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(Communicated by Suzanne Lenhart)

In treating 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. Moreover, even in the presence of drug therapy, ongoing viral replication can lead to the emergence of drug-resistant virus variances. We introduce a mathematical model that incorporates two viral strains, wild-type and drug-resistant, to theoretically and numerically investigate HIV pathogenesis during ART. A periodic model of bang-bang type is employed to estimate the drug efficacies. Furthermore, we numerically investigate the antiviral response and we characterize successful drugs or drug combination scenarios for both strains of the virus.

## 1. Introduction

Over the last few decades, the rapid spread of the human immunodeficiency virus (HIV) and the death toll of acquired immunodeficiency syndrome (AIDS) have motivated a great deal of scientific and medical research. Treatment of the HIV infection has traditionally consisted of antiretroviral therapy (ART), a regimen of pharmaceutical treatments that often produces unwanted physical side effects and can become costly over long periods of time. Moreover, 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 ART unsustainable. This in turn leads to the development of resistant strains [Kepler and Perelson 1998; Kirschner and Webb 1997; Murray and Perelson 2005; Ribeiro et al. 1998]. Since its discovery in 1984, much research has been done and researchers have increased their understanding of the virus, and consequently drugs have been

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*MSC2010:* primary 92D30; secondary 92B05, 34A34.

*Keywords:* HIV dynamics, time-varying antiretroviral treatment, drug resistance.

Read was supported by the US Department of Energy-Northwest Indiana Computational Grid Grant and a CURM mini-grant funded by the NSF grant DMS-0636648.

successful in the treatment but not the cure of the disease. In the last decade, it has become more and more evident that mathematical models are extremely useful in understanding of various biological processes. They create a powerful and inexpensive virtual laboratory where one can test and experiment different competing hypotheses.

When HIV enters the bloodstream, it primarily targets crucial components of the immune system [Fauci 1993], specifically, CD4+ T-cells or helper T-cells, whose function 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 [Bofill et al. 1992; Cohen and Boyle 2004; Fauci 1993; McMichael Winter 1996; Wilson et al. 2000; NHS 2008]. HIV is capable of infecting other immune cells, such as macrophages [Perelson and Nelson 1999], but the primary targets of infection are the CD4+ T-cells [Koup et al. 1994]. Hence, they play a central role in existing mathematical models [Adams et al. 2005; Burg et al. 2009; Huang 2008; Perelson et al. 1993; Perelson and Nelson 1999; Rapin et al. 2006; Rong et al. 2007a; 2007b; Tarfulea et al. 2011; Tarfulea 2011b; 2011a]. However, the most significant and threatening problem that HIV presents is its ability to continuously mutate in the body and form resistances to otherwise useful drugs [Shiri et al. 2005; Smith and Wahl 2005; Wahl and Nowak 2000].

Building upon the model introduced in [Tarfulea 2011b], we include two distinct viral strains (drug-sensitive and drug-resistant) and time-varying antiretroviral treatment of bang-bang type. This mathematical model is described by a system of six differential equations and is used to analyze the efficacy of different drug combinations in tandem with the evolution of the resistant strain in each case. We use the Floquet multipliers to investigate the stability properties of the infection-free steady state. We obtain the expected monotonicity property, namely if the treatment is periodic of bang-bang type and it can clear the infection, then the infection is cleared more rapidly if the treatment is more efficient or lasts longer. The multiple viral strains that this new model incorporates brought forth a much more useful understanding to the conditions faced by the antiretroviral drugs and the components of the infected immune system. Furthermore, we investigate the consequences of different scenarios of antiviral therapy, as well as 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 total viral load in the body. Thus, our model could be used to suggest which drugs or combination of drugs are optimal for a given patient, as well as to investigate the consequences of changing the treatment frequency or imperfect adherence. The effect of periodic treatment that includes pharmacokinetics on a multistrain model and the effect of STIs is an ongoing investigation.

variable	description
$T$	healthy T-cell concentration
$T_s$	drug-sensitive infected T-cell concentration
$T_r$	drug-resistant infected T-cell concentration
$V_s$	drug-sensitive virus concentration
$V_r$	drug-resistant virus concentration
$E$	concentration of CD8+ T-cells

**Table 1.** Variables used in the differential equation systems.

## 2. Formulation of the problem

**2.1. The mathematical model for the pretreatment case.** We now present the mathematical model for the dynamics of HIV before treatment (see [Tarfulea 2011b]). Building upon it, we will introduce in Section 2.2 the mathematical model with time-varying drug efficacies of bang-bang type.

A widely adopted mathematical model of HIV infection consists of a system of differential equations describing the evolution of the concentrations of healthy CD4+ T-cells, infected CD4+ T-cells, and free viruses in the body (see [Adams et al. 2005; Perelson et al. 1993; Perelson and Nelson 1999; Rapin et al. 2006; Rong et al. 2007a; 2007b; Stafford et al. 2000]).

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-cells 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 [Tarfulea et al. 2011], the authors consider a model for HIV dynamics which includes the CTLs' response.

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 the 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 the virus over time, even if the population of the drug-sensitive HIV virus was declining. Treatments which cause the population of the drug-sensitive virus to decline, but allow the population of the 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 has been utilized in [Rong et al. 2007a] to model the effects of antiretroviral therapy (ART) on the appearance of drug-resistant strains of HIV. In [Tarfulea 2011b], the author considers the following model for HIV dynamics which includes the CTLs' response:

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

together with initial data

$$T(0) = T_0, \quad T_s(0) = 0, \quad V_s(0) = V_0, \quad T_r(0) = 0, \quad V_r(0) = 0, \quad E(0) = E_0, \tag{2}$$

where  $T_0, V_0, E_0 > 0$ . The variables used in system (1) are described in Table 1 and the parameters used and their values are described in Table 2. Here  $u$  represents the rate at which drug-sensitive T-cells mutate to become drug-resistant, and it applies only when the two strains of virus differ by a single point mutation. HIV replicates at a very high rate in untreated patients. Thus, there is a realistic chance that drug-resistant variants exist even before the initiation of therapy [Ribeiro et al. 1998; Rong et al. 2007a]. Moreover, since the wild-type virus dominates the population before the initiation of therapy (see [Bonhoeffer et al. 2000; Nowak et al. 1997]), the mutation from drug-resistant to drug-sensitive is neglected. Also, it is assumed in this model that  $c$ , the clearance rate, and  $\delta$ , the infected T-cell death rate, are the same for both strains of virus.

System (1) has three possible positive steady states:

(1) The infection-free steady state:

$$S_0 := \left( T_0 = \frac{\lambda_T}{d}, T_{s0} = 0, V_{s0} = 0, T_{r0} = 0, V_{r0} = 0, E_0 = \frac{\lambda_E}{\delta_E} \right). \tag{3}$$

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

$$S_b := (T_b, T_{sb}, V_{sb}, T_{rb}, V_{rb}, E_b), \tag{4}$$

where

$$T_{sb} = 0, \quad V_{sb} = 0,$$

$$T_{rb} = \frac{c}{N_r \delta} \frac{\lambda_T - d T_b}{k_r T_b}, \quad V_{rb} = \frac{\lambda_T - d T_b}{k_r T_b}, \quad E_b = \frac{\lambda_E}{\delta_E} + \frac{c_E}{\delta_E} \frac{\lambda_T - d T_b}{k_r T_b},$$

and  $T_b$  is the positive solution of the quadratic equation  $T^2 - A_b T - B_b = 0$ , where

