Using Cross-sectional Recency Assays to Assess Prevention Efficacy: Future Trial Design and Sample Size Considerations

Fei Gao

Fred Hutchinson Cancer Research Center
Cross-sectional Incidence Estimation

• To infer incidence based on a cross-sectional sample.

• Apply recency assay to HIV-positive subjects to detect recent infections.
  • e.g., LAg avidity assay + Viral Load
Cross-sectional Incidence Estimation

- In a cross-sectional sample
  - $N_-$: number of HIV-negative subjects
  - $N_+$: number of HIV-positive subjects
  - $N_{rec}$: number of test-recent subjects

- Incidence can be estimated by
  \[
  \frac{N_{rec}}{N_- \times MDRI}
  \]
  - MDRI (mean duration of infection): the mean duration of test-recent for an HIV-positive subject.
Cross-sectional Incidence Estimation

- To correct for false recency (test-recent for long-infected subject), a modified estimator

\[\frac{N_{rec} - FRR \times N_+}{N_- \times (MDRI - FRR \times T)}\]

- T: cutoff for long-infected subject (T=2 years)
- MDRI (mean duration of infection): the mean duration of test-recent for an HIV-positive subject infected less than T.
- FRR (false-recent rate): the probability of test-recent for a long-infected subject.
Cross-sectional Incidence Estimation as Counterfactual Placebo

- Make use of the *screening population*, which can be viewed as similar to the trial population, except for HIV status and other inclusion/exclusion criteria.

- Apply recency assay to samples collected at *screening*.

- Estimate counterfactual placebo HIV incidence rate by cross-sectional incidence estimator.
Study design

- **Screen**: 
  - HIV positive $N_+$
  - HIV negative $N_-$
  - $p$ and $1-p$

- **Recency test**: 
  - $q$
  - $N_{+,\text{test}}$

- **Recency**: 
  - $N_{\text{rec}}$

- **Placebo (P)**
  - $N_{\text{rec}}$

- **Experimental (E)**
  - $N_{\text{event}}$
  - $N_{-,\text{trial}}$

- Enroll to Trial $N_{-,\text{trial}}$

- Event $N_{\text{event}}$
Hypothesis Testing

\[ H_0: \frac{E}{P} = R_0 \quad \quad H_a: \frac{E}{P} \neq R_0 \]

- Form a Z-statistic for \( E/P \)
- Reject \( H_0 \) if \( |Z| < z \)
- \( P(|Z| < z | H_0) = \alpha \)
- \( P(|Z| < z | H_a) = \beta \) for a specific \( H_a \)
Sample Size

The following design parameters must be specified for any given trial.

- **Expected placebo incidence rate**
- Recency test characteristics (FRR, MDRI, T, relative SE’s)
- Other design parameters (p, q, r, followup time)
- **Type 1 error** $\alpha$ and incidence ratio under $H_0 - R_0$
- **Desired power** $\beta$ under $H_a - R_1$
Sample size is the number of persons screened. 
Assumptions: 90% of HIV negative individuals enroll on PrEP, 90% of HIV positive specimens yield valid recency testing results, two years of follow-up on PrEP, 7% RSE on the MDRI, 25% RSE on FRR, significance level 0.05 (two-sided) and 80% power.

<table>
<thead>
<tr>
<th>US MSM</th>
<th>Incidence</th>
<th>3.42%/yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>14.5%</td>
<td></td>
</tr>
<tr>
<td>subtype</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>MDRI (days)</td>
<td>142</td>
<td></td>
</tr>
<tr>
<td>FRR</td>
<td>1.0%</td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td>2,190</td>
<td></td>
</tr>
</tbody>
</table>

Expected Numbers under $H_a$

<table>
<thead>
<tr>
<th>Recency Test</th>
<th>Experimental Product Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td># Tested</td>
<td># Test-recent</td>
</tr>
<tr>
<td>286</td>
<td>24</td>
</tr>
</tbody>
</table>
Conclusions

• We have proposed a study design for active-arm trial with counterfactual placebo based on cross-sectional incidence with recency assay.
• The approach is feasible in terms of calculated total screening sample size.
• Other operational issues.
• Extension to active-control trial.
Acknowledgments

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