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Effects of education, vaccination and treatment on HIV transmission in homosexuals with genetic heterogeneity

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Abstract

Genetic studies report the existence of a mutant allele Δ32 of CCR5 chemokine receptor gene at high allele frequencies (∼10%) in Caucasian populations. The presence of this allele is believed to provide partial or full resistance to HIV. In this study, we look at the impact of education, temporarily effective vaccines and therapies on the dynamics of HIV in homosexually active populations. In our model, it is assumed that some individuals possess one or two mutant alleles (like Δ32 of CCR5) that prevent the successful invasion or replication of HIV. Our model therefore differentiates by genetic and epidemiological status and naturally ignores the reproduction process. Furthermore, HIV infected individuals are classified as rapid, normal or slow progressors. In this complex setting, the basic reproductive number $\Re_0$ is derived in various situations. The separate or combined effects of therapies, education, vaccines, and genetic resistance are analyzed. Our results support the conclusions of Hsu Schmitz that some integrated intervention strategies are far superior to those based on a single approach. However, treatment programs may have effects which counteract each other, as may genetic resistance.

Keywords: HIV/AIDS; Genetic resistance; Vaccination; Treatment programs; Public education; Reproductive number

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1. Introduction

Currently, AIDS is the fourth leading cause of death globally and the leading cause in Africa. As of the year 1996, approximately 23 million people were HIV positive worldwide. As of 2001, 36 million people were reported to be HIV positive worldwide [1]. These data indicate an increase of approximately 13 million new infections (over 50%) in five years. The devastating global impact of HIV has increased research efforts to find an effective vaccine, or drugs that would stop the progression and transmission rate of HIV. These efforts have been mildly successful since HIV evolves resistance to drugs and mutates extremely fast. Recent genetics studies indicate a correlation of mutant genes in HIV co-receptors that may provide protection against HIV. This gives us the hope that researchers may be able to develop a drug that may mimic the resistant gene or that gene therapy may be useful in preventing HIV. This 'insertion' of a resistant gene might be able to lower the transmission rates of HIV/AIDS, and also stop the HIV infection from progressing to AIDS (in which final stage individuals have a life expectancy of about two years [2]).

Recent genetic studies [3–7] have observed that many individuals with multiple exposure to HIV-1 remain seronegative, while some of those infected by HIV-1 progress at rates significantly slower or faster than the norm. Researchers have correlated these findings with some mutant genes in HIV co-receptors. Studies found the presence of mutant alleles such as $\Delta 32$ and m303 of CCR5 suggesting resistance or protection against HIV for some individuals [8–10]. It seems that mutant alleles have somehow changed the structure of the helper T cells in such a way that it is very difficult for the virus's receptor to connect to it. Hence, the virus stops replicating, and individuals show a resistance to HIV. Individuals with two mutant alleles seem to have full protection against HIV infection. Individuals with one mutant allele seem to have partial resistance and, if infected, progress more slowly than individuals without mutant alleles. For Hsu Schmitz [11], these conclusions indicated the "existence of genetic heterogeneity with respect to susceptibility to HIV infection and to rate of AIDS progression in general populations". Using this inference, Hsu Schmitz investigated the impact of genetic heterogeneity via a deterministic model for homosexually active populations [11,12]. Hsu Schmitz concluded that treatment and vaccination were helpful in reducing the transmission rate, but they were not sufficiently effective to eradicate the disease if they were implemented alone.

Vaccines in development may only give a temporary immunity to HIV/AIDS. Antiviral drugs used in treatment, such as AZT (zidovudine), ddc (dideoxycytidine) and ddI (dideosyinosine), also worked temporarily. These antiviral drugs block the replication of the virus. However, the virus's high rate of mutation eventually catches on, and drug resistance becomes important [13,14]. Moreover, vaccination and treatment are costly at both the individual and population levels. Hence, education may play an important role in altering the course of this pandemic. Blower and McLean [15–17] studied theoretical models of partially effective HIV vaccines and the potential changes in risky behavior associated with a vaccination campaign, and found that the benefits offered by an only partly effective vaccination program may be offset by rises in potentially infectious contacts unless an education campaign accompanies it.

Following this concept and based on Hsu Schmitz's model [12], we construct a similar model in which a susceptible population is subject to vaccination, education and treatment. In our model, education means counseling to have fewer partners, abstain, and/or otherwise reduce risky behavior. Our primary goal (suggested in part by such discussions as [18]) is to investigate the

effects of education, temporary vaccination and treatment on HIV transmission in a homosexually active population with genetic heterogeneity.

This paper is divided into the following sections. Section 2 explains the complex model and includes the diagram of the compartmental model which illustrates the dynamics of the population under study. Section 3 explains in great detail the different cases for the reproductive number, R_0. Conclusions and final thoughts are in Section 4.

2. The model

Following Hsu Schmitz [12] we classify the homosexually active population into three classes of susceptible individuals: non-resistant (S_1), partially resistant (S_2) and fully resistant (S_3) to HIV infection. Infected individuals are classified as rapid (I_1), normal (I_2) and slow (I_3) progressors. Throughout this paper, the index i refers to the non-infected groups, i.e., susceptible, vaccinated and educated individuals, and the index j refers to infected classes capable of transmitting the disease, i.e., infected and treated individuals. In this model we assume that AIDS patients are sexually inactive; hence, AIDS patients do not affect the HIV transmission process (alternatively, we can define progression as the point where AIDS patients end sexual interaction with the at-risk population).

Also as in [12], we assume that recruitment into the sexually active population occurs at a constant rate, π. Of this recruitment, the three susceptible groups receive the respective fixed fractions g_i ($i = 1, 2, 3$), indicating the frequencies of relevant genotypes, where $\sum_i g_i = 1$. Because in general the frequencies of mutant alleles are lower than those of non-mutant alleles, it is reasonable to assume that

$$g_1 > g_2 > g_3; \tag{1}$$

that is, most individuals have no resistance, a small fraction have partial resistance, and an even smaller fraction have complete resistance.

In order to concentrate on investigating the effects of genetic heterogeneity, we will assume homogeneity of pairing and mixing behavior whenever possible. Because most individuals do not know their genotypes at loci related to HIV susceptibility and/or AIDS pathogenesis, we may assume, as in [11,12], that genetic heterogeneity does not influence pairing behavior. To simplify our model, we further assume that disease status does not affect pairing behavior, either, as in [11,12,15–17,19–21]. Therefore the average number of partners per unit time is given by c for all individuals. Here we assume proportional mixing of individuals [12,22]. All individuals are subject to the same per-capita natural removal rate, μ.

The infectivity of I_j individuals is described by the per-partnership transmission rate $\beta_j = b_j\beta$ ($j = 1, 2, 3$). For the sake of simplicity, we assume β and b_j are constant over incubation time as in [15,19–21]. Since we assume that fast progressors (I_1) have the highest viral load, and are therefore most infectious, while slow progressors (I_3) have the lowest viral load, and hence are least infectious, we can relate the b_j by

$$b_1 \geqslant b_2 \geqslant b_3. \tag{2}$$

If we use the transmission rate of I_2 as reference, thus rescale β and define $b_2 = 1$, then relation (2) implies that the multipliers

$$b_1 \geqslant 1 \quad \text{and} \quad 0 \leqslant b_3 \leqslant 1. \tag{3}$$

Because of S_2-individuals' partial resistance to HIV, the transmission rate $b_j\beta$ of any infected partner is reduced to $xb_j\beta$, where $0 < x < 1$ is the factor representing the partial resistance.

Newly infected S_i-individuals ($i = 1, 2$) join the three infected groups with respective fixed proportions f_{ij}, which, like the g_i, satisfy

$$0 \leqslant f_{ij} \leqslant 1 \quad \text{and} \quad \sum_{j=1}^{3} f_{ij} = 1. \tag{4}$$

We expect the new infecteds who have no resistance (S_1) to generate a larger proportion of rapid progressors (I_1) and a smaller proportion of slow (I_3) progressors than those coming from S_2, that is,

$$f_{11} > f_{21} \quad \text{and} \quad f_{13} < f_{23}. \tag{5}$$

In fact, in Section 3 we will take $f_{21} = 0$, that is, we will suppose that no partially resistant individuals become rapid progressors.

