Title
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Transient decreases in the proportion of individuals newly infected with an HIV-resistant virus (primary resistance) are documented for several cities of North America, including San Francisco. Using a staged SI deterministic model, we identified three potential causes consistent with the history of the epidemic: 1) increase in risky behavior, 2) reduction in the proportion of HIV-acutely infected individuals undergoing treatment, and 3) replacement of mono- and dual-drug therapies with triple-drug therapies. Although observed patterns resemble scenario 1 most closely, these explanations are not mutually exclusive and may have contributed synergistically to the decline. Under scenario 1 the counterintuitive situation arises where, although the proportion of primary resistance cases decreases transiently, the epidemic worsens because the actual numbers of infected individuals and of drug resistance carriers increases. Our results call for improved efforts to control the epidemic in developed nations, and highlight the usefulness of drug resistant strains as epidemiological markers.

1. INTRODUCTION

The acquisition of drug resistance by microorganisms arguably poses the biggest challenge in the fight against infectious diseases (Cohen, 2002; Velasco-Hernandez *et al.*, 2002). HIV drug-resistant strains not only limit treatment options for a particular patient, but also can be transmitted to other individuals thus creating both a clinical and an epidemiological health concern (Hirsch *et al.*, 1998; Wainberg and Friedland, 1998). Both increasing (Porter *et al.*, 2001; Grant *et al.*, 2002; Little *et al.*, 2002) and decreasing (Goudsmit *et al.*, 2001; Yerly *et al.*, 2001; Ammaranond *et al.*, 2003b) trends in the proportion of people recently infected with a drug-resistant HIV strain (primary resistance) have been observed. Interestingly, Grant and collaborators (2002) report a transient decrease in primary resistance to nucleoside reverse transcriptase inhibitors (NRTI) in the period ranging from 1997 to 1999 in San Francisco, while Little *et al.* (2002) report a transient decrease in NRTI and non-nucleoside reverse transcriptase inhibitors (NNRTI) primary resistance from 1996 to 1998 in a broad sample from North America. In both studies this decrease is followed by an increasing trend and subsequent decrease in primary resistance to NRTIs (Little *et al.*, 2002; Grant *et al.*, 2003). Although these trends could be consistent with a steady rise in primary resistance (Blower *et al.*, 2000; Porter *et al.*, 2001; Little *et al.*, 2002; Blower *et al.*, 2003), they may represent a real decrease signaling that the problem of drug resistance is being solved due to reduced transmission of resistant strains because of less risky activity, and/or diminished viremia in individuals undergoing treatment. On the other hand, the fraction of individuals with primary resistance could also decline due to a relative increase in drug sensitive cases over drug resistant cases. HIV is a non-reportable disease in North America, and thus precise information on the absolute numbers of individuals in the different disease categories is often absent. As we illustrate below, this can obscure the real cause of the observed changes in the prevalence of primary resistance.

Here we formulate a mathematical model of HIV transmission dynamics and drug resistance in order to explore the determinants of the *proportion of primary resistant to non-resistant cases*. We identify three plausible scenarios, consistent with the history of the HIV

epidemic in North America, that can generate decreases in the proportion of primary resistant cases: 1) overall increase in risky behavior, 2) reduction in the proportion of newly infected individuals undergoing drug therapy, and 3) replacement of ineffective drug treatments with more effective treatment strategies (e.g., from mono- and dual therapies to triple-drug therapies). These explanations are not mutually exclusive, and may have acted synergistically to create the trends observed. Moreover, we also investigate how the overall *prevalence of the disease* and the overall *prevalence of individuals infected with a virus resistant to treatment* respond to these three potential causes for a decrease in primary resistance. We discuss which scenario is the most likely to produce the observed trends, as well as the overall implications for the epidemic in countries with a concordant history of antiretroviral treatment.

2. MODEL DESCRIPTION

We formulated differential equations that specify the number of individuals flowing into and out of infection, disease, treatment, and drug resistance states (see below). We defined the minimum number of categories and flows that represent the key states and processes relevant to the data reported in Grant *et al.* (2002) and Little *et al.* (2002) on primary resistance trends (Table 1, Fig. 1, and Appendix A). Susceptible uninfected individuals become infected at a rate determined by the proportion of infected individuals in each category and their corresponding contact rate, in accordance with proportionate mixing (Hethcote and Van Ark, 1987; Koopman *et al.*, 1988; Castillo-Chavez *et al.*, 1989; Lloyd-Smith *et al.*, 2004). Individuals progress through the stages based on the natural progression of the disease and/or on the treatment provided. We distinguished between acute (i.e. newly infected) and chronic HIV+ individuals because the former have: 1) higher viral loads and hence are more likely to transmit the disease (Quinn *et al.*, 2000; Yerly *et al.*, 2001), and 2) are more likely to be unaware of their HIV status and engage in risky behavior (de Mendoza *et al.*, 2002). We introduced structures to consider the effects of different treatments either in isolation (case 1) or when applied sequentially in time (case 2). The unit of time is 1 year (Longini *et al.*, 1989;

Fig. 1

Table 1

4

Hethcote and Van Ark, 1992). We assume the viral population of infected individuals becomes suppressed (e.g., <500 copies/mL, Grant *et al.*, 2002) when first placed on treatment, but drug resistance is eventually generated and transmitted according to the efficacy of the treatment provided (Bonhoeffer and Nowak, 1997; Pillay *et al.*, 2000; Phillips *et al.*, 2001). In the unlikely event that a suppressed individual infects a susceptible one, it transmits wild type (the non-resistant strain) unless its original viral population prior to treatment was resistant (case 2), in which case it transmits the resistant strain. We have ignored the possibility that an infected individual can acquire a new viral strain when coming into contact with another infected individual, because this has been only been documented on an anecdotal basis (Ramos *et al.*, 2002; Koelsch *et al.*, 2003) and did not occur in cohorts of chronically infected persons (Gonzales *et al.*, 2003; Tsui *et al.*, 2004). We used Berkeley Madonna® for our numerical simulations, with the initial condition of one acutely infected individual in a population of constant influx 10,000.

2.1. *Shared flows between cases 1 and 2.* The pool of potential HIV transmitters is replenished with a continuous flow (Λ) to account for those individuals leaving the pool because of natural (μ) or disease-induced (α) removal processes. Upon risky contact with an infected individual (*c*), a susceptible can become HIV infected with probability β. We assume all individuals in the acute phase do not suffer from an additional disease removal rate above that of the background mortality, and that they progress to the corresponding chronic untreated stage after 4 months (ρ). Every year a certain fraction of untreated individuals are placed on treatment (θ); in this case acute individuals progress instantaneously to the corresponding chronic treated stage.

2.2. *Case 1: Epidemic with One Drug Therapy.* To best understand how levels of primary resistance are affected by changes in specific processes independently of treatment history, we investigated what occurs when only one kind of therapy is administered. The population is structured into 7 different categories (Table 1a, Fig. 1a). Individuals undergoing treatment and whose viral population is suppressed may stop treatment because of, for example, negative side effects, and become untreated susceptible individuals (Y_ε^T transfer to Y_s^U at rate

5

δ_ε^T). A resistant viral population will not be suppressed when exposed to treatment, so individuals under therapy are more likely to stop treatment if they are resistant *vs.* sensitive carriers (Y_R^T transfer to Y_R^U at rate δ_R^T, where $\delta_R^T > \delta_\varepsilon^T$). The high mutability of HIV determines that individuals on treatment can develop a predominantly drug resistant viral population even when under a multidrug therapy (Y_ε^T transfer to Y_R^T at rate η), and also that untreated resistant individuals may eventually have their viral population replaced by wild type (Y_R^U transfer to Y_S^U at rate σ). We assume only one kind of resistant strain can develop from the sensitive wild type virus (incorporating several strains will confound rather than clarify the question addressed here).

