Published in final edited form as:

Stat Commun Infect Dis. 2010 January ; 2(1): 1012. doi:10.2202/1948-4690.1012.

Who will Benefit from a Wide-Scale Introduction of Vaginal Microbicides in Developing Countries?*

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Abstract

Vaginal microbicides (VMB) are currently among the few biomedical interventions designed to help women reduce their risk of acquiring HIV infection. However, the microbicide containing antiretroviral (ARV-VMB) may lead to the development of antiretroviral resistance and could paradoxically become more beneficial to men at the population level.

We developed a mathematical model to study the impact of a wide-scale population usage of VMB in a heterosexual population. Gender ratios of prevented infections and prevalence reduction are evaluated in 63 different intervention schedules including continuous and interrupted ARV-VMB use by HIV-positive women. The influence of different factors on population-level benefits is also studied through Monte Carlo simulations using parameters sampled from primary ranges representative of developing countries.

Our analysis indicates that women are more likely than men to benefit from ARV-VMB use since 78-80% of the total 63,000 simulations investigated (under different parameter sets) showed a female advantage whether benefit is measured as cumulative number of infections prevented, the percentage of cumulative infections prevented, or the expected reduction in prevalence. Stratified analysis by scenarios indicates that the likelihood of a male advantage with respect to the fractions of prevented infections varies from 6% to 49% among the scenarios. It is substantial only if the risk of systemic absorption and development of resistance to ARV-VMB is high and the HIV-positive women use VMB indefinitely without interruption. Therefore, the use of ARV-VMB, with successful control measures restricting usage by HIV-positive women, is still very much a female prevention tool.

Keywords

mathematical model; HIV transmission; HIV prevention; vaginal microbicide

1 Introduction

The global fight against HIV has been going on for more than 25 years with a mixed success. The genetic diversity of the virus and its ability to undergo rapid genetic changes has seriously complicated the search for an effective vaccine [1, 2, 3]. Antiretroviral (ARV) therapies have successfully decreased the morbidity and mortality associated with AIDS, especially in the developed countries and to some extent transformed the public perception

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

of the HIV infection from disastrous to a more controllable chronic disease [4]. Unfortunately, despite some progress, the access to ARV treatment in many resource poor countries is lagging behind and HIV continues to spread unbeaten in many regions. In many of these countries, the HIV prevalence is higher among women than men [5]. This is particularly alarming given the lack of specific female preventive tools and the difficulty that women encounter in certain context to convince their male partners to use condoms. Vaginal microbicides (VMB) are among the few promising biomedical interventions designed to be used directly by women without the consent of men. Current review of research on the development of VMB yielded more than 100 studies with 45 of them in clinical stages [6]. Microbicide classes, distinguished by the mechanisms of interrupting the HIV-transmission include physico-chemical barriers, vaginal defense enhancers, surfactants, viral entry inhibitors, reverse transcriptase inhibitors, and inhibitors of HIV uptake and dissemination. Products from different classes have been tested in Phase IIb/III trials (see Table 1) but so far we do not have a proof of concept that a microbicide can prevent HIV acquisition in women. However, as pointed out by several authors [7, 8] efficacy dilution factors commonly found in microbicide trials are potentially affecting the outcome of these trials. It is biologically conceivable that a VMB would also reduce the infectiousness of HIV-positive female users to their partners but the completed trials were not designed to answer this question [9, 10, 11, 12, 13, 14, 15, 16, 17]. Parallel to the development of new VMB candidates concerns raised about possible increase in a risky sexual behavior (i.e. condom replacement, sexual disinhibition) following microbicide introduction [18] and potential long-term issues with antiretroviral (ARV) resistance for ARV-based VMB [19]. The latter modeling study highlighted that paradoxically ARV-based VMB may become more of a “men prevention” tool by preventing, under specific conditions, more infections in men than in women. Although the authors cautioned that such “paradoxical” effects could be due to some of the assumptions embedded in the model, the determinants of this shift in gender-benefits following the introduction of ARV-VMB use in a population was not formally evaluated and analyzed.

In this paper, our primary goal is to determine the likelihood that a wide-scale ARV-VMB intervention will be more beneficial for men than women and to identify under what conditions ARV-VMB use provides a greater advantage to men. This has relevance to interpret previous results and to interpret HIV trends if such product becomes widely available. The study is based on a compartmental model of HIV transmission and ART-based VMB use in a heterosexual population representative of Southern Africa. In particular, we introduce and investigate control measures to limit the usage of ARV-VMB by HIV-positive women as potential factors that influence the distribution of the benefits between genders. In all, we investigate the gender benefits under a wide range of conditions that include 63 intervention scenarios (i.e. rate of ARV-VMB introduction, probability of resistance development, and pre- and post-introductory control of the usage ARV-VMB by HIV-positive women) and 1000 randomly sampled parameter sets for each scenario. Expected population-level benefits are quantified using three indicators based on the cumulative number and the fraction of infections prevented, or on the reduction in HIV prevalence over different time periods.

