ASSESSING EFFECTIVENESS AND COST-EFFECTIVENESS OF CONCURRENCY REDUCTION FOR HIV PREVENTION

SUPPLEMENTARY APPENDIX

This supplementary Appendix provides a detailed description of the model and the results of supplemental sensitivity analyses.

MODEL DESCRIPTION

Model Overview

Our model is a stochastic microsimulation model of HIV transmission and progression in a sexual partnership network. The model is implemented in Mathworks Matlab R2008. We considered four study countries: Swaziland, Tanzania, Uganda, and Zambia. We instantiated the model separately for each of the four study countries using country-specific data wherever possible. For each country, we constructed a population reflective of that country's demographic characteristics, HIV prevalence, and pattern of concurrent sexual partnerships. We simulated the model for ten years on a month-by-month basis, capturing dynamic factors such as entry into the population, partnership formation and dissolution, HIV transmission, HIV disease progression, HIV treatment, and deaths from HIV and other causes. We calculated HIV prevalence and incidence, cumulative HIV infections, life years experienced, and deaths from HIV and other causes.

Since the model is stochastic and includes many variables drawn at random from pre-specified distributions, the results of each model iteration differed. For example, when we instantiated the population at the beginning of each simulation, individuals were assigned ages drawn from the country-specific age distribution. On average, the distribution of ages in the

model population matched the demographic data; however, any given simulation realization was different. For this reason, we performed multiple repetitions of the simulation to develop confidence intervals for estimated outcomes.

Model Structure

The model tracks the health state of all individuals in the population over time. Each individual is characterized by a set of attributes (which may or may not change over time) such as gender, age, disease state, and CD4 count. Time-varying attributes are updated over time as the model progresses. The model also tracks heterosexual partnerships in the population. This information is stored in an adjacency matrix. The adjacency matrix has dimension N_m rows by N_f columns, where N_m and N_f are the number of men and women in the population, respectively. A non-zero value in the i^{th} row and j^{th} column of the adjacency matrix indicates a sexual partnership between man i and woman j. Different non-zero values represent different types of partnerships: a value of 1 in the adjacency matrix represents a spousal partnership while a value of 2 indicates a non-spousal partnership.

Population

We created an initial population of approximately 9,000 adults 15 to 49 years old, with each individual assigned a gender, age, and HIV status. We used the most recent population pyramid of each study country to determine the age distribution in the population [1]. Similarly, we matched our population to published age- and gender-specific HIV prevalence estimates for the country of interest. Individuals who were infected prior to the model start date were initially assigned an HIV disease state and CD4 count that reflect the distribution among currently infected individuals in southern Africa [2]. Newly infected individuals follow a natural history

that depends on their treatment eligibility and access to treatment, as described below (HIV Disease Model).

We modeled a population of individuals 15 to 49 years old. Fifteen year-olds enter the population monthly. These individuals enter with a gender-specific HIV prevalence matching that of 15-year-olds in the country of interest [3-6]. The rate of entry is calculated from the population pyramid as the fraction of 14-year-olds reaching age 15 as a proportion of the current population size. We assumed that this proportion stays constant over the ten-year period of study. Individuals who reach age 50 exit the population unless they are involved in a sexual partnership; the latter individuals remain in the population until the dissolution of the partnership. Individuals also exit the population due to death. All individuals experience a monthly age-related mortality risk, determined from country-specific mortality tables [7]. Individuals infected with HIV experience an additional mortality risk that depends on their CD4 count [8].

HIV Disease Model

We modeled the progression of HIV in infected individuals using two parameters: CD4 cell count and HIV disease state. A diagram of the HIV disease states is shown in Appendix Figure 1. HIV-related mortality is determined by an individual's CD4 count, while the probability of transmission per coital act is determined by the HIV disease state (as a proxy for viral load).

An uninfected individual can become infected with HIV from an infected sex partner. We modeled the risk of infection as a monthly probability per partnership. This value subsumes in it the average number of coital acts per month and the average chance of infection per coital act. The probability of infection per coital act is primarily dependent on the HIV disease state.

We used the risk of HIV transmission per coital act by disease state found among discordant couples in Rakai, Uganda [9]. We did not model condom use and other sexually transmitted infections as explicit risk factors for HIV transmission.