We denote the per-capita progression rates for I_j individuals by γ_j ($j = 1, 2, 3$). Since $1/\gamma_j$ is the average incubation time of I_j-individuals, we must have

$$\gamma_1 > \gamma_2 > \gamma_3. \tag{6}$$

A certain proportion (p_i) of newly recruited S_i-individuals is assumed to enter the at-risk population vaccinated. As in [12,15,17], we assume that the vaccines have a 'take' proportion of ϵ ($0 < \epsilon < 1$), so that $[100 \times (1 - \epsilon)]\%$ of the vaccinated individuals are effectively unvaccinated and are as vulnerable to infection as other unvaccinated individuals. We similarly assign a vaccine efficacy of ξ ($0 < \xi < 1$) and an average protection duration of $1/\omega$ units of time: the effectively vaccinated individuals (a fraction $p_i\epsilon$ of the new recruits) of each genotype, denoted by V_i, still have $[100 \times (1 - \xi)]\%$ chance of being infected before the vaccine's protection wears off [12,15,16]. The ranges of ϵ and ξ do not include 0 and 1 because 0 implies the vaccine is useless and 1 implies the vaccine is perfect; neither is realistic. We assume no reduction in infectivity for vaccinated individuals who become infected. Although individuals might become more active (i.e., have more sexual partners per unit of time) after being treated or vaccinated, in order to focus on the role of genetic heterogeneity and for simplicity, we again assume, following [12], that neither treatment nor vaccination changes people's pairing behavior, so the common pairing activity c and the proportional mixing pattern are still in effect. (This model structure does not preclude an ongoing vaccination program: in this case, $1/\omega$ can be interpreted as the average duration of the program before individuals drop out. A vaccination program in which no one ever drops out is the special case in which $\omega = 0$.)

Moreover, a certain number of the infected I_j-individuals ($j = 1, 2, 3$) are assumed to be effectively treated at a rate m_j (rather than immediately upon infection as in [12]). We assume that treatment reduces an individual's (T_j) transmission rate from β_j to $a\beta_j$, with $0 \leqslant a < 1$, and the progression rate from γ_j to $y\gamma_j$, where $0 \leqslant y < 1$. The ranges of a and y exclude 1, as current knowledge indicates treatment does reduce infectivity and rate of progression.

To model the effects of a public education campaign, we assume that a certain number of individuals from the susceptible class S_i ($i = 1, 2, 3$) are educated at a rate α. Individuals in the E_i classes are those on whom education has had some effect in changing their behavior to reduce potentially infective contacts. We denote by Ψ the overall effectiveness of the education campaign – that is, the factor by which the average infection rate of educated individuals is reduced, relative to the infection rate of non-educated individuals. In this context, therefore, $0 < \Psi < 1$. Its range does not include 0 and 1 because 0 implies that education is useless and 1 implies that education is completely effective.

Now, let the total population be denoted by

$$\Phi := \sum_{i=1}^{3}(V_i + S_i + E_i) + \sum_{j=1}^{3}(I_j + T_j). \tag{7}$$

Then the forces of infection for S_1 and S_2 individuals are

$$\sigma_{S_1} = \beta\left(\sum_{j=1}^{3} b_j I_j + a\sum_{j=1}^{3} b_j T_j\right)\Big/\Phi, \tag{8}$$

$$\sigma_{S_2} = x\sigma_{S_1}, \tag{9}$$

for V_1- and V_2-individuals are

$$\sigma_{V_1} = (1-\xi)\sigma_{S_1}, \tag{10}$$

$$\sigma_{V_2} = x\sigma_{V_1} = x(1-\xi)\sigma_{S_1}, \tag{11}$$

and for E_1- and E_2-individuals are

$$\sigma_{E_1} = (1-\Psi)\sigma_{S_1}, \tag{12}$$

$$\sigma_{E_2} = x\sigma_{E_1} = x(1-\Psi)\sigma_{S_1}. \tag{13}$$

The numbers of newly infected S_i-, V_i- and E_i- individuals ($i = 1, 2$) are now

$$\delta_{S_i} = cS_i\sigma_{S_i}, \tag{14}$$

$$\delta_{V_i} = cV_i\sigma_{V_i}, \tag{15}$$

$$\delta_{E_i} = cE_i\sigma_{E_i}. \tag{16}$$

These newly infected individuals enter the jth ($j = 1, 2, 3$) infected group (I_j) at the rate

$$\rho_j = \sum_{i=1}^{2} f_{ij}(\delta_{S_i} + \delta_{V_i} + \delta_{E_i}). \tag{17}$$

The mathematical model is described by the following system of equations, where $i = 1, 2$ and $j = 1, 2, 3$ (see also Fig. 1; Tables 1 and 2 summarize the parameters):

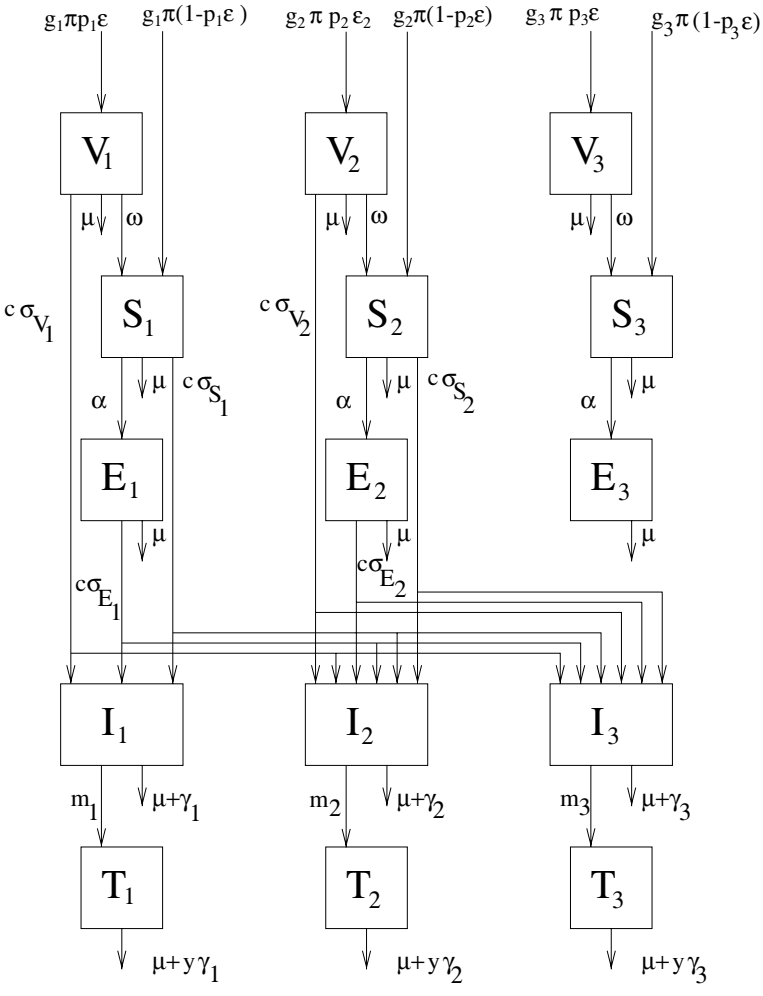

Fig. 1. Diagram of the compartmental model.

$$
\begin{aligned}
\dot{V}_i &= g_i \pi p_i \epsilon - (\mu + \omega) V_i - \delta_{V_i}, \\
\dot{V}_3 &= g_3 \pi p_3 \epsilon - (\mu + \omega) V_3, \\
\dot{S}_i &= g_i \pi (1 - p_i \epsilon) + \omega V_i - (\mu + \alpha) S_i - \delta_{S_i}, \\
\dot{S}_3 &= g_3 \pi (1 - p_3 \epsilon) + \omega V_3 - (\mu + \alpha) S_3, \\
\dot{E}_i &= \alpha S_i - \mu E_i - \delta_{E_i}, \\
\dot{E}_3 &= \alpha S_3 - \mu E_3, \\
\dot{I}_j &= \rho_j - (\mu + m_j + \gamma_j) I_j, \\
\dot{T}_j &= m_j I_j - (\mu + y\gamma_j) T_j, \\
\Phi(t) &= \sum_{k=1}^{3} (V_k + S_k + E_k + I_k + T_k).
\end{aligned}
\tag{18}
$$

Table 1
Estimates of some model parameters, from [12]