2 Methods

We developed a deterministic model of HIV transmission and disease progression in population of heterosexually active individuals to analyze the gender benefits of ARV-VMB interventions. The model is based on the compartmental model described in [19], with modifications described below. Without loss of generality of results we ignore condom use and assume 100% adherence to the product since different levels of condom use can be modeled by reduction in the transmission probabilities per act while lower adherence level

can be simulated by reduction in the VMB efficacy. In addition, we introduce flows from VMB-users to non-users to represent women's withdrawal from the product after being tested positive for HIV (see Figure 1). The modeled population is divided into three major classes: men (subscript m), women using ARV-VMB (subscript w , superscript p), and women not using ARV-VMB (subscript w) which are stratified by their HIV and disease status in susceptible (S), infected with a wild-type HIV (I), infected with a resistant-type HIV (I_r), and AIDS states (A). Men and women who become sexually active, join the community at constant rates (Λ_m and Λ_w) which are selected to balance the departure rate (μ) in a non-infected population (open but stable population). 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 functions of the number of partners per susceptible person, the number of sex acts per partnership, and the transmission probability per sex act for partners from different classes. The ranges of man-to-woman and woman-to-man transmission probabilities per act are determined based on a meta-analysis of the observational data from developing countries [20]. We distinguish between unidirectional interventions, which only reduce susceptibility of female users and bidirectional interventions, which reduce both susceptibility and infectiousness of women using ARV-VMB. Currently, the potential magnitude of the reduction (i.e. product efficacy) in susceptibility (α_s) and infectiousness (α_i) due to ARV-VMB is unknown since no product has yet been licensed. Hence, we explore a wide range of efficacy values from 0% to 90% for each mechanism of protection. We assume that if the ARV-VMB is systemically absorbed, women infected with a wild-type HIV who continue to use the ARV-VMB will develop resistance after an average period ($1/r_{max}$) which was varied from 6 months to never (i.e. infinite). Since no ARV-VMB resistance data is available we derived maximum resistance rates from existing studies of ARV resistance in developing countries [21], US [22], and Europe [23, 24, 25]. We also assumed that drug-resistant HIV strain is less transmissible due to the cost of resistance [26] and enforce mutual exclusion mechanism between resistant and non-resistant strains. Complete description of the model and the forces of infection for different classes are given in the Appendix B.

Simulated ARV-VMB interventions are introduced at time ($t=0$) into populations with ongoing HIV epidemics and equal HIV-prevalence (P) in men and women which corresponds to the current levels reported in the countries from Southern Africa [5]. The ARV-VMB is initially adopted by a fraction k_1 of the women in the population and is introduced gradually as a fraction k of the women entering the population. As a result the ARV-VMB coverage in all considered scenarios would converge to a saturation level k , at equilibrium. In reality, ARV-VMB coverage at a given time (i.e. effective coverage) will depend on the product availability and distribution as well as the willingness of the majority of the women to try it and use it regularly. Therefore, in the model, we sample the saturation level k from its full range of 0% to 100% and implement three introduction schedules (slow, intermediate, and fast). In the “slow” schedule the VMB is introduced only through the newly recruited women who adopt the product ($k_1 = 0$). In this case the ARV-VMB effective coverage reaches 55-60% of the asymptotic coverage in 20 years (Fig. 2). The “intermediate” schedule assumes that half of the asymptotic coverage is initially achieved ($k_1 = k/2$). In this case the ARV-VMB effective coverage reaches 80% of the asymptotic coverage in 20 years. The “fast” schedule assumes instantaneous uptake of the product in the female population at the asymptotic coverage level ($k_1 = k$). For each intervention schedule we define intervention scenarios based on three factors which affect the mechanisms of drug-resistance development and drug-resistance risk management and study their influence on the distribution of benefits between genders. The first factor is the intrinsic risk of systemic absorption (r_{SA}) of VMB. While there is no evidence of such absorption in clinical studies for non ARV-based VMB products such as PRO2000 [27] and dextrin sulphate [28],

quantifiable plasma drug levels were detected after intravaginal application of ARV-VMB such as for tenofovir [29] and TMC-120 [30]. Thus, we explore three distinct ranges of absorption probabilities (r_{SA}): 0% (no risk); 1-5% (low risk); and 50-90% (high risk). Since it is unclear whether such systemic absorption is associated with a substantial risk of development of drug resistance, we assume that the average time to develop resistance ($1/r_{max}$) in case of systemic absorption could vary from 6 months to never. Another factor is the pre-introductory control (PreC) that aims to limit the risk of resistance by preventing HIV-positive women from using ARV-VMB. It is implemented in the model through reduction (θ) in the fraction of the initially infected women who start on ARV-VMB. The last factor incorporated in the scenarios is the post-introductory control (PostC) which limits the risk of resistance development by encouraging ARV-VMB users who contracted HIV to stop using the product. In the model, HIV-positive women interrupt ARV-VMB application at rate δ which determines the level of success of the PostC. Although such control measures could have variable success in reality, we decided to investigate PreC and PostC at three levels, representing no, moderate, and strict control. In summary, we investigate 9 scenarios of “slow” schedules (3 levels of r_{SA} * 3 levels of PostC) and 27 scenarios of “intermediate” and “fast” schedules (3 levels of r_{SA} * 3 levels of PreC * 3 levels of PostC). The scenario-building parameters and their ranges are defined in part C of Table 3. A detailed description of the scenarios is provided in Appendix A.

For each of the 63 scenarios we perform series of 1000 simulations with biological parameters randomly selected from “primary” ranges (see Table 3) which are representative of Southern Africa. Another set of simulations is performed for the scenarios of fast VMB introduction schedules with no PreC and PostC and low and high risk of systemic absorption using biological parameters selected from “secondary” ranges proposed in [19]. This allows us to assess the sensitivity of the results to the ranges of parameters explored. For each parameter set we simulate the HIV infection in presence and in absence of ARV-VMB intervention and evaluate:

- i. the ratio $C_I(T)$ of the cumulative number of infections prevented in men and women over the period $[0, T]$ as a result of the intervention;
- ii. the ratio $F_I(T)$ of the fractions of infections prevented in men and women over the period $[0, T]$ as a result of the intervention;
- iii. the ratio $F_P(T)$ of the expected fractional changes in HIV-prevalence in men and women at time ($t = T$).

