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

by Timothy Feeney

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e: feeney@unc.edu, bsky: @tfeend.bsky.social

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Outline

RCTs

Per-protocol effects

Example using ACTG 5202 Trial
- Population
- Analysis Plan
- Results
- Limitations and Future

Randomized Trials are a gold standard

- Require clear enrollment criteria
- Unabmiguous intervention protocol
- Exchangeability: $Y^a \perp\!\!\!\perp A$ for $A \in \{0, 1\}$
- Consistency[1]: $Y = Y^{a=1}A + Y^{a=0}(1 - A)$
- Positivity[2]: $Pr(A = a \mid \mathbf{L}) > 0,\ \forall \ell$ where $f(a, \ell) > 0$

☞ This allows for unbiased estimation of treatment effects.

[1] also known as treatment variation irrelevance

[2] $\mathbf{L}$ is covariate vector

RCT estimands

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

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

[1] Hernan and Robins, NEJM 2016

[2] $\bar{a}$ is the history of treatment adherence

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 six per-protocol parameters that can be estimated[1]
- This can also depend on how the investigator(s) define adherence.

$$E\left[Y^{r=1,\bar{a}=1}\right] - E\left[Y^{r=0,\bar{a}=1}\right]$$
$$E\left[Y^{r=1,\bar{a}=1}\right] - E\left[Y^{r=0,\bar{a}=0}\right]$$
$$E\left[Y^{r=0,\bar{a}=1}\right] - E\left[Y^{r=0,\bar{a}=0}\right]$$
$$E\left[Y^{r=1,\bar{a}=1}\right] - E\left[Y^{r=1,\bar{a}=0}\right]$$
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$$E\left[Y^{r=1,\bar{a}=0}\right] - E\left[Y^{r=0,\bar{a}=0}\right]$$

[1] Rudolph *et al.* Epidemiology 2020

[2] r = randomization, $\bar{a}$ = treatment history

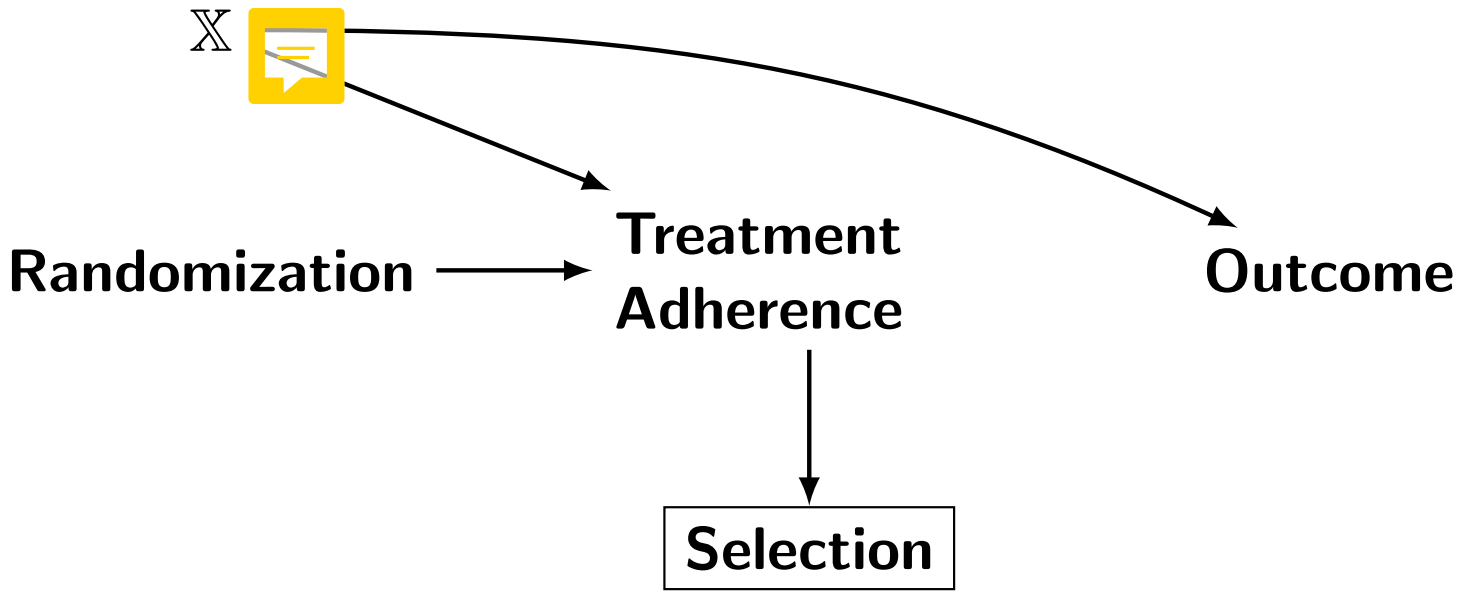
Per-protocol effects can be biased

- Frequently done by exluding those not adhering[1]
- Estimation of the per-protocol effect is much like an *observational study*
- Thus, bias can arise from non-exchangeability, non-consistency, or non-positivity

