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# The role of backward mutations on the within-host dynamics of HIV-1

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## Abstract

The quality of life for patients infected with human immunodeficiency virus (HIV-1) has been positively impacted by the use of antiretroviral therapy (ART). However, the benefits of ART are usually halted by the emergence of drug resistance. Drug-resistant strains arise from virus mutations, as HIV-1 reverse transcription is prone to errors, with mutations normally carrying fitness costs to the virus. When ART is interrupted, the wild-type drug-sensitive strain rapidly out-competes the resistant strain, as the former strain is fitter than the latter in the absence of ART. One mechanism for sustaining the sensitive strain during ART is given by the virus mutating from resistant to sensitive strains, which is referred to as backward mutation. This is important during periods of treatment interruptions as prior existence of the sensitive strain would lead to replacement of the resistant strain.

In order to assess the role of backward mutations in the dynamics of HIV-1 within an infected host, we analyze a mathematical model of two interacting virus strains in either absence or presence of ART. We study the effect of backward mutations on the definition of the basic reproductive number, and the value and stability of equilibrium points. The analysis of the model shows that, thanks to both forward and backward mutations, sensitive and resistant strains co-exist. In addition, conditions for the dominance of a viral strain with or without ART are provided. For this model, backward mutations are shown to be necessary for the persistence of the sensitive strain during ART.

### Keywords

within-host model; HIV-1; drug resistance; virus mutations


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## 1 Introduction

The Acquired Immune Deficiency Syndrome (AIDS) is one of the leading causes of death in Sub-Saharan Africa. A total of 22.4 million people in this region are estimated to be infected with Human Immunodeficiency Virus type one (HIV-1), the pathogen that causes AIDS. This total accounts for 67% of HIV-1 infections in the entire world (UNAIDS, 2009). Antiretroviral therapy (ART) against HIV-1, first introduced in 1987, showed initial promising results (Larder et al, 1989). However, the emergence of drug resistance forced the implementation of combinational therapy (Eron et al, 1995). Drug resistance is defined as the ability of the virus to replicate in the presence of drugs (Larder et al, 1989). Despite the fact that combinational therapy is effective during the first six to eighteen months, such benefits might be short-lived, particularly in patients without perfect adherence (Howard et al, 2002; Kane, 2008; Kuritzkes, 2004; Paterson et al, 2000; Wainberg and Friedland, 1998). Drug resistance was found to be mainly due to incomplete viral suppression rather than transmission of resistant strains (Deeks, 2003). Emergence of HIV-1 drug resistance represents a major challenge to the long term administration of effective ART (Burkle, 2002; Eron et al, 1995).

The high mutation rate of HIV-1 generates a background of resistance-associated mutations within a patient because the viral enzyme reverse transcriptase is error-prone and HIV-1 has no proof-reading mechanism (Mansky and Temin, 1995). Such a high mutation rate allows for virtually all possible mutations to be generated daily (Perelson et al, 1997). Mutations could either confer drug resistance, forward mutations, or revert a resistant strain back to a drug-sensitive wild-type strain, backward mutations (Hecht and Grant, 2005). Some of these mutations are beneficial to HIV-1 as they result in the virus being able to escape the effects of ART or the immune system, while others are harmful to the virus as they interfere with its replication. Therefore, among a highly diverse viral population, it is likely to find at least one strain harboring a particular mutation that confers a survival advantage in the presence of drug pressure.

Strains carrying mutations conferring drug resistance are generally less fit (in terms of infectivity and/or replication) than sensitive strains and they are easily out-competed by them (Ribeiro and Bonhoeffer, 2000; Vaidya et al, 2010). Frost et al (2000) found the resistance-conferring mutation M184V in the transcriptase inhibitor lamivudine (3TC) to reduce viral susceptibility to drugs by approximately 100-fold. This mutation also results in a lower processivity of the viral enzyme reverse transcriptase. Frost et al (2000) estimated that the relative fitness of the mutant M184V in the presence of drug pressure is approximately 10% of that of the sensitive strain prior to therapy. Despite the fact that resistant strains are significantly less fit than sensitive strains and are heavily selected against in the absence of drug pressure, it is expected that on average one cell is infected with resistant virus in an infected cell population the size of the reciprocal of the forward mutation rate (Bonhoeffer and Nowak, 1997). This means that drug-resistant strains may exist even in the absence of treatment. On the other hand, during ART the resistant strain could have better relative fitness, which has been shown to increase with drug concentration (Gonzalez et al, 2000; Kepler and Perelson, 1998; Weber et al, 2003).

Several studies have shown the effect of backward mutations on HIV-1 infected patients. For instance, for individuals originally infected with resistant mutants, replacement by emerging sensitive strains may take a few months, depending on class-specific mutations (Jain et al, 2011). On the other hand, cessation of ART leads to overgrowth of sensitive virus within 16 weeks in individuals who acquired resistant mutants during ART (Deeks et al, 2001). The rapid replacement of resistant virus during interruption of ART was mainly attributed to the resistance-associated fitness cost (Vaidya et al, 2010).

Mathematical models have been proposed to study the problem of emergence of drug resistance for both monotherapy and combinational therapy. From such modeling work, several insights about HIV-1 have been gained. McLean and Nowak (1992) showed that competition for target cells between the sensitive and resistant virus is an important determinant of which type of virus eventually emerges during the course of monotherapy treatment. Such a competition will largely depend on the effectiveness of the treatment administered and the fitness disadvantage incurred as a result of having a drug-resistance mutation. Kepler and Perelson (1998) showed that the range of drug concentrations that favors the dominance of the resistant strain is widened if spatial heterogeneity within the host is accounted for (because of non-uniform drug concentrations throughout the body), compared to a very narrow range from a single compartment assumption. Rong et al (2007) derived expressions specifying conditions under which the resistant strain is selected, and dominate the virus population in the presence of drug pressure (in the absence of backward mutations). Importantly, they showed that even with the coexistence of both sensitive and resistant strains before treatment, the resistant variants are very low in number in comparison to the sensitive ones and drug resistance is much more likely to arise for intermediate levels of treatment effectiveness. Vaidya et al (2010) analyzed the drug resistance dynamics during treatment interruptions assuming both forward and backward mutations. They showed that loss of resistant virus during (fusion inhibitor) treatment interruption was mainly the result of the resistance-associated fitness cost.

Despite the relevant implications that backward mutations have on the virus dynamics, there has not been a systematic study of their effect in a mathematical modeling approach. In order to evaluate the role played by backward mutations, we analyzed a mathematical model for the within-host dynamics of HIV-1. Such a model is defined as an extension of the one in Rong et al (2007) so that it includes backward mutation. We then analyzed the impact of the backward mutation rate on the basic reproductive number of the model, its effect on the existence and stability of infection-free and endemic equilibria, and its role in the emergence of a dominant sensitive strain during periods of ART interruptions.

## 2 Two-strain model in the absence of ART

### 2.1 Model definition

The dynamics of two interacting strains (sensitive and resistant to ART) of HIV-1 within an infected host are studied with a mathematical model based on the classical framework for within-host HIV-1 dynamics as in Nowak et al (1997) and Perelson et al (1996). It explicitly includes five compartments, namely: target $CD4^+$ T-cells, $CD4^+$ T-cells infected with sensitive virus $I_S$, $CD4^+$ T-cells infected with resistant virus $I_I$, sensitive virus $V_S$, and

resistant virus $V_r$. We make the assumption that target cells are produced at a constant rate $\lambda$ and die at a natural death rate $\gamma$. Within the plasma, free HIV-1 interacts with target CD4$^+$ T-cells leading to infection under the assumption of uniform mixing of CD4$^+$ T-cells and HIV-1. Target cells can be infected by either sensitive virus $V_s$ at a rate $\beta$ or resistant virus $V_r$ at a rate $k_1\beta$, where $k_1 \in [0, 1)$ is the relative fitness of the resistant strain in terms of infectivity. Infected cells (with either strain) are assumed to die at a virus-induced death rate $\delta$. Free virions are produced by cells infected with either sensitive or resistant virus at rates $a$ or $k_2a$, respectively, where $k_2 \in (0, 1)$ represents the relative fitness of the resistant strain in terms of viral replication. Due to virus replication errors within infected CD4$^+$ cells, it is assumed that a proportion $q$ of cells infected with sensitive virus will produce resistant virus while a proportion $z$ of cells infected with resistant virus will produce sensitive virus. The proportions $q$ and $z$ represent forward (sensitive to resistant) and backward (resistant to sensitive) mutations of the virus, respectively. Free virus is cleared from the blood plasma at a rate $c$. This model is similar to the one analyzed by Rong et al (2007), with the addition of backward mutations, and to the one used by Vaidya et al (2010) with a more general fitness and treatment effect. The dynamics of the two HIV-1 strains within a host are described graphically in Figure 1 and the corresponding equations are given in System 1.

$$\begin{aligned}
\frac{dT}{dt} &= \lambda - \gamma T - \beta T V_s - k_1 \beta T V_r \\
\frac{dI_s}{dt} &= (1-q)\beta T V_s + z k_1 \beta T V_r - \delta I_s \\
\frac{dI_r}{dt} &= q\beta T V_s + (1-z) k_1 \beta T V_r - \delta I_r \\
\frac{dV_s}{dt} &= a I_s - c V_s \\
\frac{dV_r}{dt} &= k_2 a I_r - c V_r
\end{aligned} \tag{1}$$

## 2.2 Stationary points and stability analysis

All solutions of System 1 are uniformly bounded in a proper subset $\Omega \subset \mathbb{R}^5_+$, where

$$\Omega = \left\{ (T, I_s, I_r, V_s, V_r) \in \mathbb{R}^5_+ : T + I_s + I_r \leq \frac{\lambda}{\gamma} \right\} \tag{2}$$

(Proposition 1 in Appendix).

**2.2.1 Infection-free equilibrium—**In the absence of both sensitive and resistant strains of the virus, the dynamics of CD4$^+$ T-cells are governed by $dT/dt = \lambda - \gamma T$. This leads to a single infection-free stationary point $E_0 = (\lambda/\gamma, 0, 0, 0, 0)$.

