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By

Nicoleta Tarfulea

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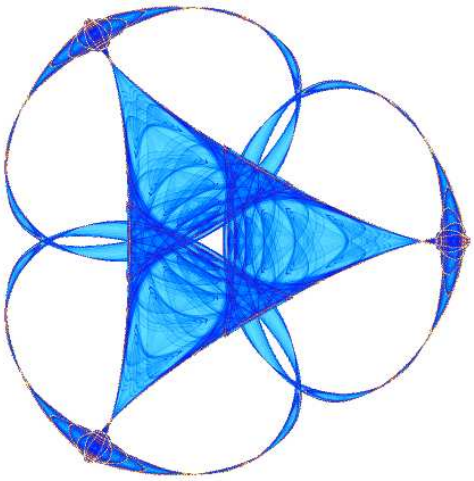


INSTITUTE FOR MATHEMATICS AND ITS APPLICATIONS

UNIVERSITY OF MINNESOTA
400 Lind Hall
207 Church Street S.E.
Minneapolis, Minnesota 55455–0436

Phone: 612-624-6066 Fax: 612-626-7370
URL: http://www.ima.umn.edu

A MATHEMATICAL MODEL FOR THE CTL EFFECT ON THE DRUG RESISTANCE DURING ANTIRETROVIRAL TREATMENT OF HIV INFECTION

NICOLETA TARFULEA

Abstract. In treating Human Immunodeficiency Virus (HIV) infection, strict adherence to drug therapy is crucial in maintaining a low viral load, but the high dosages required for this often have toxic side effects which make perfect adherence to Antiretroviral Therapy (ART) unsustainable. The imperfect patient adherence to ART and the development of resistant strains in the viral load has led to the development of alternative treatments that incorporate immunological response. This paper investigates theoretically and numerically the effect of immune effectors, such as the cytotoxic lymphocyte (CTL), in modeling HIV pathogenesis; our results suggest the significant impact of the immune response on the control of the virus during primary infection. Qualitative aspects (including positivity, boundedness, stability, uncertainty, and sensitivity analysis) are addressed. Additionally, by introducing drug therapy, we analyze numerically the model to assess the effect of treatment consisting of a combination of several antiretroviral drugs. Nevertheless, even in the presence of drug therapy, ongoing viral replication can lead to the emergence of drug-resistant virus variances. This fact is addressed in our model by including two viral strains, wild-type and drug-resistant. Our results show that the inclusion of the CTL compartment produces a higher rebound for an individual's healthy helper T-cell compartment than does drug therapy alone. Furthermore, we quantitatively characterize successful drugs or drug combination scenarios for both strains of virus.

Keywords: HIV dynamics, Cytotoxic Lymphocyte, Antiretroviral Therapy Drug resistance, Mathematical model

1. Introduction

The severe and deadly impacts of the Acquired Immunodeficiency Syndrome (AIDS) have motivated scientists to investigate them in the sequential stages of the Human Immunodeficiency Virus (HIV) infection [1, 2]. AIDS is the result of a long battle between an individual's immune system and the HIV [3, 4, 5]. The body's initial response to HIV infection is similar in nature to the response to many other viruses. Unfortunately, the virus has a demonstrated ability to evade these natural defense mechanisms, with the result that after the initial period of infection, the disease progresses to latency [6]. During this latent stage of infection, the virus can go undetected, while it continues to attack and weaken the immune system [7]. The latent period of infection is followed by the final stage, when a deteriorated immune system collapses, and the individual dies from secondary infections.

When HIV enters the bloodstream, it primarily targets crucial components of the immune system [8], specifically, CD4+ T-cells or helper T-cells, whose function

Purdue University Calumet, 2200 169th Street, Hammond, IN 46323, USA.

is to assist the response to bodily infections by releasing chemicals that signal other immune system cells, such as CD8+ (killer) T-cells, to kill infected cells or infectious particles [9, 10, 8, 11, 12, 13]. HIV is capable of infecting other immune cells, such as macrophages [14], but the primary targets of infection are the CD4+ T-cells [15]. Hence, they plays a central role in existing mathematical models [16, 17, 18, 19, 14, 20, 21, 22].

Several stages have been identified in the virus' reproduction cycle. First, an HIV viral particle attaches to a CD4+ T-cell, and the genetic material required for synthesis of new viral DNA, the viral RNA, is injected into the healthy cell. Aided by the enzyme, reverse transcriptase, which is contained in the viral shell, the virus' RNA uses the T-cell's own DNA to produce viral DNA. The viral DNA penetrates the nucleus and is integrated with the cell's chromosomes, forming part of the infected cellular DNA. The replicating mechanisms of the infected cell are then used to produce copies of this newly-integrated viral DNA, as well as copies of the original viral RNA. After the viral DNA has been replicated, an enzyme produced by the viral DNA, protease, cuts the DNA inside the cell into protein strings of proper length. These protein strings are regrouped together inside the cell with the viral RNA, and become the basis for new virus. The newly-formed viral particles can be released in a process called budding, where they exit the cell through its external membrane and become mature infectious virus. In an alternative outcome, the production of a large number of viral particles can force the infected cell to burst, killing the cell and releasing the infectious virions into the body [23, 24, 8, 25, 26, 27].

The body's immune system fails to react fast enough to prevent the virus from rapidly infecting and killing a large number of CD4+ T-cells, which subsequently they become the mechanism through which the virus population can multiply [3, 5, 28, 29, 14]. The rapid mutation of the virus can prevent proper identification of infected cells by the body's immune effectors. Infected cells flag themselves for the immune system by chopping viral proteins into pieces and attaching these to HLA cellular proteins. The molecular combination then rises to the membrane of the cell, where it becomes a signal for CD8+ T-cells to destroy the infected cell [9, 30, 12]. However, the rapid mutation of HIV can prevent the HLA molecule from properly rising to the surface of the cell, or in some cases, prevent the molecule from rising at all. As a result, the immune effector CD8+ T-cells are incapable of recognizing the cell as being infected, allowing the virus to continue replication [9, 8, 11].

The intrinsic complexity of HIV has been a crucial factor for the development of various mathematical models for the dynamics of the disease in order to predict viral evolution over time and under various conditions [18, 14, 20, 21, 22] and, more importantly, to get valuable insights into the emergence of HIV drug resistance and possible treatment scenarios [31, 32, 33, 34, 35, 36, 21, 22, 37, 38]. In this paper, building upon the standard model of within-host virus infection [39, 14], we propose a mathematical model for HIV dynamics that considers the impact of CD8+ T-cells in fighting the infection by studying their effect on the emergence of drug resistance during antiretroviral therapy. Our model incorporates multiple viral strains (drug-sensitive and drug-resistant strains) which differ by a single mutation since even a single mutation can make the mutant virus to acquire a significant degree of resistance to a drug or a class of drugs [40, 41, 42, 43]. It is worth mentioning that the model could be easily extended to include multiple resistant strains as a

result of two or more mutations. We provide analytical and numerical results of this model in the absence and presence of therapy and we investigate the evolution of the resistant strain in these cases. Furthermore, we explore the consequences of different scenarios of antiviral therapy, the influence of different combinations of the major classes of drugs available for the treatment. We also study their impact on the evolution of the disease and determine a possible optimal treatment strategy that will lower the most the viral load in the body.

2. Formulation of the problem

2.1. **Presentation of the mathematical model.** A widely adopted mathematical model of HIV infection is given by the system (1) (see [16, 19, 14, 20, 21, 22, 44]) which is composed of compartments accounting for the concentration of healthy CD4+ T-cells, HIV-infected CD4+ T-cells, and free virus in the blood.

$$\begin{aligned} \frac{dT}{dt} &= \lambda_T - dT - kVT \\ \frac{dT^*}{dt} &= kTV - \delta T^* \\ \frac{dV}{dt} &= N\delta T^* - cV \end{aligned} \tag{1}$$

Here, T, T^*, and V are the concentration of healthy CD4+ T-cells, infected CD4+ T-cells, and free virus in the body at time t, respectively. Additionally, λ_T is the recruitment rate of uninfected T - cells, k is the rate at which healthy CD4+ T-cells are infected by free HIV virus, δ is the rate at which infected CD4+ T-cells die naturally, N is the number of free virions released by an infected cell upon death, also known as the burst size, and c is the clearance rate of free virus from the body.

This system has two steady states: the infection free steady state

$$S_0 := \left(T_0 = \frac{\lambda}{d}, T_0^* = 0, V_0 = 0 \right)$$

and the infected steady state

$$S_i := \left(T_i = \frac{c}{Nk}, T_i^* = \frac{\lambda kN - cd}{kN\delta}, V_i = \frac{\lambda kN - cd}{kc} \right).$$

If we denote by

$$R_0 := \frac{k\,\lambda\,N}{d\,c},$$

the basic reproductive ration [45, 46, 21, 47], then it has been proved that the infection free steady state S_0 is globally attracting if $R_0 < 1$ and that the infected steady state S_i is globally asymptotically stable if $R_0 > 1$ [48].

The course of HIV infection varies widely across the infected population, and this is at least partially explained by individually-specific immunological responses. The primary effector of the cell-mediated immune response is the CD8+ killer T cells (CTLs). The CD8+ T cell kills infected cells bearing a specific antigen. The activation of the killer T cell is largely dependent upon the CD4+ helper T cells, which direct the immune response. Thus incorporation of cellular compartments representing both the helper and effector T cells more completely represents the

body's cellular immune system. In [49] the authors considered the following model for HIV dynamics which includes the CTLs response.

$$\begin{aligned} \frac{dT}{dt} &= \lambda_T - dT - kVT \\ \frac{dT^*}{dt} &= kTV - \delta T^* \\ \frac{dV}{dt} &= N\delta T^* - cV \\ \frac{dE}{dt} &= \lambda_E + c_E T^* - \delta_E E, \end{aligned} \tag{2}$$

together with initial data

$$T(0) = T_0, \quad T^*(0) = 0, \quad V(0) = V_0, \quad E(0) = E_0 \quad (\text{here } T_0,\, V_0,\, E_0 > 0). \tag{3}$$

Here, in addition to the variables and parameters used in the system (1), E denotes the concentration of CD8+ T-cells in the body, λ_E represents the production rate of healthy CD8+ T-cells from natural sources, δ_E represents the natural death rate of CD8+ T-cells, c_E represents the constant for CD8+ T-cell birth via their interaction with infected cells, and m represents the CD8+ T-cell-induced death rate for T^*.

