The Effects of Cycling on Drug Resistance HIV

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Abstract

Zidovudine and Didanosine are administered in cycles as a part of an HIV drug therapy. Both are Reverse Transcriptase Inhibitors (RTIs) that is, they inhibit the replication of the virus in the infected $CD4^+$ T-cells. A mathematical model is formulated that incorporates four types of viruses: wild, resistant to Zidovudine, resistant to Didanosine and resistant to both. The lower bounds for drug efficacies were found by calculating the basic reproductive number assuming constant efficacies. A systematic study of drug therapy schemes via numerical simulations with emphasis on the dynamics of viral count as a function of drug resistance is performed. The results show that although there is no optimal schedule for switching of drugs, it is generally better to switch them within shorter time periods.

1 Introduction

Over 70 million people are infected with HIV globally with a third of them expected to die from AIDS [10]. Although there is no cure for this disease, it has been observed that single-dose and combinations of antiretroviral drugs can delay the progression of HIV. The major problem associated with the control of HIV comes from the immune system's inability to control the amount and variability of viruses via mutations that are reproduced over the life span of the infected individuals.

There are four classes of antiretroviral drugs available for treatment of HIV infected individuals: non-nucleoside reverse transcriptase inhibitors (NNRTI), nucleoside/nucleotide reverse transcriptase inhibitors (NRTI), protease inhibitors (PI), and entry/fusion inhibitors (EI). The Highly Active Antiretroviral Therapy (HAART) has been shown to temporarily suppress viral loads in infected individuals to a very low level that cannot be detected by assays and tremendously increased the uninfected T-cell counts in the body [2]. Despite the variety of drug therapies, they still fail to contain the virus completely in part because of patient's non adherence to prescribed dosages, severe side effects, and development of drug resistance [1].

The evolution of drug resistant HIV is of major concern. Many mathematical models have been introduced to study the effect of drug resistance in the immune system [2, 3, 5, 8, 9, 10, 12]. Models that focus on the impact or timing of initiating an antiretroviral drug therapy with the goal of maximizing treatment effect have been studied by [2]. There Jeffrey explores the use of antiretroviral drugs as control inputs and the results show that the treatment steady states are dependent upon drug efficacy and model parameters, but are independent of when antiretroviral therapy is initiated. This idea is essential because effective drug therapy can maintain T-cell count, suppress viral level, and prolong the transition from HIV to AIDS.

With all the complications in HIV, many researchers study different methods for optimizing the control of the spread of disease throughout the immune system. There has been continuous work in the study of epidemiology and mathematic modelling in HIV for optimal control, for example [4]. The results of this paper give an insight to how important it is for drug therapy adherence. Impulsive differential equations (combinations of systems of ordinary differential equations and difference equations) have been used to examine the dynamics of drug resistance with respect to non adherence to drug protocols (failing to take prescribed dosages) [12]. Between impulses, the system is continuous and at impulse points there is an instantaneous rate of change in one or all the variables. The model shows that drug re-

sistance might appear in both intermediate and high drug concentrations whereas at low drug levels resistance would not emerge. The emergence of drug resistance during therapy is modelled in [9]. The results found in this paper show that drug resistance is more likely to emerge in the presence of antiretroviral treatment if the basic reproductive ratios of the wild-type strain and the mutant strain are very close. In addition, the author conclude that perfect adherence to regimen protocols will suppress the viral load of the drug sensitive virus while drug resistant strains develop slowly.

In this paper, we administer two RTI, and assume 100 percent adherence. We do not administer the drugs in combination, but switch between them. By computing the basic reproductive number we derive a lower bound for drug efficacy that will result in a disease free equilibrium. Numerical simulations of the model are used to evaluate how well treatment schedules suppress the viral load below 50 cells / mL.

2 Model Description

In order to study the dynamics of drug resistance within a population of individuals undergoing multi-drug treatment, we introduce a simple model that incorporates two forms of treatment.

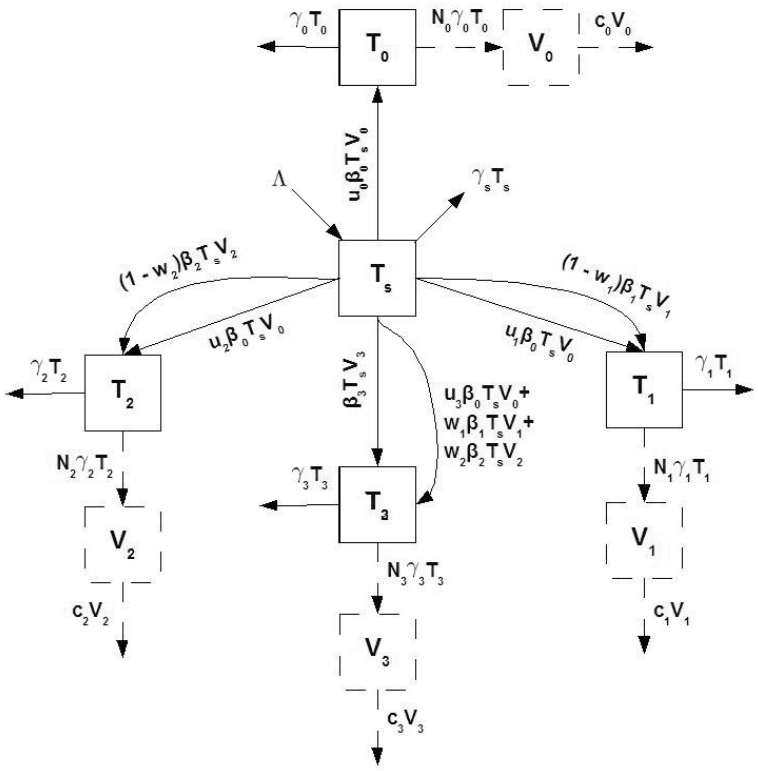


Figure 1: A wild strain of HIV and three different mutant virus strands are considered in a model describing the effects of drug therapy. The variable description of the compartment model are in Table 1.

