The Effect of Immune Response and Combination Drug Treatment on the Progression of Multi-Strain HIV

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Abstract

Rapidly mutating HIV strains pose difficulties for effective therapy. By using a mathematical model, we explore the in-host progression of mutating HIV strains considering both the immune response of the host and a combination of antiviral drugs. The first drug inhibits the entry of the HIV virus into $CD4^+$ cells, while the second is a protease inhibitor. We conduct uncertainty and sensitivity analysis of the parameters in the effective reproductive number, R_0. Deterministic simulations are performed to illustrate the random behavior of the independent HIV strains on the progression and severity of the disease.

1 Introduction

At the end of 2004, joint effort of several HIV/AIDS global research organizations, estimated about 40 million people are living with HIV, and additional 25 million have died of AIDS [1]. While there is currently no cure for HIV/AIDS, antiretroviral (AVR) therapy slows the reproduction and progression of HIV prolonging the lives of those infected. Presently, there are four groups of AVR treatments: nucleoside/nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, and fusion or entry inhibitors [2]. In order to maximize the reduction of the viral load of severely infected individuals, determining what types of drug therapies to administer and when to administer them should be a top priority. Mathematical modeling allows for predictions to be made which can aid in these determinations.

A major obstacle an effective HIV/AIDS treatment regimen must overcome is the mutating nature of the virus. The ability of HIV-1 to mutate creates diversity in the strains of the virus which generate virus resistant to treatment regimens. As suggested by Rubirio et al., 2000, drug resistance is a result of a large variance in the viral population existing prior to the initiation of drug therapy, rather than the evolution of resistant virus occurring as a result of drug therapy [3]. This suggests single drug therapies will simply apply selective pressure on the diverse viral population, allowing resistant viral strains to proliferate unchecked. The ineffectiveness of single drug therapies is discussed by Nowak et al., 1996,[4] and Bonhoeffer et al., 1997 [5]. To increase the efficiency of a treatment regimen, one should include the use of a variety of drugs. Therapies usually administer a drug which decreases the virus' ability to infect susceptible cells, such as a reverse transcriptase inhibitor or a fusion inhibitor, in combination with a drug which decreases the ability of an infected cell to produce new infective viral particles, such as a protease inhibitor.

An additional component which can aid in delaying the progression of HIV is the immune response of the host. Shortly after the initial infection with HIV, viral loads in the plasma reach a peak, triggering an immune response by the host. Without the aid of antiviral drugs, the immune system is able to decrease this initial peak in viral levels to a minimum level known as the viral set point, whereafter the asymptomatic phase of infection begins and viral levels begin to slowly increase [6]. This low level of virus in the plasma is due to the destruction of infected cells, which are the producers of infective viral particles, in addition to the low availability of $CD4^+$ cells, the targets for viral infection. Due to the low viral load at the viral set point, the viral set point may be an optimal time for initiating drug therapy [7]. The above mentioned dynamics of the interactions between the host's immune system and the HIV virus suggest immune response to HIV should be considered when constructing a drug treatment plan.

In the past, many models have been constructed in an effort to gain an understanding of the dynamics of the in-host progression of HIV. Some models are very simple and only describe the development on HIV at its most fundamental level. Other works include complications such as multiple genetic variants of

HIV as in [10],[24] or multiple drug interventions such as in [18]. Still, other models, for example [11] [12], have incorporated the effects of the host's immune response on the progression of HIV. In this paper, a mathematical model of HIV is proposed combining ideas presented separately in previous works. We consider the effects of a multi-drug treatment plan as well as the host's immune response on the progression of two genetic variants of HIV-1. Through mathematical analysis, we are able to suggest what strain of HIV to focus treatment on in order to reduce the entire viral load. The paper will first give background on immune response to HIV and HIV treatments, followed by the model and an explanation of the model. Next we conduct analysis for two scenarios, one considering viral mutations during the progression of infection and one without considering viral mutations during the infection. For each case we provide the effective reproductive number, R_0, along with the biological interpretation of R_0. Uncertainty and sensitivity analysis of the effective reproductive number, that considers viral mutations, is conducted. Deterministic simulations are provided, showing the affects of treatments, viral mutation, and immune response. The paper is concluded with results and discussion of analysis and possibilities for future work.

2 Background

2.1 Immune Response to HIV

Our immune system helps regulate invading pathogens. Leukocytes and lymphocytes are produced in the bone marrow. Pre-T, or immature lymphocytes, leave the bone marrow for the thymus where they will mature into functional T cells, which are key players in the defense against pathogens. T cells provide immunity to extracellular pathogens by signaling antibodies [11]. Helper T cells, a subgroup of the T cells with surface protein $CD4^+$, stimulate white blood cells called B cells to produce antibodies that bind to a specific pathogenic antigen and immobilize it. Thus, the invading pathogen is prevented from causing further infections [12].

For the production of antibodies, there must exist communication of $CD4^+$ T cells and B cells. Supposing helper T cells are signaling B cells and antibodies are produced, but pathogens are not being detected by the antibodies, these pathogens enter and infect cells, forever changing the host cell's dynamics. In the case of HIV, once the virus enters the cell, the viral RNA is made into DNA by the viral reverse transcriptase (RT) enzyme. This DNA is then incorporated into the host's DNA by the enzyme integrase, which results in the creation of more viral RNA during the transcription phase of protein synthesis. Viral protease then cuts the new RNA into fragments which code for specific viral proteins. These proteins are then transported to the endoplasmic reticulum where they fit into grooves on the surface of the human leukocyte antigen (HLA) molecule. This molecule then travels to the surface of the infected $CD4^+$ T cell where it is detected by $CD8^+$ T cells. Once HLA is detected by a $CD8^+$ cell,

the $CD8^+$ cell destroys the infected $CD4^+$ cell [12].

In order for HIV to successfully infect cells, it must bind to $CD4^+$ T cell receptor as well as co-receptors. It was found that the chemokine receptor CCR-5 is a co-receptor for macrophage-tropic (M-tropic) HIV-1 strains [14]. M-trophic strains are thought to transmit HIV and predominate during the asymptomatic phase of infected individuals. Mutant alleles of the CCR-5 chemokine receptor gene have been found expressed at relatively high frequencies among Caucasian populations. Even after repeated exposure to HIV, these individuals with the mutant CCR-5 receptor remain uninfected [14]. The implications of these findings have led to the evolution of pharmacological agents which block the ability of HIV to use CCR-5 as receptors.

When HIV successfully binds to a $CD4^+$ cell, the infected helper T cell will signal for killer T cells and antibodies. One of the problems with the persistence of HIV is its potential for mutation. Even in the early stages of infection, about 1 million virions are made every day of which each will mutate on average once [13]. No matter how effective our immune response is in killing off infected helper T cells, viral mutations increase the chances of escaping both antibodies and killer cells. In the progression of HIV, the immune response inevitably also depletes the number of available $CD4^+$ T cells necessary to activate $CD8^+$T cells. The virus infects faster than the $CD4^+$ T cells can replenish. The depletion of the $CD4^+$ T cells leads to the weakened immune system. Once an infected individual has a $CD4^+$ T cell count of less than 200 mm^{-3} cells, he or she is classified as having clinical AIDS.

2.2 HIV Treatments

There are currently four types of HIV treatments. Two of these treatments affect the virus once it enters the cell. Once the virus enters the host cell, the viral RNA is reverse transcribed into DNA. This DNA copy of the virus genome then goes on to create new RNA and proteins which are used to create new viruses. Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) make sure the reversed transcribed DNA is faulty, disenabling the reproduction of HIV [2]. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) reduce the spread of HIV by blocking the RT enzyme so it cannot function in the creation of viral DNA from RNA [2]. This means the cell will not make viral proteins because the DNA copy of the viral genome will not be made. Although, inhibiting RT does not stop HIV from entering cell, it does prevent the virus from successfully infecting the cell.

The third type of treatment is called protease inhibitor. Once the viral DNA, or provirus, is integrated in the host DNA, the provirus will be duplicated when a cell is activated and divides. The provirus needs to be cut at specific sites in order to code for specific proteins. Protease inhibitor treatment blocks the cleavage resulting in dysfunctional enzymes such as RT, protease and integrase, which are necessary for the proliferation of the virus. Protease inhibitors will make noninfectious viral particles, preventing the production of mature, infectious virion. [2].

