# Analysis of Drug Concentration Data in PrEP Trials

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VACCINE AND INFECTIOUS DISEASE INSTITUTE
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# Estimating prevention efficacy among compliers

**Estimating the efficacy of pre-exposure prophylaxis for HIV prevention among participants with a threshold level of drug concentration.** Dai JY, Gilbert PB, Hughes JP, Brown ER. *American Journal of Epidemiology.* In Press.

- Discuss pitfalls of standard analysis of drug concentration data in current PrEP trials
- Propose causal inference methods to estimate the efficacy among compliers

# Adherence in HIV prevention trials


Importance of assessing adherence data in prevention trials

- Corroborate or explain the primary Intent-to-treat results
- Obtain the efficacy estimate among compliers

# Drug detection as measure of adherence

- Drug concentration in blood and tissue
  - More accurate than self-report
- Case-control sampling in **active product arm** for drug assay
  - possibly matching control at the time (visit) of infection
- Standard analysis involves association of HIV infection status and drug detection
  - **Drug / Infection Association** $\neq$ **Prevention efficacy**

# The iPrEx trial

- Proof of concept for oral PrEP
- 2499 MSM randomized to FTC-TDF (Truvada) or placebo
- ITT results: 44% reduction of HIV infection rate in the FTC-TDF arm. P-value=0.005

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## Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men

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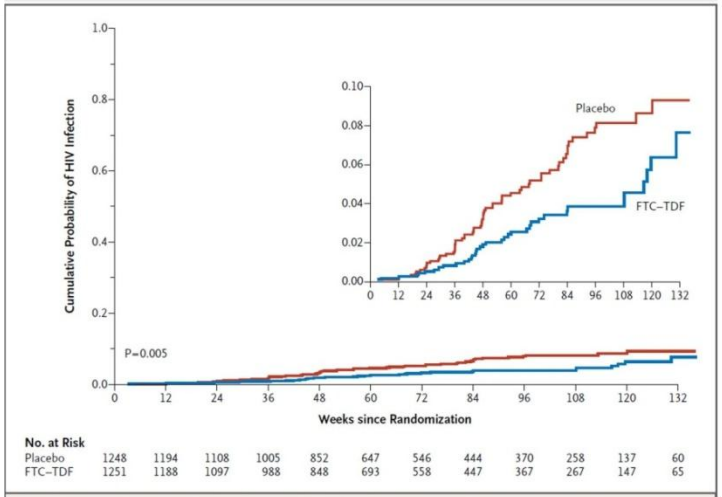
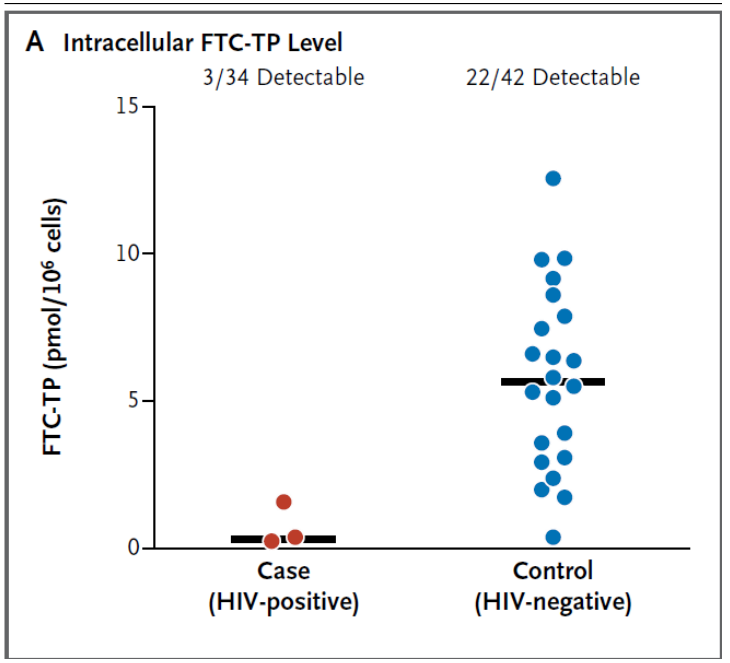



**Figure 2. Kaplan–Meier Estimates of Time to HIV Infection (Modified Intention-to-Treat Population).**
The cumulative probability of HIV acquisition is shown for the two study groups. The efficacy of preexposure prophylaxis with emtricitabine and tenofovir disoproxil fumarate (FTC–TDF) was 44%, as compared with placebo (P=0.005). The inset graph shows a more detailed version of the overall graph up to a probability of 0.10.

