

The paradoxical effects of using antiretroviral-based microbicides to control HIV epidemics

David P. Wilson*, Paul M. Coplan†, Mark A. Wainberg‡, and Sally M. Blower§¶

*National Centre in HIV Epidemiology and Clinical Research, Faculty of Medicine, University of New South Wales, Level 2, 376 Victoria Street, Sydney NSW 2010, Australia; †Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, 423 Guardian Drive, Philadelphia, PA 19104; ‡McGill University AIDS Centre, Jewish General Hospital, 3755 Côte-Ste.-Catherine Road, Montreal, QC, Canada H3T 1E2; and §Semel Institute for Neuroscience and Human Behavior and UCLA AIDS Institute, David Geffen School of Medicine, University of California, Los Angeles, CA 90095

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Vaginal microbicides, designed to prevent HIV infection in women, are one of the most promising biomedical interventions. Clinical trials of second-generation microbicides have begun; if shown to be effective, they could be licensed within 5–10 years. Because these microbicides contain antiretrovirals (ARVs), they could be highly effective. However, there is concern that, if used by HIV-positive women, ARV resistance may evolve. By analyzing a mathematical model, we find that adherence could have both beneficial and detrimental effects on trial outcomes. Most importantly, we show that planned trial designs could mask resistance risks and therefore enable high-risk microbicides to pass clinical testing. We then parameterize a transmission model using epidemiological, clinical, and behavioral data to predict the consequences of wide-scale usage of high-risk microbicides in a heterosexual population. Surprisingly, we show that reducing a participant's risk of resistance during a trial could lead to unexpectedly high rates of resistance afterward when microbicides are used in public health interventions. We also find that, paradoxically, although microbicides will be used by women to protect themselves against infection, they could provide greater benefit to men. More infections in men than in women will be prevented if there is a high probability that ARVs are systemically absorbed, microbicides are less than ~50% effective, and/or adherence is less than ~60%. Men will always benefit more than women in terms of infections prevented per resistant case; but this advantage decreases as the relative fitness of drug-resistant strains increases. Interventions that use ARV-based microbicides could have surprising consequences.

drug resistance | male advantage threshold | vaginal microbicides | mathematical model | HIV

Vaginal microbicides are being designed to prevent HIV infection of immune system cells and cervicovaginal tissue (1–3). They are currently considered to be one of the most promising biomedical interventions for preventing heterosexual transmission. Because the majority of the ~3 million HIV infections that occur each year are in women (4, 5), effective female-initiated prevention methods are urgently needed. Second-generation microbicides, containing antiretrovirals (ARVs), are now being tested for efficacy in phase III clinical trials [supporting information (SI) Table S1]. A microbicide gel containing tenofovir, a nucleotide reverse transcriptase inhibitor, will be the first to be tested for efficacy. This will be closely followed by a microbicide containing dapivirine, which belongs to the nonnucleoside reverse transcriptase inhibitor (NNRTI) class of ARVs (6); trial results will be available in 2010. Three other ARV-based microbicides, containing NNRTIs, are in earlier-phase trials (3, 5, 7–10). ARV-based microbicides are anticipated to be highly effective; however, there is concern that, if used by HIV-positive women, class-specific drug resistance may emerge. Here, we construct a mathematical model of a phase III clinical trial of an ARV-based microbicide. We use it to determine whether ARV-based microbicides that could potentially generate moderate to high levels of resistance (which we define as high-risk microbicides) could pass clinical testing. We then construct a mathematical model of heterosexual transmission and parameter-

ize it using epidemiological, clinical, and behavioral data. We use this model to predict the gender-specific epidemiological impact of wide-scale usage of high-risk and low-risk microbicides, where low-risk microbicides would only generate low levels of resistance.

Our distinction between high-risk and low-risk microbicides is in the probability that the ARVs contained in the microbicides will be systemically absorbed and subsequently have the potential to select for the emergence of drug-resistant strains of HIV. Currently, it is unknown whether ARV-based microbicides will be low-risk or high-risk. Increasing levels of systemic absorption of the ARV contained in the microbicide increase the possibility of drug resistance emerging. Assuming that ARV-based microbicides will be low-risk is reasonable because systemic absorption has not been found in phase I trials of intravaginal application of ARV-based microbicides (e.g., tenofovir, UC-781, and TMC-120) (3, 11, 12). However, assuming that they will be high-risk is also reasonable because the vagina is highly permeable (13–16) and is often an ideal route for drug administration (17–21). Hence, in all of our analyses, we investigate the potential impact of both types of microbicides.

