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The influence of anti-viral drug therapy on the evolution of HIV-1 pathogens

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Abstract. An age-structured model is used to study the possible impact of drug treatment of infections with the human immunodeficiency virus type 1 (HIV-1) on evolution of the pathogen. Inappropriate drug therapy often leads to the development of drug-resistant mutants of the virus. Previous studies have shown that natural selection within a host favors viruses that maximize their fitness. By demonstrating how drug therapy may influence the within host viral fitness we show that while a higher treatment efficacy reduces the fitness of the drug-sensitive virus, it may provide a stronger force of selection for drug-resistant viruses allowing a wider range of resistant strains to invade.

1. Introduction

Reverse transcriptase inhibitors and protease inhibitors are the two major types of drugs that have been used as inhibitors of HIV-1 replication *in vivo*. Mathematical models of HIV-1 infection under the impact of drug treatments have been studied using ordinary and/or delay differential equations (see, for example [**4, 8, 11**]). Nelson et al. developed an age-structured model of HIV-1 infection (without drug treatments) and showed that this model is a generalization of ODE and DDE models mentioned above in the absence of treatments [**9**]. Such generalized models are considered to have greater flexibility that may better represent the underlying biology of an infection [**2**]. In [**9**] the local stability of both the infection-free and the infected steady states are shown for the case when the viral production rate has a special functional form (see Eq. (2.2)). These results are applied to a similar age-structured model in [**2**] to study the effect of life history parameters of HIV-1 on maximizing within host viral fitness under various assumptions on trade-offs between the virion production rate and other parameters. Drug treatments are again not included in this model.

In this chapter we generalize the model in [**9**] by incorporating the effect of two classes of anti-HIV drugs which help to reduce the HIV replication at two different stages of the cell infection. One class is the reverse transcriptase inhibitor which

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blocks the translation of viral RNA into DNA so that CD4 cells cannot produce virion particles (the cells then become uninfected). The other class is the protease inhibitor which targets the HIV protease enzyme to prevent new copies of HIV from being made (so that some of the virion particles will remain non-infectious). Stability results are provided for a general form of the viral production rate, and the stability of the infection-free or the infected steady state is shown to depend on the reproductive ratio $\mathcal{R}$ being smaller or greater than 1. The formulation of this reproductive ratio also provides an appropriate measure for the within host viral fitness, which can be used to explore the optimal virion production rate for which $\mathcal{R}$ is maximized.

Recent clinical studies have suggested that prolonged treatment with a single anti-HIV drug may be responsible for the emergence of resistant virus [**3, 4, 5, 6, 10, 12**]. The impact of drug treatments on the dynamics of resistant stains of pathogens has been studied using age-independent mathematical models (see, for example, [**1, 4, 13**]). We show that if the viral production is linked to resistance, then higher treatment efficacy with antiretroviral agents (such as protease inhibitors) may lead to the establishment of multiple viral strains with a wider range of resistance levels.

This chapter is organized as follows: In Section 2, we formulate a mathematical model for HIV-1 infection which generalizes the age-structured model proposed in [**9**] by incorporating both types of drug treatments. Section 3 is devoted to the analysis of our model including the existence and stability of both the infection-free and the infection steady states. In Section 4, we derive a criterion for invasion by resistant strains and explore how drug treatments may affect the optimal viral fitness of resistant strains. Section 5 discusses the results.

2. Model formulation

In [**9**] the following age-structured model of HIV infection is proposed:

$$\begin{aligned} &\frac{d}{dt}T(t) = s - dT - kVT, \\ &\frac{\partial}{\partial t}T^*(a,t) + \frac{\partial}{\partial a}T^*(a,t) = -\delta(a)T^*(a,t), \\ &\frac{d}{dt}V(t) = \int_0^\infty p(a)T^*(a,t)da - cV, \\ &T^*(0,t) = kVT, \end{aligned} \tag{2.1}$$

with appropriate initial conditions. Here, $T(t)$ denotes the population of uninfected target T cells at time t, $T^*(a,t)$ denotes the density of infected T cells of infection age a (i.e. the time that has elapsed since an HIV virion has penetrated the cell) at time t, and $V(t)$ denotes the population of infectious virus at t. s is the recruitment rate of healthy T cells, d is the per capita death rate of uninfected cells, $\delta(a)$ is the age-dependent per capita death rate of infected cells, c is the clearance rate of an infectious virus, k is the rate at which an uninfected cell becomes infected by one infectious virus, and $p(a)$ is the virion production rate by an infected cell of age a.

One of the special forms of $p(a)$ considered in Model (2.1) is

$$p(a) = \begin{cases} p^* \left(1 - e^{-\theta(a-a_1)}\right) & \text{if } a \geq a_1, \\ 0 & \text{else} \end{cases} \tag{2.2}$$

where θ is a constant which determines how quickly $p(a)$ reaches the saturation level, p^*, and a_1 is the maximum age at which reverse transcription takes place.

We provide stability results in this chapter for an arbitrary function $p(a)$ which allows the possibility that an infected cell may start producing viruses before the age a_1 (i.e., in some infected cells the reverse transcription may occur earlier than a_1) and the possibility that $p(a)$ may not be a monotone function of a (e.g., it may have a peak production rate at some intermediate age). To account for the fact that an infected cell does not produce any virus before the reverse transcription has taken place we introduce a function $\beta(a)$ which describes the proportion of infected cells of age a that are not yet actively productive. Assume that $\beta(a) \in L^1[0, \infty)$ is a non-increasing function with the following properties:

$$0 \leq \beta(a) \leq 1, \quad \beta(0) = 1. \tag{2.3}$$

Then, $\beta(a)$ can be used to divide the class of infected cells, $T^*(a,t)$, into two subclasses, $T^*_{preRT}(a,t)$ and $T^*_{postRT}(a,t)$ which are defined by:

$$\begin{aligned} T^*_{preRT}(a,t) &= \beta(a) T^*(a,t), \\ T^*_{postRT}(a,t) &= (1 - \beta(a)) T^*(a,t). \end{aligned} \tag{2.4}$$

$T^*_{preRT}(a,t)$ represents the density of cells that have been "infected" by an HIV virion but reverse transcription has not been completed at infection age a, and an RT inhibitor could revert it back to uninfected class (because RT fails to occur) or reduce the probability that a preRT cell progresses to the postRT state. $T^*_{postRT}(a,t)$ represents the density of infected cells that have progressed to the postRT phase at infection age a, and the presence of a protease inhibitor could affect the rate at which new infectious virion particles are produced.

