Published in final edited form as:

J Theor Biol. 2011 November 7; 288C: 9–20. doi:10.1016/j.jtbi.2011.08.001.

Modeling the Gender-Specific Impact of Vaginal Microbicides on HIV Transmission

Dobromir T. Dimitrov^a, Marie-Claude Boily^b, Rebecca F. Baggaley^b, and Benoit Masse^{a,c}

Dobromir T. Dimitrov: dobromir@scharp.org; Marie-Claude Boily: mc.boily@ic.ac.uk; Rebecca F. Baggaley: r.baggaley@imperial.ac.uk; Benoit Masse: ben@scharp.org

^aStatistical Center for HIV/AIDS Research and Prevention, Fred Hutchinson Cancer Research Center, Seattle, WA 98109-1024 U.S.A.

^bDepartment of Infectious Disease Epidemiology, Faculty of Medicine, Imperial College, London, UK

^cCHU Sainte-Justine Research Centre, University of Montreal, Montreal, Quebec, Canada

Abstract

Vaginal microbicides (VMB) are currently among the few women-initiated biomedical interventions for preventing heterosexual transmission of HIV. In this paper we use a deterministic model of HIV transmission to assess the public-health benefits of a VMB intervention and evaluate its gender-specific impact over short (initial) and extended periods of time. We define two distinct quantitative benefit ratios (QBRs) based on infections prevented in men and women to create and study regions of male advantage in different parameter spaces. Our analysis exposes complicated temporal correlations between the QBRs and series of pre-intervention (e.g., HIV acquisition risks per act) and intervention parameters (e.g., VMB efficacy mechanisms, rates of resistance development and reversion) and indicates that different QBRs may often disagree on the gender distribution of the benefits from a VMB intervention. We also outline the strong influence of some modeling assumptions on the reported results and conclude that the assessment of VMB and other biomedical interventions must be based on more comprehensive analyses than calculations of infections prevented over a fixed period of time.

Keywords

mathematical model; epidemic; biomedical intervention; prevention; drug resistance

1. Introduction

The results from the latest vaginal microbicide (VMB) and vaccines trials present a glimpse of hope that successful products preventing HIV acquisition could be developed [1, 2]. However, experts agree that the introduction of an effective vaccine cannot be expected in the near future. Meanwhile, the HIV pandemic continues to add 2.7 million new HIV infections and to cause 2 million deaths per year [3]. The majority of these are the result of

© 2011 Elsevier Ltd. All rights reserved.

Correspondence to: Dobromir T. Dimitrov, dobromir@scharp.org.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

heterosexual transmission in developing countries, where access to antiretroviral (ARV) treatment is still limited and where women often lack the power to negotiate safe sex. VMB is a promising prevention method that women can control themselves and use to reduce their risk of heterosexual HIV transmission. A successful VMB would significantly decrease the susceptibility of the users, with no harmful side effects. Some of the current VMB candidates could potentially also reduce the infectiousness of HIV-positive users and provide protection against other sexually transmitted diseases. These different “efficacies” of the product candidates may not have the same impact on HIV transmission for males and females and on the relative benefit for each gender.

Mathematical models have been used to predict the impact of VMB use on the individual user [4, 5] and in the community [6, 7, 8]. A discussion has recently developed around which gender will benefit more in case of a wide-scale VMB intervention. A study, based on an analysis of a deterministic mathematical model, predicted that although designed for women’s protection, VMB will provide greater benefits to men [9]. A response to this study suggested that these “paradoxical” effects were mainly the result of the bi-directional protection of VMB and the reduced transmissibility (i.e. cost of resistance) of drug-resistant HIV strains assumed in the model [10]. We performed an analysis of the gender-specific benefits which confirmed this conclusion and showed that effective pre- and post-enrollment screening which restrict VMB usage by HIV-positive women may decrease the risk of resistance development among women and consequently reduce the likelihood of male advantage in VMB-prevented infections [11]. We concluded that women are more likely to benefit from VMB usage, independently of the metrics used to evaluate its impact.

The above studies discuss the distribution of the benefits from future VMB usage in different settings and include sensitivity analyses but do not further explore the influence of key parameters on the outcomes of the intervention. In this paper we focus on the main drivers which move benefit distribution toward male or female advantage. More generally, we provide an insight for when and how an intervention which is designed and initiated in one part of the community (one gender, age group) could be more beneficial for another subpopulation. We modify previously developed mathematical models of HIV epidemics in heterosexual populations [11, 9] to study the public health impact of VMB interventions. In the current version we incorporate the possibility that HIV-positive women infected with a drug-resistant HIV strain reverse back to wild-type HIV after they discontinue VMB usage based on results from ARV resistance studies [12]. Our estimates for the degree of gender advantage are based on two quantitative benefit ratios (QBRs) which compare 1) the total number and 2) the fraction of infections prevented in men and women over different periods of time up to 25 years.

The main objective of this study is to analyze the individual and combined effects of key factors such as HIV acquisition risks per sex act, VMB efficacy and the rate of resistance development, on QBRs and their evolution over time under different intervention scenarios. This extends our previous work which was focused on the impact of the pre- and post-enrollment screening and the choice of intervention schedule [11]. We also outline the strong influence of some modeling assumptions on the reported results and discuss the importance of the metrics used to assess public health impact of biomedical interventions.

2. Model description

The deterministic compartmental model employed in this study describes the course of HIV transmission in a population of heterosexually active individuals and incorporates demographic, biological, and behavioral parameters. In the model the population is divided into three major classes: men (subscript m), women using VMB (subscript w , superscript p),

and women not using VMB (subscript w), who are further stratified according to their HIV and disease status into susceptible (S), infected with a wild-type HIV strain (I), and infected with a drug-resistant strain (I_r) types. Individuals who develop AIDS are accumulated in classes A_w and A_m (see Fig. 1). Men and women who become sexually active join the community at constant rates Λ_m and Λ_w selected to balance the departure rate (μ) of an uninfected population. A fraction k of the women who enter the population start using VMB. The rates at which men and women acquire HIV infection, i.e., forces of infections for different classes ($\lambda_w^p + \lambda_{rw}^p$, $\lambda_w + \lambda_{rw}$, and $\lambda_m + \lambda_{rm}$) are derived from standard binomial models based on the average number of partnerships per year, the number of sex acts per partner, and the HIV acquisition risks per act. Individuals infected with wild-type and drug-resistant HIV develop AIDS at rate d and d_r , respectively. If VMB users become infected and continue to use the product they develop drug resistance at rate r_1 . Post-enrollment screening of the HIV status of VMB users is likely to be included in a wide-scale VMB intervention. It is integrated into the model and allows the HIV-positive users to cease product use after an average period $1/\delta$. The reversion in drug resistance status at rate r_2 , based on data for patients with failing ARV treatment [12], is an addition to the previous version of the model [11].

VMB is introduced in a population with $N_w(0) = N_m(0) = 1,000,000$ and equal HIV-prevalence (P) between sexes. While the initial distribution of the epidemic classes is not critical for the asymptotic behavior of the system, it is essential for all indicators calculated over specific periods of time after the start of the intervention. We assume that VMB is initially adopted by a proportion k_1 of the women in the population but the initial proportion among HIV-positive women is reduced to $(1 - \theta)k_1$ as a result of a pre-enrollment screening.