Once infected, an individual transitions to the acute infection state. Acute HIV infection is characterized by a rapid drop in CD4 count and a high probability of transmitting HIV to any uninfected sexual partners (8.2 infections per 1,000 coital acts) [9-11]. After the acute infection state, which we assumed lasts three months, individuals transition to the chronic HIV infection state. Chronic HIV infection is characterized by a slow and steady decline in CD4 count and a moderate risk of transmission (7 infections per 10,000 coital acts). As CD4 counts decline, an individual's risk of HIV-related mortality increases, as does the risk of an AIDS defining illness (ADI). HIV-specific mortality is a function of both CD4 count and the presence of an ADI. We used the monthly HIV-related mortality risk as a function of CD4 count estimated from a longitudinal study of HIV disease progression in South Africa [8]. We used the risk of ADI as a function of CD4 count from estimates by Holmes et al. from the Cape Town AIDS cohort data [12]. We modeled an ADI as an acute event, lasting for one month, which temporarily increases HIV-related mortality risk. The increase in HIV-related mortality due to ADI was also taken from the Cape Town AIDS cohort data [12]. The mortality risk of individuals who survive an ADI is similar to those who never had an ADI, and is primarily dependent on the CD4 count.

Once the CD4 count drops below the World Health Organization (WHO) treatment threshold, individuals become eligible for treatment. WHO guidelines advise treatment for CD4 counts less than 200 cells/μL and recommend the consideration of treatment for CD4 counts less than 350 cells/μL [13]. In sub-Saharan Africa, where resources are scarce, patients generally do not receive treatment until their CD4 counts have fallen below 200 cells/μL. Individuals are also

eligible for treatment if they have experienced an ADI, regardless of their CD4 count. Not all treatment-eligible individuals receive treatment. The fraction of eligible individuals who receive treatment in each country was determined by the antiretroviral coverage levels in 2008 [14]. This reflects the influences of imperfect linkage from testing to treatment sites, loss-to-follow-up from treatment programs, and insufficient supply of antiretroviral medications in many regions. Individuals who do receive treatment experience a recovery in CD4 count and a reduced probability of transmission (1 infection per 10,000 coital acts). Individuals who do not receive treatment experience a continued decline in CD4 count and an increasing risk of HIV-related death. Finally, individuals who receive treatment may experience treatment failure. Under failed treatment, an individual experiences a decline in CD4 counts, though at a slower rate than if untreated.

Thus, treatment has two important effects: it reduces individual risk of mortality through an elevation of CD4 and reduction of the risk of ADIs; and it reduces the risk of HIV transmission through suppression of viral load. Patients who are on effective treatment have a risk of transmitting the virus per coital act that is 7 times lower than chronically infected untreated individuals and 82 times lower than acutely infected individuals [15]. Conversely, untreated individuals or individuals on a failed regimen have an elevated risk of transmission, and a mortality risk that is primarily determined by their CD4 count.

Of those individuals who are infected with HIV at the beginning of the study period, 7% are assigned to the acute phase, reflecting current UNAIDS estimates [14]. The remaining HIV-infected individuals are assigned a CD4 count according to a normal distribution with a mean of 280 cells/μL and a standard deviation of 100 cells/μL, consistent with observed CD4 count distributions in an African population [2]. Individuals with CD4 counts above the treatment

threshold do not receive treatment. They follow the natural history as specified in our disease progression model for untreated individuals.

Sexual Partnership Network

We used a network model to explicitly track sexual partnerships between individuals. We only included heterosexual partnerships, since this is the primary mode of transmission of HIV in sub-Saharan Africa. We modeled two types of partnerships: spousal and non-spousal. Spousal partnerships are long in duration (120 months on average), while non-spousal partnerships are relatively short in duration (18 months on average). We estimated partnership durations from the duration of partners reported by surveys in Uganda and Botswana [16, 17]. At any given time, an individual can have at most one spousal partnership, though an individual can have multiple non-spousal partnerships.

The number of individuals with 0, 1, 2, or more partners was determined from Demographic Health Survey data [3-6]. Using the most recent primary dataset for each study country, we computed the proportion of individuals reporting 0, 1, 2, 3, or 4 partners in the past 12 months. We did this separately for men and women. In all the countries considered, very few individuals reported more than 4 partners. We used the number of partners in the past 12 months as a surrogate for number of concurrent partners. While this is an imperfect measure of concurrent partnerships – individuals may have multiple serially monogamous relationships in a 12-month period [18, 19] – this is an established and intuitive measure that is consistently measured across countries [20]. We addressed the issue of concurrency overestimation in sensitivity analysis. Partnerships are either spousal or non-spousal. We calculated the number of spousal partnerships in the population from the proportion of married individuals in the study country [3-6]. All additional partnerships were assumed to be non-spousal.