We track the temporal dynamics of this case with the following set of differential equations (for simplicity we use the indicator function $1_i = 1$ to imply the term is 1 when $i = 1$ and 0 otherwise, while $1_i > 1$ implies the term is 0 when $i = 1$ and 1 otherwise):

$$\frac{dX}{dt} = \Lambda - \left[\lambda_S(t) + \lambda_R(t) + \mu \right] X$$

$$\frac{d\tilde{Y}_S^U}{dt} = \lambda_S(t) X - (\rho + \tilde{\theta}_S^U(t) + \mu)\tilde{Y}_S^U$$

$$\frac{d\tilde{Y}_R^U}{dt} = \lambda_R(t) X - (\rho + \tilde{\theta}_R^U(t) + \mu)\tilde{Y}_R^U$$

$$\frac{dY_{i,S}^U}{dt} = \rho \tilde{Y}_S^U 1_{i=1} + \delta_\varepsilon^T Y_{i,\varepsilon}^T + \sigma Y_{i,R}^U - (\theta_S^U + \mu)Y_{i,S}^U + \gamma_S^U \left(Y_{i-1,S}^U 1_{i>1} - Y_{i,S}^U \right)$$

$$\frac{dY_{i,R}^U}{dt} = \rho \tilde{Y}_R^U 1_{i=1} + \delta_R^T Y_{i,R}^T - (\theta_R^U + \sigma + \mu)Y_{i,R}^U + \gamma_R^U \left(Y_{i-1,R}^U 1_{i>1} - Y_{i,R}^U \right)$$

$$\frac{dY_{i,R}^T}{dt} = \tilde{\theta}_R^U(t) \tilde{Y}_R^U 1_{i=1} + \theta_R^U Y_{i,R}^U + \eta Y_{i,\varepsilon}^T - (\delta_R^T + \mu)Y_{i,R}^T + \gamma_R^T \left(Y_{i-1,R}^T 1_{i>1} - Y_{i,R}^T \right)$$

$$\frac{dY_{i,\varepsilon}^T}{dt} = \tilde{\theta}_S^U(t) \tilde{Y}_S^U 1_{i=1} + \theta_S^U Y_{i,S}^U - (\delta_\varepsilon^T + \eta + \mu)Y_{i,\varepsilon}^T + \gamma_\varepsilon^T \left(Y_{i-1,\varepsilon}^T 1_{i>1} - Y_{i,\varepsilon}^T \right),$$

where $i = 1 \ldots n$ represents the stage number ($n = 10$, see below) and $\gamma_k^l = n\alpha_k^l$ (k = drug resistant status of viral population of an infected individual and l = treatment status of an infected individual, see Table 1). The drug sensitive and resistant forces of infection are, respectively:

$$\lambda_S(t) = \tilde{c}(t)\left[\tilde{c}(t)\tilde{\beta}_S^U \tilde{Y}_S^U + c(t)\left(\beta_S^U Y_S^U + \beta_\varepsilon^T Y_\varepsilon^T \right) \right] / w(t)$$

and

$$\lambda_R(t) = \tilde{c}(t)\left[\tilde{c}(t)\tilde{\beta}_R^U\tilde{Y}_R^U + c(t)\left(\beta_R^U Y_R^U + \beta_R^T Y_R^T\right)\right]/w(t),$$

where chronic categories represent the summation over all 10 stages (e.g., $Y_k^l = \sum_{i=1}^{10} Y_{i,k}^l$). The

weighted partnership frequency of the total population $w(t)$ is:

$$w(t) = \tilde{c}(t)(X + \tilde{Y}_S^U + \tilde{Y}_R^U) + c(t)(Y_S^U + Y_R^U + Y_R^T + Y_\varepsilon^T)$$

when we assume proportionate mixing. The rate at which individuals within a given category

initiate θ_k^l or stop treatment δ_k^l is a function of the fraction of individuals that are placed on

(F_{on}) or off (F_R^T , F_ε^T) treatment, respectively, together with the sum of the remaining

outflow rates $\left(\sum\Omega_k^l\right)$ of each particular state variable (Blower *et al.* 2000):

$$\theta_k^l = \frac{F_{on}\sum\Omega_k^l}{\left(1-F_{on}\right)} \qquad \text{and} \qquad \delta_k^l = \frac{F_{off}\sum\Omega_k^l}{\left(1-F_{off}\right)}.$$

The definition holds for both acutely and chronically infected categories. In the staged model

we present here (see below) we retained α in our calculation of treatment rates in order to

preserve consistency with its non-staged counterpart. For example, the summation of all the

outflow rates for the susceptible untreated individuals in the chronic phase of the disease Y_S^U

is $\sum\Omega_S^U = \alpha_S^U + \mu$, while that of suppressed treated individuals Y_ε^T is $\sum\Omega_\varepsilon^T = \eta + \alpha_\varepsilon^T + \mu$.

Under this one drug therapy scenario we conducted a systematic investigation to

determine how alterations to all the processes accounted for in our model affected the

dynamics of the primary resistant fraction. We scanned through reasonable changes to a set

of baseline parameter values representative of those published in the literature or based on

expert opinion (Anderson, 1989; Harrigan *et al.*, 1998; Blower *et al.*, 2000; Omrani and

Pillay, 2000; Pillay *et al.*, 2000; Bleiber *et al.*, 2001; Brenner *et al.*, 2002). We identified two

processes that could account for the observed decreases in the proportion of individuals

exhibiting primary resistance: 1) increase in risky behavior, and 2) decrease in the fraction of

individuals treated in the acute phase.

Treatment is initiated at the very start of the epidemic. For clarity, we only graph trajectories once the system has reached steady state. We then introduce a perturbation at time t=10 years. In any case, our simulations (not shown) indicate that the system responds in the same qualitative way when perturbed before it reaches steady state. The parameters values used for results reported in Figs. 2a-c and 3 (see below) are representative of HAART (Omrani and Pillay, 2000; Cohen, 2002): $\tilde{\beta}_S^U = 0.5$; $\tilde{\beta}_R^U = 0.25$; $\beta_S^U = 0.1$; $\beta_R^U = 0.06$; $\beta_R^T = 0.03$; $\beta_\varepsilon^T = 0.001$; $F_{on} = 0.4$; $F_R^T = 0.2$; $F_\varepsilon^T = 0.1$; $\rho = 3$; $\eta = .125$; $\sigma = 12$; $\alpha_S^U = 0.08$; $\alpha_R^U = 0.06$; $\alpha_R^T = 0.04$; $\alpha_\varepsilon^T = 0.033$; $\mu = 0.033$. In Appendix B we describe further explorations into the system's dynamics. We compared results: 1) of monotherapy with AZT (Lukashov *et al.*, 2000) with those for HAART (main text), and 2) when all individuals have the same contact rate regardless of their infection status, with that where uninfected and acute individuals have higher contact rates than those in the chronic stage (main text).

2.3. *Case 2: Epidemic with Two Sequential Drug Therapies.* A change in treatment efficacy was the third likely process causing a decrease in the proportion of acute individuals infected with a resistant virus. We expanded the previous model to include two submodels with the same structure as case 1, where acute and chronic untreated susceptible categories ($\tilde{Y}_S^U$ and Y_S^U) were shared for a total of 12 categories (Table 1b, Fig. 1b). Each submodel represents one of the two different drug therapy strategies. The time frames at which we apply each treatment correspond roughly to those of the HIV epidemic in San Francisco: at 30 years we introduced monotherapy with AZT (M), and at 40 years we stopped M and administered exclusively HAART (H). Accordingly, all individuals on M changed to H at a very fast rate ω at time 40: those suppressed continued being suppressed (Y_ε^M transfer to Y_ε^H), while those resistant to M became suppressed but maintained a viral population resistant to M (Y_M^M transfer to $Y_{\varepsilon M}^H$, which can potentially transmit the strain resistant to M). A $Y_{\varepsilon M}^H$ could either develop resistance to H and become an individual treated with H but not suppressed ($Y_{\varepsilon M}^H$ transfers to Y_H^H at rate η_M^H), or stop therapy before resistance to H developed (and transfer to Y_M^U at rate $\delta_{\varepsilon M}^H$). A susceptible viral population exposed to AZT or HAART developed drug resistance according to the efficacy of the treatment (at rates η^M and η^H, respectively).

