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ORIGINAL ARTICLE

Modeling the Population Level Effects of an HIV-1 Vaccine in an Era of Highly Active Antiretroviral Therapy

Wasima Rida[a,*], Sonja Sandberg[b]

[a] *American University, Washington, DC 20016, USA*
[b] *Framingham State College, Framingham, MA 01701, USA*

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Abstract First generation HIV vaccines may have limited ability to prevent infection. Instead, they may delay the onset of AIDS or reduce the infectiousness of vaccinated individuals who become infected. To assess the population level effects of such a vaccine, we formulate a deterministic model for the spread of HIV in a homosexual population in which the use of highly active antiretroviral therapy (HAART) to treat HIV infection is incorporated. The basic reproduction number R_0 is obtained under this model. We then expand the model to include the potential effects of a prophylactic HIV vaccine. The reproduction number R_f is derived for a population in which a fraction f of susceptible individuals is vaccinated and continues to benefit from vaccination. We define f^* as the minimum vaccination fraction for which $R_f \leq 1$ and describe situations in which it equals the critical vaccination fraction necessary to eliminate disease. When R_0 is large or an HIV vaccine is only partially effective, the critical vaccination fraction may exceed one. HIV vaccination, however, may still reduce the prevalence of disease if the reduction in infectiousness is at least as great as the reduction in the rate of disease progression. In particular, a vaccine that reduces infectiousness during acute infection may have an important public health impact especially if coupled with counseling to reduce risky behavior.

Keywords AIDS · Basic reproduction number · Epidemic models · HAART · HIV · Vaccines

1. Introduction

With 33.2 million persons living with HIV/AIDS and 6,800 new infections occurring each day, an effective vaccine against HIV-1 is urgently needed (UNAIDS, 2007). While vaccines for other diseases have been highly effective, first generation HIV vaccines may be only partially effective due to HIV antigenic variation and other factors. Mathematical

*Corresponding author.
E-mail address: rida@american.edu (Wasima Rida).

models have indicated that HIV vaccines that reduce susceptibility to infection by as little as 20% could prevent a significant number of infections (Anderson et al., 1995). However, two phase III trials of a recombinant glycoprotein vaccine designed to prevent infection failed to demonstrate efficacy (rgp120 HIV Vaccine Study Group, 2005; Pitisuttithum et al., 2006). A third phase III trial of a prime-boost vaccine regimen is ongoing (Rerks-Ngarm et al., 2006).

While the results of the completed phase III trials have been disappointing, the search continues for vaccines that induce broadly neutralizing antibodies that can prevent infection. Current vaccine development, however, has focused more on candidates that induce cell mediated immunity (CMI) (IAVI, 2008). Such immunity is not expected to prevent HIV infection, but might delay disease progression or reduce the infectiousness of vaccinees who become infected. The recent failure of the first phase IIb test-of-concept trial of a CMI-based vaccine has called into question the merits of such vaccines (Cohen, 2007). Others have cautioned that the trial's failure may have been due to factors such as a lack of breadth in the immune response (Watkins et al., 2008). Vaccine recipients mounted only a limited, and possibly inadequate, number of epitope-specific CTL responses against the HIV-1 Gag, Pol, and Nef transgene products. CMI-based vaccines may still prove useful. We, therefore, developed a mathematical model to explore the population level effects of a vaccine that delays disease progression or reduces infectiousness and compare those effects to a vaccine that reduces the risk of infection. Our model incorporates the effects of highly active antiretroviral therapy (HAART) to treat HIV infection which itself has population level effects on the epidemic. We also contrast the difference between population and individual level effects of the various vaccines.

In Section 2, we formulate a deterministic model for HIV transmission in a homosexual population in which the use of HAART to treat HIV infection is incorporated. Individuals are grouped into compartments reflecting their HIV status, stage of infection, and use of HAART. Sexually active individuals are assumed to mix proportionately. In Section 3, the basic reproduction number R_0 for the spread of HIV is obtained under this model. As a measure of the individual level effect of the epidemic under HAART, the average lifespan of an infective is given in Section 4. In Section 5, the model is expanded to include the potential effects of a prophylactic HIV vaccine. The reproduction number R_f is derived in Section 6 for a population in which a fraction f of susceptible individuals is effectively vaccinated and is related to the dominant eigenvalue of the next generation matrix of the epidemic (Diekmann et al., 1990). We define the vaccination fraction f^* as the minimum vaccination fraction f for which $R_f \leq 1$ and describe situations in which it equals the critical vaccination fraction necessary to eliminate disease. In particular, we address the possibility of backward bifurcation for our model where a stable endemic equilibrium coexists with the disease-free equilibrium when $R_f \leq 1$. Section 7 gives the average lifespan of an infected individual in a population where both HAART and an effective vaccine are available. Simulations using the software program Berkeley Madonna (Macey and Oster, 2000) are given in Section 8. Section 9 discusses the insights that are gained through modeling as well as the limitations of the model presented.

2. Basic HIV transmission model

We consider a deterministic model for the spread and control of HIV/AIDS in a population of homosexual men. Similar to the models of Lin et al. (1993) and Hyman et al. (1999),

our model begins by grouping individuals into compartments based on their HIV status and stage of infection. At any given time, individuals are susceptible to HIV infection or are infected and in one of five stages of infection reflecting the degree of immunodeficiency as measured by the CD4+ T cell count. The first stage of infection corresponds to acute infection when HIV RNA plasma viral load is known to peak. The second stage represents the long, asymptomatic period that follows acute infection. The third stage is reached when CD4 count falls below 350 cells/mm^3, the current level for which the initiation of highly active antiretroviral therapy (HAART) is recommended in the United States (Bartlett et al., 2006). The fourth and fifth stages correspond to CD4 counts on the order of 200 and 50 and reflect early and late stage AIDS, respectively. Infected individuals progress from the ith stage of infection to the next stage at rate τ_i for $i = 1, \ldots, 5$ in the absence of treatment. For convenience of notation, we let $\tau_5 = 0$. At the same time, untreated individuals in the ith stage die from non-HIV/AIDS and HIV/AIDS related causes at rate μ_0 and μ_i, respectively, for $i = 1, \ldots, 5$. Susceptible individuals are also assumed to die from non-HIV/AIDS causes at rate μ_0.

New susceptible individuals enter the sexually active population at rate ν per unit time such that in the absence of an HIV/AIDS epidemic the population of homosexual men remains constant. Once sexually active, susceptible individuals leave the sexually active population at rate γ due to advancing age. Likewise, infected individuals leave the sexually active population at rate γ due to age. For simplicity, we assume no infectives immigrate into the population over time. No individuals emigrate as well.

Infected individuals in the ith stage of infection are assumed to initiate HAART at rate χ_i according to prevailing treatment guidelines. For treatment naïve individuals, HAART has the effect of increasing CD4+ T cell count and reducing viral load to levels frequently below the level of detection (Jacobson et al., 2004). We let δ_1 and ζ_1 be the multiplicative effects of HAART on HIV/AIDS progression and relative infectiousness, respectively, in treatment of naïve individuals. While disease progression is delayed, infected individuals on HAART may advance to the next stage of immunodeficiency at which point the benefits of HAART may be diminished. We let δ_{j+1} and ζ_{j+1} equal the multiplicative effects of HAART on progression and relative infectiousness, respectively, for individuals who have progressed j stages ($j = 0, \ldots, 4$) while remaining on HAART. At some point, treated individuals may permanently discontinue HAART due to such factors as intolerance, drug toxicity, or loss of virologic control after exhausting the armamentarium of antiretroviral drugs which currently contains over two dozen drugs. We do not consider drug "holidays" or structured treatment interruptions as these temporary treatment discontinuations have been shown to generate drug resistant strains of HIV and are not recommended. We let ϵ_{j+1} equal the rate of treatment discontinuation for individuals who have managed to stay on HAART while progressing j stages. Individuals who discontinue HAART may have some short-term residual benefits of HAART (Sanders et al., 2005). We let $\sigma_{i,j,k}$ and $\omega_{i,j,k}$ equal the multiplicative residual effect of HAART on disease progression and infectiousness, respectively, for someone who initiated HAART at stage i, stopped HAART after progressing j stages, and has progressed k stages after stopping treatment. For simplicity, we let $\sigma_{i,j,k} = \sigma_{j+k+1}$ and $\omega_{i,j,k} = \omega_{j+k+1}$. Thus, residual effects are assumed not to depend on when one starts HAART, but only on how many stages one has progressed since starting HAART. We also assume that HAART has no effect on sexual behavior.

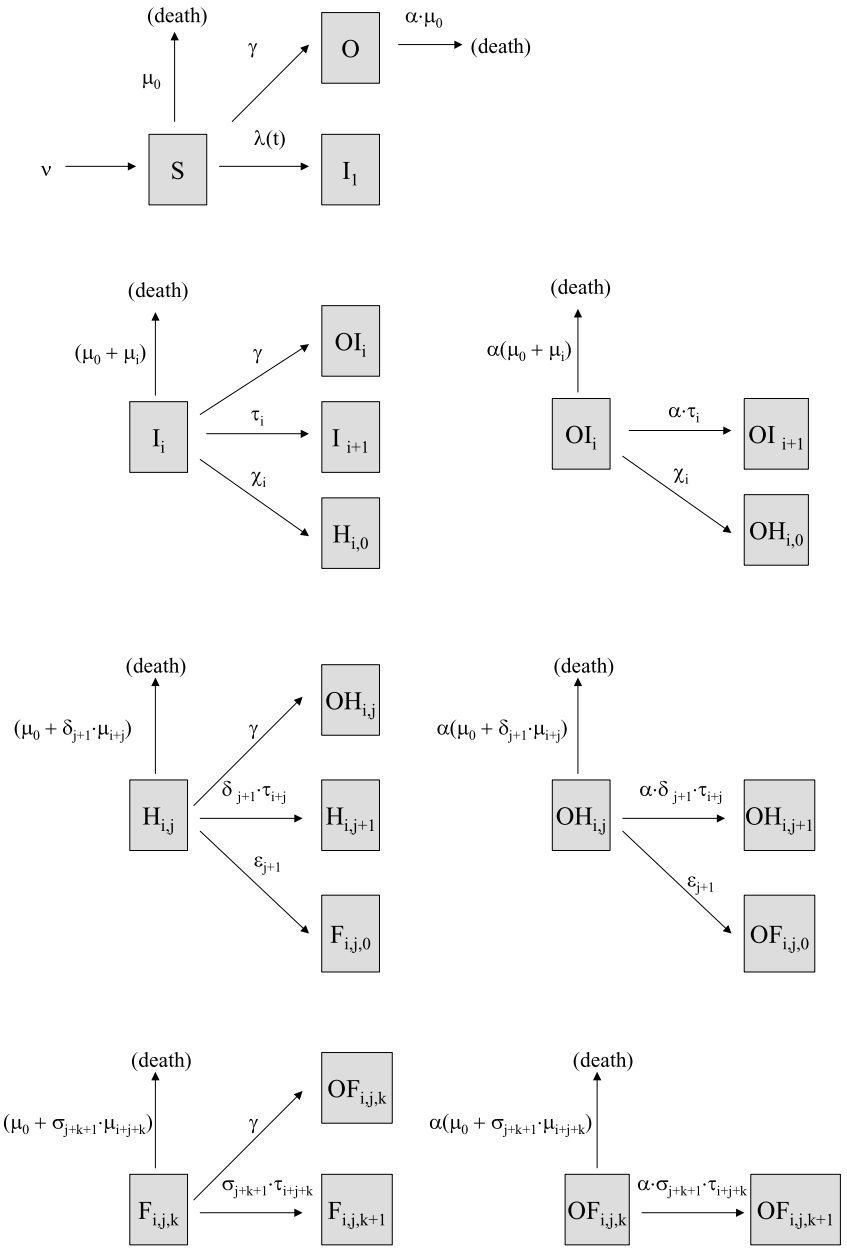

Fig. 1 Schematic of compartmental model for HIV transmission under HAART.

