Supporting Information

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SI Text

1. Introduction

This supporting information provides a complete description of our mathematical models, including their derivation and equations. First, in Section 2.1 we provide a description of our clinical trial model. The input parameters for this model are described along with their uncertainty ranges and references in Section 2.2. Some additional results of the clinical trial model that are not presented in the main text are in Sections 2.3 and 2.4; specifically, analyses of the risks versus benefits in terms of the number of infections prevented per resistant case and the results when adherence is <100%. Section 2.5 contains the mathematical solutions to the clinical trial model equations. In Section 3.1 we describe our heterosexual HIV epidemic model in detail, and in Section 3.2 we provide a complete list of parameter ranges used in this model. Sections 3.3–3.5 contain additional results of the epidemic model, including some response surface figures comparing the level of protection attained by women relative to men as influenced by key parameters and sensitivity analyses of the model.

2. Modeling a Phase III Clinical Efficacy Trial of an ARV-Based Microbicide

Currently there are various microbicides in different stages of clinical testing (see Table S1). In this study we consider second-generation microbicides, containing antiretrovirals (ARVs). We parameterize our model to match the phase III trial of dapivirine.

2.1. Model Structure. We construct a model of a phase III efficacy trial of an ARV-based microbicide. We model a placebo-controlled (i.e., two arm) clinical trial with 10,000 HIV-negative women at high risk of HIV infection (e.g., female sex workers) and simulated the trial for 12 months. We model a clinical trial carried out across a number of large settings, such as major urban cities, so that the cohort chosen to participate in the trial across all sites is a small fraction of the communities. We also assume that the duration of the trial (1 year) is sufficiently short so that the HIV prevalence does not change significantly over the timeframe of the clinical trial. We estimate the number of trial participants in each arm that become infected with HIV throughout the trial, the number of infections prevented during the trial, and the number of newly HIV-infected individuals in the microbicide arm of the trial that develop drug resistance due to continuing use of microbicides after seroconversion. We track the number of women participating in the clinical trial that are susceptible to infection (S), have very recently become infected with HIV (hence their infection is undetectable) (E), have detectable HIV infection (I), and have become infected with HIV and developed drug-resistance (R). The mathematical model is presented schematically in Fig. S1. Mathematically, our model is described by four ordinary differential equations (one for each category of women in the trial), namely,

$$\dot{S} = -(\alpha + \mu_S)S$$

$$\dot{E} = \alpha S - (\eta + \mu_E)E$$

$$\dot{I} = \eta E - (\rho + \mu_I)I$$

$$\dot{R} = \rho I - \mu_R R.$$

Here, μ_S, μ_E, μ_I, and μ_R are the rates at which each category of clinical trial participants leave the trial or are lost to follow-up, η is the rate of progression to detectable infection after seroconversion, ρ is the average rate of acquiring ARV-resistant virus, and α is the infection rate per unit time.

The primary properties of ARV-based microbicides are the efficacy of the product (which influences the infection rate α) and the average rate of emergence of ARV-resistant virus (ρ). Because these properties are unknown, in our model analysis we include them as experimental variables and explore a large uncertainty range for each parameter. We assume that if the non-nucleoside reverse transcriptase inhibitors (NNRTIs) in the ARV-based microbicide are systemically absorbed then the emergence time of drug resistance (if microbicides are used daily; i.e., adherence is 100%) could range from a minimum of 6 months (on average) to a maximum value (which we consider to be the value at which NNRTI resistance never emerges); accordingly, we define the following parameter: 6 months $< 1/\rho_{\max} < \infty$. If adherence is <100%, then we proportionally decrease the rate of emergence of drug resistance. We assume that the rate of resistance increases linearly with microbicide usage. Therefore, we model the average rate to develop resistance as the product of the maximum rate at which resistance could develop, $\rho_{\max}$, and the level of adherence (which is defined to be the proportion of days when NNRTIs are used and therefore can be absorbed). Then, $\rho = \theta p_m \rho_{\max}$, where θ is the probability that the NNRTI would be systemically absorbed during a single usage (i.e., 1 day) of the ARV-based microbicide, and p_m represents adherence. The rate of systemic drug absorption is unknown. The vagina is highly permeable (1–4) and is often considered an ideal route for drug administration (5–9); therefore, the probability of systemic absorption of NNRTIs could be high. However, preliminary results from phase I clinical trials indicate that there is only a low probability that NNRTIs will be systemically absorbed (10). Therefore, we conducted two analyses: (*i*) for high-risk ARV-based microbicides (which we define to be ARV-based microbicides that have a high probability of NNRTI absorption, ranging from 0.5 to 0.9), and (*ii*) for low-risk microbicides (which we define to be ARV-based microbicides that have a low probability of NNRTI absorption, ranging from 0.01 to 0.03).

The infection rate (α), also known as the force of infection, depends on the number of sex acts per day and the HIV transmission probabilities associated with each of these acts. In our mathematical model, we denote the probability of HIV transmission from an infected male to an uninfected female during a single unprotected act of vaginal intercourse by β_m^f. However, if a form of protection is used by a man (i.e., a condom) or a woman (i.e., a microbicide), then the probability of transmission is reduced. We consider four

types of protection: no protection (1), condoms (2), microbicides (3), and condoms used with microbicides (4). We let $\beta_i \leq \beta_m^f$ be the probability of transmission per sex act with protection type $i = (1 \ldots 4)$. The efficacy of a type of protection refers to the proportion of sex acts in which transmission is prevented that would have resulted in transmission if no protection had been used. If ε_c is the efficacy of condoms and ε_m^F is the efficacy of microbicides per sex act for women, then the transmission probabilities per sex act for each type of protection are calculated by $\beta_1 = \beta_m^f$, $\beta_2 = (1 - \varepsilon_c)\beta_m^f$, $\beta_3 = (1 - \varepsilon_m^F)\beta_m^f$, and $\beta_4 = (1 - \varepsilon_c)(1 - \varepsilon_m^F)\beta_m^f$. Then, the probability of remaining uninfected after a single sex act is $(1 - \beta_i)$. Because each discordant sex act results in either transmission of infection or not (two possible outcomes), we have a Bernoulli event. If n is the total number of sex acts per partner per unit time and p_i is the proportion of sex acts in which protection type i is used, then the probability of remaining uninfected after all np_i discordant sex acts is binomial $(1 - \beta_i)^{np_i}$. Thus, the probability of acquiring infection per HIV-infected partner per unit time is given by

$$\left\{1 - \prod_{i=1}^{4} (1 - \beta_i)^{np_i}\right\},$$

which includes all four types of protection. A sexually active woman may have multiple sex partners per unit time. If P is the HIV prevalence in the pool of male partners (in our model we take P to be constant because the trial is over 1 year, but our model could be easily modified to dynamically calculate prevalence in order to calculate results over a longer time period) and c is the average number of new sex partners per unit time, then the average number of HIV transmissions per unit time (that is, the infection rate) is

$$\alpha = cP\left\{ - \prod_{i=1}^{4} (1 - \beta_i)^{np_i}\right\}.$$

The ARV-based microbicides in the clinical trials will require daily use to sustain appropriate levels of drug concentrations, and the products are hoped to be active in protecting against HIV transmission in each serodiscordant sex act over the entire day (presumably at the same efficacy for each act). In the model design, we take the level of daily adherence to microbicides as an approximate measure for the proportion of sex acts in which microbicides confer protection. For example, if daily adherence is 70%, then we assume that microbicides offer protection (at the same efficacy) for 70% of all of their sex acts. For the analyses reported in the main text we assume complete adherence to the trial protocol by trial participants; that is, we assume that they use microbicides every day, and thus microbicides confer a degree of protection over all sex acts. In addition, in some acts condoms could be used.

We include, as do the ARV-based microbicide trials, the possibility of testing for HIV infection throughout the trial. Testing is extremely costly because of the large number of clinical sites and personnel that are necessary, required pre- and post-test counseling, the documentation that has to be collected in accordance with the guidelines for Good Clinical Practice (11), and database administration. Participants are immediately excluded from our simulated trial if HIV testing reveals that they have seroconverted. Detection for seroconversion and subsequent exclusion using rapid tests will occur in the actual trials; results from rapid tests will be available 10–15 min after testing (12). However, the rapid tests used to detect HIV infection are not highly sensitive to early detection because the test is based on HIV antibodies. This 3- to 12-week window/lag period between infection and detection is captured by our "E" compartment, representing the number of participants that have recently become infected with HIV but for which the infection is undetectable. According to our model, the duration of the clinical trial is split into a number of intervals (between each testing) where interval j refers to the time $t \in [t_{j-1}, t_j)$ and each interval between testing is of equivalent duration $\Delta t = t_j - t_{j-1}$. At the time of testing, the number of trial participants in the compartments of detectable HIV infection, namely $I(t_j)$ and $R(t_j)$, are both set to zero because the individuals represented by these compartments are excluded from the remainder of the trial, but uninfected participants and participants with undetectable HIV infection, represented by $S(t_j)$ and $E(t_j)$, respectively, remain in the trial.

2.2. Parameters. Our model is parameterized to match the phase III efficacy trial of dapivirine that is planned to be completed in 2009. We assume that participants in the modeled trial are HIV-negative women in a resource-constrained setting at high-risk for HIV infection, with an average annual incidence of 5% (13–18). We calibrated our model using the average number of new sex partners and the HIV prevalence of male partners to obtain this average (median) incidence at the beginning of the trial. Behavioral and demographic parameter values taken from the appropriate clinical, demographic, sociological, and epidemiological literature are presented in Table S2.

