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Efficacy estimates of oral pre-exposure prophylaxis for HIV prevention in cisgender women with partial adherence

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Pre-exposure prophylaxis (PrEP) with tenofovir (TFV) disoproxil fumarate and emtricitabine administered orally daily is effective in preventing human immunodeficiency virus (HIV) acquisition in both men and women with sufficient adherence; however, the adherence–efficacy relationship in cisgender women has not been well established. We calculated the adherence–efficacy curve for cisgender women by using HIV incidence and plasma TFV concentration data from three trials (FEM-PrEP, VOICE and Partners PrEP). We imputed TFV diphosphate (TFV-DP) concentrations, a measure of long-term adherence, from TFV quantification by using data from the HIV Prevention Trials Network 082 study, which measured both TFV-DP and TFV concentrations. Two, four and seven pills per week reduced HIV incidence by 59.3% (95% credible interval (CrI) 29.9–95.8%), 83.8% (95% CI 51.7–99.8%) and 95.9% (95% CI 72.6–100%), respectively. Our adherence–efficacy curve can be validated and updated by HIV prevention studies that directly measure TFV-DP concentrations. The curve suggests that high adherence confers high protection in cisgender women. However, the lower efficacy with partial adherence highlights the need for new PrEP products and interventions to increase adherence.

Pre-exposure prophylaxis (PrEP) with tenofovir (TFV) disoproxil fumarate and emtricitabine (TDF/FTC) administered orally daily is safe and highly effective in preventing human immunodeficiency virus (HIV) acquisition[1–4]. However, some studies of TDF/FTC PrEP in cisgender women have shown little or no efficacy, attributed to low product adherence[5,6]. Achieving high protection levels requires regular pill-taking during periods of exposure. Adherence in PrEP users is typically quantified through measurements of intraerythrocytic TFV diphosphate (TFV-DP) or plasma TFV concentrations[7,8]. TFV-DP has a half-life of 17 days when measured in red blood cells through dried blood spot (DBS) testing or 4–5 days when measured in peripheral blood mononuclear cells. TFV-DP concentrations can be used to estimate the average pill-taking frequency over the previous 1–2 months. By contrast, TFV has a relatively short half-life of approximately 3 days; therefore,

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its quantification can indicate whether a dose was taken within the last week but is not informative of adherence before the last dose.

In men and transgender women who have sex with men (MSM/TGW), the relationship between PrEP adherence and PrEP efficacy has been defined by comparing the TFV-DP concentrations in individuals newly diagnosed with HIV infection and those without HIV infection to the TFV-DP concentrations in individuals with known adherence to TDF/FTC PrEP from directly observed dosing[7,9]. These methods suggest that partial adherence leads to reductions in HIV incidence of 76% (95% confidence interval (CI) 56–96%), 96% (95% CI 90% to >99%) and 99% (95% CI 96% to >99%) with two, four and seven pills per week, respectively, when the TFV-DP concentration is measured in peripheral blood mononuclear cells and 84% (95% CI 12–99%) with two to three pills per week and >99% (95% CI 75% to >99%) with four to six pills per week when the TFV-DP concentration is measured in DBSs[7,9]. Repetition of this analysis in cisgender women (henceforth 'women') has been complicated by the lack of large placebo-controlled efficacy trials measuring TFV-DP concentrations. A recent analysis using data from the HIV Prevention Trials Network 084 study (HPTN 084, LIFE Study), which used TDF/FTC as an active control to assess the efficacy of cabotegravir as a long-acting PrEP agent, showed reductions in HIV incidence of 80% (95% CI 32–97%), 88% (95% CI 43–99%) and 99% (95% CI 0–99%) in participants taking two to three, four to six and seven pills per week, respectively, relative to those with no quantifiable TFV-DP; however, as the study had no placebo-control arm, these estimates may be confounded by different rates of HIV exposure between adherent and nonadherent participants[10,11].

Randomized clinical trials of PrEP that enrolled women have had mixed results due to variable adherence in the trial cohorts. The Partners PrEP and Botswana TDF2 studies reported PrEP efficacy rates of 66% (95% CI 28–84%) and 49.4% (95% CI −21.1% to 80.1%), respectively, among women[3,4]. In Partners PrEP, quantifiable plasma TFV was associated with a 94% (95% CI 41–99%) reduction in HIV incidence in women[12]. By contrast, in FEM-PrEP (PrEP Trial for HIV Prevention Among African Women), HIV prevention with TDF/FTC showed only 6% efficacy (95% CI −52% to 41%), although this improved to 18% (95% CI −36% to 51%) when follow-up time intervals during which PrEP was unavailable to the participant, either due to a missed visit or PrEP discontinuation, were excluded[5]. The VOICE (Vaginal and Oral Interventions to Control the Epidemic) trial reported a similarly low efficacy of −4.4% (95% CI −49% to 27%) for TDF/FTC[6]. Adherence, measured according to plasma TFV concentrations, was low in both the FEM-PrEP and VOICE studies; only 21% of participants newly diagnosed with HIV infection in FEM-PrEP had quantifiable TFV at the first visit after acquisition and only 37% of those newly diagnosed with HIV infection in the oral arm of VOICE had quantifiable TFV at any visit. Participants without HIV infection had quantifiable plasma TFV in 35% and 52% of samples in FEM-PrEP and VOICE, respectively, although the difference in concentration between cases and controls was not significant in either study.

Estimates of the association between PrEP adherence and PrEP efficacy are vital for informed use of PrEP and projecting its population impact. Given the lack of data on the relationship between product adherence and efficacy in women, researchers have either projected impact by assuming comparable overall adherence and effectiveness to those observed in Partners PrEP and TDF2 (refs. 13–17), assumed 'all-or-nothing' adherence and an efficacy based on the protection afforded in individuals with quantifiable plasma TFV[18–21], or a combination of both[22]. The former approach does not account for the variability seen in PrEP adherence and persistence among different populations, whereas the latter approach may not properly account for the partial protection afforded by imperfect adherence.

We combined HIV incidence and plasma TFV concentration data from three efficacy studies that enrolled women (FEM-PrEP, VOICE and Partners PrEP) with pharmacological data (TFV and TFV-DP concentrations) from another study in women (HPTN 082) to define the relationship between adherence to daily oral administration of TDF/FTC and its efficacy in reducing HIV incidence in sub-Saharan African women[23].