Model Equations

$$
\begin{aligned}
\frac{dT_s}{dt} &= \Lambda - \beta_0 T_s V_0 - \beta_1 T_s V_1 - \beta_2 T_s V_2 - \beta_3 T_s V_3 - \gamma_s T_s \\
\frac{dT_0}{dt} &= u_0 \beta_0 T_s V_0 - \gamma_0 T_0 \\
\frac{dT_1}{dt} &= u_1 \beta_0 T_s V_0 + (1 - w_1)\beta_1 T_s V_1 - \gamma_1 T_1 \\
\frac{dT_2}{dt} &= u_2 \beta_0 T_s V_0 + (1 - w_2)\beta_2 T_s V_2 - \gamma_2 T_2 \\
\frac{dT_3}{dt} &= u_3 \beta_0 T_s V_0 + w_1 \beta_1 T_s V_1 + w_2 \beta_2 T_s V_2 + \beta_3 T_s V_3 - \gamma_3 T_3 \\
\frac{dV_0}{dt} &= N_0 \gamma_0 T_0 - c_0 V_0 \\
\frac{dV_1}{dt} &= N_1 \gamma_1 T_1 - c_1 V_1 \\
\frac{dV_2}{dt} &= N_2 \gamma_2 T_2 - c_2 V_2 \\
\frac{dV_3}{dt} &= N_3 \gamma_3 T_3 - c_3 V_3
\end{aligned}
\tag{1}
$$

Table 1: Definition of Variables

Variables	Description
T_s	the concentration of non-infected $CD4^+$ T-cells.
T_0	concentration of $CD4^+$ T-cells infected with the wild virus.
T_1	concentration of $CD4^+$ T-cells infected with the a mutant virus resistant to Zidovudine.
T_2	concentration of $CD4^+$ T-cells infected with the a mutant virus resistant to Didanosine.
T_3	concentration of $CD4^+$ T-cells infected with the a mutant virus resistant both to Zidovudine and Didanosine.
V_0	concentration of wild HIV type.
V_1	the concentration of the mutant HIV that is resistant to Zidovudine.
V_2	concentration of the mutant HIV that is resistant to Didanosine.
V_3	concentration of the mutant HIV that is resistant to Zidovudine and Didanosine.

Table 2: Parameter List

Parameters	Description	Values	references
c_0	per capita clearance rate of wild virus	23 day^{-1}	[9]
c_1	per capita clearance rate of virus resistant to Zidovudine	23 day^{-1}	[9]
c_2	per capita clearance rate of virus resistant to Didanosine	23 day^{-1}	[9]
c_3	per capita clearance rate of virus resistant to both drugs	23 day^{-1}	[9]
γ_s	per capita death rate of un-infected T-cell	0.01 day^{-1}	[9]
γ_0	per capita death rate of T-cell infected with wild virus	1 day^{-1}	[9]
γ_1	per capita death rate of T-cell infected with virus resistant to Zidovudine	1 day^{-1}	[9]
γ_2	per capita death rate of T-cell infected with virus resistant to Didanosine	1 day^{-1}	[9]
γ_3	per capita death rate of T-cell infected with virus resistant to both drugs	1 day^{-1}	[9]
k_0	infection coefficient of $CD4^+$ T cells by wild virus	2.4 x 10^{-8} mL (day^{-1})	[9]
k_1	infection coefficient of $CD4^+$ T cells by virus resistant to Zidovudine	2.0 x 10^{-8} mL (day^{-1})	[9]
k_2	infection coefficient of $CD4^+$ T cells by virus resistant to Didanosine	2.0 x 10^{-8} mL (day^{-1})	[9]
k_3	infection coefficient of $CD4^+$ T cells by virus resistant to both drugs	1.67 x 10^{-8} mL (day^{-1})	approx.
Λ	net inflow constant of T-cells from proliferation and other sources	10^4 day^{-1}	[2]
N_0	average number of virions produced per T cell infected with wild virus	3000	[9]
N_1	average number of virions produced per T cell infected with virus resistant to Zidovudine	2000	[9]
N_2	average number of virions produced per T cell infected with virus resistant to Didanosine	2000	[9]
N_3	average number of virions produced per T cell infected with virus resistant to both drugs	1333.3	approx.
u_0	proportion of wild virus that remain nonresistant to to both drugs	$1-(u_1+u_2+u_3)$	—
u_1	proportion of wild virus that becomes resistant to Zidovudine during replication	3 x 10^{-5}	[7]
u_2	proportion of wild virus that becomes resistant to Didanosine during replication	3 x 10^{-5}	[7]
u_3	proportion of wild virus that becomes resistant to both drugs during replication	3 x 10^{-5}	[7]
w_1	proportion of virus resistant to Zidovudine that becomes resistant to both drugs during replication	3 x 10^{-5}	[7]
w_2	proportion of virus resistant to Didanosine that becomes resistant to both drugs during replication	3 x 10^{-5}	[7]

Susceptible T-cells have a constant input of (Λ) and death rate (γ_s). From the interaction of susceptible T-cells and each class of free virus, V_i, the T-cells become infected at a rate β_i that will enter infected classes T_i. It is assumed that these infected T-cells die at the per capita rate γ_i.

$$\beta_i = \ k_i(1-\epsilon_i) \qquad for\ i = 0, 1, 2, 3, \tag{2}$$

where k_i are the maximum rate of infection of susceptible T-cells infected by V_i. The variable ϵ_i represents the efficacy of Zidovudine or Didanosine when these drugs are applied.