2.3. Number of Infections Prevented per Resistant Case for Female Sex Workers in an ARV-Based Microbicide Clinical Trial. To assess the risks versus benefits of ARV-based microbicides for female sex workers in a clinical trial, we calculated the number of infections prevented per resistant case for both our high-risk and low-risk microbicides, using our 20,000 Monte Carlo simulations. Not surprisingly, the microbicide efficacy was found to be a key parameter in determining the risk–benefit profile [see Fig. S2, where we present a scatterplot of all 20,000 simulations of the effect of increasing microbicide efficacy on increasing the cumulative number of infections prevented per resistant case (blue data are when a low-risk microbicide is used, median 135, IQR 42–395; and red data are for when a high-risk microbicide is used, median 1, IQR 0–3)]. For low-risk microbicides, the number of infections prevented per resistant case is high, because very few cases of acquired resistance develop because of low NNRTI absorption.

2.4. Effect of Nonadherence on the Number of Infections Prevented and the Number of Cases of Acquired Resistance That Will Develop During a Clinical Trial. Although the upcoming trials will likely require daily application of the gel, it is unlikely that there will be 100% adherence. Therefore, we also analyzed different levels of adherence in conjunction with a range of microbicide efficacies. We determined that promoting high adherence rates for even moderately efficacious microbicides would have a greater impact on preventing HIV infections than increasing the efficacy of the products.

We also conducted a sensitivity analysis [by means of calculating partial rank correlation coefficients (PRCCs)] (44) of our simulated data and determined (not surprisingly) that the microbicide efficacy and adherence are the parameters that have the greatest influence on increasing the number of infections prevented during a clinical trial. In Fig. S3, we display scatterplots of the percentage of the number of infections prevented resulting from the microbicides trial versus efficacy of microbicides; in Fig. S4, we display a scatterplot of the reduction in incidence according to the average level of adherence and the efficacy combined. The bands of color in Fig. S4 represent grades of the percentage of infections prevented after 12 months of a clinical trial. For example, if a 50% effective microbicide was introduced, and on average female sex workers were 30% adherent, then 10–20% of infections would be expected to be prevented in the trial. However, if adherence could be increased to 90%, then ~40–50% of infections would be prevented. We note that for low levels of adherence, the percentage of infections prevented is almost independent of the efficacy. Increasing adherence will have a greater impact on reducing incidence than increasing microbicide efficacy, if moderately efficacious microbicides are used. The total number of drug-resistant cases that can be expected to emerge depends on whether high-risk or low-risk microbicides are used and on the average time for resistance to emerge (Fig. S5).

2.5. Mathematical Solutions to Clinical Trial Model Equations. We denote the total cumulative number of participants at the end of interval j (at time $t = \Delta t \times j$) that have been detected as seroconverters (and are consequently excluded from the remainder of the trial) and have wild-type virus and drug-resistant virus by X_j^{I} and X_j^{R}, respectively. We note that $X_0^{\mathrm{I}} = X_0^{\mathrm{R}} = 0$ and that X_j^{I} and X_j^{R} are the cumulative number of participants that have been tested at the end of each interval prior to, and including, interval j.

The closed form mathematical solutions of our clinical trial model equations, for the number of participants that are susceptible ($S(t)$), infected with undetectable HIV ($E(t)$), infected with detectable wild-type HIV ($I(t)$), and infected with detectable drug-resistant HIV ($R(t)$), at time t and participating in the clinical trial are given by

$$S(t) = S_0 \exp(-(\alpha + \mu_S)t)$$

$$E(t) = E_0 \exp(-(\eta + \mu_E)t) + \frac{\alpha S_0}{(\eta + \mu_E) - (\alpha + \mu_S)}\left[\exp(-(\alpha + \mu_S)t) - \exp(-(\eta + \mu_E)t)\right]$$

$$\begin{aligned} I(t) = {} & I_0 \exp(-(\rho + \mu_I)t)\delta_{1j} + \frac{\eta}{(\rho + \mu_I) - (\eta + \mu_E)}\left[\exp(-(\eta + \mu_E)(t - (j-1)\Delta t)) - \exp(-(\rho + \mu_I)(t - (j \right. \\ & \left. - 1)\Delta t))\right] \cdot \left\{ E_0 \exp(-(\eta + \mu_E)(j-1)\Delta t) + \frac{\alpha S_0[\exp(-(\alpha + \mu_S)(j-1)\Delta t) - \exp(-(\eta + \mu_E)(j-1)\Delta t)]}{(\eta + \mu_E) - (\alpha + \mu_S)} \right\} \\ & + \frac{\eta \alpha S_0 \exp(-(\alpha + \mu_S)(j-1)\Delta t)}{(\eta + \mu_E) - (\alpha + \mu_S)} \left[\frac{\exp(-(\alpha + \mu_S)(t - (j-1)\Delta t)) - \exp(-(\rho + \mu_I)(t - (j-1)\Delta t))}{(\rho + \mu_I) - (\alpha + \mu_S)} \right. \\ & \left. - \frac{\exp(-(\eta + \mu_E)(t - (j-1)\Delta t)) - \exp(-(\rho + \mu_I)(t - (j-1)\Delta t))}{(\rho + \mu_I) - (\eta + \mu_E)} \right] \end{aligned}$$

$$\begin{aligned} R(t) = {} & \left\{ R_0 \exp(-\mu_R t) + \frac{\rho I_0}{\mu_R - (\rho + \mu_I)}\left[\exp(-(\rho + \mu_I)t) - \exp(-\mu_R t)\right] \right\} \delta_{1j} + \frac{\rho \eta}{(\rho + \mu_I) - (\eta + \mu_E)} \\ & \cdot \left[\frac{\exp(-(\eta + \mu_E)(t - (j-1)\Delta t)) - \exp(-\mu_R(t - (j-1)\Delta t))}{\mu_R - (\eta + \mu_E)} \right. \\ & \left. - \frac{\exp(-(\rho + \mu_I)(t - (j-1)\Delta t)) - \exp(-\mu_R(t - (j-1)\Delta t))}{\mu_R - (\rho + \mu_I)} \right] \cdot \left\{ E_0 \exp(-(\eta + \mu_E)(j-1)\Delta t) \right. \\ & \left. + \frac{\alpha S_0[\exp(-(\alpha + \mu_S)(j-1)\Delta t) - \exp(-(\eta + \mu_E)(j-1)\Delta t)]}{(\eta + \mu_E) - (\alpha + \mu_S)} \right\} + \frac{\rho \eta \alpha S_0 \exp(-(\alpha + \mu_S)(j-1)\Delta t)}{(\eta + \mu_E) - (\alpha + \mu_S)} \left\{ \frac{1}{(\rho + \mu_I) - (\alpha + \mu_S)} \right. \\ & \cdot \left[\frac{\exp(-(\alpha + \mu_S)(t - (j-1)\Delta t)) - \exp(-\mu_R(t - (j-1)\Delta t))}{\mu_R - (\alpha + \mu_S)} \right. \\ & \left. - \frac{\exp(-(\rho + \mu_I)(t - (j-1)\Delta t)) - \exp(-\mu_R(t - (j-1)\Delta t))}{\mu_R - (\rho + \mu_I)} \right] - \frac{1}{(\rho + \mu_I) - (\eta + \mu_E)} \\ & \cdot \left[\frac{\exp(-(\eta + \mu_E)(t - (j-1)\Delta t)) - \exp(-\mu_R(t - (j-1)\Delta t))}{\mu_R - (\eta + \mu_E)} \right. \\ & \left. \left. - \frac{\exp(-(\rho + \mu_I)(t - (j-1)\Delta t)) - \exp(-\mu_R(t - (j-1)\Delta t))}{\mu_R - (\rho + \mu_I)} \right] \right\} \end{aligned}$$

Here, $j = \lceil t/\Delta t \rceil$ identifies the time interval (between testing) at time t, and δ_{ij} is the Kronecker delta. The number of HIV-infected participants with wild-type (X_j^{I}) and drug-resistant (X_j^{R}) virus that have been excluded from the clinical trial at the end of interval j is

$$X_j^I = I_0 \exp(-(\rho+\mu_I)\Delta t) + \frac{\eta}{(\rho+\mu_I)-(\eta+\mu_E)}[\exp(-(\eta+\mu_E)\Delta t) - \exp(-(\rho+\mu_I)\Delta t)]\cdot\left\{\frac{E_0(1-\exp(-(\eta+\mu_E)\Delta t\cdot j))}{1-\exp(-(\eta+\mu_E)\Delta t)}\right.$$
$$\left. + \frac{\alpha S_0}{(\eta+\mu_E)-(\alpha+\mu_S)}\left[\frac{1-\exp(-(\alpha+\mu_S)\Delta t\cdot j)}{1-\exp(-(\eta+\mu_S)\Delta t)} - \frac{1-\exp(-(\eta+\mu_E)\Delta t\cdot j)}{1-\exp(-(\eta+\mu_E)\Delta t)}\right]\right\}$$
$$+ \frac{\eta\alpha S_0}{(\eta+\mu_E)-(\alpha+\mu_S)}\frac{1-\exp(-(\alpha+\mu_S)\Delta t\cdot j)}{1-\exp(-(\alpha+\mu_S)\Delta t)}\left[\frac{\exp(-(\alpha+\mu_S)\Delta t) - \exp(-(\rho+\mu_I)\Delta t)}{(\rho+\mu_I)-(\alpha+\mu_S)}\right.$$
$$\left. - \frac{\exp(-(\eta+\mu_E)\Delta t) - \exp(-(\rho+\mu_I)\Delta t)}{(\rho+\mu_I)-(\eta+\mu_E)}\right]$$

