Trial Designs for Evaluating Integrated HIV Prevention Approaches

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Introduction

• Why integrated approaches?
  – ART-based biomedical intervention prevention approaches, such as TasP and PrEP, have proven efficacious in randomized trial settings.
  – Non-biomedical intervention approaches, such as linkage-to-care, risk-reduction counseling, and use of condoms, also are important to help prevent HIV transmission.
  – A continuum of HIV care is needed to avoid fragmented health services and unnecessary barriers to accessing services.
  – Integrated approaches thus hold greater promise, based on the assumption that elements of an integrated approach may interact with each other synergistically in HIV transmission risk reduction.
  – Integrated approaches are expected to improve health outcomes with more holistic, client-centered service delivery.
Introduction

• Challenges for assessing integrated approaches
  – Integrated approaches involve multiple preventive intervention elements
  – Different combinations of individual elements of an integrated approach may complicate the evaluation process, and sometimes also cause concerns on perceived study participants’ welfare
  – There is a lack of adequate insight about the statistical properties of candidate designs for assessing integrated approaches
Methods

• To provide insight about the relative merits of different trial designs that may be used to assess the effectiveness of an integrated approach
  – Perform Monte-Carlo simulation studies
  – Choose among 5 prevention interventions
  – Compare 4 prototype trial designs
Preventive intervention elements

• ART-based biomedical intervention
  – Treatment-as-Prevention (TasP)
  – PrEP

• Non-biomedical intervention
  – Linkage to Care (LtC)
  – Risk reduction counseling
  – Condom use
Candidate trial designs

• Single-factor design
  – A regimen with a single component is assessed in a controlled, randomized trial.

• Factorial design
  – All possible combinations of multiple components are assessed in a controlled, randomized trial.

• Multi-arm design
  – Multiple single component regimens are assessed in a controlled, randomized trial.

• All-in-one “kitchen-sink” design
  – A regimen with ‘all’ components in the experimental arm is assessed in a controlled, randomized trial.
Designs

Single-factor

\[ Z = 1, \text{ hazard rate: } \lambda_0 e^\beta. \]
\[ Z = 0, \text{ hazard rate: } \lambda_0. \]

\textit{coxph(Surv(time, status) ~ Z)}.

Multi-arm

Factorial

All-in-one
Designs

Single-factor

\[ Z = 1, \text{hazard rate: } \lambda_0 e^\beta. \]
\[ Z = 0, \text{hazard rate: } \lambda_0. \]

\textit{coxph(Surv(time, status) \sim Z)}.

Multi-arm

Factorial

\[
\begin{array}{c|cc}
 & Z_2 = 1 & Z_2 = 0 \\
\hline
Z_1 = 1 & \lambda_0 e^{\beta_1+\beta_2+\gamma} & \lambda_0 e^{\beta_1} \\
Z_1 = 0 & \lambda_0 e^{\beta_2} & \lambda_0 \\
\end{array}
\]

\textit{coxph(Surv(time, status) \sim Z_1 + Z_2)}

All-in-one
Designs

Single-factor

\[ Z = 1, \text{hazard rate: } \lambda_0 e^{\beta}. \]
\[ Z = 0, \text{hazard rate: } \lambda_0. \]
\[ \text{coxph}(\text{Surv}(\text{time, status}) \sim Z). \]

Factorial

\begin{array}{c|c|c}
\hline
Z_2 = 1 & Z_2 = 0 \\
\hline
Z_1 = 1 & \lambda_0 e^{\beta_1 + \beta_2 + \gamma} & \lambda_0 e^{\beta_1} \\
Z_1 = 0 & \lambda_0 e^{\beta_2} & \lambda_0 \\
\hline
\end{array}

\[ \text{coxph}(\text{Surv}(\text{time, status}) \sim Z_1 + Z_2) \]

Multi-arm

\begin{array}{c|c|c}
\hline
Z_2 = 1 & Z_2 = 0 \\
\hline
Z_1 = 1 & - & \lambda_0 e^{\beta_1} \\
Z_1 = 0 & \lambda_0 e^{\beta_2} & \lambda_0 \\
\hline
\end{array}

\[ \text{coxph}(\text{Surv}(\text{time, status}) \sim Z_1 + Z_2) \]

All-in-one
Designs

Single-factor

\[ Z = 1, \text{hazard rate: } \lambda_0 e^\beta. \]
\[ Z = 0, \text{hazard rate: } \lambda_0. \]

\[ \text{coxph}(\text{Surv}(\text{time, status}) \sim Z). \]

Multi-arm

\[
\begin{array}{c|cc}
Z_2 & Z_2 = 1 & Z_2 = 0 \\
\hline
Z_1 = 1 & \lambda_0 e^\beta_1 & - \\
Z_1 = 0 & \lambda_0 e^\beta_2 & \lambda_0 \\
\end{array}
\]

\[ \text{coxph}(\text{Surv}(\text{time, status}) \sim Z_1 + Z_2) \]

Factorial

\[
\begin{array}{c|cc}
& Z_2 = 1 & Z_2 = 0 \\
\hline
Z_1 = 1 & \lambda_0 e^{\beta_1 + \beta_2 + \gamma} & \lambda_0 e^\beta_1 \\
Z_1 = 0 & \lambda_0 e^\beta_2 & \lambda_0 \\
\end{array}
\]

\[ \text{coxph}(\text{Surv}(\text{time, status}) \sim Z_1 + Z_2) \]

All-in-one

\[ Z = 1, \text{hazard rate: } \lambda_0 e^{\beta_1 + \cdots + \beta_5 + \gamma}. \]
\[ Z = 0, \text{hazard rate: } \lambda_0. \]

\[ \text{coxph}(\text{Surv}(\text{time, status}) \sim Z). \]
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Effective</th>
<th>Less effective</th>
<th>In-between #1</th>
<th>In-between #2</th>
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<tr>
<td>PrEP</td>
<td>44%</td>
<td>10%</td>
<td>22%</td>
<td>44%</td>
</tr>
<tr>
<td>TasP</td>
<td>70%</td>
<td>70%</td>
<td>70%</td>
<td>70%</td>
</tr>
<tr>
<td>LtC</td>
<td>10%</td>
<td>0%</td>
<td>10%</td>
<td>0%</td>
</tr>
<tr>
<td>Counseling</td>
<td>20%</td>
<td>0%</td>
<td>20%</td>
<td>0%</td>
</tr>
<tr>
<td>Use of Condoms</td>
<td>30%</td>
<td>30%</td>
<td>30%</td>
<td>30%</td>
</tr>
</tbody>
</table>
Summary of results

- Sample size: 5000
- Baseline incidence rate: 2%
- Trials simulated: 1000
- About a total of 100, 300, 500 incident HIV infections observed per trial
Without interaction

• One factorial design of sample size 5000 would yield almost identical results that would otherwise need two separate single-factor trials, each of sample size 5000
• Placebo-controlled multi-arm design would yield similar results to factorial design
• All-in-one design would be most impactful
With interaction

- Single-factor design or multi-arm design would not be able to detect an interaction
- All-in-one design would reflect the interaction, but not be able to tell which two would interact, or its magnitude
- Only factorial design would be able to detect an interaction
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