Estimating counterfactual background HIV incidence and cabotegravir efficacy versus a counterfactual placebo in HPTN 083 using Bayesian modeling

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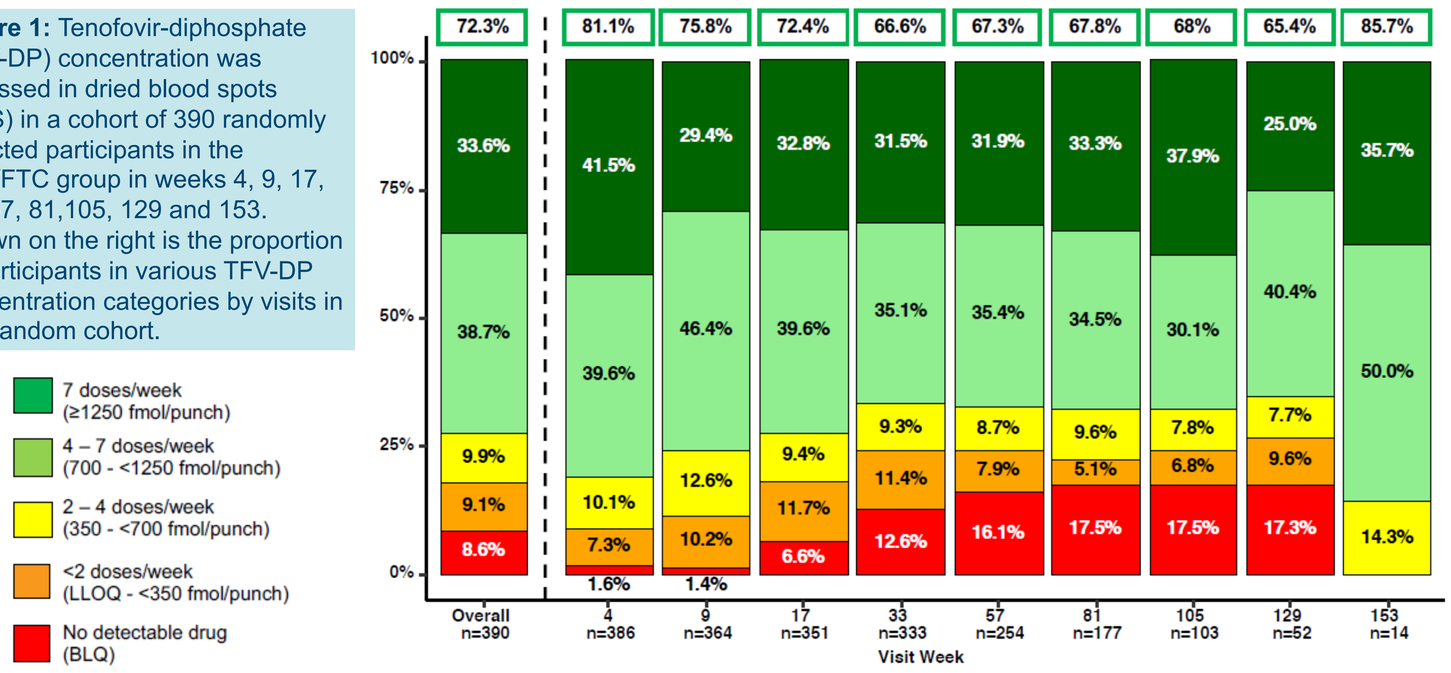
BACKGROUND

- Long-acting injectable cabotegravir (CAB-LA) reduced HIV incidence by 66% compared to daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) among men who have sex with men (MSM) in the HIV Prevention Trials Network (HPTN) 083 study, a multi-site global phase 3 registrational trial.
- Because HPTN 083 did not include a placebo group, the background HIV incidence (bHIV) in the counterfactual non-PrEP population (herein referred to as the counterfactual bHIV) cannot be observed directly. However counterfactual bHIV is essential for estimating CAB-LA efficacy versus no PrEP and for clinical messaging and future comparative prevention trial design, especially at the regional level.
- We used a Bayesian modeling approach to estimate the overall and region-specific counterfactual bHIV and the overall CAB-LA efficacy versus a counterfactual placebo using data from the blinded follow-up period of HPTN 083, including
  - Number of incident HIV infections and person-time contributed.
  - Measured drug levels in the TDF/FTC group (Figure 1).