# The drug assay data

**In the FTC-TDF (Truvada) arm**

- Case-control sampling
- 3/34 in cases; 22/42 controls
- OR=0.092, p-value <0.001
- Adds to the ITT result of 44% reduction




**Can this result be interpreted as the estimate of prevention efficacy?**

# Limitation of existing analyses

| | Drug arm HIV risk | Placebo arm HIV risk |
|---|---|---|
| Complier | A | C |
| Non-complier | B | D |

# Limitation of existing analyses

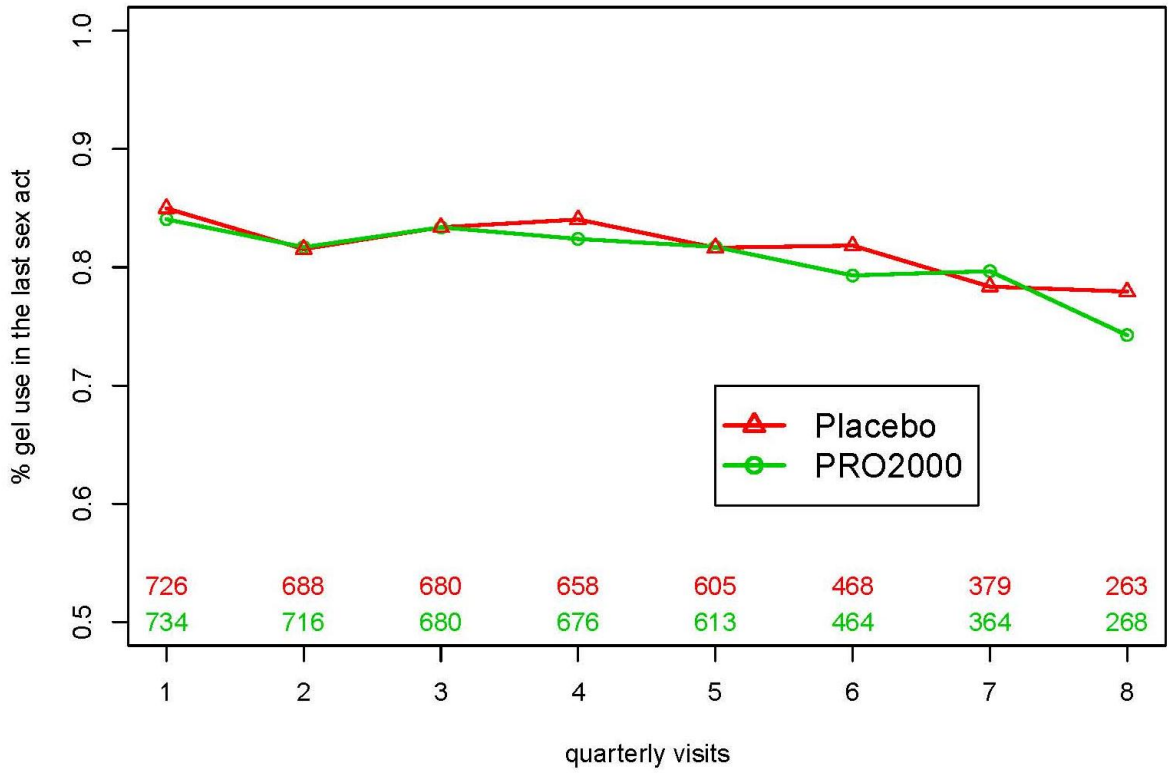
| | Drug arm HIV risk | Placebo arm HIV risk |
|---|---|---|
| Complier (drug detected) | A | C |
| Non-complier (drug undetected) | B | D |

**Complier and non-compliers may have different HIV risk-taking profiles. Are we comparing "apples" to "oranges"?**

# Characteristics of complier/non-complier in HPTN 035

- We did not have drug assay data for HPTN 035
  - Use self-reported gel use data
- The study population/product/dosing regimen are different from the iPrEx trial
  - do not generalize
- The purpose is to show an example that complier and non-complier can be quite different risk groups

# HPTN035: compare adherence between PR02000 and placebo




**OR=0.98,**
**p-value=0.75**

**No difference in adherence between three gel arms.**

# Baseline factors predicting “high/low complier’’

**Define ``high complier” to be women taking more than 85% gel**

| | Univariate OR | P-value | Multivariate OR* | P-value |
|---|---|---|---|---|
| Age > 25 | 1.43 | <0.001 | 1.37 | <0.001 |
| Own income | 1.27 | 0.004 | 1.04 | 0.67 |
| Married | 1.60 | <0.001 | 1.16 | 0.35 |
| Use condom in last sex act | 1.39 | <0.001 | 1.09 | 0.37 |
| Having more than 3 sex acts last week | 1.49 | <0.001 | 1.37 | 0.001 |

*Multivariate regression also adjusted for site.

