

Using Adherence-Efficacy Relationship of TDF/FTC to Estimate the Counterfactual Placebo Incidence in HPTN 083

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Presentation Highlights

1. What is the main issue or question the presentation addresses?

To evaluate a methodologic approach to estimate the counterfactual placebo HIV incidence rate in non-placebo-controlled trial populations, such as the HPTN 083.

2. What is the key finding or 'takeaway message'?

We can leverage the adherence-efficacy relationship of PrEP agents (like TDF/FTC) to estimate the counterfactual placebo incidence in trials such as HPTN 083.

3. How does the research advance HIV prevention efforts?

More flexible designs are required for demonstrating protective efficacy of newer PrEP agents in the field. This analysis can help inform design of such trials.

HPTN 083: Study summary


- Randomized, double-blind, double-dummy, noninferiority trial to compare CAB LA with daily oral TDF-FTC for prevention of HIV infection in at-risk populations (MSM and transgender women).
- 4,570 participants (1:1 randomized, followed for 153 weeks) at 43 sites in Argentina, Brazil, Peru, United States, South Africa, Thailand and Vietnam.
- Primary end point: Incident HIV infection.
- December 2016 – May 2020.

HPTN 083: Results

- 13 infections in CAB LA group (incidence, 0.41 per 100 PY)
- 39 in the TDF-FTC group (incidence, 1.22 per 100 PY)
- Hazard ratio, 0.34; 95% CI: (0.18, 0.62).

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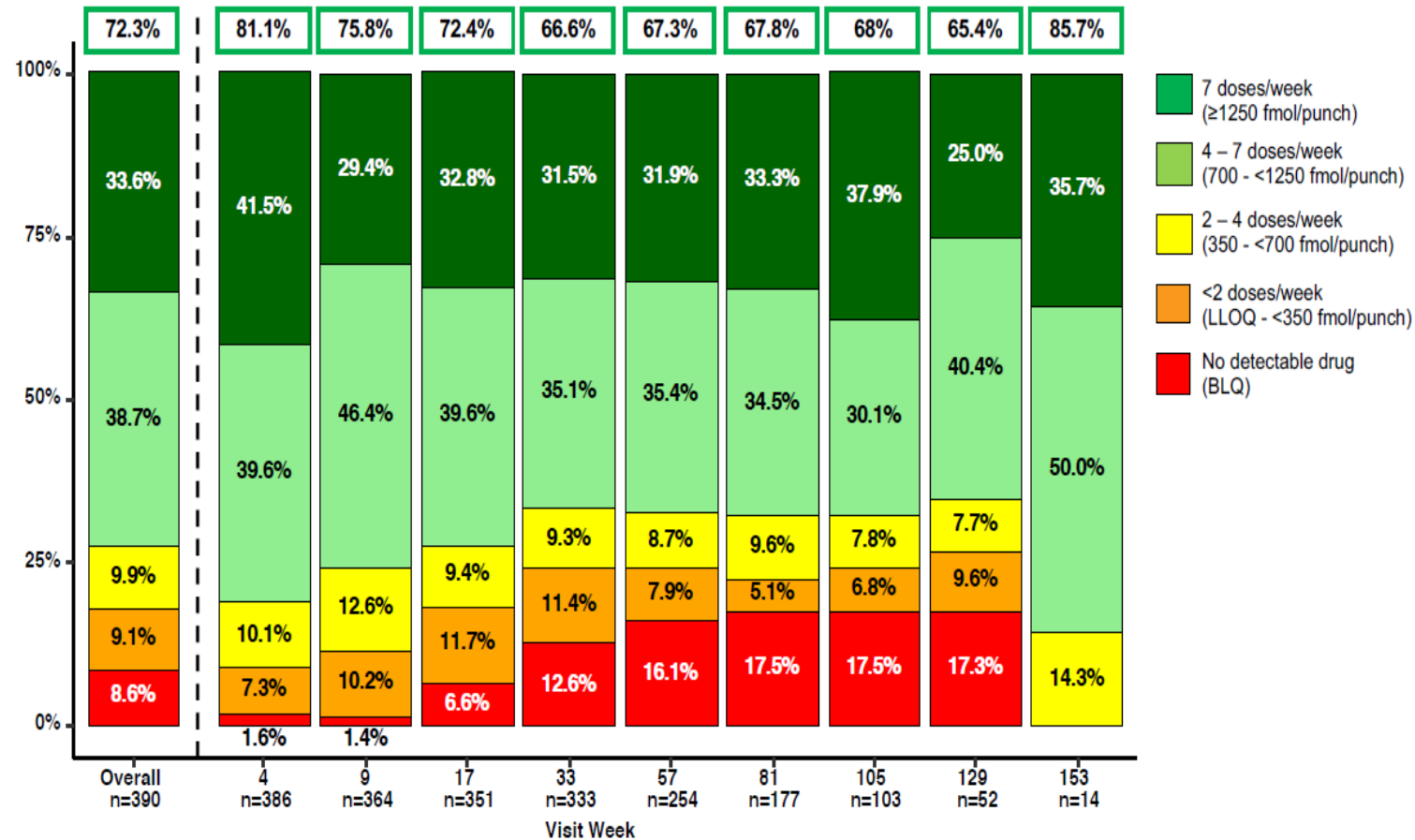
B Incident HIV Infection in Prespecified Subgroups