The fourth group of treatment is the fusion or entry inhibitors. This treatment can only be administered to patients who have already tried other treatments. These drugs do not allow HIV to bind to human surface CD4 and CCR5 proteins. The fusion inhibitors T-20 must be injected and attach to the HIV protein gp41. This prevents binding between the HIV surface proteins and human surface proteins [2]. As a result, HIV which is chemically altered by a fusion inhibitor is not able to enter a susceptible $CD4^+$ cell.

3 Model

In an effort to describe the dynamics of the interaction between multiple strains of HIV-1 and the combined antiviral forces of the host's immune system affected by multi-drug treatment, we have constructed a six-compartment non-linear ordinary differential equation model.

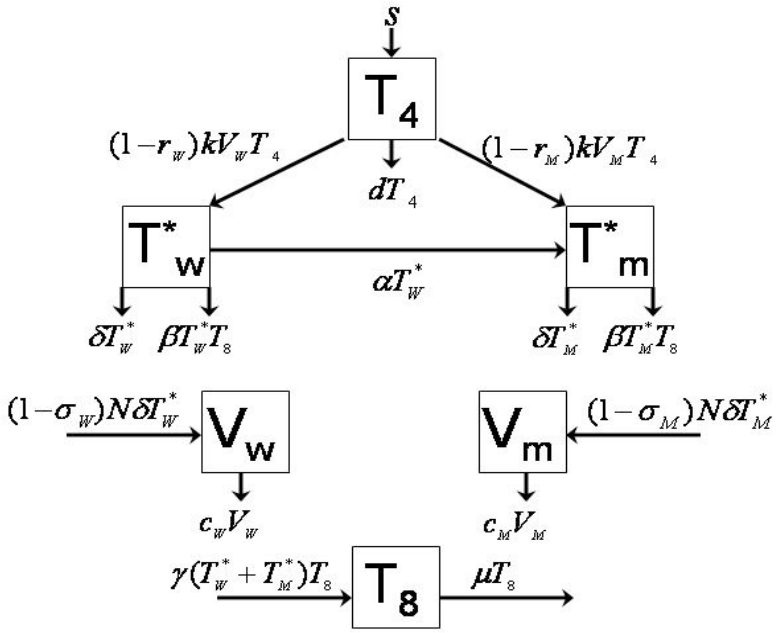

Figure 1: Two strain HIV model considering the immune system and combination drug therapy. T_4 are the susceptible $CD4^+$ T cells, T_w^* are the T cells that are infected by wild-type virus, T_m^* are the T cells that are infected by the mutated virus, V_w are the wild-type virus, and V_m are the mutated virus. See Table 1 for parameter descriptions.

$$\frac{dT_4}{dt} = s - dT_4 - (1 - r_w)kV_wT_4 - (1 - r_m)kV_mT_4 \tag{1}$$

$$\frac{dT_w^*}{dt} = (1 - r_w)kV_wT_4 - \beta T_w^*T_8 - \delta T_w^* - \alpha T_w^* \tag{2}$$

$$\frac{dT_m^*}{dt} = (1 - r_m)kV_mT_4 - \beta T_m^*T_8 - \delta T_m^* + \alpha T_w^* \tag{3}$$

$$\frac{dT_8}{dt} = \gamma(T_w^* + T_m^*)T_8 - \mu T_8 \tag{4}$$

$$\frac{dV_w}{dt} = (1 - \sigma_w)N\delta T_w^* - c_wV_w \tag{5}$$

$$\frac{dV_m}{dt} = (1 - \sigma_m)N\delta T_m^* - c_mV_m \tag{6}$$

This model incorporates a class of uninfected $CD4^+$ T cells, denoted T_4; two classes of HIV-1 virus, denoted V_w and V_m for a wild-type and a mutant type respectively; and two classes of infected $CD4^+$ T cells, T_w^* which are infected by the wild-type virus and T_m^* which are infected by the mutant-type virus. To incorporate the host's immune response to infection, a class of $CD8^+$ T cells, or killer T cells, is also included. This class is denoted by T_8. For convenience, Table 1 is provided containing a list of all parameters and state variables as well as their descriptions.

$CD4^+$ T cells, or rather helper T cells, are assumed to be recruited at a constant rate, s. The recruitment of new, uninfected, helper T cells corresponds to the maturation of precursors from the bone marrow or thymus into functional helper cells. The rate of removal of healthy helper T cells due to natural non-HIV related causes is d. Helper T cells can become infected at the same rate k by one of two of the genetic variants of the HIV-1 virus. In each case, infection is limited by an infection inhibiting drug, which can be either a reverse transcriptase inhibitor or a fusion inhibitor. The efficacy of an infection inhibiting drug is denoted r_w for the wild type strain and r_m for the mutant type strain.

The model includes two classes of infected $CD4^+$ T cells, T_w^* and T_m^*, one class corresponding to each genetic variant of the HIV virus. $CD4^+$ T cells move into one of the infected classes, T_w^* or T_m^*, when infected by a wild-type virus or a mutated virus, respectively. Infection rates are reduced by an infection inhibiting drug. Once infected by a given virus type, infected T cells may be removed from the plasma by a killer T cell. This process takes place at a rate β. For simplicity, we assume the removal rate, δ, of both kinds of infected T cells is the same. This removal of cells from the plasma represents the death of infected cells whether it be related to viral infection or natural causes. Note that the rate of removal of infected cells, δ, should be greater than the death rate, d, of uninfected cells, $\delta > d$. Since viral particles replicate within a cell, they are subject to in-cell mutation. When a wild type virus within an infected T cell becomes a mutant type virus, the infected T cell becomes a T cell infected by mutated-type virus. This process takes place at a rate α.

The immune response is taken into account through the incorporation of a $CD8^+$ class of killer T cells denoted by T_8. Although killer cells are present in the plasma which are specific to non-HIV related antigens, we consider only killer cells produced in response to the presence of the two different kinds of infected T cells. Killer cells eliminate infected T cells from the cell population. The number of killer cells produced is related to the total number of infected cells in the population. For simplicity, we assume that killer cells are produced at the same rate whether they are produced as a result of the presence of a either kind of infected T cell. This production rate is denoted by γ. Killer cells are removed from the cell population due to natural deaths, which occur at a rate μ.

Viral production takes place in infected T cells. The production of viral particles is limited by a drug which inhibits viral replication. This drug has efficacy for wild-type virus and mutated-type virus which are σ_w and σ_m respectively. The burst number, N, is defined as the average number of viral particles produced by either wild-type infected T cell or mutated-type infected T cell during its lifetime. The wild type virus class is cleared at a rate c_w, while the mutant type viruses are cleared at a rate c_m. Here, c_w is always less than c_m.

The model is initially analyzed without wild-type viral mutation ($\alpha = 0$), and then is analyzed with viral mutation ($\alpha > 0$).

4 Analysis of Steady States when $\alpha = 0$

When $\alpha = 0$, we consider the existence of both wild and mutated virus from the beginning of the infection. Wild-type infected T cells cannot produce mutated virus since mutations cannot occur in the wild-type infected T cell. We found seven steady states to our system, one non-infected steady state and six infected steady states. The non-infected steady state corresponds to a virus free system.The following points are defined using the reproductive numbers, R_w and R_m, which are defined later in this section.

The steady states are in the form of E_j=$(T_4, T_w, T_m, T_8, V_w, V_m)$, where $j = 0, 1, ..., 6$.

The disease free equilibrium (DFE), where no virus exist, is given by

$E_0 = DFE = \left(\frac{s}{d}, 0, 0, 0, 0, 0\right)$.

