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Modeling Immune System Dynamics during HIV Infection and Treatment with Differential Equations

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Abstract: An inquiry-based project that discusses immune system dynamics during HIV infection using differential equations is presented. The complex interactions between healthy T-cells, latently infected T-cells, actively infected T-cells, and the HIV virus are modeled using four nonlinear differential equations. The model is adapted to simulate long term HIV dynamics, including the AIDS state, and is used to simulate the long term effects of the traditional antiretroviral therapy (ART). The model is also used to test viral rebound over time for the combined application of ART and a new drug that blocks the reactivation of the viral genome in the infected cells and locks the HIV virus into a state of latency.

1 Introduction

Human Immunodeficiency Virus (HIV) is a devastating public health challenge that affects approximately 38.4 million people worldwide [1]. HIV is a virus that destroys a person's immune system by attacking T-helper cells and using them as hosts for viral replication. The immune system functions as a defense against antigens, foreign substances in the body which can induce an immune response. The immune system has two different paths for an immune response which interplay with each other: the adaptive immune system and the innate immune system [2]. The innate immune system is a non-discriminatory form of protection that the body employs to begin immune system responses. It consists of neutrophils and macrophages that can both "secrete highly destructive substances including enzymes that digest proteins and reactive chemicals [...and] engulf and digest what they have damaged" [2]. Macrophages are essential to the adaptive immune system as they activate the adaptive immune response by presenting antigens to CD_4+ T-helper cells [2].

The adaptive immune system's pathway has 3 general components: T-helper cells (or more simply T-cells), cytotoxic T-cells, and B-cells. Though B-cells and cytotoxic T-cells directly function as the body's defense in response to infection, T-cells are the cells which coordinate the immune response and "make antibodies [...to] send out signals to attract

macrophages and neutrophils to the site of the infection" [2]. HIV infects these T-cells and uses them as viral replicating hosts, constructing HIV viruses within the T-cell until the release of HIV viral bursts lead to T-cell death [3]. Once HIV infects T-cells, T-cells can no longer notify other immune cells of an infection; therefore, a person infected with HIV is more likely to get other "infections or infection-related cancers" [4]. As HIV replication progresses, the concentration of T-cells in the blood continues to decrease and weakens the immune system [3]. A measure of about 200 T-cells per mm^3 or less signals that HIV has progressed to acquired immunodeficiency syndrome (AIDS) [3]. The AIDS stage is extremely dangerous for the infected individual because their immune system cannot easily fight off any opportunistic illnesses or infections, and various illnesses can be life threatening, such as the cold or flu [5].

HIV infection and viral replication is a permanent process and proceeds through fusing with a cell, reverse transcribing the single-stranded HIV RNA into HIV DNA for integration with the host T-cell's DNA, producing HIV viral proteins using T-cell cellular machinery, and assembling mature HIV virions for further HIV spread [7].

Even though there is no cure, HIV can be controlled through a cocktail of antiretroviral drugs that target different stages of the HIV viral replication cycle such as HIV entry, reverse transcription, integration inhibitors, or virus assembly and production [6]. Antiretroviral therapy (ART) can dramatically prolong a patient's life and lower the chance of the patient infecting others with HIV. Before ART, people infected with HIV could progress to AIDS and die within a few years. Today, people with HIV that are treated before the disease advances to AIDS "can live nearly as long as someone who does not have HIV" [4]. Despite traditional ART treatments controlling the HIV virus while the medication is taken by the individual, treatments have many negative side effects on the long term and include loss of bone marrow, nausea, diarrhea, hypertriglyceridemia, kidney stones, gallstones, and heart disease [8]; for this reason, traditional ART treatment is often supplemented with another type of drug to form a cocktail of anti-HIV drugs. Furthermore, a major drawback of ART is that it cannot affect latently infected T-cells, which can switch to become actively producing viral hosts in time; therefore, when ART is interrupted, latently infected cells can reactivate and replenish the viral reservoirs.

A particular class of antiretroviral medications are those which target the virus assembly and production after integration of the viral genome to prevent large quantities of viral load from being produced by a single cell. These medications inhibit HIV transcription, viral assembly and production, and protease processing [6]. A new drug called didehydro-Cortistain A (dCA) blocks off reactivation of the viral genome in the infected cells and locks the HIV virus into a state of latency. This drug inhibits the HIV protein Tat that recruits the cell to initiate HIV production. When Tat is inhibited, any production, reactivation, and replenishment of the viral reservoir is stopped [9]. This medication is the first to target HIV in such early stages of its life cycle. It was tested on Bone-Liver-Thymus (BLT) mouse models; the viral rebound after stopping ART in the BLT mouse models occurred within seven days. In contrast, the viral rebound of the new dCA medication was delayed to up to 19 days. Researchers expect that "longer treatments [with the novel dCA medication] will result in longer, or even permanent, rebound delays," but further testing is necessary to evaluate the duration of the delays [9].

This promising new strategy has only been used on mice, and further exploration

of the dCA medication's therapeutic application in humans to block HIV reactivation in the T-cell's genome is a high research priority, especially as part of a combinatorial approach for treatment [10]. One way to understand the complex interactions between the human immune system, HIV, and the new drug in combination with ART is through the means of mathematical modeling. Mathematical models are useful tools that can answer questions regarding chemotherapy such as proper dosage, duration of treatment, periodicity of doses, and defining the best treatment strategy for a patient. A variety of working hypotheses may be tested through mathematical modeling to refine the most probable one, which then may be tested in clinical environment. A mathematical model is a viable tool that allows a comprehensive theoretical outlook on the effects of the variation of model's parameters before running expensive and exhaustive human trials.

This project uses mathematical modeling to simulate the effect of the novel dCA drug on HIV viral rebound over time in the human immune system. As this medication is applied together with the traditional ART treatment, a particular reverse transcription inhibitor called Zidovudine (ZDV) is used to model the ART application [11]. The long term effects of ZDV treatment and combined ZDV plus dCA treatment are assessed. For this purpose, a mathematical model of interactions between HIV and the human immune system using differential equations is derived under certain assumptions. The model is also modified to simulate the AIDS stage of the disease. The effect of the novel dCA treatment on the HIV infected human immune system is simulated by varying the level of inhibition the drug has on HIV infected cells. Parameters in the model are based on data from clinical observations of HIV patients and data from the BLT mouse tests in the *in vivo* trials of the dCA medication. The results of this study can be useful for medical practitioners to understand the dynamics of the novel HIV treatment before testing it on humans.