Figure 1 is a schematic of the compartmental model of HIV/AIDS in the presence of HAART. $S(t)$ represents the number of sexually active susceptible individuals in the population at time t while $I_i(t)$ equals the number of untreated infectives in the ith stage of infection. $H_{i,j}(t)$ expresses the number of treated individuals who initiated HAART in the ith stage of infection and have remained on HAART while progressing j stages, $j = 0, \ldots, 5-i$. At time t, they are in stage $i+j$ of infection. $F_{i,j,k}(t)$ denotes the number of infected individuals who initiated HAART in the ith stage of infection, failed or discontinued treatment after progressing j stages, and have since progressed k more stages. At time t, these individuals are in stage $i+j+k$ of infection. Finally, $O(t)$, $OI_i(t)$, $OH_{i,j}(t)$, and $OF_{i,j,k}(t)$ represent the number of susceptibles, infectives, treated individuals, and individuals who have discontinued treatment, respectively, who are no longer sexually active due to advanced age. Of note, a multiplicative factor $\alpha > 1$ is applied to the rates of HIV/AIDS disease progression and death as well to the non-HIV/AIDS mortality rate to reflect more rapid progression and death in an older population.

Using notation from the statistics field, we let Y_i, $i = 1, \ldots, 5$, be an indicator variable that individuals in the ith stage of infection as a group are no longer sexually active due to declining health. A value of 1 signifies the group is no longer contributing to the spread of HIV while a value of 0 indicates the group continues to expose susceptible individuals. At time t, the number of sexually active individuals equals

$$N(t) = S(t) + \sum_{i=1}^{5}(1-Y_i)\cdot I_i(t) + \sum_{i=1}^{5}\sum_{j=0}^{5-i}(1-Y_{i+j})\cdot H_{i,j}(t) + \sum_{i=1}^{5}\sum_{j=0}^{5-i}\sum_{k=0}^{5-(i+j)}(1-Y_{i+j+k})\cdot F_{i,j,k}(t) \tag{1}$$

whereas the number of sexually inactive individuals is

$$M(t) = \sum_{i=1}^{5} Y_i\cdot I_i(t) + \sum_{i=1}^{5}\sum_{j=0}^{5-i} Y_{i+j}\cdot H_{i,j}(t) + \sum_{i=1}^{5}\sum_{j=0}^{5-i}\sum_{k=0}^{5-(i+j)} Y_{i+j+k}\cdot F_{i,j,k}(t) + O(t) + \sum_{i=1}^{5} OI_i(t) + \sum_{i=1}^{5}\sum_{j=0}^{5-i} OH_{i,j}(t) + \sum_{i=1}^{5}\sum_{j=0}^{5-i}\sum_{k=0}^{5-(i+j)} OF_{i,j,k}(t). \tag{2}$$

We define the prevalence of HIV/AIDS at time t to equal

$$\text{HIV/AIDS}(t) = 1 - \big(S(t)+O(t)\big)\big/\big(N(t)+M(t)\big). \tag{3}$$

We assume sexually active individuals mix proportionately (Blythe and Castillo-Chavez, 1989). Under the assumption of proportionate mixing, a sexually active susceptible person's risk of infection at time t is equal to

$$\lambda(t) = \beta c\left(\sum_{i=1}^{5}(1-Y_i)\cdot\rho_i I_i(t) + \sum_{i=1}^{5}\sum_{j=0}^{5-i}(1-Y_{i+j})\cdot\rho_{i,j}H_{i,j}(t) + \sum_{i=1}^{5}\sum_{j=0}^{5-i}\sum_{k=0}^{5-(i+j)}(1-Y_{i+j+k})\cdot\rho_{i,j,k}F_{i,j,k}(t)\right)/N(t), \tag{4}$$

where β is the per contact probability that an infective in the acute stage of infection infects his susceptible partner. The term β takes into account such factors as the probability r that the susceptible partner is the receptive rather than insertive partner and the proportion of contacts ξ in which a condom is used effectively. We let

$$\beta = b\big(r + (1-r)\rho\big)(1-\xi), \tag{5}$$

where b is the per contact probability of infection when the infective is the insertive partner and he is in the acute stage of infection. The term ρ is the relative infectiousness of an infective who is the receptive rather than insertive partner. We assume HIV is transmitted only through unprotected anal intercourse. The constant c is the average number of contacts an infective has per unit time. Each contact is assumed to be with a different partner. There are no steady partnerships.

The term ρ_i is the relative infectiousness of an untreated, infected individual in stage i of infection relative to an untreated, infected individual in the acute stage of infection. Individuals in the acute stage are considered highly infectious due to high levels of virus in semenal and other body secretions. Viral load is generally lower during the long asymptomatic period and rises with disease progression. Thus, we let $\rho_1 = 1.0$ and $\rho_i \leq 1$, $i = 2, \ldots, 5$. The term $\rho_{i,j}$ is the relative infectiousness of a treated individual who initiated HAART in stage i and has remained on HAART while progressing j stages. Thus,

$$\rho_{i,j} = \zeta_{j+1}\rho_{i+j}. \tag{6}$$

Similarly, $\rho_{i,j,k}$ is the relative infectiousness of an infective who initiated HAART in stage i, failed HAART while in stage $i+j$, and is currently in stage $i+j+k$. His relative infectiousness is equal to

$$\rho_{i,j,k} = \omega_{j+k+1}\rho_{i+j+k}. \tag{7}$$

3. Basic reproduction number under HAART

An important measure of an epidemic's potential impact on a population is its basic reproduction number (Dietz, 1993). The basic reproduction number R_0 is defined as the expected number of secondary infections attributable to a single infective in a completely susceptible population. For most situations, a major outbreak of disease is only possible when R_0 is greater than one. When R_0 is less than one, the epidemic is usually not sustainable. If the goal of an intervention is to eliminate disease, then the intervention needs to reduce R_0 to a value less than one. However, an intervention that reduces R_0 by even a moderate amount can have an important impact on the prevalence of disease.

The basic reproduction number is generally defined as $R_0 = \beta c D$ where β is the per contact probability an infective infects his susceptible partner, c is the average rate of

contact, and D is the average duration of the infectious period of the infective. For the model described in the previous section, the basic reproduction number is defined as

$$R_0 = \beta c \left(\sum_{i=1}^{5} (1 - Y_i) \cdot \pi_i \rho_i D_i + \sum_{i=1}^{5} \sum_{j=0}^{5-i} (1 - Y_{i+j}) \cdot \pi_{i,j} \rho_{i,j} D_{i,j} + \sum_{i=1}^{5} \sum_{j=0}^{5-i} \sum_{k=0}^{5-(i+j)} (1 - Y_{i+j+k}) \cdot \pi_{i,j,k} \rho_{i,j,k} D_{i,j,k} \right), \tag{8}$$

where D_i, $D_{i,j}$, and $D_{i,j,k}$ are the average waiting times in states I_i, $H_{i,j}$, and $F_{i,j,k}$, respectively. The average waiting times are equal to

$$\begin{aligned} D_i &= 1/(\mu_0 + \gamma + \mu_i + \tau_i + \chi_i), \\ D_{i,j} &= 1/\big(\mu_0 + \gamma + \delta_{j+1}(\mu_{i+j} + \tau_{i+j}) + \epsilon_{j+1}\big), \quad \text{and} \\ D_{i,j,k} &= 1/\big(\mu_0 + \gamma + \sigma_{j+k+1}(\mu_{i+j+k} + \tau_{i+j+k})\big). \end{aligned} \tag{9}$$

The π_i, $\pi_{i,j}$, and $\pi_{i,j,k}$ are the probabilities of reaching states I_i, $H_{i,j}$, and $F_{i,j,k}$, respectively, once in state I_1. Thus,

$$\begin{aligned} &\pi_1 = 1.0, \\ &\pi_2 = \tau_1 D_1, \\ &\pi_i = \pi_{i-1} \tau_{i-1} D_{i-1} \quad \text{for } i = 3, 4, 5, \\ &\pi_{i,0} = \pi_i \chi_i D_i, \\ &\pi_{i,j} = \pi_{i,j-1} \delta_j \tau_{i+j-1} D_{i,j-1} \quad \text{for } j = 1, \ldots, 5 - i, \\ &\pi_{i,j,0} = \pi_{i,j} \epsilon_{j+1} D_{i,j}, \quad \text{and} \\ &\pi_{i,j,k} = \pi_{i,j,k-1} \sigma_{j+k} \tau_{i+j+k-1} D_{i,j,k-1} \quad \text{for } k = 1, \ldots, 5 - (i + j). \end{aligned} \tag{10}$$

4. Average lifespan of an infective under HAART

While R_0 reflects the population level effect of the epidemic under HAART, the average lifespan L of an infective in a population for which HAART is available is a measure of the individual level effect of the epidemic under HAART. To calculate L, we need to determine the average time that an infective is sexually active as well as sexually inactive. We let OD_i, $OD_{i,j}$, and $OD_{i,j,k}$ equal the average waiting times in states OI_i, $OH_{i,j}$, and $OF_{i,j,k}$, respectively. The average waiting times are equal to

$$\begin{aligned} OD_i &= 1/\big(\alpha(\mu_0 + \mu_i + \tau_i) + \chi_i\big), \\ OD_{i,j} &= 1/\big(\alpha\big(\mu_0 + \delta_{j+1}(\mu_{i+j} + \tau_{i+j})\big) + \epsilon_{j+1}\big), \quad \text{and} \\ OD_{i,j,k} &= 1/\big(\alpha\big(\mu_0 + \sigma_{j+k+1}(\mu_{i+j+k} + \tau_{i+j+k})\big)\big). \end{aligned} \tag{11}$$

We further let q_i, $q_{i,j}$, and $q_{i,j,k}$ equal the probabilities of reaching states OI_i, $OH_{i,j}$, and $OF_{i,j,k}$, respectively, once in state I_1. Thus,

$$\begin{aligned}
&q_1 = \pi_1 \gamma D_1,\\
&q_i = q_{i-1}\alpha\tau_{i-1}OD_{i-1} + \pi_i\gamma D_i \quad \text{for } i = 2,\ldots,5,\\
&q_{i,0} = q_i\chi_i OD_i + \pi_{i,0}\gamma D_{i,0},\\
&q_{i,j} = q_{i,j-1}\alpha\delta_j\tau_{i+j-1}OD_{i,j-1} + \pi_{i,j}\gamma D_{i,j}, \quad \text{for } j = 1,\ldots,5-i,\\
&q_{i,j,0} = q_{i,j}\epsilon_{j+1}OD_{i,j} + \pi_{i,j,0}\gamma D_{i,j,0}, \quad \text{and}\\
&q_{i,j,k} = q_{i,j,k-1}\alpha\sigma_{j+k}\tau_{i+j+k-1}OD_{i,j,k-1} + \phi_{i,j,k}\gamma D_{i,j,k}\\
&\quad \text{for } k = 1,\ldots,5-(i+j).
\end{aligned} \tag{12}$$

Average lifespan can be written as

$$\begin{aligned}
L = &\sum_{i=1}^{5}(\pi_i D_i + q_i OD_i) + \sum_{i=1}^{5}\sum_{j=1}^{5-i}(\pi_{i,j}D_{i,j} + q_{i,j}OD_{i,j})\\
&+ \sum_{i=1}^{5}\sum_{j=0}^{5-i}\sum_{k=0}^{5-(i+j)}(\pi_{i,j,k}D_{i,j,k} + q_{i,j,k}OD_{i,j,k}).
\end{aligned} \tag{13}$$

In the absence of an HIV/AIDS epidemic, the average lifespan of an individual following his sexual debut is

$$L_0 = (\alpha\mu_0 + \gamma)/\big(\alpha\mu_0(\mu_0 + \gamma)\big). \tag{14}$$

It should be noted that $L \le L_0$.

5. Incorporation of HIV vaccine effects

We assume a fraction κ_1 of the new susceptible individuals is vaccinated as they enter the sexually active population while existing susceptibles are vaccinated at rate κ_2. We let $VS(t)$ equal the number of vaccinated susceptibles at time t. Once vaccinated, an individual's per contact probability of infection is reduced by a multiplicative factor θ for $0 < \theta \le 1$. Thus, we assume a leaky rather than all-or-none type of vaccine (Smith et al., 1984). The reduction in susceptibility, however, may not be durable. Vaccinated susceptibles return to the susceptible population at rate $\eta \ge 0$ where they may be revaccinated and enter the vaccinated population again.