The set of differential equations defining this second case are:

$$\frac{dX}{dt} = \Lambda - \left[\lambda_S(t) + \lambda_M(t) + \lambda_H(t) + \mu\right] X$$

$$\frac{d\tilde{Y}_S^U}{dt} = \lambda_S(t) X - \left(\rho + \tilde{\theta}_S^M + \tilde{\theta}_S^H + \mu\right)\tilde{Y}_S^U$$

$$\frac{d\tilde{Y}_M^U}{dt} = \lambda_M(t) X - \left(\rho + \tilde{\theta}_M^M + \tilde{\theta}_M^H + \mu\right)\tilde{Y}_M^U$$

$$\frac{d\tilde{Y}_H^U}{dt} = \lambda_H(t) X - \left(\rho + \tilde{\theta}_H^H + \mu\right)\tilde{Y}_H^U$$

$$\frac{dY_{i,S}^U}{dt} = \rho \tilde{Y}_S^U 1_{i=1} + \delta_\varepsilon^M Y_{i,\varepsilon}^M + \delta_\varepsilon^H Y_{i,\varepsilon}^H + \sigma_M Y_{i,M}^U + \sigma_H Y_{i,H}^U - \left(\theta_S^M + \theta_S^H + \mu\right) Y_{i,S}^U + \gamma_S^U \left(Y_{i-1,S}^U 1_{i>1} - Y_{i,S}^U\right)$$

$$\frac{dY_{i,M}^U}{dt} = \rho \tilde{Y}_M^U 1_{i=1} + \delta_M^M Y_{i,M}^M + \delta_{\varepsilon M}^H Y_{i,\varepsilon M}^H - \left(\theta_M^M + \theta_M^H + \sigma_M + \mu\right) Y_{i,M}^U + \gamma_M^U \left(Y_{i-1,M}^U 1_{i>1} - Y_{i,M}^U\right)$$

$$\frac{dY_{i,M}^M}{dt} = \tilde{\theta}_M^M \tilde{Y}_M^U 1_{i=1} + \theta_M^M Y_{i,M}^U + \eta^M Y_{i,\varepsilon}^M - \left(\delta_M^M + \omega(t) + \mu\right) Y_{i,M}^M + \gamma_M^M \left(Y_{i-1,M}^M 1_{i>1} - Y_{i,M}^M\right)$$

$$\frac{dY_{i,\varepsilon}^M}{dt} = \tilde{\theta}_S^M \tilde{Y}_S^U 1_{i=1} + \theta_S^M Y_{i,S}^U - \left(\delta_\varepsilon^M + \eta^M + \omega(t) + \mu\right) Y_{i,\varepsilon}^M + \gamma_\varepsilon^M \left(Y_{i-1,\varepsilon}^M 1_{i>1} - Y_{i,\varepsilon}^M\right)$$

$$\frac{dY_{i,\varepsilon M}^H}{dt} = \tilde{\theta}_M^H \tilde{Y}_M^U 1_{i=1} + \theta_M^H Y_{i,M}^U + \omega(t) Y_{i,M}^M - \left(\delta_{\varepsilon M}^H + \eta_M^H + \mu\right) Y_{i,\varepsilon M}^H + \gamma_{\varepsilon M}^H \left(Y_{i-1,\varepsilon M}^H 1_{i>1} - Y_{i,\varepsilon M}^H\right)$$

$$\frac{dY_{i,H}^U}{dt} = \rho \tilde{Y}_H^U 1_{i=1} + \delta_H^H Y_{i,H}^H - \left(\theta_H^H + \sigma_H + \mu\right) Y_{i,H}^U + \gamma_H^U \left(Y_{i-1,H}^U 1_{i>1} - Y_{i,H}^U\right)$$

$$\frac{dY_{i,H}^H}{dt} = \tilde{\theta}_H^H \tilde{Y}_H^U 1_{i=1} + \theta_H^H Y_{i,H}^U + \eta_M^H Y_{i,\varepsilon M}^H + \eta^H Y_{i,\varepsilon}^H - \left(\delta_H^H + \mu\right) Y_{i,H}^H + \gamma_H^H \left(Y_{i-1,H}^H 1_{i>1} - Y_{i,H}^H\right)$$

$$\frac{dY_{i,\varepsilon}^H}{dt} = \tilde{\theta}_S^H \tilde{Y}_S^U 1_{i=1} + \theta_S^H Y_{i,S}^U + \omega(t) Y_{i,\varepsilon}^M - \left(\delta_\varepsilon^H + \eta^H + \mu\right) Y_{i,\varepsilon}^H + \gamma_\varepsilon^H \left(Y_{i-1,\varepsilon}^H 1_{i>1} - Y_{i,\varepsilon}^H\right)$$

with:

$$\lambda_S(t) = \tilde{c}\left[\tilde{c}\tilde{\beta}_S^U \tilde{Y}_S^U + c\left(\beta_S^U Y_S^U + \beta_\varepsilon^M Y_\varepsilon^M + \beta_\varepsilon^H Y_\varepsilon^H\right)\right] \Big/ w(t)$$

$$\lambda_M(t) = \tilde{c}\left[\tilde{c}\tilde{\beta}_M^U \tilde{Y}_M^U + c\left(\beta_M^U Y_M^U + \beta_M^M Y_M^M + \beta_{\varepsilon M}^H Y_{\varepsilon M}^H\right)\right] \Big/ w(t)$$

$$\lambda_H(t) = \tilde{c}\left[\tilde{c}\tilde{\beta}_H^U \tilde{Y}_H^U + c\left(\beta_H^U Y_H^U + \beta_H^H Y_H^H\right)\right] \Big/ w(t),$$

As in case 1, chronic categories represent the sum of all the corresponding stages, and:

$$w(t) = \tilde{c}\left(X + \tilde{Y}_S^U + \tilde{Y}_M^U + \tilde{Y}_H^U\right) + c\left(Y_S^U + Y_\varepsilon^M + Y_\varepsilon^H + Y_M^U + Y_M^M + Y_{\varepsilon M}^H + Y_H^U + Y_H^H\right).$$

The rate at which individuals within a given category initiate θ_k^l or stop treatment δ_k^l is

obtained following the same reasoning described above for case 1. The parameter values used

in Fig. 2d (see below) are: $c = 3$; $\tilde{c} = 6$; $\tilde{\beta}_S^U = \tilde{\beta}_M^U = 0.5$; $\tilde{\beta}_R^U = 0.25$; $\beta_S^U = \beta_M^U = 0.1$; $\beta_H^U = 0.06$; $\beta_M^M = 0.095$; $\beta_H^H = 0.03$; $\beta_\varepsilon^M = 0.02$; $\beta_\varepsilon^H = 0.001$; $\beta_{\varepsilon M}^H = 0.002$; $F_{on} = 0.4$; $\omega = 500$; $F_M^M = F_H^H = 0.2$; $F_\varepsilon^M = F_\varepsilon^H = F_{\varepsilon M}^H = 0.1$; $\rho = 3$; $\eta^M = 6$; $\eta^H = 0.125$; $\eta_M^H = 1$; $\sigma_M = 2$; $\sigma_H = 12$; $\alpha_S^U = \alpha_M^M = \alpha_M^U = 0.08$; $\alpha_H^H = 0.04$; $\alpha_M^U = 0.06$; $\alpha_\varepsilon^M = \alpha_\varepsilon^H = \alpha_{\varepsilon M}^H = 0.033$; $\mu = 0.033$.

2.3. *Staging System for the Chronically Infected*. We staged the chronic phase of the disease (Longini *et al.*, 1989; Hethcote and Van Ark, 1992) to obtain a more realistic representation of the incubation period of AIDS, and thus of the duration of time for which a person is an effective HIV transmitter (Fig. 1c). For simplicity, we chose $n = 10$ classes with the flow rate to the next class given by $n\alpha$, yielding a gamma-distributed incubation period with mean $1/\alpha$ and shape parameter n. All subcategories suffer the same background mortality μ. This structure does not alter the qualitative results of the non-staged version of the model, but the numerical results are slightly different.