The rest of the paper is organized as follows. Section 2 presents the assumptions, variables, parameters, and differential equations that make up the mathematical model. Section 3 discusses the values of the model's parameters which are derived based on real observational data. Section 4 discusses the modification of the mathematical model to simulate AIDS dynamics. In Section 5, numerical simulations are performed to study the long term behavior of the immune system's dynamics and the virus under different drug treatments using the modified model. Section 6 summarizes the important mathematical results obtained in this study and provides evidence-based answers to the biological questions that motivated this study. Some model limitations are also discussed in Section 6. *Student Exploration Exercises* are included throughout the paper, which can be used to supplement discussions and analysis of the mathematical model in the classroom.

2 Mathematical model of the immune system dynamics with HIV infection

Start from a simple mathematical model describing the rate of change of T-cells in a healthy human immune system and assume logistic growth of the T-cells. This model

was first suggested by Perelson, Kirschner, and De Boer in [12].

$$\frac{dT}{dt} = s + rT\left(1 - \frac{T}{T_{max}}\right) - \mu_T T, \tag{2.1}$$

where $T = T(t)$ is the concentration of uninfected, healthy T-cells, s is the supply rate of the T-cells from precursors in the thymus, r is the growth rate of uninfected T-cells, μ_T is the death rate of uninfected T-cells, and T_{max} is the maximum T-cell concentration.

To incorporate HIV into the immune system's dynamics, following [12], the class of T-cell concentration is split into three classes: $T = T(t)$ are the healthy T-cells, $T_1 = T_1(t)$ are the infected T-cells that are latent and do not produce virus, and $T_2 = T_2(t)$ are the infected T-cells that actively produce virus. The variable $V = V(t)$ represents the concentration of free, infectious HIV. The system of differential equations describing the dynamics between T-cells and HIV is given by the following system of ordinary differential equations

$$\begin{cases} \dfrac{dT}{dt} &= s + rT\left(1 - \dfrac{T + T_1 + T_2}{T_{max}}\right) - \mu_T T - k_1 VT \\ \dfrac{dT_1}{dt} &= k_1 VT - \mu_T T_1 - k_2 T_1 \\ \dfrac{dT_2}{dt} &= k_2 T_1 - \mu_b T_2 \\ \dfrac{dV}{dt} &= N\mu_b T_2 - k_1 VT - \mu_V V. \end{cases} \tag{A}$$

The first equation in (A) is a modified equation (2.1) and represents the rate of change of the uninfected T-cells. s is a source term and represents the rate of generation of new uninfected T-cells from precursors in the bone marrow and thymus. Uninfected T-cells have a finite life span and are assumed to die at the same rate μ_T as in an uninfected individual. It is also assumed that the latently infected T-cells (T_1) have the same death rate μ_T as the uninfected T-cells due to challenges in the immune system differentiating which T-cells are uninfected or latently infected.

To include the effects of HIV, the term $k_1 VT$ is subtracted in the right-hand side of the first equation as it models the rate at which the free virus infects healthy T-cells. Once T-cells have been infected, they become latently infected cells (T_1). Hence the same term $k_1 VT$ is added to the second differential equation that models the population dynamics of latently infected cells. The term $k_2 T_1$ models the rate at which the latently infected T-cells (T_1) are transformed to actively infected T-cells (T_2) (i.e. this term is subtracted from the second equation and is added to the third equation). The third differential equation models the rate of change of T-cells actively producing virus (T_2). The term $\mu_b T_2$ represents the rate at which T_2 cells die and exit the system. However, by the time a T_2 cell dies, it releases N free, infectious viral particles in its lifetime. Hence, the term $N\mu_b T_2$ is included in the fourth differential equation that models the rate of change of the viral load in the bloodstream. In Perelson et al.'s model [12], the parameters N and μ_b are treated as constants that are related to replication rate and are "characteristic of a particular viral species." In the fourth differential equation, the term $k_1 VT$ models the rate at which viral particles infect healthy T-cells and exit the free virus population. The last term $\mu_V V$ in the fourth differential equation represents the viral clearance rate from the patient's body.

Student Exploration 1: Understanding the model and parameters

1. The model assumes that T-cells grow logistically. What does such an assumption mean and why it is appropriate for our model? What other types of cellular population growth do you know?
2. The terms $\pm k_1 VT$ participate in both equation two and equation four in (A). They have the same coefficient k_1. What will it mean for the model if the coefficients are different?
3. The rate of change of the virus is described by the fourth equation in (A). What does the term $N\mu_b T_2$ tell us about the growth of V?

3 Discussing the values of the model's parameters

When performing numerical simulations, one of the biggest challenges is finding appropriate values for the model's parameters such that they reasonably represent the real biological processes that are modeled. For this purpose, observational studies are necessary to estimate an appropriate value or range of values for each parameter based on real life data. In this study, the parameters' values derived in [12] will be used and are provided in Table 1. Next, the process for how these parameters are obtained will be discussed in detail.

Though the number of healthy, uninfected T-cells in the bloodstream fluctuates, uninfected T-cell count is estimated at approximately 1000 mm^{-3} because the normal T-cell count in HIV-negative people is between 500-1,500 mm^{-3} [13]; thus, the initial condition for T-cells in a healthy individual is assumed to be $T(0) = 1000mm^{-3}$. Along those same biological values, the parameter T_{max} is chosen as $T_{max} = 1500mm^{-3}$ because it is the clinically relevant value of the maximum number of healthy T-cells. Next, the parameters s, r , and μ_T are chosen so that the population of T-cells in the absence of HIV is maintained at 1000 mm^{-3}. To define the growth rate r, it is conservatively assumed that the T-cells divide every 12-18 hours [14]. Therefore, the growth rate of an activated cell is conservatively approximated to be 1 day^{-1}. After this, the growth rate is multiplied by the fraction of dividing T-cells, which is 1% or 0.01. Based on observations, it is known that T-cells, when not replicating due to antigen stimulated immune responses, have a half-life of about 36 days. The death rate parameter is calculated as follows $\mu_T = (\ln 2)/36 = 0.02\ day^{-1}$. For the net rate increase of T-cells population to be 0.01, the growth rate r is chosen as $r = 0.03$ and the death rate as $\mu_T = 0.02$. For these chosen parameters and in the absence of HIV infection, the T-cells population maintains a steady state of 1000 mm^{-3} in the differential equation (2.1), which can be seen in Figure 1 for different initial concentrations of healthy T-cells.