The local stability of $E_0$ is governed by the so-called basic reproductive number which is defined as the average number of secondary infected cells arising from one infected cell being placed into an entirely susceptible cell population (Nowak and May, 2000). We employ the systematic method introduced by van den Driessche and Watmough (2002) to compute the basic reproductive number for System 1. To do this, the next generation matrix is computed by consideration of the expected numbers of secondary infections due to a single primary infection in a fully susceptible population, calculated on a class-by-class basis. In the absence of infection, the number of susceptible CD4$^+$ T-cells are $\lambda/\gamma$. A cell

infected with a sensitive strain will be responsible for $(1-q)\beta\lambda/\gamma c$ secondary infections by sensitive virus and $zk_1\beta\lambda/\gamma c$ secondary infections by resistant virus. A cell infected with a resistant strain will be responsible for $q\beta\lambda/\gamma c$ secondary infections by sensitive virus and $(1-z)k_1\beta\lambda/\gamma c$ secondary infections by resistant virus. A sensitive virus will be responsible for an average of $a/\delta$ secondary infections while a resistant virus will be responsible for an average of $k_2a/\delta$ secondary infections. Susceptible cells $T$ are not responsible for any number of secondary infections. We therefore derive the following next generation matrix for System 1:

$$\begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{(1-q)\beta\lambda}{\gamma c} & \frac{zk_1\beta\lambda}{\gamma c} \\ 0 & 0 & 0 & \frac{q\beta\lambda}{\gamma c} & \frac{(1-z)k_1\beta\lambda}{\gamma c} \\ 0 & \frac{a}{\delta} & 0 & 0 & 0 \\ 0 & 0 & \frac{k_2a}{\delta} & 0 & 0 \end{bmatrix}.$$

The spectral radius (largest eigenvalue) of this matrix defines the reproductive number for System 1. Since the matrix entries are all positive, one of the eigenvalues is simple and positive. For easier biological interpretation, we define our basic reproductive number as the square of the spectral radius of the above matrix:

$$R_0=\frac{\lambda\beta a}{2\gamma\delta c}\left[(1-q)+k_1k_2(1-z)+\sqrt{[(1-q)+k_1k_2(1-z)]^2-4k_1k_2(1-q-z)}\right] \quad (3)$$

One can recover previous (known) expressions of the basic reproductive number for models used elsewhere. For instance, when $z = 0$, i.e, when there are no backward mutations, we obtain the $R_0$ given in Rong et al (2007):

$$R_0'=\frac{\lambda\beta a(1-q)}{\gamma\delta c}.$$

Likewise, when there are no forward mutations either (i.e., $q = z = 0$), and therefore no acquired resistance, the basic reproductive number is then

$$\overline{R}_0=\frac{\lambda\beta a}{\gamma\delta c},$$

which corresponds to the basic reproductive number for a model of viral dynamics without resistance, as in Perelson et al (1996) and Nowak et al (1997).

Following Theorem 2 in van den Driessche and Watmough (2002), it is shown that the infection-free steady-state $E_0$ is locally asymptotically stable whenever $R_0 < 1$, while it is unstable otherwise. Moreover, using Theorem 1 from Castillo-Chávez et al (2002) we can show that $E_0$ is in fact globally asymptotically stable provided $R_0 < 1$ (Theorem 1 in Appendix).

**2.2.2 Endemic state—**As $R_0$ increases above 1, the infection-free stationary point loses its stability and a unique endemic steady-state in $\Omega$ emerges (Theorem 2 in Appendix). This is shown graphically as a bifurcation diagram in Figure 2. This unique endemic equilibrium $E_1 = (T^*, I_s^*, I_r^*, V_s^*, V_r^*)$ is given by

$$T^* = \frac{\lambda}{\gamma}\frac{1}{R_0}$$
$$I_s^* = \frac{z\lambda}{\delta}\frac{\left(1-\frac{1}{R_0}\right)}{\left(1-(1-q-z)\frac{\overline{R}_0}{R_0}\right)}$$
$$I_r^* = \frac{q\lambda}{\delta}\frac{\left(1-\frac{1}{R_0}\right)}{\left(1-(1-q-z)k_1k_2\frac{\overline{R}_0}{R_0}\right)}$$
$$V_s^* = \frac{a}{c}I_s^*$$
$$V_r^* = \frac{k_2 a}{c}I_r^*$$

where $\overline{R}_0$ is the basic reproductive number for the model with no mutation as given above.

It can be shown that $E_1$ is locally asymptotically stable whenever $R_0 > 1$ (Theorem 3 in Appendix). Numerical simulations (using a Latin Hypercube design to sample over the parameter space and the set of initial conditions) suggest that the endemic equilibrium $E_1$ is globally asymptotically stable whenever $R_0 > 1$.

## 2.3 Effect of mutations on viral dynamics

The above findings imply that as long as $R_0 > 1$, coexistence of sensitive and resistant strains is guaranteed. Because of fitness cost on cell infection and viral replication, the drug resistant strain is usually out-competed by the sensitive strain in terms of population abundance. This sensitive strain's dominance is shown to hold in the steady-state whenever

$$\frac{z}{q} > \frac{k_2\left(1-(1-q-z)\frac{\overline{R}_0}{R_0}\right)}{\left(1-(1-q-z)k_1k_2\frac{\overline{R}_0}{R_0}\right)} \quad (4)$$

(Theorem 5 in Appendix). From Inequality 4, the dominance of the sensitive strain only depends on forward and backward mutation rates, and the relative fitness in both infectivity and productivity of the resistant virus. The dominance of sensitive strain is favored by a less fit resistant strain (small values of $k_1$ and $k_2$) and a higher backward mutation rate $z$. Figure 3a provides an analysis of Inequality 4. In Figure 3a, the RHS of Inequality (Theorem 5 in Appendix). From Inequality 4, the dominance of the sensitive strain only depends on forward and backward mutation rates, and the relative fitness in both infectivity and productivity of the resistant virus. The dominance of sensitive strain is favored by a less fit resistant strain (small values of $k_1$ and $k_2$) and a higher backward mutation rate $z$. Figure 3a provides an analysis of Inequality 4. In Figure 3a, the RHS of Inequality 4 (in logarithmic scale) is drawn as a function of $z/q$ (also in logarithmic scale) for a few values of the resistant strain's relative fitness ($k_1 = 1$, $k_2 = 0.9, 0.999, 1$). The resulting curves are then compared to $z/q$, i.e., the LHS of Inequality 4, given by the line separating the unshaded

from the shaded region. Hence, the sensitive strain is dominant, i.e., Inequality 4 holds, whenever the curve is inside the shaded region. So, a resistant strain with a relative fitness of 90% ($k_2 = 0.9$) would be out-competed by the sensitive strain, while a resistant strain with a relative fitness as high as 99.9% ($k_2 = 0.999$) would require a forward mutation rate more than 10 times higher than the backward mutation rate (i.e., the curve corresponding to $k_2 = 0.999$ intersects the border between unshaded and shaded regions at around $\log_{10}(z/q) = -1.2$ in Figure 3a). When the resistant strain has no fitness cost (i.e., when $k_1 = k_2 = 1$), it is the balance between the forward and backward mutation rates that determine the dominant strain, with the backward mutation rate favoring the sensitive strain. Therefore, the sensitive strain will mostly out-compete the resistant strain whenever there are resistance-associated fitness costs.

Figure 4 shows the effect of a) forward and c) backward mutation rates on the equilibrium values of sensitive and resistant viral loads. As the forward mutation rate increases (and the backward mutation rate is kept constant), the resistant strain viral load increases (although still at much lower levels than the sensitive strain) while the sensitive strain viral load remains unchanged (Figure 4a). On the other hand, varying the backward mutation rate has no effect on either strain's viral load (Figure 4c).

As shown above, the value of the basic reproductive number determines the outcome of infection, into either complete clearance or infection persistence. Given the fitness cost of the resistant strain on transmission rate and viral production, the presence of forward mutations makes infection persistence more difficult to achieve $(R_0 < \overline{R}_0 \text{ and } R_0' < \overline{R}_0)$. On the other hand, whenever forward mutations are present, the presence of backward mutations increases the chance of infection persistence as the less-fit virus mutates back to the fitter one $(R_0' < R_0)$. Proofs of these statements are given in the Appendix (Theorems 6 and 7). In practice, the effect of mutation rates on the basic reproductive number is minimal as $R_0 \in [R_0', \overline{R}_0]$ with the length of the interval $\overline{R}_0 - R_0' = q\overline{R}_0$.

The above observations are consistent with an analysis of the basic reproductive number, $R_0$, as a function of forward and backward mutation rates, $q$ and $z$, respectively. Increasing the backward mutation rate $z$ leads to an increase in the basic reproductive number $R_0$, while increasing the forward mutation rate $q$ reduces the value of $R_0$ (Theorem 8 in Appendix).

## 3 Two-strain model under ART

### 3.1 Model definition

In this modeling approach, only two types of ART drugs are considered: reverse transcriptase (RT) inhibitors and protease inhibitors (PI). An RT inhibitor acts on the RT enzyme of the virus, suppressing transcription of viral RNA into viral DNA. This is modeled by decreasing the transmission rate by a factor $(1 - \varepsilon_{rt})$, where $\varepsilon_{rt} \in [0,1]$ denotes the RT drug efficiency. The efficiency of the RT inhibitor is reduced by a factor $p_1 \in [0,1)$ for the resistant strain. Therefore, its transmission rate is reduced by a factor $(1 - p_1\varepsilon_{rt})$.

Similarly, a PI acts on the protease enzyme of the virus, leading to assembly of defective viral particles (which are unable to infect other target cells). In the model, this reduces the rate of viral production per cell by a factor $(1 - \varepsilon_{pi})$, where $\varepsilon_{pi} \in [0,1]$ denotes the PI efficiency. As for the RT, the effect of the PI inhibitor on the resistant strain is reduced by a factor $p_2 \in [0,1)$, leading to a reduction factor on viral production of $(1 - p_2\varepsilon_{pi})$. Note that defective particles are still produced by infected cells under a PI inhibitor and will contribute to overall viral load, but these are not modeled explicitly as they do not contribute to new infections.

$$\begin{aligned}
\frac{dT}{dt} &= \lambda - \gamma T - (1-\varepsilon_{rt})\beta T V_s - (1-p_1\varepsilon_{rt})k_1\beta T V_r \\
\frac{dI_s}{dt} &= (1-q)(1-\varepsilon_{rt})\beta T V_s + z(1-p_1\varepsilon_{rt})k_1\beta T V_r - \delta I_s \\
\frac{dI_r}{dt} &= q(1-\varepsilon_{rt})\beta T V_s + (1-z)(1-p_1\varepsilon_{rt})k_1\beta T V_r - \delta I_r \\
\frac{dV_s}{dt} &= (1-\varepsilon_{pi})aI_s - cV_s \\
\frac{dV_r}{dt} &= (1-p_2\varepsilon_{pi})k_2 a I_r - cV_r
\end{aligned} \tag{5}$$

The full model of viral dynamics of two strains under ART is given in System 5, which is in general agreement to previous models of drug therapy from literature (Perelson, 2002; Rong et al, 2007; Vaidya et al, 2010).

### 3.2 Stationary points and stability analysis

System 5 is equivalent to System 1 under the transformations $\beta = (1 - \varepsilon_{rt})\beta$, $a = (1 - \varepsilon_{pi})a$, $k_1 = (1 - p_1\varepsilon_{rt})/(1 - \varepsilon_{rt})k_1$ and $k_2 = (1 - p_2\varepsilon_{pi})/(1 - \varepsilon_{pi})k_2$. These transformations lead to a basic reproductive number given by:

$$\hat{R}_0 = \frac{\lambda\beta a}{2\gamma\delta c}\left[\varepsilon_s(1-q) + \varepsilon_r k_1 k_2(1-z) + \sqrt{\left[\varepsilon_s(1-q) + \varepsilon_r k_1 k_2(1-z)\right]^2 - 4\varepsilon_s\varepsilon_r k_1 k_2(1-q-z)}\right] \tag{6}$$

where

$$\varepsilon_s = (1-\varepsilon_{rt})(1-\varepsilon_{pi}) > 0 \text{ and } \varepsilon_r = (1-p_1\varepsilon_{rt})(1-p_2\varepsilon_{pi}) > 0.$$

Previous results on the stability of steady-states hold by the equivalence of Systems 1 and 5. Therefore, whenever $\hat{R}_0 < 1$, solutions of 5 will approach the infection-free steady-state $\hat{E}_0 = E_0$. Indeed, $\hat{E}_0$ is globally asymptotically stable.