After a cell is infected, it begins to produce a large number of viruses until the cell ruptures and releases these, N_i, new viruses. Virus are cleared from the body at the rate c_i due to the efficacy of the drug therapy and other factors.

The formula used for drug efficacy is based on the intake of drug into the cell because it is necessary to take into account the absorbtion time of medicine [2]. Initially, there is an increase of efficacy because the cell is absorbing the drug and after the efficacy reaches its peak, the drug decays so there is a decrease in the efficacy [2]. The formula is given by

$$\epsilon(t) = \begin{cases} \eta_v + \eta_w(\frac{1}{2} - e^{\frac{-(t-t_1)}{\tau_r}}), & t_1 < t < t_{max}, \\ \eta_v + \eta_w(e^{\frac{-(t-t_{max})}{\tau_d}} - \frac{1}{2}), & t_{max} < t < t_2, \end{cases}$$

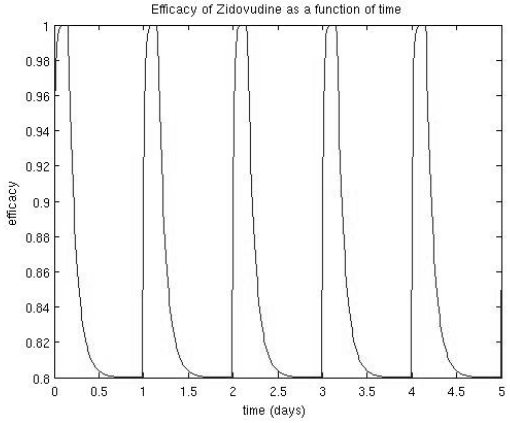
η_v is the median efficacy value, η_w is the range of efficacy values, τ_r is the rise constant, τ_d is the decay constant, and t_{max} is the time until maximum efficacy is reached. t_1 is the start time of dosage, t_2 is the end time of dosage, the values for these parameters can be found in table 3.

Let u_0, u_1, u_2, and u_3 to be the probability of T-cells infected with the wild virus that will remain unresistant to both drugs, build resistance to Zidovudine, build resistance to Didanosine, and build resistance to both drugs, respectively. Since the sum of these probabilities is 1, $u_0 = 1 - u_1 - u_2 - u_3$. Assume w_1 and w_2 are probabilities of T-cells infected with V_1 and V_2 that build resistance to both drugs respectively. Hence, the terms $(1-w_1)$ and $(1-w_2)$ denote the probability that the T-cells which are infected by V_1 and V_2 do not mutate.

Table 3: Parameters of the efficacy function

Parameters	Description	Values	references
η_v	median efficacy value	see table 4	see table 4
η_w	difference between the upper and lower efficacy bounds	.2	approx.
τ_r	rise time constant after each dose	0.0144 days	approx.
τ_d	decay time constant after each dose	0.0866 days	[6]
t_{max}	time it takes for the efficacy to reach its maximum	0.167 days	[2]

Figure 2 shows how the efficacy varies over time for a period of five days.



Since there are four viruses and two drugs, there are eight possible values for η_v depending on which drug is being administered and which virus it is affecting. The values are shown in Table 4.

Table 4: Efficacy values

V_i	efficacy of Zidovudine	reference	efficacy of Didanosine	reference
V_0	0.9	[11]	0.85	approx.
V_1	0.38	approx.	0.85	approx.
V_2	0.9	[11]	0.4	approx.
V_3	0.38	approx.	0.4	approx.

3 Mathematical Analysis

For the mathematical analysis, both drugs are administered simultaneously for a combined efficacy. Our system has a unique disease free equilibrium (DFE). The DFE is the state at which no virus or infected cells exist in the body and is denoted by

$$E_0 = (\tfrac{\Lambda}{\gamma_s}, 0, 0, 0, 0, 0, 0, 0, 0).$$

Note, that $T_s = \frac{\Lambda}{\gamma_s}$ is constant. To find the basic reproductive number we use the next generator operator method (see appendix for derivation). $\mathcal{R}_0$ is given by:

$$R_0 = max(r_0, r_1, r_2, r_3),$$

where

$$\begin{aligned} r_0 &= \frac{\Lambda}{\gamma_s} N_0 \beta_0 \left(1 - u_3 - u_1 - u_2\right) \frac{1}{c_0}, \\ r_1 &= \frac{\Lambda}{\gamma_s} N_1 \beta_1 \left(1 - w_1\right) \frac{1}{c_1}, \\ r_2 &= \frac{\Lambda}{\gamma_s} N_2 \beta_2 \left(1 - w_2\right) \frac{1}{c_2}, \\ r_3 &= \frac{\Lambda}{\gamma_s} N_3 \beta_3 \frac{1}{c_3} \end{aligned} \tag{3}$$

The biological interpretation of $\mathcal{R}_0$ is the average number of infected T-cells generated by introducing one infected T-cell in an otherwise susceptible environment during the entire infectious period.

r_0 gives the reproductive number for T-cells infected by wild virus. In other words, it is the average number of T-cells infected with wild strain generated by one T-cell infected with wild strain. Similarly, r_1, r_2, r_3 are the reproductive numbers associated with infected T-cells that are resistant to Zidovudine, Didanosine and both drugs respectively.

