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ORIGINAL ARTICLE

Theoretical Assessment of Public Health Impact of Imperfect Prophylactic HIV-1 Vaccines with Therapeutic Benefits

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Abstract This paper presents a number of deterministic models for theoretically assessing the potential impact of an imperfect prophylactic HIV-1 vaccine that has five biological modes of action, namely "take," "degree," "duration," "infectiousness," and "progression," and can lead to increased risky behavior. The models, which are of the form of systems of nonlinear differential equations, are constructed via a progressive refinement of a basic model to incorporate more realistic features of HIV pathogenesis and epidemiology such as staged progression, differential infectivity, and HIV transmission by AIDS patients. The models are analyzed to gain insights into the qualitative features of the associated equilibria. This allows the determination of important epidemiological thresholds such as the basic reproduction numbers and a measure for vaccine impact or efficacy. The key findings of the study include the following (i) if the vaccinated reproduction number is greater than unity, each of the models considered has a locally unstable disease-free equilibrium and a unique endemic equilibrium; (ii) owing to the vaccine-induced backward bifurcation in these models, the classical epidemiological requirement of vaccinated reproduction number being less than unity does not guarantee disease elimination in these models; (iii) an imperfect vaccine will reduce HIV prevalence and mortality if the reproduction number for a wholly vaccinated population is less than the corresponding reproduction number in the absence of vaccination; (iv) the expressions for the vaccine characteristics of the refined models take the same general structure as those of the basic model.

Keywords HIV · AIDS · Differential infectivity · Staged progression · Vaccine · Mathematical model · Equilibrium · Stability · Backward bifurcation

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1. Introduction

The HIV/AIDS pandemic poses an unprecedented threat to global health and human development. An estimated 34–46 million people are currently living with HIV/AIDS. More than 20 million people have died from AIDS during the last 20 years, of which an estimated 3 million deaths occurred in 2003 alone. AIDS is now the leading cause of death in sub-Saharan Africa and the fourth-leading cause of death globally. The pandemic has cut life expectancy significantly in many countries in sub-Saharan Africa. For example, life expectancy in Botswana decreased from 65 years in 1985–1990 to 40 years in 2000–2005 (WHO, 2004).

In addition to being a serious public health problem, HIV/AIDS has far reaching consequences to all social and economic sectors of society. It exacerbates poverty, reduces educational opportunities, devastates the workforce, creates large numbers of orphans, and exerts tremendous pressure on already limited health and social services (World Bank, 1997; UN, 2004). For example, HIV/AIDS has cut annual growth rates in Africa by 2–4% per year (Dixon et al., 2002). The annual economic loss of slower economic growth as a result of HIV/AIDS-related death or disability in 50 countries (US, Russia, 5 in Asia, 8 in Latin America, and 35 in sub-Saharan Africa) during 1992–2000 is estimated at $25 billion (Fleck, 2004).

The use of an effective vaccine is widely considered to be the best way to slow or curtail the HIV/AIDS pandemic (Chang et al., 2003; Esparza and Osmanov, 2003). However, it is unlikely that a highly effective vaccine will be available soon. Instead, the current expectation is that the most likely vaccine that will be developed in the foreseeable future may have lower efficacy in protecting against infection and/or result in a shorter duration of protection in successfully immunized people than most traditional vaccines. In addition, by eliciting broad cellular immune responses, such a vaccine may reduce viral RNA concentrations and reduce infectiousness in infected vaccinated individuals. The vaccine may also offer some therapeutic benefits by altering the clinical course of the disease (Shiver et al., 2002; Calarota and Weiner, 2003; Berzofsky et al., 2004; Lee et al., 2004; Santra et al., 2004; Shiver and Emini, 2004). Furthermore, due to the attributes of these vaccines as well as the behaviors associated with HIV transmission, it has been suggested that widespread vaccination may cause behavioral reversals where vaccinated people are likely to engage in more risky behaviors (Chesney et al., 1997; Griensven et al., 2004; Newman et al., 2004). The wide ranging vaccine properties, modes of transmission, and associated behavioral issues imply the need for developing adequate mathematical models to assess the community-wide impact of vaccination strategies before imperfect prophylactic HIV-1 vaccines are deployed.

Over the last decade, several compartmental mathematical models have been developed to model the transmission dynamics of HIV and assess the impact of imperfect vaccines. For instance, Blower and McLean developed a mathematical model to explore the impact of various types of imperfect HIV prophylactic vaccines (McLean and Blower, 1993; Blower and McLean, 1994; Blower and McLean, 1995). The characteristics of the vaccine considered in these studies include: having effect in some but not all people; reducing, but not fully eliminating,

susceptibility in those immunized; waning protective immunity with time; reducing the transmissibility of virus and/or reducing the mean duration of infectiousness of breakthrough infections. These four modes of action are referred to as "take," "degree," "duration," and "reduced infectiousness," respectively. Other studies that build on this model include Massad et al. (2001), and Porco and Blower (1998, 2000). The latter model was also used to predict the impact of vaccination programs when two HIV subtypes are circulating.

In addition to the four modes of actions discussed above, recent mathematical studies have considered characteristics of imperfect HIV-1 vaccines that include lengthening of the incubation period (by slowing "progression" to AIDS) and increasing risky behaviors (see, for instance, Anderson and Garnett, 1996; Massad et al., 2001; Blower et al., 2002; Smith and Blower, 2004; Anderson and Hanson, 2005). Generally, these models have several equilibrium solutions, including the perverse outcome of higher prevalence and AIDS-related mortality following vaccination.

This paper provides a rigorous qualitative analysis of a basic HIV-1 vaccination model that incorporates the key features of these models. It also offers several extensions to this basic model. First, the contribution of AIDS patients in the transmission of HIV is often ignored in most HIV epidemic models by imposing the simplifying assumptions that AIDS mortality is instantaneous or that AIDS patients are not capable of mixing and acquiring new sex partners. Usually no empirical support is offered to justify these assumptions. In this paper, a model that incorporates the contribution of HIV-infected people in the AIDS stage on the transmission dynamics of HIV-1 is developed and analyzed. Second, studies of HIV RNA in infected individuals show that viral levels vary widely between individuals, with individuals having higher viral loads during the chronic phase tending to develop AIDS more rapidly. Because RNA levels are correlated with infectiousness (e.g., Gray et al., 2001), earlier HIV models need to be extended to study the impact of an HIV vaccine given the variations in infectiousness and the increase in the average progression time from infection to AIDS that goes along with a decreased viral load during the chronic phase of infection (Hyman et al., 1999). This paper presents a differential infectivity model to investigate the effects of vaccination on the distribution of infected individuals in different RNA strata. Finally, it is well-known that an HIV-infected individual typically passes through several infection stages, being highly infectious during the preantibody phase (primary infection stage), maintaining low infectivity during the asymptomatic phase (secondary infection stage), and becoming highly infectious as s/he progresses toward AIDS (AIDS stage) (Longini et al., 1989; Hethcote and Ark, 1992; Fauci et al., 1996; Hyman et al., 1999; Perelson and Nelson, 1999; McCluskey, 2003). These multiple infection stages are essential part of HIV transmission dynamics and are considered in this study via the use of a staged progression model. A staged progression model is designed to study the variation of infectiousness in a given individual over time and to capture the effects of vaccination on HIV transmission as infected individuals pass through these different stages.

The paper is organized as follows. A basic model for assessing the impact of an anti-HIV prophylactic vaccine with certain characteristics is developed

and analyzed in Section 2. The model is then extended to incorporate the effect of HIV transmission by individuals in the AIDS stage in Section 3. Further extensions to incorporate differential infectivity and staged progression are given in Sections 4 and 5, respectively. The work is summarized in Section 6.

2. Basic HIV-1 vaccine model

We begin by analyzing a deterministic model of HIV-1 transmission dynamics to assess the impact of an imperfect vaccine (McLean and Blower, 1993; Anderson and Garnett, 1996; Blower et al., 2002; Smith and Blower, 2004). The model stratifies the homogeneously mixing sexually-active population into five classes: susceptibles (X), vaccinated who are not infected yet (V), infecteds who are not vaccinated (Y), vaccinated who acquired infection (W), and AIDS cases (A). It is assumed that, at any moment in time, new recruits enter the sexually active population at a rate Λ. These individuals are assumed to be susceptible (i.e., they are categorized in the X class) and a proportion p of these individuals are successfully vaccinated (and moved to the vaccinated class V). As in other models (e.g., McLean and Blower, 1993; Anderson and Garnett, 1996; Blower et al., 2002), we consider only cohort vaccination where only the new recruits into the sexually-active community (i.e., pre- and early-adolescents) are vaccinated (see also Clements et al., 2004 for further discussion). Other studies have investigated different strategies such as vaccinating a proportion of all sexually-active members of the community (e.g., Kribs-Zaleta and Velasco-Hernández, 2000; Gumel et al., 2004) or vaccinating a fraction of both newborns and susceptible individuals (e.g., Arino et al., 2003). The parameter p is a composite measure ($p = \epsilon\,\tilde{p}$) of vaccine take (ϵ) and coverage ($\tilde{p}$). Susceptible individuals acquire HIV infection at time-dependent rate λ. Upon effective contact with an infected individual (so that transmission occurs), a susceptible individual moves into the Y class of infected individuals. It is assumed that vaccinated people engage in increased risky behavior at a factor r compared to unvaccinated people, and that the vaccine-induced immunity acquired by vaccinated individuals wanes, so that these vaccinated people eventually move to the X class of susceptible individuals at a rate γ. Once there, these individuals assume the same risky behavior of susceptibles. Vaccinated individuals can experience break-through infection (due to the incomplete protection provided by the vaccine) and become infected at a rate $qr\,\lambda$. Upon becoming infected with HIV, vaccinated individuals enter the class W of vaccinated-infected people. The relative risk of infectiousness of individuals in this category compared to those in unvaccinated category Y is modeled by the parameter s. Infected individuals (whether vaccinated or not) can progress to full-blown AIDS stage at a rate $\theta\sigma$ if vaccinated and σ if not vaccinated. AIDS patients have an additional disease-induced mortality rate α. The temporal dynamics of the aforementioned variables can then be monitored using the following deterministic model (see Fig. 1A for a transfer

diagram):

$$\begin{aligned} \mathrm{d}X/\mathrm{d}t &= (1-p)\Lambda - \mu X - \lambda X + \gamma V, \\ \mathrm{d}V/\mathrm{d}t &= p\Lambda - \mu V - qr\lambda V - \gamma V, \\ \mathrm{d}Y/\mathrm{d}t &= \lambda X - (\mu+\sigma)Y, \\ \mathrm{d}W/\mathrm{d}t &= qr\lambda V - (\mu+\theta\sigma)W, \\ \mathrm{d}A/\mathrm{d}t &= \sigma Y + \theta\sigma W - (\mu+\alpha)A. \end{aligned} \tag{1}$$

The infection rate, λ, depends on the transmission probability per partnership, the number of partners of infected individuals (in categories Y and W) and the proportion of infected individuals in each category. The probability of HIV transmission from a person in category Y to a susceptible person in category X or V is β whereas that from a person in category W is adjusted by the degrees of infectiousness s and increased risk behavior r. The number of partners is subsumed in β. Assuming homogeneous mixing, this gives

$$\lambda = \beta\frac{Y}{N} + rs\beta\frac{W}{N}, \tag{2}$$

where N is total number of people in the sexually active population at time t. An imperfect HIV vaccine could have a wide range of properties, including the possibility of reducing susceptibility to infection ($q < 1$), reducing the transmissibility of the virus ($s < 1$), and/or reducing the rate of progression of breakthrough infections to AIDS ($\theta < 1$). In addition, vaccinated individuals may exhibit increased risky behavior ($r \geq 1$) (Chesney et al., 1997; Newman et al., 2004).

It should be noted, however, that the basic model (1) does not currently incorporate a few other useful aspects associated with the dynamics of HIV-1 such as gender, age, heterogeneity of mixing between different sexual activity groups, and other modes of HIV transmission (sharing contaminated needles by IV drug users, mother-to-child transmission, blood transfusion, etc.). The model also assumes that other strategies such as the use of condoms, HIV testing and counseling, and antiretroviral therapy are not used (this allows us to focus on assessing the singular role of anti-HIV preventive vaccine on curtailing the spread of HIV in a given community). A common assumption frequently imposed in models of HIV epidemiology is that AIDS patients do not acquire new sex partners, requiring the exclusion of AIDS patients from the sexually active population. In this case,

$$N = X + V + Y + W. \tag{3}$$

Thus, the equation for the rate of change of the population of AIDS patients in (1) can be discarded (since the model assumes that individuals in the AIDS class do

not interact with the rest of the population). The implications of including AIDS patients in the sexually active community will be discussed in Section 3.

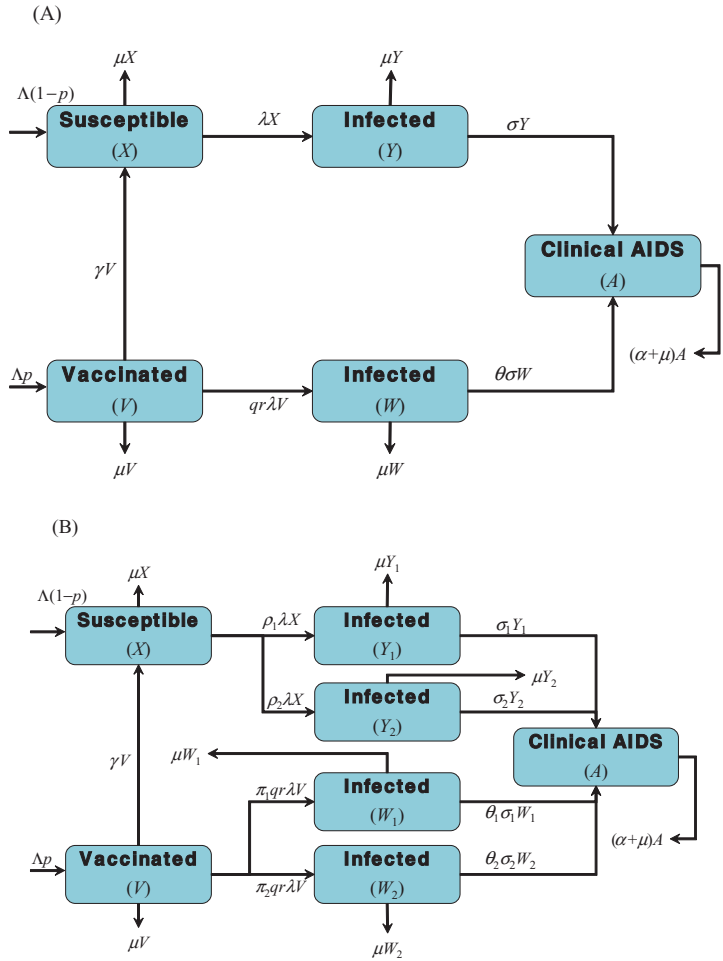

Fig. 1 (A) The basic HIV-1 vaccine model divides the population into five groups according to their susceptibilities, infectiousness, and differences in rates of progression to AIDS. The properties of the vaccine include coverage/take ($p = \epsilon\,\tilde{p}$), degree protection (q), waning immunity (γ), induced increases in risk behavior (r), lower infectiousness of vaccinated infected (s), and slower progression to AIDS (θ). (B) The differential infectivity model stratifies the population into seven groups according to their susceptibilities, infectiousness, and differences in rates of progression to AIDS. The vaccine acts through take (p), degree protection (q), waning immunity (γ), infectiousness (s_i), slowing progression to AIDS (θ_j), and inducing increases in risk behavior (r). (C) The staged-progression model stratifies the population into seven groups according to their susceptibilities, infectiousness, and differences in stages of progression to AIDS. The vaccine acts through take (p), degree protection (q), waning immunity (γ), infectiousness (s_i), slowing progression between stages (θ_j), and inducing increases in risk behavior (r).

