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A Mathematical Model of HIV Transmission in Homosexuals With Genetic Heterogeneity

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Several AIDS cohort studies observe that the incubation period between HIV infection and AIDS onset can be shorter than 3 years in about 10% seropositive individuals, or longer than 10 years in about 10–15% individuals. On the other hand, many individuals remain seronegative even after multiple exposures to HIV. These distinct outcomes have recently been correlated with some mutant genes in HIV co-receptors (e.g., CCR5,CCR2 and CXCR4). For instance, the mutant alleles Δ32 and m303 of CCR5 may provide full protection against HIV infection in homozygotes and partial protection in heterozygotes; moreover, infected heterozygotes may progress more slowly than individuals who have no mutant alleles. Frequencies of these mutant alleles are not very low in Caucasian populations, therefore, their effects may not be insignificant. Based on available data, we propose a one-sex model with susceptibles classified as having no, partial or full natural resistance to HIV infection, and infecteds classified as rapid, normal or slow progressors. Our goals are to investigate the impact of such heterogeneity on the spread of HIV and to identify key parameters. The basic reproductive number R_0 is derived from a simplified model. The relative contributions to R_0 from the three groups of infecteds are investigated. We present a rough estimating procedure making use of limited data to estimate some new parameters specific to our model. Finally the rough estimating procedure is applied to an example focusing on CCR5-Δ32 in San Francisco gay men. The relative contributions to R_0 among the three infected groups are compared using two different classifying criteria for infecteds. Under given assumptions, we conclude that, without any intervention, HIV infection will continue to spread in this population and the epidemic is mainly driven by the normal progressors. The transmission rates from infecteds are identified as key parameters.

Keywords: HIV, AIDS, mathematical model, R_0, homosexual, genetics, mutation, CCR5

1 INTRODUCTION

The studies of Sheppard, Lang and Ascher (1993) and Phair (1994) find that about 10–15% of HIV infected individuals remain AIDS free for 10 years or longer (non-progressors), while another 10% progress within the first 2–3 years (rapid progressors). On the other hand, many individuals remain seronegative even after multiple exposures to HIV from infected partners (Detels *et al.* 1994, Paxton *et al.* 1996, Fowke *et al.* 1996). These distinct outcomes pose an interesting question to HIV/AIDS researchers: What

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makes the difference? Genetic heterogeneity among individuals may contribute significantly. Several recent studies have demonstrated the protective effects of certain mutant genes on HIV infection or/and AIDS pathogenesis. For instance, Samson *et al.* (1996) show that a mutant allele, $\Delta 32$, of CCR5 chemokine receptor gene is present at a high frequency of 0.092 in Caucasian populations. The frequencies of homozygotes and heterozygotes for the mutation are about 1% and 16%, respectively. However, 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 $\Delta 32$ alleles are found. These observations suggest $\Delta 32$ may provide, at least partial, resistance to HIV-1 infection. Dean *et al.* (1996) report the same mutant allele with a similar frequency ($\sim$ 10%) in the Caucasian population of the United States. Their results indicate that the homozygotes with two $\Delta 32$ alleles may escape from HIV-1 infection and heterozygous infecteds may have a slower progression than other infecteds.

Recently Quillent *et al.* (1998) characterize another CCR5 gene mutation, m303, which is present among Europeans at an allele frequency of under 1%. Individuals with genotype m303/m303 or $\Delta 32$/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, Smith *et al.* (1997) describe a mutation, 64I, which occurs at an allele frequency of 10–15% among Caucasians and African Americans. Although this mutant gene dose not seem to provide protection against HIV-1 infection, it does indicate a 2–4 years delay of progression among infecteds. Moreover, the effects of CCR5-$\Delta 32$ and CCR2-64I on AIDS progression are determined as genetically independent. Among rapid progressors (AIDS onset less than 3 years since infection), about 38–45% do not have either of the two mutant alleles, $\Delta 32$ and 64I; while among non-progressors (avoid AIDS for 16 years or more), about 28–29% can be explained by a mutant allele in either gene.

In stromal-derived factor (SDF-1, the principal ligand for CXCR4), Winkler *et al.* (1998) also identify a gene variant, 3'A, that shows recessive restriction on AIDS pathogenesis. HIV infected individuals with SDF1–3'A/3'A (homozygous recessive) 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 SDF1 protection seem to be additive.

All the information above clearly indicates the existence of genetic heterogeneity with respect to susceptibility to HIV infection and to rate of AIDS progression in general populations. Such kind of heterogeneity has not been studied in the modeling literature. Our special interest in this paper is to investigate, using mathematical models, the impact of such heterogeneity on the spread of HIV and to identify key parameters. To accommodate the genetic heterogeneity on one side and being limited by data availability on the other side, we propose a deterministic one-sex model with susceptibles classified as having no, partial or complete resistance to HIV infection and infecteds as rapid, normal or slow progressors. The details of the general model are presented in Section 2. Under some simplifying assumptions, the basic reproductive number, R_0 (Diekmann *et al.* 1990), is obtained in terms of model parameters in Section 3. Based on the limited available information and scarce data, a rough estimation of some parameters is carried out in Section 4. In Section 5 the rough estimating procedure is applied to an example focusing on CCR5-$\Delta 32$ among gay men in San Francisco. The relative contributions to R_0 among the three infected groups are compared under two different classifying criteria for infecteds. Finally some concluding remarks are provided in Section 6.

2 MODEL DESCRIPTION

As the first step in our efforts to incorporate genetic heterogeneity in epidemiological models, we focus on the simplest possible scenario, i.e., a homosexually-active homogeneously-mixing population, to investigate the role of differential

susceptibility and pathogenesis in HIV infected populations.