Likewise, for $\hat{R}_0 > 1$, there is a unique endemic equilibrium $\hat{E}_1 = (\hat{T}^*, \hat{I}_s^*, \hat{I}_r^*, \hat{V}_s^*, \hat{V}_r^*)$ in $\Omega$ given by

$$\hat{T}^*=\frac{\lambda}{\gamma}\frac{1}{\hat{R}_0}$$
$$\hat{I}_s^*=\frac{z\lambda}{\delta}\frac{\left(1-\frac{1}{\hat{R}_0}\right)}{\left(1-(1-q-z)\varepsilon_s\frac{\overline{R}_0}{\hat{R}_0}\right)}$$
$$\hat{I}_r^*=\frac{q\lambda}{\delta}\frac{\left(1-\frac{1}{\hat{R}_0}\right)}{\left(1-(1-q-z)\varepsilon_r k_1 k_2\frac{\overline{R}_0}{\hat{R}_0}\right)}$$
$$\hat{V}_s^*=\frac{(1-\varepsilon_{pi})a}{c}\hat{I}_s^*$$
$$\hat{V}_r^*=\frac{(1-p_2\varepsilon_{pi})k_2 a}{c}\hat{I}_r^*$$

obtained by applying the transformations above. Thus, it follows that $\hat{E}_1$ is locally asymptotically stable (and presumably globally stable) whenever $\hat{R}_0>1$.

### 3.3 Effect of mutations on viral dynamics

As ART gives the resistant strain an advantage over the sensitive strain on transmission and viral replication, the resistant strain will now dominate the dynamics (in the long run) for most parameter combinations. In fact, the sensitive strain would be dominant only if

$$\frac{z}{q}>\frac{(1-p_2\varepsilon_{pi})}{(1-\varepsilon_{pi})}\frac{k_2\left(1-(1-q-z)\varepsilon_s\frac{\overline{R}_0}{R_0}\right)}{\left(1-(1-q-z)\varepsilon_r k_1 k_2\frac{\overline{R}_0}{R_0}\right)} \quad (7)$$

which is harder to achieve when increasing either the drug efficacy on the sensitive strain (lower $\varepsilon_s$) or the drug escape by the resistant strain (larger $\varepsilon_r$) (Theorem 9 in Appendix). From Inequality 7, the factors determining whether or not the resistant strain will out-compete the sensitive strain include forward and backward mutations, the relative fitness of the resistant virus, and the drug efficacies to either strain. Figure 3b provides an analysis of Inequality 7. Analogous to the case without ART (Figure 3a), the RHS of Inequality 7 is drawn as a function of the ratio of mutation rates ($z/q$) and compared to $z/q$ (the LHS of Inequality 7); so that the sensitive strain is dominant whenever the curve is inside the shaded region (Figure 3b). For the curves given as examples, the resistant strain's relative fitness is fixed to $k_1 = 1$ and $k_2 = 0.9$, and its drug sensitivity is taken as $p_1 = p_2 = 0$ (i.e., fully resistant), while the drug efficacy on the sensitive strain is varied as $\varepsilon_{rt} = 0$, $\varepsilon_{pi} = 0, 0.1, 0.9$. When $\varepsilon_{pi} = 0$, we are into the case where ART is not present and the sensitive strain is always dominant. As the drug efficacy increases, the inhibitory effect of the drug on the sensitive strain counter balances the fitness cost of the resistant strain. For instance, when $\varepsilon_{pi} = 0.1$ (for $k_2 = 0.9$), there is a perfect balance between strains and therefore, the dominant strain i determined by the mutation rates (with the forward mutation rate favoring the resistant strain). As soon as $\varepsilon_{pi} > 0.1$, a greater backward mutation rate (relative to the forward mutation rate) is required to allow the dominance of the sensitive strain. For instance, for a drug efficacy of $\varepsilon_{pi} = 0.9$, the backward mutation rate would have to be around 40 times faster than the forward mutation rate.

Figure 4 (right column) shows the effect of forward and backward mutation rates on the viral load of both strains. Contrary to the case where ART is not present, the backward mutation rate $z$ plays a major role in the steady-state value of the sensitive strain viral load with approximately a 10-fold increase (decrease) in viral load for each 10-fold increase (decrease) in the backward mutation rate (Figure 4b). On the other hand, the forward mutation rate does not have any impact on either viral load (Figure 4b). The effect of forward and backward mutations on $\hat{R}_0$ is reversed in the presence of ART, that is, increasing the forward mutation rate $q$ increases $\hat{R}_0$ while increasing the backward mutation rate $z$ decreases $\hat{R}_0$, with the extra requirement that $k_1 k_2 \varepsilon_r > \varepsilon_s$ (Theorem 10 in Appendix).

### 3.4 Role of backward mutations during treatment interruptions

As discussed above, the sensitive strain mostly dominates dynamics in the absence of ART, while during ART it is easier for the resistant strain to out-compete the sensitive strain. Simulated dynamics of System 5 for two different scenarios are shown in Figure 5. In each case, the simulations were run for a period of one year without ART followed by two treatment windows separated by a period of one month off ART. In the first scenario, it is assumed that the backward mutation rate is zero, $z = 0$ (Figure 5a), while in the second case, the backward mutation rate is non-zero (Figure 5b). The rest of the parameters are the same for both simulations. In both cases, the sensitive strain is dominant during the period without ART. On introduction of ART, the resistant strain becomes the dominant strain in both cases. However, in the absence of backward mutations, the population of the sensitive strain dies out and cannot re-emerge on interruption of treatment (Figure 5a). In Figure 5b, the sensitive strain quickly dominates dynamics on interruption of ART but is replaced by the resistant strain when ART is resumed. In both cases, the steady-state values remain the same after the treatment interruption as the interruption only acts to perturb the equilibrium value, which is quickly restored on resumption of ART. An increase in steady-state target cells is noted during ART administration (Figure 5c), which is explained by the direct effect of ART on the sensetive strain and the fitness cost of the resistant (see $\hat{T}^*$ above).

## 4 Discussion

We have shown that for the within-host model of two strains of HIV-1 with both forward and backward mutations, in either the absence or presence or ART (Systems 1 and 5, respectively), there is only one endemic state inside the feasible region (with coexistence of sensitive and resistant strains). The existence and stability of this point is determined by the basic reproduction number. Furthermore, numerical simulations suggest this unique endemic equilibrium is globally asymptotically stable. The uniqueness of the endemic equilibrium in the model with backward mutations contrasts with that of a two-strain model with forward mutations only, which has two endemic equilibria in the feasible region (Rong et al, 2007). One of these equilibria provides coexistence of strains, as in the model discussed here, while the other implies extinction of the sensitive strain. Our findings show that this latter equilibrium is pushed outside the feasible region when backward mutations are introduced.

Our results also include conditions necessary for a specific strain to out-compete the other (in terms of relative abundance, since as discussed above, both strains coexist or both die

out). In the absence of treatment, the condition for the dominance of the sensitive strain is given in terms of both mutation rates and the relative fitness of the resistant strain (Inequality 4). Not surprisingly, it is easier for the sensitive strain to dominate the dynamics because of the fitness cost of drug resistance. Although the mutation rates could theoretically overcome the effect of fitness cost, it would require unrealistic values for such rates. On introduction of ART, the condition for the dominance of the sensitive strain becomes also dependent on drug efficacies, so that, as the efficacies of treatment increase, it becomes increasingly difficult for the sensitive strain to dominate and hence the resistant strain takes over (Inequality 7).

For the model where ART is not present, forward mutations have the greatest effect on the steady-state value for the resistant strain, while backward mutations do not play any significant role on equilibrium values (Figure 4). Introduction of treatment swaps the roles of forward and backward mutations, with changes in forward mutations being insignificant on steady-state values and changes in backward mutations having the greatest effect on the sensitive strain (Figure 4). The above results are expected, as in each case either mutation favors the strain that is less fit for that specific environment (absence or presence of ART). A similar pattern is observed for the basic reproductive number. In the absence of ART, the basic reproductive number increases as the backward mutation rate increases, while it decreases as the forward mutation rate increases. This relationship is reversed in the presence of ART, with the basic reproductive number decreasing with an increase in the backward mutation rate and increasing with an increase in the forward mutation rate.

Vaidya et al (2010) showed that the rapid replacement of resistant virus during therapy interruptions is mainly due to the resistance-associated fitness loss rather than backward mutations. However, as shown in Figure 5, backward mutations are essential to the eventual emergence of the sensitive strain as they provide a mechanism for the persistence of the sensitive strain within a host during ART. On interruption of ART, the prior existence of a fitter sensitive strain within a host leads to a swift emergence of the sensitive virus as the dominant strain. Nonetheless, this may not be the only mechanism for persistence of the sensitive strain during ART. For instance, it has been shown that long-lived latently infected cells are the main contributor for a slowdown of virus decay during treatment (Perelson et al, 1997), which may help a less fit virus strain to survive until the environment changes (e.g., treatment interruptions). Similarly, the variability of drug efficacies in different tissues (Boffito et al, 2005) may provide a reservoir for the sensitive strain, which would allow it to survive during ART and re-emerge when treatment is suspended.

There are several limitations to the present study. For instance, only a single resistant strain was considered, although many other resistant strains could be present and these may possess different fitness costs and mutation rates. A multi-strain model taking all this into consideration could be analyzed to further study the role of backward mutations. Moreover, it was assumed that the drug efficacies for both RT and PI were constant throughout the treatment period. This may not be always true since drugs are assimilated at different rates by the body and their distribution can vary between tissues. Compartmentalization of HIV-1 infection, which allows for evolution of distinct HIV-1 variants in different parts of the host, cannot be reproduced by the present model. This present model could be extended to a

multi-compartment model, although detailed data on the dynamics of viral strains in each compartment would be required for a meaningful parameterization of the model.

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## Appendix: Proofs of results

**Proposition 1 Boundedness of solutions:** *The closed positive 5-dimensional orthant, defined as* $\mathbb{R}^5_+ = \left\{x \in \mathbb{R}^5 \backslash x \geq 0\right\}$ *is positive invariant for System 1 and there exists* $M > 0$ *such that all solutions satisfy* $T(t)$, $I_s(t)$, $I_r(t)$, $V_s(t)$, $V_r(t) < M$ *for all large* $t$.

*Proof* Positive invariance follows from the fact that all solutions are uniformly bounded in a proper subset $\Omega$. To show that solutions of System 1 are bounded, let $\hat{T}$ be the steady-state of susceptible cells present before infection. In a healthy individual, the T-cell population dynamics are regulated by $f(T) = \lambda - \gamma T$, where, $f(T)$ is a smooth function and $f(T) > 0$ for $0 < T < \hat{T}$. Furthermore, $f(\hat{T}) = 0$ with $f'(\hat{T}) < 0$ and $f(T) < 0$ whenever $T > \hat{T}$.