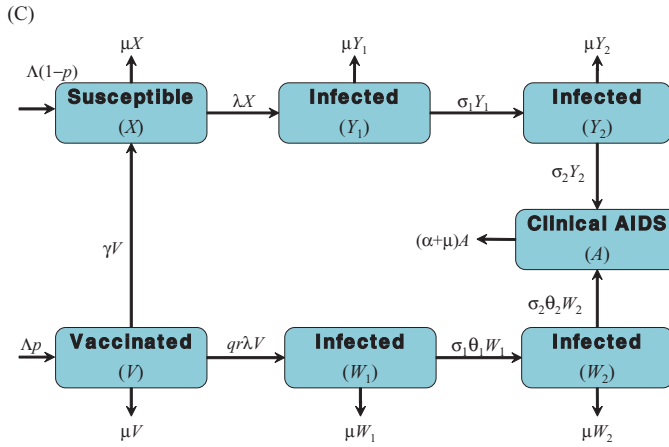

Fig. 1 Continued.

2.1. Basic properties

All parameters of the model are assumed to be nonnegative. Furthermore, since the model (1) monitors human populations, it is assumed that all the state variables are nonnegative at time $t = 0$. Consider the biologically-feasible region

$$\mathfrak{D} = \{(X, V, Y, W) \in \Re_+^4 : X + V + Y + W \leq \Lambda/\mu\}.$$

It can be shown that all solutions of the system starting in $\mathfrak{D}$ remain in $\mathfrak{D}$ for all $t \geq 0$. Thus, $\mathfrak{D}$ is positively-invariant and it is sufficient to consider the dynamics of the flow generated by (1) in this positively-invariant domain $\mathfrak{D}$. It can be shown that unique solutions exist in $\mathfrak{D}$ for all positive time. Thus, the model is epidemiologically and mathematically well posed (see Hethcote, 2000 for further discussion).

2.2. Equilibria, stability, and reproduction numbers

2.2.1. The model without vaccination

We consider, first of all, the model (1) in the absence of vaccination. In this case, $p = \gamma = V = W = 0$, and the model reduces to the following two-dimensional system:

$$\mathrm{d}X/\mathrm{d}t = \Lambda - \mu X - \beta \frac{Y}{N} X, \quad \mathrm{d}Y/\mathrm{d}t = \beta \frac{Y}{N} X - (\mu + \sigma) Y. \tag{4}$$

The equilibria of this model are obtained by setting the right-hand sides of (4) to zero. It follows then that (4) has a disease-free equilibrium $e_0 = (X^*, Y^*) = (\Lambda/\mu, 0)$ which can be shown (via linearization for instance) to be locally asymptotically stable if $\mathcal{R}_0 = \beta/(\mu + \sigma) < 1$ and unstable if $\mathcal{R}_0 > 1$.

Furthermore, for $\mathcal{R}_0 > 1$, the model has a unique and locally asymptotically stable endemic equilibrium, given by

$$e_1 = (X^{**}, Y^{**}) = \left(\frac{\Lambda D_u}{\mathcal{R}_0 - 1 + \mu D_u}, \frac{\Lambda(\mathcal{R}_0 - 1) D_u}{\mathcal{R}_0 - 1 + \mu D_u} \right), \tag{5}$$

where $D_u = 1/(\mu + \sigma)$ denotes the average duration of infectiousness for unvaccinated individuals. Using Dulac criterion (see, e.g., Perko, 1996), with a Dulac function $D = 1/Y$, it is easy to show that there are no periodic solutions in the associated feasible region $\mathfrak{D} = \{(X, Y) \in \Re^2_+ : X + Y \leq \Lambda/\mu\}$. Thus, e_0 is globally asymptotically stable if $\mathcal{R}_0 < 1$, and the unique endemic equilibrium is globally asymptotically stable if $\mathcal{R}_0 > 1$. In other words, for the model without vaccination, HIV will be eliminated if $\mathcal{R}_0 < 1$ and will persist if $\mathcal{R}_0 > 1$. The threshold quantity $\mathcal{R}_0$ is the *basic reproduction number* of infection which defines the number of new HIV infections generated by a single infected individual in a completely susceptible population (see, e.g., Anderson and May, 1991; Hethcote, 2000). Mathematically, $\mathcal{R}_0$ is defined as the spectral radius (dominant eigenvalue) of the next generation matrix (see, e.g., Diekmann et al., 1990; van den Driessche and Watmough, 2002).
Having established the above results, we now return to the vaccination model (1).

2.2.2. Stability of equilibria for vaccination model
The vaccination model (1) has a disease-free equilibrium given by

$$\mathcal{E}_0 = (X^*, V^*, Y^*, W^*) = \left(\frac{[\gamma + (1-p)\mu]\Lambda}{\mu(\mu + \gamma)}, \frac{p\Lambda}{\mu + \gamma}, 0, 0 \right). \tag{6}$$

To find the conditions under which this equilibrium is locally asymptotically stable, the Jacobian matrix of the system (1) is evaluated at the disease-free equilibrium $\mathcal{E}_0$ to give,

$$J(\mathcal{E}_0) = \begin{pmatrix} -\mu & \gamma & -\left(1 - \frac{p\mu}{\gamma+\mu}\right)(\mu+\sigma)\mathcal{R}_0 & -rs\left(1 - \frac{p\mu}{\gamma+\mu}\right)(\mu+\sigma)\mathcal{R}_0 \\ 0 & -(\gamma+\mu) & -\frac{pqr\mu(\mu+\sigma)\mathcal{R}_0}{\gamma+\mu} & -\frac{pqr^2s\mu(\mu+\sigma)\mathcal{R}_0}{\gamma+\mu} \\ 0 & 0 & -(\mu+\sigma)[1-\mathcal{R}_0(1-\frac{p\mu}{\gamma+\mu})] & rs(\mu+\sigma)\mathcal{R}_0(1-\frac{p\mu}{\gamma+\mu}) \\ 0 & 0 & \frac{pqr\mu(\mu+\sigma)\mathcal{R}_0}{\gamma+\mu} & -(\mu+\theta\sigma) + \frac{pqr^2s\mu(\mu+\sigma)\mathcal{R}_0}{\gamma+\mu} \end{pmatrix}.$$

Clearly, two eigenvalues of $J(\mathcal{E}_0)$ are $-\mu$ and $-(\gamma + \mu)$, both negative. It can be shown that the remaining two eigenvalues (obtained from the 2×2 matrix in the lower corner of $J(\mathcal{E}_0)$) have negative real parts if and only if

$$R(p) = \mathcal{R}_0 \left\{ 1 - \frac{p\,\mu}{\gamma + \mu} \left[1 - \frac{q\,r^2\,s\,(\mu + \sigma)}{(\mu + \theta\,\sigma)} \right] \right\} < 1. \tag{7}$$

Furthermore, it can be seen that at least one of these eigenvalues has a positive real part if $R(p) > 1$. Thus, we have established the following result.

Lemma 1. *The disease-free equilibrium $\mathcal{E}_0$ of (1) is locally asymptotically stable if $R(p) < 1$ and unstable if $R(p) > 1$.*

The threshold quantity $R(p)$ is known as the *vaccinated reproduction number* (see, e.g., Blower et al., 2002). Biologically-speaking, this measures the number of new secondary infections generated by a single HIV-infected individual in a community where anti-HIV vaccines are used as a control strategy. Notice that in the absence of vaccination ($p = 0$), $R(p) = R(0) = \mathcal{R}_0 = \beta/(\mu + \sigma)$.

Lemma 1 establishes that if the disease-free equilibrium exists, it is locally asymptotically stable if and only if $R(p) < 1$. However, the disease-free equilibrium may not be globally asymptotically stable even if $R(p) < 1$. There is the possibility of backward bifurcation (bistability), where a stable endemic equilibrium co-exist with the disease-free equilibrium when $R(p) < 1$ (see, e.g., Kribs-Zaleta and Velasco-Hernández, 2000; Arino et al., 2003; Corbett et al., 2003). To investigate this, we substitute the force of infection λ into (1) and show that (at steady-state) the endemic equilibria of (1) satisfy the following polynomial:

$$\lambda(B_1\lambda^2 + B_2\lambda + B_3) = 0, \tag{8}$$

where

$$\begin{aligned} B_1 &= qr[\mu + \theta\sigma + p(1-\theta)\sigma], \\ B_2 &= (\gamma + \mu + p\,\sigma)(\mu + \theta\,\sigma) - pqr^2s(\mu + \sigma)^2\mathcal{R}_0 \\ &\quad + qr(\mu + \sigma)[(\mu + \theta\sigma)(1 - p)(1 - \mathcal{R}_0) + \mu p], \\ B_3 &= (\gamma + \mu)\,(\mu + \sigma\,)(\mu + \theta\,\sigma)[1 - R(p)]. \end{aligned}$$

$\lambda = 0$ gives the disease-free equilibrium while the quadratic in (8) can be analyzed for the possibility of multiple equilibria. It should be noted that in the case of a perfect vaccine ($q = 0$), $B_1 = 0$, $B_2 > 0$ and the quadratic equation becomes linear in λ (with $\lambda = -B_3/B_2$). In this case, the vaccination model (1) has a unique endemic equilibrium if and only if $B_3 > 0$ (i.e., $R(p) > 1$), ruling out the possibility of backward bifurcation in this case. It is worth noting that the coefficient B_1 is always positive when the vaccine is imperfect (since $0 < \theta \leq 1$) and B_3 is positive (negative) if $R(p)$ is less than (greater than) unity, respectively. Hence, we have the following result:

Lemma 2. *The vaccination model (1) has*

(i) *a unique endemic equilibrium if $B_3 < 0 \Leftrightarrow R(p) > 1$;*

(ii) *a unique endemic equilibrium if* $B_2 < 0$, *and* $B_3 = 0$ *or* $B_2^2 - 4B_1B_3 = 0$;
(iii) *two endemic equilibria if* $B_3 > 0$, $B_2 < 0$ *and* $B_2^2 - 4B_1B_3 > 0$;
(iv) *no endemic equilibrium otherwise.*

To find the backward bifurcation point when $R(p) < 1$, we set the discriminant $B_2^2 - 4B_1B_3$ to zero and solve for the critical value of $R(p)$. This gives

$$R^c(p) = 1 - \frac{B_2^2}{4(\gamma+\mu)(\mu+\sigma)(\mu+\theta\sigma)B_1}, \tag{9}$$

from which it can be shown that backward bifurcation occurs for values of $R(p)$ in the inequality $R^c(p) < R(p) < 1$.

To numerically illustrate this fact, the model (1) is simulated using the following arbitrary set of parameters: $\Lambda = 1$, $p = 0.9$, $\mu = 0.02$, $r = 1$, $s = 1$, $\theta = 0.5$, $q = 1$, $\gamma = 0.1$, $\sigma = 0.4$, $\beta = 0.36$ so that $\mathcal{R}_0 = 0.857 < 1$, $R(p) = 0.9740 < 1$, and $R^c(p) = 0.9737 < R(p)$. The simulation results, depicted in Fig. 2A, show that the model has a disease-free equilibrium (corresponding to $\lambda = 0$) and two endemic equilibria (corresponding to $\lambda = 0.024$ and $\lambda = 0.03$, respectively). The figure shows that one of the endemic equilibria ($\lambda = 0.03$) is locally stable, the other endemic equilibrium ($\lambda = 0.024$) is unstable (a saddle), and the disease-free equilibrium is locally stable. This clearly shows the co-existence of two stable equilibria when $R(p) < 1$, confirming that (1) undergoes the phenomenon of backward bifurcation. The epidemiologic implication of this backward bifurcation phenomenon is that a sufficiently large initial number of infected individuals (above the stable manifold of the saddle endemic equilibrium given by $\lambda = 0.024$) will cause the system to settle at the locally asymptotically stable endemic equilibrium (corresponding to $\lambda = 0.03$ for this example), causing HIV persistence in the community. It should be noted, however, that since $\mathcal{R}_0 = 0.857 < 1$ for this numerical example, the disease is guaranteed to die out without vaccination because (as shown in Section 2.2.1) the disease-free equilibrium of the model without vaccination is globally asymptotically stable for $\mathcal{R}_0 < 1$. Clearly, this is an example where vaccination is detrimental to the community: the disease dies out without a vaccine (if $\mathcal{R}_0 < 1$) but persists with a vaccine (even though $\mathcal{R}_0 < 1$). This clearly shows that, unlike in previous models (e.g., Kribs-Zaleta and Velasco-Hernández, 2000), the disease-free equilibrium for the vaccination model (1) is not globally asymptotically stable for all $\mathcal{R}_0 < 1$. Further simulations, using the same parameters values as above except now $p = 0.8$, implying $R(p) = 0.961$ and $R^c(p) = 0.987$, are carried out and the results are depicted in Fig. 2B. This figure shows convergence to the unique disease-free equilibrium. The simulations shown in Fig. 2B also suggest that the disease-free equilibrium is also globally asymptotically stable since all trajectories with initial conditions in $\mathfrak{D}$ approach this equilibrium. Figure 2C shows convergence to the unique stable endemic equilibrium (here, $\beta = 0.5$, $s = 0.5$, $p = 0.9$, $\mathcal{R}_0 = 1.190$, $R(p) = 1.182$). Further simulations (Fig. 2C–F) suggest that the endemic equilibrium is globally asymptotically stable for $R(p) > 1$.