Based on the level of natural resistance to HIV, susceptibles are classified into three groups: 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 AIDS pathogenesis, infecteds are classified into three groups: rapid progressor (I_1), normal progressor (I_2) and slow progressor (I_3). AIDS patients are assumed sexually inactive, thus they do not play a role in HIV transmission and are not included in our model. Throughout this paper, the index i refers to group of susceptibles and the index j to group of infecteds.

We assume that recruitment occurs at a constant rate, π, 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. Although genotype frequencies usually change with time due to random fluctuation or/and the disease, the frequencies in the homosexual population do not affect the frequencies among the newcomers, who are progeny of heterosexual populations. However, heterosexual populations are not included in our model and the dynamic of g_i is unknown. Hence, we assume, for convenience, that g_i are constant. Because frequencies of mutant alleles are relatively small, it is expected that

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

that is, a large fraction of individuals has no resistance, a small fraction has partial resistance, and an even smaller fraction has complete resistance.

All individuals are subject to the common per-capita natural removal rate, μ. The average number of partners per unit time is denoted by c_i ($i = 1, 2, 3$) for S_i-individuals and by d_j ($j = 1, 2, 3$) for I_j-individuals. The per-capita progression rates for I_j individuals are denoted by γ_j ($j = 1, 2, 3$). Because $1/\gamma_j$ is the average incubation time of I_j-individuals, it is obvious that

$$\gamma_1 > \gamma_2 > \gamma_3. \tag{2}$$

The infectiousness of I_j individuals is reflected by the per-partnership transmission rate, β_j ($j = 1, 2, 3$). We assume that rapid progressors (I_1) have the highest viral load, thus are most infectious; and that slow progressors (I_3) have the lowest viral load, thus are least infectious. More specifically, we hypothesize the following relation:

$$\beta_1 \geq \beta_2 \geq \beta_3. \tag{3}$$

It has been shown that the viral load and the infectiousness may change dramatically during the incubation period. However, to incorporate this fact we would need to keep track of the "age" of infection for each individual and end up with a complicated model. For the sake of simplicity, here we assume β_j are constant as in Anderson, Gupta and May (1991) and in McLean and Blower (1993).

During the partnership between an S_2-individual and an I_j-individual, the transmission rate β_j of the infected partner is reduced to $x_j\beta_j$, with $0 < x_j < 1$ to account for 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}, which satisfy

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

We expect the new infecteds who come from S_1 to generate a larger fraction of rapid progressors (I_1) and a smaller fraction of slow progressors (I_3) than those coming from S_2, that is,

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

Because we are looking at a homosexually active population, processes of pair formation and dissolution are not followed explicitly, instead, a proportional mixing pattern is assumed. The total number of sexual partnerships is defined as

$$\Lambda := \sum_{i=1}^{3} c_i S_i + \sum_{j=1}^{3} d_j I_j. \tag{6}$$

For a susceptible, given he pairs (i.e., forms a pair with an individual), the chance of pairing with an I_j-individual is $d_j I_j/\Lambda$ (Busenberg and Castillo-Chavez 1991). Thus, the force of infection for S_1-individuals is

$$\sigma_1 := \sum_{j=1}^{3} \beta_j d_j I_j/\Lambda, \tag{7}$$

and for S_2-individuals is

$$\sigma_2 := \sum_{j=1}^{3} x_j \beta_j d_j I_j / \Lambda. \tag{8}$$

Hence, the rate of new infections in S_i-individuals ($i = 1, 2$), or the incidence from S_i, is

$$\delta_i := c_i S_i \sigma_i. \tag{9}$$

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

$$\rho_j := \sum_{i=1}^{2} f_{ij} \delta_i, \tag{10}$$

called "birth" rate or the incidence of I_j. We denote the overall incidence by Ω as

$$\Omega := \sum_{i=1}^{2} \delta_i = \sum_{j=1}^{3} \rho_j, \tag{11}$$

where equality holds because of condition (4). We are now ready to present our mathematical model:

$$\begin{aligned}
\dot{S}_1 &= g_1 \pi - \mu S_1 - \delta_1 \\
\dot{S}_2 &= g_2 \pi - \mu S_2 - \delta_2 \\
\dot{S}_3 &= g_3 \pi - \mu S_3 \\
\dot{I}_1 &= \rho_1 - (\mu + \gamma_1) I_1 \\
\dot{I}_2 &= \rho_2 - (\mu + \gamma_2) I_2 \\
\dot{I}_3 &= \rho_3 - (\mu + \gamma_3) I_3
\end{aligned} \tag{12}$$

In order to make this model analytically tractable, some simplifications are required. A simplified model and the derived basic reproductive number are presented in the next section.