Student Exploration 2: T-cells population behavior in the absence of infection
Recreate Figure 1 by solving the model (2.1) with the following initial values for the T-cells: $T_0 = 250, 500, 1200, 1500$; students can use the *ode45* built in differential equation solver in MATLAB. What could be said about the long term behaviour of the immune system of a healthy person? Does the long term immune cell count depend on the initial condition?

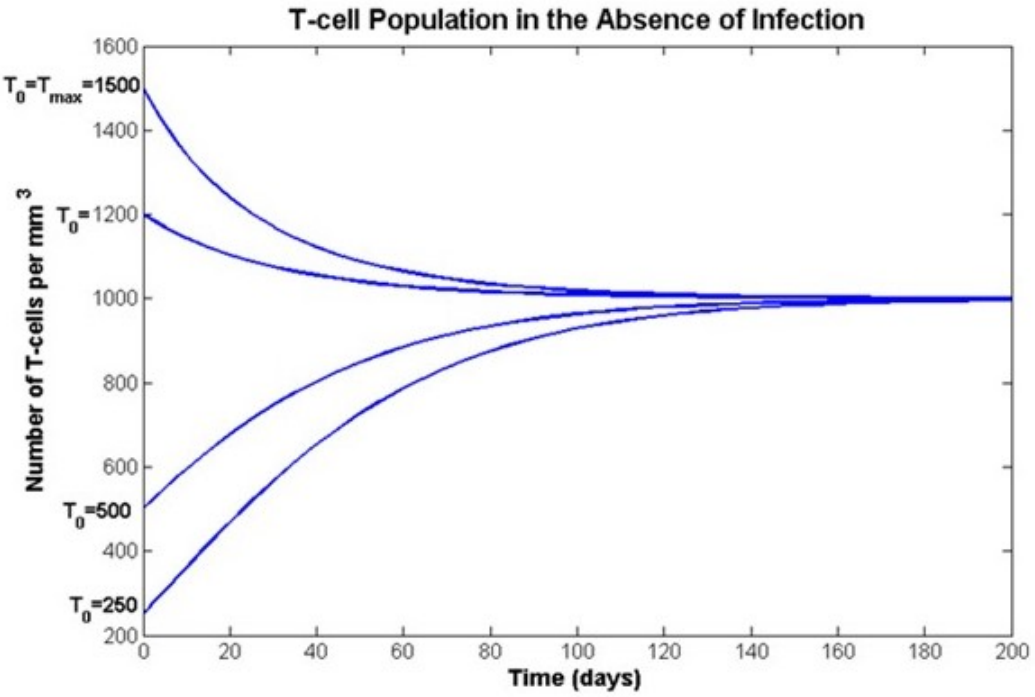

Figure 1: T-cell population distribution in a healthy individual. Four initial values T_0 for the T-cell concentration are considered: 250, 500, 1200, and the maximum of 1500 cells per cubic millimeter. The stationary value for each case is 1000 cells per mm^3.

The parameter k_1 in the differential equations is a bimolecular rate constant that represents the rate of infection of the healthy T-cells by the HIV virus particles, and it has a dimension of $mm^{-3}day^{-1}$. To estimate this parameter, it is scaled such that the product k_1T_0 has the units day^{-1}. The reason for such scaling is based on the fact that viral infection of a cell occurs when it "encounter[s] the cell, bind[s to] CD_4 or some other receptor, and then enter[s] the cell" [12]. Then, to create an upper limit for the term k_1T_0, the Smoluchowski's formula [15, 16] for diffusion-limited rate constants is applied, and this product is estimated to be bounded by $k_1T_0 \leq 0.36h^{-1}$. Furthermore, assuming that $k_1T_0 = 0.001h^{-1} = 0.024days^{-1}$ as only 2-3% of the T-cells become actively infected T-cells when viral particles attach and attempt to infect them; hence, $k_1 = 2.4 \times 10^{-5}mm^{-3}day^{-1}$ [12].

To estimate the value of μ_b, the death rate of actively infected T-cells (T_2), it is assumed based on observational studies that HIV-infected cells are viable up to 62 hours after infection. Parameter μ_b is hence estimated such that $\mu_b = 0.24\ day^{-1}$ using 2.58 days as the half-life for the actively infected cells.

To estimate the parameter μ_V, it is assumed that the free virus in the body lost half of its infectivity in 4 to 6 hours such that $\mu_V = 2.4\ day^{-1}$. For the parameter k_2, which represents the rate at which latently infected T-cells transform into actively infected T-cells, it is assumed that this parameter would be much smaller than the growth rate r; hence, $k_2 = 0.1r = 0.003\ day^{-1}$ as the "conversion process may not be 100 % efficient" [12].

The parameter N represents the number of infectious viral particles released by an actively infected T-cell over its lifespan. This number depends on many factors and some observational studies estimated N between 1,000 and 3,000 [17]. For the purpose of modeling, N is varied in the low range between 1000 and 1500 as this model is applicable to HIV strains that do not produce immune response and such strains are believed to be low viral producers [18].

Stability analysis of the system (A), which is left as *Student exploration 3*, reveals that this system has two equilibrium states - one uninfected steady state and one infected steady state. It also finds that N must be larger than a certain critical threshold number N_{crit} for the HIV infection to develop into AIDS. If $N \leq N_{crit}$, the virus decays and the system would return to an uninfected state. If $N = N_{crit}$, the virus remains constant at a practically undetectable level of $10^{-5}\ mm^{-3}$. Finally, if $N \geq N_{crit}$, the free viral particle concentration grows. This analysis indicates that N_{crit} is a bifurcation parameter that shows how viral replication affects the course of the infection; if infected T-cells die without producing enough virus, then there would not be enough virus with each generation that could sustain the HIV infection. It could be shown that when $N \leq N_{crit}$, then the uninfected steady state equilibrium is asymptotically stable; when $N \geq N_{crit}$, then the endemically infected steady state equilibrium becomes stable. This proof is left as a *Student exploration 4*.

Student Exploration 3: Stability analysis of system (A): Finding system's equilibrium solutions.

Find the two equilibrium values E_1, E_2 of the system (A).