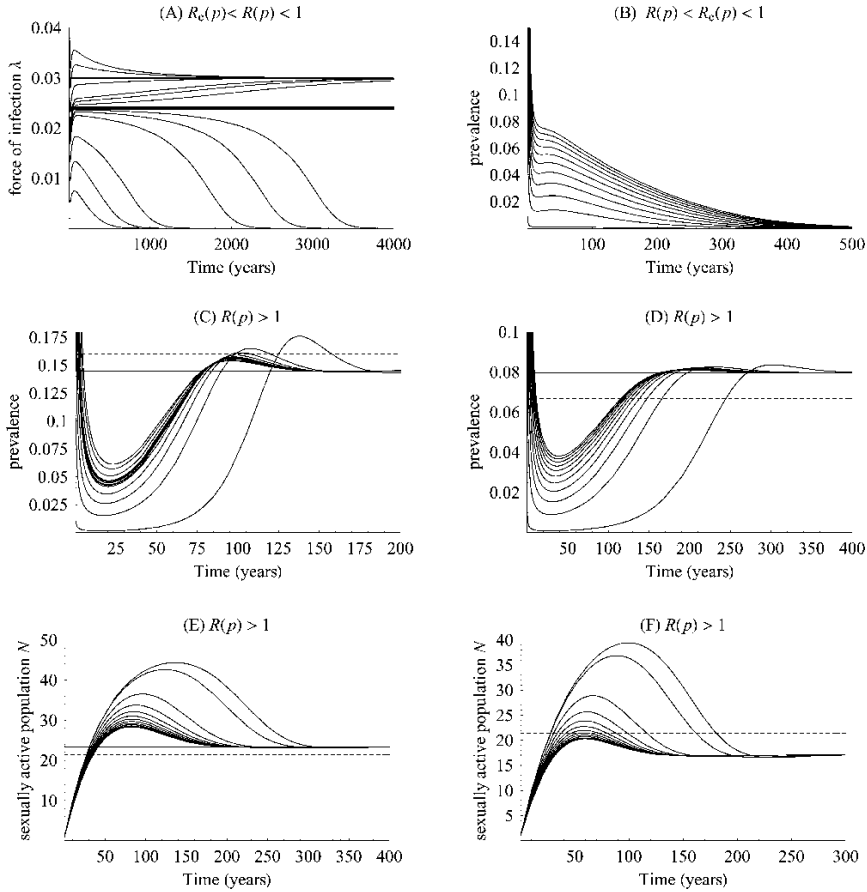

Fig. 2 Basic HIV-1 vaccination model: Force of infection λ, prevalence, or number of sexually-active people, versus time since vaccination for various values of the parameters. *Dotted lines* denote prevaccination values. *Thick gray line* denotes unstable endemic equilibrium. Common parameters: $\Lambda = 1, \mu = 0.02, r = 1, q = 1, \gamma = 0.1, \sigma = 0.4$. Other parameters: (A) $\beta = 0.36, s = 1, \theta = 0.5, p = 0.9$; (B) $\beta = 0.36, s = 1, \theta = 0.5, p = 0.8$; (C) $\beta = 0.5, s = 0.5, \theta = 0.5, p = 0.9$; (D) $\beta = 0.45, s = 0.45, \theta = 0.4, p = 0.9$; (E) same as (D); (F) $\beta = 0.45, s = 1, \theta = 0.9, p = 0.9$.

2.2.3. Endemic equilibrium with vaccination

The analysis in the preceding section shows that if $R(p)$, as defined in Eq. (7), is greater than one, then disease elimination is ruled out and endemic prevalence is certain. Suppose, for simplicity, $R(p) > 1$. It follows from Lemma 2 that model (1) has a unique endemic equilibrium given by $\mathcal{E}_1 = (X^*, V^*, Y^*, W^*)$ where

$$X^* = \frac{[\gamma + (1-p)(q\,r\,\lambda^* + \mu)\,]\Lambda}{(\lambda^* + \mu)\,(\gamma + q\,r\,\lambda^* + \mu)}, \quad V^* = \frac{p\,\Lambda}{\gamma + q\,r\,\lambda^* + \mu},$$

$$Y^* = \frac{[\gamma + (1-p)(q\,r\,\lambda^* + \mu)]\lambda^*\,\Lambda\,D_u}{(\lambda^* + \mu)\,(\gamma + q\,r\,\lambda^* + \mu)}, \quad W^* = \frac{p\,q\,r\,\lambda^*\,\Lambda\,D_v}{\gamma + q\,r\,\lambda^* + \mu},$$

with $\lambda^* = (-B_2 + \sqrt{B_2^2 - 4B_1B_3})/(2B_1)$, where $D_v = 1/(\mu + \theta\sigma)$ denotes the average incubation period from HIV infection to AIDS for the vaccinated persons.

2.2.4. Vaccine impact

Following Blower et al. (2002), we now consider model (1) such that the population consists entirely of vaccinated individuals. In this case, it can be shown that the associated basic reproduction number is given by

$$R_{0v} = \frac{qr^2s\beta}{\mu + \theta\sigma}, \tag{10}$$

where the quantity R_{0v} is average number of secondary infections that one vaccinated individual who becomes infected can produce during his/her sexually active life if introduced into a wholly vaccinated population. Using this definition, and that for $\mathcal{R}_0$, allows us to rewrite the vaccinated reproduction number $R(p)$ as

$$R(p) = \mathcal{R}_0\left[1 - p\frac{\mu}{\mu + \gamma}\left(1 - \frac{R_{0v}}{\mathcal{R}_0}\right)\right]. \tag{11}$$

It will be shown that the vaccine reproduction number for each of the models considered in this paper can be written in the form (11).

A measure of vaccine impact for model (1) can then be defined as (see McLean and Blower, 1993; Blower and McLean, 1994)

$$\phi = \frac{p\,\mu}{\gamma + \mu}\left[1 - \frac{q\,r^2\,s\,(\mu + \sigma)}{(\mu + \theta\,\sigma)}\right] = p\frac{\mu}{\mu + \gamma}\left(1 - \frac{R_{0v}}{\mathcal{R}_0}\right). \tag{12}$$

This is a generalization of the concept of vaccine efficacy that captures waning immunity (γ), take (p), therapeutic effect (θ), degree of protection ($1 - q$), effect on infectiousness (s), and increased risky behavior (r). Thus, other things being equal, the vaccine impact on HIV transmission (ϕ) is greater, when the duration of protection (smaller γ) is longer, vaccine take (larger p) or degree of protection (smaller q) are higher, the vaccine effect on infectiousness (smaller s) is larger, the vaccine therapeutic effect (larger θ) is smaller, and the change in risky behavior (smaller r) is smaller. It should be noted that a vaccine with therapeutic effects ($\theta < 1$) has a lower impact on HIV transmission compared with a vaccine that does not provide any therapeutic benefits ($\theta = 1$). However, the impact of the former on life expectancy can be larger than the latter as will be shown below. Note also that $R(p) \leq \mathcal{R}_0$ if and only if $\phi \geq 0$, and $R(p) > \mathcal{R}_0$ if and only if $\phi < 0$. That is, a vaccine will have a positive impact in terms of reducing HIV transmission (and, therefore, HIV prevalence) if the reproduction number for a wholly vaccinated population is less than the corresponding reproduction number without vaccination. The vaccine will have no impact on HIV prevalence if these

two numbers are equal. The impact of the vaccine on HIV prevalence is negative (detrimental) if the reproduction number for a wholly vaccinated population is greater than the reproduction number without vaccination. However, as will be shown below, even an imperfect vaccine with negative impacts in terms of higher prevalence can reduce AIDS-related mortality. A key goal of public health programs is to reduce premature deaths from diseases (measured in this model by the size of the population, N). Therefore, a vaccine that helps ensure a larger total population even if it results in higher prevalence can still be quite useful.

We now state the strategy followed for obtaining the conditions under which the following outcomes occur as a result of vaccination: (i) lower prevalence and larger population, (ii) higher prevalence and larger population, and (iii) higher prevalence and smaller population. We first set the right-hand side of the system (1) to zero and linearize the resulting system of equations around the endemic equilibrium with no vaccination e_1. This entails totally differentiating the system with respect to X, V, Y, W, N, and p and evaluating the result at equilibrium e_1. The differentials are then rearranged and used to solve for the expressions for the partial derivatives of the associated variables with respect to p (e.g., $\partial W/\partial p$). This will indicate infinitesimal changes from the prevaccination (endemic) equilibrium. This *sensitivity analysis* method, of studying how a variable (e.g., W) responds to changes in its environment (e.g., vaccination $p > 0$), is also known as *comparative statics* method in other disciplines such as economics (see, e.g., Varian, 1992; Takayama, 1993). The method essentially compares the "before" and "after" equilibrium situations (hence the term comparative). The term "statics" refers to the fact that the comparison is made after all adjustments have taken place (e.g., prevaccination endemic equilibrium vs. postvaccination endemic equilibrium). The same results can be obtained by differentiating the components of the endemic equilibrium $\mathcal{E}_1$ with respect to p and evaluating the result at $p = 0$. Thus,

$$\frac{\partial W^*}{\partial p}\,|_{p=0} = \frac{\Lambda q r(\mu+\sigma)(\mathcal{R}_0-1)}{(\mu+\theta\,\sigma)[(\gamma+\mu)+qr(\mu+\sigma)(\mathcal{R}_0-1)]} > 0 \quad \text{iff} \quad \mathcal{R}_0 > 1.$$

Therefore, if $\mathcal{R}_0 > 1$, the number of infected people who were vaccinated will increase as a result of vaccination. The condition $\mathcal{R}_0 > 1$ is needed for the existence of the prevaccination endemic equilibrium.

For prevalence $(Y/N + W/N)$, similar calculations reveal that:

$$\frac{1}{N^*}\left(\frac{\partial Y^*}{\partial p}+\frac{\partial W^*}{\partial p}-\frac{Y^*}{N^*}\frac{\partial N^*}{\partial p}\right)\Bigg|_{p=0}$$
$$= -\frac{\Lambda[(\mu+\theta\,\sigma)-qr^2 s(\mu+\sigma)]}{N^{**}(\mu+\theta\,\sigma)[(\gamma+\mu)+qr(\mu+\sigma)(\mathcal{R}_0-1)]},$$

where, $N^{**} = \Lambda\mathcal{R}_0 D_u/(\mathcal{R}_0 - 1 + \mu D_u)$. Clearly, the sign of the denominator of the above expression is positive as long as $\mathcal{R}_0 > 1$. Thus, a necessary and sufficient condition for prevalence to decrease following vaccination is

$$1 - \frac{q\,r^2\,s\,(\mu+\sigma)}{(\mu+\theta\,\sigma)} = 1 - \frac{R_{0\mathrm{v}}}{\mathcal{R}_0} > 0. \tag{13}$$

This result is summarized below:

Lemma 3. *For the vaccination model (1), an imperfect vaccine will reduce steady-state HIV prevalence if and only if* $R_{0\mathrm{v}} < \mathcal{R}_0$.

It is worth mentioning that, based on further analysis, adding AIDS patients in the computation of prevalence (i.e., prevalence $= Y/N + W/N + A/N$) does not change the above result. Condition (13) is likely to be satisfied for smaller values of q, s, r, and σ and larger values of μ and θ. That is, the vaccine is likely to reduce HIV transmission if the degree of protection it offers is high (smaller q), vaccinated individuals (with "breakthrough" infections) are less infectious (smaller s) and progress faster to AIDS (larger θ), the risky behavior induced by vaccination is small (smaller r), the duration in the sexually active population is short (larger μ), and progression of infected unvaccinated persons to AIDS is slow (smaller σ). It should be noted that, in this paper, risk behavior is modeled exogenously using the parameter r. This result indicates that the vaccine impact is lower if the expected increase in risk behavior among vaccinees is high. Figure 2C illustrates the situation where introducing a vaccine with the characteristics $p = 0.9, r = 1, s = 0.5, \theta = 0.5, q = 1, \gamma = 0.1$, and $\sigma = 0.4$ and assuming $\beta = 0.5$ can lead to a reduction in prevalence. Choosing a vaccine with the characteristic $p = 0.9, r = 1, s = 0.45, \theta = 0.4, q = 1, \gamma = 0.10$, and $\sigma = 0.4$, and assuming $\beta = 0.45$ so that $R_{0\mathrm{v}} = 1.125 > \mathcal{R}_0 = 1.071$ and $\phi = -0.0075$, leads to a higher postvaccine prevalence in comparison to prevaccination prevalence (Fig. 2D).

To assess the effect of vaccination on the size of the sexually active population N, we investigate the sign of the derivative of N^* with respect to p evaluated at $p = 0$. This is given by

$$\left.\frac{\partial N^*}{\partial p}\right|_{p=0} = \frac{\mathcal{R}_0\Lambda\sigma[(\mu+\theta\,\sigma)+qr(1-\theta)(\mathcal{R}_0-1)(\mu+\sigma)-qr^2s(\mu+\sigma)]}{[\mathcal{R}_0(\mu+\sigma)-\sigma](\mu+\theta\,\sigma)[(\gamma+\mu)+qr(\mathcal{R}_0-1)(\mu+\sigma)]}.$$

The sign of the above expression depends on the sign of the numerator. It follows that the sign of the above derivative is positive if and only if

$$(\mu+\theta\,\sigma)+qr(1-\theta)(\mathcal{R}_0-1)(\mu+\sigma)-qr^2s(\mu+\sigma) > 0. \tag{14}$$

Thus, the total population (N) increases as a result of vaccination if the above condition is true. It can be shown that the effect of vaccination on steady-state mortality (as measured by $1/N$, $1/(N+A)$, or $(\alpha+\mu)A$) also depends on condition (14). Clearly, condition (14) is likely to be satisfied for smaller values of s. That is, the less infectious vaccinated infected individuals are, the more likely the vaccine will succeed in reducing AIDS-related mortality. Intuitively, condition (14) is likely to be satisfied for smaller values of q, θ, and r. That is, a vaccine that can reduce transmission, provide therapeutic benefits, and does not induce increased risky behavior is expected to reduce AIDS-related mortality. However, intuition

may fail in this case because some of these vaccine properties have contradictory effects. For example, a vaccine with therapeutic effects is likely to slow the progression of vaccinated infected individuals to AIDS and make them live longer, and presumably continue to infect others. Consequently, by extending the life expectancy of these infected individuals, the vaccine also increases their contribution to HIV transmission. Thus, the overall result will depend on which of these effects is dominant.

In the forthcoming extended models, condition (14) will be expressed in the following convenient format:

$$1 + qr(\mathcal{R}_0 - 1)\frac{(D_v/D_u - 1)}{(1 - D_u/L)} - \frac{R_{0v}}{\mathcal{R}_0} > 0, \tag{15}$$

where $L = 1/\mu$ is average duration in the sexually active population. It should be noted that condition (15) is automatically satisfied if condition (13) is met. If both conditions are violated, then vaccination will be detrimental to the community since, in this case, both prevalence and mortality will be higher compared to prevaccination levels. This result is summarized below:

Lemma 4. *For the vaccination model (1), an imperfect vaccine will reduce steady-state mortality if and only if condition (15) holds.*

Numerical simulations, depicted in Fig. 2D and E, show that a vaccine with certain characteristics can lead to lower mortality even in the presence of a higher postvaccination prevalence. In Fig. 2F, where $p = 0.9, r = 1, s = 1, \theta = 0.9, q = 1, \gamma = 0.1, \sigma = 0.4$, and $\beta = 0.45$ (so that $\phi = -0.0158$), it is clear that using such a vaccine is detrimental to the community since it resulted in higher postvaccination prevalence and lower size of the sexually active population (in comparison to prevaccination case).