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

parameter	description	value	reference
$\lambda_T$	Recruitment rate of uninfected cells	$d \cdot T(0)$	1
$d$	Death rate of uninfected cells	$0.01 \text{ day}^{-1}$	1, 2
$k_s$	Infection rate of T-cells by the wild-type virus	$2.4 \cdot 10^{-5} \mu\text{l day}^{-1}$	1, 3, 4
$k_r$	Infection rate of T-cells by the drug-resistant virus	$2.4 \cdot 10^{-5} \mu\text{l day}^{-1}$	1, 3, 4
$\delta$	Death rate of infected cells	$0.3 \text{ day}^{-1}$	5
$m_1$	Immune-induced clearance rate for infected $T_s$ cells	$10^{-2} \mu\text{l day}^{-1}$	3
$m_2$	Immune-induced clearance rate for infected $T_r$ cells	$10^{-2} \mu\text{l day}^{-1}$	3
$N_s$	Virions produced per infected drug-sensitive cell	5000	1
$N_r$	Virions produced per infected drug-resistant cell	5000	1
$c$	Clearance rate of free virus	$23 \text{ day}^{-1}$	1
$\lambda_E$	Immune effector production (source) rate	$10^{-3} \mu\text{l day}^{-1}$	3
$c_E$	Stimulation of CTL proliferation	$0.3 \text{ day}^{-1}$	5
$\delta_E$	Death rate of immune effectors	$0.1 \text{ day}^{-1}$	3, 5
$u$	Mutation rate from sensitive strain to resistant strain	$3 \cdot 10^{-5}$	1

**Table 2.** Parameter definitions and values used in numerical simulations. Key for references: 1 = [Rong et al. 2007a]; 2 = [Mohri et al. 1998]; 3 = [Adams et al. 2005]; 4 = [Perelson et al. 1993]; 5 = [Bonhoeffer et al. 2000].

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

$$S_i := (T_i, T_{si}, V_{si}, T_{ri}, V_{ri}, E_i), \quad (5)$$

where

$$T_i = \frac{\lambda_T c}{dc + \delta(k_s N_s T_{si} + k_r N_r T_{ri})}, \quad V_{si} = \frac{\delta N_s T_{si}}{c},$$

$$V_{ri} = \frac{\delta N_r T_{ri}}{c}, \quad E = \frac{\lambda_E + c_E(T_{si} + T_{ri})}{\delta_E},$$

and  $T_{si}$  and  $T_{ri}$  are the solutions of the system

$$\begin{cases} \frac{(1-u)k_s N_s \delta \lambda_T}{dc + \delta(k_s N_s T_s + k_r N_r T_r)} - \delta - \frac{m_1(\lambda_E + c_E(T_s + T_r))}{\delta_E} = 0, \\ \frac{\delta \lambda_T (uk_s N_s T_s + k_r N_r T_r)}{dc + \delta(k_s N_s T_s + k_r N_r T_r)} - \delta T_r - \frac{m_2(\lambda_E + c_E(T_s + T_r))T_r}{\delta_E} = 0. \end{cases} \quad (6)$$

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:

$$S_w := (T_w, T_{sw}, V_{sw}, T_{rw}, V_{rw}, E_w), \quad (7)$$

where

$$T_{rw} = 0, \quad V_{rw} = 0,$$

$$T_{sw} = \frac{c}{N_s \delta} \frac{\lambda_T - d T_w}{k_s T_w}, \quad V_{sw} = \frac{\lambda_T - d T_w}{k_s T_w}, \quad E_w = \frac{\lambda_E}{\delta_E} + \frac{c_E}{\delta_E} \frac{\lambda_T - d T_w}{k_s T_w},$$

and  $T_w$  is the positive solution of the quadratic equation  $T^2 - A_w b T - B_w = 0$ , where

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

The other steady states  $S_0$  and  $S_b$  are the same.

Let

$$R_s := \frac{N_s \delta k_s \lambda_T}{cd(\delta + m_1 \frac{\lambda_E}{\delta_E})} \quad \text{and} \quad R_r := \frac{N_r \delta k_r \lambda_T}{cd(\delta + m_2 \frac{\lambda_E}{\delta_E})} \quad (8)$$

denote the basic reproductive ratios of the wild-type strain and the drug-resistant strain, respectively, and let  $\sigma = (k_s N_s)/(k_r N_r)$ . In [Tarfulea 2011b], it was shown that the infection-free steady state  $S_0$  is locally asymptotically stable if  $R_r < 1$  and  $R_s < 1/(1-u)$ , and it is unstable if  $R_r > 1$  or  $R_s > 1/(1-u)$ . In the case that  $u = 0$  in model (1) (i.e., there is no mutation), 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  $R_s > 1$ .

**2.2. Model with antiretroviral therapy.** 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) [Cohen and Boyle 2004; Cohen 2005a; 2005b; El-Sadr et al. 2006; Nowak et al. 1997; Sharomi and Gumel 2008] designed to limit the virus' ability to mutate and develop drug-resistant strains. Nucleoside reverse transcriptase inhibitors (NRTIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs) 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 rates for the wild-type and the drug-resistant viruses. 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 [Casiday and Frey 2001], and 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 introducing drug-efficacy parameters, which are extensively used in numerous models, such as [Adams et al. 2005; Perelson and Nelson 1999; Rong et al. 2007a; 2007b]. We consider  $\varepsilon_{RT}^s$  and  $\varepsilon_{RT}^r$  to represent the efficacies of RTIs and  $\varepsilon_{PI}^s$  and  $\varepsilon_{PI}^r$  to be the efficacies of PIs, for drug-sensitive and drug-resistant strains. These drugs are incorporated into model (1) to obtain the following system (the initial condition used is the values for the infected steady state in the no-treatment case given by (5) and the parameter values used are from Table 2):

$$\begin{aligned}
 \frac{dT}{dt} &= \lambda_T - Td - k_s(1 - \varepsilon_{RT}^s)V_sT - k_r(1 - \varepsilon_{RT}^r)V_rT, \\
 \frac{dT_s}{dt} &= (1 - u)k_s(1 - \varepsilon_{RT}^s)TV_s - \delta T_s - m_1ET_s, \\
 \frac{dV_s}{dt} &= N_s(1 - \varepsilon_{PI}^s)\delta T_s - cV_s, \\
 \frac{dT_r}{dt} &= uk_s(1 - \varepsilon_{RT}^s)TV_s + k_r(1 - \varepsilon_{RT}^r)V_rT - \delta T_r - m_2ET_r, \\
 \frac{dV_r}{dt} &= N_r(1 - \varepsilon_{PI}^r)\delta T_r - cV_r, \\
 \frac{dE}{dt} &= \lambda_E + c_E(T_s + T_r) - \delta_E E.
 \end{aligned} \tag{9}$$

The case of constant drug efficacies has been addressed in several models (see [Adams et al. 2005; Perelson and Nelson 1999; Rong et al. 2007a; 2007b; Tarfulea et al. 2011; Tarfulea 2011b]). In this case,  $\varepsilon_{RT}^s$ ,  $\varepsilon_{PI}^s$ ,  $\varepsilon_{RT}^r$ , and  $\varepsilon_{PI}^r$  lie in  $[0, 1]$ . In



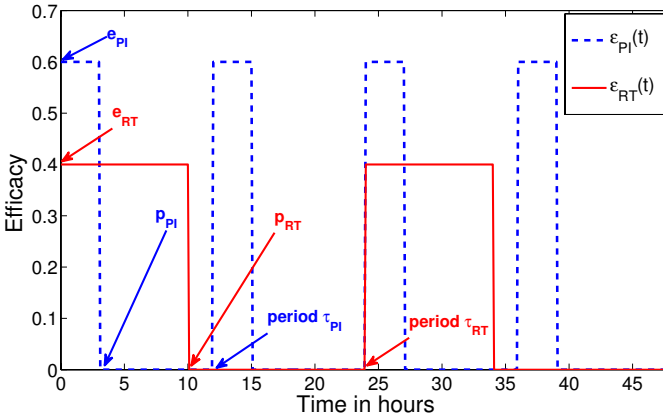
the case that all are zero, i.e., no treatment, we obtain system (1); if all are 1, then we obtain a complete cure of the disease since  $dV_s/dt < 0$  and  $dV_r/dt < 0$ . Moreover, we have that  $\varepsilon_{RT}^s > \varepsilon_{RT}^r$  and  $\varepsilon_{PI}^s > \varepsilon_{PI}^r$  since the wild-type 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  $0 < \alpha < 1$  and  $\alpha$  represents the HIV mutants' level of resistance; as  $\alpha$  decreases, there is more resistance to the used drug for the drug-resistant strains. However, in reality, the drug efficacies are not constant in time; thus the main purpose of this paper is to investigate the effect of including periodic antiretroviral therapy of bang-bang type.