Several assumptions are incorporated into the model to reflect the observed population dynamics and the VMB mechanisms to influence the HIV transmission:

- Entry rates Λ_w and Λ_m in both men and women are assumed to preserve the size of a population which have not been exposed to HIV.
- Men and women are assumed to have a fixed number of sex acts per year. Sexual partnerships are not balanced in this version of the model. Sexual activity of women does not change if they start using VMB (no risk compensation) but it ceases upon development of AIDS for both, men and women.
- The use of VMB reduces the HIV susceptibility and infectiousness and leads to a decrease in the HIV acquisition risks per sex act.
- Drug-resistant HIV strains are less transmissible due to the cost of the drug resistance [12].
- The rate of resistance development r_1 depends on the maximum rate of resistance development and the probability of systemic absorption of the product in the bloodstream as explained in B.
- The model assumes 100% adherence to the VMB, i.e., users apply the product regularly without interruptions. Lower adherence levels can be simulated by reduction in the VMB efficacy and do not affect the risk of resistance development.
- The use and availability of other HIV prevention measures and ARV treatments including condom use, male circumcision, and highly active ARV treatment (HAART) are not considered separately. Their effects on HIV transmission are aggregated in the HIV acquisition probabilities per act.

Complete description of the model including all dynamic equations and initial conditions is given in B.

3. Intervention scenarios and benefit ratios

It has been proposed that the predicted male advantage in the cumulative number of prevented infections is due to the combined effects of the reduced transmissibility of the drug-resistant HIV and the bi-directional protection of the VMB [10]. Results from multivariate sensitivity analysis confirmed the significance of these factors and identified several more intervention and transmission parameters as highly influential on the QBRs over different periods of time including the VMB efficacy in reducing susceptibility (α_s) and infectiousness (α_i), the HIV acquisition risk per act for women (β_w) and men (β_m), and the rate of resistance development (r_1) (see Fig.7 in [11]). Analysis of their individual and combined effects is the main objective of the current study. Four groups of intervention scenarios are considered:

- biR: Bi-directional intervention (i.e. VMB reduces both HIV susceptibility and infectiousness);
- biNR: Bi-directional intervention assuming no resistance development ($r_1 = 0$);
- uniR: Uni-directional intervention (i.e. VMB does not reduce infectiousness and therefore has no effect on onward HIV transmission, $\alpha_i = 0$);
- uniNR: Uni-directional intervention assuming no resistance development ($\alpha_i = 0$, $r_1 = 0$).

All four groups assume no reversion in resistance ($r_2 = 0$). In addition we simulate scenarios *biRr* which allow reversion of resistance at rate $r_2 > 0$ and scenarios *biRa* in which HIV acquisition risk for women is assumed to be higher than for men ($\beta_w > \beta_m$) to study the impact of these modeling decisions on the results.

In the baseline scenarios of each group, the epidemic parameters in the model are fixed at their baseline values, which represent developing countries in Southern Africa (see Table 1). When varied, the ranges of the acquisition risks per act are determined based on a meta-analysis of data from low-income countries [13]. The baseline value of 0.5 for the VMB reduction in susceptibility is in agreement with the efficacy observed in the CAPRISA-004 trial for high adherers [1]. However, a wide range (from 0% to 90%) for both susceptibility and infectiousness reductions is explored. The annual rate of resistance development is varied from 0 to 1 which corresponds to an average period of 1 year to never (infinite) for HIV-positive VMB users to develop drug resistance. A complete description of the scenarios simulated in different sections of this paper is given in A.

For each scenario we simulate an HIV epidemic in absence and in presence of VMB intervention which is always introduced at time $t=0$. We define two quantitative benefit ratios (QBRs) to study the gender distribution of benefits:

- The cumulative indicator $C_f(T)$ is the ratio of the cumulative number of infections prevented in men and women over the period $[0, T]$ as a result of the VMB intervention;
- The fractional indicator $F_f(T)$ is the ratio of the fractions of infections prevented in men and women over the period $[0, T]$ as a result of the VMB intervention.

Each of the QBR $C_f(T)$ and $F_f(T)$ indicates that men or women benefit more from the VMB intervention over the period $[0, T]$ if its value is greater or less than one, respectively.

4. Results

Initial benefit distribution

Our first goal is to analyze the benefit distribution shortly after the introduction of VMB in the population. To calculate the initial level of the ratio C_I (F_I), the number (fraction) of infections prevented in men and women over a small initial interval Δt is estimated. Using the initial population distribution, accounting for the immediate changes in HIV transmission inflicted by VMB usage, and assuming equal sexual activity for both genders ($n_m = n_w$) we find (see B for details):

$$\begin{aligned}\lim_{\Delta t \rightarrow 0} C_I(\Delta t) &\approx (1 - \theta) \frac{\alpha_i \beta_m}{\alpha_s \beta_w} \\ \lim_{\Delta t \rightarrow 0} F_I(\Delta t) &\approx (1 - \theta) \frac{\alpha_i}{\alpha_s},\end{aligned}\tag{1}$$

Note that the initial ratio of the prevented fractions F_I depends only on intervention parameters such as the ability of the VMB to reduce susceptibility and infectiousness of the users and the level of pre-enrollment screening. On the other hand the ratio of the prevented infections C_I is sensitive to the acquisition risks per act. This may be affected by condom use, circumcision, or use of ARV treatment. The VMB intervention provides initially more benefits to men in terms of F_I only if the VMB efficacy in reducing infectiousness is higher than its efficacy in reducing susceptibility ($\alpha_i > \alpha_s$) and pre-enrollment screening is not

perfect ($\theta < 1 - \frac{\alpha_s}{\alpha_i}$). In the special case when $\alpha_i = \alpha_s$, the initial level of F_I is close to $1 - \theta$, i.e., the intervention is always more beneficial to women initially. Conversely, the initial ratio of the number of cumulative infections prevented C_I may show immediate male advantage even if the reduction in infectiousness is less than the reduction in susceptibility ($\alpha_i < \alpha_s$). However, it occurs only if the HIV acquisition risk for men is larger than for

women ($\frac{\beta_m}{\beta_w} > \frac{\alpha_s}{\alpha_i} > 1$) provided that the pre-enrollment screening is not effective enough ($\theta < 1 - \frac{\alpha_s \beta_w}{\alpha_i \beta_s}$).

If the intervention is uni-directional ($\alpha_i = 0$) then both QBRs are initially zero, i.e., the VMB usage protects only women (Fig. 2A, B). The starting level ($1 - \theta$) of the fractional indicator (F_I) in the bi-directional scenarios (*biR* and *biNR*) correlates with the pre-enrollment screening effectiveness while the initial level of cumulative indicator C_I is slightly higher due to the assumed relation between HIV acquisition risks for men and women ($\beta_w > \beta_m$). As predicted by expressions (1), drug resistance development does not affect the initial level of either indicator but its influence increases over time (*biR* and *uniR* vs. *biNR* and *uniNR*). Note that indicators may disagree on which gender receives more benefits soon after the start of the interventions (Fig. 2C). Cumulative indicator (C_I) predicts immediate male advantage for small θ while fractional indicator (F_I) gives initial advantage to women regardless of the success of pre-enrollment screening.

Asymptotic benefit distribution

Next, we investigate analytically and numerically (Fig.3) the dynamical trends in QBRs when a VMB intervention is implemented over a very long period of time. In what follows we assume that the original local settings remain unchanged and the HIV epidemic has enough time to stabilize at an equilibrium state. The basic reproductive number R_0 in the settings with no intervention is often used to study the ability of an epidemic to establish and persist within a “naive” population. It measures the number of secondary infections produced by a typical infected individual during his entire period of infectiousness in a

completely susceptible population [19]. Generally, if $R_0 > 1$ the infection persists and the infected population stabilizes at an endemic fixed point while if $R_0 < 1$ the infection naturally dies out. If the use of biomedical products such as VMB reduces the individual risk of infection without increasing the duration of the infectious period, the reproductive number decreases, i.e., the effective reproductive number $\bar{R}_0$ is less than the reproductive number in absence of intervention, R_0 . If $\bar{R}_0 < 1$ the population becomes HIV-free after some time and no new infections arise after this, with or without intervention. Therefore, the cumulative number of infections prevented in each gender as a result of the intervention stabilize after some initial period and QBR remain unchanged afterward (see Fig.3A,B).

