Improving Inferences from Randomized Trials: Using per-protocol analyses obtain better estimated 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
- Unabmiguous intervention protocol
- Exchangeability: $Y^a \perp\!\!\!\perp A \qquad$ for $A \in \{0, 1\}$
- Consistency: $Y = Y^{a=1}A + Y^{a=0}(1 - A)$
- Positivity[1]: $Pr(A = a) > 0,\ \forall \ell$ where $f(a) > 0$

☞ This allows for unbiased estimation of treatment effects.

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

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]

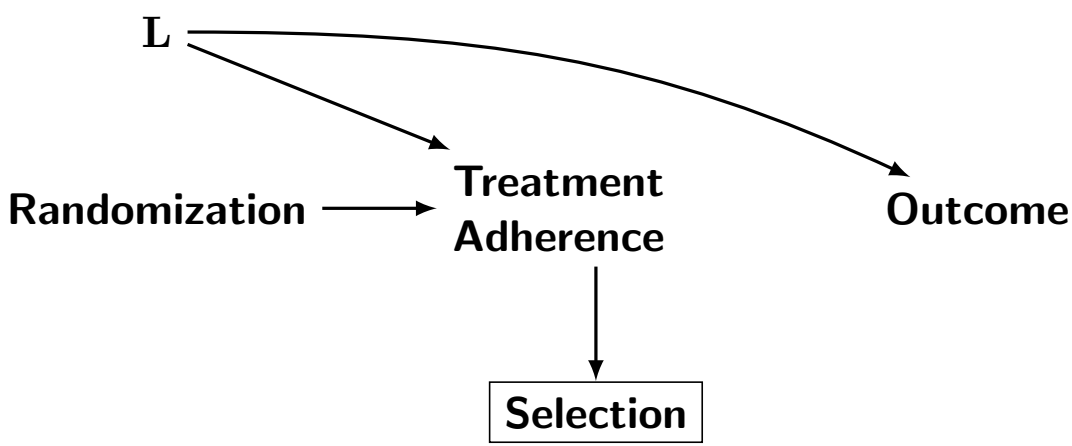
r = randomization; $\bar{a}$ = history of treatment adherence

[1] Hernan and Robins, NEJM 2016

Per-protocol effects can be biased

- Frequently done by excluding those not adhering[1]
- Susceptible to selection bias

☞ Can be addresed: e.g with inverse probability weighting (see next talk)



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

[0] $\mathbf{L}$: 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 $k \in \{1, \ldots, \infty\}$ protocols depending on how the investigator(s) define adherence.

[1] Rudolph *et al.* Epidemiology 2020

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

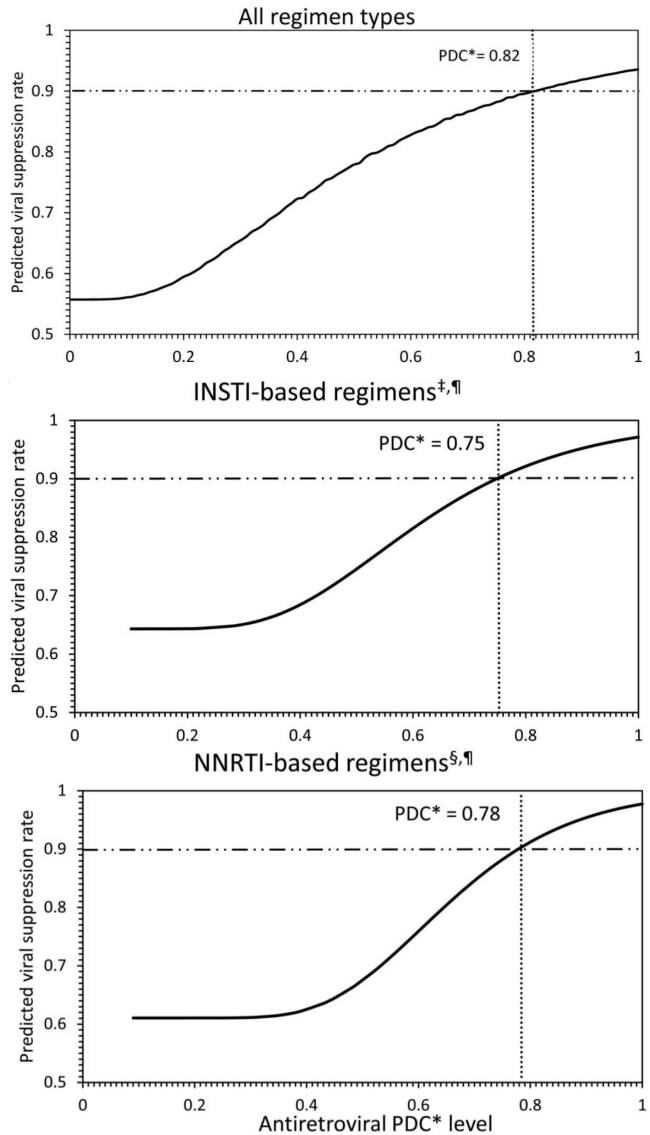
Y =outcome, C=censoring, A = treatment , L = covariates, t =time point from $0 \ldots t$, g is a deterministic treatment strategy, overbar denotes history of values

