

Improving Inferences from Randomized Trials: Using per-protocol analyses obtain better estimates of HIV treatment effects.

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Outline

RCTs

Per-protocol effects

Example using ACTG 5202 Trial

- Population

- Analysis Plan

- Results

- Limitations and Future

Closing Remarks

Randomized Trials are a gold standard

- Require clear enrollment criteria.
- Unambiguous intervention protocol.
- Exchangeability: $Y^a \perp\!\!\!\perp A$ for $A \in \{0, 1\}$
- Consistency: $Y = Y^{a=1}A + Y^{a=0}(1 - A)$
- Positivity: $Pr(A = a) > 0$

☞ This allows for unbiased estimation of treatment effects.

Y^a = counterfactual outcome under treatment $A = a$, Y = observed outcome, A = treatment

RCT estimands

- Intention-to-treat (ITT) effect: $E[Y^{r=1}] - E[Y^{r=0}]$
- This is the effect of treatment assignment on outcomes.
- Public health focused.

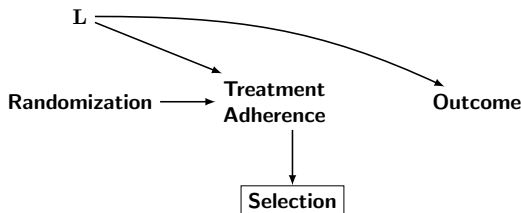
- *Typical* Per-protocol (PP) effect: $E[Y^{r=1, \bar{a}=1}] - E[Y^{r=0, \bar{a}=0}]$
- This is the effect of treatment assignment and adherence on outcomes.
- Patient focused.¹

R = randomization; \bar{A} = history of treatment

¹Hernan and Robins, NEJM 2016

Per-protocol effects can be biased

- Frequently done by excluding those not adhering.¹
 - Susceptible to selection bias.
- 👉 Can be addressed: e.g with inverse probability weighting (see next talk).



¹Cole *et al.* JAMA Net. Open 2023, Dodd *et al.* Trials 2012

L : vector of covariates

There is no *one* per-protocol effect

Accounts for adherence.

"Doc, what if I take all my doses like you tell me to?"

There are *at least* 6 per-protocol parameters that can be estimated.¹

There are also $k \geq 1$ protocols depending on how the investigator(s) define adherence.

¹Rudolph *et al.* Epidemiology 2020

Per Protocol Causal Identification

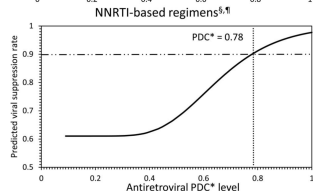
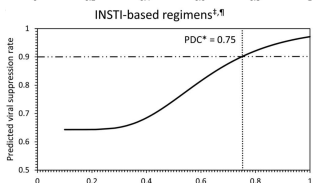
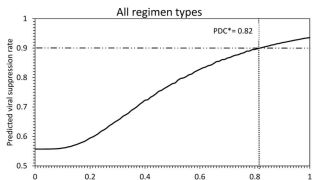
Let g be a deterministic treatment strategy and overbar denote a history of values

- Conditional Exchangeability:
 $Y^g \perp\!\!\!\perp (A_t, C_{t+1}) \mid (\bar{A}_{t-1} = \bar{a}_{t-1}^g, \bar{L}_t = \bar{\ell}_t, C_t = Y_t = 0) \quad \forall t$
- Consistency: if $\bar{A}_t = \bar{A}_t^g$ then $\bar{Y}_t = \bar{Y}_t^g$
- Positivity: $f(a_t^g, C_t = 0 \mid \bar{a}_{t-1}^g, \bar{\ell}_t, C_t = Y_t = 0) > 0 \quad \forall t$
- No missclassification and correct model specification.

Y = outcome, C = censoring, A = treatment, L = covariates, t = time point.
Wen *et al.* Biometrics 2019

Example: adherence in HIV treatment

- Adherence needed for HIV viral suppression varies by treatment regimen.
- Blanket recommendations fail.
- ☞ Understanding of how adherence impacts efficacy is *critical*^a for:
 - Developing new treatments.
 - Maximizing current treatments.



