

Supplementary Material
to
Predicted effectiveness of daily and non-daily PrEP
for MSM based on sex and pill-taking patterns from
HPTN 067/ADAPT

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1 Agent-Based Model Description

1.1 Stratifying Sexual Behavior by Risk

Individuals in the model were divided into low-risk and high-risk groups based on their propensity for concurrent stable partnerships. High-risk participants in the model may have up to two concurrent partners, one of which may be long-term, and may engage in casual sex outside of their partnerships, while low-risk participants are serially monogamous. The proportion of participants in each risk group in the model was informed by responses to the HPTN 067/ADAPT behavioral questionnaire: the proportion in the low-risk group was estimated as the proportion of men who reported at most one partner in the last three months prior to enrollment, the proportion in the high-risk group from those who reported two or more partners. Some of the high-risk participants also practiced one-time casual sex with partners of unknown HIV status. The proportion of high-risk men engaging in one-time casual contacts and the frequency of those contacts were estimated from participants who reported more than three partners. In addition to having fewer partners, low-risk individuals/partners also have lower HIV incidence and prevalence than high-risk individuals/partners.

1.2 Partnerships

Partnerships are categorized as either casual, short term, or long term. Casual partnerships last only a single act and are only engaged in by individuals from the high-risk group. The frequency of these acts will be discussed later. All other partnerships start as short term (see Table S1). Every day these short term partnerships have a daily probability to break up or to transition into long term partnerships. The rate of dissolution of short term partnerships was assumed to be once every 120 days on average. The rate of dissolution of the long term partnership is set to the inverse of the length of the main partnership of 1130 days given in [7]. The transition rate from short term to long term was calibrated to match the 41% of partnerships in MSM [6].

Low-risk individuals are assumed to only have one partnership at a time. In contrast, high-risk individuals can have up to two partners at a time, but only one long term partnership. When in a long term partnership, we assume that they acquire new partnerships at only half the rate as they would otherwise. Moreover, we assume that their long term relationships are twice as likely to dissolve if they have a concurrent short term partnership. Finally, in the absence of any other partners, high-risk individuals acquire partners at twice the rate of low-risk individuals.

High-risk MSM who engage in casual sex form casual partnerships for a single act. These participants are assumed to select one-time partners from the high-risk participants. However, for simplicity, we assume that these participants only have one main partner (i.e., either short or long term partner) at a time.

Sexual acts in the model occurred randomly in time. The average frequency of sexual acts in each partnership was assigned at partnership initiation and remained constant for its duration. For those who practice casual sex, the frequency of casual sex was assigned at the start of the simulation to match the difference in sex frequency between subgroups with ≥ 4 partners and the rest in the trial. The average proportion of sex acts protected by condoms was assumed to be the same for stable and casual partnerships. No correlation between condom use and PrEP coverage was assumed, reflecting the self-reported data from the trial (see Table S12). The HIV acquisition risk per sex act was differentiated by the partners stage of infection (acute, asymptomatic, or late), and treatment status. Differences in transmission risk due to sexual positioning were not considered.

1.3 HIV status

Each sex partner infected with HIV is in one of three HIV stages when assigned to a participant in the cohort: acute, asymptomatic or late. HIV stage is used in the model to determine the HIV infection risk per sex act (see below). Partners in the acute and late phases have a 9.2- and 7.3-fold higher per-act probability of transmitting HIV than the asymptomatic phase [4]. Based on the definitions used in [4], we set the length of the acute and late phases to be 5 and 15 months long, respectively (when not on antiretroviral therapy, ART). The asymptomatic phase is 115 months to give a total of ten years before individuals enter the late phase

Table S1: Partnership parameters

Parameter	Value	Source
Rate of acquiring short-term partner:low-risk	0.5 months ⁻¹	Assumed
Rate of acquiring short-term partner:high-risk	1 month ⁻¹	Assumed
Relative partner acquisition rate with 1 short term partner:low-risk	0.0	Assumed
Relative partner acquisition rate with 1 short term partner:high-risk	1.0	Assumed
Relative partner acquisition rate with 1 long term partner:low-risk	0.0	Assumed
Relative partner acquisition rate with 1 long term partner:high-risk	0.5	Assumed
Relative partner acquisition rate with 2 partners:high-risk	0.0	Assumed
Dissolution rate of short term partnership	0.25 month ⁻¹	Assumed
Dissolution rate of long term partnership	0.33 years ⁻¹	[7]
Relative dissolution rate of long term partnership with 2 partners	2	Assumed
Transition rate of short to long	2 years ⁻¹	[6]

(when not on ART). After the late phase, individuals enter the extended phase which lasts by the end of the simulation. In the extended phase, individuals have sex 40% less frequently[7].

Table S2: Duration and relative infectivity of HIV phases. All numbers derived from [4].