As in [15]:
Per-capita natural removal rate $\mu = 1/32$ yr^{-1}
Recruitment rate $\pi = 2000$ yr^{-1}
Product of per-partnership transmission rate of normal progressors and pairing activity $\beta c = 0.62$ yr^{-1}
Estimated from data in [8]:
Genotype frequencies $g_1 = 0.75$, $g_2 = 0.23$, $g_3 = 0.02$
Implied by [9]:
Reduction factor for susceptibility $x = 0.65$
As in [11]:
Per-capita rates of progression for rapid progressors $\gamma_1 = 1/2$ yr^{-1}
Per-capita rates of progression for normal progressors $\gamma_2 = 1/8$ yr^{-1}
Per-capita rates of progression for slow progressors $\gamma_3 = 1/16$ yr^{-1}
Distributing fractions of infected groups for individuals without resistance $f_{11} = 0.128$, $f_{12} = 0.655$, $f_{13} = 0.217$
Distributing fractions of infected groups for individuals with partial resistance $f_{21} = 0.063$, $f_{22} = 0.605$, $f_{23} = 0.332$

Table 2
Parameters related to vaccination, education and treatment

Parameters related to vaccination:	
p_i	proportion of S_i-individuals who enter the population vaccinated
ϵ	proportion of vaccinated individuals in whom the vaccine 'takes'
ξ	vaccine efficacy (infection reduced by a factor of $(1-\xi)$)
ω	inverse of average duration of vaccine protection
Parameters related to education:	
α	rate at which susceptibles are successfully educated
Ψ	efficacy of education (infection reduced by a factor of $(1-\Psi)$)
Parameters related to treatment:	
m_j	rate at which I_j-individuals enter treatment
a	treatment-induced reduction factor for infectivity
y	treatment-induced reduction factor for progression to AIDS

2.1. Global stability of disease-free equilibrium

Under certain conditions the disease-free equilibrium (DFE) $I_j = T_j = 0$ $(j = 1, 2, 3)$ is globally stable, as the following result shows using a Lyapunov function.

Theorem 2.1. *Suppose that*

$$c\beta \max_j \left(\frac{b_j}{\mu + \gamma_j}, \frac{ab_j}{\mu + y\gamma_j} \right) < 1. \tag{19}$$

Then the disease-free equilibrium is globally stable.

Proof. Let $L = \sum_j (I_j + T_j)$ be our Lyapunov function. Certainly $L = 0$ at the DFE only.

$$
\begin{aligned}
L'(t) = \sum_{j=1}^{3} \Bigg\{ & -(\mu+\gamma_j)I_j - (\mu+y\gamma_j)T_j + \frac{c\beta}{\Phi}\sum_{k=1}^{3} b_k(I_k + aT_k) \times [f_{1j}(S_1 + (1-\xi)V_1 \\
& + (1-\Psi)E_1) + x f_{2j}(S_2 + (1-\xi)V_2 + (1-\Psi)E_2)] \Bigg\} \\
< {} & c\beta\left[\sum_{k=1}^{3} b_k(I_k + aT_k)\right]\sum_{j=1}^{3}\left(f_{1j}\frac{S_1+V_1+E_1}{\Phi} + x f_{2j}\frac{S_2+V_2+E_2}{\Phi}\right) \\
& - \sum_{j=1}^{3}\left[(\mu+\gamma_j)I_j + (\mu+y\gamma_j)T_j\right] = c\beta\left[\sum_{k=1}^{3} b_k(I_k + aT_k)\right]\left(\frac{S_1+V_1+E_1}{\Phi} + x\frac{S_2+V_2+E_2}{\Phi}\right) \\
& - \sum_{j=1}^{3}\left[(\mu+\gamma_j)I_j + (\mu+y\gamma_j)T_j\right] < c\beta\left[\sum_{k=1}^{3} b_k(I_k + aT_k)\right] - \sum_{j=1}^{3}\left[(\mu+\gamma_j)I_j + (\mu+y\gamma_j)T_j\right] \\
= {} & \left[c\beta\sum_{j=1}^{3} b_j I_j - \sum_{j=1}^{3}(\mu+\gamma_j)I_j\right] + \left[ac\beta\sum_{j=1}^{3} b_j T_j - \sum_{j=1}^{3}(\mu+y\gamma_j)T_j\right] \\
= {} & \sum_{j=1}^{3}(\mu+\gamma_j)\left[c\beta\frac{b_j}{\mu+\gamma_j} - 1\right]I_j + \sum_{j=1}^{3}(\mu+y\gamma_j)\left[c\beta\frac{ab_j}{\mu+y\gamma_j} - 1\right]T_j.
\end{aligned}
$$

By hypothesis (19) we get $L' < 0$ because each of the terms in the sum over j is negative. Therefore the disease-free equilibrium is globally stable. □

Note that the expression $\frac{c\beta b_j}{\mu+\gamma_j}$ in the hypothesis represents the overall infection rate of an I_j individual $c\beta b_j$ multiplied by the average time spent in that stage, $1/(\mu+\gamma_j)$, in a situation where most of the population is susceptible and there is no vaccination, education or treatment. Likewise the expression $\frac{ac\beta b_j}{\mu+y\gamma_j}$ represents the overall infection rate of a T_j individual, multiplied by the average duration in that stage, $1/(\mu+y\gamma_j)$. If (19) holds, then these expressions are all ($j = 1, 2, 3$) less than 1, meaning that even in the absence of control measures the disease is doing a poor job of reproducing itself. Under these circumstances, it is not surprising that the disease is guaranteed to die out.

If we compare the respective reproductive measures for I_j and T_j given above, we see marked similarities, the differences stemming from the reduced infectivity and removal rate of the treated classes. In general one cannot say which of the two expressions is larger, because the reductions in the two rates act counter to each other with respect to disease persistence in the population. It will be useful to define the factor by which the removal rate is reduced,

$$
H_j \equiv \frac{\mu + y\gamma_j}{\mu + \gamma_j}, \tag{20}
$$

the ratio of the reduced removal rate to the original removal rate. Note

$$
H_i = 1 - (1-y)\frac{\gamma_i}{\mu+\gamma_i} \quad \text{so} \quad \gamma_i < \gamma_j \Longleftrightarrow H_i > H_j;
$$

by assumption of (6) we have $H_1 < H_2 < H_3$.

For each j, if $a < H_j$, then the reduced infectivity 'outweighs' the factor by which mortality is reduced, and T_j individuals contribute less to the spread of HIV than do I_j individuals. If in fact $a < H_1$, then (19) reduces to

$$c\beta \max_j \frac{b_j}{\mu + \gamma_j} < 1.$$

If instead $a > H_j$ for a given j, then the removal rate is reduced more than the infectivity for that class, and a treated j-class individual actually contributes more to further infection than an untreated j-class infective. In this case the treatment benefits the individual more than the population at large. If in fact $a > H_3$ then (19) reduces to

$$c\beta \max_j \frac{ab_j}{\mu + y\gamma_j} < 1.$$

In the following section we shall extend the analysis of HIV's capacity to persist by computing the disease's overall reproductive number, to see how disease control strategies may affect it.

3. The basic reproductive number

3.1. Computation of $\Re_0$

As mentioned in [23] the reproductive number ($\Re_0$) is the effected number of secondary cases produced by a typical infected individual during its entire period of infectiousness in a demographically steady susceptible population. Therefore, in order to study whether HIV will invade a population or stabilize over a given region we must investigate $\Re_0$. We now compute the reproductive number when treatment, education and vaccination are applied to the population, following the 'next-generation operator' method of [23,24]. The computation is done by linearizing our system (18) around the disease-free state and looking for conditions that guarantee the growth of the three infected classes, I_j, as well as the three treated classes, T_j.

