Supplemental Digital Content 1
to
Recruitment of Female Sex Workers in HIV Prevention Trials: Can Efficacy Endpoints Be Reached More Efficiently?

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1 Model Description

1.1 HIV Risk Per Sex Act

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

$$P = (1 - c\alpha_c)\,(1 - t\alpha_T)\,(1 - p\alpha_p)\,\gamma_A^{\tau}\phi_X\beta$$

where:

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

t - treatment status variable (t=0 untreated, t=1 on ART)

p - prevention status variable (p=0 no prevention, p=1 prevention)

α_c - condom efficacy per act

α_T - ART efficacy per act

α_p - HIV prevention efficacy per act (80% is used in the main analysis, 50% is used in alternative analysis)

τ - variable representing the type of act (τ=0 for vaginal, τ=1 for anal act)

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

ϕ_X - relative HIV acquisition risk by the stage of HIV infection (acute [X=ac], asymptomatic [X=as], late [X=l]) of the infected partner compared to asymptomatic ($\phi_{as} = 1$)

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

1.2 Simulation Procedure

1. Cohorts of 3600 women are assigned with risk group, number and type of current partnerships. Female sex workers (FSW) are assumed to have similar partnership characteristics as low-risk participants. This means that FSW have the same partner acquisition probabilities, break up probabilities, and number of partnerships as low-risk participants (we do, however, assume that FSW have proprtional mixing rather than assortative mixing with respect to acquisition of high/low risk partnerships).

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 start between 30 and 210 days prior to the start of the simulation

   (b) partners risk level (high or low). 35% of partners are assumed high-risk (no partners are assumed to be sex workers)

   (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 male sexual partners was randomly assigned based on assumed HIV prevalence and ART coverage among the male partners by risk group (high and low)

   (f) practicing anal sex (yes, no)

3. Daily each participant may:

(a) initiate a new partnership. High-risk non-FSW were assumed to initiate new partnerships at a lower rate when they were in active short-term (relative rate 0.54) and long-term (relative rate 0.17) partnerships compared to women who did not have a partner.

(b) have sex with some of her 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 woman is HIV negative and her 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

(c) practice sex work (if participant is a sex worker). The HIV and ART status of FSW clients was randomly assigned based on assumed HIV prevalence and ART coverage among clients. HIV transmission may occur if the woman is HIV negative and her client is HIV positive. The probability of HIV acquisition depends on the type of the act (vaginal vs. anal), the client'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 to once per month

(g) short-term partnerships convert into long-term after 9 months provided that the participant had no other active long-term partners at the time

(h) break up a partnership. Long- and short-term partnerships were assumed to dissolve at different rates, corresponding to expected partnership duration, with a faster dissolution rate when a woman was in concurrent partnerships.

4. Trial Management:

(a) For the event-driven trial, during the first 12 months of the trial, 150 participants are enrolled in the active and control arms each month (totalling 300 participants enrolled per month). Participants are followed for up to 3 years, till dropping out, till diagnosed with HIV or till 120 infections have been recorded; whatever occurs first.

(b) For the fixed-duration all participants are enrolled on the same day, and followed for 3 years, till dropping out or till diagnosed with HIV.

(c) At the end of each month participants are tested for HIV, and if tested positive, participants are removed from the trial

(d) At the end of each month participants may drop-out of the trial, in which case they are no longer followed

1.3 Mixing Patterns

- The probability for a high-risk woman to acquire a partner from the high-risk group is: $(1-\epsilon)+\epsilon\cdot$(proportion of high-risk partners).
- The probability for a low-risk woman to acquire a partner from the high-risk group is: $\epsilon\cdot$(proportion of high-risk partners).
- The probability for a sex worker to acquire a partner from the high-risk group is the proportion of high-risk partners.

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.

Table S1: Targeted distribution per risk group with respect to existing partnerships by type (short- and long-term) [5, 11]. Sex workers have same distribution as low-risk women.