If $\mathcal{R}_0 < 1$ then the DFE is locally asymptotically stable, meaning that the virus is eradicated. Using this criteria and equation (2), we derive the following expressions for the lower bounds of the drug efficacies.

$$\begin{aligned}
\epsilon_0 &> \frac{-\gamma_s c_0}{N_0 k_0 \Lambda (1 - u_1 - u_2 - u_3)} + 1 \\
\epsilon_1 &> \frac{-\gamma_s c_1}{N_1 k_1 \Lambda (1 - w_1)} + 1 \\
\epsilon_2 &> \frac{-\gamma_s c_2}{N_2 k_2 \Lambda (1 - w_2)} + 1 \\
\epsilon_3 &> \frac{-\gamma_s c_3}{N_3 k_3 \Lambda} + 1.
\end{aligned}$$

Figure 2 shows that the virus populations' solutions approach DFE when $\mathcal{R}_0 < 1$. When $\mathcal{R}_0 > 1$ they approach another equilibrium point as shown in Figure 3. The parameter values used are from Table 2 except for ϵ_i which are varied.

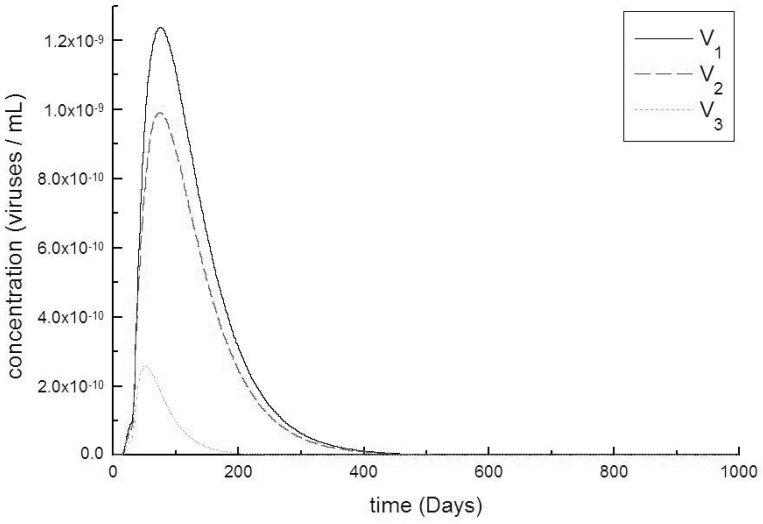


Figure 2: Numerical simulation using $\epsilon_0 = 0.6905$, $\epsilon_1 = 0.4349$, $\epsilon_2 = 0.4349$ and $\epsilon_3 = 0.001$. In this case $\mathcal{R}_0 < 1$.

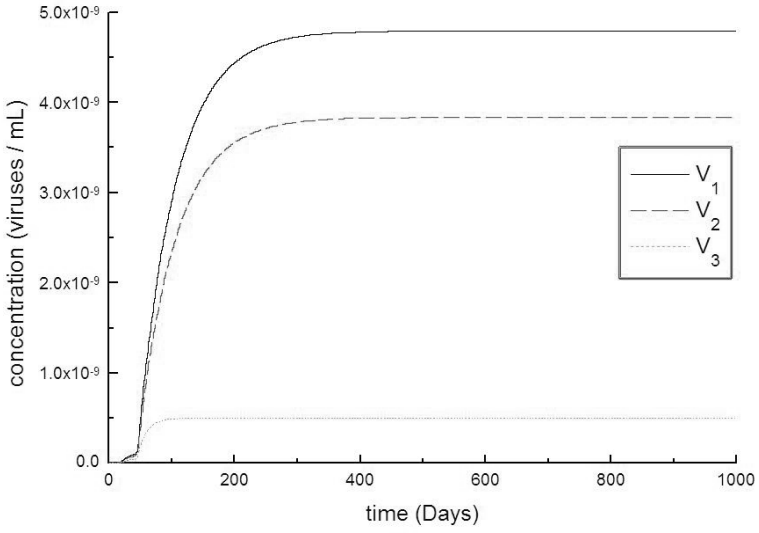


Figure 3: Numerical simulation using $\epsilon_0 = .6805$, $\epsilon_1 = 0.4349$, $\epsilon_2 = 0.4349$ and $\epsilon_3 = 0.001$. In this case $\mathcal{R}_0 > 1$.

4 Numerical Simulation

The main focus of the numerical simulations is to measure the effectiveness of drug cycling. Single simulations are run to study the dynamics of the concentrations of the virus. Multiple runs are used to vary the time between switching drug therapies. The multiple simulations are run over approximately a ten year span because this is the average time it takes an HIV infected patient to develop AIDS [6]. When running these simulations we consider schedules for switching drugs that suppress virus concentration below 50 viruses per mL, the level that physicians consider to be successful [13]. The multiple simulations are run for all possible combinations of treatment periods ranging from 10 days to 200 days in increments of 10 days. We keep a record of how many plots meet these criteria and record the results in Figure 4. We also performed a sensitivity analysis with respect to the parameters N_i, c_i, k_i, and γ_i.

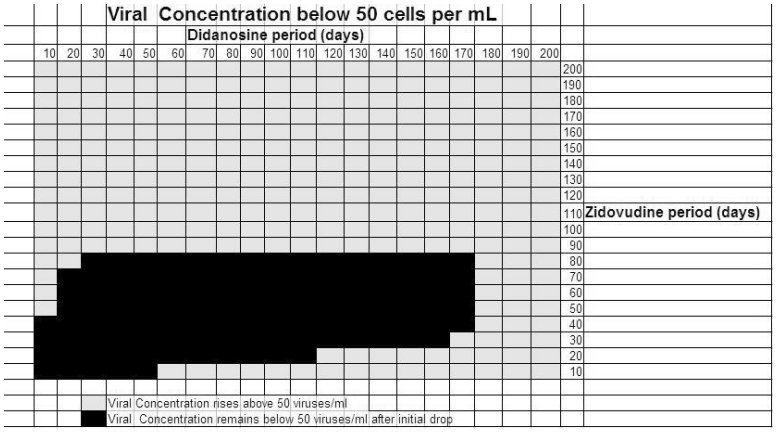


Figure 4: Using the parameters from Table 2 with the initial conditions $T_s = 10^6$ cells/ml and $V_0 = 500$ viruses/ml we run multiple simulations. The times for the treatment periods are given on the sides of the grid.

