Developing Placebo Counterfactuals for PrEP Studies

Jim Hughes, Ph.D.
SCHARP
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Introduction

• Current PrEP trials use an “active” control arm
  – HPTN 083/084 use TDF/FTC control
• Nonetheless, there is interest in understanding the effect of new PrEP agents versus placebo
  – Supplementary evidence of efficacy
  – Understanding population impact
Introduction

• External, contemporaneous trials with placebo arms may be used to form a “counterfactual” placebo arm for an active control trial
  – Overlap in populations
  – Overlap in time
  – Overlap in eligibility criteria
<table>
<thead>
<tr>
<th>Study design description</th>
<th>HPTN 084</th>
<th>ECHO</th>
<th>HVTN 702</th>
<th>AMP (HVTN 703/HPTN081)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compare HIV incidence between PrEP options; 1:1 randomization to TDF/FTC daily pills or CAB LA injectable; double blind, double dummy</td>
<td>Compare HIV incidence between contraceptive options; 1:1:1 randomization to DMPA, copper IUD, or LNG implant; open-label</td>
<td>Determine efficacy of an HIV vaccine candidate for HIV prevention; 1:1 randomization to placebo or vaccine; double blind</td>
<td>Determine efficacy of mAb for HIV prevention; 1:1:1 to VRC01 30mg / VRC01 10mg / Placebo; double blind</td>
<td></td>
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<tr>
<td>Population</td>
<td>HIV-seronegative women aged 18–45 years</td>
<td>HIV-seronegative women aged 16-35 years</td>
<td>HIV-seronegative men and women aged 18–35 years</td>
<td>HIV-seronegative women aged 18–40 years</td>
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<tr>
<td>Sample size</td>
<td>Target: N = 3200 PY = 7125</td>
<td>Included: N = 7103 PY = 9594</td>
<td>Included: N = 1886 Y = 2782</td>
<td>Included: N = 1393 PY = 2266</td>
</tr>
</tbody>
</table>
Methods

• Target trial (e.g. HPTN 084)
  – s subgroups (sites/countries/regions)
  – \( m_i \) = person-years in subgroup i
  – \( O \) = observed HIV incidence in experimental arm in s subgroups

• External trial (e.g. ECHO)
  – Same s subgroups (sites/countries/regions)
  – \( I_i \) = HIV incidence in (placebo arm of) subgroup i

\[
c_P = \frac{\sum_i m_i I_i}{\sum_i m_i}
\]
Methods

- Counterfactual relative risk (cRR)
  - Compare cP to observed incidence in the target trial across the subgroups
  - $cRR = O/cP$
- Confidence intervals for cP, cRR may be computed on log scale
Example – ECHO and HPTN 084

- HIV-uninfected women in SSA
- 1:1:1 randomization to DMPA, copper IUD, or LNG implant; open-label
- No difference between arms – combine all arms
- Overlapping countries with HPTN 084: eSwatini, Kenya, South Africa

<table>
<thead>
<tr>
<th>Country</th>
<th>084 Person Years</th>
<th>ECHO Incidence (%/yr)</th>
<th>Expected 084 incidence (%/yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kenya</td>
<td>65</td>
<td>1.36</td>
<td>3.50</td>
</tr>
<tr>
<td>South Africa</td>
<td>802</td>
<td>4.64</td>
<td>3.50</td>
</tr>
<tr>
<td>Eswatini</td>
<td>77</td>
<td>4.97</td>
<td>3.50</td>
</tr>
</tbody>
</table>

- \( cP = 4.44\% / \text{yr} \) (95% CI: 4.02 – 4.89)
Summary

• Further stratification could be done by age or other demographics, though the data start to get thin.

• Counterfactual estimates do not have the strength of evidence of a randomized comparison
  – Combine with other evidence e.g. adherence and HIV incidence in active control arm

• Utility of this approach may decline as contemporaneous placebo arm data become less available
Collaborators

- Deborah Donnell
- Fei Gao
- Barbra Richardson
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