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Predicting the Impact of a Partially Effective HIV Vaccine and Subsequent Risk Behavior Change on the Heterosexual HIV Epidemic in Low- and Middle-Income Countries *A South African Example*

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Summary

We developed a mathematical model to simulate the impact of various partially effective preventive HIV vaccination scenarios in a population at high risk for heterosexually transmitted HIV. We considered an adult population defined by gender (male/female), disease stage (HIV-negative, HIV-positive, AIDS, and death), and vaccination status (unvaccinated/vaccinated) in Soweto, South Africa. Input data included initial HIV prevalence of 20% (women) and 12% (men), vaccination coverage of 75%, and exclusive male negotiation of condom use. We explored how changes in vaccine efficacy and post-vaccination condom use would affect HIV prevalence and total HIV infections prevented over a 10-year period. In the base-case scenario, a 40% effective HIV vaccine would avert 61,000 infections and reduce future HIV prevalence from 20% to 13%. A 25% increase (or decrease) in condom use among vaccinated individuals would instead avert 75,000 (or only 46,000) infections and reduce the HIV prevalence to 12% (or only 15%). Furthermore, certain combinations of increased risk behavior and vaccines with <43% efficacy could worsen the epidemic. Even modestly effective HIV vaccines can confer enormous benefits in terms of HIV infections averted and decreased HIV prevalence. However, programs to reduce risk behavior may be important components of successful vaccination campaigns.

Keywords

AIDS vaccines; mathematical models; sexual behavior; heterosexual transmission; Africa; condoms; models/projections

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Despite a lack of success in HIV vaccine development to date,¹ there are 35 HIV vaccine candidates currently progressing through various clinical trials around the world and many more in development.² Because of the scientific challenges in vaccine design,³ clinical trials are using a minimum efficacy value of 30% for evaluating the effectiveness of potential vaccine candidates.⁴ Given the urgent need for an HIV vaccine, vaccines with only partial efficacy are likely to be used initially in populations at high risk for HIV infection.⁵ The potential for post-vaccination risk-taking behavior to increase poses a significant threat to the successful use of partially effective vaccines in future vaccination programs.^{5–8} Individuals might increase their risk-taking behavior, assuming they are completely protected from HIV when, in reality, they might have only limited protection or none at all.^{9–14}

Models have shown that even a partially effective HIV vaccine with minimal efficacy could have an enormous population impact on the HIV epidemic in high-risk groups or areas with a high prevalence of HIV, such as sub-Saharan Africa,^{15–22} but that the magnitude of this impact depends on a fine balance between the efficacy of the vaccine, the vaccine coverage level, and the change in risky behavior.^{18,20,23–27} Although decreases in individual risk behavior would augment the population benefits of such vaccination programs in terms of HIV infections prevented, increases in risk behavior might negate those benefits or even worsen the HIV epidemic. Although we are unable to predict what might occur in a future mass vaccination campaign,⁷ results from the few completed vaccine trials to date in North America, Europe, and Asia show that risk behavior generally did not increase,^{28–32} despite early reports of increased risk behavior in several small trials.³³ Nine African countries are preparing or already enrolling participants for HIV vaccine trials,^{2,34,35} however, and preliminary studies indicate that sexual risk behavior might increase in response to vaccination.^{6,36,37} To what degree increased risk behavior might potentially offset the benefits of vaccination remains a question largely unanswered in the African setting.

The impact of partially effective vaccines and potential risk behavior change on future vaccination campaigns in South Africa has not yet been examined. With an estimated 5.5 million people living with HIV/AIDS as of 2006 and HIV prevalence in some areas of 30% to 40%,^{38–40} South Africa is experiencing the type of severe HIV epidemic that is present or developing in many low- and middle-income countries. Additionally, because of South Africa's burden of HIV, political support for HIV vaccines, participation in international HIV vaccine trials, and status as a middle-income country with a relatively strong health infrastructure for vaccine purchase and delivery, it may be one of the first countries in sub-Saharan Africa to consider the use of early generations of licensed HIV vaccines. Therefore, we estimated the effect of various potential preventive* vaccination scenarios on the heterosexual HIV epidemic in the urban township of Soweto, South Africa with a mathematic simulation model, using different levels of vaccine efficacy and changes in post-vaccination condom use.

Methods

We developed a dynamic compartmental epidemic model for heterosexual HIV transmission and disease progression to simulate the impact of various partially effective preventive HIV vaccination scenarios and subsequent changes in risk behavior in a population at high risk for heterosexually transmitted HIV in Soweto, South Africa.

*For this study, a preventive vaccine is defined as a vaccine that prevents primary infection with HIV, and a partially effective vaccine (low-efficacy vaccine, imperfect vaccine) is defined as a vaccine with less than 100% efficacy, or ability to prevent transmission of HIV.

Model Description

The model defines 6 “compartments,” with each representing a particular health “state,” to simulate the process of HIV transmission and disease progression: (1) unvaccinated HIV-negative, (2) vaccinated HIV-negative, (3) unvaccinated asymptomatic HIV-positive, (4) vaccinated asymptomatic HIV-positive, (5) symptomatic HIV-positive, and (6) AIDS. There are separate states for men and women, for a total of 12 compartments overall. Rates of movement of individuals are specified by a set of 12 deterministic differential equations that govern allowable transitions between the population subgroups. The model considers a population of sexually active adults who enter the simulation on reaching sexual maturity and can leave the simulation because of death from non-AIDS-related or AIDS-related causes. Only heterosexual transmission of HIV is considered in this analysis.

The model accounts for the immunologic and behavioral effects of a preventive HIV vaccine. HIV-negative men and women who are vaccinated are protected from HIV infection in sexual partnerships with HIV-infected individuals a certain proportion of the time, which is the efficacy of the vaccine. Therefore, if the vaccine is 40% effective, vaccinated HIV-negative individuals are then protected from HIV infection in 40% of partnerships with infected heterosexual partners. Because we modeled HIV transmission on a per-partnership basis, this 40% reduction applies to the probability of HIV transmission over the entire course of a partnership between a man and woman rather than to a per-sex act probability of transmission. Additionally, individuals may change their sexual risk-taking behavior, such as condom use, sex act type and frequency, and number of sex partners, in response to vaccination. For example, they might increase their risky behavior because they feel protected by the vaccine, or they might decrease their risky behavior as a response to the counseling that may be given in a mass vaccination campaign. Specifically, we examine post-vaccination changes in male-negotiated condom use behavior.