Each of the quantitative ratios $C_I(T)$, $F_I(T)$, and $F_P(T)$ indicates that men or women benefit more from the intervention if its value is greater or less than one, respectively. We study the cumulative distribution of these indicators over all of the 63,000 simulations (63 scenarios times 1000 simulations) as well as stratified by scenarios. Correlations between levels of pre- and post-introductory control and quantitative indicators in time are studied by comparison of two-dimensional contour plots of the indicators over the parameter space of the control variables (θ and δ). Identical analysis is performed with another set of simulations assuming unidirectional intervention to reveal the influence of the reduction in the infectiousness of the HIV-positive ARV-VMB users on the gender-specific benefits. Multivariate sensitivity analysis is conducted to determine the effects of biological and intervention parameters on the quantitative indicators. Partial rank correlation coefficients are calculated and compared for periods of 5, 10, and 20 years after the start of the intervention.

3 Results

Our “primary” analysis uses the initial HIV prevalence and the transmission probabilities per act from data representative for the countries in Southern Africa which is the world region most heavily affected by the HIV epidemic (see Appendix B, Table 3). Most simulations, included in this analysis, produce stable or increasing epidemics in absence of a ARV-VMB intervention with basic reproductive number $R_0 > 1$ in 99.9% of all 63,000 simulations. In contrast, the majority of the simulations, conducted with parameters sampled from their “secondary” ranges produce declining epidemics in absence of a ARV-VMB intervention with basic reproductive number $R_0 < 1$ in 99.7% of the simulations included in the “secondary” analysis. Not surprisingly, most simulated epidemics in the “secondary” analysis decline fast following the introduction of ARV-VMB and show significantly decreased incidence rates after the initial period of 10 years.

Figure 3 A,B shows the temporal variations of the qualitative indicators $C_I(T)$, $F_I(T)$, and $F_P(T)$ for specific ARV-VMB interventions from the “primary” analysis. It illustrates simulations of two interventions of the intermediate schedule with high r_{SA} , no PostC, and different levels of PreC. For each scenario, the overall dynamics of the three indicators is qualitatively similar but predict quite variable benefit distributions between genders over time, which outline the importance of the choice of the quantitative indicator and the time period chosen for the evaluation. The level of PreC dramatically influences the indicators during the early stages of the intervention by modifying the ratio of susceptible to HIV-positive ARV-VMB users which affects the ratio of direct benefits received by each genders. When the HIV-prevalence in ARV-VMB users stabilizes (in 10 to 15 years) the advantage in benefits depends on the balance between the increase in the fraction of ARV-VMB users among non-infected women (benefiting women through reduced susceptibility) and the arising drug-resistant fraction among HIV-positive women (benefiting men through reduced infectivity). These dynamical fluctuations in the benefit ratios justify the detailed study of the three quantitative indicators over different periods of time. The intervention using a “secondary” parameter set in absence of PreC (Fig.3-C) initially shows a male advantage similar to that of the “primary” simulation (Fig.3-B). However, all benefit indicators decline toward unity at a slower pace due to the declining epidemic which diminishes the influence of the increasing fraction of ARV-VMB users among susceptible women on the benefit distribution. This drives the likelihood of male advantage in the “secondary” scenarios significantly higher than the corresponding “primary” scenarios (Fig. 5).

The cumulative distributions of the indicators over 10 and 20 years over all “primary” simulations highlight that women tend to benefit more than men from a ARV-VMB-intervention whether benefit is measured as cumulative number of infections prevented, the percentage of cumulative infections prevented, and the expected reduction in prevalence (Fig.4). Independently of the indicator, about 80% of the total number of simulations predict greater benefits for women and more than 40% of the simulations estimate the expected benefits for women to be at least twice than for men. Note that the cumulative percentage of simulations that predict male advantage is not substantially affected by the period of the analysis despite the temporal variations of each indicator discussed above (Fig. 3). This suggests that the selected periods of time span far enough to capture the major dynamical changes in the benefit distribution which due to the intervention. However, the overwhelming female advantage reported in Fig.4 does not necessarily mean that women are more likely to benefit from a VMB-intervention since not all scenarios are necessarily equally probable.

Thus, for each scenario, we explore the percentage of interventions with bidirectional and unidirectional ARV-VMB that predict a male advantage in prevented fractions ($F_I(T)$) over periods of 10 and 20 years (Fig.5, A and B). In addition, the distribution of the indicator (we report 50th[5th,95th] percentiles in the text) helps us to assess the magnitude of the male benefit. The scenario (highlighted Pf002) with highest likelihood of a male benefit predicts a male advantage in nearly 50% of simulations over 10 and 20 years as it assumes high risk of systemic absorption combined with no PreC and PostC of ARV-VMB usage by HIV-positive women. In such case, the magnitude of the male benefit among all simulations is a medium to high with $F_I(10)$ at 0.9895[0.47,1.93]. A moderate likelihood (30%-50%) of male advantage in F_I is obtained in 11 out of 63 scenarios over a period of 10 years and the median level of $F_I(10)$ in these scenarios varies between 0.7 and 0.9. A closer look shows that 9 of them assume no PostC while the other 2 assume combinations of high rate of resistance development, moderate PostC, and no to moderate PreC. All scenarios without resistance (Fig.5A, $Z = 0$, see caption), which is also equivalent to transmissibility of the resistant strain being similar to that of the wild-type HIV, resulted in a low likelihood (below 30%) of a male advantage and median level of $F_I(10)$ between 0.33 and 0.76. Similarly, for unidirectional interventions (Fig.5B) the likelihood of male advantage and median level of $F_I(10)$ remain low across all scenarios. These results highlight the determinant role of the reduced transmissibility of the ART-resistant HIV and bidirectional protection of ART-VMB on the relative level of male benefits. If both factors are absent male advantage is not observed in any of the simulated scenarios (see Fig.5B, $Z = 0$) and the median level of $F_I(10)$ remains close to 0.5 which means that the percentage of infections prevented is nearly 2 times larger in females than in males. Note that the benefit ratio is significantly influenced by the efforts to reduce ARV-VMB usage by HIV-positive women. In all scenarios with strict PostC the simulations which report more infection prevented in men are less than 25% while only 2 of the scenarios with strict PreC report male advantage in more than 30% of the simulations. Similar results were obtained for $C_I(T)$ and $F_P(T)$ (not shown).