3. Extension (I): HIV transmission by AIDS patients

The assumptions described when discussing the basic model (1) pose several additional questions. These include: are AIDS patients infectious? Are AIDS patients capable of mixing with the rest of the community? If so, what are the epidemiologic implications of HIV transmission by AIDS patients? The answer to the first question is in the affirmative. Numerous epidemiologic and biological data suggest that a diagnosis of AIDS is a strong predictor of infectiousness. It is generally accepted that there is a strong association between host infectiousness and the concentration of virus in the blood or genital tract. Several studies reported higher viral loads in blood and semen of AIDS patients (Royce et al., 1997). Epidemiologic evidence also supports the hypothesis that AIDS patients are capable of, and do engage in, risky sexual behavior defined in terms of inconsistent condom use or having multiple sex partners (Lansky et al., 2000). For example, in a study of HIV-1-infected transfusion male recipients and their female sex partners, O'Brien et al. (1994) show that advanced AIDS patients are more likely to infect their partners

(odd ratio 7.9) compared to recipient with no advanced immunodeficiency. Similar findings, reported in the cross-sectional study of HIV-infected females and their male sex partners (Nicolosi et al., 1994), show that out of 242 couples, only 18 (their disease status is not stated) reported to have not been sexually active for at least 1 year, 51% of the remaining couples reported to have never used a condom. Another 18% of the study participants reported to have used condoms "sometimes," and among men who were aware of the seropositivity of their female partners, 18% never used condoms. Compared to asymptomatic HIV-infected women, the adjusted odd ratio of a symptomatic woman HIV transmission to her male partner is 2.4.

In this section, the basic model (1) is extended to incorporate the transmission of HIV by infected individuals in the AIDS stage. The model equations are the same as those given in (1) except, now,

$$\lambda = \beta_1 \frac{Y}{N} + rs\beta_1 \frac{W}{N} + \beta_A \frac{A}{N}, \quad \text{and} \quad N = X + V + Y + W + A, \tag{16}$$

where the parameters β_1 and β_A are the probabilities of HIV transmission from an asymptomatic (unvaccinated) and AIDS patient to a susceptible partner, respectively. Hence, β_A/β_1 measures the infectiousness of an AIDS patient relative to an asymptomatic, unvaccinated, HIV-infected person (see Fig. 1A for a schematic description of this model). Consider the biologically-feasible region

$$\mathfrak{D}_1 = \left\{(X, V, Y, W, A) \in \Re_+^5 : X + V + Y + W + A \leq \Lambda/\mu\right\}.$$

Since individuals in the AIDS category are also infectious, the quantities $1/(\mu + \sigma)$ and $1/(\mu + \theta\sigma)$ no longer measure the average durations of infectiousness. Instead, they only measure the average waiting times in the HIV state for unvaccinated and vaccinated individuals, respectively. The average duration of infectiousness should be redefined to take into account the time spent in the AIDS stage, $1/(\alpha + \mu)$, and the probability of an HIV-infected individual developing AIDS, σ. Thus, the respective average durations of infectiousness for unvaccinated and vaccinated individuals are given by

$$D_{u1} = \frac{1}{\mu + \sigma} + \frac{\sigma}{(\mu + \sigma)(\alpha + \mu)}, \; D_{v1} = \frac{1}{\mu + \theta\sigma} + \frac{\theta\sigma}{(\mu + \theta\sigma)(\alpha + \mu)}. \tag{17}$$

3.1. Equilibria, stability, and reproduction numbers

3.1.1. The model without vaccination

In the absence of vaccination, the disease-free equilibrium is locally asymptotically stable if and only if

$$\mathcal{R}_{01} = \frac{\beta_1}{(\mu + \sigma)} + \frac{\sigma\beta_A}{(\mu + \sigma)(\alpha + \mu)} < 1, \tag{18}$$

where $\mathcal{R}_{01}$ is the basic reproduction number of the second model ((1) with (16)) in the absence of vaccination. If $\mathcal{R}_{01} > 1$, the model has a unique and locally

asymptotically stable endemic equilibrium, given by

$$\tilde{e}_1 = (X^*, Y^*, A^*) = \left(\frac{\Lambda D_{u1}}{\mathcal{R}_{01} - 1 + \mu D_{u1}}, \frac{\Lambda(\mathcal{R}_{01} - 1)}{(\mu + \sigma)(\mathcal{R}_{01} - 1 + \mu D_{u1})}, \right.$$
$$\left. \frac{\Lambda(\mathcal{R}_{01} - 1)(\mu D_{u1} - 1)}{\alpha(\mathcal{R}_{01} - 1 + \mu D_{u1})} \right). \tag{19}$$

3.1.2. Disease-free equilibrium with vaccination

With vaccination, the model ((1) with (16)) has a disease-free equilibrium given by

$$\mathcal{E}_{01} = (X^*, V^*, Y^*, W^*, A^*) = \left(\frac{\Lambda[\gamma + (1-p)\mu]}{\mu(\mu + \gamma)}, \frac{p\Lambda}{\mu + \gamma}, 0, 0, 0 \right),$$
$$N^* = \frac{\Lambda}{\mu}, \tag{20}$$

which is locally-asymptotically stable if and only if

$$R_1(p) = \mathcal{R}_{01} \left\{ 1 - \frac{p\,\mu}{\gamma + \mu} \left[1 - \frac{(\mu + \sigma)}{(\mu + \theta\,\sigma)} \frac{q\,r^2\,s(\alpha + \mu)\beta_1 + qr\theta\sigma\beta_A}{(\alpha + \mu)\beta_1 + \sigma\beta_A} \right] \right\} < 1.$$

As in model (1), $R_1(p)$ can be rewritten as

$$R_1(p) = \mathcal{R}_{01} \left[1 - p \frac{\mu}{\mu + \gamma} \left(1 - \frac{R_{0v1}}{\mathcal{R}_{01}} \right) \right], \tag{21}$$

where

$$R_{0v1} = q\,r^2\,s \frac{\beta_1}{\mu + \theta\,\sigma} + qr \frac{\theta\sigma\beta_A}{(\alpha + \mu)(\mu + \theta\,\sigma)}, \tag{22}$$

is the basic reproduction number when the entire population consists of vaccinated individuals. Again, a measure of vaccine impact can be derived as

$$\phi_1 = p \frac{\mu}{\mu + \gamma} \left(1 - \frac{R_{0v1}}{\mathcal{R}_{01}} \right). \tag{23}$$

Compared to the original model (1), it can be shown (using the sensitivity analysis detailed earlier on ϕ_1 around $\beta_A = 0$) that the impact of the vaccine on this revised model depends on whether θ is greater or less than rs. If $\theta < rs$ (that is, the positive effect on delaying the onset of AIDS is dominated by the net effect of reducing infectiousness and increasing risky behavior), then the impact of the vaccine will be higher ($\phi_1 > \phi$) if the contribution of AIDS transmission is taken into account. It should be noted that the revised model with AIDS patients contributing to HIV

transmission has longer durations of infectiousness ($D_{u1} > D_u$, $D_{v1} > D_v$), higher reproduction numbers ($\mathcal{R}_{01} > \mathcal{R}_0$, $R_{0v1} > R_{0v}$), and higher prevalence.

As in model (1), there may exist a pair of endemic equilibria that compete with the disease-free equilibrium $\mathcal{E}_{01}$ if ${R_1}^c(p) < R_1(p) < 1$, where ${R_1}^c(p)$ denotes some critical value of $R_1(p)$ below unity (i.e., the revised model is susceptible to undergoing backward bifurcation).

3.1.3. Endemic prevalence with vaccination

Using the same methods used for analyzing model (1), it can be shown that disease prevalence, defined by $Y/N + W/N + A/N$, for the revised model will be lower in the postvaccination equilibrium if and only if the following expression is positive:

$$1 - \frac{1}{\mathcal{R}_{01}}\left[\frac{q\,r^2\,s\beta_1}{\mu + \theta\,\sigma} + \frac{qr\theta\sigma\beta_A}{(\alpha+\mu)(\mu+\theta\,\sigma)}\right]. \tag{24}$$

This can be rewritten in the following, familiar, alternative format:

$$1 - \frac{R_{0v1}}{\mathcal{R}_{01}}. \tag{25}$$

Consequently, prevalence falls (rises) if R_{0v1} is smaller (larger) than $\mathcal{R}_{01}$. Furthermore, the size of the population will be larger or smaller in the postvaccination equilibrium depending on the sign of the following expression:

$$1 + \frac{qr(1-\theta)(\mu+\sigma)(\alpha+\mu)(\mathcal{R}_{01}-1)}{(\alpha+\mu+\sigma)(\mu+\theta\sigma)} - \frac{1}{\mathcal{R}_{01}}\left[\frac{q\,r^2\,s\beta_1}{\mu+\theta\,\sigma} + \frac{qr\theta\sigma\beta_A}{(\alpha+\mu)(\mu+\theta\,\sigma)}\right].$$

This can be rewritten in this alternative format:

$$1 + qr(\mathcal{R}_{01}-1)\frac{(D_{v1}/D_{u1}-1)}{(1-D_{u1}/L)} - \frac{R_{0v1}}{\mathcal{R}_{01}}. \tag{26}$$

These expressions differ from those in the previous model by the new terms in the expressions for D_{u1}, D_{v1}, $\mathcal{R}_{01}$, and R_{0v1}. Note that if α approaches infinity, all previous results for model (1) hold. Also, if θ is less than rs (the positive effect on delaying the onset of AIDS is dominated by the net effect of reducing infectiousness and increasing risky behavior), then the vaccine will more likely increase the size of the population and reduce HIV prevalence if the contribution of AIDS transmission is taken into account.

4. Extension (II): Differential infectivity (DI) and progression to AIDS

Studies of HIV RNA in infected individuals show that viral levels vary widely between individuals, where individuals with higher viral loads during the chronic phase tend to develop AIDS more rapidly (Mellors et al., 1997). Because studies have shown that RNA levels are correlated with infectiousness (Quinn et al.,

2000; Gray et al., 2001), HIV vaccine models need to incorporate the variations in infectiousness and the increase in the average time from primary HIV infection to AIDS stage that goes along with a decreased viral load during the chronic phase of infection (Hyman et al., 1999).

For simplicity, the unvaccinated infected population is subdivided into two subgroups of varying RNA levels namely Y_1 and Y_2. Upon infection, an individual enters the high HIV RNA subgroup (Y_1) with probability ρ_1 and the low HIV RNA subgroup (Y_2) with probability ρ_2 ($\rho_2 = 1 - \rho_1$). It is assumed that people in these subgroups develop AIDS at rates σ_1 and σ_2 ($\sigma_1 > \sigma_2$), respectively. Similarly, the vaccinated infected population is subdivided into two subgroups of high and low viral loads (W_1 and W_2) with respective probabilities π_1 and π_2 ($\pi_2 = 1 - \pi_1$). Notice the assumption that the vaccine can alter the fraction of people going into the high HIV RNA group (W_1 instead of Y_1) if $\pi_1 \neq \rho_1$. The respective progression rates to AIDS for these groups are $\theta_1\sigma_1$ and $\theta_2\sigma_2$. The relative degrees of infectiousness of individuals in these subgroups compared with those in subgroups Y_1 and Y_2 are given by s_1 and s_2, respectively. It is assumed that once an infected individual is in any of these subgroups, s/he remains there until developing AIDS. As in the original model (1), it is assumed here that once a person develops AIDS, s/he is removed from the sexually active population. This assumption will be relaxed in Section 4.1.2 below. The model has the following structure (see Fig. 1B):

$$\begin{aligned}
\mathrm{d}X/\mathrm{d}t &= (1-p)\Lambda - \mu X - \lambda X + \gamma V,\\
\mathrm{d}V/\mathrm{d}t &= p\Lambda - \mu V - qr\lambda V - \gamma V,\\
\mathrm{d}Y_1/\mathrm{d}t &= \rho_1\lambda X - (\mu+\sigma_1)Y_1,\\
\mathrm{d}Y_2/\mathrm{d}t &= \rho_2\lambda X - (\mu+\sigma_2)Y_2,\\
\mathrm{d}W_1/\mathrm{d}t &= \pi_1 qr\lambda V - (\mu+\theta_1\sigma_1)W_1,\\
\mathrm{d}W_2/\mathrm{d}t &= \pi_2 qr\lambda V - (\mu+\theta_2\sigma_2)W_2,\\
\mathrm{d}A/\mathrm{d}t &= \sigma_1 Y_1 + \sigma_2 Y_2 + \theta_1\sigma_1 W_1 + \theta_2\sigma_2 W_2 - (\alpha+\mu)A,\\
\lambda &= \sum_{i=1}^{2}\left(\beta_i\frac{Y_i}{N} + rs_i\beta_i\frac{W_i}{N}\right), \quad N = X + V + \sum_{i=1}^{2}(Y_i + W_i).
\end{aligned} \tag{27}$$

A more detailed model with $I + J + 1$ arbitrary infection stages is given in Appendix A.

For the model (27), it can be shown that the following feasible region is positively-invariant:

$$\mathfrak{D}_2 = \left\{(X, V, Y, W) \in \Re_+^6 : X + V + \sum_{i=1}^{2}(Y_i + W_i) \leq \Lambda/\mu\right\},$$

where $Y = (Y_1, Y_2) \in \Re_+^2$, $W = (W_1, W_2) \in \Re_+^2$.

4.1. Equilibria, stability, and reproduction numbers

4.1.1. Disease-free equilibrium with vaccination

For model (27), it is straightforward to show that the corresponding disease-free equilibrium is locally asymptotically stable if and only if

$$R_2(p) = \mathcal{R}_{02}\left[1 - p\frac{\mu}{\gamma+\mu}\left(1 - \frac{R_{0v2}}{\mathcal{R}_{02}}\right)\right] < 1, \tag{28}$$

where

$$\mathcal{R}_{02} = \frac{\rho_1\beta_1}{\mu+\sigma_1} + \frac{\rho_2\beta_2}{\mu+\sigma_2}, \quad \text{and} \quad R_{0v2} = q\,r^2\left(\frac{\pi_1 s_1\beta_1}{\mu+\theta_1\sigma_1} + \frac{\pi_2 s_2\beta_2}{\mu+\theta_2\sigma_2}\right). \tag{29}$$

Here, $\mathcal{R}_{02}$ is the basic reproduction number of the model (27) in the absence of vaccination and R_{0v2} denotes the basic reproduction number of the model (27) if the entire population consists of vaccinated individuals. As in the preceding models, a measure of vaccine efficacy can be derived as

$$\phi_2 = p\frac{\mu}{\mu+\gamma}\left(1 - \frac{R_{0v2}}{\mathcal{R}_{02}}\right), \tag{30}$$

and the possibility of the existence of multiple equilibria that compete with the disease-free equilibrium when $R_2(p) < 1$ cannot be ruled out (i.e., the differential infectivity model (27) may also exhibit backward bifurcation).