Risk group	No partners	1 short-term	2 short-term	1 long-term	1 long-term 1 short-term
High-risk	0%	62%	14%	16%	8%
Low-risk	0%	35%	0%	65%	0%

1.4 Confidence Interval Calculations

The confidence intervals of the product efficacy estimated in RCT and used in Figure 4D in the main text are based on a normal approximation of the log of the incidence rate ratio (see [10, pp. 243–244]). We have confidence interval $[\underline{E}, \bar{E}]$ where

$$\underline{E},\ \bar{E} = 1 - \exp\left[\log(\hat{IR}) \pm 1.96 \cdot \hat{SD}\left(\log(\hat{IR})\right)\right]$$

and

$$\hat{IR} = \frac{A_1/T_1}{A_0/T_0}$$

is the estimate for the incidence rate ratio where A_1 and A_0 are the number of infected participants and T_1 and T_0 are the total follow up times in the active and control arms respectively and

$$\hat{SD}\left(\log(\hat{IR})\right) = \sqrt{1/A_1 + 1/A_0}.$$

1.5 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 becoming lost- to- follow-up or completing the trial without becoming infected. The trial duration was estimated from

the time of the first enrollment to the time when the targeted number of infections was reached. 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 efficacy in the RCTs was calculated as one minus the incidence rate ratio (IRR) of acquiring HIV, defined as the ratio of the HIV incidence rate in the active vs control arm.

2 Calibration Procedure

We estimate the HIV incidence among FSW assuming that FSW have no sex partners other than clients. The model parameters which influence the HIV acquisition by FSW from clients were sampled randomly from their ranges (see Table S2) until 1000 parameters sets which result in annual HIV incidence between 4% - 8% are selected. Using these parameters, the model is used to simulate RCTs by randomly sampling the remaining parameters.

Table S2: Parameters used in the model calibration.

Calibration Parameters	**Symbol**	**Value**	**Sources**
Relative risk per receptive anal compared to vaginal intercourse	γ_A	5 - 20	[1]
Rate of condom use by sex workers per vaginal sex act	c	0.8 - 1.0	[9]
Condom efficacy against HIV	α_C	0.66 - 0.94	[4, 13]
Female HIV acquisition risk per unprotected vaginal act with partner/client in asymptomatic HIV stage	β	0.002 - 0.004	[2, 4]
Relative risk per sex act with partner/client in acute HIV compared to asymptomatic HIV stage	ϕ_{ac}	4.5 - 18.8	[2]
Relative risk per sex act with partner/client in late HIV compared to asymptomatic HIV stage	ϕ_l	4.5 - 11.9	[2]
HIV prevalence, high-risk partners/clients	π	0.128 - 0.163	[11]
Proportion of sex acts which are anal sex for sex workers	a	0.01 - 0.2	[9]
ART efficacy in reducing infectiousness	α_T	0.9	[3]
Proportion of infected clients in the acute HIV stage	ρ_{ac}	0.0365	proportional to stage duration
Proportion of infected clients in the asymptomatic HIV stage	ρ_{as}	0.7883	proportional to stage duration
Proportion of infected clients in the late HIV stage	ρ_l	0.1752	proportional to stage duration
Proportion of infected clients in the asymptomatic HIV stage who are on ART	t_{as}	0.173	assumed
Proportion of infected clients in the late HIV stage who are on ART	t_l	0.65	assumed
Expected number of clients having penetrative sex per sex worker per day in main scenario (in low incidence scenario)	n	1.429 (0.286)	[9]

We estimate the primary HIV risk from clients for female sex workers. Let X be the probability to acquire HIV during sex from a random client. We can then define $X = \pi\beta CAR$, where

$$C = \begin{cases} 1 & \text{w.p. } 1-c \\ 1-\alpha_C & \text{w.p. } c, \end{cases}$$

$$A = \begin{cases} 1 & \text{w.p. } 1-a, \\ \gamma_A & \text{w.p. } a, \end{cases}$$

$$R = \begin{cases} \phi_{ac} & \text{w.p. } \rho_{ac}, \\ T_{as} & \text{w.p. } \rho_{as}, \\ T_l\phi_l & \text{w.p. } \rho_l, \end{cases}$$