Figure 1: Tenofovir-diphosphate (TFV-DP) concentration was assessed in dried blood spots (DBS) in a cohort of 390 randomly selected participants in the TDF/FTC group in weeks 4, 9, 17, 33, 57, 81,105, 129 and 153. Shown on the right is the proportion of participants in various TFV-DP concentration categories by visits in this random cohort.



In HPTN 083, the counterfactual background HIV incidence was **4.4** infections per 100 person-years.
Assignment to long-acting injectable cabotegravir (CAB-LA) was associated with a **90.5% reduction in HIV incidence** versus no PrEP use.

METHODS

- Tenofovir diphosphate (TFV-DP) concentrations in dried blood spots (DBS) were assessed for 10% of randomly selected TDF/FTC group participants throughout the follow-up (Figure 1), as well as in all 39 TDF/FTC group seroconverters at the first visit they were found HIV positive and at any previous visits where DBS were collected. TFV-DP levels were categorized into three adherence categories (Table 1).
- We extended a Bayesian model developed by Glidden et al. to analyze the TFV-DP concentration data from the TDF/FTC group and the HIV incidence data from both study groups at the regional level in the blinded phase of HPTN 083.
- The model used a prior distribution derived from published relationships between TFV-DP and HIV prevention efficacy in the iPrEx Study Open Label Extension(OLE) (Table 1) and allowed for different counterfactual bHIV and TDF/FTC adherence patterns by region (Box 1).
- Posterior estimates of region-specific and overall counterfactual bHIV and CAB-LA efficacy versus counterfactual placebo were obtained via Markov chain Monte Carlo (MCMC).

Glidden et al. 2021 doi: 10.1002/jia2.25744; Grant et al. 2010 doi: 10.1056/NEJMoa1011205

Box 1. Mathematical representation of the Bayesian model.

- In an at-risk population not on PrEP in region j , we assume HIV infections occur following a Poisson process, where the time to infection follows an exponential distribution with a constant region-specific hazard rates $\lambda_{bHIV,j}$:

$$\lambda_{bHIV,j} = exp(\alpha_j)$$
$$\alpha_j \sim Normal\ (\mu_\alpha, \sigma_\alpha)$$

- The region-specific incident infections in the CAB-LA group of the trial follow a Poisson distribution:

$$d_{CAB,j} \sim Pois\ (\lambda_{CAB,j} \times T_{CAB,j})$$
$$\lambda_{CAB,j} = exp(\alpha_j + \beta_1)$$

where $T_{CAB,j}$ is the total person-years (PY) in the CAB-LA group at region j.

- As such, the efficacy of the CAB-LA against placebo can be estimated as:

$$\delta_{CAB,bHIV} = 1 - exp(\beta_1)$$

- Among the cases and the random cohort (i.e., case-cohort) in the TDF/FTC group at region j, the total number of infections in each adherence category $d_{TDFC,aj}$ have the following distribution:

$$d_{TDFC,aj} \sim Pois\ (\lambda_{TDF,aj} \times T_{TDFC,aj})$$

where:

  - $\lambda_{TDF,aj} = exp(\alpha_j + \beta_2 + \beta_3 \times (a-1))$ is the hazard rate for adherence category a.
  - $T_{TDFC,aj}$ is the total PY in adherence category a within case-cohort.

- The total PY in the three adherence categories follow a multinomial distribution:

$$[T_{TDFC,1j}, T_{TDFC,2j}, T_{TDFC,3j}] \sim Multinomial\ (\rho_{1j}, \rho_{2j}, \rho_{3j})$$
$$[\rho_{1j}, \rho_{2j}, \rho_{3j}] \sim \text{Dirichlet}\ (\mu_{\rho 1}, \mu_{\rho 2}, \mu_{\rho 3})$$

where:

  - ρ_{aj} is the region-level expected proportion of total PY in adherence category a at region j.
  - $\frac{\mu_{\rho a}}{\sum_a \mu_{\rho a}}$ is the overall expected proportion of total PY in adherence category a in the TDF/FTC group.

- The number of infections among people in the TDF/FTC group who were not cases nor selected to be in the random cohort (i.e., non-case-cohort) at region j, $d_{TDFN,j}$, which equals 0, follows:

$$d_{TDFN,j} \sim Pois\ (\mu_{TDFN,j})$$
$$\mu_{TDFN,j} = -m_j\ log(k_{1j} + k_{2j} + k_{3j})$$
$$k_{aj} = exp(-\lambda_{TDF,aj} \times \tau_j) \times \rho_{aj}$$

where:

  - m_j = the total number of people in the non-case-cohort.
  - $t_{TDFN,j}$ = the total PY in the non-case-cohort.
  - $\tau_j = \frac{t_{TDFN,j}}{m_j}$ = the average total PY per person in the non-case-cohort.

