Effects of treatment or/and vaccination on HIV transmission in homosexuals with genetic heterogeneity

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Abstract

Several mutant genes in HIV co-receptors (e.g., CCR5, CCR2 and CXCR4) have been correlated with susceptibility to HIV or/and rate of progression to AIDS. Some of these genes have high allele frequencies in general populations. Their effects on the HIV/AIDS dynamics may be significant. To study such genetic heterogeneity, Hsu Schmitz [S.-F. Hsu Schmitz, A mathematical model of HIV transmission in homosexuals with genetic heterogeneity, J. Theoret. Med. (to appear)] proposed a one-sex model with susceptibles classified by genotype as having no, partial or full natural resistance to HIV infection and infecteds classified as rapid, normal or slow progressors. The example of CCR5-D32 mutation in San Francisco gay men indicated that the normal progressors are most responsible for disease spread. The per-partnership transmission rates of rapid and slow progressors are identified as key parameters. The present manuscript extends the previous one by considering the intervention of treatment or/and vaccination. Detailed investigations are illustrated by using the same example of CCR5-D32 mutation in San Francisco gay men. Treating only newly infected individuals or vaccinating only newly recruited susceptibles is not effective enough for disease control. When both measures are applied, the epidemic may be eradicated if the transmission rate of slow progressors is not too large, and treatments and vaccines in use are of decent quality. © 2000 Elsevier Science Inc. All rights reserved.

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1. Introduction

About 10–15% of HIV infected individuals remain AIDS free for 10 yr or longer (non-progressors), while another 10% progress within the first 2–3 yr (rapid progressors) [1,2]. On
the other hand, there are many individuals who remain seronegative even with multiple exposures to HIV from infected partners [3–5]. To the question what makes the difference in the outcome of HIV infection and AIDS pathogenesis, partial answers have been given by recent discovery of some mutant genes in HIV co-receptors that are correlated with susceptibility to HIV or/and rate of progression to AIDS. For instance, the mutant allele, Δ32, of CCR5 chemokine receptor gene is present at a high frequency of 0.092 in Caucasian populations [6]. The frequencies of homozygotes and heterozygotes for the mutation are about 1% and 16%, respectively. In a cohort of HIV-1 infected Caucasian patients, the heterozygote frequency is 35% lower than in the general population and no homozygotes with two Δ32 alleles are found. These observations suggest Δ32 may provide, at least partial, resistance to HIV-1 infection. Dean et al. [7] discover the same mutant allele with similar frequency (~10%) in the Caucasian population of the US. Their results indicate that the homozygotes with two Δ32 alleles may escape from HIV-1 infection and heterozygous infecteds may have a slower progression than other infecteds. Another CCR5 gene mutation, m303, is present among Europeans at an allele frequency of under 1% [8]. Individuals with genotype m303/m303 or Δ32/m303 acquire resistance to HIV-1 infection. Similarly, the m303 heterozygosity may give partial protection against infection and slow down the progression once infected. In another chemokine, CCR2, the mutation, 64I, occurs at an allele frequency of 10–15% among Caucasians and African Americans [9]. This mutant gene indicates a 2–4 yr delay of progression among infecteds and its effects are genetically independent of CCR5-Δ32. In stromal-derived factor (SDF-1, the principal ligand for CXCR4), the gene variant, 3'A, shows recessive restriction on AIDS pathogenesis [10]. HIV infected individuals with SDF-1-3'A/3'A genotype have a significantly lower relative hazard to AIDS onset and the protection is approximately twice that seen with CCR2 or CCR5 protection. Moreover, CCR and SDF-1 protection seem to be additive.

All the information above clearly indicates the existence of genetic heterogeneity in susceptibility to HIV infection and in rate of progression to AIDS in general populations. Because some of these mutant genes have relatively high allele frequencies, their effects on the HIV/AIDS dynamics may be significant. Such kind of genetic heterogeneity has not been specifically studied in the modeling literature although the effects of heterogeneity on disease invasion have been investigated in more general ways [11,12].

As driven by available data, Hsu Schmitz [13] proposes a specific one-sex model with susceptibles classified by genotype as having no, partial or full resistance to HIV infection and infecteds classified as rapid, normal or slow progressors. The basic reproductive number of this model is derived according to [14]. Using the example of CCR5-Δ32 mutation in San Francisco gay men, some parameters are estimated from available data and the normal progressors are found to be most responsible for disease spread. In addition, the per-partnership transmission rates of rapid and slow progressors are identified as key parameters in this population. Compared with the general model in [11] where transmission rate does not depend on the infectious individual, this specific model allows such dependence. In contrast to the model in [12] where heterogeneity was described by frailty, i.e., a random variable with certain probability distribution for each individual, this specific model treats heterogeneity as a fixed characteristic within each group as in [11], i.e., within-group variation is ignored.
The present manuscript is an extension to the previous one by implementing treatment or/and vaccination to evaluate the feasibility of HIV disease elimination and to provide some hints about strategies of HIV prevention and treatment. Section 2 briefly describes the basic model where treatment and vaccination are not applied [13]. Section 3 presents the general model incorporating treatment and vaccination. The basic reproductive numbers under treatment alone, vaccination alone, and treatment and vaccination together are derived and compared. Section 4 presents practical considerations on treatment and vaccination through an example focusing on CCR5-Δ32 mutation among gay men in San Francisco. Finally some concluding remarks are provided in Section 5.