$$X_j^R = R_0\exp(-\mu_R\Delta t) + \frac{\rho I_0}{\mu_R-(\rho+\mu_I)}[\exp(-(\rho+\mu_I)\Delta t) - \exp(-\mu_R\Delta t)] + \frac{\rho\eta}{(\rho+\mu_I)-(\eta+\mu_E)}$$
$$\cdot\left[\frac{exp(-(\eta+\mu_E)\Delta t) - exp(-\mu_R\Delta t)}{\mu_R-(\eta+\mu_E)} - \frac{\exp(-(\rho+\mu_I)\Delta t) - \exp(-\mu_R\Delta t)}{\mu_R-(\rho+\mu_I)}\right]\cdot\left\{\frac{E_0(1-\exp(-(\eta+\mu_E)\Delta t\cdot j))}{1-\exp(-(\eta+\mu_E)\Delta t)}\right.$$
$$\left. + \frac{\alpha S_0}{(\eta+\mu_E)-(\alpha+\mu_S)}\left[\frac{1-\exp(-(\alpha+\mu_S)\Delta t\cdot j)}{1-\exp(-(\alpha+\mu_S)\Delta t)} - \frac{1-\exp(-(\eta+\mu_E)\Delta t\cdot j)}{1-\exp(-(\eta+\mu_E)\Delta t)}\right]\right\}$$
$$+ \frac{\rho\eta\alpha S_0}{(\eta+\mu_E)-(\alpha+\mu_S)}\frac{1-\exp(-(\alpha+\mu_S)\Delta t\cdot j)}{1-\exp(-(\alpha+\mu_S)\Delta t)}\left\{\frac{1}{(\rho+\mu_I)-(\alpha+\mu_S)}\left[\frac{\exp(-(\alpha+\mu_S)\Delta t) - \exp(-\mu_R\Delta t)}{\mu_R-(\alpha+\mu_S)}\right.\right.$$
$$\left. - \frac{\exp(-(\rho+\mu_I)\Delta t) - \exp(-\mu_R\Delta t)}{\mu_R-(\rho+\mu_I)}\right] - \frac{1}{(\rho+\mu_I)-(\eta+\mu_E)}\left[\frac{\exp(-(\eta+\mu_E)\Delta t) - \exp(-\mu_R\Delta t)}{\mu_R-(\eta+\mu_E)}\right.$$
$$\left.\left. - \frac{\exp(-(\rho+\mu_I)\Delta t) - \exp(-\mu_R\Delta t)}{\mu_R-(\rho+\mu_I)}\right]\right\}$$

The number of participants that have dropped out of the clinical trial from each of the categories [susceptible ($L_S(t)$), undetectable infection ($L_E(t)$), detectable wild-type infection ($L_I(t)$), and detectable drug-resistant infection ($L_R(t)$)] at time t is

$$L_S(t) = \frac{\mu_S S_0}{\alpha+\mu_S}[1-\exp(-(\alpha+\mu_S)t)]$$

$$L_E(t) = \frac{\mu_E E_0}{\eta+\mu_E}[1-\exp(-(\eta+\mu_E)t)] + \frac{\mu_E\alpha S_0}{(\eta+\mu_E)-(\alpha+\mu_S)}\left[\frac{1-exp(-(\alpha+\mu_S)t)}{(\alpha+\mu_S)} - \frac{1-\exp(-(\eta+\mu_E)t)}{(\eta+\mu_E)}\right]$$

$$L_I(t) = \frac{\mu_I I_0}{\rho+\mu_I}[1-\exp(-(\rho+\mu_I)t)]\delta_{1j} + \frac{\mu_I\eta}{(\rho+\mu_I)-(\eta+\mu_E)}\left[\frac{1-\exp(-(\eta+\mu_E)(t-(j-1)\Delta t))}{(\eta+\mu_E)}\right.$$
$$\left. - \frac{1-\exp(-(\rho+\mu_I)(t-(j-1)\Delta t))}{(\rho+\mu_I)}\right]\cdot\left\{E_0\exp(-(\eta+\mu_E)(j-1)\Delta t)\right.$$
$$\left. + \frac{\alpha S_0[\exp(-(\alpha+\mu_S)(j-1)\Delta t) - \exp(-(\eta+\mu_E)(j-1)\Delta t)]}{(\eta+\mu_E)-(\alpha+\mu_S)}\right\}$$
$$+ \frac{\eta\alpha\mu_I S_0\exp(-(\alpha+\mu_S)(j-1)\Delta t)}{(\eta+\mu_E)-(\alpha+\mu_S)}\left[\frac{1}{(\rho+\mu_I)-(\alpha+\mu_S)}\left\{\frac{1-\exp(-(\alpha+\mu_S)(t-(j-1)\Delta t))}{(\alpha+\mu_S)}\right.\right.$$
$$\left. - \frac{1-\exp(-(\rho+\mu_I)(t-(j-1)\Delta t))}{(\rho+\mu_I)}\right\} - \frac{1}{(\rho+\mu_I)-(\eta+\mu_E)}\left\{\frac{1-\exp(-(\eta+\mu_E)(t-(j-1)\Delta t))}{(\eta+\mu_E)}\right.$$
$$\left.\left. - \frac{1-\exp(-(\rho+\mu_I)(t-(j-1)\Delta t))}{(\rho+\mu_I)}\right\}\right] + \left\langle\frac{\mu_I I_0}{\rho+\mu_I}[1-\exp(-(\rho+\mu_I)\Delta t)]\right.$$
$$+ \frac{\mu_I\eta}{(\rho+\mu_I)-(\eta+\mu_E)}\left[\frac{1-\exp(-(\eta+\mu_E)\Delta t)}{(\eta+\mu_E)} - \frac{1-\exp(-(\rho+\mu_I)\Delta t)}{(\rho+\mu_I)}\right]\cdot\left\{E_0\left(\frac{1-\exp(-(\eta+\mu_E)(j-1)\Delta t)}{1-\exp(-(\eta+\mu_E)\Delta t)}\right)\right.$$
$$+ \frac{\alpha S_0}{(\eta+\mu_E)-(\alpha+\mu_S)}\left[\frac{\exp(-(\alpha+\mu_S)\Delta t) - \exp(-(\alpha+\mu_S)(j-1)\Delta t)}{1-\exp(-(\alpha+\mu_S)\Delta t)}\right.$$
$$\left.\left.\left. - \frac{\exp(-(\eta+\mu_E)\Delta t) - \exp(-(\eta+\mu_E)(j-1)\Delta t)}{1-\exp(-(\eta+\mu_E)\Delta t)}\right]\right\}$$

$$+\frac{\eta\alpha\mu_I S_0}{(\eta+\mu_E)-(\alpha+\mu_S)}\left[\frac{1}{(\rho+\mu_I)-(\alpha+\mu_S)}\left\{\frac{1-\exp(-(\alpha+\mu_S)\Delta t)}{(\alpha+\mu_S)}-\frac{1-exp(-(\rho+\mu_I)\Delta t)}{(\rho+\mu_I)}\right\}-\frac{1}{(\rho+\mu_I)-(\eta+\mu_E)}\right.$$
$$\left.\cdot\left\{\frac{1-\exp(-(\eta+\mu_E)\Delta t)}{(\eta+\mu_E)}-\frac{1-\exp(-(\rho+\mu_I)\Delta t)}{(\rho+\mu_I)}\right\}\right]\cdot\left[\frac{1-\exp(-(\alpha+\mu_S)(j-1)\Delta t)}{1-\exp(-(\alpha+\mu_S)\Delta t)}\right]\Bigg\rangle(1-\delta_{1j})$$