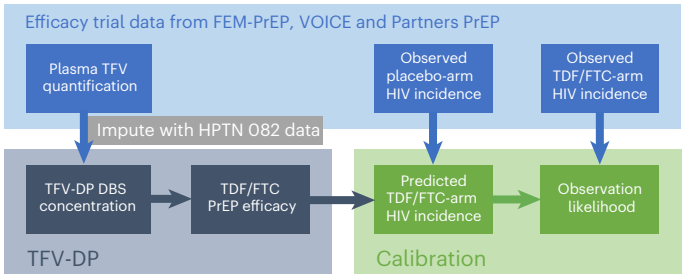

Fig. 1 | Flowchart of TDF/FTC efficacy estimation. Our method relied on data from three randomized clinical trials (FEM-PrEP, VOICE and Partners PrEP) and TFV-DP measurements from HPTN 082. For each trial, we first imputed TFV-DP measurements using data from HPTN 082 and then computed TDF/FTC efficacy using the imputed values. Next, we combined the computed efficacy with the placebo-arm HIV incidence from each trial to predict the HIV incidence stratified by TFV detectability. Finally, this HIV incidence was compared to the observed incidence to estimate the likelihood of the observation. Using this likelihood function, we calibrated the model through Markov chain Monte Carlo (MCMC) methods.

We calibrated an adherence–efficacy curve mapping TFV-DP concentrations in DBSs to the reduction in HIV incidence relative to placebo in women (Fig. 1). We used data from three randomized, placebo-controlled efficacy studies of TDF/FTC in adult women in sub-Saharan Africa (FEM-PrEP, VOICE and Partners PrEP). These studies did not measure TFV-DP concentrations but assessed adherence through plasma TFV quantification. We imputed TFV-DP values in the three efficacy studies by using data from HPTN 082 (a TDF/FTC implementation study in African women that measured both plasma TFV and TFV-DP concentrations). We fit the adherence–efficacy curve to the number of new HIV diagnoses with and without quantifiable plasma TFV in the active arms of the three studies, accounting for the difference in the placebo-arm HIV incidence in each study (Supplementary Fig. 1). As a sensitivity analysis, we considered three functional forms of the adherence–efficacy curve, each making different assumptions. We also considered models that directly predict the active-arm HIV incidence from plasma TFV data without imputation, but these models performed slightly worse according to the deviance information criterion (Supplementary Table 1). For more details, please see Methods.

We next estimated the reduction in HIV incidence imparted by TDF/FTC as a function of TFV-DP DBS concentrations measured in femtomoles per punch (that is, the standardized paper disc used in DBS assays). In our base model, we assumed that (1) the HIV incidence among individuals not adherent to TDF/FTC was the same as that in the placebo arm and (2) the HIV incidence approaches zero with increasing TDF/FTC use (Fig. 2). Under these assumptions, we estimated that TFV-DP DBS concentrations of 350, 700 and 1,250 fmol per punch were associated with reductions in HIV incidence of 53.8% (95% CrI 26.1–94.1%), 78.7% (95% CrI 45.3–99.7%) and 93.7% (95% CrI 66.0–100.0%), respectively.

These values were robust to the model assumptions (Extended Data Table 1). Using our first alternative model, which allowed the HIV incidence among individuals with no adherence to TDF/FTC to differ from the incidence in the placebo group (Extended Data Fig. 1), we estimated that TFV-DP DBS concentrations of 350, 700 and 1,250 fmol per punch were associated with reductions in HIV incidence of 48.4% (95% CrI 19.4–91.5%), 75.7% (95% CrI 44.8–99.5%) and 92.7% (95% CrI 66.6–100.0%), respectively. Using our second alternative model, which allowed the maximum efficacy to be <100% (Extended Data Fig. 2), we estimated that TFV-DP DBS concentrations of 350, 700 and 1,250 fmol per punch were associated with reductions in HIV incidence of 52.4%

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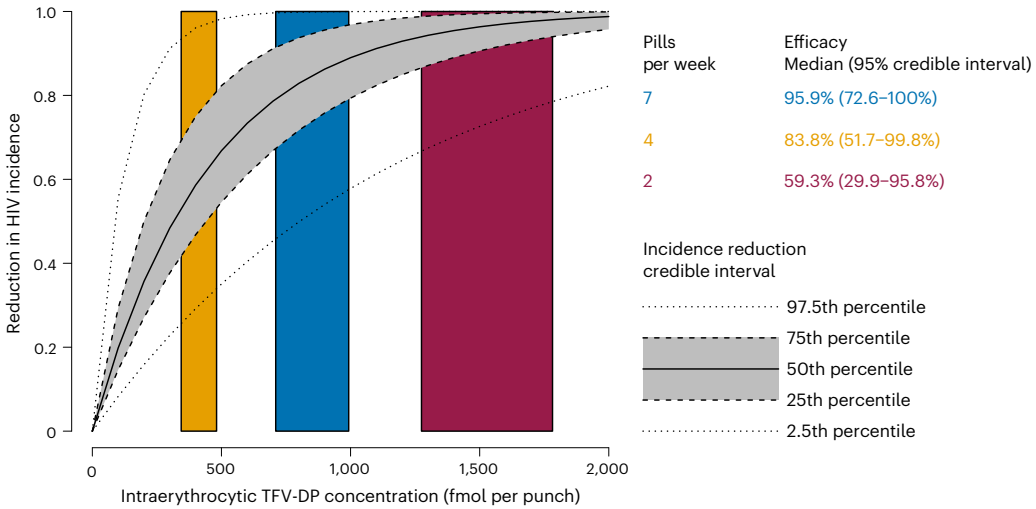

Fig. 2 | Efficacy of TDF/FTC according to TFV-DP measurements. The reduction in HIV incidence is shown as a function of TFV-DP concentrations in DBSs according to model h_1. The gray ribbon indicates the IQR. Dashed lines indicate the 95% credible interval. Colored rectangles represent the IQR of TFV-DP measurements associated with pill-taking frequencies of two, four and seven pills per week derived from directly observed dosing[8].

(95% CrI 28.5–83.8%), 76.8% (95% CrI 48.6–97.1%) and 92.0% (95% CrI 67.7–99.8%), respectively.

