Utilizing a “Counterfactual Placebo” to Establish Efficacy of Novel HIV Prevention Agents

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1. What is the main issue or question the presentation addresses?
   • Traditional designs for efficacy trial may not be feasible in evaluating novel HIV prevention agents, given current landscape for HIV prevention.

2. What is the key finding or ‘takeaway message’?
   • Active-controlled trial augmented by a “counterfactual placebo” may be conducted to evaluate efficacy of an experimental HIV prevention agent with a reasonable sample size.

3. How does the research advance HIV prevention efforts?
   • An efficacy trial is necessary to establish the efficacy of a novel HIV prevention agent and to lay the foundation for ultimate licensure of future HIV prevention products.
The past decade has seen tremendous progress in the development of biomedical agents that are effective as pre-exposure prophylaxis (PrEP) for HIV prevention.

- Oral PrEP: TDF/FTC, F/TAF
- Long-acting injectable PrEP: CAB-LA

For evaluation of new HIV prevention agents, current designs may not be feasible.
Trial Design for Evaluating Efficacy of Novel HIV Prevention Agents

**Placebo-Controlled Trial Design**

- Randomize
  - Novel Prevention Agent
  - Placebo

Follow-up to estimate incidence

- \( \lambda_E \)
- \( \lambda_P \)

Superiority comparison

Randomizing individuals to placebo arm may not be ethical.

**Active-Controlled Trial Design**

- Randomize
  - Novel Prevention Agent
  - Active-control (e.g., TDF/FTC, CAB-LA)

Follow-up to estimate incidence

- \( \lambda_E \)
- \( \lambda_A \)

Superiority or non-inferiority (NI) comparison

Active-control has been demonstrated efficacious in a previous trial.

With highly effective active-control (and new agent), the sample size are likely to be prohibitively large.
Active-Control Design with TDF/FTC as active-control (HPTN 083)

- HPTN 083: evaluate efficacy of long-acting cabotegravir (CAB-LA) in MSM/TGW population, with daily oral TDF/FTC as active-control.

Step 1: Determine NI Margin ($\delta$): what we meant by non-inferiority to the active-control.
- Margin M1: active-control efficacy
- Margin M2: proportion preservation of active-control efficacy

It also defines the acceptable prevention efficacy for the experimental agent.

<table>
<thead>
<tr>
<th>NI Margin</th>
<th>Margin M1 (95% CI lower bound of Active-Control efficacy)</th>
<th>Margin M2 (preservation of Active-Control efficacy)</th>
<th>Non-inferiority</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\delta = \left( \frac{1}{1 - M_1} \right)^{1-M_2}$</td>
<td>1.23</td>
<td>34.2%</td>
<td>50%</td>
</tr>
<tr>
<td>1.23</td>
<td>34.2%</td>
<td>50%</td>
<td>PE &gt; 44%</td>
</tr>
</tbody>
</table>

Step 2: Study Design using the NI margin – power = 90%

<table>
<thead>
<tr>
<th>Efficacy: Active-Control</th>
<th>Efficacy: Experimental Agent</th>
<th>PY in Each Arm (3% incidence)</th>
<th># Event: Active-Control</th>
<th># Event: Exper. Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>54.5%</td>
<td>66%</td>
<td>8,733</td>
<td>99</td>
<td>74</td>
</tr>
</tbody>
</table>
Active-Control Design with CAB-LA as active-control: A future study design

• For a future trial to evaluate efficacy for a novel PrEP agent, we may use CAB-LA as active-control.

Step 1: Determine NI Margin ($\delta$): what we meant by non-inferiority to the active-control.

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</tr>
</thead>
<tbody>
<tr>
<td>$\delta = \left( \frac{1}{1 - M_1} \right)^{1-M_2}$</td>
<td>85%</td>
<td>31%</td>
<td>PE &gt; 44%</td>
</tr>
</tbody>
</table>

The NI margin is large mainly due to high efficacy of CAB-LA as active-control.

Step 2: Study Design using the NI margin – power = 90%

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</thead>
<tbody>
<tr>
<td>90%</td>
<td>80%</td>
<td>13,486</td>
<td>40</td>
<td>81</td>
</tr>
</tbody>
</table>
Utilizing Counterfactual Placebo

Active-Controlled Trial Design
Augmented by a “Counterfactual Placebo”

Randomize

Novel Prevention Agent

Active-control Prevention Agent

Follow-up to estimate incidence

$\hat{\lambda}_E$  $\hat{\lambda}_A$

Counterfactual Placebo

$\hat{\lambda}_P$

Counterfactual placebo: the HIV incidence that would have been observed had a placebo arm been included

Historical placebo arm

HIV recency data at screening

Incidence of other STIs

May help to determine efficacy of experimental agent
• Non-inferiority comparison between $\lambda_E$ and $\lambda_A$ is equivalent as a relative efficacy comparison under a constancy assumption for the efficacy of the active control

$$H_0: \frac{\log \lambda_P - \log \lambda_E}{\log \lambda_P - \log \lambda_A} \leq \gamma \text{ vs } H_a: \frac{\log \lambda_P - \log \lambda_E}{\log \lambda_P - \log \lambda_A} > \gamma$$

• $\gamma$ is the M2 margin in the non-inferiority trial design, which indicates relative efficacy of the experimental agent and active-control.

• Such a hypothesis can also be evaluated utilizing the counterfactual placebo incidence estimate $\hat{\lambda}_A$ through the test statistic

$$T = \frac{\log \hat{\lambda}_P^* - \log \hat{\lambda}_E}{\log \hat{\lambda}_P^* - \log \hat{\lambda}_A} - \gamma$$

• We may then strengthen evidence on efficacy of experimental agent utilizing “counterfactual placebo”.

Utilizing Counterfactual Placebo
Active-Control Design with CAB-LA as active-control: A future study design

Counterfactual Placebo based on data from external cohorts with 5,500 PYs.

Required counterfactual placebo PYs increased by 1.5 relative to randomized placebo, to offset greater uncertainty in estimating incidence.

Study Design – power = 90%

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</thead>
<tbody>
<tr>
<td>90%</td>
<td>80%</td>
<td>8,522</td>
<td>26</td>
<td>51</td>
</tr>
</tbody>
</table>

Active-Controlled Trial Design Augmented by a “Counterfactual Placebo”

May help to determine efficacy of experimental agent
Summary

- Traditional designs for efficacy trial may not be feasible in evaluating novel HIV prevention agents, given current landscape for HIV prevention.

- Active-controlled trial augmented by a “counterfactual placebo” may be conducted to evaluate efficacy of an experimental HIV prevention agent with a reasonable sample size.
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