[0] Wen *et al.* Biometrics 2019

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

Role of adherence in HIV treatment efficacy

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



[a] Adimora, Cole and Eron CID 2017

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:

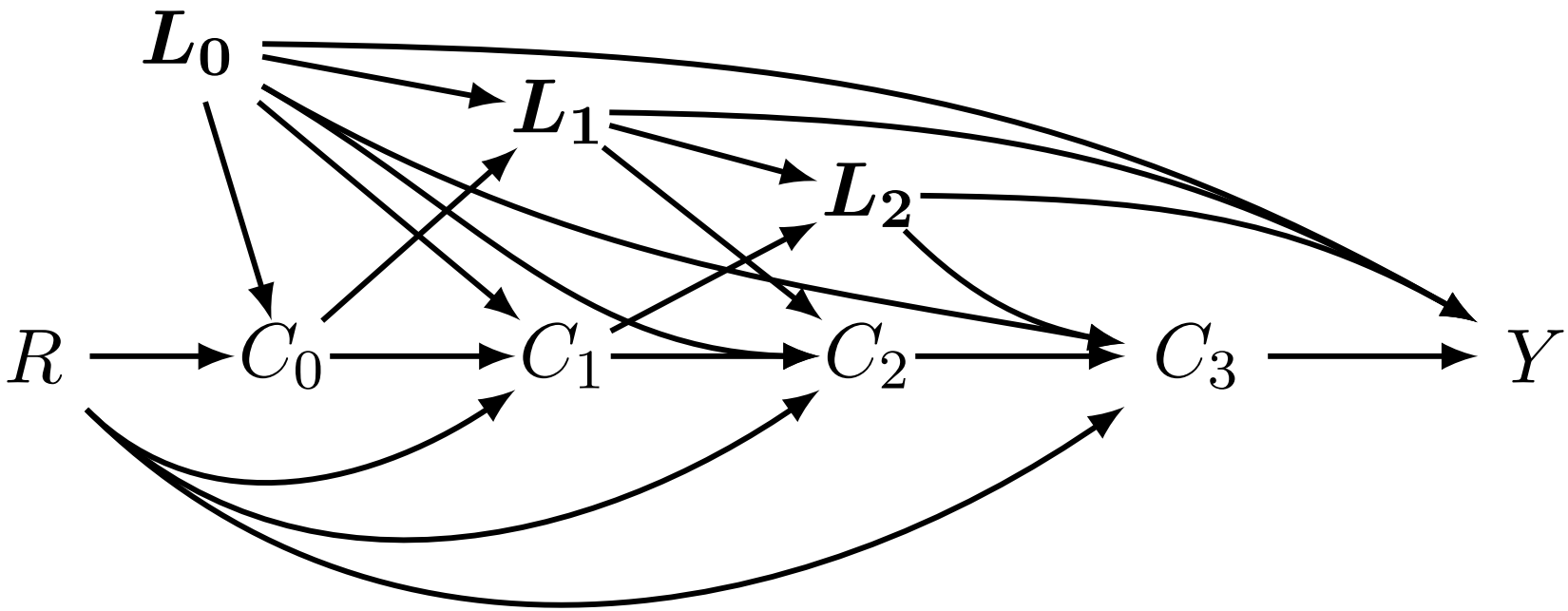
- Estimand: $E\left[Y^{r=1,\bar{a}=1}\right] - E\left[Y^{r=0,\bar{a}=0}\right]$ at 48 weeks
- Modulating treatment protocol $\bar{a}$.
- Protocol will depend on number of doses missed