3 THE BASIC REPRODUCTIVE NUMBER

Most individuals do not know their genotypes at loci related to HIV susceptibility or/and AIDS pathogenesis, hence, it is reasonable to assume that genetic heterogeneity does not influence pairing behavior. The assumption that all individuals of a given disease status have the same average number of partners per unit time, i.e., $c_i = c$ for all i and $d_j = d$ for all j, is thus not too limiting. To make our model simpler, we further assume that disease status does not affect pairing behavior, i.e., $c = d$, as in Anderson, Gupta and May (1991) and McLean and Blower (1993). In addition, we reparameterize the transmission rates via $\beta := \beta_2$, or more specifically,

$$\beta_1 = b_1 \beta \text{ and } \beta_3 = b_3 \beta. \tag{13}$$

Relation (3) implies that the multipliers

$$b_1 \geq 1 \text{ and } b_3 \leq 1. \tag{14}$$

Currently there are no data that throw some light on whether or not the reduction factors x_j for β_j depend on j. To continue our goal of analyzing the simplest possible genetic-epidemiological model, we assume that $x_j = x$ for all j. Relevant variables can now be simplified as follows:

$$\Lambda = c \left(\sum_{i=1}^{3} S_i + \sum_{j=1}^{3} I_j \right); \tag{15}$$

$$\begin{aligned}
\sigma_1 &= c\beta \sum_{j=1}^{3} b_j I_j / \Lambda \\
&= \beta \sum_{j=1}^{3} b_j I_j \Big/ \left(\sum_{i=1}^{3} S_i + \sum_{j=1}^{3} I_j \right);
\end{aligned} \tag{16}$$

$$\sigma_2 = c\beta x \sum_{j=1}^{3} b_j I_j / \Lambda = x \sigma_1; \tag{17}$$

$$\delta_1 = c S_1 \sigma_1; \tag{18}$$

$$\delta_2 = c S_2 \sigma_2 = x c S_2 \sigma_1; \tag{19}$$

$$\rho_j = c \sigma_1 (f_{1j} S_1 + x f_{2j} S_2), \quad j = 1, 2, 3. \tag{20}$$

To study the potential of disease spreading, we shall compute the basic reproductive number, R_0 (Diekmann *et al.* 1990), which indicates whether a disease may invade a population in demographic steady state when there is no disease present. The computation is done by linearizing our system (12) around the disease-free state and looking for conditions that guarantee the growth of the three infected classes, I_j. The resulting 3-dimensional system is represented in the following form:

$$\dot{\mathbf{X}} = (\mathbf{M} - \mathbf{D})\mathbf{X}, \tag{21}$$

where

$$\mathbf{X} = \begin{bmatrix} I_1 \\ I_2 \\ I_3 \end{bmatrix}, \quad \mathbf{M} = c\beta \begin{bmatrix} b_1\tau_1 & \tau_1 & b_3\tau_1 \\ b_1\tau_2 & \tau_2 & b_3\tau_2 \\ b_1\tau_3 & \tau_3 & b_3\tau_3 \end{bmatrix},$$

$$\mathbf{D} = \begin{bmatrix} \mu+\gamma_1 & 0 & 0 \\ 0 & \mu+\gamma_2 & 0 \\ 0 & 0 & \mu+\gamma_3 \end{bmatrix}, \tag{22}$$

with

$$\tau_j = f_{1j}g_1 + xf_{2j}g_2. \tag{23}$$

The three eigenvalues of the matrix $\mathbf{MD}^{-1}$ are 0, 0 and λ, where

$$\lambda = c\beta\left\{\frac{b_1\tau_1}{\mu+\gamma_1} + \frac{\tau_2}{\mu+\gamma_2} + \frac{b_3\tau_3}{\mu+\gamma_3}\right\} \tag{24}$$

$$= K\{Q_1 + 1 + Q_3\} \tag{25}$$

with

$$K = c\beta\frac{\tau_2}{\mu+\gamma_2},$$

$$Q_1 = b_1\left(\frac{\mu+\gamma_2}{\mu+\gamma_1}\right)\left(\frac{\tau_1}{\tau_2}\right)$$

$$\text{and } Q_3 = b_3\left(\frac{\mu+\gamma_2}{\mu+\gamma_3}\right)\left(\frac{\tau_3}{\tau_2}\right). \tag{26}$$

Because all elements on the right hand side of (24) are positive, it is clear $\lambda > 0$. Therefore, λ is the dominant eigenvalue of $\mathbf{MD}^{-1}$, which is also referred to the basic reproductive number, R_0 (Diekmann *et al.* 1990). If $R_0 > 1$, then the disease will successfully invade. Hence, it is important to evaluate the relative contribution of each infected group, determined by b_j, τ_j and γ_j, to R_0. If $Q_1 < 1$ and $Q_3 < 1$, then the group of normal progressors, I_2, contributes the major part, K, to R_0. Under this situation, if $K > 1$, then certainly $R_0 > 1$, which implies the disease will spread; if $K < 1$, it may still be possible to have $R_0 > 1$ when K, Q_1 and Q_3 are not too small. The definitions of γ_j (2) and b_j (14) imply that, in Q_1, $b_1 \geq 1$ and $(\mu+\gamma_2)/(\mu+\gamma_1) < 1$. The third term τ_1/τ_2 may be larger or smaller than unity, depending on f_{ij}. Similarly in Q_3, $b_3 \leq 1$ and $(\mu+\gamma_2)/(\mu+\gamma_3) > 1$, while the third term τ_3/τ_2 is indeterminant. Overall, it is difficult to compare the magnitudes of Q_1 and Q_3 without knowing more precisely the values or ranges of the parameters involved. Further issues about R_0 are discussed in Section 5, where known values of most parameters are used.