### 3. Time-varying drug efficiency

In this section, we include time-varying drug efficacy functions to model various treatment regimens. Thereafter, we consider the model (9) where  $\varepsilon_{RT}^s(t)$ ,  $\varepsilon_{RT}^r(t)$ ,  $\varepsilon_{PI}^s(t)$ , and  $\varepsilon_{PI}^r(t)$  are functions of time with range the interval  $[0, 1]$  and they represent the time-varying drug efficacies of the RTIs and PIs for drug-sensitive and drug-resistant strains. When  $\varepsilon_{RT}^s(t)$ ,  $\varepsilon_{RT}^r(t)$  or  $\varepsilon_{PI}^s(t)$ ,  $\varepsilon_{PI}^r(t)$  are close to zero, the drug has almost no effect, while if they are near 1, the viral replication is almost completely inhibited. The shapes of these functions are determined by the pharmacokinetics that describe what happens to a drug after the moment of intake and before starting to be active at the infection site [De Leenheer 2009]. It is characterized by a fast rise to the peak value immediately after the drug intake, followed by a slower decay. Thus, we consider that each of the drug efficacies considered,  $\varepsilon_{RT}^s(t)$ ,  $\varepsilon_{RT}^r(t)$ ,  $\varepsilon_{PI}^s(t)$ , and  $\varepsilon_{PI}^r(t)$ , is periodic, that is  $\varepsilon_{RT}^s(t) = \varepsilon_{RT}^s(t + \tau_{RT}^s)$  and  $\varepsilon_{PI}^s(t) = \varepsilon_{PI}^s(t + \tau_{PI}^s)$  for all  $t$ , where  $\tau_{RT}^s, \tau_{PI}^s > 0$  are the principal periods for the RTIs and PIs for the sensitive strain. We have similar relations for the efficiency of the drug-resistant strain. For example, the period is 1 if medication is taken daily or 0.5 for a twice a day treatment schedule. Moreover, we assume the efficiency functions to be of the bang-bang type, i.e., at any time during treatment, the drug is either active or inactive. It is clear that is just an approximation of the real shape of  $\varepsilon(t)$  determined by the pharmacokinetics, but some key properties are to be revealed from this case. These functions are given by

$$\begin{aligned} \varepsilon_{RT}^s(t) &= \begin{cases} e_{RT}^s, & \text{for } t \in [0, p_{RT}^s], \\ 0, & \text{for } t \in (p_{RT}^s, \tau_{RT}^s), \end{cases} \\ \varepsilon_{PI}^s(t) &= \begin{cases} e_{PI}^s, & \text{for } t \in [0, p_{PI}^s], \\ 0, & \text{for } t \in (p_{PI}^s, \tau_{PI}^s), \end{cases} \end{aligned} \quad (10)$$

with a similar behavior for  $\varepsilon_{RT}^r$  and  $\varepsilon_{PI}^r$ . An example of such functions is illustrated in Figure 1. Here  $p_{RT}^s \in (0, \tau_{RT}^s)$  is the time duration when the RT drug is active with efficacy  $e_{RT}^s \in [0, 1]$ , and  $p_{PI}^s$  and  $e_{PI}^s$  are defined similarly. The drug is assumed to be totally inefficient during the remaining part of the corresponding



**Figure 1.** An example of periodic drug efficacies functions of the bang-bang type,  $\varepsilon_{RT}(t)$  (solid line) and  $\varepsilon_{PI}(t)$  (dotted line). Here RTI drug has the period  $\varepsilon_{RT} = 1$  (i.e., 24 h), is active for 10 h (i.e.,  $p_{RT} = 0.42$ ) with efficacy  $e_{RT} = 0.4$ ; PI drug has the period  $\varepsilon_{PI} = 0.5$  (i.e., 12 h), is active for 4 h (i.e.,  $p_{PI} = 0.17$ ) with efficacy  $e_{PI} = 0.6$ .

period. The same relations hold for drug-resistant drug efficacies. Furthermore, 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  $\varepsilon_{RT}^r = \alpha_1 \varepsilon_{RT}^s$  or that  $\varepsilon_{PI}^r = \alpha_2 \varepsilon_{PI}^s$ , where  $0 < \alpha_1, \alpha_2 < 1$  and  $\alpha_1, \alpha_2$  represent the HIV mutants' level of resistance; as  $\alpha_1$  or  $\alpha_2$  decreases, there is more resistance to the used drug for the drug-resistant strains.

In order to compare our results with results from related models using constant efficacies, we define the average drug efficacy for each type of drug used, given by

$$\bar{\varepsilon}_{RT}^s := \frac{1}{\tau_{RT}^s} \int_0^{\tau_{RT}^s} \varepsilon_{RT}^s(t) dt \quad \text{and} \quad \bar{\varepsilon}_{PI}^s := \frac{1}{\tau_{PI}^s} \int_0^{\tau_{PI}^s} \varepsilon_{PI}^s(t) dt, \quad (11)$$

and thus,

$$\bar{\varepsilon}_{RT}^s = \frac{e_{RT}^s p_{RT}^s}{\tau_{RT}^s} \quad \text{and} \quad \bar{\varepsilon}_{PI}^s = \frac{e_{PI}^s p_{PI}^s}{\tau_{PI}^s},$$

for the sensitive strain, and

$$\bar{\varepsilon}_{RT}^r := \frac{1}{\tau_{RT}^r} \int_0^{\tau_{RT}^r} \varepsilon_{RT}^r(t) dt \quad \text{and} \quad \bar{\varepsilon}_{PI}^r := \frac{1}{\tau_{PI}^r} \int_0^{\tau_{PI}^r} \varepsilon_{PI}^r(t) dt, \quad (12)$$

and thus,

$$\bar{\varepsilon}_{RT}^r = \frac{e_{RT}^r p_{RT}^r}{\tau_{RT}^r} \quad \text{and} \quad \bar{\varepsilon}_{PI}^r = \frac{e_{PI}^r p_{PI}^r}{\tau_{PI}^r},$$

for the resistant strain. Moreover, we introduce the overall treatment effects

$$\varepsilon^s = 1 - (1 - \bar{\varepsilon}_{RT}^s)(1 - \bar{\varepsilon}_{PI}^s) \quad \text{and} \quad \varepsilon^r = 1 - (1 - \bar{\varepsilon}_{RT}^r)(1 - \bar{\varepsilon}_{PI}^r) \quad (13)$$

for the wild-type and mutant strains, respectively.

There are two parameters which can vary in the efficacies  $\varepsilon(t)$  (for both RTIs and PIs), namely the efficacy of the drug  $e$  and the time duration  $p$ . In the remaining part of this section, we investigate their effect on the Floquet multipliers of systems (15) and (16).