HIV phase	Duration	Relative infectivity
Acute	5 months	9.2
Asymptomatic	115 months	1
Late	15 month	7.3
Extended	-	7.3

1.4 HIV incidence and prevalence

Let $I_{L,H}$ and $P_{L,H}$ be the incidence and prevalence in the low and high-risk populations, respectively. We assume that

$$\begin{aligned} I_L &= \psi_1 I_H \\ P_L &= \psi_2 P_H \end{aligned}$$

Based on [12] which compared the HIV prevalence and HIV incidence among individuals with and without concurrent partnerships, we explore $\psi_1 \in [0.1, 0.5]$ and $\psi_2 \in [0.5, 0.75]$.

We then calculate the HIV incidence and HIV prevalence in the high and low-risk populations so that the overall incidence and prevalence match data from

epidemiological studies in Table S3.

$$I_H = (\text{Overall Incidence}) / ((1 - q_L) + \psi_1 q_L)$$

$$P_H = (\text{Overall Prevalence}) / ((1 - q_L) + \psi_2 q_L)$$

Here q_L is the fraction of the population that is low-risk.

Table S3: Overall HIV incidence and prevalence assumed for Harlem and Bangkok. The confidence intervals for incidence were used to accept/reject possible parameter choices.

Quantity	Value	Source
HIV incidence: Bangkok (per person year)	0.059 (CI 0.052-0.068)	[1]
HIV incidence: Harlem (per person year)	0.025 (CI 0.013-0.044)	[10]
HIV prevalence: Bangkok (%)	21.3	[1]
HIV prevalence: Harlem (%)	19.0	[7]

CI: Confidence Interval

We assume that individuals select partners from the same risk group as themselves with probability $1 - \epsilon$ and from population at large with probability ϵ , the mixing degree. $\epsilon = 1$ is the case where low and high-risk partners mix homogeneously and $\epsilon = 0$ is the case where low-risk have exclusively low-risk partners. Let $C_{L,H}$ be the probabilities that low and high-risk individuals choose high-risk partners respectively.

$$C_L = \epsilon(1 - q_L)$$

$$C_H = \epsilon q_L + (1 - \epsilon)(1 - q_L)$$

The incidence and prevalence of HIV in the sexual partners of trial participants is then calculated via

$$\text{Partner Incidence} = C I_H + (1 - C) I_L$$

$$\text{Partner Prevalence} = C P_H + (1 - C) P_L$$

1.5 ART status and efficacy

ART is assumed to decrease the probability of infection and also slow the progression of HIV. The ART initiation does not occur during the acute phase, while in the late phase it is assumed 10-fold more likely than in the asymptomatic phase. In average, 0%, 48%, and 90% are on ART in the acute, asymptomatic, and late phases, respectively. This results in overall 51% of the HIV infected population on ART. This is similar to the values reported in [9], although we allow these rates to vary due to uncertainty. Our midpoint parameter choices also predict that in a

given year, roughly four times as many individual will initiate ART while in the asymptomatic phase than in the late phase. This ratio agrees with the ratio of individuals without/with AIDS at HIV diagnosis in New York City [2].

ART efficacy is also uncertain. In both the U.S. and Thailand, viral suppression is at least 80% of those on ART [9]. We assume that efficacy is 100% in these individuals, but varies between 30% and 70% for virally unsuppressed. Therefore, we assume that overall ART efficacy is in the range 86%-94%.

1.6 PrEP efficacy per act

We first estimated the number of pills taken within a week around each sex act (five days before and two days after) reported at the HPTN 067/ADAPT sites in Harlem and Bangkok. (see Figure S2) Then we averaged PrEP efficacy for each group of covered acts (fully and partially) assuming 0%, 76% and 96% protection for acts with 0-1, 2-3 and 4+ pills taken within a week. In the main analysis we used the efficacy estimates for each regimen, based on the pill-taking behaviors at each site. We also considered that the PrEP efficacy per partially covered acts may be overestimated given that for an overwhelming proportion of these acts the post-exposure pill is not taken (Figure 2 in [8]). Studies exploring PrEP protection against repeated rectal challenges in macaques demonstrated the importance of the post-exposure dose.[5] Thus, we assessed the sensitivity of our results by exploring a conservative scenario assuming reduced PrEP efficacies for partially covered acts (50% of the data-based estimates used in the main analysis).

1.7 Heterogeneity in PrEP coverage among participants

In our main scenario we distributed the total number of covered acts among the modelled MSM cohort using the HPTN 067/ADAPT trial data. To do this we stratified trial participants into three subgroups with respect to the percentage of sexual acts fully covered by PrEP and calculated the average percentage of sexual acts which are fully and partially covered in each subgroup. We assessed the sensitivity of our effectiveness estimates to the way covered acts are distributed among the participants in the simulated cohort. To this end we compared our main projections with two alternative distributions of the covered acts: i) a uniform PrEP scenario, where all participants have the same proportions of fully and partially covered acts and ii) a concentrated PrEP scenario, where participants are divided into three subgroups in which participants have all of their sexual acts fully covered, partially covered or not covered, respectively. All three simulated scenarios are constructed to have the same overall proportion of fully and partially covered acts for the entire cohort.