☞ This can lead to biased estimates

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

Per-protocol effects can be biased



Can be addresed: inverse probability weighting (IPW), the g-formula, TMLE, can be used to account for selection bias (see next talk)

[0] $\mathbb{X}$: vector of covariates

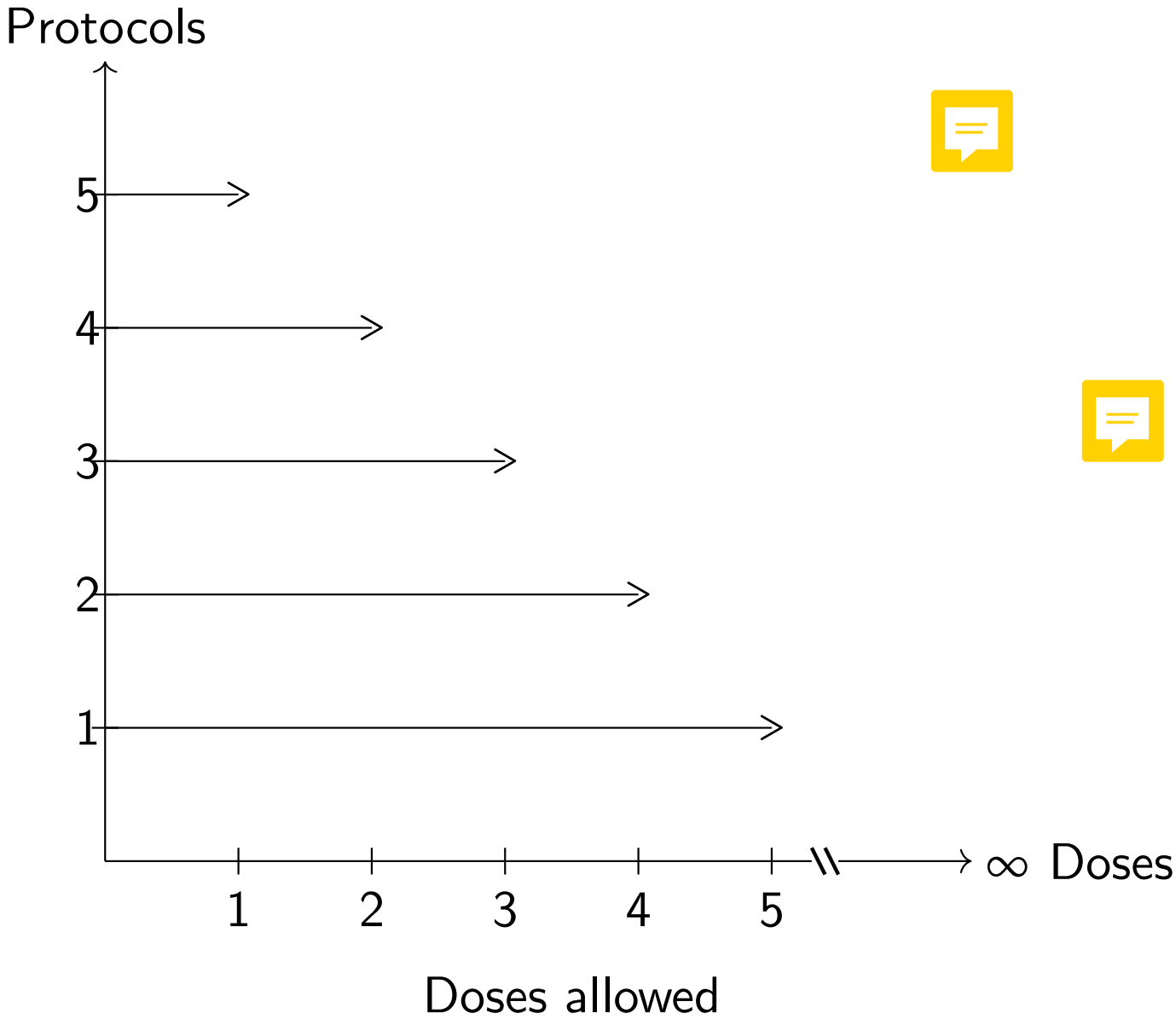
Per Protocol Causal Identification

- Conditional Exchangeability:
  $Y^g \perp\!\!\!\perp (A_t, C_{t+1}) \mid \left(\bar{A}_{t-1} = \bar{a}^g_{t-1}, \bar{L}_t = \bar{\ell}_t, C_t = Y_t = 0\right) \quad \forall t$
- Consistency: if $\bar{A}_t = \bar{A}^g_t$ then $\bar{Y}_t = \bar{Y}^g_t$
- Positivity: $f(a^g_t, C_t = 0 \mid \bar{a}^g_t, \bar{\ell}_t, C_t = Y_t = 0) > 0$ where
  $f(\bar{a}^g_t, \bar{\ell}_t, C_t = Y_t = 0) > 0 \quad \forall t$
- No interference: $\bar{A}^g_{it} \perp\!\!\!\perp \bar{Y}^g_{jt}$ where $i \neq j$
- No missclassification and correct model specification