$$L_R(t)=\left\{R_0(1-\exp(-\mu_R t))+\frac{\mu_R\rho I_0}{\mu_R-(\rho+\mu_1)}\left[\frac{1-\exp(-(\rho+\mu_1)t)}{\rho+\mu_1}-\frac{1-\exp(-\mu_R t)}{\mu_R}\right]\right\}\delta_{1j}+\frac{\mu_R\rho\eta}{(\rho+\mu_1)-(\eta+\mu_E)}$$
$$\cdot\left[\frac{1}{\mu_R-(\eta+\mu_E)}\left\langle\frac{1-\exp(-(\eta+\mu_E)(t-(j-1)\Delta t))}{\eta+\mu_E}-\frac{1-\exp(-\mu_R(t-(j-1)\Delta t))}{\mu_R}\right\rangle-\frac{1}{\mu_R-(\rho+\mu_1)}\right.$$
$$\left.\cdot\left\langle\frac{1-\exp(-(\rho+\mu_1)(t-(j-1)\Delta t))}{\rho+\mu_1}-\frac{1-\exp(-\mu_R(t-(j-1)\Delta t))}{\mu_R}\right\rangle\right]\cdot\left\{E_0\exp(-(\eta+\mu_E)(j-1)\Delta t)\right.$$
$$\left.+\frac{\alpha S_0}{(\eta+\mu_E)-(\alpha+\mu_S)}[\exp(-(\alpha+\mu_S)(j-1)\Delta t)-\exp(-(\eta+\mu_E)(j-1)\Delta t)]\right\}+\frac{\mu_R\rho\eta\alpha S_0\exp(-(\alpha+\mu_S)(j-1)\Delta t)}{(\eta+\mu_E)-(\alpha+\mu_S)}$$
$$\cdot\left\{\frac{1}{(\rho+\mu_1)-(\alpha+\mu_S)}\left[\frac{1}{\mu_R-(\alpha+\mu_S)}\left\langle\frac{1-\exp(-(\alpha+\mu_S)(t-(j-1)\Delta t))}{\alpha+\mu_S}-\frac{1-\exp(-\mu_R(t-(j-1)\Delta t))}{\mu_R}\right\rangle\right.\right.$$
$$\left.\left.-\frac{1}{\mu_R-(\rho+\mu_1)}\left\langle\frac{1-\exp(-(\rho+\mu_1)(t-(j-1)\Delta t))}{\rho+\mu_1}-\frac{1-\exp(-\mu_R(t-(j-1)\Delta t))}{\mu_R}\right\rangle\right]-\frac{1}{(\rho+\mu_1)-(\eta+\mu_E)}\right.$$
$$\left.\cdot\left[\frac{1}{\mu_R-(\eta+\mu_E)}\left\langle\frac{1-\exp(-(\eta+\mu_E)(t-(j-1)\Delta t-\frac{1-\exp(-\mu_R(t-(j-1)\Delta t))}{\eta+\mu_E}}{\mu_R}\right\rangle-\frac{1}{\mu_R-(\rho+\mu_1)}\right.\right.$$
$$\left.\left.\cdot\left\langle\frac{1-\exp(-(\rho+\mu_1)(t-(j-1)\Delta t))}{\rho+\mu_1}-\frac{1-\exp(-\mu_R(t-(j-1)\Delta t))}{\mu_R}\right\rangle\right]\right\}+\left\langle R_0(1-\exp(-\mu_R\Delta t))+\frac{\mu_R\rho I_0}{\mu_R-(\rho+\mu_1)}\right.$$
$$\left.\cdot\left[\frac{1-\exp(-(\rho+\mu_1)\Delta t)}{\rho+\mu_1}\right)-\frac{1-\exp(-\mu_R\Delta t)}{\mu_R}\right]+\frac{\mu_R\rho\eta}{(\rho+\mu_1)-(\eta+\mu_E)}\left[\frac{1}{\mu_R-(\eta+\mu_E)}\left\langle\frac{1-\exp(-(\eta+\mu_E)\Delta t)}{\eta+\mu_E}\right.\right.$$
$$\left.\left.-\frac{1-\exp(-\mu_R\Delta t)}{\mu_R}\right\rangle-\frac{1}{\mu_R-(\rho+\mu_1)}\left\langle\frac{1-\exp(-(\rho+\mu_1)\Delta t)}{\rho+\mu_1}\right)\right.$$
$$\left.-\frac{1-\exp(-\mu_R\Delta t)}{\mu_R}\right\rangle\cdot\left\{E_0\left(\frac{1-\exp(-(\eta+\mu_E)(j-1)\Delta t)}{1-\exp(-(\eta+\mu_E)\Delta t)}\right)+\frac{\alpha S_0}{(\eta+\mu_E)-(\alpha+\mu_S)}\right.$$
$$\left.\cdot\left[\frac{\exp(-(\alpha+\mu_S)\Delta t)-\exp(-(\alpha+\mu_S)(j-1)\Delta t)}{1-\exp(-(\alpha+\mu_S)\Delta t)}-\frac{\exp(-(\eta+\mu_E)\Delta t)-\exp(-(\eta+\mu_E)(j-1)\Delta t)}{1-\exp(-(\eta+\mu_E)\Delta t)}\right]\right\}$$
$$+\frac{\mu_R\rho\eta\alpha S_0}{(\eta+\mu_E)-(\alpha+\mu_S)}\left\{\frac{1}{(\rho+\mu_1)-(\alpha+\mu_S)}\left[\frac{1}{\mu_R-(\alpha+\mu_{s_S})}\left\langle\frac{1-\exp(-(\alpha+\mu_S)\Delta t)}{\alpha+\mu_S}-\frac{1-\exp(-\mu_R\Delta t)}{\mu_R}\right\rangle\right.\right.$$
$$\left.\left.-\frac{1}{\mu_R-(\rho+\mu_1)}\left\langle\frac{1-\exp(-(\rho+\mu_1)\Delta t)}{\rho+\mu_1}-\frac{1-\exp(-\mu_R\Delta t)}{\mu_R}\right)\right\rangle\right]$$
$$-\frac{1}{(\rho+\mu_1)-(\eta+\mu_E)}\left[\frac{1}{\mu_R-(\eta+\mu_E)}\left\langle\frac{1-\exp(-(\eta+\mu_E)\Delta t)}{\eta+\mu_E}-1-\exp(-\mu_R\Delta t)\mu_R\right.\right.$$
$$\left.\left.-\frac{1}{\mu_R-(\rho+\mu_1)}\left\langle\frac{1-\exp(-(\rho+\mu_1)\Delta t)}{\rho+\mu_1}\right)-\frac{1-\exp(-\mu_R\Delta t)}{\mu_R}\left(\frac{1-\exp(-(\alpha+\mu_S)(j-1)\Delta t)}{1-\exp(-(\alpha+\mu_S)\Delta t)}\right)(1-\delta_{1j})\right.\right.$$

The sum of all groups, $S(t)+E(t)+I(t)+R(t)\,L_{\mathrm{S}}(t)+L_{\mathrm{E}}(t)+L_{\mathrm{I}}(t)+L_{\mathrm{R}}(t)+X_j^{\mathrm{I}}+X_j^{\mathrm{R}}=C_0$, the total initial cohort size (a constant), so that the population size is conserved as required.

If testing for HIV seropositivity is performed at the end of regular intervals of duration Δt, then the total number of susceptible women tested, over all tests, is

$$S_0\left(\frac{\exp(-(\alpha+\mu_S)\Delta t)-\exp(-(\alpha+\mu_S)(T+\Delta t))}{1-\exp(-(\alpha+\mu_S)\Delta t)}\right),$$

and the total number of women with undetectable infection tested, over all tests, is

$$\left(E_0 - \frac{\alpha S_0}{(\eta + \mu_E) - (\alpha + \mu_S)}\left(\frac{\exp(-(\eta + \mu_E)\Delta t) - \exp(-(\eta + \mu_E)(T + \Delta t))}{1 - \exp(-(\eta + \mu_E)\Delta t)}\right) + \frac{\alpha S_0}{(\eta + \mu_E) - (\alpha + \mu_S)}\right.$$
$$\left.\cdot\left(\frac{\exp(-(\alpha + \mu_S)\Delta t) - \exp(-(\alpha + \mu_S)(T + \Delta t))}{1 - \exp(-(\alpha + \mu_S)\Delta t)}\right)\right.$$

The total number of women with detectable infection that have been tested, over all tests, is $X^{\mathrm{I}}_{T/\Delta t} + X^{\mathrm{R}}_{T/\Delta t}$, where T is the duration of the trial.

3. Modeling a Heterosexual HIV Epidemic When ARV-Based Microbicides Are Used in a Public Health Intervention

3.1. Model Structure. We consider the situation where vaginal ARV-based microbicides are made available for use by women in a community in a general high-prevalence resource-constrained setting (i.e., in the general population and not specifically for female sex workers). We develop a model of heterosexual transmission and track the number of men and women that are susceptible (S_{M} and S_{F}), infected with wild-type virus (I_{M} and I_{F}), or infected with drug-resistant virus (R_{M} and R_{F}). However, since not all women will use microbicides, we divided the female populations into those that use microbicides and those who choose not to use microbicides; we let $S^{\mathrm{U}}_{\mathrm{F}}$, $I^{\mathrm{U}}_{\mathrm{F}}$, and $R^{\mathrm{U}}_{\mathrm{F}}$ represent the number of women that use microbicides, in each of the corresponding model compartments, and we let S_{F}, I_{F}, and R_{F} represent the number of women who choose not to use microbicides. We define the coverage rate, κ, as the proportion of women using microbicides. For these women we also investigate a range in adherence (0–100%). We assume that adherence is indicative of the proportion of acts in which the products will confer a given protective efficacy against HIV infection. In our model drug resistance can be acquired by HIV-infected females using microbicides, and it can subsequently be transmitted sexually from females to males and then from males to females. We present a schematic of our population model in Fig. S6; and the model is described mathematically by the following ordinary differential equations for women in the community:

$$\dot{S}^U_F = \kappa\pi_F - \mu_F S^U_F - \frac{c_F\beta^{FU}_M S^U_F I_M}{N_M} - \frac{c_F\beta^{FU}_{RM} S^U_F R_M}{N_M}$$

$$\dot{I}^U_F = \frac{c_F\beta^{FU}_M S^U_F I_M}{N_M} - (\mu_F + \delta^S_F + \rho)I^U_F$$

$$\dot{R}^U_F = \frac{c_F\beta^{FU}_{RM} S^U_F R_M}{N_M} + \rho I^U_F - (\mu_F + \delta^R_F)R^U_F$$

$$\dot{S}_F = (1 - \kappa)\pi_F - \mu_F S_F - \frac{c_F\beta^F_M S_F I_M}{N_M} - \frac{c_F\beta^F_{RM} S_F R_M}{N_M}$$

$$\dot{I}_F = \frac{c_F\beta^F_M S_F I_M}{N_M} - (\mu_F + \delta^S_F)I_F$$

$$\dot{R}_F = \frac{c_F\beta^F_{RM} S_F R_M}{N_M} - (\mu_F + \delta^R_F)R_F;$$

and the following equations for men in the community:

$$\dot{S}_M = \pi_M - \mu_M S_M - \frac{c_M(\beta^M_F I_F + \beta^M_{FU} I^U_F)S_M}{N_F} - \frac{c_M(\beta^M_{RF} R_F + \beta^M_{RFU} R^U_F)S_M}{N_F}$$

$$\dot{I}_M = \frac{c_M(\beta^M_F I_F + \beta^M_{FU} I^U_F)S_M}{N_F} - (\mu_M + \delta^S_M)I_M$$

$$\dot{R}_M = \frac{c_M(\beta^M_{RF} R_F + \beta^M_{RFU} R^U_F)S_M}{N_F} - (\mu_M + \delta^R_M)R_M.$$