Let r_{rt} and r_p denote the efficacy of the treatment therapy with reverse transcriptase inhibitors and protease inhibitors, respectively ($0 \leq r_{rt},\ r_p \leq 1$), and let η denote the maximal (age-independent) per capita rate at which preRT cells of become uninfected. Then the rate at which preRT cells become uninfected is given by

$$\int_0^\infty r_{rt} \eta T^*_{preRT}(a,t) da,$$

and new infectious virion particles are produced at the rate

$$\int_0^\infty (1 - r_p) p(a) T^*_{postRT}(a,t) da.$$

Incorporating these drug treatments in the equations for T, T^* and V in Model (2.1) we have:

$$\frac{d}{dt}T(t) = s - dT - kVT + \int_0^\infty r_{rt}\eta T^*_{preRT}(a,t)da,$$

$$\frac{\partial}{\partial t}T^*(a,t) + \frac{\partial}{\partial a}T^*(a,t) = -\delta(a)T^*(a,t) - r_{rt}\eta T^*_{preRT}(a,t),$$

$$\frac{d}{dt}V(t) = \int_0^\infty (1-r_p)p(a)T^*_{postRT}(a,t)da - cV.$$

Thus, using the relation (2.4) we modify Model (2.1) to get the following model:

$$\begin{aligned}
&\frac{d}{dt}T(t) = s - dT - kVT + \int_0^\infty r_{rt}\eta\beta(a)T^*(a,t)da,\\
&\frac{\partial}{\partial t}T^*(a,t) + \frac{\partial}{\partial a}T^*(a,t) = -\delta(a)T^*(a,t) - r_{rt}\eta\beta(a)T^*(a,t),\\
&\frac{d}{dt}V(t) = \int_0^\infty (1-r_p)(1-\beta(a))p(a)T^*(a,t)da - cV,\\
&T^*(0,t) = kVT,\\
&T(0) = T_0 > 0, \quad T^*(a,0) = T^*_0(a) \geq 0, \quad V(0) = V_0 > 0.
\end{aligned} \tag{2.5}$$

As mentioned earlier, we allow the virion production rate $p(a)$ to be an arbitrary function (e.g., it does not have to be a monotone function). $p(a)$ and $\delta(a)$ are assumed to be bounded.

System (2.5) can be reformulated as a system of Volterra integral equations. To simplify expressions we introduce the following notation:

$$\begin{aligned}
&K_0(a) = e^{-\int_0^a (\delta(\tau)+r_{rt}\eta\beta(\tau))d\tau}\\
&K_1(a) = r_{rt}\eta\beta(a)K_0(a)\\
&K_2(a) = (1-r_p)(1-\beta(a))p(a)K_0(a)\\
&\mathcal{K}_i = \textstyle\int_0^\infty K_i(a)da, \quad i = 0,1,2.
\end{aligned} \tag{2.6}$$

$K_0(a)$ is the probability of an infected cell remaining infected at age a, hereafter the age-specific survival probability of an infected cell. $K_1(a)$ gives the probability that an infected cell becomes noninfected at age a given that the cell has not died at age a. The probability that an infected cell has not died at age a is

$$e^{-\int_0^a \delta(\tau)d\tau}. \tag{2.7}$$

The probability that an infected cell is still in the preRT stage and has not been treated at age a by an RT inhibitor is $e^{-\int_0^a r_{rt}\eta\beta(\tau)d\tau}$ and hence the probability

that the cell becomes noninfected at age a due to an RT inhibitor is

$$\frac{d}{dt}\left(1-e^{-\int_0^a r_{rt}\eta\beta(\tau))d\tau}\right)=r_{rt}\eta\beta(a)e^{-\int_0^a r_{rt}\eta\beta(\tau))d\tau}. \tag{2.8}$$

$K_1(a)$ is the product of the two probabilities given by (2.7) and (2.8). $K_2(a)$ is a product of the the age-specific survival probability of an infected cell and the rate, $(1-r_p)(1-\beta(a))p(a)$, at which infectious virion particles are produced by an actively productive cell of age a. Thus, the integral of $K_2(a)$ over all ages, i.e.,

$$\mathcal{K}_2=\int_0^\infty (1-r_p)(1-\beta(a))p(a)K_0(a)da$$

gives the total amount of infectious virion particles produced by one infected cell in its lifespan. This is an important quantity which will be used later to define the viral fitness.

For mathematical convenience we introduce the new variable, $B(t)$, to describe the rate at which an uninfected T cell becomes infected at time t,

$$B(t)=kV(t)T(t). \tag{2.9}$$

Integrating the T^* equation in System (2.5) along the characteristic lines, $t-a=$ constant, we get the following formula

$$T^*(a,t)=\begin{cases} B(t-a)K_0(a) & \text{for } a<t,\\ T_0^*(a-t)\dfrac{K_0(a)}{K_0(a-t)} & \text{for } a\geq t. \end{cases} \tag{2.10}$$

Substituting (2.10) into the T and V equations in (2.5):

$$\begin{aligned} \frac{d}{dt}T(t)&=s-dT-B(t)+\int_0^t K_1(a)B(t-a)da+\tilde{F}_1(t),\\ \frac{d}{dt}V(t)&=\int_0^t K_2(a)B(t-a)da-cV+\tilde{F}_2(t), \end{aligned} \tag{2.11}$$

where

$$\begin{aligned} \tilde{F}_1(t)&=\int_t^\infty r_{rt}\eta\beta(a)T_0^*(a-t)\frac{K_0(a)}{K_0(a-t)}da,\\ \tilde{F}_2(t)&=\int_t^\infty (1-r_p)(1-\beta(a))p(a)T_0^*(a-t)\frac{K_0(a)}{K_0(a-t)}da. \end{aligned} \tag{2.12}$$

Clearly, $\tilde{F}_1(t)\to 0$ as $t\to\infty$. Integrating the T equation in (2.11) and changing the order of integration:

$$\begin{aligned} T(t) &= T_0e^{-dt}+\int_0^t e^{-d(t-u)}\Big[s-B(u)\\ &\quad +\int_0^u B(u-\tau)K_1(\tau)d\tau+\tilde{F}_1(u)\Big]du\\ &=\int_0^t\left[e^{-d\,(t-u)}\,(s-B(u))+B(u)H_1(t-u)\right]du+F_1(t), \end{aligned} \tag{2.13}$$

where

$$H_1(t) = e^{-d\,t}\int_0^t e^{d\,\tau}K_1(\tau)d\tau,$$
$$F_1(t) = T_0e^{-d\,t} + \int_0^t e^{-d\,(t-u)}\tilde{F}_1(u)du. \tag{2.14}$$

For the derivation of (2.13) we have used the following fact:

$$\begin{aligned}
&\int_0^t e^{-d\,(t-u)}\int_0^u B(u-\tau)K_1(\tau)d\tau du\\
&= \int_0^t e^{-d\,(t-u)}\int_0^u B(\alpha)K_1(u-\alpha)d\alpha du\\
&= \int_0^t B(\alpha)\int_\alpha^t e^{-d\,(t-u)}K_1(u-\alpha)du d\alpha\\
&= \int_0^t B(\alpha)e^{-d\,(t-\alpha)}\int_0^{(t-\alpha)} e^{d\,\sigma}K_1(\sigma)d\sigma d\alpha\\
&= \int_0^t B(\alpha)H_1(t-\alpha)d\alpha.
\end{aligned}$$

Similarly, by integrating the V equation in (2.11) we get

$$\begin{aligned}
V(t) &= V_0e^{-ct} + \int_0^t e^{-c(t-u)}\left[\int_0^u B(u-\tau)K_2(\tau)d\tau + \tilde{F}_2(u)\right]du\\
&= \int_0^t B(u)H_2(t-u)du + F_2(t),
\end{aligned} \tag{2.15}$$

where

$$H_2(t) = e^{-ct}\int_0^t e^{c\tau}K_2(\tau)d\tau,$$
$$F_2(t) = T_0e^{-ct} + \int_0^t e^{-c(t-u)}\tilde{F}_2(u)du. \tag{2.16}$$

Equations (2.13) and (2.15), with $B(t)$ replaced by $kV(t)T(t)$, form a system of Volterra integral equations which is equivalent to the original system (2.5). Hence, for the discussion of existence and uniqueness of the solutions we only need to consider the following system

$$\begin{aligned}
T(t) &= \int_0^t \left[e^{-d\,(t-u)}\left(s - kV(u)T(u)\right) + kV(u)T(u)H_1(t-u)\right]du\\
&\quad + F_1(t),\\
V(t) &= \int_0^t kV(u)T(u)H_2(t-u)du + F_2(t),
\end{aligned} \tag{2.17}$$

where H_i and F_i $(i = 1, 2)$ are given in (2.14) and (2.16).