1.8 Simulation Procedure

1. Cohorts of 3600 men are assigned with risk group, number and type of current partnerships, pre-exposure propylaxis (PrEP) adherence, trial arm, and

tendency to form partnerships with women (in the case of the Harlem site).

- (a) Individuals were assigned to either low or high-risk groups as some of the high-risk MSM are allowed to engage in casual sex. low-risk individuals have at most one partner at a time and are more likely to partner with a low-risk than high-risk MSM. high-risk individuals, who don't practice casual sex can have up to two concurrent partnerships. high-risk individuals, who practice casual sex are assumed to have a single 'main partner', but select other casual partners daily from the high-risk population.
 - (b) The initial number and type of individual partnerships are given in Table S4.
 - (c) Depending on the coverage scenario being simulated, individuals are stratified in different coverage groups. The PrEP coverage group determines the probability that an act will be fully or partially covered, as well as the efficacy of this coverage. In the 'homogeneous' scenario, all individuals belong to a single group, with the probability of partial and full coverage the same for everyone. In the 'concentrated' scenario, individuals are pre-assigned to groups with all sex acts fully covered, partially covered, or not covered. Finally, in the 'data-driven' scenario, individuals are grouped by the proportion of fully covered acts (high, medium or low) with coverage level and per act efficacy informed by the trial data (see main text).
 - (d) Individuals are assigned to either daily, time-driven, or event-driven PrEP. The pill taking behavior is not explicitly modeling. Instead the rates of full and partial coverage, as well as the efficacy associated with these coverage levels, is determined for each coverage type from the trial data (see main text).
 - (e) At the Harlem site, many individuals reported vaginal sex acts. Therefore, we allowed for having female partners.
2. Existing partnerships are initialized with the following attributes:
- (a) starting day of the partnership with respect to the start of the simulation. All long-term partnerships are assumed a year old while short-term partnerships are initiated between 30 and 180 days prior to the start of the simulation,
 - (b) partners risk level (high or low), the fraction of high-risk partnerships depends on the risk group of the individual,
 - (c) frequency of sexual activity,
 - (d) daily probability to break up,
 - (e) current HIV and ART status of the partner. The HIV and ART status of sexual partners was randomly assigned based on assumed HIV prevalence and ART coverage among the partners by risk group (high and low)

- (f) practicing vaginal sex (yes, no)
3. On each day, for each participant, we simulate:
- (a) Initiation of new partnerships. High-risk individuals were assumed to initiate new partnerships at a lower rate when they were in an active long-term partnership compared to men who did not have a long term partner (relative rate 0.5). Note that low-risk and high-risk individuals practicing casual sex may only have one stable partner at a time.
 - (b) Sex acts with current partners based on the frequency of acts for each partnership. Probability of condom use depends on the type of partnership. HIV transmission may occur if the partner is HIV positive. The probability of HIV acquisition depends on the type of the act (vaginal vs. anal), the partner's HIV stage and ART status, and if the act is protected by condom. The probability of having sex on the first day of a new partnership is 100%.
 - (c) Casual sex acts (if participant is in the high-risk group practicing casual sex). The HIV and ART status of casual partners is randomly assigned based on assumed HIV prevalence and ART coverage among the high-risk population. HIV transmission may occur if the partner is HIV positive. The probability of HIV acquisition depends on the type of the act (vaginal vs. anal), the partner's HIV stage and ART status, and if the act is protected by condom.
 - (d) Active partner(s) may acquire HIV outside the relationship depending on his risk level.
 - (e) Active infected partner(s) who are not on ART may initiate ART depending on their current HIV phase (excluding the acute HIV phase).
 - (f) If an infected partner in the late HIV phase exceeds the late HIV phase duration, expected sexual activity is reduced by 40%.
 - (g) Short-term partnerships convert into long-term after six months provided that the participant had no other active long-term partners at the time.
 - (h) Dissolution of partnerships. Long- and short-term partnerships were assumed to dissolve at different rates, corresponding to expected partnership duration, with a faster dissolution rate when in concurrent partnerships.
4. Simulation Management:
- (a) Cohort participants are simulated for one year or until HIV infection, whichever occurs first.
 - (b) At the end of each month participants are tested for HIV, and if tested positive, participants are removed from follow up.

- (c) The reference group for estimating PrEP efficacy is simulated by creating a copy of each individual, with the same simulated partnerships and sex acts assuming that PrEP efficacy is zero.