Here, $N_{\mathrm{F}} = S^{\mathrm{U}}_{\mathrm{F}} + I^{\mathrm{U}}_{\mathrm{F}} + R^{\mathrm{U}}_{\mathrm{F}} + S_{\mathrm{F}} + I_{\mathrm{F}} + R_{\mathrm{F}}$, and $N_{\mathrm{M}} = S_{\mathrm{M}} + I_{\mathrm{M}} + R_{\mathrm{M}}$ are the total number of women and men in the community respectively, π_{M} and π_{F} are the rates of entry of susceptible people into the sexually active population, and μ_{M} and μ_{F} are the rates of departure from the pool of people selecting for sex partners, for men and women, respectively. Women have an average of c_{F} sex partnerships with men, and men have an average of c_{M} sex partnerships with women. We ensure that there is conservation of partnerships such that $c_{\mathrm{F}}N_{\mathrm{F}} = c_{\mathrm{M}}N_{\mathrm{M}}$, we let each woman have a constant c_{F} number of sex partners and then the number of sex partners that each man will have is $c_{\mathrm{M}} = c_{\mathrm{F}}N_{\mathrm{F}}/N_{\mathrm{M}}$ (45). Serodiscordant partnerships can result in transmission of HIV (wild-type strains) with probability $\beta^{\mathrm{M}}_{\mathrm{F}}$ or $\beta^{\mathrm{M}}_{\mathrm{FU}}$ from an infected woman to a susceptible man, $\beta^{\mathrm{F}}_{\mathrm{M}}$ or $\beta^{\mathrm{FU}}_{\mathrm{M}}$ from an infected man to a susceptible woman, $\beta^{\mathrm{M}}_{\mathrm{RF}}$ or $\beta^{\mathrm{M}}_{\mathrm{RFU}}$ from a woman with drug-resistant HIV to a susceptible man, and $\beta^{\mathrm{F}}_{\mathrm{RM}}$ or $\beta^{\mathrm{FU}}_{\mathrm{RM}}$ from a man with drug-resistant HIV to a susceptible woman; state variables with an additional subscript/superscript "U" represent women that use microbicides.

Transmission probabilities are calculated in a similar manner to the transmission probability constructs for the clinical trial model. For example, the overall probability of HIV transmission from a woman (who is not using a microbicide) and is infected with drug-resistant virus to a susceptible man is given by $\beta^{\mathrm{M}}_{\mathrm{RF}} = 1 - (1 - \beta^{\mathrm{m}}_{\mathrm{rf}})^{n_{\mathrm{M}}(1-q_2)}(1 - (1 - \varepsilon_{\mathrm{c}})\beta^{\mathrm{m}}_{\mathrm{rf}})^{n_{\mathrm{M}}q_2}$, where n_{M} is the total number of vaginal sex acts men have per sex partner per year, $\beta^{\mathrm{m}}_{\mathrm{rf}}$ is the transmission probability per unprotected sex act, q_2 is the proportion of sex acts in which condoms are used, and ε_{c} is the efficacy of condoms per sex act. We model the survival time for HIV-infected

individuals with the δ parameters. Similar to the clinical trial model, we let ρ be the rate of developing drug resistance in HIV-infected women who use microbicides; that is, $\rho = \theta p_m \rho_{max}$, where θ is the probability that systemic NNRTI absorption will occur, p_m is the level of adherence, and ρ_{max} is the maximum rate of developing drug resistance. We present the ranges of parameter values specific for this model in Table S3.

3.2. Parameters. In Table S3 we present the parameter values for the heterosexual population model where ARV-based microbicides are used in a public health intervention.

3.3 Risk Versus Benefits of ARV-Based Microbicides for Men Versus Women. To evaluate the benefits for men versus women of ARV-based microbicides in preventing infections, we calculated the ratio (women to men) of the cumulative number of infections after 10 years of microbicide usage in each of our 20,000 Monte Carlo simulations; 10,000 simulations of high-risk microbicides and 10,000 simulations of low-risk microbicides. Cumulative distribution functions of this measure are presented in Fig. S7 for high-risk (red) and low-risk (blue) microbicides; this figure indicates the male advantage threshold (MAT) and the proportion of simulations that benefit men or women the most.

To assess the risks versus benefits of ARV-based microbicides for men and women when ARV-based microbicides are available in the general population, we calculated the number of infections prevented per resistant case in each of our 20,000 Monte Carlo simulations; 10,000 simulations of high-risk microbicides and 10,000 simulations of low-risk microbicides. In Fig. S8, we present cumulative distribution functions of the number of infections prevented per resistant case after 10 years of microbicide usage for both men [dark blue data (low-risk microbicides) and light blue data (high-risk microbicides)] and women [pink (low-risk microbicides) and mauve data (high-risk microbicides)]. It can be seen that in terms of the cumulative number of infections prevented per resistant case, regardless of the level of systemic drug absorption, ARV-based microbicides will always be of greater benefit to men than women (Fig. S8).

3.4. Low-Risk Microbicides and the Male Advantage Threshold. In the main text, we present response surfaces of the ratio (men to women) of the cumulative number of infections prevented after 10 years of ARV-based microbicide use in a general population as a function of the dominant parameters for the case of high-risk microbicides. In Fig. S9, we present the analogous response surfaces for the case of low-risk microbicides and their corresponding male advantage thresholds (MATs).

3.5. Sensitivity Analyses. We carried out sensitivity analyses to determine the importance of the input parameters in influencing the model outcome variables. We calculated standardized regression coefficients as a measure of sensitivity (results shown in Table S4). For both women and men, for high-risk and low-risk microbicides, the most important factor in determining the effectiveness of an ARV-based microbicide intervention in reducing the incidence of HIV epidemics in a heterosexual population is the degree of coverage of the microbicide. Adherence and product efficacy for women were also found to be important, albeit modestly, in reducing HIV incidence (Table S4). The most important factor in determining the degree of benefit for men over women in terms of the ratio (men to women) of the number of infections prevented per resistant case was found to be the fitness of drug-resistance strains relative to wild-type strains, followed by the microbicide efficacy for women and microbicide efficacy for men.

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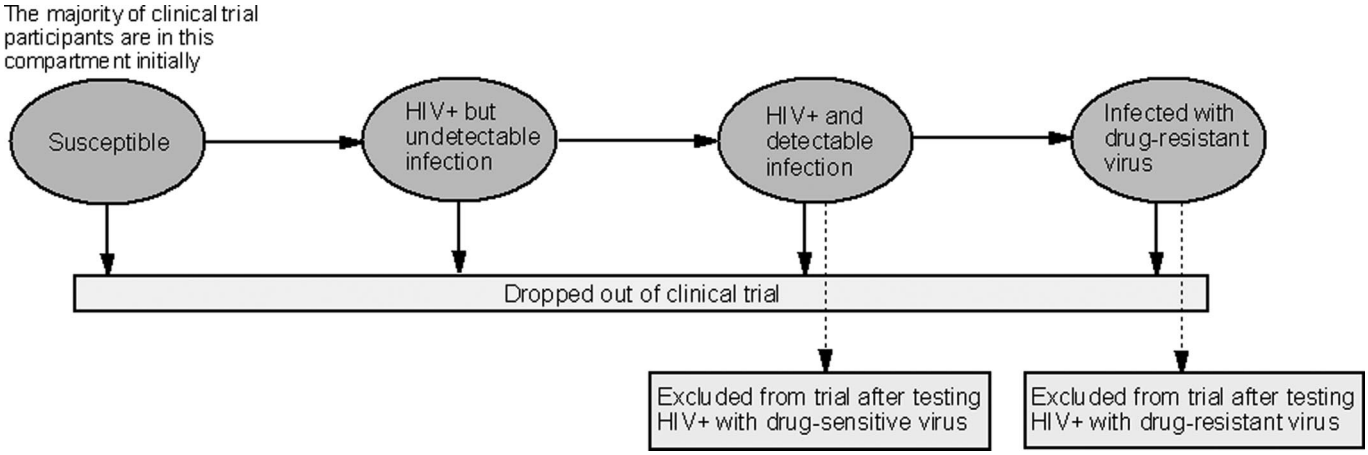

Fig. S1. Schematic diagram of the compartments of individuals in a phase III clinical efficacy trial of ARV-based microbicides and the flow in and out of these compartments according to our mathematical model. The dashed arrows denote exclusion from the trial once detected to be a seroconverter; this protocol is to reduce the risk of the participant developing drug-resistant HIV due to ARV-based microbicide usage.

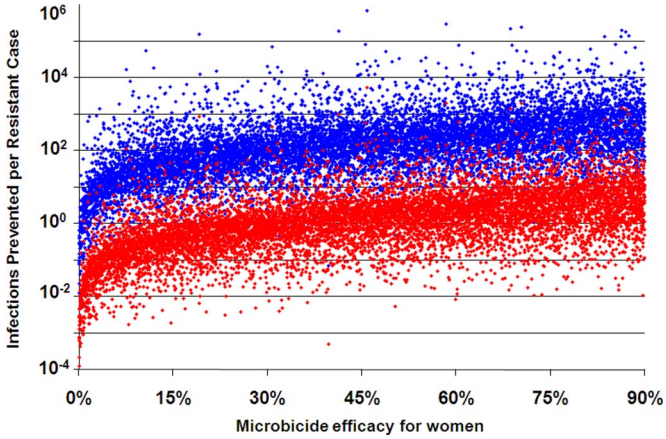

Fig. S2. Scatterplot of the cumulative number of infections prevented per resistant case predicted by our clinical trial model versus the efficacy of microbicides in preventing HIV infection in women (assuming 100% adherence). The blue data are when low-risk microbicides are used, and the red data for when high-risk microbicides are used.