3. Model analysis

In this section we provide analytic results on the existence of positive solutions as well as possible steady states and their stability.

3.1. Existence of positive solutions. Let $x(t) = (T(t), V(t))$. System (2.17) can be written in the form

$$x(t) = \int_0^t \kappa(t-u)g(x(u))du + f(t),$$

where $f(t) = (F_1(t), F_2(t))$ is a continuous function from $[0,\infty)$ to $[0,\infty)^2$, κ is the following 2×2 matrix with entries being locally integrable functions on $[0,\infty)$,

$$\kappa(t) = \begin{pmatrix} se^{-dt} & H_1(t) - e^{-dt} \\ 0 & H_2(t) \end{pmatrix},$$

and g is defined by,

$$g(x) = (1, kVT).$$

Obviously, $f \in C([0,\infty); \mathbf{R}^2)$, $g \in C(\mathbf{R}^2, \mathbf{R}^2)$, and $\kappa \in L^1_{loc}([0,\infty); \mathbf{R}^{2\times 2})$. Theorem 1.1 in Gripenberg *et al.* (1990), Section 12.1, now provides us with a continuous solution defined on a maximal interval such that the solution goes to infinity if this maximal interval is finite.

To see that all solutions will remain non-negative for positive initial data, we use the following system (see (2.9) and (2.11)) which is also equivalent to System (2.5):

$$\begin{aligned} \frac{d}{dt}T(t) &= s - dT - B(t) + \int_0^t K_1(a)B(t-a)da + \tilde{F}_1(t), \\ \frac{d}{dt}V(t) &= \int_0^t K_2(a)B(t-a)da - cV + \tilde{F}_2(t), \\ B(t) &= kV(t)T(t), \end{aligned} \tag{3.1}$$

where $\tilde{F}_i$ is given in Eq. (2.12) and $\tilde{F}_i(t) > 0$, $\lim_{t\to\infty} \tilde{F}_i(t) = 0$ for $i = 1, 2$.

Suppose that there exists a $\bar{t} > 0$ such that $T(\bar{t}) = 0$ and $T(t), V(t) > 0$ for $0 \le t < \bar{t}$. Then $B(\bar{t}) = kV(\bar{t})T(\bar{t}) = 0$, $B(t) = kV(t)T(t) > 0$ for $0 \le t < \bar{t}$, and thus from the T equation in (3.1) we have

$$\frac{d}{dt}T(\bar{t}) = s + \int_0^{\bar{t}} K_1(a)B(\bar{t}-a)da + \tilde{F}_1(\bar{t}) > 0.$$

Hence, $T(t) \ge 0$ for all $t \ge 0$. Similarly we can show that $V(t) \ge 0$ and $B(t) \ge 0$ for all $t \ge 0$ and for all positive initial data.

3.2. Steady states and their stability. We use System (3.1) for our stability analysis. According to [**7**], any equilibrium of System (3.1), if it exists, must be

a constant solution of the limiting system:

$$\begin{aligned}
&\frac{d}{dt}T(t) = s - dT - B(t) + \int_0^\infty K_1(a)B(t-a)da,\\
&\frac{d}{dt}V(t) = \int_0^\infty K_2(a)B(t-a)da - cV, \qquad (3.2)\\
&B(t) = kV(t)T(t).
\end{aligned}$$

System (3.2) has two constant solutions: the infection-free steady state

$$\bar{E} = (\bar{T}, \bar{V}, \bar{B}) = (\frac{s}{d}, 0, 0), \qquad (3.3)$$

and the infected steady state

$$E^\diamond = (T^\diamond, V^\diamond, B^\diamond) \qquad \text{where}$$

$$T^\diamond = \frac{c}{k\mathcal{K}_2}, \qquad V^\diamond = \frac{sk\mathcal{K}_2 - dc}{kc(1-\mathcal{K}_1)}, \quad B^\diamond = kT^\diamond V^\diamond \qquad (3.4)$$

with $\mathcal{K}_1$ and $\mathcal{K}_2$ given in (2.6). Notice that $\beta(a) = 0$ for $a \geq a_1$ and

$$\begin{aligned}
\mathcal{K}_1 &< \int_0^\infty r_{rt}\eta\beta(a)e^{-\int_0^a r_{rt}\eta\beta(s)ds}da\\
&= -\int_0^\infty \frac{d}{da}\left(e^{-\int_0^a r_{rt}\eta\beta(s)ds}\right)da\\
&= 1 - e^{-\int_0^\infty r_{rt}\eta\beta(s)ds}\\
&\leq 1.
\end{aligned}$$

Thus, $V^\diamond > 0$ if and only if $sk\mathcal{K}_2 - dc > 0$, or $\mathcal{R} > 1$, where

$$\mathcal{R} = \frac{sk\mathcal{K}_2}{dc}. \qquad (3.5)$$

Clearly, the infected steady state (3.4) is feasible if and only if $\mathcal{R} > 1$. We can interpret $\mathcal{R}$ by noticing that s/d is the cell density in the absence of infection; k and c are the cell infection and viral clearance rates, respectively; and $\mathcal{K}_2$ gives the infectious virion particles produced by one infected cell during its entire life. Therefore, $\mathcal{R}$ is the reproductive ratio of the virus under the impact of drug treatments.

We now consider the stability of steady states. Let us first consider the infection-free steady state $\bar{E}$. The following result suggests that the population sizes of virus and infected cells will go to zero as $t \to \infty$ if the reproductive ratio is less than 1.

Result 1 *$\bar{E}$ is locally asymptotically stable if $\mathcal{R} < 1$, and it is unstable if $\mathcal{R} > 1$.*

This stability result can be verified as the follows. Using System (3.2) we get the characteristic equation at the steady state $\bar{E}$

$$\det\begin{bmatrix} -d-\lambda & -ks/d & \hat{K}_1(\lambda) \\ 0 & -c-\lambda & \hat{K}_2(\lambda) \\ 0 & ks/d & -1 \end{bmatrix} = 0, \qquad (3.6)$$

where λ is an eigenvalue and $\hat{K}_i(\lambda)$ denotes the Laplace transform of $K_i(a)$, i.e.,

$$\hat{K}_i(\lambda) = \int_0^\infty K_i(a)e^{-\lambda a}da, \quad i = 1, 2. \tag{3.7}$$

The characteristic equation (3.6) can be written as

$$(\lambda + d)\big[\lambda + c - \frac{sk}{d}\hat{K}_2(\lambda)\big] = 0. \tag{3.8}$$

One negative root of Eq. (3.8) is $\lambda = -d$ and all other roots are given by the equation

$$\lambda + c = \frac{sk}{d}\hat{K}_2(\lambda), \tag{3.9}$$

which can be rewritten as

$$\frac{\lambda}{c} + 1 = \mathcal{R}\frac{\hat{K}_2(\lambda)}{\mathcal{K}_2}. \tag{3.10}$$

Notice that $|\hat{K}_2(\lambda)| \le \mathcal{K}_2$ for all complex roots λ with non-negative real part (i.e., $\Re\lambda \ge 0$). Hence, the modulus of the right-hand side of Eq. (3.10) is less than 1 provided that $\mathcal{R} < 1$. Since the modulus of the left hand side of Eq. (3.10) is always greater than 1 if $\Re\lambda \ge 0$, we conclude that all roots of (3.9) have negative real part if $\mathcal{R} < 1$. It follows that $\bar{E}$ is locally asymptotically stable when $\mathcal{R} < 1$.

