Technical Appendix

to

PrEP adherence patterns strongly impact individual HIV risk and observed efficacy in randomized clinical trials.

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1. HIV risk per sex act

The probability of HIV acquisition per act with infected partner is determined based on the type of the act (vaginal vs. anal), if the act is protected by condom as follows:

$$P = (1-\alpha_p(t))(1-c\alpha_c)r^A R\beta$$

where:

$\alpha_p(t)$ - PrEP efficacy per act depending on the time t since the last dose taken

c - condom use variable (c=0 for unprotected, c=1 for protected act)

α_c - condom efficacy per act

A – variable representing the type of act (A=0 for vaginal, A=1 for anal act)

r - relative HIV acquisition risk per anal act compared to vaginal act

R - relative HIV acquisition risk by the stage of HIV infection of the infected partner

β- HIV acquisition risk per unprotected vaginal act with infected partner in asymptomatic HIV stage

2. Probability to acquire HIV during a single sex act

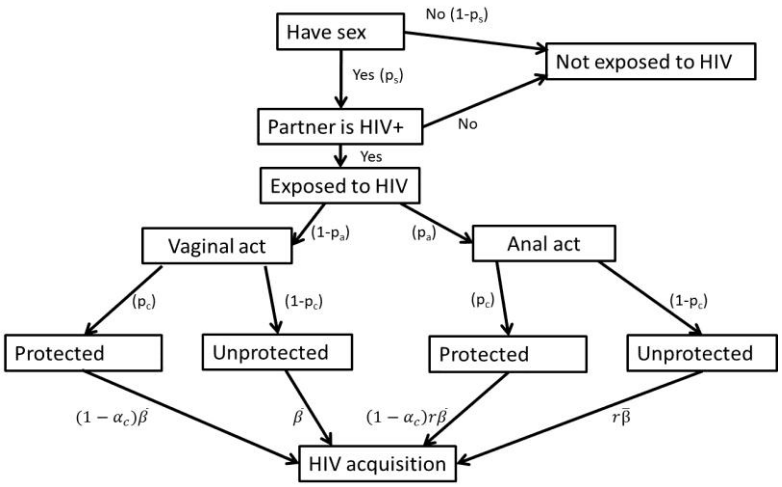

Figure S1. Decision-tree diagram used to determine HIV exposure and HIV risk.

If the sex act is with infected partner the probability that the participant acquires HIV is determined by the decision tree in Figure S1 and depends on the parameters in Table S1 as follows:

- probability to have sex (p_s) depends on the frequency of sex acts specified for each partnership
- probability to have anal sex act (p_a) depends on the proportion of the male partners who practice anal sex and on the proportion of anal sex acts specified for each partnerships
- probability of condom use (p_c) depend on the type of partnership (long- vs. short-term) and is specified for each partnership
- probability of HIV acquisition per vaginal act ($\bar{\beta} = (1-\alpha_p(t))\, R\beta$) depends on the HIV stage of the infected partner and the usage of PrEP before the act (see also the formula of the HIV risk per act in Section 1).

An active partner could be infected at the start of the simulation or when the partnership is initiated which depends on the HIV prevalence among male partners assumed. He can also acquire HIV outside the partnership which depends on the HIV incidence among male partners assumed.

3. Simulation procedure and bookkeeping

1) 2000 women are assigned in 2 risk groups (high or low) with number and type of current partnerships (short- or long-term) based on data representative for South Africa. The high risk assignment implies propensity to concurrent partnerships. Low-risk participants are serially monogamous while high-risk participants have up to 2 concurrent partnerships.
2) Existing partnerships are initialized with the following attributes:
    - starting day of the partnership with respect to the start of the simulation. All long-term partnerships are assumed to be a year old (starting day = -365) while short-term partnerships are initiated between 90 and 210 days prior the simulation
    - partner's risk level (high or low). The high risk group characterizes with higher HIV prevalence and HIV incidence
    - Frequency of sexual activity
    - Daily probability to break up
    - Current HIV status of the partner
    - Anal sex practices (yes, no) and frequency of anal sex

3) Daily each participant may :
    - Initiate a new partnership. Always starts as a short-term. Initiation rate depends on the risk group of the participant
    - Have sex with some of her current partners based on the frequency of acts for each partnership. Probability of condom use and HIV acquisition risk per act depend on the type of partnership. HIV transmission may occur if the woman is HIV- and her partner is HIV+. The probability of HIV acquisition depends on the type of the act (vaginal vs. anal), if the act is protected by condom, partner's HIV stage and if PrEP is recently used to provide protection (see the risk formula and diagram above).
    - Active partners may acquire HIV outside the relationship depending on their risk level
    - Short-term partnership convert into long-term when 9 months limit is reached

- Break up a partnership. That depends on the type of the partnership and the current concurrency status. May be forced if short-term partnership reaches 9 months but another long-term partnership is in place.