From the first equation of System 1, we note that $\frac{dT}{dt} \leq f(T)$. This means that there exists a $t_0 > 0$ such that $T(t) < \hat{T} + 1$ for $t > t_0$. Let $S = \max_{T \geq 0} f(T)$. Adding the first three equations of System 1, we obtain

$$\frac{dT}{dt} + \frac{dI_s}{dt} + \frac{dI_r}{dt} = f(T) - \delta(I_s + I_r) \leq S - \delta(I_s + I_r).$$

Let $A, B > 0$ be such that $\delta(A + B) > S + 1$. Then as long as

$$T(t) + I_s(t) + I_r(t) \geq A + B + \hat{T} + 1$$

and $t > t_0$, we have that

$$\frac{dT}{dt} + \frac{dI_s}{dt} + \frac{dI_r}{dt} < -1.$$

Clearly, there exists $t_1 > t_0$ such that

$$T(t) + I_s(t) + I_r(t) < A + B + \hat{T} + 1$$

for all $t > t_1$.

Adding the last two equations, we get





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$$\frac{dV_s}{dt}+\frac{dV_r}{dt}=aI_s+k_2aI_r-c(V_s+V_r).$$

The asymptotic bound for $I_s$ is $I_s(t)<A+\hat{T}+1$ while that of $I_r$ is $I_r(t)<B+\hat{T}+1$. Considering the asymptotic bounds for both $I_s$ and $I_r$ together with the differential inequality

$$\frac{dV_s}{dt}+\frac{dV_r}{dt}\leq -c(V_s+V_r)+a(A+k_2B+(1+k_2)\hat{T}+1+k_2),$$

which holds for large $t$, yields the asymptotic bound below;

$$c^{-1}a(A+k_2B+(1+k_2)\hat{T}+1+k_2).$$

**Theorem 1 Global stability of infection-free state:** *The infection-free equilibrium $E_0$ is globally asymptotically stable provided $R_0 < 1$.*

*Proof* To prove global stability of the disease free equilibrium $E_0$, we use Theorem 1 adopted from Castillo-Chávez et al (2002). We can write System 1 in the form

$$X'(t)=F(X,Y)$$
$$Y'(t)=G(X,Y),\quad G(X,0)=0$$

where $X = (T)$ and $Y = (I_s, I_r, V_s, V_r)$ with $X\in \mathbf{R}_+$ and $Y \in \mathbb{R}^4_+$.

Taking $F(X, 0) = [\lambda - \gamma T]$,

$$A=\begin{bmatrix} -\delta & 0 & (1-q)\beta\lambda/\gamma & zk_1\beta\lambda/\gamma \\ 0 & -\delta & q\beta\lambda/\gamma & (1-z)k_1\beta\lambda/\gamma \\ a & 0 & -c & 0 \\ 0 & k_2a & 0 & -c \end{bmatrix}$$

and

$$\hat{G}(X,Y)=\begin{bmatrix} (1-q)\beta\lambda V_s/\gamma+zk_1\beta\lambda V_r/\gamma-(1-q)\beta TV_s-zk_1\beta TV_r \\ q\beta\lambda V_s/\gamma+(1-z)k_1\beta\lambda V_r/\gamma-q\beta TV_s-(1-z)k_1\beta TV_r \\ 0 \\ 0 \end{bmatrix}.$$

Since $\limsup_{t\to\infty} T(t)\leq \frac{\lambda}{\gamma}$, we have that $\hat{G}(X, Y) \geq 0$ for all $(X, Y) \in \Omega$.

Therefore $G(X, Y) = AY - \hat{G}(X, Y)$, where $\hat{G}(X, Y) \geq 0$ for $(X, Y) \in \Omega$, and applying Theorem 1 from Castillo-Chávez et al (2002), the fixed point $E_0$ is globally asymptotically stable, provided, $R_0 < 1$.

**Theorem 2 Uniqueness of endemic equilibrium:** *$E_1$ is in $\Omega$ if and only if $R_0 > 1$. Moreover, $E_1$ is a unique endemic equilibrium in $\Omega$ whenever it exists.*

*Proof* Substituting $E_1=(T^*, I_s^*, I_r^*, V_s^*, V_r^*)$ into System 1 shows that $E_1$ is a stationary point. From second and third equations of System 1, we obtain

$$I_s^*+I_r^*=\frac{1}{\delta}(\lambda-\gamma \mathrm{T}^*),$$

then

$$T^*+I_s^*+I_r^*=\frac{\lambda}{\gamma}\frac{1}{R_0}+\frac{1}{\delta}\left(\lambda-\gamma\frac{\lambda}{\gamma}\frac{1}{R_0}\right)=\frac{\lambda}{\gamma}\frac{1}{R_0}+\frac{\lambda}{\delta}\left(1-\frac{1}{R_0}\right)\leq\frac{\lambda}{\delta}$$

as long as $\delta \geq \gamma$.

Note that, as $k_1k_2 < 1$,

$$(1-q-z)-(1-q-k_1k_2z)<0.$$

Thus,

$$(1-q-z)^2-(1-q-z)[(1-q)+k_1k_2(1-z)]<-k_1k_2(1-q-z)$$

(under the assumption that $1 - q - z > 0$). Multiplying by 4 and adding $[(1 - q) + k_1k_2(1 - z)]^2$ to both sides of the inequality leads to

$$\{2(1-q-z)-[(1-q)+k_1k_2(1-z)]\}^2<[(1-q)+k_1k_2(1-z)]^2-4k_1k_2(1-q-z).$$

Therefore,

$$2(1-q-z)-[(1-q)+k_1k_2(1-z)]<\sqrt{[(1-q)+k_1k_2(1-z)]^2-4k_1k_2(1-q-z)}.$$

and so

$$2(1-q-z)<\frac{1}{2}\left\{(1-q)+k_1k_2(1-z)+\sqrt{[(1-q)+k_1k_2(1-z)]^2-4k_1k_2(1-q-z)}\right\}.$$

Hence, multiplying by $\overline{R}_0=\frac{a\beta\lambda}{\delta\gamma c}$, we obtain $(1-q-z)\overline{R}_0<R_0$ (and then $(1-q-z)k_1k_2\overline{R}_0<R_0$). Therefore $I_s^*>0$ (and $I_r^*$) if and only if $R_0 > 1$, which implies $E_1 \in \Omega$ iff $R_0 > 1$

To show that $E_1$ is the only endemic equilibrium in $\Omega$, assume that there is another such equilibrium $E_2=(\hat{T},\hat{I}_s,\hat{I}_r,\hat{V}_s,\hat{V}_r)$ in $\Omega$. Note that by solving for stationary points, $\hat{T}$ must be a solution of the quadratic equation

$$\left(\frac{a\beta}{c}\right)^2(1-q-z)k_1k_2\hat{T}^2-[(1-q)+(1-z)k]\left(\frac{a\beta}{c}\right)\delta\hat{T}+\delta^2=0.$$

Then

$$\hat{T}=\frac{c\delta}{2k_1k_2a\beta(1-q-z)}\left[(1-q)+k_1k_2(1-z)+\sqrt{[(1-q)+k_1k_2(1-z)]^2-4k_1k_2(1-q-z)}\right]$$

(note that the other root of the above quadratic equation is $T^*$). As for $E_1$, $\hat{I}_s+\hat{I}_r=\lambda-\gamma\hat{T}$, so if $\lambda-\gamma\hat{T}<0$, then $E_2\notin\Omega$. So assume that $\lambda-\gamma\hat{T}>0$. Thus

$$\hat{I}_r=\frac{q(\lambda-\gamma\hat{T})}{\delta-(1-q-z)\frac{a\beta}{c}\hat{T}}.$$

Since $k_1k_2<1$ we have

$$k_1k_2+(1-q-z)<(1-q)+k_1k_2(1-z)$$

and then

$$(2k_1k_2)^2-4k_1k_2[(1-q)+k_1k_2(1-z)]<-4k_1k_2(1-q-z).$$

This implies that

$$\{2k_1k_2-[(1-q)+k_1k_2(1-z)]\}^2<[(1-q)+k_1k_2(1-z)]^2-4k_1k_2(1-q-z)$$

and so

$$2k_1k_2-[(1-q)+k_1k_2(1-z)]<\sqrt{[(1-q)+k_1k_2(1-z)]^2-4k_1k_2(1-q-z)}.$$

Thus

$$1<\frac{1}{2k_1k_2}\left\{[(1-q)+k_1k_2(1-z)]+\sqrt{[(1-q)+k_1k_2(1-z)]^2-4k_1k_2(1-q-z)}\right\}.$$

This implies that $\delta-(1-q-z)\frac{a\beta}{c}\hat{T}<0$ and so $\hat{I}_r<0$. Therefore $E_2\notin\Omega$.

**Theorem 3 Local stability of endemic equilibrium:** *If* $R_0 > 1$, *the unique endemic equilibrium* $E_1$ *is locally asymptotically stable*.

Using the standard linearization of the model to determine the local stability of $E_1$ is very laborious to track mathematically. For this reason, we employ the centre manifold theory (Carr, 1981) as described in Castillo-Chávez and Song (2004) to establish the local asymptotic stability of $E_1$.

Making the following change of variables; $T = x_1$, $I_s = x_2$, $I_r = x_3$, $V_s = x_4$ and $V_r = x_5$. Therefore, we get

$$\frac{dX}{dt} = F = (f_1, f_2, f_3, f_4, f_5)^T$$

such that

$$\begin{aligned} x'_1(t) &= f_1 = \lambda - \gamma x_1 - \beta x_1 x_4 - k_1 \beta x_1 x_5 \\ x'_2(t) &= f_2 = (1-q)\beta x_1 x_4 + z k_1 \beta x_1 x_5 - \delta x_2 \\ x'_3(t) &= f_3 = q\beta x_1 x_4 + (1-z) k_1 \beta x_1 x_5 - \delta x_3 \\ x'_4(t) &= f_4 = a x_2 - c x_4 \\ x'_5(t) &= f_5 = k_2 a x_3 - c x_5 \end{aligned}$$

The corresponding Jacobian matrix at the disease free equilibrium is given by

$$J(E_0) = \begin{bmatrix} -\gamma & 0 & 0 & \frac{-\beta\lambda}{\gamma} & -\frac{k_1\beta\lambda}{\gamma} \\ 0 & -\delta & 0 & \frac{(1-q)\beta\lambda}{\gamma} & \frac{z k_1 \beta\lambda}{\gamma} \\ 0 & 0 & -\delta & \frac{q\beta\lambda}{\gamma} & \frac{(1-z)k_1\beta\lambda}{\gamma} \\ 0 & a & 0 & -c & 0 \\ 0 & 0 & k_2 a & 0 & -c \end{bmatrix}.$$

If $\beta$ is taken as the bifurcation point and we consider the case when $R_0 = 1$, then

$$\beta = \beta^* = \frac{2\delta\gamma c}{a\lambda(k_1 k_2(1-z) + (1-q) + \sqrt{[(1-q) + k_1 k_2(1-z)]^2 - 4k_1 k_2(1-q-z))}}.$$