$$T_{as} = \begin{cases} 1 & \text{w.p. } 1-t_{as}, \\ 1-\alpha_T & \text{w.p. } t_{as}, \end{cases}$$

$$T_l = \begin{cases} 1 & \text{w.p. } 1-t_l, \\ 1-\alpha_T & \text{w.p. } t_l, \end{cases}$$

where C represents condom use, A represents performing anal sex, R represents the HIV phase of the client and T_{as} and T_l represents the client's ART status given that the client is in the asymptomatic and late HIV phases respectively. Here C, A, and R are assumed independent, which implicitly assumes that condom use and efficacy are the same for both vaginal and anal sex acts.

We assume that $Y \sim \text{Poisson}(n)$ is the number of clients per day. Let Z represent the daily number of encounters in which an infection would occur, that is $Z|X, (Y = k) \sim \text{Binomial}(k, X)$ so that $Z|X \sim \text{Poisson}(nX)$. Then the daily probability of infection is given by

$$\lambda := \mathbf{P}(Z \geqslant 1) = \sum_x \mathbf{P}(Z \geqslant 1|X = x)\mathbf{P}(X = x) = \sum_x (1 - e^{-nx})\mathbf{P}(X = x).$$

We can then estimate the expected incidence rate by considering the average number of days before a sex worker is infected. Let $D \sim \text{Geometric}(\lambda)$ so that $\mathbf{P}(D = k) = \lambda(1-\lambda)^k$ for $k = 1, 2, \ldots$. Thus the expected number of days before infection is $\mathbf{E}[D] = (1-\lambda)/\lambda$. Thus we have the estimated yearly incidence rate of

$$\text{Yearly Incidence Rate} = 365.242\frac{\lambda}{1-\lambda},$$

where 365.242 is the average number of days in a year. We sample the parameter space, and keep sets of parameters which give a yearly incidence rate between 0.04 and 0.08.

2.1 Parameterization

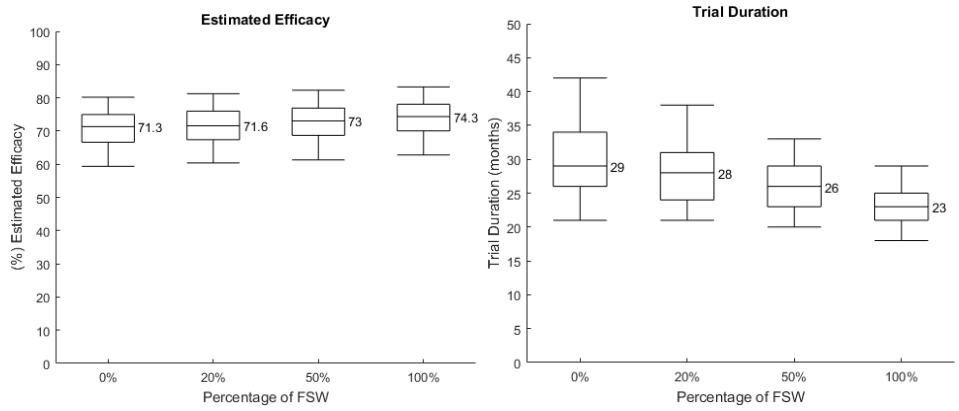
Table S3: Other epidemic parameters used in the analysis.

Epidemic Parameters	**Value**	**Sources**
Duration of acute HIV stage	5 months	[2]
Duration of asymptomatic HIV stage	9 years	[12]
Duration of late HIV stage	2 years	[2]
Relative HIV prevalence, low-risk partners	0.75	assumed
HIV incidence, high-risk partners	0.02 - 0.04	assumed
Relative HIV incidence, low-risk partners	0.75	assumed
Fraction of infected partners who receive ART after acute HIV stage	0.25	[11]
ART multiplier of the HIV stage durations	3	assumed

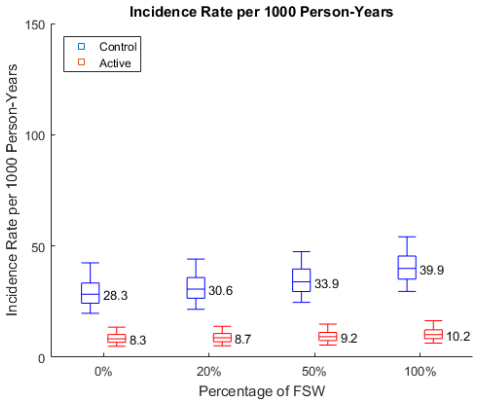
Table S4: Other behavioral parameters used in the analysis.