For the case of $\mathcal{R} > 1$, let

$$f(\lambda) = \frac{\lambda}{c} + 1 - \mathcal{R}\frac{\hat{K}_2(\lambda)}{\mathcal{K}_2}. \tag{3.11}$$

Clearly, any real root of $f(\lambda) = 0$ is also a root of (3.9). Recognizing that

$$f(0) = 1 - \mathcal{R} < 0, \quad \lim_{\lambda\to\infty} f(\lambda) = \infty, \tag{3.12}$$

we know that $f(\lambda) = 0$ has at least one positive root $\lambda^* > 0$ which is a positive eigenvalue of the characteristic equation (3.8). This shows that the infection-free steady state is unstable when $\mathcal{R} > 1$.

Next, we consider the stability of the infected steady state $E^\diamond$. As noted earlier, this steady state exists if and only if $\mathcal{R} > 1$. The following result suggests that the virus population will be established if the reproductive ratio is greater than 1.

Result 2 *The infected steady state $E^\diamond$ is locally asymptotically stable if $\mathcal{R} > 1$.*

For the verification of Result 2 we now look at the characteristic equation at the steady state $E^\diamond$:

$$\det\begin{bmatrix} -d - kV^\diamond - \lambda & -kT^\diamond & \hat{K}_1(\lambda) \\ 0 & -c - \lambda & \hat{K}_2(\lambda) \\ kV^\diamond & kT^\diamond & -1 \end{bmatrix} = 0$$

or equivalently

$$\big[(\lambda + \frac{sk\mathcal{K}_2 - dc\mathcal{K}_1}{c(1-\mathcal{K}_1)}\big]\big[\lambda + c - c\frac{\hat{K}_2(\lambda)}{\mathcal{K}_2}\big] = \frac{sk\mathcal{K}_2 - dc}{c(1-\mathcal{K}_1)}\big[(\lambda + c)\hat{K}_1(\lambda) - c\frac{\hat{K}_2(\lambda)}{\mathcal{K}_2}\big].$$

Using the notation $\mathcal{R} = sk\mathcal{K}_2/dc$ we can rewrite the above equation as

$$\big[(1-\mathcal{K}_1)\lambda + d(\mathcal{R} - \mathcal{K}_1)\big]\big[\lambda + c - c\frac{\hat{K}_2(\lambda)}{\mathcal{K}_2}\big] = d(\mathcal{R}-1)\big[(\lambda + c)\hat{K}_1(\lambda) - c\frac{\hat{K}_2(\lambda)}{\mathcal{K}_2}\big]$$

or as

$$\left(1+\frac{\lambda}{c}\right)\left(A(\lambda+d)+1-\hat{K}_1(\lambda)\right)=\frac{\hat{K}_2(\lambda)}{\mathcal{K}_2}A\big(\lambda+d\big), \tag{3.13}$$

where

$$A=\frac{1-\mathcal{K}_1}{d(\mathcal{R}-1)}. \tag{3.14}$$

The possibility of a negative real root of Eq. (3.13) can be excluded as follows. Suppose $\lambda \geq 0$. Then

$$\hat{K}_1(\lambda) \leq \hat{K}_1(0)=\mathcal{K}_1<1. \tag{3.15}$$

It follows that $A>0$ and

$$\left(1+\frac{\lambda}{c}\right)\left(A(\lambda+d)+1-\hat{K}_1(\lambda)\right) \geq A(\lambda+d).$$

From (3.13) we have

$$\frac{\hat{K}_2(\lambda)}{\mathcal{K}_2}>1. \tag{3.16}$$

However, since $\lambda \geq 0$, $\hat{K}_2(\lambda) \leq \hat{K}_2(0)=\mathcal{K}_2$, which contradicts with (3.16). Thus, Equation (3.13) has no non-negative real roots.

We can show that Eq. (3.2) or Eq. (3.13) has no complex roots λ with non-negative real part. Suppose not, then Eq. (3.2) has a root $\lambda=x_0+iy_0$ with $x_0 \geq 0$, $y_0>0$. If $\mathcal{R}\to 1$, from (3.2) we have

$$(\lambda+d)\left(\lambda+c-c\frac{\hat{K}_2(\lambda)}{\mathcal{K}_2}\right)=0. \tag{3.17}$$

i) If $x_0>0$ then using a similar argument as in Result 1 we know that $\lambda=x_0+iy_0$ cannot be a root. ii) If $x_0=0$ then (3.17) has one negative root $-d$ and other roots that are determined by the equation

$$1+\frac{\lambda}{c}=\frac{\hat{K}_2(\lambda)}{\mathcal{K}_2}$$

or

$$1+\frac{y_0}{c}i=\frac{\int_0^\infty K_2(a)\cos(ya)da}{\mathcal{K}_2}-\frac{\int_0^\infty K_2(a)\sin(ya)da}{\mathcal{K}_2}i. \tag{3.18}$$

Comparison of the real parts of both sides yields that $\cos(ya)=1$. Thus, $\sin(ya)=0$ which implies that (3.18) does not hold. Therefore, (3.2) has no roots with non-negative real part when $\mathcal{R}\to 1$.

For general $\mathcal{R}$, by the continuous dependence of roots of the characteristic equation on $\mathcal{R}$ we know that the curve determined by the roots must cross the imaginary axis as $\mathcal{R}$ decreases and close to 1. That is, the characteristic equation (3.13) has a pure imaginary root, say, iy, with $y>0$. Replacing λ in (3.13) with iy we see that the modulus of the left-hand side of (3.13) satisfies

$$\begin{aligned} |LHS| &> |Ayi+Ad+1-\hat{K}_1(iy)| \\ &= \left|Ad+1-\int_0^\infty K_1(a)\cos(ya)da+i\left(Ay+\int_0^\infty K_1(a)\sin(ya)da\right)\right|. \end{aligned} \tag{3.19}$$