Fig.5C compares the median fraction of prevented infections and the prevalence of drug-resistance among the HIV-positive population after 10 years of ARVVMB intervention. It clearly shows that the scenarios with high risk of systemic absorption and no PostC, which tend to have the highest likelihood of male advantage in $F_I(10)$ (Fig.5A), also prevent the largest fraction of infections in the population. Unfortunately, it comes at the steep cost of high prevalence of drug-resistant HIV in the population. If ARV-VMB usage by HIV-positive women is limited, then the prevalence of drug-resistance reduces by more than 60% (compare Pf002 and Pf222). Figure 5 also permits to compare the results of two specific intervention scenarios obtained with “primary” (Pf001, Pf002) and “secondary” (Sf001, Sf002) parameter sets. Interestingly, the likelihood of a male benefit and the levels of $F_I(10)$ are higher with the secondary range (Sf 002: 73% likelihood of male advantage and $F_I(10) = 1.307[0.67,3.64]$) compared to the primary range (Pf 002: 49% likelihood of male advantage and $F_I(10) = 0.9895[0.47,1.93]$). Similarly the overall fraction of infection prevented over 10 years is 28.5% Sf002 compared to 22% for Pf002 (Fig.5C). The level of resistance predicted is also larger for the secondary range. The difference between these estimates can be explained by the overly “optimistic” assumptions embedded in the “secondary” set of parameters since most epidemics have R_0 of less than one which implies fast decline in the epidemics even in absence of ARV-VMB.

To better understand the impact of PreC and PostC on the benefit ratios we sampled uniformly the control parameters δ and θ for a scenario with high probability of resistance development while keeping the other biological parameters fixed. We looked at variations in indicators after 5, 10, and 20 years evaluated over the parameter space of the control variables (θ and δ). Figure 6-A shows that a male advantage over the initial 5-year period

can be expected only for a combination of low rates of pre- and post-introductory control. The influence of the PreC declines in time (flatter slopes) because it alters the initial population distribution but not the later infection dynamics (Fig. 6-B,C). Over 20 years, the ARV-VMB intervention produces greater male benefits only for low rates of PostC. These particular interventions prevent higher percentage of female infections regardless of the level of PreC as long as the HIV-positive women on ARV-VMB withdraw from the product within the first 7 years following their infection ($\delta > 0.14$). This suggests that a relatively small screening effort would result in a female advantage in the prevented fractions. However, significantly stronger effort will be needed if high level of resistance development is expected.

Finally, we present results (Fig. 7) from the multivariate sensitivity analysis of the influence of biological and intervention parameters on the benefit distribution measured by the quantitative indicators $C_I(T)$, $F_I(T)$, and $F_P(T)$. Our analysis shows strong negative correlation of the reduction in susceptibility (a_s) of the ARV-VMB with all benefit ratios, indicating that the likelihood for male advantage declines when the efficacy of the product increases. Reduced infectiousness (a_i) has larger positive influence early on than later for all benefit ratios, indicating that its increase boosts the possibility of male advantage. This correlations were expected since the reduced susceptibility (a_s) is the major factor that contribute to female benefits from the intervention while the importance of reduced infectiousness (a_i) to the male benefits falls with the increasing influence of the resistance. Transmission probabilities per act (β_w and β_m) express strong correlation with the prevented fractions ratio $F_I(T)$ and increasing correlation with $F_P(T)$. However, their influence on the cumulative ratio of infections $C_I(T)$ changes dynamically in time. High man-to-woman transmission (β_w) initially yields more prevented infections in women because epidemics with $\beta_w > \beta_m$ characterize with higher HIV-prevalence in women and even small percentage reduction in new female infections results in a big cumulative number. The correlation reverses later in time when higher β_w boosts the prevalence of drug-resistance in HIV-positive women and contributes to more cumulative infections prevented in men. Other factors that bring in relatively more male benefits are the asymptotic VMB coverage (k) and the maximum resistance rate (r_{max}) while the increase in drug-resistance fitness (a_r) leads to relatively more benefits to women.

4 Discussion

The most recent AIDS epidemic update shows equal worldwide prevalence of HIV-infections among women and men. However, women are disproportionately affected in Southern Africa where they account for 61% of HIV-infected individuals [5]. Some HIV-preventive measures can be successfully used to reduce the probability of HIV-transmission during a coital act. Male condoms, when used consistently and correctly, provide high levels of protection against HIV and other sexually transmitted infections. However, it is often difficult for women to negotiate its use on a regular basis. Some analyses have shown evidence that male circumcision decreases the woman-to-man transmissibility [31, 32] but its protection effects to women are still unclear [33, 34]. VMB are designed to address the need for a female-controlled method for HIV-prevention. Although the VMB are developed as female preventive tool to reduce their risk to contract HIV during heterosexual contacts, a wide-scale intervention will prevent a lot of male infections as well. These additional benefits are neither surprising nor unwelcome [35, 36]. The question of which gender will benefit more from a VMB-intervention has little practical importance compared to the question of who is able to use the product effectively and consistently. In this study we discuss gender benefits from ARV-VMB to provide scientific insights on how a preventive tool used and controlled by women can provide more benefits to men and to evaluate the

likelihood of such male advantage to be recorded. This has relevance to interpret previous results and to interpret HIV trends if such product becomes widely available.