The system (2) has two possible steady states within the nonnegative orthant, that is, the infection free steady state

$$S_0 := \left(T_0 = \frac{\lambda_T}{d}, T_0^* = 0, V_0 = 0, E_0 = \frac{\lambda_E}{\delta_E} \right) \tag{4}$$

and the infected steady state

$$S_i := \left(T_i, T_i^* = \frac{c}{N\delta} \cdot \frac{\lambda_T - dT_i}{kT_i}, V_i = \frac{\lambda_T - dT_i}{kT_i}, E_i = \frac{\lambda_E}{\delta_E} + \frac{c_E}{\delta_E} \cdot \frac{\lambda_T - dT_i}{kT_i} \right), \tag{5}$$

where T_i is the positive solution of the quadratic equation $T^2 - A \cdot T - B = 0$, with

$$A = \frac{c}{N\delta k} \left(\delta + m\frac{\lambda_E}{\delta_E} - md\frac{c}{N\delta k}\frac{c_E}{\delta_E} \right) \text{ and } B = m \left(\frac{c}{N\delta k} \right)^2 \frac{c_E}{\delta_E} \lambda_T.$$

If we let

$$R := \frac{N\delta k \lambda_T}{cd \left(\delta + m\frac{\lambda_E}{\delta_E} \right)}$$

denote the basic reproductive ratio, then the uninfected steady state S_0 is stable if and only if $R < 1$. Moreover, the infected steady state is stable for any choice of the parameters in the considered range (see [49]).

To model the emergence of drug resistance and a possible treatment method, a new model is required which accounts for the presence of drug-sensitive and drug-resistant strains of virus separately, rather than aggregating them. In this manner, one could determine whether a certain treatment regimen was producing an increase in the drug-resistant concentration of virus over time, even if the population of drug-sensitive HIV virus was declining. Treatments which cause the population of drug-sensitive virus to decline, but the population of drug-resistant virus to increase over time are postponing the inevitable, as they do not provide a long-term benefit to an individual infected with HIV. A model incorporating two strains of HIV

TABLE 1. Parameter definitions and values used in numerical simulations

Parameter	Description	Value	Ref.
λ_T	Recruitment rate of uninfected cells	$d \cdot T(0)$	[21]
d	Death rate of uninfected cells	0.01 day $^{-1}$	[50, 21]
k_s	Infection rate of T-cells by the wild-type virus	$2.4 \cdot 10^{-5} \mu$l day^{-1}	[16, 19, 21]
k_r	Infection rate of T-cells by the drug-resistant virus	$2.4 \cdot 10^{-5} \mu$l day^{-1}	[16, 19, 21]
δ	Death rate of infected cells	0.3 day^{-1}	[51]
m_1	Immune-induced clearance rate for infected T_s cells	$10^{-2} \mu$l day^{-1}	[16]
m_2	Immune-induced clearance rate for infected T_r cells	$10^{-2} \mu$l day^{-1}	[16]
N_s	Virions produced per infected drug-sensitive cell	5000	[21]
N_r	Virions produced per infected dru-resistant cell	5000	[21]
c	Clearance rate of free virus	23 day^{-1}	[21]
λ_E	Immune effector production (source) rate	$10^{-3} \mu$l day^{-1}	[16]
c_E	Stimulation of CTL proliferation	0.3 day^{-1}	[51]
δ_E	Death rate of immune effectors	0.1 day^{-1}	[16, 51]

has been utilized extensively in [21] to model the effects of Antiretroviral Therapy (ART) on the arisal of drug-resistant strains of HIV.

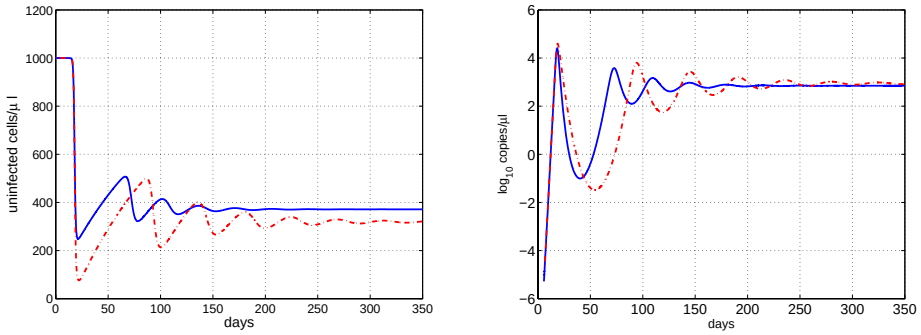
Drawing from the multiple-strain model of infection and the CD8+-inclusive models [52, 53, 54], we consider the following model for our purpose.

$$\begin{aligned}
\frac{dT}{dt} &= \lambda_T - dT - k_s V_s T - k_r V_r T \\
\frac{dT_s}{dt} &= (1-u) k_s T V_s - \delta T_s - m_1 E T_s \\
\frac{dV_s}{dt} &= N_s \delta T_s - c V_s \\
\frac{dT_r}{dt} &= u k_s T V_s + k_r V_r T - \delta T_r - m_2 E T_r \\
\frac{dV_r}{dt} &= N_r \delta T_r - c V_r \\
\frac{dE}{dt} &= \lambda_E + c_E (T_s + T_r) - \delta_E E,
\end{aligned} \tag{6}$$

together with initial data

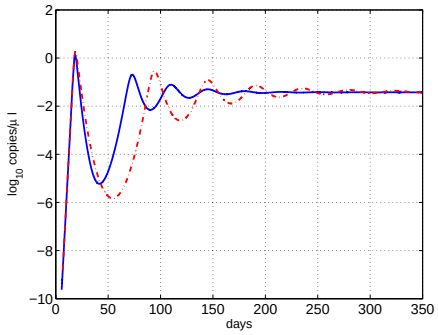
$$T(0) = T_0,\ T_s(0) = 0,\ V_s(0) = V_0,\ T_r(0) = 0,\ V_r(0) = 0,\ E(0) = E_0, \tag{7}$$

where $T_0,\ V_0,\ E_0 > 0$.

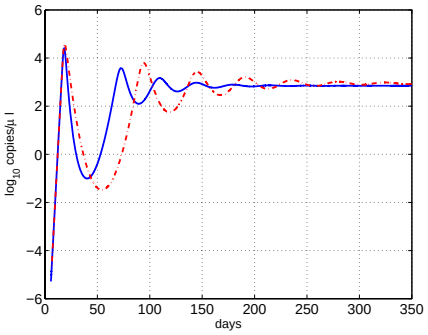


(a) Uninfected cells $T(t)$

(b) Wild-type virus $V_s(t)$



(c) Resistant virus $V_r(t)$



(d) Total virus

FIGURE 1. Simulation over the first 350 days of infection; (-.-) line for the system in [21] with initial conditions $T(0) = 10^3$ cells/ μl, $T_s(0) = 0$ cells/μl, $T_r(0) = 0$ cells/μl, $V_s(0) = 10^{-3}$ copies/μl, and $V_r(0) = 0$ cells/μl,; (–) line for (6) with additional initial condition $E(0) = 10^{-3}$ cells/ μl.

In this model, T represents the healthy T-cell concentration, T_s and V_s represent the drug-sensitive infected T-cell and drug-sensitive virus concentration, respectively, T_r and V_r represent the drug-resistant infected T-cell and drug-resistant virus concentration, respectively, and E represents the concentration of CD8+ T-cells in the body. Moreover, λ_T represents the production rate of healthy CD4+ T-cells from natural sources, λ_E represents the production rate of healthy CD8+ T-cells from natural sources, δ represents the death rate of infected T-cells, δ_E represents the natural death rate of CD8+ T-cells, d_T represents the natural death rate of uninfected CD4+ T-cells, m_1 represents the CD8+ T-cell-induced death rate for T_s, m_2 represents the CD8+ T-cell-induced death rate for T_r. Additionally, u represents the rate at which drug-sensitive T-cells mutate to become drug-resistant, while k_r and k_s are the drug-resistant and drug-sensitive infection rates of target cells by free virus, respectively. It is assumed, in this model, that c, the viral clearance rate, and δ, the infected T-cell death rate, are the same for both strains of virus.

Figure 1 presents simulation results for the CD4+ T cell concentration, the wild type virus, the resistant virus, and the total viral load before treatment using the systems in [21] and (6). The values of the common parameters are the same, and all values are listed in Table 1. As is expected, CD8+ T-cell response is very important in the evolution of HIV and this aspect is captured by the system that we consider. While the two cases produce similar behavior, the healthy T-cell concentration is higher in the second case, and, consequently, the total viral load is lower in this case. Moreover, the limiting solution is lower as well.

2.2. **Analysis of the model.** We start the analysis by showing that the solution of the initial-value problem (6)–(7) is nonnegative and bounded. The following lemmas are relatively simple, but useful tools for proving these facts.

Lemma 1. *Let P and Q be two continuous functions on the interval $[a, b)$ ($b < \infty$ or $b = \infty$), with Q nonnegative everywhere. Then, the solution to the initial-value problem*

$$\frac{dy}{dt} + P(t)y = Q(t) \text{ for } t \in (a, b); \quad y(a) = \alpha, \text{ with } \alpha \geq 0, \tag{8}$$

is nonnegative everywhere. Moreover, if either $\alpha > 0$ or $Q(a) > 0$, then the solution y is strictly positive in (a, b).

Proof. Let $\mu(t) := \exp\Big(\int_a^t P(s)ds\Big)$ be the integrating factor of the first-order linear ordinary differential equation in (8). Then, it is well-known that the solution of the initial-value problem (8) is given by

$$y(t) = \frac{1}{\mu(t)}\Big(\int_a^t \mu(s)Q(s)ds + \alpha\Big) \text{ for } t \in [a, b).$$

Since $\mu(t) > 0$ for all $t \in [a, b)$, the conclusion of the lemma follows easily. □

Lemma 2. *Let $y : [a, b) \to \mathbf{R}$ ($b < \infty$ or $b = \infty$) be a function differentiable on (a, b). If there exist two positive constants α, $\beta > 0$ such that $y'(t) \leq \alpha - \beta y(t)$ in (a, b), then the function y is bounded from above.*

Proof. Observe that $[(e^{\beta s}y(s)]' \leq \alpha e^{\beta s}$ in (a, b). Then, by integration with respect to s over the interval $[a, t]$, with $t \in [a, b)$, it follows that

$$e^{\beta t}y(t) - e^{\beta a}y(a) \leq \frac{\alpha}{\beta}(e^{\beta t} - e^{\beta a}),$$

and so

$$y(t) \leq \frac{e^{\beta a}}{e^{\beta t}}y(a) + \frac{\alpha}{\beta}(1 - \frac{e^{\beta a}}{e^{\beta t}}) \leq |y(a)| + \frac{\alpha}{\beta}, \quad \text{for all } t \in [a, b),$$

which proves the claim. □

First of all, we observe that the first equation of the system (6) can be reformulated as a standard first-order linear ODE

$$\frac{dT}{dt} + (d + k_s V_s + k_r V_r)T = \lambda_T. \tag{9}$$

Because $T(0) = T_0 > 0$, by Lemma 1 it follows that $T(t) > 0$ for all $t > 0$ for which the solution of the initial-value problem (6)–(7) exists.

