
- Slow (some protection up to 5 days)
Results: Uniform adherence

Average adherence 50%

33% difference

26% difference

~30% observed efficacy
Results: Mixed adherence

Mix adherence 20% & 80%. Slow loss of protection.

Participants:
Half with 20% adh
Half with 80% adh

Adherence pattern is more important to poor adherers
Results: Risk-driven adherence
Summary

• Both, protection waning and adherence patterns may have substantial impact on the PrEP efficacy observed in placebo-controlled RCTs

• The adherence pattern seems to be most important for low adherence provided that PrEP retains some protection for longer than a day.

• Block adherence is associated with lowest PrEP efficacy. Note that theoretically it may be self-reported as 100% adherence and confirmed by PK testing if participants “remember” to take PrEP before scheduled visits

• Risk-driven adherence is associated with better PrEP efficacy provided strong correlation between “expected” and “actual” sex acts
Future directions

- Continue to investigate different (more realistic, more exotic, really crazy … ) scenarios. Suggestions for alternative protection functions and adherence patterns are welcome!
- Expand the analysis to PrEP interventions at community level looking to optimize the uptake and consistent usage of PrEP
- Explore the potential impact of adherence patterns on the drug-resistance due to PrEP use
Acknowledgements

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- **Deborah Donnell**, PI of the HPTN SDMC
Results: Uniform adherence

Average adherence 20%

- Red: fast loss
- Blue: intermediate loss
- Green: slow loss

Observed PrEP efficacy (1-RR)

Adherence pattern:
- Periodic
- Random
- Block
Results: Uniform adherence

Average adherence 80%

Observed PrEP efficacy (1-RR)

- Periodic
- Random
- Block

- fast loss
- intermediate loss
- slow loss