- The priors for β_2 and β_3 were specified based on iPrEx OLE (Table 1)

$$\beta_2 \sim Normal(0.176, 0.230)$$
$$\beta_3 \sim Normal\ (-2.14, 0.875)$$

- Diffuse priors were specified for $\beta_1, \mu_\alpha, \sigma_\alpha$ and $\mu_{\rho a}$.

Table 1. Adherence categories, the corresponding TFV-DP levels, and the published relationships between TFV-DP and HIV prevention efficacy in the iPrEx Study Open Label Extension (OLE).

Adherence category	TFV-DP levels (fmol/punch)	Average F/TDF intake over previous month (tablets/week)	Estimates from iPrEx OLE		Efficacy vs. placebo in the model $\left(1 - \frac{\lambda_{\text{TDF,a}}}{\lambda_{bHIV}}\right)$
			Relative risk vs. placebo (95% CI)	Efficacy vs. placebo (%)	
Low ($a = 1$)	<350	<2	1.19 (0.76, 1.87)	0	$\exp(\beta_2)$
Medium ($a = 2$)	350 – 700	2 to 3	0.14 (0.02, 0.76)	86	$\exp(\beta_2 + \beta_3)$
High ($a = 3$)	≥700	≥4	0.02 (0.00, 0.49)	98	$\exp(\beta_2 + \beta_3 \times 2)$

RESULTS

- The overall counterfactual bHIV without PrEP was **4.4** infections per 100 person-years (95% credible interval CrI: 1.4 – 13.9), ranging from 3.7 in the US (95% CrI: 1.9 – 6.9) to 6.1 in Africa (95% CrI: 1.7 – 18.9) (Table 2).
- **Assignment to CAB-LA** was estimated to reduce the overall HIV incidence by **90.5%** versus no PrEP use (95% CrI: 79.2 – 95.7%), ranging from 82.1% in Africa (95% CrI: 34.7 – 94.2%) to 92.9% in the US (95%CrI: 86.5 – 96.2%) (Table 2).

Table 2. The posterior medians and 95% credible intervals for counterfactual background HIV incidence (bHIV) and reduction in incidence by CAB-LA (as-used) by region. The overall reduction in incidence is estimated using a parameter in the Bayesian model, and the region-level reduction in incidence is calculated as 1-(observed CAB-LA incidence/estimated counterfactual bHIV) for each region.

Region	Estimated counterfactual bHIV (per 100 person-years)	Estimated reduction in incidence by CAB-LA (as-used)
Africa	6.1 (1.7, 18.9)	82.1% (34.7%, 94.2%)
Asia	4.2 (1.7, 9.6)	91.7% (79.1%, 96.3%)
Latin America	4.3 (2.1, 8.5)	86.2% (71.6%, 93.0%)
US	3.7 (1.9, 6.9)	92.9% (86.5%, 96.2%)
Overall	4.4 (1.4, 13.9)	90.5% (79.2%, 95.7%)

CONCLUSIONS

- These findings suggest high CAB-LA efficacy versus no PrEP and add to the data from HPTN 083 which showed high efficacy versus oral PrEP, supporting CAB-LA's use as a potent biomedical prevention option in diverse regions.
- The estimates align with indirect comparisons from prior CAB-LA trials, reinforcing confidence in the high preventive efficacy of CAB-LA despite the absence of placebo arms.
- These efficacy estimates were based on as-used CAB-LA in the trial, not perfect adherence to the prescribed regimen.

ACKNOWLEDGMENTS

We would like to thank Dr. Dave Glidden for his helpful discussions on the Bayesian model. We would also like to thank the HPTN 083 study team and trial participants, without whom this work would not be possible.

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Overall support for the HIV Prevention Trials Network (HPTN) is provided by the National Institute of Allergy and Infectious Diseases (NIAID), Office of the Director (OD), National Institutes of Health (NIH), National Institute on Drug Abuse (NIDA), the National Institute of Mental Health (NIMH), and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) under Award Numbers UM1AI068619 (HPTN Leadership and Operations Center), UM1AI068617 (HPTN Statistical and Data Management Center), and UM1AI068613 (HPTN Laboratory Center).

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Presented at AIDS 2026,
The 26th International AIDS Conference
Rio de Janeiro, Brazil
Poster Number: WEPEC190

AIDS 2026
26–31 July