While a vaccine's ability to reduce susceptibility to HIV infection may be limited, it may delay the onset of AIDS or reduce the infectiousness of vaccinees who become infected. These effects of vaccination could have an important public health impact on the epidemic. We let ψ_i and ϕ_i be the multiplicative effect of vaccination on disease progression and infectiousness, respectively, for an infected vaccinee in the ith stage of infection. We further assume these effects remain multiplicative in the presence of

HAART. However, vaccination is assumed not to affect the rate of HAART uptake or discontinuation.

Finally, vaccination may have an effect on risky behavior. We assume vaccination does not change the rate of contact. We also assume proportionate mixing still holds and individuals do not select partners on the basis of their vaccination status. Instead, we let o be the multiplicative effect of vaccination on a vaccinee's likelihood of using a condom for a given contact. When both partners are vaccinated, the multiplicative effect equals o^2. Thus, the per contact probability of infection under vaccination is

$$\beta\left(1-o^X\xi\right)/(1-\xi), \tag{15}$$

where X equals the number of vaccinated individuals in a partnership (i.e., 0, 1, or 2). Given that condoms are used in a fraction ξ of contacts between unvaccinated individuals, we have the constraint $0 \le o^X \le 1/\xi$. When $o < 1$, the vaccine has the effect of decreasing condom usage. When $o > 1$, vaccinees actually increase condom usage. In situations where $o^X > 1/\xi$, the per contact probability of infection is set equal to 0.

We define $VI_i(t)$, $VH_{i,j}(t)$, $VF_{i,j,k}(t)$, $VO(t)$, $VOI_i(t)$, $VOH_{i,j}(t)$, and $VOF_{i,j,k}(t)$ as the number of vaccinated individuals in the various states of the epidemic. The system of differential equations with the use of HAART and vaccination is given in Appendix A.

Under the assumption of proportionate mixing, an unvaccinated susceptible's risk of infection at time t in a vaccinated population is equal to

$$\begin{aligned}\lambda_U(t) = \beta c\Bigg(&\sum_{i=1}^{5}(1-Y_i)\cdot\rho_i I_i(t) + \sum_{i=1}^{5}\sum_{j=0}^{5-i}(1-Y_{i+j})\cdot\rho_{i,j}H_{i,j}(t)\\ &+\sum_{i=1}^{5}\sum_{j=0}^{5-i}\sum_{k=0}^{5-(i+j)}(1-Y_{i+j+k})\cdot\rho_{i,j,k}F_{i,j,k}(t)\\ &+\upsilon_1\Bigg(\sum_{i=1}^{5}(1-Y_i)\cdot\phi_i\rho_i VI_i(t) + \sum_{i=0}^{5}\sum_{j=0}^{5-i}(1-Y_{i+j})\cdot\phi_{i+j}\rho_{i,j}VH_{i,j}(t)\\ &+\sum_{i=0}^{5}\sum_{j=0}^{5-i}\sum_{k=0}^{5-(i+j)}(1-Y_{i+j+k})\cdot\phi_{i+j+k}\rho_{i,j,k}VF_{i,j,k}(t)\Bigg)\Bigg)/N(t),\end{aligned} \tag{16}$$

where $\upsilon_1 = (1-o\xi)/(1-\xi)$. A vaccinated susceptible's risk of infection is equal to

$$\begin{aligned}\lambda_V(t) = \theta\beta c\Bigg(&\upsilon_1\Bigg(\sum_{i=1}^{5}(1-Y_i)\cdot\rho_i I_i(t) + \sum_{i=1}^{5}\sum_{j=0}^{5-i}(1-Y_{i+j})\cdot\rho_{i,j}H_{i,j}(t)\\ &+\sum_{i=1}^{5}\sum_{j=0}^{5-i}\sum_{k=0}^{5-(i+j)}(1-Y_{i+j+k})\cdot\rho_{i,j,k}F_{i,j,k}(t)\Bigg)\end{aligned}$$

$$+\upsilon_2\Bigg(\sum_{i=1}^{5}(1-Y_i)\cdot\phi_i\rho_i VI_i(t)+\sum_{i=0}^{5}\sum_{j=0}^{5-i}(1-Y_{i+j})\cdot\phi_{i+j}\rho_{i,j}VH_{i,j}(t)$$

$$+\sum_{i=0}^{5}\sum_{j=0}^{5-i}\sum_{k=0}^{5-(i+j)}(1-Y_{i+j+k})\cdot\phi_{i+j+k}\rho_{i,j,k}VF_{i,j,k}(t)\Bigg)\Bigg)/N(t), \tag{17}$$

where $\upsilon_2=(1-o^2\xi)/(1-\xi)$.

6. Reproduction number under HAART and vaccination

To calculate the reproduction number under HAART and vaccination, we take into account the vaccination status of susceptible and infected individuals. We let $R_0(v,u)$ represent the expected number of secondary infections attributable to an infected vaccinee in an entirely susceptible and unvaccinated population. This number can be expressed as

$$R_0(v,u)=\beta c\upsilon_1\Bigg(\sum_{i=1}^{5}(1-Y_i)\cdot\pi_i^*\rho_i^*D_i^*+\sum_{i=1}^{5}\sum_{j=0}^{5-i}(1-Y_{i+j})\cdot\pi_{i,j}^*\rho_{i,j}^*D_{i,j}^*$$

$$+\sum_{i=1}^{5}\sum_{j=0}^{5-i}\sum_{k=0}^{5-(i+j)}(1-Y_{i+j+k})\cdot\pi_{i,j,k}^*\rho_{i,j,k}^*D_{i,j,k}^*\Bigg), \tag{18}$$

where D_i^*, $D_{i,j}^*$, and $D_{i,j,k}^*$ are the average waiting times of an infected vaccinee in states VI_i, $VH_{i,j}$, and $VF_{i,j,k}$, respectively. The average waiting times are equal to

$$\begin{aligned}
&D_i^*=1/\big(\mu_0+\gamma+\psi_i(\mu_i+\tau_i)+\chi_i\big),\\
&D_{i,j}^*=1/\big(\mu_0+\gamma+\psi_{i+j}\delta_{j+1}(\mu_{i+j}+\tau_{i+j})+\epsilon_{j+1}\big),\quad\text{and}\\
&D_{i,j,k}^*=1/\big(\mu_0+\gamma+\psi_{i+j+k}\sigma_{j+k+1}(\mu_{i+j+k}+\tau_{i+j+k})\big).
\end{aligned} \tag{19}$$

The ρ_i^*, $\rho_{i,j}^*$, and $\rho_{i,j,k}^*$ are the relative infectiousness of an infective in state VI_i, $VH_{i,j}$, and $VF_{i,j,k}$, respectively, compared to an unvaccinated infective in state I_1. These parameter are equal to

$$\begin{aligned}
&\rho_i^*=\phi_i\rho_i,\\
&\rho_{i,j}^*=\phi_{i+j}\rho_{i,j},\quad\text{and}\\
&\rho_{i,j,k}^*=\phi_{i+j+k}\rho_{i,j,k}.
\end{aligned} \tag{20}$$

The π_i^*, $\pi_{i,j}^*$, and $\pi^*i_{,j,k}$ are the probabilities of reaching states VI_i, $VH_{i,j}$, and $VF_{i,j,k}$, respectively, once in state VI_1. Thus,

$$\begin{aligned}
&\pi_1^*=1.0,\\
&\pi_2^*=\psi_1\tau_1D_1^*,
\end{aligned}$$

$$
\begin{aligned}
&\pi_i^* = \pi_{i-1}^* \psi_{i-1} \tau_{i-1} D_{i-1}^* \quad \text{for } i = 3, 4, 5, \\
&\pi_{i,0}^* = \pi_i^* \chi_i D_i^*, \\
&\pi_{i,j}^* = \pi_{i,j-1}^* \psi_{i+j-1} \delta_j \tau_{i+j-1} D_{i,j-1}^* \quad \text{for } j = 1, \ldots, 5-i, \\
&\pi_{i,j,0}^* = \pi_{i,j}^* \epsilon_{j+1} D_{i,j}^*, \quad \text{and} \\
&\pi_{i,j,k}^* = \pi_{i,j,k-1}^* \psi_{i+j+k-1} \sigma_{j+k} \tau_{i+j+k-1} D_{i,j,k-1}^* \quad \text{for } k = 1, \ldots, 5-(i+j).
\end{aligned} \tag{21}
$$

We similarly define $R_0(v, v)$ as the expected number of secondary infections due to a vaccinated infective in an entirely vaccinated population in which the effects of vaccination are durable. Thus, $R_0(v, v) = \theta(\upsilon_2/\upsilon_1) R_0(v, u)$. Likewise, we define $R_0(u, v)$ as the expected number of secondary infections from an unvaccinated infective in an entirely vaccinated population again in which vaccine effects are durable. It follows that $R_0(u, v) = \theta \upsilon_1 R_0$. Finally, we let $R_0(u, u) = R_0$.

For a population in which a fraction f of susceptible individuals is in the vaccinated state VS at the disease-free or endemic equilibrium, we define R_f as the dominant eigenvalue of the next generation matrix M_f of the epidemic process under HAART and vaccination where

$$
M_f = \begin{bmatrix} (1-f) R_0(u, u) & (1-f) R_0(v, u) \\ f R_0(u, v) & f R_0(v, v) \end{bmatrix}. \tag{22}
$$

Heuristically, if we think of infected individuals as being infectious for a single unit of time, then the product of the next generation matrix and the vector of unvaccinated and vaccinated infectives at time t is the vector of expected unvaccinated and vaccinated infectives at time $t+1$ conditional on the number at time t. Specifically,

$$
M_f \cdot \begin{bmatrix} I(t) \\ VI(t) \end{bmatrix} = \begin{bmatrix} I(t+1) \\ VI(t+1) \end{bmatrix}. \tag{23}
$$

Note that when $f = 0$, R_f reduces to R_0. Also, when there is no change in risky behavior,

$$
R_f = (1-f) R_0(u, u) + f R_0(v, v) = (1-f) R_0(u, u) + f \theta R_0(v, u). \tag{24}
$$

Implicit in our derivation of R_f is the assumption that the degree of risky behavior change does not depend on the fraction f. As an alternative, we could define υ_1 and υ_2 as some function of the vaccination parameters κ_1 and κ_2.

The vaccination fraction f is defined as the proportion of susceptibles in the vaccinated state at the disease-free or endemic equilibrium where the hazard of infection λ_U given by Eq. (16) equals zero or a positive constant, respectively. f depends on the parameters κ_1, κ_2, and η as well as the rate at which susceptibles leave the sexually active population. At an endemic equilibrium, f has the following expression.

$$
f = \frac{\kappa_1(\mu_0 + \gamma + \lambda_U + \kappa_2/\kappa_1)}{\mu_0 + \gamma + \eta + \kappa_2 + \kappa_1 \lambda_U + (1-\kappa_1)\theta \lambda_U}. \tag{25}
$$

See Appendix B for the derivation of f. At the disease-free equilibrium, f reduces to

$$f = \frac{\kappa_1(\mu_0 + \gamma + \kappa_2/\kappa_1)}{\mu_0 + \gamma + \eta + \kappa_2}. \tag{26}$$

We emphasize that when $\eta > 0$, f does not represent the proportion of susceptibles who have been vaccinated. Instead, f represents the proportion of susceptibles who have been vaccinated and remain protected by vaccination.

We define f^* as the minimum vaccination fraction for which R_f equals one. For f^* satisfying $\inf\{f : R_f \leq 1\}$, we determine κ_1^* and κ_2^* that satisfy Eq. (26) with f set equal to f^*. For example, if $R_0 = 1.49$, $1/(\mu_0 + \gamma) = 35$ years, $\theta = 1$, $\psi_i = \phi_i = 0.2$, $\upsilon_1 = \upsilon_2 = 1$, and $1/\eta = 10$ years, then $R_0(v, v) = 0.85$ and $f^* = 0.77$. Thus, $\kappa_1^* = 0.9$ and $\kappa_2^* = 0.0259$ per month will reduce the reproduction number to one. Similarly, $\kappa_1^* = 0.50$ and $\kappa_2^* = 0.0300$ per month have the same effect on the reproduction number. If no new recruits are vaccinated, then existing susceptibles need to be vaccinated at a rate of 0.0350 per month to reduce the reproduction number to one. Of note, κ_2 reflects the rate of catch-up vaccination as well as revaccination of vaccinees who have lost protection.