Behavioral Parameters	**Value**	**Sources**
Annual drop-out rate of sex worker participants	0.05 - 0.5	explored
Annual drop-out rate of high-risk participants	0.05	[8]
Annual drop-out rate of low-risk participants	0.05	[8]
Proportion of women who are sex workers	0.0 - 1	explored
Proportion of women who are not sex workers who are likely to have concurent partnerships (high-risk group)	0.25	[5]
Proportion of partners who are likely to have concurent partnerships (high-risk group)	0.35	[5]
Monthly frequency of sex acts in long-term partnerships	3-9	[5]
Monthly frequency of sex acts in short-term partnerships	3-9	[5]
Monthly frequency of sex acts for partnerships in which partners in the late HIV stage exceed the late HIV stage duration	1	assumed
Rate of condom use in long-term partnerships	0.2	[5]
Rate of condom use in short-term partnerships	0.5	[5]
Annual ART initiation rate for infected parners in the asymptomatic HIV stage	0.1	assumed
Annual ART initiation rate for infected parners in the late HIV stage	0.5	assumed
Proportion of partnerships in which anal sex is practiced	0.1 - 0.3	[7]
Probability for sex acts with a partner who practices anal sex to include anal intercourse	0.2 - 0.6	[6]
Time to convert from short- to long-term partnership	9 months	assumed
Degree of assortative mixing between risk groups	0.56	[5]
Average time between partnerships for low-risk women	9 months	assumed
Average time between partnerships for high-risk women	3 months	assumed
Relative partner acquisition rate for high-risk women who already have a short- term partner	0.54	[5]
Relative partner acquisition rate for high-risk women who already have a long- term partner	0.17	[5]
Average duration of an active long-term partnership if not in concurrent partnerships	10 years	assumed
Expected duration of a newly formed partnership if not in concurrent partnerships	1 year	assumed
Relative dissolution rate for long-term partnerships when in concurrent partnerships	4	assumed
Relative dissolution rate for short-term partnerships when in concurrent partnerships	2	assumed

3 Additional Results

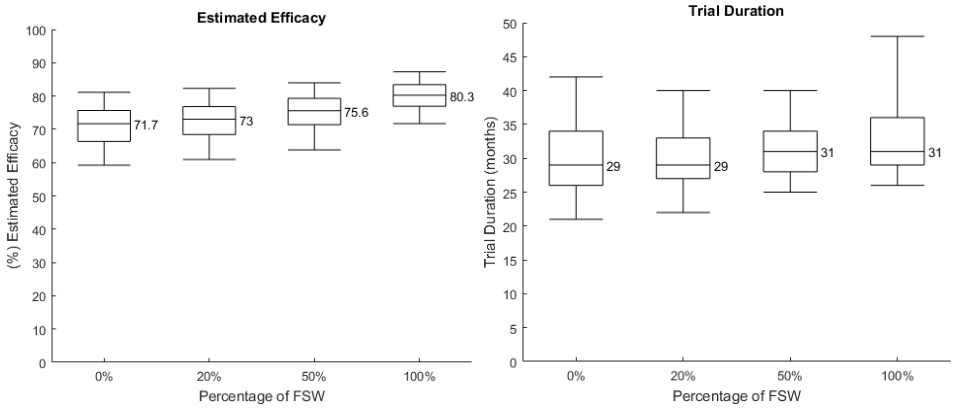


(a) estimated efficacy (b) trial duration



(c) projected HIV incidence rate by arm

Figure S1: Simulations of event-driven trials assuming low incidence due to sex work. Fixed true efficacy of 80% in reducing HIV susceptibility per act and 5% annual drop-out rate are assumed over the course of the trial. Box plots (5th, 25th, 75th, and 95th percentiles) reflect estimated variation over 1000 trials simulated.