Show that it has one uninfected steady state: $E_1 = (T^*, T_1^*, T_2^*, V^*)$, where

$$T^* = \frac{T_{max}}{2r}\left(r - \mu_T + \sqrt{(r-\mu_t)^2 + \frac{4sr}{T_{max}}}\right), T_1^* = T_2^* = V^* = 0$$

and one infected steady state: $E_2 = (\overline{T}, \overline{T}_1, \overline{T}_2, \overline{V})$, where

$$\overline{T} = \frac{\mu_V}{\alpha}, \quad \alpha = \left(\frac{Nk_2}{\mu_T + k_2} - 1\right)k_1; \quad \overline{T}_1 = \frac{\mu_V V}{Nk_2 - k_3}; \quad \overline{T}_2 = \frac{k_2\mu_V V}{\mu_b(Nk_2 - k_3)}, k_3 = k_2 + \mu_T$$

$$\overline{V} = \frac{s\alpha^2 + (r-\mu_T)\alpha\mu_V - \gamma\mu_V^2}{k_1\mu_V(\alpha + \beta\mu_V)}, \quad \beta = \frac{\gamma}{k_3}\left(1 + \frac{k_2}{\mu_b}\right), \quad \gamma = \frac{r}{T_{max}}.$$

Student Exploration 4: Stability analysis of system (A): Finding the critical threshold number and bifurcation parameter N_{crit}.

Using the Jacobian of the system (A), study the stability of the two equilibria E_1 and E_2. Show that the uninfected equilibrium E_1 will be asymptotically stable for $N < N_{crit}$, where $N_{crit} = \dfrac{k_3(k_1T_0 + \mu_V)}{k_1k_2T_0}$.

Student Exploration 5: Numerical simulations of the long term HIV-immune system dynamics

Recreate Figure 2 of the dynamics of healthy, latently, and actively infected T-cells and the free virus by numerically solving system (A) using values from Table 1. The bursting parameter N is varies at three different values: 1000, 1200, and 1400.

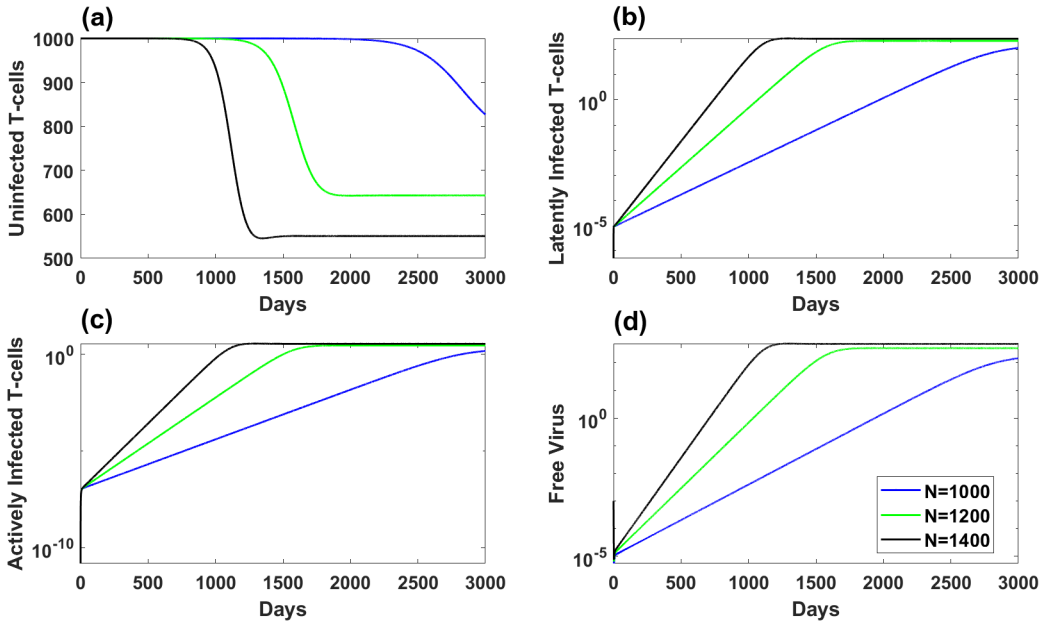

Figure 2: Immune system dynamics simulations under HIV infection using model (A) for different values of the parameter N: N=1000 in blue, N=1200 in green, and N=1400 in black. Panels represent (a) uninfected T-cells, (b) latently infected T-cells, (c) actively infected T-cells, and (d) free viral particles.

Next, numerical simulations of the healthy, latently, and actively infected T-cells and the free virus using (A) are illustrated in Figure 2. All graphs and numerical simulations are created using MATLAB, the numeric computing environment developed by MathWorks. From Figure 2, observe that the healthy T-cells decrease significantly in a HIV-infected person after about 600-700 days (or about 2 years) and eventually reach a value between 500 and 600 cells per mm^3 when the lysing (bursting) parameter $N = 1400$. This means

that this model does not reproduce the AIDS state, which is when the number of uninfected T-cells in a HIV infected individual falls under 200 cells per mm^3. In the next section, the model is modified so that it simulates AIDS dynamics.

Variables	**Description**	**Initial or default values**
$T(t)$	T-cells of the healthy immune system	500-1500 mm^{-3}
$T_1(t)$	latently infected T-cells	0
$T_2(t)$	actively infected T-cells	0
$V(t)$	free HIV virus	10^{-3} mm^{-3}
Parameters		
s	supply rate of T-cells from the thymus	10 $day^{-1}mm^{-3}$
r	growth rate parameter of T-cells	0.03 day^{-1}
μ_T	death rate parameter of T-cells	0.02 day^{-1}
k_1	infection rate parameter of the virus	$2.4 \times 10^{-5} mm^3 day^{-1}$
k_2	rate of transforming from T_1 to T_2	$3 \times 10^{-3} day^{-1}$
μ_b	death rate parameter of infected T-cells	0.24 day^{-1}
μ_v	viral clearance rate parameter	2.4 day^{-1}
N	bursting number parameter	varies (50 - 1500)

Table 1: The functions and parameters in the model (A) and their initial or default values.