4.1.2. Endemic prevalence with vaccination

Prevalence, $(Y_1 + Y_2 + W_1 + W_2)/N$, will be lower in the postvaccination equilibrium if and only if the sign of the following quantity is positive:

$$1 - \frac{q\,r^2}{\mathcal{R}_{02}}\left(\frac{\pi_1 s_1\beta_1}{\mu+\theta_1\sigma_1} + \frac{\pi_2 s_2\beta_2}{\mu+\theta_2\sigma_2}\right) = 1 - \frac{R_{0v2}}{\mathcal{R}_{02}}. \tag{31}$$

The size of the population will be larger in the postvaccination equilibrium if and only if the sign of the following expression is positive:

$$1 + qr(\mathcal{R}_{02} - 1)\frac{(D_{v2}/D_{u2} - 1)}{(1 - D_{u2}/L)} - \frac{R_{0v2}}{\mathcal{R}_{02}}. \tag{32}$$

The definition and interpretation of each of these quantities (e.g., D_{u2}) change from that for a single group as in model (1) to a mean of all subgroups. Thus, D_{u2} and D_{v2} are now defined as

$$D_{u2} = \frac{\rho_1}{\mu+\sigma_1} + \frac{\rho_2}{\mu+\sigma_2}, \quad D_{v2} = \frac{\pi_1}{\mu+\theta_1\sigma_1} + \frac{\pi_2}{\mu+\theta_2\sigma_2}, \tag{33}$$

and interpreted as the mean duration of infectiousness for infected unvaccinated and vaccinated individuals, respectively.

If the contribution of AIDS cases to HIV transmission is taken into account, the following expressions for basic and vaccinated reproduction numbers are derived as

$$\tilde{\mathcal{R}}_{02} = \frac{\rho_1\beta_1}{\mu+\sigma_1} + \frac{\rho_2\beta_2}{\mu+\sigma_2} + \frac{\beta_A}{\alpha+\mu}\left(\frac{\rho_1\sigma_1}{\mu+\sigma_1} + \frac{\rho_2\sigma_2}{\mu+\sigma_2}\right), \tag{34}$$

$$\tilde{R}_2(p) = \tilde{\mathcal{R}}_{02}\left[1 - p\frac{\mu}{\gamma+\mu}\left(1 - \frac{\tilde{R}_{0v2}}{\tilde{\mathcal{R}}_{02}}\right)\right],$$

where $\tilde{R}_{0v2}$ is now defined as

$$\tilde{R}_{0v2} = q\,r^2\left(\frac{\pi_1 s_1\beta_1}{\mu+\theta_1\sigma_1} + \frac{\pi_2 s_2\beta_2}{\mu+\theta_2\sigma_2}\right) + \frac{qr\beta_A}{\alpha+\mu}\left(\frac{\pi_1\theta_1\sigma_1}{\mu+\sigma_1\theta_1} + \frac{\pi_2\theta_2\sigma_2}{\mu+\theta_2\sigma_2}\right). \tag{35}$$

To analyze the importance of various vaccine characteristics, a generalized version of model (27), where four unvaccinated differential infectivity subgroups Y_i ($i = 1, 2, 3, 4$) and four differential breakthrough infectivity subgroups W_i ($i = 1, 2, 3, 4$) are assumed (See Appendix A), is simulated using the parameters in Table 1. Following Hyman et al. (1999, 2001), the probability of transmission per partnership is estimated using the expression $\beta_i = 1 - (1 - \zeta_i)^{h(z)}$, where ζ_i is the transmission probability per contact, $h(z) = 104z^{-\eta} + 1$ denotes the average number of contact per partnership. The initial conditions for all simulations of the differential infectivity model are the equilibrium values without vaccination (see Hyman et al., 2001, for discussion on the importance of initial conditions).

Figure 3A illustrates the impact of a vaccine with a 10-year duration of effect ($\gamma = 0.1$) and 50% reduction in infectiousness of "breakthrough" cases ($s_i = 0.5$) for various rates of vaccination coverage. This figure shows a marked decrease in postvaccination steady-state prevalence with increasing coverage rate (thus, the vaccine has a positive impact). A scenario where breakthrough infections are 90% less infectious ($s_i = 0.1$), in addition to the two vaccine characteristics above, is depicted in Fig. 3B, where it is evident that such a vaccine offers a far better reduction in prevalence compared to the vaccine in Fig. 3A (underlying the importance of vaccine-induced reduction of infectiousness). A scenario where the vaccine reduces breakthrough infectiousness by 50% ($s_i = 0.5$) and offers lifelong effect ($\gamma = 0$) is shown in Fig. 3C, from which it can be deduced that such a vaccine is slightly better than those in Fig. 3A and B.

Further simulations with a vaccine that offers a 25% degree protection ($q = \theta_i = 0.75$) that lasts for 20 years ($\gamma = 0.05$) with breakthrough infections being 90% ($s_i = 0.1$) less infectious are carried out. The results, depicted in Fig. 3D, show that similar patterns as those observed in Fig. 3A–C. Figure 3D also shows that HIV can be eliminated from the community with high vaccination coverage rates. Figures 3E and F illustrate the case where a vaccine that reduce infectiousness and

Table 1 Data for the differential infectivity (DI) and staged-progression (SP) models

Description	Symbol	Value	Reference
New recruits into population	Λ	0.99μ	Assumed
Mean transmission per contact	$\bar{\zeta}$	0.0011	Gray et al. (2001, 2003)
Partner acquisition rate	z	5	Hyman et al. (1999)
Sexually active removal rate	μ	0.07	Hyman et al. (1999)
DI parameters			
Distribution of newly infected	ρ_i	(0.05, 0.33, 0.5, 0.12)	O'Brien et al. (1996)
Progression rates	σ_i	(0.19, 0.096, 0.058, 0.028)	O'Brien et al. (1996)
Relative per contact transmission	ζ_i	(23, 14, 13, 1)	Gray et al. (2001, 2003)
SP parameters			
Progression rates	σ_i	(13., 0.2355, 0.2355, 0.47)	Hyman *et al.* (1999)
Relative per contact transmission	ζ_i	$(23, 1, 1, 14) \times 4.8 \times 10^{-4}$	Gray et al. (2001, 2003)

progression rates by 25% ($\theta_i = s_i = 0.75$), provides 25% degree protection ($q = 0.75$) lasting for 10 years ($\gamma = 0.1$), and increases risk behavior by 25% ($r = 1.25$) can result in higher postvaccination HIV prevalence and higher postvaccination total population size, respectively. Note that even though the postvaccination prevalence rate is higher (Fig. 3E), the size of the population is larger compared with prevaccination level (Fig. 3F). Furthermore, the prevalence ratio is below unity (i.e., prevalence is falling) for the first 20 years before rising and exceeding unity after about 70 years.

5. Extension (III): Staged progression

The staged progression model accounts for the variation of infectiousness in a given individual over time. It has been widely observed that an HIV-infected person passes through infectious stages, being highly infectious during the preantibody phase, maintaining low infectivity during the asymptomatic phase, and becoming highly infectious as s/he progresses toward AIDS (Longini et al., 1989; Hethcote and Ark, 1992; Hyman et al., 1999; McCluskey, 2003). We assume three progression stages, where Y_1 and W_1 now represent the classes of unvaccinated and vaccinated infected individuals in the primary infection stage, respectively. Similarly, Y_2 and W_2 represent the populations of unvaccinated and vaccinated infecteds at the secondary infection stage. Unvaccinated and vaccinated individuals in the last infection stage (AIDS) are lumped in the A compartment (Appendix B includes a generalized staged-progression model, with I and J stages of infection for the unvaccinated and vaccinated individuals, respectively). Compared to the model (27) (taking HIV transmission by AIDS patients into account), only the following equations are changed (see Fig. 1C):

$$\begin{aligned} \mathrm{d}Y_1/\mathrm{d}t &= \lambda X - (\mu + \sigma_1)Y_1, \\ \mathrm{d}Y_2/\mathrm{d}t &= \sigma_1 Y_1 - (\mu + \sigma_2)Y_2, \\ \mathrm{d}W_1/\mathrm{d}t &= qr\lambda V - (\mu + \theta_1\sigma_1)W_1, \end{aligned} \tag{36}$$

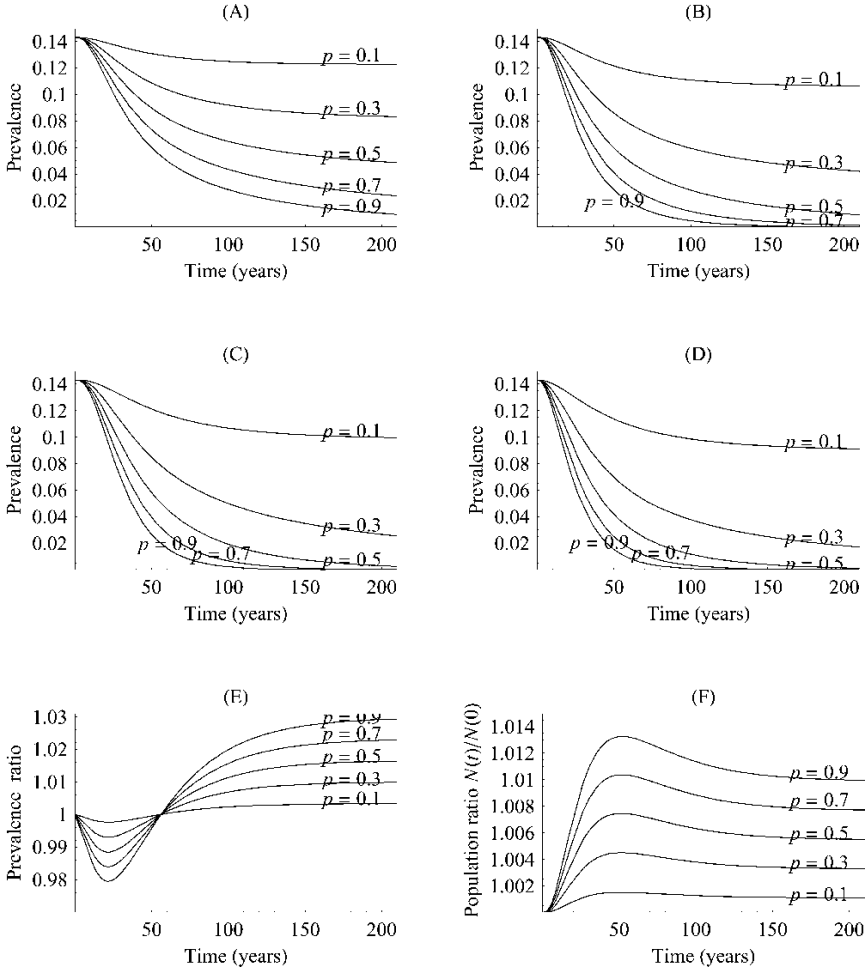

Fig. 3 Differential infectivity (DI) HIV-1 vaccination model: Prevalence or number of sexually-active people, versus time since vaccination for various values of the parameters. Common parameters: Table 1 and $\pi_i = \rho_i$. Other parameters: (A) $\theta_i = 1, \gamma = 0.1, s_i = 0.5, q = 1, r = 1$; (B) same as in (A) except $s_i = 0.1$; (C) same as in (A), except $\gamma = 0$; (D) $\theta_i = q = 0.75, s_i = 0.1, \gamma = 0.05, r = 1$; (E) $\theta_i = s_i = q = 0.75, \gamma = 0.1, r = 1.25$; (F) same as (E).

$$\mathrm{d}W_2/\mathrm{d}t = \theta_1\sigma_1 W_1 - (\mu + \theta_2\sigma_2)W_2,$$
$$\mathrm{d}A/\mathrm{d}t = \sigma_2 Y_2 + \theta_2\sigma_2 W_2 - (\alpha + \mu)A.$$

Note that $1/\sigma_i$ (and $1/\theta_i\sigma_i$ for the vaccinated and infected persons) now measures average waiting time in stage i. A suitable domain is

$$\mathfrak{D}_3 = \left\{ (X, V, Y, W, A) \in \Re_+^7 : X + V + \sum_{i=1}^{2} (Y_i + W_i) + A \leq \Lambda/\mu \right\},$$

where $Y = (Y_1, Y_2) \in \Re_+^2$, $W = (W_1, W_2) \in \Re_+^2$.

For this model, it can be shown that the disease-free equilibrium is locally asymptotically stable if and only if

$$R_3(p) = \mathcal{R}_{03}\left[1 - p\frac{\mu}{\gamma + \mu}\left(1 - \frac{R_{0v3}}{\mathcal{R}_{03}}\right)\right] < 1, \tag{37}$$

where

$$\mathcal{R}_{03} = \frac{\beta_1}{\mu + \sigma_1} + \frac{\sigma_1\beta_2}{(\mu + \sigma_1)(\mu + \sigma_2)} + \frac{\beta_A\sigma_1\sigma_2}{(\alpha + \mu)(\mu + \sigma_1)(\mu + \sigma_2)}, \tag{38}$$

and

$$R_{0v3} = q\,r^2\left[\frac{s_1\beta_1}{\mu + \theta_1\sigma_1} + \frac{\theta_1\sigma_1 s_2\beta_2}{(\mu + \theta_1\sigma_1)(\mu + \theta_2\sigma_2)}\right] + \frac{qr\beta_A\theta_1\sigma_1\theta_2\sigma_2}{(\alpha + \mu)(\mu + \theta_1\sigma_1)(\mu + \theta_2\sigma_2)}. \tag{39}$$

In this case, prevalence would fall (rise) after vaccination if R_{0v3} is less (greater) than $\mathcal{R}_{03}$. The size of the population will be larger (smaller) in the postvaccination equilibrium if and only if

$$1 + qr(\mathcal{R}_{03} - 1)\frac{(D_{v3}/D_{u3} - 1)}{(1 - D_{u3}/L)} - \frac{R_{0v3}}{\mathcal{R}_{03}} \tag{40}$$

is positive (negative), where

$$D_{u3} = \frac{1}{\mu + \sigma_1} + \frac{\sigma_1}{(\mu + \sigma_1)(\mu + \sigma_2)} + \frac{\sigma_1\sigma_2}{(\alpha + \mu)(\mu + \sigma_1)(\mu + \sigma_2)}, \tag{41}$$

$$D_{v3} = \frac{1}{\mu + \theta_1\sigma_1} + \frac{\theta_1\sigma_1}{(\mu + \theta_1\sigma_1)(\mu + \theta_2\sigma_2)} + \frac{\theta_1\sigma_1\theta_2\sigma_2}{(\alpha + \mu)(\mu + \theta_1\sigma_1)(\mu + \theta_2\sigma_2)}.$$

To analyze the importance of various vaccine characteristics, a generalized version of model (36) is simulated using the parameters in Table 1. We assume that there are four stages of progression ($i = 1, 2, \ldots, 4$) (See Appendix B).