Finally, we estimated the reduction in HIV incidence associated with specific weekly pill-taking frequencies. We sampled across the range of TFV-DP DBS measurements by dose as established using directly observed dosing[8]. Assuming a log-normal distribution, the TFV-DP DBS concentrations were 407 (interquartile range (IQR) 344–481), 840 (IQR 710–993) and 1,507 (IQR 1,275–1,782) fmol per punch for two, four and seven pills per week, respectively, in women of African descent (Fig. 2, colored rectangles). The reduction in HIV incidence with each dose, based on all available data from the efficacy trials, was estimated by averaging the adherence–efficacy curve across the associated TFV-DP concentration range estimated from directly observed dosing.

Using the base model, as defined above, we estimated that two, four and seven pills per week were associated with reductions in HIV incidence of 59.3% (95% CrI 29.9–95.8%), 83.8% (95% CrI 51.7–99.8%) and 95.9% (95% CrI 72.6–100%), respectively. These estimates were again robust to the model structure (Extended Data Table 1). Using our first alternative model (h_2), we estimated that two, four and seven pills per week were associated with reductions in HIV incidence of 54.3% (95% CrI 25.3–93.8%), 81.6% (95% CrI 52–99.7%) and 95.3% (95% CrI 72.8–100%), respectively (Extended Data Fig. 1). Using our second alternative model (h_3), we estimated that two, four and seven pills per week were associated with reductions in HIV incidence of 57.8% (95% CrI 32.6–87.3%), 82% (95% CrI 54.9–98.2%) and 94.5% (95% CrI 72.7–99.9%), respectively (Extended Data Fig. 2).

Oral PrEP with TDF/FTC reduces the incidence of HIV infection in both MSM/TGW and women with high adherence. The relationship between the number of pills taken per week and the efficacy of PrEP has been quantified for MSM/TGW by using TFV-DP concentrations in DBSs as an objective surrogate measure of PrEP adherence. Recently, data have emerged on the relationship between adherence and efficacy among women. We calibrated an adherence–efficacy curve for women by combining (1) HIV incidence and plasma TFV quantification data from three placebo-controlled efficacy trials in women with (2) pharmacological data from HPTN 082 on the relationship between plasma TFV and TFV-DP concentrations in DBSs. The framework allows for easy updates when new evidence becomes available.

We estimated that women with TFV-DP concentrations associated with pill-taking frequencies of two, four and seven pills per week had 59%, 84% and 96% lower HIV incidence, respectively, than those not taking PrEP. These reductions are only slightly lower than those estimated in MSM/TGW at the same levels of adherence[7,9], suggesting that the lower observed efficacy in PrEP trials in women is primarily due to adherence. This is consistent with subgroup analyses in Partners PrEP and HPTN 084 that found high effectiveness in women with quantifiable plasma TFV and TFV-DP concentrations consistent with taking two or more pills per week[11,12], as well as with a recent meta-analysis that found high levels of protection in women consistently taking four to six pills per week in PrEP demonstration projects[24].

On an individual level, the number of pills taken per week does not uniquely determine the reduction in HIV incidence conferred. The efficacy of TDF/FTC relies on accumulation of the active metabolites TFV-DP and FTC triphosphate in the target cells of HIV, systemically and in mucosal tissues (for exposures through sexual contact) or in the blood (for exposures through the use of injection drugs)[25–27]. Pharmacokinetic modeling of TDF/FTC predicts that active metabolites reach protective levels in colorectal tissues and peripheral blood with only two weekly doses, whereas three doses may be required to reach protective levels in the female genital tract. Therefore, both weekly adherence and exposure route likely have important roles in determining the efficacy of TDF/FTC. Consistent with our findings, these models predict greater 'forgiveness' for missed doses in MSM/TGW, in whom exposure is likely to be in colorectal tissues, than in women, in whom exposure is likely to be in the female genital tract[27,28]. Currently, on-demand '2–1–1' PrEP consisting of two pills before and two pills after sex is not recommended for women owing to a longer interval before detection and lower concentrations in the female genital tract, although there have been no 2–1–1 efficacy trials in women[27,29]. Although our results indicate that four weekly pills can provide upward of an 80% reduction in HIV incidence, we did not investigate the impact of pill-taking timing relative to sexual acts. Women taking on-demand PrEP will likely have better protection than predicted by our curve as effective use requires high adherence only during periods of exposure; thus, individuals with infrequent exposure may be highly protected despite having low TFV-DP concentrations (a measure of cumulative adherence). Pharmacokinetic modeling will be crucial for projecting the efficacy of TDF/FTC in nondaily PrEP regimens and in understudied populations such as heterosexual men and people who inject drugs[28].

Our adherence–efficacy curve will aid the evaluation of new PrEP products. Daily oral TFV alafenamide fumarate, long-acting injectable cabotegravir and long-acting oral lenacapavir are being evaluated in superiority and/or noninferiority trials against an active-control regimen of daily oral TDF/FTC, given its high effectiveness. The preventive

efficacy of these new products can only be derived from counterfactual placebo estimates of incidence[30]. Such counterfactual placebo estimates often rely on baseline estimates of recent infection in the enrolled population[31], markers of HIV exposure (for example, sexually transmitted infections)[32] or propensity scores[33]. For MSM/TGW, counterfactual estimates can also be constructed from the active placebo arm by using the adherence–efficacy relationship[34]; our work will allow that method to be extended to studies on women. In brief, (1) the incidence in the TDF/FTC arm should be the product of the incidence in the counterfactual placebo arm and the hazard ratio (1 – efficacy) due to product use; (2) this hazard ratio can be estimated using the TFV-DP measurements from a representative sample of individuals in the TDF/FTC arm; and (3) the incidence in the counterfactual placebo arm can then be estimated by dividing the incidence in the TDF/FTC arm by the calculated hazard ratio.

Our adherence–efficacy curve can also be incorporated into projections of PrEP impact. Mathematical models of PrEP-based initiatives aimed at reducing HIV incidence rely on assumptions about efficacy in the target population[13–22]. In both controlled trials and demonstration projects, women who take PrEP often have only partial adherence[11,23,24]. Our curve will allow future modeling studies of PrEP to (1) account for HIV prevention among women with partial adherence and (2) estimate the impact of interventions intended to increase PrEP adherence in this population.