We begin by investigating the effect of only one drug in the system at a time. Let us assume first that the efficiencies  $\varepsilon_{RT}^s(t)$  and  $\varepsilon_{RT}^r(t)$  are periodic (as described above) and  $\varepsilon_{PI}^s(t) = 0$  and  $\varepsilon_{PI}^r(t) = 0$ , i.e., only RTIs are administered in the system. Notice that the infection-free steady state

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

is still an equilibrium solution of the model (9), regardless the inclusion of the drug efficiency. Moreover, in our investigation we use only this steady state since its stability implies that the treatment can clear the infection. Thus, we linearize the system (9) about  $S_0$  and obtain the linear system

$$\frac{dx}{dt} = A(t)x, \quad (14)$$

where

$$A(t) = \begin{pmatrix} -d & 0 & -a_{RT}^s(t) & 0 & -a_{RT}^r(t) & 0 \\ 0 & -\delta - m_1 E_0 & (1-u)a_{RT}^s(t) & 0 & 0 & 0 \\ 0 & N_s \delta & -c & 0 & 0 & 0 \\ 0 & 0 & ua_{RT}^s(t) & -\delta - m_2 E_0 & a_{RT}^r(t) & 0 \\ 0 & 0 & 0 & N_r \delta & -c & 0 \\ 0 & c_E & 0 & c_E & 0 & -\delta_E \end{pmatrix},$$

with  $a_{RT}^s(t) = k_s(1 - \varepsilon_{RT}^s(t))T_0$  and  $a_{RT}^r(t) = k_r(1 - \varepsilon_{RT}^r(t))T_0$ . Here  $x$  is the six-dimensional vector function whose components are the perturbations corresponding to the main variables  $T$ ,  $T_s$ ,  $V_s$ ,  $T_r$ ,  $V_r$ , and  $E$ , respectively. The local stability properties of  $S_0$  for system (9) are determined by the Floquet multipliers of (14) (see [De Leenheer and Smith 2003]) which, given the block-triangular structure of  $A(t)$ , are  $e^{-d\tau}$ ,  $\lambda_2$ ,  $\lambda_3$ ,  $\lambda_4$ ,  $\lambda_5$ , and  $e^{-\delta_E \tau}$ , where  $\lambda_2$  and  $\lambda_3$  are the Floquet multipliers of the planar  $\tau$ -periodic system

$$\begin{pmatrix} \dot{x}_2 \\ \dot{x}_3 \end{pmatrix} = \begin{pmatrix} -\delta - m_1 E_0 & (1-u)k_s(1 - \varepsilon_{RT}^s(t))T_0 \\ N_s \delta & -c \end{pmatrix} \begin{pmatrix} x_2 \\ x_3 \end{pmatrix}, \quad (15)$$

and  $\lambda_4$  and  $\lambda_5$  are the Floquet multipliers of the planar  $\tau$ -periodic system

$$\begin{pmatrix} \dot{x}_4 \\ \dot{x}_5 \end{pmatrix} = \begin{pmatrix} -\delta - m_2 E_0 & (1-u)k_r(1 - \varepsilon_{RT}^r(t))T_0 \\ N_r \delta & -c \end{pmatrix} \begin{pmatrix} x_4 \\ x_5 \end{pmatrix}. \quad (16)$$

The infection-free steady state  $S_0$  is locally asymptotically stable for system (9) if the Floquet multipliers of system (14) are contained in the unit disk of the complex plane, which is satisfied if  $|\lambda_2|, |\lambda_3|, |\lambda_4|, |\lambda_5| < 1$ . Unfortunately it is well known that for general functions  $\varepsilon(t)$  this condition is difficult to verify. If we consider the drug efficacies  $\varepsilon_{RT}^s(t)$  and  $\varepsilon_{RT}^r(t)$  of the bang-bang form given by (10), we get that the Floquet multipliers  $\lambda_2$  and  $\lambda_3$  of system (15) are the eigenvalues of the matrix

$$\Phi(e_{RT}^s, p_{RT}^s) := \exp((\tau_{RT}^s - p_{RT}^s)B(0)) \exp(p_{RT}^s B(e_{RT}^s)), \quad (17)$$

where the matrix function  $B(\cdot)$  is defined by

$$B(e_{RT}^s) := \begin{pmatrix} -\delta - m_1 E_0 & (1-u)k_s(1 - e_{RT}^s)T_0 \\ N_s \delta & -c \end{pmatrix}, \quad (18)$$

for any value of  $e_{RT}^s$ . Using the approach in [De Leenheer and Smith 2003], we obtain that the Floquet multipliers are contained in the interior of the unit disk of the complex plane if and only if the spectral radius  $\rho(\Phi(e_{RT}^s, p_{RT}^s))$  of the matrix  $\Phi(e_{RT}^s, p_{RT}^s)$  is less than 1. Furthermore, by applying Proposition 2 in [De Leenheer and Smith 2003] to our system, we get the expected monotonicity properties: the spectral radius is decreasing in each of its arguments. That is, if the treatment is periodic of the bang-bang type and it can eradicate the virus, then the infection is cleared more rapidly when the treatment is more effective or it lasts longer. These effects are confirmed by the results obtained from the numerical investigations described in the second part of this section.

We obtain a similar result if we consider the effect of only PIs, in which case

$$B(e_{PI}^s) := \begin{pmatrix} -\delta - m_1 E_0 & (1-u)k_s T_0 \\ N_s(1 - e_{PI}^s)\delta & -c \end{pmatrix},$$

or if we consider a cocktail of drugs where both inhibitors are present, in which case

$$B(e_{RT}^s, e_{PI}^s) = \begin{pmatrix} -\delta - m_1 E_0 & (1-u)k_s(1 - e_{RT}^s)T_0 \\ N_s(1 - e_{PI}^s)\delta & -c \end{pmatrix}.$$

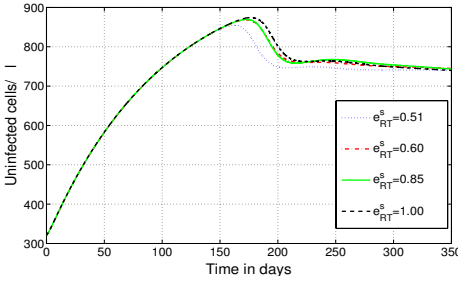
**3.1. Numerical results.** In this section, we analyze our results from the numerical investigations performed. We created MATLAB codes in order to solve the system numerically which allowed us to test and validate the mathematical mode and to explore various scenarios. We used `ode45` and `ode15s`, two MATLAB functions for the numerical solutions for our systems of differential equations (`ode45` is based on an explicit Runge–Kutta (4,5) formula, the Dormand–Prince pair, a one-step

solver that needs only the solution at the immediately preceding time point, whereas ode15s is a variable order solver based on the backward differentiation formulas, Gear's method, a multistep solver for stiff problems).

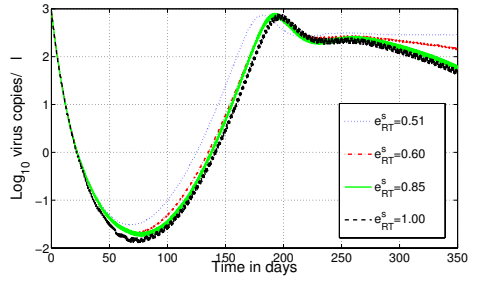
Our focus is placed on the following areas of interest: quantity of viral load and uninfected cell count for individual drug intake where average drug efficacies ( $\bar{\varepsilon}_{RT}^s$ ,  $\bar{\varepsilon}_{PI}^s$ ) are fixed and the time duration when the drug is active is varied, quantity of viral load and uninfected cell count for both classes of drugs taken in conjunction where drug efficacies are fixed and the time duration when the drug is active is varied, the effect on viral load and uninfected cell count for both drugs taken in conjunction where the ratio of their corresponding efficacies are varied over the same period, the effect on viral load and uninfected cell concentration while strictly varying the total efficacy of either drug, and the effect on viral load when the level of resistances ( $\alpha_1$ ,  $\alpha_2$ ) for the resistant-type viruses are varied.