3. RESULTS AND DISCUSSION

3.1. *Analysis of Case 1: Increase in Risky Contact Rates at the Onset of HAART*. After the introduction of triple-drug therapies in 1995, there was optimism that AIDS may become a curable disease. Many studies report a subsequent increase in risky behaviour (contact rate c in our model) that in turn led to an increase in the number of new HIV infections (Dukers *et al.*, 2001; Law *et al.*, 2001; Stolte *et al.*, 2001; Katz *et al.*, 2002). We explored how this change in c could affect drug resistance dynamics. We first considered the scenario where uninfected and acutely infected individuals have a contact rate that is 2 times that of the chronically infected ($\tilde{c} = 2c$) throughout the course of the simulation, irrespective of the viral strain they carry. Here we describe the situation where c (and in consequence $\tilde{c}$) doubles once the epidemic reaches the steady state (i.e., equilibrium), but in any case the greater the increase in the contact rates, the more pronounced the changes described below. Simulations (not shown) indicate that the qualitative behaviour of the system is the same whether or not the perturbation occurs at steady state, as presented below.

Fig. 2

Fig. 2 illustrates the temporal dynamics of the overall prevalence of the disease in the host population Y, the overall resistance prevalence in the host population r, and the proportion of individuals infected with a resistant virus among those in the acute phase $\tilde{r}$ (equations are given in Appendix A). A greater contact rate c (Fig. 2a) implies an increase in both Y and r in the host population that scales in a nonlinear mode with c (Sattenspiel *et al.*, 1990; Blower *et al.*, 2000; Katz *et al.*, 2002). When individuals have on average 1 risky contact per year the disease dies out, while when $c \geq 4$ at equilibrium over 80% of the population is infected ($0.8 < Y < 1.0$) and less than half the population carries a resistant HIV strain ($0.4 < r < 0.5$).

This increase in the prevalence of the disease Y and of drug resistance r in the *overall population* does not imply a parallel increase in the *proportion* of resistant individuals *within* the infected categories (Figs. 2a, b). In actuality, there is an initial decrease in $\tilde{r}$ when c increases. Likewise, the proportion of individuals infected with a resistant virus among all of the infected and among those in the chronic phase also decreases (results not shown). There is a subsequent increase in these three proportions (resistant carriers among acute, chronic, and total infected). The trough reflects the relationship between the transient dynamics of the wild type and resistant strains: when c increases, the prevalence of untreated individuals with acute wild type infections $\tilde{Y}_S^U$ increases to a higher magnitude and at a slightly faster rate than that of untreated individuals with an acute resistant infection ($\tilde{Y}_R^U$) because wild type has a higher transmission rate per risky contact (β) than resistant strains (Bleiber *et al.*, 2001; Dukers *et al.*, 2001; Porco *et al.*, 2004). This translates into a decrease of individuals infected with a resistant strain (Y_R^U) vs. those infected with a wild type strain (Y_S^U) among those in the chronic phase of the disease, once the delay effect stemming from the progression of acute to chronic has come into effect. In a relatively short time span the virus' transient dynamics caused by the change in c are resolved and all host categories level off to their new steady state. Even though c plays a role in determining both the transient dynamics and the equilibria of the percent prevalence of infection (Y) and percent of individuals with resistant strains among infected (r), Figs. 2a and b show how for the percent of primary resistant cases $\tilde{r}$ all

runs settle down to the *same steady state* independently of the contact rate c. Likewise, we obtain the same steady state values for the fraction of individuals that carry a resistant strain among the chronic and all of the infected individuals.

Because transient trajectories behave very similarly for contact rates c above approximately 8 risky encounters per year, and at higher c the transients approach the steady state at a faster pace, the trough generated in $\tilde{r}$ is more noticeable at lower contact rates (Fig. 2b). In consequence, if we were to look at the fraction resistant among infected categories in populations with high contact rates, we may not be able to infer substantial increases in contact rates as compared to populations with relatively low values of this parameter. Grant *et al.* (2002) report a 15-25% decrease in NRTI resistance prevalence among the acutely infected, and their trough occurs within a 4-year period. The magnitude of the trough indicates that if an increase in c has played a major role in determining observed primary NRTI resistance trends, the average contact rates in these populations are probably not above 4 per year. On the other hand, the short duration of the trough in the empirical data indicates that c in North America may be much higher. In any case, we must keep in mind that our model represents a noticeable oversimplification of the HIV epidemic (e.g., we did not consider core groups that could accelerate the system's dynamics), such that any quantitative results should be interpreted with caution.

The dynamics represented in Figs. 2a and b are influenced by the distinct abilities of wild type and resistant strains to be generated, maintained, and transmitted throughout the host population. The relative value of the transmission rates is the most critical factor determining the dynamical differences of the two strains under reasonable values of the parameter space, with these differences being more pronounced as the disparity in transmissibility of the two strains increases (Fig. 3). Other authors have also found transmission rates to play a decisive role in the spread and prevalence of drug resistant HIV strains (Blower *et al.*, 2001; Ammaranond *et al.*, 2003a). To investigate how these parameters affect the proportion resistant among the acutely infected individuals $\tilde{r}$, we quantified their relationship in terms of the ratio of the rates according to disease and treatment status: acute

untreated ($\tilde{\beta}_R^U / \tilde{\beta}_S^U$), chronic untreated ($\beta_R^U / \beta_S^U$), and chronic treated ($\beta_R^T / \beta_\varepsilon^T$). The relative importance of these transmission rates β will be weighted at each time point by the prevalence of each category, which is affected by the various other forces acting on the system, and the contact rates (λ_S and λ_R, see above). We focus only on the ratios of the untreated individuals, because (i) the transmission rate of treated and suppressed individuals (β_ε^T) is very small, and (ii) even though the prevalence of treated and resistant individuals (Y_R^T) is high, transmission is substantially lower in treated than untreated individuals, e.g. $\beta_R^T < \beta_R^U$ (Blower *et al.*, 2000). We assume the transmission advantage of wild type over the resistant strain is the same among untreated individuals in the acute and chronic phases, and that all other parameters of the model are constant. Fig. 3 shows changes in primary resistance proportions $\tilde{r}$ over time as a function of increasing values of the ratios $\tilde{\beta}_R^U / \tilde{\beta}_S^U = \beta_R^U / \beta_S^U$ from 0.1 to 2. As in Figs. 2a and b, there is a transient phase after which all runs return to their particular equilibrium value because the β ratio remains a constant. On the other hand, the shape of the transient trough is greatly affected by the value of the ratio, such that for values <1 (i.e. the resistant strain is less transmissible than wild type) there is an initial decrease in $\tilde{r}$. As the ratio approaches 1 the trough becomes smaller. Once the ratio is >1 (i.e. the resistant strain is more transmissible than wild type) $\tilde{r}$ increases, and the magnitude of the increase is larger as the ratio increases. When all three ratios are 1 the transient dynamics reflect the relative importance of the other processes at work in the system. Near steady state all trajectories behave in a similar fashion because then their courses are determined largely by parameters that have remained unchanged across the different runs.

3.2. *Analysis of Case 1: Decrease in Fraction Treated.*

Due to the long-term negative side effects of antiretroviral therapies (ARVT), the benefits to initiating treatment early in the infection have not proven sufficient to outweigh the costs. Delaying therapy has progressively become more widely accepted (Pomerantz, 2001). We found that a decrease in the treated fraction of individuals in the acute phase causes a decrease in the proportion resistant among the acutely infected $\tilde{r}$ for all relevant values of the parameters. However,

this scenario differs substantially from the increase in risky contact rates discussed above: now disease prevalence Y increases because treatment has a greater relative impact on transmission than on mortality (Volberding, 2003), while resistance prevalence in the overall population r decreases (Fig. 2c). In parallel to $\tilde{r}$, the proportion resistant among all the infected individuals and among those in the chronic phase of the disease also decrease. These basic trends, albeit with nonlinear dynamics and equilibria, are consistent across treatment values ranging from 0-1.

In reality, a decrease in the fraction of acute cases treated has probably not been the most important factor in determining the observed decrease in primary resistance because of the simultaneous large increase in the treatment of chronic-phase individuals, which are substantially more numerous than those in the acute stage (Goudsmit *et al.*, 2001; Schwarcz *et al.*, 2001). For example, treatment rates of HAART (Highly Active Antiretroviral Therapy) in a broad US sample of the adult HIV-infected population receiving regular medical care increased from <10% in 1996 to almost 50% in 1998 in HIV infected individuals with CD4 counts above 0.5×10^9/L (Shapiro *et al.*, 1999).