This work has two major limitations. First, the efficacy trials in women did not collect TFV-DP DBS measurements from participants, so we relied on data from HPTN 082 to impute TFV-DP measurements from plasma TFV quantification. This assumes the same distribution of TFV-DP concentrations conditional on plasma TFV concentrations. Pill-taking patterns may differ across populations owing to geographic, temporal or demographic factors. In this case, the population from HPTN 082 is comparable to the populations in the efficacy studies with regard to region and time but is younger. Second, there is evidence that trial participants may adjust TDF/FTC usage depending on HIV exposure[35,36]; however, we assumed uniform exposure at all levels of TDF/FTC usage. Incorporating self-reported behavioral data from study participants could identify and correct this potential bias.

Increased PrEP uptake is an important part of ending the HIV epidemic and will likely depend on the availability of multiple PrEP options[37]. Providing the best PrEP option for individuals in high-incidence populations requires knowledge of preventive efficacy against HIV at different levels of adherence. Building on previous work that showed the high efficacy of oral PrEP among women with quantifiable plasma TFV[12], we developed an adherence–efficacy curve based on TFV-DP measurements to better quantify the benefits of HIV prevention for women at all levels of TDF/FTC adherence. Our results indicate that the relationship between PrEP adherence and PrEP efficacy in MSM/TGW and women may be more similar than has been appreciated.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-023-02564-5.

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Methods

TFV-DP models for preventive efficacy estimation

We assumed that the protection afforded by TDF/FTC against HIV acquisition could be predicted based on the TFV-DP DBS measure X_D through a TFV-DP model, $f(X_D)$. Following previous work, we assumed that f is an exponentially decaying function and considered three different models relating HIV incidence reductions to TFV-DP DBS concentrations (Extended Data Fig. 3)[7]. Our base model, f_1, assumed that individuals with no quantifiable TFV-DP have the same HIV incidence as individuals from the trial population concurrently randomized to placebo and that the HIV incidence approaches zero with increasing TFV-DP drug concentrations. The second model, f_2, allowed individuals with low TFV-DP concentrations to have greater or lower HIV incidence than individuals on placebo, reflecting findings from prior studies. For example, MSM/TGW with the lowest PrEP adherence in the iPrEx open-label extension study had higher HIV incidence than those not taking PrEP[7], but women have been found to decrease their pill-taking during periods of low potential exposure[35,36]. The third model, f_3, allowed for the possibility that even high PrEP adherence may not lead to complete protection, so efficacy approaches k_3 with full adherence.

$$
\begin{aligned}
f(X_D, \mathbf{k}) &\equiv \frac{\text{Hazard rate in individuals on PrEP with TFV-DP concentration of } X_D}{\text{Hazard rate in off-PrEP individuals}} \\
f_1(X_D|k_1) &= \exp(-X_D \ln 2/k_1) \\
f_2(X_D|k_1, k_2) &= \exp(-X_D \ln 2/k_1)\, k_2 \\
f_3(X_D|k_1, k_3) &= \exp(-X_D \ln 2/k_1)(1 - k_3) + k_3
\end{aligned}
$$

k_1, k_2 and k_3 are free parameters that need to be estimated. For each model, the parameter k_1 represents the IC_{50}, that is, the concentration of TFV-DP required to achieve half the maximum theoretical reduction in HIV incidence. That is

$$
f(0) - f(k_1) = \left(f(0) - \lim_{X_D \to \infty} (f(X_D))\right)/2
$$

Imputation of TFV-DP values from plasma detectability

The three randomized, placebo-controlled PrEP-efficacy trials in women—FEM-PrEP (ClinicalTrials.gov identifier: NCT00625404), Partners PrEP (NCT00557245) and VOICE (NCT00705679)—measured product adherence through the detection of plasma TFV concentrations, which reflect pill-taking patterns within the last 2 weeks. Each trial dichotomized plasma TFV concentrations according to a different quantification threshold (Extended Data Table 2), ranging from >0.3 ng ml^{-1} at any visit to >10 ng ml^{-1} at a given visit. In contrast, HPTN 082 (NCT02732730) longitudinally measured both plasma TFV concentrations and intraerythrocytic TFV-DP concentrations in DBSs but was not placebo-controlled[23]. To determine the HIV incidence with increasing TFV-DP concentrations, we used data from the three placebo-controlled efficacy trials and applied our model by imputing the trial participants' TFV-DP measurements based on data from HPTN 082. For each trial, we used its TFV quantification threshold to categorize HPTN 082 participants into the positive or negative quantification group (Extended Data Fig. 4). We then sampled from these groups to impute TFV-DP concentrations for participants of the three placebo-controlled trials. We denote the distribution of TFV-DP measurements associated with plasma quantification, $P \in \{+, -\}$, and the trial, T, as Δ_{PT} (Extended Data Fig. 4).

The above imputation combined with the TFV-DP models (f_1, f_2 and f_3) generated three quantification models of PrEP efficacy as a function of plasma quantification ($P \in \{+, -\}$) and the trial (T): h_1, h_2 and h_3. None of the three randomized, placebo-controlled trials that measured TDF/FTC efficacy in women collected TFV-DP DBS measurements. Therefore, the above estimates relied on imputed DBS measurements given plasma TFV quantification data from HPTN 082. We thus evaluated whether a more direct approach—estimation of PrEP efficacy from plasma TFV quantification alone—might predict PrEP efficacy in trial cohorts better than imputed DBS measurements. Specifically, we considered two additional and simplified quantification models that directly use plasma TFV quantification without imputing a TFV-DP concentration (h_4 and h_5).

$$
\begin{aligned}
h(P|T, \mathbf{k}) &\equiv \frac{\text{Hazard rate in individuals on PrEP with TFV quantifiability of } P}{\text{Hazard rate in off-PrEP individuals}} \\
h_i(P|T, \mathbf{k}) &\sim f_i(X_D|\mathbf{k})\; i \in \{1, 2, 3\}\; X_D \sim \Delta_{PT} \\
h_4(P|T, \mathbf{k}) &= \begin{cases} k_4 & P = + \\ k_5 & P = - \end{cases} \\
h_5(P|T, \mathbf{k}) &= \begin{cases} k_4 & P = + \\ 1 & P = - \end{cases}
\end{aligned}
$$

Calibration of efficacy parameters

Each quantification model was calibrated using data from the three randomized, placebo-controlled efficacy trials (Extended Data Table 2) by using MCMC methods to estimate the unknown model parameters $\mathbf{k}$. In this procedure, the likelihood of a given set of proposed values for $\tilde{\mathbf{k}}$ and a model h must be computed at each step (see the next section). In total, we ran 100 MCMC chains of 1,100 steps each for a total of 110,000 parameter sets for each model. Extended Data Table 3 shows the median and 95% Bayesian credible interval estimated for each model parameter. As these estimates relied on prior assumptions about the joint distribution of TFV-DP and TFV concentrations, our uncertainty intervals for both parameters and model outputs cannot be viewed as CIs but instead as Bayesian credible intervals.