We rewrite the resulting six-dimensional system in the following form:

$$\dot{\mathbf{X}} = (\mathbf{M} - \mathbf{D})\mathbf{X},$$

where

$$\mathbf{X} = \begin{bmatrix} I_1 \\ I_2 \\ I_3 \\ T_1 \\ T_2 \\ T_3 \end{bmatrix}, \qquad \mathbf{D} = \begin{bmatrix} \eta_1 & 0 & 0 & 0 & 0 & 0 \\ 0 & \eta_2 & 0 & 0 & 0 & 0 \\ 0 & 0 & \eta_3 & 0 & 0 & 0 \\ 0 & 0 & 0 & \varphi_1 & 0 & 0 \\ 0 & 0 & 0 & 0 & \varphi_2 & 0 \\ 0 & 0 & 0 & 0 & 0 & \varphi_3 \end{bmatrix},$$

$$\mathbf{M} = c\beta \begin{bmatrix} b_1\tau_1 & \tau_1 & b_3\tau_1 & ab_1\tau_1 & a\tau_1 & ab_3\tau_1 \\ b_1\tau_2 & \tau_2 & b_3\tau_2 & ab_1\tau_2 & a\tau_2 & ab_3\tau_2 \\ b_1\tau_3 & \tau_3 & b_3\tau_3 & ab_1\tau_3 & a\tau_3 & ab_3\tau_3 \\ m_1 & 0 & 0 & 0 & 0 & 0 \\ 0 & m_2 & 0 & 0 & 0 & 0 \\ 0 & 0 & m_3 & 0 & 0 & 0 \end{bmatrix}, \tag{21}$$

and

$$\tau_1 = f_{11}(\delta_{S_1} + \delta_{E_1} + \delta_{V_1}),$$

$$\tau_2 = f_{12}(\delta_{S_1} + \delta_{E_1} + \delta_{V_1}) + xf_{22}(\delta_{S_2} + \delta_{E_2} + \delta_{V_2}),$$

$$\tau_3 = f_{13}(\delta_{S_1} + \delta_{E_1} + \delta_{V_1}) + xf_{23}(\delta_{S_2} + \delta_{E_2} + \delta_{V_2}),$$

$$\eta_j = \mu + m_j + \gamma_j,$$

$$\varphi_j = \mu + y\gamma_j.$$

The six eigenvalues of the matrix $\mathbf{MD}^{-1}$ are 0, 0, 0, 0, λ_- and λ_+, which are given by

$$\lambda_- = \frac{1}{2}\left(\Re_{0_I} - \sqrt{\Re_{0_I}^2 + 4a\vec{\Re}_I \cdot \vec{\Re}_T}\right) \quad \text{and} \quad \lambda_+ = \frac{1}{2}\left(\Re_{0_I} + \sqrt{\Re_{0_I}^2 + 4a\vec{\Re}_I \cdot \vec{\Re}_T}\right), \tag{22}$$

where

$$\begin{aligned} \Re_{0_I} &= c\left[k_1\left(f_{11}\frac{\beta_1}{\eta_1} + f_{12}\frac{\beta_2}{\eta_2} + f_{13}\frac{\beta_3}{\eta_3}\right) + xk_2\left(f_{22}\frac{\beta_2}{\eta_2} + f_{23}\frac{\beta_3}{\eta_3}\right)\right], \\ \vec{\Re}_I &= c\left(\frac{k_1 f_{11}\beta_1}{\eta_1}, (k_1 f_{12} + xk_2 f_{22})\frac{\beta_2}{\eta_2}, (k_1 f_{13} + xk_2 f_{23})\frac{\beta_3}{\eta_3}\right), \\ \vec{\Re}_T &= \left(\frac{m_1}{\varphi_1}, \frac{m_2}{\varphi_2}, \frac{m_3}{\varphi_3}\right), \end{aligned} \tag{23}$$

and

$$k_i = g_i\left[\left(1 - \frac{\alpha}{\mu + \alpha}\Psi\right)\left(1 - \frac{\mu}{\mu + \omega}p_i\epsilon\right) + (1 - \xi)\left(\frac{\mu}{\mu + \omega}p_i\epsilon\right)\right]. \tag{24}$$

Because all elements in the expression for λ_+ are positive, it is clear $\lambda_+ > 0$. Therefore, λ_+ is the dominant eigenvalue of $\mathbf{MD}^{-1}$; this is the basic reproductive number, $\Re_0$ [23].

We can see from the form of (22) and (23) that the reproductive number for the model is a combination of the secondary infections caused by the infected and treated classes. Notice that the square root denotes the two-step process required for a treated individual to 'generate' another treated person, since when s/he infects a person, the person must become infected first before being treated. $\Re_{0_I}$ is the reproductive number in the absence of treatment, while $\vec{\Re}_I$ and $\vec{\Re}_T$ represent the two stages (initial infection and entering treatment) involved in replacing a treated individual.

In the following sections we shall interpret more precisely the factors involved in $\Re_0$.

3.2. Simple model

To facilitate the interpretation of $\Re_0$ for our complex model, we first consider a homogeneous population and a single progression rate; note that the presence of only a single genotype and progression rate will eliminate the g_i and f_{ij} and remove the remaining subscripts. By doing so we obtain a five-dimensional model with the following reproductive number (where the subscript S denotes 'simple'):

$$\Re_{0_S} = \frac{1}{2}\left\{ \frac{c\beta k}{\mu + m + \gamma} + \sqrt{\left(\frac{c\beta k}{\mu + m + \gamma} \right)^2 + 4a\left(\frac{c\beta k m}{(\mu + y\gamma)(\mu + m + \gamma)} \right)} \right\}, \tag{25}$$

where

$$k = \left(1 - \frac{\alpha}{\mu + \alpha}\Psi\right)\left(1 - \frac{\mu}{\mu + \omega}p\epsilon\right) + (1 - \xi)\left(\frac{\mu}{\mu + \omega}p\epsilon\right). \tag{26}$$

It is worthwhile to notice that k contains only parameters involving education and vaccination. The two factors of the first term denote the reduction factor for education and the proportion of non-vaccinated individuals respectively. The factors of the other term represent the reduction factor for vaccination and the proportion of vaccinated individuals respectively. Notice that the range of k will always be between 0 and 1, which implies that education and vaccination will always reduce the value of $\Re_{0_S}$. (A more detailed analysis is given for the full model in the next section.)

For convenience let

$$\Re_{0_{SI}} = \frac{c\beta k}{\mu + m + \gamma} \quad \text{and} \quad \Re_{0_{ST}} = \frac{m}{\mu + y\gamma}; \tag{27}$$

by making these substitutions we can write $\Re_{0_S}$ as follows:

$$\Re_{0_S} = \frac{1}{2}\left(\Re_{0_{SI}} + \sqrt{\Re_{0_{SI}}(\Re_{0_{SI}} + 4a\Re_{0_{ST}})} \right), \tag{28}$$

which parallels the structure of (22). The square root in $\Re_0$ represents the two-step process that a treated person takes before s/he can actually generate another treated individual. This form has been seen before in other models for diseases with multiple infectious stages (cf. [25,26]). We can also observe that

$$\Re_{0_{SI}} < \Re_{0_S} < \Re_{0_{SI}} + \sqrt{\Re_{0_{SI}}\Re_{0_{ST}}};$$

epidemiologically, the first inequality follows from the fact that treated individuals contribute to infections, and the second comes from the overlap between the two 'replacement' processes (replacing I-individuals and T-individuals). An analogous statement holds for the full model (18).

We have seen above that vaccination and education always reduce the value of $\Re_{0_S}$; however, we have also seen that while treatment reduces an individual's infectivity, it also prolongs the individual's time as an infective. Therefore, in order to analyze the effect of treatment on $\Re_{0_S}$, we

shall take the derivative of (25) with respect to the treatment rate m, and show under what circumstances

$$\frac{\partial \Re_{0_S}}{\partial m} < 0.$$

Substituting this derivative into the above inequality yields

$$2a\frac{\mu+\gamma}{\mu+y\gamma} - \frac{c\beta k}{\mu+m+\gamma} - \sqrt{\left(\frac{c\beta k}{\mu+m+\gamma}\right)^2 + 4a\frac{c\beta km}{(\mu+y\gamma)(\mu+m+\gamma)}} < 0,$$

which gives the following inequality:

$$a < \frac{c\beta k}{\mu+\gamma}\left(\frac{\mu+y\gamma}{\mu+\gamma}\right),$$

which we can rewrite as

$$\frac{a}{H} < \Re_{0_S}|_{m=0}, \tag{29}$$

where $H \equiv \frac{\mu+y\gamma}{\mu+\gamma}$ represents the factor by which treatment reduces the rate of progression to AIDS. Hence, treatment will reduce $\Re_{0_S}$ (and benefit the population at large as well as the individual) when it reduces infectivity at least $\Re_{0_S}|_{m=0}$ as many times as it reduces the removal rate.