A more detailed description of the model and the assumptions underlying its specification is provided in the Appendix.

Simulations

We conducted simulations as if a vaccine was currently available and a vaccination program was implemented for a period of 10 years. We then evaluated the effects of various vaccination scenarios by examining the total number of HIV infections averted and the change in population HIV prevalence. We calculated these values by comparing model outputs under the vaccine program simulation with a simulation without a vaccination program.

We first simulated a base-case scenario, in which a vaccination program was implemented using a vaccine with 40% efficacy and in which there was no post-vaccination change in risk behavior (male-negotiated condom use). We compared model predictions from the base-case scenario with other vaccination scenarios with varying vaccine efficacies and post-vaccination changes in male condom use. We performed all model simulations using Excel 2003 spreadsheet software (Microsoft Corporation, Redmond, WA).

Input Parameters, Assumptions, and Initial Conditions

We derived input parameters for the model from published data sources and assumptions. Input parameters are listed in Table 1, along with their associated model equation symbols. We modeled the urban township population of Soweto using an initial population size of 823,000, including only men and women aged 17 years or older,⁴¹ a mean age of 25.1 years,⁴² and a life expectancy of 60.8 years from birth in the absence of deaths attributable to AIDS.⁴³ Based on regional and national studies of sexual debut in South Africa, we

estimated that all individuals in Soweto are sexually active by this age.^{44–47} Using national and province-specific HIV prevalence data for individuals aged 15 to 49 years,⁴⁷ we estimated an initial HIV prevalence of 11.6% for men and 20.0% for women. We assumed an antiretroviral (ARV)-naïve population.

We modeled a preventive HIV vaccine that produced an immunologic effect in all recipients (100% take, $\psi = 1$); provided protection for a mean duration of 10 years ($1/\omega = 10$); and affected only HIV transmission, with no effect on infectivity or disease progression in those who were HIV-positive.^{19,25,48,49} For our base-case scenario, we used a 40% effective vaccine ($\epsilon = 0.4$), a figure that was subsequently varied. We simulated a program in which vaccines were given to unvaccinated asymptomatic men and women aged 17 years or older without testing individuals for HIV; therefore, vaccines were given to uninfected and asymptomatic HIV-positive individuals. We assumed that no members of the population were vaccinated initially and that the vaccine would be administered in a highly coordinated and effective mass vaccination campaign in which 75% of those eligible for vaccination were vaccinated in the first year and in each year thereafter ($\chi(t) = 0.75$). Although a high estimate, we believe that this coverage level would be feasible, given the apparent devastating epidemic in South Africa and the needs of both individuals and the government for additional HIV prevention methodologies. We also performed additional sensitivity analyses for a more modest coverage level of 50% ($\chi(t) = 0.50$), however.

In the model, we varied the number of sexual partners a man or woman has and the probability of HIV transmission within those sexual partnerships according to disease stage. We estimated that uninfected and asymptomatic HIV-positive men and women had, on average, 3 sexual partnerships per year ($\rho_0, \rho_1 = 3$),^{37,50} symptomatic HIV-positive men and women had only 1 sexual partnership per year ($\rho_2 = 1$), and individuals with AIDS had no sex partners ($\rho_3 = 0$). We used Ugandan data to calculate values for per-partnership probability of HIV transmission from asymptomatic ($\beta_{M1,j} = 0.0684$; $\beta_{W1,j} = 0.1112$) and symptomatic ($\beta_{M2,j} = 0.1657$; $\beta_{W2,j} = 0.2697$) HIV-positive men and women (see Appendix for further details).^{18,51–53} We based our infectivity parameters on monogamous serodiscordant couple studies, which represent conservative estimates compared with transmission data from multiple-partnership studies.⁵⁴ Because research into the biologic and social bases for observed gender differences in HIV transmission is inconclusive to date,^{18,51,53–57} we performed additional sensitivity analyses in which the male-to-female (MTF) and female-to-male (FTM) infectivity rates were exchanged and in which the symptomatic FTM infectivity rate was decreased by 2- and 10-fold.

We used the median time from HIV seroconversion to AIDS in an African setting and previously published lengths for HIV disease stages to estimate the duration of asymptomatic HIV disease ($1/\mu_{1,j} = 6.8$ years) and symptomatic HIV disease ($1/\mu_{2,j} = 2.6$ years) in the model.^{19,25,58} We used the median time from AIDS development to death of 9.2 months ($1/\mu_{3,j} = 0.8$ years) for the duration of AIDS.⁵⁸ These disease progression times were based on studies from a cohort in rural Uganda before the availability of ARV therapy in this area.

From studies of condom use in South Africa,^{44–47,50} we estimated that baseline condom use was 50% in all sexual partnerships ($h_{i0} = 0.5$). We used a condom failure rate of 14% over the course of each sexual partnership ($f = 0.14$).⁵⁹ For our base-case simulation, we examined a scenario in which post-vaccination condom use did not change from baseline levels of 50% (0% change in condom use, $\Delta = 1.0$); subsequent analyses examined values from 25% (50% decrease, $\Delta = 0.5$) to 75% (50% increase, $\Delta = 1.5$) to explore a wide range of potential changes in risk behavior. In addition, based on research showing a significant gender difference in the ability of women in many South African settings to negotiate

condom use successfully with their sexual partners,^{60–63} we assumed that condom use was negotiated exclusively by the male in the relationship. Therefore, we used a likelihood function for condom use in a given partnership based entirely on the preference of the male partner (see Appendix for further details).

