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RESEARCH ARTICLE

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Combining information to estimate adherence in studies of pre-exposure prophylaxis for HIV prevention: Application to HPTN 067

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In trials of oral HIV pre-exposure prophylaxis (PrEP), multiple approaches have been used to measure adherence, including self-report, pill counts, electronic dose monitoring devices, and biological measures such as drug levels in plasma, peripheral blood mononuclear cells, hair, and/or dried blood spots. No one of these measures is ideal and each has strengths and weaknesses. However, accurate estimates of adherence to oral PrEP are important as drug efficacy is closely tied to adherence, and secondary analyses of trial data within identified adherent/non-adherent subgroups may yield important insights into real-world drug effectiveness. We develop a statistical approach to combining multiple measures of adherence and show in simulated data that the proposed method provides a more accurate measure of true adherence than self-report. We then apply the method to estimate adherence in the ADAPT study (HPTN 067) in South African women.

KEYWORDS

adherence, HIV, latent variable, pharmacokinetic model, pre-exposure prophylaxis

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1 | INTRODUCTION

HIV-uninfected individuals may reduce their risk of sexual acquisition of HIV by taking antiretroviral drugs as pre-exposure prophylaxis (PrEP). The first, and most widely used, PrEP agent approved for use in both men and women is a combination of the antiretroviral drugs emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF), an orally administered tablet (brand name—Truvada®). However, multiple phase 3 clinical trials of TDF/FTC, conducted across different geographic, gender, sexual orientation, and sexual relationship groups, have yielded differing estimates of efficacy.[1-8] In these trials, researchers have also noted large variations in pill-taking adherence as measured by concentrations of the drug present in plasma. It is widely believed that variable adherence may explain the variation in efficacy results.[9,10]

In spite of the critical role that adherence plays in determining PrEP efficacy, measuring individual-level adherence during a trial remains challenging. Some common approaches to measuring adherence include:[11]

- Self-report—Participants report on doses taken or not taken as prescribed; data may be collected on a daily time scale or over longer intervals; results may be quantitative counts (0/1 for daily pill taking, or percent over longer intervals) or semi-quantitative estimates (eg, took pills always, usually, sometimes, seldom, never).
- Pill counts—The number of pills returned at the end of an interval is subtracted from the number of pills dispensed to determine the number of pills taken, which can then be used to estimate (the maximum possible) adherence over the interval; counts may be made by a clinician or self-reported.
- Pharmacy records—Days covered by dispensed drug divided by days between dispensation and refill, typically done over several refills; failure to obtain a refill is assumed to be evidence of nonadherence; as with pill counts, refills provide a best-case estimate of pill-taking.
- Electronic dose monitoring devices (eg, WisePill™, MEMSCap™)—Pills are kept in a device that records each opening of the device; openings are assumed to correspond to pill taking.
- Pharmacologic measures [eg, drug levels in urine, plasma, dried blood spots (DBS), peripheral blood mononuclear cells (PBMC), hair]—Levels of drug or drug metabolites are measured in a biological compartment periodically over follow-up.

Each approach has strengths and weaknesses. Self-report and electronic dose monitoring devices can collect data daily. However, these measures, as well as pill counts, can be manipulated by the participant and claims of over-reporting are common.[12] In addition, openings of electronic dose monitoring devices do not necessarily correspond to pill taking[13] and the devices may be lost or (rarely) fail to operate properly. Pharmacologic measures are more objective but only provide a snapshot in time. For example, following a dose of tenofovir, the activated form of the drug (TFV) is only detectable in plasma for approximately 7 days after ingestion. Slower metabolism of TFV in DBS, PBMC, and hair provides a longer look-back period but dose timing is difficult to determine.[14] In addition, so-called "white coat dosing" (taking a pill just before a scheduled follow-up visit) can give misleading estimates of adherence for biologic measures with short half-lives (eg, plasma) when considered in isolation.[15]

In practice, investigators often rely on multiple measures and informally attempt to combine them to estimate participant adherence. Our objective is to develop a formal method for combining multiple measures of adherence that can be used to characterize a participant's true adherence to medication during a clinical study. We propose a latent variable approach that allows us to combine multiple sources of observed data, data from external pharmacokinetic studies, and assumptions about over/under-reporting in an internally consistent model. We develop the model and estimation

TABLE 1 HPTN 067 sample collection schedule

	Directly observed therapy								Self-administered					
Weeks after trial initiation	**0**	**1**	**2**	**3**	**4**	**4**	**5**	**6**	**10**	**14**	**18**	**22**	**26**	**30**
Directly observed dosing (1 per week)	X	X	X	X	X									
Randomization								X						
Self-administered medication (daily)									X	X	X	X	X	X
Plasma					X	D D			X	S	X	S	S	X
PBMC					X	D D	X	X	X	S	X	S	S	X

Note: X indicates samples that have been collected and analyzed and are available for the current analysis. Each D indicates a hypothetical time of collection of an additional sample for the "Extra DOT" simulations described in Section 3 and S indicates the hypothetical time of collection of an additional sample for the "Extra SA" simulation, also described in Section 3.

methods in Section 2, evaluate the model on simulated data in Section 3, and apply the methods to data from an HIV prevention study, HPTN 067, in Section 4. We discuss the potential for future applications and development of the approach in Section 5.

2 | METHODS

2.1 | Data source

HPTN 067 (the ADAPT Study) was a phase 2, randomized, open-label, pharmacokinetic, and behavioral study designed to assess the coverage (proportion of sex events protected by adequate dosing of PrEP), acceptability and safety of daily vs intermittent dosing regimens of Truvada®.[16] Individuals enrolled in HPTN 067 initially underwent a 6-week period of once-weekly directly observed therapy (DOT) during which a single pill of Truvada® was ingested at the beginning of weeks 1 to 5. Biologic samples (eg, blood, hair) were collected at the end of weeks 4 to 6. Participants were then randomized at the end of week 6 to one of three different pill-taking regimens—daily, time-driven (2 pills per week plus a post-exposure boost) or event-driven (pre- and post-exposure dosing)—for a 24-week period of self-administered (SA) dosing.

During the SA phase participants used an electronic dose monitoring (EDM) device to store pills and the EDM generated a log of device opening events and times. This log was then used as a guide for clinic staff during weekly phone calls with each participant to assess sexual behavior and pill-taking during the previous week. Participants were asked about the accuracy of the EDM device pill-taking record and were given the opportunity to add or subtract pill-taking events from the electronic record, or adjust the timing of pill-taking. The type and timing of sex acts were also ascertained during these calls (necessary for calculating adherence to event-based regimens). The results of the weekly interviews are the final record of EDM-advised self-reported adherence and sexual behavior. Participants were also scheduled to have a clinic visit every four weeks during the self-administered phase. At each clinic visit, biological samples were collected for drug concentration measurement. Drug concentrations have been analyzed in plasma at weeks 4, 10, 18, and 30, and in PBMC at weeks 4, 5, 6, 10, 18, and 30. The study design and data collection scheme are illustrated in Table 1.