Next we want to determine the criteria for E_0 to be locally asymptotically stable (LAS). We linearize the system around E_0 and find the characteristic equation for the jacobian. This steady state is stable if each of the eigenvalues have negative real parts. The Routh-Hurwitz Theorem is used to find criteria

Table 1: Population and parameter definitions

Populations	**Description**
T_4	Target or uninfected $CD4^+$ T cells
T_w^*	$CD4^+$ T cells infected by wild virus
T_m^*	$CD4^+$ T cells infected by mutant virus
T_8	$CD8^+$ T cells, immune response to virus
V_w	Wild viral concentration
V_m	Mutant viral concentration
Parameters	**Description**
s	Recruitment rate of $CD4^+$ T cells
d	Natural death rate of uninfected cells
r_w	Efficacy of RT or entry inhibitor on wild viruses
r_m	Efficacy of RT or entry inhibitor n mutant viruses
k	Infectivity rate
β	Rate at which CD8 T cells kill infected $CD4^+$ T cells
δ	Rate of loss of virus producing cells
γ	Rate of activation of $CD8^+$ T cells
μ	Death rate of $CD8^+$ T cells
α	Rate of mutation from T_w^* to T_m^*
σ_w	Efficacy of protease inhibitor on wild viruses
σ_m	Efficacy of protease inhibitor on mutant viruses
N	Ave. no. of virus particles produced by an infected cell during its lifetime
c_w	Rate of clearance of wild viruses
c_m	Rate of clearance of mutant viruses

to ensure stability. The general jacobian is as follows:

$$J = \begin{pmatrix} G & 0 & 0 & 0 & -(1-r_w)kT_4 & -(1-r_m)kT_4 \\ (1-r_w)kV_w & -\beta T_8 - \delta & 0 & -\beta T_w^* & (1-r_w)kT_4 & 0 \\ (1-r_m)kV_m & 0 & -\beta T_8 - \delta & -\beta T_m^* & 0 & (1-r_m)kT_4 \\ 0 & \gamma T_8 & \gamma T_8 & \gamma(T_w^* + T_m^*) - \mu & 0 & 0 \\ 0 & (1-\sigma_w)N\delta & 0 & 0 & -c_w & 0 \\ 0 & 0 & (1-\sigma_m)N\delta & 0 & 0 & -c_m \end{pmatrix}$$

where $G = -d - (1-r_w)kV_w - (1-r_m)kV_m$.

The jacobian J evaluated at E_0 is

$$J(E_0) = \begin{pmatrix} -d & 0 & 0 & 0 & -(1-r_w)k\frac{s}{d} & -(1-r_m)k\frac{s}{d} \\ 0 & -\delta & 0 & 0 & (1-r_w)k\frac{s}{d} & 0 \\ 0 & 0 & -\delta & 0 & 0 & (1-r_m)k\frac{s}{d} \\ 0 & 0 & 0 & -\mu & 0 & 0 \\ 0 & (1-\sigma_w)N\delta & 0 & 0 & -c_w & 0 \\ 0 & 0 & (1-\sigma_m)N\delta & 0 & 0 & -c_m \end{pmatrix}.$$

By inspection, $-d$ and $-\mu$ are negative eigenvalues. We reduce the matrix to a 4×4 and find the characteristic equation for the new matrix. The characteristic equation, $F(\lambda)$, is:

$$F(\lambda) = A(\lambda)B(\lambda),$$

where

$$A(\lambda) = \big(-(\delta+\lambda)(c_w+\lambda)(1-r_w)k(1-\sigma_w)N\delta\big),$$
$$B(\lambda) = \big(-(\delta+\lambda)(c_m+\lambda) + (1-r_m)k(1-\sigma_m)N\delta\big).$$

All eigenvalues have negative real parts when

$$N < min\bigg(\frac{c_w d}{(1-r_w)k(1-\sigma_w)}, \frac{c_m d}{(1-r_m)k(1-\sigma_m)}\bigg). \tag{7}$$

We define the reproductive number as

$$R_0 := max(R_w, R_m),$$

where

$$R_w = \frac{sk(1-r_w)}{d}\frac{N(1-\sigma_w)}{c_w},$$

and

$$R_m = \frac{sk(1-r_m)}{d}\frac{N(1-\sigma_m)}{c_m}.$$

Then for $R_0 < 1$, Equation 7 holds.

The reproductive number is the average number of secondary virus produced by one virus in a mostly susceptible population of $CD4^+$ T cells. Since HIV can be modeled as a host-vector system, there are two types dynamic behaviors occurring during the progression of HIV: the virus infects the $CD4^+$ T cell and the infected cells produces more virus. In the equation of R_w, $\frac{sk(1-r_w)}{d}$ denotes the average number of T cells that become infected resulting from the introduction of one virus, which contribute to creating more wild virus. $\frac{N(1-\sigma_w)}{c_w}$ denotes the average number of wild virus that one infected T cell produces. R_m can be interpreted similarly.

If $R_0 < 1$, then, on average, less than one virus is produced, implying the disease will disappear. If $R_0 > 1$, then, on average, each virus will produce more than one virus.

R_w and R_m the individual effective reproductive numbers of a system free of mutant virus or wild-type virus, respectively. We can see this when we linearize the system of ODE's about the non-infection steady state when one of the viral strains is non-existent. For example, one can consider the system without

mutant strain virus.

$$\begin{aligned}
\frac{dT_4}{dt} &= s - dT_4 - (1-r_w)kV_wT_4 \\
\frac{dT_w^*}{dt} &= (1-r_w)kV_wT_4 - \beta T_w^*T_8 - \delta T_w^* \\
\frac{dT_8}{dt} &= \gamma T_w^*T_8 - \mu T_8 \\
\frac{dV_w}{dt} &= (1-\sigma_w)N\delta T_w^* - c_wV_w
\end{aligned}$$

We want to show that when mutant virus does not exist, the effective reproductive number is R_w. To do this we linearize the new system about the disease free equilibrium , $DFE^* = (\frac{s}{d}, 0, 0, 0)$. The linearization is:

$$J = \begin{pmatrix} -d & 0 & 0 & -(1-r_w)k\frac{s}{d} \\ 0 & -\delta & 0 & (1-r_w)k\frac{s}{d} \\ 0 & 0 & -\mu & 0 \\ 0 & (1-\sigma_w)N\delta & 0 & -c_w \end{pmatrix}.$$

We find the characteristic equation for this system, and after some calculation, it can be proved that DFE^* is LAS when $R_w < 1$. Similarly, we can show that R_m is the effective reproductive number for the system when there are no wild-type virus. However, if both strains of HIV-1 persist, then R_0 is the maximum of the reproductive numbers, R_w and R_m.

Due to the nature of the parameters defining R_0, it is reasonable to expect a value $R_0 > 1$. This means the disease is not eradicated from a person's body after the introduction infection. Since R_0 depends on the efficacy of both treatments on both the wild and mutant virus, to reduce R_0 to a value less than one, the efficacy of either one of the treatments would have to be 100%. Thus far, no single treatment or combination therapy is 100% effective. Our goal is to determine whether treatment regimens that specify drugs which target particular subsets of virus are effective.

The infected steady states are defined below.

$$E_1 = \left(\frac{s}{dR_m}, 0, \frac{s-dT_4}{\delta}, 0, 0, \frac{(1-\sigma_m)N\delta T_m^*}{c_m}\right),$$

which exists when $R_m > 1$ and $s < (\frac{\mu}{\gamma}\frac{\delta}{R_m - 1})$.

$$E_2 = \left(\frac{s}{dR_w}, \frac{s-T_4d}{\delta}, 0, 0, \frac{(1-\sigma_w)N\delta T_w^*}{c_w}, 0\right)$$

which exists when $R_w > 1$ and $s < (\frac{\mu}{\gamma}\frac{\delta}{R_w - 1})$.

$$E_3 = \left(\frac{s}{d + (1 - r_m)V_m k}, 0, \frac{\mu}{\gamma}, \frac{\delta}{\beta} \left(\frac{R_m d T_4}{s} - 1 \right), 0, \frac{(1 - \sigma_m) N \delta T_m^*}{c_m} \right)$$

which exists when $s > \frac{\mu}{\gamma}$ and $R_m > \frac{s\gamma}{s\gamma - \mu}$.

$$E_4 = \left(\frac{s}{d + (1 - r_w)V_w k}, \frac{\mu}{\gamma}, 0, \frac{\delta}{\beta} \left(\frac{R_w d T_4}{s} - 1 \right), \frac{(1 - \sigma_w) N \delta T_w^*}{c_w}, 0 \right)$$

which exists when $s > \frac{\mu}{\gamma}$ and $R_w > \frac{s\gamma}{s\gamma - \mu}$.

In the case of having both wild and mutant virus infecting, and if

$$A = \frac{(1 - r_w)(1 - \sigma_w)}{c_w} = \frac{(1 - r_m)(1 - \sigma_m)}{c_m},$$

then

$$E_5 = \left(\frac{s}{dR_m}, \frac{s}{\delta}(1 - \frac{1}{R_m}) - A, A, 0, \frac{(1 - \sigma_w) N k \delta T_w^*}{c_w}, \frac{(1 - \sigma_m) N k \delta T_m^*}{c_m} \right)$$

where A is an arbitrary number less than $\frac{s}{\delta}(1 - \frac{1}{R_m})$. This point exists when $R_m = R_w > 1$.

$$E_6 = \left(\frac{\frac{s}{d}}{1 + \frac{\delta R_m \mu}{s\delta}}, \frac{\mu}{\gamma} - A, A, \frac{\delta}{\beta}(\frac{d R_m T_4}{s} - 1), \frac{(1 - \sigma_w) N k \delta T_w^*}{c_w}, \frac{(1 - \sigma_m) N k \delta T_m^*}{c_m} \right)$$

where $A < \frac{\mu}{\gamma}$.
This point also exists when $R_m = R_w > \frac{1}{1 - \frac{\delta \mu}{s\gamma}}$ and $\frac{\delta \mu}{s\gamma} < 1$.