Based on the work of Diekmann et al. (1990) on the basic reproduction number for infectious diseases in heterogeneous populations, it follows that the epidemic reaches a unique endemic equilibrium when $R_f > 1$. When $R_f \leq 1$, the epidemic model may exhibit a globally asymptotically stable disease-free equilibrium. However, backward bifurcation may occur where a stable endemic equilibrium coexists with the disease-free equilibrium for $f^* \leq f \leq f_c$ for some critical vaccination fraction f_c.

Simple epidemic models in which multiple types of infectives or susceptibles exist have exhibited backward bifurcation for certain values for model parameters. See the work of Safan et al. (2006), Elbasha and Gumel (2006), Arino et al. (2004), Kribs-Zaleta and Velasco-Hernández (2000), Dushoff (1996), and Huang et al. (1992). van den Driessche and Watmough (2002) give conditions for the existence and stability of super and subthreshold equilibria for R_f near one. The conditions involve the derivative of the Jacobian for the model's differential equations. The Jacobian for the differential equations given in Appendix A is a 114×114 matrix if one includes infectives with advance AIDS in the epidemic process. To date, we have not been able to demonstrate that our model satisfies these conditions.

Elbasha and Gumel (2006) consider a simpler model for the population level effects of an HIV vaccine in which there is only a single stage of infection before infected individuals develop AIDS. Only vaccination of new susceptibles is permitted. Vaccination of existing susceptibles is not considered. Using this model, they establish criteria for when a unique endemic equilibrium exists as well as when two endemic equilibria exist. One criterion for a unique endemic equilibrium is that the vaccination reproduction number is greater than one. They also derive an expression for determining the backward bifurcation point. Their derivation of the vaccine reproduction number, however, is notably different than ours. They define the reproduction number in which a fraction κ_1 of new susceptibles is vaccinated as

$$R(\kappa_1) = \left(1 - \frac{\kappa_1(\mu_0 + \gamma)}{\mu_0 + \gamma + \eta}\right) R_0 + \frac{\kappa_1(\mu_0 + \gamma)}{\mu_0 + \gamma + \eta} R_0(v, v). \tag{27}$$

For $R_0 > 1$, $R_0(v, v) < R_0$, $\theta = 1$, $\upsilon_1 = \upsilon_2 = 1$, and κ_1 insufficient to achieve a disease-free equilibrium, $R(\kappa_1) > R_f > 1$ where f satisfies Eq. (25) with $\kappa_2 = 0$. For $\theta < 1$,

situations can arise in which $R(\kappa_1) < R_f$. In general, $R_f > 1$ if and only if $R(\kappa_1) > 1$. Likewise, $R_f < 1$ if and only if $R(\kappa_1) < 1$.

For backward bifurcation to occur in our model, an endemic equilibrium with $\lambda_U > 0$ would have to exist such that

$$f\left(\kappa_1^*, \kappa_2^*, \lambda_U > 0\right) > f\left(\kappa_1^*, \kappa_2^*, \lambda_U = 0\right). \tag{28}$$

Such an equilibrium may be possible if

$$\kappa_1^*\left(1-\kappa_1^*\right)(1-\theta)(\mu_0+\gamma) + \kappa_1^*\eta - \theta\left(1-\kappa_1^*\right)\kappa_2^* > 0. \tag{29}$$

When $\theta = 1$, condition (29) reduces to

$$\kappa_1^*\eta/\left(1-\kappa_1^*\right) > \kappa_2^* \tag{30}$$

for $\kappa_1^* < 1$. Returning to our previous example with $R_0 = 1.49$ if we let $\kappa_1^* = 0.9$ and $\kappa_2^* = 0.0259$ per month, then condition (30) is satisfied. However, when $\kappa_1^* \leq f^* = 0.77$, condition (30) cannot be satisfied. We postulate that the above approach can identify situations in which backward bifurcation might occur.

7. Average lifespan of an infective under HAART and vaccination

To calculate the average lifespan L^* of an infected vaccinee, we let OD_i^*, $OD_{i,j}^*$, and $OD_{i,j,k}^*$ equal the average waiting times in states VOI_i, $VOH_{i,j}$, and $VOF_{i,j,k}$, respectively. The average waiting times are equal to

$$\begin{aligned}
&OD_i^* = 1/\left(\alpha\left(\mu_0 + \psi_i(\mu_i+\tau_i)\right) + \chi_i\right),\\
&OD_{i,j}^* = 1/\left(\alpha\left(\mu_0 + \psi_{i+j}\delta_{j+1}(\mu_{i+j}+\tau_{i+j})\right) + \epsilon_{j+1}\right), \quad \text{and}\\
&OD_{i,j,k}^* = 1/\left(\alpha\left(\mu_0 + \psi_{i+j+k}\sigma_{j+k+1}(\mu_{i+j+k}+\tau_{i,j,k})\right)\right).
\end{aligned} \tag{31}$$

We further let q_i^*, $q_{i,j}^*$, and $q_{i,j,k}^*$ equal the probabilities of reaching states VOI_i, $VOH_{i,j}$, and $VOF_{i,j,k}$, respectively, once in state VI_1. Thus,

$$\begin{aligned}
&q_1^* = \pi_1^*\gamma D_1^*,\\
&q_i^* = q_{i-1}^*\alpha\psi_{i-1}\tau_{i-1}OD_{i-1}^* + \pi_i^*\gamma D_i^*, \quad \text{for } i = 2,\ldots,5,\\
&q_{i,0}^* = q_i^*\chi_i OD_i^* + \pi_{i,0}^*\gamma D_{i,0}^*,\\
&q_{i,j}^* = q_{i,j-1}^*\alpha\psi_{i+j-1}\tau_{i+j-1}OD_{i,j-1}^* + \pi_{i,j}^*\gamma D_{i,j}^*, \quad \text{for } j = 1,\ldots,5-i,\\
&q_{i,j,0}^* = q_{i,j}^*\epsilon_{j+1}OD_{i,j}^* + \pi_{i,j,0}^*\gamma D_{i,j,0}^*, \quad \text{and}\\
&q_{i,j,k}^* = q_{i,j,k-1}^*\alpha\psi_{i+j+k-1}\sigma_{j+k}\tau_{i+j+k-1}OD_{i,j,k-1}^* + \pi_{i,j,k}^*\gamma D_{i,j,k}^*\\
&\quad \text{for } k = 1,\ldots,5-(i+j).
\end{aligned} \tag{32}$$

Average lifespan can be written as

$$L^* = \sum_{i=1}^{5}\left(\pi_i^* D_i^* + q_i^* OD_i^*\right) + \sum_{i=1}^{5}\sum_{j=0}^{5-i}\left(\pi_{i,j}^* D_{i,j}^* + q_{i,j}^* OD_{i,j}^*\right) + \sum_{i=1}^{5}\sum_{j=0}^{5-i}\sum_{k=0}^{5-(i+j)}\left(\pi_{i,j,k}^* D_{i,j,k}^* + q_{i,j,k}^* OD_{i,j,k}^*\right). \tag{33}$$

Again, $L^* \leq L_0$. Furthermore, $L^* \geq L$ if $\psi_i \leq 1$ for $i = 1, \ldots, 5$.

8. Simulations

To assess the population level effects of a prophylactic HIV vaccine, we simulated an epidemic in a hypothetical population of 20,000 homosexual men. Men make their sexual debut at rate $\nu = 32.06$ new susceptibles per month such that the size of the population remains constant in the absence of an HIV/AIDS epidemic. Men leave the sexually active population at rate $\gamma = 0.00105$ per month due to age and die from non-HIV/AIDS causes at rate $\mu_0 = 0.00133$ per month. A multiplication factor of $\alpha = 1.25$ is applied to the mortality rate for men who leave the sexually active population. Thus, a man is sexually active on average for $1/(\gamma + \mu_0) = 35$ years in the absence of HIV/AIDS and has an average lifespan $L_0 = 57$ years following his sexual debut.

We choose values for the contact rate, transmission probabilities, relative infectiousness parameters, and rates of disease progression and HIV/AIDS mortality such that the basic reproduction number equals 1.68 before the introduction of HAART. In particular, we assume that infectives in the acute stage of infection are eight times more infectious than individuals in the long asymptomatic stage (Pilcher et al., 2004). And as infectives progress from the asymptomatic phase, they become more infectious. However, we assume that once individuals reach the advance stage of AIDS they are too ill to be sexually active. The average lifespan of an HIV-infected individual is 9.2 years before the introduction of HAART.

Once infected, men do not initiate HAART until they reach the third stage of infection. At this stage, about 75% of the infected men commence HAART. In subsequent stages, 75% who did not start HAART in the previous stage begin HAART. We also assume that condoms are used effectively in $\xi = 0.45$ of contacts. This value is compatible with the 55% of men who reported always using condoms in 1999 by the Stop AIDS Project and reflects a decrease in condom usage following the introduction of HAART in 1996 (Katz et al., 2002). Other HAART parameters are chosen such that HAART is equally effective in delaying disease progression as it is in reducing infectiousness. We assume $\delta_i = \zeta_i$ and $\delta_i = \sqrt{\delta_{i-1}}$. In our simulations, R_0 under HAART is equal to 1.49. While HAART has a modest impact on the basic reproduction number, average lifespan of an infected person is increased to 18.4 years. The complete list of model parameters is given in Appendix C.

Although not shown here, when the effect of HAART on disease progression δ_i is similar to its effect on infectiousness ζ_i, the basic reproduction number does not changed appreciably and the HIV/AIDS prevalence remains fairly stable over time in a population that has already reached steady state. When $\delta_i = \zeta_i$, there is some modest shrinkage in R_0

since infectives are more likely to leave the sexually active population before they die from HIV/AIDS related causes. When $\delta_i > \zeta_i$, both R_0 and HIV/AIDS prevalence decrease. When $\delta_i \gg \zeta_i$, R_0 can fall below one and HIV/AIDS prevalence will gradually go to zero. However, when $\delta_i \ll \zeta_i$, R_0 and HIV/AIDS prevalence can increase dramatically. In this case, average lifespan under HAART might increase, but so does HIV/AIDS prevalence.

To assess the potential impact of vaccination on the HIV/AIDS epidemic, we fixed the HAART parameters as given in Appendix C. We also assume an initial HIV/AIDS prevalence of approximately 28% that reflects the average prevalence among men who have sex with men in five US cities (Sifakis et al., 2005). In all simulations, we assume a continual 75% vaccination of new susceptible individuals. Existing susceptibles are vaccinated at a rate of 0.0001 per month. The effects of vaccination are assumed to be durable. Thus, at the disease-free equilibrium, 77% of sexually active susceptibles are vaccinated. For these simulations, we assume there is no change in risky behavior following vaccination.

8.1. Impact of vaccination on HIV/AIDS prevalence

Figure 2(a) shows the HIV/AIDS prevalence over 150 years for an HIV-1 vaccine that reduces susceptibility to infection, but has no effect on disease progression or infectiousness. We define vaccine efficacy on susceptibility as $VE(S) = (1-\theta)100\%$. In the absence of an effective vaccine, prevalence remains near a steady state prevalence of about 28%. As expected, when R_f is less than one, prevalence decreases toward zero. In the case of an 80% efficacious vaccine, $R_f = 0.59$ and prevalence drops to below 1% after about 92 years. Figure 2(b) illustrates the prevalence for a vaccine that does not reduce susceptibility, but delays disease progression. The vaccine has no effect on the infectiousness of vaccinees who become infected. We assume $\psi_i = \psi$ for all stages of infection. We define vaccine efficacy on disease progression as $VE(P) = (1 - \psi)100\%$ which equals the percent reduction in the rate of progression to AIDS and death due to vaccination. While such a vaccine is beneficially on an individual level, prevalence increases due to the longer infectious period of infected individuals. When $VE(P) = 80\%$, prevalence increases to a new steady state of 69%. Figure 2(c) depicts prevalence for a vaccine that delays disease progression and reduces infectiousness, but does not prevent infection. We assume $\phi_i = \phi$ for all stages of infection and define vaccine efficacy on infectiousness as $VE(I) = (1 - \phi)100\%$. The steady state prevalence of disease is reduced somewhat when $\psi_i = \phi_i$ owing to infectives leaving the sexually active population before progressing to advance AIDS. Finally, Fig. 2(d) presents the "altruistic" vaccine (Burr, 1998). In this situation, the vaccine neither reduces susceptibility to infection nor delays disease progression. It simply reduces transmission from infected vaccinees. Of note, the value of R_f is nearly identical to that of a vaccine that reduces susceptibility to infection by $\theta = \phi$. However, in the situations where R_f is less than one, prevalence decreases at a slower rate. For example, when $VE(I) = 80\%$, prevalence falls below 1% after about 110 years.