Results

We simulated vaccination scenarios for an initial population of 823,000 sexually active heterosexual men and women with an HIV prevalence of 12% and 20%, respectively, of whom 75% were effectively vaccinated each year with vaccines that provided an average of 10 years of protection. In the absence of HIV prevention interventions in Soweto, the model predicted that HIV prevalence would increase over the next 50 years from 16% currently to 26%, with 743,000 new HIV infections occurring during that period. Within the next 10 years alone, simulations predicted that the overall population prevalence would rise to 20% and that 161,000 new HIV infections would occur.

For vaccination scenarios with no change in post-vaccination risk behavior, increases in vaccine efficacy produced greater numbers of HIV infections averted (Fig. 1), with concurrent decreases in overall population HIV prevalence. A vaccination program using a 20% effective vaccine would avert 32,000 infections over 10 years and decrease the 10-year overall population HIV prevalence from 20% to 17%. Similarly, a 30% effective vaccine would avert 47,000 infections and decrease prevalence to 15% over 10 years. In contrast, a 100% effective vaccine would avert 128,000 infections in the same time period and decrease HIV prevalence to 7%.

We next examined specific combinations of vaccine efficacy and changes in risk behavior (Fig. 2). Figure 2A shows the results for our base-case vaccination scenario using a 40% effective vaccine with no change in condom use after vaccination. Over 10 years, this vaccination program could prevent 61,000 new HIV infections in Soweto and reduce the population HIV prevalence from 20% to 13%.

We then examined changes in risk behavior by varying post-vaccination condom use. We simulated a vaccination scenario in which a 40% effective vaccine was used, as in the base-case scenario, but in which post-vaccination condom use increased by 25% (see Fig. 2B). In this case, the beneficial effects of the base-case vaccination program increased: cumulative infections averted would increase from 65,000 to 75,000, and the prevalence of HIV would decrease even further, from 20% to 12%. In contrast, a vaccination scenario in which post-vaccination condom use decreased by 25% would reduce the beneficial effects of the base-case vaccination program (see Fig. 2C). The cumulative number of infections averted would decrease from 65,000 to 46,000, and the prevalence of HIV would only decrease from 20% to 15%.

Depending on the particular combination of vaccine efficacy and change in risk behavior, some vaccination programs we simulated would be detrimental. As an example, we show a vaccination program that used a 20% effective vaccine but resulted in a 50% decrease in post-vaccination condom use (see Fig. 2D). This scenario created a perverse outcome in which the negative behavioral effects outweighed the protective effects of the vaccine. This vaccination program would actually cause an additional 14,000 infections beyond what would be expected without any vaccination campaign and would increase the prevalence of HIV over 10 years from 20% to 22%.

Given these observations and the uncertainty of future mass vaccination campaign conditions, we then examined the relation between varying vaccine efficacy values and levels of risk behavior change. We estimated all combinations of vaccine efficacy and

changes in post-vaccination condom use for vaccination scenarios that would prevent the same 61,000 HIV infections as the base-case scenario over a period of 10 years (Fig. 3A). At one extreme, an imperfect vaccine would be less effective than a program to change condom use behavior: any HIV prevention program that could increase condom use to at least 80% (eg, increase condom use by more than 58% over baseline levels), in the absence of a vaccine, would prevent more infections than a 40% effective vaccine in the base-case vaccination scenario. At the other extreme, an imperfect vaccine with adequate efficacy could offset the negative effects of any decreases in post-vaccination condom use: if all individuals ceased using condoms entirely after being vaccinated (eg, condom use decreased 100% from baseline levels of 50%), any HIV vaccine that was more than 66% effective would still prevent more infections than a 40% effective vaccine in the base-case vaccination scenario.

To examine whether various vaccination programs might be beneficial or harmful at the population level, we also estimated which combinations of vaccine efficacy and changes in condom use would result in a net decrease in the number of HIV infections (see Fig. 3B). As the efficacy of the vaccine increased, HIV infections were still reduced, even with decreasing condom use. All vaccination programs that generated any increase in condom use over baseline levels would be beneficial in terms of infections prevented, regardless of the efficacy of the vaccine used. All vaccination programs that used a vaccine with an efficacy of at least 43% would be beneficial in terms of infections prevented, regardless of changes in male-negotiated condom use after vaccination—a result that is robust even if condom use were to cease entirely after the vaccination campaign. Any vaccination programs that used a vaccine with an efficacy <43% and also caused a decrease in condom use from baseline levels could be beneficial or harmful in terms of infections prevented, depending on the particular combination of vaccine efficacy and risk behavior change.

Because of the uncertainty in the published literature regarding the existence of gender differences in HIV transmission rates, we performed additional sensitivity analyses in which the MTF and FTM transmission parameters were exchanged. In addition, we performed sensitivity analyses on the symptomatic FTM infectivity parameter (0.27 probability of transmission per partnership per year), because our calculations yielded a relatively high value for this probability. We examined outcomes for simulations in which the FTM infectivity parameter was reduced to 50% and 10% of our calculated value. We also explored the effects of a 50% vaccination program coverage goal rather than a 75% goal. In all cases, although the quantitative benefits of the programs change (data not shown), the analyses remain robust to our qualitative conclusions regarding the impact of partially effective vaccines.

Discussion

We designed a mathematical model to simulate heterosexual transmission and disease progression of HIV in low- or middle-income country populations. We simulated vaccination programs using preventive vaccines with varying levels of efficacy and post-vaccination changes in risk behavior, which, for this study, was represented by condom use. We specifically examined the impact of these vaccination programs on the HIV epidemic in Soweto, South Africa in terms of HIV infections prevented and changes in HIV prevalence over time. We found that vaccines with only 30% or 40% efficacy can confer substantial health benefits; this is significant because most vaccines in use today for other diseases have much higher efficacies than this. We also found that the effects of changes in risk behavior, post-vaccination condom use in this instance, can be significant and that condom use merits close attention in future vaccination campaigns. Finally, we found that even with increases in risk behavior, sufficiently effective vaccines could still be beneficial.

