Causal Inference Issues in the iPrEx Trial

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http://www.epibiostat.ucsf.edu/dave/talks.html
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iPrEx Trial

- Funded by NIAID/Gates
- 3,000 high risk HIV- MSM
- Randomized double-blinded
- Daily TDF/FTC (truvada) or placebo
- Followed for HIV infection, safety
PrEP

• **Pre-Exposure Prophylaxis for HIV**
• Anti-HIV drugs taken before HIV exposure
• New/Old concept: ACTG 076
• Chemoprophylaxis successful for malaria, TB, meningitis
• Raises difficult issues: safety, cost, behavior
• HIV prevention trials: 4 for 25 (Padian 2007)
TDF/FTC (truvada)

- Dosing: long intracellular half life
- Tolerable
- Positive animal data
- Co-formulated into single daily pill
  TDF = tenofovir + FTC = emtricitabine
- Both patented by Gilead
- FDA approved: fewer regulatory hurdles
  unlike microbicides, vaccines
Power/Sample Size

• 1,500 subjects/arm, 10% loss to follow-up
• Follow-up until 48 weeks for last person
• 85 events (3% seroincidence yearly)
• $H_0$: 30% efficacy, $H_a$: 60% efficacy
• Power: 1-sided power 0.83, 2-sided 0.74
Study Power - 85 Events

The graph illustrates the power of a study as a function of percent efficacy. Two hypotheses are considered:

- H0: 0% Efficacy
- H0: 30% Efficacy

The power increases as the percent efficacy increases. For H0: 0% Efficacy, the power is lower compared to H0: 30% Efficacy.
Trial Outcomes

• HIV Seroconversion
• Adverse events (especially renal, liver)
• Adherence
• HIV-RNA, CD4 count, resistance
  if participant is infected with HIV
## Hypothetical Results

<table>
<thead>
<tr>
<th></th>
<th>HIV+</th>
<th>HIV-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Truvada</td>
<td>20</td>
<td>1480</td>
</tr>
<tr>
<td>Placebo</td>
<td>65</td>
<td>1435</td>
</tr>
</tbody>
</table>

HR = 0.30, 95% Confidence Int. (0.18, 0.55)
Mutations

• Does truvada promote resistance virus?
• Resistance diminishes treatment options
• Maybe be used in resource limited settings
• Mutation is a trait of infected participants creates a causal inference issue
Mutation Data

- Proportion of mutants
  - Placebo: 23%
  - TDF/FTC: 75%
- Pearson $\chi^2$: 18.1, $p < 0.001$
- Does TDF/FTC promote resistance?
Mutation Data

• Proportion of mutants
  • Placebo: 23% = 15/65 (15 MT, 50 WT)
  • TDF/FTC: 75% = 15/20 (15 MT, 5 WT)
• Pearson $\chi^2$: 18.1, $p < 0.001$
• Does TDF/FTC promote resistance?
Note

• Analyses involves only 85 participants
• 65 on placebo and 20 on FTC/TDF
• Spirit of clinical trials: like v. like
  compare similar populations
• Are these two groups similar?
Intention to Treat

• Compare outcomes in comparable population
• Only true comparable population is all randomized subjects
• Answer can be unsatisfying
### Intent to Treat

<table>
<thead>
<tr>
<th></th>
<th>HIV+/MT</th>
<th>HIV- or WT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Truvada</strong></td>
<td>15</td>
<td>1485</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>15</td>
<td>1485</td>
</tr>
</tbody>
</table>

*Mixes up HIV infection and mutations*
A Scenario

• Mutations due to infection with resistant virus

• TDF/FTC does not protect against resistant virus

• Exposures to HIV similar in the two groups
Placebo Group

- 1,500 total participants
- 500 exposed to HIV (450 WT, 50 MT)
- 50/450 WT exposed are infected
- 15/50 MT exposed are infected
- 65 HIV+: 50 WT, 15 MT
TDF/FTC Group

- 1,500 total participants
  - 500 exposed to HIV (450 WT, 50 MT)
  - 5/450 WT exposed are infected
  - 15/50 MT exposed are infected
- 20 HIV+: 5 WT, 15 MT
# TDF/FTC Group

## Placebo

<table>
<thead>
<tr>
<th></th>
<th>HIV+</th>
<th>HIV-</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>MT</td>
<td>50</td>
<td>400</td>
<td>1,000</td>
</tr>
<tr>
<td>WT</td>
<td>15</td>
<td>35</td>
<td>1,000</td>
</tr>
<tr>
<td>None</td>
<td>0</td>
<td>1,000</td>
<td>1,000</td>
</tr>
<tr>
<td></td>
<td>65</td>
<td>1,500</td>
<td></td>
</tr>
</tbody>
</table>

## FTC/TDF

<table>
<thead>
<tr>
<th></th>
<th>HIV+</th>
<th>HIV-</th>
</tr>
</thead>
<tbody>
<tr>
<td>MT</td>
<td>5</td>
<td>495</td>
</tr>
<tr>
<td>WT</td>
<td>15</td>
<td>35</td>
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<tr>
<td>None</td>
<td>0</td>
<td>1,000</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>1,500</td>
</tr>
</tbody>
</table>
Comparison