3.3. *Analysis of Case 2: Increased Effectiveness of Drug Therapy.* Even though the HIV epidemic in San Francisco began approximately in the 1970s (Bacchetti and Moss, 1989; Lukashov and Goudsmit, 2002; Robbins *et al.*, 2003) and monotherapy with AZT was initiated in 1987 (Ezzell, 1987), a substantial drop in the rate at which individuals progress to AIDS did not occur until 1995-96, when patients began taking three or more drugs simultaneously (Li *et al.*, 1998). Under these conditions we can expect the dynamics of the epidemic to be very much transformed, and the levels of resistance in the population could be affected (Mocroft *et al.*, 1998; Palella *et al.*, 1998; Goudsmit *et al.*, 2001; Yerly *et al.*, 2001; Louie *et al.*, 2002). Not surprisingly, the introduction of HAART has preceded the time point of decrease in the incidence of primary NRTI resistance in San Francisco, and of primary NRTI and NNRTI in North America.

We investigated how the transition from a less to a more effective drug therapy strategy changes the population dynamics of drug resistance in HIV (equations provided in Appendix A). Fig. 2d shows how the percentages of individuals infected Y, of individuals infected with a resistant strain r, and of individuals that carry a resistant strain among the acutely infected $\tilde{r}$, suffer a permanent decrease with the change in treatment strategy (although they do increase slightly after reaching a minimum value). The proportion resistant among all of the infected and among the chronically ill also decrease.

Even though resistant individuals progress to AIDS on average at a lower rate α under HAART than under monotherapy, the decrease in $\tilde{r}$ occurs because drug resistance takes longer to appear (smaller η), resistance is lost at a faster pace in untreated individuals (larger σ), and, most importantly, the probability of transmitting a resistant strain is substantially decreased (smaller β) as compared to strains resistant to monotherapy. Drug resistance dynamics can therefore be very different in drug-naïve populations *vs.* those where strategies of increased effectiveness are applied sequentially in time.

For reasonable values of the parameter space: 1) All parameters had the expected effect on the trough, i.e., any force that decreases the prevalence and/or duration of a resistant category will increase the depth and length of the trough, with the exception of the rate α_H^U at which untreated individuals resistant to HAART (Y_H^U) progress to AIDS. A faster progression of such individuals produces a slightly smaller trough because this category reverts to wild type at a very high rate σ. As σ decreases to approximately 5 this effect is reversed and a higher α_H^U produces a somewhat bigger trough in length and height. Because individuals infected by a resistant strain will not have reservoirs of wild type they will, on average, revert to wild type at a much slower rate σ than those that have a predominantly resistant strain due to treatment of an initial wild type viral population (Brenner *et al.*, 2002). We have chosen to ignore this distinction between the two routes of becoming a chronic resistant untreated individual (Y_M^U or Y_H^U) and consider they all have one common σ within each treatment (i.e., monotherapy or HAART), because there are no qualitative or noticeable quantitative effects on $\tilde{r}$ when we vary σ between 0.1–12.0. All other mortality rates cause the expected trend in

the trough, and do not play as substantial a role as the transmission rates in determining its height and length. 2) The resistant category whose transmission rate β has the greatest effect on $\tilde{r}$ (with a smaller β implying a greater trough with delayed dynamics) is that of the chronically infected individuals resistant to but treated with HAART (Y_H^H); this is not surprising because within a year this category becomes the one with the highest prevalence among the resistant carriers. 3) Lower resistance emergence rates η and higher resistance reversal rates σ cause an expected bigger trough, although they do not have a considerable effect on either its height or length (except for extremely low values of η).

4. GENERAL DISCUSSION

Primary drug resistance trends vary in space and time because of differences in behavior, demography, timing and composition of treatment regimens, guidelines for defining drug resistance and primary individuals, etc. (Chiesi *et al.*, 1999; Pillay *et al.*, 2000; Schwarcz *et al.*, 2001; Ghani *et al.*, 2002). Transient declines in the proportion of individuals recently infected with an NRTI-drug resistant HIV strain have been reported for San Francisco and ten other cities of North America (Grant *et al.*, 2002; Little *et al.*, 2002; Grant *et al.*, 2003). Because NRTI have been administered for a longer time and to a greater fraction of HIV-infected individuals than NNRTI or protease inhibitors, PI, observed NRTI patterns may hold more information on recent epidemic trends than NNRTI or PI. We identified three potential causes for these dynamics: changes in contact rates, treatment levels, and therapy efficacy. We investigated how these changes impact the prevalence levels of HIV infected individuals and viral drug resistance in the host population. We looked at a wide range of parameter values, and even though the exact quantitative results vary, the overall qualitative results are consistent across all scenarios.

Although all three scenarios depicted generate a decrease in the proportion of resistant individuals among the newly infected $\tilde{r}$ with nonlinear dynamics and equilibria, the transient and steady state patterns of the decrease vary. For a representative set of the parameter space,

under scenario (1), which corresponds to the increase in risky contact rates, the decrease is temporary and ultimately the system settles to the one unique equilibrium value of $\tilde{r}$ for all contact rates. In scenario (2), where a smaller fraction of those individuals in the acute phase of the disease are placed on treatment, the decrease is permanent and monotonic. In the last case (3) where we analyze the possible effects of switching the population to a more successful treatment strategy, $\tilde{r}$ first decreases, then increases but to a lower level than the initial point of change in treatment. The observed transient dynamics of $\tilde{r}$ exhibit a good resemblance with the first scenario, which is the only one that shows a decrease and a convincing increase followed by another decrease. Moreover, in San Francisco it does appear that in 1996 there was a change in the system that may have generated a new and lower attraction point for $\tilde{r}$ (Grant *et al.*, 2002). It is very likely that one or even both of the other two scenarios has contributed to a permanent decrease in $\tilde{r}$, and produced the patterns observed in combination with the first scenario.

Most interestingly, the transient dynamics and equilibria of other key variables characterizing the system also vary under the different scenarios. Disease prevalence increases in (1) and (2), but decreases in (3), while drug resistance prevalence increases in (1) but decreases in (2) and (3). The decrease in the proportion of drug resistant carriers among recently infected individuals can be optimistically interpreted as an indicator of reduced drug resistance prevalence in the HIV epidemic, consistent with scenarios (2) and (3). However, if (1) is the major contributing factor to the epidemic's dynamics, we have the counter-intuitive situation where following an increase in risky contact rates the proportion of newly infected drug resistant cases decreases transiently as the epidemic worsens. Our results underscore how additional information needs to be collected and evaluated for the correct interpretation of time-trends in primary drug resistance, because this decrease is consistent with both an increase and a decrease in the absolute numbers of infected and resistant individuals. This information should include estimates of the fraction of recent and chronic infections that are treated, and the overall incidence rate of new HIV-1 infections.

Drug resistant strains can therefore serve as population-level markers, because their relative prevalence can be tracked temporally and spatially to help detect overall epidemic trends. These strains may be particularly informative as epidemiological flags in countries where it is not mandatory to report the infectious status of an individual, but relative frequencies of the different strains can be obtained from monitored groups such as antenatal clinics. For example, an increase in primary cases may reflect better surveillance with no related change in the epidemic's dynamics. If the viral population is monomorphic (i.e., one strain) the data may not provide further information. However, unless individuals infected with a drug sensitive strain are more inclined than drug-resistant carriers to undergo an HIV test when in the initial infection stage, the change in the relative proportions of the two strains among the primary cases is a strong indicator that changes have occurred that affect the system's dynamics. Information on composite variables that reflect the relative proportions of drug resistant and drug sensitive strains can help us make more accurate predictions as to the present and future trends of the epidemic in general, and of drug resistance in particular.