Anderson et al. [19], using a similar model in which vaccination and treatment are the same, ongoing therapy (which is assumed to be permanent and non-preventative), derived a similar conclusion: if $a = 1$, then $\Re_{0_S}|_{m=0} > 1 + \frac{\gamma}{\mu+\gamma}$ must hold (their inequality 1a) in order for the community at large, as well as individuals, to benefit from implementing a new treatment program. (For comparison purposes, inequality (29) can be rewritten $\Re_{0_S}|_{m=0} > 1 + (1-y)\frac{\gamma}{\mu+\gamma}$.) More generally, they found that the condition analogous to (29) is

$$a < \left[(1-y)\Re_{0_S}|_{m=0} + y\right] - (1-y)\frac{\gamma}{\mu+\gamma}.$$

Note that the condition (29) for overall effectiveness of a treatment program resembles the condition $a/H_j < 1$ considered at the end of Section 2.1, under which T_j-individuals contribute less to the spread of infection than do I_j-individuals. It is interesting to note that if $\Re_{0_S}|_{m=0} > 1$ and the disease is endemic in the population, then condition (29) is less restrictive than $a/H < 1$, that is, treatment may reduce $\Re_{0_S}$ even if it reduces the removal rate more than it reduces infectivity (as long as (29) holds). This fact may seem counterintuitive until one notices that

$$\lim_{m\to\infty} \Re_{0_S} = \sqrt{\frac{a}{H}\Re_{0_S}|_{m=0}}, \tag{30}$$

that is, treatment can only reduce (or, if (29) does not hold, increase) $\Re_{0_S}$ to the geometric mean of a/H and its original value. Therefore, if a treatment program prolongs an individual's sexually active lifetime more than it reduces the individual's infectivity ($a/H > 1$), it can never reduce $\Re_{0_S}$ below 1.

The analysis of this homogeneous population will be helpful in understanding the analysis of $\Re_0$ for the heterogeneous population, which is presented in the following sections.

3.3. Effects of vaccination and education

If m_j is set to 0 ($j = 1, 2, 3$), which implies that no treatment is applied to the population, $\Re_0$ will simplify to the following expression, similar to $\Re_{0_I}$ as given in (23):

$$\Re_0 = c\left[k_1\left(f_{11}\frac{\beta_1}{\mu+\gamma_1} + f_{12}\frac{\beta_2}{\mu+\gamma_2} + f_{13}\frac{\beta_3}{\mu+\gamma_3}\right) + xk_2\left(f_{22}\frac{\beta_2}{\mu+\gamma_2} + f_{23}\frac{\beta_3}{\mu+\gamma_3}\right)\right],$$

and the only thing that will change when either vaccination or education, or both, are applied is k_i.

Let us first consider the simplest case, which is when only three susceptible classes S_1, S_2 and S_3 and the three infected classes I_1, I_2 and I_3 are taken into consideration (that is, in the absence of any disease control measures). Then, k_i will be denoted by

$$k_i = g_i, \tag{31}$$

and thus $\Re_0$ is given by the sum of the secondary infections caused by each of the infected classes contained in our model.

Now, if only vaccination is applied to the population, then k_i will be given by

$$k_i = g_i\left(1 - \xi\frac{\mu}{\mu+\omega}p_i\epsilon\right), \tag{32}$$

$\Re_0$ will be reduced based on the fact that g_i is being multiplied by a factor which is always less than 1. This factor is the reduction term due to the vaccine, and depends on the efficacy and duration of the vaccine and the proportion of people who are vaccinated.

If only education is applied to the population, then k_i will take the following form:

$$k_i = g_i\left(1 - \frac{\alpha}{\mu+\alpha}\Psi\right); \tag{33}$$

multiplying g_i is the reduction factor due to education, which is always less than 1, regardless of the proportion $\frac{\alpha}{\mu+\alpha}$ who are educated and the efficacy Ψ of the program – in other words, every little bit helps (to reduce $\Re_0$).

If both vaccination and education are applied to the population, then the value of k_i is given by (24). (We can see that the expression in (24) has $k_i < g_i$ by considering it as a weighted average of the expressions given in (32) and (33).) This expression implies that the joint intervention of education and vaccination will have an effect on the basic reproductive number which is intermediate between that of vaccination alone and that of education alone; however, this conclusion is an artifact of our modeling decision to limit complexity by educating only non-vaccinated individuals (education of vaccinated individuals would add more classes to our already-large model), and in reality the two reduction factors should be cumulative rather than alternative. A realistic comparison for policy purposes should also include a measure of cost for both types of program.

3.4. Effects of treatment

When treatment is applied to the population, the basic reproductive number, denoted by $\Re_{0_T}$ with T indicating treatment, is as given in Section 3.1:

$$\Re_{0_T} = \frac{1}{2}\left(\Re_{0_I} + \sqrt{\Re_{0_I}^2 + 4a\vec{\Re}_I \cdot \vec{\Re}_T}\right), \tag{34}$$

where

$$\Re_{0_I} = c\left[k_1\left(f_{11}\frac{\beta_1}{\eta_1} + f_{12}\frac{\beta_2}{\eta_2} + f_{13}\frac{\beta_3}{\eta_3}\right) + xk_2\left(f_{22}\frac{\beta_2}{\eta_2} + f_{23}\frac{\beta_3}{\eta_3}\right)\right],$$

$$\vec{\Re}_I = c\left(\frac{k_1 f_{11}\beta_1}{\eta_1}, (k_1 f_{12} + xk_2 f_{22})\frac{\beta_2}{\eta_2}, (k_1 f_{13} + xk_2 f_{23})\frac{\beta_3}{\eta_3}\right),$$

$$\vec{\Re}_T = \left(\frac{m_1}{\varphi_1}, \frac{m_2}{\varphi_2}, \frac{m_3}{\varphi_3}\right).$$

Notice again that the square root appears in $\Re_{0_T}$ when treatment is present due to the two-step process required for a treated individual to generate another treated. The analysis of the previous section with regard to the effects of vaccination and education holds in the presence of treatment: the only difference is again in the k_i, and reducing the k_i reduces $\Re_0$. We therefore proceed to an analysis of treatment's effects on $\Re_0$.

To examine the effectiveness of treatment not only in the individual level, but also in the population level to slow down the spread of the disease, we take the partial derivatives of $\Re_{0_T}$ with respect to m_i and look for conditions under which the derivatives are less than 0. For convenience, let

$$F_1 = ck_1 f_{11}\beta_1, \qquad F_2 = c(k_1 f_{12} + xk_2 f_{22})\beta_2, \qquad F_3 = c(k_1 f_{13} + xk_2 f_{23})\beta_3,$$

so that

$$\Re_{0_T} = \frac{1}{2}\left\{\left[\vec{\Re}_I \cdot (1,1,1)\right] + \sqrt{\left[\vec{\Re}_I \cdot (1,1,1)\right]^2 + 4a\vec{\Re}_I \cdot \left(\frac{m_1}{\varphi_1}, \frac{m_2}{\varphi_2}, \frac{m_3}{\varphi_3}\right)}\right\}.$$

Now, taking the partial derivative of $\Re_{0_T}$ with respect to m_1 and setting $\frac{\partial \Re_{0_T}}{\partial m_1} < 0$ we obtain the following:

$$\frac{\partial \Re_{0_T}}{\partial m_1} < 0 \Longleftrightarrow \frac{a}{H_1} < \vec{\Re}_I \cdot \left(1 + \frac{m_1}{\varphi_1}H_1, 1 + \frac{m_2}{\varphi_2}H_1, 1 + \frac{m_3}{\varphi_3}H_1\right),$$

which we can rewrite as

$$\frac{\partial \Re_{0_T}}{\partial m_1} < 0 \Longleftrightarrow \frac{a}{H_1} < \vec{F} \cdot \left(1, 1 + \frac{m_2}{\eta_2}\left(\frac{H_1}{H_2} - 1\right), 1 + \frac{m_3}{\eta_3}\left(\frac{H_1}{H_3} - 1\right)\right), \tag{35}$$

where

$$\vec{F} = \left(\frac{F_1}{\mu + \gamma_1}, \frac{F_2}{\mu + \gamma_2}, \frac{F_3}{\mu + \gamma_3}\right) \quad \text{and} \quad \vec{F} \cdot (1,1,1) = \Re_{0_T}|_{m_1 = m_2 = m_3 = 0}.$$

We can likewise derive conditions

$$\frac{\partial \Re_{0_T}}{\partial m_2} < 0 \Longleftrightarrow \frac{a}{H_2} < \vec{F} \cdot \left(1 + \frac{m_1}{\eta_1}\left(\frac{H_2}{H_1} - 1\right), 1, 1 + \frac{m_3}{\eta_3}\left(\frac{H_2}{H_3} - 1\right)\right) \tag{36}$$

and

$$\frac{\partial \Re_{0_T}}{\partial m_3} < 0 \Longleftrightarrow \frac{a}{H_3} < \vec{F} \cdot \left(1 + \frac{m_1}{\eta_1}\left(\frac{H_3}{H_1} - 1\right), 1 + \frac{m_2}{\eta_2}\left(\frac{H_3}{H_2} - 1\right), 1\right). \tag{37}$$