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



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

Adherence and Protocol

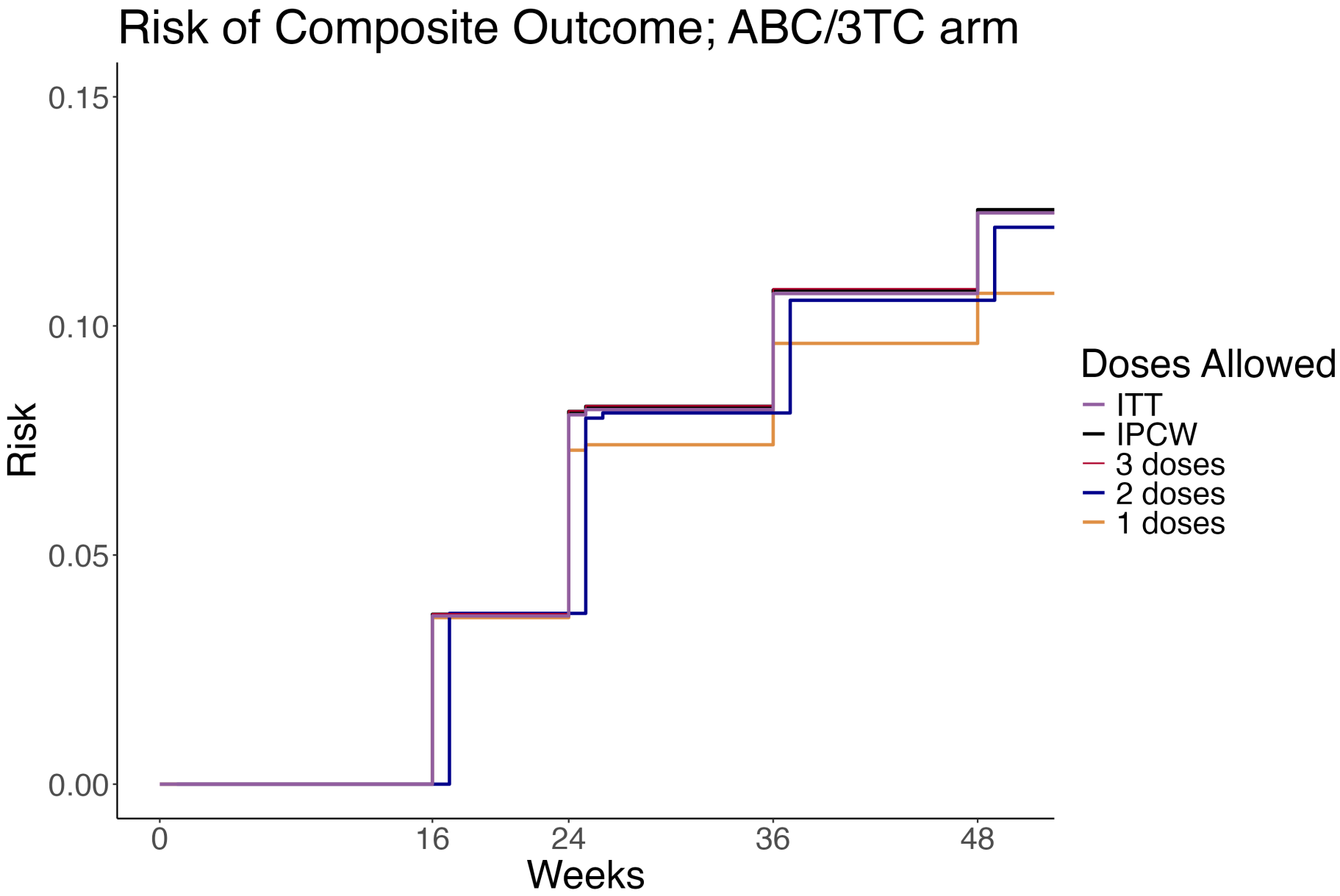
Adherence evaluated in-person at 8, 24, 48, 72, 96, then every 24 weeks and either at the final study evaluation or after virologic failure.