2.2 | Statistical model

We now describe a general statistical framework for combining multiple measurements of drug adherence. Our goal is to estimate the true daily adherence to a study drug. Let A_{ij} denote the true pill-taking for participant i on day j where $A_{ij} = 1$ means participant i took a pill on day j and $A_{ij} = 0$ means no pill taken. In general, except for the DOT period, A_{ij} is unobserved. However, a number of measures of adherence may be observed. In the current model, we consider three measures—R_{ij}, self-reported pill-taking by person i on day j at time t_{ij}; P_{ij}, plasma drug concentration; and B_{ij}, drug concentration in PBMC. P_{ij} and B_{ij} are both measured in person i on day j at time u_{ij}. Additional measures of adherence

may be added in a straightforward manner, as described below. Note that P_{ij} and B_{ij} will be missing on most days. Our goal is to estimate $P(A_i|R_i, P_i, B_i)$ where A_i, R_i, P_i, and B_i are vectors over all days. Assuming (i) independence between the self-reported data and the biological measures, conditional on true pill-taking (ie, $R_i \perp (P_i, B_i)|A_i$), (ii) that reported pill-taking on day j depends only on true pill-taking on day j (again, conditional on true pill-taking), and (iii) that plasma and PBMC levels depend only on past history of pill-taking, we may write

$$\begin{aligned} P(A_i|R_i, P_i, B_i) &\propto P(R_i, P_i, B_i|A_i)P(A_i) \\ &= P(R_i|A_i)P(P_i, B_i|A_i)P(A_i) \\ &= \prod_j P(R_{ij}|A_{ij})P(P_{ij}, B_{ij}|A_{i\tau_{ij}})P(A_{ij}), \end{aligned} \tag{1}$$

where τ_{ij} is the set $\{k : t_{ik} < u_{ij}\}$ (ie, all pill-taking times prior to the drug measurement time u_{ij}). This approach can be extended in an obvious way if additional measures of adherence are collected, provided one can assume conditional independence of the measures or provide a joint model of appropriate subsets of the measures. To complete the model, each of the terms on the right-hand side of (1) must be parameterized. In general, the parameterization will depend on the design of the study being analyzed. Here, we outline the specific approaches used to analyze the HPTN 067 daily arm data.

2.2.1 | Adherence

$P(A_{ij})$ plays the role of a prior probability in (1) and may be thought of as the intrinsic or background probability of adherence to daily pill-taking for participant i on day j in the absence of information on self-reports, biological measurements or other observed measures of adherence. The simplest model for $P(A_{ij})$ is to assume that each person has his or her own intrinsic true adherence probability, namely,

$$\begin{aligned} P(A_{ij} = 1) &= p_i, \\ p_i &\sim \text{beta}(a_1, b_1), \end{aligned} \tag{2}$$

that is constant over the course of follow-up. $P(A_{ij})$ could also be modeled as a function of time and/or external covariates, Z, as

$$\begin{aligned} \text{logit}(P(A_{ij} = 1|Z_i)) &= \beta_{i0} + \beta_{i1}j + \beta_2 Z_{i1} + \cdots \\ \beta_{i0} &\sim N(\beta_0, \sigma_0^2) \\ \beta_{i1} &\sim N(\beta_1, \sigma_1^2) \\ &\vdots \end{aligned} \tag{3}$$

or could be modeled as a Markov process,[17] for example

$$\begin{aligned} P(A_{ij} = 1|A_{ij-1} = s) &= p_{is}, \\ p_{i0} &\sim \text{beta}(a_{10}, b_{10}), \\ p_{i1} &\sim \text{beta}(a_{11}, b_{11}), \end{aligned} \tag{4}$$

which would be appropriate if it was anticipated that participants might experience intervals of risk, and dose accordingly. Informal evaluation of the posterior estimates and distributions of model parameters (eg, β_{i1} in (3) or $p_{i0} - p_{i1}$ in (4)) can be used to guide model choice.

2.2.2 | Self-reports

Each individual is assumed to have a personal probability of over- and under-reporting adherence, given as $P(R = 1|A = 0)$ and $P(R = 0|A = 1)$, respectively. These (mis)reporting probabilities are assumed to depend only on the current day's true

pill-taking,

$$\begin{aligned} P(R_{ij} = 1|A_{ij} = 0) &= \phi_i, \\ P(R_{ij} = 0|A_{ij} = 1) &= \psi_i, \\ \phi_i &\sim \text{beta}(a_2, b_2), \\ \psi_i &\sim \text{beta}(a_3, b_3), \end{aligned} \tag{5}$$

with the identifiability constraint[18] $\psi_i + \phi_i < 1$. If under-reporting is thought to be rare then one might assume $\psi_i = 0$.

2.2.3 | Drug concentration

Let $h(\theta_i, u_{ij} - t_{ik})$ denote the expected contribution to the total drug concentration at time u_{ij} from a pill ingested at time t_{ik} for an individual with pharmacokinetic parameters θ_i (see description of pharmacokinetic model below). Then, assuming dose-additivity,[19] the total expected drug concentration at time u_{ij} is

$$C_{ij} = \sum_{k:t_{ik}<u_{ij}} A_{ik} h(\theta_i, u_{ij} - t_{ik}). \tag{6}$$

We assume that the measured (log) drug concentration at time u_{ij}, Y_{ij}, follows a normal distribution

$$Y_{ij}|A_i, \theta_i, \sigma \sim N(\log(C_{ij}), \sigma^2). \tag{7}$$

If the measurement assay has a lower (log) detection limit of ν (assumed known), then we write the likelihood contribution of the log concentration measurement as

$$\ell(Y_{ij}|A_i, \theta_i, \sigma) \sim \begin{cases} \phi(Y_{ij}|A_i, \theta_i, \sigma), & \text{if } Y_{ij} \geq \nu, \\ \Phi(\nu|A_i, \theta_i, \sigma), & \text{if } Y_{ij} < \nu, \end{cases} \tag{8}$$

where ϕ and Φ are the normal density and distribution functions, respectively.

The pharmacokinetic model of Burns et al[20] is used to define the expected TFV concentrations. They used data from the MTN-001 study[21] to develop and fit a model for plasma TFV and PBMC TFV-DP in healthy volunteers using a method that accounts for nonadherence[22] to provide unbiased parameter estimation. Specifically, plasma TFV concentrations are modeled by a two-compartment first-order absorption/elimination model and linked to PBMC tenofovir diphosphate (TFV-DP) concentration by first-order uptake with first-order elimination (Figure 1).

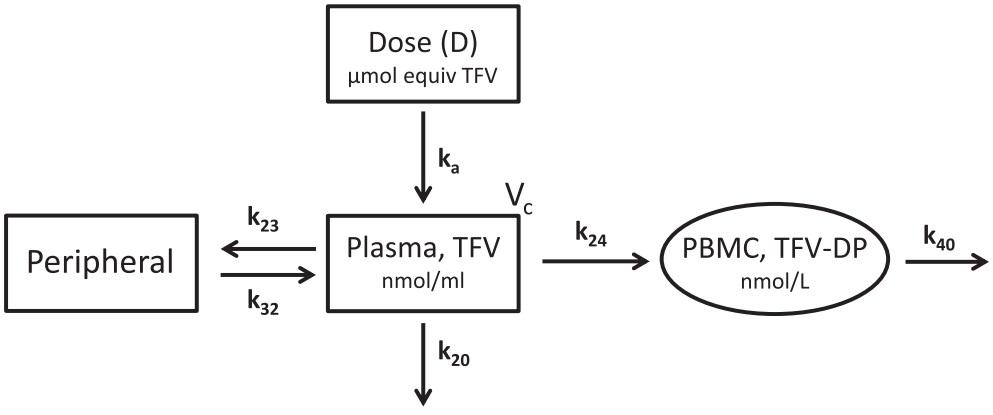

FIGURE 1 Pharmacokinetic model for oral tenofovir in plasma and PBMC

TABLE 2 Conversion of input and outputs from the Burns et al[20] model units to measurement units used in HPTN 067

Quantity	Model units	Measurement units	Conversion	LLOQ
Dose (D)	472 μmol TFV (136 mg TFV)	300 mg TDF	μmol TFV = 1.57 * mg TDF	-
TFV	nmol/mL	ng/mL	ng/mL = 288.1 * nmol/mL	0.31 ng/mL
TFV-DP	nmol/L	fmol/million cells	fmol/million cells = 0.282 * nmol/L	≈0.6 fmol/million cells

Abbreviation: LLOQ, lower limit of quantitation.