4 Modified mathematical model that simulates the AIDS dynamics

In the equation for the rate of change of the virus in system (A), the term $N\mu_b T_2$ is replaced with a nonlinear growth term $\frac{N\mu_b t^2}{b^2+t}T_2$. The idea for this nonlinear growth term comes from a similar term $\frac{\beta B^2}{\alpha^2+B^2}$ used in [19], where it determines the scale of budworm densities at which saturation of predators will take place. While in [19] the budworm density B term is squared in both the numerator and denominator, t (time) is squared only in the numerator of model (B) to mimic the exponential growth of the virus.

$$\begin{cases} \frac{dT}{dt} &= s + rT\left(1 - \frac{T+T_1+T_2}{T_{max}}\right) - \mu_T T - k_1 VT \\ \frac{dT_1}{dt} &= k_1 VT - \mu_T T_1 - k_2 T_1 \\ \frac{dT_2}{dt} &= k_2 T_1 - \mu_b T_2 \\ \frac{dV}{dt} &= \frac{N\mu_b t^2}{b^2+t} T_2 - k_1 VT - \mu_V V. \end{cases} \tag{B}$$

Here, the parameter b is introduced and represents the scale of virus in the bloodstream at which saturation of virus takes place. The upper limit for viral load saturation in the

bloodstream is incredibly difficult to calculate and varies depending on the patient. As clinical guidelines indicate that viral load above 100,000 copies is generally considered 'high,' the parameter b is estimated to saturate when $b^2 \geq 100,000 mm^{-3}$, and $b = 316 mm^{-3}$ in this study [13]. In the modified model (B), as b is the absolute clinical minimum, AIDS occurs in approximately 2 years; however, for real patients, viral load saturation can be dramatically higher depending on the individual and AIDS would occur over a longer timescale. This relationship can be seen in Figure 3.

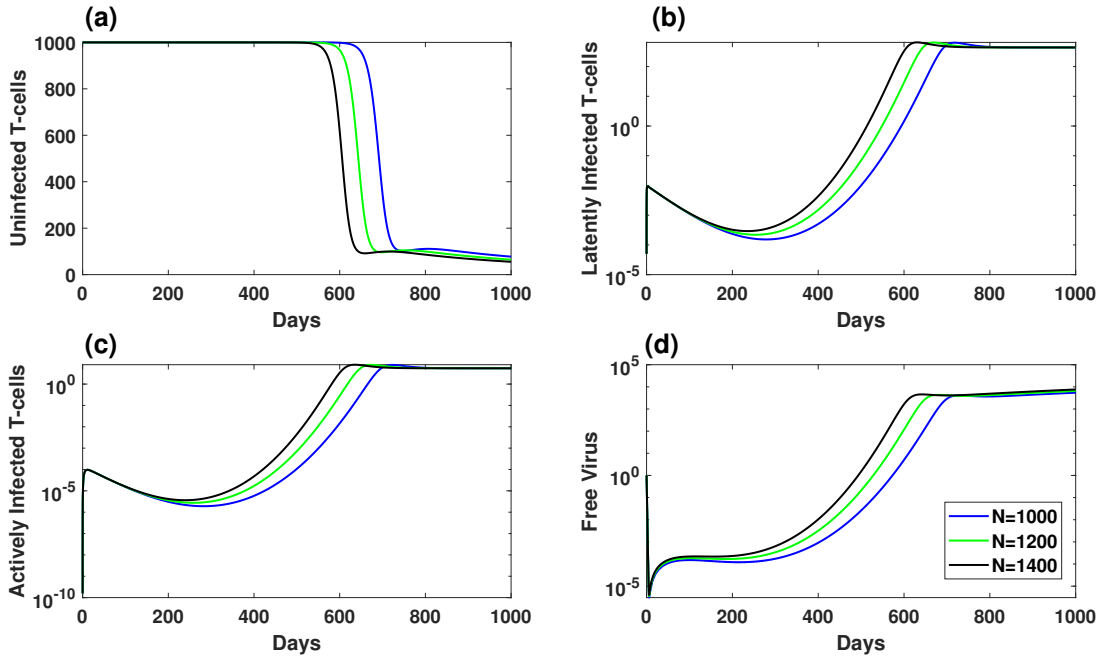

Figure 3: AIDS dynamics simulations using model (B) with the nonlinear growth term for different values of viral load produced by actively infected T-cells over their lifetimes N: N=1000 in blue, N=1200 in green, and N=1400 in black. Panels represent (a) uninfected T-cells, (b) latently infected T-cells, (c) actively infected T-cells, and (d) free viral particles.

The nonlinear growth term enables a switch from slow to rapid replication of the virus and thereby accounts for the very fast viral growth characteristic of HIV during the AIDS stage. This term also implicitly models mutations in HIV, as the more HIV virus is produced, the more likely it is that there are new forms of the virus that can more effectively infect T-cells and escape detection and death by the immune system, thereby propagating a faster spread of the infection. Furthermore, the addition of this term addresses another deficiency in the model (A) where the number of free virus is relatively low at about an order of 10^3 in comparison to viral load tests in actual patients which is $> 10^4$. As evident in Figure 3, the scale of the free virus in the bloodstream better approaches clinical values and is at a scale of 10^4.

Furthermore, the new model (B) is quite stable when the parameter N is varied. This contrasts the original model (A) which, as Figure 2 shows, is quite sensitive when N is varied. The new model's behavior is more realistic and in line with HIV dynamics as the parameter N may vary. As HIV is a chronic disease, it cannot be cured even when there is

an immune response actively trying to clear the virus from the patient's system [4]. In the next section, this new model is used to simulate the effect of some HIV treatments.

5 Simulating the effect of HIV/AIDS treatment

One antiretroviral medication that is frequently used to inhibit HIV infection of the cell is ZDV. ZDV is a reverse transcriptase inhibitor that prevents the RNA genome of HIV from being converted into DNA [11]. ZDV targets the process of viral genome integration into the cell, which occurs early in the viral replication cycle of HIV. Medications that inhibit early parts of the pathway before integration of HIV's genome to the host cell's DNA can "block" the pathway for infection. To simulate such treatment using the derived model, it is assumed that this medication can inhibit the transition from a healthy T-cell to a latently infected T-cell. Hence, the term k_1VT in the model B changes to k_1VTR. The new model C is given below:

$$\begin{cases} \dfrac{dT}{dt} &= s + rT\left(1 - \dfrac{T + T_1 + T_2}{T_{max}}\right) - \mu_T T - k_1 VTR \\ \dfrac{dT_1}{dt} &= k_1 VTR - \mu_T T_1 - k_2 T_1 \\ \dfrac{dT_2}{dt} &= k_2 T_1 - \mu_b T_2 \\ \dfrac{dV}{dt} &= \dfrac{N\mu_b t^2}{b^2 + t} T_2 - k_1 VT - \mu_V V. \end{cases} \tag{C}$$