Subgroup	Cabotegravir no. of events/PY (incidence per 100 PY)	TDF-FTC no. of events/PY (incidence per 100 PY)	Hazard Ratio (95% CI)
Overall	13/3205 (0.41)	39/3187 (1.22)	 0.34 (0.18–0.62)

Landovitz, R.J., et al., 2021. Cabotegravir for HIV prevention in cisgender men and transgender women. *New England Journal of Medicine*, 385(7), pp.595-608.

HPTN 083: CASE-COHORT sampling of drug concentrations in TDF-FTC group

- Tenofovir diphosphate (TFV-DP) conc. assessed in DBS samples of 390 randomly selected participants in TDF-FTC arm.
- TFV-DP conc. also assessed in those with incident HIV infection (39 total), at first positive visit and at selected previous visits.
- A case-cohort sample of 425 participants (386 controls, 39 cases).



The analysis roadmap: Utilizing adherence measures in the TDF-FTC arm

- First, we categorize adherence measurements as low (< 350 fmol/punch), medium (350-700 fmol/punch), and high (≥ 700 fmol/punch).
- Then for each participant, total follow-up (F/U) time is divided into contribution to each adherence category (low, medium, high).
- For cases, events are assigned to the adherence category observed at their first positive visit.
- For controls, follow up is considered till the last adherence measurement before study-end.

Counterfactual placebo HIV incidence rate (cHIV) calculation

We pursue a Bayesian modeling technique following the approach in Glidden et al. (2021)

- Specifies Poisson likelihood for the observed data, adjusted for case cohort sampling
- Incorporates drug level data from case cohort samples in the TDF-FTC arm, with aggregate data on follow-up and HIV infections by adherence category.
- Incorporates follow-up data for non-case-cohort samples from the TDF-FTC arm, as well from the CAB-LA arm.

Glidden, David V., et al. "Using the adherence-efficacy relationship of emtricitabine and tenofovir disoproxil fumarate to calculate background HIV incidence: a secondary analysis of a randomized, controlled trial." *Journal of the International AIDS Society* 24.5 (2021): e25744.

Modeling the likelihood (brief steps)

- Counterfactual placebo infections are modeled as Poisson with rate λ_0 .
- HIV infections in CAB LA are modeled as Poisson with rate λ_1 , where $\lambda_1 = \exp\{\log(\lambda_0) + \alpha\}$.
- For those in TDF-FTC selected for case-cohort sampling,
 - HIV infections in adherence stratum l are modeled as Poisson with rate λ_{2l} , $\lambda_{2l} = \exp\{\log(\lambda_0) + \beta_l\}$, where $(l = 0, 1, 2)$ are the adherence categories.
 - Follow-up time in each adherence category are modeled as multinomial with parameter ρ_l (defined as fraction of follow-up time with drug level l).
- Those not selected for case-cohort sampling in TDF-FTC are modeled as a Poisson mixture, with mixing weights ρ_l .