2. Basic model

This section briefly describes the simpler one-sex model in [13] as the basic model for this manuscript. A population consisting of sexually active individuals is considered. Based on the level of natural resistance to HIV, susceptibles are classified, according to genotype, into three groups: with no resistance \((S_1)\), partial resistance \((S_2)\) and complete resistance \((S_3)\). We assume that \(S_3\)-individuals never become infected. Similarly, based on rate of progression, infecteds are classified into three groups: rapid progressor \((I_1)\), normal progressor \((I_2)\) and slow progressor \((I_3)\). Throughout this paper, the index \(i\) refers to group of susceptible/vaccinated individuals and the index \(j\) refers to group of infected/treated individuals.

We assume recruitment occurs at a constant rate, \(\pi\), to replenish the three susceptible groups with respective fractions, \(g_i\) \((i = 1, 2, 3\) and \(\sum_i g_i = 1\)), which are related to the frequencies of relevant genotypes. All individuals are subject to the common per-capita natural removal rate, \(\mu\). As in [15,16], we assume all susceptibles and infecteds have the same average number of partners per unit time, \(c\). This assumption seems to be reasonable in our case because for the present not many individuals know their genotypes at those loci related to HIV/AIDS, hence, genetic heterogeneity does not influence pairing behavior. The per-capita progression rates for \(I_j\)-individuals are denoted by \(\gamma_j\) \((j = 1, 2, 3)\) with \(1/\gamma_j\) equal to the average incubation time of \(I_j\)-individuals. The infectiousness of \(I_j\)-individuals is reflected by the per-partnership transmission rate, \(\beta_j\) \((j = 1, 2, 3)\). As in [13], we use \(\beta := \beta_2\) as reference and reparameterize \(\beta_j = b_j \beta\) with \(b_2 \equiv 1\). When an \(S_2\)-individual pairs with an \(I_j\)-individual, the transmission rate \(\beta_j\) is reduced to \(\beta x\beta_j\), with \(0 < x < 1\) to account for the partial resistance to HIV in \(S_2\)-individuals. Newly infected \(S_i\)-individuals \((i = 1, 2)\) join the three infected groups with respective proportions \(f_{ij}\), where \(0 \leq f_{ij} \leq 1\) and \(\sum_{j=1}^{3} f_{ij} = 1\).

The proportional mixing pattern [17] is assumed for contacts among individuals. More specifically, for a susceptible, given he pairs, the chance of pairing with an \(I_j\)-individual is \(cI_j/\Phi_0\), where \(\Phi_0 := \sum_{i=1}^{3} S_i + \sum_{j=1}^{3} I_j\) with \(n\) indicating null, i.e., the basic model. The force of infection for \(S_1\)-individuals is then \(\sigma_1 = \beta \sum_{j=1}^{3} b_j I_j/\Phi_0\) and for \(S_2\)-individuals is \(\sigma_2 = x\sigma_1\). The number of newly infected \(S_i\)-individuals \((i = 1, 2)\) is \(\delta_i = cS_i \sigma_i\). These newly infected individuals enter \(I_j\) \((j = 1, 2, 3)\) group at the rate \(\rho_j = \sum_{i=1}^{3} f_{ij} \delta_i\). The mathematical model is described by the following system of equations:

\[
\begin{align*}
\dot{S}_1 &= g_1 \pi - \mu S_1 - \delta_1, \\
\dot{S}_2 &= g_2 \pi - \mu S_2 - \delta_2,
\end{align*}
\]
The basic reproductive number of this model is

\[ R_{0n} = c \beta E_n, \]  

where

\[ E_n := \frac{b_1 \tau_1}{\mu + \gamma_1} + \frac{\tau_2}{\mu + \gamma_2} + \frac{b_3 \tau_3}{\mu + \gamma_3} \]

and

\[ \tau_j := f_{ij} g_1 + x f_{2j} g_2. \]

Because \( f_{ij}, g, \) and \( x \) are positive, \( \tau_j \) and \( E_n \) are also positive.

The estimates of per-partnership transmission rates of rapid and slow progressors (i.e., \( \beta_1 \) and \( \beta_3 \), or \( b_1 \) and \( b_3 \)) are not available. Sensitivity analyses show that these two parameters have important impact on the relative group contributions to \( R_{0n} \) [13]. The extended model incorporating treatment and vaccination is described in the following section.

3. Extended model

For convenience, we consider an ideal situation in which certain proportions \( (m_j) \) of newly infected \( I_j \)-individuals \( (j = 1, 2, 3) \) are effectively treated and certain proportions \( (p_i) \) of newly recruited \( S_i \)-individuals \( (i = 1, 2) \) are vaccinated. We assume that the transmission rate of effectively treated individuals \( (T_i) \) is reduced from \( \beta_j \) to \( z \beta_j \) with \( 0 \leq z < 1 \), and the progression rate is reduced from \( \gamma_j \) to \( y \gamma_j \) with \( 0 \leq y < 1 \). The value of 1 is not included in the ranges of \( z \) and \( y \) because it means treatment does not reduce infectiousness and rate of progression at all, which does not sound reasonable based on current knowledge. As in [16], we assume that the vaccines have a ‘take’ proportion of \( \epsilon \) \( (0 < \epsilon < 1) \), an efficacy of \( \Psi \) \( (0 < \Psi < 1) \) and a protection duration of \( 1/\omega \) units of time. The ranges of \( \epsilon \) and \( \Psi \) do not include 0 and 1 because 0 implies the vaccine is useless and 1 implies the vaccine is perfect; both are not realistic. These vaccine parameters indicate \( [100 \times (1 - \epsilon)]\% \) vaccinated individuals are not effectively vaccinated and they are in principle like other unvaccinated individuals. Those effectively vaccinated individuals (in a proportion of \( p_i \epsilon \)), denoted by \( V_i \), still have \( [100 \times (1 - \Psi)]\% \) chance to be infected within the protection duration of \( 1/\omega \) units of time. No reduction in infectiousness for infecteds who have been vaccinated is assumed. Although individuals might become more active (i.e., having more sexual partners per unit of time) after being treated or vaccinated, for simplicity we assume that neither...
the treatment nor the vaccination changes people’s pairing behavior, so the common pairing
activity c and the proportional mixing pattern in the basic model are still in effect. Let