Given a participant's central compartment volume, V_c, the expected concentrations for plasma TFV levels and PBMC TVF-DP levels are given by the following expressions:

$$h_2(\theta,t) = \frac{D}{V_c}k_a\left[\frac{k_{32}-k_a}{(\alpha-k_a)(\beta-k_a)}e^{-k_a t} + \frac{k_{32}-\alpha}{(k_a-\alpha)(\beta-\alpha)}e^{-\alpha t} + \frac{k_{32}-\beta}{(k_a-\beta)(\alpha-\beta)}e^{-\beta t}\right],$$

$$h_4(\theta,t) = Dk_ak_{24}\left[\frac{k_{32}-k_a}{(k_{40}-k_a)(\alpha-k_a)(\beta-k_a)}e^{-k_a t} + \frac{k_{32}-k_{40}}{(k_a-k_{40})(\alpha-k_{40})(\beta-k_{40})}e^{-k_{40}t}\right.$$
$$\left. + \frac{k_{32}-\alpha}{(k_a-\alpha)(k_{40}-\alpha)(\beta-\alpha)}e^{-\alpha t} + \frac{k_{32}-\beta}{(k_a-\beta)(k_{40}-\beta)(\alpha-\beta)}e^{-\beta t}\right],$$

$$\alpha = 0.5\times\left(W + \sqrt{W^2 - 4k_{32}(k_{20}+k_{24})}\right),$$

$$\beta = 0.5\times\left(W - \sqrt{W^2 - 4k_{32}(k_{20}+k_{24})}\right), \text{ and}$$

$$W = k_{23} + k_{32} + k_{20} + k_{24},$$

where θ is a vector of the pharmacokinetic parameters $(k_a, k_{23}, \ldots)$, D is the initial (oral) dose, and $h_2(\theta,t)$ and $h_4(\theta,t)$ are the expected plasma TFV and PBMC TFV-DP drug levels, respectively, at time t after pill-taking. Table 2 gives factors for conversion of units between the Burns et al model input/output and measurement units used in HPTN 067.

V_c is modeled as a function of participant weight (kg):

$$V_c = a_0 + a_1(73 - wt). \tag{9}$$

Burns et al[20] find evidence of individual-level variability for the parameters k_a, k_{20}, k_{24}, and a_0 while k_{23}, k_{32}, k_{40}, and a_1 are modeled as population-level parameters. In the next section, we discuss our approach to parameter estimation, and in particular highlight areas where our decisions regarding parameter variability differs from that of Burns et al.

2.3 | Parameter estimation

Markov chain Monte Carlo (MCMC) methods, implemented with the JAGS software package, are used for parameter estimation.[23] Our primary interest is in estimating individual-level average adherence (p_i) and under- and over-reporting (ψ_i, ϕ_i, respectively). We are also interested in estimating adherence on individual days, $P(A_{ij}|R_i, P_i, B_i)$. However, HPTN 067 was not designed to estimate the parameters of a PK model for TDF/FTC and the sampling frequency is not adequate to provide useful PK parameter estimates (to fit a PK model for TDF/FTC, participants are typically seen at 1, 2, 4, 6, 8 hours post-dosing as in Burns et al[20]). Instead, we use informative priors (Table 3) for the PK parameters based on the values published by Burns et al.[20] Consistent with Burns et al the parameters k_{20}, k_{24}, and a_0 include individual-level variability while the parameters k_{23}, k_{32}, k_{40}, and a_1 are fit at the population level. Although Burns et al also found evidence of individual-level variability for k_a, preliminary simulations with HPTN 067-like data showed that inclusion of individual-level variability in this parameter led to substantial model instability and failure of some PK parameters to converge over the MCMC chain; fixing k_a at the population-level value of 9.79 h^{-1} solved this issue and this approach is used for the remainder of the analyses. All pharmacokinetic parameters use lognormal priors to ensure positivity and certain constraints on the pharmacokinetic parameters, described by Burns et al, are implemented to ensure identifiability. Uninformative priors are used for individual-level average adherence and the self-reporting parameters (see Table 3).

TABLE 3 Parameters and priors

Parameter		Value (%RSE)[a]	%BPV (%RSE)[a]	Prior	Hyperpriors
Pharmacokinetic parameters					
k_a	Absorption rate constant (h^{-1})	9.79 (65.18)	160.2 (169.1)	$\log(k_a) \sim N(\mu_{k_a}, \sigma^2_{k_a})$	$\mu_{k_a} \sim N(\log(9.79), 0.6518^2)$ $\log \sigma_{k_a} \sim N(\log(1.602), 1.691^2)$
k_{23}	Plasma to peripheral rate constant (h^{-1})	0.631 (24.7)	-	$\log(k_{23}) \sim N(\log(0.631), 0.247^2)$	
k_{32}	Peripheral to plasma rate constant (h^{-1})	0.396 (23.24)	-	$\log(k_{32}) \sim N(\log(0.396), 0.2324^2)$	
k_{20}	Plasma elimination rate constant (h^{-1})	0.13 (17.81)	36.22 (33.99)	$\log(k_{20i}) \sim N(\mu_{k_{20}}, \sigma^2_{k_{20}})$	$\mu_{k_{20}} \sim N(\log(0.13), 0.1781^2)$ $\log \sigma_{k_{20}} \sim N(\log(0.3622), 0.3399^2)$
k_{24}	Plasma to PBMC rate constant (h^{-1})	0.017 (72.48)	159.49 (69.95)	$\log(k_{24i}) \sim N(\mu_{k_{24}}, \sigma^2_{k_{24}})$	$\mu_{k_{24}} \sim N(\log(0.017), 0.7248^2)$ $\log \sigma_{k_{24}} \sim N(\log(1.595), 0.6995^2)$
k_{40}	PBMC elimination rate constant (h^{-1})	0.013 (16.63)	-	$\log(k_{40}) \sim N(\log(0.013), 0.1663^2)$	
a_0	Vol. of distribution base value (L)	385.71 (14.84)	19.3 (45.1)	$\log(a_{0i}) \sim N(\mu_{a_0}, \sigma^2_{a_0})$	$\mu_{a_0} \sim N(\log(385.71), 0.1484^2)$ $\log \sigma_{a_0} \sim N(\log(0.193), 0.451^2)$
a_1	Vol. of distribution weight scalar (L/kg)	−2.16 (34.52)	-	$a_1 \sim N(-2.16, 0.745^2)$[b]	
σ_{TFV}	SD (nmol/mL)	0.2748 (0.0524)	-	$\log(\sigma_{\text{TFV}}) \sim N(\log(0.2748), 0.0524^2)$	
$\sigma_{\text{TFV-DP}}$	SD (nmol/L)	0.3118 (0.0721)	-	$\log(\sigma_{\text{TFV-DP}}) \sim N(\log(0.3118), 0.0721^2)$	
Adherence parameters					
p	True adherence probability	-	-	$p_i \sim \text{beta}(\alpha_1, \beta_1)$[c] $\alpha_1 = \eta_1 \times \zeta_1,\ \beta_1 = \zeta_1 \times (1 - \eta_1)$	$\zeta_1 \sim \text{gamma}(3, 1)$ $\eta_1 \sim \text{beta}(1, 1)$
Self-reporting parameters					
ϕ	Over-reporting probability	-	-	$\phi_i \sim \text{beta}(\alpha_2, \beta_2)$[c] $\alpha_2 = \eta_2 \times \zeta_2, \beta_2 = \zeta_2 \times (1 - \eta_2)$	$\zeta_2 \sim \text{gamma}(3, 1)$ $\eta_2 \sim \text{beta}(1, 1)$
ψ	Under-reporting probability	-	-	$\psi_i \sim \text{beta}(\alpha_3, \beta_3)$[c] $\alpha_3 = \eta_3 \times \zeta_3,\ \beta_3 = \zeta_3 \times (1 - \eta_3)$	$\zeta_3 \sim \text{gamma}(3, 1)$ $\eta_3 \sim \text{beta}(1, 1)$

Note: Parameters that include random person effects are indexed by i. Informative priors for PK parameters are based on data from Burns et al.[20]

Abbreviations: BPV, between-participant variability expressed as a coefficient of variation; RSE, relative standard error expressed as a coefficient of variation.