Let $R_0 > 1$ and $(S_w^*, I_w^*, S_m^*, I_m^*)$ be the equilibrium population distribution (susceptible women, HIV-positive women, susceptible men, HIV-positive men) reached in the absence of the VMB, while $(\bar{S}_w^*, \bar{I}_w^*, \bar{S}_m^*, \bar{I}_m^*)$ represents the equilibrium population distribution assuming VMB usage. Here $\bar{S}_w^*$ aggregates both susceptible female classes S_w^p and S_w , $\bar{I}_w^*$ aggregates sexually active HIV-positive female classes, and $\bar{I}_m^*$ aggregates both HIV-positive male classes I_m and I_{mm} . Explicit expressions of the reproductive number R_0 and the endemic equilibrium $(S_w^*, I_w^*, S_m^*, I_m^*)$ for the epidemic without intervention are obtained in B. Similar expressions for the model with intervention cannot be derived but the equilibrium values $(\bar{S}_w^*, \bar{I}_w^*, \bar{S}_m^*, \bar{I}_m^*)$ are estimated through numerical simulations. We obtained the following asymptotic limits of the quantitative indicators:

$$\begin{aligned} \lim_{T \rightarrow \infty} C_l(T) &= \frac{I_m^* - \bar{I}_m^*}{I_w^* - \bar{I}_w^*} \\ \lim_{T \rightarrow \infty} F_l(T) &= \left(\frac{I_m^* - \bar{I}_m^*}{I_w^* - \bar{I}_w^*} \right) \frac{I_w^*}{I_m^*} \end{aligned} \quad (2)$$

by comparing the number of new infections in men and women over a small time interval (see B). If an effective VMB intervention is able to decrease the basic reproductive number R_0 below one ($\bar{R}_0 < 1$) then $(\bar{S}_w^*, \bar{I}_w^*, \bar{S}_m^*, \bar{I}_m^*)$ is a disease-free equilibrium ($\bar{I}_w^* = \bar{I}_m^* = 0$). In this

case the fractional QBR (F_l) tends to one while the cumulative QBR (C_l) approaches $\frac{I_m^*}{I_w^*}$ (not shown). Both limits do not depend on any intervention parameters and are predetermined by the HIV epidemic settings in the absence of the VMB. It is worth noting that such an effective VMB intervention will always have equal long-term effects for both genders in terms of the cumulative fractions of prevented infections (F_l). However, higher cumulative number of infections will be averted in the gender which is predisposed to larger absolute numbers of HIV-positives at the non-VMB equilibrium state. This is not necessarily the gender with higher HIV prevalence, since the epidemic may differentially affect the number of individuals by gender in the population [20]. These asymptotic results highlight that a long-term analysis based on different QBR may predict an advantage to different genders regardless of the effectiveness of the intervention. The simulations in Fig.3 represent interventions which asymptotically prevent more cumulative HIV infections in men ($C_l > 1$) but higher cumulative fractions of HIV infections in women ($F_l < 1$). Note that the pre-enrollment screening effectiveness (θ) does not influence the asymptotic levels of the benefit indicators when $R_0 > 1$ but remains a factor if $R_0 < 1$. This implies that when the intervention is introduced into a population with a declining epidemic, the initial effort to prevent the usage of VMB by HIV-positive women will be much more important for the long-term gender-specific impact of the intervention.

Although the asymptotic estimates of the QBRs are useful to predict the long-term trends in the benefit distribution, from a public health perspective it is more important to analyze the

variations in the indicator values over more practical time intervals (up to 25 years) and study how they are affected by the epidemic and intervention parameters. In what follows we investigate wide ranges of the most influential parameters and study the regions of male advantage (RMA) associated with the cumulative and the fractional indicators (C_I and F_I) over different parameter spaces. All other parameters remain fixed at baseline values (see Table 1).

Effects of VMB susceptibility and infectiousness reduction

Figure 4 presents the temporal changes in the RMA in the $\alpha_s - \alpha_i$ parameter space assuming no post-enrollment screening. The regions expand with time but the changes are distinctive only with respect to C_I . The steep boundary slope indicates that the susceptibility reduction (α_s) has stronger influence than the reduction of infectiousness (α_i). Naturally, if the VMB is not effective in decreasing the susceptibility of its users then the pool of infected women using VMB will grow faster. The drug resistance developing in this pool leads to more benefits for men even if VMB is completely inefficient in reducing infectiousness ($\alpha_i = 0$) provided that the transmissibility of the resistant HIV strain is considerably lower than that of wild-type. The reverse in the acquisition risk for men and women ($\beta_w > \beta_m$) results in a slight expansion in RMA (dotted lines) with respect to the fractional indicator (F_I). The increased female acquisition risk elevates the influence of the resistance factor which must be balanced with greater susceptibility reduction. The same assumption ($\beta_w > \beta_m$) has opposite effects on the RMA associated with the cumulative indicator (C_I) which reduce substantially. It confirms that the dependence of C_I on the HIV acquisition risk, which we noticed during the initial period after the start of the intervention, remains strong in the long term. Assuming higher female acquisition risk, the VMB interventions with moderate efficacy (in the region between dotted lines in Fig.4A and Fig.4B) will prevent more female infections (as a total number) but higher percentage of infections in men over 25 years. Effective post-enrollment screening will decrease both QBRs and therefore will reduce the size of the RMA (not shown).

Effects of the gender-specific HIV acquisition risks per act

We continue to study the influence of the HIV acquisition risk per act for men (β_m) and women (β_w) which had sizable impact on the results in the previous section. In the next set of simulations (Fig. 5) it is assumed that the VMB elicits an equal reduction in susceptibility and infectiousness ($\alpha_s = \alpha_i$). The vast majority of the simulated interventions prevent more cumulative female infections but avert a higher cumulative fraction of male infections, or vice versa. The RMA associated with the cumulative QBR (C_I) include only interventions with higher male acquisition risk ($\beta_m > \beta_w$). In these settings the initial advantage that the VMB provides to women due to effective pre-enrollment screening ($\theta = 0.5$) is compensated by the difference in the HIV acquisition risk and soon VMB prevents more infections in the male population where the total number of new infections is higher. The resistance which arises is more beneficial to men and additionally boosts C_I . Conversely, the male advantage in prevented fractions (F_I) occurs only if the male acquisition risk is lower ($\beta_m < \beta_w$), which ensures a larger proportion of HIV-positive women over time. That, in turn, increases the effects from reduced infectiousness and the growing impact of drug resistance which are primarily beneficial for men. The dotted lines in Fig. 5 represent the boundaries of the RMA when uni-directional VMB is simulated ($\alpha_i = 0$). Such VMB intervention always prevents more infections in women if the female acquisition risk is high (Fig. 5A). The lack of reduction in infectiousness significantly decreases the chance of male advantage in terms of the fractional indicator F_I which is recorded only for extreme combinations of high female and low male acquisition risks (Fig. 5B).

Efficacy vs. resistance

The combined effects of VMB efficacy and resistance on the QBRs are presented in Fig.6. Almost vertical boundaries of the RMA suggest that the influence of efficacy (α_s) is stronger than the influence of the resistance rate (r_1) when latter is substantial (above 10%). However, the VMB products which are currently under development show limited or no systemic absorption in the bloodstream [21, 22, 23, 24] which implies that the expected rate of resistance development will be small (far below 10%). Therefore, the specific level of resistance risk will be an important consideration when the issue of gender-specific impact is discussed, especially if the product provides uni-directional protection only. Note that the RMA are not just reduced when VMB does not affect infectiousness but they completely exclude the areas with small resistance rates (Fig.6 C,D). This clearly supports the proposition that the “male advantage phenomenon” is driven by the bi-directional protection of the VMB and/or the reduced transmission of drug-resistant HIV. Higher female than male acquisition risk ($\beta_w > \beta_m$) leads to substantial reduction in the likelihood of male advantage in C_I (see dotted lines in Fig.6 A,C). The effect on the RMA associated with the fractional QBR (F_I) is much smaller expansion (Fig.6 B,D).