Figure 4A illustrates the impact of a vaccine with a 10-year duration of effect ($\gamma = 0.1$), and 50% reduction in infectiousness and rates of progression of "breakthrough" cases ($\theta_i = s_i = 0.5$), no increase in risky behavior ($r = 1$), and no reduction of susceptibility to infection ($q = 1$) for various rates of vaccination coverage. This figure shows a reduction in postvaccination prevalence as a function of vaccine coverage. In Fig. 4B, same parameters as in Fig. 4A were used except now breakthrough infections are assumed to be 75% less infectious and progress slower

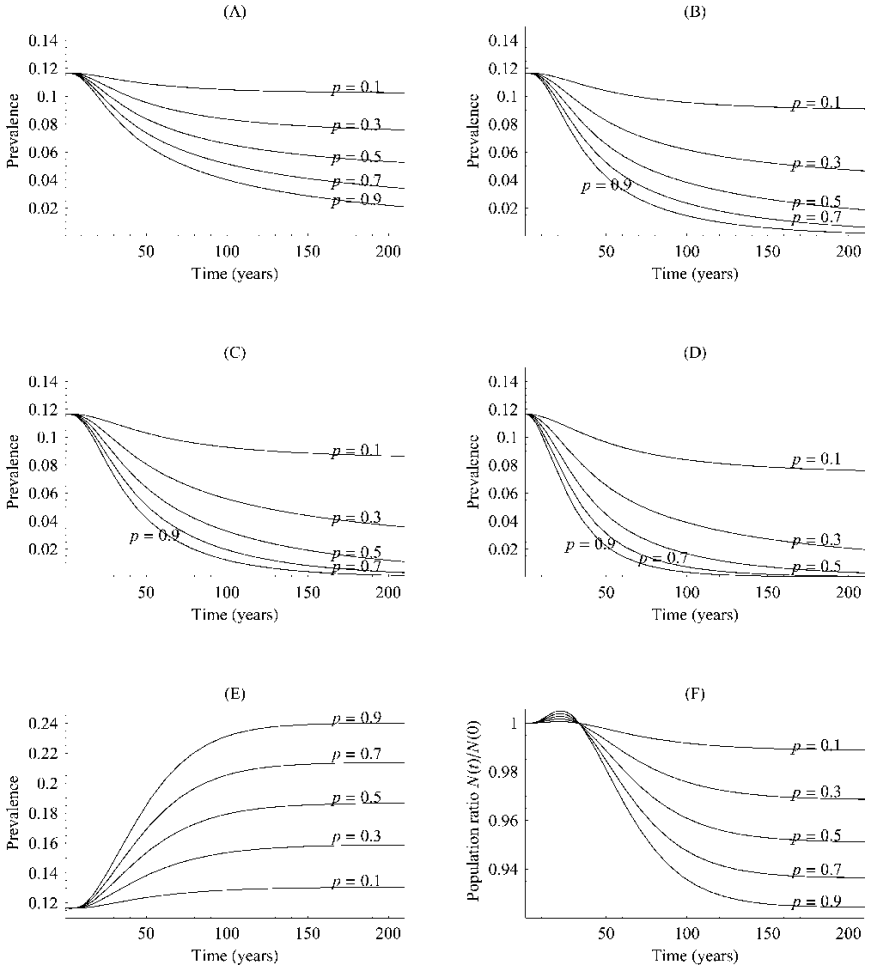

Fig. 4 Staged-Progression (SP) HIV-1 vaccination model: Prevalence, ratio of postvaccination and prevaccination prevalence, number of sexually-active people, or ratio of postvaccination and prevaccination number of sexually-active people, versus time since vaccination for various values of the parameters. Common parameters: Table 1 and $\pi_i = \rho_i$. Other parameters: (A) $\theta_i = s_i = 0.5, \gamma = 0.1, q = 1, r = 1$; (B) same as in (A), except $\theta_i = s_i = 0.25$; (C) same as in (A) except $\gamma = 0$; (D) $\theta_i = s_i = 0.25, q = 0.75, \gamma = 0.05, r = 1$; (E) $s_i = 1, \theta_i = q = 0.75, \gamma = 0.1, r = 1.25$; (F) same as (E).

to the next stage ($\theta_i = s_i = 0.25$), giving similar (but reduced) prevalence profile as in Fig. 4A.

In Fig. 4C, we simulate the same vaccine as in Fig. 4A with the additional characteristic of offering lifelong effect ($\gamma = 0$). The reduction in prevalence, in comparison to the scenario in Fig. 4A, is quite dramatic, underlying the importance of lifelong vaccine effect ($\gamma = 0$). Figure 4D depicts the case of a vaccine that provides a 25% degree protection ($q = 0.75$) that lasts for 20 years ($\gamma = 0.05$)

with breakthrough infections being 75% less infectious and slower in progression ($\theta_i = s_i = 0.25$). This gives results that are marginally better than those in Fig. 4C. In Fig. 4E and F, we illustrate the case where a vaccine that reduces progression rates by 25% ($\theta_i = 0.75$), provides 25% degree protection ($q = 0.75$) lasting for 10 years ($\gamma = 0.1$), and increases risk behavior by 25% ($r = 1.25$) can have detrimental effects. This is because, in this case, the postvaccination prevalence rate is higher and the size of the sexually-active population is smaller compared with prevaccination levels.

6. Summary and concluding remarks

In this paper, we have presented and analyzed four mathematical models for assessing the impact of an imperfect HIV-1 vaccine in curtailing the spread of HIV in a given community. We started by analyzing a simple deterministic, compartmental, mathematical model for monitoring the temporal dynamics of the susceptible, vaccinated, and infected individuals (excluding those in the AIDS class) in the presence of an imperfect vaccine. This basic model is then progressively refined to incorporate key issues pertaining to HIV epidemiology and vaccine characteristics. First, the contribution of AIDS cases in HIV transmission is included in the basic model, thereby relaxing the widely-used assumption that AIDS patients do not partake in the transmission of HIV. Second, the impact of an imperfect HIV-1 vaccine is studied by extending the basic model to incorporate the variations in infectiousness and the increase in the average time from infection to AIDS that goes along with a decreased viral load during the chronic phase of infection. Finally, the variation of infectiousness in a given individual over time is incorporated resulting in a staged progression model, which also monitors the effects of vaccination on HIV transmission as infected individuals pass through different stages of infection. The resulting models are then qualitatively analyzed for the existence and stability of their associated equilibria. In addition to allowing the determination of various epidemiologic thresholds (such as the reproduction numbers), the analysis also enables us to gain deeper insights into the stability and bifurcations of the various models (notably the possibility of backward bifurcations was established). We show, via numerical simulations using a reasonable set of parameters, that two endemic equilibria and a disease-free equilibrium can coexist, and have separate basins of attraction, for some values of the vaccinated reproduction number, $R(p)$, less than unity.

The analysis of the basic model shows that the introduction of an imperfect vaccine will result in a reduction in HIV prevalence and AIDS-related mortality if the basic reproduction number in the absence of vaccination, $\mathcal{R}_0$, exceeds the basic reproduction number when the entire population is vaccinated, R_{0v}. Furthermore, this study shows that even if this condition is violated, and prevalence is higher in the postvaccination era, the introduction of an imperfect vaccine can still succeed in reducing AIDS-induced mortality provided R_{0v} is not "too" high relative to $\mathcal{R}_0$ and other parameters.

Our analysis on the effect of HIV transmission by infected individuals in the AIDS stage of infection shows that vaccine impact depends on whether the positive therapeutic effect of delaying the onset of AIDS (θ) is less or more dominant than the net effect of reducing infectiousness and increasing risky behavior (rs). The former shows that the impact of the vaccine will be higher if the contribution of AIDS transmission is taken into account. Furthermore, HIV transmission by AIDS patients resulted in longer durations of infectiousness ($D_{u1} > D_u$, $D_{v1} > D_v$), higher reproduction numbers ($\mathcal{R}_{01} > \mathcal{R}_0$, $R_{0v1} > R_{0v}$), and higher prevalence in comparison to the basic model (where HIV transmission by individuals with AIDS is not taken into account).

This study shows that the results obtained from the basic model extend to the more general models, provided the quantities $\mathcal{R}_0$, R_{0v}, and durations of infectiousness are defined appropriately. These quantities include the main characteristics of an imperfect HIV-1 vaccine that need to be measured for the impact of vaccination to be assessed. We have shown that these expressions turn out to be more complicated for the more realistic (extended) models.

The models considered in this study do not incorporate other important features of HIV transmission such as heterogeneities in susceptibility to infection, variations in sexual behavior, gender, and age. A natural extension of this work is to include some of these features. Investigating the global dynamics of the models is another area of interest (and a subject of a separate study).

Several candidate HIV-1 vaccines are currently in development. This study provides useful tools for assessing the effectiveness and analyzing the potential population level impact of vaccines with various properties and taking into account increases in risk behaviors following widespread vaccination. It is important that the effectiveness and impact of candidate vaccines be assessed using appropriate tools before any vaccination programs are implemented. The study highlights important key parameters to be considered in assessing the public health impact of such vaccines and indicates the possibility that vaccine effectiveness can, in some scenarios, be undermined or even more than offset. For example, it is shown that deploying an imperfect vaccine that slows progression to AIDS without reducing susceptibility to infection or infectiousness of vaccinated individuals may result in a detrimental public health outcome. Overall, the study shows that the prospect of effective HIV control is promising using an imperfect vaccine with certain desirable features. In order to maximize the benefit of such vaccines, effective behavioral interventions may need to be implemented simultaneously with HIV vaccines.

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Appendix A: Generalized differential infectivity vaccination model

This appendix describes the derivation and analysis of a generalized version of the differential infectivity model (27) which, additionally, takes into account the transmission of HIV by AIDS patients. The model, which is an extension of the models of McLean and Blower (1993), Anderson and Garnett (1996), Hyman et al. (1999), and Blower et al. (2002), assumes a constant in-flow of new sexually-active individuals, assumed susceptible, into the community at a rate Λ. Furthermore, susceptible individuals acquire HIV infection at time dependent rate λ. The rate λ depends on the transmission probability per partner and number of new sex partners (β_i) of infected individuals in subgroup i, the relative infectiousness (s_j), and increases in risky behavior (r) of vaccinated infected individuals, the transmission probability from AIDS patients to their susceptible sex partners (β_A) and the proportions of individuals in these various subgroups, Y_i/N, W_j/N, A/N.

Upon acquiring HIV infection, a susceptible enters the class of unvaccinated infected individuals (Y). This infected unvaccinated population is divided into I subgroups, $Y_1, Y_2, \ldots, Y_I$, representing the different strata of HIV RNA concentrations of infected individuals. The probability an infected unvaccinated individual entering subgroup i is denoted by ρ_i, and individuals in subgroup i develop AIDS at rate σ_i. It is assumed that a fraction p of susceptible individuals are vaccinated and placed in the vaccinated class (V). It is further assumed that the vaccine-induced immunity acquired by vaccinated individuals wanes at a rate γ (so that vaccinated individuals move to the susceptible class at a rate γ). Since vaccinated individuals are not fully protected against infection (owing to the vaccine imperfection), it is assumed that vaccinated individuals acquire infection at a rate that is q times lower than that of unvaccinated susceptible individuals. Infected vaccinated individuals are placed in class W. Another essential aspect of this model is the assumption that the vaccine alters the distribution of people going into the different HIV RNA groups upon infection. In other words, it is assumed that the vaccinated infected population is subdivided into J subgroups, $W_1, W_2, \ldots, W_J$, with respective probabilities $\pi_1, \pi_2, \ldots, \pi_J$. The progression rate to AIDS for subgroup j is $\theta_j\sigma_j$ $(0 < \theta_j \leq 1)$, so that if HIV RNA subgroup n is defined consistently in the two infection classes Y and W, θ_n will measure the effectiveness of the vaccine in slowing progression to AIDS in infected individuals who are supposed to be in the infected unvaccinated subgroup n but, due to the vaccine, they enter subgroup n of the vaccinated infected class. The relative degree of infectiousness of individuals in subgroup W_n compared with those in subgroup Y_n is given by s_n $(0 < s_n \leq 1)$. AIDS patients have an additional disease-induced mortality rate α. Thus, the generalized differential infectivity model is given by

$$\mathrm{d}X/\mathrm{d}t = (1-p)\Lambda - \mu X - \lambda X + \gamma V,$$

$$\mathrm{d}V/\mathrm{d}t = p\Lambda - \mu V - qr\lambda V - \gamma V,$$

$$
\begin{aligned}
\mathrm{d}Y_i/\mathrm{d}t &= \rho_i \lambda X - (\mu + \sigma_i) Y_i, \qquad i = 1, 2, \ldots, I \\
\mathrm{d}W_j/\mathrm{d}t &= \pi_j q r \lambda V - (\mu + \theta_j \sigma_j) W_j, \qquad j = 1, 2, \ldots, J \\
\mathrm{d}A/\mathrm{d}t &= \sum_{i=1}^{I} \sigma_i Y_i + \sum_{j=1}^{J} \theta_j \sigma_j W_j - (\alpha + \mu) A, \\
\lambda &= \sum_{i=1}^{I} \beta_i \frac{Y_i}{N} + \sum_{j=1}^{J} r s_j \beta_j \frac{W_j}{N} + \beta_A A, \\
N &= X + V + \sum_{i=1}^{I} Y_i + \sum_{j=1}^{J} W_j + A.
\end{aligned}
\tag{A.1}
$$

A suitable domain for this model is

$$
\mathfrak{D}_{\mathfrak{a}} = \left\{ (X, V, Y, W, A) \in \Re_+^{3+I+J} : X + V + \sum_{i=1}^{I} Y_i + \sum_{j=1}^{J} W_j + A \leq \Lambda/\mu \right\},
$$

where $Y = (Y_1, Y_2, ..., Y_I) \in \Re_+^I$, $W = (W_1, W_2, ..., W_J) \in \Re_+^J$.