We claim that $\int_0^\infty K_1(a)\sin(ya)da \geq 0$. In fact, notice that

$$\int_0^\infty K_1(a)\sin(ya)da = \int_0^{a_1} K_1(a)\sin(ya)da. \tag{3.20}$$

Notice also that $K_1(0) = r_{rt}\eta$ and $K_1'(a) = r_{rt}\eta[\beta'(a)K_0(a) + \beta(a)K_0'(a)] \leq 0$ almost everywhere on $[0,\infty)$. Integrating $\int_0^{a_1} K_1(a)\sin(ya)da$ by parts,

$$\begin{aligned}
\int_0^{a_1} K_1(a)\sin(ya)da &= \frac{r_{rt}\eta}{y} - \frac{1}{y}K_1(a_0)\cos(ya_1) + \frac{1}{y}\int_0^{a_1} K_1'(a)\cos(ya)da \\
&\geq \frac{r_{rt}\eta}{y} - \frac{1}{y}K_1(a_1)\cos(ya_1) + \frac{1}{y}\int_0^{a_1} K_1'(a)da \\
&= \frac{1}{y}K_1(a_1)(1-\cos(ya_1)) \\
&\geq 0.
\end{aligned}$$

Thus $\int_0^\infty K_1(a)\sin(ya)da \geq 0$. We also observe that $1 - \int_0^\infty K_1(a)\cos(ya)da \geq 1 - \mathcal{K}_1 > 0$. It follows from (3.19) that

$$|LHS| > A|d+iy|. \tag{3.21}$$

On the other hand, the modulus of the right-hand side of (3.13) satisfies

$$|RHS| \leq A|d+iy|. \tag{3.22}$$

This leads to a contradiction.

We conclude that the characteristic equation (3.13) has no roots with nonnegative real part. Therefore, Result 2 holds.

It is obvious that the threshold condition $\mathcal{R} > 1$ and the magnitude of $\mathcal{R}$ play a key role in the maintenance of the virus. In the following section we use these results to demonstrate how drug efficacy may affect the invasion of drug resistant strains.

4. Influence of drug therapy on viral fitness

In this section we focus on the issue concerning the impact of drug treatments on evolution of pathogens. In particular we consider the development of mutant strains mediated by drug therapy.

Suppose that the drug-sensitive strain of HIV-1 infection is at the infected steady state $E^\diamond = (T^\diamond, V^\diamond, B^\diamond)$ (see (3.4)), and that a small number of drug resistant virus have been introduced into the population. We derive an invasion criterion for a resistant strain by using a heuristic argument as is done in [**2**]. Denote the reproductive ratio of the sensitive strain by $\mathcal{R}_s$ (which is the same $\mathcal{R}$ as defined in (3.5)). From results in Section 2 we know that $\mathcal{R}_s > 1$ and that the population size of uninfected cells is $T^\diamond = s/(d\mathcal{R}_s)$ (see (3.4)). Let $\tilde{K}_0(a)$ denote the age-specific survival probability of a T cell infected with the resistant strain (an equivalent quantity for the sensitive strain is given in (2.6)), $\tilde{r}_{rt}$ and $\tilde{r}_p$ denote the efficacy of the two types of drugs for the resistant strain, and $\tilde{p}(a)$ denote the virion production rate of the resistant strain. For ease of illustration we assume that all other parameters are the same for both strains. We derive the invasion criterion for the case when both types of drugs are included. This criterion will be applied to different scenarios of chemotherapy such as a single-drug therapy (e.g., $r_p > 0$ and $r_{rt} = 0$) or combination therapy (i.e., $r_p > 0$ and $r_{rt} > 0$).

Since $T^\diamond$ is the amount of available uninfected T cells, a typical resistant virus can infect $kT^\diamond/c$ cells in its lifespan. Each of these infected cells can produce a total of

$$N_r = \int_0^\infty (1-\tilde{r}_p)(1-\beta(a))\tilde{p}(a)\tilde{K}_0(a)da$$

virion particles during its whole life time (burst size). Thus the reproductive ratio of the resistant strain (when the sensitive strain is at its positive equilibrium), $\mathcal{R}_r^\diamond$, is

$$\mathcal{R}_r^\diamond = \frac{kT^\diamond}{c}\int_0^\infty (1-\tilde{r}_p)(1-\beta(a))\tilde{p}(a)\tilde{K}_0(a)da,$$

and the invasion criterion is $\mathcal{R}_r^\diamond > 1$. Substituting $s/(d\mathcal{R}_s)$ for $T^\diamond$ we obtain the condition for the resistant strain to invade the sensitive strain:

$$\mathcal{R}_r > \mathcal{R}_s \tag{4.1}$$

where the quantity

$$\mathcal{R}_r = \frac{s}{d}\frac{k}{c}\int_0^\infty (1-\tilde{r}_p)(1-\beta(a))\tilde{p}(a)\tilde{K}_0(a)da \tag{4.2}$$

actually represents the reproductive ratio of the resistant strain when the equilibrium density of uninfected cells is s/d (which is the value of T at the infection-free state). We use the quantity $\mathcal{R}_r$ as a measure of fitness of a resistant virus. Eq. (4.1) shows that natural selection within a host favors viruses that maximize its reproductive ratio. We can also define a relative viral fitness (cf. [**2**]) by dividing the reproductive ratio by the factor $(s/d)(k/c)$ in both $\mathcal{R}_s$ and $\mathcal{R}_r$ since they are assumed equal for both sensitive and resistant strains.

Next, for the calculation of the optimal reproductive ratio we consider the case when the viral production rates for both strains have the form given in (2.2). That is,

$$\tilde{p}(a) = \begin{cases} \tilde{p}^*\left(1-e^{-\theta(a-a_1)}\right) & \text{if } a \geq a_1, \\ 0 & \text{else} \end{cases} \tag{4.3}$$

where $\tilde{p}^*$ is the saturation level for the resistant strain. Accordingly, we choose $\beta(a)$ to be (see (2.3))

$$\beta(a) = \begin{cases} 1, & 0 \leq a < a_1, \\ 0, & a \geq a_1. \end{cases} \tag{4.4}$$

The death rate of cells is assumed to be the same for both strains with form

$$\delta(a) = \begin{cases} \delta_0, & 0 \leq a < a_1, \\ \delta_0 + \mu, & a \geq a_1, \end{cases} \tag{4.5}$$

where δ_0 and μ are positive constants with δ_0 representing a background death rate of cells and μ representing an extra death rate for actively reproductive cells.

Drug resistance is incorporated by assuming that the efficacy of chemotherapy for the resistant strain is lower than that for the sensitive strain by a factor σ, $0 \leq \sigma \leq 1$, i.e.,

$$\tilde{r}_{rt} = \sigma_{rt} r_{rt}, \quad \tilde{r}_p = \sigma_p r_p. \tag{4.6}$$

For ease of demonstration we assume in this chapter that $\sigma_{rt} = \sigma_p = \sigma$ which could be relaxed in later studies. $\sigma = 0$ corresponds to the completely resistant strain while $\sigma = 1$ corresponds to the completely sensitive strain. Other strains have an intermediate value $0 < \sigma < 1$. To incorporate the cost that resistant strains pay

for the development of resistance we consider a trade-off between drug resistance and virion production rate $\tilde{p}(a)$. Various functional forms for the cost can be used. Herein, we consider two types of costs by which the saturation level p^* is reduced according to the following formulas

$$\text{Type I}: \quad \tilde{p}(a) = \sigma p^* \big(1 - e^{-\theta(a-a_1)}\big), \tag{4.7}$$

$$\text{Type II}: \quad \tilde{p}(a) = e^{-\phi(1/\sigma - 1)} p^* \left(1 - e^{-\theta(a-a_1)}\right), \tag{4.8}$$

where ϕ is a measure for the level of cost. We provide analytic results for Type I cost and illustrate that the qualitative properties of the two types of costs are similar. To make the calculation transparent we rewrite the reproductive ratio $\mathcal{R}_r$ using (4.4) – (4.7) as