Next, let us prove that V_s is nonnegative. Arguing by contradiction, suppose that V_s changes sign. It follows that there exists a minimal positive time t_0 when

$V_s(t_0) = 0$. Since $V_s(t) > 0$ in $[0, t_0)$, one obtains $V_s'(t_0) \leq 0$. From the third equation of the system (6), it follows that $T_s(t_0) \leq 0$. However, the second equation of (6) together with the initial condition $T_s(0) = 0$, gives $T_s(t)$ in the form

$$T_s(t) = \frac{1}{\mu_{T_s}(t)} \Big[\int_0^t \mu_{T_s}(\theta)(1-u)k_s T(\theta)V_s(\theta)d\theta \Big], \tag{10}$$

with

$$\mu_{T_s}(t) := \exp\Big[\int_0^t (\delta + m_1 E(\theta))d\theta \Big].$$

From (10), we observe that $T_s(t_0)$ must be strictly positive, which is in clear contradiction with $T_s(t_0) \leq 0$. This proves that $V_s(t)$ must be positive on its domain of definition. Since both $T(t)$ and $V_s(t)$ are positive wherever defined, from Lemma 1 applied to the second equation of (6) one gets the positivity of $T_s(t)$ on its domain of definition. From the fourth equation of (6) and the initial condition $T_r(0) = 0$, we can solve for T_r and write the solution in the form

$$T_r(t) = \frac{1}{\mu_{T_r}(t)} \int_0^t \mu_{T_r}(\theta)(uk_s T(\theta)V_s(\theta) + k_r V_r(\theta)T(\theta))d\theta, \tag{11}$$

where

$$\mu_{T_r}(t) := \exp\big(\int_0^t (\delta + m_2 E(\theta))d\theta \big).$$

Since $\mu_{T_r}(t) > 0$, for all $t \geq 0$, and $uk_s T(0)V_s(0) + k_r V_r(0)T(0) = uK_s T_0 V_0 > 0$, the equation (11) implies that there is $t_0 > 0$ such that $T_r(t) > 0$ in $(0, t_0)$. Assume that $t_0 < \infty$ is maximal with this property, that is, $T_r(t) > 0$ for all $t < t_0$ and $T_r(t_0) = 0$ (if $t_0 = \infty$, then obviously $T_r(t) > 0$ for all $t > 0$ and the positivity of T_r is proven completely). By Lemma 1, fifth equation of (6), and the initial data $V_r(0) = 0$, one obtains that $V_r(t) > 0$ on $(0, t_0]$. But this, together with the positivity of the other terms of the right-hand side of equation (11), is in contradiction with $T_r(t_0) = 0$. Thus, we conclude that $T_r(t) > 0$ on its domain of definition. Furthermore, Lemma 1 and the last two equations of (6), combined with the just proven positivity of both T_r and T_s, show that V_r and E must be positive wherever defined as well.

The boundedness of the solution of (6) can be proven as follows. From (6), first observe that

$$\frac{d}{dt}(T+T_s+T_r) = \lambda_T - dT - \delta T_s - m_1 E T_s - \delta T_r - m_2 E T_r \leq \lambda_T - \min(d, \delta)(T+T_s+T_r). \tag{12}$$

Then, by Lemma 2, the function $T + T_s + T_r$ is bounded from above. Because T, T_s, and T_r are also nonnegative, we obtain that each of them is a bounded function. From the third, fifth, and sixth equations of (6), we see that

$$V_s'(t) \leq C - cV_s(t), \quad V_r'(t) \leq C - cV_r(t), \quad E'(t) \leq C - \delta_E E(t),$$

respectively, where in each inequality C is a constant that bounds $N_s \delta T_s$, $N_r \delta T_r$, and $\lambda_E + c_E(T_s + T_r)$, respectively. Then, by applying Lemma 2, we obtain that the functions V_s, V_r, and E are also bounded.

Let $\bar{S} := (\bar{T}, \bar{T}_s, \bar{V}_s, \bar{T}_r, \bar{V}_r, \bar{E})$ denote a steady state (constant solution) of the system (6) in the nonnegative orthant $\mathbf{R}^6_+$. That is, $\bar{S}$ is a nonnegative solution of

the algebraic system

$$\begin{aligned}
&\lambda_T - dT - k_s V_s T - k_r V_r T = 0\\
&(1-u)k_s T V_s - \delta T_s - m_1 E T_s = 0\\
&N_s \delta T_s - c V_s = 0\\
&u k_s T V_s + k_r V_r T - \delta T_r - m_2 E T_r = 0\\
&N_r \delta T_r - c V_r = 0\\
&\lambda_E + c_E(T_s + T_r) - \delta_E E = 0,
\end{aligned} \tag{13}$$

Solving for T, V_s, V_r, and E with respect to T_s and T_r in (13) gives

$$\begin{aligned}
T &= \frac{\lambda_T c}{dc + \delta(k_s N_s T_s + k_r N_r T_r)}\\
V_s &= \frac{\delta N_s T_s}{c}\\
V_r &= \frac{\delta N_r T_r}{c}\\
E &= \frac{\lambda_E + c_E(T_s + T_r)}{\delta_E}
\end{aligned} \tag{14}$$

Substituting back into equation (13), one finds that the system (6) has three possible positive steady states:

(1) the infection free steady state

$$S_0 := \left(T_0 = \frac{\lambda_T}{d}, T_{s0} = 0, V_{s0} = 0, T_{r0} = 0, V_{r0} = 0, E_0 = \frac{\lambda_E}{\delta_E}\right), \tag{15}$$

(2) the boundary steady state S_b, when only the drug-resistant strain is present

$$S_b := (T_b, T_{sb}, V_{sb}, T_{rb}, V_{rb}, E_b), \tag{16}$$

where $T_{sb} = 0, V_{sb} = 0$, $T_{rb} = \frac{c}{N_r \delta} \cdot \frac{\lambda_T - dT_b}{k_r T_b}$, $V_{rb} = \frac{\lambda_T - dT_b}{k_r T_b}$, $E_b = \frac{\lambda_E}{\delta_E} + \frac{c_E}{\delta_E} \cdot \frac{\lambda_T - dT_b}{k_r T_b}$, and T_b is the positive solution of the quadratic equation $T^2 - A_b \cdot T - B_b = 0$, where

$$A_b = \frac{c}{N_r \delta k_r}\left(\delta + m_2 \frac{\lambda_E}{\delta_E} - m_2 d \frac{c}{N_r \delta k_r}\frac{c_E}{\delta_E}\right) \text{ and } B_b = m_2 \left(\frac{c}{N_r \delta k_r}\right)^2 \frac{c_E}{\delta_E}\lambda_T.$$

(3) the interior steady state S_i, when both the wild-type and the resistant strains coexist

$$S_i := (T_i, T_{si}, V_{si}, T_{ri}, V_{ri}, E_i), \tag{17}$$

where $T_i = \frac{\lambda_T c}{dc + \delta(k_s N_s T_{si} + k_r N_r T_{ri})}$, $V_{si} = \frac{\delta N_s T_{si}}{c}$, $V_{ri} = \frac{\delta N_r T_{ri}}{c}$, $E = \frac{\lambda_E + c_E(T_{si} + T_{ri})}{\delta_E}$, and T_{si} and T_{ri} are the solutions of the system

$$\begin{cases}
\dfrac{(1-u)k_s N_s \delta \lambda_T}{dc + \delta(k_s N_s T_s + k_r N_r T_r)} - \delta - \dfrac{m_1[\lambda_E + c_E(T_s + T_r)]}{\delta_E} = 0\\
\dfrac{\delta \lambda_T (u k_s N_s T_s + k_r N_r T_r)}{dc + \delta(k_s N_s T_s + k_r N_r T_r)} - \delta T_r - \dfrac{m_2[\lambda_E + c_E(T_s + T_r)]T_r}{\delta_E} = 0
\end{cases} \tag{18}$$

Let

$$R_s := \frac{N_s \delta k_s \lambda_T}{cd\left(\delta + m_1 \frac{\lambda_E}{\delta_E}\right)} \text{ and } R_r := \frac{N_r \delta k_r \lambda_T}{cd\left(\delta + m_2 \frac{\lambda_E}{\delta_E}\right)} \tag{19}$$

denote the basic reproductive ratios of the wild-type strain and the drug-resistant strain, respectively, and let $\sigma = \dfrac{k_s N_s}{k_r N_r}$.

The second equation in (18) is of the form

$$T_r^3 + a_1 T_r^2 + a_2 T_r - a_3 = 0, \tag{20}$$

where

$$\begin{aligned} a_1 &= \frac{\lambda_E}{c_E} + \frac{\delta \delta_E}{m_2 c_E} + (1+\sigma) T_s + \alpha > 0 \\ a_2 &= -\frac{\lambda_T \delta_E}{m_2 c_E} + (\sigma T_s + \alpha)\left(T_s + \frac{\lambda_E}{c_E} + \frac{\delta \delta_E}{m_2 c_E}\right) \\ a_3 &= u \lambda_T \sigma T_s > 0, \end{aligned}$$

and $\alpha = \dfrac{dc}{\delta k_r N_r}$.