4 ESTIMATION OF NEW PARAMETERS

Estimates of most social-demographic and biomedical parameters (e.g., per-capita natural removal rate, μ; recruitment rate, π; average number of partners per unit time, c; overall per-partnership transmission rate, β; and overall per-capita rate of progression, γ) are readily available in the literature. The additional parameters specific to our model include the distributing fractions (g_i) for newly accrued susceptibles, per-partnership transmission rates (β_j) and per-capita rates of progression (γ_j) for different infected groups, reduction factor (x) for β_j, and distributing fractions (f_{ij}) for newly infected individuals. The g_i can be estimated from allele or genotype frequencies. The definitions of rapid, normal and slow progressors should give some hints about γ_j. However, there is no direct information about β_j, x and f_{ij}. For the moment we treat β_j and x as free parameters. To have an educated guess at the values of f_{ij}, some "retrospective" information, like frequencies of protective genotypes among infecteds categorized by incubation duration (e.g., Figure 2 in Smith *et al.* 1997 and Figure 2(B) in Winkler *et al.* 1998), is used. Let h_{ji} denote the observed fraction of infecteds in I_j who were in S_i; that is, h_{ji} give "retrospective" information on f_{ij}. By definition, $\sum_{i=1}^{2} h_{ji} = 1$ for $j = 1, 2, 3$. The rough estimates of the fractions of rapid, normal and slow progressors, denoted respectively by q_1, q_2 and q_3 with $\sum_{j=1}^{3} q_j = 1$, among all infecteds are also available (e.g., Sheppard, Lang and Ascher 1993, Phair 1994 and Smith *et al.* 1997). The h_{ji} and q_j are usually estimated based on data cumulatively collected over long periods of time in cohort studies. They do not refer to prevalence nor to incidence, but may be viewed as "average" fractions for the given period of time. Using our simplified model together with some additional assumptions, we now show how the "retrospective" h_{ji} can be used to give an estimate of its "prospective" counterpart, f_{ij}.

First we let $\theta := S_2/S_1$. Since the majority of susceptibles are in S_1, it is expected that $0 < \theta < 1$. From expressions (11), (18) and (19), we obtain the following:

$$\delta_2 = x\theta\delta_1, \tag{27}$$

$$\Omega = (1 + x\theta)\delta_1. \tag{28}$$

The available h_{ij} and q_j are obtained from cohort studies where individuals did not become seropositive all at the same time. Moreover, the longitudinal patterns of h_{ji} and q_j are not known. To make rough use of these fractions, we assume that they are constant over time. This assumption helps relate them with the incidence associated with individuals who seroconverted at about the same time. With the given q_j, the incidence of I_j can be expressed as

$$\rho_j = q_j\Omega = q_j(1 + x\theta)\delta_1. \tag{29}$$

In our notation and under the above-mentioned assumption, the "retrospective" information about the incidence is described by

$$h_{j1} := \frac{f_{1j}\delta_1}{\rho_j} = \frac{f_{1j}}{q_j(1 + x\theta)}, \tag{30}$$

$$h_{j2} := \frac{f_{2j}\delta_2}{\rho_j} = \frac{f_{2j}x\theta}{q_j(1 + x\theta)}, \tag{31}$$

for $j = 1, 2, 3$. Rearranging the above equations, the f_{ij} can then be expressed as

$$f_{1j} = h_{j1}q_j(1 + x\theta), \tag{32}$$

$$f_{2j} = h_{j2}q_j(1 + x\theta)/x\theta. \tag{33}$$

Summing the above two equations over j and making use of condition (4), one obtains

$$1 = (1 + x\theta)\eta_1, \tag{34}$$

$$1 = \left(\frac{1 + x\theta}{x\theta}\right)\eta_2, \tag{35}$$

where

$$\eta_1 = \sum_j h_{j1}q_j \text{ and } \eta_2 = \sum_j h_{j2}q_j \tag{36}$$

are known quantities. Here the unknown quantity involving $x\theta$ can be evaluated by either

$$1 + x\theta = \frac{1}{\eta_1} \tag{37}$$

or

$$\frac{1 + x\theta}{x\theta} = \frac{1}{\eta_2} = \frac{1}{1 - \eta_1}. \tag{38}$$

Plugging the results of expressions (37) and (38) respectively into Equations (32) and (33) gives the required estimates for f_{ij}.

We are aware of a potential problem with this rough estimating procedure. The quantities η_1 and η_2 come from q_j and h_{ji} which are assumed constant over time. This assumption may result in strange behaviors. For instance, from expression (37) one obtains

$$x\theta = \frac{1}{\eta_1} - 1 = \frac{1 - \eta_1}{\eta_1}. \tag{39}$$

With constant x and η_1, Equation (39) implies θ should be constant as well, which is not true in general, but is true when the population is at equilibrium. However, when the population is not at equilibrium, the estimates of f_{ij} may still be reasonable if θ does not change much over time.

Although the above estimating procedure does not have a sound statistical base and depends on strong assumptions, it may provide sensible guesses, which may be useful especially under the current situation. Furthermore, it is important to note that, in some sense, this is the best that we can hope for given the fact that the available clinical data were not collected to address the questions raised by our model. Lack of data should not constrain the type of questions that may be raised. In fact, we hope that our model results may motivate the collection of the data required here. The application of this rough estimating procedure will be illustrated in the following example.

5 EXAMPLE

We choose the population of gay men in San Francisco as target with the focus on the mutation CCR5-Δ32 to illustrate the estimating procedure for f_{ij} as

well as to assess the relative contributions of the three infected groups to R_0. Whenever possible, we take parameter values specific for this population; otherwise we take values from other Caucasian AIDS cohorts.