At the beginning of the study (the initialization of the simulation), men and women were partnered with 0, 1, 2, 3, or 4 partners. The distribution of partnerships corresponded to the observed partnership distribution in the population. To do this, we assigned a partnership number to each individual so that the proportion of men and women assigned 0, 1, 2, 3, or 4 partners matches the proportion of men and women reporting 0, 1, 2, 3, or 4 partners in the study country [3-6]. We then randomly matched men and women until all the partnerships were assigned. Finally, a certain number of partnerships were designated as spousal partnerships to match the observed proportion of married individuals in the population.

The total number of partnerships among men in the network must equal the total number of partnerships among women in the network (since each partnership involves one man and one woman). Men in the study countries reported more sexual partners than women reported [3-6]. As a result, the number of women in the network was greater than the number of men. To ensure that the total number of partnerships among men equaled the total number of partnerships among women, we used a fixed male population of 4,000 and adjusted the number of women in the population appropriately. This resulted in total population sizes between 8,000 and 9,000, depending on the country. The resulting male-to-female ratio in the model is compared to the ratio predicted by demographic data in Appendix Table 1. The reported gender-specific concurrency behaviors are more consistent with male-to-female ratios in some countries (Swaziland and Tanzania) than others (Uganda and Zambia). This highlights the need for better data measuring sexual behavior patterns in these countries. In sensitivity analysis, we evaluated the impact of adjusting the male-to-female ratio compared to other methods for reconciling gender-related discrepancies in sexual behavior reporting.

Network Dynamics

The sexual partnership network evolves over time: each month, partnerships are lost and partnerships are gained. The probability of partnership dissolution is different for the different types of partnerships, and is determined by the average partnership duration; thus, each spousal and non-spousal partnership has a constant monthly probability of dissolution of 1/120 and 1/18, respectively. We calculated the probability of partnership formation to balance the probability of partnership dissolution, as well as new individuals entering the population at age 15 without partnerships, so that the proportion of individuals with 0, 1, 2, 3, or 4 partners is approximately constant over time. The probability that an individual gains a new partnership depends on the number of partners he or she currently has. This probability also differs by gender and by type of partnership to be gained. To find these probabilities, we solved a convex optimization problem: we found the partnership formation probabilities that result in a steady-state partnership distribution as close to the observed partnership distribution as possible [21]. In practice, we found that the calculated partnership formation probabilities resulted in stable partnership distributions over time (Appendix Figure 2).

Behavior Change Scenarios

We used the model to evaluate three potential behavior change scenarios:

1) Increased Monogamy: individuals with more than one partnership change to having at most one partnership at any one time.
2) High-Risk Partnership Reduction: individuals with the highest number of concurrent partnerships reduce their number of partners, but do not necessarily become monogamous.

3) Untargeted Partnership Reduction: individuals with more than one partnership reduce their number of sexual partners.

Each behavior change scenario represents a modification of the degree distribution in the population. Thus, a 10% increase in monogamy means that we generate a new degree distribution by taking 10% of non-monogamous individuals and making them monogamous. We then simulate using this new degree distribution.

To facilitate the comparison of these scenarios, we removed the same number of partnerships in each scenario. The number of partnerships to be removed in each scenario was determined by the number of partnerships removed under the Increased Monogamy scenario. In the base case, where we consider all scenarios as being 10% effective, we mean that in each scenario we remove the number of partnerships removed under a 10% increased in monogamy. The difference between scenarios is in how those partnerships are removed (only among high-risk individuals or randomly among individuals with concurrent partnerships).

Primary Outcomes

As described above, the model is probabilistic: to initialize the model we randomly assigned characteristics to individuals, and then events (e.g., disease transmission and progression, death, and partnership formation and dissolution) occur randomly over time. We simulated the model for ten years in one-month time increments. For each run of the model, we calculated a variety of outcome measures, including HIV incidence and prevalence over time, new HIV infections, life years experienced, and deaths from HIV and other causes. We then ran the model 500 times with random initialization to develop a mean value and range for each outcome measure. We chose 500 runs for each scenario because we found that, for more than 500 runs, the standard deviation of each outcome measure was unchanged. To illustrate the

variability in our results, we show the distribution of the number of infections for the Status Quo and the three behavior change scenarios in Appendix Figure 3.

