Causal Inference Issues in the iPrEx Trial

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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

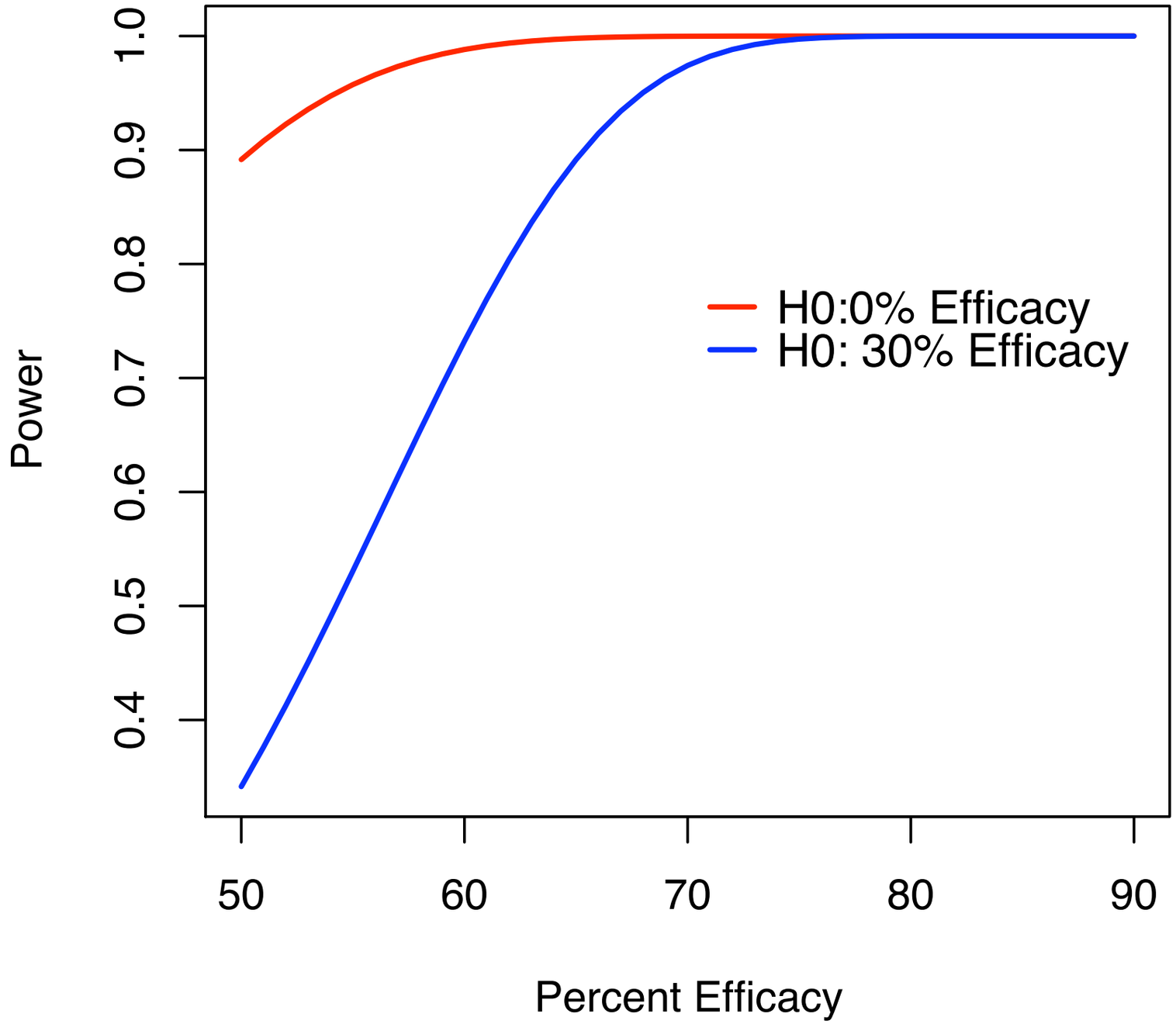
(truvada)

- 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



Trial Outcomes

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

Hypothetical Results

	HIV+	HIV-
Truvada	20	1480
Placebo	65	1435

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 χ^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 χ^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

	HIV+/MT	HIV- or WT
Truvada	15	1485
Placebo	15	1485

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

	HIV+	HIV-	
MT	50	400	450
WT	15	35	50
None	0	1,000	1,000
	65		1,500

FTC/TDF

	HIV+	HIV-	
MT	5	495	450
WT	15	35	50
None	0	1,000	1,000
	20		1,500

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,.....,n
- Counterfactual: (Y_{i0}, Y_{i1})
  Y_{i0} : ith outcome, assigned to placebo
  Y_{i1} : ith 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 $P_1,...P_K$
- Causal effect with P_k is
  $pr(Y_{i1}=1)/pr(Y_{i0}=1)$ 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

	$Y_{i1}=1$	$Y_{i1}=0$
$Y_{i0}=1$	p_{11}	p_{10}
$Y_{i0}=0$	p_{01}	p_{00}

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

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

Principal Strata

- Latent
- But conceptually exist *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

	MT	WT
Truvada		
Placebo		

Answers a Question

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

-Gilbert et al (2003)

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
  data for i not affected by rx for j
  suspect in small sexual networks

- $pr(Y_{i0}=1, Y_{i1}=0)=0 \Rightarrow pr(Y_{i0}=1 | Y_{i1}=1)$
  HIV+ on TDV: belong to Group 4

Placebo HIV+

- RE = 1-RR
- RR = $(p_{11} + p_{01})/(p_{11}+p_{10})$ =>
  RE = $p_{01}/(p_{11}+p_{10})$ =
  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(grp 4| HIV+ placebo, Y=y)
- logit(p(y)) = $\alpha + \beta y$
- β indexes selection

Selection Model

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

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