We first consider a treatment scenario with only the reverse transcriptase inhibitor (RTI) drug where we fix the average efficacy,  $\bar{\varepsilon}_{RT}^s$  and vary the step-function parameters,  $e_{RT}^s$  and  $p_{RT}^s$ . Note that  $\varepsilon^s = 1 - (1 - \bar{\varepsilon}_{RT}^s)(1 - \bar{\varepsilon}_{PI}^s)$ , as defined by (13) (the same relation holds for  $\varepsilon^r$ ). We choose  $\varepsilon^s = 0.51$  and since we are only considering the RTI drug, we choose  $\bar{\varepsilon}_{PI}^s = 0.00$  and therefore  $\bar{\varepsilon}_{RT}^s = 0.51$ . We also note that in the periodic step-function, we have  $\bar{\varepsilon}_{RT}^s = (e_{RT}^s p_{RT}^s) / \tau_{RT}^s$ . We therefore pick the convenient ordered pair values for  $(e_{RT}^s, p_{RT}^s) \in \{(0.51, 1.00), (0.60, 0.85), (0.85, 0.60), (1.00, 0.51)\}$ . As intuition would lead us to expect, we see that the total viral load is lowest at the time when the drug is active is the largest (i.e., the case for which  $(e_{RT}^s, p_{RT}^s) = (0.51, 1.00)$ ). However, we also see the result in which the uninfected cell concentration has an inverse relationship to the viral load, due to the resistant strain virus. The wild-type viral load behaves similarly to the uninfected CD4+ T-cells. More specifically, the uninfected cell concentration peaks the highest and also converges to the highest steady state when the period over which the drug is released is the shortest (i.e., the case for which  $(e_{RT}^s, p_{RT}^s) = (1.00, 0.51)$ ) (see Figure 2). This is a result similar to the case when constant efficiencies  $\varepsilon_{RT}$ ,  $\varepsilon_{PI}(t)$  are used (see [Rong et al. 2007a; Tarfulea 2011b]). An analogous conclusion is obtained when investigating the effects on viral load and uninfected cell concentration when considering a treatment such that  $\bar{\varepsilon}_{RT}^s = 0.00$  and  $\bar{\varepsilon}_{PI}^s = 0.51$ , in other words, a treatment using only protease inhibitors (PIs) and varying the step-function parameters as done for RTIs. In all the above mentioned cases, we consider  $\alpha_1 = \alpha_2 = 0.2$ .

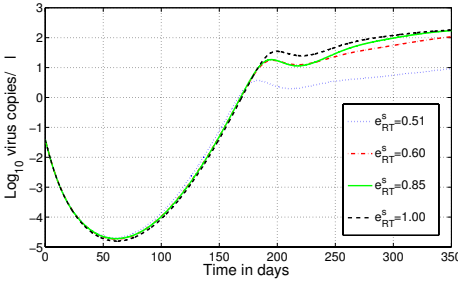
We now consider a treatment scenario in which RTIs and PIs are used in conjunction. Our first investigation begins with setting the efficacies of both drugs to be equal (i.e.,  $\varepsilon_{RT}^s = \varepsilon_{PI}^s$ ). Therefore, we again choose  $\varepsilon^s = 0.51$  (with  $\alpha_1 = \alpha_2 = 0.2$ ), and therefore it follows from  $\varepsilon^s = 1 - (1 - \bar{\varepsilon}_{RT}^s)(1 - \bar{\varepsilon}_{PI}^s)$  that  $\bar{\varepsilon}_{RT}^s = \bar{\varepsilon}_{PI}^s = 0.30$ . Thus, the equivalence of the ordered pairs  $(e_{RT}^s, p_{RT}^s)$  and  $(e_{PI}^s, p_{PI}^s)$  follows. We



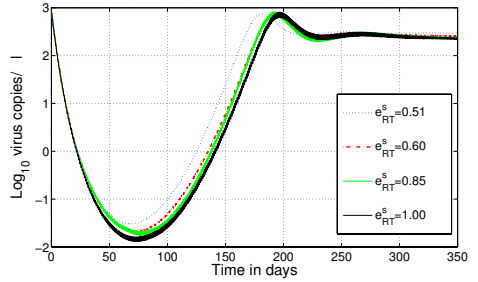
(a) Uninfected cells  $T(t)$ .



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



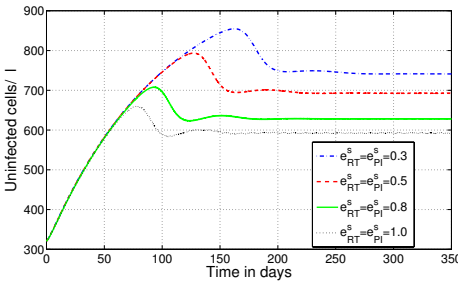
(c) Resistant virus  $V_r(t)$ .



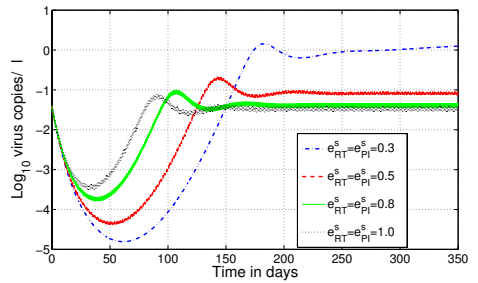
(d) Total virus.

**Figure 2.** Simulation over the first 350 days of infection with  $\bar{e}_{RT}^s = 0.51$  and  $\bar{e}_{PI}^s = 0.00$ ; thus  $\varepsilon^s = 0.51$  (see text for details).

therefore choose the convenient ordered pair values for  $(e_{RT}^s, p_{RT}^s) = (e_{PI}^s, p_{PI}^s) \in \{(0.3, 1.0), (0.5, 0.6), (0.8, 0.375), (1.0, 0.3)\}$ . This simulation yields results which are opposed that of the results when the two drugs were used individually and are presented in [Figure 3](#) for the uninfected T-cell and resistant strain virus concentrations. The lowest viral peak with a convergence to the lowest steady state came from the highest drug efficacy and shortest time release period (i.e.,  $e_{RT}^s = e_{PI}^s = 1.0$  and  $p_{RT}^s = p_{PI}^s = 0.3$ ); that is, it is better if the drug is effective longer than if it

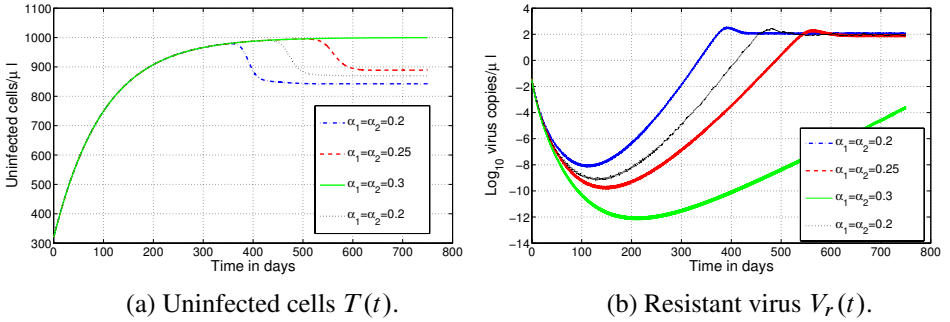


(a) Uninfected cells  $T(t)$ .