SUPPLEMENTAL SENSITIVITY ANALYSES

Our base case analyses explored the impact of concurrency reduction in different demographic and epidemiological settings by modeling four different sub-Saharan African countries – which was a form of sensitivity analysis. We also conducted sensitivity analyses on a variety of potentially influential model parameters, such as the level of access to HIV treatment, HIV treatment eligibility criteria, the average duration of non-spousal partnerships, and the risk of HIV transmission through non-spousal partnerships. These results are summarized for Tanzania for the case of 10% program effectiveness (Appendix Table 2). Although the number of infections averted changed with different parameter values, the rank ordering of the different behavior change scenarios was the same over the ranges of values considered.

We varied the level of HIV treatment coverage of eligible individuals by ± 20%. The number of infections averted by concurrency reduction was not significantly changed. We also considered an increased CD4 count threshold for the initiation of HIV treatment: our original analysis was conducted with an HIV treatment threshold of 200 cells/μL; revised guidelines now advise initiation of treatment at 350 cells/μL [22]. This change in HIV treatment policy also did not significantly impact the number of infections averted by concurrency reduction.

We varied the average duration of non-spousal partnerships by ± 6 months. This had little effect on the number of infections averted under the Increased Monogamy and Untargeted Partnership Reduction behavior change scenarios. The number of infections averted under the

High-Risk Partnership Reduction scenario increased as partnership duration increased. However, the rank order of the different behavior change scenarios was preserved.

We also considered changes in non-spousal HIV transmission probability by ± 20%, representing a decrease or increase in levels of condom use or other risk reduction behaviors as compared to our base case analysis. The number of infections averted by concurrency reduction was reduced as the risk of HIV transmission through these partnerships declined. Again, the rank ordering of the behavior change scenarios was not affected.

We based on our analysis on sexual behavior survey data to estimate concurrency behavior in the study countries. These surveys did not explicitly report the number of concurrent partnerships; instead we used the number of partners reported in the past 12 months. An analysis of sexual behavior survey responses in the Caribbean found that the number of partners reported in the past 12 months overestimated the level of concurrent partners by approximately 50% [19]. To explore the effects of possible overestimation of concurrency behaviors, we evaluated concurrency reduction for one study country (Tanzania) under the assumption that the number of partners reported in the past 12 months overestimates the level of concurrent partners by 50%. To do so, we changed 50% of individuals reporting concurrent partnerships to having a single partnership, but kept the relative levels of individuals reporting 2, 3, and 4 partners the same. This resulted in 10% of men and 6% of women having >1 sex partners (versus 20% of men and 12% of women reporting >1 sex partner in the past 12 months [3]). The results of this analysis are shown in Appendix Figure 4. As expected, the number of infections averted by concurrency reduction is smaller when there is less concurrency behavior in the population. However, the relative effectiveness of the different types of behavior change remains unchanged.

The reported gender-specific degree distributions suffered from inconsistencies in the number of sexual partners reported by men compared to the number of sexual partners reported by women. We adjusted the male-to-female ratio in the model population to reconcile these discrepancies, but this calculated ratio did not always match demographic estimates. Instead of adjusting the male-to-female ratio, one might consider adjusting the reported sexual partnership distributions – for example, by averaging the partnership distributions reported by men and women and then applying this average distribution to both genders. We looked at the effects of using an averaged partnership distribution to evaluate concurrency reduction in Zambia, which has the most divergent male-to-female ratio from demographic estimates. This resulted in 11% of both men and women having >1 sex partners (versus 20% of men and 2% women reporting >1 sex partner [6]). Results of this sensitivity analysis are shown in Appendix Figure 5. Concurrency reduction averts fewer infections when the partnership distributions are averaged. However, the relative effects of the different types of behavior change are not qualitatively affected.