The existence and stability criteria for each point is summarized in Table 2 and detailed calculations can be found in the appendix.

This analysis with $\alpha = 0$, while mathematically informative, is somewhat unrealistic. This is illustrated by the strict conditions that must be satisfied to have co-existence of viral strains. From literature we also know that viral mutations are common [15]. Therefore for the rest of paper, we conduct analysis for when $\alpha > 0$.

5 Analysis of Steady States when $\alpha > 0$

We now analyze the model which considers wild-type mutations. This means that wild-type virus can mutate at a constant rate α inside a wild-type infected

Table 2: Conditions for the existence and local stability for each steady state, considering no mutations.

Steady State	**Criteria to Exist**	**Criteria to be LAS**
DFE	always exist	$R_0 < 1$
E_1 (V_m persist, $T_8 = 0$)	$R_m > 1$ and $s < (\frac{\mu}{\gamma}\frac{\delta}{R_m - 1})$	$R_m > R_w$
E_2 (V_w persist, $T_8 = 0$)	$R_w > 1$ and $s < (\frac{\mu}{\gamma}\frac{\delta}{R_w - 1})$	$R_w > R_m$
E_3 (V_m persist, $T_8 \neq 0$)	$s > \frac{\mu}{\gamma}$ and $R_m > \frac{s\gamma}{s\gamma - \mu}$	$R_m > R_w$
E_4 (V_w Persist, $T_8 \neq 0$)	$s > \frac{\mu}{\gamma}$ and $R_w > \frac{s\gamma}{s\gamma - \mu}$	$R_w > R_m$
E_5 (V_w, V_m co-exist, $T_8 = 0$)	$R_m = R_w > 1$	
E_6 (V_w, V_m co-exist, $T_8 \neq 0$)	$R_m = R_w$	

T cell. This model yields five steady states. The disease free equilibrium (F_0) is given by $F_0 = DFE = \left(\frac{s}{d}, 0, 0, 0, 0, 0\right)$ and its stability can be found by linearizing the system about the F_0.

The DFE stability can be found by the same method as described in the the subsection with analysis on steady states when $\alpha = 0$. The following is the general jacobian:

$$J = \begin{pmatrix} G & 0 & 0 & 0 & -(1-r_w)kT_4 & -(1-r_m)kT_4 \\ (1-r_w)kV_w & -(\beta T_8 + (\delta + \alpha)) & 0 & -\beta T_w^* & (1-r_w)kT_4 & 0 \\ (1-r_m)kV_m & \alpha & -(\beta T_8 + delta) & \beta T_m^* & 0 & (1-r_m)kT_4 \\ 0 & \gamma T_8 & \gamma T_8 & \gamma(T_w^* + T_m^*) - \mu & 0 & 0 \\ 0 & (1-\sigma_w)N\delta & 0 & 0 & -c_w & 0 \\ 0 & 0 & (1-\sigma_m)N\delta & 0 & 0 & -c_m \end{pmatrix}$$

where

$$G = -d - (1-r_w)kV_w - (1-r_m)kV_m.$$

To find the stability of the DFE for $\alpha > 0$, evaluate the jacobian J at F_0 and find the characteristic equation.

$$J(DFE) = J(F_0) = \begin{pmatrix} -d & 0 & 0 & 0 & -(1-r_w)k\frac{s}{d} & -(1-r_m)k\frac{s}{d} \\ 0 & -(\delta+\alpha) & 0 & 0 & (1-r_w)k\frac{s}{d} & 0 \\ 0 & \alpha & -\delta & 0 & 0 & (1-r_m)k\frac{s}{d} \\ 0 & 0 & 0 & -\mu & 0 & 0 \\ 0 & (1-\sigma_w)N\delta & 0 & 0 & -c_w & 0 \\ 0 & 0 & (1-\sigma_m)N\delta & 0 & 0 & -c_m \end{pmatrix}$$

The characteristic equation is the following:

$$h(\lambda) = X(\lambda)Y(\lambda)$$

where

$$X(\lambda) = \left(\frac{(1-r_m)ks(1-\sigma_m)N\delta}{d} - (\delta+\lambda)(c_m+\lambda)\right),$$

and

$$Y(\lambda) = \left(\frac{(1-r_w)ks(1-\sigma_w)N\delta}{d} - ((\delta+\alpha)+\lambda)(c_w+\lambda)\right).$$

For all the eigenvalues to have negative real parts, we derive the following conditions:

$$c_m\delta - \frac{(1-r_m)ks(1-\sigma_m)N\delta}{d} > 0$$

and

$$c_w(\delta+\alpha) - \frac{(1-r_w)ks(1-\sigma_)N\delta}{d} > 0.$$

From these conditions, we define the effective reproductive number, R_0^*. In order to satisfy both conditions,

$$R_0^* = max\big(R_w^*, R_m^*\big)$$

where

$$R_w^* = \left(\frac{(1-r_w)ks}{d(\delta+\alpha)}\frac{(1-\sigma_w)N\delta}{c_w}\right),$$

and

$$R_m^* = \left(\frac{(1-r_m)ks}{d}\frac{(1-\sigma_m)N}{c_m}\right).$$

R_w^* has analogous interpretation to R_w. However, α adds to the removal of wild-type infected T cells. Therefore, $\frac{(1-r_w)ks}{d(\delta+\alpha)}$, is the average number of T cells that become infected with the initiation of one virus. The second fraction of R_w^* has the same interpretation as R_w. R_m^* can be described similarly as R_m.

The following points are the infected steady states: two boundary cases, and two of coexistence.

In the case of the mutant virus persisting, having no immune response to the virus, $F_1 = \left(\frac{s}{d}\frac{1}{R_m^*}, 0, \frac{s}{\delta}(1 - \frac{1}{R_m^*}), 0, 0, \frac{(R_m^* - 1)d}{(1 - r_m)k}\right)$,

which exists when $R_m^* > 1$.

We also observe the persistence of the mutant virus, and an immune response, $F_2 = \left(\frac{s}{d}\frac{1}{1 + \frac{\delta R_m^* \mu}{s\gamma}}, 0, \frac{\mu}{\gamma}, \frac{\delta}{\beta}\frac{R_m^*}{1 + \frac{\delta R_m^* \mu}{s\gamma}} - 1, 0, \frac{\delta\mu}{\gamma}\frac{\delta N(1 - \sigma_m)}{c_m}\right)$,

which exists when $R_m^* > \frac{1}{1 - \frac{\delta\mu}{s\gamma}}$, and $\frac{\delta\mu}{s\gamma} < 1$.

Now, if the case that both strains persist, and we do not observe an immune response to the virus, $F_3 =$
$\left(\frac{s}{R_w^* d}, \frac{s}{\delta}(1 - \frac{1}{R_m^*}) - T_m^*, \frac{R_w^* - 1}{\frac{(\delta+\alpha)\delta R_w^*}{s\alpha} - \frac{R_m^* \delta^2}{s\alpha}}, 0, \frac{(1 - \sigma_w)N\delta T_w^*}{c_w}, \frac{(1 - \sigma_m)N\delta T_m^*}{c_m}\right)$,

which exists when $R_w^* > R_m^*$ and $R_w^* > 1$.

In the case of coexistence and an immune response, $F_4 =$
$\left(\frac{s - \frac{\alpha\mu}{\gamma}}{d(\Psi)}, \frac{\mu}{\gamma} - T_m^*, \frac{\frac{\alpha\mu}{\gamma}\Psi}{(1 - \frac{\alpha\mu}{s\gamma})(\delta R_m^* - (\delta + \alpha)R_w^*)}, \frac{\delta + \alpha}{\beta}(\frac{d}{s}R_w^* T_4 - 1), \frac{d(\delta + \alpha)}{sk(1 - r_w)}R_w^* T_w^*, \frac{d\delta}{sk(1 - r_m)}R_m^* T_m^*\right)$

where $\Psi = 1 + \frac{(\delta+\alpha)\mu}{s\gamma}R_w^*$. which exists when $1 > \frac{\alpha\mu}{s\gamma}, R_m^* > \frac{(\delta+\alpha)R_w^*}{\delta}$, and

$\frac{d}{s}R_w^* T_4 > 1$.