Table S4: Initial partnership status distribution by risk group. The stable partnerships of high-risk individuals practicing casual sex are distributed as in the low-risk group.

Risk group	No partners	1 short-term	2 short-term	1 long-term	1 long-term 1 short-term
High-risk	0%	6%	8%	28%	56%
Low-risk	10%	13%	0%	77%	0%

1.9 Outcomes of Interest

The follow-up time for each participant was measured from the time of enrollment to the time of infection for those infected during follow up, and from the time of enrollment to the time of last visit for those who remain uninfected. The annual HIV incidence rate in each trial arm was calculated as the number of recorded infections divided by the total follow up time in years, which is the sum of the follow up time of all participants. The estimated effectiveness for each simulation was calculated as one minus the incidence rate ratio (IRR) of acquiring HIV, defined as the ratio of the HIV incidence rate when all cohort participants use PrEP vs when nobody use PrEP.

2 Markov Model Description

To help calibrate various parameters, we developed a probabilistic description of partnerships, sex acts, and infections using a Markov Chain model. Individuals are classified by their current number of partnerships as well as their types of partners (categorized by HIV status and frequency of anal sex). As an individual’s risk group is assumed to be fixed throughout the trial period, we define three separate Markov processes for low-risk individuals, high-risk without casual sex and high-risk with casual sex.

2.1 Transmission, Sex, Infection, and Partner Acquisition Probabilities

The total number of possible states for a trial participant then depends on the possible concurrencies of short and long term stable partners, the HIV statuses of these partners, and whether the partnerships engage in anal or vaginal sex. We track a total of $N_h = 8$ possible partner HIV statuses (uninfected, acute, asymptomatic, asymptomatic on ART, late, late on ART, extended, and extended

Table S5: Enumeration of states in the Markov Model. Indices, up to 33 apply to both low-risk and high-risk individuals. Casual sex is still possible for high-risk individuals who practice it. Indices of 34 or greater describe participants who have more than one partner and are therefore only used by high-risk individuals who don't engage in casual sex.

Index	Meaning
1	No main partners
2	One short term male partner, HIV negative
3	One short term male partner, HIV positive, acute phase
4	One short term male partner, HIV positive, asymptomatic phase
5	One short term male partner, HIV positive, asymptomatic phase, on ART
6	One short term male partner, HIV positive, late phase
7	One short term male partner, HIV positive, late phase, on ART
8	One short term male partner, HIV positive, extended phase
9	One short term male partner, HIV positive, extended phase, on ART
10-17	One short term female partner (enumerate all possible HIV phases)
18-33	One long term partner (male or female)
34-545	Two partners (only used for high-risk individuals)

on ART) and two possible sex partner types (anal sex only, vaginal sex only) to give a total of $N_p = 16$ partner types. Low-risk and high-risk individuals practicing casual sex can have either one short term or one long term partner so they have a total of $N_L = 1 + 2N_p = 33$ states. High-risk individuals who don't engage in casual sex have a total of $N_H = 1 + 2N_p + 2N_p^2 = 545$ states.

For each risk group, we then define the following probability matrices

- The transition matrices $A_L, A_C \in \mathbb{R}^{N_L \times N_L}$ and $A_H \in \mathbb{R}^{N_H \times N_H}$ represent the transition probabilities between all possible states. For these transition matrices the entry in the i th row and j th column represents the daily probability of transitioning from state j to state i .
- The rates of anal and vaginal sex $S_L^v, S_L^a, S_C^v, S_C^a \in \mathbb{R}^{N_L \times N_L}$ and $S_H^v, S_H^a \in \mathbb{R}^{N_H \times N_H}$. These rates represent the expected number of sex acts that occur on a given day, with the actual number being Poisson distributed. The daily rate of anal and vaginal sex depends not only on the current state of an individual, but also on the previous state, as new partnerships are guaranteed to have sex on the first day of their existence. The i th row and j th column represents the sex rate for individuals in the state i who were previously in state j . If a partner is in the extended phase of HIV, then the sex rate is reduced by a factor $k_E < 1$. It is assumed that participants do not form new partnerships with individuals already in the extended phase. If an individual is in concurrent partnerships, the sex rate of each is reduced by a factor of two

Table S6: Sex rates based on partner health and time since start of relationship. Sex acts with a given partner are assumed to be either all vaginal or all anal.

Status	Mean Sex Acts
Healthy, older than one day	μ
Extended, older than one day	$k_E \mu$
Healthy, new partnership	$1 + \mu$

(except for the '+1' of a new partnership). Individuals who practice casual sex are assumed to have an average of μ_C casual encounters per day. We assume that f_a are anal and $1 - f_a$ are vaginal. Therefore their anal and vaginal sex rates are incremented by $\mu_C f_a$ and $\mu_C(1 - f_a)$, respectively.