Where, C=censoring, t =time point from $0 \ldots t$, g is a deterministic treatment strategy, overbar denotes history of values

[0] Wen *et al.* Biometrics 2019

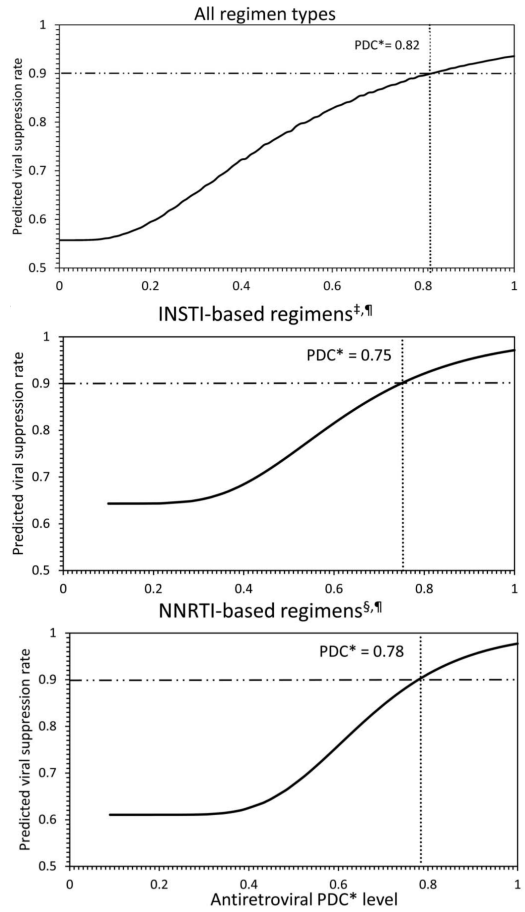
More on Protocol Definition



An example using an HIV Trial: AIDS Clinical Trial Group (ACTG) 5202

Role of adherence in HIV treatment efficacy

- Adherence needed for viral suppression varies by treatment regimen.
- Blanket recommendations fail to capture differences.
- ☞ Understanding of how adherence impacts efficacy is *critical*[1] for:
  - Developing new treatments.
  - Maximizing current treatments.



[1] Adimora, Cole and Eron CID 2017

Example: ACTG 5202 Reanalysis

Overview:

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

Objective:

- Per-protocol analysis modulating protocol definition.
- Target population: The population of HIV+ individuals in the United States
- Estimand: $E\left[Y^{r=1,\bar{a}=1}\right] - E\left[Y^{r=0,\bar{a}=0}\right]$ at 48 weeks