(b) Resistant virus  $V_r(t)$ .

**Figure 3.** Simulation over the first 350 days of drug treatment with  $\varepsilon^s = 0.51$  and  $\bar{e}_{RT}^s = \bar{e}_{PI}^s = 0.3$ .

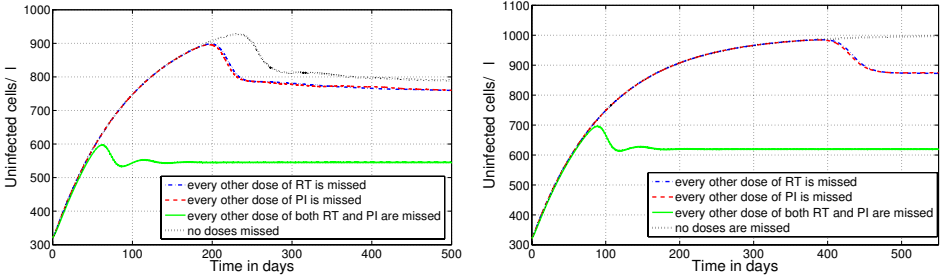


**Figure 4.** Simulation over the first 750 days of drug treatment, varying the HIV mutants' level of resistance. For all but black dotted line,  $\bar{\varepsilon}_{RT}^s = \bar{\varepsilon}_{PI}^s = 0.71$ , and for the black dotted line,  $\bar{\varepsilon}_{RT}^s = \bar{\varepsilon}_{PI}^s = 0.81$

has a higher peak. However, as in the case of the individual drug treatment cases, the uninfected cell concentration had inverse results to the resistant strain viral concentration and behaves similarly to the wild-type viral concentration.

Our next analysis considers the effects on the viral load and uninfected cell concentrations while varying the efficacies for both drugs. We continue to consider a fixed overall treatment effect where  $\varepsilon^s = 0.51$ . We then examine the average efficacy values  $(\bar{\varepsilon}_{RT}^s, \bar{\varepsilon}_{PI}^s) \in \{(0.51, 0.0), (0.41, 0.17), (0.3, 0.3), (0.17, 0.41)\}$ . Here again  $\alpha_1 = \alpha_2 = 0.2$ . We considered the results of  $(\bar{\varepsilon}_{RT}^s, \bar{\varepsilon}_{PI}^s) = (0.51, 0.0)$  in a previous section and used these values again for comparison. It is not surprising to see that this is, in fact, the least efficient scenario since the others involve a drug cocktail as opposed to this one-drug treatment. It is noted that the best result, having the lowest viral peak and convergent steady state with the highest uninfected cell concentration, comes from a drug cocktail in which the drug efficacy ratio (RTI:PI) is 1:4. Moreover, as we would expect, administering any cocktail of drugs with any chosen efficacies (without keeping a constant overall efficacy) gives better results than the individual classes of drugs alone.

Recall that we use resistance rates,  $\alpha_1$  and  $\alpha_2$ , such that  $\varepsilon_{RT}^r = \alpha_1 \varepsilon_{RT}^s$  and  $\varepsilon_{PI}^r = \alpha_2 \varepsilon_{PI}^s$ , with  $\alpha_1, \alpha_2 \in (0, 1)$ . We consider the effects on viral load for varying levels of resistance. We let  $\alpha_1, \alpha_2 \in \{0.25, 0.5, 0.75, 1.0\}$ . Note that when  $\alpha_1 = \alpha_2 = 1.0$ , the efficacy for the drugs against the mutant virus is equal to that of the drug-sensitive-type virus. We see the intuitive results that demonstrate that when  $\alpha_1, \alpha_2$  get closer to 1, the total viral load for the resistant-type, the mutant virus decreases. We next consider fixing one of the resistant rates (i.e., the resistant rate for one of the drugs) and vary the other. We observe the total viral load in the case where we fix  $\alpha_2 = 0.25$  and vary  $\alpha_1 \in \{0.25, 0.5, 0.75, 1.0\}$ . It is noted that, again, we see the lowest viral load is obtained when  $\alpha_1 = 1.0$ , and as  $\alpha_1$  becomes closer



(a)  $\bar{\epsilon}_{RT}^s = \bar{\epsilon}_{PI}^s = 0.51$  and  $\alpha_1 = \alpha_2 = 0.2$ . (b)  $\bar{\epsilon}_{RT}^s = \bar{\epsilon}_{PI}^s = 0.71$  and  $\alpha_1 = \alpha_2 = 0.3$ .

**Figure 5.** Uninfected T-cell concentration  $T(t)$  under suboptimal treatment.

to 1, the viral load of the resistant-type virus decreases. An analogous observation is made for fixing  $\alpha_1$  and varying  $\alpha_2$ . In Figure 4, we consider the efficacies for the two classes of drugs to be  $\bar{\epsilon}_{RT}^s = \bar{\epsilon}_{PI}^s = 0.71$ , which guarantees that the wild-type virus is suppressed. We let  $p_{RT}^s = p_{PI}^s = 0.71$  and we see that for values for  $\alpha_1$  and  $\alpha_2$  lower than 0.3, the drug-resistant strain persists. Moreover, if we increase the drug efficacies to 0.81, for  $\alpha_1 = \alpha_2 = 0.2$ , the drug-resistant strain still persists.

One of the critical obstacles to successful HIV drug therapy is the imperfect adherence to a prescribed drug regimen due to its complexity or severe side effects. Receiving treatment for HIV is expensive and people can be careless; therefore we want to look into the effects of missing doses. We investigate numerous efficacy combinations and RTI/PI individual and/or combined treatments. The results unanimously indicate that skipping a dose of either drug at any combination has certain undesirable effects which included a weaker drop in viral load and lower overall uninfected cell concentration. In Figure 5, we present the dynamics of uninfected T-cell concentration when every other dose of RTIs, PIs, or both are missed and compare with the dynamics of a regular treatment. In Figure 5(a) we consider  $\bar{\epsilon}_{RT}^s = \bar{\epsilon}_{PI}^s = 0.51$ ,  $p_{RT}^s = p_{PI}^s = 0.51$ , and  $\alpha_1 = \alpha_2 = 0.2$ , whereas in Figure 5(b) we consider  $\bar{\epsilon}_{RT}^s = \bar{\epsilon}_{PI}^s = 0.71$ ,  $p_{RT}^s = p_{PI}^s = 0.71$ , and  $\alpha_1 = \alpha_2 = 0.3$ . In the latter case, the viral load is eradicated under perfect adherence, but the uninfected T-cell concentration decreases and both strains of virus persist even when only one drug is missed.

### 4. Conclusions

We have developed and analyzed a mathematical model that accounts for multiple viral strains during the course of antiretroviral therapy with periodic antiretroviral therapy of bang-bang type. There were many different circumstances that we investigated thoroughly. The first area of interest was determining how the system behaves when only the presence of one antiretroviral class of drugs is used. This was done for each of the two classes of interest, namely protease inhibitors and



reverse transcriptase inhibitors. It was noted, based on the periodic step-function used for our analysis, that, upon taking only one of the two available drugs, when the efficacy of either drug was increased and the period over which the drug would be active, the total viral load decreased. There was an identical scenario for either drug taken alone.