Our analysis indicates that a wide-scale introduction of ARV-VMB will more likely provide greater population benefits to women by preventing more total cumulative infections as well as higher percentage of cumulative infections in women than in men and will more likely lead to higher reduction in the female HIV-prevalence. From 63 scenarios analyzed, under a variety of parameter assumptions, none predicted a likelihood of male advantage in prevented fractions greater than 50% over extended periods of time while in only 11 scenarios the expectation for more infections prevented in men was greater than 30%. Slightly more than 20% of the total simulations gave advantage to men versus women. In order to explain how a preventive tool designed to protect women can provide more benefits to men one needs to understand the mechanisms of ARV-VMB impact on the HIV-dynamics at the population level. The primary source of influence is the “efficacy” mechanism which acts through reduction in the susceptibility and the infectiousness of the users of ARV-VMB. If it is possible to develop drug resistance then an additional “resistance” mechanism will play a major role by reducing transmissibility of the drug-resistant HIV-strain [26]. Both mechanisms provide population benefits by preventing infections in women and men which we measure here as total numbers on prevented infections, percentage of cumulative infections prevented, and percentage decrease in HIV-prevalence over different periods of time. Since the intervention is introduced in the female subpopulation the “efficacy” mechanism prevents infections in females from the moment when first users enter the population while its direct impact on the male infections depends on the existence of a pool of HIV-positive women who use the product. Therefore, any measures that restrict the use of ARV-VMB by HIV-positive women will limit the direct male benefits from the “efficacy” mechanism. On the other hand, drug-resistance will develop in HIV-positive women using VMB and therefore the “resistance” mechanism will be more beneficial to men, if there is a cost of the resistance which reduces transmissibility. If the rate of resistance development is high and HIV-positive women continue using the product indefinitely then the fraction of women infected with drug-resistant HIV will grow and ultimately lead to reduced woman-to-man transmission.

Bidirectional efficacy combined with significant reduction in the transmissibility of drug-resistant HIV can produce scenarios with more male benefits. This explanation, first proposed by Heise and Philpott [35], is supported by our analysis which shows that if one of those two assumptions is not met the likelihood of male advantage is less than 30% (see Fig. 5). If both assumptions are not met the male advantage is practically impossible. In addition, we showed that even if both assumptions are fulfilled ARV-VMB will be more likely to benefit women as a result of preventive measures to contain the risk of resistance development which will also limit the benefits to men. An important question is how feasible is to expect that such control measures will be successful. First, PreC and PostC will most likely occur naturally even without coordinated measures to restrict product use since HIV-positive women who know (or learn) their HIV status will probably not start (nor continue) using ARV-VMB. The proportion of the Southern African women who are aware of their HIV-status is estimated at 21% [37]. However, it is likely that the acceptance of voluntary testing decreases with the increase in the self-perceived HIV risk [38] which reduces the potential impact of the natural control. Second, the potential problem of drug-resistance with the use of ARV-based microbicides is being investigated in ongoing trials [39]. Therefore, it is unlikely that such products will be introduced without initial and periodic screening of the users in order to prevent prolonged ARV-VMB usage by HIV-positive women after contracting HIV. Those measures will more likely lead to at least moderate levels of PreC and PostC. A “pessimistic” scenario which assumes high risk of systemic absorption combined with moderate levels of PreC and PostC gives about 33%

chance for male prevalence in prevented fractions and prevalence reduction over 20 years. Therefore, even moderate levels of pre-introductory control (PreC) and post-introductory control (PostC) will make male-dominated scenarios very unlikely. The analysis outlined as most beneficial for men the scenario assuming bidirectional ARV-VMB intervention with high risk of systemic absorption in absence of PreC and PostC (Fig.5). It provides compatible benefits to men and women due to the reduced susceptibility and infectiousness of the VMB users while the growing fraction of women infected with drug-resistant HIV strain often gives an advantage to men. Not surprisingly, the same scenario predicts the most substantial drug-resistance prevalence after the initial period of ARV-VMB usage. If the same scenario is simulated with parameter values from the “secondary” ranges it predicts higher likelihood of male advantage in prevented fractions over 10 years. We attributed the discrepancy between these estimates to the fact that the epidemics in the “secondary” analysis predominately have basic reproduction number (R_0) less than one. This can only be possible if other drastic measures are currently in place to reduce the HIV-incidence in the countries from Southern Africa. However, the current AIDS reports do not show a sign that the epidemic in the region is declining. This also highlight the sensitivity of model prediction to R_0 at the time of introduction and also, often forgotten, to the range of parameter explored.

Finally, 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, aggregate the level of condom use in the transmission probabilities per act, and ignore the availability and possible effects of antiretroviral treatments for HIV-positive individuals. Although important for the overall public health impact of a wide-scale ARV-VMB intervention these factors will introduce symmetric effects on the gender benefits and therefore we believe they have very little influence on the benefit indicators. Our model does not allow for drug-resistant HIV to reverse back to wild type in the non-users of ARV-VMB. The existing data suggests that in patients with failing ARV therapy such reversion can be expected from 12 to 16 weeks after the therapy interruption while transmitted drug-resistance can persist longer than 4 years [26]. Since we identified the reduced transmissibility of the drug-resistant HIV as a factor in benefit distribution this modeling decision influences the balance between genders. In fact, it is favorable to men because the majority of the resistant cases arise in women and possible reversion to wild type will increase more the woman-to-man transmission probability. As a result, our analysis tends to overestimate the likelihood of male advantage.

In conclusion, ARV-VMB is still very much a female prevention tool. Successful control measures that restrict ARV-VMB usage by HIV-positive women will reduce significantly the risk of resistance development and further increase the likelihood of female advantage in ARV-VMB-prevented infections. Man and woman benefits will be roughly the same only if ARV-VMB is introduced without any HIV monitoring combined with an ARV-VMB inducing a very high rate of systemic absorption, an unlikely scenario for a wide-scale intervention. A ARV-VMB intervention will reduce HIV-incidence regardless which gender has an advantage in benefits but the male advantage in most case is not desirable only because it correlates with high prevalence of drug-resistance among HIV-positive population.