APPENDIX A

The composite variables we focused on in our analysis are the overall disease prevalence Y, the overall resistance prevalence in the host population r, and the proportion of individuals infected with a resistant virus among those in the acute phase $\tilde{r}$. The corresponding equations for case 1 are:

$$Y = \frac{\tilde{Y}_S^U + \tilde{Y}_R^U + Y_S^U + Y_R^U + Y_R^T + Y_\varepsilon^T}{X + \tilde{Y}_S^U + \tilde{Y}_R^U + Y_S^U + Y_R^U + Y_R^T + Y_\varepsilon^T} = \frac{y}{N},$$

$$r = \frac{\tilde{Y}_R^U + Y_R^U + Y_R^T}{N},$$

$$\tilde{r} = \frac{\tilde{Y}_R^U}{\tilde{Y}_R^U + \tilde{Y}_S^U}.$$

For case 2 they are:

$$Y = \frac{\tilde{Y}_S^U + \tilde{Y}_M^U + \tilde{Y}_H^U + Y_S^U + Y_M^U + Y_M^M + Y_\varepsilon^M + Y_{\varepsilon M}^H + Y_H^U + Y_H^H + Y_\varepsilon^H}{X + \tilde{Y}_S^U + \tilde{Y}_M^U + \tilde{Y}_H^U + Y_S^U + Y_M^U + Y_M^M + Y_\varepsilon^M + Y_{\varepsilon M}^H + Y_H^U + Y_H^H + Y_\varepsilon^H} = \frac{y}{N},$$

$$r = \frac{\tilde{Y}_M^U + \tilde{Y}_H^U + Y_M^U + Y_M^M + Y_{\varepsilon M}^H + Y_H^U + Y_H^H}{N},$$

$$\tilde{r} = \frac{\tilde{Y}_M^U + \tilde{Y}_H^U}{\tilde{Y}_S^U + \tilde{Y}_M^U + \tilde{Y}_H^U}.$$

N represents the total population size and y represents the total number of infected.

APPENDIX B

Here we describe additional explorations we conducted to best understand the system's dynamics, regarding the effects of treatments of varying efficacy (e.g., AZT) and modifications in the contact rates and fraction of individuals under treatment of the different host categories.

C.1. *Increase in risky contact rates under AZT.* To verify whether the trends described in Figs. 2a and 2b (main text) are consistent across treatments, we explored how a population

under monotherapy with AZT is affected by an increase in the rate c of risky contacts (parameter values are as those provided in the main text). As with HAART c determines y in a highly non-linear fashion, although now the disease can attain higher prevalence levels: when $c =1$ HIV does not go extinct as occurs with HAART, but maintains itself at the steady state of $Y = 0.243$; when $2 < c < 4$ this value is $> 70\%$, and prevalence levels close to 90% are attained with contact rates as low as 4. In addition, under AZT an increase in c also leads to an increase in r, although for any given c the population harbors a greater resistant fraction with the less efficacious treatment: at the steady state $r > 0.5$ for values of $c > 3$. Other theoretical studies have also found that treatments of low efficacy will generate high levels of drug resistance in the population (Blower *et al.*, 2001; Goudsmit *et al.*, 2001). Accordingly, although $\tilde{r}$'s response to an increase in c follows the pattern displayed under HAART, with AZT the steady state value is greater (0.633 vs. 0.305) and the trough is less pronounced. The transient dynamics of the epidemic resolve faster under AZT, particularly at high contact rates, as compared to HAART.

We obtained higher disease and resistance prevalence in a population treated with AZT than with HAART at equal contact rates (Katz *et al.*, 2002). Therefore, as treatment efficacy increases, so does the minimum contact rate required to maintain the virus in the population while disease prevalence at the steady state decreases. A more effective treatment also leads to a greater decrease in the proportion of resistant carriers with respect to wild type carriers.

C.2. *Increase in risky behaviour when all individuals have the same contact rate c.* We analysed what happens when uninfected individuals and those in the acute phase of HIV infection engage on average in the same number of risky behavioral acts as do those in the chronic phase ($\tilde{c} = c$). Under this scenario, for any given c the drug sensitive and resistant forces of infection are, respectively:

$$\lambda_S(t) = c(t) \frac{\tilde{\beta}_S^U \tilde{Y}_S^U + \beta_S^U Y_S^U + \beta_\varepsilon^T Y_\varepsilon^T}{X + \tilde{Y}_S^U + \tilde{Y}_R^U + Y_S^U + Y_R^U + Y_R^T + Y_\varepsilon^T},$$

and

$$\lambda_R(t) = c(t)\frac{\tilde{\beta}_R^U \tilde{Y}_R^U + \beta_R^U Y_R^U + \beta_R^T Y_R^T}{X + \tilde{Y}_S^U + \tilde{Y}_R^U + Y_S^U + Y_R^U + Y_R^T + Y_\varepsilon^T} \ .$$

The trends are the same as in the case of two different contact rates, but now: a) disease and b) resistance prevalence are lower, and c) for any given c the decrease in the proportion of resistant carriers when we double the contact rate is more pronounced. As expected given the reduced population level contact rate, the transient dynamics occur at a slower pace.

C.3. *Decrease in fraction treated.* In addition we investigated what happens to a population that suffers a decrease in the fraction of individuals that are treated in the acute phase of the disease under the following assumptions: 1) under monotherapy with AZT, 2) when all individuals have the same contact rate regardless of their infection status, and 3) when we decrease the fraction treated among both acute and chronic individuals. Again the patterns were parallel to the ones described above and in the main text.

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Figure 1. Flow diagrams depicting the transmission dynamics of an HIV epidemic under drug therapy. (a) Case 1: Epidemic with one drug therapy. (b) Case 2: Epidemic with two sequential drug therapies. Category notations and parameters are identified in Table 1. *Color code* for the categories' encircling ovals: black = uninfected, purple = infected with wild type, red = infected with a drug resistant to therapy (case 1), blue = infected with a strain resistant to monotherapy (case 2), and green = infected with a strain resistant to HAART (case 2). *Background code* of oval categories: no fill = untreated, gray = under drug therapy; in case 2 dotted gray = monotherapy, and solid gray = HAART. *Dash code* for the categories' encircling ovals: solid = no staging (uninfected and acutely infected) and fractioned = staged categories (individuals in the chronic phase).
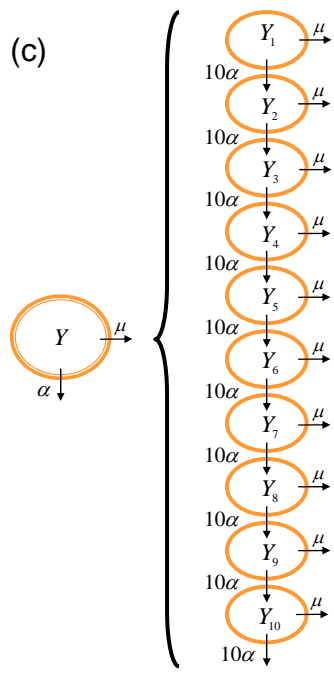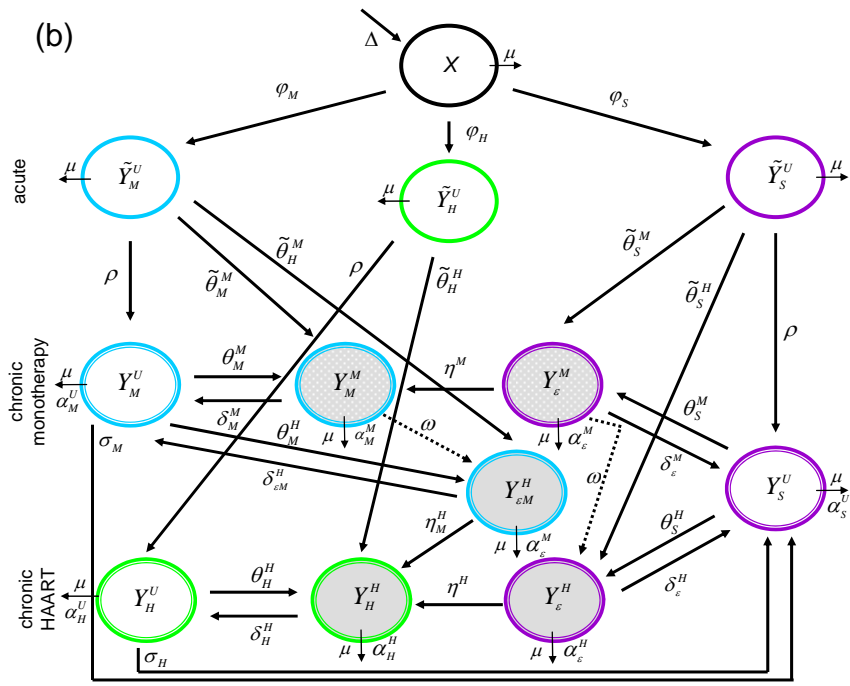
(b)