Gilbert et al. (2003) have suggested that a vaccine that delays disease progression by at least 40% would be useful. From an individual level, such a vaccine would increase the lifespan of a vaccinated infective from 18.4 to more than 25.5 years in our model. Figure 3 shows the relationship between $VE(P)$ and expected lifespan. However, when $VE(S)$ is near zero, the vaccine's effect on infectiousness will determine its impact on the epidemic. The more the vaccine reduces infectiousness, the more the reproduction

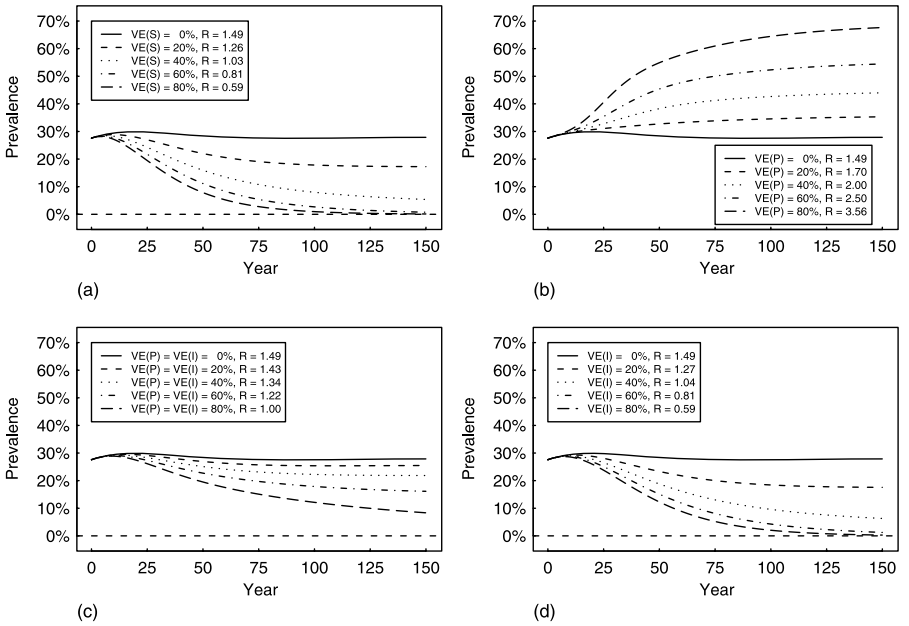

Fig. 2 HIV/AIDS prevalence over time for various HIV vaccine effects. In (a), a vaccine that only reduces susceptibility to infection is considered in a population where $R_0 = 1.49$. No change in risky behavior ($\upsilon_1 = \upsilon_2 = 1$) is assumed. The effect of vaccination is assumed durable ($\eta = 0$). Seventy-five percent of new susceptible is vaccinated while existing susceptible are vaccinated at rate 0.0001 per month. In (b), the vaccine only delays the time to AIDS while in (c) the vaccine both delays disease progression and reduces the infectiousness of vaccinees who become infected. In (d), an "altruistic" vaccine is considered in which only the infectiousness of infected vaccinees is reduced.

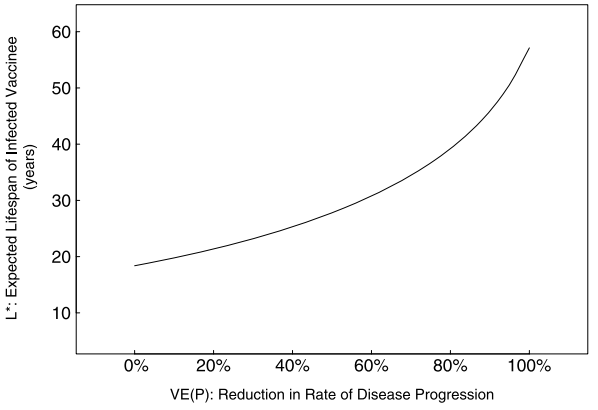

Fig. 3 Effect of vaccination of lifespan L^* of infected vaccinees.

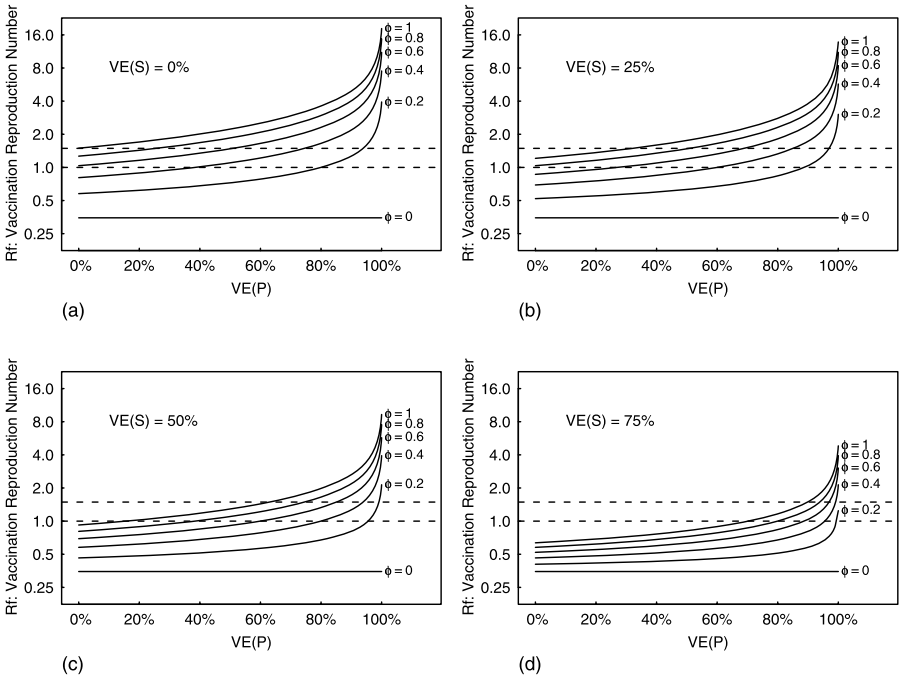

Fig. 4 Effect of vaccination on the reproduction number R_f. In (a), $VE(S)$ is set equal to 0% while $VE(P)$ and $VE(I)$ are varied in a population where $R_0 = 1.49$. No change in risky behavior ($\upsilon_1 = \upsilon_2 = 1$) is assumed. The effect of vaccination is assumed durable ($\eta = 0$). Seventy-five percent of new susceptible is vaccinated while existing susceptible are vaccinated at rate 0.0001 per month. In (b)–(d), $VE(S)$ is fixed at 25%, 50%, and 75%, respectively, while $VE(P)$ and $VE(I)$ are varied.

number and HIV/AIDS prevalence will decrease. If it has no effect on infectiousness, both the reproduction number and prevalence could increase.

Figure 4(a) demonstrates the relationship between R_f and a vaccine that delays disease progression and/or reduces infectiousness given $VE(S)$ equals zero. As in the previous figures, the vaccination fraction f equals 77%. When $VE(P)$ equals 40%, $VE(I)$ has to be greater than 30% for R_f to be less than 1.49. Interestingly, when $VE(I) \geq 60\%$, R_f falls below one. Figure 4(b) illustrates the situation in which $VE(S)$ is 25%. When $VE(P)$ equals 40%, R_f will be less than 1.49 and 1.0 if $VE(I)$ is greater than 10% and 50%, respectively. Figures 4(c) and 4(d) consider the situation in which $VE(S)$ equals 50% and 75%, respectively. In these situations, when $VE(P)$ is greater than 80% and 90%, prevalence increases unless $VE(I)$ is greater than 20%.

8.2. Impact of vaccination on the size of the sexually active population

For certain vaccine effects, we might have the perverse situation where $R_f < R_0$, but the size N of the sexually active population falls below the steady state size of an unvaccinated population. Figure 5 displays the impact of the various vaccine effects on the size of the sexually active population over time. If there were no AIDS epidemic, the size would

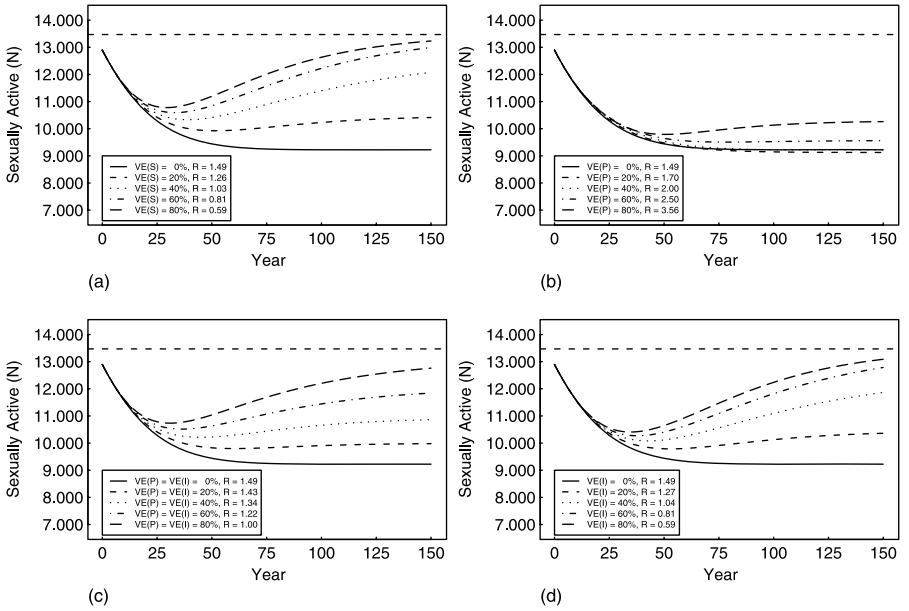

Fig. 5 Impact of vaccine effects on the size N of the sexually active population. In (a), a vaccine that only reduces susceptibility to infection is considered in a population where $R_0 = 1.49$. No change in risky behavior ($\upsilon_1 = \upsilon_2 = 1$) is assumed. The effect of vaccination is assumed durable ($\eta = 0$). Seventy-five percent of new susceptible is vaccinated while existing susceptible are vaccinated at rate 0.0001 per month. In (b), the vaccine only delays the time to AIDS while in (c) the vaccine both delays disease progression and reduces the infectiousness of vaccinees who become infected. In (d), an "altruistic" vaccine is considered in which only the infectiousness of infected vaccinees is reduced.

equal $\nu/(\gamma + \mu_0) = 13{,}471$. With the AIDS epidemic, there are 12,895 individuals in the sexually active class at time zero. In the absence of vaccination, this number drops to a steady state level of 9,223. In Fig. 5(a), we see that a vaccine that reduces susceptibility to infection increases N toward the pre-AIDS level. A vaccine that delays disease progression without reducing infectiousness has a more subtle impact on N. In Fig. 5(b), we have a slight decrease in N for $VE(P) = 20\%$ while the number increases for $VE(P)$ greater than 40%. When a vaccine delays progression and reduces infectiousness, N increases as depicted in Fig. 5(c). Figure 5(d) shows how a vaccine that only reduces the infectiousness of vaccinees who become infected behaves much like a vaccine that reduces susceptibility. In general, N at the epidemic steady state can be approximated by

$$N \approx \frac{(1-f)\nu}{\mu_0 + \gamma + \lambda_u}\left(1 + \frac{\lambda_U}{\mu_0 + \gamma + \mu_H}\right) + \frac{f\nu}{\mu_0 + \gamma + \theta\lambda_U}\left(1 + \frac{\theta\lambda_U}{\mu_0 + \gamma + \psi\mu_H}\right), \tag{34}$$

where λ_U is the hazard of infection for an unvaccinated susceptible at steady state given by Eq. (16) and μ_H is the average HIV/AIDS mortality rate of an unvaccinated infective who has HAART available to him. When $\theta = \phi$ and $\psi < 1$, λ_U increases as ψ decreases