Effects of reversion of resistance

Drug resistance emergence is among the strongest concerns when an ARV-based biomedical HIV intervention is considered for wide-scale introduction. We have previously demonstrated that if such a problem exists with a VMB product it can be minimized through preand post-enrollment HIV testing of VMB users [11]. This result was obtained assuming that people who develop drug resistance continue to harbor the resistant strains as dominant quasiespecies indefinitely. However, experimental studies show that the interruption of failing ARV therapy in patients with acquired drug resistance leads to reemergence of wild-type HIV over 12 to 16 weeks [25]. In contrast, transmitted resistance has been shown to persist for up to 3 years in ARV-naive patients [26]. Here we study the effects of the reversion of resistance (at rate r_2) on the prevalence of resistance and the VMB benefit distribution over 50 years after VMB introduction (Figure 7). Initially (over the first 2–3 years) r_2 has little influence on resistance prevalence but on longer term it can be responsible for a 5-fold reduction in expected resistance levels (Figure 7A) which leads to decrease in QBRs (Figure 7B, C). Even a moderate rate of resistance reversion $r_2 = 1$, which gives an average time of 1 year for the wild type variants to reemerge and dominate the viral population, leads to manageable levels of resistance prevalence of about 2%. However, this scenario could be overly optimistic if the VMB shares ARV components with the available HAART regimens and promotes the same resistance. We must point out that the reversion of resistance influences the HIV epidemic only if HIV-positive women gradually stops using VMB, i.e., when post-enrollment screening is successful ($\delta > 0$). Otherwise, the vast majority of women who have developed resistance continue to use VMB, which preserves their resistance status. Therefore, periodic HIV screening of VMB users is essential. The simulations presented in Figure 7 assume that HIV-positive women interrupt the usage of VMB after an average period of 1 year. If the post-infection VMB usage is longer then the effect of resistance reversion will be smaller.

5. Discussion

VMB interventions, similar to vaccination programs, induce both direct and indirect effects on HIV transmission dynamics. Protective effects from reduced susceptibility of the women using VMB are classified as direct while the other protective or detrimental effects which result from the intervention-induced changes in transmission are classified as indirect effects. These include effects from reduced infectiousness of VMB users, reduced

transmissibility of drug resistant HIV strains, and decreased HIV prevalence reducing the risk of contacts with infected partners.

We studied the mechanisms which contribute to the VMB benefits for each gender during the short-, intermediate-, and long-term phases of intervention implementation. Since the intervention is introduced in the female subpopulation, the number of female infections due to reduced susceptibility should be impacted from the moment that VMB usage begins. On the other hand, men benefit from the combination of reduced infectiousness of the HIV-positive users and reduced transmissibility of drug-resistant HIV. A decline in the number of male infections should be expected later in time, once enough HIV-positive women are using VMB and a fraction of them have developed resistance. Intuitively we would expect an initial female advantage in benefits regardless of the evaluation method. In contrast, we found that the initial advantage with respect to the cumulative indicator (C_I) heavily depended on pre-existing population settings at the start of the intervention such as HIV acquisition risks per sex act. The same factors do not affect the fractional indicator (F_I). The influence of the pre-enrollment screening which prevents the usage of VMB by HIV-positive women is initially strong because it controls the rate of drug-resistance development and affects the risk of transmission from women to men in case of bi-directional protection. This influence diminishes over an extended intervention period for HIV epidemics with basic reproductive number $R_0 > 1$ in the absence of the VMB (Fig.3C,D). The pre-enrollment screening effectiveness (θ) remains a factor if the reproductive number $R_0 < 1$ in which case the number of new HIV infections decreases substantially over time (Fig.3A,B) and the impact of the intervention is limited in time.

The analytical assessment of the initial and asymptotic QBR provides an insight into the dynamical trends of the gender-specific benefit distribution. However, investigators and decision makers are more often interested in the public-health impact of the interventions over fixed periods of 5, 10, or 20 years after their initiation. We studied numerically how different epidemic and intervention parameters may influence the conclusions based on such analysis and identified parameter combinations which make an intervention designed and initiated in women to provide more benefits to men. We demonstrated that the choice of the evaluation period could taint the results, especially if it is not presented in connection with the dynamical trends in the HIV epidemic. Our analysis of the regions of male advantage (RMA) indicated complicated temporal correlations (Fig.4–6) between the QBRs and a series of pre-intervention (e.g., HIV acquisition risks per act) and intervention parameters (e.g., VMB efficacy mechanisms, rates of resistance development and reversion). When taken out of the complete dynamical picture, some of the observed patterns seem unexpected or counterintuitive but they all have reasonable explanations when the interaction between the mechanisms embedded in the mathematical model are discussed. In general, the RMA grow over the 25 year period after the introduction of VMB. However, the expansion rate significantly slows down toward the end of the period when the HIV epidemic, modified by VMB usage, approaches its new equilibrium state. Although independent from the intervention, the relative acquisition risk per act, male versus female, plays an important role in determining the size of the RMA. Its decline leads to a sizable reduction in the likelihood of male advantage associated with the cumulative indicator (C_I) while the RMA associated with the fractional indicator (F_I) grows (see Fig.4, 6).

These results highlight the importance of the combined effects of some epidemic and intervention parameters for the conclusions based on modeling studies. Investigators often spend some effort justifying the choice of individual parameter ranges but do not elaborate on how suitable their integrated parameter space is for the particular problem or environment. This is especially true in modeling biomedical interventions, where attention is focused on the changes in the epidemic inflicted by a newly developed product, while the

“original” epidemiological settings are often neglected. This paper presents evidence demonstrating that the appropriateness of the pre-intervention settings has to be carefully evaluated. Long-term benefit distributions of VMB interventions introduced in communities where the HIV epidemic has low basic reproductive number ($R_0 \approx 1$ or smaller) are quite different from those where the reproductive number is high ($R_0 \gg 1$) because the interventional effects are limited in duration and magnitude by the declining epidemics. Moreover, the likelihood of male advantage changes when HIV acquisition risks for the genders are varied relative to each other. Therefore, the pre-intervention epidemic environment must be studied carefully before being used as a baseline for intervention evaluations.

Next, we would like to address some simplifying assumptions incorporated in our modeling study and their impact on the reported results. In the epidemic model (Fig. 1), we average the transmission rates over different phases of HIV infections and aggregate possible effects of ARV treatments in HIV acquisition risks per act. These factors will introduce symmetric effects on the gender benefits and therefore have little influence on the QBR and RMA. Risk compensation due to VMB usage is not considered but could impact the QBR especially if condoms, which provide protection to both gender, are replaced by VMB which protects only women. An inclusion of this factor will further decrease the likelihood of male advantage. The model allows former VMB users who have developed drug-resistance to reverse back to wild type dominance and assumes that the reversion rate is the same for acquired and transmitted resistance. Data collected in patients with failing ARV therapy suggest that such reversion can be expected from 12 to 16 weeks after therapy interruption, while data from ARV-naïve people shows that transmitted drug-resistance can persist for more than 4 years [12]. However, the uniform treatment of all female drug-resistant cases has little impact on the epidemic because the prevalence of transmitted compared to acquired drug resistance among HIV-positive women is extremely small. As a result, our analysis slightly overestimates the impact of resistance reversion on the HIV epidemic.