[a]Values from Burns et al.[20]

[b]$0.745 = 2.16 \times 0.3452$.

[c]η and ζ may be interpreted as the mean and "effective sample size" of the prior distribution, respectively. In each case, $E(\eta) = 0.5$ and $E(\zeta) = 3$.

TABLE 4 Estimated adherence and mis-reporting parameters and convergence criteria from base case simulation

	True	Posterior estimates				$\hat{R}$				
	Mean	Mean	25th	50th	75th	Min.	25th	50th	75th	Max.
p	0.667	0.680	0.567	0.715	0.814	1	1.004	1.012	1.024	2.062
ϕ	0.333	0.266	0.160	0.238	0.315	1	1.003	1.007	1.013	1.974
ψ	0.020	0.029	0.010	0.016	0.028	1	1.010	1.035	1.120	2.152

Note: $\hat{R}$ is a measure of convergence with values close to 1.0 being optimal.

TABLE 5 Correlation between estimated and true values of p, ϕ, and ψ for base case simulation and simulations where priors for some PK parameters are misspecified (generating distributions for k_{20}, k_{24}, and k_{40} having means equal to half the priors given in Table 3), where PBMC data are missing, where plasma data are missing and where self-reports are missing

	Base case	Extra DOT	Extra SA	Biased PK	Missing PBMC	Missing plasma	Missing self-report
p	0.92	0.94	0.96	0.95	0.84	0.93	0.87
ϕ	0.65	0.73	0.79	0.75	0.58	0.67	NA
ψ	0.41	0.48	0.43	0.28	0.15	0.21	NA

Note: When self-reports are missing, estimation of mis-reporting parameters is not possible.

The constraint on the misreporting parameters mentioned in Equation (5) was implemented using a dummy Bernoulli variable with probability mass depending on a step function of the constraint (Spiegelhalter et al,[24] examples vol III).

Model fitting for the simulation analyses was run for 80 000 iterations (70 000 as burnin). The analysis of the HPTN 067 data was run for 180 000 iterations (170 000 as burnin). Unless otherwise noted, mean values of parameters over all iterations (minus the burnin) are reported. Convergence of key parameters was evaluated using the Gelman and Rubin convergence diagnostic (R).[25]

3 | SIMULATIONS

Our first (base case) simulation was based on the HPTN 067 design and data collection schedule (Table 1). The simulated dataset consisted of 100 participants with a 6-week DOT period followed by a 24-week period of self-administered daily drug dosing. Drug concentrations were generated based on the model described in Section 2.2 using the central values of the parameters given in Table 3 and including individual level variability for k_a, k_{20}, k_{24}, and a_0 (*Note*: Data were simulated with individual level variability for k_a but our model fit k_a as fixed at 9.79 h^{-1}, as described in Section 2.3). In addition, individual-level average adherence, over-, and under-reporting were simulated from the distributions

$$p_i \sim \text{beta}(4, 2),$$
$$\phi_i \sim \text{beta}(2, 4),$$
$$\psi_i \sim \text{beta}(1, 49).$$

(*Note*: Although we impose the identifiability constraint $\psi_i + \phi_i < 1$, the probability of this constraint being violated with the distributions given here is <0.000001; thus, the mean and standard deviations of the generating distributions follow directly from the beta distributions.)

The values of p_i, ϕ_i, and ψ_i were then estimated as described in Section 2.3. Figure 2 ("Base") shows the true simulated values of these three parameters vs estimated values based on the posterior means from the MCMC sample. The estimates of individual-level average adherence, p_i, are generally quite accurate while the over- and under-reporting probabilities, ϕ_i and ψ_i, are estimated less well—ϕ_i shows shrinkage (slope less than 1) and downward bias (mean estimate over all individuals equal to 0.27 compared to expected value of 0.33 based on the generating distribution) and the correlation of $\hat{\psi}_i$ with the true values is relatively low; see Tables 4 and 5. The correlation between the average estimated pill-taking (average of the estimated $P(A_{ij}|R_i, P_i, B_i)$) and the average true pill-taking (average of the simulated A_{ij})—both averaged