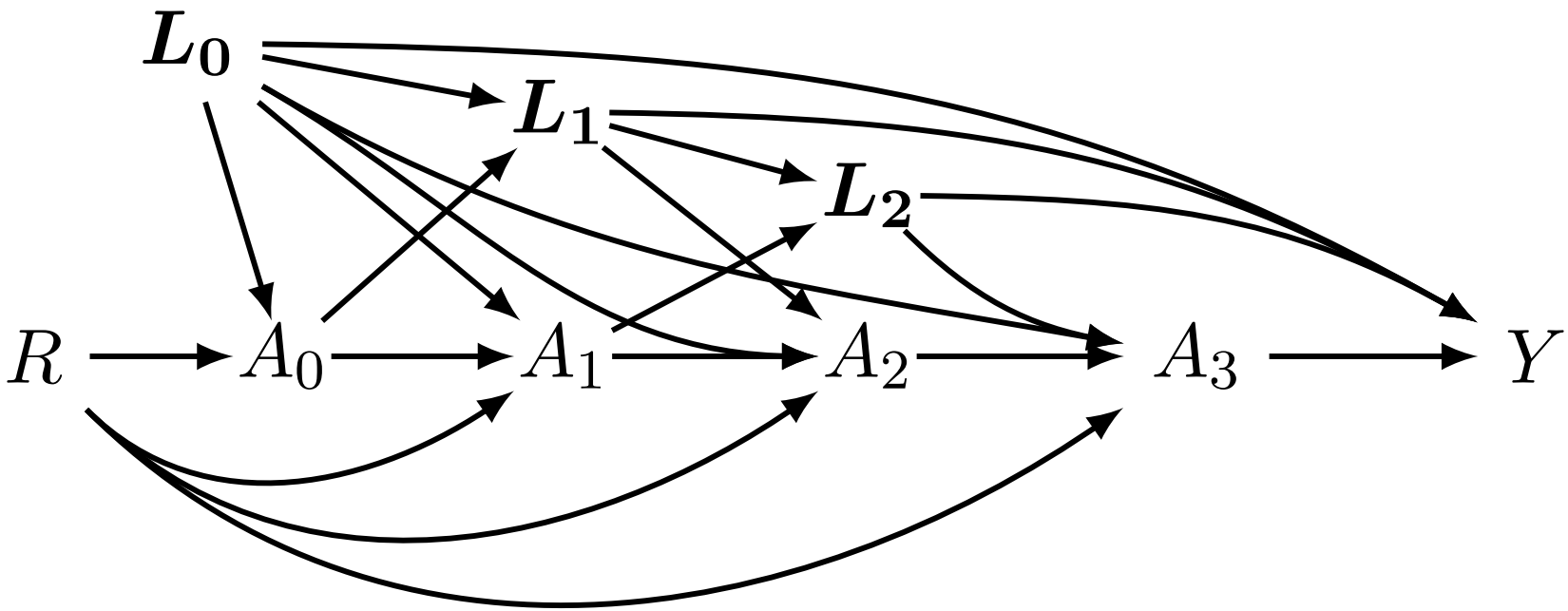
Outcomes: Virologic Failure defined as:

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

ACTG 5202 Study Population

	ABC/3TC		TDF/FTC	
	+ATV	+EFV	+ATV	+EFV
n	463	465	465	464
Female (%)	75 (16.2)	98 (21.1)	78 (16.8)	71 (15.3)
Age Group (%)				
0-25 year	51 (11.0)	43 (9.2)	52 (11.2)	46 (9.9)
25-49 years	353 (76.2)	362 (77.8)	339 (72.9)	356 (76.7)
≥ 50 years	59 (12.7)	60 (12.9)	(15.9)	62 (13.4)
Baseline log RNA (med [IQR])	4.64 [4.31, 5.14]	4.68 [4.34, 4.96]	5 [4.31, 5.05]	4.65 [4.35, 4.91]
Baseline CD4 (med [IQR])	236 [73, 345]	225 [103, 324]	224 [87, 327]	233 [104, 334]
AIDS Hx (%)	84 (18.1)	88 (18.9)	69 (14.8)	71 (15.3)

DAG



j: follow up time, $\mathbf{L_j}$: vector of covariates at follow up time j
A_j: tx adherence at follow up time j, R: randomization, Y: viral failure or death