The resultant linearized system of the transformed model with $\beta = \beta^*$ has a simple zero eigenvalue. This means that the centre manifold theory (Carr, 1981) can be employed to analyze the dynamics of the model near the bifurcation parameter value $\beta^*$. The Jacobian, $J(E_0)$ at $\beta^*$ has a right eigenvector associated with the zero eigenvalue given by $u = [u_1, u_2, u_3, u_4, u_5]$, where

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$$u_1=\frac{k_1\beta\lambda[(1-q-z)a\beta\lambda-\delta c\gamma]}{\gamma^2[\delta c\gamma-(1-q)a\beta\lambda]}u_5,$$
$$u_2=\frac{zk_1\beta\lambda c}{\delta c\gamma-(1-q)a\beta\lambda}u_5,$$
$$u_3=\frac{c}{k_2 a}u_5,$$
$$u_4=\frac{zk_1\beta\lambda a}{\delta c\gamma-(1-q)a\beta\lambda}u_5,$$
$$u_5=u_5>0.$$

The left eigenvector for $J(E_0)$ associated with the zero eigenvalue is given by $v = [v_1, v_2, v_3, v_4, v_5]$, where

$$v_1=0,$$
$$v_2=\frac{qk_2a^2\beta\lambda}{\delta[\delta c\gamma-(1-q)a\beta\lambda]}v_5,$$
$$v_3=\frac{k_2 a}{\delta}v_5,$$
$$v_4=\frac{qk_2a\beta\lambda}{\delta c\gamma-(1-q)a\beta\lambda}v_5,$$
$$v_5=v_5>0.$$

We state without proof, Theorem 4 as outlined in Castillo-Chávez and Song (2004).

**Theorem 4 Castillo-Chávez and Song:** *Consider the following general system of ordinary differential equations with a parameter* $\phi$

$$\frac{dx}{dt}F(x,\phi), f:\mathbb{R}^n\times\mathbb{R}\, and\, f\in\mathbb{R}^2(\mathbb{R}^n\times\mathbb{R}), \quad (8)$$

*where* 0 *is the equilibrium of the system i.e,* $f(0, \phi) = 0$ *for all* $\phi$ *and assume*

**A1:** $A=D_x f(0,0)=\left(\frac{\partial f_i}{\partial x_j}(0,0)\right)$ *is the linearization of System 8 around the equilibrium* 0 *evaluated with* $\phi = 0$. *Then, zero is a simple eigenvalue of A and other eigenvalues of A have negative real parts.*

**A2:** *Matrix A has a right eigenvector u and a left eigenvector v corresponding to the zero eigenvalue.*

*Let* $f_k$ *be the kth component of f and*

$$\hat{a}=\sum_{k,i,j=1}^{n} v_k u_i u_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0),$$

$$\hat{b}=\sum_{k,i=1}^{n} v_k u_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0,0).$$

*The local dynamics of 8 are completely governed by* $\hat{a}$ *and* $\hat{b}$ *as follows:*

**(i)** $\hat{a} > 0, \hat{b}_{>0}$. *When* $\phi < 0$ *with* $|\phi| << 1$, 0 *is locally asymptotically stable and there exists a positive unstable equilibrium; when* $0 < \phi << 1$, 0 *is unstable and there exists a negative and locally asymptotically stable equilibrium*.

**(ii)** $\hat{a} < 0, \hat{b}_{<0}$. *When* $\phi < 0$ *with* $|\phi| << 1$, 0 *is unstable; when* $0 < \phi << 1$, 0 *is locally asymptotically stable and there exists a positive unstable equilibrium*.

**(iii)** $\hat{a} > 0, \hat{b}_{<0}$. *When* $\phi < 0$ *with* $|\phi| << 1$, 0 *is unstable and there exists a locally asymptotically stable negative equilibrium; when* $0 < \phi << 1$, 0 *is stable and a positive unstable equilibrium appears*.

**(iv)** $\hat{a} < 0, \hat{b}_{>0}$. *When* $\phi$ *changes from negative to positive*, 0 *changes its stability from stable to unstable. Correspondingly, a negative unstable equilibrium becomes positive and locally asymptotically stable*.

*4.0.1 Computation of* $\hat{a}$ *and* $\hat{b}$

For System 1, the associated nonzero partial derivatives of $F$ at the disease free equilibrium $E_0$ are given by

$$\frac{\partial^2 f_1}{\partial x_1 \partial x_4} = -\beta, \frac{\partial^2 f_1}{\partial x_1 \partial x_5} = -k_1\beta, \frac{\partial^2 f_2}{\partial x_1 \partial x_4} = (1-q)\beta, \frac{\partial^2 f_2}{\partial x_1 \partial x_5} = zk_1\beta, \frac{\partial^2 f_3}{\partial x_1 \partial x_4} = q\beta \frac{\partial^2 f_3}{\partial x_1 \partial x_5} = (1-z)k_1\beta.$$

Therefore, it follows that

$$\begin{aligned}\hat{a} &= -\beta^* v_1 u_1 u_4 - k_1\beta^* v_1 u_1 u_5 + (1-q)\beta^* v_2 u_1 u_4 + zk_1\beta^* v_2 u_1 u_5 + q\beta^* v_3 u_1 u_4 + (1-z)k_1\beta^* v_3 u_1 u_5 \\ &= (1-q)\beta^* v_2 u_1 u_4 + zk_1\beta^* v_2 u_1 u_5 + q\beta^* v_3 u_1 u_4 + (1-z)k_1\beta^* v_3 u_1 u_5 \\ &= \frac{k_1^2 k_2 a\beta^{*2}\lambda[(1-q-z)a\beta^*\lambda - \delta\gamma c]\theta}{\delta\gamma^2[\delta c\gamma - (1-q)a\beta^*\lambda]^3}\end{aligned}$$

(9)

where

$$\theta = [z(1-q)qa^2\beta^{*2}\lambda^2 + (za\beta^*\lambda + qza\lambda)(\delta c\gamma - (1-q)a\beta^*\lambda) + (1-z)(\delta c\gamma - (1-q)a\beta^*\lambda)^2]$$

It is observed that

$$\delta c\gamma - (1-q)a\beta^*\lambda > 0$$

for all possible parameter values. Assume that $\delta c\gamma - (1-q)a\beta^*\lambda < 0$, then, substituting for the value of $\beta^*$, gives

$$k_1k_2(1-z) + (1-q) + \sqrt{[(1-q) + k_1k_2(1-z)]^2 - 4k_1k_2(1-q-z)} - 2(1-q).$$

This simplifies to

$$k_1k_2qz<0$$

which is clearly not possible. Therefore, $\delta c\gamma-(1-q)a\beta^*\lambda$ is always positive.

We note that $\hat{a}>0$ provided $\delta c\gamma-(1-q)a\beta^*\lambda>0$ and $(1-q-z)a\beta^*c-\delta c\gamma>0$. Substituting for the value of $\beta^*$, we get that $\hat{a}>0$ whenever;

$$k_1k_2(1-z)+\sqrt{[(1-q)+k_1k_2(1-z)]^2-4k_1k_2(1-q-z))}>(1-q)$$

and

$$k_1k_2(1-z)+\sqrt{[(1-q)+k_1k_2(1-z)]^2-4k_1k_2(1-q-z))}+2z<(1-q).$$

This means that

$$k_1k_2(1-z)+\Delta+2z<1-q<k_1k_2(1-z)+\Delta$$

where $\Delta=\sqrt{[(1-q)+k_1k_2(1-z)]^2-4k_1k_2(1-q-z))}$. This is clearly not possible. Therefore $\hat{a}<0$.

The value of the parameter $b$ is associated with following non-vanishing partial derivatives of $F$,

$$\frac{\partial^2 f_1}{\partial x_4\partial\beta^*}=-\frac{\lambda}{\gamma},\ \frac{\partial^2 f_1}{\partial x_5\partial\beta^*}=-\frac{k_1\lambda}{\gamma},\ \frac{\partial^2 f_2}{\partial x_4\partial\beta^*}=\frac{(1-q)\lambda}{\gamma},\ \frac{\partial^2 f_2}{\partial x_5\partial\beta^*}=\frac{zk_1\lambda}{\gamma},\ \frac{\partial^2 f_3}{\partial x_4\partial\beta^*}=\frac{q\lambda}{\gamma},\ \frac{\partial^2 f_3}{\partial x_5\partial\beta^*}=\frac{(1-z)k_1\lambda}{\gamma}.$$

Therefore, it follows that

$$\begin{aligned}\hat{b}&=\tfrac{(1-q)\lambda}{\gamma}v_2u_4+\tfrac{zk_1\lambda}{\gamma}v_2u_5+\tfrac{q\lambda}{\gamma}v_3u_4+\tfrac{(1-z)k_1\lambda}{\gamma}v_3u_5\\&=\tfrac{qzk_1k_2a^2\beta^*\lambda^2cv_5u_5}{[\delta c\gamma-(1-q)a\beta^*\lambda]^2}+\tfrac{k_1k_2a\lambda[(1-z)\delta c\gamma-(1-q-z)a\beta^*\lambda]v_5u_5}{\gamma\delta[\delta c\gamma-(1-q)a\beta^*\lambda]}\end{aligned}\quad(10)$$

Since $\delta c\gamma-(1-q)a\beta^*\lambda>0$, in order to show that $\hat{b}>0$, it is enough to show that $(1-z)\delta c\gamma-(1-q-z)a\beta^*\lambda>0$. If we assume that $(1-z)\delta c\gamma-(1-q-z)a\beta^*\lambda<0$, then

$$(1-z)\sqrt{[(1-q)+k_1k_2(1-z)]^2-4k_1k_2(1-q-z)}<(1-q-z)-k_1k_2(1-z)^2-qz.$$

This reduces to

$$2qz(1-q-z)<0$$

which is not possible since $q, z << 1$. Therefore $\hat{b}>0$.

Thus $\hat{a}<0$ and $\hat{b}>0$ and from Theorem 4 item(iv), if $R_0 > 1$, the unique endemic equilibrium $E_1$ is locally asymptotically stable.

**Theorem 5 Sensitive strain dominance:** *The sensitive strain is dominant at endemic equilibrium* $E_1$ $(\text{i. e. }, \ V_s^* > V_r^*)$ *whenever*

$$\frac{z}{q} > \frac{k_2\left(1-(1-q-z)\frac{\overline{R}_0}{R_0}\right)}{\left(1-(1-q-z)k_1k_2\frac{\overline{R}_0}{R_0}\right)}.$$

*Proof* The sensitive strain will dominate dynamics when $V_s^* > V_r^*$ This happens when

$$\frac{a}{c}I_s^* > \frac{k_2 a}{c}I_r^*.$$

Substituting for $I_s^*$ and $I_r^*$ and simplifying, we get

$$z\left(1-(1-q-z)k_1k_2\frac{\overline{R}_0}{R_0}\right) > k_2 q\left(1-(1-q-z)\frac{\overline{R}_0}{R_0}\right).$$

Therefore, for the sensitive strain to be dominant, it is required that

$$\frac{z}{q} > \frac{k_2\left(1-(1-q-z)\frac{\overline{R}_0}{R_0}\right)}{\left(1-(1-q-z)k_1k_2\frac{\overline{R}_0}{R_0}\right)}.$$

**Theorem 6 Effect of forward mutations on $R_0$:** *Given positive forward mutations,* $q > 0$, *and positive fitness cost of resistant strain,* $k_1, k_2 < 1$, *we have* $R_0 \leq \overline{R}_0$.