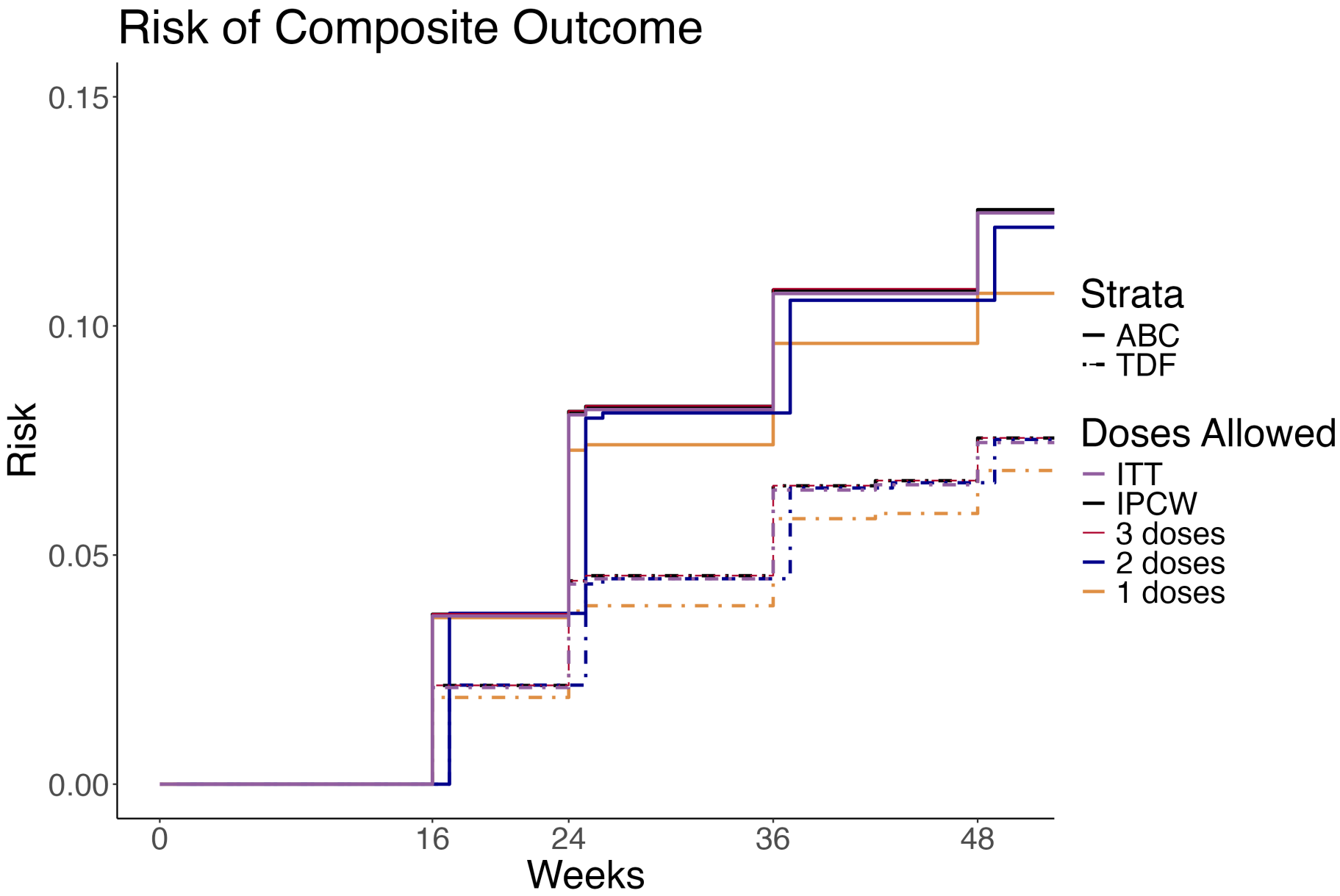
Last Time Missed Medication	**How Close Was Dose Schedule Followed**
Never	Never
>3 months ago	Some of the time
1-3 months ago	About half the time
2-4 weeks ago	Most of the time
1-2 weeks ago	All the time
Within the past week	

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 ≥ 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 Composite Outcome; ABC/3TC arm
0.15
0.10
0.05
0.00
Risk
0
16
24
36
48
Weeks
Doses Allowed
ITT
IPCW
3 doses
2 doses
1 doses