(4.9)

$$\begin{aligned} \mathcal{R}_r &= \frac{s}{d}\frac{k}{c}\int_{a_1}^{\infty} \big(1 - \sigma r_p\big)\sigma p^* \big[1 - e^{-\theta(a-a_1)}\big] e^{-(\delta_0 + \sigma r_{rt}\eta)a_1} e^{-(\delta_0+\mu)(a-a_1)} da \\ &= \big(1 - \sigma r_p\big)\sigma e^{-(\delta_0 + \sigma r_{rt}\eta)a_1} D, \end{aligned}$$

where

$$D = \frac{s}{d}\frac{k}{c}\int_0^{\infty} p^* \big(1 - e^{-\theta u}\big) e^{-(\delta_0+\mu)u} du$$

is a quantity that is independent of σ, r_{rt}, r_p, and a_1. Similarly we can rewrite $\mathcal{R}_s$ in the form

$$\mathcal{R}_s = (1 - r_p) e^{-(\delta_0 + r_{rt}\eta)a_1} D. \tag{4.10}$$

From Eqs (4.9) and (4.10) we get the following relationship between $\mathcal{R}_r$ and $\mathcal{R}_s$:

$$\mathcal{R}_r = \frac{\sigma(1 - \sigma r_p) e^{-r_{rt}\eta(1-\sigma)a_1}}{1 - r_p} \mathcal{R}_s. \tag{4.11}$$

Consider $\mathcal{R}_r = \mathcal{R}_r(\sigma)$ as a function of σ. A resistant strain with resistance σ can invade the sensitive strain if $\mathcal{R}_r(\sigma) > \mathcal{R}_s$, which (from the fact that $\mathcal{R}_r(1) = \mathcal{R}_s$) is possible only if $\frac{d\mathcal{R}_r(\sigma)}{d\sigma} < 0$ for some $\sigma \in (0, 1)$. Notice that

$$\frac{d\mathcal{R}_r}{d\sigma} \begin{cases} < 0 & \text{if} \quad \sigma_- < \sigma < \sigma_+ \\ = 0 & \text{if} \quad \sigma = \sigma_-, \sigma_+ \\ > 0 & \text{else,} \end{cases} \tag{4.12}$$

where

$$\sigma_\pm = \frac{2r_p + a_1 r_{rt}\eta \pm \sqrt{4r_p^2 + a_1^2 r_{rt}^2 \eta^2}}{2a_1 r_p r_{rt}\eta},$$

if $r_p > 0$ and $r_{rt} > 0$. Since

$$\sqrt{4r_p^2 + a_1^2 r_{rt}^2 \eta^2} = \sqrt{(2r_p + a_1 r_{rt}\eta)^2 - 4a_1 r_p r_{rt}\eta} \le 2r_p + a_1 r_{rt}\eta$$

we know that $\sigma_\pm \geq 0$. Clearly $\mathcal{R}_r(\sigma) \leq \mathcal{R}_s$ for all $\sigma \in (0,1)$ if $\sigma_- \geq 1$, i.e., if r_p and r_{rt} satisfy

$$\frac{2r_p + a_1 r_{rt}\eta - \sqrt{4r_p^2 + a_1^2 r_{rt}^2 \eta^2}}{2a_1 r_p r_{rt}\eta} \geq 1. \tag{4.13}$$

Obviously the condition (4.13) is not easy to use to draw conclusions. Let us first derive some analytic understanding for a simpler case in which only a single-drug therapy with a protease inhibitor is considered, i.e., $r_p > 0$ and $r_{rt} = 0$. The case of combined therapy will be explored numerically.

Single-drug therapy. In this case, since $r_p > 0$ and $r_{rt} = 0$, Eq. (4.11) simplifies to

$$\mathcal{R}_r(\sigma) = \frac{\sigma(1-\sigma r_p)}{1-r_p}\mathcal{R}_s. \tag{4.14}$$

It is easy to check that in order to have $\mathcal{R}_r(\sigma) \geq \mathcal{R}_s$ for some $\sigma \in (0,1)$ it is necessary that $r_p > \frac{1}{2}$, in which case

$$\frac{d\mathcal{R}_r(\sigma)}{d\sigma} < 0, \quad \text{for} \quad \frac{1}{2r_p} < \sigma < 1.$$

The above inequalities suggest that there exists a maximum level of resistance, $\sigma_{\max}$, such that

$$\mathcal{R}_r(\sigma) > \mathcal{R}_s \quad \text{if and only if} \quad \sigma_{\max} < \sigma < 1. \tag{4.15}$$

(Remark: A higher resistance level corresponds to a smaller value of σ.) That is, strains with resistance $\sigma < \sigma_{\max}$ cannot invade. We can determine $\sigma_{\max}$ by noticing that it must be a solution of the equation $\mathcal{R}_r(\sigma) = \mathcal{R}_s$, from Eq. (4.14) we know that $\sigma_{\max}$ satisfies

$$\frac{\sigma(1-\sigma r_p)}{1-r_p} = 1. \tag{4.16}$$

Two solutions of (4.16) are

$$\sigma_1 = 1, \quad \sigma_2 = \frac{1-r_p}{r_p}.$$

Since the condition $r_p > \frac{1}{2}$ guarantees that $\frac{1-r_p}{r_p} < 1$, we have

$$\sigma_{\max} = \sigma_2 = \frac{1-r_p}{r_p} < 1, \quad \text{if} \quad r_p > \frac{1}{2},$$

and

$$\begin{cases} \mathcal{R}_r(\sigma) > \mathcal{R}_s, & \sigma_{\max} < \sigma < 1, \\ \mathcal{R}_r(\sigma) < \mathcal{R}_s, & \sigma < \sigma_{\max}, \\ \mathcal{R}(\sigma) = \mathcal{R}_s, & \sigma = 1, \sigma_{\max} \end{cases} \tag{4.17}$$

(see Figure 1). Clearly, if $r_p < \frac{1}{2}$ then $\sigma_{\max} > 1$ and hence $\mathcal{R}_r < \mathcal{R}_s$ for all σ. This indicates that when the drug efficacy is very low, the sensitive strain is favored. The intuitive reason for this is that if the cost of resistance is high, one would not