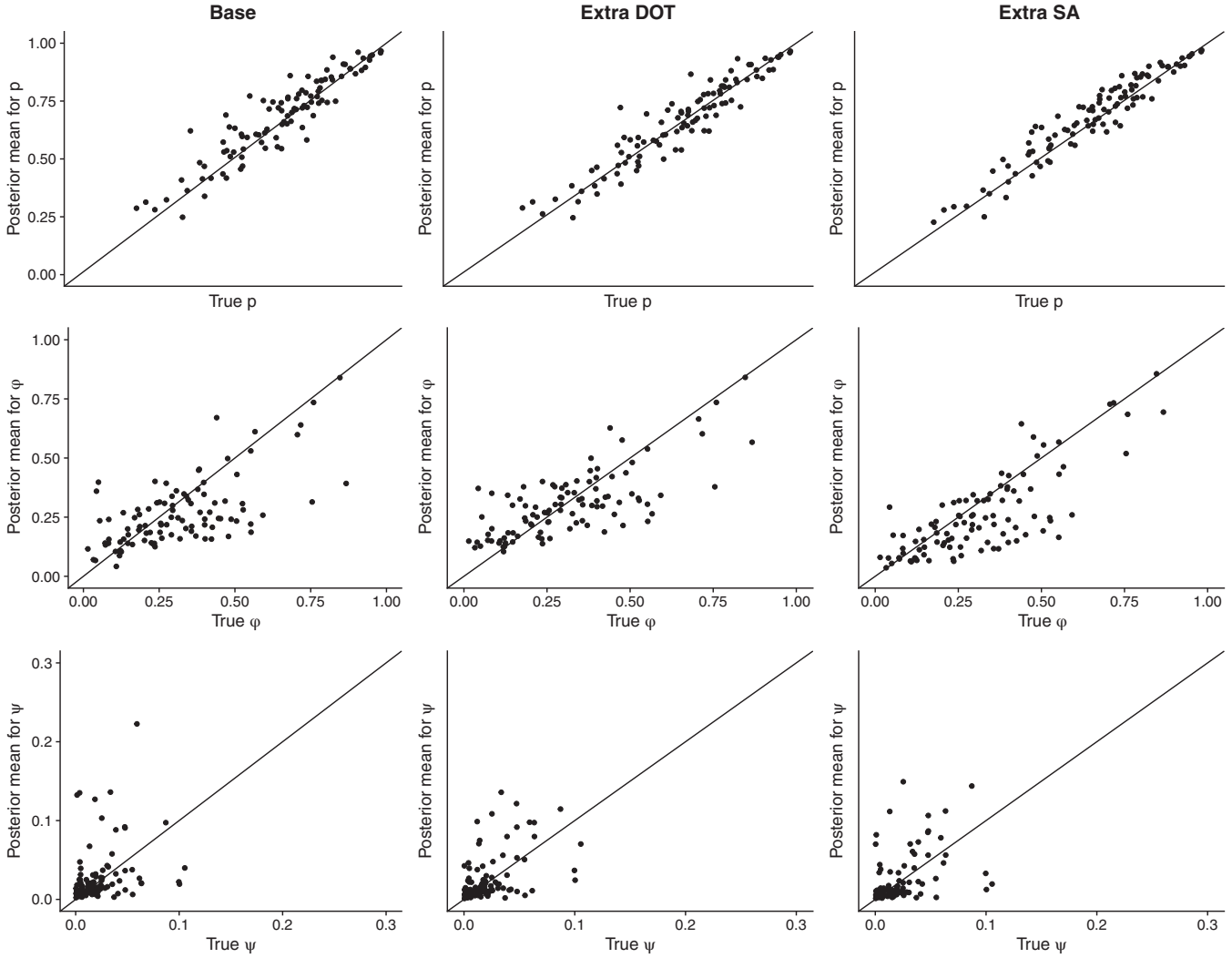

FIGURE 2 Comparison of estimated values for adherence (p), over-reporting (ϕ), and under-reporting (ψ) vs true values from simulations based on the HPTN 067 design and data collection schedule as designed, with additional samples during the DOT period, and with additional samples during the SA period

over the SA-phase of follow-up—is 0.96; this is notably higher than the correlation (0.87) between the average self-reported pill-taking (average of the R_{ij}) and the average true pill-taking.

The posterior distributions of the PK parameters vary in their width, reflecting greater or lesser uncertainty (see Appendix Table A1) but are within reason, likely because of the relatively strong priors provided. We hypothesize that the PK model is not fully identifiable given the data collection schedule of HPTN 067. However, this partial non-identifiability does not prevent accurate estimation of adherence and over/under-reporting as seen in Figure 2.

We also investigated alternative data collection schedules via simulation. In a second (extra DOT) simulation, we augment the HPTN 067 blood sampling schedule by collecting two additional blood samples during the DOT period (Figure 2, "Extra DOT"). Specifically, additional samples are collected at 1 and 3 days after the week 4 sample shown in Table 1. Finally, in a third (extra SA) simulation, we augment the HPTN 067 blood sampling schedule by collecting three additional samples at weeks 14, 22, and 26 during the SA period (Figure 2, "Extra SA"). In either scenario, we see only small improvements in estimation of adherence and mis-reporting parameters (Table 5), suggesting that much denser sampling (eg, within the 24-hour period immediately after a directly observed dose) would be necessary to meaningfully improve estimation of individual-level adherence or mis-reporting parameters.

We conducted additional simulations to investigate the sensitivity of the estimates of p, ϕ, and ψ to (i) misspecification of pharmacokinetic parameter priors; (ii) loss of information from one of PBMC, plasma and self-reports. The results are

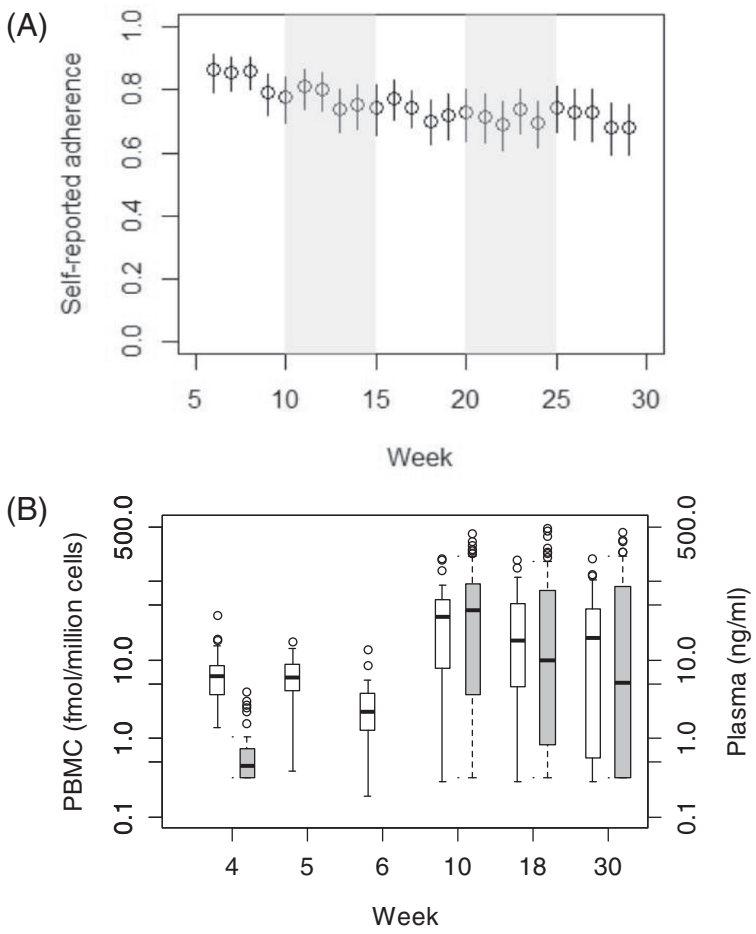

FIGURE 3 Data for HPTN 067 Cape Town daily arm participants over follow-up: (A) Weekly average self-reported adherence during the self-administered dosing phase, with 95% confidence intervals, beginning with week 6. (B) Boxplots of plasma (shaded boxes) and PBMC (white boxes) drug levels at blood sampling times. By design, plasma samples were not collected at weeks 5 and 6

summarized in Table 5 as correlations between the estimated and true values of p, ϕ, and ψ. We see that the estimates of p, ϕ are robust (similar or higher correlation to the base case) to misspecification of priors for the PK parameters k_{20}, k_{24}, and k_{40} as well as loss of plasma information, but more sensitive to loss of PBMC information. Correlation of $\hat{\psi}$ with ψ is lower than the base case in all scenarios. When self-reports are missing, estimates of p are only modestly worse compared to the base case but estimation of ϕ and ψ is not possible. In addition, estimation of daily adherence (A_{ij}) is much worse in this case—for example, when self-reports are missing the variance of the estimated daily adherence, $\hat{A}_{ij}$, increases by a factor of 2.4 compared to the base case.

4 | RESULTS FROM THE HPTN 067 STUDY

We analyzed data for 59 women randomized to daily dosing in the HPTN 067 Cape Town site. Participants' median weight was 74 kg (IQR: 62-90 kg). Average total follow-up was 213 days and women provided 239 evaluable plasma TFV samples and 329 evaluable PBMC samples. During the SA phase (9921 total person-days; average 168 days) self-reported adherence information was available on 9756 days (98%) and women reported taking PrEP on 75% of those days. Median plasma TFV during the SA phase was 18.8 ng/mL (IQR: 0.57-82.7; max = 457) and median PBMC TFV-DP was 13.4 fmol/million cells (IQR: 1.4-46.5; max = 197). Figure 3 summarizes the self-reported, plasma, and PBMC data over follow-up.