(c)
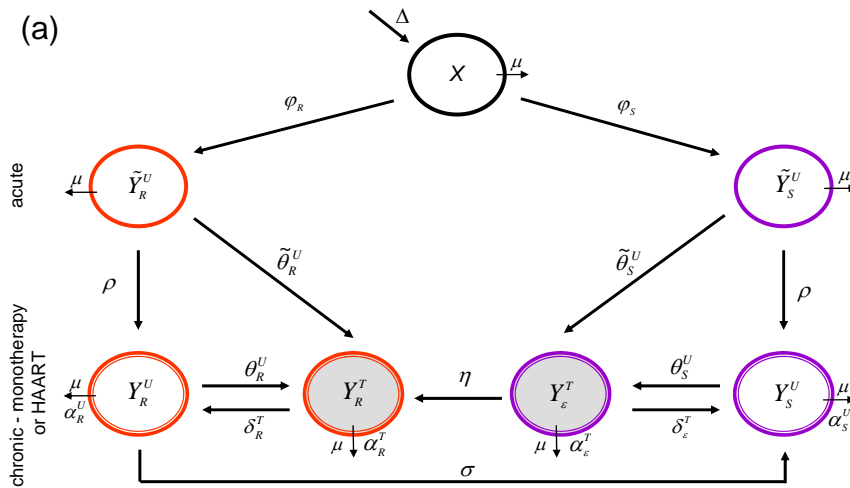
Figure 2. Drug resistance dynamics and its relationship to HIV incidence. A decrease in the proportion of individuals infected with an HIV drug resistant strain among those recently infected can correlate both with an increase and a decrease in the number of infected individuals and of drug resistant carriers in the host population. We plotted the response of the fraction of infected individuals Y, the fraction of individuals infected with a drug resistant strain r, and the fraction of individuals infected with a drug resistant strain among those recently infected individuals $\tilde{r}$, in response to three different historical processes: (a) increase in the risky contact rates in the whole population c and in the acutely infected group $\tilde{c}$; (b) resistance prevalence among acutely infected individuals when c and $\tilde{c}$ increase; (c) decrease in fraction of individuals treated F_{on} in the acute stage of HIV infection; (d) increase in drug therapy efficacy from AZT to HAART. Graphs (a)-(c) follow case 1 (see Model Description) with parameter values representative of HAART. In graphs (a) and (b), $F_{on} = 0.4$; in graph (c), $c = 3$. Graph (d) follows case 2.

(b)

c doubles

resistance prevalence among acute

c = 2 to 4	
c = 4 to 8	
c = 8 to 16	
c = 16 to 32	
c = 32 to 64	
c = 64 to 128	

years

(c)

solid
F_{on} = 0.4 to 0.1

dotted
F_{on} = 0.6 to 0.05

prevalence

disease prevalence in population Y	
resistance prevalence in population r	
resistance prevalence among acute $\tilde{r}$	

decrease in fraction acute treated

years

33
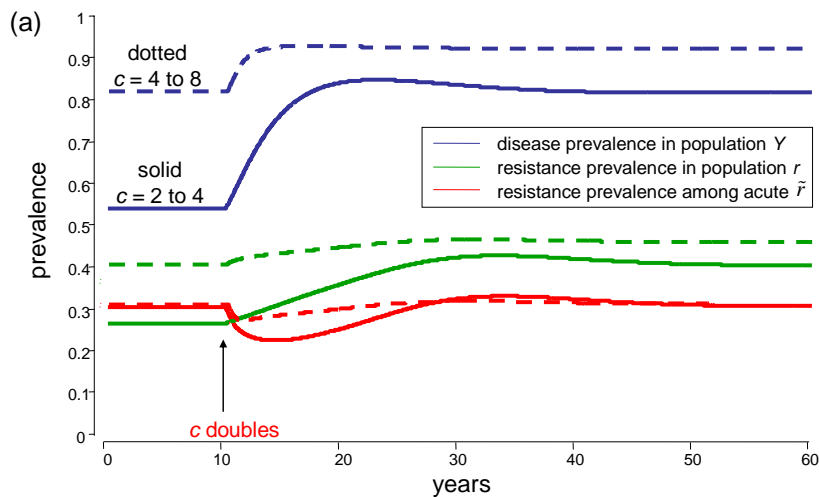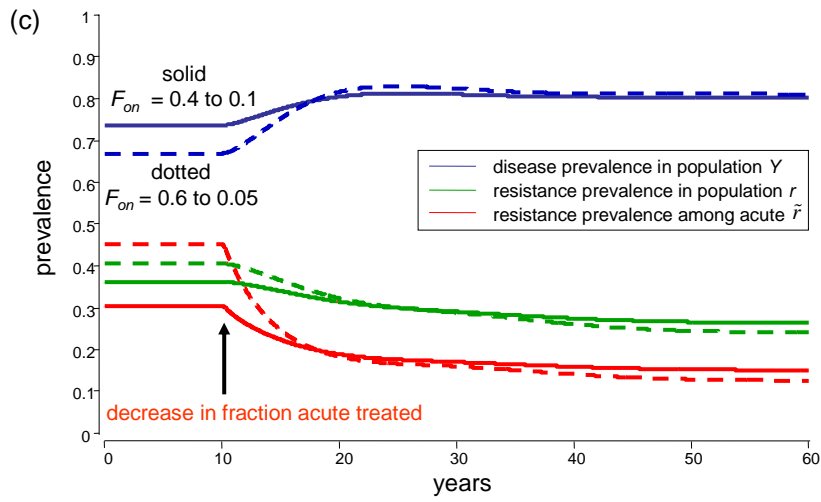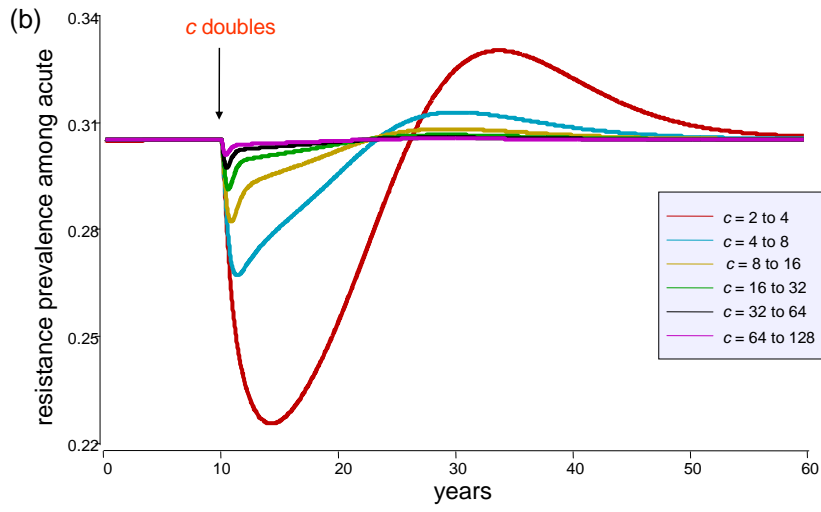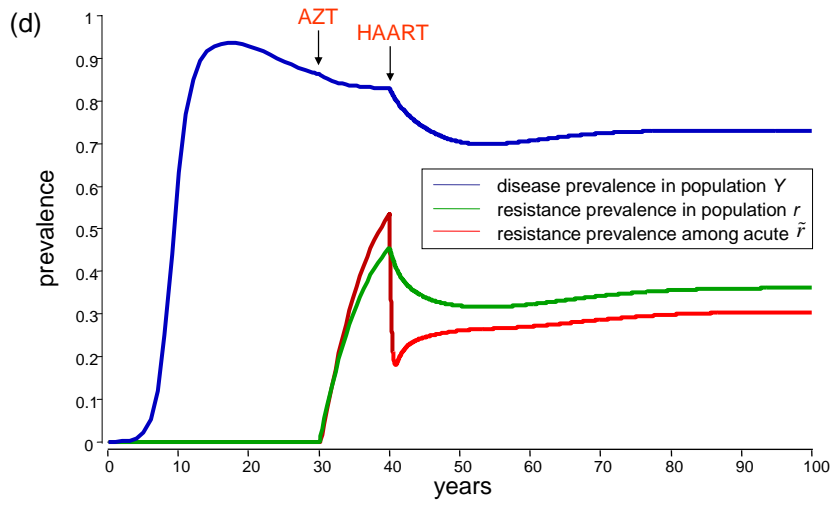
Figure 3. Relationship between the transmission rates (β) of drug resistant and wild type HIV strains. This relationship determines the dynamics of the proportion of individuals infected with a drug resistant strain among those recently infected $\tilde{r}$. We simulated what occurs when we double the contact rate c for values of the ratio of the transmission rates of resistant strains and wild type in acutely and chronically infected individuals ($\tilde{\beta}_R^U / \tilde{\beta}_S^U = \beta_R^U / \beta_S^U$) ranging from 0.1 to 2 (with fixed $\tilde{\beta}_S^U = 0.5$ and $\beta_S^U = 0.1$, and increasing values of $\tilde{\beta}_R^U = 0.05$, 0.24, 0.43, 0.62, 0.81, 1.0 and $\beta_R^U = 0.01$, 0.048, 0.086, 0.124, 0.162, 0.2). All other parameters are representative of HAART (case 1, see Model Description), with the initial $c = 3$ and the fraction of individuals treated among the chronic and acute $F_{on} = 0.4$.
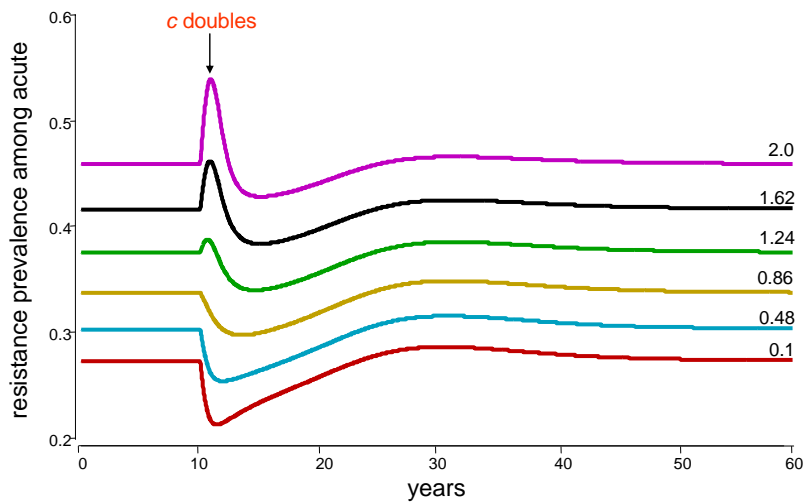
Table 1. Summary of the properties and parameters characterizing the different disease categories.