Risk of Composite Outcome
0.15
0.10
0.05
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Risk
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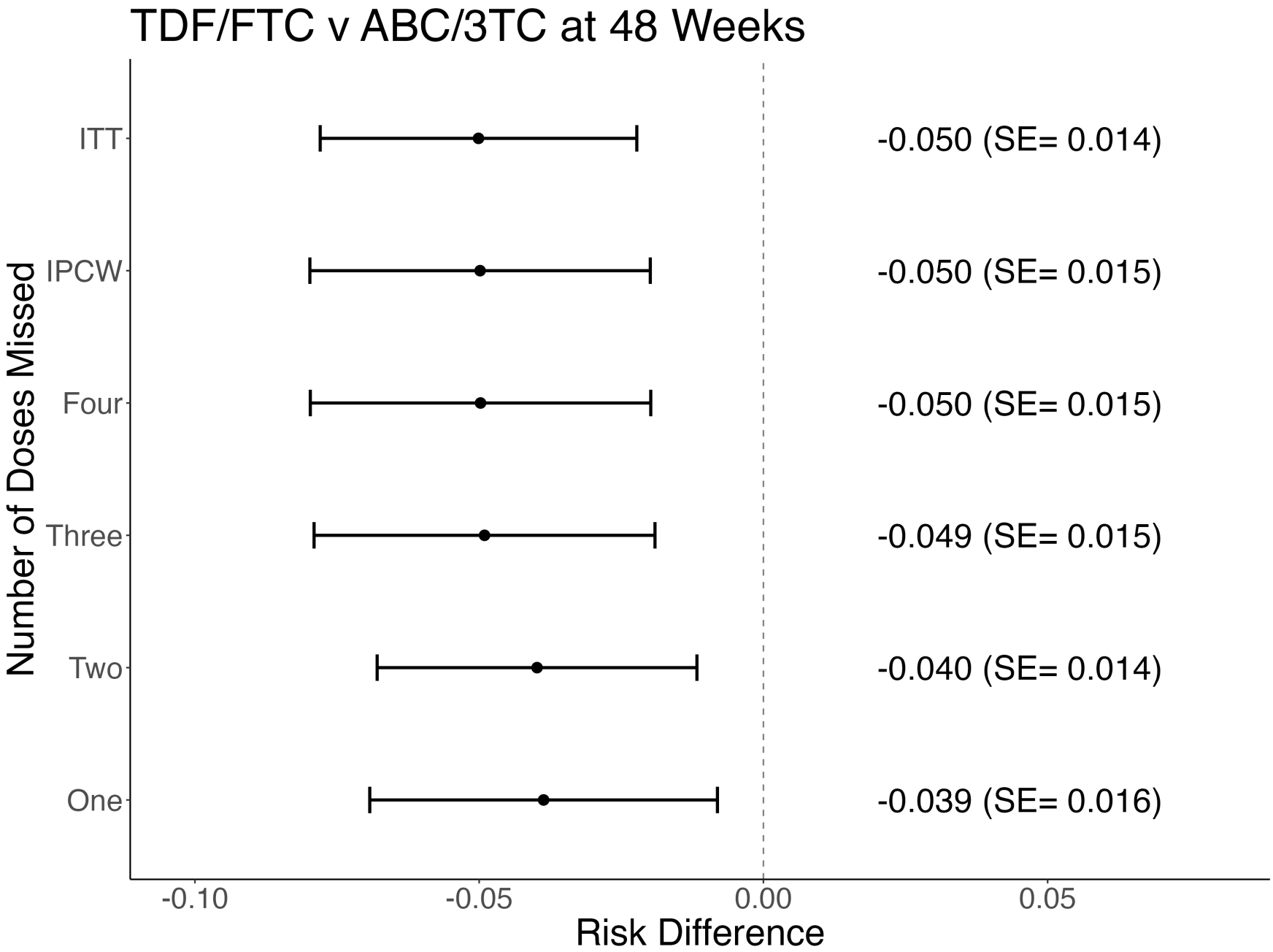
16
24
36
48
Weeks
Strata
ABC
TDF
Doses Allowed
ITT
IPCW
3 doses
2 doses
1 doses


TDF/FTC v ABC/3TC at 48 Weeks
Number of Doses Missed
ITT
IPCW
Four
Three
Two
One
-0.050 (SE= 0.014)
-0.050 (SE= 0.015)
-0.050 (SE= 0.015)
-0.049 (SE= 0.015)
-0.040 (SE= 0.014)
-0.039 (SE= 0.016)
-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, and extending to different diseases.

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

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

Takeaways

- Per protocol analysis should be treated like an observational analysis.
- Time varying analysis needs to be accounted for.
- 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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- ACTG 5202 Particpants
- 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