As the treatment serves to reduce viral infectivity, it is included in the system (C) by modifying the term k_1VT. The treatment depends on time because the medication is applied for a certain number of days and also depends on the frequency of medication application. In the long term, the residual concentration of the medication in the blood-stream will stabilize at a certain level that can be calculated and is denoted by R. The derivation of the formula representing the long term residual level of the medication is given in Giordano et al. [20] and is left as *Student Exploration 6*. To simulate the treatment with ZDV, the residual $R = \dfrac{C_0}{e^{kp} - 1}$ is used. The parameter p represents how frequently the medication must be taken, which in this case is assumed $p = 1$ day. The daily dose of the drug is $C_0 = 600$ for ZDV [21]. Finally, k is the elimination constant of the drug that is defined based on the half-life of the medication used, which for ZDV is $k = 16.64$ (based on the fact that the half-life for the ZDV is one hour).

> *Student Exploration 6: Calculating the drug accumulation with repeated doses.*
> Calculate the residual value for the concentration of a drug when it is applied with a period p, has a half-life k, and a dose C_0. Show that the residual value of the drug's concentration in the blood on the long term will be given by $R = \dfrac{C_0}{e^{kp} - 1}$.

Both Figure 4 and Figure 5 explore the dynamics of the model (C) with ZDV treatment over different time durations. Figure 4 illustrates the recovery of the immune system

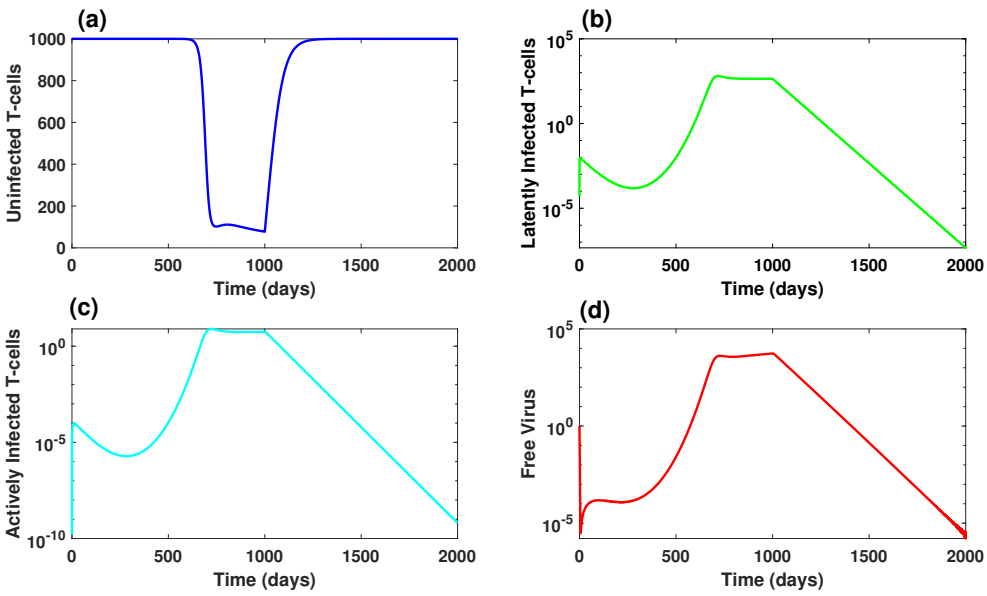

Figure 4: Simulation of a continuous ZDV treatment applied after day 1000, once the AIDS stage is reached, with N = 1000. Panels represent (a) uninfected T-cells, (b) latently infected T-cells, (c) actively infected T-cells, and (d) free viral particles.

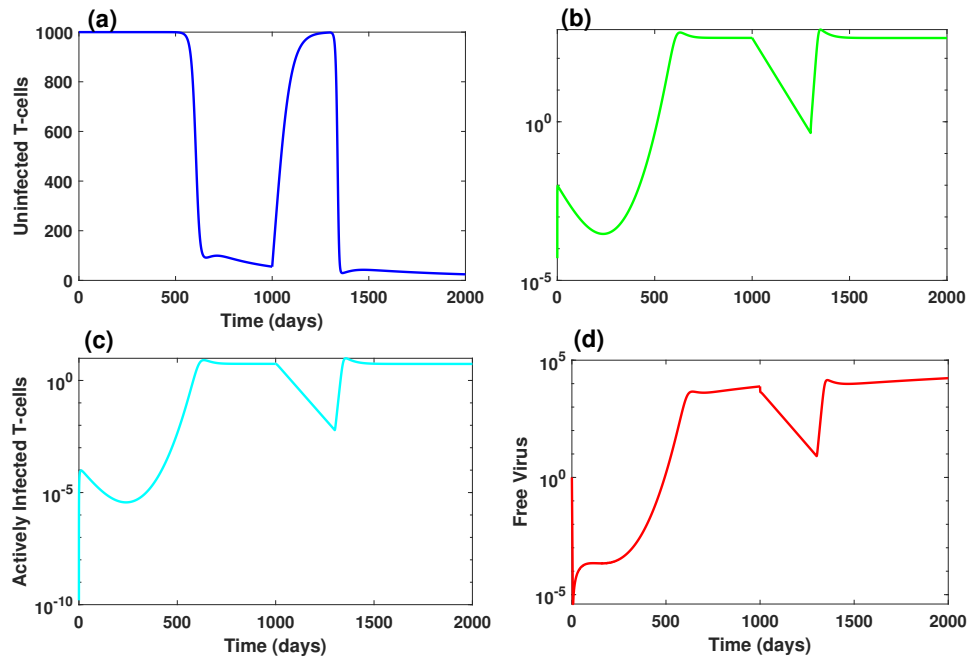

Figure 5: Simulation of a short 300 days ZDV treatment applied after day 1000, once the AIDS stage is reached, with N = 1000. Panels represent (a) uninfected T-cells, (b) latently infected T-cells, (c) actively infected T-cells, and (d) free viral particles.

throughout continuous application of the medication as the viral load decreases and the

T-cells increase up to healthy levels. In Figure 5, the medication was applied for 300 days starting at day 1000 once the AIDS level for healthy T-cells is reached. The graph illustrates the immune system's recovery from AIDS conditions when ZDV medication is applied for 300 days, but then it returns to AIDS state once the medication is stopped.