Since the y intercept is below the x axis and $a_1 > 0$, the equation (20) has only one positive solution which guaranties the existence of the infected steady state value for T_r. Now the first equation in (18) is a quadratic equation in T_s

$$T_s^2 + b_1 T_s + b_2 = 0, \tag{21}$$

where

$$\begin{aligned} b_1 &= \frac{\lambda_E}{c_E} + \frac{\delta \delta_E}{m_1 c_E} + T_r(1+\sigma) + \alpha > 0, \\ b_2 &= -\frac{(1-u)\lambda_T \delta_E}{m_1 c_E} + (\alpha + T_r)\left(\frac{\delta \delta_E}{m_1 c_E \sigma} + \frac{\lambda_E}{c_E \sigma} + \frac{1}{\sigma} T_r\right), \end{aligned}$$

and whose discriminant is

$$\Delta = \left[\frac{m_1 c_E}{\delta_E}(1-\sigma) T_r + m_1\left(\alpha \frac{c_E}{\delta_E} - \sigma \frac{\lambda_E}{\delta_E}\right)\sigma \delta\right]^2 + 4 \frac{c_E}{\delta_E} \sigma^2 \lambda_T m_1 (1-u) > 0,$$

which guaranties the existence of real solutions for the equation (21). Since $b_1 > 0$ this equation can have at most one positive solution. The necesary and sufficient condition for the existence of a positive solution is $b_2 < 0$, which implies that $R_s > \dfrac{1}{1-u}$.

In the special case that there is no mutation, i.e., $u = 0$, the interior steady state S_i reduces to another boundary steady state S_w when only the wild-type strain is present.

$$S_w := (T_w, T_{sw}, V_{sw}, T_{rw}, V_{rw}, E_w), \tag{22}$$

where $T_{rw} = 0, V_{rw} = 0$, $T_{sw} = \dfrac{c}{N_s \delta} \cdot \dfrac{\lambda_T - dT_w}{k_s T_w}$, $V_{sw} = \dfrac{\lambda_T - dT_w}{k_s T_w}$, $E_w = \dfrac{\lambda_E}{\delta_E} + \dfrac{c_E}{\delta_E} \cdot \dfrac{\lambda_T - dT_w}{k_s T_w}$, and T_w is the positive solution of the quadratic equation $T^2 - A_w b \cdot T - B_w = 0$, where

$$A_w = \frac{c}{N_s \delta k_s}\left(\delta + m_1 \frac{\lambda_E}{\delta_E} - m_1 d \frac{c}{N_s \delta k_s} \frac{c_E}{\delta_E}\right) \text{ and } B_w = m_1 \left(\frac{c}{N_s \delta k_s}\right)^2 \frac{c_E}{\delta_E} \lambda_T.$$

The other steady states S_0 and S_b are the same.

The Jacobian matrix of the system (6) is

$$J = \begin{pmatrix} -d - k_s V_s - k_r V_r & 0 & -k_s T & 0 & -k_r T & 0 \\ (1-u)k_s V_s & -\delta - m_1 E & (1-u)k_s T & 0 & 0 & -m_1 T_s \\ 0 & N_s \delta & -c & 0 & 0 & 0 \\ uk_s V_s + k_r V_r & 0 & uk_s T & -\delta - m_2 E & k_r T & -m_2 T_r \\ 0 & 0 & 0 & N_r \delta & -c & 0 \\ 0 & c_E & 0 & c_E & 0 & -\delta_E \end{pmatrix}.$$

Let $J(S_0)$ be the Jacobian matrix evaluated at the steady state S_0. This steady state is asymptotically stable if and only if the eigenvalues of the matrix $J(S_0)$ have negative real parts. The characteristic equation $\det(J(S_0) - \xi I_6) = 0$ is

$$(d+\xi)(\delta_E+\xi)\left[\xi^2 + \left(\delta + c + m_2\frac{\lambda_E}{\delta_E}\right)\xi + \delta c + m_2 c\frac{\lambda_E}{\delta_E} - k_r N_r \delta \frac{\lambda_T}{d}\right]$$
$$\left[\xi^2 + \left(\delta + c + m_1\frac{\lambda_E}{\delta_E}\right)\xi + \delta c + m_1 c\frac{\lambda_E}{\delta_E} - (1-u)k_s N_s \delta \frac{\lambda_T}{d}\right] = 0$$

One can see that the sum of the roots of each of the quadratic factors is negative. Thus, the necessary and sufficient condition for the roots to have negative real parts is that their product be positive. Therefore, we just proved the following stability result.

Proposition 1. (1) *The infection-free steady state S_0 is locally asymptotically stable if $R_r < 1$ and $R_s < \dfrac{1}{1-u}$, where R_s and R_r are the basic reproductive ratios of the wild-type strain and the drug-resistant strain, respectively, given by* (19)*, and it is unstable if $R_r > 1$ or $R_s > \dfrac{1}{1-u}$.*

(2) *In the case that $u = 0$ in model* (6) *(i.e., there is no mutation), then the infection-free steady state S_0 is locally asymptotically stable if $R_r < 1$ and $R_s < 1$, and it is unstable if $R_r > 1$ or $R_s > 1$.*

Note that if the infection-free steady state S_0 is stable, then the system (6) does not have the interior steady state S_i (since in this case $T_{si} < 0$).

For the boundary steady state S_b, the characteristic equation $\det(J(S_b) - \xi I_6) = 0$, is of the form

$$(\xi^2 + (k_2 + c)\xi + ck_2 - N_s k_s \delta(1-u)T_b)(\xi^4 + \alpha_1\xi^3 + \alpha_2\xi^2 + \alpha_3\xi + \alpha_4) = 0, \quad (23)$$

where $k_1 = d + k_r V_{rb}$, $k_2 = \delta + m_1 E_b$, $k_3 = \delta + m_2 E_b$, $k_4 = m_2 T_{rb}$, and the coefficients are

$$\begin{aligned} \alpha_1 &= c + k_3 + k_1 + \delta_E > 0, \\ \alpha_2 &= (k_1 + k_3)(c + \delta_E) + c\delta_E + k_1 k_3 + k_4 c_E - k_r N_r \delta T_b, \\ \alpha_3 &= (c + k_1)(c_E k_4 + \delta_E k_3) + ck_1(\delta_E + k_3) - k_r N_r \delta(d + \delta_E)T_b, \\ \alpha_4 &= ck_1(c_E k_4 + \delta_E k_3) - k_r N_r \delta \delta_E d T_b. \end{aligned}$$

The stability condition for this boundary steady state is that the roots of the characteristic equation (23) have negative real parts. The first factor of this equation is quadratic with the sum of its roots negative. Thus, the necesary and sufficient

condition for these two roots to have negative real parts is that their product to be positive, relation that translates into

$$N_s k_s \delta (1-u) T_b < c(\delta + m_1 E_b).$$

Since $T(t)$ is bounded above by $\dfrac{\lambda_T}{d}$ and $E_b > \dfrac{\lambda_E}{\delta_E}$, we find that a sufficient condition for the above relation to hold is $R_s < \dfrac{1}{1-u}$.

For the second factor of (23) we use the Routh-Hurwitz criteria [55], that is

$$D_1 = \alpha_1 > 0, \quad D_2 = \begin{vmatrix} \alpha_1 & \alpha_3 \\ 1 & a_2 \end{vmatrix} > 0, \quad D_3 = \begin{vmatrix} \alpha_1 & \alpha_3 & 0 \\ 1 & \alpha_2 & \alpha_4 \\ 0 & \alpha_1 & \alpha_3 \end{vmatrix} > 0, \quad \text{and } \alpha_4 > 0.$$

In our case, D_1 is a sum of positive terms, so it is always positive. Last condition is equivalent to

$$k_r N_r \delta \delta_E d T_b < c k_1 (c_E k_4 + \delta_E k_3),$$

and a sufficient condition for it to hold is $R_r < 1$. We can state the following result.

Proposition 2. *The local stability of the infection free steady state S_0 implies the local stability of the boundary steady state S_b.*

Using the values of the parameters in the model (6) from Table 1 and a 10% variation centered at these values we find that both S_0 and S_b are unstable steady states (see Section 2.3).

To study the interior steady state S_i given by (17) we make the assumption that the CD8+ T-cell induced death rates for T_s and T_r are the same, denoted by m. Thus, one can find the analytical expressions for T_{si} and T_{ri} to be

$$\begin{aligned} T_{si} &= -\frac{k_r N_r - (1-u) k_s N_s}{k_s N_s (k_r N_r - k_s N_s)} \cdot \frac{A_i - \sqrt{B_i}}{2 m c_E \delta (1-u)} \\ T_{ri} &= \frac{u}{k_r N_r - k_s N_s} \cdot \frac{A_i - \sqrt{B_i}}{2 m c_E \delta (1-u)}, \end{aligned} \tag{24}$$

where

$$\begin{aligned} A_i &= m c_E d c + N_s k_s \delta (1-u)(\delta \delta_E + m \lambda_E) \\ B_i &= [m c_E d c - N_s k_s \delta (1-u)(\delta \delta_E + m \lambda_E)]^2 + 4 m c_E \lambda_T \delta_E [N_s k_s \delta (1-u)]^2 \end{aligned}$$

The characteristic equation $\det(J(S_i) - \xi I_6) = 0$ is a six order polynomial in ξ. Using the parameters in Table 1 in the same range as in the case of the boundary steady state S_b, we find S_i to be a stable steady state in all the aforementioned cases (see Section 2.3).

Since the drug resistant variants of HIV preexist before the initiation of therapy [56, 21], it is important to consider the case when there is no mutation during the initial stage of the disease. Thus, the interior steady state S_i reduces to the second boundary steady state S_w given by (22). In this case, the characteristic equation is

$$[\xi^2 + (k_3 + c)\xi + c k_3 - N_r k_r \delta T_w](\xi^4 + \beta_1 \xi^3 + \beta_2 \xi^2 + \beta_3 \xi + \beta_4) = 0, \tag{25}$$

where $k_1 = d + k_s V_{sw}$, $k_2 = \delta + m_1 E_w$, $k_3 = \delta + m_2 E_w$, $k_4 = m_1 T_{sw}$, and the coefficients are

$$\begin{aligned}
\beta_1 &= c + k_2 + k_1 + \delta_E > 0,\\
\beta_2 &= (k_1 + k_2)(c + \delta_E) + c\delta_E + k_1 k_2 + k_4 c_E - k_s N_s \delta T_w,\\
\beta_3 &= (c + k_1)(c_E k_4 + \delta_E k_2) + c k_1(\delta_E + k_2) - k_s N_s \delta (d + \delta_E) T_w,\\
\beta_4 &= c k_1 (c_E k_4 + \delta_E k_2) - k_s N_s \delta \delta_E d T_w.
\end{aligned}$$

With a similar analysis as in the case of the boundary steady state S_b, we can state the following result for the steady state S_w.