Due to time constraints, and the complexity of the system being analyzed, we did not establish conditions for local stability of each of the above steady states.

Next, we conduct uncertainty analysis to investigate the variability in the effective reproductive number due to the uncertainty in the parameter distributions. Sensitivity analysis is then conducted to find out what parameter, with a given distribution, affects R_0 the most.

6 Uncertainty and Sensitivity Analysis

This analysis is conducted with $\alpha > 0$.

6.1 Uncertainty

Uncertainty analysis is a way to evaluate the variability in the value of R_0^* due to the uncertainty in the input parameter values. We are interested seeing the effects of combination drug therapy in two different cases:

$$1)\ r_w > r_m \text{ and } \sigma_m > \sigma_w \text{ and,}$$
$$2)\ r_m > r_w \text{ and } \sigma_w > \sigma_m.$$

Therefore, we perform this analysis for each case. Then we compare the uncertainty of R_0^* and sensitivity of the parameters. In each case, we use Monte Carlo sampling simulations, in which we assign each parameter a distribution. To evaluate R_0^*, we sample from each of the parameters' distributions at random. This sampling is carried out 10^3 times. A histogram for case 1 is provided (see Figure 2). [25] advises, that when a parameter distribution is unknown, a triangular distribution should be used for that parameter. Therefore, we create triangular distributions based on the data provided in the literature of [18], [19], [20], [21], [5], [22], [23], [17], [16], [15], and [24]. To see the effects of treatment we assign different distributions for the treatment efficacies corresponding to case 1) and 2). See Table 4 and 5 for the specific values used in uncertainty and sensitivity analysis.

From these sampling simulations, we can find the probability of R_0^* being than certain values for the particular distributions given to each parameter. Please refer to Table 3.

Table 3: Results of the R_0^* histogram showing the probability R_0^* is less than given value Q

Q	Prob($R_0^* < Q$)
50	0.012
100	0.047
250	0.185
500	0.418

We did not include the histogram for the second case because it is similar to the histogram of case 1. The results of the histogram agree with the biological behavior of HIV because R_0^* will never be less than one after the introduction of one HIV virus, meaning that the disease will not be rid from the human body. Once people are infected with HIV, they will always have HIV. In fact, we notice R_0^* will very few times even be near 1. We observed a consist low frequency for values of $5 < R_0^* < 750$. Instead, the effective reproductive number is concentrated in intervals around magnitude $10^2 and 10^3$.

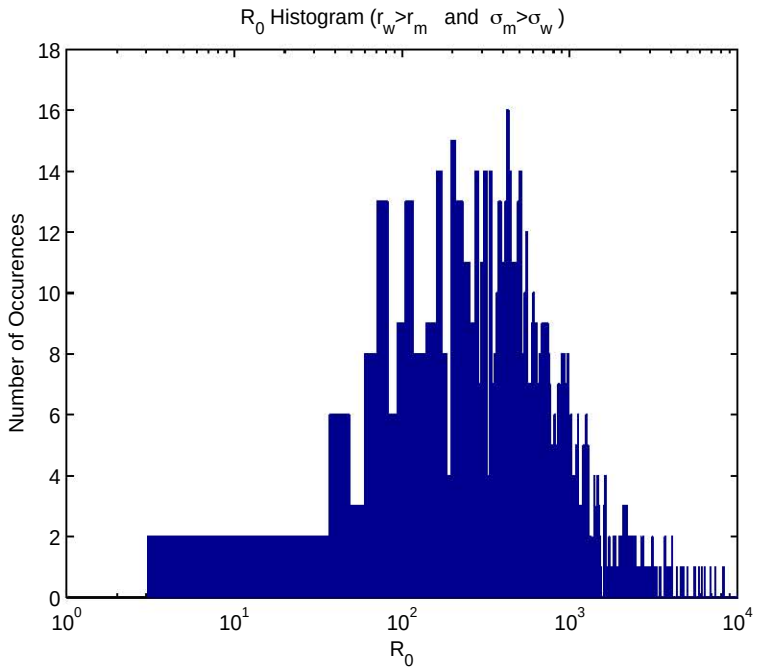

Figure 2: This is the histogram for R_0^* in the case of $r_w > r_m$ and $\sigma_m > \sigma_w$. This shows that upon the introduction of one virus, R_0^* will never be less than one, when denotes that the disease will disappear. Biologically, this is correct because once a person is HIV positive, he or she will always have the virus. The characteristics of the histogram are as follows: mean = 946, standard deviation = 1130, and median = 605.

Table 4: Assigned intervals for each treatment parameter, from which triangular distributions were constructed. We investigate two cases: 1) $r_w > r_m$ and $\sigma_m > \sigma_w$ and 2)$r_m > r_w$ and $\sigma_w > \sigma_m$.

Parameter	**Min Value**	**Estimated Mode**	**Max Value**
Case 1			
r_w	.51	.75	1
r_m	0	.25	.5
σ_w	0	0.25	0.5
σ_m	0.51	0.75	1
Case 2			
r_w	0	.25	.5
r_m	.51	.75	1
σ_w	0.51	0.75	1
σ_m	0	0.25	0.5

6.2 Sensitivity

Sensitivity of R_0^* is conducted by calculating the partial rank correlation coefficient (PRCC) of each parameter with respect to R_0^*. We consider the cases 1 and 2 as used in uncertainty analysis. To get the PRCC, we first had to use regression analysis to find both the residuals of R_0^* with respect to each one of the parameters and the residuals of each parameter. For example, to find the PRCC of parameter y, first let R_0^* denote the response variable and use regression against all parameters, except for y. The parameters which are used in the regression are called the predictors. Regression will allow one to see if the predictors give an accurate prediction of the value of R_0^*. The predictions are given as the residuals in the regression process. Residuals are the errors in how the predictor parameters can explain R_0^*. Next, we use y as the response variable and regress against every other parameter in the expression of R_0^*. If this plot is random, meaning that y does not have a linear relationship will all other parameters, then the residuals are high. Therefore, y is an important parameter to have in the calculation of R_0^*. A linear relationship means that all the predictor parameters would be yielding the same information as y. Therefore, since y is redundant information, one can explain R_0^* using only the predictor parameters. More random plots lead to higher residuals and less relationship between the response parameter and predictor parameters. Less random, or linear relationships, lead to lower residuals and higher correlations between the parameters.

However, if the regression of R_0^* on the parameters without y is good, then y is not needed in the model. Since the model is deterministic, if y is not needed, then the model is wrong if it includes y as a parameter.

After obtaining both the residuals of R_0^* with respect to each one of the parameters and the residuals of each parameter, one can then rank the residuals and compute the partial rank correlation coefficient(PRCC) of the parameters

Table 5: Assigned intervals for non-treatment parameters. These distributions are the same for both cases: 1) $r_w > r_m$ and $\sigma_m > \sigma_w$ and 2) $r_m > r_w$ and $\sigma_w > \sigma_m$.

Parameter	**Min Value**	**Estimated Mode**	**Max Value**	**Sources**
N	100	550	1000	[18], [19], [20], [21]
k	0.00005	0.500025	1	[18], [19], [20], [21], [5], [22], [23], [17], [16], [24]
s	1	5	10	[18], [21], [5], [22], [23], [17], [16], [15], [18]
d	0.0042	0.0521	.1	[18], [19], [21], [5], [22], [23], [17], [16], [24]
δ	0.172	0.336	0.5	[18], [19], [20], [21], [5], [22], [23], [17], [16], [15]
α	0.74	2.87	5	[18], [15]
c_w	0.2	2.6	5	
c_m	0.2	5.4	10.6	

with respect to R_0^*. In order to visualize the value of the PRCC, one can create a scattered plot of the R_0^* residuals of one parameter against the residuals of that same parameter; the slope of the fitted line through the scattered plots will represent the PRCC.

PRCC's vary from [-1,1]. Positive PRCC means the parameter and R_0^* have a positive correlation. So if the parameter increases, then R_0^* increases, and if the parameter decreases, then R_0^* also decreases. If the PRCC is negative then the parameter has a negative effect on R_0^*. If the parameter increases, R_0^* decreases, and if the parameter decreases, R_0^* increases. PRCC's close to zero imply no matter how much a parameter is increased or decreased, R_0^* will not be effected.