Adherence and Protocol

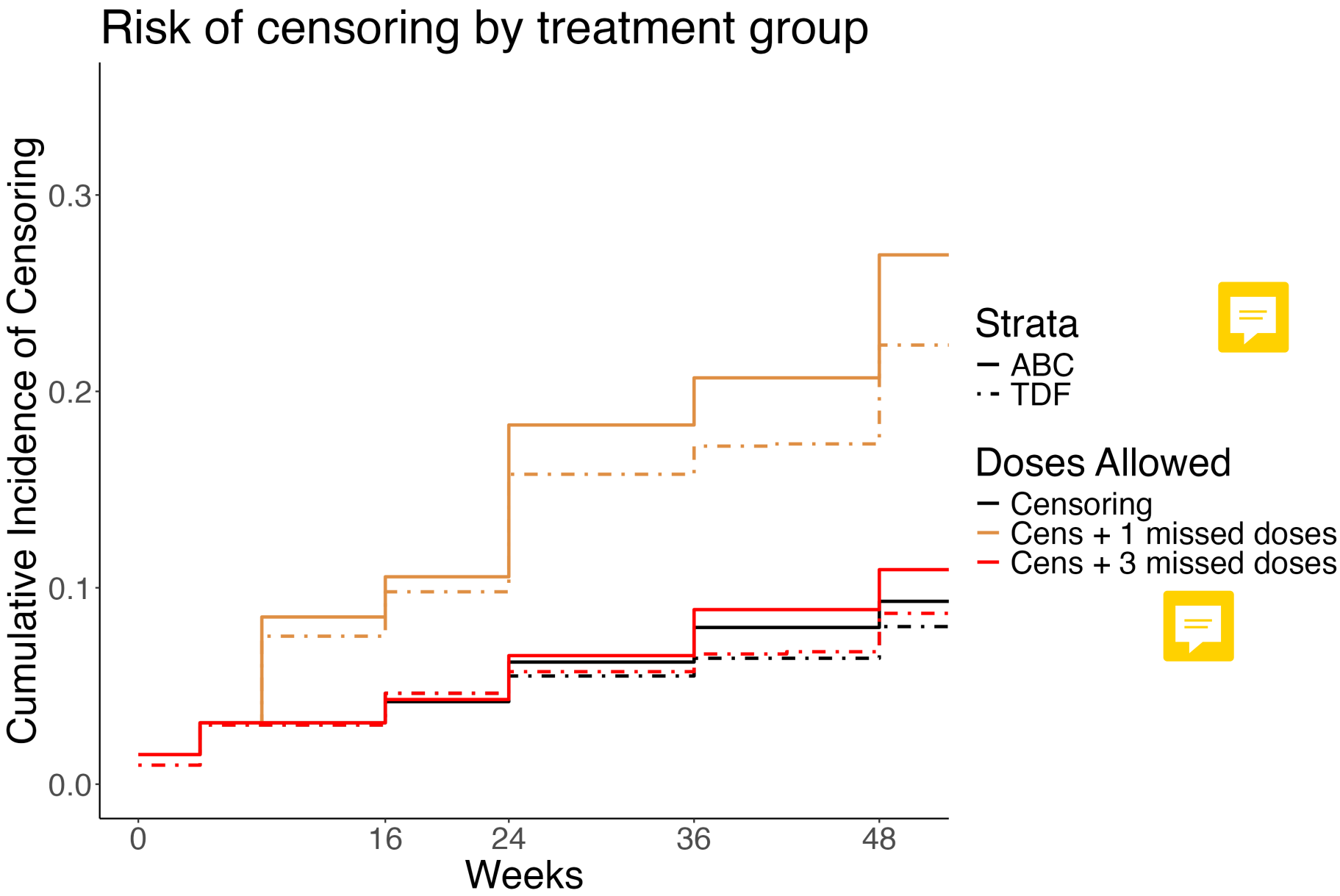
Adherence evaluated in-person at 8, 24, 48, 72, 96, then every 24 weeks and either at the final study evaluation or after virologic failure.