4.1 Drug treatment time

One point that arises from the idea of switching between two drugs is the optimal time to switch. One could choose among any possible combination of treatment period. Figure 4 shows that for the initial parameters, cycling quickly keeps viral concentration lower than cycling slowly. The virus initially has a concentration of 500 viruses/ml that quickly drop below 50 viruses/ml due to treatment. After this point, we consider a successful treatment one that maintains the suppression of the virus below 50 viruses/ml. If a drug is given for too much time, the virus concentration that is resistant to the drug will be able to increase above 50 viruses/ml. Thus, in general, short time spans are more successful at keeping virus concentration low.

However, as Figure 4 shows, decreasing the period for one drug is not always advantageous in keeping virus concentrations low. For instance, when Zidovudine is administered for 50 days, changing the treatment time for Didanosine from 20 days to 10 days results in a higher viral concentration. This occurs because the separation between the periods of the two drugs is very large. Thus, one can conclude that switching very quickly for both drugs would be the best way to keep viral concentration low.

Unfortunately, there are some exceptions for this rule. Figure 5 shows

the result of increasing the burst size and the infection rate of V_3. Even though both rise above 50 viruses/ml, it takes more time for the second plot to reach that mark. Thus, the periods used in the second plot keep virus concentration low for a longer period of time. Therefore, cycling very quickly is not always the most successful way to keep virus concentration low.

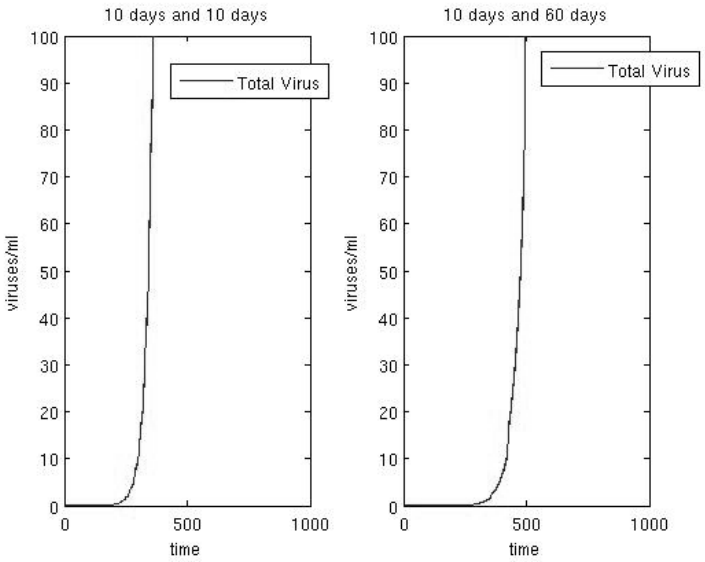


Figure 5: Changing $k_3 = 1.67\text{x}10^{-8}$ to $k_3 = 1.9\text{x}10^{-8}$ and $N_3 = 1333.3$ to $N_3 = 1900$ gives us these figures. The first plot is when Zidovudine is given for 10 days and Didanosine is given for 10 days. The second plot is when Zidovudine is given for 10 days and Didanosine is given for 60 days. Notice that the first plot reaches 50 viruses/ml at around 400 days and the second plot reaches 50 viruses/ml at around 500 days.

4.2 Sensitivity Analysis

We determine the sensitivity of a parameter according to how significantly the dynamics of the system change when the parameter is changed. A sensitivity analysis is performed by varying parameters values for infection rate (k_i), burst size (N_i), clearance rate (c_i), and rate for infected T-cells (γ_i). One can conclude that increasing infection rate, burst size, and T-cell death

rate and decreasing clearance rate produces a higher virus concentration. Thus, to test the sensitivity each infection rate, burst size, and T-cell death rate are increased by 10 percent one at a time and each clearance rate is decreased by 10 percent. The effects of increasing k_0 on the dynamics of virus concentration are shown in Figure 6.

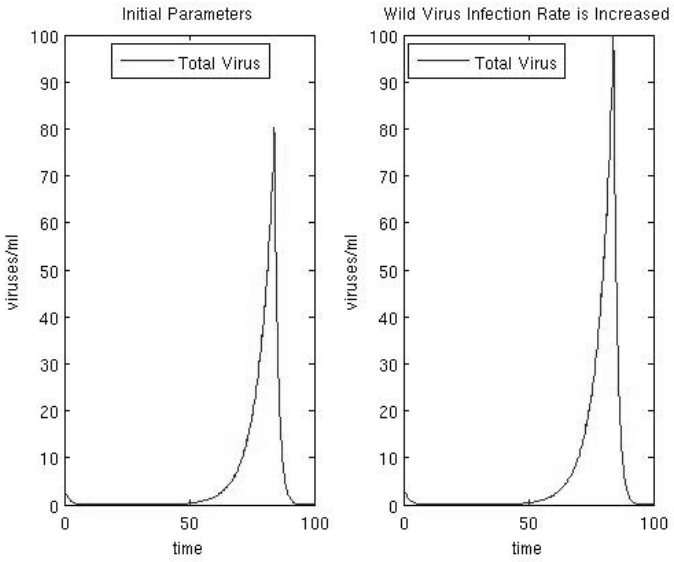


Figure 6: The first plot is for the parameters in Table 2. The second plot is when $k_0 = 2.4\text{x}10^{-8}$ is changed to $k_0 = 2.64\text{x}10^{-8}$.