Relationship between seroconversion and TFV-DP DBS levels

We can utilize knowledge from previous studies to infer on the relationship between seroconversion and TFV-DP DBS level

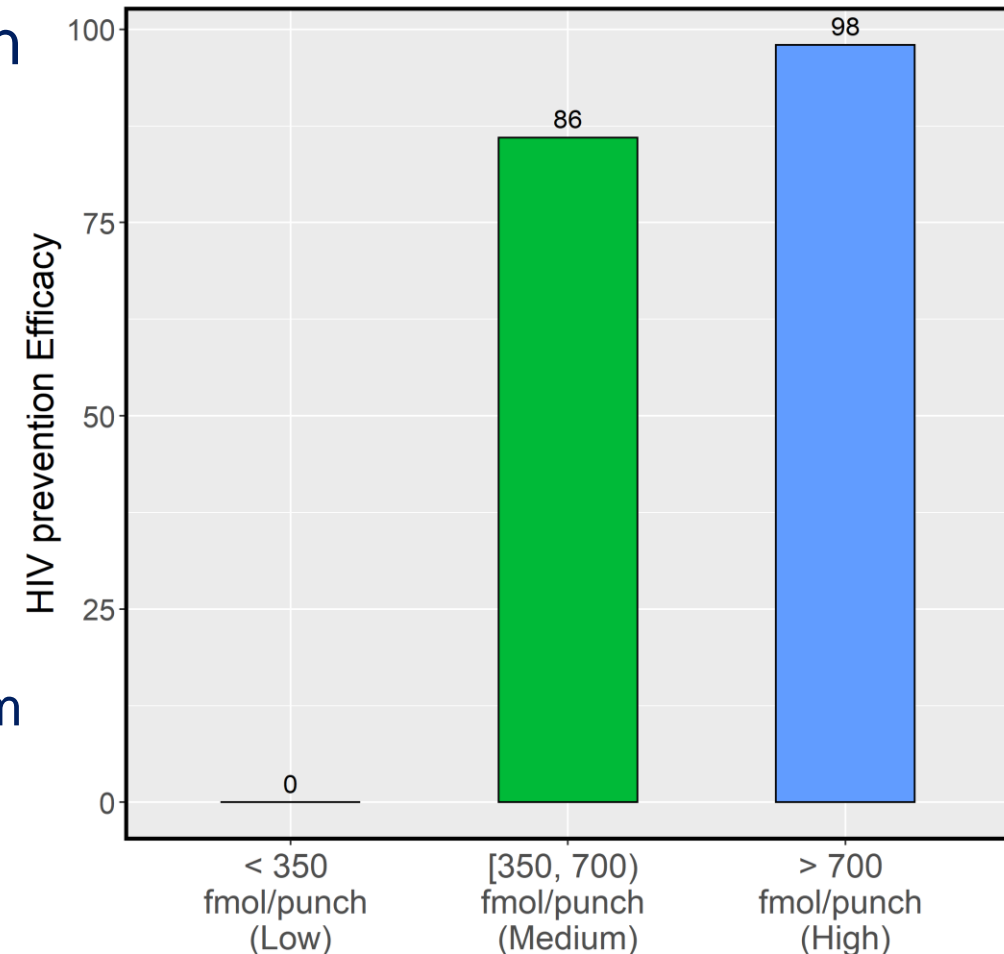
$$\beta_l = \beta_0 + \beta_1 l$$

$l = 0$ if TFV-DP DBS level < 350 fmol/punch,

$l = 1$ if TFV-DP DBS level $\in [350, 700)$ fmol/punch,

$l = 2$ if TFV-DP DBS level ≥ 700 fmol/punch

Developed from a study of TDF-FTC, by pooling data from iPrEx randomized and OLE phases (Glidden et al. 2021).



Applying these methods to data from a Hypothetical Trial (A simulation study)

- We simulate data from a hypothetical trial, inspired by what we may expect to find in HPTN 083.
 - Two-armed trial of TDF-FTC vs CAB-LA
 - Around 1952 participants in each arm.
 - Total infections: 47 (36 in TDF-FTC arm and 11 in CAB-LA arm).
 - Case-cohort sampling of 291 participants for DBS measurement.
- We demonstrate the usefulness of these methods by applying them to data from this hypothetical trial.