A Intervention schedules and scenarios

In out “primary” analysis we simulate ARV-VMB interventions in 63 distinct scenarios assuming different introduction schedules and different levels of PreC, PostC, and r_{SA} . The “secondary” analysis consists of 2 scenarios assuming fast introduction schedules and no PreC and PostC. The list of all scenarios with their characteristics is presented in Table 2.

The abbreviation of the scenarios (AbXYZ) should be read as follows: (A) denotes the parameter set used - primary (P) or secondary (S); (b) denotes the introduction schedule - slow (s), intermediate (i), or fast (f); (X,Y,Z) represent levels of PostC, PreC, and r_{SA} used - no (0), low/moderate (1), or high/strict (2). For each scenarios we simulate 1000 ARV-VMB interventions using parameters which are uniformly sampled from their “primary” or “secondary” ranges.

B Model's Description

We use a deterministic model of HIV transmission and disease progression in population of heterosexually active individuals to analyze the gender benefits of ARVVMB interventions. The flow diagram of the model is presented in Figure 1. The mathematical model is described by the following system of equations:

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

where S_m , S_w , and S_w^p represent susceptible men, susceptible women not using ARV-VMB, and susceptible women using ARV-VMB, respectively, I_w^p (I_{rw}^p) are the HIV-positive women using ARV-VMB infected with the wild (drug-resistant) strain, I_w (I_{rw}) are the HIV-positive women not using VMB infected with the wild (drug-resistant) strain, I_m (I_{rm}) are the HIV-positive men infected with the wild (drug-resistant) strain, respectively, and A_w (A_m) accumulates all infected women (men) who develop AIDS and are not sexually active. Entry rates Λ_w and Λ_m in men and women are assumed to preserve the size of a HIV-free population, i.e., $\Lambda_w = \mu N_w$ and $\Lambda_m = \mu N_m$. The rate of resistance development r is a product of the maximum rate of resistance development r_{max} and the probability of systemic absorption r_{SA} , i.e., $r = r_{max} r_{SA}$. The rates at which men and women acquire HIV-infection, i.e., forces of infections for different classes are derived from standard binomial models based on the number of partners per susceptible person, the number of sex acts per partnership, and the transmission probability per sex act for partners from different classes:

$$\begin{aligned}
 \lambda_w^p &= \rho_w \left(1 - (1 - (1 - \alpha_s) \beta_w)^{n_w/\rho_w} \right) \frac{I_m}{N_m} \\
 \lambda_{rw}^p &= \rho_w \left(1 - (1 - \alpha_r (1 - \alpha_s) \beta_w)^{n_w/\rho_w} \right) \frac{I_{rm}}{N_m} \\
 \lambda_w &= \rho_w \left(1 - (1 - \beta_w)^{n_w/\rho_w} \right) \frac{I_m}{N_m} \\
 \lambda_{rw} &= \rho_w \left(1 - (1 - \alpha_r \beta_w)^{n_w/\rho_w} \right) \frac{I_{rm}}{N_m} \\
 \lambda_m &= \rho_m \left(1 - (1 - \beta_m)^{n_m/\rho_m} \right) \frac{I_w}{N_w} + \rho_m \left(1 - (1 - (1 - \alpha_i) \beta_m)^{n_m/\rho_m} \right) \frac{I_w^p}{N_w} \\
 \lambda_{rm} &= \rho_m \left(1 - (1 - \alpha_r \beta_m)^{n_m/\rho_m} \right) \frac{I_{rw}}{N_w} + \rho_m \left(1 - (1 - \alpha_r (1 - \alpha_i) \beta_m)^{n_m/\rho_m} \right) \frac{I_{rw}^p}{N_w}
 \end{aligned} \tag{2}$$

where $N_w = S_w^p + S_w + I_w^p + I_w + I_{rw}^p + I_{rw}$ and $N_m = S_m + I_m + I_{rm}$ represent the sexually active women and men in the population, respectively.

Biological meaning and ranges of all parameters are given in Table 3. The model assumes 100% adherence to the product, i.e., the VMB users apply the product regularly without interruption. This is not a strong limitation since lower adherence level can be simulated by reduction in the VMB efficacy.

Each ARV-VMB intervention is introduced in a population with $N_w(0) = N_m(0) = 1,000,000$ and equal HIV-prevalence (P) in men and women. Initial distribution of the epidemic classes is set as follow:

$$\begin{aligned} S_w^p(0) &= k_1 (1 - P) N_w(0) \\ S_w(0) &= (1 - k_1) (1 - P) N_w(0) \\ S_m(0) &= (1 - P) N_m(0) \\ I_w^p(0) &= (1 - \theta) k_1 P N_w(0) \\ I_w(0) &= (1 - (1 - \theta) k_1) P N_w(0) \\ I_m(0) &= P N_m(0) \\ I_{rw}^p(0) &= I_{rw}(0) = I_{rm}(0) = 0. \end{aligned} \quad (3)$$

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Figure 1.

Flow diagram of the deterministic model of HIV transmission and disease progression in presence of a ARV-VMB intervention in heterosexual population divided in men (subscript m), women using ARV-VMB (subscript w , superscript p), and women not using ARV-VMB (subscript w) stratified as susceptible (S), infected with a wild-type HIV (I), infected with a resistant-type HIV (I_r), or in AIDS state (A). Forces of the infection (λ_w^p , λ_{rw}^p , λ_w , λ_{rw} , λ_m , and λ_{rm}) are described in Appendix B.

Figure 2.

Dynamics of the effective coverage of a ARV-VMB intervention over time defined as a proportion of the female population using VMB. The simulation assumes asymptotic coverage $k = 40\%$ and represents different introduction schedules - slow ($k_1 = 0$), intermediate ($k_1 = k/2$), and fast ($k_1 = k$).