A major conclusion of this analysis is that the cumulative and fractional indicators may disagree on important issues related to the distribution of the benefits from a VMB intervention. Therefore, these indicators must undergo a careful consideration before being used as a basis for public health projections. Our analysis shows that for many feasible parameter settings, simulated VMB interventions prevent more infections in one gender but avert a larger fraction of infections in the other. The results are especially difficult to interpret when HIV acquisition risks per act are varied (see Fig.5) because the RMA associated with C_I and F_I over 25 years are mutually exclusive but in combination they cover almost completely the entire parameter space. This discrepancy is embedded in the theoretical formulations of the QBRs, which is based on the difference in the number of new HIV infections in the presence and absence of VMB usage. However, the HIV epidemics without intervention, which are used as reference points, do not have identical dynamical behavior, but express significant variation with respect to pre-intervention parameters. For instance, when the female HIV acquisition risk is higher ($\beta_w > \beta_m$) the HIV epidemic produces substantially more female than male infections. Therefore, significantly more infections must be prevented in women to avert the same percentage infections as in men. It is difficult to say which indicator is more relevant and informative when benefit distribution is discussed. The reduced sensitivity of the fractional indicators to the pre-intervention parameters makes it more suitable for studies where those parameters are not precisely estimated. We suggest that both indicators must be evaluated and compared in any formal analysis.

Moreover, we believe that other indicators, such as the relative reduction in HIV prevalence and incidence must be considered to avoid the ambiguity associated with indicators based on

the absolute number of prevented infections. We illustrate our concern with an example of a hypothetical VMB intervention which reduces the susceptibility of the users by 56%, infectiousness by 59.5%, and is used by 42% of the women in the community. The comparison of the number of new HIV infections accumulated each year with and without intervention shows that during the initial 10–15 years the use of VMB implies fewer new infections per year (Fig.8A). However, during the next 15–20 years the pattern reverses and the number of new infections in the scenario with VMB surpasses those in the scenario without intervention. Is that enough to conclude that the HIV epidemic will worsen after the initial 15 years and should we recommend this product only for a limited period of time? Obviously, that is not the case because the simulated intervention provides good bi-directional protection which remains unchanged over time. The alarming readings of this indicator are the result of the intervention being effective in slowing down the HIV epidemic, which after 15 years has significantly affected the population size (Fig. 8B). The big size difference between the HIV-negative subpopulations leads to more new infections in the intervention scenario which does not imply that the community will be better off if the product is withdrawn at that point. In fact, other indicators, such as HIV prevalence and incidence, continue to support the positive VMB impact up to 50 years after its introduction (Fig.8C). Therefore, QBR based on HIV prevalence and incidence can be a useful addition to any intervention evaluation, as shown for the gender-specific effects in Fig.8D. This example confirms our conclusion that the assessment of ongoing and future VMB (or other biomedical) interventions must be based on more comprehensive analyses than calculations of infections prevented over a fixed period of time. Although focused on the gender-specific effects, this study raises the awareness that a careful consideration of the pre-intervention epidemic conditions as well as the dynamical behavior of the qualitative indicators must be integrated in all studies reporting results obtained through mathematical modeling.

A. Intervention scenarios

The sets of parameter values and ranges used in the intervention scenarios simulated throughout the paper are summarized in Table 2. Parameters not included in each scenario description are fixed at their baseline values (see Table 1).

B. Model description and technical details

Model equations and initial conditions—The model is formulated by the following system of differential equations:

$$\begin{aligned}
 \frac{dS_w^p}{dt} &= k\Lambda_w - (\lambda_w^p + \lambda_{rw}^p)S_w^p - \mu S_w^p \\
 \frac{dS_w}{dt} &= (1-k)\Lambda_w - (\lambda_w + \lambda_{rw})S_w - \mu S_w \\
 \frac{dS_m}{dt} &= \Lambda_m - (\lambda_w + \lambda_{rm})S_m - \mu S_m \\
 \frac{dI_w^p}{dt} &= \lambda_w^p S_w^p - (\mu + d + r_1 + \delta)I_w^p \\
 \frac{dI_{rw}^p}{dt} &= \lambda_{rw}^p S_w^p + r_1 I_w^p - (\mu + d_r + \delta)I_{rw}^p \\
 \frac{dI_w}{dt} &= \lambda_w S_w + \delta I_w^p + r_2 I_{rw} - (\mu + d)I_w \\
 \frac{dI_{rw}}{dt} &= \lambda_{rw} S_w + \delta I_{rw}^p - (\mu + d_r + r_2)I_{rw} \\
 \frac{dI_m}{dt} &= \lambda_m S_m - (\mu + d)I_m \\
 \frac{dI_{rm}}{dt} &= \lambda_{rm} S_m - (\mu + d_r)I_{rm} \\
 \frac{dA_w}{dt} &= d(I_w + I_w^p) + d_r(I_{rw} + I_{rw}^p) \\
 \frac{dA_m}{dt} &= dI_m + d_r I_{rm}.
 \end{aligned} \tag{3}$$

Entry rates $\Lambda_w = \mu_w N_w$ and $\Lambda_m = \mu_m N_m$ are selected to balance the departure rates in population which have not been exposed to HIV. Here

$N_w = S_w^p + S_w + I_w^p + I_w + I_{rw}^p + I_{rw}$ ($N_m = S_m + I_m + I_{rm}$) represents the sexually active women (men) in the population. The rate of resistance development r_1 is a product of the maximum rate of

resistance development and the probability of systemic absorption. Since no VMB resistance data is available we study a wide range for the likelihood of systemic absorption (from 0 to 100%) and assume that if absorbed VMB causes drug-resistance after an average period which varies from 1 year to never (i.e. infinite). The resulting range for r_1 (from 0 to 1) is used in the analysis (see Fig.6 and Table 2). All other variables and parameters are described in section 2 and Table 1.

$$\begin{aligned}
 \lambda_w^p &= \rho_w(1 - (1 - (1 - \alpha_s)\beta_w)^{n_w/\rho_w}) \frac{I_m}{N_m} \\
 \lambda_{rw}^p &= \rho_w(1 - (1 - \alpha_r(1 - \alpha_s)\beta_w)^{n_w/\rho_w}) \frac{I_m}{N_m} \\
 \lambda_w &= \rho_w(1 - (1 - \beta_w)^{n_w/\rho_w}) \frac{I_m}{N_m} \\
 \lambda_{rw} &= \rho_w(1 - (1 - \alpha_r\beta_w)^{n_w/\rho_w}) \frac{I_m}{N_m} \\
 \lambda_m &= \rho_m(1 - (1 - \beta_m)^{n_m/\rho_m}) \frac{I_w}{N_w} + \rho_m(1 - (1 - (1 - \alpha_i)\beta_m)^{n_m/\rho_m}) \frac{I_w^p}{N_w} \\
 \lambda_{rm} &= \rho_m(1 - (1 - \alpha_r\beta_m)^{n_m/\rho_m}) \frac{I_{rw}}{N_w} + \rho_m(1 - (1 - \alpha_r(1 - \alpha_i)\beta_m)^{n_m/\rho_m}) \frac{I_{rw}^p}{N_w}.
 \end{aligned} \tag{4}$$

Here ρ_w (ρ_m) is the average number of sex partners that women (men) have per year, n_w (n_m) is the average number of sexual acts that women (men) have per year, β_w (β_m) is the female (male) HIV-acquisition risk per act, α_s (α_i) measures the efficacy of VMB in reducing susceptibility (infectiousness) of VMB users, and α_r is the relative fitness of drug-resistant HIV strains compared to the wild-type HIV.

VMB interventions are initiated at time $t = 0$ in populations with $N_w(0) = N_m(0) = 1,000,000$ and equal HIV-prevalence (P) in men and women. VMB is initially used by proportion k_1 of the HIV-negative women and reduced proportion of $(1-\theta)k_1$ of the HIV-positive women. The state of HIV epidemic at the start of a VMB intervention is set as follows:

$$\begin{aligned}
 S_w^p(0) &= k_1(1 - P)N_w(0) \\
 S_w(0) &= (1 - k_1)(1 - P)N_w(0) \\
 S_m(0) &= (1 - P)N_m(0) \\
 I_w^p(0) &= (1 - \theta)k_1PN_w(0) \\
 I_w(0) &= (1 - (1 - \theta)k_1)PN_w(0) \\
 I_m(0) &= PN_m(0) \\
 I_{rw}^p(0) &= I_{rw}(0) = I_{rm}(0) = 0 \\
 A_w(0) &= A_m(0) = 0.
 \end{aligned} \tag{5}$$

Simulation of a VMB intervention—Figure 8 presents variations in population size, HIV prevalence and incidence as well as HIV infections prevented per year for a VMB intervention which reduces the susceptibility of the users by 56%, infectiousness by 59.5%, and is used by 42% of the women in the community.