Inputs for the Bayesian analysis: Summary infection data

Summary data from the hypothetical trial

TDF-FTC Arm

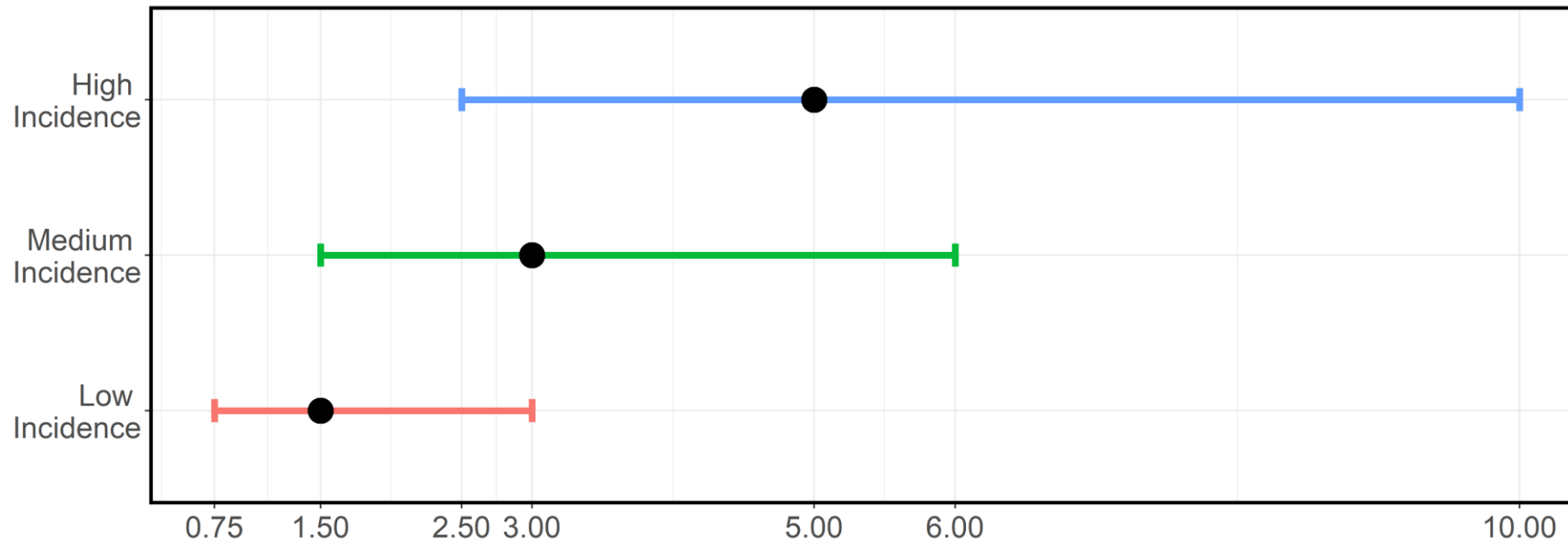
TDF-FTC CC samples				TDF-FTC non-CC samples	Total
	Adherence Categories				
N = 291	Low < 350 fmol/punch	Medium 350-700 fmol/punch	High ≥ 700 fmol/punch	N = 1661, $\tau = 1.446$	N = 1952
Person Years	99 (26.3%)	40 (10.6%)	238 (63.1%)	2402	2779
Events	34	1	1	0	36

CAB-LA Arm

CAB-LA samples	
Person Years	2712
Events	11

Inputs for the Bayesian analysis: Priors

- In Bayesian analysis, we need to specify prior (probability) distributions for the different model parameters.
- To specify prior for cHIV incidence (λ_0), we use the following strategies
 1. Flat (non-informative) prior
 2. Informative prior with log-normal distribution