We begin by constructing a mathematical model of a phase III efficacy trial of an ARV-based microbicide. Our model is constructed to match the original design of the dapivirine trial, which is a 12-month, two-arm, placebo-controlled, double-blind trial of ~10,000 women who are at high risk of HIV infection (e.g., female sex workers) with an average annual pretrial incidence of ~5%. The dapivirine trial protocol is once-daily application of microbicide regardless of the number of daily sex acts. This protocol will be used because it is expected that the concentration of dapivirine will be sustained over a 24-h period. Trial participants will be monitored for adherence throughout the trial. To conduct an ethical trial that will protect participants from acquiring drug resistance, they will be checked monthly for seroconversion using rapid testing with results available 10–15 min afterward. Seroconverters will be excluded from the trial to reduce their likelihood of developing drug resistance. However, the rapid tests are not highly sensitive to early detection because the test is based on HIV antibodies; therefore, there will be a 3- to 12-week window/lag period between when an individual becomes infected and when the test can detect their infection. Therefore, rapid testing will not detect early-stage seroconverters who will, because of their microbicide usage, be at risk of acquiring ARV resistance. Hence, even monthly testing may not prevent some seroconverters from acquiring drug resistance.

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¶To whom correspondence should be addressed. E-mail: sblower@mednet.ucla.edu.

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The timing of seroconversion will need to be accounted for when the trial results are analyzed.

Our clinical trial model enables us to track participants (separately in the placebo and microbicide arms) in four states: uninfected with HIV (state 1); recently infected with wild-type strains of HIV but with an undetectable infection (state 2); infected with detectable levels of wild-type strains of HIV (state 3); and infected with detectable levels of NNRTI-resistant virus (state 4). At the beginning of the trial all participants are in state 1. When the model is used to simulate a trial some participants in both arms of the trial (because the microbicide is not 100% effective) become infected and move from state 1 to state 2. Participants who are in the microbicide arm of the trial and in state 2 are not detected as seroconverters and are therefore at risk of acquiring resistance; hence, some HIV-infected participants who continue to use ARV-based microbicides acquire class-specific drug-resistant HIV and move directly to state 4. The remaining individuals in state 2 in the microbicide arm and all of the individuals in the placebo arm move to state 3 after 3–12 weeks. The model includes testing all participants for seroconversion and subsequent exclusion of seroconverters; seroconverters who are excluded are either in state 3 or state 4. It is assumed that before the trial participants either use condoms or no protection. We then allow participants in the microbicide arm of the trial to use one of four protection options: condoms, microbicides, condoms plus microbicides, or no protection (22). Each of the four options provides a different level of protection against infection; see *SI Text* for how these protection options are modeled. The model allows participants in the placebo arm to only use one of two protection options: condoms or no protection. Condom use during the trial is assumed not to change. The possibility of participants dropping out of the trial is also included. Further description of the model is given in *Materials and Methods*, *SI Text* (section 2.1), and *Fig. S1*.

We used our clinical trial model to calculate the number of infections prevented and the number of participants who acquire drug resistance. We conducted two analyses, assuming that microbicides could be either low-risk or high-risk. For each of these analyses, we conducted 10,000 Monte Carlo simulations (23, 24) (see *Materials and Methods* and *SI Text* for further details). To conduct our simulations, we sampled ranges for all parameters rather than using point estimates; clinical data guided the estimation of any unknown parameters [see *Table S2* and *SI Text* (section 2.2)]. This procedure allowed us to include estimation uncertainty and also use certain model parameters as experimental variables. The parameter that determined the risk level of the microbicides (i.e., the probability of systemic absorption) was varied from 0.01 to 0.03 for low-risk microbicides and from 0.5 to 0.9 for high-risk microbicides. Because the biological properties of ARV-based microbicides are unknown, we also varied two other parameters: (i) their clinical efficacy (i.e., the degree of protection that they will provide against HIV infection) (range 50–90%), and (ii) the length of time that it would take an HIV-infected women to acquire NNRTI resistance if the ARV is systemically absorbed (range 6 months to never). We also sampled adherence rates ranging from 0% to 100%, with 100% adherence signifying that microbicides are used daily [see *SI Text* (*Table S2*)]. To assess the potential impact of testing frequency on the number of cases of acquired resistance, we varied this parameter from weekly, fortnightly, monthly, every two months, every three months, every four months, every six months, to only once at the end of the trial (i.e., after 12 months).