4) Sexual activity is simulated for a year prior the trial enrollment with all sexual acts recorded. Trial participants are enrolled from the cohort over 1 year period based on the simulated sexual activity using inclusion criteria employed in concluded RCTs. [1] Enrolled participants are assigned to an active (PrEP) or control (placebo) arms with 1:1 allocation ratio.
5) Event-driven trials are simulated, i.e., trials conclude when a specific number of infections have been reached.

All sexual acts are recorded. Each record consists of:

- Participant identifier
- Day of the act
- Partner identifier
- Current partnership type (long- vs. short-term)
- Risk level of the partner
- HIV status of the partner. If infected the day of HIV acquisition is recorded.
- Type of the sex act (vaginal vs. anal)
- Use of protection
- If the sex act results in HIV transmission

4. Mixing patterns

The probability for a high-risk woman to acquire a partner from the high-risk group is:

$(1-\varepsilon)+ \varepsilon * (\text{proportion of high-risk men})$

The probability for a low-risk woman to acquire a partner from the high-risk group is:

$\varepsilon * (\text{proportion of high-risk men})$

The degree of assortative mixing (ε) takes values between 0 and 1 and control the level of preferential pairing between partners from the same risk groups. We explore assortative mixing ($\varepsilon=0.56$) in which women from high-risk group have greater chance to pair with men from high risk group compared to women from the low-risk group.

5. Parameterization and calibration

Table S1. Parameters values used in the main analysis

Parameter Description	Values and ranges	Reference
A. Epidemic parameters		
Female HIV acquisition risk per unprotected vaginal act with short-term partner in asymptomatic HIV stage	0.0065	[2]
Female HIV acquisition risk per unprotected vaginal act with long-term partner in asymptomatic HIV stage	0.0024	[2]
Condom efficacy against HIV per sex act	90%	[3]
Relative risk per sex act with partner in acute HIV compared to asymptomatic HIV stage	9.2	[4]
Relative risk per sex act with partner in late HIV compared to asymptomatic HIV stage	7.3	[4]
Duration of acute HIV stage	4 months	[5]
Duration of asymptomatic HIV stage	8 years	[5]
Duration of late HIV stage	1 year	[5]
Relative risk per receptive anal compared to vaginal intercourse	10	[6]
HIV prevalence among high -(low-)risk male partners	20% (15%)	assumed, [7, 8]
HIV incidence among high -(low-)risk male partners	2% (1%)	assumed, [8]
B. Behavioral parameters		

Average rate (range) of condom use in long-term partnerships	15% (10%-20%)	[2]
Average rate (range) of condom use in short-term partnerships	40% (30%-50%)	[2]
Proportion of partnerships in which anal sex is practiced	20%	[9]
Average proportion (range) of anal sex acts with a partner who practice anal sex	40% (20%-60%)	[10]
Minimal duration of a partnership	30 days	assumed
Time to convert from short- to long-term partnership	270 days	assumed
Proportion of women who are likely to have concurent partnerships (high-risk group)	25%	[2]
Proportion of men who are likely to have concurent partnerships (high-risk group)	35%	[2]
Degree of assortative mixing between risk groups	0.56	[2]
Average time between partnership for high- (low-) risk women	30 (60) days	[2]
Relative partner acquisition rate for high-risk women who already have a short- (long-) term partner	0.54 (0.17)	[2]
Average duration of an active short- (long-) term partnership if not in concurrent partnerships	7 (120) months	assumed
Relative risk to break an active short- (long-) term partnership when in concurrent partnerships	2 (4)	assumed
Monthly frequency (range) of sex acts per partnerships	5.25 (3-7.5)	[2]
C. Intervention parameters		
Efficacy of PrEP in reducing HIV acquisition risk within 24 hours after a pill is taken	70%	[11, 12]

Table S2. Distribution of risk groups with respect to existing partnerships by type (short- and long-term) at the start of the simulations

Risk group	No partners	1 short-term	2 short-term	1 long-term	1 long-term 1 short-term
High-risk	8%	60%	12%	14%	6%
Low-risk	11%	29%	0%	60%	0%

Table S3. Characteristics of the simulated female cohort at enrollment based on previous sexual activity

Characteristics	Mean (Range)	Baseline VOICE [9] (description)
Proportion of high-risk women	24% (21.7%-26.5%)	22% (multiple partners last 3m)
Average number of sexual acts per year for women in the cohort	68 – 72	130 (based on # acts weekly)
Average number of partners at enrolment	1.11 (1.08-1.13)	
Average number of new partners during trial	1.04 (0.94-1.14)	
HIV prevalence among partners	19% (17.3%-20.6%)	
Proportion of partnerships practicing anal sex	19.5% (17.6%-21.2%)	17% (anal sex last 3 m)
Overall prevalence of anal sex	7.5% (6.8%-8.4%)	
Proportion acts protected by condom	29.9% (29.2%-30.8%)	85% (condom use last act)
HIV incidence in the control arm	5.1% (3.8%-7.2%)	[4.6%, 6.8%] (HIV incidence in [oral, gel] placebo arms)

