Accounting for variable adherence and sexual risk behavior patterns in the design and analysis of PrEP trials, and when modeling the impact of PrEP implementation

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New HIV prevention routes promising

Å Oral and topical PrEP: mixed results

Å Main explanations for variability in effects:¹
- Statistical chance (unlikely)
- Biological paths (mostly unclear)
- Non-adherence (most plausible)

Å Modeling paper suggests even more complex situation²

Å Implications possibly relevant for current discussions

Goals talk

Â Explain the key concepts model paper. Steps:
   1. Factors that influence absolute risk (AR).
   2. ..also influence on relative risk (RR) in trials..
   3. ..and the adherence - RR relationship

Â Apply cumulative probability model to MB trial data:
   í True method effectiveness 50% per-contact risk reduction
   í Per-contact infection risk of .003\(^1\) with HIV+ partner
   í Per-contact risk reduction condom use 80%\(^2\)

Â Possible implications for trial design, analyses and models

(1) Coverage = adherence percentage?

HIV treatment study:
- Adherence = (# pills taken / # pills prescribed) * 100
- 70 pills taken in 100 days for QD = 70% adherence
- Represents 30 ‘uncovered days’ (under certain assumptions)

- PrEP trial (examples for microbicide)
- Adherence = (# doses inserted / # contacts) * 100
- 70% over 100 days can be 30/100 or 3/10 ‘uncovered’ contacts
- Control for # of contacts when predicting AR infection

- Relevant in RCTs, i.e. does it carry over to relative risk?
What does this illustrate?

1. Direct effect of adherence on AR & RR
2. Direct effect of contact frequency on AR & RR
3. Contact frequency affect adherence – AR & adherence - RR relation
(2) Riskiness of the contact

- Evident that riskiness of a contact influences AR
  - Vaginal/anal, STD, treatment coverage area, condom use

- Riskiness effect on RR and adherence-RR relation?

<table>
<thead>
<tr>
<th>Number contacts</th>
<th>Adh 50%, no condom</th>
<th>Adh 50%, condom</th>
<th>Adh 100%, no condom</th>
<th>Adh 100%, condom</th>
<th>Ratio 50/100 no condom</th>
<th>Ratio 50/100 condom</th>
</tr>
</thead>
<tbody>
<tr>
<td>400</td>
<td>0.85</td>
<td>0.77</td>
<td>0.65</td>
<td>0.53</td>
<td>1.31</td>
<td>1.45</td>
</tr>
</tbody>
</table>

- Separate adherence % for high-risk & low-risk encounters
(3) Number of partners

Å In real life not a single partner, and the more partners, the larger the probability of contact with an HIV+ partner.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>AR + Adh 50%</th>
<th>AR + Adh 100%</th>
<th>RR+ Adh 50%</th>
<th>RR + Adh 100%</th>
<th>Ratio 50/100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1p * 400c</td>
<td>0.14</td>
<td>0.12</td>
<td>0.09</td>
<td>0.65</td>
<td>0.85</td>
<td>1.31</td>
</tr>
<tr>
<td>10p * 40c</td>
<td>0.21</td>
<td>0.16</td>
<td>0.11</td>
<td>0.54</td>
<td>0.78</td>
<td>1.44</td>
</tr>
</tbody>
</table>

p = partner * c = contacts = 400

Å AR, RR and adherence–RR relation depends on # partners.
All these factors simultaneously...

- Influence absolute and relative risks
- Influence the relationship adherence → relative risk
- Obscure the true method effectiveness (TME) in trials
Implications and illustrations

Â Role of (dominant) sexual behavior patterns:
1. Abdool Karim: few contacts, few partners, high condom
2. Skoler-Karpoff: more frequent, less condom use
3. Feldblum: more frequent & partners, high condom use

Â Role of single vs high-risk & low-risk adherence rates

Â Caprisa parameters as in de Bruin e.a. (2012)¹

¹ de Bruin e.a, PLoS one, 2012; 7(8):e44029
Trial design implications

- Trial power for different sexual risk behavior patterns

<table>
<thead>
<tr>
<th>Study</th>
<th>Probability control</th>
<th>Probability intervention</th>
<th>Cumulative RR</th>
<th>Required sample size/arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.134</td>
<td>0.085</td>
<td>0.634</td>
<td>669</td>
</tr>
<tr>
<td>2</td>
<td>0.247</td>
<td>0.195</td>
<td>0.789</td>
<td>1034</td>
</tr>
<tr>
<td>3</td>
<td>0.620</td>
<td>0.418</td>
<td>0.674</td>
<td>101</td>
</tr>
</tbody>
</table>

- Dito for general vs separate adherence % high & low risk

- Implication 1: Consider effect modifiers in sample size computations and update based on actual participant behavior

- Implication 2: Accurately measure all relevant variables and patterns (e.g. adherence high-low risk encounters)
Trial analysis implications

• RR is a unique product of trial behavior * time * TME (*other)

• TME can be compared and used as input for (CE) models

• Implication 3: In order to identify the true treatment effect, primary trial analyses may have to control for effect modifiers (not just overall adherence)

• Effect differential adherence on TME conclusions, Caprisa
  - 70% vs. 78% low & 44% high risk (1.8 times lower adherence)
  - TME estimate 57% versus 68%
Implications for (CE) models

- Modest changes in parameters can have large influence on projections (e.g. TME 67% or 58%)

- (CE) Models advanced but assume general adherence percentage:
  - 61% overall: 580 infections prevented
  - 78% low vs 44% high risk (average 61%): 460 prevented (21% pts less)

- Implication 4: (CE) models require accurate TME estimates and actual population behavior estimates (e.g. adherence, condom use, etc)

- Implication 5: (CE) models may need to differentiate between adherence levels at high vs low risk encounters

Conclusion & limitations

**Conclusions:**
- Trial design, analyses and modeling studies could benefit from considering the influences described.

**Future research:**
- Empirically test model-based assumptions
- Improve measures and obtain accurate population data

**Limitations:**
- Illustrations based on average trial data
- Scenario’s somewhat different for oral versus topical
- Not all relevant variables included, e.g. frailty

1- O’Hagan e.a., AIDS, 2012;26(2):123-6