As in McLean and Blower (1993), we use $1/\mu = 32$ years, $\pi = 2000$/year and $1/\alpha = 5/3$ years. As for the value of βc, because normal progressors are the majority in the infected population, we assume $\beta_2 c$ can be described by the parameter values estimated for the whole infected population, e.g., $\beta_2 c = \beta c = 0.62$/year. No information about β_1 and β_3, or equivalently about b_1 and b_3, is available, thus they are considered as free parameters. According to data on homosexually active men in the San Francisco City Clinic Cohort (SFCC) presented in Dean *et al.* (1996, Table II), the frequencies of the three genotypes are estimated as $g_1 = 0.75$, $g_2 = 0.23$ and $g_3 = 0.02$. Based on pooled data of Caucasians in five AIDS cohorts (including SFCC) presented in Smith *et al.* (1997, Figure 3), we define that rapid progressors have an incubation time of less than 3.5 years, slow progressors of more than 13 years, and normal progressors of in between 3.5 and 13 years; i.e., $1/\gamma_1 < 3.5$ years, 3.5 years $\leq 1/\gamma_2 \leq 13$ years and $1/\gamma_3 > 13$ years. Accordingly we choose $\gamma_1 = 1/2$, $\gamma_2 = 1/8$ and $\gamma_3 = 1/16$ as an educated reasonable guess. When the AIDS criterion of 1993 is applied to these data (top panel in Figure 3 of Smith *et al.* 1997), the fractions of these three groups are approximated by $q_1 = 0.115$, $q_2 = 0.645$ and $q_3 = 0.240$, and the within group distributions are approximated by $h_{11} = 0.89$, $h_{12} = 0.11$, $h_{21} = 0.81$, $h_{22} = 0.19$, $h_{31} = 0.72$ and $h_{32} = 0.28$. These values are only approximations due to three reasons: 1) they are estimated from a figure, not directly from counts; 2) this figure is constructed based on pooled data of five AIDS cohorts; and 3) in the figure CCR2-64I mutation is also considered in addition to CCR5-Δ32 mutation. However, these are the best approximations that we can get from published, aggregated data. We note that the frequency of heterozygotes in two European cohorts of seropositive Caucasians is 35% lower than in the general populations (Samson *et al.* 1996). Hence, we select the value of $x = 1 - 0.35 = 0.65$.

With the above values of q_j and h_{ji} the η_1 in (36) is calculated as 0.799, resulting in $(1 + x\theta) = 1.254$. Using (32) and (33), we obtain $f_{11} = 0.128$, $f_{12} = 0.655$, $f_{13} = 0.217$, $f_{21} = 0.063$, $f_{22} = 0.605$ and $f_{23} = 0.332$. These fractions look reasonable and satisfy conditions (4) and (5). Together with other parameters, the magnitude of R_0 and relative contributions from the three infected groups can be assessed using (25). Because the value of x is suggested from geographically distinct populations, we decide to treat x first as a free parameter and then take the value of 0.65 for further investigation.

As shown in Figure 1, the relative contribution of rapid progressors, Q_1, is rather small, ranging between 0.05 and 0.23 with $b_1 \in [1, 4]$ and $x \in (0, 1)$, and is more sensitive to b_1 than to x. The upper bound of b_1 is chosen for illustrative purpose. With $b_3 \in (0, 1]$ and $x \in (0, 1)$,the relative contribution of slow progressors, Q_3, is mostly larger than Q_1, but still less than unity with a range between 0 and 0.63. As can be seen from Figure 2, the value of Q_3 is also more sensitive to b_3 than to x. Because $Q_1 < 1$ and $Q_3 < 1$, the normal progressors contribute the most to R_0, with K evaluated by

$$K = 1.949 + 0.552x. \tag{40}$$

For $0 < x < 1$, we obtain $1.95 < K < 2.50$, which "guarantees" the disease will continue to spread in this population.

When x is fixed at 0.65, the magnitude of R_0 for different values of b_1 and b_3 can be calculated using (25) as follows:

$$R_0 = 2.308(0.053b_1 + 1 + 0.609b_3), \tag{41}$$

which is also plotted in Figure 3. Because the coefficient of b_3 is about 11.5 times of that of b_1, R_0 is much more sensitive to value of b_3 than to b_1. With $b_1 \in [1, 4]$ and $b_3 \in (0, 1]$, we obtain $0.053 \leq Q_1 \leq 0.212$ and $0 < Q_3 \leq 0.609$, which are clearly less than unity. Hence, the normal progressors gives the major contribution to R_0 with $K = 2.308 > 1$ (this fact is generally true for $x \in (0, 1)$ as presented in (40)). The resulting range of R_0 is between 2.43 and 4.20. When $b_1 = 1$ and $b_3 = 1$, we obtain $R_0 = 3.84$ with $Q_1 = 0.053 < Q_3 = 0.609$; while when $b_1 = 4$ and