After the HIV viral genome is integrated into the host T-cell, then a second type of HIV medications can target the HIV viral replication process and reduce the viral load produced because of the infection. One such medication is the dCA inhibitor [9]. To simulate its inhibiting effect on viral replication, an assumption is made that less amounts of virus N will be produced by a single actively infected T-cell when dCA is applied. Thus, to model the long-term effects of dCA application, the magnitude of the parameter N was varied from $N = 1000$ to $N = 500$, $N = 200$, $N = 100$, and $N = 50$, to simulate 50%, 80%, 90%, and 95% inhibition respectively, and the results are given in Figure 6.

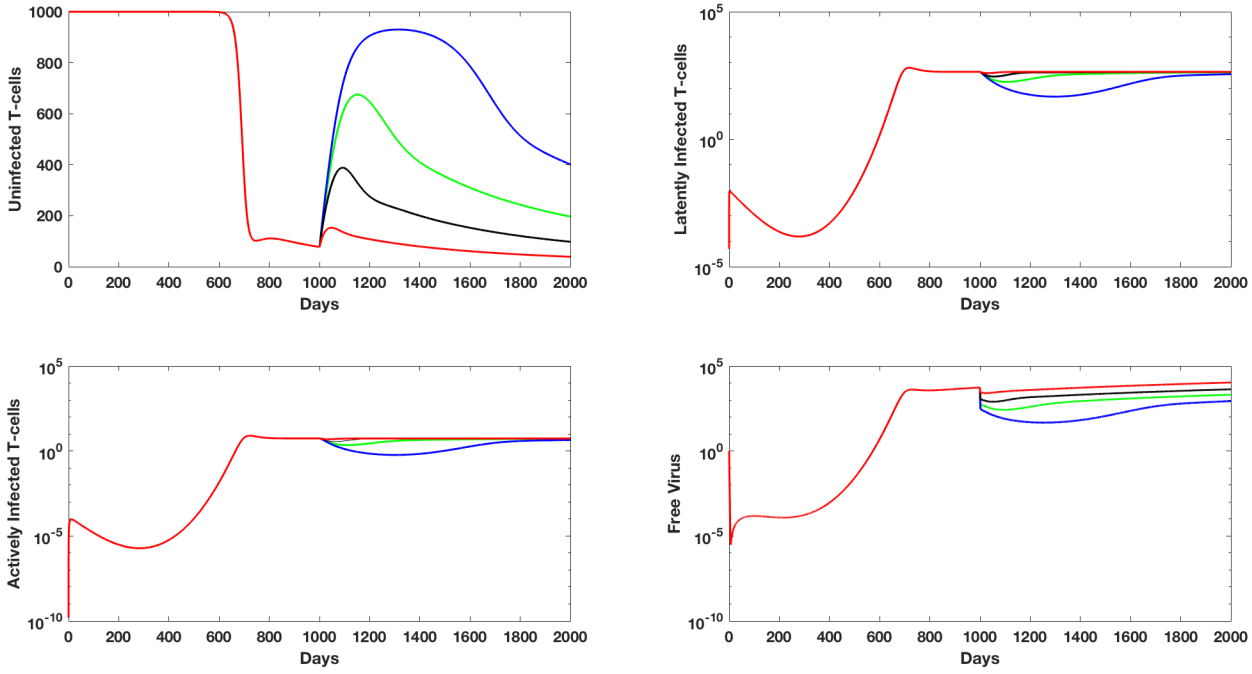

Figure 6: Immune system dynamics over 2000 days when the dCA inhibitor is applied after day 1000. Bursting parameter is initially set at $N = 1000$. 50% inhibition ($N = 500$) is given in red; 80% inhibition ($N = 200$) is given in black; 90% inhibition ($N = 100$) in green; and 95% inhibition ($N = 50$) in blue. Panels represent (a) uninfected T-cells, (b) latently infected T-cells, (c) actively infected T-cells, and (d) free viral particles.

Figure 6 illustrates that even when the virus's production is inhibited through the application of dCA drug, an increase in the uninfected T-cells up to a healthy level can only be observed when there is 95% inhibition (or $N = 50$). As this model does not include immune responses as a mechanism for clearing the virus, it is reasonable that the uninfected T-cell population recovers after a certain time before it starts to decline again because the immune system cannot fight the virus. However, as there is much less

virus being produced due to the dCA application throughout the course of infection, the rate of uninfected T-cell decline is much slower in comparison to the original dynamics establishing AIDS in the system as seen in Figure 3.