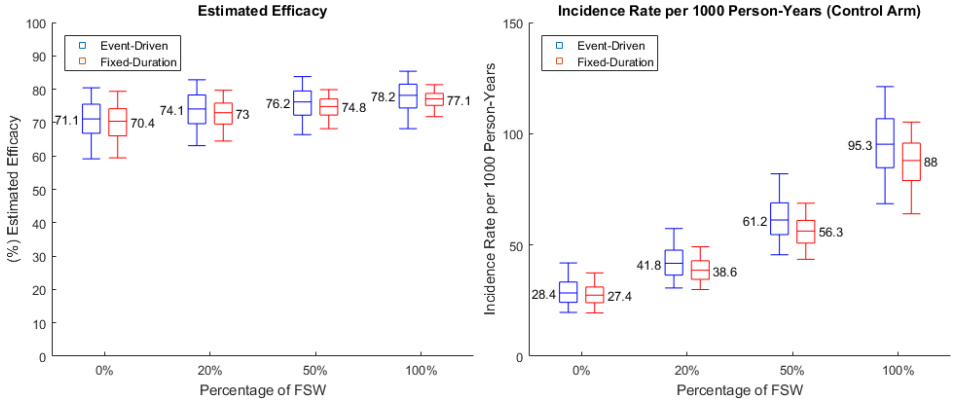


(a) estimated efficacy (b) trial duration

(c) projected HIV incidence rate by arm

Figure S2: Simulations of event-driven trials assuming that FSWs do not have partners and their HIV incidence (exclusively from sex work) is similar to the main scenarios without FSW. Fixed true efficacy of 80% in reducing HIV susceptibility per act over the course of the trial and 5% annual drop-out rate are assumed over the course of the trial. Box plots (5th, 25th, 75th, and 95th percentiles) reflect estimated variation over 1000 trials simulated.

We have investigated if the reduced trial duration when more FSW are enrolled could be the reason for the improved efficacy estimates. We have simulated RCTs in which participants are enrolled simultaneously and followed for a fixed duration of 3 years (Fig. S3). Our analysis suggests a 1-2 percentage points lower efficacy estimates and less than 0.7 percentage points lower annual HIV incidence compared to the event-driven RCTs in the main scenario. However, the differences in efficacy between simulated RCTs with different proportions of FSW remain unaffected.



(a) estimated efficacy (b) projected HIV incidence rate by arm

Figure S3: Comparison of trials with 3-year follow up to event-driven trials. Fixed true efficacy of 80% in reducing HIV susceptibility per act and 5% annual drop-out rate among non-FSW and FSW are assumed over the course of the trial. Box plots (5th, 25th, 75th, and 95th percentiles) reflect estimated variation over 1000 trials simulated.

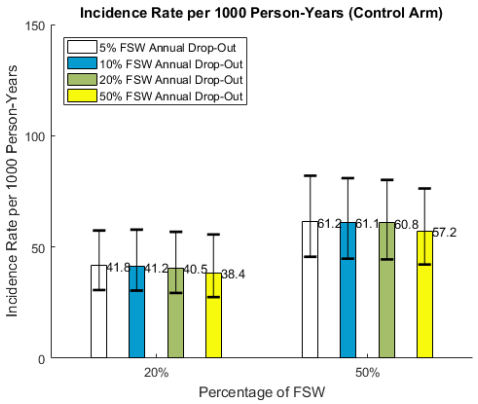


Figure S4: HIV incidence rate in the control arms of trials with different drop-out rates among FSW. Fixed true efficacy of 80% in reducing HIV susceptibility per act and 5% annual drop-out rate among non-FSW are assumed over the course of the trial. Bars represent the median estimate and range plots (5th and 95th percentiles) reflect estimated variation over 1000 trials simulated.

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