If microbicides are used in public health interventions and become widely available, they may be used by HIV-positive women who are unaware that they are infected. These HIV-positive women will be at risk of acquired resistance, and men will subsequently be at risk of transmitted resistance. We therefore constructed an epidemic model of heterosexual transmission and predicted, over a 10-year period, the potential gender-specific epidemiological impact of public health interventions

based on using either low-risk or high-risk microbicides. Each analysis consisted of 10,000 Monte Carlo simulations (23, 24). Our model tracks men in three states: susceptible, infected with wild-type virus, or infected with NNRTI-resistant virus. It separately tracks two groups of women: women who use microbicides and women who choose not to use microbicides. Each group of women can also be in one of the three states: susceptible, infected with wild-type virus, or infected with NNRTI-resistant virus. By tracking these nine states, we model both acquired and transmitted resistance. In our model, the women who are using microbicides and are infected with wild-type strains can develop acquired resistance (i.e., become infected with NNRTI-resistant strains). NNRTI-resistant strains can then be transmitted from women infected with NNRTI-resistant strains to uninfected men, and from men infected with NNRTI-resistant strains to uninfected women. Our model structure also allows us to vary the coverage rate (i.e., the proportion of women using microbicides), adherence (for women using microbicides), and the relative fitness of NNRTI-resistant strains [see *Materials and Methods*, *SI Text* (section 3.1), *Fig. S6*, and *Table S3* for a more detailed model description]. We used the model to predict the cumulative number of infections prevented, the incidence of transmitted resistance, the prevalence of resistance, and the cumulative number of infections prevented per resistant case. To make our predictions, we assumed that there would be no wide-scale, population-level surveillance and testing for seroconversion and resistance.

We parameterized our model using clinical, behavioral, and epidemiological data [see *SI Text* (section 3.2) and *Table S3*]. Microbicides were characterized by the same parameter ranges as in the clinical trial model, but in addition we included a fourth characteristic: clinical efficacy in protecting men against HIV infection. ARV-based microbicides are currently only being evaluated for efficacy in protecting women. However, it is biologically plausible that they may, by reducing viral loads in cervical-vaginal fluid in infected woman, protect men (to some degree) from infection (i.e., they may have clinical efficacy in protecting men who have sex with HIV-infected women). Clinical efficacy for each gender was treated as an experimental variable, varied between 0% and 90% and sampled independently [see *SI Text* (section 3.2) and *Table S3*].

Results

Our results show that the same number of infections will be prevented during a clinical trial regardless of whether the dapivirine-based microbicide (or any subsequently tested microbicide) is high-risk or low-risk (*Table 1*). Not surprisingly, the clinical efficacy of microbicides is the main determinant of the number of infections prevented (see *Figs. S3* and *S4*). However, the adherence rate is also extremely important in preventing infections; high rates will be extremely beneficial (*Fig. 1A*). Only 36 [median value; interquartile range (IQR) 11–100] infections will be prevented by the end of the dapivirine trial if adherence is ~50% (median value; range 0–100%) (*Table 1*), but 133 (median value; IQR 96–171) infections will be prevented if adherence is 100%. We find that testing monthly for seroconversion (as planned for the dapivirine trial) will prevent the same number of infections as any other testing frequency.

Although high adherence will have a beneficial effect by preventing many infections (*Fig. 1A*), it could also have a very detrimental effect (if high-risk microbicides are evaluated) by generating a large number of resistant cases (*Fig. 1B*). The number of cases of acquired resistance that will develop during the dapivirine trial will mainly be determined by whether it (or any subsequently tested ARV-based microbicide) is high-risk or low-risk (*Table 1* and *Fig. S5*), but high-risk microbicides will also be strongly affected by adherence (*Fig. 1B*). If adherence is high then a high-risk microbicide could generate many resistant cases