Since $H_1 < H_2 < H_3 < 1$, we have that

$$1 < 1 + \frac{m_1}{\eta_1}\left(\frac{H_2}{H_1} - 1\right) < 1 + \frac{m_1}{\eta_1}\left(\frac{H_3}{H_1} - 1\right),$$

$$1 + \frac{m_2}{\eta_2}\left(\frac{H_1}{H_2} - 1\right) < 1 < 1 + \frac{m_2}{\eta_2}\left(\frac{H_3}{H_2} - 1\right),$$

$$1 + \frac{m_3}{\eta_3}\left(\frac{H_1}{H_3} - 1\right) < 1 + \frac{m_3}{\eta_3}\left(\frac{H_2}{H_3} - 1\right) < 1,$$

so that if we multiply (35)–(37) by H_1, H_2 and H_3 respectively, we see that

$$\frac{\partial \Re_{0_T}}{\partial m_1} < 0 \;\Rightarrow\; \frac{\partial \Re_{0_T}}{\partial m_2} < 0 \;\Rightarrow\; \frac{\partial \Re_{0_T}}{\partial m_3} < 0.$$

Therefore, the condition under which *any* (small) increase in treatment will reduce $\Re_{0_T}$ is (35). If currently $m_1 = m_2 = m_3 = 0$ and we wish to begin a treatment program, this condition becomes

$$\frac{a}{H_1} < \vec{F} \cdot (1, 1, 1) = \Re_{0_T}|_{m_1 = m_2 = m_3 = 0}.$$

As treatment rates rise, (35) becomes more strict, approaching

$$\frac{a}{H_1} < \vec{F} \cdot \left(1, \frac{H_1}{H_2}, \frac{H_1}{H_3}\right). \tag{38}$$

If this latter condition is met, then increasing any m_j always reduces $\Re_{0_T}$.

If we make the simplifying assumption that treatment does not differentiate among types of progressors, then we have $m_1 = m_2 = m_3 = m$, and we obtain a condition of similar form,

$$\frac{\partial \Re_{0_T}}{\partial m} < 0 \Longleftrightarrow \frac{a}{H_0} < \vec{F} \cdot \left(1 + \frac{m}{\eta_1}\left(\frac{H_0}{H_1} - 1\right), 1 + \frac{m}{\eta_2}\left(\frac{H_0}{H_2} - 1\right), 1 + \frac{m}{\eta_3}\left(\frac{H_0}{H_3} - 1\right)\right), \tag{39}$$

where H_0 is an average removal rate reduction factor,

$$\frac{1}{H_0} = \frac{\vec{W} \cdot \left(\frac{1}{H_1}, \frac{1}{H_2}, \frac{1}{H_3}\right)}{\vec{W} \cdot (1, 1, 1)},$$

weighted by

$$\vec{W} = \left(\frac{F_1}{\eta_1^2}, \frac{F_2}{\eta_2^2}, \frac{F_3}{\eta_3^2}\right).$$

When $m = 0$, (39) simplifies to $\frac{a}{H_0} < \Re_{0_T}|_{m=0}$. As $m \to \infty$, (39) approaches $\frac{a}{H_0} < \vec{F} \cdot \left(\frac{H_0}{H_1}, \frac{H_0}{H_2}, \frac{H_0}{H_3}\right)$. If both conditions are met, then increasing m always reduces $\Re_{0_T}$ (regardless of m).

In either case (m_j distinct or identical), the interpretation of these conditions remains the same as that of Section 3.2: a new treatment program will reduce $\Re_{0_T}$ when it reduces infectivity at least $\Re_{0_T}|_{m_j=0\,\forall j}$ as many times as it reduces the removal rate. We should start a treatment program only under such conditions. The only difference for the heterogeneous model is that in considering whether to step up an existing treatment program, the condition becomes a weighted sum of the infection classes' (j) contributions to the epidemic. (It is also true that the treatment rates enter the conditions, but we may consider instead the limiting conditions given above, which guarantee improvement regardless of the m_j.)

It is again true in general that a treatment program which prolongs individuals' sexually active lifespans more than it reduces their infectivity cannot be used to reduce $\Re_0$ below 1; we offer as justification the simple observation (cf. (30)) that, in the case where $m_j = m\ \forall j$,

$$\lim_{m\to\infty} \Re_{0_T} = \sqrt{a\left(\frac{1}{H_1}, \frac{1}{H_2}, \frac{1}{H_3}\right) \cdot \vec{F}}.$$

We can see from the form of (34) that treatment does not interfere with the effects of vaccination or education, in the sense that the presence of a treatment program ($m_j > 0$ for some j) does not prevent vaccination or education from reducing $\Re_{0_T}$ via the k_i. (The k_i do affect the weighted sums discussed above, however, through the F_j.) Comparing the effects of treatment to those of vaccination or education, however, is difficult analytically, and enlightening only when we consider particular parameter values, as will be done in Section 3.6.

3.5. Effects of genetic resistance

The form of $\Re_{0_T}$ also yields information on the effects of genetic resistance on the spread of the HIV epidemic. Because genetic resistance slows progression rate as well as reduces the likelihood of infection, there is the potential for the same counteractive effects on $\Re_{0_T}$ as with treatment programs, if the partial protection provided to S_2 individuals prolongs their eventual infective period more than it reduces their risk of infection. The complete genetic resistance provided to S_3 individuals obviously benefits the population as a whole, but if slower progressors cause more infections than faster progressors, we need to establish some conditions under which partial genetic resistance in some proportion of the population also benefits everyone. We shall therefore consider when the presence of partial genetic resistance reduces $\Re_{0_T}$. Also, in order to simplify the analysis and resulting conditions, for the remainder of this section we will assume a uniform vaccination policy $p_i = p$; similar results hold when the p_i are distinct.

$\Re_{0_T}$ as given is less than $\Re_{0_T}|_{g_1=1}$ if the two components seen in (34) are reduced:

$$\Re_{0_I} < \left(\Re_{0_I}|_{g_1=1}\right) \quad \text{and} \quad a\vec{\Re}_I \cdot \vec{\Re}_T < a\left(\vec{\Re}_I \cdot \vec{\Re}_T|_{g_1=1}\right), \tag{40}$$

that is, if the average number of secondary infections caused by an infective or treated individual, respectively, decreases when $g_2, g_3 > 0$. From (34) we see that in order for $\Re_{0_T}$ to be reduced, it is necessary that at least one of the two conditions in (40) hold, and sufficient that both of them

hold. In order to put conditions (40) into a form which allows us to compare the two effects of partial genetic resistance, we will define two quantities,

$$K_I = \frac{ck\sum_{j=1}^{3}\frac{\beta_j}{\eta_j}f_{1j}}{ck\sum_{j=1}^{3}\frac{\beta_j}{\eta_j}f_{2j}} \quad \text{and} \quad K_T = \frac{ack\sum_{j=1}^{3}\frac{m_j}{\eta_j}\frac{\beta_j}{\varphi_j}f_{1j}}{ack\sum_{j=1}^{3}\frac{m_j}{\eta_j}\frac{\beta_j}{\varphi_j}f_{2j}}. \tag{41}$$

K_I is the ratio of the average number of infections caused by an infected S_1 individual while in the I classes to the average number of infections caused by an infected S_2 individual while in the I classes. If $K_I < 1$, the redistribution of progression rates (the f_{2j}) caused by partial genetic resistance actually increases the overall number of secondary infections from untreated infectives. Similarly, K_T is the ratio of the average number of infections caused by an infected S_1 individual while in the T classes to the average number of infections caused by an infected S_2 individual while in the T classes; the factors m_j/η_j are the proportions of each type of infective who get treatment. If $K_T < 1$, the redistribution of progression rates caused by partial genetic resistance increases the number of secondary infections from treated infectives. These definitions allow us to rewrite (40) as

$$\frac{x}{K_I} < 1 + \frac{g_3}{g_2} \quad \text{and} \quad \frac{x}{K_T} < 1 + \frac{g_3}{g_2}. \tag{42}$$