- The per-act risk matrices $R_L^v, R_L^a, R_C^v, R_C^a \in \mathbb{R}^{N_L \times N_L}$ and $R_H^v, R_H^a \in \mathbb{R}^{N_H \times N_H}$ which depend primarily on the HIV status of the partners, and whether those partnership practice anal sex. However, when there is partner concurrency, we must take into account the difference in sex rates on the first day of the partnership.

$$\text{Per Act Risk} = \frac{\sum_k (\text{Per act risk from partner } k \times \text{sex rate with partner } k)}{\sum_k \text{sex rate with partner } k}$$

For example, consider an individual that has one HIV negative partner and then acquires a second partner who is HIV positive with per act risk ρ . On the first day of the relationship they will be much more likely to have sex with the HIV positive partner so the per act risk will be

$$\text{Per Act Risk on day 1} = \frac{\rho \times (1 + \mu/2) + 0 \times \mu/2}{1 + \mu} \approx \rho$$

However, on subsequent days sex acts with each partner are equally likely and the per act exposure risk for this individual will drop.

$$\text{Per Act Risk after day 1} = \frac{\rho \times \mu/2 + 0 \times \mu/2}{\mu} = \rho/2$$

Therefore, the risk matrix must have the same structure as the sex matrices, with the entry in the i th row and j th column representing the per act sex risk for an individual who just moved to the i th state from the j th state

- The daily probabilities of acquiring a new partner $D_L, D_C \in \mathbb{R}^{N_L \times N_L}$ and $D_H \in \mathbb{R}^{N_H \times N_H}$. These are essentially the A matrices with the dissolution and transition probabilities set to zero.

Table S7: Notation for the Markov model.

Notation	Description
$p_L \in \mathbb{R}^{N_L}, p_C \in \mathbb{R}^{N_C}, p_H \in \mathbb{R}^{N_H}$	Vector representing the probability of being in each state
$A_L \in \mathbb{R}^{N_L \times N_L}, A_C \in \mathbb{R}^{N_L \times N_L}, A_H \in \mathbb{R}^{N_H \times N_H}$	Transition matrices
$S_L^{a,v} \in \mathbb{R}^{N_L \times N_L}, S_C^{a,v} \in \mathbb{R}^{N_L \times N_L}, S_H^{a,v} \in \mathbb{R}^{N_H \times N_H}$	Sex matrices
$R_L^{a,v} \in \mathbb{R}^{N_L \times N_L}, R_C \in \mathbb{R}^{N_L \times N_L}, R_H \in \mathbb{R}^{N_H \times N_H}$	Risk matrices
$D_L \in \mathbb{D}^{N_L \times N_L}, D_C \in \mathbb{R}^{N_L \times N_L}, D_H \in \mathbb{D}^{N_H \times N_H}$	Acquisition matrices

3 Calibration Procedure

3.1 Sexual behavior parameters

Using the trial data, we calibrated several model parameters. As we assumed that condom use was independent of risk behavior and partnership status, we calculated condom frequency by dividing the total number of acts with a condom by the total number of acts. This yielded a condom frequency of 43% in Harlem and 83% in Bangkok.

The sex frequency of short and long term partnerships (μ), the frequency of casual sex (μ_C), the fraction of partnerships practicing anal sex, the fraction of casual partners practicing anal, and the proportions of individuals in low-risk group (q_L), high-risk group without casual sex (q_H) and high-risk group with casual sex (q_C) were all estimated via maximum likelihood. Specifically, we calculate the likelihood of each participant's daily number of sex acts and the number of partners reported at baseline.

$$\begin{aligned}
 \text{Likelihood } L &= \prod_k L_k \\
 \text{For individual } k \quad L_k &= \text{Prob}\left(\mathbf{y}_k^{a,v}, X_k | \theta\right) \\
 \text{low-risk} &= \text{Prob}\left(\mathbf{y}_k^{a,v}, x_k | \{A_0, S^{a,v}, D\}_L(\theta)\right) q_L \\
 \text{high-risk} &+ \text{Prob}\left(\mathbf{y}_k^{a,v}, x_k | \{A_0, S^{a,v}, D\}_H(\theta)\right) q_H \\
 \text{Casual risk} &+ \text{Prob}\left(\mathbf{y}_k^{a,v}, x_k | \{A_0, S^{a,v}, D\}_C(\theta)\right) q_C \\
 \text{Parameters } \theta &= [\mu, \mu_C, f_a, g_a, q_L, q_H, q_C]
 \end{aligned}$$

Where $\mathbf{y}_k^{a,v}$ are vectors of anal, vaginal sex acts (by day) and X_k is number of sex partners reported at baseline for the k th participant. The matrices S and D are defined as above. The matrix A_0 is similar to A except that the incidence and prevalence of HIV is assumed to be zero. This simplification greatly aids computational efficiency as we no longer have to keep track of partner HIV status, which is assumed to be independent of sexual behavior. (Note: We assume the reduction in sex frequency when partners reach the extended phase is ignored for

Table S8: Probability of the number of sex partners in previous 90 days for each risk group.