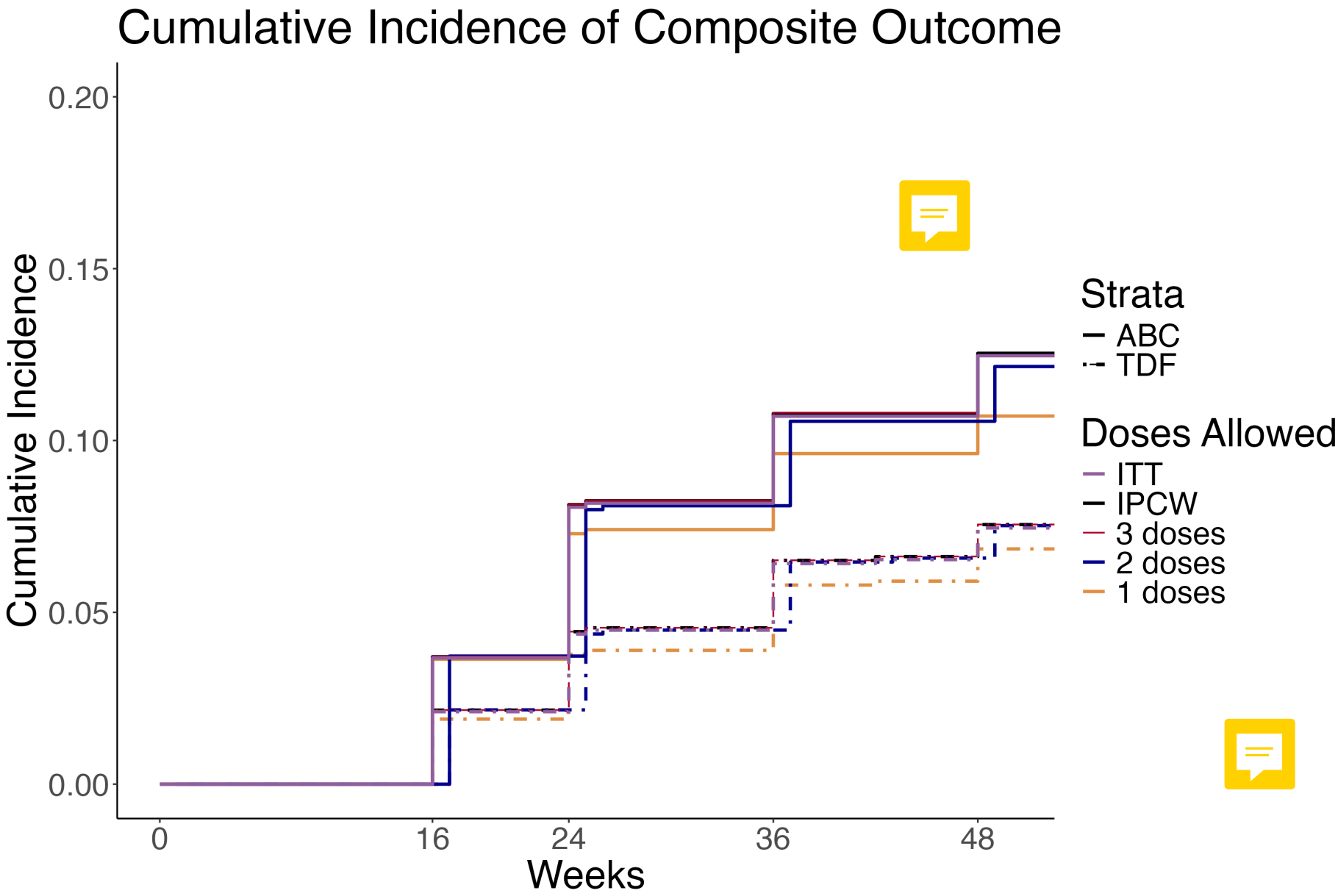
Last Time Missed Medication	**How Close Was Dose Schedule Followed**
Never	Never
>3 months ago	Some of the time
1-3 months ago	About half the time
2-4 weeks ago	Most of the time
1-2 weeks ago	All the time
Within the past week	