Heterosexually transmitted HIV is responsible for more than 80% of adult HIV infections worldwide,⁵⁹ and more than 98% of new HIV infections are occurring in low- and middle-income countries.⁴⁰ In the South African setting, Amirfar and colleagues²² used a Markov model to examine the impact of a preventive HIV vaccine in a cohort of adolescent girls, whereas a study by Blower et al⁶⁴ used a dynamic transmission model to investigate the impact of disease-modifying HIV vaccines in a homogeneous population. Our analysis extends this work by using a dynamic transmission model to simulate the impact of preventive HIV vaccines and changes in sexual risk behavior on heterosexual HIV transmission and disease progression in South Africa and represents one of a small number of HIV vaccination program simulations for heterosexually transmitted HIV in low- and middle-income country populations.^{15–18,20} Despite using different methodology and population assumptions, our findings of the beneficial impact of partially effective vaccines were consistent with previous models, simple and complex, of the effects of preventive HIV vaccines^{15,16,19,21,48} and their sensitivity to changes in risk behavior.^{18,23,25}

To our knowledge, this also represents the first time that differential condom use behavior between men and women has been incorporated into a model of HIV disease transmission. Although Western models of HIV transmission have specified that condom use between 2 partners with differing practices is the greater of the 2 (eg, if one person uses condoms 70% of the time and another person uses condoms 30% of the time, condom use in that particular partnership is 70%),²⁵ we believe that this does not accurately reflect condom use negotiation in the African setting. We assumed exclusive male negotiation of condom use in our model to reflect the decreased ability of South African women to negotiate condom use in heterosexual partnerships,^{60–63} a disadvantage attributable to cultural and economic barriers that is found in many countries throughout sub-Saharan Africa and, in part, explains the shift toward a female-dominated epidemic.⁴⁰ Therefore, in our model, the likelihood of condom use in a given sexual partnership was exclusively linked to the condom use rate of the male partner; as a result, changes in risk behavior were linked to male-determined changes in condom use.

The absence of ARV therapy is a limitation of this model, but we expect that our qualitative conclusions would not be substantially different. To simplify the model, our current analyses have assumed an ARV-naïve population, because few people in the South African public sector presently have access to ARV therapy.⁶⁵ In addition to prolonging life, ARV therapy decreases viral loads in HIV-infected individuals, and decreased viral loads have been shown to result in decreased sexual transmission of HIV.^{18,51,53,56} The effects of the national plan for widespread public sector distribution of ARV therapy to South Africans infected with HIV⁶⁶ need to be included in future analyses of the impact of HIV vaccination programs once significant coverage of ARV therapy for HIV-positive individuals is achieved.

Another limitation of this model is that we have only simulated the impact of a preventive, or prophylactic, vaccine. We believe that this approach is justified, because preventive vaccines have the greatest potential to control the epidemic;²⁶ novel design approaches and numerous clinical trials for preventive vaccines are still underway,^{2,3,67} and few studies have explored the impact of preventive vaccines on heterosexual HIV transmission in African populations—notably in Uganda, Kenya, and Zimbabwe.^{15–18,20} We believe that an examination of the impact of a preventive vaccine on heterosexual HIV transmission in South Africa is necessary as an initial step and simplifies the discussion surrounding the dynamic trade-off between vaccine efficacy and changes in post-vaccination risk behavior. Because of current scientific challenges in developing preventive vaccines that stimulate broadly neutralizing antibody responses, however, disease-modifying vaccines that stimulate a cytotoxic T-lymphocyte (CTL)–based response are also currently under development.^{3,68}

Similar to ARV therapy, these disease-modifying vaccines might be able to decrease viral load (and therefore infectivity) and disease progression in those already infected. Although they may not prevent HIV infection at the individual level, disease-modifying vaccines might decrease HIV transmission, and thus HIV prevalence, at the population level over time.⁶⁹ Other models have investigated the impact of disease-modifying vaccines,^{15,19–21,25–27,48,64,70} but further exploration of the impact of disease-modifying vaccines and risk behavior change on heterosexual HIV transmission in Africa in particular is merited.

Despite the uncertainty about the efficacy of a vaccine, we have been able to make general conclusions for communities such as the township of Soweto regarding the use of partially effective vaccines and the implications of risk behavior change. In addition to the consideration of potential disease-modifying vaccines and widespread access to ARV therapy, future analyses would benefit from the incorporation of migration and heterogeneous risk behavior groups into the model. Vaccination scenarios varying other parameters, such as vaccination coverage levels, vaccine take, and duration of protection as well as the timing, length, costs, and benefits of vaccination campaigns, should also be considered when a potential vaccine candidate has been identified for use and decisions must be made regarding its implementation. Because so little is currently known about the potential for risk behavior change in the African setting, studies to evaluate whether risk behavior changes might occur in future vaccination campaigns are greatly needed.

Because of the significant effects of changes in risk behavior on the potential benefits of mass vaccination campaigns, programs to reduce risk behavior may be important components of successful vaccination campaigns for South Africa and other countries with similar epidemic profiles, particularly when lower efficacy vaccines are used. Programs to reduce risk behavior, such as those used during the rollout of ARV therapy or other HIV prevention campaigns in African countries, may serve as templates for risk behavior reduction strategies.^{57,71} Because of the decreased ability of women to negotiate condom use in their relationships and the higher risk behaviors found in men throughout sub-Saharan Africa, programs specifically targeting men should also be considered. More immediately, risk behavior assessment must remain an important component of HIV vaccine clinical trials because it provides one of the only means of predicting changes in risk behavior that might occur at the population level in an actual mass vaccination campaign. The reductions in HIV prevalence and new HIV infections that can result from using partially effective vaccines are substantial, however, even in the presence of increased risk behavior; therefore, development of preventive vaccines should remain a high priority despite concerns that these vaccines may have only moderate efficacy.

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Appendix

Appendix:

Detailed information on the mathematical model used for the evaluation of various HIV vaccination program scenarios is provided here.