Equilibrium population and basic reproductive number R_0 in absence of VMB intervention—Our analysis shows that the benefit distribution of VMB intervention strongly depends on the pre-intervention settings. Basic reproductive number R_0 is a key characteristic which is used to determine the long-term outcome of the HIV epidemic. If $R_0 > 1$ the infection persists and the infected population stabilizes at an endemic fixed point while if $R_0 < 1$ the infection naturally dies out and the population stabilizes at its disease-free equilibrium. In absence of VMB the system (3) reduces to 4 equations with variables S_w , S_m , I_w , and I_m . The disease-free equilibrium of the system is given by:

$$S_w = \frac{\Lambda_m}{\mu}, S_m = \frac{\Lambda_m}{\mu}, I_w = I_m = 0.$$

From the condition for local stability of the disease-free equilibrium we calculate

$$R_0 = \frac{\sqrt{b_m b_w}}{d + \mu},$$

where $b_m = \rho_m(1 - (1 - \beta_m)^{n_m/\rho_m})$ and $b_w = \rho_w(1 - (1 - \beta_w)^{n_w/\rho_w})$. When $R_0 > 1$ the system (3) in absence of VMB possesses an endemic equilibrium given by:

$$\begin{aligned} S_w &= \Lambda_w \frac{b_m + d + \mu}{b_m(b_w + \mu) - d(d + \mu)} \\ S_m &= \Lambda_m \frac{b_w + d + \mu}{b_w(b_m + \mu) - d(d + \mu)} \\ I_w &= \Lambda_w \frac{b_m b_w - (d + \mu)^2}{(d + \mu)(b_m(b_w + \mu) - d(d + \mu))} \\ I_m &= \Lambda_m \frac{b_m b_w - (d + \mu)^2}{(d + \mu)(b_w(b_m + \mu) - d(d + \mu))} \end{aligned} \quad (6)$$

Estimates of the initial values of QBR—To estimate the initial values of the ratios

C_I and F_I we calculate the limits $\lim_{\Delta t \rightarrow 0} C_I(\Delta t)$ and $\lim_{\Delta t \rightarrow 0} F_I(\Delta t)$. Let $\Sigma_w(\Delta t)$ ($\bar{\Sigma}_w(\Delta t)$) be the cumulative number of new HIV infections in women over the initial period Δt with (without) VMB usage. Similarly, $\Sigma_m(\Delta t)$ ($\bar{\Sigma}_m(\Delta t)$) is the cumulative number of new HIV infections in men over the initial period Δt with (without) VMB usage. Therefore, $C_{Iw}(\Delta t) = \Sigma_w(\Delta t) - \bar{\Sigma}_w(\Delta t)$ and $C_{Im}(\Delta t) = \Sigma_m(\Delta t) - \bar{\Sigma}_m(\Delta t)$ are the number of infections prevented in women and men over the period Δt . Using these notations we obtain:

$$\lim_{\Delta t \rightarrow 0} C_I(\Delta t) = \lim_{\Delta t \rightarrow 0} \frac{C_{Im}(\Delta t)}{C_{Iw}(\Delta t)} = \frac{\lim_{\Delta t \rightarrow 0} \frac{\Sigma_m(\Delta t) - \bar{\Sigma}_m(\Delta t)}{\Delta t}}{\lim_{\Delta t \rightarrow 0} \frac{\Sigma_w(\Delta t) - \bar{\Sigma}_w(\Delta t)}{\Delta t}} = \frac{\lim_{\Delta t \rightarrow 0} \frac{\Sigma_m(\Delta t)}{\Delta t} - \lim_{\Delta t \rightarrow 0} \frac{\bar{\Sigma}_m(\Delta t)}{\Delta t}}{\lim_{\Delta t \rightarrow 0} \frac{\Sigma_w(\Delta t)}{\Delta t} - \lim_{\Delta t \rightarrow 0} \frac{\bar{\Sigma}_w(\Delta t)}{\Delta t}} = \frac{\lambda_m(0)S_m(0) - \bar{\lambda}_m(0)\bar{S}_m(0)}{(\lambda_w(0)S_w(0) - (\bar{\lambda}_w(0)\bar{S}_w(0) + \bar{\lambda}_w^p(0)\bar{S}_w^p(0)))}. \quad (7)$$

Here the barred variables are calculated in the presence of VMB while the non-barred variables are calculated assuming no VMB usage. To approximate the forces of infections (λ) we use that $(1 - x)^n \approx 1 - nx$ when $nx \ll 1$. Replacing the initial conditions (5) the following hold:

$$\begin{aligned} \lambda_m(0) &\approx n_m \beta_m P \\ \bar{\lambda}_m(0) &\approx n_m \beta_m (1 - (1 - \theta)k_1)P + n_m \beta_m (1 - \alpha_i)(1 - \theta)k_1 P \\ \lambda_w(0) &\approx n_w \beta_w P \\ \bar{\lambda}_w(0) &\approx n_w \beta_w P \\ \bar{\lambda}_w^p(0) &\approx n_w \beta_w (1 - \alpha_s)P. \end{aligned} \quad (8)$$

Thus, $\lim_{\Delta t \rightarrow 0} C_I(\Delta t) \approx (1 - \theta) \frac{\alpha_i \beta_m n_m}{\alpha_s \beta_w n_w}$. Assuming equal sexual activity for both genders ($n_m =$

n_w) we end up with the expression for C_I in (1). The expression $\lim_{\Delta t \rightarrow 0} F_I(\Delta t) \approx (1 - \theta) \frac{\alpha_i}{\alpha_s}$ is obtained similarly.

Asymptotic estimates of the QBR—Let $(S_w^*, I_w^*, S_m^*, I_m^*)$ be the equilibrium population (susceptible women, HIV-positive women, susceptible men, HIV-positive men) reached in the absence of the VMB, while $(\bar{S}_w^*, \bar{I}_w^*, \bar{S}_m^*, \bar{I}_m^*)$ represents the equilibrium population assuming an VMB usage. Here $\bar{S}_w^*$ aggregates both susceptible female classes S_w^p and S_w , $\bar{I}_w^*$ aggregates sexually active HIV-positive female classes, and $\bar{I}_w^*$ aggregates HIV-positive

male classes I_m and I_{Im} . When the system is already at equilibrium the amount of the new infections (inflow) for each gender is equal to the number of the individuals leaving the infected classes (outflow). Therefore, the number of infections prevented in women $C_{Iw}(\Delta t)$ and men $C_{Im}(\Delta t)$ over the period Δt can be estimated by the difference in the outflow with and without VMB usage:

$$C_{Iw}(\Delta t) = (d + \mu)(I_w^* - \bar{I}_w^*)\Delta t, \quad C_{Im}(\Delta t) = (d + \mu)(I_m^* - \bar{I}_m^*)\Delta t. \quad (9)$$

Provided that $I_w^* > 0$ and $I_m^* > 0$ ($R_0 > 1$) the fractions of the infections prevented in women $F_{Iw}(\Delta t)$ and men $F_{Im}(\Delta t)$ over the same period are:

$$F_{Iw}(\Delta t) = \frac{(d + \mu)(I_w^* - \bar{I}_w^*)\Delta t}{(d + \mu)I_w^*\Delta t} = 1 - \frac{\bar{I}_w^*}{I_w^*}, \quad F_{Im}(\Delta t) = 1 - \frac{\bar{I}_m^*}{I_m^*}. \quad (10)$$

Since these estimates remain unchanged over time the asymptotic limits of the quantitative indicators will be:

$$\lim_{T \rightarrow \infty} C_I(T) = \frac{C_{Im}(\Delta t)}{C_{Iw}(\Delta t)} = \frac{I_m^* - \bar{I}_m^*}{I_w^* - \bar{I}_w^*}, \quad \lim_{T \rightarrow \infty} F_I(T) = \frac{F_{Im}(\Delta t)}{F_{Iw}(\Delta t)} = \left(\frac{I_m^* - \bar{I}_m^*}{I_w^* - \bar{I}_w^*} \right) \frac{I_w^*}{I_m^*} \quad (11)$$

We study the public-health benefits of interventions of vaginal microbicides.
 We evaluate gender-specific impact using two indicators based on prevented HIV.
 Our analysis exposes complicated correlations between parameters and indicators.
 Comparison of infections prevented over a fixed period of time may be misleading.
 We recommend more comprehensive analysis based on additional indicators.

