Future Trial Designs for HIV Prevention

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Key Takeaways

• What is your main question?
  • We have multiple ARV-based forms of HIV protection – most recently an injection of cabotegravir every 8 weeks that prevents 90% of HIV infections in both men and women. With such effective prevention available, how will we approach future testing of potential HIV vaccines or other novel biologics?

• What did you find?
  • When novel biologics are also expected to be highly effective, a potential strategy is to estimate the infection rate we would have expected if no product were used, using a “counterfactual placebo” strategy. Several ways to estimate this placebo counterfactual rate are available and being evaluated.

• Why is it important?
  • We need to ensure that we have reliable evidence of the effectiveness of novel products, even as we have multiple proven choices available for HIV prevention.
Three eras of HIV prevention trials

1. No effective biomedical prevention
   - Adult trials all placebo controlled

2. Oral FTC/TDF approved for prevention
   - ARV-based: Active control FTC/TDF
   - Vaccine and mAb: allowed concurrent use of FTC/TDF

3. CAB-LA approved for prevention
   - With uptake and access can prevent ~90% of infections
   - Future: ???
Comparison for future prevention trials

1. Experimental vs. Active Agent(s)
   - Selected agent or choice
   - Experimental = unproven agent e.g. triple mAb, monthly pill, vaccine
   - Active agent = a proven agent e.g. TDF/FTC, CAB-LA

2. Experimental vs. Placebo
   - All with access to active agent(s)

3. Experimental vs. Placebo
   - Among persons not currently choosing to use any active agent
Comparison for future prevention trials

1. Experimental vs Active Agent(s)
   Selected agent or choice

2. Experimental vs. Placebo
   All with access to active agent(s)

3. Experimental vs. Placebo
   All persons not choosing any active agent
### HIV incidence in recent trials of HIV prevention

<table>
<thead>
<tr>
<th><strong>ACTIVE CONTROL</strong></th>
<th><strong>Countries</strong></th>
<th><strong>N enrolled</strong></th>
<th><strong>Number of infections</strong></th>
<th><strong>Incidence rate/100 PY</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
<tr>
<td>DISCOVER (MSM)</td>
<td>Europe, UK, Canada and Untied States</td>
<td>5399</td>
<td>7 vs 16</td>
<td>0.16</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.34</td>
</tr>
<tr>
<td>HPTN 083 (MSM/TGW)</td>
<td>United States, Peru, Brazil, Argentina, Thailand, Vietnam, South Africa</td>
<td>4541</td>
<td>13 vs 39 (stopped early)</td>
<td>0.41</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.22</td>
</tr>
<tr>
<td>HPTN 084 (Women)</td>
<td>South Africa, Botswana, Eswatini, Zimbabwe, Malawi, Kenya, Uganda.</td>
<td>3224</td>
<td>4 vs 36 (stopped early)</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>1.86</td>
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</table>

<table>
<thead>
<tr>
<th><strong>PLACEBO CONTROL (FTC/TDF background use)</strong></th>
<th><strong>Incidence rate/100 PY</strong></th>
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<tbody>
<tr>
<td></td>
<td>Experimental</td>
</tr>
<tr>
<td>AMP MSM/TG (HVTN 704/HPTN 085)</td>
<td>United States, Peru, Brazil, Switzerland</td>
</tr>
<tr>
<td>AMP Women (HVTN 703/HPTN 081)</td>
<td>South Africa, Zimbabwe, Malawi, Botswana, Kenya, Mozambique, Tanzania</td>
</tr>
<tr>
<td>HVTN 702 (Men and Women)</td>
<td>South Africa</td>
</tr>
</tbody>
</table>
Usual strategy: Active-controlled non-inferiority trial

- Constancy assumption: Effectiveness of Active Control applies in new setting
- NI margin defined to ensure effectiveness of experimental

RR = Relative risk
Sample size for randomized non-inferiority trials with highly effective active control

**Illustration**: HPTN 083

Goal: Establish CAB-LA is non-inferior to FTC/TDF in MSM+TG

- **Assumed CAB-LA is 25% better than FTC/TDF**
- **Assumed FTC/TDF modestly effective**

**HPTN 083 Trial Size**

<table>
<thead>
<tr>
<th>Future active control incidence</th>
<th>FTC/TDF incidence 2.1%</th>
<th>FTC/TDF incidence 1.0%</th>
<th>FTC/TDF incidence 0.5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental</td>
<td>25% more effective</td>
<td>Experimental has same effectiveness</td>
<td>Experimental has same effectiveness</td>
</tr>
<tr>
<td>Person Years</td>
<td>9,600</td>
<td>40,000</td>
<td>80,000</td>
</tr>
<tr>
<td>People</td>
<td>4,500</td>
<td>100,000</td>
<td>200,000</td>
</tr>
</tbody>
</table>
New strategy proposed: Active-controlled trial with placebo counterfactual