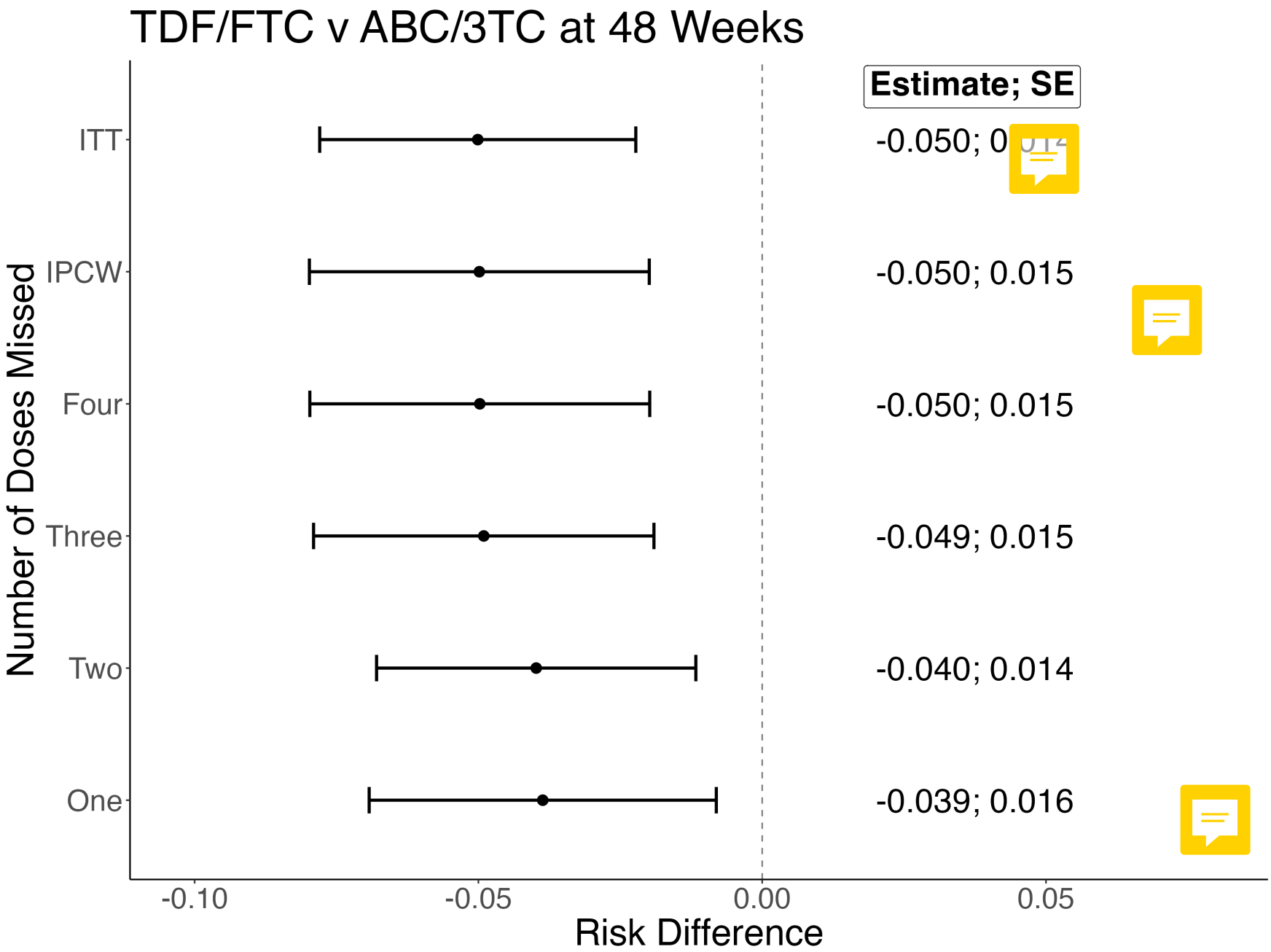
Adherence Definition	**Definition of Variable**
0 dose missed OK	No report of missed medication doses
1 dose missed OK	Participant with only one report of missed medication doses
⋮	⋮
4 doses missed OK	Participant with ≥ 10 reported missed medication doses without overlap in reported timing

Deviation from Defined Protocols

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


Risk of censoring by treatment group
Cumulative Incidence of Censoring
0.0
0.1
0.2
0.3
0
16
24
36
48
Weeks
Strata
ABC
TDF
Doses Allowed
Censoring
Cens + 1 missed doses
Cens + 3 missed doses


Cumulative Incidence of Composite Outcome
Cumulative Incidence
0.20
0.15
0.10
0.05
0.00
0
16
24
36
48
Weeks
Strata
ABC
TDF
Doses Allowed
ITT
IPCW
3 doses
2 doses
1 doses


TDF/FTC v ABC/3TC at 48 Weeks
Estimate; SE
ITT
IPCW
Four
Three
Two
One
-0.050; 0.014
-0.050; 0.015
-0.050; 0.015
-0.049; 0.015
-0.040; 0.014
-0.039; 0.016
Number of Doses Missed
-0.10
-0.05
0.00
0.05
Risk Difference

Limitations and Future Plans

1. Completed with public access data[1]
2. Reliance on coarse, self-reported medication adherence
3. Assume identification conditions met.[2]
4. Future directions include repeating analysis with g-formula, considering additional protocols.

[1] Approved for more granular data from ACTG, awaiting dataset

[2] NB: not guaranteed in per-protocol setting even though it is a trial

Thank you!

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I'd like to acknowledge:

- Steve Cole
- Paul Zivich
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- ACTG 5202 Particpants
- Cole Lab Members

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