\[ \Phi_e := \sum_{i=1}^{3} S_i + \sum_{i=2}^{3} V_i + \sum_{j=1}^{3} (I_j + T_j) \]  

(5)

with e indicating the extended model, then the forces of infection for \( S_1 \)- and \( S_2 \)-individuals are

\[ \sigma_{S1} = \beta \left( \sum_{j=1}^{3} b_j I_j + z \sum_{j=1}^{3} b_j T_j \right) / \Phi_e \]  

(6)

\[ \sigma_{S2} = x \sigma_{S1} \]  

(7)

and for \( V_1 \)- and \( V_2 \)-individuals are

\[ \sigma_{V1} = (1 - \Psi) \sigma_{S1}, \]  

(8)

\[ \sigma_{V2} = x \sigma_{V1} = x(1 - \Psi) \sigma_{S1}. \]  

(9)

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

\[ \delta_{Si} = c S_i \sigma_{Si}, \]  

(10)

\[ \delta_{Vi} = c V_i \sigma_{Vi}. \]  

(11)

These newly infected individuals enter \( j \)th \((j = 1, 2, 3)\) infected group \((I_j \) and \( T_j)\) at the rate

\[ \rho_j = \sum_{i=1}^{2} f_{ij} (\delta_{Si} + \delta_{Vi}). \]  

(12)

The following system of equations describes the extended mathematical model:

\[ \dot{S}_1 = g_1 \pi (1 - p_1) e + \omega V_1 - \mu S_1 - \delta_{S1}, \]

\[ \dot{S}_2 = g_2 \pi (1 - p_2) e + \omega V_2 - \mu S_2 - \delta_{S2}, \]

\[ \dot{S}_3 = g_3 \pi - \mu S_3, \]

\[ \dot{V}_1 = g_1 \pi p_1 e - (\mu + \omega) V_1 - \delta_{V1}, \]

\[ \dot{V}_2 = g_1 \pi p_2 e - (\mu + \omega) V_2 - \delta_{V2}, \]

\[ \dot{I}_1 = (1 - m_1) \rho_1 - (\mu + \gamma_1) I_1, \]

\[ \dot{I}_2 = (1 - m_2) \rho_2 - (\mu + \gamma_2) I_2, \]

\[ \dot{I}_3 = (1 - m_3) \rho_3 - (\mu + \gamma_2) I_3, \]

\[ \dot{T}_1 = m_1 \rho_1 - (\mu + \gamma_1) T_1, \]

\[ \dot{T}_2 = m_2 \rho_2 - (\mu + \gamma_2) T_2, \]

\[ \dot{T}_3 = m_3 \rho_3 - (\mu + \gamma_3) T_3, \]  

(13)

The effects of treatment or/and vaccination on the epidemic are investigated in the following subsections.
3.1. Effects of treatment

If only treatment is applied to the population, the basic reproductive number, denoted by \( R_{0t} \) with \( t \) indicating treatment, is

\[
R_{0t} = c\beta F_t,
\]

where

\[
F_t := \frac{(1 - m_1)b_1\tau_1}{\mu + \gamma_1} + \frac{(1 - m_2)b_2\tau_2}{\mu + \gamma_2} + \frac{(1 - m_3)b_3\tau_3}{\mu + \gamma_3} + \frac{m_1z b_1\tau_1}{\mu + y\gamma_1} + \frac{m_2z\tau_2}{\mu + y\gamma_2} + \frac{m_3z b_3\tau_3}{\mu + y\gamma_3}
\]

and \( \tau_j \) has the same definition as in (4) for the basic model. The difference between \( R_{0n} \) and \( R_{0t} \) is denoted by

\[
D_t : = R_{0n} - R_{0t} = c\beta(m_1b_1\tau_1H_1 + m_2\tau_2H_2 + m_3b_3\tau_3H_3),
\]

where

\[
H_j := \frac{1}{\mu + \gamma_j} - \frac{z}{\mu + y\gamma_j}.
\]

If we require that the treatment is effective not only in the individual level, but also in the population level to slow down the spread of the disease, then we expect \( D_t > 0 \), which implies not all \( H_j \) can be negative. For given \( \mu \) and \( \gamma_j \), \( H_j \) can become negative when \( y \to 0 \) and \( z \to 1 \), i.e., treatment significantly prolongs the incubation period, but does not reduce the infectiousness. Fortunately, recent clinical trials (see [18,19] for example) with highly active antiretroviral therapy (HAART) have shown that such treatments reduce the plasma HIV–RNA to undetectable levels. Due to the reduction of viral load, the infectiousness may be reduced.