We first analyze the disease-free equilibrium in the absence of vaccination. This equilibrium is given by: $e_{0a} = (X^*, Y_i^*, A^*) = (\Lambda/\mu, 0, 0)$ for $i = 1, 2, \ldots, I$. Linearizing the above system (A.1) around the disease-free equilibrium e_{0a} gives the following Jacobian:

$$
J(e_{0a}) = \begin{pmatrix}
-\mu & -\beta_1 & \cdots & -\beta_i & \cdots & -\beta_I & -\beta_{\mathrm{A}} \\
0 & \rho_1\beta_1 - \mu - \sigma_1 & \cdots & \rho_1\beta_i & \cdots & \rho_1\beta_I & \rho_1\beta_{\mathrm{A}} \\
\vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\
0 & \rho_i\beta_1 & \cdots & \rho_i\beta_i - \mu - \sigma_i & \cdots & \rho_i\beta_I & \rho_i\beta_{\mathrm{A}} \\
\vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\
0 & \rho_I\beta_1 & \cdots & \rho_I\beta_i & \cdots & \rho_I\beta_I - \mu - \sigma_I & \rho_I\beta_{\mathrm{A}}
\end{pmatrix}.
$$

Using the methods described in Hyman et al. (1999), it can be shown that each eigenvalue of this Jacobian matrix has negative real part (so that the disease-free equilibrium is locally asymptotically stable) if and only if

$$
\mathcal{R}_{0a} = \sum_{i=1}^{I} \left(\frac{\rho_i \beta_i}{\mu + \sigma_i} + \frac{\beta_{\mathrm{A}}}{\alpha + \mu} \frac{\rho_i \sigma_i}{\mu + \sigma_i} \right) < 1. \tag{A.2}
$$

Similarly, the disease-free equilibrium in the presence of vaccination is given by

$$
\mathcal{E}_{0a} = (X^*, V^*, Y_i^*, W_j^*, A^*) = \left(\frac{\Lambda}{\mu} - \frac{p\Lambda}{(\gamma + \mu)}, \frac{p\Lambda}{\gamma + \mu}, 0, 0, 0 \right) \tag{A.3}
$$

for $i = 1, 2, \ldots, I$; $j = 1, 2, \ldots, J$. The associated Jacobian is $J(\mathcal{E}_{0a}) =$

$$\begin{pmatrix}
-\mu & \gamma & \cdots & -\beta_i\left(1-\frac{\mu p}{\gamma+\mu}\right) & \cdots & -rs_j\beta_j\left(1-\frac{\mu p}{\gamma+\mu}\right) & \cdots & -\beta_{\mathrm{A}}\left(1-\frac{\mu p}{\gamma+\mu}\right) \\
0 & -\mu-\gamma & \cdots & -\beta_i qr\frac{\mu p}{\gamma+\mu} & \cdots & -rs_j\beta_j qr^2\frac{\mu p}{\gamma+\mu} & \cdots & -\beta_{\mathrm{A}} qr\frac{\mu p}{\gamma+\mu} \\
\vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\
0 & 0 & \cdots & \rho_i\beta_i\left(1-\frac{\mu p}{\gamma+\mu}\right)-\mu-\sigma_i & \cdots & \rho_i\beta_j(1-\frac{\mu p}{\gamma+\mu}) & \cdots & \rho_i\beta_{\mathrm{A}}\left(1-\frac{\mu p}{\gamma+\mu}\right) \\
\vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\
0 & 0 & \cdots & \pi_j\beta_i qr\frac{\mu p}{\gamma+\mu} & \cdots & \pi_j\beta_j s_j qr^2\frac{\mu p}{\gamma+\mu}-\mu-\theta_j\sigma_j & \cdots & \pi_j\beta_{\mathrm{A}} qr\frac{\mu p}{\gamma+\mu} \\
\vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\
0 & 0 & \cdots & \sigma_i & \cdots & \theta_j\sigma_j & \cdots & -\alpha-\mu
\end{pmatrix}.$$

A straightforward calculation reveals that all eigenvalues have negative real parts if and only if

$$R_a(p) = \mathcal{R}_{0a}\left[1 - p\frac{\mu}{\gamma+\mu}\left(1-\frac{R_{0\mathrm{v}a}}{\mathcal{R}_{0a}}\right)\right] < 1, \tag{A.4}$$

where

$$R_{0\mathrm{v}a} = \sum_{j=1}^{J}\left(q\,r^2\frac{\pi_j s_j\beta_j}{\mu+\theta_j\sigma_j} + qr\frac{\beta_{\mathrm{A}}}{\alpha+\mu}\frac{\pi_j\theta_j\sigma_j}{\mu+\theta_j\sigma_j}\right). \tag{A.5}$$

Furthermore, the endemic equilibrium in the absence of vaccination is given by $\mathcal{E}_{1a} = (X^*, V^*, Y_i^*, W_j^*, A^*)$, where

$$X^* = \frac{\Lambda D_{\mathrm{u}a}}{\mathcal{R}_{0a}-1+\mu D_{\mathrm{u}a}},\ V^* = 0,\ Y_i^* = \frac{\rho_i\Lambda(\mathcal{R}_{0a}-1)}{(\mu+\sigma_i)(\mathcal{R}_{0a}-1+\mu D_{\mathrm{u}a})}, \tag{A.6}$$

$$W_i^* = 0,\ A^* = \frac{\Lambda(\mathcal{R}_{0a}-1)}{(\alpha+\mu)(\mathcal{R}_{0a}-1+\mu D_{\mathrm{u}a})}\sum_{i=1}^{I}\frac{\rho_i\sigma_i}{\mu+\sigma_i},$$

with

$$D_{\mathrm{u}a} = \sum_{i=1}^{I}\left(\frac{\rho_i}{\mu+\sigma_i} + \frac{1}{\alpha+\mu}\frac{\rho_i\sigma_i}{\mu+\sigma_i}\right). \tag{A.7}$$

An infinitesimal change from (a small perturbation of) this equilibrium as a result of vaccination can be calculated using the equation

$$\mathbf{Z} = J(\mathcal{E}_{1a})^{-1}\mathbf{P},$$

where $J(\mathcal{E}_{1a}) =$

$$\begin{pmatrix}
-\mu - K_{11} & \gamma + K_{12} & -K_{13} & \cdots \\
0 & -\mu - \gamma - qrK_{12} & 0 & \cdots \\
\rho_1 K_{11} & -\rho_1 K_{12} & rho_1 K_{13} - \mu - \sigma_1 & \cdots \\
\vdots & \vdots & \vdots & \vdots \\
\rho_I K_{11} & \rho_I K_{12} & \rho_I K_{13} & \cdots \\
0 & \pi_1 qr K_{12} & 0 & \cdots \\
\vdots & \vdots & \vdots & \vdots \\
0 & \pi_J qr K_{12} & 0 & \cdots \\
0 & 0 & \sigma_1 & \cdots
\end{pmatrix}$$

$$\begin{pmatrix}
-K_{I3} & -K_{14} & \cdots & -K_{J4} & -K_{\mathrm{A}} \\
0 & 0 & \cdots & 0 & 0 \\
\rho_1 K_{I3} & \rho_1 K_{14} & \cdots & \rho_1 K_{J4} & \rho_1 K_{\mathrm{A}} \\
\vdots & \vdots & \vdots & \vdots & \vdots \\
\rho_I K_{I3} - \mu - \mu - \sigma_I & \rho_I K_{14} & \cdots & \rho_I K_{J4} & \rho_I K_{\mathrm{A}} \\
0 & -\mu - \theta_1 \sigma_1 & \cdots & 0 & 0 \\
\vdots & \vdots & \vdots & \vdots & \vdots \\
0 & 0 & \cdots & -\mu - \theta_J \sigma_J & 0 \\
\sigma_I & \theta_I \sigma_I & \cdots & \theta_J \sigma_J & -\alpha - \mu
\end{pmatrix}$$

with

$$K_{11} = \frac{(R_0 - 1)^2}{D_{\mathrm{u}} R_0},\ K_{12} = \frac{R_0 - 1}{D_{\mathrm{u}} R_0},\ K_{i3} = \frac{\beta_i D_{\mathrm{u}} + 1 - R_0}{D_{\mathrm{u}} R_0},$$

$$K_{i4} = \frac{rs_i \beta_i D_{\mathrm{u}} + 1 - R_0}{D_{\mathrm{u}} R_0},$$

$$K_{\mathrm{A}} = \frac{\beta_{\mathrm{A}} D_{\mathrm{u}} + 1 - R_0}{D_{\mathrm{u}} R_0},$$

$$\mathbf{Z} = \left(\frac{\mathrm{d}X}{\mathrm{d}p}, \frac{\mathrm{d}V}{\mathrm{d}p}, \frac{\mathrm{d}Y_1}{\mathrm{d}p}, \frac{\mathrm{d}Y_2}{\mathrm{d}p}, \ldots, \frac{\mathrm{d}Y_I}{\mathrm{d}p}, \frac{\mathrm{d}W_1}{\mathrm{d}p}, \frac{\mathrm{d}W_2}{\mathrm{d}p}, \ldots \frac{\mathrm{d}W_J}{\mathrm{d}p}, \frac{\mathrm{d}A}{\mathrm{d}p}\right)^{\mathrm{T}},$$

$$\mathbf{P} = (1, -1, 0, 0, \ldots, 0, 0, 0, \ldots, 0, 0)^{\mathrm{T}},$$

and T denoting transpose of a matrix.

It follows that the effect of vaccination on endemic HIV prevalence $(\sum_{i=1}^{I} Y_i + \sum_{j=1}^{J} W_j + A)/N$ is given by the sign of the expression

$$1 - \frac{R_{0va}}{\mathcal{R}_{0a}}. \tag{A.8}$$

Thus, prevalence falls following vaccination if and only if $R_{0va} < \mathcal{R}_{0a}$. Furthermore, the effect of vaccination on the size of the population depends on the sign of the following expression:

$$1 + qr(\mathcal{R}_{0a} - 1)\frac{(D_{va}/D_{ua} - 1)}{(1 - D_{ua}/L)} - \frac{R_{0va}}{\mathcal{R}_{0a}}, \tag{A.9}$$

where the average durations of infectiousness for the vaccinated groups (D_{va}) and duration in the sexually-active (excluding AIDS patients) population (L) are given by

$$D_{va} = \sum_{j=1}^{J}\left[\frac{\pi_j}{\mu + \theta_j\sigma_j} + \frac{1}{(\alpha+\mu)}\frac{\pi_j\theta_j\sigma_j}{(\mu+\theta_j\sigma_j)}\right], \; L = \frac{1}{\mu}. \tag{A.10}$$

Appendix B: Generalized staged-progression vaccination model

For the generalized staged-progression model, the unvaccinated infected population (Y) is subdivided into I infected subgroups namely $Y_1, Y_2, \ldots, Y_I$. Similarly, the vaccinated infected class (breakthrough infections) is subdivided into J subgroups $W_1, W_2, \ldots, W_J$. We assume one AIDS category. Suppose $1/\sigma_i$ $(1/\theta_i\sigma_i)$ denotes the average waiting time in the unvaccinated (vaccinated) subgroup i, then the generalized staged-progression model is given by

$$\begin{aligned}
\mathrm{d}X/\mathrm{d}t &= (1-p)\Lambda - \mu X - \lambda X + \gamma V,\\
\mathrm{d}V/\mathrm{d}t &= p\Lambda - \mu V - qr\lambda V - \gamma V,\\
\mathrm{d}Y_1/\mathrm{d}t &= \lambda X - (\mu+\sigma_1)Y_1,\\
\mathrm{d}Y_i/\mathrm{d}t &= \sigma_{i-1}Y_{i-1} - (\mu+\sigma_i)Y_i, \qquad i = 2,3,\ldots,I,\\
\mathrm{d}W_1/\mathrm{d}t &= qr\lambda V - (\mu+\theta_1\sigma_1)W_1,\\
\mathrm{d}W_j/\mathrm{d}t &= \theta_{j-1}\sigma_{j-1}W_{j-1} - (\mu+\theta_j\sigma_j)W_j, \qquad j = 2,3,\ldots,J,\\
\mathrm{d}A/\mathrm{d}t &= \sigma_I Y_I + \theta_J\sigma_J W_J - (\alpha+\mu)A,
\end{aligned} \tag{B.1}$$

$$\lambda = \sum_{i=1}^{I} \beta_i \frac{Y_i}{N} + \sum_{j=1}^{J} rs_j \beta_j \frac{W_j}{N} + \beta_{\mathrm{A}} \frac{A}{N},$$

$$N = X + V + \sum_{i=1}^{I} Y_i + \sum_{j=1}^{J} W_j + A.$$

A suitable domain for this model is

$$\mathfrak{D}_{\mathfrak{b}} = \left\{ (X, V, Y, W, A) \in \Re_+^{3+I+J} : X + V + \sum_{i=1}^{I} Y_i + \sum_{j=1}^{J} W_j + A \leq \Lambda/\mu \right\}.$$

where $Y = (Y_1, Y_2, ..., Y_I) \in \Re_+^I$, $W = (W_1, W_2, ..., W_J) \in \Re_+^J$.

The disease-free equilibrium in the absence of vaccination is given by: $e_{0b} = (X^*, Y_i^*, A^*) = (\Lambda/\mu, 0, 0)$ for $i = 1, 2, \ldots, I$. The associated Jacobian matrix is

$$J(e_{0b}) = \begin{pmatrix} -\mu & -\beta_1 & -\beta_2 & \cdots & -\beta_i & \cdots & -\beta_I & -\beta_{\mathrm{A}} \\ 0 & \beta_1 - \mu - \sigma_1 & \beta_2 & \cdots & \beta_i & \cdots & \beta_I & \beta_{\mathrm{A}} \\ 0 & \sigma_1 & -\mu - \sigma_1 & \cdots & 0 & \cdots & 0 & 0 \\ \vdots & \vdots & & \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & 0 & \cdots & -\mu - \sigma_i & \cdots & 0 & 0 \\ \vdots & \vdots & & \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & 0 & \cdots & 0 & \sigma_{I-1} & -\mu - \sigma_I & 0 \\ 0 & 0 & 0 & \cdots & 0 & \cdots & \sigma_I & -\alpha - \mu \end{pmatrix},$$

so that the disease-free equilibrium in the absence of vaccination is locally asymptotically stable if and only if

$$\mathcal{R}_{0b} = \sum_{i=1}^{I} \left[\frac{\beta_i}{(\mu + \sigma_i)} \prod_{j=1}^{i-1} \frac{\sigma_j}{(\mu + \sigma_j)} \right] + \frac{\beta_{\mathrm{A}}}{(\alpha + \mu)} \prod_{h=1}^{I} \frac{\sigma_h}{(\mu + \sigma_h)} < 1. \tag{B.2}$$

The disease-free equilibrium with vaccination is given by

$$\mathcal{E}_{0b} = (X^*, V^*, Y_i^*, W_j^*, A^*) = \left(\frac{\Lambda}{\mu} - \frac{p\Lambda}{(\gamma + \mu)}, \frac{p\Lambda}{\gamma + \mu}, 0, 0, 0 \right) \tag{B.3}$$

for $i = 1, 2, \ldots, I$ and $j = 1, 2, \ldots, J$. The Jacobian matrix evaluated at this equilibrium is

$$J(\mathcal{E}_{0b}) =$$

$$\begin{pmatrix}
-\mu & \gamma & \cdots & -\beta_i\left(1-\frac{\mu p}{\gamma+\mu}\right) & \cdots & -rs_j\beta_j\left(1-\frac{\mu p}{\gamma+\mu}\right) & \cdots & -\beta_{\mathrm{A}}\left(1-\frac{\mu p}{\gamma+\mu}\right) \\
0 & -\mu-\gamma & \cdots & -\beta_i qr\frac{\mu p}{\gamma+\mu} & \cdots & -rs_j\beta_j qr^2\frac{\mu p}{\gamma+\mu} & \cdots & -\beta_{\mathrm{A}} qr\frac{\mu p}{\gamma+\mu} \\
0 & 0 & \cdots & \beta_i\left(1-\frac{\mu p}{\gamma+\mu}\right) & \cdots & rs_j\beta_j\left(1-\frac{\mu p}{\gamma+\mu}\right) & \cdots & \beta_{\mathrm{A}}\left(1-\frac{\mu\, p}{\gamma+\mu}\right) \\
\vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\
0 & 0 & \cdots & -\mu-\sigma_i & \cdots & 0 & \cdots & 0 \\
\vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\
0 & 0 & \cdots & \beta_i qr\frac{\mu\, p}{\gamma+\mu} & \cdots & \beta_j s_j qr^2\frac{\mu p}{\gamma+\mu} & \cdots & \beta_{\mathrm{A}} qr\frac{\mu p}{\gamma+\mu} \\
\vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\
0 & 0 & \cdots & 0 & \cdots & -\mu-\theta_j\sigma_j & \cdots & 0 \\
\vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\
0 & 0 & \cdots & 0 & \cdots & 0 & \cdots & -\alpha-\mu
\end{pmatrix},$$

from which it follows that this equilibrium is locally asymptotically stable if and only if

$$R_b(p) = \mathcal{R}_{0b}\left[1 - p\frac{\mu}{\gamma+\mu}\left(1 - \frac{R_{0\mathrm{v}b}}{\mathcal{R}_{0b}}\right)\right] < 1, \tag{B.4}$$

where

$$R_{0\mathrm{v}b} = qr^2\sum_{i=1}^{J}\left[\frac{s_i\beta_i}{(\mu+\theta_i\sigma_i)}\prod_{j=1}^{i-1}\frac{\theta_j\sigma_j}{(\mu+\theta_j\sigma_j)}\right]$$

$$+ qr\frac{\beta_{\mathrm{A}}}{(\alpha+\mu)}\prod_{h=1}^{I}\frac{\theta_h\sigma_h}{(\mu+\theta_h\sigma_h)} < 1. \tag{B.5}$$