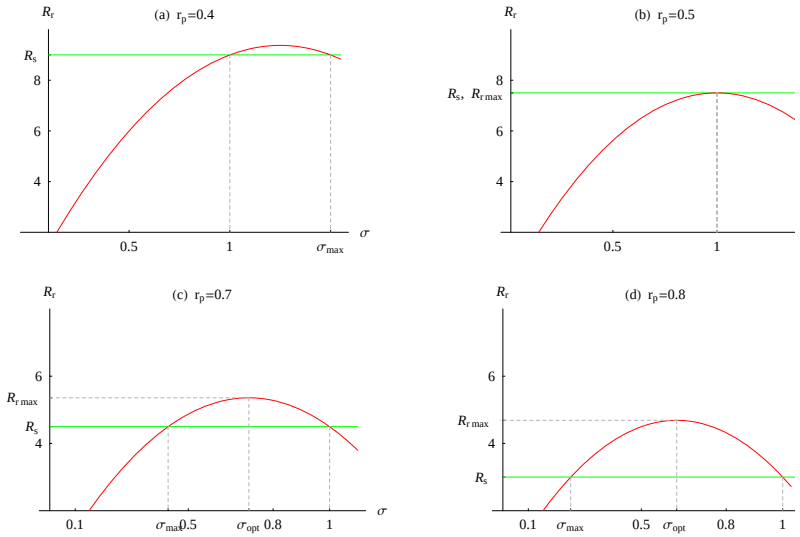

FIGURE 1. Plots of the reproductive ratio $\mathcal{R}_r$ vs. the resistant level $1/\sigma$ for different treatment efficacy r_p (r_{rt} is chosen to be 0). In (a) and (b) it is shown that $\mathcal{R}_r < \mathcal{R}_s$ for all $\sigma < 1$. Therefore, no resistant strains can invade. In (c) and (d) it is shown that resistant strains with resistance σ in $(\sigma_{\max}, 1)$ can invade. The optimal resistance is σ_{opt} at which $\mathcal{R}_r$ reaches its maximum $\mathcal{R}_{r\,\max}$.

expect resistance when there is little selection pressure from the drugs. Other non-resistant strains would outcompete it under these conditions. Resistant strains can only increase in frequency when the selection pressure (drug efficacy) is high.

We can also determine an optimal resistance, σ_{opt}, which maximizes the reproductive ratio. In fact, we can easily check that $\mathcal{R}_r(\sigma)$ has only one critical point in the interval $(\sigma_{\max}, 1)$, $\sigma = \frac{1}{2r_p}$, at which $\frac{d\mathcal{R}_r(\sigma)}{d\sigma} = 0$. Hence,

$$\sigma_{opt} = \frac{1}{2r_p} \tag{4.18}$$

(see Figure 1).

We summarize the following results for the case of a single-drug therapy. Recall that a resistant strain with resistance σ can invade the sensitive strain if and only if $\mathcal{R}_r(\sigma) > \mathcal{R}_s$.

1. There exists a threshold drug efficacy r_p^* ($r_p^* = 1/2$ for Type I cost) below which no resistant strains can invade (see Figure 1 (a) (b)). Analytically this is due to the fact that $\sigma_{\max} \geq 1$ when $r_p < r_p^*$. Hence $\mathcal{R}_r(\sigma) < \mathcal{R}_s$ for all $\sigma < 1$.
2. When the drug efficacy is above the threshold r_p^* there is a range of resistance levels for which the resistant strains are able to invade. This is because, analytically, $\sigma_{\max} < 1$ when $r_p > r_p^*$, and $\mathcal{R}_r(\sigma) > \mathcal{R}_s$ for all σ in $(\sigma_{\max}, 1)$.

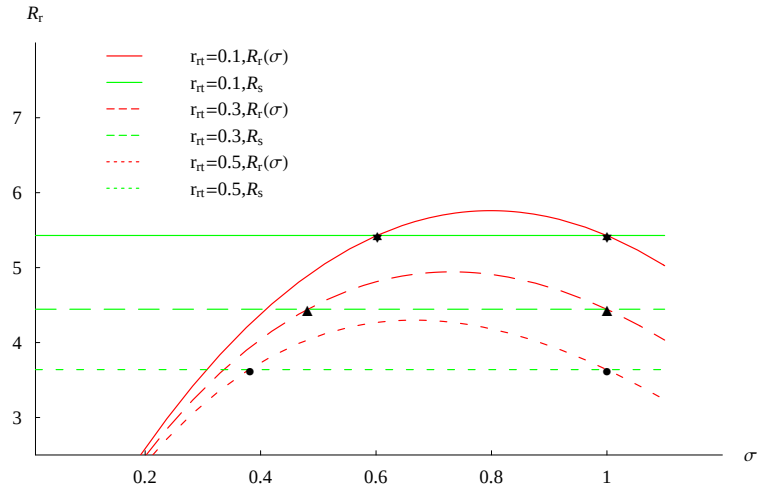

FIGURE 2. Plots of the reproductive ratio $\mathcal{R}_r$ vs. resistance σ for $r_{nt} = 0.1$ (solid), $r_{rt} = 0.3$ (long dashed), $r_{rt} = 0.5$ (short dashed). The value of r_p is fixed at $r_p = 0.6$ for which invasion is possible in the absence of the an RT drug (i.e., if $r_{rt} = 0$). For each given r_{rt}, the values of σ for which $\mathcal{R}_r(\sigma) > \mathcal{R}_s$ give the range for resistance invasion, which is the range between the two intersection points of the two corresponding curves.

3. When $\sigma_{\max} < 1$, the range of invasion strains, $(\sigma_{\max}, 1)$, increase with the drug efficacy r_p. The optimal resistance, σ_{opt}, decrease with the drug efficacy r_p (a more resistant strain corresponds to a smaller σ value, see Figure 1 (c) (d)). This increasing property is also clear from the formulas $\sigma_{\max} = (1 - r_p)/r_p$ and $\sigma_{opt} = 1/(2r_p)$.
4. As the drug efficacy increases, the optimal viral fitness, $\mathcal{R}_r(\sigma_{opt})$, decreases (see Figure 1 (c) (d)). We can also see this from the formula $\mathcal{R}_{r\,\max} = \mathcal{R}_r(\sigma_{opt}) = D/(4r_p)$ which is a decreasing function of r_p.

Combination therapy. We now consider the case of combination therapy, i.e., $r_p > 0$ and $r_{rt} > 0$. For simplicity we choose $\eta = 1$. From (4.9) and (4.10) we have

$$\mathcal{R}_r = \frac{\sigma(1 - \sigma r_p)e^{-r_{rt}(1-\sigma)a_1}}{1 - r_p}\mathcal{R}_s. \tag{4.19}$$

Again, consider $\mathcal{R}_r = \mathcal{R}_r(\sigma)$ as a function of σ. Then $\mathcal{R}_r(\sigma) > \mathcal{R}_s$ if and only if σ satisfies the inequality

$$\frac{\sigma(1 - \sigma r_p)e^{-r_{rt}(1-\sigma)a_1}}{1 - r_p} > 1. \tag{4.20}$$

To explore the role of r_{rt} we fix r_p (e.g., $r_p = 0.7$ in Figure 2). Eq. (4.20) cannot be solved analytically for σ. However, plots of $\mathcal{R}_r(\sigma)$ for different values of r_{rt} suggest that, as r_{rt} increases, the range for $\mathcal{R}_r(\sigma) > \mathcal{R}_s$ also increases (see Figure 2). Figure 3 illustrates the joined effect of r_{rt} and r_p on the reproductive ratios $\mathcal{R}_s$