Based on the formula of (14) or (16), the critical value of each treatment related parameters (i.e., \( m_j, y, z \)) to have \( R_{0t} < 1 \) can be calculated. Because we have only one equation, we can solve for only one unknown parameter. Hence, we examine one parameter at a time. For example, if \( m_1 = m_2 = m_3 = m \), the common treatment proportion with given \( R_{0n} \) has to be

\[
m > m^* : = \frac{R_{0n} - 1}{c\beta U},
\]

where

\[
U := b_1\tau_1H_1 + \tau_2H_2 + b_3\tau_3H_3 = E_n - zE_y
\]

with

\[
E_y := \frac{b_1\tau_1}{\mu + y\gamma_1} + \frac{\tau_2}{\mu + y\gamma_2} + \frac{b_3\tau_3}{\mu + y\gamma_3}.
\]

Because \( 0 < y < 1 \), all three terms in \( E_y \) are larger than the corresponding terms in \( E_n \); thus, \( E_y > E_n \). If \( 100 \times m \)% newly infected individuals are effectively treated and \( m > m^* \), then the epidemic will eventually die out. Expression (18) holds only when \( U > 0 \). If \( U < 0 \), which is equivalent to \( H_j < 0 \) for all \( j \), then this treatment is not effective in the population level and should not be applied. As a proportion, \( m^* \) is constrained in the range of \((0,1]\). The value 0 is not included.
here because it means no treatment. The condition \( m^\ast > 0 \) requires \((R_{0n} - 1)U > 0\). When \( R_{0n} > 1 \), which is the usual case for the current HIV/AIDS epidemic, it requires

\[
U > 0.
\]

As expected, we get negative \( m^\ast \) and \( \Delta_t \) if \( U < 0 \). Also, because \( U \) is in the denominator of (18), it cannot be zero. On the other hand, the condition \( m^\ast \leq 1 \) requires

\[
U \geq U_m := \frac{R_{0n} - 1}{c\beta}.
\]

or equivalently

\[
z \leq z_m := \frac{1}{c\beta E_y}.
\]

When \( R_{0n} > 1 \), the \( U \)'s satisfying (22) also satisfy (21). If conditions (22) or (23) is not satisfied, we obtain \( m^\ast > 1 \), which is not realistic. Thus either of these two conditions can be used to check the possibility of disease eradication with the given treatment. If it proves possible, then the required common treatment proportion can be calculated by expression (18).

Alternatively, for given \( m \) and \( y \), the reduction factor for infectiousness has to be

\[
z < z^\ast := \frac{1 + R_{0n}(m - 1)}{c\beta m E_y}
\]

to eliminate the disease by the treatment. Note that when \( m = 1 \), \( z^\ast \) is equivalent to \( z_m \) in expression (23). Again, as a proportion, \( z^\ast \) is constrained in the range of \([0,1)\). The value 1 is not included here because it means the treatment has no effect in reducing infectiousness. The condition \( z^\ast \geq 0 \) requires

\[
m \geq 1 - \frac{1}{R_{0n}}.
\]

If condition (25) is not satisfied, we would get negative \( z^\ast \). The other condition \( z^\ast < 1 \) requires

\[
m > \frac{R_{0n} - 1}{R_{0n} - c\beta E_y} = \frac{R_{0n} - 1}{c\beta (E_y - E_n)}.
\]

If \( R_{0n} > 1 \), then the right-hand side is negative and any \( m \in (0,1) \) will satisfy (26). If \( R_{0n} < 1 \), then the disease will die out by itself and treatment is not necessary for disease control in the population level. In brief, only condition (25) has to be satisfied for having a realistic \( z^\ast \) if \( R_{0n} > 1 \).

To obtain the critical value of reduction factor for rate of progression, \( y^\ast \), with given \( m \) and \( z \), one needs to solve the following polynomial for \( y \):

\[
0 = \gamma_1\gamma_2\gamma_3 K y^3 + \{\gamma_1\gamma_2(\mu K - \tau_1 b_1) + \gamma_1\gamma_3(\mu K - \tau_2) + \gamma_2\gamma_3(\mu K - \tau_3 b_3)\} y^2
+ \{\gamma_1(\mu K - \tau_2 - \tau_3 b_3) + \gamma_2(\mu K - \tau_2 b_1 - \tau_3 b_3) + \gamma_3(\mu K - \tau_1 b_1 - \tau_2)\} y
+ (\mu K - \tau_1 b_1 - \tau_2 - \tau_3 b_3) \mu,
\]

where
\[ K := \frac{1 - (1 - m)R_{0n}}{c \beta m z}. \]  

(28)

There are three solutions to this polynomial, but only the solution satisfying \( 0 \leq y < 1 \) should be chosen. The value 1 is not included here because it means the treatment has no effect in reducing rate of progression. For the situations with \( m_j \) not all equal, the value of \( z^* \) or \( y^* \) can also be obtained, but the equation to be solved will become even messier.