Furthermore, it can be shown that the endemic equilibrium for the model (B-2) in the absence of vaccination is given by $\mathcal{E}_{1b} = (X^*, V^*, Y_i^*, W_j^*, A^*)$, where

$$X^* = \frac{\Lambda D_{\mathrm{u}b}}{\mathcal{R}_{0b} - 1 + \mu D_{\mathrm{u}b}},$$

$$Y_i^* = \frac{\rho_i\Lambda(\mathcal{R}_{0b}-1)}{(\mu+\sigma_i)(\mathcal{R}_{0b}-1+\mu D_{\mathrm{u}b})}\prod_{j=1}^{i-1}\frac{\sigma_j}{(\mu+\sigma_j)},\ V^* = 0, \tag{B.6}$$

$$W_j^* = 0,\ A^* = \frac{\Lambda(\mathcal{R}_{0b} - 1)}{(\alpha + \mu)(\mathcal{R}_{0b} - 1 + \mu D_{\mathrm{u}b})} \sum_{j=1}^{I} \frac{\sigma_j}{\mu + \sigma_j},$$

where

$$D_{\mathrm{u}b} = \sum_{i=1}^{I} \left[\frac{1}{(\mu + \sigma_i)} \prod_{j=1}^{i-1} \frac{\sigma_j}{(\mu + \sigma_j)} \right] + \frac{1}{(\alpha + \mu)} \prod_{h=1}^{I} \frac{\sigma_h}{(\mu + \sigma_h)}. \tag{B.7}$$

An infinitesimal change from this equilibrium as a result of vaccination can be calculated using the equation

$$\mathbf{Z} = J(\mathcal{E}_{1b})^{-1}\mathbf{P},$$

where $J(\mathcal{E}_{1b}) =$

$$\begin{pmatrix}
-\mu - K_{11} & \gamma + K_{12} & -K_{13} & \cdots & -K_{I3} & -K_{14} & \cdots & -K_{J4} & -K_{\mathrm{A}} \\
0 & -\mu - \gamma - qrK_{12} & 0 & \cdots & 0 & 0 & \cdots & 0 & 0 \\
K_{11} & -K_{12} & K_{13} - \mu - \sigma_1 & \cdots & K_{I3} & K_{14} & \cdots & K_{J4} & K_{\mathrm{A}} \\
\vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\
0 & 0 & 0 & \cdots & -\mu - \sigma_I & 0 & \cdots & 0 & 0 \\
0 & qrK_{12} & 0 & \cdots & 0 & -\mu - \theta_1\sigma_1 & \cdots & 0 & 0 \\
\vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\
0 & 0 & 0 & \cdots & 0 & 0 & \cdots & -\mu - \theta_J\sigma_J & 0 \\
0 & 0 & 0 & \cdots & \sigma_I & 0 & \cdots & \theta_J\sigma_J & -\alpha - \mu
\end{pmatrix},$$

and $\mathbf{Z}$, $\mathbf{P}$, and K_{ij} are defined earlier. The effect of vaccination on endemic HIV prevalence $(\sum_{i=1}^{I} Y_i + \sum_{j=1}^{J} W_j + A)/N$ is given by the sign of the expression

$$1 - \frac{R_{0\mathrm{v}b}}{\mathcal{R}_{0b}}. \tag{B.8}$$

The effect of vaccination on the size of the population depends on the sign of the following expression:

$$1 + qr(\mathcal{R}_{0b} - 1)\frac{(D_{\mathrm{v}b}/D_{\mathrm{u}b} - 1)}{(1 - D_{\mathrm{u}b}/L)} - \frac{R_{0\mathrm{v}b}}{\mathcal{R}_{0b}}, \tag{B.9}$$

where the average durations of infectiousness for the vaccinated groups ($D_{\mathrm{v}b}$) and duration in the sexually active (excluding AIDS patients) population (L) are given

by

$$D_{vb} = \sum_{i=1}^{J} \left[\frac{1}{(\mu + \theta_i \sigma_i)} \prod_{j=1}^{i-1} \frac{\theta_j \sigma_j}{(\mu + \theta_j \sigma_j)} \right] + \frac{1}{(\alpha + \mu)} \prod_{h=1}^{I} \frac{\theta_h \sigma_h}{(\mu + \theta_h \sigma_h)}, \quad L = \frac{1}{\mu}. \tag{B.10}$$

References

Anderson, R.M., May, R.M., 1991. Infectious Diseases of Humans: Dynamics and control, Oxford University Press, Oxford.

Anderson, R.M., Garnett, G.P., 1996. Low-efficacy HIV vaccines: Potential for community-based intervention programmes. Lancet 348, 1010–1013.

Anderson, R.M., Hanson, M., 2005. Potential public health impact of imperfect HIV type 1 vaccines. J. Infect. Dis. 191(Suppl. 1), S85–S96.

Arino, J., McCluskey, C.C., van den Driessche, P., 2003. Global results for an epidemic model with vaccination that exhibits backward bifurcation. SIAM J. Appl. Math. 64, 260–276.

Berzofsky, J., Ahlers, A., Janik, J., Morris, J., Sangkon, O., et al., 2004. Progress on new vaccine strategies against chronic viral infections. J. Clin. Invest. 114, 450–462.

Blower, S., McLean, A., 1994. Prophylactic vaccines, risk behavior change, and the probability of eradicating HIV in San Francisco. Science 265, 1451–1454.

Blower, S., McLean, A., 1995. AIDS: Modeling epidemic control. Science 267, 1250–1253.

Blower, S., Koelle, K., Mills, J., 2002. Health policy modeling: Epidemic control, HIV vaccines, and risky behavior. In: Kaplan and Brookmeyer (Eds.), Quantitative Evaluation of HIV Prevention Programs. Yale University Press, pp. 260–289.

Chang, M.L., Vitek, C., Esparza, J., 2003. Public health considerations for the use of a first generation HIV vaccine. Report from a WHO-UNAIDS-CDC consultation, Geneva, 20–21 November 2002. AIDS 17, W1–W10.

Chesney, M., Chambers, D., Kahn, J., 1997. Risk behavior for HIV infection in participants in preventive HIV vaccine trials: A cautionary note. J. Acquir. Immune. Defic. Syndr. Hum. Retrovirol. 16, 266–271.

Calarota, S., Weiner, D., 2003. Present status of human HIV vaccine development. AIDS 17(Suppl. 4), S73–S84.

Clements, C.J., Abdool-Karim, Q., Chang, M.L., Nkowane, B., Esparza, J., 2004. Breaking new ground—are changes in immunization services needed for the introduction of future HIV/AIDS vaccines and other new vaccines targeted at adolescents? Vaccine 22, 2822–2826.

Corbett, B.D., Moghadas, S.M., Gumel, A.B., 2003. Subthreshold domain of bistable equilibria for a model of HIV epidemiology. IJMMS 58, 3679–3698.

Diekmann, O., Heesterbeek, J.A.P., Metz, J.A.J., 1990. On the definition and the computation of the basic reproduction ratio R_0 in models for infectious diseases in heterogeneous populations. J. Math. Biol. 28, 503–522.

Dixon, S., McDonald, S., Roberts, J., 2002. The impact of HIV and AIDS on Africa's economic development. BMJ 324, 232–234.

Esparza, J., Osmanov, S., 2003. HIV vaccines: A global perspective. Curr. Mol. Med. 3, 183–193.

Fauci, A.S., Pantaleo, G., Stanley, S., Weissman, D., 1996. Immunopathogenic mechanisms of HIV infection. Ann. Intern. Med. 124, 654–663.

Fleck, F., 2004. Developing economies shrink as AIDS reduces workforce. BMJ 329, 129.

Gray, R., Wawer, M., Brookmeyer, R., Sewankambo, N., et al., for the Rakai Project Study Group, 2001. Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-discordant couples in Rakai, Uganda. Lancet 357, 1149–1153.

Gray, R., Li, X., Wawer, M., Gange, S., Serwadda, D., et al. (2003). Stochastic simulation of the impact of antiretroviral therapy and HIV vaccines on HIV transmission; Rakai, Uganda. AIDS 17, 1941–1951.

Gumel, A.B., Moghadas, S.M., Mickens, R.E., 2004. Effect of a preventive vaccine on the dynamics of HIV transmission. Commun. Nonlinear Sci. Numer. Simul. 9, 649–659.
Hethcote, H.W., 2000. The mathematics of infectious diseases. SIAM Rev. 42, 599–653.
Hethcote, H.W., Van Ark, J., 1992. Modeling HIV transmission and AIDS in the United States. Lecture Notes in Biomathematics vol. 95. Springer-Verlag, New York.
Hyman, J.M., Li, J., Stanley, E.A., 1999. The differential infectivity and staged progression models for the transmission of HIV. Math. Biosci. 208, 227–249.
Hyman, J.M., Li, J., Stanley, E.A., 2001. The initialization and sensitivity of multigroup models for the transmission of HIV. J. Theor. Biol. 155, 77–109.
Kribs-Zaleta, C., Velasco-Hernández, J., 2000. A simple vaccination model with multiple endemic states. Math. Biosci. 164, 183–201.
Lansky, A., Nakashima, A., Jones, J., 2000. Risk behaviors related to heterosexual transmission from HIV-infected persons. Sex. Transm. Dis. 27, 483–489.
Lee, D., Graham, B., Chiu, Y.-L., Gilbert, P., McElrath, M., et al., 2004. Breakthrough infections during phase 1 and 2 prime-boos HIV-1 vaccine trials with canarypox vectors (ALVAC) and booster dose of recombinant gp120 or gp160. J. Infect. Dis. 190, 903–907.
Longini, I., Clark, W., Byers, R., 1989. Statistical analysis of the stages of HIV infections using a Markov model. Stat. Med. 8, 831–843.
Massad, E., Coutinho, F., Burattini, M., Lopez, L., Struchiner, C.J., 2001. Modeling the impact of imperfect HIV vaccines on the incidence of the infection. Math. Comput. Model. 34, 345–351.
McCluskey, C., 2003. A model of HIV/AIDS with staged progression and amelioration. Math. Biosci. 181, 1–16.
McLean, A., Blower, S., 1993. Imperfect vaccines and herd immunity to HIV. Proc. R. Soc. Lond. B 253, 9–13.
Mellors, J., Munoz, A., Giorgi, J., Margolick, J., Tassoni, C., et al., 1997. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. Ann. Intern. Med. 126, 946–954.
Newman, P., Duan, N., Rudy, E., Johnston-Roberts, K., 2004. HIV risk and prevention in a post-vaccine context. Vaccine 22, 1954–1963.
Nicolosi, A., Musicco, M., Saracco, A., Lazzarin, A., 1994. Risk factors for woman-to-man sexual transmission of the human immunodeficiency virus. J. Acquir. Immune. Defic. Syndr. 7, 296–300.
O'Brien, T., Busch, M., Donegan, E., Ward, J., Wong, L., et al., 1994. Heterosexual transmission of human immunodeficiency virus type 1 from transfusion recipients to their sex partners. J. Acquir. Immune. Defic. Syndr. 7, 705–710.
Perko, L., 1996. Differential equations and dynamical systems. Springer-Verlag, New York.
Perelson, A., Nelson, P., 1999. Mathematical analysis of HIV-1 dynamics in vivo. SIAM Rev. 41, 3–44.
Porco, T., Blower, S., 1998. Designing HIV vaccination policies: Subtypes and cross-immunity. Interfaces 28, 167–190.
Porco, T., Blower, S., 2000. HIV vaccines: The effect of the mode of action on the coexistence of HIV subtypes. Math. Popul. Stud. 8, 205–229.
Quinn, T.C., Wawer, M.J., Sewankambo, N., et al., for the Rakai Project Study Group, 2000. Viral load and heterosexual transmission of human immunodeficiency virus. N. Engl. J. Med. 342, 921–929.
Royce, R., Sena, A., Cates, W., Cohen, M., 1997. Sexual transmission of HIV. N. Engl. J. Med. 336, 1072–1078.
Santra, S., Barouch, D., Korioth-Schmitz, B., Lord, C., Beddall, M., et al., 2004. Recombinant pox virus boosting of DNA-primed rhesus monkeys augments peak but not memory T lymphocyte responses Proc. Natl. Acad. Sci. 101, 11088–11093.
Shiver, J., Fu, T.-M., Chen, L., Casimiro, D., Davies, M.-A., et al., 2002. Replication-incompetent adenoviral vaccine vector elicits effective anti-immunodeficiency-virus immunity. Nature 415, 331–335.
Shiver, J., Emini, E., 2004. Recent advances in the development of HIV-1 vaccines using replication-incompetent adenovirus vectors. Ann. Rev. Med. 55, 355–372.
Takayama, A., 1993. Analytical Methods in Economics. University of Michigan Press, Ann Arbor.
United Nations Department of Economic and Social Affairs/Population Division, 2004. The Impact of AIDS. United Nations, New York.

van den Driessche, P., Watmough, J., 2002. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. Math. Biosci. 180, 29–48.
van Griensven, F., Keawkungwal, J., Tappero, J., Sangkum, U., Pitisuttithum, P., et al., 2004. Lack of increased HIV risk behavior among injection drug users participating in the AIDSVAX B/E HIV vaccine trial in Bangkok, Thailand. AIDS 18, 295–301.
Varian, H., 1992. Microeconomic Analysis, 3rd edn, W.W. Norton, New York.
World Bank, 1997. Confronting AIDS: Public Priorities in a Global Epidemic. Oxford University Press, Oxford.
WHO, 2004. The World Health Report: Changing History. World Health Organization, 1211 Geneva 27, Switzerland.