Figure 4 shows the marginal distributions of estimates of p, ψ, and ϕ from the HPTN 067 Cape Town participants (see Appendix Tables A2 and A3 for estimated adherence and PK model parameters and convergence criteria). Median

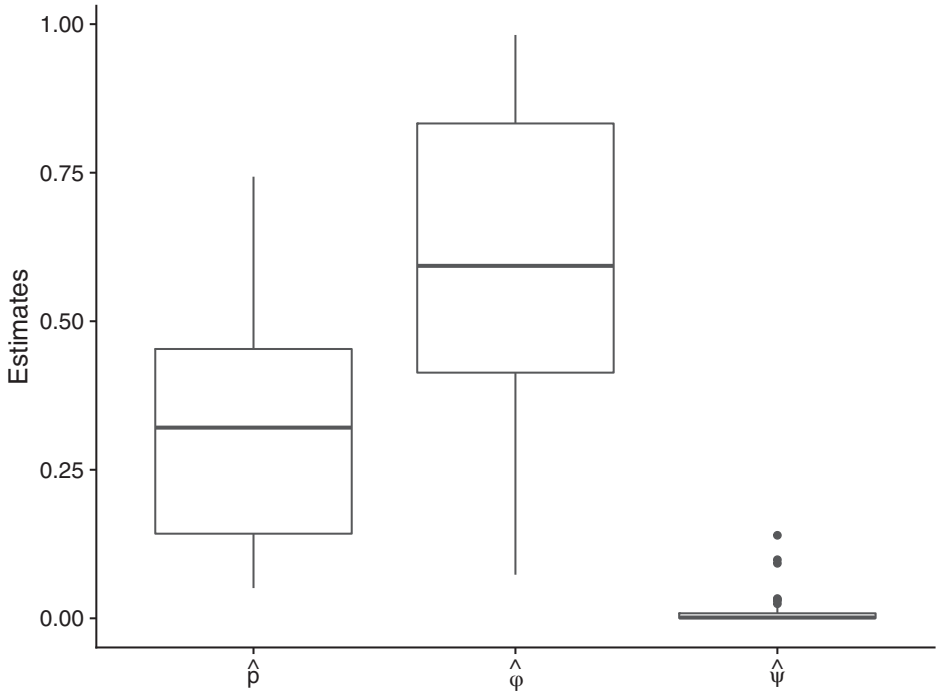

FIGURE 4 Estimated posterior means for adherence ($\hat{p}_i$), over-reporting ($\hat{\phi}_i$), and under-reporting ($\hat{\psi}_i$) for HPTN 067 Cape Town daily arm participants

estimated individual-level average adherence, $\hat{p}_i$, was 32% (IQR: 14%-45%) (compared to median self-reported adherence of 75%), over-reporting was common, and under-reporting was less common. Seven of 59 women (12%) had estimated adherence greater than (the equivalent of) four doses per week ($\hat{p}_i > 0.57$) and none had estimated adherence greater than 6 doses per week ($\hat{p}_i > 0.86$), a level that is thought to be necessary for consistent protection from HIV infection in women.[26] In Figure 5, all estimated values for average individual-level adherence are less than the average self-reported adherence, suggesting frequent over-reporting of adherence ($\psi > 0$) and little underreporting ($\phi \approx 0$).

Figure 6 shows the relationship between plasma drug levels and the number of pills taken in the prior week as measured by (A) self-report and (B) average estimated pill-taking (average $P(A_{ij} = 1|R_i, P_i, B_i)$), both in the past week; and the relationship between PBMC drug levels and the number of pills taken in the prior two weeks as measured by (C) self-report and (D) average estimated pill-taking, both in the past 2 weeks. Among women who report 0 or 1 pill in the past week, plasma levels are uniformly low, consistent with our finding of little under-reporting of pill-taking. However, for women who report 2 or more pills in the past week, there is large variation in the observed plasma drug levels, even among women who report identical numbers of pills taken. This may partly reflect variations in timing of pill taking but also likely reflects variable levels of over-reporting. In contrast, women with estimated pill-taking consistent with 3 or more pills in the past week (>5/14) (Figure 6B) show much less variation in plasma drug levels within adherence categories, suggesting that the estimated pill-taking measure has correctly adjusted for over-reporting (note that none of the participants have estimated adherence in the highest category of >13/14). Interestingly, however, and in contrast to the self-reported pill taking data, women with low estimated pill-taking (<5/14, equivalent of 1-2 pills in the past week) have variable plasma drug levels. The women with low estimated pill-taking and high plasma levels (the "outliers" in the second and third from left boxes in Figure 6B) typically report taking 3 or more pills in the past week. Further investigation shows, however, that these women have low levels of drug in PBMC. This combination of high plasma drug levels and low PBMC drug levels suggests dosing recently before blood sampling. This may represent so-called "white-coat dosing" (taking a pill right before coming into the research clinic) or regular but non-daily dosing (with a dose or doses close to the time of sampling). In either event this leads to a low estimated pill-taking in the past week in spite of the self-report of pill taking and high plasma drug levels.

Comparison of Figure 6C,D shows a striking improvement in the ability of estimated adherence to predict PBMC drug levels compared to self-reported pill-taking—much less variability of PBMC drug levels is seen within categories of estimated adherence compared to categories of self-reported pill-taking. The only exception is, once again, for low levels

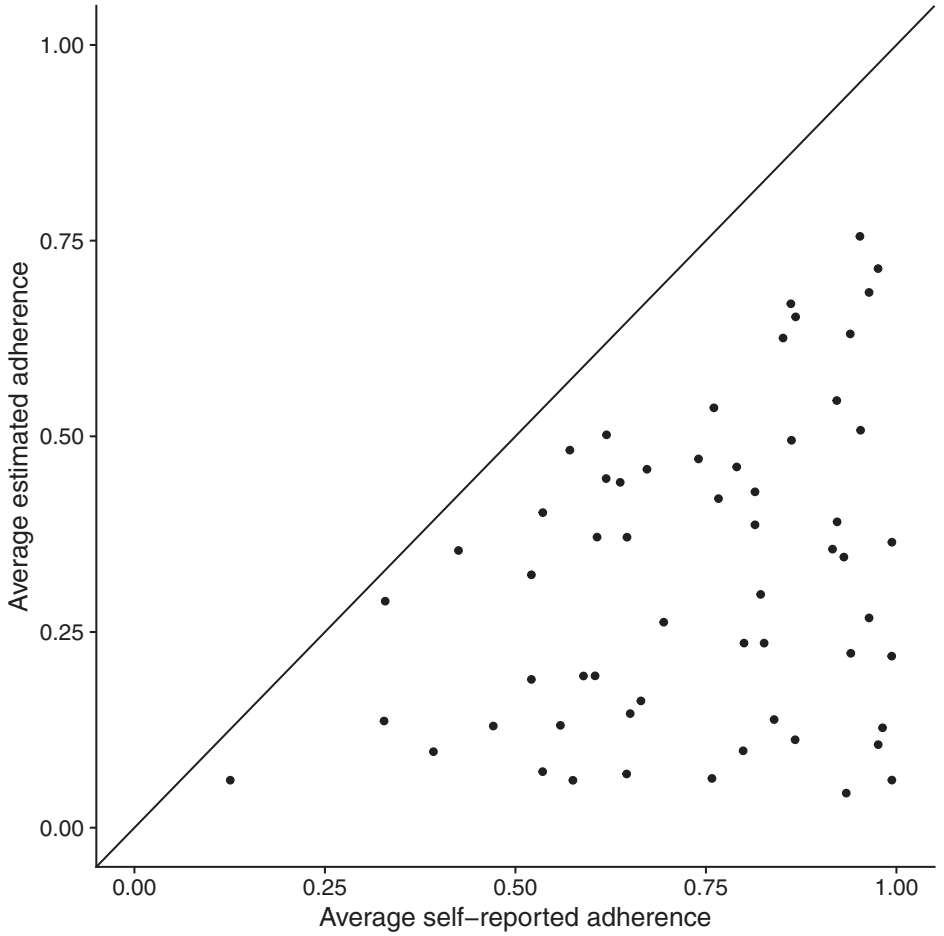

FIGURE 5 Estimated individual-level average adherence ($\hat{p}_i$) vs average self-reported adherence for HPTN 067 Cape Town daily arm participants

of estimated adherence. Since "white coat dosing" has less influence on PBMC drug levels, these variations may be due to variations in the exact timing of the (estimated) 1 or 2 pills taken in the past two weeks. Although one cannot distinguish white-coat dosing from consistent non-daily dosing with plasma levels alone, the addition of PBMC does allow us to distinguish these different scenarios.