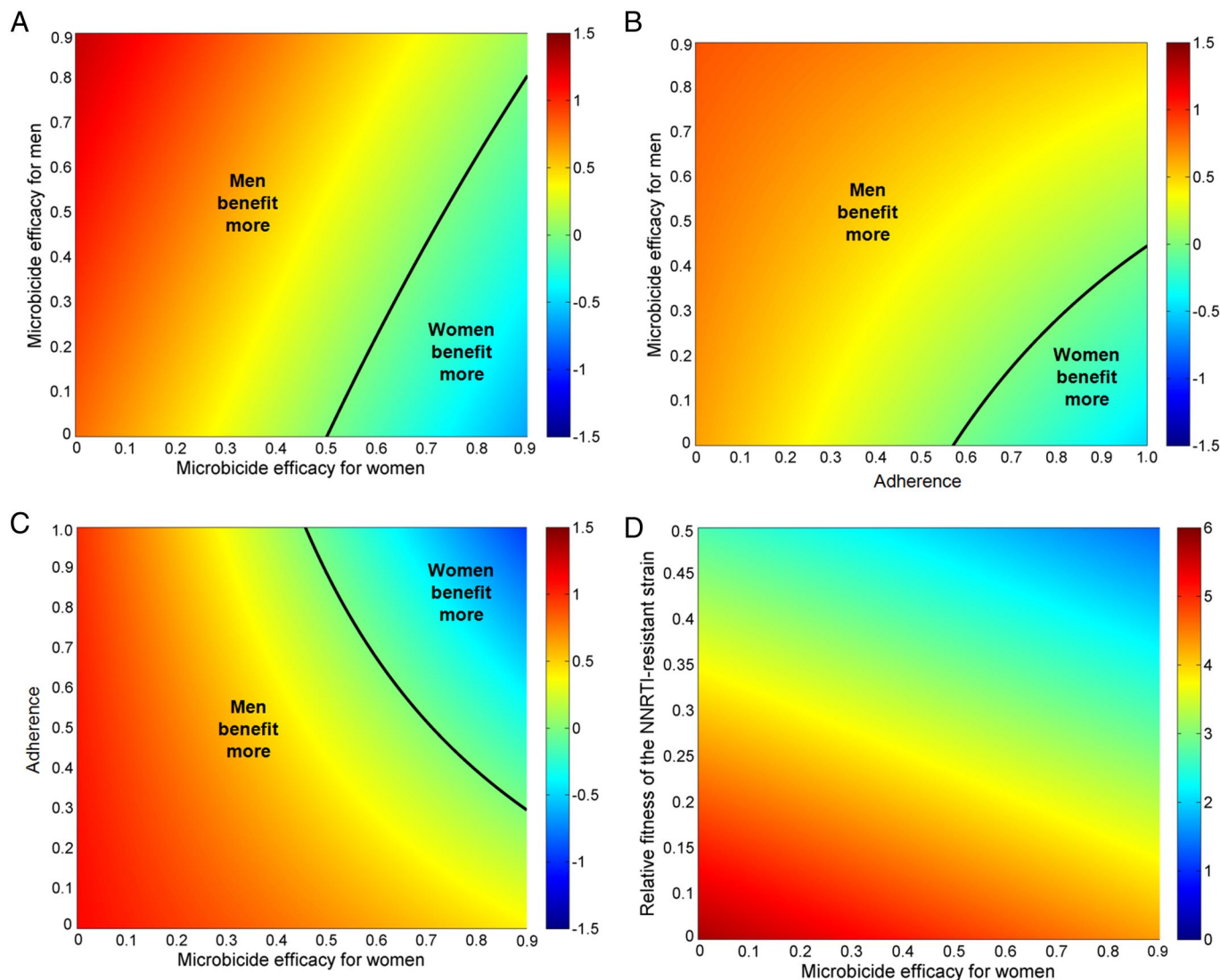


Fig. 2. Nonlinear response surfaces with interaction terms, constructed from data generated from our epidemic model of heterosexual transmission with high-risk NNRTI microbicides used in public health interventions. The black curve delimits the male advantage threshold (MAT), where the ratio (men to women) of the cumulative number of infections prevented (RNIP) is 1; above this curve, microbicides are more beneficial for men than for women (i.e., $RNIP > 1$). Response surfaces for the degree of benefit for men over women in terms of the RNIP, on a \log_2 scale, are presented as a function of efficacy in protecting men against HIV infection versus efficacy in protecting women against HIV infection (A), efficacy in protecting men against HIV infection versus adherence (B), and adherence versus efficacy in protecting women against HIV infection (C). (D) Response surface for the ratio (men to women) of infections prevented per NNRTI-resistant case (on \log_2 scale) as a function of the relative fitness of the NNRTI-resistant strain and efficacy of the microbicide in preventing HIV infection in women.

NNRTIs are likely to be absorbed from microbicides at different rates, and they should be well characterized before marketing authorization. It is also possible, but unlikely, that selection for resistance could occur in the vaginal cavity, and that systemic absorption would not be necessary. ARV-based microbicides, like any therapeutic product, may cause other adverse events apart from resistance that should also be monitored. They should also be evaluated during clinical trials to determine whether they show differential effectiveness against different HIV subtypes (29).