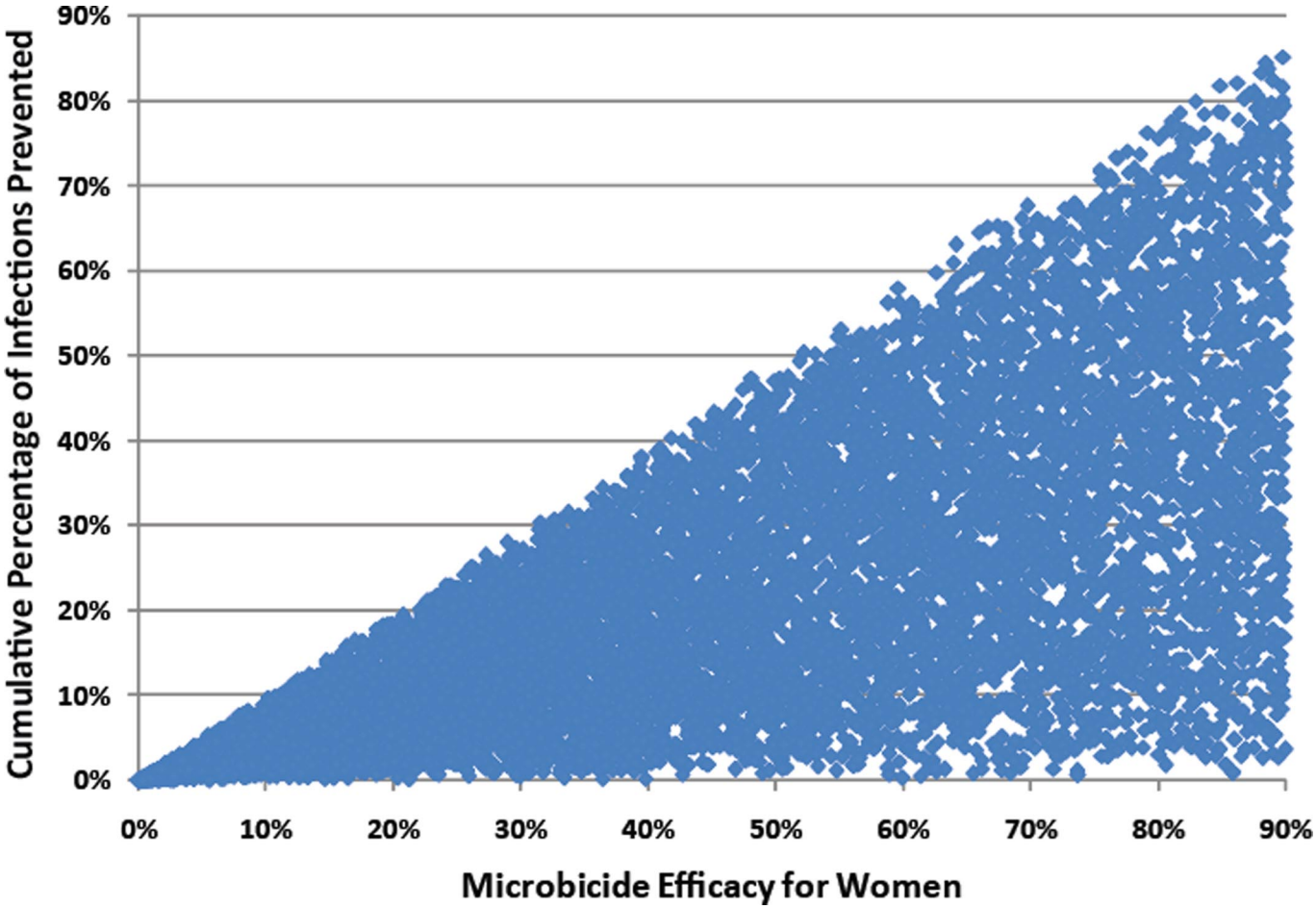

Fig. S3. Scatterplot of the cumulative percentage of infections prevented predicted by our clinical trial model versus the efficacy of microbicides in protecting women against infection. Adherence levels ranged from 0% to 100%.

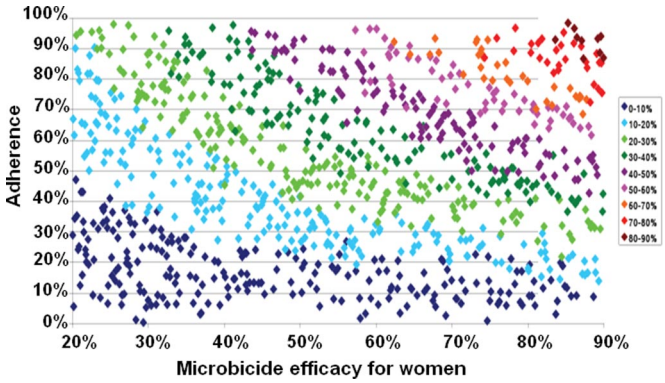

Fig. S4. Scatterplot of the cumulative percentage of infections prevented predicted by our clinical trial model for a given microbicide efficacy and adherence level. The bands of color represent grades of the percentage of infections prevented after 12 months.

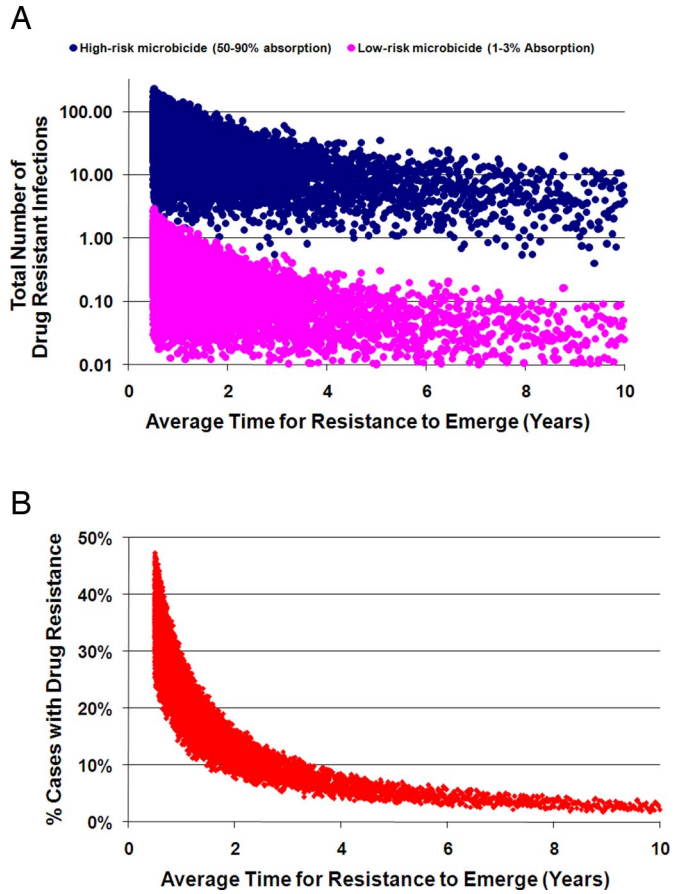

Fig. S5. (*A*) Scatterplot of the cumulative number of NNRTI-resistant cases that can be expected after 12 months of a 10,000-participant ARV-microbicide clinical trial with 100% adherence versus the average time for NNRTI resistance to emerge. (*B*) The effect of increasing the average time to acquire resistance (for a high-risk microbicide) on decreasing the percentage of cases of acquired resistance in a 12-month phase III clinical trial of an NNRTI-containing microbicide gel without testing during the trial (predictions are based upon 10,000 Monte Carlo simulations).