For the assigned triangular distributions of the parameters, figure 3 depicts the scattered plots of the R_0^* residuals against the particular parameter residuals

when $r_w > r_m$ and $\sigma_m > \sigma_w$. The PRCC is represented as the slope of the fitted line in the plot (see Table 6 for values).

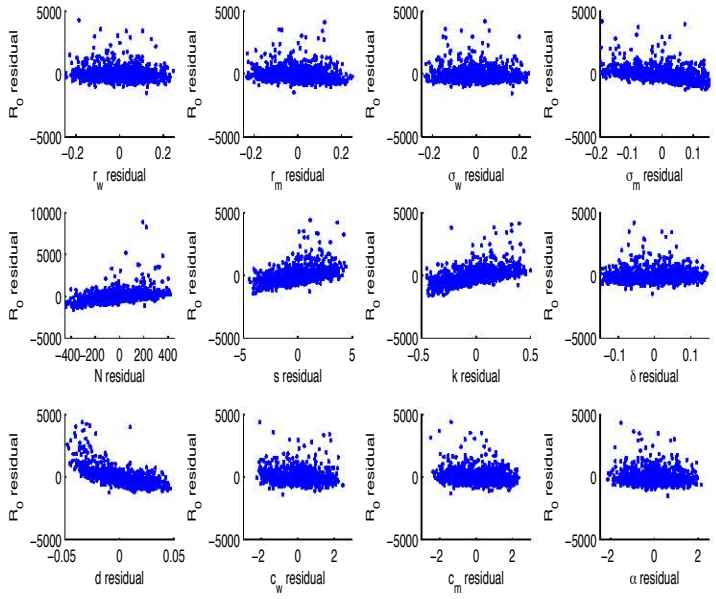

Figure 3: Residual Plots of R_0^* with respect to each parameter vs. Residuals of each parameter. The Partial Rank Correlation is the slope of a fitted line through the scattered plots.

The following is a table of the Partial Rank Correlation Coefficients (PRCC) of each parameter with respect to R_0^* for the two cases.

In case 1, $r_w > r_m$ and $\sigma_m > \sigma_w$, it is interesting to see that r_m, RT treatment efficacy for the mutated virus, has a stronger correlation to R_0^*, even though r_w, RT treatment efficacy for the wild virus, is higher. This also occurs in the second case, $r_m > r_w$ and $\sigma_w > \sigma_m$, even though $\sigma_w > \sigma_m$, σ_m has a higher correlation to R_0^* than σ_w. So if one is to make a policy of what treatment to provide and what virus to target, he or she should focus the resources on controlling the mutated virus population. This policy would reduce R_0^* most efficiently. Another surprising result is that the mutating rate, α, is not sensitive in the expression of R_0^*. Parameter α has very low correlation to the effective reproductive number. The highest correlated parameters are N, s, d, and k. Rather, R_0^* is sensitive to the beginning number of susceptible T cells, the infection rate, and the number of virus produced by one infected T cell.

Table 6: Partial Rank Correlation Coefficients (PRCC) for the parameters with respect to R_0^* in two different cases: 1) $r_w > r_m$ and $\sigma_m > \sigma_w$ and 2) $r_m > r_w$ and $\sigma_w > \sigma_m$.

Parameter	PRCC $r_w > r_m$ and $\sigma_m > \sigma_w$	PRCC $r_m > r_w$ and $\sigma_w > \sigma_m$
r_w	-0.070	-0.001
r_m	-0.222	-0.543
σ_w	-0.021	-0.067
σ_m	-0.551	-0.232
N	0.529	0.510
s	0.577	0.540
k	0.600	0.616
δ	0.054	0.026
d	-0.664	-0.620
c_w	-0.130	-0.078
c_m	-0.226	-0.167
α	-0.092	-0.010

7 Simulations

We are considering a simple model of HIV with immune response, treatments, two viral strains, and mutation of free virus. Most literature does not include these dynamics in combination when modeling the mutating nature of HIV and its progression. Particularly, we are interested in the administration of targeted treatment towards each strain. Recall r_w and r_m are the efficacy corresponding to the treatment aimed at reducing the susceptibility of helper T cells, while σ_w and σ_m are the efficacy corresponding to the treatment that reduces the infectivity of infected T cells. Now, if we have a regimen with the boundary cases for the level of efficacy each treatment can have,

$$r_w = 0, r_m = 1,$$
$$\sigma_w = 1, \sigma_m = 0$$
$$\text{or,}$$
$$r_w = 1, r_m = 0,$$
$$\sigma_w = 0, \sigma_m = 1,$$

we know R_w^* and R_m^* are both equal to zero. Thus, the concentration of both wild-type and mutant virus will eventually be cleared from the host (see Figure 4.

We explore what happens to the viral concentrations when the efficacy of treatment is within the boundary. First, we study the effect of the immune response and mutation rate on the viral load. As expected, we observe that including the effect of the immune response to infection will decrease the viral load. Likewise, constant treatment decreases the viral load even further than

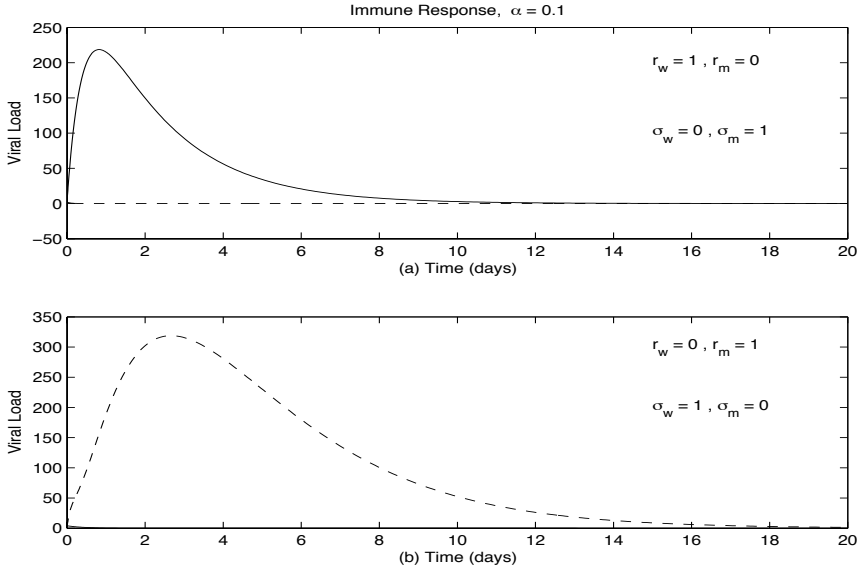

Figure 4: Boundary Treatment for Wild and Mutant Strains
(–) Wild-Type Virus, (-) Mutant Virus

solely considering having an immune response to infection. Parameter values and initial conditions used in simulations can be found listed in Table 7.

The results for the effect of the mutation on solutions were counterintuitive. At a mutation rate of $\alpha = 0.1$ and the given parameter values, the viral load did not greatly differ from simulations performed with $\alpha = 0$. The general trajectory of viral concentration for both the wild-type and mutant-type did not alter with the consideration of mutations, only the levels of viral load achieved where modified. However, considering an immune response to different regimens of treatment efficacy resulted in large differences in viral load and trajectory (see Figure 5. Also, we observed a sustained level of wild virions but extinction of mutant virions, corresponding to steady state E_4. Even though for the parameters used, we observe mutant virus extinction, we know from analysis parameter α is necessary for a larger region of coexistence.

The steady states of interests are those which sustain coexistence of the wild and mutant strains when $\alpha > 0$. The rest of the simulations are with mutations.

Simulations to determine the effect of efficacy in case 1 and case 2 on R_0^* were performed. For $\sigma_w < \sigma_m$, R_0^* increases almost linearly as we vary the RT or entry inhibitor efficacy. In this case, low levels of the effective reproductive number can be sustained by high levels of r_m in combination with mostly all values of r_w. in these plots, we include a plane at $R_0^* = 1$, to see the level of efficacy necessary to ensure $R_0^* < 1$. The levels of treatment must be extremely high to reduce R_0^* below 1.