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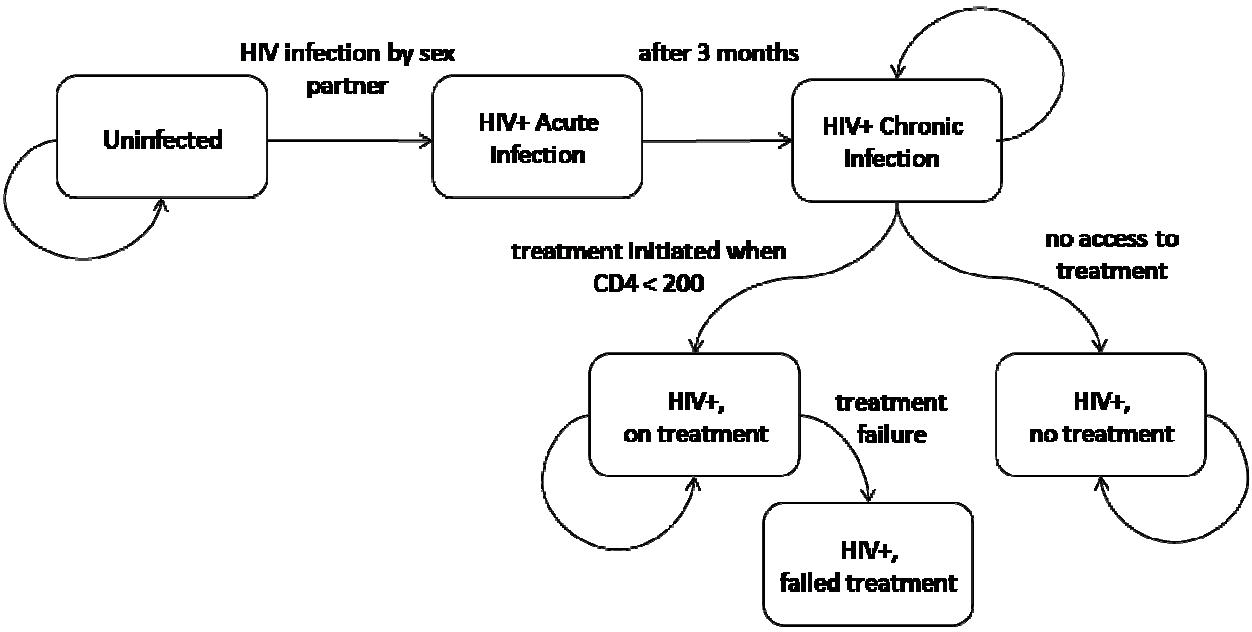
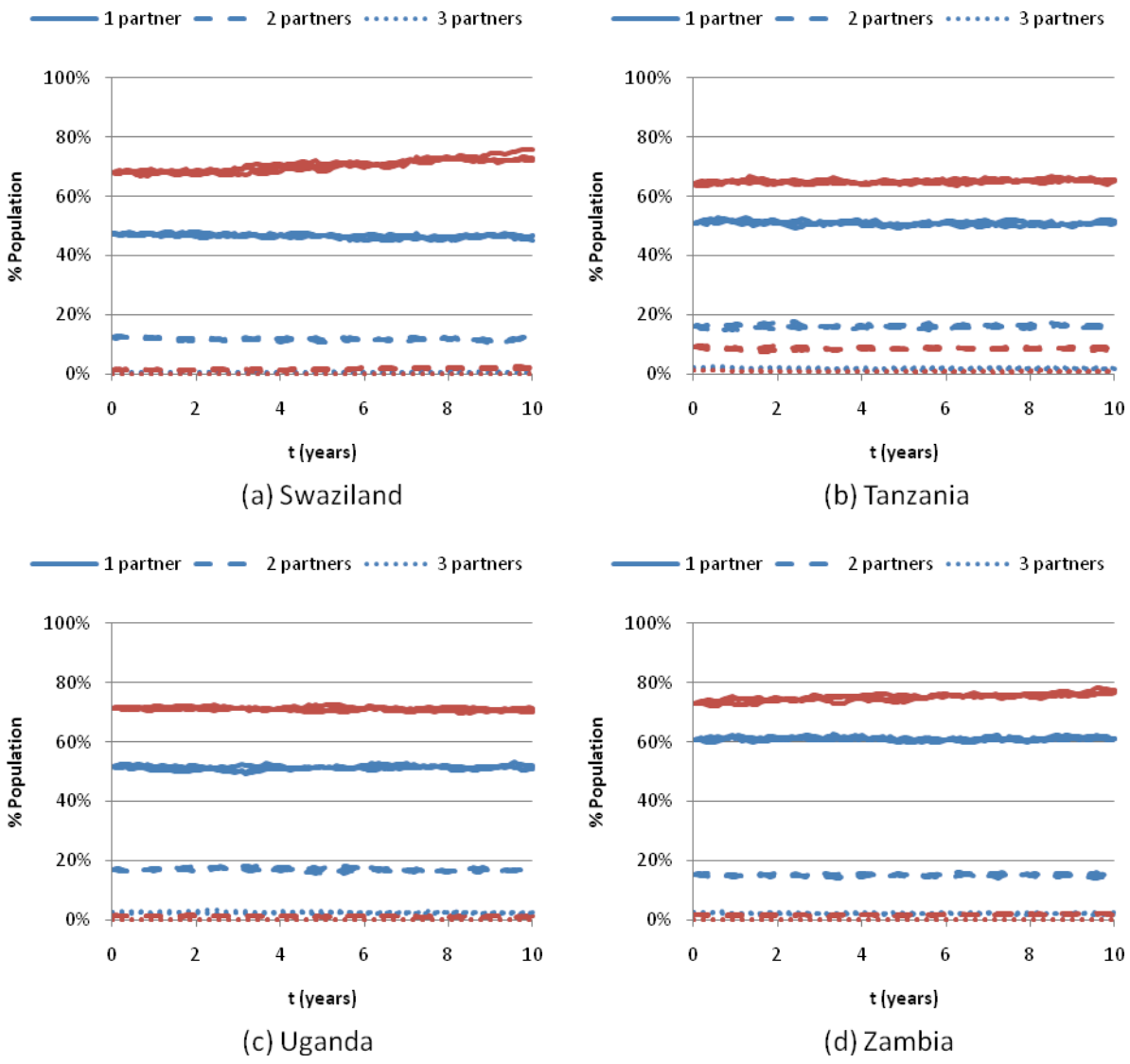
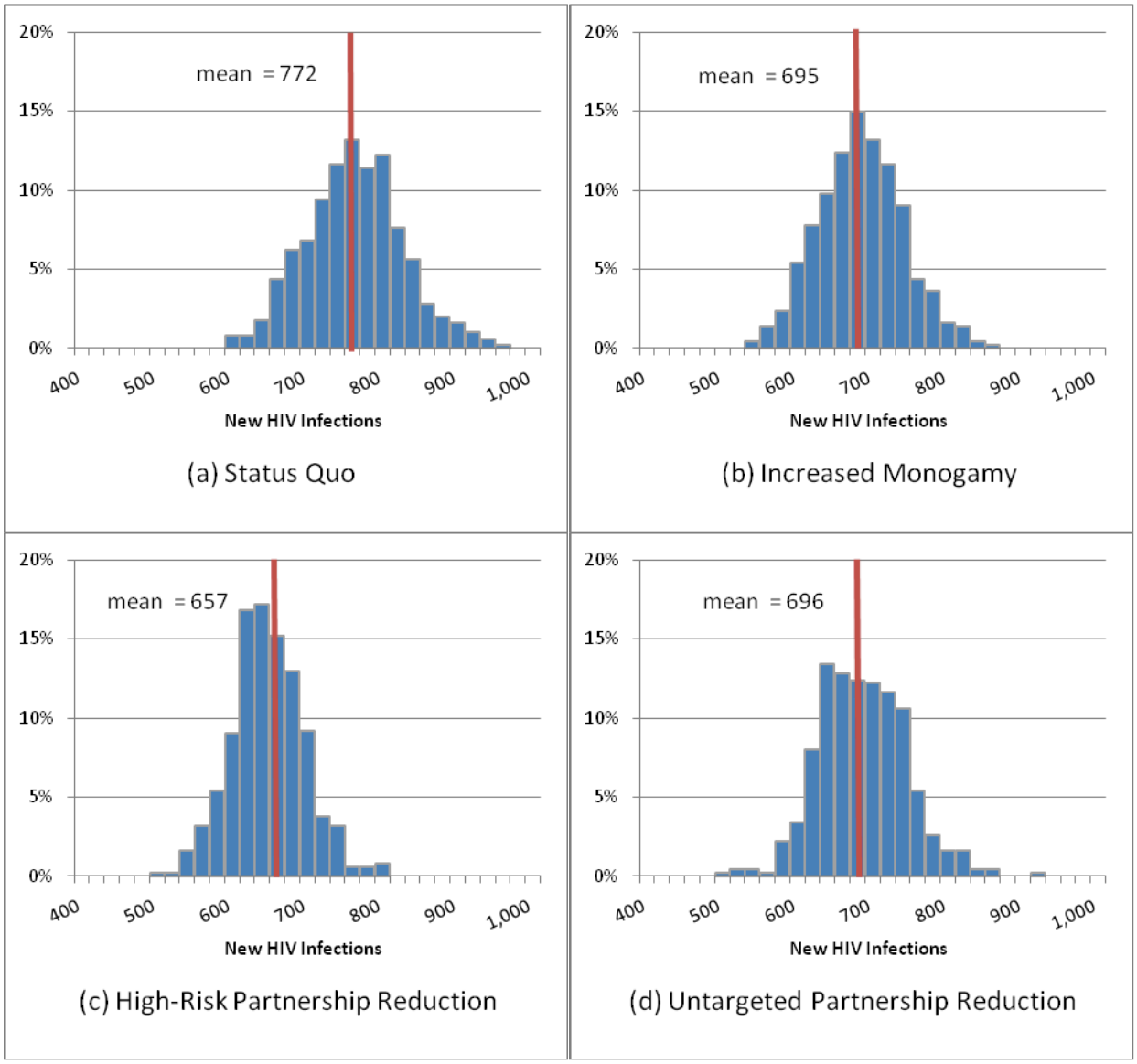
Appendix Figure 1: Schematic diagram of HIV disease model.