- Constancy assumption: Effectiveness of Active Control applies in new setting
- Expected infections on active control too small to achieve statistical accuracy
- Decrease in infections compared to no protection expected to be large
Estimating efficacy relative to “Counterfactual” placebo

How do we do this?
Estimate counterfactual placebo incidence rate
1. Placebo data from external trials
2. HIV incidence in registrational cohort
3. Cross-sectional incidence assessed using recency assay during screening for enrollment in “untreated” participants
4. Estimating placebo incidence using reliable predictor(s) of HIV exposure risk

Estimate efficacy of active control compared to counterfactual placebo
5. Using adherence-efficacy relationship of active control
6. Using immune biomarkers of effective vaccine/mAb as mediators of prevention efficacy (monoclonal Ab and vaccine)
1. Historical data for specific populations

HIV-1 Incidence Estimates among Female Placebos in sub-Saharan Africa

Credit: Holly Janes
# 1. Counterfactual efficacy using external trial data

**IDEA:** HIV incidence data from other trials in the same regions and population remains a valid estimate of current HIV incidence

<table>
<thead>
<tr>
<th>Counterfactual study</th>
<th>CAB-LA Incidence</th>
<th>Counterfactual Placebo Incidence</th>
<th>Efficacy of CAB-LA versus Placebo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Five Country (HVTN 703)</td>
<td>0.19</td>
<td>2.62</td>
<td>93% (76%-98%)</td>
</tr>
<tr>
<td>Three Country (ECHO)</td>
<td>0.23</td>
<td>4.47</td>
<td>95% (79%-99%)</td>
</tr>
<tr>
<td>South Africa (HVTN 702 Vaccine)</td>
<td>0.28</td>
<td>4.21</td>
<td>93% (73%-98%)</td>
</tr>
</tbody>
</table>

Historical data is not updated for current TasP and PrEP use
2. Registrational cohort as counterfactual

- A Phase II, three-arm, two-stage prophylactic HIV vaccine trial with a concurrent randomisation to compare F/TAF PrEP to TDF/FTC PrEP

Increasingly expect effective use of PrEP in the registration cohort

**PrEPVacc Registration cohort**

**VACC part**
- n=563
- Vaccine A
- Vaccine B
- Placebo

**PrEP part**
- n=834
- Offer of Descovy (F/TAF 200/25 mg)
- Offer of Truvada (F/TDF 200/300 mg)

Endpoints relevant to PrEP w 0-26

Endpoints relevant to vaccines after w 26
2. Counterfactual using Recency Testing Algorithm (RITA) at Screening

- Limiting Antigen Avidity Enzyme Immunoassay (LAg) results (normalized optical density ODn)
- Viral load
- LAg avidity and viral load results:\(^1-^3\)
  - ODn > 1.5 classify as long-term infection (no viral load testing)
  - ODn ≤ 1.5 + VL ≥ 1000 copies/ml classify as recent infections
  - ODn ≤ 1.5 + VL < 1000 copies /ml classify as long-term infection
- Incidence estimate validated for 2 year window

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3. Oliver et al; Validation of the Limiting Antigen Avidity Assay in Rakai, Uganda; https://doi.org/10.1089/aid.2018.0207
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Representative of eligible population who were uninfected two years ago

Eligible Population at screening

HIV Testing (rapid tests)

HIV positive

HIV LAg avidity testing

ODn ≤1.5

Viral load testing

≥1000 copies/ml Classify as recent infection

Calculate baseline incidence

<1000 copies/ml Classify as long-term infection

ODn > 1.5 Classify as long-term infection

HIV negative

Frequent testing and early ART make viral suppression in recent infection more common

HIV testing every 3 months

Observed incidence on PrEP

3. Oliver et al.; Validation of the Limiting Antigen Avidity Assay in Rakai, Uganda: https://doi.org/10.1089/aid.2018.0207
4. Estimating HIV incidence using biomarker of HIV exposure

IDEA: Biomarker of sexual exposure (b/c correlated with HIV exposure, e.g. Rectal GC in MSM) can be used to estimate risk of HIV infection

Assumptions
- Multiple observations with “placebo” HIV incidence and exposure biomarker
- Relationship between placebo HIV incidence and exposure biomarker holds across trials
- Biomedical intervention in future trials does not affect exposure biomarker

Statistical precision is challenging

Lack good candidate biomarker of exposure for women

Clinical trials, Zhu, under revision
Conclusions

• Long-acting PrEP, when readily available and widely used, will create a challenge for assessing the prevention efficacy of new products

• Efficacy estimates based on counterfactual placebo approach offers a path forward
  • FDA “Considerations for the Design and Conduct ofExternally Controlled Trials for Drug and Biological Products” (Draft Guidance 2023)
  • Careful and thoughtful engagement with regulators, clinical trialists, biostatisticians, community stakeholders needed to navigate this path (e.g. Forum for Collaborative Research PrEP project)

• Our common goal is to ensure a future with a multiple highly effective, readily available and widely used biologics
Thank you

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