Risk Group	Number of Partners					
	0	1	2	3	4	5+
Low	2.3%	90.4%	6.7%	0.5%	0.1%	0.0%
High	0.1%	6.3%	63.9%	25.6%	3.8%	0.3%
Casual (Bangkok)	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%
Casual (Harlem)	0.0%	0.0%	0.2%	1.0%	2.8%	96.0%

these calculations.) The likelihood is calculated separately for each risk class, then added together to get the total likelihood for the individual.

3.1.1 Likelihood of number of baseline partnerships

We define \mathbf{b}^* to be the steady state of the transition process $A_0\mathbf{b}^* = \mathbf{b}^*$. Then define the i th entry of \mathbf{b}_{nm} to be the probability that a participant had m partners in the last n days and is now in state i . We iteratively solve for \mathbf{b} via

$$\mathbf{b}_{nm} = (A_0 - D)b_{n-1,m} + Db_{n-1,m-1}$$

$$b_{0mi} = \begin{cases} b_i^* & i = 1, m = 0 \\ b_i^* & i \in [2, 33], m = 1 \\ b_i^* & i > 33, m = 2 \\ 0 & \text{otherwise} \end{cases}$$

Setting the initial conditions this way makes sure that we count the partnerships that had initiated prior to baseline window of three months. The values of $\mathbf{b}_{90,m}$ give the probability of having m sex partners in the previous 90 days.

3.1.2 Likelihood of anal and vaginal sex acts during trial

Let the i th entry \mathbf{p}_n^k be the probability that on day n of the trial, the k th participant is in state i , given the number of sex acts that they have had. On day zero, we assume that

$$\mathbf{p}_0^k = \mathbf{b}_{90,x_k}$$

where x_k is the number of partners in the last 90 days at baseline. In the rare case that the number of partners is missing. We set $\mathbf{p}_0^k = \tilde{\mathbf{b}}_{180}$, which is calculated under the assumption that participant has had sex at least once in the last six month:

$$\mathbf{a}_n = A_0\mathbf{a}_{n-1} - \tilde{H}\mathbf{a}_{n-1}$$

$$\tilde{\mathbf{b}}_n = A_0\tilde{\mathbf{b}}_{n-1} + \tilde{H}\mathbf{a}_{n-1}$$

$$\tilde{H}_{ij} = (1 - e^{B_{ij}})A_{0ij}$$

where \tilde{H}_{ij} are the entries of \tilde{H} .

We iteratively solve for \mathbf{p}_n^k via

$$\begin{aligned} y_{kn}^a &= \text{Anal sex acts on day } n \\ y_{kn}^v &= \text{Vaginal sex acts on day } n \\ H_{knij} &= A_{0ij} (S_{ij}^a)^{y_{kn}^a} (S_{ij}^v)^{y_{kn}^v} \frac{e^{-S_{ij}^a - S_{ij}^v}}{y_{kn}^a! y_{kn}^v!} \\ \mathbf{p}_n^k &= H_{kn} \mathbf{p}_{n-1}^k \end{aligned}$$

where H_{knij} are the entries of H_{kn} .

Finally we can calculate the likelihood for a given risk group via

$$\text{Prob}\left(\mathbf{y}_k^{a,v}, x_k | \{A_0, S^{a,v}, D\}\right) = \sum_i p_{n_k i}^k$$

Where n_k is the number of follow up days for individual k .

The maximum likelihood estimates (Table S9) were calculated using the Nelder-Mead algorithm as implemented via `optim` in R.

3.2 Epidemiological parameters

Other parameters, such as the mixing degree, per act infection risk, and rate of ART initiation, could not be estimated directly from the trial data or from the literature. These parameters were calibrated using the following procedure:

1. We first defined parameter ranges for each unknown parameter value, informed as much as possible by the literature (see Table S10 for the ranges).
2. For each model simulation select a parameter values within the predefined ranges.
3. Generate the matrices $A_{L,H,C}$, $S_{L,H,C}^{a,v}$ and $R_{L,H,C}^{a,v}$.
4. Calculate the incidence per person-day by adding up the probability of infection in each state multiplied by the probability of being in each state:

$$\begin{aligned} \text{Daily Incidence} &= \underbrace{q_L \mathbf{1}_L^T ((R_L^a * S_L^a + R_L^v * S_L^v) * A_L)}_{\text{low-risk}} \mathbf{b}_L^* \\ &+ \underbrace{q_H \mathbf{1}_H^T ((R_H^a * S_H^a + R_H^v * S_H^v) * A_H)}_{\text{High Risk}} \mathbf{b}_H^* \\ &+ \underbrace{q_C \mathbf{1}_C^T ((R_C^a * S_C^a + R_C^v * S_C^v) * A_C)}_{\text{Casual Risk}} \mathbf{b}_C^* \end{aligned}$$

Where $\mathbf{1}_{L,H,C}$ are vectors of all ones with length N_S .