*Proof* It is enough to show that

$$(1-q)+k_1k_2(1-z)+\sqrt{[(1-q)+k_1k_2(1-z)]^2-4k_1k_2(1-q-z)} \leq 2.$$

When $q = z = 0$ and $k_1 = k_2 = 1$, we have

$$(1-q)+k_1k_2(1-z)+\sqrt{[(1-q)+k_1k_2(1-z)]^2-4k_1k_2(1-q-z)}=2$$

and $R_0=\overline{R}_0$. This is the case when we have no drug resistance but a single sensitive strain. Let $q \neq 0$, $z \neq 0$ and $k_1, k_2 \in (0,1)$, and suppose that

$$(1-q)+k_1k_2(1-z)+\sqrt{[(1-q)+k_1k_2(1-z)]^2-4k_1k_2(1-q-z)}>2.$$

This means that

$$\sqrt{[(1-q)+k_1k_2(1-z)]^2-4k_1k_2(1-q-z)}>2-k_1k_2(1-z)-(1-q). \quad (11)$$

Since $k_1$, $k_2 \in (0,1)$, $q \neq 0$, $z \neq 0$ and $q$, $z << 1$, then $0 < k_1k_2(1-z) + (1-q) < 2$. Squaring both sides of (4), we get

$$[(1-q)+k_1k_2(1-z)]^2-4k_1k_2(1-q-z)>4+k_1^2k_2^2(1-z)^2+(1-q)^2-4k_1k_2(1-z)-4(1-q)+2k_1k_2(1-z)(1-q).$$

On simplification,

$$k_1k_2z(1-q)-k_1k_2(1-q)>1-k_1k_2(1-z)-(1-q).$$

Collecting like terms,

$$q[k_1k_2(1-z)-1]>0$$

which is a contradiction since $k_1k_2(1-z)-1<0$. Therefore,

$$R_0<\overline{R}_0.$$

**Theorem 7 Effect of backward mutations on $R_0$:** *Whenever* $q > 0$ *and* $k_1$, $k_2 < 1$, *the presence of backward mutations* $z > 0$ *increases the basic reproductive number* $(i.e., R_0>R_0^{'})$.

*Proof*. We need to show that

$$(1-q)<\frac{1}{2}\left[(1-q)+k_1k_2(1-z)+\sqrt{[(1-q)+k_1k_2(1-z)]^2-4k_1k_2(1-q-z)}\right]$$

which is equivalent to

$$(1-q)-k_1k_2(1-z)<\sqrt{[(1-q)+k_1k_2(1-z)]^2-4k_1k_2(1-q-z)}.$$

We proceed by assuming the opposite, i.e.,

$$(1-q)-k_1k_2(1-z)\geq\sqrt{[(1-q)+k_1k_2(1-z)]^2-4k_1k_2(1-q-z)}$$

then, squaring both sides

$$[(1-q)-k_1k_2(1-z)]^2 \geq [(1-q)+k_1k_2(1-z)]^2 - 4k_1k_2(1-q-z)$$

which reduces to

$$(1-q)(1-z) \leq 1-q-z$$

or equivalently,

$$qz \leq 0$$

which contradicts our assumptions.

**Theorem 8 Rate of change of $R_0$ with respect to mutations:** *Given $R_0$ as described in 3,*

$$\frac{\partial R_0}{\partial q} < 0 \; and \; \frac{\partial R_0}{\partial z} > 0.$$

*Proof*

$$\frac{\partial R_0}{\partial q} = \frac{a\beta\lambda}{2\delta\gamma c}\left[-1+\frac{[k_1k_2z+(k_1k_2+q-1)]}{\sqrt{[(1-q)+k_1k_2(1-z)]^2-4k_1k_2(1-q-z)}}\right]$$

and

$$\frac{\partial R_0}{\partial z} = \frac{k_1k_2a\beta\lambda}{2\delta\gamma c}\left[-1+\frac{[k_1k_2z+(1+q-k_1k_2)]}{\sqrt{[(1-q)+k_1k_2(1-z)]^2-4k_1k_2(1-q-z)}}\right].$$

$\frac{\partial R_0}{\partial q} < 0$ iff

$$[k_1k_2z+(k_1k_2+q-1)] < \sqrt{[(1-q)+k_1k_2(1-z)]^2-4k_1k_2(1-q-z)}.$$

Since the term inside the square root is positive ($k_1$, $k_2 \in (0, 1)$ and $q$, $z << 1$), it is enough to show that

$$[k_1k_2z+(k_1k_2+q-1)]^2 < k_1^2k_2^2z^2+2k_1k_2z(1+q-k_1k_2)+(k_1k_2+q-1)^2.$$

This reduces to

$$2k_1k_2z(k_1k_2-1)<2k_1k_2z(1-k_1k_2) \text{ or } k_1k_2<1$$

which is satisfied in our region of interest, i.e., when $k_1$, $k_2 \in (0,1)$.

Similarly, $\frac{\partial R_0}{\partial z}>0$ iff

$$[k_1k_2z+(1+q-k_1k_2)]>\sqrt{k_1^2k_2^2z^2+2k_1k_2z(1+q-k_1k_2)+(k_1k_2+q-1)^2}.$$

It is enough to show that

$$[k_1k_2z+(1+q-k_1k_2)]^2>k_1^2k_2^2z^2+2k_1k_2z(1+q-k_1k_2)+(k_1k_2+q-1)^2$$

which reduces to

$$4q>4qk_1k_2 \text{ or } 1>k_1k_2$$

which is satisfied in our region of interest, i.e., when $k_1$, $k_2 \in (0,1)$. Therefore,

$$\frac{\partial R_0}{\partial q}<0 \text{ and } \frac{\partial R_0}{\partial z}>0.$$

**Theorem 9 Sensitive strain dominance during ART:** *The sensitive strain dominates dynamics at the endemic equilibrium during treatment if*

$$\frac{z}{q}>\frac{(1-p_2\varepsilon_{pi})}{(1-\varepsilon_{pi})}\frac{k_2\left(1-(1-q-z)\varepsilon_s\frac{\overline{R}_0}{R_0}\right)}{\left(1-(1-q-z)\varepsilon_rk_1k_2\frac{\overline{R}_0}{R_0}\right)}.$$

*Proof* The proof follows same argument as for Theorem 5.

**Theorem 10 Rate of change of $R_0$ with respect to mutations during ART:** *Given $\hat{R}_0$ as described in 6,*

$$\frac{\partial \hat{R}_0}{\partial q}>0 \; and \; \frac{\partial \hat{R}_0}{\partial z}<0$$

*whenever $k_1k_2\varepsilon_r>\varepsilon_s$.*

*Proof*




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$$\frac{\partial \hat{R}_0}{\partial q}=\frac{a\beta\lambda\varepsilon_s}{2\delta\gamma c}\left[-1+\frac{-\varepsilon_s(1-q)+k_1k_2\varepsilon_r(1+z)}{\sqrt{[\varepsilon_s(1-q)+\varepsilon_rk_1k_2(1-z)]^2-4\varepsilon_s\varepsilon_rk_1k_2(1-q-z)}}\right]$$

and

$$\frac{\partial \hat{R}_0}{\partial z}=\frac{k_1k_2a\beta\lambda\varepsilon_r}{2\delta\gamma c}\left[-1+\frac{\varepsilon_s(1+q)-k_1k_2\varepsilon_r(1-z)}{\sqrt{[\varepsilon_s(1-q)+\varepsilon_rk_1k_2(1-z)]^2-4\varepsilon_s\varepsilon_rk_1k_2(1-q-z)}}\right].$$

$\frac{\partial \hat{R}_0}{\partial q}>0$ iff

$$-\varepsilon_s(1-q)+k_1k_2\varepsilon_r(1+z)>\sqrt{[\varepsilon_s(1-q)+\varepsilon_rk_1k_2(1-z)]^2-4\varepsilon_s\varepsilon_rk_1k_2(1-q-z)}.$$

Since the term inside the square root is positive ($k_1$, $k_2 \in (0,1)$ and $q$, $z << 1$), it is enough to show that

$$[-\varepsilon_s(1-q)+k_1k_2\varepsilon_r(1+z)]^2>[\varepsilon_s(1-q)+\varepsilon_rk_1k_2(1-z)]^2-4\varepsilon_s\varepsilon_rk_1k_2(1-q-z).$$

This reduces to

$$k_1k_2\varepsilon_rz+\varepsilon_s(1-q-z)>\varepsilon_s(1-q) \text{ or } k_1k_2\varepsilon_r>\varepsilon_s$$

which is satisfied depending on the parameters $k_1$ and $k_2$ and the treatment parameters $p_1$, $p_2$, $\varepsilon_{rt}$ and $\varepsilon_{pi}$.

Similarly, $\frac{\partial \hat{R}_0}{\partial z}<0$ iff

$$\varepsilon_s(1+q)-k_1k_2\varepsilon_r(1-z)<\sqrt{[\varepsilon_s(1-q)+\varepsilon_rk_1k_2(1-z)]^2-4\varepsilon_s\varepsilon_rk_1k_2(1-q-z)}.$$

It is enough to show that

$$[\varepsilon_s(1+q)-k_1k_2\varepsilon_r(1-z)]^2<[\varepsilon_s(1-q)+\varepsilon_rk_1k_2(1-z)]^2-4\varepsilon_s\varepsilon_rk_1k_2(1-q-z)$$

which reduces to

$$q\varepsilon_s+\varepsilon_rk_1k_2(1-q-z)<\varepsilon_rk_1k_2(1-z) \text{ or } \varepsilon_s<k_1k_2\varepsilon_r$$

which is satisfied depending on the parameters $k_1$ and $k_2$ and the treatment parameters $p_1$, $p_2$, $\varepsilon_{rt}$ and $\varepsilon_{pi}$. Therefore,

$$\frac{\partial \hat{R}_0}{\partial q} > 0 \text{ and } \frac{\partial \hat{R}_0}{\partial z} < 0$$

whenever $k_1 k_2 \varepsilon_r > \varepsilon_s$.