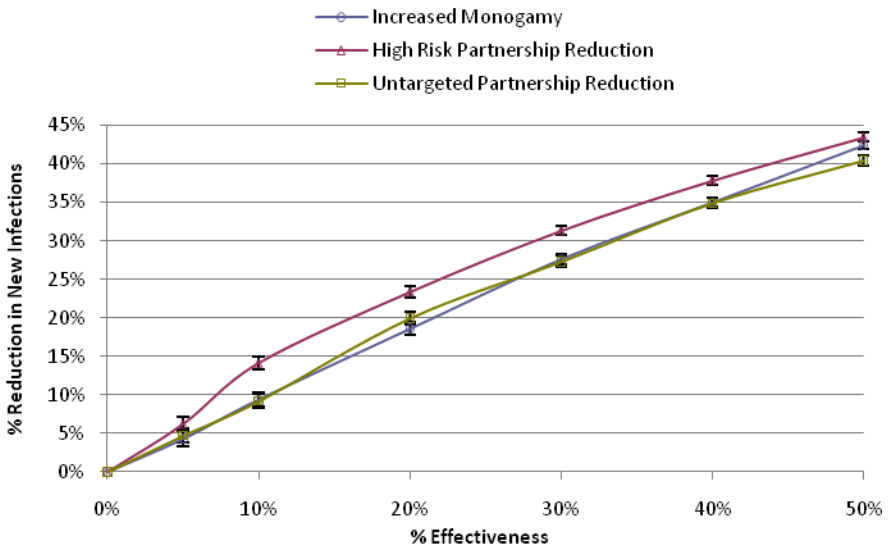
Appendix Figure 2: Partnership distributions for men (blue) and women (red) over time for 3 simulation runs.