Proposition 3. *The local stability of the infection free steady state S_0 implies the local stability of the boundary steady state S_w when only the wild-type strain is presnt.*

2.3. **Uncertainty and sensitivity analysis of the model.** From the analysis in the previous section it follows that the basic reproductive ratios R_s and R_r play an important role in predicting the evolution of HIV. Therefore, we perform

TABLE 2. Statistics for R_s from Monte Carlo samples of 10^5 repetitions and PRCC value for each parameter

Parameter	Mean	Std. Dev.	Median	PRCC
λ_T	3.1305	0.0905	3.1307	1.000
d	2.9833	0.0820	2.9813	-0.9997
k_s	3.1301	0.0904	3.1303	1.000
δ	3.1301	0.0090	3.1301	0.9997
m_1	3.1301	0.0090	3.1301	-1.000
N_s	3.1285	0.6016	3.1235	1.000
c	3.6916	1.5271	3.1910	-0.9389
λ_E	3.1301	0.0090	3.1301	-1.000
δ_E	3.1301	0.0090	3.1301	0.9997

an uncertainty and sensitivity analysis to determine how these ratios vary due to the uncertainty in the estimation of parameters used in the model. Here N_s and N_r are sampled from an uniform distribution over the interval $(2000, 4000)$ and $(1000, 3000)$ [21], with the mean 3000 and 2000, respectively (values that we have been used in numerical simulations); c is sampled from a distribution over the interval $(9, 36)\text{day}^{-1}$ [21, 57]; all other parameters being sampled from a 10% distribution centered at their values which are given in Table 1.

Statistical results obtained by generating 5 Monte Carlo samples of 10^5 repetitions chosen from the above distributions are listed in Table 2 for R_s, Table 3 for R_r, and Table 4 for the uninfected steady states T_0 and V_0. To address the sensitivity analysis, we assess the partial rank correlation coefficients (PRCCs) (see [21]) between R_s and R_r and each considered parameter, respectively. A closer value to 1 suggests a stronger correlation; thus, we find that the most influential parameters in this case are λ_T, λ_E (the recruitment rate of uninfected CD4+ T-cells and the production rate of healthy CD8+ T-cells, respectively), and k_s, k_r, N_s, N_r, m_1, and m_2 (the infection rate of CD4+ T-cells, the number of free virions released

TABLE 3. Statistics for R_r from Monte Carlo samples of 10^5 repetitions and PRCC value for each parameter

Parameter	Mean	Std. Dev.	Median	PRCC
λ_T	1.7392	0.0503	1.7393	1.000
d	1.6574	0.0456	1.6563	-0.9997
k_r	1.7390	0.0502	1.7392	1.000
δ	1.7390	0.0050	1.7390	0.9997
m_2	1.7390	0.0050	1.7390	-1.000
N_r	1.7400	0.5011	1.7409	1.000
c	2.0509	0.8484	1.7728	-0.9389
λ_E	1.7390	0.0050	1.7390	-1.000
δ_E	1.7390	0.0050	1.7390	0.9997

by an infected cell upon death, and the immune effectors - induced death rate for T_s, T_r, respectively); that is, decreasing the infection rate or the burst size (for example, increasing the drug efficacy of RT or PI inhibitors) or decreasing the death rate $m_i, i = 1, 2$ is more effective in reducing R_s or R_r. This result supports our approach in the treatment case considered in the next section.

TABLE 4. Statistics for the infection free steady states T_0 and E_0 from Monte Carlo samples of 10^5 repetitions for each parameter

for T_0	Parameter	Mean	Std. Dev.	Median
	λ_T	1000.1	28.9163	1000.2
	d	953.0816	26.2072	952.4442
for E_0				
	λ_E	0.0100	2.8926e-004	0.0100
	δ_E	0.0100	2.8914e-004	0.0100

Having decided the most influential parameters, we investigate their effect on the infected steady state S_i. Statistical results for T_i, V_{si}, and V_{ri}, that is for the

TABLE 5. Statistics for T_i from Monte Carlo samples of 10^5 repetitions and PRCC value for each parameter

Parameter	Mean	Std. Dev.	Median	PRCC
ks	462.3418	5.1067	462.0640	-0.9998
kr	462.0788	6.9800e-010	462.0788	5.7489e-007
Ns	474.0013	7.8848	462.3059	-0.9900
N_r	462.0788	6.9800e-010	462.0788	6.4769e-006
m	462.0600	2.6122	462.0875	1.000

healthy CD4+ T-cell density, the drug sensitive and drug resistant viral loads, are

presented in Tables 5, 6, and 7, respectively. The p-value < 0.01 in each considered case. From the partial rank correlation coefficients (PRCCs) between T_i,V_{si}, and

TABLE 6. Statistics for V_{si} from Monte Carlo samples of 10^5 repetitions and PRCC value for each parameter

Parameter	Mean	Std. Dev.	Median	PRCC
ks	484.8274	3.6580	485.0474	0.9997
kr	485.0371	0.0012	485.0371	-0.9995
Ns	485.7595	4.9811	484.5943	1.0000
N_r	485.0315	0.0169	485.0373	-0.9318
m	485.1027	5.0987	485.0203	-0.999

V_{ri}, and each parameter (coefficients that measure the independent influence of these parameters on the variation of T_i, V_{si}, V_{ri} respectively), we observe that there is a strong correlation between these steady state values and the values of the considered parameters. The strongest correlation appears to be between these

TABLE 7. Statistics for V_{ri} from Monte Carlo samples of 10^5 repetitions and PRCC value for each parameter

Parameter	Mean	Std. Dev.	Median	PRCC
ks	0.0219	4.4797e-004	0.0218	-0.9982
kr	0.0219	7.8957e-004	0.0218	0.9995
Ns	0.0239	0.0054	0.0218	-0.8802
N_r	0.0296	0.0202	0.0217	0.9318
m	0.0218	2.2946e-004	0.0218	-0.999

steady states and the immune effectors induced death rates for the infected T-cells with both strains of virus. Increasing these rates is more efficient in rising the number of healthy T-cells and decreasing the wild-type and the resistant virus. This is a strong evidence that supports the inclusion of CTL's effect in our model. Also, both classes of antiviral drugs, RTIs and PIs, but only the ones affecting the sensitive strain, influence the steady state level of CD4+ T-cells. Interestingly enough, the infection rates are the most influential parameters for both strains of viral load; the RT inhibitors (see model (26) in Section 3) have a stronger effect in reducing the viral load.

3. Model with Antiretroviral Therapy

When HIV infects the body, it attacks the CD4+ lymphocytes. Since HIV is a retrovirus, it contains no DNA of its own, and has to use the enzyme reverse transcriptase to facilitate its replication. This enzyme allows HIV's RNA to become incorporated into the DNA of the helper T-cells of the body, which continue to replicate the HIV RNA in its own DNA. Additional enzymes help bring together the pieces of RNA to form complete HIV viruses, eventually causing the infected cell to burst and release more HIV into the system to attack uninfected helper T

cells. The process of reverse transcription is prone to errors, so many different strains of the virus may survive to replicate in the body.

There are two major classes of antiretroviral drugs which are utilized in HIV treatment: the reverse transcriptase inhibitors (RTI) and the protease inhibitors (PI). Combinations of these are used in a regimen known as Highly Active Antiretroviral Therapy (HAART) [10, 58, 59, 35, 1, 2] designed to limit the virus' ability to mutate and develop drug-resistant strains. Nucleoside Reverse Transcriptase Inhibitors (NRTI's) and Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI's) inhibit reverse transcription enzymes. Entry inhibitors prevent the virus from attaching to the surface of the lymphocytes. This class of drugs in our model would have an impact on reducing k_s and k_r, the infection rate for wild-type and drug resistant virus, respectively. Protease inhibitors inhibit the protein enzymes that cut viral proteins to the correct size. PIs go to work after the process of reverse transcription by inhibiting the activity of protease, an enzyme needed by the virus for the production of new virions in infected lymphocytes [23]. In our model this would impact N_s and N_r, the number of virions produced per infected drug-sensitive and drug-resistant cell, respectively.

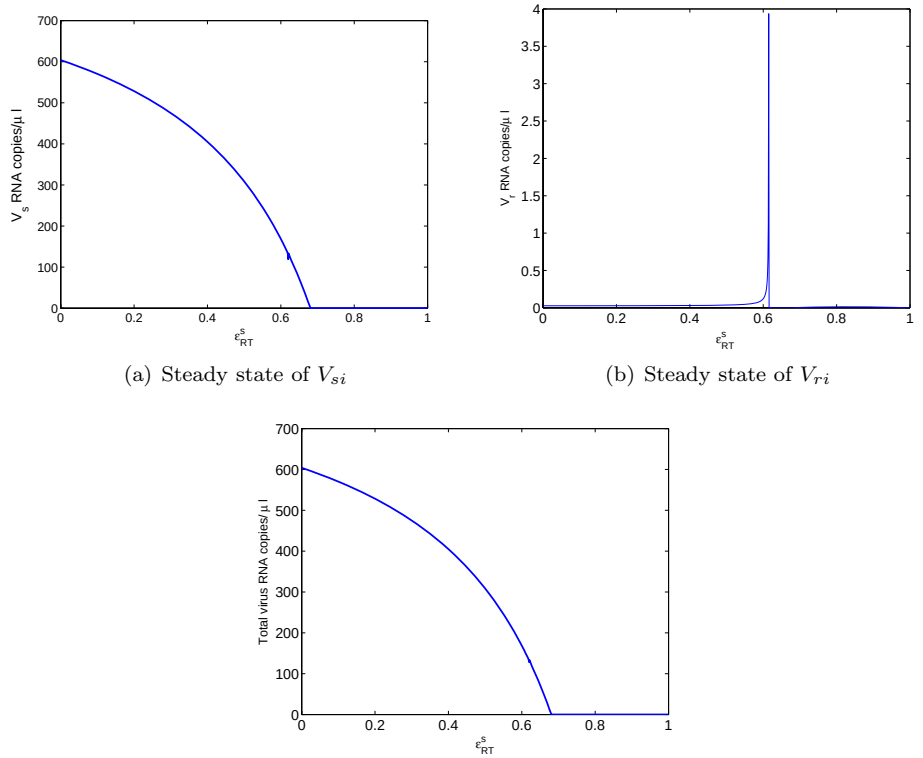
We study the antiretroviral drug therapy in this system by introduction of drug-efficacy parameters, which are extensively used in numerous models, such as [16, 14, 21, 22]. We consider ε_{RT}^s and ε_{RT}^r to represent the efficacies of RTIs and ε_{PI}^s and ε_{PI}^r to be the efficacies of PIs drug-sensitive and drug-resistant strains, respectively. Thus, incorporating the effect of these drugs into the system (6) we obtain the following equations.