We compared the five quantification models—three using imputed DBS measurements and two using plasma TFV quantifiability only—to reproduce the number of HIV diagnoses stratified by plasma TFV quantification (Supplementary Fig. 1). According to the deviance information criterion, which accounts for both the goodness of model fit and model complexity, the three models using imputed DBS measurements outperformed those using plasma TFV quantifiability only (Supplementary Table 1).

Likelihood estimation

The likelihood of the observed data was estimated using the following procedure:

1. From the total number of new HIV diagnoses and person-quarters of follow-up time in the placebo arm of each efficacy trial ($S_{0,T}$ and $Q_{0,T}$, respectively), we randomly sampled the probability that an individual will have an HIV diagnosis during a given quarterly visit, r_T, from a beta distribution.

$$
r_T \sim \beta(1 + S_{0,T}, 1 + Q_{0,T} - S_{0,T})
$$

2. From the number of participants with and without quantifiable TFV among those with no HIV diagnosis ($Y_{+,T}$ and $Y_{-,T}$, respectively) and the total follow-up time in the active arm of each trial, $Q_{1,T}$, we randomly sampled the total number of quarterly visits with and without quantifiable TFV.

$$
\begin{aligned}
Q_{+,T} &\sim Q_{1,T}\beta(1 + Y_{+,T}, 1 + Y_{-,T}) \\
Q_{-,T} &= Q_{1,T} - Q_{+,T}
\end{aligned}
$$

3. For each trial, we calculated the HIV hazard ratio of individuals with and without quantifiable TFV compared to the placebo group, $h^{(\pm|T,\tilde{\mathbf{k}})}$. For models h_1, h_2 and h_3, we imputed TFV-DP values as described above. We drew $Q_{+,T}$ and $Q_{-,T}$ values for follow-up time with and without quantifiable TFV, respectively.

The probability of HIV acquisition with and without quantifiable TFV in each trial was then averaged across all follow-up times.

$$p_{\pm,T} = \left(\sum_{j=1}^{Q_{\pm,T}} 1 - (1 - r_T)^{h^{(j)}(\pm|\tilde{\mathbf{k}},T)} \right) / Q_{\pm,T}$$

For models h_4 and h_5, there is no imputation step, so the hazard ratio was completely determined by TFV quantification.

$$p_{\pm,T} = 1 - (1 - r_T)^{h(\pm|\tilde{\mathbf{k}},T)}$$

4. The likelihood was computed by comparing the rate, $p_{P,T}$, to the observed number of seroconversions in the active arm of each trial, $S_{P,T}$, and the amount of follow-up time, $Q_{P,T}$.

$$L\left(\tilde{\mathbf{k}}, \text{Data}\right) = \exp \prod_{P,T} \text{PBinom}\left(S_{P,T}; Q_{P,T}, p_{P,T}\right)$$

5. Steps 1–4 were repeated ten times, and the final likelihood is the average across each repetition.

Statistics and reproducibility

In this work, we reanalyzed HIV incidence and plasma TFV quantifiability data from three randomized, blinded, placebo-controlled clinical trials—FEM-PrEP, Partners PrEP and VOICE—and plasma TFV and TFV-DP concentration data from the implementation study HPTN 082, whose statistical methods have been described elsewhere[3,5,6]. No data were excluded from these analyses. No statistical method was used to predetermine the sample size. Sample sizes were instead fixed according to the endpoints of the original studies. Uncertainty intervals were reported as 95% credible intervals, which were calculated as the 2.5% and 97.5% quantiles for each estimand across all MCMC-derived samples. Model calibration was performed in R (version 4.1.2) using the adaptMCMC package (version 1.4).

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The data used in this study are available on GitHub (https://github.com/FredHutch/PrEPCiswomen).

Code availability

Model and calibration code is available on GitHub (https://github.com/FredHutch/PrEPCiswomen).

Acknowledgements

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Author contributions

All authors contributed to the preparation of the manuscript. S.D.-M., L.-G.B., N.M.M. and C.L.C. led the HIV Prevention Trials Network 082 trial. Laboratory testing of tenofovir diphosphate concentrations in dried blood spot samples was supervised by P.L.A. M.M. wrote the R code, ran the calibration and wrote the initial draft of the manuscript. D.J.D. and D.D. supervised the analysis of the project. D.J.D., D.D., M.-C.B., K.M.M. and S.S. provided feedback on methodology.

Competing interests

P.L.A. has received personal fees from Gilead, ViiV and Merck, as well as research support from Gilead, paid to his institution. L.-G.B. has received honoraria for advisories to Gilead Sciences, Merck (Pty) Ltd, ViiV Healthcare and Janssen; these are not ongoing. K.M.M. has received teaching payments from Pfizer, outside the submitted work. All other authors declare no competing interests.

Additional information

Extended data is available for this paper at https://doi.org/10.1038/s41591-023-02564-5.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41591-023-02564-5.