^a Adimora, Cole and Eron CID 2017

An example using an HIV Trial: ACTG 5202

Study Population

Phase 3b RCT at 59 sites, US and Puerto Rico

	ABC/3TC	TDF/FTC
N	928	929
Male at birth %	81.4	84.0
Age Group %		
≤ 25	10.1	10.5
26-49	77.0	74.8
≥ 50	12.8	14.6
Baseline \log_{10} RNA copies/mL (med [IQR])	4.66 [4.31, 5.06]	4.65 [4.34, 4.96]
Baseline CD4 count/mL (med [IQR])	229 [84, 338]	230 [97, 330]

Example: ACTG 5202 Reanalysis

Objective:

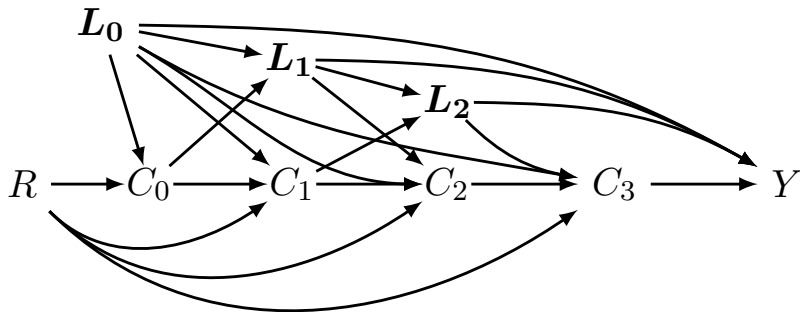
- Estimand: $E[Y^{r=1, \bar{a}=1}] - E[Y^{r=0, \bar{a}=0}]$ at 48 weeks.
- Will vary protocol definition depending on the number of doses missed.

Outcomes: Composite virologic failure and all-cause mortality.

Methods: IPW analysis accounting for

- Age, Sex, Ethnicity
- Baseline CD4
- Baseline HIV RNA and screening RNA
- Time varying CD4
- Time varying HIV RNA

DAG



t : follow up time, \mathbf{L}_t : vector of covariates at follow up time t
 C_t : protocol deviation at follow up time t , R : randomization, Y : viral failure or death

Adherence and Protocol

Adherence evaluated in-person at 8, 24, 48, 72, 96, then every 24 weeks and either at the final study evaluation or after virologic failure.

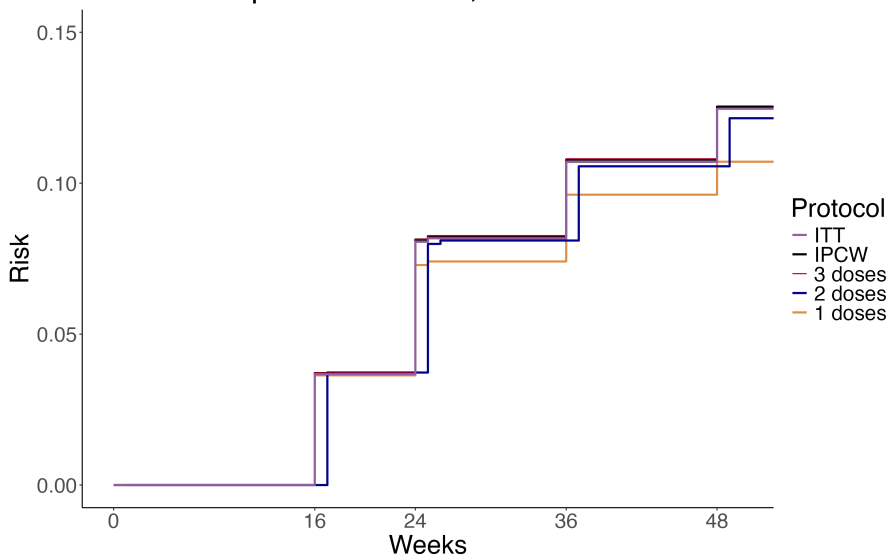
Last Time Missed Medication	How Close Was Dose Schedule Followed
Never	Never
>3 months ago	Some of the time
1-3 months ago	About half the time
2-4 weeks ago	Most of the time
1-2 weeks ago	All the time
Within the past week	

Protocol Definition	Description of Protocol
0 dose missed OK	No report of missed medication doses
1 dose missed OK	Participant with only one report of missed medication doses
⋮	⋮
4 doses missed OK	Participant with ≥ 4 reported missed medication doses without overlap in reported timing