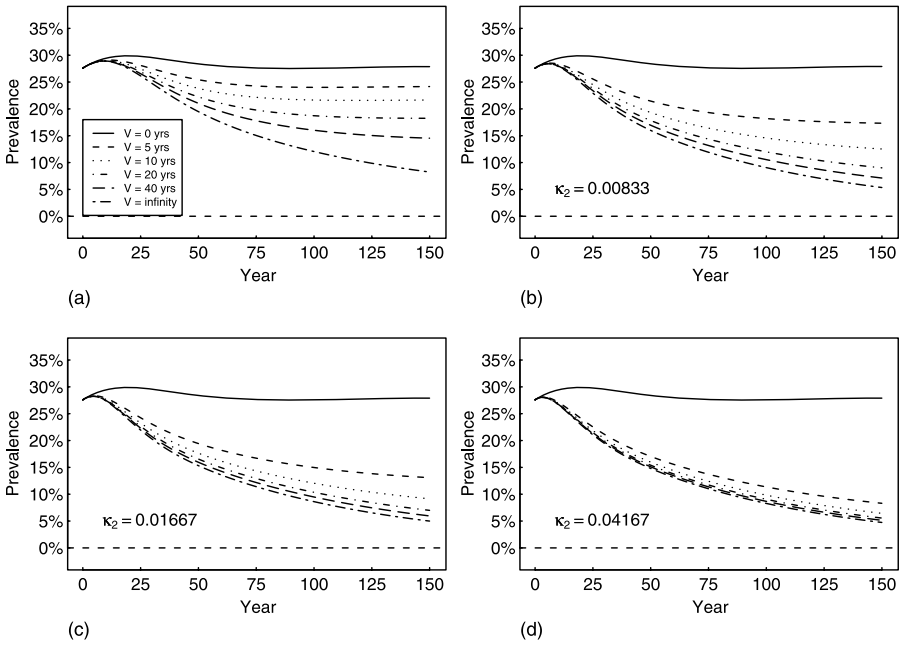

Fig. 6 Impact of vaccine duration V on HIV/AIDS prevalence. A vaccine that does not reduce susceptibility to infection, but reduces the rate of disease progression and the level of infectiousness by 80% is administered to 77% of new susceptibles in a population where $R_0 = 1.49$. Vaccine duration ranges from zero years (i.e., no benefit of vaccination) to lifelong protection. In (a), there is no catch-up vaccination of existing susceptibles and no revaccination of uninfected vaccinees who return to the unvaccinated susceptible class (i.e., $\kappa_2 = 0$). In (b)–(d), catch-up and revaccination occur at rates $\kappa_2 = 0.00833$, 0.01667, and 0.04167 per month corresponding to an average time of 10, 5, and 2 years to revaccination after losing protection.

from one and expression (34) can give a value less than that of an unvaccinated population at steady state.

8.3. Impact of vaccine duration and revaccination on HIV/AIDS prevalence

We next explored the impact of the duration of vaccine protection on HIV/AIDS prevalence. Vaccines with limited duration may have modest impact unless revaccination can be implemented when protection has been lost. We consider a vaccine that does not reduce susceptibility to infection, but reduces the rate of disease progression and level of infectiousness by 80%. When $R_0 = 1.49$ and the vaccine has lasting protection, $R_f = 1.0$ with an effective vaccination fraction of 77%. Thus, in this situation, vaccination can eliminate disease. Holding the vaccination fraction of new susceptibles κ_1 fixed at 77%, we varied the expected duration of vaccine protection $V = 1/\eta$ from 0 to 40 years. We also varied the vaccination rate of existing susceptibles κ_2 to reflect a revaccination program that takes into account the expected duration of vaccine protection. Figure 6(a) illustrates the impact of vaccine duration on HIV/AIDS prevalence when there is no revaccination (i.e., $\kappa_2 = 0$). Figure 6(b) shows how revaccination 10 years on average after a vaccinee returns to the susceptible pool restores some of the benefits of vaccination. Similarly,

Fig. 6(c) and Fig. 6(d) demonstrate the advantage of revaccination 5 and 2 years after losing protection, respectively. For a vaccine that loses protection at rate η, vaccinating existing susceptibles including those who have lost protection from earlier vaccination at a rate

$$\kappa_2 = \frac{f^*(\mu_0 + \gamma + \eta) - \kappa_1(\mu_0 + \gamma)}{1 - f^*} \tag{35}$$

can maintain the population level benefits of vaccination.

8.4. Backward bifurcation

Given that backward bifurcation is known to occur in simpler HIV transmission and vaccine models, we looked for possible backward bifurcation with our model. We did so by examining the impact of varying the initial prevalence of HIV/AIDS from 1% to 70% on the long-term outcome of vaccination for the vaccines described above. For values of $VE(S)$, $VE(P)$, and $VE(I)$ that gave a value of one for R_f, the epidemic was always eliminated. Time to elimination depended on initial prevalence with a longer time to elimination with higher initial prevalence. We also examined situations in which $VE(P) = VE(I)$ and $VE(S)$ was chosen such that R_f equalled one. Again, the epidemic was eventually eliminated.

We took a closer look at a vaccine for which $VE(S) = 0\%$ and $VE(I) = VE(P) = 80\%$ with $R_0 = 1.49$. In this situation, the vaccination fraction necessary to reduce the reproduction number to one is $f^* = 0.77$. We varied κ_1^*, κ_2^*, and η and looked closely at those values for which $\kappa_1^*\eta/(1 - \kappa_1^*) > \kappa_2^*$. The previous simulations had assumed a vaccine with durable effects (i.e., $\eta = 0$). We again varied the initial HIV/AIDS prevalence from 1% to 70%. In all scenarios we simulated, all epidemics were eliminated. To date, we have not encountered a situation in which backward bifurcation occurred with our model.

8.5. Impact of behavior change in a vaccinated population

To assess the impact of behavior change on the epidemic after the introduction of an HIV vaccine, we consider a vaccine that delays disease progression or reduces infectiousness, but does not reduce susceptibility to infection. For simplicity, we assume the effects of vaccination are durable. For a given vaccination fraction f, $\psi_i = \psi$, and $\phi_i = \phi$, we determine the decrease in condom use $1 - o_L$ among vaccinees that would completely negate the benefits of vaccination. Similarly, we determine the increase in condom use $o_U - 1$ among vaccinees that would further reduce the reproduction number to a value less than one. The hope is that the combination of a partially effective vaccine and increase in condom use could eliminate disease.

Table 1 displays the values of o_L and o_U for various vaccination fractions and values of ψ and ϕ. For a vaccine that delays disease progression and reduces infectiousness by 80% (i.e., $\psi = \phi = 0.2$), the reproduction number is reduced to a value less than one when at least 77% of susceptible individuals are vaccinated. In this situation, if condom use by a vaccinated person were reduced by 56.5%, the net effect would be to return the reproduction number back to its prevaccination value of 1.49. For a vaccine that delays disease progression and reduces infectiousness by 60% (i.e., $\psi = \phi = 0.4$), there is no

Table 1 Percent decrease ($1 - o_L$) and percent increase ($o_U - 1$) in condom use among vaccinated individuals to undo the effects of vaccination and reduce the reproduction number to a value ≤ 1.0, respectively

f	$\psi = \phi = 0.2$, $L^* = 39.6$ years			$\psi = \phi = 0.4$ $L^* = 31.2$ years			$\psi = \phi = 0.6$ $L^* = 25.5$ years		
	R_f	o_L	o_U	R_f	o_L	o_U	R_f	o_L	o_U
0.0	1.49			1.49			1.49		
0.1	1.43	0.590	*	1.46	0.814	*	1.47	0.909	*
0.2	1.36	0.577	*	1.42	0.813	*	1.45	0.909	*
0.3	1.30	0.563	*	1.38	0.809	*	1.43	0.908	*
0.4	1.24	0.546	1.508	1.35	0.806	1.603	1.41	0.908	1.644
0.5	1.17	0.526	1.259	1.31	0.802	1.361	1.39	0.907	1.402
0.6	1.11	0.503	1.129	1.28	0.798	1.252	1.38	0.906	1.299
0.7	1.04	0.474	1.044	1.24	0.794	1.182	1.36	0.905	1.235
0.8	0.98	0.435	0.981	1.20	0.790	1.134	1.34	0.904	1.190
0.9	0.91	0.379	0.930	1.17	0.785	1.097	1.32	0.903	1.157
1.0	0.85	0.271	0.885	1.13	0.780	1.069	1.30	0.902	1.132
f	$\psi = 0.4, \phi = 0.2$ $L^* = 31.2$ years			$\psi = 0.5, \phi = 0.2$ $L^* = 28.1$ years			$\psi = 0.6, \phi = 0.2$ $L^* = 25.5$ years		
	R_f	o_L	o_U	R_f	o_L	o_U	R_f	o_L	o_U
0.0	1.49			1.49			1.49		
0.1	1.40	0.200	*	1.39	0.038	*	1.39	0	*
0.2	1.31	0.158	*	1.29	0	*	1.28	0	*
0.3	1.21	0.106	*	1.19	0	*	1.17	0	*
0.4	1.12	0.039	1.374	1.09	0	1.318	1.07	0	1.266
0.5	1.03	0	1.065	0.99	0	0.978	0.96	0	0.897
0.6	0.94	0	0.887	0.89	0	0.775	0.86	0	0.667
0.7	0.84	0	0.754	0.79	0	0.612	0.75	0	0.470
0.8	0.75	0	0.633	0.69	0	0.446	0.64	0	0.240
0.9	0.66	0	0.498	0.59	0	0.193	0.54	0	0
1.0	0.57	0	0.245	0.49	0	0	0.43	0	0

*The reproduction number cannot be reduced to a value ≤ 1.0 even if all vaccinated individuals were to use condoms with all contacts

vaccination fraction that will reduce the reproduction number to one. However, when the vaccination fraction equals 0.6 and condom use among vaccinees increases by 25.2%, the reproduction number equals one and the epidemic would eventually be eliminated in this population. For a vaccine that delays disease progression and reduces infectiousness by 40% (i.e., $\psi = \phi = 0.6$), again there is no vaccination fraction that will eliminate disease. Furthermore, in this situation, a 10% decrease in condom use by vaccinees would completely negate the benefits of vaccination.

From the bottom half of Table 1, we see that a vaccine that reduces infectiousness more than it delays disease progression has a larger impact from an epidemic standpoint. For a vaccine that delays progression by 40% (i.e., $\psi = 0.6$) while reducing infectiousness by

80% (i.e., $\phi = 0.2$), the reproduction number can be reduced to a value less than one by vaccinating 50% of susceptibles. Interestingly, if all vaccinees were to stop using condoms entirely, the effect of vaccination would not be removed completely. In this situation, the reproduction number would equal 1.32, somewhat less than the prevaccination number of 1.49.

9. Discussion

Our primary aim has been to contrast the population level effects of an HIV vaccine that prevents infection with one that delays disease or reduces infectiousness of vaccinees who become infected in a population where HAART is available. We began by constructing a system of differential equations for the transmission of HIV that incorporates the use of HAART by infected individuals. We point out that our model for the use of HAART differs in some respects from other published models. McCluskey (2003), for example, considers a staged progression model for HIV disease in which infected individuals in stage $i + 1$ can return to stage i due to treatment. However, once a treated individual returns to stage i, he progresses to the next stage at the rate of an untreated infective. Our model, on the other hand, permits treated individuals to progress at a different and potentially slower rate.

Baggaley et al. (2006) have also developed a treatment model to assess the impact of antiretroviral use in resource-poor settings. Their model differs from ours in some important respects. It takes account of whether infected individuals are infected with strains of HIV-1 that are sensitive to HAART. It permits individuals with AIDS to return to the sexually active population 6 months after initiating antiretovirals. Our model could likewise permit individuals with advanced AIDS who are on HAART to return to the sexually active population by defining the indicator variables $Y_{i,j} = 0$ for all i and j, $Y_{i,j,k} = 0$ for $i + j + k < 5$ and $Y_{i,j,k} = 1$ for $i + j + k = 5$. Baggaley et al. (2006) also assume an initial increase in mortality from HAART due to immune reconstitution inflammatory syndrome (IRIS) (Goebel, 2005). However, as IRIS becomes better understood and managed in HAART patients, potential negative effects of HAART should be reduced. Also, if one believes that HAART can eliminate infectiousness (i.e., $\zeta_i = 0$) as suggested by Montaner et al. (2006), one might argue that by treating all 33 million infected individuals worldwide the epidemic could be eradicated in 45 years. One important aspect that our model does not address is the potential emergence of drug resistant strains of HIV.