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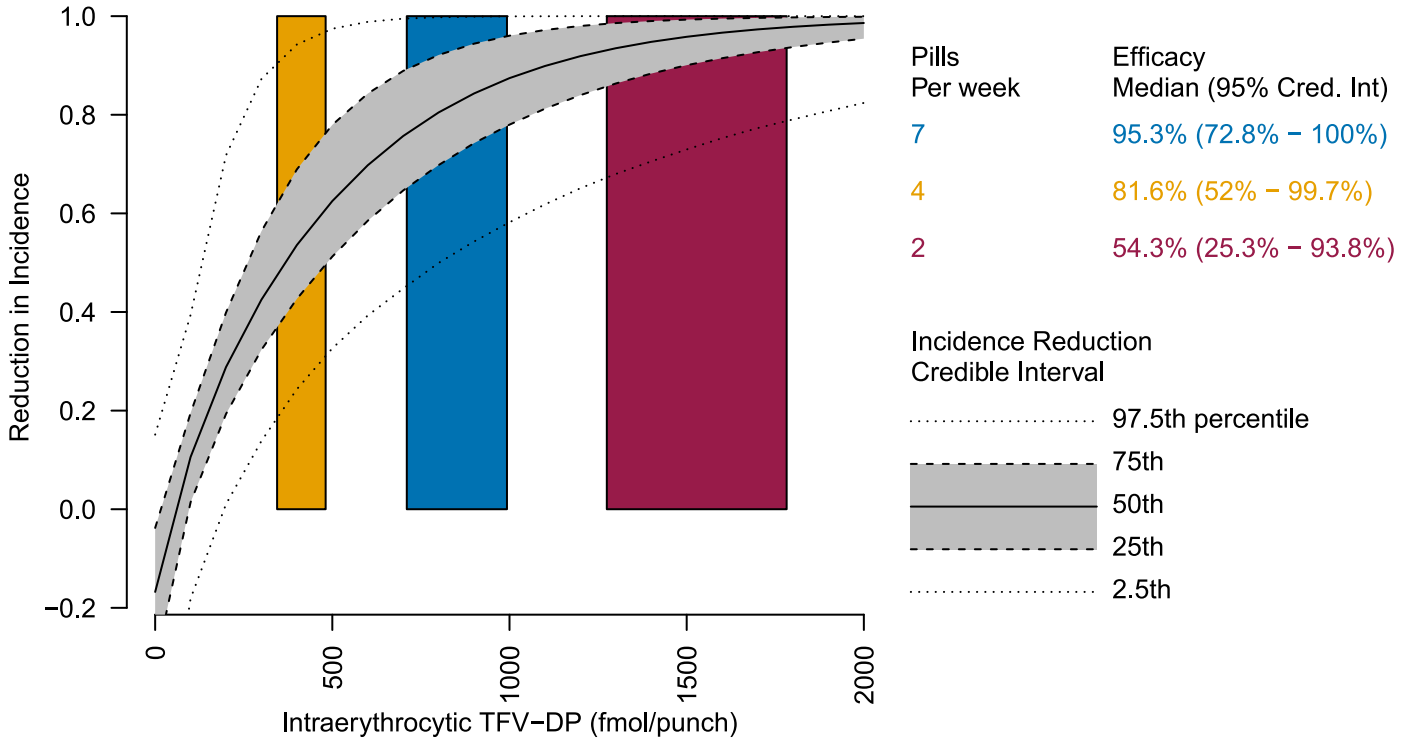
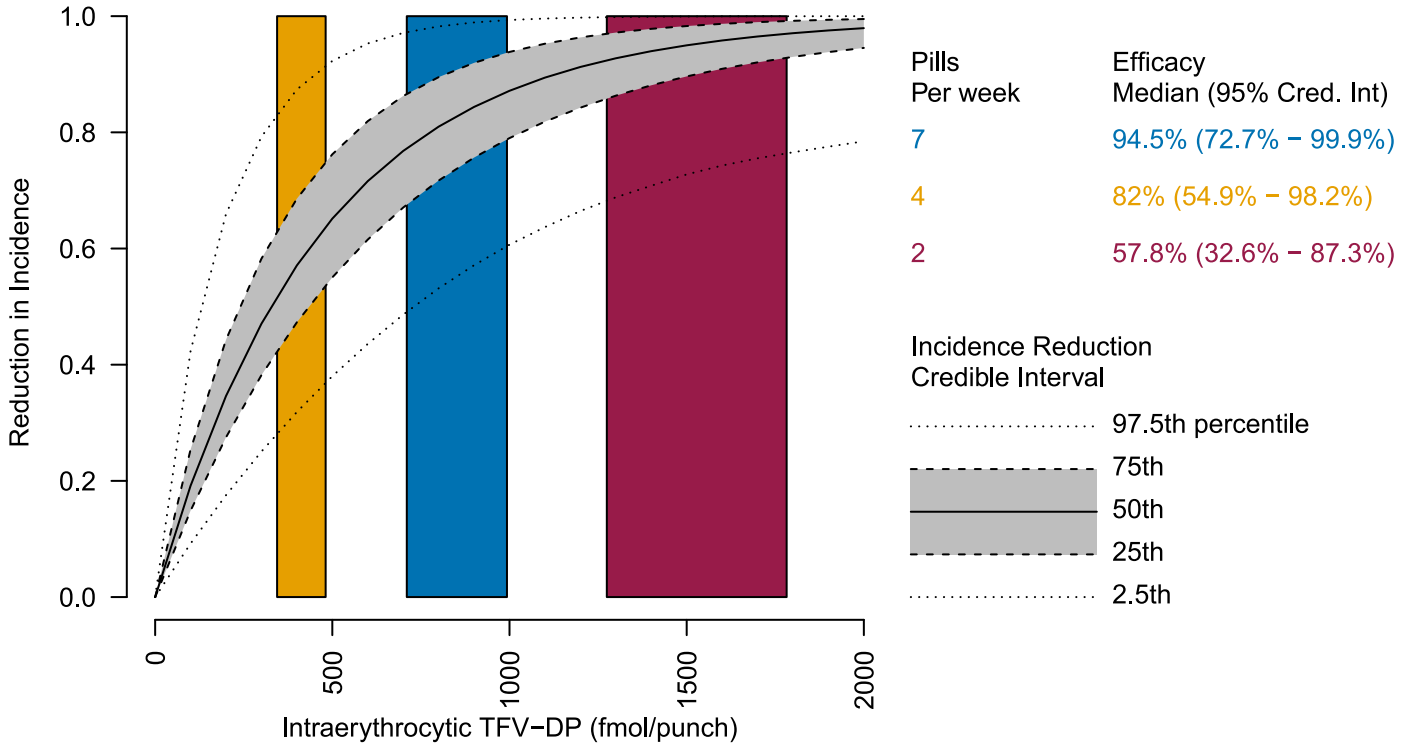