3.2. Effects of vaccination

If only vaccination is applied to the population, the basic reproductive number, denoted by \( R_{0v} \) with \( v \) indicating vaccination, is defined as

\[ R_{0v} = c \beta E_\kappa, \]  

(29)

where

\[ E_\kappa = \frac{b_1 \kappa_1}{\mu + \gamma_1} + \frac{\kappa_2}{\mu + \gamma_2} + \frac{b_3 \kappa_3}{\mu + \gamma_3} \]  

(30)

and

\[ \kappa_j := \tau_j - \phi \xi_j \]  

(31)

with

\[ \xi_j := f_j g_1 p_1 + x f_2 g_2 p_2 \]  

(32)

and

\[ \phi := \frac{\mu e \Psi}{\mu + \omega}, \]  

(33)

which is called vaccine impact in [16]. Since all parameters are positive, we have \( \xi_j > 0 \) and \( \phi > 0 \). The difference between \( R_{0n} \) and \( R_{0v} \) is denoted by \( \Delta_v \) as

\[ \Delta_v := R_{0n} - R_{0v} = c \beta \phi E_\xi, \]  

(34)

where

\[ E_\xi := \frac{b_1 \xi_1}{\mu + \gamma_1} + \frac{\xi_2}{\mu + \gamma_2} + \frac{b_3 \xi_3}{\mu + \gamma_3}. \]  

(35)

Because all parameters on the right-hand side of (35) are positive, we have \( E_\xi > 0 \) and thus \( \Delta_v > 0 \), i.e., vaccination is always helpful for reducing the basic reproductive number. However, positivity of \( \Delta_v \) does not guarantee the epidemic will eventually die out, which requires a stronger condition, i.e., \( R_{0v} < 1 \). Based on the formula in (29) or (34), the critical value of each vaccination related parameter (i.e., \( p_1 \) and \( \phi \) (as function of \( \mu, \epsilon, \Psi \) and \( \omega \))) to have \( R_{0v} < 1 \) can be calculated. For instance, for given \( p_1 \) and \( p_2 \), the vaccine impact has to be

\[ \phi > \phi^* := \frac{R_{0n} - 1}{c \beta E_\xi}. \]  

(36)
When $R_{0n} > 1$, the numerator of (36) is positive; hence $\phi^* > 0$ as required. Alternatively, if $p_1 = p_2 = p$, then $\xi_j = pt_j$ and $E_\xi = pE_n$. This common vaccination proportion with given $R_{0n}$ has to be

$$p > p^* := \frac{1}{\phi} \left( 1 - \frac{1}{R_{0n}} \right).$$

(37)

The condition $p^* > 0$ requires $R_{0n} > 1$. That is, if $R_{0n} < 1$, the epidemic will eventually die out even without any intervention; thus it is not necessary to have vaccination. However, if one would like to shorten the time to disease elimination, it would be certainly helpful to add vaccination (because $A_v > 0$). The condition $p^* \leq 1$ requires

$$\phi \geq \phi_p := 1 - \frac{1}{R_{0n}}.$$  

(38)

Since $R_{0n} > 1$ is the usual case, only condition (38) is required to check the feasibility of disease elimination with the given vaccination program. Also note that $\phi_p$ is equivalent to $\phi^*$ in (36) when $p = 1$.

3.3. Effects of treatment and vaccination

If both treatment and vaccination are applied to the population, the basic reproductive number is

$$R_{0tv} = c\beta F_\kappa,$$

where

$$F_\kappa := \frac{(1 - m_1)b_1\kappa_1}{\mu + \gamma_1} + \frac{(1 - m_2)b_2\kappa_2}{\mu + \gamma_2} + \frac{(1 - m_3)b_3\kappa_3}{\mu + \gamma_3} + \frac{m_1zb_1\kappa_1}{\mu + y\gamma_1} + \frac{m_2zb_2\kappa_2}{\mu + y\gamma_2} + \frac{m_3zb_3\kappa_3}{\mu + y\gamma_3}.$$  

(40)

The difference between $R_{0n}$ and $R_{0tv}$ is denoted by $A_{tv}$ as

$$A_{tv} := R_{0n} - R_{0tv} = c\beta \{ \phi E_\xi + b_1m_1\kappa_1H_1 + m_2\kappa_2H_2 + b_3m_3\kappa_3H_3 \}.$$  

(41)

If $H_j > 0$ for all $j$, then we are sure $A_{tv} > 0$, i.e., the joint intervention of treatment and vaccination can reduce the basic reproductive number. However, if not all $H_j > 0$, then it is still possible to have $A_{tv} > 0$.

Since treatments are readily available in many countries, it is probably more interesting to investigate the additional effect of vaccination after treatment is given. More precisely, we are interested in

$$A_{v+} := R_{0n} - R_{0tv} = c\beta \phi F_\xi,$$  

(42)

where

$$F_\xi := \frac{(1 - m_1)b_1\xi_1}{\mu + \gamma_1} + \frac{(1 - m_2)b_2\xi_2}{\mu + \gamma_2} + \frac{(1 - m_3)b_3\xi_3}{\mu + \gamma_3} + \frac{m_1zb_1\xi_1}{\mu + y\gamma_1} + \frac{m_2zb_2\xi_2}{\mu + y\gamma_2} + \frac{m_3zb_3\xi_3}{\mu + y\gamma_3}.$$  

(43)

Since all parameters on the right-hand side of (43) are positive and $m_j \leq 1$, we have $F_\xi > 0$ and thus $A_{v+} > 0$, i.e., vaccination can further reduce the basic reproductive number after treatment is
given. To have $R_{0tv} < 1$ with given $m_j$, $y$, $z$ and $p$, the critical value of vaccine impact can be calculated using (39) or (42) as follows:

$$\phi > \phi^*_v := \frac{R_{0t} - 1}{c\beta F^*_v}.$$ 

(44)

If $R_{0t} > 1$, then $\phi^*_v > 0$ as required.