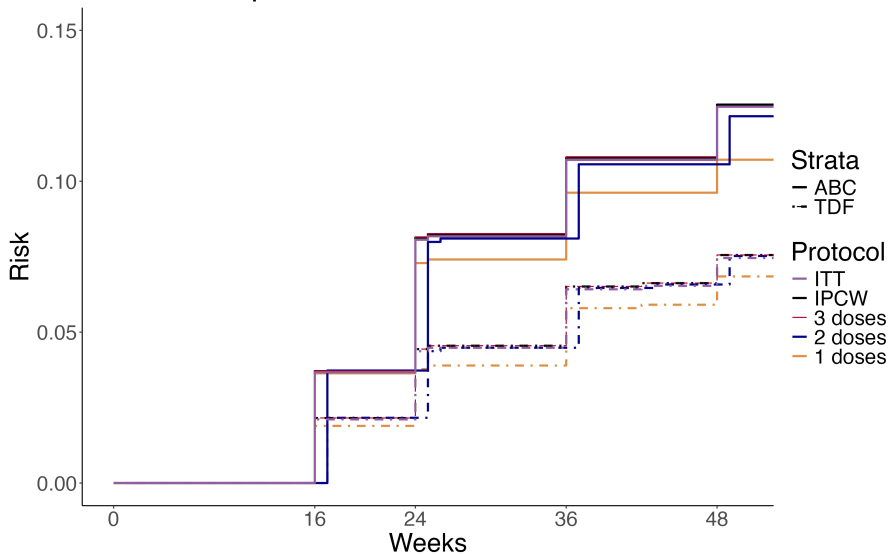
Deviation from Defined Protocols

Treatment Group	LTFU	Doses Missed					Total
		1	2	3	4	5	
ABC/3TC	234	276	110	57	18	7	928
TDF/FTC	211	263	79	38	23	7	929

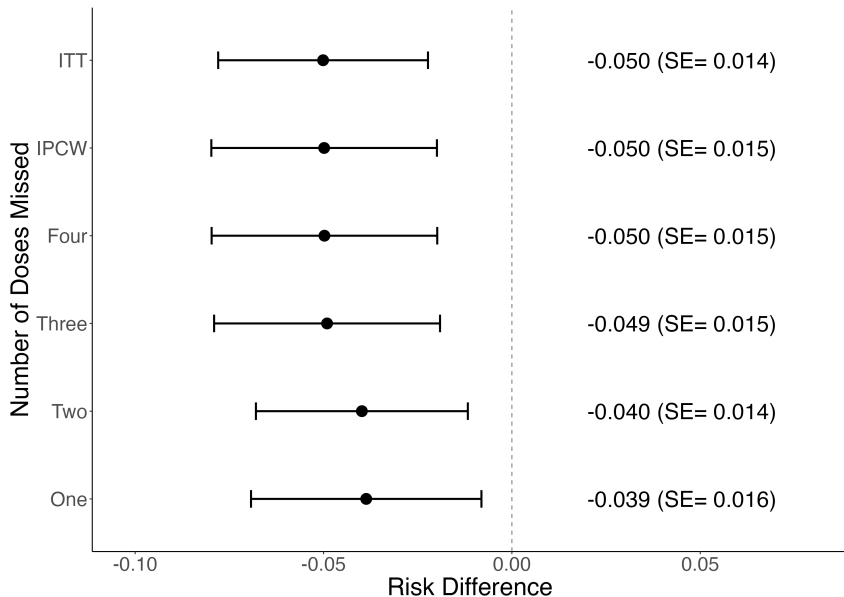
Risk of Composite Outcome; ABC/3TC arm




Risk of Composite Outcome



TDF/FTC v ABC/3TC at 48 Weeks



Limitations and Future Plans

1. Completed with public access data.¹
2. Reliance on coarse, self-reported medication adherence.
3. Assume identification conditions met.
 Not guaranteed even though in a trial. Just like observational studies.
4. Future directions include repeating analysis with g-formula, considering additional protocols, and extending to different diseases.

¹Approved for more granular data from ACTG, awaiting dataset

Takeaways

- Per protocol analysis should be treated like an observational analysis.
- Time varying covariates need to be taken into account.
- There are many ways protocols can be defined.
- The way protocol is defined can have meaningful impacts on estimates.

Thank you!



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I'd like to acknowledge:

- Steve Cole
- Paul Zivich
- Catherine Li
- ACTG 5202
- ACTG 5202 Participants
- Cole Lab Members



My website where you can find a link to my github.

Outcome Definition

- plasma HIV-1 RNA level ≥ 1000 copies /mL between 16 weeks and 24 weeks
- or ≥ 200 copies/mL at or after 24 weeks
- all cause mortality

Censoring Risk

Risk of censoring by treatment group