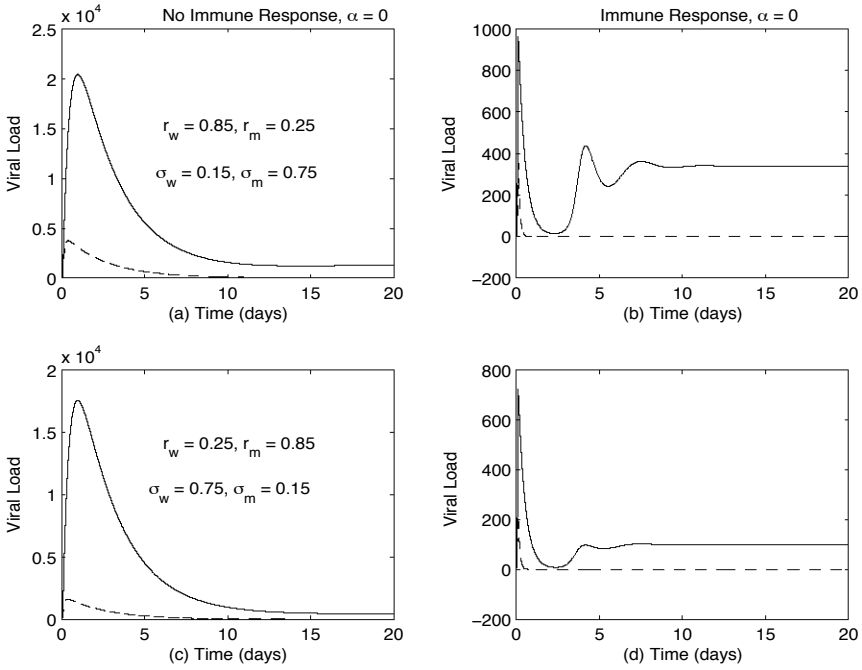

Figure 5: (–) Wild-Type Viral Load, (- -) Mutant Viral Load
(a) No Immune, Case 1 of Efficacy, (b) Immune Response, Case 1 of Efficacy, (c) No Immune Response, Case 2 of Efficacy, (d) Immune Response, Case 2 of Efficacy

Variable	**Initial Value**	
$T_4(0)$	100	mm^{-3}
$T_w^*(0)$	3	mm^{-3}
$T_m^*(0)$	2	mm^{-3}
$T_8(0)$	1	mm^{-3}
$V_w(0)$	4	mm^{-3}
$V_m(0)$	2	mm^{-3}
Parameter	**Value**	**Unit**
r_w	varies	
r_m	varies	
σ_w	varies	
σ_m	varies	
s	6	mm^{-3}
d	0.1	day^{-1}
k	0.1	$\text{mm}^3\ \text{day}^{-1}$
β	0.35	day^{-1}
δ	0.4	day^{-1}
γ	0.55	day^{-1}
μ	2	day^{-1}
α	0.1 or 0	day^{-1}
N	659	
c_w	2.4	day^{-1}
c_m	10.6	day^{-1}

Table 7: Initial conditions and parameter values used in the simulations performed. The values of the treatment efficacy were varied.

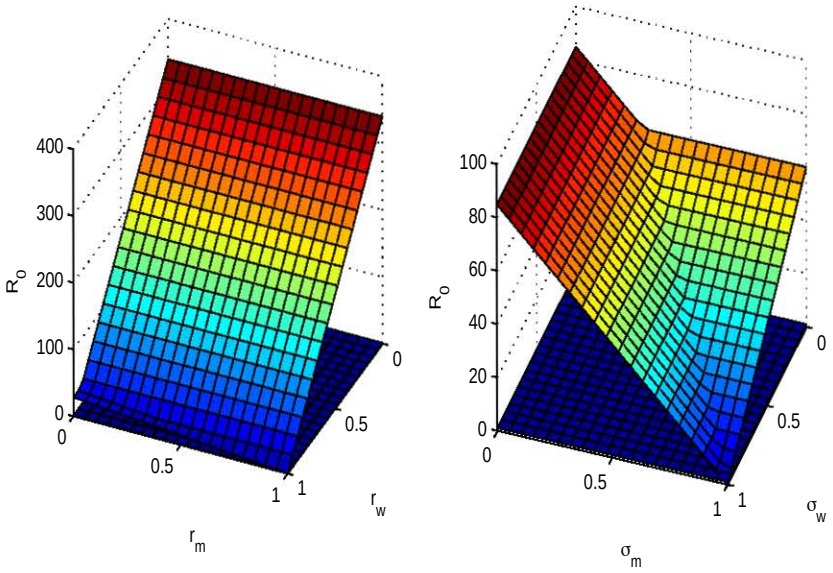

Figure 6: R_0^* vs. RT Treament and R_0 vs. PI Treatment Efficacy when $r_w = 0.85, r_m = 0.25, \sigma_w = 0.15, \sigma_m = 0.75$, and $\alpha = 0.1$

For case 1, where we fixed the RT or entry inhibitor efficacy and vary the PI efficacy, we observe low levels of R_0^* are maintained for high levels of σ_w and σ_m. In fact, we can maintain R_0^* below 60, for $\sigma_m > 0.4$ in combination with any σ_w. Please refer to **??**.

For case 2, minimal levels of R_0^*, less than 50, are achieved when $r_w > 0.40$, for the PI treatment efficacy of $\sigma_w = 0.75$ and $\sigma_m = 0.15$. When we fix $r_w = 0.25$ and $r_m = 0.85$, and vary PI efficacy, we observe a low level of R_0^* for $\sigma_w > 0.50$ and all values of σ_m. Please refer to 7.

While considering ranges of treatments gives allows us to observe the range for which R_0^* will be maintained low, it is not reasonable to assume efficacy of all treatments constant over time. A more realistic approach is to simulate viral loads after viral set point, and with nonconstant efficacy. To achieve this, we introduce a time delay for all treatments. We do not initiate treatment for 10 days after infection. When we do, we make it constant for 5 days. After day 15, the level of efficacy behaves according to a sinusoidal curve.

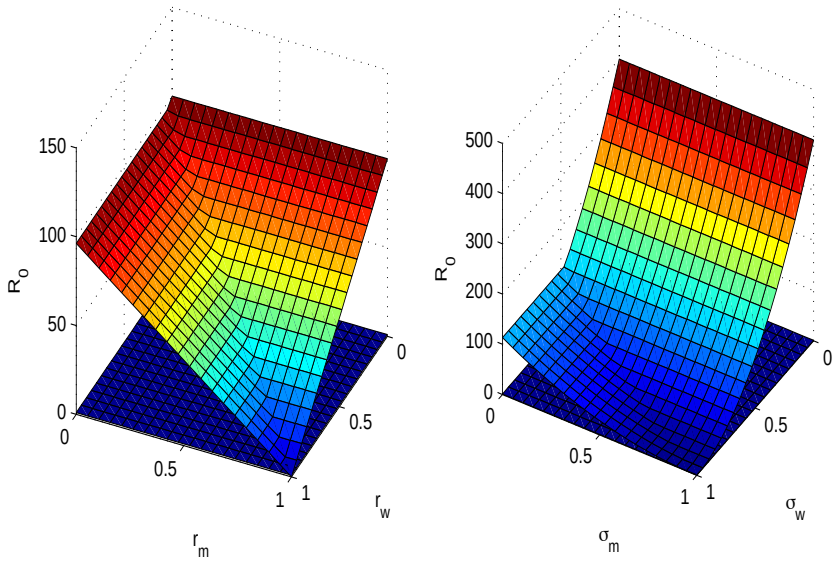

Figure 7: R_0^* varying RT and PI treatment efficacies, where $r_w = 0.25, r_m = 0.85, \sigma_w = 0.75, \sigma_m = 0.15$ and $\alpha = 0.1$

The combination of time delayed treatment causes an increase in viral concentration. When we have a higher RT efficacy on wild-type virus, and low PI efficacy of wild-type virus, we have high levels of wild-type virus with and without immune response. Having a time delay on treatment only considers the problem with constant efficacy, however, also including immune response time delay would be appropriate in this model.