$$\begin{aligned}
\frac{dT}{dt} &= \lambda_T - dT - k_s(1-\varepsilon_{RT}^s)V_sT - k_r(1-\varepsilon_{RT}^r)V_rT \\
\frac{dT_s}{dt} &= (1-u)k_s(1-\varepsilon_{RT}^s)TV_s - \delta T_s - m_1ET_s \\
\frac{dV_s}{dt} &= N_s(1-\varepsilon_{PI}^s)\delta T_s - cV_s \\
\frac{dT_r}{dt} &= uk_s(1-\varepsilon_{RT}^s)TV_s + k_r(1-\varepsilon_{RT}^r)V_rT - \delta T_r - m_2ET_r \\
\frac{dV_r}{dt} &= N_r(1-\varepsilon_{PI}^r)\delta T_r - cV_r \\
\frac{dE}{dt} &= \lambda_E + c_E(T_s+T_r) - \delta_E E,
\end{aligned} \tag{26}$$

The initial conditions are the values for the interior infected steady states S_i (given by (17)) in the no-treatment case. Here ε_{RT}^s, ε_{PI}^s, ε_{RT}^r, and $\varepsilon_{PI}^r \in [0,1]$. In the case that all are zero, i.e., no treatment, we obtain the system (6); if all are 1, then we obtain a complete cure of the disease since $\frac{dV_s}{dt} < 0$ and $\frac{dV_r}{dt} < 0$. Moreover, we have that $\varepsilon_{RT}^s > \varepsilon_{RT}^r$ and $\varepsilon_{PI}^s > \varepsilon_{PI}^r$ since the wild-type virus is more susceptible to drugs. Therefore we can consider that $\varepsilon_{RT}^r = \alpha\varepsilon_{RT}^s$ or that $\varepsilon_{PI}^r = \alpha\varepsilon_{PI}^s$, where $0 < \alpha < 1$ represents the HIV mutants' level of resitance; the smaller α, the more resistance to the used drug for the drug-resistant strains.

The analysis of this system does not change from the previous case since the positive coefficients k_s, k_r and N_s, N_r in (6) have been replaced by $k_s(1-\varepsilon_{RT}^s), k_r(1-\varepsilon_{RT}^r)$ and $N_s(1-\varepsilon_{PI}^s), N_r(1-\varepsilon_{PI}^r)$, respectively, in (26) which are positive as well.

Therefore, the nonnegative orthant $\mathbf{R}^6_+$ is an invariant for the solution and the system has three steady states in this region, $\bar{S}_0$, $\bar{S}_b$, and $\bar{S}_i$ obtained in a similar way as before.



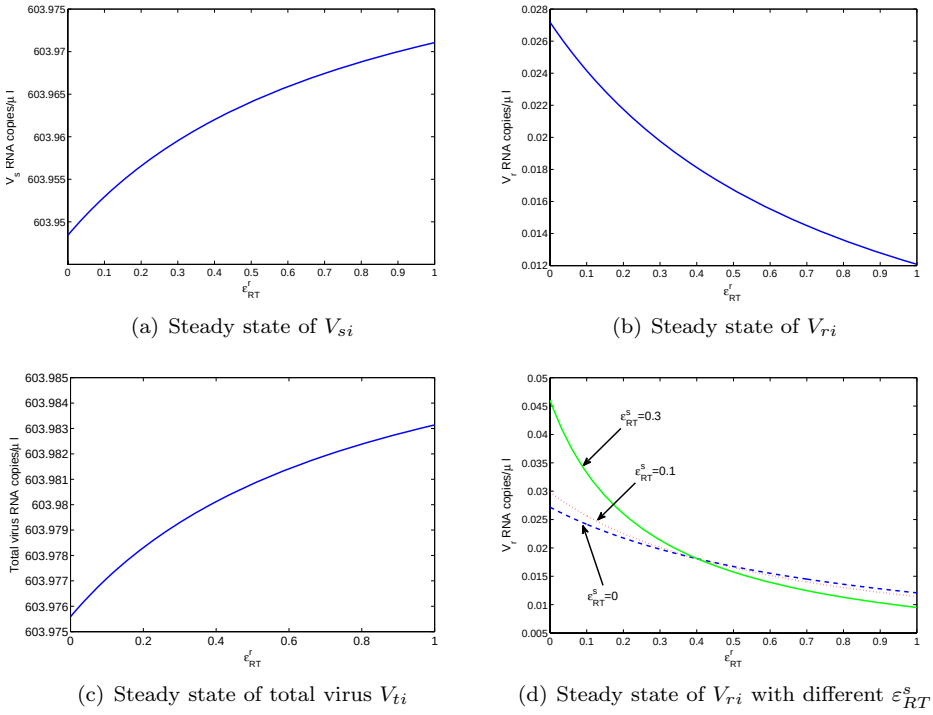
(a) Steady state of V_{si}

(b) Steady state of V_{ri}

(c) Steady state of total virus V_{ti}

FIGURE 2. Steady state of the virus in model (26) as a function of ε^s_{RT}, with $\varepsilon^r_{RT} = \alpha\varepsilon^s_{RT}$, ε^s_{PI} and ε^r_{PI} are zero, and $\alpha = 0.5$

We begin by investigating the effect of only one class of antiretroviral drugs in the system. First off we consider that $\varepsilon^r_{RT} = \alpha\varepsilon^s_{RT}$ and $\varepsilon^r_{PI} = \varepsilon^s_{PI} = 0$. Figure 2 shows the variation of the steady states V_{si}, V_{ri}, for wild type and drug-resistant strains respectively, and the total virus as ε^s_{RT} varies over the interval $(0, 1)$, with $\alpha = 0.5$. One can see that drug-sensitive strain V_{si} decreases with the increase of drug efficacy ε^s_{RT} until it becomes zero for $\varepsilon^s_{RT} = 0.68$. However, this is not the case with the drug-resistant strain V_{ri}. At first it changes very slowly as the efficacy ε^s_{RT} increases. When ε^s_{RT} approaches 0.6, V_{ri} increases substantially until it reaches its maximum value. As ε^s_{RT} varies from 0.6 to 0.62, the value of this steady state decreases from its peak to zero. Thus, for $\varepsilon^s_{RT} = 0.68$, both values for steady states reach zero, so the virus is eradicated. Next, we investigate the effect of varying ε^r_{RT} in the interval $(0, 1)$, on the steady states V_{si} and V_{ri}, with $\varepsilon^s_{RT} = 0$ and $\varepsilon^s_{PI} = \varepsilon^r_{PI} = 0$ as well. As one can see from Figure 3, ε^r_{RT} alone has little or no effect on drug sensitive strain, which in fact shows an insignificant increase. Although V_{ri} decreases with the increase of ε^r_{RT}, it never reaches zero even with a perfect



(a) Steady state of V_{si}

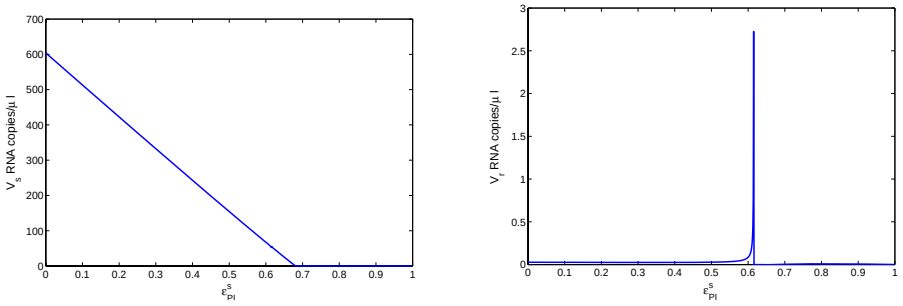
(b) Steady state of V_{ri}

(c) Steady state of total virus V_{ti}

(d) Steady state of V_{ri} with different ε^s_{RT}

FIGURE 3. Steady state of the virus in model (26) as a function of ε^r_{RT}, with ε^s_{PI} and ε^r_{PI} are zero; $\varepsilon^s_{RT} = 0$ for (a), (b), and (c).

adherence to this treatment. Moreover, the total virus exhibits the same behavior as the wild type. This implies that a RTI drug targeting only the strain-resistant virus does not have any effect on the total virus concentration. In Figure 3(d) we



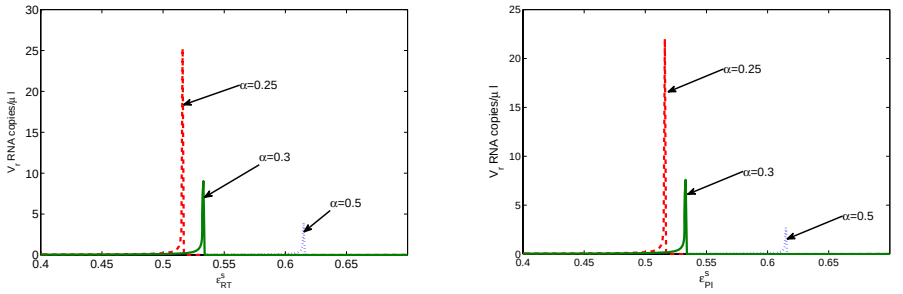
(a) Steady state of V_{si}

(b) Steady state of V_{ri}

FIGURE 4. Steady state of the virus in model (26) as a function of ε^s_{PI} with $\varepsilon^r_{PI} = \alpha\varepsilon^s_{PI}$, and ε^s_{RT} and ε^r_{RT} are zero and $\alpha = 0.5$

gradually introduce RTIs for the wild-type virus. Even though V_{ri} reaches lower values as ε^s_{RT} increases (as expected), it does not change dramatically the evolution

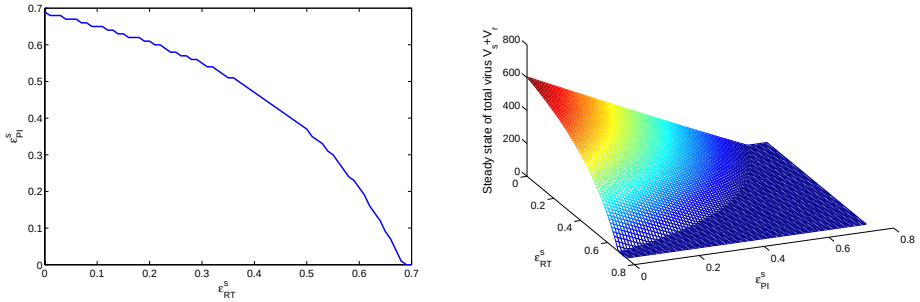
of the system in this considered situations. Therefore, this result gives additional support to our assumption that $\varepsilon^s_{RT} > \varepsilon^r_{RT}$. We perform a similar analysis using



(a) $\varepsilon^s_{PI} = \varepsilon^r_{PI} = 0$ (b) $\varepsilon^s_{RT} = \varepsilon^r_{RT} = 0$

FIGURE 5. Steady state of V_r with $\varepsilon_r = \alpha\varepsilon_s$, for different values of α

only PIs, that is $\varepsilon^r_{PI} = \alpha\varepsilon^s_{PI}$ and $\varepsilon^s_{RT} = \varepsilon^r_{RT} = 0$ and the results for the two steady states are shown in Figure 4. It is not surprising to see a similar behavior as before. However, in this case V_{si} decreases almost linear (i.e., faster than in the other case) and V_{ri} has a lower maximum value obtained for $\varepsilon^s_{PI} = 0.62$. It appears that PIs are slightly more efficient than RTIs when considered in a non-cocktail regimen (see Figure 5); also, as the resistant strain is less resistant (i.e., the values for α are greater), the maximum values for this steady states gets smaller, as expected, which is another evidence for our assumption.