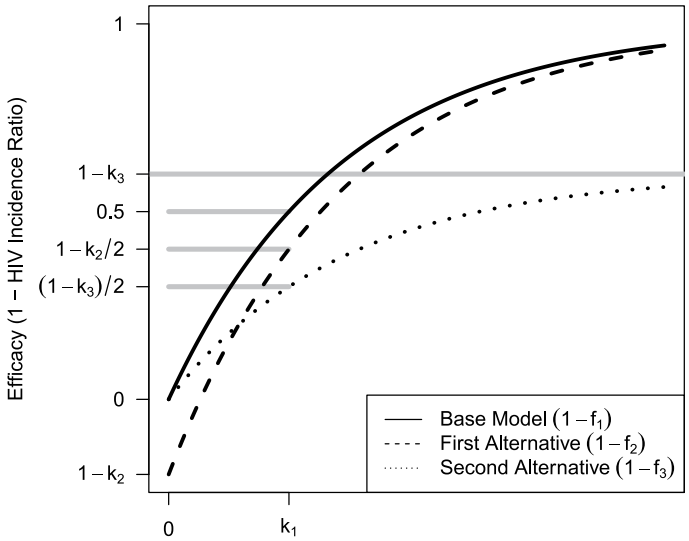
Extended Data Fig. 1 | Efficacy of TDF/FTC by TFV-DP measurement in model h_2. Reduction in incidence in HIV as a function of tenofovir diphosphate (TFV-DP) levels in dried blood spots measurement according to model h_2. Grey ribbon = IQR, Dashed line = 95% Credible Interval. Colored rectangles represent the IQR of TFV-DP measurements associated with two pills per week (red), four pills per week (blue) and seven pills per week (green) derived from directly observed dosing[8].

https://doi.org/10.1038/s41591-023-02564-5



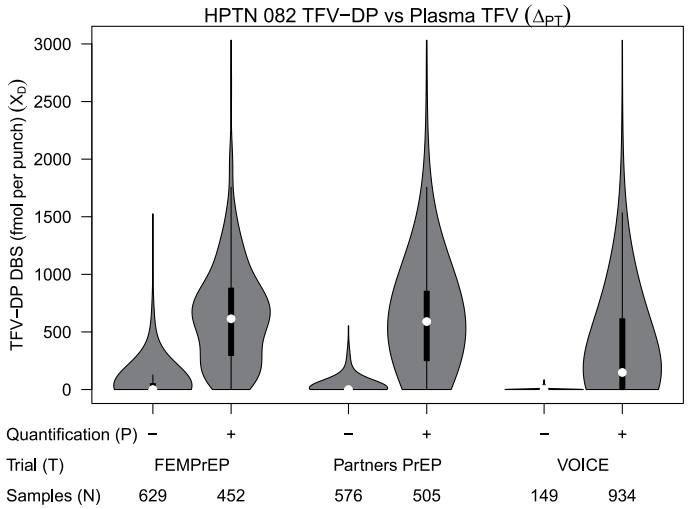
Extended Data Fig. 2 | Efficacy of TDF/FTC by TFV-DP measurement in model h_3. Reduction in incidence in HIV as a function of tenofovir diphosphate (TFV-DP) levels in dried blood spots measurement according to model h_3. Grey ribbon = IQR, Dashed line = 95% Credible Interval. Colored rectangles represent the IQR of TFV-DP measurements associated with two pills per week (red), four pills per week (blue) and seven pills per week (green) derived from directly observed dosing[8].

https://doi.org/10.1038/s41591-023-02564-5



Extended Data Fig. 3 | Adherence-efficacy model curves. Assumed functional forms for PrEP efficacy as a function of intraerythrocytic tenofovir diphosphate, testing assumptions that individuals with no quantifiable TFV-DP have the same HIV incidence as individuals concurrently randomized to placebo and that HIV incidence approaches zero with increasing TFV-DP. f_1 includes both assumptions. f_2 challenges the first assumption by allowing individuals with low PrEP adherence to have lower (or higher) efficacy k_2 than those on placebo. f_3 challenges the second assumption as efficacy approaches k_3.

https://doi.org/10.1038/s41591-023-02564-5



Extended Data Fig. 4 | Imputation of TFV-DP concentration from plasma TFV quantifiability. Measurements of intraerythrocytic TFV-DP among HPTN 082 participants with quantifiable or unquantifiable plasma TFV using the quantification threshold of each trial (see Extended Data Table 2). Plots are based on a total of N = 1083 samples, which are divided into positive and negative depending on the quantification threshold. For FEMPrEP and partners PrEP, the total is only 1081 because for two samples the quantification threshold could not be evaluated due to missing data. Width = frequency, white dot = median, black rectangle = interquartile range, black line = upper and lower adjacent values.

 https://doi.org/10.1038/s41591-023-02564-5

Extended Data Table 1 | Estimates of Efficacy

	Efficacy estimates in women			Previous results in MSM/TGW	
TFV-DP/adherence	h_1	h_2	h_3	Anderson et al[9]	Grant et al[7]
350 fmol/punch	53.8% (26.1 - 94.1)	48.4% (19.4 - 91.5%)	52.4% (28.5 - 83.8)		68.0% (17.3 - 87.7)
700 fmol/punch	78.7% (45.3 - 99.7)	75.7% (44.8 - 99.5%)	76.8% (48.6 - 97.1)		93.5% (75.1 - 98.2)
1250 fmol/punch	93.7% (66.0 - 100.0)	92.7% (66.6 - 100.0)	92.0% (67.7 - 99.8)		99.4% (96.0 - 99.9)
Two pills per week	59.3% (29.9 - 95.8)	54.3% (25.3 - 93.8)	57.8% (32.6 - 87.3)	76% (56 - 96)	
Four pills per week	83.8% (51.7 - 99.8)	81.6% (52.0 - 99.7)	82% (54.9 - 98.2)	96% (90 - >99)	
Seven pills per week	95.9% (72.6 - 100)	95.3% (72.8 - 100)	94.5% (72.7 - 99.9)	99% (96 - >99)	100% (57 – 100)