Certainly, the optimal scenario for drug treatment is by means of a patient taking a cocktail of both classes of drugs. Therefore, it was of great importance to investigate the functionality of using both drugs of interest simultaneously. When the two drugs were taken in conjunction, they had an inverse effect on the infected body. In other words, when we increased initial efficacy of the drug cocktail and decreased the period, the total viral load decreased. For any of the scenarios investigated, however, the total uninfected cell count responded inversely to the response of the resistant strain viral load. This led us to the conclusion that the drug cocktail was not only the proper choice, but we also observed that it was most effective given at a 4:1 ratio (protease inhibitors: reverse transcriptase inhibitors). Furthermore, the examination of the effects of using different ratios of both drugs to further optimize the efficacy of the treatment was also of substantial interest. Scenarios for both varying efficacy and varying the level of resistance to the drug therapy by the drug-resistant-type virus were examined. As the level of drug efficacy increased, there were noticeable increases in the uninfected cell count as well as a stronger decrease in the total viral load. When the level of resistance was increased, we noted an increase in viral load as we expected. Although seemingly intuitive, we were also sure to investigate the functionality of the system when varying both drug efficacies, individually and in tandem, and the results of the evolution of drug resistance.

Given the staggering percentage of infected people that are either unable to obtain the appropriate drug therapies or simply cannot take all the recommended doses, we also numerically investigated the effect of imperfect adherence to the prescribed treatment regimen. That is, we investigated what would happen when someone is under a drug regimen and particular doses were skipped. The last area of results we obtained consisted of scenarios where the infected person missed a certain number of doses for either drug and for both drugs together. Skipping doses for either drug alone had nearly identical effects; there was significantly less of a drop in viral load and the uninfected cell count was much lower. The results of missing doses when the drug cocktail was being administered followed directly from the individual missed doses as well.

## Appendix

The following table contains all of the symbols used throughout the paper (in the order of appearance).

symbol	description
$T$	healthy T-cell concentration
$T_s$	drug-sensitive infected T-cell concentration
$T_r$	drug-resistant infected T-cell concentration
$V_s$	drug-sensitive virus concentration
$V_r$	drug-resistant virus concentration
$E$	concentration of CD8+ T-cells
$\lambda_T$	recruitment rate of uninfected cells
$d$	death rate of uninfected cells
$k_s$	infection rate of T-cells by the wild-type virus
$k_r$	infection rate of T-cells by the drug-resistant virus
$\delta$	death rate of infected cells
$m_1$	immune-induced clearance rate for infected $T_s$ cells
$m_2$	immune-induced clearance rate for infected $T_r$ cells
$N_s$	virions produced per infected drug-sensitive cell
$N_r$	virions produced per infected drug-resistant cell
$c$	clearance rate of free virus
$c_E$	stimulation of CTL proliferation
$\delta_E$	death rate of immune effectors
$u$	mutation rate from sensitive strain to resistant strain
$S_0$	vector $(T_0, T_{s0}, V_{s0}, V_{r0}, E_0)$ with the infection-free steady state
$S_b$	vector $(T_b, T_{sb}, V_{sb}, V_{rb}, E_b)$ with the boundary steady state
$S_i$	vector $(T_i, T_{si}, V_{si}, V_{ri}, E_i)$ with the interior steady state
$S_w$	vector $(T_w, T_{sw}, V_{sw}, V_{rw}, E_w)$ with the wild-type steady state
$R_s$	basic reproductive ratio of the wild-type strain
$R_r$	basic reproductive ratio of the drug-resistant strain
$\varepsilon_{RT}^s$	efficacy of RTIs for drug-sensitive strain
$\varepsilon_{RT}^r$	efficacy of RTIs for drug-resistant strain
$\varepsilon_{PI}^s$	efficacy of PIs for drug-sensitive strain
$\varepsilon_{PI}^r$	efficacy of PIs for drug-resistant strain
$\alpha$	HIV mutants' level of resistance
$\tau_{RT}^s$	principal period for the RT inhibitors for the sensitive strain
$\tau_{PI}^s$	principal period for the P inhibitors for the sensitive strain

symbol	description
$p_{RT}^S$	time duration when the RT drug for the sensitive strain is active
$p_{RT}^R$	time duration when the RT drug for the resistant strain is active
$p_{PI}^S$	time duration when the P drug for the sensitive strain is active
$p_{PI}^R$	time duration when the P drug for the resistant strain is active
$e_{RT}^S$	efficacy of RT drugs for the sensitive strain
$e_{RT}^R$	efficacy of RT drugs for the resistant strain
$e_{PI}^S$	efficacy of P drugs for the sensitive strain
$e_{PI}^R$	efficacy of P drugs for the resistant strain
$\alpha_1$	HIV mutants' level of resistance for the RT drug
$\alpha_2$	HIV mutants' level of resistance for the P drug
$\bar{e}_{RT}^S$	average efficacy of RT drugs for sensitive strain
$\bar{e}_{RT}^R$	average efficacy of RT drugs for resistant strain
$\bar{e}_{PI}^S$	average efficacy of P drugs for sensitive strain
$\bar{e}_{PI}^R$	average efficacy of P drugs for resistant strain
$\varepsilon^S$	overall treatment effect on the sensitive strain
$\varepsilon^R$	overall treatment effect on the resistant strain

## References

- [Adams et al. 2005] B. M. Adams, H. T. Banks, M. Davidian, H.-D. Kwon, H. T. Tran, S. N. Wynne, and E. S. Rosenberg, “HIV dynamics: modeling, data analysis, and optimal treatment protocols”, *J. Comput. Appl. Math.* **184**:1 (2005), 10–49. MR 2006h:92020 Zbl 1075.92030
- [Bofill et al. 1992] M. Bofill, G. Janossy, C. A. Lee, D. MacDonald-Burns, A. N. Phillips, C. Sabin, A. Timms, M. A. Johnson, and P. B. Kernoff, “Laboratory control values for CD4 and CD8 T lymphocytes: implications for HIV-1 diagnosis”, *Clin. Exp. Immunol.* **88**:2 (1992), 243–252.
- [Bonhoeffer et al. 2000] S. Bonhoeffer, M. Rembiszewski, G. M. Ortiz, and D. F. Nixon, “Risks and benefits of structured antiretroviral drug therapy interruptions in HIV-1 infection”, *AIDS* **14**:15 (2000), 2313–2322.
- [Burg et al. 2009] D. Burg, L. Rong, A. U. Neumann, and H. Dahari, “Mathematical modeling of viral kinetics under immune control during primary HIV-1 infection”, *J. Theor. Biol.* **259**:4 (2009), 751–759. MR 2973193
- [Casiday and Frey 2001] R. Casiday and R. Frey, “Drug strategies to target HIV: enzyme kinetics and enzyme inhibitors”, preprint, Washington University, St. Louis, MO, 2001, <http://www.chemistry.wustl.edu/~edudev/LabTutorials/HIV/DrugStrategies.html>.
- [Cohen 2005a] C. J. Cohen, “EuroSIDA study confirms ability of most HAART regimens to decrease rates of illness and death”, in *The 12th Conference on Retroviruses and Opportunistic Infections* (Boston, 2005), The Body Pro, New York, February 24, 2005.