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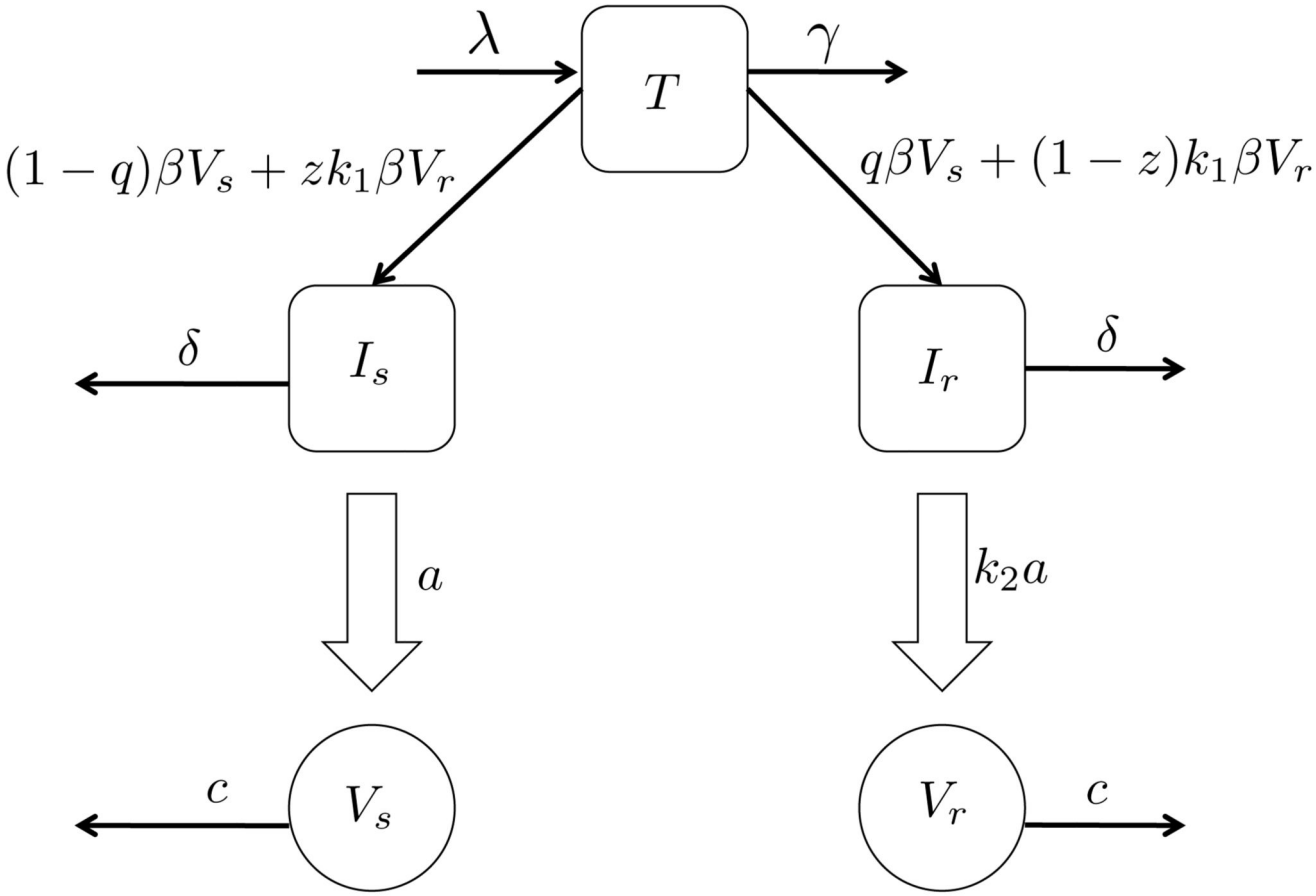


**Fig. 1.**

Schematic diagram showing infection dynamics of System 1. $CD4^+$ T-cells are classified into uninfected $T$, and infected with ART-sensitive or ART-resistant virus, $I_s$ and $I_r$, respectively. Virus strains are either sensitive, $V_s$, or resistant, $V_r$, to ART. See text for details.

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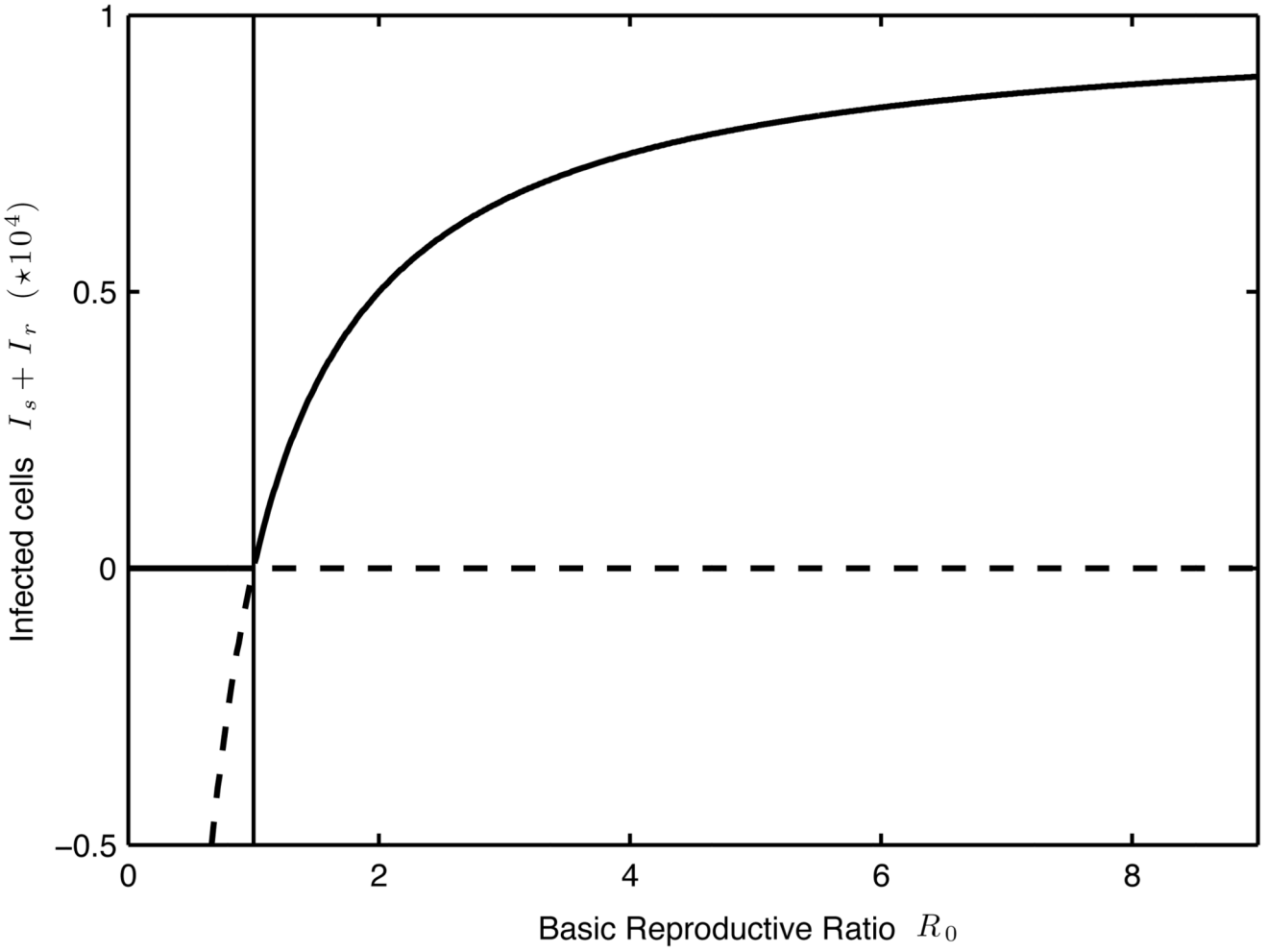


**Fig. 2.**

A bifurcation diagram for System 1. Number of infected cells for equilibrium points $E_0$ and $E_1$ are shown according to their stability status (solid curve when stable, dashed curve when unstable). At $R_0 = 1$ there is a transcritical bifurcation on the number of infected cells. Parameter estimates as listed in Table ??

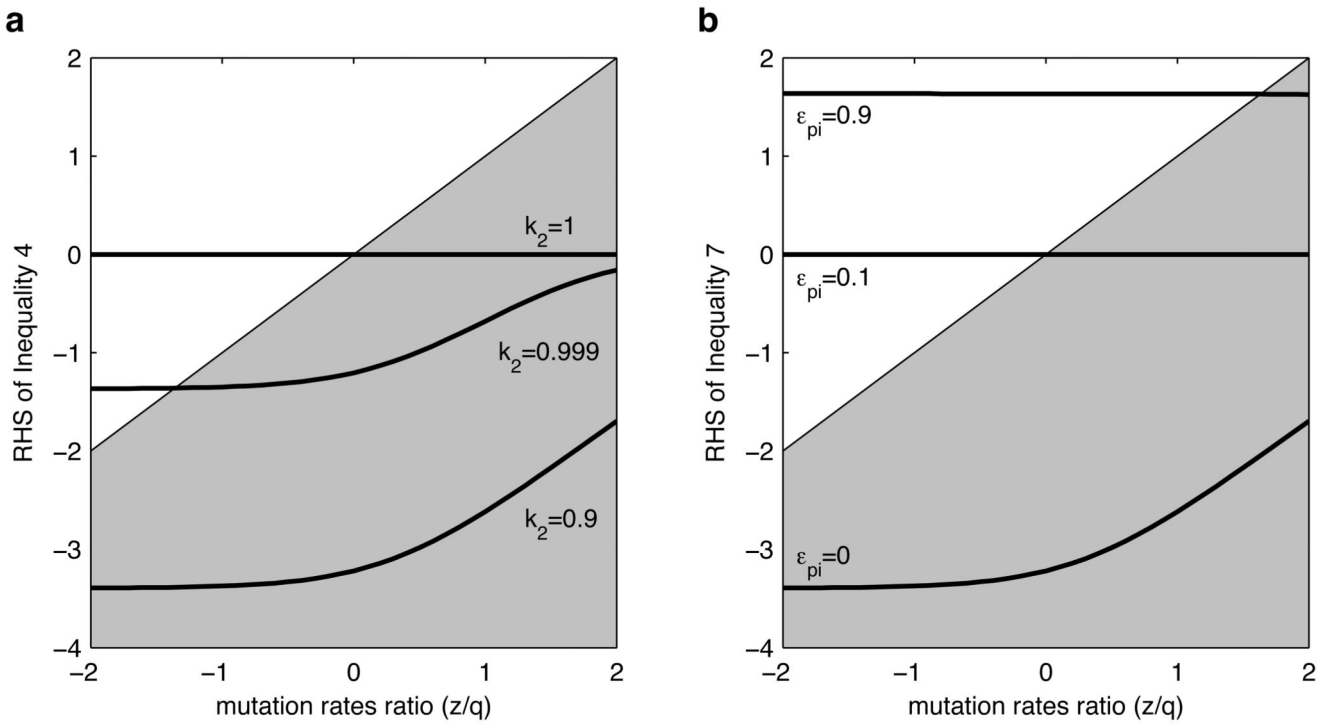


**Fig. 3.**

Analysis of the sensitive strain dominance. Solid curves show the RHS of inequalities **a)** 4 and **b)** 7, corresponding to absence or presence of ART, respectively. The sensitive strain is dominant whenever the curve is inside the shaded region. **a)** Without ART, a few values for fitness cost of resistance are considered ($k_1 = 1$, $k_2 = 1, 0.999, 0.9$). **b)** With ART, a few values for drug efficacy are considered ($k_1 = 1$, $k_2 = 0.9$, $p1 = p2 = 0$, $\varepsilon_{rt} = 0$, $\varepsilon_{pi} = 0, 0.1, 0.9$). The rest of the parameter estimates are fixed to the values in Table 1. All measurements are in logarithmic scale