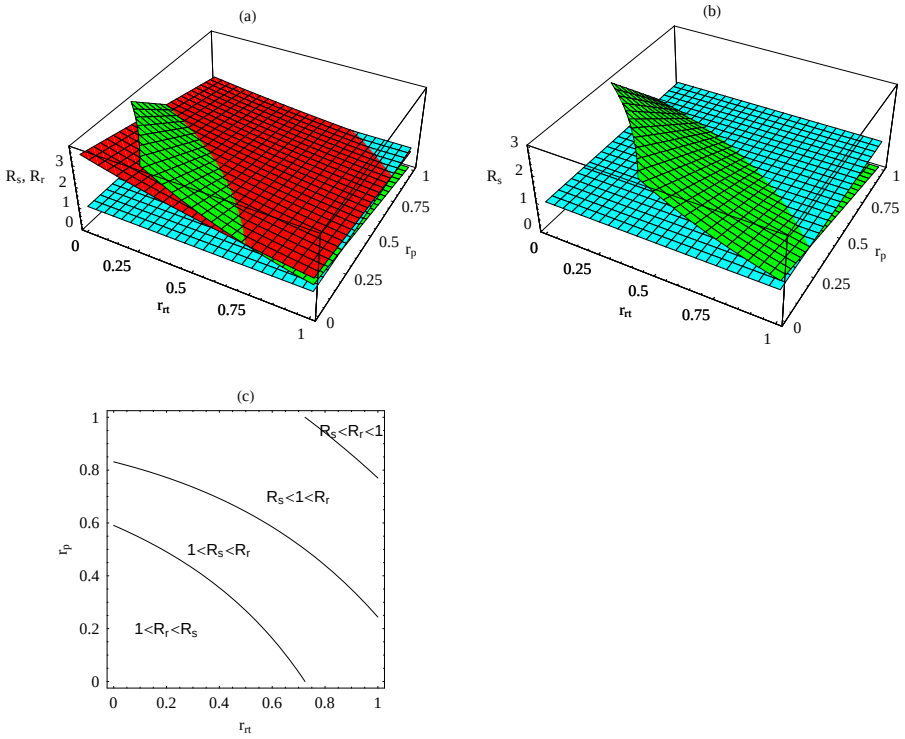

FIGURE 3. Plots of the reproductive ratios $\mathcal{R}_s$ and $\mathcal{R}_r$ as functions of r_{rt} and r_p. Three surfaces are plotted in Figure 3(a): $\mathcal{R}_r(r_{rt}, r_p)$ (the top surface near the origin), $\mathcal{R}_s(r_{rt}, r_p)$ (middle surface) and the constant 1 (the bottom surface). The intersection of the top two surfaces is the curve on which $\mathcal{R}_r = \mathcal{R}_s$. In Figure 3(b) two surfaces, $\mathcal{R}_s(r_{rt}, r_p)$ and the constant 1, are plotted to show the curve on which $\mathcal{R}_s = 1$. Figure 3(c) is a contour plot of the surfaces $\mathcal{R}_r(r_{rt}, r_p)$ and $\mathcal{R}_s(r_{rt}, r_p)$.

and $\mathcal{R}_r$. From the contour plot (see Figure 3(c)) we see that when the drug efficacy is low (the region in the lower-left corner in which $\mathcal{R}_s > \mathcal{R}_r > 1$) the resistant strain cannot invade. Neither strain can survive when the drug efficacy is high (the top-right region in which $\mathcal{R}_s < 1$ and $\mathcal{R}_r < 1$). In the middle region the invasion of resistant strains are possible as $\mathcal{R}_r > \mathcal{R}_s$.

Figure 4 shows that when Type II cost is used the qualitative property of the reproductive ratio $\mathcal{R}_r$ as a function of σ is very similar to those when Type I cost is used. For example, the function $\mathcal{R}_r(\sigma)$ admits a unique $\sigma_{\max}$ and a unique σ_{opt} for sufficiently small values of ϕ.

5. Discussion

We have formulated an age-structured model for HIV-1 infection with drug treatments to study the impact of chemotherapy on the emergence of resistant HIV-1 strains. We have exhibited the reproductive ratio of the drug sensitive strain $\mathcal{R}_s$,

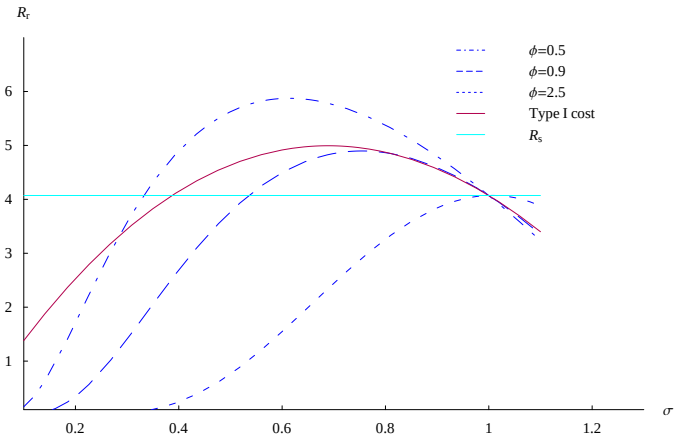

FIGURE 4. Plots of the reproductive ratio $\mathcal{R}_r$ vs. resistance σ when Type II cost is considered. The value of ϕ measures the level of cost. Invasion is possible for σ in the range between the two intersection points at which $\mathcal{R}_r = \mathcal{R}_s$. It also shows that invasion is impossible if the cost is too high (e.g., $\phi = 2.5$).

and demonstrated the asymptotical stability of the infection-free steady state $\bar{E}$ if $\mathcal{R}_s < 1$ and the infected steady state $E^\diamond$ if $\mathcal{R}_s > 1$. We have considered two types of drug treatments with reverse transcriptase inhibitors and protease inhibitors and the possible development of drug resistance. The cost for resistant strains is assumed to be a reduced viral production rate. We have calculated the reproductive ratio for the resistant strain $\mathcal{R}_r(\sigma)$ with resistance σ, and provided a criterion for the potential invasion of resistant strains, $\mathcal{R}_r(\sigma) > \mathcal{R}_s$, in an environment where the wild strain is already established. We argue that natural selection within a host favors viruses that maximize the reproductive ratio which is consistent with earlier findings (see, for example, [**2**]). Consequently, we show that natural selection should favor viral strains that have an intermediate level of resistance, and the optimal resistance (σ_{opt}) decreases with increasing drug efficacy (see Figure 1 and Figure 2). Mathematically, increasing the values of r_p and r_{rt} results in: (i) a reduction in the reproductive ratio $\mathcal{R}_s$ of the drug sensitive strain (see Figure 4) and hence a reduction in the equilibrium level of infection (see $T^\diamond$ and $V^\diamond$ in Eq. (3.4)); (ii) a decrease in the optimal viral fitness $\mathcal{R}_{r\,\max}$ of the resistant strain and a decrease in the optimal resistance σ_{opt} (see Figure 1 and Figure 3); and (iii) an increase in the range $\sigma_{\max} < \sigma < 1$ of resistance (that is, $\sigma_{\max}$ decreases with both r_p and r_{rt}, see Figure 1 and Figure 2). These are strains that has a high fitness (i.e., $\mathcal{R}_r(\sigma) > \mathcal{R}_s$) are hence are able to invade a host population. On the other hand, if r_p and r_{rt} are small such that $\sigma_{\max}$ is greater than 1, then $\mathcal{R}_r(\sigma) < \mathcal{R}_s$ for all resistance σ. These strains will not be maintained in a population.

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