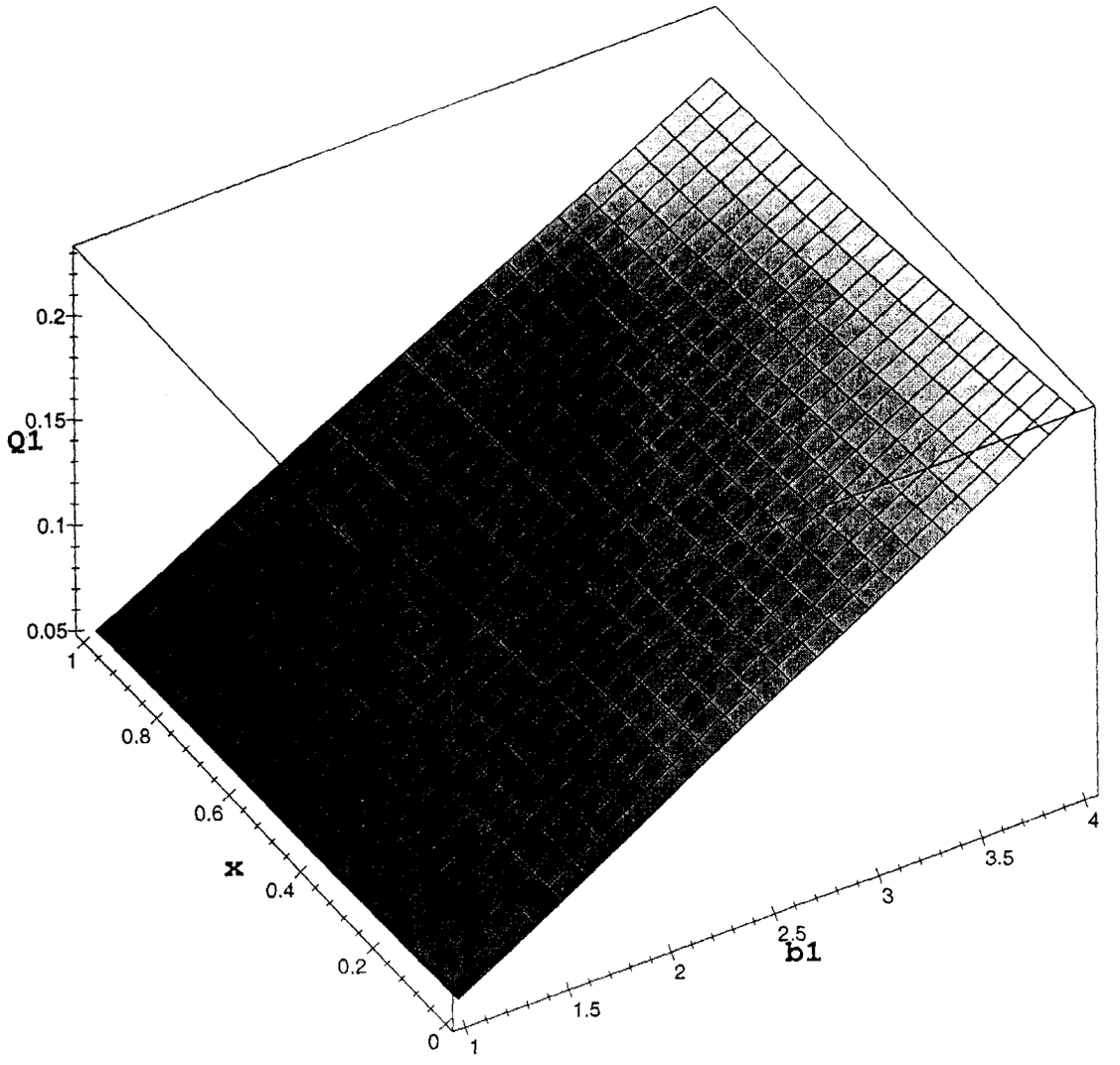

FIGURE 1 Relative contribution to basic reproductive number, R_0, from the rapid progressors, Q_1, as a function of the corresponding multiplier of reference transmission rate, b_1, and the reduction factor for the per-partnership transmission rate, x.

$b_3 = 0.25$, $R_0 = 3.15$ with $Q_1 = 0.212 > Q_3 = 0.152$. Thus, depending on the values of b_1 and b_3, the relative contribution of rapid progressors may be smaller or larger than that of slow progressors.

The way we classify rapid, normal and slow progressors based on incubation period in the above example is somehow arbitrary. However, there does not seem to be a standard classification presented in the literature. To investigate the effects of the classification, we now repeat the same evaluation with a different cut-off value, $\geq$16 years, for slow progressors. More specifically, we define rapid progressors as before, but slow progressors have an incubation period of at least 16 years, and thus normal progressors lie between 3.5 and 16 years. The new values for the rates of progression are chosen as $\gamma_2 = 1/10$ and $\gamma_3 = 1/18$. The relevant fractions approximated from Smith *et al.* (1997, Figure 3) are $q_2 = 0.845$, $q_3 = 0.040$, $h_{21} = 0.79$, $h_{22} = 0.21$, $h_{31} = 0.77$ and $h_{32} = 0.23$. The prospective fractions are calculated as $f_{11} = 0.128, f_{12} = 0.834, f_{13} = 0.038$, $f_{21} = 0.063$, $f_{22} = 0.890$ and $f_{23} = 0.047$, which again