The model design was based on a mathematical model for homosexual HIV transmission and disease progression simulating the effects of HIV vaccination programs in men who have sex with men in San Francisco,^{19,25} which had incorporated characteristics of previously published models of HIV disease.^{48,49,72} We developed the current epidemic model for the heterosexual transmission of HIV that occurs in African populations. We adapted the model in the following ways: (1) to account for 2 different populations (male and female) linked by heterosexual HIV transmission; (2) to account for HIV transmission conditions in sub-Saharan Africa, including male-driven negotiation of condom use and lack of knowledge of one's HIV status; and (3) to assess the impact of a preventive vaccine only. Model input parameters and assumptions were also chosen to reflect the African setting.

The model defines 6 health states, which differ for men and women, for a total of 12 states overall. Movement of individuals from the unvaccinated HIV-negative (state 1) to the vaccinated HIV-negative (state 2) compartment and from the unvaccinated asymptomatic HIV-positive (state 3) to the vaccinated asymptomatic HIV-positive (state 4) compartment is determined by effective vaccination with an HIV vaccine, whereas movements in the reverse direction are determined by vaccine protection waning over time. Movement of individuals from the unvaccinated HIV-negative (state 1) to the unvaccinated asymptomatic HIV-positive (state 3) compartment and from the vaccinated HIV-negative (state 2) to the vaccinated asymptomatic HIV-positive (state 4) compartment is determined by acquisition of HIV infection from a heterosexual partner. Movement of individuals from the unvaccinated and vaccinated asymptomatic HIV-positive (states 3 and 4) compartments to the symptomatic HIV-positive (state 5) compartment and, subsequently, to the AIDS (state 6) compartment is determined by disease progression in those who become infected with HIV. Other movements between compartments in the model are not allowed. For model simulations, transitions between the 12 population subgroups were calculated annually to determine the number of men and women in each compartment.

We modeled a heterogeneous population with respect to gender and disease stage and a homogeneous population with respect to risk behavior and vaccination coverage (eg, except for changes in behavior based on vaccination or disease progression, sexual risk behavior was uniform throughout population subgroups, mixing of sexual partnerships was random, and vaccination was not targeted to individuals at higher risk of HIV infection). Specifically, behavioral heterogeneity was incorporated into the model by (1) varying the number of sexual partnerships per year according to disease stage; (2) modeling changes in condom use behaviors after vaccination; (3) incorporating differential condom use behaviors between men and women; and (4) simulating HIV transmission on a per-partnership basis, such that a partnership involving a single high-risk sex act could convey the same probability of HIV transmission as a partnership involving many lower risk sex acts.

Table 1A lists a description of the variables used in the model equations. Table 2A lists the 12 differential equations that define transitions between various health states in the model. For example, Equation 1 describes the rate of change of the male ($M_{i,j}$), unvaccinated ($j = 0$), HIV-negative ($i = 0$) sexually active population at time t :

$$\frac{dM_{0,0}(t)}{dt} = I_{M0,0} - \psi v(t) M_{0,0}(t) - \mu M_{0,0}(t) - \rho_0 \lambda_M(t) M_{0,0}(t) + \omega M_{0,1}(t) \quad (1)$$

This rate depends on the following factors, which are each terms in Equation 1: (a) $I_{M0,0}$, the number of unvaccinated HIV-negative men who arrive into the sexually active population each year on reaching the age of 17 years; (b) $\psi v(t) M_{0,0}(t)$, the number of unvaccinated HIV-negative men [$M_{0,0}(t)$] who are vaccinated each year [proportion of the population

vaccinated, $\psi(t)$ and in whom the vaccine has an effect (take, ψ); (c) $\mu M_{0,0}(t)$, the number of unvaccinated HIV-negative men $[M_{0,0}(t)]$ who die each year as a result of non-AIDS-related causes (non-AIDS-related mortality rate, μ); (d) $\rho_0 \lambda_M(t) M_{0,0}(t)$, the number of unvaccinated HIV-negative men $[M_{0,0}(t)]$ who become infected with HIV [per-partnership probability of an unvaccinated man acquiring HIV from any woman at time t , $\lambda_M(t)$] each year from a female partner (number of female partners per year for an uninfected man, ρ_0); and (e) $\omega M_{0,1}(t)$, the number of vaccinated ($j = 1$) HIV-negative men $[M_{0,1}(t)]$ for whom protection from the vaccine wanes each year (rate of vaccine waning, ω), returning them to the immunologic and behavioral “unvaccinated” state. Rates of change for other population subgroups are determined in a similar fashion.

We assumed, in accordance with the theoretic framework of McLean and Blower,⁴⁹ that a vaccine could fail to protect an individual from HIV infection in 3 different ways. The vaccine might not produce an immunologic response in the individual (imperfect, or $<100\%$, take, ψ); in those who produce an immunologic response, the vaccine might provide only partial protection to individuals (imperfect, or $<100\%$, degree or efficacy, ε); and the duration of protection (mean duration in years, $1/\omega$) afforded by the vaccine may not last for the entire sexually active life of the vaccine recipient. Because this analysis considered a vaccine with 100% take and 10 years' duration of protection, however, only imperfect vaccine efficacy is examined as a significant source of vaccine failure in the current study. Because different combinations of vaccine imperfections produce different outcomes,⁴⁹ our model allows for future analyses varying vaccine take and duration in addition to efficacy.

We assumed that an HIV vaccine protected an uninfected individual from acquiring HIV infection when exposed to an HIV-positive heterosexual partner and that vaccines with $<100\%$ efficacy did not provide complete protection from HIV infection. We modeled this incomplete protection as partial protection on an individual level (eg, a 40% effective vaccine [$\varepsilon = 0.4$] would only provide protection from 40% of sexual partnerships with an HIV-positive partner). As shown in Equations 3 and 4 in Table 2A, a partially effective vaccine reduces the rate of HIV infection by a factor of $(1 - \varepsilon)$. Therefore, a 40% effective vaccine reduces the probability of HIV infection from sexual partnerships with HIV-positive individuals to 60%.