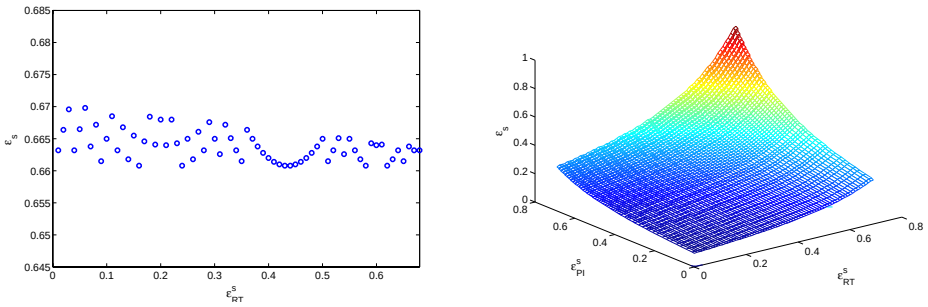


(a) The relation between ε^s_{RT} and ε^s_{PI} when the infected steady state $V_{ti} = 0$ (b) Steady state of the total virus V_{ti}

FIGURE 6. Variation of ε^s_{RT} and ε^s_{PI}

Next we simulate a combination of both types of drugs, RTIs and PIs, for both wild-type and drug-resistant strains. Having concluded that the drugs affecting only the drug-resistant virus for both classes of antiretroviral drugs have very little effect when not combined with the ones for the drug sensitive virus, we consider that $\varepsilon^r_{RT} = \alpha_1\varepsilon^s_{RT}$ and $\varepsilon^r_{PI} = \alpha_2\varepsilon^s_{PI}$, with $\alpha_{1,2} \in (0, 1)$ representing the HIV mutants' level of resistance. These values for α's are not necessarily equal. The relationship between ε^s_{RT} and ε^s_{PI} such that the steady state for total virus $V_{ti} = V_{si} + V_{ri}$ is

zero is given in Figure 6(a) (here $\alpha_1 = \alpha_2 = 0.25$).The coordinates of any point on this curve give the necessary and sufficient combined drug sensitive efficacies for the perfect treatment, i.e., eradication of the disease in the case of constant drug efficacies. The drug-resistant efficacies can be calculated as well using the above mentioned relation. Figure 6(b) shows the levels of the steady state of the total virus V_{ti} as the drug sensitive efficacies vary in the interval $[0, 1]$, with $\alpha_1 = \alpha_2 = 0.25$. Let us define the drug-sensitive and drug-resistant overall treatment effect [21] to



(a) (b)

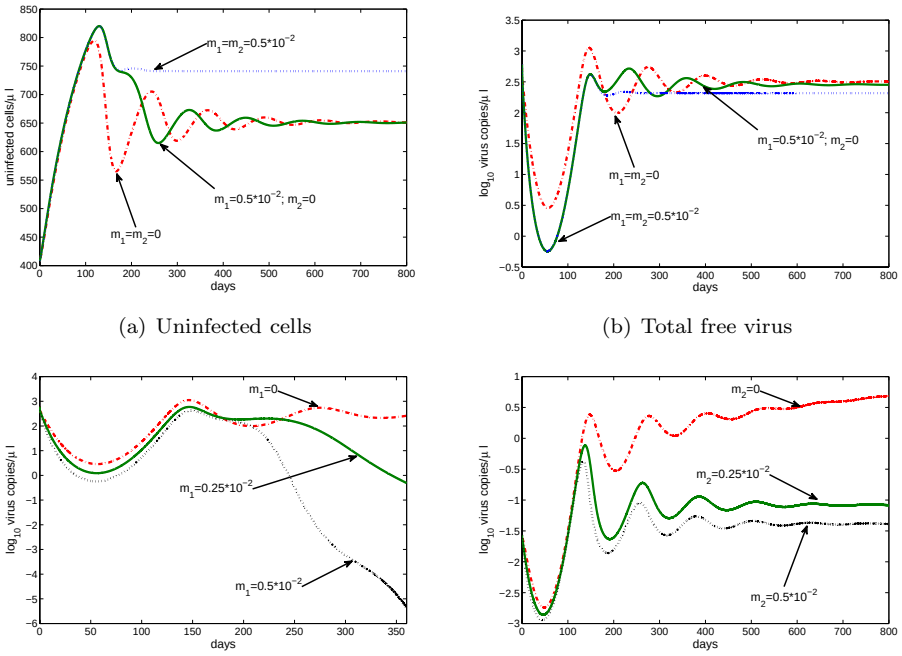
FIGURE 7. The relation between ε_s and ε^s_{RT}, ε^s_{PI} such that the infected steady state V_{ti} is zero, i.e., effective treatment

be

$$\varepsilon_s = 1 - (1 - \varepsilon^s_{RT})(1 - \varepsilon^s_{PI}) \text{ and } \varepsilon_r = 1 - (1 - \varepsilon^r_{RT})(1 - \varepsilon^r_{PI}), \tag{27}$$

respectively. Using the previously mentioned relation between drug sensitive and drug-resistant efficacies, it is enough to restrict our analysis to ε_s, since ε_r depends on ε_s through α_1 and α_2. Its variation as $\varepsilon^s_{RT}, \varepsilon^s_{PI} \in (0, 1)$ such that $V_{ti} = 0$ is given in Figure 7 (b). Not surprisingly, the overall effect increases as a cocktail of drugs is used in the treatment regimen. Furthermore, we investigate the optimum combination of RTIs and PIs for potential maximum efficiency. For the pairs $(\varepsilon^s_{RT}, \varepsilon^s_{PI})$ at which $V_{ti} = 0$ we calculate the drug sensitive overall efficacy ε_s as ε^s_{RT}varies in the interval $(0, 0.7)$ and we plot the results in Figure 7(a). It is clear that the treatment is more effective when a cocktail of drugs is used. Moreover, there are different combinations at which it attends its maximum values (such as $\varepsilon^s_{RT} = 0.04$, or $\varepsilon^s_{RT} = 0.08$); it appears that ε_s varies almost periodically for $\varepsilon^s_{RT} \in (0, 0.25)$. However, as ε^s_{RT} approaches 0.65, ε_s does not change significantly. This suggests that a more effective treatment should contain a cocktail with both type of antiretroviral drugs, RTIs and PIs. Likewise, this dependence of the overall efficacies ε_s and ε_r could be obtained for any desired threshold values for the steady states of the drug sensitive, drug-resistant, or total free virus. Then an optimum treatment strategy could be design for each patient.

In our proposed model we consider the influence of CD8 T lymphocytes (CTLs), thus we investigate the dynamics of our system (26) when the immune-induced clearance rates are zero and different from zero. We use the steady state values of the pretreatment model (6) (see Figure 1) as the initial conditions in all these simulations. Figure 8 (a) and (b) illustrates the evolution of the uninfected T cells and the total free virus over a period of 800 days. Here the overall treatment effect



(a) Uninfected cells

(b) Total free virus

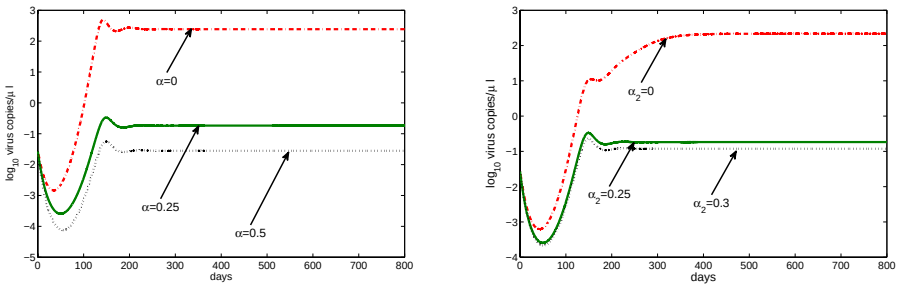
(c) Drug sensitive virus with $m_2 = 0$

(d) Drug-resistant virus with $m_1 = 0$

FIGURE 8. Time evolution of uninfected T cells and the viral load with and without the influence of immune effectors; $\alpha = 0.2$, $\varepsilon_s = 0.51$ with $\varepsilon^s_{RT} = \varepsilon^s_{PI} = 0.3$

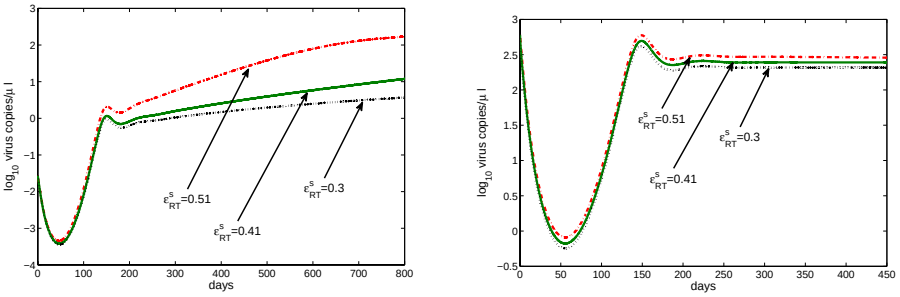
for the drug sensitive strain is $\varepsilon_s = 0.51$ ($\varepsilon^s_{RT} = \varepsilon^s_{PI} = 0.3$) and the HIV mutants' resistance level is $\alpha = 0.2$. Clearly, the inclusion of CTLs has a significant effect on the steady state levels of uninfected T cells and the total viral load, as well as on the overall dynamics of the system. The virus concentration decreases when the immune clearance rate is not zero (for the drug sensitive strain or for both strains) as the density of the CD4+ T cells converges to a higher level. Furthermore, we investigate the effect of each clearance rate of the corresponding virus' strains and the results are plotted in Figure 8 (c) and (d). Under the same conditions, we consider $m_2 = 0$ and we vary m_1; we see a substantial decrease of the sensitive strain. Moreover it is eradicated under these assumptions when $m_1 = 0.5 \cdot 10^{-2} \mu\text{l cell}^{-1}\text{day}^{-1}$ (see Figure 8 (c)). We observe a similar behavior when $m_1 = 0$ and we vary m_2; the level of the resistant virus in the system decreases considerable (see Figure 8 (d)).