Figure 3.

Temporal dynamics of the quantitative indicators $C_I(T)$, $F_I(T)$, and $F_P(T)$ for intermediate interventions with high $r_{SA} = 0.7$ and no PostC. Assumed A) strict ($\theta = 0.8$) and B)-C) no ($\theta = 0$) PreC. The “primary” values used in A)-B) are $\beta_m = 0.0038$, $\beta_w = 0.003$, and $\mu = 1/35$ while the “secondary” values in C) are $\beta_m = 0.00127$, $\beta_w = 0.001$, and $\mu = 2/35$. All other parameters remain fixed at values: $k = 0.6$, $a_s = a_i = 0.5$, $a_r = 0.2$, $r_{max} = 1$, $d = d_r = 0.1$, $P = 0.2$, $n_w = n_m = 125$, and $\rho_w = \rho_m = 1.2$.

Figure 4.

Cumulative distribution functions (i.e. fraction of all simulations where the indicator is less than the value on the x-axis) of the quantitative indicators $C_I(T)$, $F_I(T)$, and $F_P(T)$ over periods of 10 and 20 years, for the 63,000 simulations included in the “primary” analysis. The black vertical lines indicate the points where the male and the female benefits are equal. Dotted lines separate regions where one of the genders receives more than double the benefits of the other from the simulated VMB interventions

Figure 5.

Percentage of 1,000 simulations per scenario that predict a male advantage in prevented fractions ($F_I(T)$), over periods of 10 and 20 years for A) bidirectional (reduce both susceptibility and infectiousness of ARV-VMB users) and B) unidirectional (only reduce susceptibility) ART-VMB interventions. Boxplots represent 5, 25, 50, 75, and 95 percentiles in the distribution of $F_I(10)$ for each scenario. The horizontal lines indicate the level at which the likelihood for male advantage is 50% (right scale) and the male and the female benefits are equal (left scale). In C): Comparison of the median fraction of prevented infections and the prevalence of drug-resistance among the HIV-positive population over a period of 10 years. The abbreviation of the scenarios (AbXYZ) should be read as follows: (A) denotes the parameter set used - primary (P) or secondary (S); (b) denotes the introduction schedule - slow (s), intermediate (i), or fast (f); (X,Y,Z) represent levels of PostC, PreC, and r_{SA} used - no (0), low/moderate (1), or high/strict (2). The highlighted “primary” scenarios are comparable to the “secondary” scenarios by introduction schedule, resistance risk and control levels.

Figure 6.

Contour plots of the quantitative indicator $F_I(T)$ in the domain of pre- and post-control levels assuming fast introduction of ARV-VMB and high risk of systemic absorption $r_{SA} = 0.5$ over periods of A) 5 years, B) 10 years, and C) 20 years. All other parameters remain fixed at values: $k = 0.7$, $\alpha_s = 0.4$, $\alpha_i = 0.6$, $\alpha_r = 0.2$, $\beta_m = 0.0038$, $\beta_w = 0.003$, $r_{max} = 1$, $\mu = 1/35$, $d = d_r = 0.1$, $P = 0.2$, $n_w = n_m = 125$, and $\rho_w = \rho_m = 1.2$. $F_I(T)$ in excess of one (shaded region) indicates male advantage.

Figure 7.

Partial rank correlation coefficients (PRCC) between input parameters and quantitative indicators $C_I(T)$, $F_I(T)$, and $F_P(T)$ for the scenario (Pf112) of fast introduction of VMB with high r_{SA} and moderate PreC and PostC.

Table 1

Selected Phase II/III double-blinded trials of VMB products

Product	Study characteristics			Period	Results RR (95%CI)
	Design (Endpoints needed)	Sample size (endpoints observed)	Population		
Surfactants:					
Nonoxonyl-9, 70 mg [9]	Phase III 2 arms (88)	1170 (94)	18-45 yrs, FSW ⁷	1994-1996	1.0 (0.7-1.5)
Nonoxonyl-9, 52.5 mg (Col-1492) [10]	Phase II/III 2 arms (100)	1005 (104)	FSW ⁷	1996-2000	1.5 (1.0-2.2)
C31G, 1% (Savvy) [11]	Phase III 2 arms (66)	2153 (33) ¹	18-35 yrs ⁷	2004-2006	1.7 (0.9-3.5)
C31G, 1% (Savvy) [12]	Phase III 2 arms (66)	2142 (17) ¹	18-35 yrs ⁷	2004-2006	0.88 (0.33-2.27)
Viral entry inhibitor:					
Carrageenan (Carraguard/PC515) [13]	Phase III 2 arms (194)	6202 (285)	older than 16 yrs ⁷	2004-2007	0.87 (0.69-1.09)
Cellulose sulfate 6% (Ushercell) CONRAD [14]	Phase III 2 arms (66)	1398 (41) ²	older than 18 yrs ⁷	2005-2007	1.61 (0.86-3.01)
Cellulose sulfate 6% (Ushercell) [15]	Phase III 2 arms (66)	1644 (23) ³	18-35 yrs ⁷	2004-2007	0.8 (0.3-1.8)
Naphthalen sulfonate (PRO2000 0.5%)-HPTN-035 [16]	Phase II/IIb 4 arms ⁴ (192)	3009 (194)	sexually active ⁷	2005-2008	0.7 ⁵ (0.46-1.08)
Naphthalen sulfonate (PRO2000 0.5%)-MDP-301 [17]	Phase III 3 arms ⁸	9385 (374)	sexually active ⁷	2005-2009	0.67 ⁶ (0.44-1.02)
Naphthalen sulfonate (PRO2000 2%)-MDP-301 [17]	Phase III 3 arms ⁸	9385 (374)	sexually active ⁷	2005-2008	1.11 (0.82-1.51)
Vaginal defense enhancer:					
Carbopol 974P- HPTN-035 (BufferGel) [16]	Phase II/IIb 4 arms ⁴ (192)	3009 (194)	sexually active ⁷	2005-2008	1.1 ⁵ (0.77-1.62)
					1.05 ⁶ (0.72-1.55)

¹ stopped early - low incidence

² stopped early - harm

³ stopped early due to CONRAD trial results

- ⁴ Arms: PRO2000, BufferGel, placebo-gel, no gel
- ⁵ Product vs. placebo-gel
- ⁶ Product vs. no gel
- ⁷ Enrolment criteria vary among trials
- ⁸ Arms: PRO2000 0.5%, PRO2000 2%, placebo-gel. PRO2000 2% was discontinued in Feb 2008.