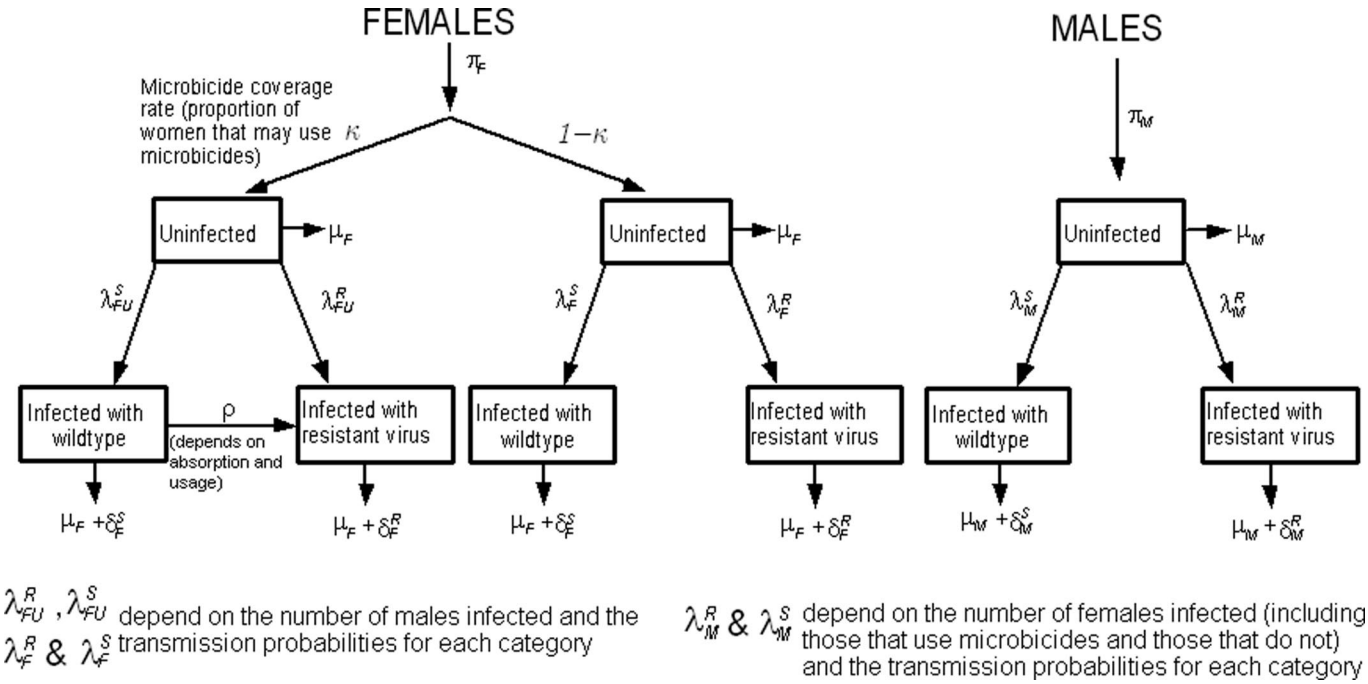

Fig. S6. Schematic flow diagram of our population-level mathematical model of heterosexual transmission of HIV when microbicides are used as public health interventions.

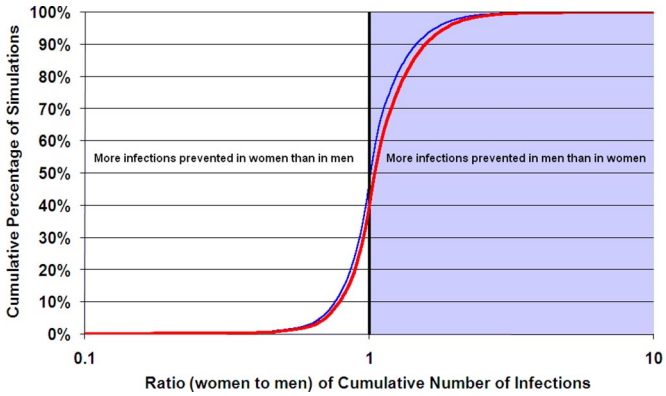

Fig. S7. Cumulative distribution functions, generated by using Monte Carlo simulation data from the analyses of high-risk and low-risk microbicides, of the ratio (women to men) of the cumulative number of infections after 10 years of microbicide usage predicted from our heterosexual transmission epidemic model (red data generated assuming high-risk microbicides are used, and blue data generated assuming low-risk microbicides are used). The black line shows the male advantage threshold (MAT); at this threshold the cumulative number of infections prevented is equally reduced for both men and women; the blue region to the right of the MAT shows when microbicides would be more beneficial for men than women. Adherence levels ranged from 0% to 100%.

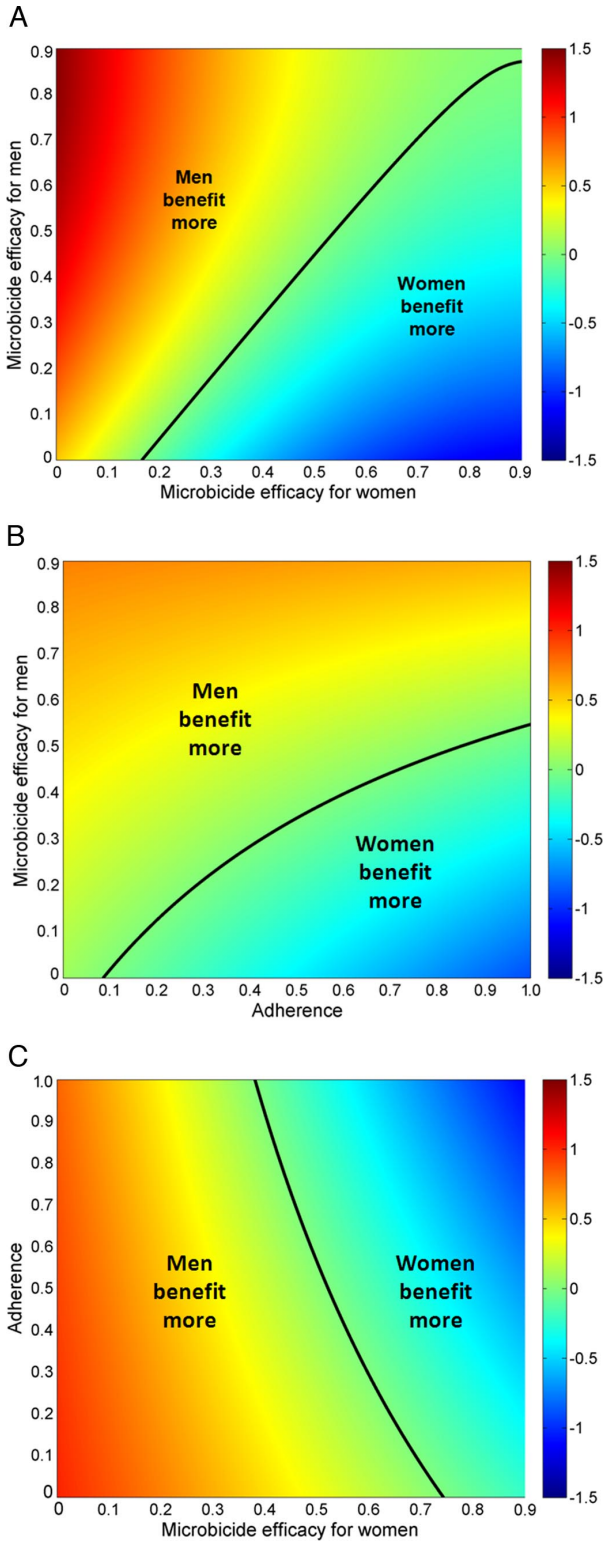

Fig. S8. Response surfaces of the ratio (men to women) of the cumulative number of infections prevented (in a heterosexual population where microbicides are widely available) in the case of low-risk microbicides, on a $\log_2$ scale, as a function of microbicide efficacy in protecting men against infection versus microbicide efficacy in protecting women against infection (*A*), microbicide efficacy in protecting men against infection versus adherence (*B*), and adherence versus microbicide efficacy in protecting women against infection (*C*). The black curve delimits the male advantage threshold (MAT).

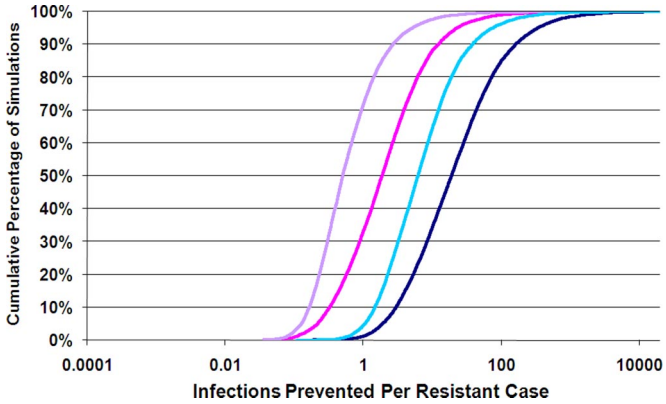

Fig. S9. Cumulative distribution functions of the number of infections prevented per resistant case (in a heterosexual population where microbicides are widely available) after 10 years of microbicide usage for both men [dark blue data (when a low-risk microbicide is used) and light blue data (when a high-risk microbicide is used)] and women [pink (when a low-risk microbicide is used) and mauve data (when a high-risk microbicide is used)]. Adherence levels ranged from 0% to 100%.

Table S1. Investigational microbicides in clinical trials by testing stage

Investigational microbicide	Class	Mechanism of HIV inhibition	Clinical phase	Start* of pivotal efficacy trials	Size of efficacy trials
Carraguard	Sulfonated polyanion	Anionic binding to cationic charge on HIV-1	III	2004	6,639
Pro2000[†]	Sulfonated polyanion	Anionic binding to cationic charge on HIV-1	III	2005	12,000 + 3,220
BufferGel	Vaginal acid-buffering	Low pH	IIB	2005	3,220
Dapivirine (TMC120)	ARV (NNRTI)	Replication	I/II	2008	10,000
Tenofovir	ARV (NtRTI)	Replication	I/II	2007/2008	1,200
UC-781	ARV (NNRTI)	Replication	I/II	TBD	TBD
MIV-150[‡]	ARV (NNRTI)	Replication	I	TBD	TBD
VivaGel	Sulfonated polyanion	Anionic binding to cationic charge on HIV-1	I	TBD	TBD
Acidform	Vaginal acid-buffering	Low pH	I	TBD	TBD

Currently, three microbicides that do not contain antiretrovirals are being investigated. Two are in phase III trials to determine whether their efficacy levels are sufficient for Food and Drug Administration approval, and one is in a phase IIB trial. TBD, to be determined.

*Actual start date if in past; predicted start date in the future.

[†]Buffergel and Pro2000 are being tested in one phase IIB trial with 3,220 subjects.

[‡]MIV-150 is being tested in combination with Carraguard.