- Compare the daily incidence to the estimates for MSM in Harlem and Bangkok (Table S3). If the prediction lies within the 95% confidence interval, accept the parameter choice and proceed to the full agent based model simulation.

Table S9: Parameters derived from HPTN067 Trial data using maximum likelihood.

Calibration Parameters	symbol	Bangkok	Harlem
Daily sex rate with ongoing partners	μ_E	0.13	0.19
Daily sex rate with casual partners	μ_C	0.15	0.09
Fraction of ongoing partners practicing AI		1.00	0.62
Fraction of casual partners practicing AI		1.00	0.94
Fraction low-risk participants	q_L	0.24	0.23
Fraction high-risk participants, no casual sex	q_H	0.45	0.31
Fraction high-risk participants practicing casual sex	q_C	0.31	0.46
Fraction sex acts using with condom		0.83	0.43

Table S10: Parameters varied during simulation. The following parameters were sampled uniformly from the given ranges. If the incidence was predicted to fall inside [1.31-4.42]% for Harlem or [5.2-6.8]% for Bangkok the parameter set was accepted for the agent based simulation. The Harlem and Bangkok columns indicate the range of parameters accepted by the calibration procedure for the individual sites.

Parameters	Range	Sources	Bangkok	Harlem
Ratio of HIV prevalence in low vs high-risk partners	0.50-0.75	[12]	0.50-0.75	
Ratio of HIV incidence in low vs high-risk partners	0.1-0.5	[12]	0.10-0.50	
Mixing degree between low and high-risk partners	0-1	-	0-1	
Condom efficacy	0.71-0.94	[11]	0.71-0.74	0.71-0.94
HIV infection risk from anal sex in asymptomatic phase (%)	0.10-2.50	[3] ¹	0.78-0.83	0.15-0.74
ART initiation rate, asymptomatic phase ($\text{days}^{-1} * 10^{-4}$)	3.0-6.0	[2, 9]	3.0-4.1	3.0-6.0
ART initiation rate, late phase ($\text{days}^{-1} * 10^{-3}$)	3.0-6.0	[2, 9]		3.0-6.0
ART efficacy	0.86-0.94	[9]	0.86-0.94	

¹ We use half the lower bound to account for insertive as well as receptive acts.

4 Supplementary Results

4.1 Sex act coverage from HPTN 067/ADAPT at Bangkok and Harlem by arm

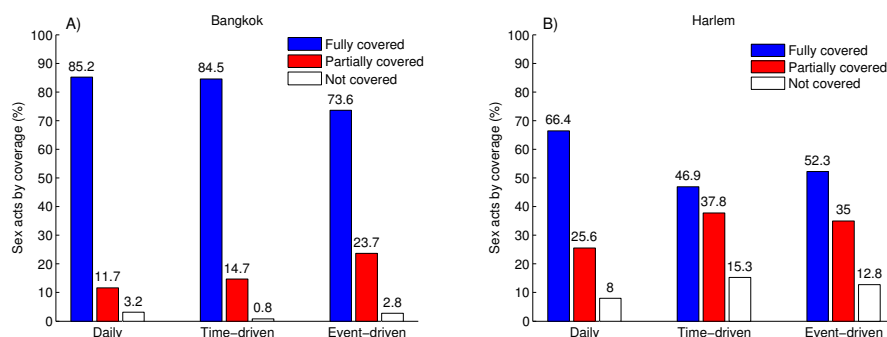


Figure S1: PrEP coverage based on results from HPTN 067/ADAPT. Overall proportion of sex acts in A) Bangkok and B) Harlem which are fully and partially covered by trial arm. A sex act is fully covered if a pill is taken within 96 hours before the act and another pill is taken within 24 hours after the act. An act is classified as partially covered if only one of these pills is taken, either before or after the act.