8 Results and Conclusions

In an effort to gain further understanding of the dynamics of HIV infection, we have developed a mathematical model which considers the effects of immune response and multi-drug treatment on the in-host progression of two genetic variants of HIV. Mathematical analysis was conducted for the case when no viral mutation occurred as well as for when viral mutations took place. In each case, multiple equilibria were found. We determined both coexistence and exclusion

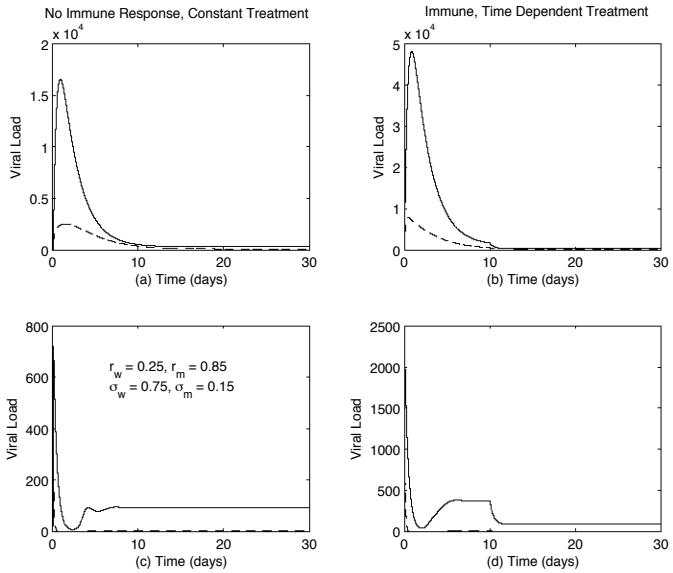

Figure 8: Case 2, (-) Wild Virions, (- -) Mutant Virions, (a) and (c) Do not consider an immune response and have constant treatment, (c) and (d) Consider an Immune Response and Time Dependent Treatment

equilibria as well as existence criteria for each of these points. For the case where the mutation rate was zero, we determined criteria which ensured the stability of each exclusion equilibria. In both the mutation and the non-mutation case, the conditions for stability of F_0 and E_0, the non-infected steady states, were used to derive the effective reproductive numbers R_0 and R_0^*, which are defined as the average number of secondary viruses produced by the introduction of a single virus into a pool of uninfected $CD4^+$ cells.

Once the effective reproductive number was determined, we carried out uncertainty and sensitivity analysis. The uncertainty analysis gave insight to how uncertain the value of R_0^* was given the uncertainty of the parameters in R_0^*, while sensitivity analysis revealed which parameters had the greatest relative effect on the value of R_0^*. Through uncertainty analysis, it was found that, given a number, Q, the probability that R_0^* is less than Q is positively correlated with Q. In particular, for very low values of N, the probability that R_0^* is less than N is extremely low. This agrees with the fact that once a person is successfully infected with HIV, it is highly improbable for viral levels to decrease to zero. The results of the sensitivity analysis were somewhat surprising. We discovered that, in both treatment cases, R_0^* was least sensitive to the mutation rate. The T cell infection rate, the recruitment and death rates of $CD4^+$ cells, and the burst number were among the parameters to which R_0^* was most sensitive in both treatment cases. Finally, considering only treatment parameters, the

effective reproductive number was most sensitive to treatment efficacy for the mutant type virus. These results suggest that it is crucial to have drugs which can decrease the susceptibility of T cells and reduce the infectivity of the virus.

In addition to mathematical and sensitivity analysis, numerical simulations were conducted to provide further insight to the model. In these simulations, we considered two separate cases. In one case, the infection inhibiting drug had a high efficacy for the wild type virus and a low efficacy for the mutant type virus, while the viral replication inhibiting drug had high efficacy for the mutant type virus and a low efficacy for the wild type virus. In the other case, the infection inhibiting drug had a high efficacy for the mutant type virus and a low efficacy for the wild type virus, while the viral replication inhibiting drug had high efficacy for the wild type virus and a low efficacy for the mutant type virus. In each of these cases, a specific type of drug is used to target a specific genetic variant of the HIV virus. We found that only a small range of treatment parameter values would yield an effective reproductive number less than unity, which would result in eradication of the viral population. These parameter values correspond to very high efficacy of treatments. Furthermore, our model suggests using specific types of drugs to target specific strains of HIV is an ineffective way to treat HIV. In order to keep the progression of HIV to a minimum, at least one drug should have high efficacy for multiple genetic variants of the virus.

9 Future Work

Due to complexity of the HIV, we made assumptions of the nature of the parameters to simplify our calculations. To improve on the amount of information captured by the model, one alteration to our model would be the inclusion of the β, effectiveness of CD7 cells in killing infected helper T cells, in the $\frac{dV_w}{dt}$ and $\frac{dV_m}{dt}$ terms. This would assure the β term would appear in the effective reproductive number in order to consider immune response in maintaining R_0^* at a minimum level. While this model accounts for immune response and treatment on two strains of HIV, it does not account for the time delays associated with immune response and treatment. Formulating a time delay model could aid in determining the role of responses of immune to infection and to treatment. Not only are parameters associated with immune response and treatment efficacy time dependent, but other parameters such as supply of CD4 T cells, mutation rate, and infectivity rate among others should also be made time dependent. This would provide a framework for understanding the balancing of immune response and treatment to viral load, helper T cell count and killer T cell count. We notice results vary due to parameter estimations used during simulations. Finding ways to make more accurate estimations of parameters would improve the quantitative results presented in this paper.

10 Appendix

10.1 Routh-Hurwitz Theorem

1. Find Jacobian Matrix (J) of system at the steady point (p) of interest, ($J(p)$).
2. Find characteristic equation for system jacobian by takeing the determinate of ($J(p) - \lambda I$), where J is the system Jacobian matrix and I is the identity matrix.
   To ensure eigenvalues have real negative part, use Routh-Hurwitz Method as follows:

- For $\lambda^2 + \lambda a_1 + a_2 = 0$

$$a_1, a_2 > 0$$

- For $\lambda^3 + \lambda^2 a_1 + \lambda a_2 + a_3 = 0$

$$a_1, a_3 > 0$$

and

$$a_1 a_2 > a_3$$

- For $\lambda^4 + \lambda^3 a_1 + \lambda^2 a_2 + \lambda a_3 + a_4 = 0$

$$a_1, a_2, a_4 > 0$$

and

$$a_3(a_1 a_2 - a_4) > a_1^2 a_4$$

10.2 Local stability criteria for each steady point when $\alpha = 0$

Stability For Steady Point E_1

$$J(E_1) = \begin{pmatrix} -d - (1-r_m)kV_m & 0 & 0 & 0 & -(1-r_w)kT_4 & -(1-r_m)kT_4 \\ 0 & -\delta & 0 & 0 & (1-r_w)kT_4 & 0 \\ (1-r_m)KV_m & 0 & -\delta & \beta T_m^* & 0 & (1-r_m)kT_4 \\ 0 & 0 & 0 & \gamma T_m^* - \mu & 0 & 0 \\ 0 & (1-\sigma_w)N\delta & 0 & 0 & -c_w & 0 \\ 0 & 0 & (1-\sigma_m)N\delta & 0 & 0 & -c_m \end{pmatrix}$$

Characteristic Equation: $Det(J(E_1) - \lambda I) = ABC$
where

$$A = \big(\lambda - \gamma T_m^* + \mu\big)$$
$$B = \big(\lambda^2 + (\delta + c_w)\lambda + \delta c_w - \frac{R_w \delta c_w}{R_m}\big)$$
$$C = \big(\lambda + \delta + (1 - r_M)kV_m\big)\big(\lambda^2 + (\delta + c_m)\lambda\big) + \big(dc_m\delta(R_m - 1)\big)$$

Stability For Steady Point E_2 This point is symmetric to Point E_1.

Stability For Steady Point E_3

$$J(E_1) = \begin{pmatrix} -d - (1 - r_m)kV_m & 0 & 0 & 0 & -(1 - r_w)kT_4 & -(1 - r_m)kT_4 \\ 0 & -\beta T_8 - \delta & 0 & 0 & (1 - r_w)kT_4 & 0 \\ (1 - r_m)kV_m & 0 & -\beta T_8 - \delta & \beta T_m^* & 0 & (1 - r_m)kT_4 \\ 0 & \gamma T_8 & \gamma T_8 & \gamma T_m^* - \mu & 0 & 0 \\ 0 & (1 - \sigma_w)N\delta & 0 & 0 & -c_w & 0 \\ 0 & 0 & (1 - \sigma_m)N\delta & 0 & 0 & -c_m \end{pmatrix}$$

Characteristic Equation:

$$Det(J(E_3) - \lambda I) = AB$$

where

$$A = \big(\lambda^2 + (\beta T_8 + \delta + c_w)\lambda + (\beta T_8 + \delta)c_w - \frac{dR_w c_w \delta T_4}{s}\big)$$

and

$$B = \left(\frac{-s}{T_4}\big(-\lambda(\lambda + \beta T_8 + \delta)(\lambda + c_m) + \frac{R_m c_m d\delta T_4}{s}\lambda - \beta\mu T_8\lambda + c_m)\big) + \frac{R_m c_m d\delta\lambda(s - dT_4)}{s}\right)$$

Stability For Steady Point E_4 is similar.

Stability for E_5 and E_6 is difficult due to the nature of the system. Only a range of numerical results were obtained to show the stability of the steady states.

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