As detailed in the model equations, the rate of HIV infection for individuals in the model depends on the following factors: an individual's vaccination status, the efficacy of the vaccine used, the number of sexual partners per year, the probability of choosing an HIV-positive partner from the population at any point in time, the probability that HIV is transmitted (infectivity) in a particular partnership, the condom use in a particular partnership, and the change in male-negotiated condom use behavior that occurs after vaccination. Table 2A also lists the 3 equations [for lambda probabilities $\lambda_M(t)$, $\lambda_{M\psi}(t)$, and $\lambda_{\mu}(t)$] that define the probability of acquiring HIV from any partner at a given time to which an uninfected man or woman is exposed.

The lambda probability depends partially on the probability of transmission of HIV from a particular sexual partnership. The probability of HIV transmission per sex act varies within and between sexual partnerships.⁷³ Rather than using infectivity parameters for the probability of HIV transmission per sex act, we use infectivity parameters for the probability of HIV transmission over the course of a sexual partnership. The probability of HIV transmission from a given sexual partnership is determined by the likelihood of choosing an HIV-infected partner and the likelihood of HIV being transmitted during the course of that partnership if an HIV-infected partner is chosen, both of which depend on the disease stage of the HIV-infected partner, given all possible potential heterosexual partnerships that exist.

The lambda probability also depends on condom use. Condom use is captured by the term $n_{Mi,j}$, which is the probability that a particular sexual partnership between a man with disease stage i and vaccination stage j and a woman (with any disease stage and vaccination status) is not protected by condoms. This is determined by the baseline condom use $h_{i,0}$; the change in condom use as a result of a vaccination program, Δ ; and the likelihood of condom failure, f (see Table 1A for equations). Because we assume that condom use is negotiated by the man in the partnership, only changes in male post-vaccination risk behavior affected condom use in heterosexual partnerships. The lambda probability to be applied to an uninfected woman (regardless of vaccination status), however, includes a condom use term based only on his own condom use behavior, $n_{M0,0}$. Similarly, the lambda probability that a vaccinated uninfected man experiences includes a condom use term based on his own condom use behavior, which may have changed after vaccination, $n_{M0,1}$. The lambda probability to be applied to an uninfected woman (regardless of vaccination status) includes a condom use term based on the male condom use behaviors for all her potential

$$\text{partnerships, } \sum_{i=1}^{i=3} \sum_{j=0}^{j=1} n_{Mi,j}.$$

HIV transmission was modeled to occur only via heterosexual contact; transmission from mother to child and transmission through blood transfusions, intravenous drug use, or homosexual contact were not included in the model equations. Epidemics driven by other routes of transmission, such as injection drug use or men who have sex with men, would be better addressed with models specifying the particular transmission and risks of HIV in those populations. Of these alternate infection routes, mother-to-child transmission is a significant contributor to the HIV epidemic in South Africa. We have allowed for early HIV infection in the model, however, by specifying that a proportion of arriving 17-year-olds are already HIV-positive. Adolescents who were infected through mother-to-child transmission at birth and have not yet succumbed to AIDS and adolescents who acquired HIV through early sexual activity are included in this group.

HIV transmission was modeled on a per-partnership basis; thus, rates of HIV transmission were used for the probability of transmission over the entire duration of a partnership between a man and a woman rather than on a per-contact or per-sex act basis. We note that the total number of sexual partnerships that men have with women and women have with men each year are not strictly balanced; however, this difference in partnerships is small (<4%, data not shown) and does not significantly affect the outcomes predicted by the model.

We assumed uniform HIV transmission risk across different partnerships, such that having risky sex in a partnership (because of chosen partner, type of sex act, or use of condoms) just a few times might be equivalent to having less risky sex many times in a different sexual partnership.⁷⁴ For the per-partnership probability of HIV transmission calculations, we used transmission data from rural Uganda^{18,51} and assumed that transmissions per person per year in a serodiscordant monogamous sexual relationship would accurately estimate transmissions per partnership per year. We derived an asymptomatic infectivity parameter that is 41% of the symptomatic infectivity parameter, which approximates results by other studies.^{52,53,72} Although European and US data indicate that HIV infectivity from MTF transmission is greater than that from FTM transmission, African studies have indicated that infectivity is equal from MTF and FTM transmission, is greater from FTM transmission than from MTF transmission, and/or is instead dependent on other factors such as age, viral load, genital ulceration, pregnancy, circumcision, and type of sexual partnership (monogamous vs. casual partner).^{18,51,53–57,75} We also assumed that men in the model were not circumcised, which is an issue that we are addressing in a separate study.^{37,76}

We modeled a stable population size over time except for deaths attributable to AIDS. In the simulation, men and women join the sexually active heterosexual population on reaching the age of 17 years, defined as the age by which all individuals are sexually active.^{44–47} These new arrivals enter the model at a constant rate (determined by the number of men and women who die as a result of non–AIDS-related causes) into the uninfected or HIV-infected asymptomatic compartment population. We assumed that no one is vaccinated before the age of 17 years. Some individuals have already been infected with HIV; we estimated that 3% of 17-year-old men and 10% of 17-year-old women are HIV-positive.^{45–47,77}

Acquisition of HIV infection before the age of 17 years (and thus before entry into the model's compartment populations) may have occurred through mother-to-child transmission or other means such as early sexual activity, as described previously. We assumed that all the arriving HIV-positive 17-year-olds would still be in the asymptomatic stage of the disease because they acquired the infection recently or because individuals infected at birth through mother-to-child transmission who have developed AIDS would no longer be alive and that disease progression to symptomatic HIV and further to AIDS would not occur until after entry into the model. Individuals can leave the model from any population subgroup as a result of non–AIDS-related mortality or from the AIDS subgroup population as a result of AIDS-related death.

We assumed equal numbers of men and women in the initial population. We assumed that the percentage of people initially in each HIV disease stage was proportional to the time spent in that stage. We assumed that the vaccine would provide equal protection against all HIV subtypes. Because we assumed that the vaccine had an impact only on initial HIV transmission but had no effect on disease progression or infectivity (eg, through a reduction in viral load) in those who became HIV infected before or after vaccination, we have not described the vaccinated symptomatic HIV-positive and AIDS states as separate from the unvaccinated symptomatic HIV-positive and AIDS states, respectively, or their respective infectivity values, despite the model allowing for such differentiation.