# How much compliers/non-compliers differ in HIV risk even when they receive placebo gel?

**HPTN 035 Trial**

| | HIV incidence in placebo gel arm |
|---|---|
| High complier(>85% ) | 4.4 |
| Low complier (<85%) | 3.2 |

**In the placebo arm, hazard ratio of high-complier vs low-complier is 1.48 (p-value 0.18).**

# Back to iPrEx: What is the causal (unbiased) comparison?

**If compliance in drug arm and placebo arm is similar,**

| | Drug arm HIV risk | Placebo arm HIV risk |
|---|---|---|
| Complier | A | C |
| Non-complier | B | D |

**Complier average causal effect (CACE)**

**We do not have drug assay as surrogate of adherence for placebo arm!**

# Complier in the placebo arm is not identified

**Observe E – HIV incidence in the placebo arm as a whole**

| | ARV HIV risk | Placebo HIV risk |
|---|---|---|
| Complier | A | C = ? |
| Non-complier | B | D = ? |

E

**Suppose the proportion of compliers is p, the HIV incidence in the placebo arm E = p*C + (1-p)*D.**

# Exclusion Restriction

**If we assume B=D, i.e., non-compliers do not get any protection from randomization to ARV, then C is identified.**

| | ARV HIV risk | Placebo HIV risk |
|---|---|---|
| Complier | A | C = (E-(1-p)*D)/p |
| Non-complier | B | D = B |

**Causal comparison is identified by assuming exclusion restriction.**

# Applying to the iPrEx data

**Using maximum likelihood method and accounting for case-control sampling**

| | ARV HIV risk | Placebo HIV risk | OR | P-value |
|---|---|---|---|---|
| complier | 0.005 | 0.050 | 0.093 | 0.004 |
| non-complier | 0.052 | = 0.052 | 1.0 | --- |

**Not very different from association analysis, but reassuring….**

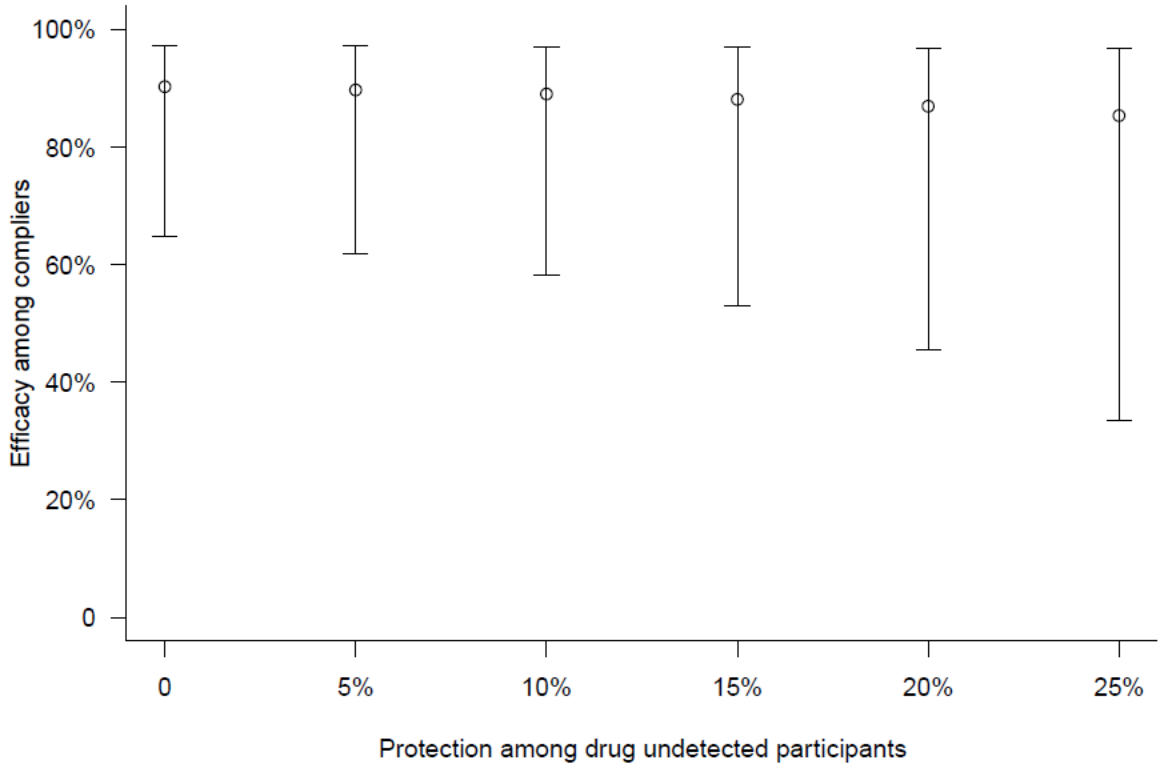
# Compare compliers and non-compliers in HIV risk-taking

| | ARV HIV risk | Placebo HIV risk | OR | P-value |
|---|---|---|---|---|
| complier | 0.005 | 0.050 | 0.093 | 0.004 |
| non-complier | 0.052 | 0.052 | 1.0 | --- |

**Compliers and non-compliers in this MSM population have similar HIV risk-taking.**

# Sensitivity analysis

- **Exclusion restriction may not hold exactly because drug assay was done at a single time for each participant**




In the iPrEx trial, efficacy among compliers is around 80%-90%.

# Related works

- Use baseline covariates, and other compliance data in the placebo arm, to predict the true compliance  in the placebo arm.
- Estimate the **drug concentration – prevention efficacy** curve
- Apply these analytical techniques to VOICE

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