5. Patterns of pill-taking explored

The following pill-taking patterns have been simulated and compared (see Figure S1):

1) PrEP doses are skipped randomly (random pattern);
2) PrEP doses skipped at regular intervals (periodic pattern);
3) PrEP doses skipped in larger blocks (block pattern).
4) Risk-driven pill-taking in which the daily decision to take PrEP is based on the personal expectation to have sex. Two scenarios with respect to the ability to correctly predict sexual activity are simulated (see Table S1)

Table S4. Definition of risk-driven pill-taking scenarios

Risk-driven pill-taking	Days in which sex is	
	Expected	Not expected
Take PrEP	80%	20%
Have sex Scen1:	57%	20%
Scen2:	60%	10%

6. Estimating PrEP efficacy and PrEP coverage

The overall PrEP coverage is calculated based on the simulated PrEP usage over 12 months as follows:

1) Daily coverage provided by PrEP is determined by the protection profile assumed and the time since the last PrEP dose is taken
2) The number of days with full or partial coverage is counted
3) The overall PrEP coverage is calculated as $\frac{\sum_{days} Daily\ PrEP\ coverage}{\#\ of\ days}$.

The overall sex act coverage is calculated based on the simulated PrEP usage and sexual activity over 12 months as follows:

1) Individual act coverage, provided by PrEP is determined by the protection profile assumed and the time between the last PrEP dose taken and the sex act
2) The number of sex acts with full or partial coverage is counted
3) The overall PrEP coverage is calculated as $\frac{\sum_{acts} Sex\ act\ PrEP\ coverage}{\#\ of sex\ acts}$.

The efficacy of oral PrEP is calculated based on the simulated trial results as follows:

1) HIV incidence by arm is calculated: HIV incidence (by arm) $= \frac{\#\ \text{infections}}{\text{total follow up time in years}}$
2) Relative risk to acquire HIV is calculated: RR= $\frac{\text{HIV incidence (active arm)}}{\text{HIV incidence (control arm)}}$
3) The observed PrEP efficacy is calculated: Eff=1-RR;

7. Sensitivity analysis

We have simulated clinical trials using 1000 randomly sampled sets of behavioral and epidemic parameters to study the sensitivity of our results (projected PrEP efficacy) to specific modeling assumptions. For each parameter set an event-driven trial is simulated 10 times. List of parameter, their sensitivity ranges are presented in Table S5. Parameters are ordered by their partial-rank correlation with the PrEP efficacy averaged over the 10 simulations per parameter set. In all simulations we have simulated 50% uniform adherence scenario with random pill-taking pattern and long protection profile of PrEP.

Table S5. Parameters ranges used in the sensitivity analysis

Parameter Description	*Range*	*PRCC*[1]
HIV prevalence among high-risk male partners	**0.1-0.2**	**0.266857**
Partners acquisition rate for low-risk women without partners (daily)	0.005-0.02	0.15036
HIV prevalence among low-risk male partners (multiplier of high-risk)	0.5-1	0.130346
Proportion of women who are likely to have concurent partnerships (high-risk group)	0.2-0.5	0.130215
Relative partner acquisition rate for high-risk women who already have a long-term partner	0.1-0.3	0.100444
Initial fraction of low-risk women without partners	0-0.1	0.094502
Rate of dissolution of long-term partnerships in absence of other partners	$1.4x10^{-4}$-$5.6x10^{-4}$	0.090386
Average rate of condom use in long-term partnerships	0.1-0.3	0.078416
Rate of dissolution of long-term partnerships in presence of short-term partner	1-8	0.075491
Partners acquisition rate for high-risk women without partners (multiplier of low-risk)	1-3	0.070951
Rate of dissolution of short-term partnerships in absence of other partners	0.25-1	0.06375
Proportion of men who are likely to have concurrent partnerships (high-risk group)	0.2-0.5	0.037335
Female HIV acquisition risk per unprotected vaginal act with short-term partner in asymptomatic HIV stage (multiplier of long-term)	1-3	0.03223
Relative partner acquisition rate for high-risk women who already have a short- term partner	0.3-0.7	0.020911
Initial fraction of high-risk women with multiple partners	0.1-0.3	0.017531
Initial fraction of high-risk women with 1 partner who have long-term partner	0.1-0.3	0.011042
Relative frequency of sex acts in short-term partnerships	0.5-1	0.00278
Initial fraction of low-risk women with 1 partner who have long-term partner	0.5-0.8	-0.02042
HIV incidence among male partners (multiplier of HIV prevalence)	0.08-0.12	-0.03325
Average rate of condom use in short-term partnerships	0.3-0.5	-0.03965
Initial fraction of high-risk women without partners	0-0.1	-0.05076
Degree of assortative mixing between risk groups	0-1	-0.06684
Condom efficacy against HIV per sex act	0.8-0.95	-0.06725
Initial fraction of high-risk women with multiple partner who have long-term partner	0.2-0.5	-0.07348
Female HIV acquisition risk per unprotected vaginal act with long-term partner in asymptomatic HIV stage	0.002-0.003	-0.11586
Average proportion of anal sex acts with a partner who practice anal sex	0.2-0.6	-0.12817
Relative risk per sex act with partner in acute HIV compared to asymptomatic HIV stage	4.5-19	-0.13822
Monthly frequency of sex acts in long-term partnerships	4-8	-0.15762
Relative risk per sex act with partner in late HIV compared to	4.5-12	-0.18838