- [Cohen 2005b] C. J. Cohen, “Ritonavir-boosted protease inhibitors, 1: Strategies for balancing efficacy with effects on lipids”, *AIDS Read.* **15**:9 (2005), 462–465, 470–471, 474, 477.
- [Cohen and Boyle 2004] C. J. Cohen and B. A. Boyle, “Antiretroviral therapy: the ‘when to start’ debates”, *Clin. Infect. Dis.* **39**:11 (2004), 1705–1708.
- [De Leenheer 2009] P. De Leenheer, “Within-host virus models with periodic antiviral therapy”, *Bull. Math. Biol.* **71**:1 (2009), 189–210. MR 2010c:92044 Zbl 1169.92024
- [De Leenheer and Smith 2003] P. De Leenheer and H. L. Smith, “Virus dynamics: a global analysis”, *SIAM J. Appl. Math.* **63**:4 (2003), 1313–1327. MR 2004b:34136 Zbl 1035.34045
- [El-Sadr et al. 2006] W. M. El-Sadr et al., “CD4+ count-guided interruption of antiretroviral treatment”, *N. Engl. J. Med.* **355**:22 (2006), 2283–2296.
- [Fauci 1993] A. S. Fauci, “Immunopathogenesis of HIV infection”, *J. Acquir. Immune Defic. Syndr.* **6**:6 (1993), 655–662.
- [Huang 2008] Y. Huang, “Long-term HIV dynamic models incorporating drug adherence and resistance to treatment for prediction of virological responses”, *Comput. Stat. Data Anal.* **52**:7 (2008), 3765–3778. MR 2427379 Zbl 05564736
- [Kepler and Perelson 1998] T. B. Kepler and A. S. Perelson, “Drug concentration heterogeneity facilitates the evolution of drug resistance”, *Proc. Natl. Acad. Sci. USA* **95**:20 (1998), 11514–11519. Zbl 0919.92023
- [Kirschner and Webb 1997] D. E. Kirschner and G. F. Webb, “Understanding drug resistance for monotherapy treatment of HIV infection”, *Bull. Math. Biol.* **59**:4 (1997), 763–786.
- [Koup et al. 1994] R. A. Koup, J. T. Safrit, Y. Cao, C. A. Andrews, G. McLeod, W. Borkowsky, C. Farthing, and D. D. Ho, “Temporal association of cellular immune responses with the initial control of viremia in primary human immunodeficiency virus type 1 syndrome”, *J. Virol.* **68**:7 (1994), 4650–4655.
- [McMichael Winter 1996] A. J. McMichael, “How HIV fools the immune system”, *MRC News* (Winter 1996).
- [Mohri et al. 1998] H. Mohri, S. Bonhoeffer, S. Monard, A. S. Perelson, and D. D. Ho, “Rapid turnover of T lymphocytes in SIV-infected rhesus macaques”, *Science* **279**:5354 (1998), 1223–1227.
- [Murray and Perelson 2005] J. M. Murray and A. S. Perelson, “Human immunodeficiency virus: quasi-species and drug resistance”, *Multiscale Model. Simul.* **3**:2 (2005), 300–311. MR 2122990 Zbl 1068.92027
- [NHS 2008] National Health Service, “HIV and AIDS”, 2008, <http://www.nhs.uk/Conditions/HIV>.
- [Nowak et al. 1997] M. A. Nowak, A. L. Lloyd, G. M. Vasquez, T. A. Wiltout, L. M. Wahl, N. Bischofberger, J. Williams, A. Kinter, A. S. Fauci, V. M. Hirsch, and J. D. Lifson, “Viral dynamics of primary viremia and antiretroviral therapy in simian immunodeficiency virus infection”, *J. Virol.* **71**:10 (1997), 7518–7525.
- [Perelson and Nelson 1999] A. S. Perelson and P. W. Nelson, “Mathematical analysis of HIV-1 dynamics in vivo”, *SIAM Rev.* **41**:1 (1999), 3–44. MR 1669741 Zbl 1078.92502
- [Perelson et al. 1993] A. S. Perelson, D. E. Kirschner, and R. De Boer, “Dynamics of HIV infection of CD4+ T cells”, *Math. Biosci.* **114**:1 (1993), 81–125. Zbl 0796.92016
- [Rapin et al. 2006] N. Rapin, C. Kesmir, S. Frankild, M. Nielsen, C. Lundegaard, S. Brunak, and O. Lund, “Modelling the human immune system by combining bioinformatics and systems biology approaches”, *J. Biol. Phys.* **32**:3–4 (2006), 335–353.

- [Ribeiro et al. 1998] R. M. Ribeiro, S. Bonhoeffer, and M. A. Nowak, “The frequency of resistant mutant virus before antiviral therapy”, *AIDS* **12**:5 (1998), 461–465.
- [Rong et al. 2007a] L. Rong, Z. Feng, and A. S. Perelson, “Emergence of HIV-1 drug resistance during antiretroviral treatment”, *Bull. Math. Biol.* **69**:6 (2007), 2027–2060. MR 2008e:92022 Zbl 1298.92053
- [Rong et al. 2007b] L. Rong, M. A. Gilchrist, Z. Feng, and A. S. Perelson, “Modeling within-host HIV-1 dynamics and the evolution of drug resistance: trade-offs between viral enzyme function and drug susceptibility”, *J. Theor. Biol.* **247**:4 (2007), 804–818. MR 2009m:92133
- [Sharomi and Gumel 2008] O. Sharomi and A. B. Gumel, “Dynamical analysis of a multi-strain model of HIV in the presence of anti-retroviral drugs”, *J. Biol. Dyn.* **2**:3 (2008), 323–345. MR 2009g:92129 Zbl 1154.92033
- [Shiri et al. 2005] T. Shiri, W. Garira, and S. D. Musekwa, “A two-strain HIV-1 mathematical model to assess the effects of chemotherapy on disease parameters”, *Math. Biosci. Eng.* **2**:4 (2005), 811–832. MR 2170427 Zbl 1097.92031
- [Smith and Wahl 2005] R. J. Smith and L. M. Wahl, “Drug resistance in an immunological model of HIV-1 infection with impulsive drug effects”, *Bull. Math. Biol.* **67** (2005), 783–813. MR 2006k:34017
- [Stafford et al. 2000] M. A. Stafford, L. Corey, Y. Cao, E. S. Daar, D. D. Ho, and A. S. Perelson, “Modeling plasma virus concentration during primary HIV infection”, *J. Theor. Biol.* **203**:3 (2000), 285–301.
- [Tarfulea 2011a] N. E. Tarfulea, “A mathematical model for HIV treatment with time-varying antiretroviral therapy”, *Int. J. Comput. Math.* **88**:15 (2011), 3217–3235. MR 2834516 Zbl 1237.92034
- [Tarfulea 2011b] N. E. Tarfulea, “A mathematical model for the CTL effect on the drug resistance during antiretroviral treatment of HIV infection”, IMA Preprint Series #2377, Institute for Mathematics and its Applications, Minneapolis, MN, August 2011, <http://www.ima.umn.edu/preprints/pp2011/2377.pdf>.
- [Tarfulea et al. 2011] N. E. Tarfulea, A. Blink, E. Nelson, and D. Turpin, Jr., “A CTL-inclusive mathematical model for antiretroviral treatment of HIV infection”, *Int. J. Biomath.* **4**:1 (2011), 1–22. MR 2012c:92088
- [Wahl and Nowak 2000] L. M. Wahl and M. A. Nowak, “Adherence and drug resistance: predictions for therapy outcome”, *Proc. R. Soc. Lond. B* **267**:1445 (2000), 835–843.
- [Wilson et al. 2000] J. D. K. Wilson, G. S. Ogg, R. L. Allen, C. Davis, S. Shaunak, J. Downie, W. Dyer, C. Workman, J. S. Sullivan, A. J. McMichael, and S. L. Rowland-Jones, “Direct visualization of HIV-1-specific cytotoxic T lymphocytes during primary infection”, *AIDS* **14**:3 (2000), 225–233.

Received: 2011-07-06

Revised: 2013-08-08

Accepted: 2014-05-31

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Involve (ISSN 1944-4184 electronic, 1944-4176 printed) at Mathematical Sciences Publishers, 798 Evans Hall #3840, c/o University of California, Berkeley, CA 94720-3840, is published continuously online. Periodical rate postage paid at Berkeley, CA 94704, and additional mailing offices.

Involve peer review and production are managed by EditFLOW<sup>®</sup> from Mathematical Sciences Publishers.

PUBLISHED BY

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2015

vol. 8

no. 3

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