These conditions automatically hold true if, on average, slower progressors infect fewer individuals than faster progressors. In this case, both effects of genetic resistance are beneficial to the population as a whole. That is, if an average I_3 individual causes fewer infections before removal than an average I_2 individual, and likewise for I_2 with respect to I_1, which we can write

$$ck\frac{\beta_3}{\eta_3} < ck\frac{\beta_2}{\eta_2} < ck\frac{\beta_1}{\eta_1}, \tag{43}$$

then

$$\begin{aligned}\sum_{j=1}^{3}\frac{\beta_j}{\eta_j}f_{2j} &= \left(\frac{\beta_1}{\eta_1}-\frac{\beta_2}{\eta_2}\right)f_{21} + \left(\frac{\beta_2}{\eta_2}-\frac{\beta_3}{\eta_3}\right)(f_{21}+f_{22}) + \frac{\beta_3}{\eta_3}\\ &< \left(\frac{\beta_1}{\eta_1}-\frac{\beta_2}{\eta_2}\right)f_{11} + \left(\frac{\beta_2}{\eta_2}-\frac{\beta_3}{\eta_3}\right)(f_{11}+f_{12}) + \frac{\beta_3}{\eta_3}\\ &= \sum_{j=1}^{3}\frac{\beta_j}{\eta_j}f_{1j},\end{aligned}$$

which implies that $K_I > 1$. (The inequality above comes from (5).) We can show a similar result in the case that an average slow progressor causes fewer infections while in the treated class than an average normal progressor, and likewise for normal progressors with respect to fast progressors, i.e.,

$$\frac{m_3}{\eta_3}ack\frac{\beta_3}{\varphi_3} < \frac{m_2}{\eta_2}ack\frac{\beta_2}{\varphi_2} < \frac{m_1}{\eta_1}ack\frac{\beta_1}{\varphi_1} \;\Rightarrow\; \sum_{j=1}^{3}\frac{m_j}{\eta_j}\frac{\beta_j}{\varphi_j}f_{2j} < \sum_{j=1}^{3}\frac{m_j}{\eta_j}\frac{\beta_j}{\varphi_j}f_{1j} \;\Rightarrow\; K_T > 1. \tag{44}$$

Under the hypotheses (43) and (44) both of the conditions in (42) clearly hold (since $x < 1$).

Finally, even if slower progressors do cause more infections on average than faster progressors (K_I, $K_T < 1$), partial genetic resistance in some of the population can reduce $\Re_{0_T}$ if x is sufficiently small, or if g_3 is sufficiently large relative to g_2 (cf. (42)). In other words, genetic resistance acts to

limit the spread of HIV if it prevents infections more than it prolongs infectivity. Otherwise, as can be true with treatment, partial genetic resistance may be beneficial at the individual level but detrimental at the population level.

3.6. Parameter analysis

We now estimate values for our model parameters in order to draw some conclusions based on the above analysis of the reproductive number. In the discussion below, we will use parameter values derived in [11,12] for the example of gay men in San Francisco and the CCR5-Δ32 allele mutation. Here rapid progressors are defined as those with an incubation time less than 3.5 years, slow progressors as those whose incubation time is greater than 13 years, and normal progressors as those with intermediate incubation times. Table 1, reproduced from [12], lists these parameters (note $f_{21} > 0$ here, so it has been incorporated into $\Re_0$). In addition, we fix values for the remaining parameters as follows (except as noted in the figures, where two parameters at a time are varied).

The two remaining parameters inherent to the infection process are b_1 and b_3, the infectivity multipliers for rapid and slow progressors, respectively, relative to the infectivity of normal progressors. Data are not currently readily available to predict infectivity based on progression rate, so for illustrative purposes we will take $b_1 = 4$ and $b_3 = 1/2$. Likewise, no vaccine against HIV is readily available at present, so for the sake of argument we will consider 75% vaccination $p_1 = p_2 = 0.75$, a take proportion $\epsilon = 0.9$, 95% protection ($\xi = 0.95$), and a mean duration of $1/\omega = 20$ yr. Similarly, to illustrate the effects of a hypothetical public education campaign we will take an 'education rate' of $\alpha = 1/32$ yr^{-1}, comparable with the removal rate μ (so that in the absence of infection about half the population would be reached before leaving the at-risk population), and again (to parallel vaccine efficacy) 95% effectiveness, $\Psi = 0.95$. (One study of two gay populations in America [27] found a reduction in risky behavior of roughly 20–30% following an education campaign. Using $\alpha = \mu$ as above, this corresponds to a more moderate efficacy $\Psi \in [0.4, 0.6]$, but as discussed in the next paragraph, even this may be enough to make a difference.) Finally, of the treatment parameters there is some evidence that currently available treatments may reduce the rate of progression to AIDS by as much as 50%, so we take $y = 1/2$. There are not, however, data readily available to indicate how much treatment reduces infectivity; for illustration we consider likewise a 50% reduction, $a = 1/2$. We will also consider no discrimination of treatment rate by type of progressor, and therefore take $m_1 = m_2 = m_3 = 1/2$ yr^{-1} (which corresponds to about 75% of infectives being treated before leaving the sexually active population).

By plotting the reproductive number for the complex model as a function of α and Ψ, we obtain the graph shown in Fig. 2, which describes the impact of education on the spread of HIV. It can be seen in this graph that $\Re_0 < 1$ as long as α (the rate at which susceptibles go to the educated class) is not close to 0 (approximately $\alpha > 1/20$) and Ψ (effectiveness of education) is at least 60% effective. This means that educating even some small portion of susceptible individuals about the dangers of HIV will have a significant effect in reducing the next generation of newly infective persons, i.e., $\Re_0$. Hence, education appears to be an effective control measure.

To see the impact of vaccination on the reproductive number, we graph $\Re_0$ as a function of ξ (vaccine effectiveness) and ω (duration of protection against HIV). The result, in Fig. 3, shows that $\Re_0 < 1$ only if ω is close to 0 (i.e., the mean duration of protection is considerably longer than the 20 years estimated above), and ξ is approaching one. That is, the program is effective only

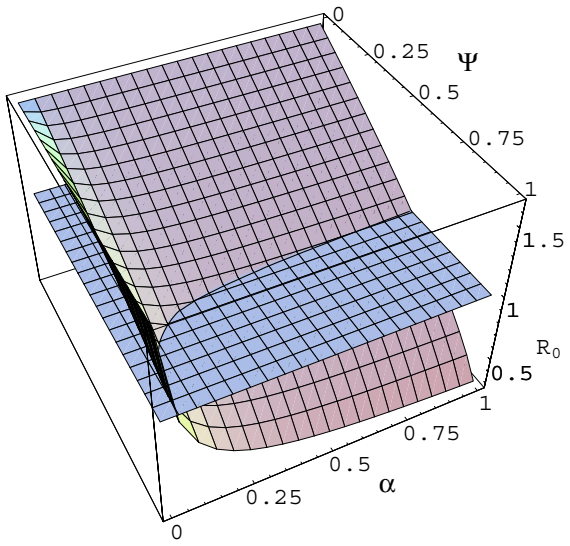

Fig. 2. $\Re_0$ for education as a function of $\Psi \in (0, 1]$ and $\alpha \in (0, \infty)$ intercepted with $\Re_0 = 1$ plane.

when the vaccine's protection is essentially complete, and either lasts indefinitely or is renewed regularly before it can wane. Given the limitations of vaccines currently under development and the possibility of dropouts even for ongoing programs, these conditions may be unrealistic. Calculations also show that for a vaccine with duration and take proportion as estimated above, $\Re_0$ remains above one even if everyone is vaccinated ($p_i = 1$) and protection is complete ($\xi = 1$). Since $\epsilon = 0.9$ is fairly optimistic, this appears to place the onus of protection on the longevity of the vaccine ($1/\omega$).

The graphs in Fig. 4 depict the effects of a uniform treatment program on $\Re_0$. In Fig. 4(a) we see that the effect of the uniform treatment rate m saturates quickly (for approximately $m > 1/4$), and, given the estimate $y = 1/2$, $\Re_0 < 1$ for $a < 0.4$ or so, and almost any treatment rate. In other words, if treatment can reduce infectivity by 60% or more, the infection may be contained. However, Fig. 4(b) shows that this threshold for a moves with y, as described in Section 3.4: in order for treatment to reduce $\Re_0$ below one, treatment must reduce infectivity more than progression rate, by a factor here of $\Re_0|_{m=0} \approx 1.4$ (in comparison, our parameter estimates give $a/H_1 = 0.94$ and $a/H_0 = 0.84$). This result, coupled with the analysis of Section 3.4, signals a focus for researchers and treatment developers to study the reduction in infectivity a program affords.

Finally, we can consider the effects of partial genetic resistance in a heterogeneous population. For these estimates, the relevant quantities defined in the previous section have values $K_I = 1.16$ and $K_T = 1.01$, suggesting that slower progressors do contribute less to infection than faster progressors, in which case both effects of partial genetic resistance are beneficial to the population as a whole. Note, however, that these quantities depend significantly on the values of b_1 and b_3, accurate data for which is not available.