- 3 strata defined by exposure to HIV
  *no exposure/wild-type/mutant*

- Comparison by strata:
  *no excess risk of mutation*

- Coherent picture of effect of FTC/TDF by mutation

- Must believe strata are comparable
Causal Inference

• Theory largely developed by Rubin

• Define population $P: i=1,\ldots,n$

• Counterfactual: $(Y_{i0}, Y_{i1})$
  $Y_{i0}$: $i$th outcome, assigned to placebo
  $Y_{i1}$: $i$th outcome, assigned to TDF/FTC

• Compare $Pr(Y_{i1}=1)/Pr(Y_{i0}=1)$
Causal Inference

• Can’t observe counterfactuals
• Either observed $Y_{i0}$ or $Y_{i1}$
• Randomization does the “right” thing
• Provides a rigorous causal framework
Extended to subsets

• Imagine there are $K$ strata in the popn
• Suppose $P$ is composed of $P_1, \ldots, P_K$
• Causal effect with $P_k$ is
  $\Pr(Y_i = 1)/\Pr(Y_i = 0)$ for $i$ in $P_k$
• Can define subset at baseline
  (e.g., age, # of partners at enrollment)
Principal Stratification

- Define latent subgroups
- Group 1: Never infected ($Y_{i0} = Y_{i1} = 0$)
- Group 2: Infected under PLC ($Y_{i0} = 1, Y_{i1} = 0$)
- Group 3: Infected under drug ($Y_{i0} = 0, Y_{i1} = 1$)
- Group 4: Always infected ($Y_{i0} = Y_{i1} = 1$)
Latent Groups

<table>
<thead>
<tr>
<th></th>
<th>$Y_{i1}=1$</th>
<th>$Y_{i1}=0$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Y_{i0}=1$</td>
<td>$p_{11}$</td>
<td>$p_{10}$</td>
</tr>
<tr>
<td>$Y_{i0}=0$</td>
<td>$p_{01}$</td>
<td>$p_{00}$</td>
</tr>
</tbody>
</table>

$$RR = \frac{(p_{11} + p_{01})}{(p_{11} + p_{10})}$$

$H_0: p_{10} = p_{01}$
Principal Strata

- Latent
- But conceptually exist \textit{a priori}
- Not affected by the treatment
- Form a possible causal framework
Effect by Strata

- Group 1: Never infected
  *no benefit or harm from rx -- no mutations*

- Group 2: Infected under PLC
  *PLC worse even if virus is MT*

- Group 3: Infected under drug
  *drug worse even if virus is MT*

- Group 4: Always infected
  *MT comparison is very relevant*
Casual Comparison

Restricted to Stratum 4

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Answers a Question

“If infected despite TDF/FTC, what is chance of mutant virus compared to if he had forgone PrEP treatment?”

Our Problem

• The strata are latent

• Have some information:
  \( HIV^+ \) on TDV: in either Groups 3 or 4
  \( HIV^+ \) on placebo: either Group 2 or 4

• Strata membership unknowable
  need to make external assumptions
  can make meaningful sensitivity analyses
Some Previous Work

- Frankgakis & Rubin, Biometrics 58: 21-29
- Gilbert et al, Biometrics, 59:531-41
- Shepherd et al, Biometrics, 62:332-342
Some Assumptions

• Classic causal assumption: SUTVA
  \textit{data for i not affected by rx for j suspect in small sexual networks}

• $$\Pr(Y_{i0}=1, Y_{i1}=0)=0 \implies \Pr(Y_{i0}=1|Y_{i1}=1)$$

HIV+ on TDV: belong to Group 4
Placebo HIV+

- \( RE = 1 - RR \)
- \( RR = \frac{p_{11} + p_{01}}{p_{11} + p_{10}} \Rightarrow RE = \frac{p_{01}}{p_{11} + p_{10}} = \) probability in group 2 given HIV on placebo
- Fraction of HIV+ on placebo in the always infected = 70%
- About 20 in always infected on placebo
Sensitivity Analysis

- Want to compare prevalence of mutations in group 4 between placebo and truvada
- By assumption, truvada = 15/20
- For placebo = ??/ ~20
- can explore values for ?? with 15 mutations can between 0 and 15
Gilbert et al

• Considered comparison of HIV-RNA in HIV+ in a vaccine study
• Y denotes HIV-RNA after infection
• \( p(y) = \Pr(\text{grp 4} | \text{HIV+ placebo}, Y=y) \)
• \( \logit(p(y)) = \alpha + \beta y \)
• \( \beta \) indexes selection
Selection Model

• $\beta > 0$, higher VL $\Rightarrow$ more likely in group 4
  high VLs on placebo compared to TDF/FTC

• $\beta < 0$, higher VL $\Rightarrow$ less likely in group 4
  low VLs on placebo compared to TDF/FTC

• $\beta=0$, no VL difference between group 3 & 4
  direct comparison of mean VL

• Higher the VE, the wider effects of sensitivity are
Principal Stratification

• Clarifying framework

• Puts these comparisons in causal framework

• But, not identifiable. Permits informed sensitivity analyses

• Especially if drug effect is adverse bounds post-randomization bias

• Can give wide interval if RE is large
Wide Applications

- Missing Data due to death
- Informative dropouts
- Adjustment for compliance
Many Thanks

- Tor
- Estie
- NIAID
- Bill and Melinda Gates Foundation