Table 2

Intervention scenarios

Name	PostC	PreC	r_{SA}	Name	PostC	PreC	r_{SA}	Name	PostC	PreC	r_{SA}
<i>A. Primary scenarios assuming slow introduction schedule:</i>											
Ps000	no	n/a	no	Ps001	no	n/a	low	Ps002	no	n/a	high
Ps100	mod.	n/a	no	Ps101	mod.	n/a	low	Ps102	mod.	n/a	high
Ps200	strict	n/a	no	Ps201	strict	n/a	low	Ps202	strict	n/a	high
<i>B. Primary scenarios assuming intermediate introduction schedule:</i>											
Pi020	no	strict	no	Pi021	no	strict	low	Pi022	no	strict	high
Pi120	mod.	strict	no	Pi121	mod.	strict	low	Pi122	mod.	strict	high
Pi220	strict	strict	no	Pi221	strict	strict	low	Pi222	strict	strict	high
Pi010	no	mod.	no	Pi011	no	mod.	low	Pi012	no	mod.	high
Pi110	mod.	mod.	no	Pi111	mod.	mod.	low	Pi112	mod.	mod.	high
Pi210	strict	mod.	no	Pi211	strict	mod.	low	Pi212	strict	mod.	high
Pi000	no	no	no	Pi001	no	no	low	Pi002	no	no	high
Pi100	mod.	no	no	Pi101	mod.	no	low	Pi102	mod.	no	high
Pi200	strict	no	no	Pi201	strict	no	low	Pi202	strict	no	high
<i>C. Primary scenarios assuming fast introduction schedule:</i>											
Pf020	no	strict	no	Pf021	no	strict	low	Pf022	no	strict	high
Pf120	mod.	strict	no	Pf121	mod.	strict	low	Pf122	mod.	strict	high
Pf220	strict	strict	no	Pf221	strict	strict	low	Pf222	strict	strict	high
Pf010	no	mod.	no	Pf011	no	mod.	low	Pf012	no	mod.	high
Pf110	mod.	mod.	no	Pf111	mod.	mod.	low	Pf112	mod.	mod.	high
Pf210	strict	mod.	no	Pf211	strict	mod.	low	Pf212	strict	mod.	high
Pf000	no	no	no	Pf001	no	no	low	Pf002	no	no	high
Pf100	mod.	no	no	Pf101	mod.	no	low	Pf102	mod.	no	high
Pf200	strict	no	no	Pf201	strict	no	low	Pf202	strict	no	high
<i>D. Secondary scenarios assuming fast introduction schedule:</i>											
Sf001	no	no	low	Sf002	no	no	high				

Table 3

Ranges of biological and intervention parameters

Param.	Description	Parameter ranges		Refs.
		Primary	Secondary	
A. Biological parameters in absence of VMB:				
β_w	Man-to-woman transmission probability per act	0.0014-0.0063	0.0008-0.00i8	[20, 19]
β_m	Woman-to-man transmission probability per act	0.0013-0.011	0.0005-0.00i5	[20, 19]
$1/\mu$	Average time (in years) to remain sexually active	30-40	2-20	[40, 5, 19]
d, d_r	Per capita annual rates of progression to AIDS of people infected with wild- and resistant-type HIV	1/12-1/7	1/12-1/7	[41, 42, 19]
P	Initial HIV-prevalence in both men and women	0.15-0.30	0.01-0.60	[5, 19]
n_w, n_m	Average number of sexual contacts per year for women and men	100-150	60-150	[43, 19]
ρ_w, ρ_m	Average number of sexual partners per year for women and men	0.5-1.5	0.5-1.5	[43, 19]
R_0	Range of basic reproduction number in absence of VMB	0.8066-6.8786	0.0725-1.1904	calculated
B. Intervention parameters:				
k	Fraction of the women entering the population who decide to use VMB	0-1	0-1	exp. var. [19]
α_s, α_i	VMB efficacy in reducing susceptibility and infectiousness	0-0.90	0-0.90	exp. var. [19]
a_r	Relative transmissibility of drug-resistant HIV compared to wild HIV	0.05-0.5	0.05-0.5	exp. var. [19]
r_{max}	Maximum annual rate of resistance development for HIV-positive woman using VMB	0-2	0-2	exp. var. [19]
C. Parameters which determine intervention schedules and scenarios:				
k_1	Fraction of the initial female population who decide to use VMB	0 (slow), $k/2$ (intermediate), k (fast [*])		
r_{SA}	Risk of systemic absorption of VMB per application	0% (no risk), 1-5% (low risk [*]), 50-90% (highrisk [*])		
θ	Pre-introduction control (PreC). Reduction in the initial fraction of HIV-positive women who decide to use VMB	0% (no control [*]), 30-50% (moderate control), 80-100% (strict control)		
$1/\delta$	Post-introduction control (PostC). Duration of continuous usage of VMB by HIV-positive women	for life (no control [*]), 3-5 yrs (moderate control), 1-2 yrs (strict control)		

* The scenarios included in the “secondary” analysis assume fast VMB introduction with low and high risk of systemic absorption (r_{SA}) and no PreC and PostC.