Empiric data for the parameters in this model were not available historically for Soweto; therefore, we have parameterized the model to simulate HIV prevalence starting from the present. Further, HIV prevalence data specifically for the community of Soweto have not been collected to date. Despite the lack of population HIV prevalence data for Soweto, we validated the model using overall predicted trends for the population HIV prevalence of Gauteng province (which includes Soweto township).⁷⁸ In the absence of vaccination programs, predicted trends for the HIV prevalence of Soweto in the sexually active population in our model matched predicted trends for the HIV prevalence of Gauteng province in adults aged 20 to 64 years within 5% to 15% each year for 10 years (data not shown).

Table 1A
Definition of Model Variables

Description of Variable	Symbol
Disease stage (<i>i</i>)	
Uninfected (HIV-negative)	$i = 0$
Infected (HIV-positive) asymptomatic	$i = 1$
Infected (HIV-positive) symptomatic	$i = 2$
AIDS	$i = 3$
Vaccination status (<i>j</i>)	

Description of Variable	Symbol
Unvaccinated	$j = 0$
Vaccinated	$j = 1$
Disease stage-specific variables	
No. men in disease stage i with vaccination status j at time t	$M_{ij}(t)$
No. women in disease stage i with vaccination status j at time t	$W_{ij}(t)$
Probability of a man acquiring the infection at time t from any 1 female partner	$\lambda_M(t)$
Probability of a man acquiring the infection at time t from any 1 female partner, under behavior modifications attributable to male vaccination	$\lambda_{Mv}(t)$
Probability of a woman acquiring the infection at time t from any 1 male partner, regardless of female vaccination status	$\lambda_w(t)$
Per-partner infectivity (chance of transmitting HIV) of a man in disease stage i with vaccination status j	$\beta_{Mi,j}$
Per-partner infectivity (chance of transmitting HIV) of a woman in disease stage i with vaccination status j	$\beta_{Wi,j}$
Contact rate (no. new partners per year) of men or women in disease stage i	ρ_i
Mean duration (y) of disease stage i under vaccination status j	$1/\mu_{i,j}$
Annual immigration of men in disease stage i with vaccination status j	$I_{Mi,j}$
Annual immigration of women in disease stage i with vaccination status j	$I_{Wi,j}$
Probability a partnership between an uninfected unvaccinated man and a woman with disease stage i and vaccination status j is not protected by condoms*	$n_{M0,0}$
Probability a partnership between an uninfected vaccinated man and a woman with disease stage i and vaccination status j is not protected by condoms*	$n_{M0,1}$
Probability a partnership between an uninfected woman (regardless of vaccination status) and a man with disease stage i and vaccination status j is not protected by condoms*	$n_{Mi,j}$
Population variables	
Non-AIDS-related annual death rate	μ
Preventive-vaccine variables	
Annual percent of uninfected or asymptomatic HIV-positive men or women who receive preventive vaccine	$v(t)$
Vaccine take (proportion of those vaccinated in whom vaccine stimulates an immune response)	ψ
Vaccine efficacy (percent of partnerships protected from infection)	ε
Mean duration (y) of vaccine protection	$1/\omega$

* $n_{Mi,j} = fg_{i,j} + (1 - g_{i,j})$, where $g_{i,0} = h_{i,0}$ and $g_{i,1} = \Delta h_{i,0}$ (f = condom failure rate for all partnerships; $h_{i,0}$ = baseline condom use for all partnerships, with no vaccination program; Δ = change in condom use after vaccination; $g_{i,j}$ = condom use for all partnerships after implementation of a vaccination program).

Table 2A
Model Equations*

State Equation	
1	$\frac{dM_{0,0}(t)}{dt} = I_{M0,0} - \psi v(t) M_{0,0}(t) - \mu M_{0,0}(t) - \rho_0 \lambda_M(t) M_{0,0}(t) + \omega M_{0,1}(t)$
2	$\frac{dW_{0,0}(t)}{dt} = I_{W0,0} - \psi v(t) W_{0,0}(t) - \mu W_{0,0}(t) - \rho_0 \lambda_w(t) W_{0,0}(t) + \omega W_{0,1}(t)$
3	$\frac{dM_{0,1}(t)}{dt} = \psi v(t) M_{0,0}(t) - \mu M_{0,1}(t) - \rho_0 (1 - \varepsilon) \lambda_{Mv}(t) M_{0,1}(t) - \omega M_{0,1}(t)$