Acknowledgments

BRM and DD are supported by a grant from the National Institutes of Health (grant number 5 U01 AI068615-03).

The authors thank the anonymous referees for many useful comments on an earlier draft.

References

1. Abdool Karim Q, Abdool Karim S, Frohlich J, Grobler A, Baxter C, Mansoor L, Kharsany A, Sibeko S, Mlisana K, Omar Z, Gengiah T, Maarschalk S, Arulappan N, Mlotshwa M, Morris L, Taylor D, Group CT. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science*. 2010; 329(5996):1168–1174. [PubMed: 20643915]
2. Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, Kaewkungwal J, Chiu J, Paris R, Prensri N, Namwat C, de Souza M, Adams E, Benenson M, Gurunathan S, Tartaglia J, McNeil JG, Francis DP, Stablein D, Birx DL, Chunsuttiwat S, Khamboonruang C, Thongcharoen P, Robb ML, Michael NL, Kunasol P, Kim JH. Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand. *New England Journal of Medicine*. 2009; 361:2209–2220. [PubMed: 19843557]
3. UNAIDS/WHO. Geneva: UNAIDS/World Health Organization; 2009. AIDS epidemic update: November 2009. http://data.unaids.org/pub/Report/2009/jc1700_epi_update_2009_en.pdf
4. Foss AM, Vickerman PT, Heise L, Watts CH. Shifts in condom use following microbicide introduction: should we be concerned? *AIDS*. 2003; 17:1227–1237. [PubMed: 12819525]

5. Smith RJ, Bodine EN, Wilson DP, Blower SM. Evaluating the potential impact of vaginal microbicides to reduce the risk of acquiring HIV in female sex workers. *AIDS*. 2005; 19:413–421. [PubMed: 15750395]
6. Vickerman P, Watts C, Delany S, Alary M, Rees H, Heise L. The importance of context: Model projections on how microbicide impact could be affected by the underlying epidemiologic and behavioral situation in 2 African settings. *Sexually Transmitted Diseases*. 2006; 33:397–405. [PubMed: 16721331]
7. Vickerman PD, Foss AP, Watts CP. Using Modeling to Explore the Degree to Which a Microbicide's Sexually Transmitted Infection Efficacy May Contribute to the HIV Effectiveness Measured in Phase 3 Microbicide Trials. *JAIDS*. 2008; 48(4):460–467. [PubMed: 18614928]
8. Foss AM, Vickerman PT, Alary M, Watts CH. How much could a microbicide's sexually transmitted infection efficacy contribute to reducing HIV risk and the level of condom use needed to lower risk? Model estimates. *Sexually Transmitted Infections*. 2009; 85:276–282. [PubMed: 19208696]
9. Wilson DP, Coplan PM, Wainberg MA, Blower SM. The paradoxical effects of using antiretroviral-based microbicides to control HIV epidemics. *Proceedings of The National Academy of Sciences of The United States of America*. 2008; 105:9835–9840. [PubMed: 18606986]
10. Heise L, Philpott S. Predicting the unpredictable real-world impact of ARV-based microbicides. *Proceedings of The National Academy of Sciences of The United States of America*. 2008; 105:E73–E73. [PubMed: 18974215]
11. Dimitrov DT, Masse B, Boily M-C. Who Will Benefit from a Wide-Scale Introduction of Vaginal Microbicides in Developing Countries? *Statistical Communications in Infectious Diseases*. 2010; Vol. 2(Iss. 1) Article 4.
12. Little SJ, Frost SDW, Wong JK, Smith DM, Pond SLK, Ignacio CC, Parkin NT, Petropoulos CJ, Richman DD. Persistence of transmitted drug resistance among subjects with primary human immunodeficiency virus infection. *Journal of Virology*. 2008; 82:5510–5518. [PubMed: 18353964]
13. Boily MC, Baggaley RF, Wang L, Masse B, White RG, Hayes RJ, Alary M. Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies. *Lancet Infectious Diseases*. 2009; 9:118–129. [PubMed: 19179227]
14. Ferry B, Carael M, Buve A, Auvert B, Laourou M, Kanhonou L, de Loenzien M, Akam E, Chege J, Kaona F. Comparison of key parameters of sexual behaviour in four African urban populations with different levels of HIV infection. *AIDS*. 2001; 15:S41–S50. [PubMed: 11686464]
15. Morgan D, Mahe C, Mayanja B, Okongo JM, Lubega R, Whitworth JAG. HIV-1 infection in rural Africa: is there a difference in median time to AIDS and survival compared with that in industrialized countries? *AIDS*. 2002; 16:597–603. [PubMed: 11873003]
16. Porter K, Zaba B. The empirical evidence for the impact of HIV on adult mortality in the developing world: data from serological studies. *AIDS*. 2004; 18:S9–S17. [PubMed: 15319739]
17. Wawer MJ, Gray RH, Sewankambo NK, Serwadda D, Li XB, Laeyendecker O, Kiwanuka N, Kigozi G, Kiddugavu M, Lutalo T, Nalugoda F, Wabwire-Mangen F, Meehan MP, Quinn TC. Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda. *Journal of Infectious Diseases*. 2005; 191:1403–1409. [PubMed: 15809897]
18. Kalichman SC, Simbayi LC, Cain D, Jooste S. Heterosexual anal intercourse among community and clinical settings in Cape Town, South Africa. *Sexually Transmitted Infections*. 2009; 85:411–415. [PubMed: 19429569]
19. Diekmann O, Heesterbeek JAP, Metz JAJ. On the definition and the computation of the basic reproduction ratio R_0 in models for infectious-diseases in heterogeneous populations. *Journal of Mathematical Biology*. 1990; 28:365–382. [PubMed: 2117040]
20. Anderson RM, May RM, Boily MC, Garnett GP, Rowley JT. The Spread of HIV-1 in Africa - Sexual Contact Patterns and the Predicted Demographic-Impact of AIDS. *Nature*. 1991; 352:581–589. [PubMed: 1865922]
21. Lacey CJN, Wright A, Weber JN, Profy AT. Direct measurement of in-vivo vaginal microbicide levels of PRO 2000 achieved in a human safety study. *AIDS*. 2006; 20:1027–1030. [PubMed: 16603855]