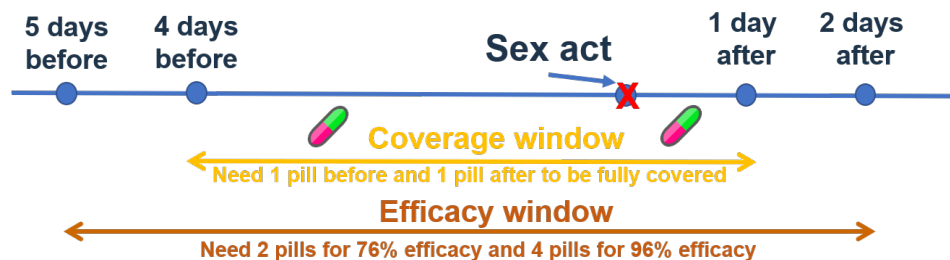


Figure S2: Diagram of PrEP coverage and PrEP efficacy window. Coverage window is consistent with the definition from HPTN 067/ADAPT. A sex act is fully covered if a pill is taken within 96 hours before the act and another pill is taken within 24 hours after the act. An act is classified as partially covered if only one of these pills is taken, either before or after the act. Efficacy window is used to count the number of pills taken within a week around each sex act in order to estimate the PrEP efficacy for each act assuming 0%, 76% and 96% protection for acts with 0-1, 2-3 and 4+ pills taken within a week.

4.2 Distribution of sex acts within coverage groups

Table S11: PrEP coverage of the sex acts of participants in different coverage groups determined by percentage fully-covered acts. It is based on data from Bangkok and Harlem sites of HPTN 067/ADAPT.

Coverage groups	Distribution of sex acts within each coverage group		
	% fully covered	% partially covered	% not covered
Bangkok: Daily PrEP:			
Low (0%-40%)	18.4	58.1	23.5
Medium (40%-80%)	71.8	24.0	4.2
High (80%-100%)	100.0	0.0	0.0
Bangkok: Time-driven PrEP:			
Low (0%-40%)	0.0	100.0	0.0
Medium (40%-80%)	66.9	30.3	2.8
High (80%-100%)	90.2	9.4	0.4
Bangkok: Event-driven PrEP:			
Low (0%-40%)	36.5	62.2	1.3
Medium (40%-80%)	59.7	34.6	5.7
High (80%-100%)	87.5	12.2	0.3
Harlem: Daily PrEP:			
Low (0%-40%)	21.8	51.7	26.5
Medium (40%-80%)	67.1	1.4	1.4
High (80%-100%)	100.0	0.0	0.0
Harlem: Time-driven PrEP:			
Low (0%-40%)	24.0	52.7	23.3
Medium (40%-80%)	61.0	30.6	8.4
High (80%-100%)	93.7	6.0	0.3
Harlem: Event-driven PrEP:			
Low (0%-40%)	27.0	49.4	23.6
Medium (40%-80%)	61.2	33.9	4.9
High (80%-100%)	94.1	4.1	1.8

4.3 Self-reported condom use data by HPTN 067/ADAPT participants in Bangkok and Harlem

Table S12: Percentage of acts unprotected by condoms within each PrEP coverage category and overall for each PrEP regimen.

	Reported percentage unprotected acts			
	Daily	Time-driven	Event-driven	Overall
Bangkok				
Not covered	29.8%	0.0%	3.6%	17.4%
Partially covered	34.3%	14.7%	6.6%	17.0%
Fully covered	28.0%	13.6%	5.1%	17.4%
Harlem				
Not covered	62.4%	56.1%	71.4%	63.2%
Partially covered	63.5%	56.7%	54.7%	57.3%
Fully covered	56.9%	59.5%	51.8%	55.8%

4.4 Sensitivity analysis

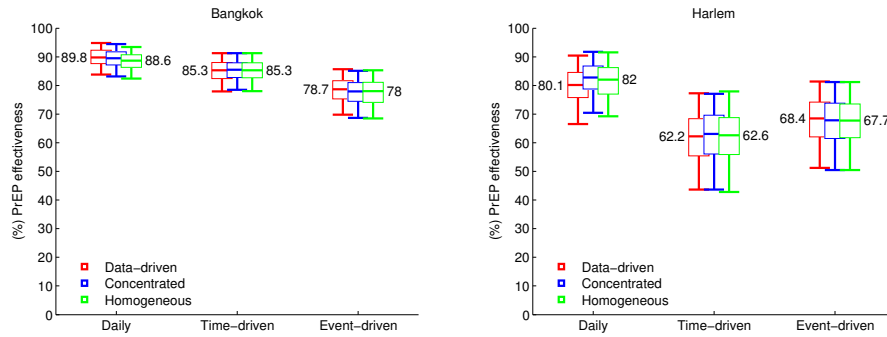


Figure S3: Sensitivity of the PrEP effectiveness to the assumed distribution of covered acts among the MSM in the simulated cohorts. Projected reduction in HIV incidence due to PrEP use under different distributions of fully and partially covered acts using the PrEP efficacy estimates per fully and partially covered acts from the main analysis. Concentrated distribution assumes that a group of MSM has all acts fully covered, another group has all acts partially covered while the rest have no acts covered. Data-driven distribution is informed by the site-specific data collected in HPTN 067/ADAPT as described in Methods. Homogeneous distribution assumes that all MSM have the same proportion of acts fully and partially covered.

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