The median drug levels associated with the estimated adherence categories in Figure 6B,D tend to be higher than comparable values reported from DOT studies such as HPTN 066.[9] However, such studies typically collect blood samples just prior to dosing, when drug levels are at their nadir. In contrast, HPTN 067 participants likely took their pills at various times prior to their blood draw. This likely contributes to the overall higher median levels (as well as high variability) seen in the drug levels in these data.

Taken together, the plots in Figure 6 suggest that estimated adherence is a more accurate reflection of pill taking than self-reports. These results also suggest that a joint pharmacokinetic model that includes biological compartments with both short and long-term half-lives (eg, plasma and PBMC) is necessary to capture true drug adherence. Reflecting the robustness of the results to prior misspecification seen in the simulations, the results shown in Figures 4 to 6 show little change if the prior means for k_{20}, k_{24}, k_{40} are halved (see also Supplemental Tables S1 and S2).

5 | DISCUSSION

The approach developed here allows one to combine data from multiple sources to estimate the hypothetical "true" adherence to a daily oral medication. The approach can, in theory, be extended to work with any combination of data sources and arbitrarily complex models. In practice, however, a pharmacokinetic model with good prior parameter

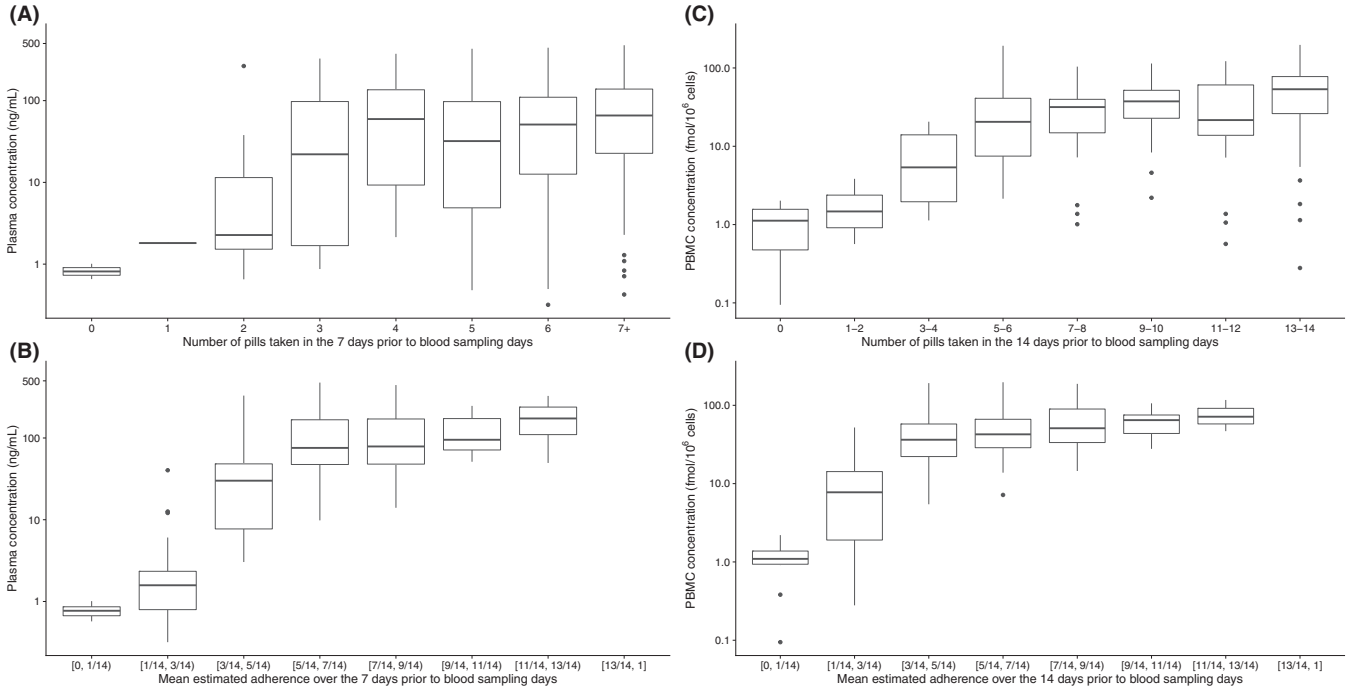

FIGURE 6 Plasma (plots A and B) and PBMC drug levels (plots C and D) vs number of pills taken in the past week (plasma) or two weeks (PBMC) as measured by self-report (A and C) and average estimated pill-taking (average $P(A_{ij} = 1|R_i, P_i, B_i)$) (B and D)

information will generally be necessary to implement these methods since the biologic sampling from most clinical trials will not typically be dense enough to support estimation of the pharmacokinetic parameters. In particular, the first assumption given in Equation (1)—independence between the self-reported data and the biological measures of adherence, conditional on true pill-taking—seems intuitively reasonable but further assumptions of conditional independence between biological measures may be less tenable. Other model assumptions could be assessed by fitting a more complex model to the data that included the assumptions as a special case and then comparing model fit (eg, as noted in Equations 3 and 4).

The strength of this approach is that it combines all available information to make quantitative statements about individual-level adherence and misreporting at the finest time scale available in the observed data. For example, in the HPTN 067 data the method provides an estimated probability that a participant took a pill on any given day as well as an average probability of pill-taking over the entire self-administered dosing period of follow-up. In practice, however, after accounting for the self-report, these daily estimates of adherence are less useful than one might hope. We found that, aside from the days immediately preceding each blood sample, there is little temporal variation in the estimated daily adherence. More specifically, outside of the days immediately preceding the blood sample, the estimated probability of pill-taking for an individual on a given day is typically one of two values, depending on the self-report for that day and the likelihood of under and over-reporting for that participant. We present figures in the Appendix (Appendix Figure A1) showing the time course of estimated probability of pill-taking for representative participants with low, high and intermediate estimated adherence.

Initially, we speculated that additional plasma samples, collected closer to the time of pill-taking during the DOT phase, would improve estimation of individual-level adherence and misreporting probabilities by providing more information on person-level pharmacokinetic parameters. In our limited experiment here, however, more frequent daily sampling during the DOT or SA phase did not lead to a noticeable improvement in estimation. It is possible that more intensive intraday sampling (ie, 1-12 hours post-DOT dose) could lead to improved estimation.

When these methods were applied to data from women taking daily oral PrEP in South Africa, we found evidence of significant over-reporting and minor under-reporting of pill-taking; the net effect is that average adherence to daily dosing is estimated to be lower than reported in most participants. The mean estimated pill-taking in the weeks immediately prior to blood sampling predicted plasma and PBMC drug levels very well, and noticeably better than self-reported pill-taking when the estimated number of pills taken is high. When the estimated number of pills taken in the prior week is low, plasma levels at the time of sampling may still be high, which likely reflects dosing shortly before the sampling. These

findings are specific to the women in this sample and may not be representative or other women in South Africa or elsewhere, or of men using TDF/FTC.