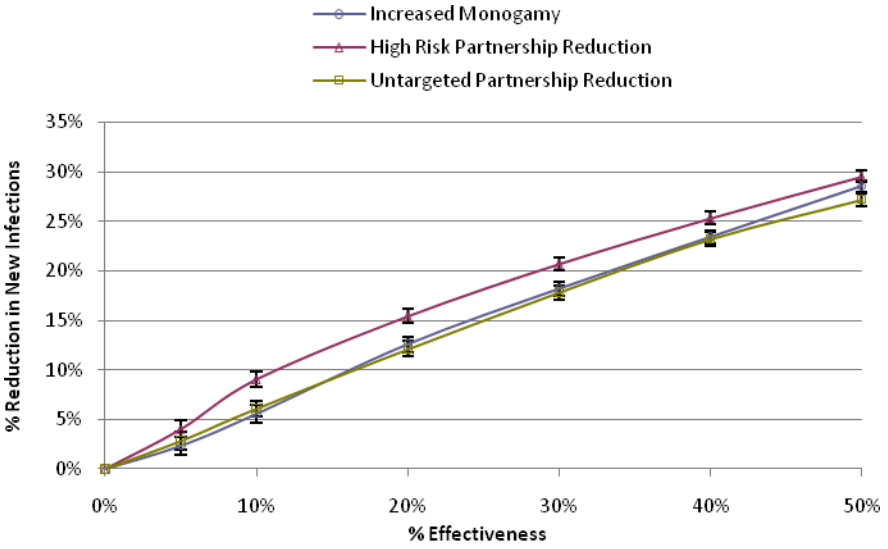
Appendix Figure 3: Mean and distribution of number of new HIV infections for the Status Quo and three behavior change scenarios over 500 runs.



Appendix Figure 4: Sensitivity analysis on using the reported partnership distribution versus adjusting for 50% over-reporting of concurrent partnerships in Tanzania. 95% confidence intervals are indicated for each sample point.