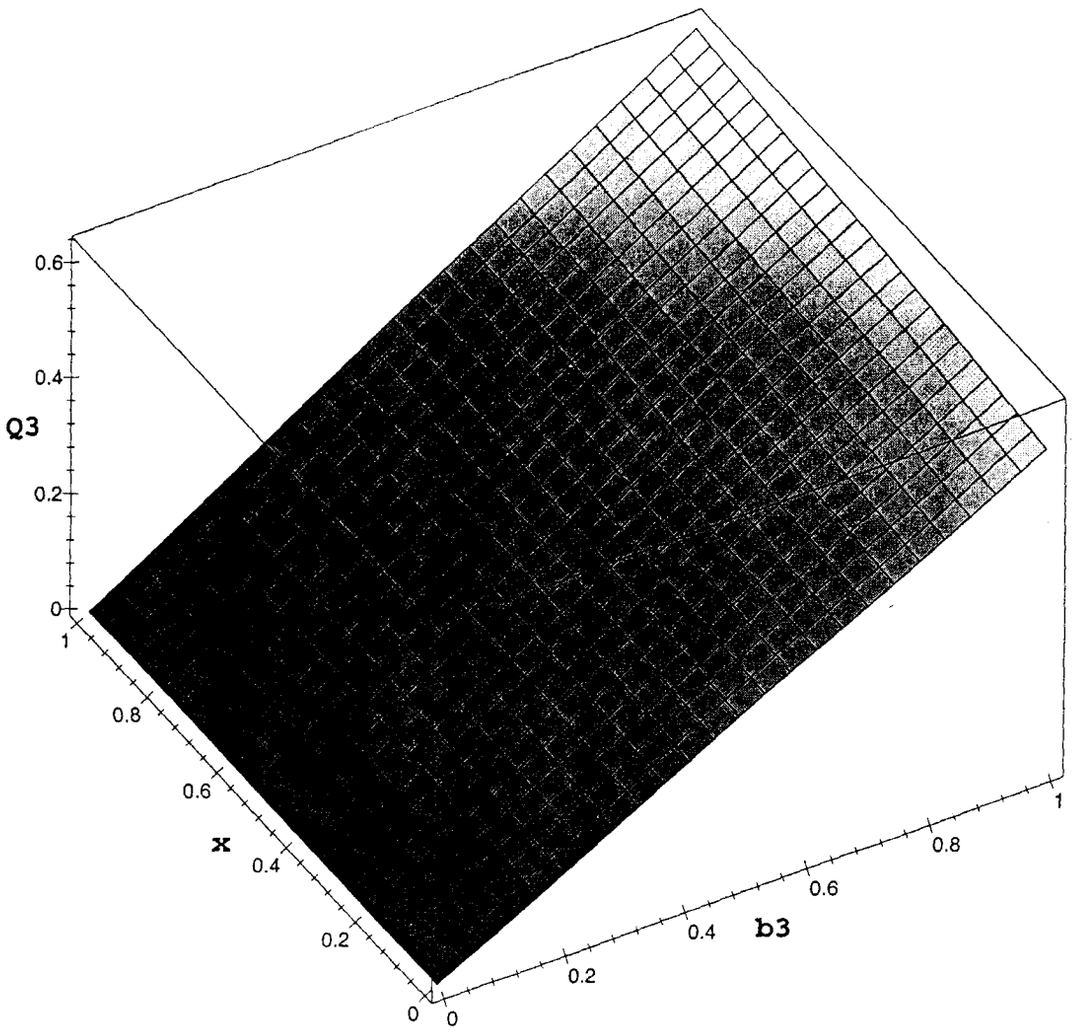

FIGURE 2 Relative contribution to basic reproductive number, R_0, from the slow progressors, Q_3, as a function of the corresponding multiplier of reference transmission rate, b_3, and the reduction factor for the per-partnership transmission rate, x.

satisfy conditions (4) and (5). When x is fixed at 0.65, the magnitude of R_0 for different values of b_1 and b_3 can be calculated by the following formula:

$$R_0 = 3.583(0.034b_1 + 1 + 0.071b_3), \qquad (42)$$

which is also more sensitive to b_3 than to b_1; however, the coefficient of b_3 is only about 2 times of that of b_1. With $b_1 \in [1, 4]$ and $b_3 \in (0, 1]$, we obtain $0.034 \leq Q_1 \leq 0.136$ and $0 < Q_3 \leq 0.071$, which are clearly less than unity. Moreover, Q_1 and Q_3 here are smaller than the earlier evaluation due to larger f_{12} and f_{22} in τ_2 and a smaller γ_2. For Q_3 the additional influence comes from much smaller f_{13} and f_{23} in τ_3 and a smaller γ_3. The contribution to R_0 from normal progressors is $K = 3.583$, which is larger than the $K = 2.308$ in the earlier evaluation also due to larger f_{12} and f_{22} in τ_2 and a smaller γ_2. The value of R_0 ranges between 3.70 and 4.32, which is also larger than the earlier evaluation. When $b_1 = 1$ and $b_3 = 1$, we obtain $R_0 = 3.96$ with $Q_1 = 0.034 < Q_3 = 0.071$; while when $b_1 = 4$ and $b_3 = 0.25$, $R_0 = 4.14$ with $Q_1 = 0.137 > Q_3 = 0.018$. As before, the relative magnitude between Q_1 and Q_3 depends on the values of b_1 and b_3.