To measure the sensitivity we measure the time it takes to reach 50 viruses/ml and stay below that concentration. Table 5 shows these times for changing each of the parameters by 10 percent when Zidovudine is administered first and when Didanosine is administered first. From the table, it is evident that infection rate, burst size, and clearance rate are more sensitive than infected T-cell death rate. In addition, when Zidovudine is administered first the parameters associated with the virus resistant to Zidovudine (V_1) are more sensitive and when Didanosine is administered first the parameters associated with the virus resistant to Didanosine (V_2) are more sensitive. The most sensitive parameters are average amount of viral production of virus resistant to Zidovudine (N_1) and the clearance rate of the virus resistant to Didanosine c_2 depending on which drug is given first.

Another way to measure the sensitivity is to examine the region of effective control while varying the times that each drug is administered. k_0 is increased by 10 percent and the effects are shown in Figure 7. Notice that there are less treatment times that maintain virus concentration below 50 viruses/ml. The number of treatment times that maintain low levels of virus concentration are shown in Table 6. The fewer number of treatment times that are effective implies that the parameter is more sensitive. Thus, the parameters associated with V_1 are the most sensitive. From this analysis, k_1, N_1, N_2, and c_1 are the most sensitive parameters.

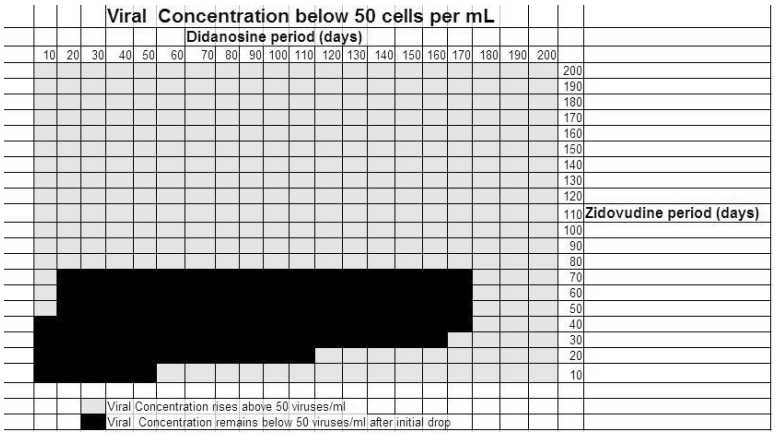


Figure 7: This region of effective control differs from Figure 4 because $k_0 = 2.4\text{x}10^{-8}$ is changed to $k_0 = 2.64$ x 10^{-8}.

Table 5: In this table we consider the time it takes the total virus to decrease and remain below 50 virus/mL. In each row, we vary the indicated parameter to the value that is specified.

Parameter Values	Zidovudine given 1^{st}	Didanosine given 1^{st}
Parameters values in Table 2	84.91	0.11
$k_0 = 2.64$ x 10^{-8}	85.12	0.11 days
$k_1 = 2.2$ x $10^{-}8$	99.29	0.11 days
$k_2 = 2.2$ x 10^{-8}	84.81	102.55 days
$k_3 = 1.83$ x 10^{-8}	84.9	0.11 days
$c_0 = 20.91$	84.94	0.12 days
$c_1 = 20.91$	99.63	0.11 days
$c_2 = 20.91$	84.81	102.66 days
$c_3 = 20.91$	84.9	0.11 days
$N_0 = 3300$	84.93	0.14 days
$N_1 = 2200$	99.46	0.11 days
$N_2 = 2200$	84.78	102.75 days
$N_3 = 1466.7$	84.79	0.11 days
$\gamma_0 = 1.1$	84.86	0.11 days
$\gamma_1 = 1.1$	86.74	0.11 days
$\gamma_2 = 1.1$	84.76	90.82 days
$\gamma_3 = 1.1$	84.89	0.11 days

Table 6: This table shows the number of times that virus concentration is maintained at 50 virus/mL with the specified Zidovudine and Didanosine cycle time. The parameters vary in the same manner as Table 5.

Parameter Values	# of boxes filled on the grid
initial Parameters	113
$k_0 = 2.64$ x 10^{-8}	98
$k_1 = 2.2$ x $10^{-}8$	47
$k_2 = 2.2$ x 10^{-8}	57
$k_3 = 1.83$ x 10^{-8}	113
$c_0 = 20.91$	113
$c_1 = 20.91$	47
$c_2 = 20.91$	57
$c_3 = 20.91$	113
$N_0 = 3300$	113
$N_1 = 2200$	47
$N_2 = 2200$	47
$N_3 = 1466.7$	113
$\gamma_0 = 1.1$	113
$\gamma_1 = 1.1$	113
$\gamma_2 = 1.1$	103
$\gamma_3 = 1.1$	113

4.3 Conclusions

First we assumed a constant efficacy for each virus. This gave critical values for ϵ_i that would produce a DFE. If RTI treatment remained this effective, the virus will eventually be eradicated resulting in a cure for HIV.

However, the efficacies are not constant because of mutations that cause resistance to the drugs. Thus, we had to complicate the analysis by making the efficacies change with time. After cycling and non-constant efficacies were added to the model, numerical analysis had to be used analyze the dynamics of the system. A combination of single runs as well as multiple runs were used to analyze the dynamics of this more complicated model.

Using numerical simulations we study the effects of changing the amount of time that each drug is given. The results show that in general cycling in shorter periods of time keeps viral concentration lower than cycling in longer periods of time. In addition, choosing two periods that are far apart does not allow enough time for one of the viruses to decrease resulting in a higher virus concentration.

When the infection rate and burst size for V_3 are increased Figure 5 shows a situation when quickly cycling between drugs is not the optimal treatment for keeping virus concentration low. When infection rate and burst size for V_3 are increased, the lower bound for ϵ_3 becomes high enough to be able to compete against V_1 and V_2. When this occurs, using Didanosine lowers the rate of growth more since it has a higher efficacy for the V_3. Thus, a longer period for Didanosine will keep virus concentration below 50 viruses/ml longer.