The attentive reader will have noticed that the values of $\Re_0$ in all the graphs are close to 1. In fact, for the set of parameters given above, $\Re_0 = 1.13$; improvement of one or more of the control program parameters as described above is sufficient to make $\Re_0 < 1$. This number, together with

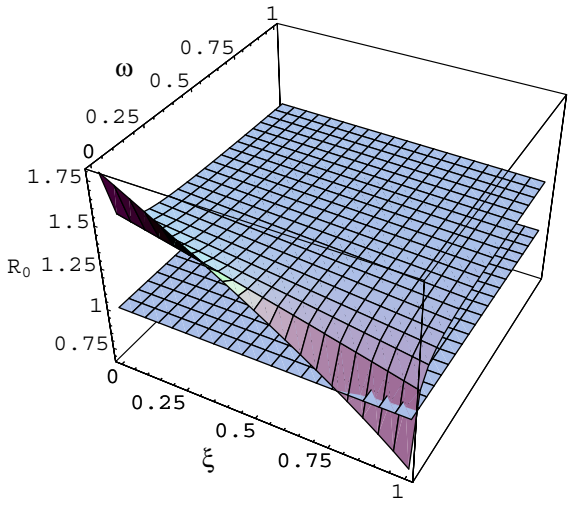

Fig. 3. $\Re_0$ for vaccine as a function of $\xi \in (0,1]$ and $\omega \in (0,\infty)$ intercepted with the plane $\Re_0 = 1$.

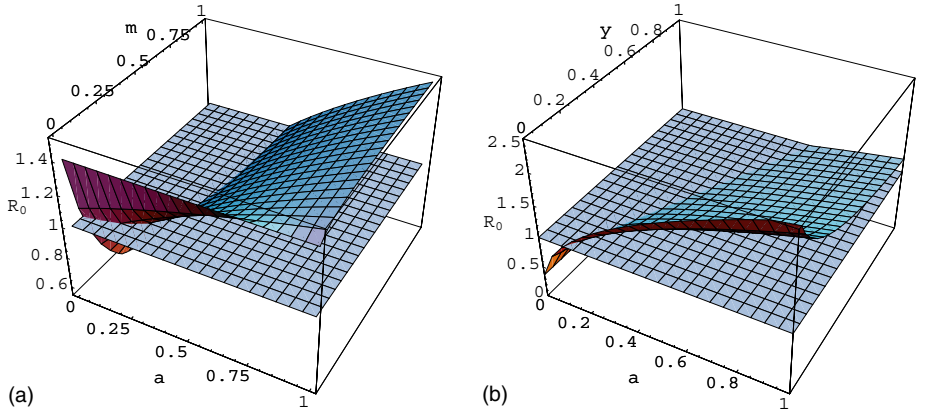

Fig. 4. $\Re_0$ for treatment as a function of (a) a and m, (b) a and y, intercepted with the plane $\Re_0 = 1$.

the graphs, suggests that it is possible to bring the spread of HIV under control by the joint interventions of education, vaccination and treatment. Without any of these interventions we find $\Re_0 = 3.5$, in accordance with the ranges given in [11,12]. Multiple control measures are therefore much more likely to be effective than any single one.

It should be noted that this paper has concentrated purely on analysis of the reproductive number, and given no consideration to the possible existence of endemic equilibria when $\Re_0 < 1$, as has been observed in some highly structured models (e.g., [28,29]). Due to the complexity of our HIV model, we leave investigation of endemic equilibria to future work, although we note our model lacks the cyclic mobility between classes of different vulnerabilities to infection and the multiple stages of non-linear transition rates commonly observed in models which exhibit such behavior.

4. Conclusions

We have presented a novel model to incorporate genetic heterogeneity into HIV/AIDS epidemiology, in conjunction with three disease control measures. We have used the basic reproductive number for this model to discuss the relative contributions of each feature to reducing the spread of HIV. Our results support the conclusions of Hsu Schmitz and Blower & McLean that some integrated intervention strategies (e.g., vaccination, education and treatment together) are far superior to those based on a single approach. However, treatment programs or features such as partial genetic resistance, which protect an individual, may also complicate disease control in the population as a whole by prolonging the infective period. Blower and McLean found that a partially effective HIV vaccination campaign could make matters worse if it created a feeling of invulnerability among the vaccinated that led to a significant rise in risky behavior; with the treatment program and genetic diversity modeled here, however, the complication is inherent in the nature of the protection provided.

In order for treatment programs or partial genetic resistance to benefit the population as a whole, they must reduce infectivity more than they prolong it. In the case of treatment, a, the reduction factor for infectivity, must be sufficiently small compared to the H_j, the reduction factors in the removal rates (cf. (35) and (39)), just as Anderson et al. found for a homozygous model. Treatment programs reduce $\Re_0$ if the infectivity is reduced more than the infective lifespan is prolonged. This result emphasizes improvement of treatments over increase of treatment rates when viewed from a disease control perspective.

As regards genetic resistance, the complete resistance to infection afforded a few individuals naturally benefits everyone, as those are decoupled from the entire process. However, in cases where slower progressors may actually infect more people than rapid progressors by remaining sexually active longer, the tendency of partial genetic resistance to slow the progression rate of HIV may benefit the individual but not the population. Genetic resistance helps lower HIV's ability to reproduce when it reduces (x) the risk of infection more than it prolongs (K_I, K_T) the infective period by redistributing (f_{2j}) progression rates (cf. (42)). The parameter estimates developed in this paper for genetic resistance and a hypothetical treatment program do suggest that both phenomena will benefit the population as a whole, by acting to lower the reproductive number of HIV.

Our numerical analysis appears to signal a high potential for a public education campaign to reduce the spread of HIV (through $\Re_0$) compared to a vaccination campaign under the conditions simulated in our model. The graph in Fig. 2 suggests that effectively educating at least some small portion of the susceptible individuals will reduce the generation of secondary infections significantly, whereas Fig. 3 shows a shallower response (of $\Re_0$) to vaccination parameters, suggesting that a vaccine program like the one modeled would be effective only when the vaccine grants almost complete immunity to HIV for a long period of time. However, it is important to separate the effects of the model structure from the effects of actual campaigns: in this paper we have studied a system in which (following McLean & Blower and Hsu Schmitz, among others) participation in vaccination programs (whether onetime or ongoing) is determined before (or at) entry into the at-risk population and may end at any time, whereas education is targeted to those already susceptible, and is assumed to have permanent effects. Neither program is assumed to be affected by incidence levels. This system corresponds most closely to a population in which both the disease and a vaccination program are established, and a sustained public education campaign

is introduced as an additional control measure. In such a situation, an education campaign does appear to have high potential for disease control. However, it would also be possible to consider control programs with other characteristics (including a model in which these two programs switch features with each other), and our conclusions may depend on the structures we model.

At present, an education program therefore appears to be a good option in reducing the further spread of HIV, in part because (as observed, e.g., in [18]) reliable vaccination and treatment programs are not yet readily available, and in part because as a population-level effort it is less costly than individual-level efforts like vaccines and treatment. With sufficient thought and creativity, a sustained, dynamic education campaign should also not suffer the same kind of diminishing returns as the vaccination and treatment programs presently in use or envisioned seem biologically obliged to do: the protection afforded by vaccines may wane over time, and antiviral drugs used in treatment are not 100% effective because after some time the highly mutable virus can still replicate even in the presence of these drugs. However, this conclusion is not a recommendation against vaccination or treatment: we cannot ethically abandon those already infected, or our efforts to prevent new infections. Instead, researchers must work to continue improving the effectiveness of such biological disease control measures in reducing infectivity, whether they are new vaccines or medical therapies trying to keep ahead of HIV's ability to mutate. Gene therapy, which has already proven successful in some limited experimental cases, seems likely to develop into a major research area, so the effects of genetic resistance investigated in this article may soon join the ranks of the other disease control measures modeled.

At present obviously $\mathfrak{R}_0 > 1$ for the spread of HIV in populations across the world. Public education campaigns frequently follow the outbreak of HIV in many of these populations. Medical treatment has become available in some areas, and research continues to advance in the search for preventative medical measures such as vaccines. The model studied in this paper suggests that the joint intervention of all these measures may be effective in overcoming the virus's ability to invade a population, even when the disease spreads effectively in the absence of these measures (e.g., $\mathfrak{R}_0 = 3.5$ for the partially hypothetical homosexual population studied).

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