Alternatively, when $\phi$ is given, the common vaccination proportion has to be

$$p > p^*_v := \frac{1}{\phi} \left( 1 - \frac{1}{R_{0t}} \right),$$

(45)

which is due to $F^*_v = p F_v$. The condition $p^*_v > 0$ requires

$$R_{0t} > 1.$$ 

(46)

That is, if $R_{0t} < 1$, the epidemic will eventually die out under the given treatment; thus it is not necessary to add vaccination to the existing intervention. However, if one would like to shorten the time to disease elimination, it would be certainly helpful to add vaccination (because $\Delta_{v+} > 0$). The condition $p^*_v \leq 1$ requires

$$R_{0t} \leq \frac{1}{1 - \phi},$$

(47)

which makes sense with $0 < \phi < 1$. Thus (47) is the condition to check if it is feasible to eliminate the disease with a common vaccination proportion added to treatment intervention.

The formulas and conditions derived from basic reproductive numbers in this section are applied to the evaluation of feasibility of disease elimination by treatment or/and vaccination in a homosexual population in the following section.

4. Example

4.1. Background information

As in [13], we choose the population of gay men in San Francisco with the focus on the CCR5-Δ32 mutation as an example. Susceptibles without Δ32 genes have no resistance to HIV infection ($S_1$); those with one Δ32 gene have partial resistance ($S_2$); and those with two Δ32 genes have complete resistance ($S_3$) and never become infected. Based on data presented in Fig. 3 of [9] and using the AIDS criterion of 1993, we define rapid progressors ($I_1$) as having an incubation time of less than 3.5 yr, slow progressors ($I_3$) of more than 13 yr, and normal progressors ($I_2$) of in between 3.5 and 13 yr, i.e., $1/\gamma_1 < 3.5$ yr, $3.5$ yr $\leq 1/\gamma_2 \leq 13$ yr and $1/\gamma_3 > 13$ yr. Table 1 lists the estimates of parameters taken from the literature.

No information about $\beta_1$ and $\beta_3$, or equivalently $b_1$ and $b_3$, is available, thus they are considered as free parameters within respective ranges: $1 \leq b_1 \leq 4$ (this upper bound is chosen for illustrative purpose) and $0 \leq b_3 \leq 1$. Sensitivity analyses are carried out using different values of $b_1$ and $b_3$. Without any treatment and vaccination intervention, the magnitude of $R_{0n}$, defined in (2), for different values of $b_1$ and $b_3$ can be calculated by the following formula:

$$R_{0n} = 2.308(0.053b_1 + 1 + 0.609b_3).$$

(48)
Even under the ‘best’ situation with the minimum values of $b_1$ and $b_3$, $R_0$ is still larger than unity with the major contribution coming from normal progressors. This implies that the disease will continue spreading out in this population.

4.2. With treatment

When certain proportions ($m_i$) of newly infected individuals are effectively treated, the basic reproductive number will be changed to $R_{0t}$, as defined in (14). Newly infected individuals from either $S_1$ or $S_2$ group will join one of the three infected groups, i.e., individuals of different genotypes may enter the same infected group. From practical point of view, it is difficult to distinguish rapid, normal or slow progressors from each other at time of infection or seroconversion only by checking their genotypes; hence a common treatment proportion, $m$, seems to reasonable.

Based on expression (23), Fig. 1 presents the allowable upper bounds of the treatment-induced reduction factor for transmission rate $z$, i.e., $z_m$, for the treatment-induced reduction factor for progression rate $y$ under four different ($b_1, b_3$) situations: ‘best’ with $b_1 = 1$ and $b_3 = 0$, ‘intermediate’ with $b_1 = 2$ and $b_3 = 0.5$, ‘neutral’ with $b_1 = b_3 = 1$, and ‘worst’ with $b_1 = 4$ and $b_3 = 1$. Under all four situations, the $z_m$ increases nearly linearly with $y$; that is, the larger the $y$ is, the larger the upper bound for $z$ is allowed; or equivalently, the smaller reduction in progression rate is, the smaller reduction in transmission rate is required. Also the $z$ has to be relatively smaller than $y$, which suggests more efforts should be given to reduction of transmission rate than to reduction of progression rate induced by the treatment. For any given value of $y$, the order of the $z_m$ is ‘best’ > ‘intermediate’ > ‘neutral’ > ‘worst’; that is, the better the situation, the larger the upper bound for $z$ is allowed, thus the less strength in reduction of transmission rate from the treatment is required. For instance, when $y = 0.5$, the $z_m$s of these four situations are $0.245, 0.186, 0.162$ and $0.145$, respectively. Compared with the ‘neutral’ situation where the three