State Equation	
4	$\frac{dW_{0,1}(t)}{dt} = \psi v(t) W_{0,0}(t) - \mu W_{0,1}(t) - \rho_0 (1 - \varepsilon) \lambda_w(t) W_{0,1}(t) - \omega W_{0,1}(t)$
5	$\frac{dM_{1,0}(t)}{dt} = I_{M1,0} - \psi v(t) M_{1,0}(t) - \mu M_{1,0}(t) + \rho_0 \lambda_M(t) M_{0,0}(t) + \omega M_{1,1}(t) - \mu_{1,0} M_{1,0}(t)$
6	$\frac{dW_{1,0}(t)}{dt} = I_{W1,0} - \psi v(t) W_{1,0}(t) - \mu W_{1,0}(t) + \rho_0 \lambda_w(t) W_{0,0}(t) + \omega W_{1,1}(t) - \mu_{1,0} W_{1,0}(t)$
7	$\frac{dM_{1,1}(t)}{dt} = \psi v(t) M_{1,0}(t) - \mu M_{1,1}(t) + \rho_0 (1 - \varepsilon) \lambda_{M_v}(t) M_{0,1}(t) - \omega M_{1,1}(t) - \mu_{1,1} M_{1,1}(t)$
8	$\frac{dW_{1,1}(t)}{dt} = \psi v(t) W_{1,0}(t) - \mu W_{1,1}(t) + \rho_0 (1 - \varepsilon) \lambda_w(t) W_{0,1}(t) - \omega W_{1,1}(t) - \mu_{1,1} W_{1,1}(t)$
9	$\frac{dM_{2,0}(t)}{dt} = I_{M2,0} + \sum_{j=0}^{j=1} \mu_{1,j} M_{1,j}(t) - \mu M_{2,0}(t) - \mu_{2,0} M_{2,0}(t)$
10	$\frac{dW_{2,0}(t)}{dt} = I_{W2,0} + \sum_{j=0}^{j=1} \mu_{1,j} W_{1,j}(t) - \mu W_{2,0}(t) - \mu_{2,0} W_{2,0}(t)$
11	$\frac{dM_{3,0}(t)}{dt} = \mu_{2,0} M_{2,0}(t) - \mu M_{3,0}(t) - \mu_{3,0} M_{3,0}(t)$
12	$\frac{dW_{3,0}(t)}{dt} = \mu_{2,0} W_{2,0}(t) - \mu W_{3,0}(t) - \mu_{3,0} W_{3,0}(t)$
13, 14	$\lambda_{M(t)} = \frac{n_{M0,0} \sum_{i=1}^{i=3} \sum_{j=0}^{j=1} \rho_i \beta_{w_{i,j}} W_{i,j}(t)}{\sum_{i=0}^{i=3} \sum_{j=0}^{j=1} \rho_i W_{i,j}(t)}, \lambda_{M_v}(t) = \frac{n_{M0,1} \sum_{i=1}^{i=3} \sum_{j=0}^{j=1} \rho_i \beta_{w_{i,j}} W_{i,j}(t)}{\sum_{i=0}^{i=3} \sum_{j=0}^{j=1} \rho_i W_{i,j}(t)}$
15	$\lambda_w(t) = \frac{\sum_{i=0}^{i=3} \sum_{j=0}^{j=1} n_{M_{i,j}} \rho_i \beta_{M_{i,j}} M_{i,j}(t)}{\sum_{i=0}^{i=3} \sum_{j=0}^{j=1} \rho_i M_{i,j}(t)}$

* Model equations adapted from Owens et al.¹⁹ and Edwards et al.²⁵

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Figure 1. Sensitivity analysis showing cumulative HIV infections averted over 10 years for vaccination programs using vaccines with varying efficacy values (20%, 40%, 60%, 80%, and 100%).

Figure 2.

Changes in population HIV prevalence compared with a no-vaccine simulation over 10 years for various vaccination program scenarios: base-case scenario using a 40% effective vaccine with no postvaccination change in risk behavior (A); decreased risk behavior scenario using a 40% effective vaccine with a 25% increase in postvaccination condom use (B); increased risk behavior scenario using a 40% effective vaccine with a 25% decrease in postvaccination condom use (C); and a scenario to demonstrate the potential for epidemic worsening, using a 20% effective vaccine with a 50% decrease in postvaccination condom use (D).

Figure 3.

Equivalence graph showing various combinations of vaccine efficacy and changes in postvaccination condom use in vaccination scenarios that would result in the same number of cumulative infections averted: all combinations of programs preventing 61,000 new HIV infections, which is the number of infections prevented in the base-case scenario (A), and all combinations of programs with no net effect, or 0 infections prevented, such that combinations of programs falling above the curve would prevent infections, whereas those falling below the curve would lead to additional infections (B).

Table 1
Parameter Values*

Parameter Name	Symbol	Value [†]
Preventive vaccine parameters		
Percentage of uninfected or asymptomatic HIV-positive men and women vaccinated annually	$v(t)$	0.75 (0.50 to 0.75)
Vaccine take (proportion of those vaccinated in whom vaccine stimulates an immune response)	ψ	1
Vaccine efficacy (percent of partnerships protected from infection)	e	0.40 (0 to 1.0)
Change in (male-negotiated) condom use after vaccination [‡]	Δ	1.0 (0.5 to 1.5)
Mean duration (y) of vaccine protection	$1/\omega$	10
HIV transmission parameters		
Male infectivity (per-partner probability of transmission to a woman)		
Asymptomatic period of HIV infection	$\beta_{M,j}$	0.0684 (0.06 to 0.11)
Symptomatic period of HIV infection	$\beta_{M,j}$	0.1657 (0.16 to 0.27)
Female infectivity (per-partner probability of transmission to a man)		
Asymptomatic period of HIV infection	$\beta_{W,j}$	0.1112 (0.06 to 0.11)
Symptomatic period of HIV infection	$\beta_{W,j}$	0.2697 (0.03 to 0.27)
Contact rate (no. new partners annually) of men or women		
Uninfected	ρ_0	3
HIV infected, asymptomatic period	ρ_1	3
HIV infected, symptomatic period	ρ_2	1
HIV infected, AIDS	ρ_3	0
Baseline (male-negotiated) condom use for all partnerships (no vaccination program)	h_{i0}	0.5
Condom failure rate for all partnerships	f	0.14
HIV disease duration parameters		
Asymptomatic HIV infection (y)	$1/\mu_{1,j}$	6.8
Symptomatic HIV infection (y)	$1/\mu_{2,j}$	2.6
AIDS (y)	$1/\mu_{3,j}$	0.8
Initial population parameters, heterosexual men/women >16 years old		
Total population size		823,000
Initial HIV prevalence, male population (%)		11.6
Initial HIV prevalence, female population (%)		20.0
Mean age (y)		25.1
Non-AIDS life expectancy (y)		60.8
Non-AIDS-related annual mortality rate	μ	0.028 [§]

* Model variable terminology adapted from Owens et al.¹⁹ and Edwards et al.²⁵

[†] See text for parameter value references and assumptions; values in parentheses are ranges used in sensitivity analyses.

[‡] For example, for $\Delta = 1.0$, no change in condom use; for $\Delta = 1.25$, 25% increase in condom use; for $\Delta = 0.75$, 25% decrease in condom use.

[§] Non-AIDS-related mortality rate calculated as follows: $1/\mu + (\text{population mean age}) + (\text{non-AIDS-related population life expectancy})$.