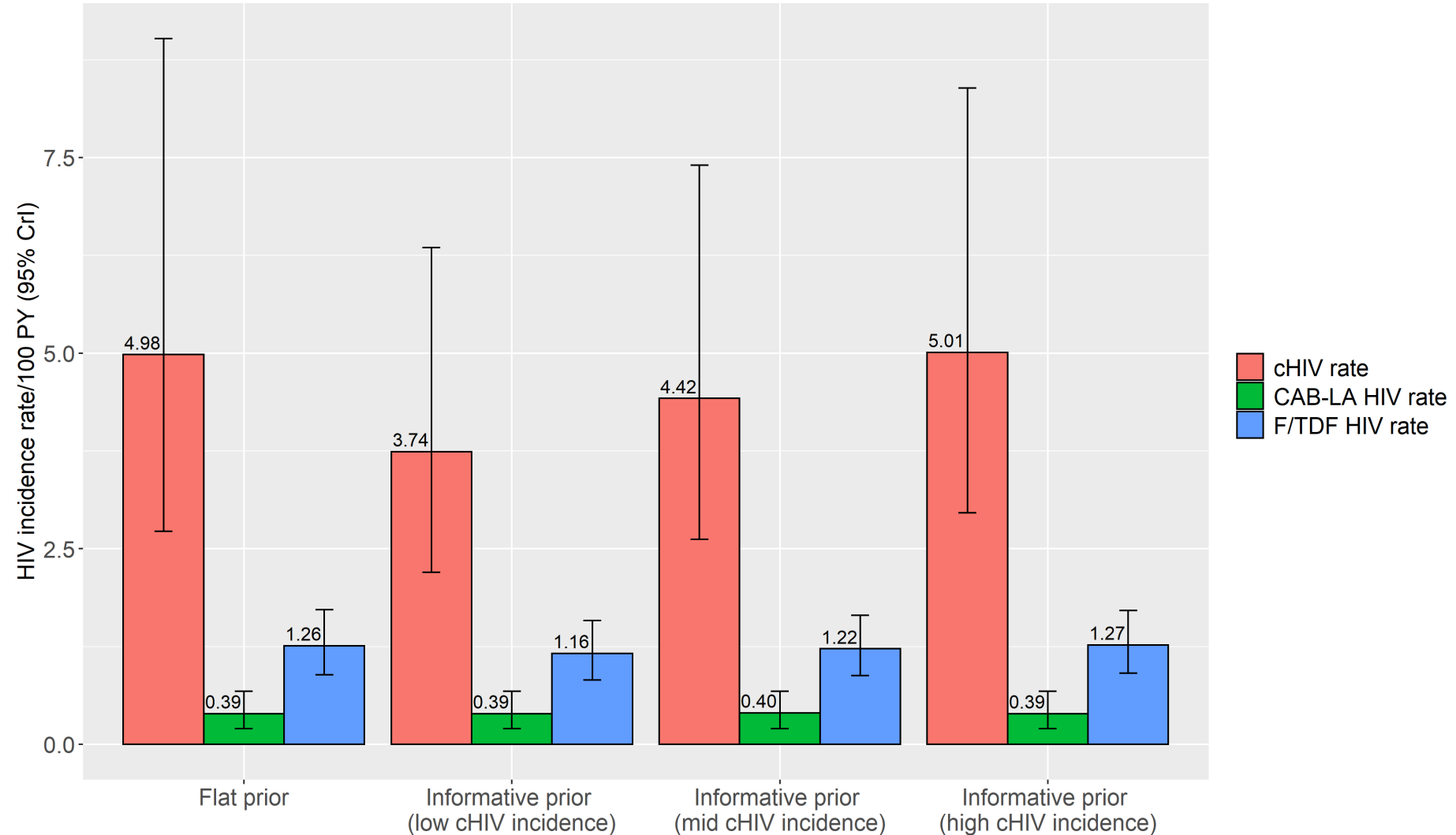


Dot whisker plot of median, 10th and 90th quantile of prior distribution

Results from the Hypothetical trial

- CAB-LA incidence rate ~ 0.39 events per 100 PY
- TDF-FTC incidence rate ~ 1.16 - 1.27 events per 100 PY
- cHIV incidence rate ~ 3.74 - 5.01 events per 100 PY