### Table 1

<table>
<thead>
<tr>
<th>Estimates and sources of some model parameters</th>
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<tbody>
<tr>
<td>As in [16]:</td>
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<tr>
<td>Per-capita natural removal rate $\mu = 1/32$ yr$^{-1}$</td>
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<tr>
<td>Recruitment rate $\pi = 2000$ yr$^{-1}$</td>
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<tr>
<td>Product of per-partnership transmission rate of normal progressors and pairing activity $\beta c = 0.62$ yr$^{-1}$</td>
</tr>
<tr>
<td>Estimated from data in [7]:</td>
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<tr>
<td>Genotype frequencies $g_1 = 0.75, g_2 = 0.23, g_3 = 0.02$</td>
</tr>
<tr>
<td>Implied by [6]:</td>
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<tr>
<td>Reduction factor for susceptibility $x = 0.65$</td>
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<tr>
<td>As in [13]:</td>
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<tr>
<td>Per-capita rates of progression for rapid progressors $\gamma_1 = 1/2$ yr$^{-1}$</td>
</tr>
<tr>
<td>Per-capita rates of progression for normal progressors $\gamma_2 = 1/8$ yr$^{-1}$</td>
</tr>
<tr>
<td>Per-capita rates of progression for slow progressors $\gamma_3 = 1/16$ yr$^{-1}$</td>
</tr>
<tr>
<td>Distributing fractions of infected groups for individuals without resistance $f_{11} = 0.128, f_{12} = 0.655, f_{13} = 0.217$</td>
</tr>
<tr>
<td>Distributing fractions of infected groups for individuals with partial resistance $f_{21} = 0.063, f_{22} = 0.605, f_{23} = 0.332$</td>
</tr>
</tbody>
</table>
Fig. 2. Minimum common treatment proportion \( (m') \) required to have the basic reproductive number \( R_0 \leq 1 \), as a function of \( b_1 \) and \( b_3 \) (see Fig. 1 legend and text for definition) with treatment-induced reduction factor for progression rate \( y = 0.5 \) and treatment-induced reduction factor for per-partnership transmission rate \( z = 0.14 \).
Fig. 3. Minimum vaccine impact ($\phi'$) required to have the basic reproductive number $R_{0v} \leq 1$, as a function of vaccination proportion ($p_2$) for the newly recruited susceptibles who have partial resistance to HIV ($S_2$) under ‘best’, ‘intermediate’, ‘neutral’ and ‘worst’ situations (see Fig. 1 legend and text for definition) when all newly recruited susceptibles who have no resistance to HIV ($S_1$) are vaccinated ($p_1 = 1$).

Fig. 4. Basic reproductive number $R_{0t}$ under treatment with a common treatment proportion $m = 0.8$, treatment-induced reduction factor for progression rate $\gamma = 0.4$ and treatment-induced reduction factor for per-partnership transmission rate $z = 0.4$, as a function of $b_1$ and $b_3$ (see Fig. 1 legend and text for definition).
Fig. 5. Minimum vaccine impact ($\phi^*$) required to have the basic reproductive number $R_{0tv} \leq 1$, as a function of vaccination proportion ($p_2$) for the newly recruited susceptibles who have partial resistance to HIV ($S_2$) under ‘best’, ‘intermediate’, ‘neutral’ and ‘worst’ situations (see Fig. 1 legend and text for definition) when all newly recruited susceptibles who have no resistance to HIV ($S_1$) are vaccinated ($p_1 = 1$). The common treatment proportion is $m = 0.8$ with treatment-induced reduction factor for progression rate $y = 0.4$ and treatment-induced reduction factor for per-partnership transmission rate $z = 0.4$.

Fig. 6. Basic reproductive number $R_0t$ under treatment with a common treatment proportion $m = 0.8$, treatment-induced reduction factor for progression rate $y = 0.4$ and treatment-induced reduction factor for per-partnership transmission rate $z = 0.2$, as a function of $b_1$ and $b_3$ (see Fig. 1 legend and text for definition).
infected groups have the same transmission rate, the consideration of heterogeneity in transmission rate among infected groups may make the same treatment more effective under the ‘best’ situation or less effective under the ‘worst’ situation. Moreover, the difference between situations also increases with \( y \). If the treatment yields \( y = 0.5 \), then the \( z \) has to be less than or equal to 0.145 in order to eliminate the disease under the ‘worst’ situation. Fig. 2 presents the critical values of the common treatment proportion, \( m^* \), for \( b_1 \in [1, 4] \) and \( b_3 \in [0, 1] \) with \( y = 0.5 \) and \( z = 0.14 \). The value of \( m^* \) increases with \( b_1 \) as well as with \( b_3 \), but is much more sensitive to \( b_3 \). Thus, it is recommended to obtain a good estimate of \( b_3 \). With currently available treatments, it is possible to reduce the progression rate by 50% (i.e., \( y = 0.5 \)), but there is little information about reduction of transmission rate. Although plasma HIV–RNA can be reduced to undetectable levels with HA-ART [18,19], it has not been determined how much the transmission rate may be reduced. It might be difficult to reduce this rate by 86% (i.e., \( z = 0.14 \)) as required. Additional intervention, e.g., using condoms, might be necessary to help in this context. Overall, depending on \( b_1 \) and \( b_3 \), treatment alone might not be able to eliminate the disease in this population.

4.3. With vaccination

To check the possibility of eradicating the epidemic by vaccination, we now consider an ideal situation with 100% of the newly recruited \( S_1 \)-individuals vaccinated, i.e., \( p_1 = 1 \). The minimum
values of vaccine impact, \( \phi^* \), required to have \( R_{0v} \leq 1 \) for \( p_2 \in [0, 1] \) under four different \((b_1, b_3)\) situations are plotted in Fig. 3. The \( \phi^* \) decreases as \( p_2 \) increases; that is, the more newly recruited \( S_2 \)-individuals are vaccinated, the smaller the vaccine impact is required. From economical point of view, a common vaccination proportion would be more appropriate if it is expensive to distinguish between \( S_1 \)- and \( S_2 \)-individuals before vaccination. For any given \( p_2 \), the order of the \( \phi^* \) under the four situations is ‘worst’ > ‘neutral’ > ‘intermediate’ > ‘best’; that is, the better the situation is, the smaller the vaccine impact and the less strength from the vaccines is required. Compared with the ‘neutral’ situation, the consideration of heterogeneity in transmission rate among infected groups may make the same vaccine more effective under the ‘best’ situation or less effective under the ‘worst’ situation. Under the most advantageous condition with \( p_1 = p_2 = 1 \) and the ‘best’ \( b_1 \) and \( b_3 \), we require a vaccine impact of \( \phi \geq \phi^* = 0.589 \), which may be reached by a vaccine with ‘take’ \( \epsilon = 0.95 \), efficacy \( \Psi = 0.95 \) and protection duration \( 1/\omega = 60 \) yr. Such vaccine is currently not available and will probably also not be in the future. The standard required for the vaccines is even higher if \( p_1 < 1 \) or \( p_2 < 1 \) or \( b_1 > 1 \) or \( b_3 > 0 \), all of which result in \( \phi^* > 0.589 \). Thus, vaccination alone does not seem to be able to eliminate the disease in this population.