Furthermore, a sensitivity analysis is run to find which parameters should be changed in order to lower virus concentration to a greater degree. The results show that infection rate, burst size, and clearance rate are more sensitive than infected T-cell death rate. Also parameters that are associated with V_1 were more sensitive than parameters that were associated with the other viruses. Finally, it seemed that N_1 was the most sensitive parameter. This information is important in identifying ways to optimize treatment using this drug switching method. Since infection rate, burst size, and clearance rate were the most sensitive parameters, treatments that change these parameters would be the most effective. In addition, since N_1 is the most sensitive parameter, adding a protease inhibitor, which lowers the number of infectious viruses that are produced [2], could be very effective for this treatment method.

5 Future Works

Further study is required to fully understand the effects and benefits of antiretroviral drug therapy on the progression of HIV. To better understand the immune response to HIV and drug therapy, we can alter the model by introducing a class of CD8+ T-cells. This CD8+ T-cell compartment will capture the effects of how CD8 cells help kill infected T-cells. To this end, we could also model the input of drugs that helps boost the strength of these cells in the body. In this model, we consider the time switching of drug therapy. However, the model does not account for the time delays associated with the immune response and treatment of the wild strain of HIV-1. Modeling this time delay will exhibit the actual development of immune responses caused by infection and absorption of treatments. Another idea we could explore in this paper is optimal drug therapies and strategies based on variable switching time parameters that could further delay the progression of HIV.

6 Acknowledgments

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A Appendix Next Generator Operator Method

Let $\dot{\vec{x}} = \vec{F} - \vec{V}$, where $\dot{\vec{x}}$ is define as a vector whose elements are the differential equation of the model, $\vec{F}$ represents rate of appearance of new infections in the compartment of infected T-cells and $\vec{V}$ represents the rate of interaction between viruses and T-cells in each compartment. $\vec{F}$ and $\vec{V}$ are denoted as follows.

$$\vec{F} = \begin{bmatrix} 0 \\ (1-u_1-u_2-u_3)\,\beta_0 T_s V_0 \\ u_1\beta_0 T_s V_0 + (1-w_1)\,\beta_1 T_s V_1 \\ u_2\beta_0 T_s V_0 + (1-w_2)\,\beta_2 T_s V_2 \\ u_3\beta_0 T_s V_0 + w_1\beta_1 T_s V_1 + w_2\beta_2 T_s V_2 + \beta_3 T_s V_3 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix},$$

$$\vec{V} = \begin{bmatrix} -\Lambda + \beta_0 T_s V_0 + \beta_1 T_s V_1 + \beta_2 T_s V_2 + \beta_3 T_s V_3 + \gamma_s T_s \\ \gamma_0 T_0 \\ \gamma_1 T_1 \\ \gamma_2 T_2 \\ \gamma_3 T_3 \\ -N_0\gamma_0 T_0 + c_0 V_0 \\ -N_1\gamma_1 T_1 + c_1 V_1 \\ -N_2\gamma_2 T_2 + c_2 V_2 \\ -N_3\gamma_3 T_3 + c_3 V_3 \end{bmatrix}$$

The Jacobian matrix of $\vec{F}$ and $\vec{V}$ vectors are:

$$J_{\vec{F}} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ (1-u_1-u_2-u_3)\,\beta_0 V_0 & 0 & 0 & 0 & 0 & (1-u_1-u_2-u_3)\,\beta_0 T_s & 0 & 0 & 0 \\ u_1\beta_0 V_0 + (1-w_1)\,\beta_1 V_1 & 0 & 0 & 0 & 0 & u_1\beta_0 T_s & (1-w_1)\,\beta_1 T_s & 0 & 0 \\ u_2\beta_0 V_0 + (1-w_2)\,\beta_2 V_2 & 0 & 0 & 0 & 0 & u_2\beta_0 T_s & 0 & (1-w_2)\,\beta_2 T_s & 0 \\ u_3\beta_0 V_0 + w_1\beta_1 V_1 + w_2\beta_2 V_2 + \beta_3 V_3 & 0 & 0 & 0 & 0 & u_3\beta_0 T_s & w_1\beta_1 T_s & w_2\beta_2 T_s & \beta_3 T_s \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

$$J_{\vec{V}} = \begin{bmatrix} \beta_0 V_0 + \beta_1 V_1 + \beta_2 V_2 + \beta_3 V_3 + \gamma_s & 0 & 0 & 0 & 0 & \beta_0 T_s & \beta_1 T_s & \beta_2 T_s & \beta_3 T_s \\ 0 & \gamma_0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \gamma_1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \gamma_2 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \gamma_3 & 0 & 0 & 0 & 0 \\ 0 & -N_0\gamma_0 & 0 & 0 & 0 & c_0 & 0 & 0 & 0 \\ 0 & 0 & -N_1\gamma_1 & 0 & 0 & 0 & c_1 & 0 & 0 \\ 0 & 0 & 0 & -N_2\gamma_2 & 0 & 0 & 0 & c_2 & 0 \\ 0 & 0 & 0 & 0 & -N_3\gamma_3 & 0 & 0 & 0 & c_3 \end{bmatrix}$$