asymptomatic HIV stage		
Proportion of partnerships in which anal sex is practiced	**0-0.4**	**-0.38301**
Relative risk per receptive anal compared to vaginal intercourse	**5-20**	**-0.39045**

[1] Partial rank correlation coefficients (PRCC) between the parameters and the mean PrEP efficacy observed in 10 simulations of clinical trials per parameter set.

The largest absolute PRCCs correspond to the parameters which govern the prevalence and frequency of anal sex in the cohort and the HIV prevalence among male partners (in bold). The comparison of the observed PrEP efficacy in the main analysis (100 simulations with fixed behavior and epidemic parameters) and the sensitivity analysis (10000 simulations with varying behavior and epidemic parameters) shows little difference in the median, quartile and 90% uncertainty estimates (Fig. S3).

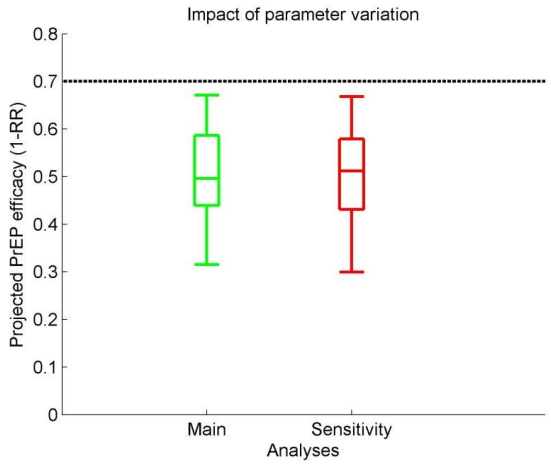

Figure S2. Comparison between the observed PrEP efficacy in the main and sensitivity analyses. Long PrEP protection profile, uniform 50% adherence and random pill-taking pattern are assumed. Box plots (5th, 25th, 50th, 75th, and 95th percentiles) reflect estimated variation over 100 trials simulated in the main analysis and 10000 trials simulated in the sensitivity analysis.

8. Scenarios assuming 90% effective PrEP

Results from concluded clinical trials suggest that PrEP may be highly protective (efficacy per act of 90% or above) in some high-risk populations such as MSM. Results from additional scenarios in which PrEP is 90% effective for reducing the HIV acquisition risk per act are presented below. The most optimistic estimates of PrEP efficacy can be matched and even exceeded with 50% actual adherence if PrEP is highly effective and has long-lasting protection. Notably, if block pill-taking is the prevalent then low to intermediate efficacy will be recorded.

Comment [DD1]: Thea: Effective for reducing or effective in reducing?

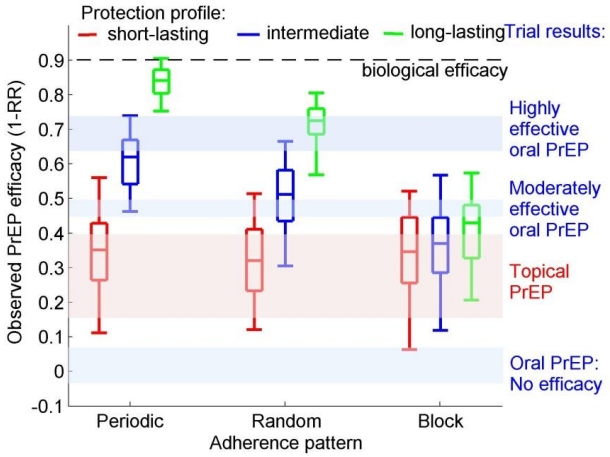

Figure S3. Observed PrEP efficacy under different PrEP protection profiles and pill-taking patterns. Uniform 50% adherence of each participant is assumed. Box plots (5th, 25th, 50th, 75th, and 95th percentiles) reflect estimated variation over 100 trials simulated. Shaded regions illustrate the efficacy estimates obtained in concluded RTCs

References

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