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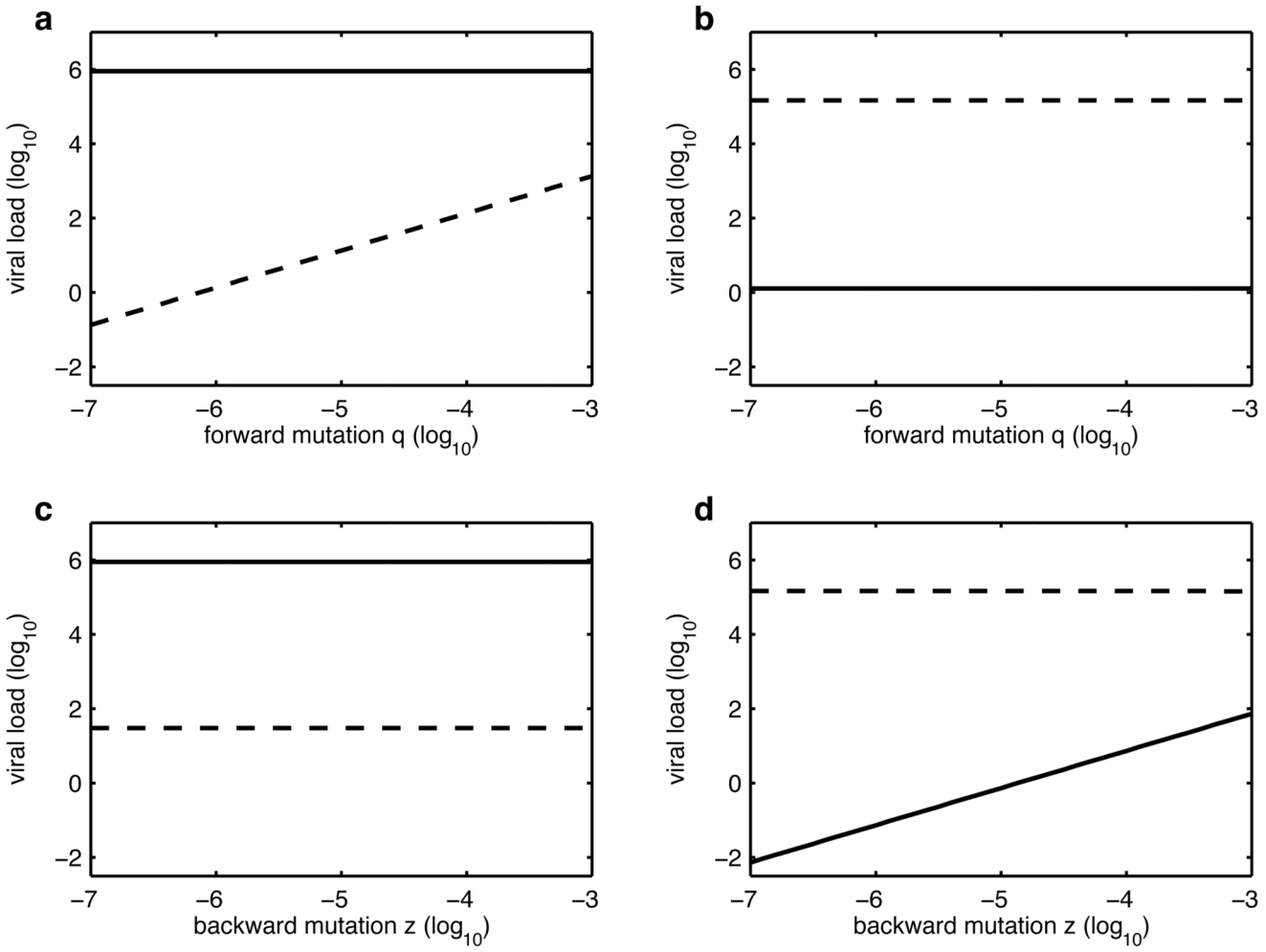


**Fig. 4.**

Equilibrium viral loads for sensitive (solid) and resistant (dashed) strains as forward or backward mutation rates are varied. Left panel: In the absence of ART, **a)** varying forward mutation rate, $q$, and **c)** varying backward mutation rate, $z$. Right panel: In the presence of ART, **b)** varying forward mutation rate, $q$, and **d)** varying backward mutation rate, $z$. Only one mutation rate is varied at a time while the other is fixed to its baseline value in Table 1. Values used for drug efficacy parameters: $\varepsilon_{rt} = 0.8$, $\varepsilon_{pi} = 0.75$, $p_1 = 0.1$, and $p_2 = 0.1$

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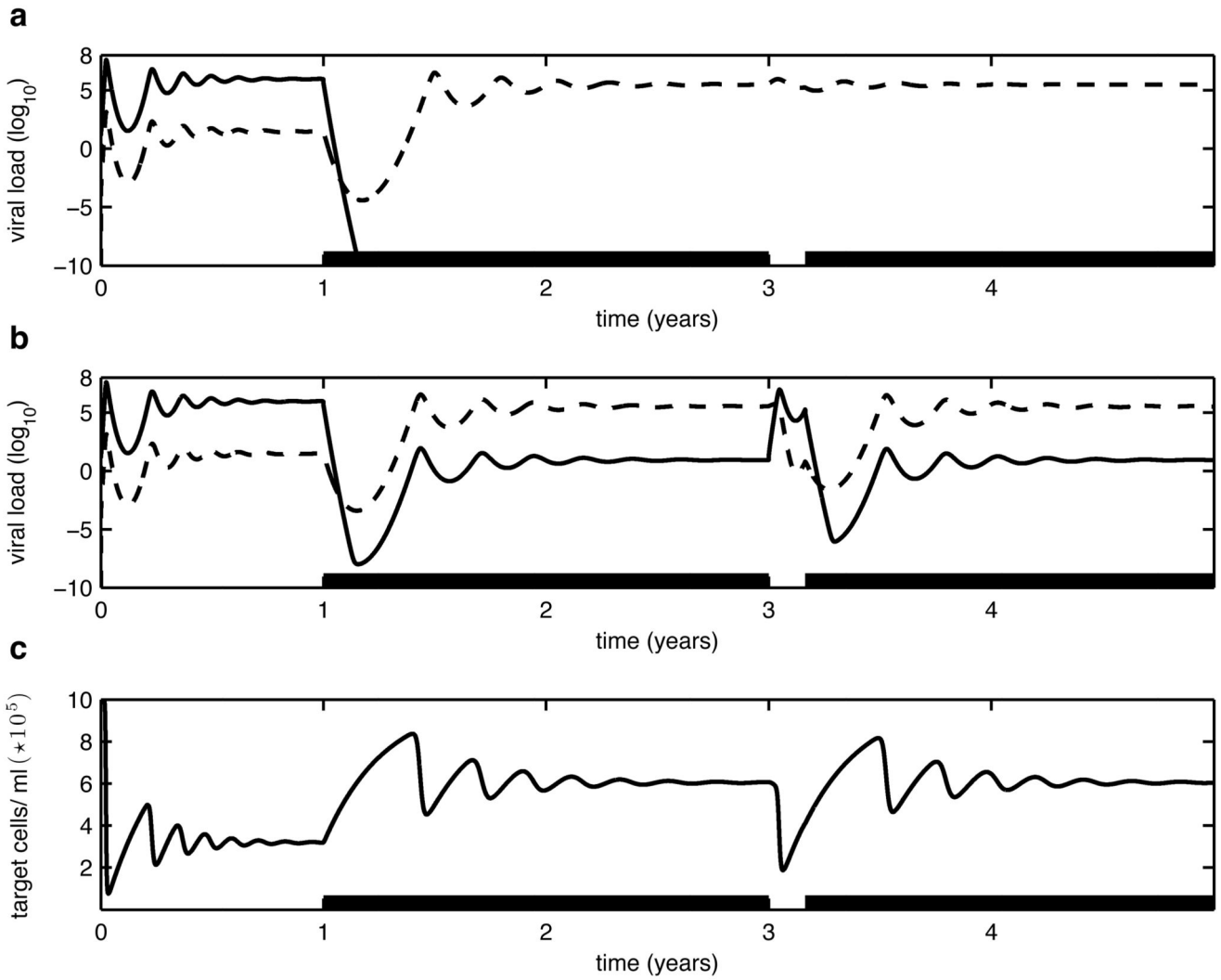


**Fig. 5.**

Infection dynamics within the host in the presence or absence of ART. The bold line on the x-axis shows the periods when ART is administered: ART is present from year 1 after infection to year 3, followed by an interruption of 1 month, after which ART is present until the end of the simulations. Dynamics of sensitive (solid) and resistant (dashed) strains for the model **a)** without backward mutations ($z = 0$) **b)** with backward mutations ($z = 1.73 \times 10^{-5}$). **c)** Dynamics of uninfected $CD4^+$ T-cells for the model with backward mutations. Values used for drug efficacy parameters: $\varepsilon_{rt} = 0.8$, $\varepsilon_{pi} = 0.75$, $p_1 = 0.1$, and $p_2 = 0.1$. The rest of the parameters are fixed to values in Table 1

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## Table 1

Parameter values used in simulations

| Parameter | Definition | Value/Range | Reference |
|---|---|---|---|
| $T_0$ | Initial target cell count | $10^6$ cells/ml | Buckley and Gluckman (2002) |
| $\gamma$ | Death rate of target cells | 0.01 $d^{-1}$ | Mohri et al (1998) |
| $\lambda$ | Recruitment rate of target cells | $10^4$ cells/ml $d^{-1}$ | Defined as $T_0/\gamma$ |
| $\beta$ | Infection rate of target cells by $V_s$ | $2.4 \times 10^{-8}$ ml $d^{-1}$ | Perelson et al (1993) |
| $k_1$ | Relative fitness of $V_r$ infectivity | 5/6 | $k_r/k_s$ in Rong et al (2007) |
| $\delta$ | Death rate of infected cells | 1.0 $d^{-1}$ | Markowitz et al (2003) |
| $a$ | Rate of virus production | 3000 $(\text{cells/ml})^{-1}d^{-1}$ | $\delta N_s$ in Rong et al (2007) |
| $k_2$ | Relative fitness of $V_r$ replication | 2/3 | $N_r/N_s$ in Rong et al (2007) |
| $c$ | Clearance rate of free virus | 23 $d^{-1}$ | Ramratnam et al (1999) |
| $q$ | Forward mutation rate | $2.24 \times 10^{-5}$ | Vaidya et al (2010) |
| $z$ | Backward mutation rate | $1.73 \times 10^{-5}$ | Vaidya et al (2010) |
| $\varepsilon_{rt}$ | RT drug efficacy | (0, 1) | Varied |
| $\varepsilon_{pi}$ | PI drug efficacy | (0, 1) | Varied |
| $P_1$ | Relative RT efficacy for $V_r$ | (0, 1) | Varied |
| $P_2$ | Relative PI efficacy for $V_r$ | (0, 1) | Varied |