Estimated reduction in HIV incidence TDF/FTC at select concentrations of TFV-DP concentration and adherence. Table shows median values and 95% credible intervals

 https://doi.org/10.1038/s41591-023-02564-5

Extended Data Table 2 | Data from three randomized placebo-controlled efficacy trials of daily oral PrEP in women

	Quantifiable plasma TFV			Incidence (per 100 Person-Year)	
Trial	HIV diagnosis	No HIV diagnosis	Quantification Threshold	Placebo	Treatment
FEMPrEP	7/33 (21%)	35/95 (37%)	>10 ng/ml at visit	5.0	4.7
Partners PrEP	1/8 (13%)	135/175 (77%)	>0.3 ng/ml at visit	2.8	1.0
VOICE	24/61 (39%)	77/148 (52%)	>0.3 ng/ml at any visit	4.2	4.7

In each trial the quantification of plasma TFV was assessed in each newly diagnoses individual as well as a subset of the individuals without HIV in treatment arm. HIV incidence is per 100 person-years. Each trial used a slightly different of plasma quantification threshold.

 https://doi.org/10.1038/s41591-023-02564-5

Extended Data Table 3 | Model Parameters

Model	Parameter	Description	Median (95%CI)
h_1	k_1	TFV-DP DBS IC50	299 (126 - 801)
h_2	k_1	TFV-DP DBS IC50	314 (86 - 803)
	k_2	RR of those with unquantifiable TFV-DP DBS	1.17 (0.85 - 1.65)
h_3	k_1	TFV-DP DBS IC50	322 (120 - 702)
	k_3	Minimum possible RR	0 (0 - 0.16)
h_4	k_4	RR of those with quantifiable plasma TFV	0.49 (0.32 - 0.74)
	k_5	RR of those with unquantifiable plasma TFV	1.2 (0.87 - 1.65)
h_5	k_4	RR of those with quantifiable plasma TFV	0.47 (0.31 - 0.7)

Parameter values with medians and credible intervals as estimated using MCMC. IC50=TFV-DP DBS measure required to achieve half the maximum theoretical incidence reduction. RR = relative incidence compared to the placebo arm.

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Corresponding author(s): Mia Moore

Last updated by author(s): May 13, 2023

Reporting Summary

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☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
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☒	☐ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
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☒	☐ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☐	☒ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
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Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	No software was used
Data analysis	R version 4.1 was used for analysis. Package adaptMCMC version 1.4 used for Markov Chain Monte Carlo

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

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All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
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The data underlying the results presented in the study are available from SCHARP data management center, HPTN-data-access@scharp.org

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	All data is from cisgender women
Reporting on race, ethnicity, or other socially relevant groupings	Calibration of efficacy curves did not use race and ethnicity information. Self-identification of African American was used to adjust TFV-DP ranges associated with 2, 4 and 7 pills per week, however that analysis was performed in a prior study which we cite.
Population characteristics	All subjects were cisgender women in sub-Saharan Africa. Age distributions were HPTN 082: 16-24 (median 21); FEMPrEP:18-35 (median 23); VOICE: 18-40 (median 24), and Partner's PrEP:18+ (median 25-34). In HPTN 082 34% reported having more than one sex partner, compared to 26% in FEMPrEP, 23% in VOICE, and 8% in Partner's PrEP. Full information on their characteristics is given in the primary manuscripts for HPTN 082, VOICE, FEMPrEP and Partners PrEP.
Recruitment	Subjects were recruited to all studies based on factors associated elevated rates of HIV acquisition. Individuals in Partners PrEP had a primary partner known to be living with HIV. Individuals in HPTN 082 were recruited based on a VOICE risk score of five or more. This information is available in the primary manuscripts for all studies.
Ethics oversight	The study was reviewed and approved by the HIV Prevention Trials Network (HPTN).

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

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Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	There were no sample size calculations in this work. Instead, they were determined by the prior studies to address their primary endpoints. The precision of our efficacy estimates is limited by the existing data, however it is no longer ethical to collect data of this kind and the scientific question remains important. Therefore, we describe the adherence-efficacy curve to the greatest precision that the data permits.
Data exclusions	There was no data excluded from this study
Replication	The study described is computational. The code has been preserved so that it is fully reproducible. It is no longer ethical to conduct placebo controlled, randomized PrEP efficacy trials so these studies cannot be repeated in the same manner.
Randomization	In this work, we use HIV incidence data from three groups: 1) those assigned placebo , 2a) those assigned TDF/FTC with quantifiable TFV and 2b) those assigned TDF/FTC without quantifiable TFV. The underlying studies FEM-PrEP, Partners PrEP, and VOICE randomized participants to either receive placebo or TDF/FTC, ie group 1 vs 2a/b. However the quantifiability of TFV, a measure of study product adherence, could not be randomized. As with the issue of sample size, it would no longer be ethical to conduct a randomized trial of this sort, in which individuals are assigned a sub-optimal pill-taking frequency. We include this limitation in the discussion.
Blinding	All studies were blinded during follow-up and analysis.

Reporting for specific materials, systems and methods

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n/a	Involved in the study
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☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	VOICE: NCT00705679; FEMPrEP:NCT00625404; Partners PrEP: NCT00557245; HPTN 082: NCT02732730
Study protocol	VOICE: 10.1056/NEJMoa1402269; FEMPrEP: 10.1056/NEJMoa1202614; Partners PrEP: 10.1056/NEJMoa1108524; HPTN 082: doi.org/10.1371/journal.pmed.1003670
Data collection	VOICE: South Africa, Uganda, Zimbabwe 2009-2012; FEMPrEP: Kenya, South Africa, Tanzania 2009-2012; Partners PrEP: Kenya, Uganda 2008-2010; HPTN 082: South Africa, Zimbabwe 2016-2018
Outcomes	VOICE, FEMPrEP and Partners PrEP had HIV acquisition (as measured by seroconversion) as the primary outcome. They also collected data on adherence as plasma tenofovir quantifiability as a secondary outcome. The threshold of quantifiability in each study was slightly different as described in the manuscript. VOICE required >0.3 ng/ml at any follow-up visit, Partners PrEP >0.3 ng.ml at the time of seroconversion, and FEMPrEP >10ng/ml at time of seroconversion. In HPTN 082, TFV-DP concentration in DBS throughout followup was the primary endpoint and TFV concentration in plasma was the secondary endpoint.