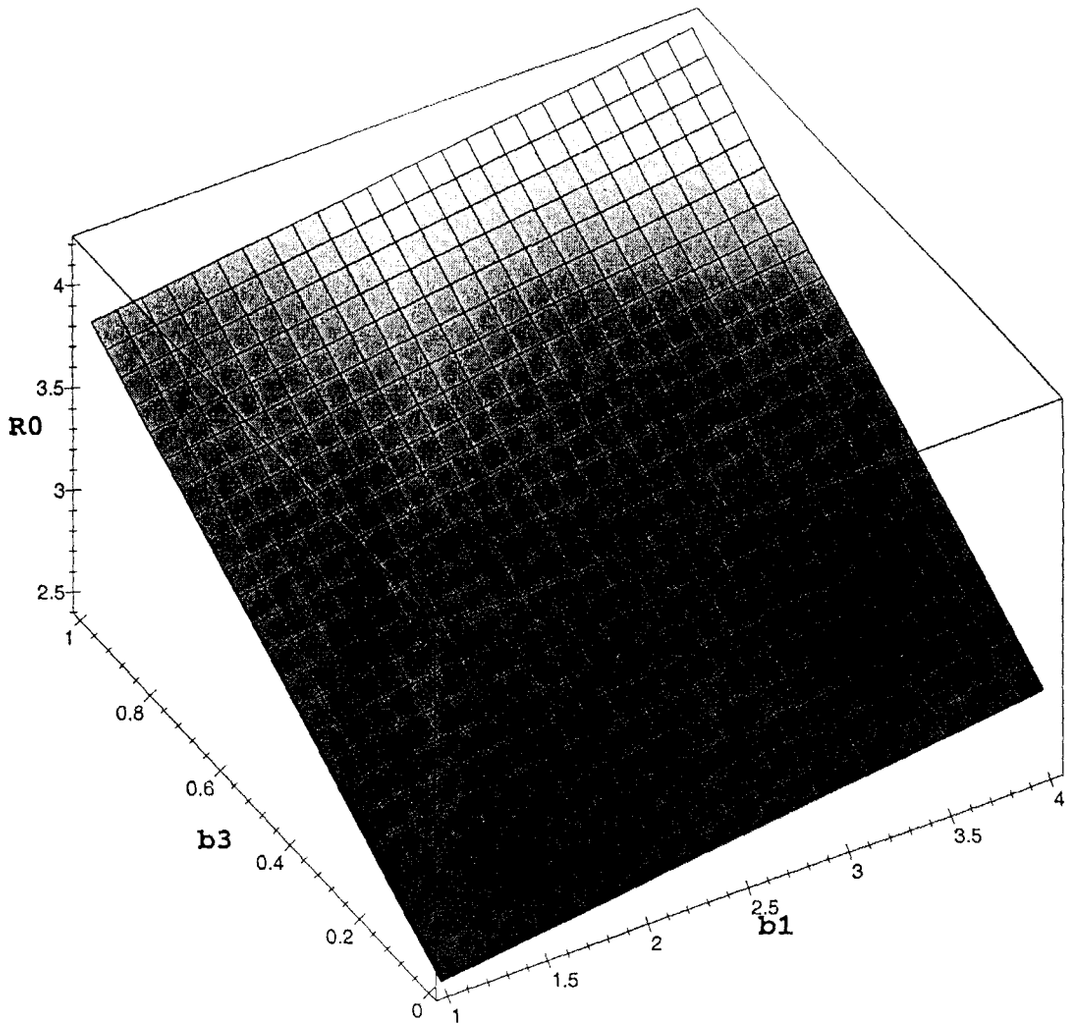

FIGURE 3 Basic reproductive number, R_0, as a function of the multipliers of reference transmission rate, b_1 and b_3, with the reduction factor for the per-partnership transmission rate, $x = 0.65$.

6 CONCLUDING REMARKS

We have presented a novel model to incorporate genetic heterogeneity into HIV / AIDS epidemiology. The basic reproductive number for this model has been derived and the relative contributions from different infected groups have been discussed. Because published data are limited, values of some parameters are not available and have to be estimated in a rough way. Our rough estimating procedure for distributing fractions of infecteds, f_{ij}, has provided reasonable estimates in the above example. To improve the accuracy of this estimation, data collected in a prospective manner, e.g., keeping track of how many S_i individuals become I_j individuals, would be very helpful. However, it may take a long time and a lot of efforts to observe a sufficient number of new infection cases and follow them until AIDS onset. The alternative is to develop more sophisticated estimating procedures to make use of the retrospective data.

Among the three free parameters, i.e., x, b_1 and b_3, the basic reproductive number R_0 for the homosexual population in San Francisco seems to be more

sensitive to factors of transmission rates, b_1 and b_3, than to the reduction factor, x. Therefore, more efforts should be devoted to the estimation of b_j, or equivalently the transmission rates β_j. When $x = 0.65$, the value of R_0 lies between 2.43 and 4.32, depending on classifying criterion for infecteds and values of b_1 and b_3. Anyway, it clearly indicates that HIV infection will continue to spread in this population and the major contribution to R_0 is from the normal progressors, who are the majority among infecteds. This implies HIV prevention and treatment interventions should certainly include this major group. Further investigation on effects of treatment and vaccination in this population will be published elsewhere (Hsu Schmitz 1999). The relative contribution from rapid progressors may be smaller or larger than that from slow progressors, again depending on classifying criterion for infecteds and values of b_1 and b_3. A standard classifying criterion for infecteds will be welcomed and is awaited, so we will have less confusion when several studies are compared.

The estimation and evaluation applied to the example are mainly for illustrative purpose. The assumptions required by the model and the rough estimating procedure might not all be satisfied in the example population. For instance, the fractions q_j and h_{ji} might not be constant. Furthermore, treatment is commonly used in this population in recent years. Our model without considering treatment effects might not reflect the real epidemic. However, the main purposes of this exercise are: 1) to motivate clinical researchers to collect required data (e.g., γ_j, β_j, x and f_{ij}) and to standardize the classifying criterion for infecteds; and 2) to identify key parameters, e.g., b_1 and b_3.

In our model infecteds coming from S_1 and those from S_2 are pooled together. It would be more informative, and probably also more realistic, to have three infected groups specifically for S_1-individuals and another three infected groups for S_2-individuals. However, this will give three equations more in the model and make the analysis and interpretation more difficult. Moreover, this requires additional parameters to be estimated from more detailed data, which are not readily available.

As mentioned in the Introduction, there are several mutant alleles of different loci related to susceptibility to HIV or/and rate of progression to AIDS. Thus, it may be more appropriate to consider a combined locus accommodating several relevant loci, instead of focusing on a single locus. For instance, Smith *et al.* (1997) combine the CCR5 locus and the CCR2 locus into a compound locus. More data should also be collected to cover this aspect.

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