ARV-based microbicides protect against HIV infection by averting transmission in a similar manner as preexposure prophylaxis (PrEP). PrEP, based on a combination of tenofovir and another NRTI, emtricitabine, is currently being tested in clinical trials (30). It is currently unknown how effective PrEP will be, and it could be possible that people will use PrEP and microbicides simultaneously to increase effectiveness. There are some similarities between ARV-based microbicides and PrEP. For

individuals using either of these protection options, drug-resistance may develop and so second- or third-line drug regimes could be required for therapy. Public health interventions based on PrEP could have similar population-level consequences for resistance as ARV-based microbicides and may also have some similar gender-specific differences. Important issues for both protection options include the responsibility to prevent secondary spread of drug-resistant infection and the need for frequent medical monitoring. However (unlike with condoms), it may well be possible to achieve high coverage and adherence to microbicides and/or PrEP because these interventions may be more acceptable to partners (27, 31). The cost-effectiveness of scaling up either intervention, which is currently unknown, will also be an important consideration in their public health assessment. The relative efficacies and expected adherence levels of both of these interventions will be crucial in evaluating their potential effectiveness and acceptability; these factors are still to be determined.

We have shown that even if ARV-based microbicides are high-risk and only moderately efficacious, they could reduce HIV incidence. Currently, only condoms and male circumcision are available for protection, and both are highly effective but not widely used. Therefore, the potential combined benefit of male circumcision, and/or condoms, together with the usage of microbicides could substantially reduce rates of heterosexual transmission. However, ARV-based microbicides could lead to relatively high levels of ARV resistance arising. Therefore, we recommend that careful and regular population-level monitoring occur to monitor for resistance if, and when, ARV-based microbicides are used in public health interventions. Our results imply that monitoring for resistance should occur when PrEP is widely used. However, it is important to note that if resistance does emerge as a result of either ARV-based microbicides or PrEP, the strains that will evolve will only be resistant to the specific class of drugs in the products (3, 32). Susceptibility to other classes of ARVs will be unaffected, and hence therapeutic options for the individuals who acquire resistance will be reduced but not eliminated. In addition, recently approved second-generation NNRTI drugs retain efficacy against most HIV variants that are resistant to first-generation NNRTI drugs (33, 34). Other ARV-based microbicides could use different classes of drugs such as entry inhibitors, CCR5 antagonists, such as the Rantes derivatives, have the potential to be highly cost-effective and less likely to select for resistance (35, 36).

Obviously, it is advantageous for microbicides to prevent infections in both men and women. However, vaginal microbicides are being developed for preventing infections in women and to empower women, particularly in resource-constrained countries. They are a prevention tool that can only be used by women. Nevertheless, we have found that ARV-based microbicides may, under certain conditions, benefit men more than

women. Whether this will occur will be determined by (i) the degree to which women adhere to microbicides, (ii) microbicide efficacy, and (iii) the viral fitness of drug-resistant strains. It is paradoxical that men may benefit more than women because of the development of effective microbicides; this paradoxical effect will be exacerbated if high-risk microbicides are used. We predict, therefore, that the population-level consequences of public health interventions that use ARV-based microbicides could well be surprising.

Materials and Methods

We constructed clinical trial and epidemic-level mathematical models. For the clinical trial model, we tracked 10,000 women (female sex workers) at high risk of HIV infection in both a microbicide arm and a placebo-control arm; the pretrial average annual incidence was 5%. HIV transmission rates were calculated according to per sex act transmission probabilities, the number of vaginal sex acts per partner, the average number of new sex partners per year, the protection afforded by condoms and microbicides, and the proportion of acts in which each protection type is used. These factors were incorporated into a mechanistic binomial formulation (37) to calculate the cumulative transmission probability per woman over the duration of the trial; see *SI Text* (section 2.1) for model equations and further description.

We also constructed an epidemiological model of heterosexual transmission in a high prevalence resource-constrained community where ARV-based microbicides are used in a public health intervention. The model is described by a system of nine ordinary differential equations [see *SI Text* (section 3.1), *Fig. S6*, and *Table S3*]. To identify maximum beneficial and detrimental effects, we modeled the introduction of microbicides into a treatment-naïve population without ambient resistance, and we did not include the possibility of large-scale testing for HIV infection.

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