Multiple investigators have modeled the potential impact of an imperfect HIV vaccine. See, for example, the work of Massad et al. (2001), Davenport et al. (2004), Smith and Blower (2004), Anderson and Hanson (2005), Gumel et al. (2006), and Abu-Raddad et al. (2007). Anderson and Hanson, in particular, present simple mathematical models for the spread and control of HIV/AIDS with a vaccine that reduces susceptibility to infection, delays disease progression, and reduces infectiousness of vaccinees who become infected. Their models also assume a fraction ϵ of vaccinees is completed protected from infection. Susceptible vaccinees lose their protection at rate γ. Their models, however, do not include the effects of treatment of HIV-infected individuals although the effects of HAART can be incorporated into the estimate of R_0. Under these models, they give a lower bound

for the vaccination fraction needed to reduce the reproduction number to a value less than one.

Anderson and Hanson's expression for the lower bound for the critical vaccination fraction involves R_{0v}, the reproduction number in an entirely vaccinated population. This number is analogous to our $R_0(v, v)$. For the Anderson and Hanson model, the vaccine will have a positive impact on the epidemic only when $R_{0v} < R_0$. In our model, the vaccine will have a positive impact at the population level when $R_f < R_0$. When there is no change in risky behavior, R_f can be expressed as a weighted average of R_0 and $R_0(v, v)$ as given in Eq. (24). In this case, R_f is less than R_0 if and only if $R_0(v, v)$ is less than R_0. When risky behavior changes due to vaccination, we can have situations in which $R_f < R_0 < R_0(v, v)$. For example, a vaccine that does not prevent infection, does not reduce infectiousness, but slows the rate of disease progression by 40%, has a durable effect, and is given to 50% of susceptible individuals will increase $R_0 = 1.49$ to $R_f = 1.83$ if risky behavior does not change. However, if counseling of vaccinees increases condom use by 20%, then $R_f = 1.47$ while $R_0(v, v) = 1.81$. It should be pointed out that our parameterization of the effect of change in risky behavior on risk of HIV infection is different from that of Anderson and Hanson. In their parameterization, they let r equal the multiplicative effect on risk of infection due to the change in risky behavior of a vaccinee. If both the susceptible and infective are vaccinated, the risk of infection is multiplied by r^2. In our model, we let υ_1 be the multiplicative effect when only a single member of a partnership is vaccinated while υ_2 is the multiplicative effect when both members are vaccinated. However, $\upsilon_2 \neq \upsilon_1{}^2$.

Several investigators have modeled the joint impact of HIV treatment and vaccination on the epidemic. Kgosimore and Lungu (2004), for example, consider a model in which the vaccine reduces susceptibility to infection, delays disease progression and reduces infectiousness in those who become infected, and has durable effects. New susceptibles are not vaccinated at the time of their sexually debut. Instead, existing susceptibles are vaccinated at rate ϕ. Unvaccinated infectives initiate treatment at rate α while vaccinated infectives initiate treatment at rate σ. However, once an infective starts treatment, he progresses to AIDS at a rate that does not depend on his vaccination status. Also, the effects of treatment are assumed durable. There are no treatment failures. And there are no changes in risky behavior. With this model, they derive the effective reproduction number R under treatment and vaccination which is nearly identical to our expression for R_f when we equate $R_0(u, u)$ to their $R_{UT}(\alpha)$ (i.e., reproduction number due to unvaccinated infectives in an unvaccinated population that receives treatment) and we equate $R_0(v, u)$ to their $R_{VT}(\sigma)$ (i.e., reproduction number due to vaccinated infectives in an unvaccinated population that receives treatment). Our vaccination fraction f at the disease-free equilibrium equals $\kappa_2/(\mu_0 + \gamma + \eta + \kappa_2)$ while their fraction equals $\phi/(b + \phi)$ where b is the birth rate which is assumed equal to the non-HIV/AIDS mortality rate.

Our model can be expanded in a number of important ways. First, we assumed that all sexually active individuals have the same rate of sexual contact and that they do not form steady partnerships. Other models for sexual behavior include models in which there are several sexual activity classes and individuals select partners either through assortative or preferred mixing (Jacquez et al., 1988). Kretzschmar and Dietz (1998) considered populations in which there is pair formation. And Morris and Kretzschmar (1997) examined models of concurrent partnerships on the spread of HIV.

We have not considered the possibility that unvaccinated individuals might change their risky behavior in the belief that many of their potential partners are vaccinated. We could multiply their rate of effective condom usage by a factor υ_1 that reflects the vaccination parameters κ_1 and κ_2 to account for this change in risky behavior.

We assumed all uninfected individuals are equally susceptible to HIV. However, there are data to support genetic heterogeneity in susceptibility. Hsu Schmitz (2000) and Del Valle et al. (2004) construct models in which uninfected individuals are classified as non-resistant, partially resistant, or fully resistant based on the existence of one or two mutant allele $\Delta 32$ of the CCR5 chemokine receptor gene. In this situation, the susceptible class would be divided into two or more groups and risk of infection modified accordingly.

Given the genetic diversity of HIV, it is conceivable that a vaccine could prevent infection or delay disease only for strains that are antigenically similar to the vaccine. If the vaccine prevents infection by certain strains, then over time the vaccine will become less effective as it no longer matches the prevalent strains. Furthermore, if the prevalent strains are more pathogenic and cause a more rapid disease progression, the impact of vaccination at the individual as well as population level could be deleterious. Blower et al. (2005), for example, considers the problem of HIV subtypes in South Africa where clades A, B, C, and D are prevalent. In future work, we hope to model an epidemic in which there are two predominant strains with different rates of disease progression and infectiousness and examine the impact of a vaccine that reduces the risk of infection to one but not the other strain.

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Appendix A: Differential equations

$$\frac{dS}{dt} = (1-\kappa_1)\nu + \eta VS - (\mu_0 + \gamma + \kappa_2 + \lambda)S,$$

$$\frac{dVS}{dt} = \kappa_1\nu + \kappa_2 S - (\mu_0 + \gamma + \eta + \theta\lambda)VS,$$

$$\frac{dI_i}{dt} = \lambda S \cdot 1\{i=1\} + \tau_{i-1}I_{i-1} \cdot 1\{i>1\} - (\mu_0 + \gamma + \mu_i + \tau_i + \chi_i)I_i,$$

$$i = 1, \ldots, 5,$$

$$\frac{dVI_i}{dt} = \theta\lambda VS \cdot 1\{i=1\} + \psi_{i-1}\tau_{i-1}VI_{i-1} \cdot 1\{i>1\} - \big(\mu_0 + \gamma + \psi_i(\mu_i + \tau_i) + \chi_i\big)VI_i, \quad i = 1, \ldots, 5,$$

$$\frac{dH_{i,j}}{dt} = \chi_i I_i \cdot 1\{j=0\} + \delta_j \tau_{i+j-1} H_{i,j-1} \cdot 1\{j>0\} - \big(\mu_0 + \gamma + \delta_{i+j}(\mu_{i+j} + \tau_{i+j}) + \epsilon_{i+j}\big) H_{i,j},$$

$$i = 1, \ldots, 5, \quad j = 0, \ldots, 5-i,$$

$$\frac{dVH_{i,j}}{dt} = \chi_i VI_i \cdot 1\{j=0\} + \psi_{i+j-1}\delta_j \tau_{i+j-1} VH_{i,j-1} \cdot 1\{j>0\} - \big(\mu_0 + \gamma + \psi_{i+j}\delta_{i+j}(\mu_{i+j} + \tau_{i+j}) + \epsilon_{i+j}\big) VH_{i,j},$$

$$i = 1, \ldots, 5, \quad j = 0, \ldots, 5-i,$$

$$\frac{dF_{i,j,k}}{dt} = \epsilon_{j+1} H_{i,j} \cdot 1\{k=0\} + \sigma_{j+k}\tau_{i+j+k-1} F_{i,j,k-1} \cdot 1\{k>0\} - \big(\mu_0 + \gamma + \sigma_{j+k+1}(\mu_{i+j+k} + \tau_{i+j+k})\big) F_{i,j,k},$$

$$i = 1, \ldots, 5, \quad j = 0, \ldots, 5-i, \quad k = 0, \ldots, 5-(i+j),$$

$$\frac{dVF_{i,j,k}}{dt} = \epsilon_{j+1} VH_{i,j} \cdot 1\{k=0\} + \psi_{i+j+k-1}\sigma_{j+k}\tau_{i+j+k-1} VF_{i,j,k-1} \cdot 1\{k>0\} - \big(\mu_0 + \gamma + \psi_{i+j+k}\sigma_{j+k+1}(\mu_{i+j+k} + \tau_{i+j+k})\big) VF_{i,j,k},$$

$$i = 1, \ldots, 5, \quad j = 0, \ldots, 5-i, \quad k = 0, \ldots, 5-(i+j),$$

$$\frac{dO}{dt} = \gamma S - \alpha\mu_0 O,$$

$$\frac{dVO}{dt} = \gamma VS - \alpha\mu_0 VO,$$

$$\frac{dOI_i}{dt} = \gamma I_i + \alpha\tau_{i-1} OI_{i-1} \cdot 1\{i>1\} - \alpha(\mu_0 + \mu_i + \tau_i) OI_i - \chi_i OI_i,$$

$$i = 1, \ldots, 5,$$

$$\frac{dVOI_i}{dt} = \gamma VI_i + \alpha\psi_{i-1}\tau_{i-1} VOI_{i-1} \cdot 1\{i>1\} - \alpha\big(\mu_0 + \psi_i(\mu_i + \tau_i)\big) VOI_i - \chi_i VOI_i, \quad i = 1, \ldots, 5,$$

$$\frac{dOH_{i,j}}{dt} = \gamma H_{i,j} + \chi_i OI_i \cdot 1\{j=0\} + \alpha\delta_j \tau_{i+j-1} OH_{i,j-1} \cdot 1\{j>0\} - \alpha\big(\mu_0 + \delta_j(\mu_{i+j} + \tau_{i+j})\big) OH_{i,j} - \epsilon_{j+1} OH_{i,j},$$

$$i = 1, \ldots, 5, \quad j = 0, \ldots, 5-i,$$

$$\frac{dVOH_{i,j}}{dt} = \gamma VH_{i,j} + \chi_i VOI_i \cdot 1\{j=0\} + \alpha\psi_{i+j-1}\delta_j \tau_{i+j-1} VOH_{i,j-1} \cdot 1\{j>0\} - \alpha\big(\mu_0 + \psi_{i+j}\delta_j(\mu_{i+j} + \tau_{i+j})\big) VOH_{i,j} - \epsilon_{j+1} VOH_{i,j},$$

$$i = 1, \ldots, 5, \quad j = 0, \ldots, 5-i,$$

$$\frac{dOF_{i,j,k}}{dt} = \gamma F_{i,j,k} + \epsilon_{j+1} OH_{i,j} \cdot 1\{k=0\} + \alpha\sigma_{j+k}\tau_{i+j+k-1} OF_{i,j,k-1} \cdot 1\{k>0\} - \alpha\big(\mu_0 + \sigma_{j+k+1}(\mu_{i+j+k} + \tau_{i+j+k})\big) OF_{i,j,k},$$

$$i = 1,\ldots,5,\ j = 0,\ldots,5-i,\ \ k = 0,\ldots,5-(i+j),$$

$$\frac{dVOF_{i,j,k}}{dt} = \gamma VF_{i,j,k} + \epsilon_{j+1} VOH_{i,j} \cdot 1\{k=0\} + \alpha\psi_{i+j+k-1}\sigma_{j+k}\tau_{i+j+k-1} VOF_{i,j,k-1} \cdot 1\{k>0\} - \alpha\big(\mu_0 + \psi_{i+j+k}\sigma_{j+k+1}(\mu_{i+j+k} + \tau_{i+j+k})\big) VOF_{i,j,k},$$

$$i = 1,\ldots,5,\ j = 0,\ldots,5-i,\ k = 0,\ldots,5-(i+j),$$

where $\lambda = \lambda_U$ given by Eq. (16) and $1\{\}$ is an indicator function that equals one when the condition is met and zero otherwise.