Given that we consider in our treatment scenarios that efficacies for drug resistant strains depend on the efficacies of the drug sensitive strains via the HIV mutants' resistance levels, we investigate the effect of this parameter on the dynamics of the drug resistant virus and we present the results in Figure 9. Without a doubt, the steady state values of the resistant strains are lower as the virus is less resistant to either class of antiretroviral drugs used (see Figure 9 (a)); furthermore, with the same RTIs' resistance level, it is more efficient to have a better adherence to the class of PI drugs (see Figure 9 (b)).



(a) $\alpha_1 = \alpha_2 = \alpha$ (b) $\alpha_1 = 0.25$

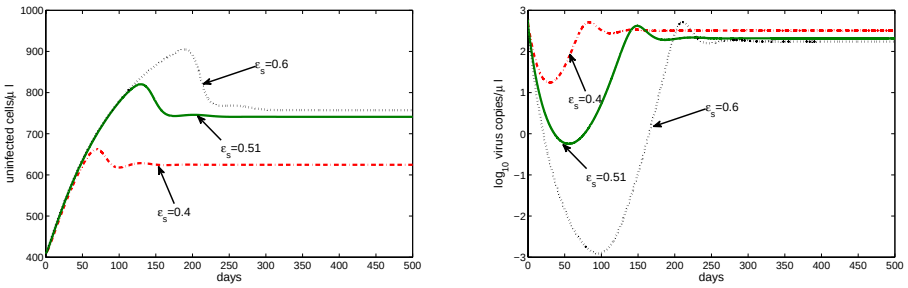
FIGURE 9. The dynamics of the drug-resistant virus for different mutants' resistant levels; $\varepsilon_s = 0.51$ with $\varepsilon^s_{RT} = \varepsilon^s_{PI} = 0.3$



(a) Drug-resistant virus (b) Total free virus

FIGURE 10. The evolution of the resistant and total virus concentrations for different combinations of therapy, with $\varepsilon_s = 0.51$ and $\alpha = 0.2$

In the last part, we analyze different treatment scenarios. First off, we investigate the effect of different combinations of RTIs and PIs for both strains. We consider a fixed overall treatment effect for the sensitive strain (e.g., $\varepsilon_s = 0.51$ in Figure 10) and fixed resistance rates ($\alpha_1 = \alpha_2 = 0.2$). We investigate different possibilities for $\varepsilon^s_{RT}, \varepsilon^s_{PI}$ and $\varepsilon^r_{RT} = \alpha_1\varepsilon^s_{RT}, \varepsilon^r_{PI} = \alpha_2\varepsilon^s_{PI}$ connected by the relation (27). Figure 10 (a) and (b) shows the dynamics of the resistant strain and the total free virus , respectively, when $(\varepsilon^s_{RT}, \varepsilon^s_{PI}, \varepsilon^r_{RT}, \varepsilon^r_{PI}) \in \{(0.51, 0, 0.102, 0), (0.41, 0.17, 0.082, 0.034), (0.3, 0.3, 0.06, 0.06)\}$, i.e., we start with only RTIs and progressively incorporate PIs. It is not surprising to see that the least efficient scenario appears when there is no combination of these two classes of drugs. In this case, the viral loads decrease the least compared to the other cases and converge to higher steady states. As expected, the level of mutant virus increases the most when a no combination therapy is administered. Moreover, from these numerical experiments we obtain a similar conclusion as before, that PIs are more effective in the cocktail of drugs when ε^s_{RT} belongs to the first third of the interval as seen in Figure 6 (b).



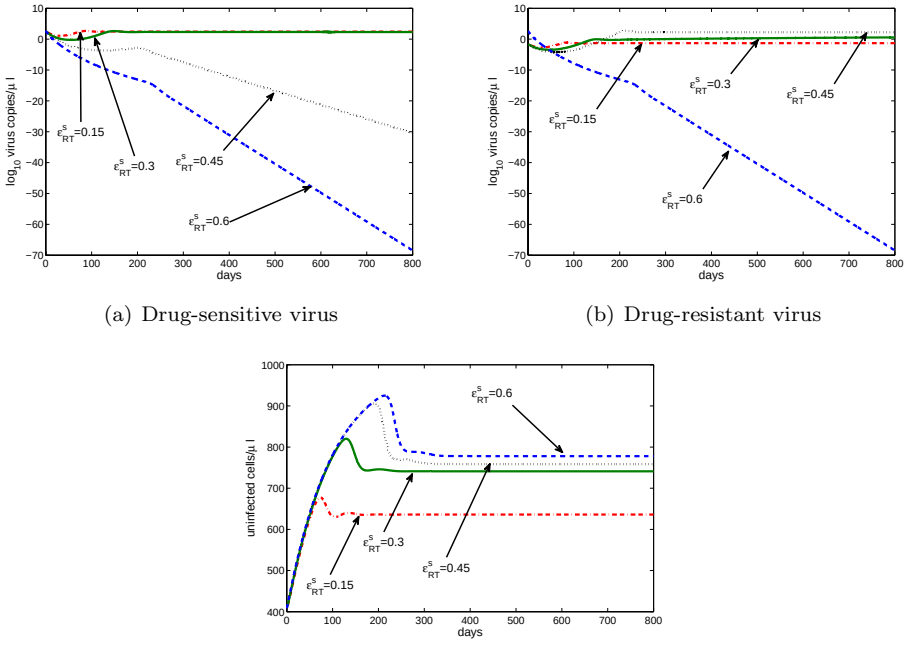
(a) Uninfected cells (b) Total free virus

FIGURE 11. The dynamics of the uninfected T cells and total free virus for different ε_s, with $\alpha = 0.2$ and $\varepsilon^s_{RT} = \varepsilon^s_{PI}$ given by (27)

Secondly, we investigate the effect of different treatment effects ε_s for the sensitive strain in the interval $(0, 0.65)$ (for values greater than 0.65, the viral population is eradicated), with $\alpha = 0.2$ (that is, a mutant strain more resistant to the drug), and the same ration of RTIs and PIs. We present the results in Figure 11 for $\varepsilon_s = 0.41, 0.51$, and 0.61 with $\varepsilon^s_{RT} = \varepsilon^s_{PI} = 0.15, 0.31$, and 0.37, thus $\varepsilon^r_{RT} = \varepsilon^r_{PI} = 0.03, 0.06$, and 0.074, respectively. We clearly observe that the number of uninfected T cells converges to a higher level as the drug efficacy increases (see Figure 11 (a)), while the amplitude of the viral peak and the value of the steady state decrease. However, a higher drug efficacy causes the viral load to reach its first peak at a later time than a lower drug efficacy (see Figure 11 (b)). Likewise, if we consider $\varepsilon^s_{PI} = 0.3$, varying ε^s_{RT} in a range of $(0.15, 0.3)$ has a small effect on V_{si} and V_{ri}; however, for $\varepsilon^s_{RT} = 0.45$ only the resistant strain persists, whereas when $\varepsilon^s_{RT} = 0.6$ both strains are eradicated (Figure 12); in turn, healthy T-cell concentration converges to higher levels as the efficacy increases, as expected.

4. Disscusion

Mathematical models of HIV's dynamics have been intensively utilized in the common effort to accurately predict the course that HIV takes under different circumstances [21, 20, 14, 18, 22]. many of them are composed of a system of differential equations describing the evolution of the uninfected T-cells, infected T-cells, and the free virus in the body. In this paper we perform further analysis that considers the impact of CD8+ T-cells in fighting the infection, by including their effect on a multiple strain system. Our results show that that the presence of the active-immune effectors reduces the infected cell concentration, driving drug-sensitive, drug-resistant, and the total viral concentrations to stabilize at lower levels, and allowing the concentration of healthy CD4+ T-cells to reach a higher steady-state (Figure 1). The analysis of our mathematical model shows that the solution of the initial value problem (6)–(7) is non-negative and bounded. Stability and sensitivity analysis is performed on the system (6) to show that it has three positive steady states: the unstable infection free and boundary steady states and stable interior steady state. In addition, through the results of Monte-Carlo simulations, we analyze the sensitivity of the interior steady state to key parameters. We find that the



(a) Drug-sensitive virus

(b) Drug-resistant virus

(c) Uninfected cells

FIGURE 12. The dynamics of the wild-type, the resistant virus, and uninfected T cells for different ε^s_{RT}, with $\alpha = 0.2$ and $\varepsilon^s_{PI} = 0.3$

inclusion of the effector-cell compartment suggests stimulation of the immune system, through Structured Treatment Interruption or antigenic boosts, can produce a positive outcome with a suppressed viral load and an immune system capable of controlling the infection.

Exploring new means of treating HIV that are meant to supplement traditional pharmaceutical regimens appears to be an intriguing new field of research. Finding ways for the immune system to cope with an HIV infection that do not involve large amounts of pharmaceutical treatment could be a necessary step in fighting the HIV epidemic. In this paper we also explore the impact of the antiretroviral therapy on an HIV plagued immune system while accounting for the presence of CD8+ T-lymphocytes (CTLs), as well as their impact on the emergence of drug resistance variance. Our results show that when the activity of immune effectors is incorporated into the model and antiretroviral treatment is simulated, the concentration of healthy helper T-cells increases relative to that of a system without immune effectors (see Figure 8). Additionally, our results confirm the fact that a more efficient drug therapy requires a combination of RTIs and PIs for both strains of virus, wild-type and resistant; nevertheless, we prove that a more effective treatment should contain a cocktail with both drugs, but the ratio of RTIs to PIs should be about 1:4 (Figure 7 (a)), that is PIs are slightly more effective in the combination therapy. These results yield promise for newer treatment methods such as STIs and antigenic stimulation of the immune system.

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Purdue University Calumet, 2200 169th Street, Hammond, IN 46323, USA