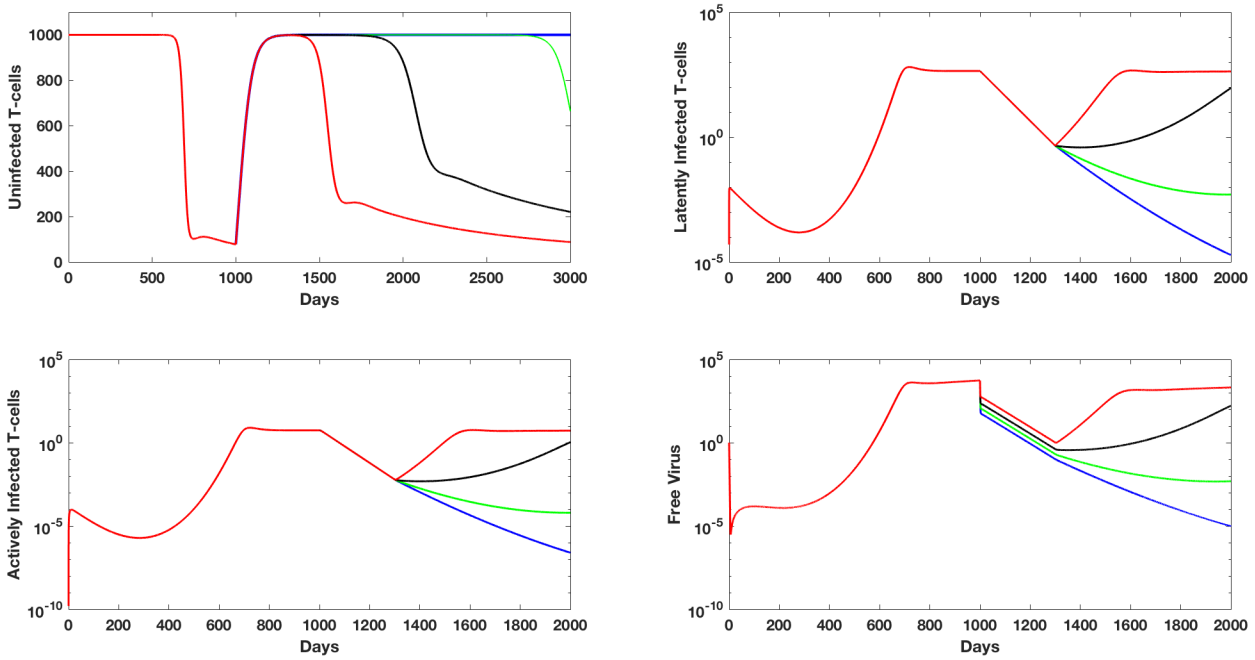

Figure 7: Immune system dynamics over 2000 days when combined treatment with ZDV and dCA is applied after day 1000. ZDV is applied for 300 days, while dCA inhibitor is applied continuously. Bursting parameter is initially set at $N = 1000$. Application of dCA with 50% inhibition ($N = 500$) is given in red; 80% inhibition ($N = 200$) is given in black; 90% inhibition ($N = 100$) in green; and 95% inhibition ($N = 50$) in blue. Panels represent (a) uninfected T-cells, (b) latently infected T-cells, (c) actively infected T-cells, and (d) free viral particles.

Figure 7 depicts the long term effects of the combined treatment with ZDV and dCA drugs applied after 1000 days once the AIDS stage of the HIV infection is established. ZDV is applied for 300 days and is afterwards stopped. Observe that the uninfected T-cell population recovers with the "cocktail" of combined antiretroviral drugs. Even more, the viral rebound is much slower when the treatment is terminated due to the continuous inhibition effects of dCA. When $50 \leq N \leq 200$, as in Figure 7 (green and blue lines), the production of healthy T-cells increases to a healthy concentration and the viral load decreases dramatically. This indicates that with the novel dCA medication, there is an increased delay in the recovery time of the virus in comparison to traditional antiretroviral therapy as illustrated in Figure 5. Hence, this conclusion reinforces the hypothesis that a cocktail of antiretroviral drugs is most effective when treating HIV as both stages of HIV replication can be suppressed in the cell.

6 Discussion and Conclusion

Starting from the immune system population dynamics of a healthy individual, a mathematical model of the complex interactions between the immune system and HIV is derived. The model replicates the clinical levels of both the uninfected T-cells and the free viral particles in the bloodstream, making the model's behavior realistic and in line with HIV dynamics as a chronic disease that cannot be cured even when there is an immune response actively trying to clear the virus from the patient's system [4].

The model is used to study the effects of various treatments on viral suppression and compare their long-term effects on the immune system's dynamics. The effects of two "classes" of medications for HIV treatment are compared in an effort to better understand the biological processes behind HIV infection. The first type of antiretroviral medications is represented by the ZDV drug and affects early stages of the HIV infection pathway prior to the integration of the viral genome to the host T-cell's DNA. The second type targets the HIV viral replication process and reduces the viral load produced because of the infection, represented by dCA drug.

Numerical simulations showed that the first class of medications are much more effective than the second class. When the model was used to simulate the HIV viral population under combined ZDV and dCA application, it was found that the HIV virus rebounds to a level that can be controlled by the uninfected T-cells if the dCA drug inhibits at least 50 % of actively infected cells. In addition, when comparing Figures 4, 6, and 7, the time for the viral rebound when the combined treatment of dCA and ZDV is stopped is extended in comparison to ZDV or dCA treatments alone. This indicates that with the application of the dCA medication, there is an increased delay in the recovery time of the viral load in comparison to traditional antiretroviral therapy (application of ZDV only). Therefore, this supports a hypothesis that a cocktail of antiretroviral drugs is most effective when treating HIV because both stages of HIV infection and replication can be suppressed in the cell.

These results are in compliance with the laboratory study of Kessing et al. [9], where they observed that the viral rebound was delayed up to 19 days after the combined treatment of ART and dCA was interrupted in their mouse-model. When human T-cells, isolated from infected individuals, were used to test the novel dCA and ART treatment *in vitro*, the addition of dCA to ART promoted rapid HIV suppression. They also observed that the viral rebound when the treatment is interrupted is about twice as slow compared to the traditional ART treatment; similar effects were also obtained with the mathematical model.

Next, if the novel drug inhibits at least 50% of actively infected T-cells, Figure 7 shows that the virus rebounds to a low level. Even more, when the inhibition is at least 80%, the uninfected T-cells recover to healthy levels. Similar behavior was observed in a laboratory study by Mousseau et. al. [22], where they applied the dCA inhibitor in human cells during an *in vitro* study. dCA inhibits the viral production of *in vitro* human cells at about 80% to 100% in most of the studied subjects. Only for one subject was the viral inhibition at 55%. For this reason, a variety of estimates of dCA inhibition on viral rebound were studied with the model, including the more conservative assumption of 50% inhibition.

The results of this study improve the knowledge of the underlying dynamics between

HIV infection and the human immune system. The developed mathematical model gives a comprehensive theoretical outlook on the effects of the novel dCA medication on the HIV infected human immune system dynamics before running expensive and exhaustive human trials. The model also can be used in development of new pharmacological strategies for treatment of the disease.

In mathematical modeling, it is also critical to understand applicability and discuss limitations of the constructed model. Even though the modification of the non-linear term used in this study may account for viral mutations over time, one limitation of the model is that it does not explicitly include mutations; the predictions of the immune system being able to control the virus at the steady state may not be true in a real case scenario. However, the predictions of the effects of the novel dCA medication on the virus will not necessarily be affected by viral mutations, as dCA targets the virus before the virus can infect the cell and mutate. Therefore, the predictions of the model about the effects of the novel dCA drug treatment on the viral rebound are valid even under the assumption of no mutations.

One direction for future improvement of this model is to account for the mutations of the HIV virus over time by introducing more variables for the virus $V_i, i = 1, 2, \ldots n$ in the system of differential equations. However, this will significantly effect the theoretical tractability of this model. To further improve the biological accuracy of the model, an external source term could be included. Finally, a mechanism for the immune system to fight back against HIV infection would enable the discussion of the role of medications in the system to become more nuanced and would improve the modeling of the dynamics of HIV and the medications.

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