Table S2. Parameter values for ARV-based microbicide clinical trial model, parameterized for female sex workers (FSWs)

Parameter	Description	Parameter range		Refs. and notes
		Minimum	Maximum	
β_m^f	Probability of transmission per vaginal sex act from male (infected with wild-type strains of HIV) to female	0.0001	0.0011	15, 16, 18–22
ε_m^F	Efficacy (per sex act) of microbicides in protecting women against HIV infection	0	0.90	Experimental variable
ε_c	Efficacy (per sex act) of condoms	0.80	0.95	23–27
q_2	Proportion of sex acts where a condom is used (before and during the trial)	0.40	0.70	28–33
c	Average number of new sex partners per day (for a FSW)	1	4	14, 28, 34, 35
n	Average number of vaginal sex acts per partner per day (for a FSW)	0	2	Experimental variable
P	Prevalence of HIV among men paying for sex in a resource-constrained setting	0.10	0.60	36–39
$1/\eta$	Average number of weeks after seroconversion for infection to become detectable by a rapid test	3	12	40–43
$1/\rho_{max}$	Average number of months to develop drug resistance if ARV-based microbicides are used daily and the NNRTI is systemically absorbed into the blood stream	6	Never	Experimental variable*
θ	Probability per sex act that systemic NNRTI absorption occurs (when a NNRTI-based microbicide is used)	High probability = 0.50; Low probability = 0.01	High probability = 0.90; Low probability = 0.03	Experimental variable
p_1	Proportion of sex acts where no protection is used (during a trial)	$p_1 = 1 - p_2 - p_3 - p_4$		†
p_2	Proportion of sex acts where only condoms are used (during a trial)	$p_2 = \alpha_1 \cdot q_2$, where $0 < \alpha_1 < 1$		‡
p_3	Proportion of sex acts where only microbicides are used (during a trial)	0	$1 - q_2$	
p_4	Proportion of sex acts where both a condom and a microbicide are used (during a trial)	$p_4 = q_2 - p_2$		
p_m	Adherence (defined as the proportion of days in which microbicides are used during a trial)	0 ($p_m = p_3 + p_4$)	1 ($p_m = p_3 + p_4$)	

*We model the average rate to develop resistance, ρ, as the product of the maximum rate at which resistance could develop, ρ_{max}, and the level of adherence. Then, $\rho = \theta p_{m\rho\,max}$, where θ is the probability that systemic NNRTI absorption would occur with a single usage (i.e., 1 day) of the NNRTI-based microbicide, and p_m is the level of adherence.

†This equation ensures that the proportions of the four types of protection during sex acts sum to 1 as required.

‡These constraints are defined such that "condom replacement" does not occur (i.e., condom usage before the trial = condom usage during the trial), and that the maximum proportions of microbicide use and condom use cannot exceed 1.

Table S3. Parameter values for a general heterosexual population where ARV-based microbicides are used in a public health intervention

Parameter	Description	Parameter range		Refs. and notes
		Minimum	Maximum	
κ	Microbicide coverage: the proportion of women using microbicides	0	1	Experimental variable
ε_m^F	Efficacy (per sex act) of microbicides for women	0	0.90	Experimental variable
ε_m^M	Efficacy (per sex act) of microbicides for men	0	0.90	(see main text)
ε_c	Efficacy (per sex act) of condoms	0.80	0.95	23–27
c_F	Average number of new sex partners women acquire each year	0.5	1.5	46–51
c_M	Average number of new sex partners men acquire each year	$c_M = c_F N_F/N_M$		*
n_F	Number of vaginal sex acts women have per partner per year	$60/c_F$	$150/c_F$	46, 49, 52, 53
n_M	Number of vaginal sex acts men have per partner per year	$60/c_M$	$150/c_M$	
P	Initial prevalence of HIV in both men and women before microbicides are available	0.01	0.60	36–39, 48, 54–56
α_1	Multiplier for drug-resistant transmissibility (this ensures that drug-resistant strains are less transmissible than wild-type strains)	0.05	0.5	57, 58
β_m^f	Transmissibility per vaginal sex act from a man (infected with wild-type strains of HIV) to a woman	0.0008	0.0018	16, 18–20
β_{rm}^f	Transmissibility per vaginal sex act from a man (infected with drug-resistant strains of HIV) to a woman	$\alpha_1\beta_m^f$		†
β_f^m	Transmissibility per vaginal sex act from a woman (infected with wild-type strains of HIV) to a man	0.0005	0.0015	16, 18–20
β_{rf}^m	Transmissibility per vaginal sex act from a woman (infected with drug-resistant strains of HIV) to a man	$\alpha_1\beta_f^m$		†
q_2	Proportion of sex acts where a condom is used (pre-microbicide introduction)	0	0.50	33, 47, 52, 53, 59–62
p_1	Proportion of sex acts where no protection is used (when microbicides are available)	$p_1 = 1 - p_2 - p_3 - p_4$		‡
p_1	Proportion of sex acts where only a condom is used (when microbicides are available)	$p_2 = \alpha_1 \cdot q_2$, where $0 < \alpha_1 < 1$		§
p_3	Proportion of sex acts where only a microbicide is used (when microbicides are available)	0	$1 - q_2$	
p_1	Proportion of sex acts where both a condom and a microbicide are used (when microbicides are available)	$p_4 = q_2 - p_2$		
p_m	Adherence	$p_m = p_3 + p_4$ 0–100%		
$1/\rho_{max}$	Average number of months to develop drug-resistance if ARV-based microbicides are used daily and the NNRTIs are systemically absorbed into the blood stream	6	Never	Experimental variable¶
θ	Probability per vaginal sex act that systemic NNRTI absorption will occur (if an NNRTI-based microbicide is used)	High probability = 0.50; Low probability = 0.01	High probability = 0.90; Low probability = 0.03	Experimental variable
$1/\mu_F$	Average number of years over which new sex partners are acquired by women	2	20	51
$1/\mu_M$	Average number of years over which new sex partners are acquired by men	2	20	51
$1/\delta_F^S$	Average survival time for women infected with wild-type strains of HIV (in years)	7	12	16, 63
$1/\delta_M^S$	Average survival time for men infected with wild-type strains of HIV (in years)	$1/\delta_F^S$		‖
$1/\delta_F^R$	Average survival time for women infected with drug-resistant strains of HIV (in years)	7	14	16, 58, 63
$1/\delta_M^R$	Average survival time for men infected with drug-resistant HIV (years)	$1/\delta_F^R$		‖

*Balances the total number of sexual partnerships to ensure conservation. Here, N_F and N_M are the total number of females and males, respectively, in our model and are calculated dynamically.

†It is known that viral mutation is associated with decreased replication capacity. We model the chance of transmitting HIV for someone infected with a drug-resistant virus as a multiplicative factor (α_1) between 0.05 and 0.5 relative to someone infected with wild-type virus.

‡This equation ensures that the proportions of the four types of protection during sex acts sum to 1 as required.

§These constraints are defined such that "condom replacement" does not occur (i.e., condom usage before the trial = condom usage during the trial), and that the maximum proportions of microbicide use and condom use cannot exceed 1.

¶Similar to the clinical trial, we model the average rate to develop resistance, ρ, as the product of the maximum rate of developing resistance, ρ_{max}, and the level of adherence. Then, $\rho = \theta\, p_{m\rho\,max}$, where θ is the probability that systemic NNRTI absorption would occur with a single usage (i.e., during 1 day) of the NNRTI-based microbicide, and p_m is the level of adherence.

‖We assume that the rate of disease progression is the same for men and women.

Table S4. Standardized regression coefficients indicating the importance of the key parameters in influencing the outcome variables

	High-risk microbicides				Low-risk microbicides			
Input parameter (outcome variable)	% Infections prevented (women)	% Infections prevented (men)	Ratio (men to women) of % infections prevented	Ratio (men to women) of infections prevented per NNRTI-resistant case	% Infections prevented (women)	% Infections prevented (men)	Ratio (men to women) of % infections prevented	Ratio (men to women) of infections prevented per NNRTI-resistant case
Coverage (κ)	0.59	0.71	0.07	−0.04	0.49	0.58	0.06	−0.03
Adherence (p)	0.37	0.33	−0.29	0.08	0.48	0.47	−0.18	0.11
Efficacy of protection of microbicides for women (ε_m^F)	0.25	0.08	−0.60	−0.27	0.36	0.11	−0.65	−0.31
Efficacy of protection of microbicides for men (ε_m^M)	0.03	0.23	0.22	0.24	0.09	0.34	0.38	0.31
Degree of absorption of NNRTIs (θ)	0.09	0.20	0.14	0.03	0.02	0.03	0.05	0.03
Average time to acquire drug resistance ($1/\rho_{time}$)	−0.11	−0.23	−0.16	−0.049	−0.035	−0.08	−0.11	−0.06
Transmission probability (per act) from men to women for wild-type HIV (β_m^f)	−0.12	−0.07	0.25	0.09	−0.15	−0.08	0.24	0.09
Transmission probability (per act) from women to men for wild-type HIV (β_f^m)	−0.09	−0.24	−0.17	−0.20	−0.12	−0.24	−0.16	−0.19
Relative fitness of drug-resistant strains (α_1)	−0.01	−0.08	−0.16	−0.61	0.01	0.01	−0.06	−0.55

High-risk microbicides are defined to be those that have a high probability (0.5–0.9) that the NNRTIs contained in the microbicide will be systemically absorbed, and low-risk microbicides are defined to be those that have a low probability (0.01–0.03) that NNRTIS will be systemically absorbed.