The Jacobian matrices $J_{\vec{F}}$ and $J_{\vec{V}}$ evaluated at the DFE are:

$$J_{\vec{F}}(DFE) = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \frac{(1-u_1-u_2-u_3)\beta_0\Lambda}{\gamma_s} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \frac{u_1\beta_0\Lambda}{\gamma_s} & \frac{(1-w_1)\beta_1\Lambda}{\gamma_s} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \frac{u_2\beta_0\Lambda}{\gamma_s} & 0 & \frac{(1-w_2)\beta_2\Lambda}{\gamma_s} & 0 \\ 0 & 0 & 0 & 0 & 0 & \frac{u_3\beta_0\Lambda}{\gamma_s} & \frac{w_1\beta_1\Lambda}{\gamma_s} & \frac{w_2\beta_2\Lambda}{\gamma_s} & \frac{\beta_3\Lambda}{\gamma_s} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

$$J_{\vec{V}}(DFE) = \begin{bmatrix} \gamma_s & 0 & 0 & 0 & 0 & \frac{\beta_0\Lambda}{\gamma_s} & \frac{\beta_1\Lambda}{\gamma_s} & \frac{\beta_2\Lambda}{\gamma_s} & \frac{\beta_3\Lambda}{\gamma_s} \\ 0 & \gamma_0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \gamma_1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \gamma_2 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \gamma_3 & 0 & 0 & 0 & 0 \\ 0 & -N_0\gamma_0 & 0 & 0 & 0 & c_0 & 0 & 0 & 0 \\ 0 & 0 & -N_1\gamma_1 & 0 & 0 & 0 & c_1 & 0 & 0 \\ 0 & 0 & 0 & -N_2\gamma_2 & 0 & 0 & 0 & c_2 & 0 \\ 0 & 0 & 0 & 0 & -N_3\gamma_3 & 0 & 0 & 0 & c_3 \end{bmatrix}$$

The inverse of the Jacobian of $J_{\vec{V}}(DFE)$ is:

$$J_{\vec{V}}^{-1}(DFE) = \begin{bmatrix} {\gamma_s}^{-1} & -\frac{N_0\beta_0\Lambda}{{\gamma_s}^2 c_0} & -\frac{N_1\beta_1\Lambda}{{\gamma_s}^2 c_1} & -\frac{N_2\beta_2\Lambda}{{\gamma_s}^2 c_2} & -\frac{N_3\beta_3\Lambda}{{\gamma_s}^2 c_3} & -\frac{\beta_0\Lambda}{{\gamma_s}^2 c_0} & -\frac{\beta_1\Lambda}{{\gamma_s}^2 c_1} & -\frac{\beta_2\Lambda}{{\gamma_s}^2 c_2} & -\frac{\beta_3\Lambda}{{\gamma_s}^2 c_3} \\ 0 & {\gamma_0}^{-1} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & {\gamma_1}^{-1} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & {\gamma_2}^{-1} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & {\gamma_3}^{-1} & 0 & 0 & 0 & 0 \\ 0 & \frac{N_0}{c_0} & 0 & 0 & 0 & {c_0}^{-1} & 0 & 0 & 0 \\ 0 & 0 & \frac{N_1}{c_1} & 0 & 0 & 0 & {c_1}^{-1} & 0 & 0 \\ 0 & 0 & 0 & \frac{N_2}{c_2} & 0 & 0 & 0 & {c_2}^{-1} & 0 \\ 0 & 0 & 0 & 0 & \frac{N_3}{c_3} & 0 & 0 & 0 & {c_3}^{-1} \end{bmatrix}$$

The Multiplication of $J_{\vec{F}}(DFE)$ and $J_{\vec{V}}^{-1}(DFE)$ is:

$$= \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \frac{(1-u_1-u_2-u_3)\beta_0\Lambda N_0}{\gamma_s c_0} & 0 & 0 & 0 & \frac{(1-u_1-u_2-u_3)\beta_0\Lambda}{\gamma_s c_0} & 0 & 0 & 0 \\ 0 & \frac{N_0\beta_0\Lambda u_1}{\gamma_s c_0} & \frac{(1-w_1)\beta_1\Lambda N_1}{\gamma_s c_1} & 0 & 0 & \frac{u_1\beta_0\Lambda}{\gamma_s c_0} & \frac{(1-w_1)\beta_1\Lambda}{\gamma_s c_1} & 0 & 0 \\ 0 & \frac{N_0\beta_0\Lambda u_2}{\gamma_s c_0} & 0 & \frac{(1-w_2)\beta_2\Lambda N_2}{\gamma_s c_2} & 0 & \frac{u_2\beta_0\Lambda}{\gamma_s c_0} & 0 & \frac{(1-w_2)\beta_2\Lambda}{\gamma_s c_2} & 0 \\ 0 & \frac{N_0\beta_0\Lambda u_3}{\gamma_s c_0} & \frac{w_1\beta_1\Lambda N_1}{\gamma_s c_1} & \frac{w_2\beta_2\Lambda N_2}{\gamma_s c_2} & \frac{\beta_3\Lambda N_3}{\gamma_s c_3} & \frac{u_3\beta_0\Lambda}{\gamma_s c_0} & \frac{w_1\beta_1\Lambda}{\gamma_s c_1} & \frac{w_2\beta_2\Lambda}{\gamma_s c_2} & \frac{\beta_3\Lambda}{\gamma_s c_3} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

The eigenvalues obtained from $J_{\vec{F}}(DFE)J_{\vec{V}}^{-1}(DFE)$ matrix are:

$$\begin{aligned} \lambda_6 &= \frac{\Lambda}{\gamma_s} N_0\beta_0 \left(1 - u_3 - u_1 - u_2\right) \frac{1}{c_0}, \\ \lambda_7 &= \frac{\Lambda}{\gamma_s} N_1\beta_1 \left(1 - w_1\right) \frac{1}{c_1}, \\ \lambda_8 &= \frac{\Lambda}{\gamma_s} N_2\beta_2 \left(1 - w_2\right) \frac{1}{c_2}, \\ \lambda_9 &= \frac{\Lambda}{\gamma_s} N_3\beta_3 \frac{1}{c_3}. \end{aligned} \tag{4}$$

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