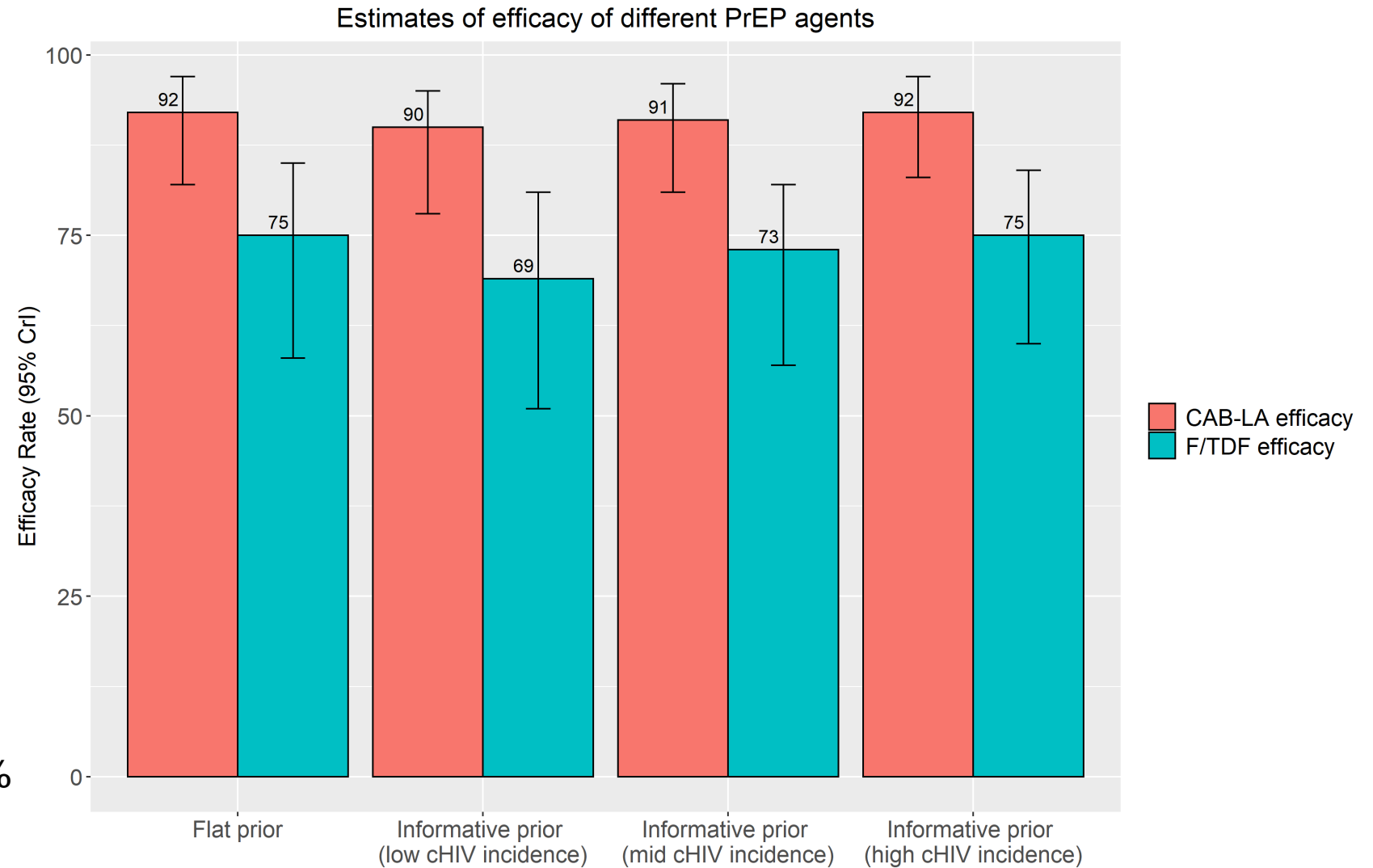
Estimates of HIV incidence without PrEP, as well as in presence of intervention



Vertical lines represent 95% credible intervals

Results from the Hypothetical trial

- CAB-LA efficacy bet. 90% - 92%
- TDF-FTC efficacy bet. 69% - 75%



Conclusions from the simulation study

- Some (expected) variability in the median cHIV incidence, based on which prior was used.
 - Unless we have an objective idea about the background incidence rate prior to the analysis, it is probably more optimal to use a flat prior.
- Estimated median incidence (and efficacy) for TDF-FTC varied slightly across priors.
 - Interdependence of model parameters
- Estimated median incidence (and efficacy) for CAB-LA were similar across priors.

Next Step

Apply these methods to adherence and infection data
from HPTN 083.

Placebo Data

- If we have follow-up data collected in a non-PrEP period, we can use that to enhance information available to estimate the counterfactual placebo HIV incidence.
 - It may be possible to borrow information from other trials that share similar subpopulations, similar geographical locations, etc.

Heterogeneity across (latent) TDF-FTC adherence categories

- We can also allow for varying (counterfactual) incidence rate heterogeneity across (latent) TDF-FTC adherence categories.

Possible extensions

Addition of individual level data

- Leverage detailed individual level information if available in the trial
 - To capture subgroup effect: HIV incidence can vary by factors such as age, cohort, race, and location.
 - To adjust for population differences when borrowing information from other studies (for example, while importing placebo data from other trials).
 - To use participant characteristics to build a predictive model for adherence and impute adherence profiles for non-case-cohort TDF-FTC participants.

References

1. Landovitz, R.J., Donnell, D., Clement, M.E., Hanscom, B., Cottle, L., Coelho, L., Cabello, R., Chariyalertsak, S., Dunne, E.F., Frank, I. and Gallardo-Cartagena, J.A., 2021. Cabotegravir for HIV prevention in cisgender men and transgender women. *New England Journal of Medicine*, 385(7), pp.595-608.
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Thank you

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