4.4. With treatment and vaccination

Since either treatment alone or vaccination alone is not good enough to control the epidemic, we now consider to add vaccination to an existing treatment program with a common treatment proportion \( m = 0.8 \) and \( y = z = 0.4 \). With such treatment, we still have \( R_{0t} > 1 \), which is illustrated in Fig. 4 for given ranges of \( b_1 \) and \( b_3 \). As in \( R_{0t} \) and \( m^* \) (Fig. 2), \( R_{0t} \) is more sensitive to \( b_3 \) than to \( b_1 \). Similar to Fig. 3, the minimum values of vaccine impact, \( \phi^*_v \), required to have \( R_{0tv} \leq 1 \) with \( p_1 = 1 \) and \( p_2 \in [0, 1] \) under four different \((b_1, b_3)\) situations are plotted in Fig. 5. Again, the more newly recruited \( S_2 \)-individuals are vaccinated or the better the \((b_1, b_3)\) situation is, the smaller the vaccine impact is required. The consideration of heterogeneity in transmission rate among infected groups may make the same vaccine more effective under the ‘best’ situation or less effective under the ‘worst’ situation when compared with the ‘neutral’ situation. Under the most advantageous condition with \( p_1 = p_2 = 1 \) and the ‘best’ \( b_1 \) and \( b_3 \), we require \( \phi \geq \phi^*_v = 0.499 \), which may be reached by a vaccine with \( \epsilon = \Psi = 0.9 \) and \( 1/\omega = 51.3 \) yr.

If the treatment yields \( z = 0.2 \) instead of 0.4, then the situation is much better. The \( R_{0t} \) becomes much smaller, although still larger than unity (Fig. 6). The required minimum values of vaccine impact also become smaller, but in the same pattern (Fig. 7). Under the most advantageous condition with \( p_1 = p_2 = 1 \) and the ‘best’ \( b_1 \) and \( b_3 \), we require \( \phi \geq \phi^*_v = 0.195 \), which may be reached by a vaccine with \( \epsilon = \Psi = 0.8 \) and \( 1/\omega = 14 \) yr or a vaccine with \( \epsilon = \Psi = 0.7 \) and \( 1/\omega = 21.2 \) yr. The standard required for the vaccines is certainly lower than under vaccination alone, but still quite demanding.

5. Concluding remarks

We have presented a model accommodating heterogeneous susceptibility and rate of progression related to genotype of certain locus, and allowing one or both of the following intervention programs:
1. Certain proportions of newly recruited susceptible individuals who have no or only partial resistance to HIV to be immunized by vaccines with certain vaccine impact.

2. Certain proportions of newly infected individuals to be effectively treated by treatments inducing reduction in transmission rate and progression rate.

In agreement with [15], our results show that treatments which prolong the incubation period but do not reduce transmission rate at the same time may even enlarge the epidemic. In the example of gay men in San Francisco, we have observed that the limiting factor for the treatment to be effective in the population level is the treatment-induced reduction factor for the transmission rate and that the required treatment proportion is more sensitive to the transmission rate of slow progressors than to that of rapid progressors. We therefore suggest medical researchers to focus more on reducing transmission rates than on reducing progression rates when developing new treatments and to collect data for estimating the transmission rate of at least the slow progressors in addition to that of normal progressors. Compared with the ‘neutral’ situation with homogeneous transmission rate among infected groups, the consideration of heterogeneity in transmission rate may make the same treatment more effective under the ‘best’ situation or less effective under the ‘worst’ situation. If slow progressors have about the same transmission rate as the normal progressors ($b_1 \approx 1$) and rapid progressors have a very high transmission rate ($b_3 \approx 4$), then treatment alone might not be able to eliminate the disease in this population because the required treatment-induced reduction factor for the transmission rate is difficult to be reached.

Vaccination is helpful to slow down the spread of disease, but only highly efficacious and long-lasting vaccines have the potential to eradicate the epidemic. In the example of gay men in San Francisco, we have observed that the vaccine impact has to be at least 0.589 even under the most advantageous condition. It does not seem to be possible to eliminate the disease only with such program using potential vaccines. Compared with the ‘neutral’ situation, the consideration of heterogeneity in transmission rate may make the same vaccines more effective under the ‘best’ situation or less effective under the ‘worst’ situation. The combination of treatment and vaccination is a promising approach to controlling the epidemic. However, the treatments and vaccines still need to be of decent quality.

Possible extension to our model may take into account heterogeneous sensitivity to treatments, incomplete treatment due to patient refusal, drug resistance, additional treatments for patients at later disease stages, heterogeneous transmission rates during incubation period, repeated vaccination, change in pairing behavior after treatment or/and vaccination, etc. Some of these issues will be covered elsewhere.

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References