22. McCormack S, Jespers V, Low-Beer N, Gabe R, Kaganson N, Chapman A, Nunn A, Lacey C, Van Damme L. A dose-ranging phase I study of dextrin sulphate, a vaginal microbicide, in HIV-Negative and HIV-Positive female volunteers. *Sexually Transmitted Diseases*. 2005; 32:765–770. [PubMed: 16314774]
23. Mayer KH, Maslankowski LA, Gai F, El-Sadr WM, Justman J, Kwiecien A, Masse B, Eshleman SH, Hendrix C, Morrow K, Rooney JF, Soto-Torres L. Safety and tolerability of tenofovir vaginal gel in abstinent and sexually active HIV-infected and uninfected women. *AIDS*. 2006; 20:543–551. [PubMed: 16470118]
24. Jespers VA, Van Roey JM, Beets GI, Buve AM. Dose-ranging phase 1 study of TMC120, a promising vaginal microbicide, in HIV-negative and HIV-positive female volunteers. *JAIDS*. 2007; 44:154–158. [PubMed: 17106275]
25. Deeks SG, Wrin T, Liegler T, Hoh R, Hayden M, Barbour JD, Hellmann NS, Petropoulos CJ, McCune JM, Hellerstein MK, Grant RM. Virologic and immunologic consequences of discontinuing combination antiretroviral-drug therapy in HIV-infected patients with detectable viremia. *New England Journal of Medicine*. 2001; 344:472–480. [PubMed: 11172188]
26. Pao D, Andradu U, Clarke J, Dean G, Drake S, Fisher M, Green T, Kumar S, Murphy M, Tang A, Taylor S, White D, Underhill G, Pillay D, Cane P. Long-term persistence of primary genotypic resistance after HIV-1 seroconversion. *JAIDS-Journal Of Acquired Immune Deficiency Syndromes*. 2004; 37:1570–1573.

Figure 1.
Flow diagram of a vaginal microbicide (VMB) intervention in a heterosexual population.
The departure rates μ from each compartment are omitted for simplicity.

Figure 2. Initial dynamics (up to 1 year after the start of the intervention) of the QBR for A)–B) baseline scenarios *biR*, *biNR*, *uniR*, and *uniNR*; C) *biR* scenarios with different levels of pre-enrollment screening. Marked horizontal lines ($y = 1$) represent the level at which both genders benefit the same.

Figure 3.

Long-term dynamics of the QBRs for A)–B) *biR* scenarios with $R_0 < 1$ ($\alpha_i = 0.4$, $\alpha_s = 0.5$, $\beta_w = 0.001$, $\beta_m = 0.002$); C)–D) *biR* scenarios with $R_0 > 1$ ($\alpha_i = 0.4$, $\alpha_s = 0.5$, $\beta_w = 0.002$, $\beta_m = 0.004$) and different levels of pre-enrollment screening. Marked horizontal lines ($y = 1$) represent the level at which both genders benefit the same.

Figure 4.

Regions of male advantage (RMA) in the α_s – α_i parameter space over 5, 10, 15, 20, and 25 years with respect to A) the cumulative indicator (C_l) and B) the fractional indicator (F_l) for *biR* scenarios. Dotted lines represent the boundaries of the 25-year region assuming higher HIV acquisition risk for women than for men (*biRa* scenarios).

Figure 5. Regions of male advantage (RMA) in the $\beta_w - \beta_m$ parameter space over 5, 10, 15, 20, and 25 years with respect to A) the cumulative indicator (C_l) and B) the fractional indicator (F_l) for *biR* scenarios ($\alpha_i = \alpha_s$). Dotted lines represent the boundaries of the 25 year region assuming uni-directional protection (*uniR* scenarios, $\alpha_i = 0$).

Figure 6.

Regions of male advantage (RMA) in the $\alpha_s - r$ parameter space over 5, 10, 15, 20, and 25 years for interventions with A)–B) bi-directional protection assuming equal VMB efficacy in reducing susceptibility and infectiousness (*biR* scenarios, $\alpha_i = \alpha_s$) and C)–D) uni-directional protection (*uniR* scenarios, $\alpha_i = 0$). The dotted lines represent the boundaries of the 25-year region for the scenario assuming that the acquisition risk for women is higher than for men (*biRa* scenarios, $\alpha_i = \alpha_s$).

Figure 7.

Dynamics of A) the prevalence of drug-resistance, B) the cumulative indicator (C_I), and C) the fractional indicator (F_I) for biRr scenarios with different rates of resistance reversion per year and active post-enrollment screening ($\delta = 1$). The rate of resistance development is assumed relatively high ($r_1 = 0.7$).

Figure 8.

Characteristics of a hypothetical VMB intervention: A) yearly number of new infections; B) population size; C) HIV-prevalence and incidence; D) QBR based on cumulative prevented infections (C_I), cumulative prevented fractions (F_I), reduction in HIV-prevalence (F_P) and incidence (F_{inc}).

Table 1

Parameter description

Param.	Description	Baseline value	Refs.
<i>A. Pre-intervention parameters:</i>			
β_m	Male HIV acquisition risk per act	0.003	[13]
β_w	Female HIV acquisition risk per act	0.0038	[13]
$1/\mu$	Average time (in years) to remain sexually active	35	[14, 3]
Λ_m	Rate at which men become sexually active	$\mu\beta_m$	calculated
Λ_w	Rate at which women become sexually active	$\mu\beta_w$	calculated
d, d_r	Annual rates of progression to AIDS of people infected with wild- and resistant-type HIV	0.1	[15, 16]
n_w, n_m	Average number of sexual acts per year for women and men	60	[17, 18]
ρ_w, ρ_m	Average number of sexual partners per year for women and men	1.5	[17, 18]
P	Initial HIV prevalence	0.05	[3]
<i>B. Intervention parameters:</i>			
k	Asymptotic VMB coverage	0.5	assumed
k_1	Initial VMB coverage	0.5	assumed
α_s	VMB efficacy in reducing susceptibility per act	0.5	assumed, [1]
α_i	VMB efficacy in reducing infectiousness per act	0.5	assumed
θ	Reduction in the initial fraction of HIV+ women who start on VMB as a result of pre-enrollment screening	0.5	assumed
δ	Annual withdrawal rate from VMB by HIV+ women as a result of post-enrollment screening	0	assumed
α_r	Relative transmissibility of drug-resistant HIV	0.25	assumed, [12]
r_1	Rate of resistance development by HIV+ users of VMB	0.5	assumed
r_2	Rate of resistance reversion in former users of VMB	0	assumed

Table 2

Simulated intervention scenarios by figure

Figure	Scenario ^l	α_s	α_i	β_m	β_w	r_1	r_2	θ	δ
<i>A. Baseline scenarios:</i>									
Fig.2AB	biR	0.5	0.5	0.0038	0.003	0.5	0	0.5	0
Fig.2AB	biNR	0.5	0.5	0.0038	0.003	0	0	0.5	0
Fig.2AB	uniR	0.5	0	0.0038	0.003	0.5	0	0.5	0
Fig.2AB	uniNR	0.5	0	0.0038	0.003	0	0	0.5	0
<i>B. Initial and long-term dynamics:</i>									
Fig.2C,3CD	biR, $R_0 > 1$	0.5	0.4	0.004	0.002	0.5	0	0.1–0.7	0
Fig.3AB	biR, $R_0 < 1$	0.5	0.4	0.002	0.001	0.5	0	0.1–0.7	0
Fig.7	biRr	0.5	0.5	0.0038	0.003	0.7	0–4	0.5	1
<i>C. Regions of male advantage:</i>									
Fig.4 (regions)	biR	0–0.9	0–0.9	0.0038	0.003	0.5	0	0.5	0
Fig.4 (dotted)	biRa	0–0.9	0–0.9	0.003	0.0038	0.5	0	0.5	0
Fig.5 (regions)	biR	0.5	0.5	0.001–0.006	0.001–0.006	0.5	0	0.5	0
Fig.5 (dotted)	uniR	0.5	0	0.001–0.006	0.001–0.006	0.5	0	0.5	0
Fig.6 (regions)	biR	0–0.9	0–0.9	0.0038	0.003	0–1	0	0.5	0
Fig.6 (dotted)	biRa	0–0.9	0–0.9	0.003	0.0038	0–1	0	0.5	0

^l Scenario categories are discussed in Section 3. All other parameters are fixed on their baseline values from Table 1.