(a) Case 1: Epidemic with one drug therapy (monotherapy or HAART)

	phase	virus	Rx	in	cont	trans	on Rx	off Rx	prog	R gain	R loss	out	mort
X	U	NA	NA	Λ	$\tilde{c}$	–	–	–	–	–	–	–	μ
$\tilde{Y}_S^U$	A	S	U	–	$\tilde{c}$	$\tilde{\beta}_S^U$	$\tilde{\theta}_S^U$	–	ρ	–	–	–	μ
$\tilde{Y}_R^U$	A	R	U	–	$\tilde{c}$	$\tilde{\beta}_R^U$	$\tilde{\theta}_R^U$	–	ρ	–	–	–	μ
Y_S^U	C	S	U	–	c	β_S^U	θ_S^U	–	–	–	–	α_S^U	μ
Y_R^U	C	R	U	–	c	β_R^U	θ_R^U	–	–	σ	–	α_R^U	μ
Y_R^T	C	R	T	–	c	β_R^T	–	δ_R^T	–	–	–	α_R^T	μ
Y_ε^T	C	ε	T	–	c	β_ε^T	–	δ_ε^T	–	η	–	α_ε^T	μ

(b) Case 2: Epidemic with two sequential drug therapies

	phase	virus	Rx	in	cont	trans	on Rx	Rx transf	off Rx	prog	R gain	R loss	out	mort
X	X	NA	NA	Λ	$\tilde{c}$	–	–	–	–	–	–	–	–	μ
$\tilde{Y}_S^U$	A	S	U	–	$\tilde{c}$	$\tilde{\beta}_S^U$	$\tilde{\theta}_S^M$ $\tilde{\theta}_S^H$	–	–	ρ	–	–	–	μ
$\tilde{Y}_M^U$	A	R-M	U	–	$\tilde{c}$	$\tilde{\beta}_M^U$	$\tilde{\theta}_M^M$ $\tilde{\theta}_M^H$	–	–	ρ	–	–	–	μ
$\tilde{Y}_H^U$	A	R-H	U	–	$\tilde{c}$	$\tilde{\beta}_H^U$	$\tilde{\theta}_H^H$	–	–	ρ	–	–	–	μ
Y_S^U	C	S	U	–	c	β_S^U	θ_S^M θ_S^H	–	–	–	–	–	α_S^U	μ
Y_M^U	C	R-M	U	–	c	β_M^U	θ_M^M θ_M^H	–	–	–	–	σ_M	α_M^U	μ
Y_H^U	C	R-H	U	–	c	β_H^U	θ_H^H	–	–	–	–	σ_H	α_H^U	μ
Y_M^M	C	R-M	M	–	c	β_M^M	–	ω	δ_M^M	–	–	–	α_M^M	μ
Y_H^H	C	R-H	H	–	c	β_H^H	–	–	δ_H^H	–	–	–	α_H^H	μ
Y_ε^M	C	ε	M	–	c	β_ε^M	–	ω	δ_ε^M	–	η^M	–	α_ε^M	μ
Y_ε^H	C	ε	H	–	c	β_ε^H	–	–	δ_ε^H	–	η^H	–	α_ε^H	μ

$Y_{\varepsilon M}^{H}$	C	R–M	H	–	c	$\beta_{\varepsilon M}^{H}$	–	–	$\delta_{\varepsilon M}^{H}$	–	η_{M}^{H}	–	$\alpha_{\varepsilon M}^{H}$	μ
ε														

A tilde indicates the category or parameter pertains to the acute phase of the disease. Subscripts refer to the status of the viral population infecting the individual, and superscripts describe its treatment status. Heading explanations: phase = individual's disease status, virus = drug resistant status of viral population of an infected individual, Rx = treatment status of infected individuals, in = inflow rate, cont = rate at which individuals engage in risky contacts, trans = transmission rate, e.g., probability of transmitting the virus given a risky encounter between an uninfected and an infected individual, on Rx = rate at which individuals initiate treatment, Rx transf = rate at which individuals transfer from monotherapy to HAART (relevant only for Case 2), off Rx = rate at which individuals cease treatment, prog = rate at which individuals progress from the acute to the chronic stage of the disease, R gain = rate at which a susceptible viral population within an infected individual acquires drug resistance mutations, R loss = rate at which a drug resistant viral population within an infected individual loses mutations that confer drug resistance and becomes drug sensitive, out = disease induced removal rate from the pool of active HIV transmitters, mort = average background mortality rate. Abbreviations for categories and parameters: X = uninfected, A = acute, C = chronic, NA = not applicable, S = infected with drug sensitive strain, R = infected with a drug resistant strain, M = monotherapy, H = HAART, ε = viral population suppressed, U = untreated.

$Y_{\varepsilon M}^{H}$	C	R–M	H	–	c	$\beta_{\varepsilon M}^{H}$	–	–	$\delta_{\varepsilon M}^{H}$	–	η_{M}^{H}	–	$\alpha_{\varepsilon M}^{H}$	μ