This model may be extended in a number of ways. In particular, one could allow the individual-level average adherence (p_i) to vary over time or by other covariates (as in Equation 3) or as a function of an impending follow-up visit (ie, explicitly parameterizing the possibility of whitecoat dosing); additional biologic measures (eg, hair) could be incorporated, although this would require a well-characterized joint pharmacokinetic model of plasma, PBMC and hair, or the possibly unrealistic assumption of conditional independence between hair and the blood compartments. Any of these approaches would considerably expand the number of model parameters and make model fitting and convergence more challenging.

We believe the approach outlined here provides researchers with a coherent approach to combining multiple sources of information about adherence to pill-taking, together with prior information on PK parameters and measurements following directly observed dosing, to provide a more accurate estimate of true pill consumption. Such estimates can then be used in secondary trial analyses to identify "adherers" and to study correlates of adherence.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The protocol was approved by the Ethical Review Committee for Research in Human Subjects of the Thailand Ministry of Public Health, and by Institutional Review Boards of the U.S. CDC and Columbia University Medical Center. The protocol was registered at ClinicalTrials.gov (identifier NCT01327651; https://www.hptn.org/research/studies/82).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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APPENDIX

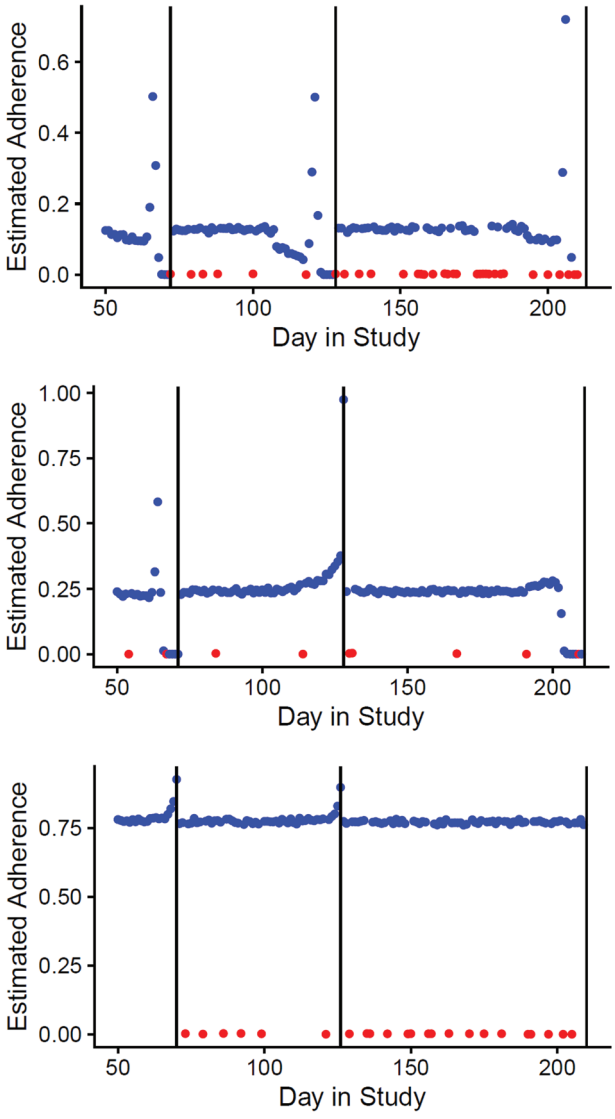

FIGURE A1 Estimated adherence over the self-administered dosing phase of the study for three participants. Vertical lines represent blood sampling times. Days when the participant self-reported taking a pill are in blue and estimated adherence associated with self-reports of no pill taking are depicted in red

TABLE A1 Estimated PK parameters and convergence criteria from base-case simulation with k_a fixed at 9.79 (see Section 2.3)

		Posterior	Posterior	95% credible interval		$\hat{R}$				
	True value	Mean	Median	Lower	Upper	Min.	25th	50th	75th	Max.
k_a	9.790	9.777	9.778	9.712	9.839	-	-	1.001	-	-
k_{23}	0.631	0.628	0.627	0.510	0.751	-	-	1.062	-	-
k_{32}	0.396	0.369	0.368	0.326	0.420	-	-	1.160	-	-
k_{40}	0.013	0.013	0.013	0.012	0.013	-	-	1.225	-	-
k_{24} mean	0.017	0.045	0.044	0.034	0.058	1	1.062	1.133	1.300	38.449
k_{24} SD	0.009	0.007	0.000	0.003	0.043	-	-	-	-	-
k_{20} mean	0.130	0.152	0.151	0.117	0.193	1	1.052	1.147	1.322	57.953
k_{20} SD	1.527	0.020	0.005	0.018	0.044	-	-	-	-	-
a_0 mean	385.710	417.239	412.047	300.473	563.773	1	1.031	1.072	1.154	7.705
a_0 SD	76.553	67.504	30.374	62.649	125.484	-	-	-	-	-
a_1	−2.160	−2.172	−2.173	−3.623	−0.660	-	-	1.002	-	-

Note: True values are based on parameter estimates given by Burns et al.[20] For parameters simulated with between-subject variability (k_{24}, k_{20}, a_0), the true values represent the empirical means and standard deviations in the simulated dataset. $\hat{R}$ is a measure of convergence with values close to 1.0 being optimal. For population parameters only a single value of R exists and is given as the "median" R; for individual-level parameters quantiles of the distribution of the values of R are shown.

TABLE A2 Estimated adherence and mis-reporting parameters and convergence criteria from Cape Town data

	Posterior estimates				$\hat{R}$				
	Mean	25th	50th	75th	Min.	25th	50th	75th	Max.
p	0.32	0.14	0.32	0.45	1.00	1.00	1.01	1.04	1.37
ϕ	0.61	0.41	0.59	0.83	1.00	1.00	1.01	1.06	1.34
ψ	0.011	0.000	0.001	0.008	1.01	1.14	1.33	1.46	8.87

Note: $\hat{R}$ is a measure of convergence with values close to 1.0 being optimal.

TABLE A3 Estimated PK parameters and convergence criteria from Cape Town data

		Posterior	Posterior	95% credible interval		$\hat{R}$				
	True value	Mean	Median	Lower	Upper	Min.	25th	50th	75th	Max.
k_a	9.741	9.740	9.682	9.800	NA	NA	1.000	NA	NA	
k_{23}	0.477	0.480	0.323	0.619	NA	NA	1.072	NA	NA	
k_{32}	0.532	0.528	0.382	0.725	NA	NA	1.006	NA	NA	
k_{40}	0.005	0.004	0.004	0.005	NA	NA	1.023	NA	NA	
k_{24} mean	0.004	0.004	0.002	0.010	1.000	1.003	1.011	1.037	1.801	
k_{24} SD	0.002	0.000	0.002	0.005	NA	NA	NA	NA	NA	
k_{20} mean	0.066	0.065	0.049	0.088	1.001	1.042	1.133	1.381	7.213	
k_{20} SD	0.010	0.006	0.008	0.018	NA	NA	NA	NA	NA	
a_0 mean	643.644	558.505	225.056	1503.702	1.016	1.080	1.180	1.612	13.162	
a_0 SD	341.150	129.784	241.357	932.940	NA	NA	NA	NA	NA	
a_1	−2.217	−2.215	−3.596	−0.794	NA	NA	1.004	NA	NA	

Note: In this analysis, k_a was effectively fixed at 9.74 (see Section 2.3). $\hat{R}$ is a measure of convergence with values close to 1.0 being optimal. For population parameters only a single value of R exists and is given as the "median" R; for individual-level parameters quantiles of the distribution of the values of R are shown.