Predicting the individual-level effectiveness of daily and non-daily PrEP based on study results from HPTN 067 ADAPT

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A Phase II, Randomized, Open-Label, Pharmacokinetic and Behavioral Study of the Use of Intermittent Oral PrEP

Evaluate the feasibility of intermittent dosing of PrEP regimen among HIV-uninfected MSM/TGW and WSM at high risk of acquiring HIV infection (178 MSM/TGW in Bangkok, 179 MSM/TGW in New York and 179 WSM in Cape Town)

Pill taking is informed by an electronic dispensing device (Wisepill ™) that recorded each opening

Treatment regimen:
- daily dosing
- time-driven dosing (2 per week + within 2h after sex)
- event-driven dosing (within 2d before + within 2h after sex).
HPTN 067: Modelling Centre involvement

Trial endpoints: Total number of pills taken, Sex acts coverage

Modelling: predict HIV incidence reduction by arm and site

Analysis of coverage data by arm and site

Connect coverage data with PrEP efficacy per act

Model development

Model calibration

Effectiveness analysis estimate HIV incidence reduction
Sex coverage per protocol

• Sexual activity is based on weekly interviews by phone or in person, i.e., entirely based on self-reported data.

• Pill taking is informed by an electronic dispensing device that recorded each opening.

• Sex coverage was defined as follows:
  • Fully covered acts - pills taken within 4 days before and 1 day after an act.
  • Partially covered acts - only before or after pill is taken.
  • This definition guarantees that all sex acts are fully covered with all 3 treatment regimens (daily, time-driven, event-driven) assuming perfect adherence.
iPrEx analysis suggests that PrEP is protective for MSM even if taken only twice a week (Anderson et al., Sc.Trans.Med. 2012). Non-daily regimens of PrEP also showed efficacy (McCormack, Lancet 2016; Molina, CROI 2015) when used by MSM.

Trials testing daily PrEP on women suggest strong dependence on adherence and less forgiveness for missed doses (Baeten, NEJM 2012; Van Damme, NEJM 2012, Marrazzzo, NEJM 2015).

Later studies suggest that women need more frequent PrEP dosing than men to protect against HIV (Cottrell, JID 2016).

HPTN 067 definition of coverage is unlikely to provide protection for women.

Sex acts covered by this definition are unlikely to be equally protected even for MSM.
We define sex acts to be protected by PrEP as follows:

- **Fully protected acts** - pills taken within 2 days before and 1 day after an act. This definition is more restrictive than the definition used in the trial protocol.
- **Partially protected acts** - only before or after pill is taken
Protected vs. covered sex acts

- Difference in distribution of covered and protected sex acts based on data from Cape Town site

Small differences in the daily arm:
- >70% fully covered (protected)
- >20% partially covered (protected)

Significant differences in the non-daily arms:
- 15%-20% less fully protected than fully covered
- 10%-15% more partially protected than covered
Protected acts by site and arm

Cape Town

Harlem

Bangkok
Distribution of protected sex acts based on data from HPTN 067

Division of Cape Town participants by % of fully covered acts:

- **Daily**
  - Low (below 40%)
  - Medium (40%-80%)
  - High (above 80%)

- **Time-driven**

- **Event-driven**

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Bar charts showing:

- Proportion of acts per participant:
  - Fully protected
  - Partially protected

- Subgroups by proportion of fully protected acts:
  - Low
  - Medium
  - High
Model development

- Stochastic individual-based mathematical model simulates HIV acquisition among a cohort of uninfected individuals.

- Participants are assigned in 2 risk groups with number and type of current partnerships based on data from Cape Town, New York and Bangkok.

- For each PrEP regimen the cohort is followed for 1 year under 2 distinct scenarios:
  - PrEP is used and the distribution of sex acts protected by PrEP is based on data from HPTN 067 by site and arm.
  - PrEP is not used

- Presented results are based on 1000 simulations per scenario
Model development

Probability to acquire HIV depends on:
- the type of the act (vaginal or anal)
- the use of condom
- partner’s HIV stage and ART status
- PrEP protection (by regimen)

Rates of initiation and dissolution of partnerships, frequency, type, and protection of sexual acts are calibrated for Cape Town, New York and Bangkok.
**Scenarios and Effectiveness Metric**

- **PrEP protection:**
  - *90% efficacy* in reducing the HIV acquisition risk per fully protected acts for MSM.
  - *70% efficacy* in reducing the HIV acquisition risk per fully protected acts for women.

- Scenarios on partially protected acts:
  - **No PrEP efficacy** retained for partially protected acts
  - **Half of the PrEP efficacy** retained for partially protected acts

\[
\text{Effectiveness} = 1 - \frac{\text{HIV incidence rate with PrEP}}{\text{HIV incidence rate without PrEP}}
\]
PrEP Effectiveness – Cape Town

Key assumption:
70% efficacy per fully protected act

Alternatives:
50% efficacy
90% efficacy

No efficacy for partial protection
Half efficacy for partial protection
How important is the distribution of protected sex acts?

Cape Town

No efficacy for partial protection

- Red: concentrated
- Blue: from HPTN 067 data
- Green: homogeneous

Reduction in HIV risk

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Reduction in HIV risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily</td>
<td>0.45</td>
</tr>
<tr>
<td>Time-driven</td>
<td>0.20</td>
</tr>
<tr>
<td>Event-driven</td>
<td>0.25</td>
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</tbody>
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Comparison across sites

No efficacy for partial protection

Reduction in HIV risk

- Cape Town
- Harlem
- Bangkok

Trial arms:
- Daily
- Time-driven
- Event-driven
Summary

• Non-daily PrEP is unlikely to be as effective as daily PrEP in reducing HIV incidence among females in South Africa and among MSM in USA and Thailand due to higher proportion of sex acts protected with daily use.
• The analysis of the three sites suggests that PrEP will be most effective among MSM in Thailand and least effective among women in South Africa
• Uncertainty in the PrEP efficacy associated with non-daily regimens should be further investigated to provide more reliable estimates of effectiveness
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