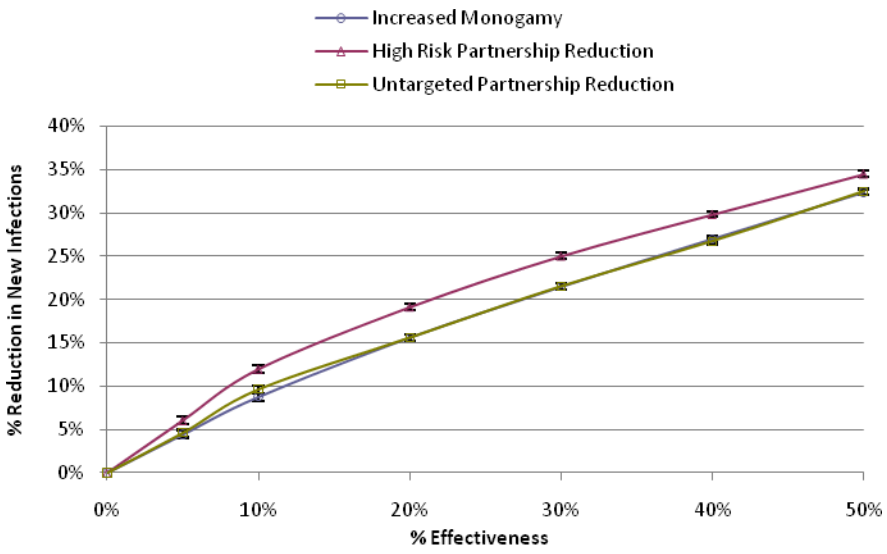


(a) Reported partnership distribution

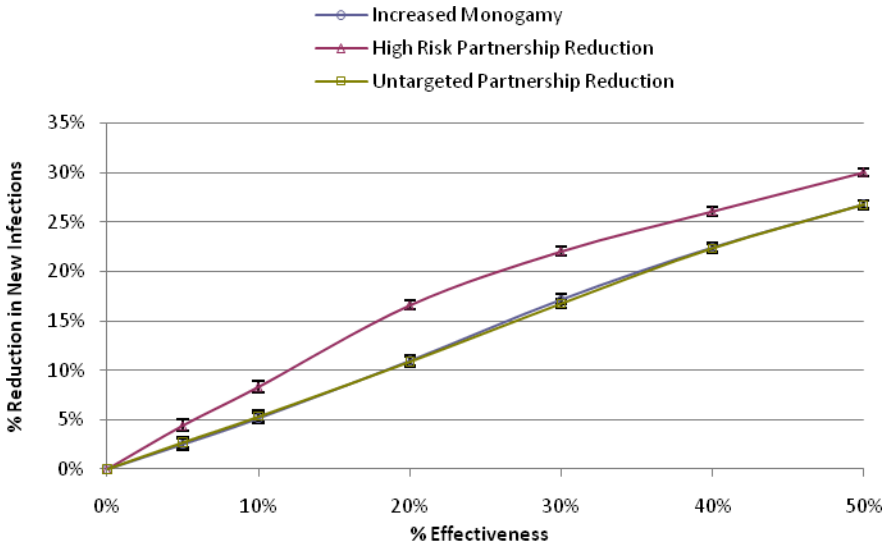


(b) Adjusted partnership distribution

Appendix Figure 5: Sensitivity analysis on adjusting the male-to-female ratio versus averaging gender-specific partnership distributions in Zambia to reconcile discrepancies between reported number of partners between men and women. 95% confidence intervals are indicated for each sample point.



(a) Adjusted male-to-female ratio



(b) Average partnership distribution

Appendix Table 1: Male-to-female ratio from demographic data and as adjusted in the model to reconcile differences in reported number of partnerships by men and women.

Male-to-female ratio among 15-49 year-olds	**Swaziland**	**Tanzania**	**Uganda**	**Zambia**
Actual	1:1.06	1:1.02	1:1.00	1:1.00
Model	1:1.08	1:1.09	1:1.31	1:1.40

Appendix Table 2: Sensitivity analysis results showing percentage of total infections averted in Tanzania over 10 years for varying input parameters with 10% program effectiveness.

	Behavior Change Scenario		
Parameter Scenario	**Increased Monogamy**	**High-Risk Partnership Reduction**	**Untargeted Partnership Reduction**
Base Case	9.4%	14.2%	9.2%
HIV treatment coverage level			
10%	10.2%	14.6%	9.9%
50%	9.2%	14.4%	9.3%
HIV treatment threshold			
350 cells/μL	9.4%	14.9%	10.5%
Non-spousal partnership duration (years)			
1.0	10.0%	11.9%	9.5%
2.0	10.3%	16.9%	10.1%
Non-spousal HIV transmission risk (relative risk)			
0.8	8.4%	11.9%	8.6%
1.2	12.0%	18.4%	11.7%