The initial values are:

$$S(0) = 2{,}145.5, \quad VS(0) = 6{,}436.5,$$
$$I_1(0) = 109, \quad I_2(0) = 1{,}358, \quad I_3(0) = 220,$$
$$I_4(0) = 19, \quad I_5(0) = 7,$$
$$H_{30}(0) = 2{,}093, \quad H_{31}(0) = 152, \quad H_{32}(0) = 72, \quad H_{40}(0) = 294,$$
$$H_{41}(0) = 82, \quad H_{50}(0) = 107,$$
$$F_{300}(0) = 46, \quad F_{301}(0) = 10, \quad F_{302}(0) = 13, \quad F_{310}(0) = 8,$$
$$F_{311}(0) = 11, \quad F_{320}(0) = 16,$$
$$F_{400}(0) = 4, \quad F_{401}(0) = 4, \quad F_{410}(0) = 8, \quad F_{500}(0) = 2,$$
$$O(0) = 5{,}900, \quad OI_1(0) = 1, \quad OI_2(0) = 67, \quad OI_3(0) = 15,$$
$$OI_4(0) = 2, \quad OI_5(0) = 1,$$
$$OH_{30}(0) = 574, \quad OH_{31}(0) = 50, \quad OH_{32}(0) = 33, \quad OH_{40}(0) = 56,$$
$$OH_{41}(0) = 23, \quad OH_{50}(0) = 30,$$
$$OF_{300}(0) = 14, \quad OF_{301}(0) = 3, \quad OF_{302}(0) = 5, \quad OF_{310}(0) = 2,$$
$$OF_{311}(0) = 1, \quad OF_{320}(0) = 1,$$
$$OF_{400}(0) = 1, \quad OF_{401}(0) = 1, \quad OF_{410}(0) = 2, \quad OF_{500}(0) = 1.$$

All other variables have an initial value of 0.

Appendix B: Derivation of the vaccination fraction f at an endemic equilibrium

At an endemic equilibrium,

$$\frac{dS}{dt} = (1-\kappa_1)\nu + \eta VS - (\mu_0 + \gamma + \kappa_2 + \lambda)S = 0, \tag{B.1}$$

$$\frac{dV}{dt} = \kappa_1 \nu + \kappa_2 S - (\mu_0 + \gamma + \eta + \theta\lambda)VS = 0, \tag{B.2}$$

$$\frac{d(S+VS)}{dt} = \nu - (\mu_0 + \gamma + \lambda)S - (\mu_0 + \gamma + \theta\lambda)VS = 0. \tag{B.3}$$

Equation (B.3) implies

$$\nu = (\mu_0 + \gamma + \lambda)S + (\mu_0 + \gamma + \theta\lambda)VS \tag{B.4}$$

while Eq. (B.2) implies

$$\begin{aligned} VS &= \frac{\kappa_1 \nu + \kappa_2 S}{\mu_0 + \gamma + \eta + \theta\lambda} \\ &= \frac{(\kappa_1(\mu_0 + \gamma + \lambda) + \kappa_2)S + \kappa_1(\mu_0 + \gamma + \theta\lambda)VS}{\mu_0 + \gamma + \eta + \theta\lambda}. \end{aligned} \tag{B.5}$$

Equation (B.5) implies

$$S = \frac{(\mu_0 + \gamma + \eta + \theta\lambda - \kappa_1(\mu_0 + \gamma + \theta\lambda))VS}{\kappa_1(\mu_0 + \gamma + \lambda) + \kappa_2}. \tag{B.6}$$

Adding VS to Eq. (B.6) yields

$$S + VS = \frac{(\mu_0 + \gamma + \eta + \kappa_2 + \kappa_1\lambda + (1 - \kappa_1)\theta\lambda)VS}{\kappa_1(\mu_0 + \gamma + \lambda) + \kappa_2}. \tag{B.7}$$

Thus,

$$f = \frac{VS}{S + VS} = \frac{\kappa_1(\mu_0 + \gamma + \lambda) + \kappa_2}{\mu_0 + \gamma + \eta + \kappa_2 + \kappa_1\lambda + (1 - \kappa_1)\theta\lambda}, \tag{B.8}$$

where $\lambda = \lambda_U$ as given by Eq. (16).

Appendix C: Parameter values

Table C.1 Population parameters[1]

Parameter	Value	Description	Reference
γ	0.00105	Rate at which individuals leave the sexually active population due to age	Model assumption
μ_0	0.00133	Non-HIV/AIDS mortality rate	Hoyert et al. (2005)
ν	32.06	Number of new susceptibles per month	Estimated to keep the population size stable in a population without HIV

[1] Rates are expressed as rates per month

Table C.2 HIV epidemic parameters[1]

Parameter	Value	Description	Reference
α	1.25	Multiplicative factor of advanced age on disease progression and mortality	Model assumption
β		$\beta = b \cdot (r + (1-r) \cdot \rho)(1-\xi)$	
μ_1	$0.5\mu_0$	HIV/AIDS mortality rate in Stage 1	Louie et al. (2002); Lyles et al. (2000)
μ_2	$2.5\mu_0$	HIV/AIDS mortality rate in Stage 2	Louie et al. (2002); Lyles et al. (2000)
μ_3	$5\mu_0$	HIV/AIDS mortality rate in Stage 3	Louie et al. (2002); Lyles et al. (2000)
μ_4	$10\mu_0$	HIV/AIDS mortality rate in Stage 4	Louie et al. (2002); Lyles et al. (2000)
μ_5	$20\mu_0$	HIV/AIDS mortality rate in Stage 5	Louie et al. (2002); Lyles et al. (2000)
ρ	0.0732	Relative infectiousness of an infective who is the receptive partner to that of an infective who is the insertive partner	Quinn et al. (2000)
ρ_1	1		
ρ_2	0.2608	Relative infectiousness of Stage 2 to Stage 1	Pilcher et al. (2004); Quinn et al. (2000)
ρ_3	0.3262	Relative infectiousness of Stage 3 to Stage 1	Quinn et al. (2000)
ρ_4	0.4082	Relative infectiousness of Stage 4 to Stage 1	Quinn et al. (2000)
ρ_5	1	Relative infectiousness of Stage 5 to Stage 1	Quinn et al. (2000)

[1]Rates are expressed as rates per month

Table C.3 HIV epidemic parameters (continued)[1]

Parameter	Value	Description	Reference
τ_1	0.231	Rate of disease progression from Stage 1 to Stage 2	Lyles et al. (2000); Babiker et al. (2000)
τ_2	0.0124	Rate of disease progression from Stage 2 to Stage 3	Lyles et al. (2000); Babiker et al. (2000)
τ_3	0.0169	Rate of disease progression from Stage 3 to Stage 4	Lyles et al. (2000); Babiker et al. (2000)
τ_4	0.0416	Rate of disease progression from Stage 4 to Stage 5	Babiker et al. (2000)
τ_5	0		
b	0.0314	Per contact probability that a susceptible person who is the receptive partner of an infectious individual in the first stage of infection becomes infected	Pilcher et al. (2004); Quinn et al. (2000); Gray et al. (2001); Porco et al. (2004); Vittinghoff et al. (1999);
c	6	Average number of contacts per month	Model assumption
r	0.5	Probability that the infective is the insertive partner	Model assumption
ξ	0.45	Fraction of contacts in which a condom is used effectively	Katz et al. (2002)

[1]Rates are expressed as rates per month

Table C.4 HAART parameters[1]

Parameter	Value	Description	Reference
δ_1	0.1	Multiplicative effect of HAART on disease progression in an anti-retroviral naïve individual	Sanders et al. (2005); Quinn et al. (2000); Paltiel et al. (2005); Thiebaut et al. (2005)
δ_2	$\sqrt{\delta_1}$	Multiplicative effect of HAART on disease progression after progressing one stage	Toth et al. (2000)
δ_3	$\sqrt{\delta_2}$	Multiplicative effect of HAART on disease progression after progressing two stages	Toth et al. (2000)
δ_4	$\sqrt{\delta_3}$	Multiplicative effect of HAART on disease progression after progressing three stages	Toth et al. (2000)
δ_5	$\sqrt{\delta_4}$	Multiplicative effect of HAART on disease progression after progressing four stages	Toth et al. (2000)

[1]Rates are expressed as rates per month

Table C.5 HAART parameters[1] (continued)

Parameter	Value	Description	Reference
ϵ_1	0.0005	Rate of HAART discontinuation for an individual who has not progressed	Sanders et al. (2005); Paltiel et al. (2005); Thiebaut et al. (2005)
ϵ_2	0.0034	Rate of HAART discontinuation for an individual who has progressed 1 stage	Sanders et al. (2005)
ϵ_3	0.0063	Rate of HAART discontinuation for an individual who has progressed 2 stages	Sanders et al. (2005); King Jr. et al. (2003); Deeks (2003)
ϵ_4	–	Rate of HAART discontinuation for an individual who has progressed 3 stages	Sanders et al. (2005); King Jr. et al. (2003); Deeks (2003)
ϵ_5	–	Rate of HAART discontinuation for an individual who has progressed 4 stages	Sanders et al. (2005); King Jr. et al. (2003); Deeks (2003)

[1]Rates are expressed as rates per month

Table C.6 HAART parameters[1] (continued)

Parameter	Value	Description	Reference
ζ_1	δ_1	Effect of HAART on infectiousness in an antiretroviral nave individual	Porco et al. (2004)
ζ_2	δ_2	Effect of HAART on infectiousness for an individual who has progressed one stage	Porco et al. (2004)
ζ_3	δ_3	Effect of HAART on infectiousness for an individual who has progressed two stages	Porco et al. (2004)
ζ_4	δ_4	Effect of HAART on infectiousness for an individual who has progressed three stages	Porco et al. (2004)
ζ_5	δ_5	Effect of HAART on infectiousness for an individual who has progressed four stages	Porco et al. (2004)
σ_1	$\sqrt{d3}$	Residual effect of HAART on disease progression when $j+k=0$	Sanders et al. (2005)
σ_2	1	Residual effect of HAART on disease progression when $j+k=1$	Sanders et al. (2005)
σ_3	1	Residual effect of HAART on disease progression when $j+k=2$	Sanders et al. (2005)
σ_4	1	Residual effect of HAART on disease progression when $j+k=3$	Sanders et al. (2005)
σ_5	1	Residual effect of HAART on disease progression when $j+k=4$	Sanders et al. (2005)

[1] Rates are expressed as rates per month

Table C.7 HAART parameters[1] (continued)

Parameter	Value	Description	Reference
χ_1	0	HAART uptake rate in Stage 1	Model assumption
χ_2	0	HAART uptake rate in Stage 2	Model assumption
χ_3	$3\tau_3$	HAART uptake rate in Stage 3	Model assumption
χ_4	$3\tau_4$	HAART uptake rate in Stage 4	Model assumption
χ_5	$3\mu_5$	HAART uptake rate in Stage 5	Model assumption
ω_1	1	Residual effect of HAART on infectiousness when $j+k=0$	Model assumption
ω_2	1	Residual effect of HAART on infectiousness when $j+k=1$	Model assumption
ω_3	1	Residual effect of HAART on infectiousness when $j+k=2$	Model assumption
ω_4	1	Residual effect of HAART on infectiousness when $j+k=3$	Model assumption
ω_5	1	Residual effect of HAART on infectiousness when $j+k=4$	Model assumption

[1] Rates are expressed as rates per month

Table C.8 HIV vaccination parameters[1]

Parameter	Value	Description	Reference
η	$\eta \geq 0$	Rate at which vaccinated susceptibles return to the unvaccinated susceptible population	Variable
o	$0 \leq o^X \leq \frac{1}{\xi}$	Effect of vaccination on condom use	Variable
θ	$0 < \theta \leq 1$	Effect of vaccination on susceptibility to HIV infection	Variable
κ_1	0.75	Proportion of susceptibles who are vaccinated at sexual debut	Model assumption
κ_2	0.0001	Rate at which existing susceptibles are vaccinated	Model assumption
ϕ	$0 < \phi \leq 1$	Effect of vaccination on infectiousness	Variable
ψ	$0 < \psi \leq 1$	Effect of vaccination on rate of disease progression and mortality	Variable
f	0.77	Vaccination fraction	Model assumption

[1]Rates are expressed as rates per month

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