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HIGHLY ACTIVE ANTIRETROVIRAL THERAPY: MODELING AND OPTIMIZING HIV TREATMENT

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ABSTRACT. Highly active antiretroviral therapy (HAART) is the current standard treatment for the Human immunodeficiency virus (HIV). We will introduce an existing system of ordinary differential equations (ODEs) describing the interaction of the HIV virus with the human immune system. Next we will modify this system to incorporate variables representing typical HAART treatment with two different classes of drugs (reverse transcriptase and protease inhibitors). We define an optimal control that seeks to maximize the benefits of these drugs while minimizing their harmful side effects. We will prove existence of an optimal control, find the optimality condition, and solve the system numerically using a Runge-Kutta algorithm. We will illustrate our numerical solution and discuss the uses and limitations of this type of biological model.

Key Words: HAART, HIV model, Optimal Control, Two treatments, ODE model

AMS Subject Classification. 49K15, 92D30.

1. INTRODUCTION

In the last 30 years, AIDS (Acquired Immunodeficiency Syndrome) has become a global pandemic, affecting people on every continent in the world, most notably in Sub-Saharan Africa. AIDS is a devastating condition, caused by the Human Immunodeficiency Virus (HIV), which results in a complete breakdown of the immune system, quickly leading to disability and death if left untreated. In the 2013 UN Report on the Global AIDS Epidemic, it was estimated that there are currently 35.3 million people living with HIV, with 25 million (about 70%) of these people in Sub-Saharan Africa [23]. The same report attributed 1.6 million deaths to AIDS in the year 2012. The number of new HIV infections has been on a downward trend in recent years, but there were still 2.3 million new HIV infections in 2012. This leaves much that can be done in the way of HIV treatment. There is currently no vaccine for HIV, so treatment is limited to drugs that can delay the onset of AIDS in a patient. More effective treatment programs can increase the lifespan and quality of life for the

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millions of people currently living with HIV. However, as treatment regimens for HIV become more and more aggressive, adverse drug side-effects can become almost as serious as the disease itself, causing the quality of life of patients on drug treatment regimens to become a major concern [21]. The optimal control approach to solving for a treatment regimen addresses this issue in that it weighs the benefits of a stronger immune system versus the extreme toxicity of the drugs used to treat HIV.

Although it infects many types of cells, HIV works primarily by targeting and infecting CD4+ T-cells, commonly called "helper T-cells", which it then uses to reproduce itself. These cells are lymphocytes (a type of white blood cell and part of the immune system) which are specifically vital to the organization of other immune system cells in the attack on infectious diseases. CD4+ T-cells do not attack the viruses themselves, but instead direct other lymphocytes, such as CD8+ T-cells, to kill the virus and infected cells. CD4+ T-cells are produced in the thymus at a constant rate, which does not change with HIV infection. When they are first created, CD4+ T-cells are called "naive", "quiescent", or "un-activated" because they do not become active in immune system responses until they are "activated" by exposure to an antigen such as HIV (or any other molecule recognized by the immune system). CD4+ T-cells are generally not targeted by HIV until they become activated [10], which is why we will use the model proposed by Guedj, et. al. [10] in this paper, as it is one of the few existing models to differentiate between these two types of CD4+ T-cells.

HIV infection causes a depletion and deterioration of these vital CD4+ T-cells in a few different ways. In one way, stimulation of the immune system (caused by HIV) increases the rate of replication of these cells, which increases their rate of mutation, causing a general functional deterioration of CD4+ T-cells over time [7]. More significantly, CD4+ T-cells infected with HIV have a much shorter lifespan than uninfected CD4+ T-cells (the death rates of un-activated, activated (non-infected), and activated (infected) CD4+ T-cells are respectively .00014 day^{-1}, 0.12 day^{-1}, and 0.67 day^{-1}) [10]. While these infected CD4+ T-cells are dying much faster than normal due to a shorter half-life and being eliminated by the immune system through CD8+ T-cells, the thymus does not change the rate at which it replaces these cells, causing a gradual decline in the number of CD4+ T-cells in the bloodstream until the immune system cannot function properly [12]. An individual is generally considered to have AIDS when the number of CD4+ T-cells in their bloodstream drops to below 400 per microliter of blood from a normal concentration of 1000 to 1200 per microliter [21].

After infecting a CD4+ T-cell, since HIV is a retrovirus (meaning it consists of single-stranded RNA), it uses a protein called reverse transcriptase to convert itself into double-stranded DNA that can infiltrate the nucleus of the cell and be

integrated into the cell's genome. The cell's nucleus then rapidly produces copies of the original viral RNA, which are "cut" into useable copies of new HIV virus by a protein, protease, and then released into the bloodstream to infect new CD4+ T Cells. HAART treatment (Highly Active Anti-Retroviral Therapy) is the most widely used therapy regimen for patients with HIV. It consists of a "cocktail" of three or more drugs, most commonly two belonging to the reverse-transcriptase inhibitor (RTI) class and one belonging to the protease inhibitor class (PI). The RTIs affects the virus's ability to infect new cells, while the PI affects its ability to replicate itself properly after it has already infected a cell. Note that for our model, we will combine the multiple RTIs into one variable representing their combined effectiveness.

Both of these drugs are toxic and have adverse side affects. The RTI is by far the more toxic of the two, but it is also the most effective. In Section 2 of this paper, we will modify an already existing ODE model of the interaction between HIV and the human immune system in order to incorporate "control" variables (representing treatment with an RTI and a PI) as well as an "objective functional" that represents the cumulative health benefit of these drugs. This will give us a system from which we can derive an optimal "treatment plan" using these drugs. In Section 3 we will establish the existence of a pair of optimal solutions for the variables representing RTI and PI treatment that will maximize the objective functional (cumulative health benefits) subject to the modified "state" system of ODEs. In Section 4, we will use Pontryagin's Maximum Principle to derive a solution for this optimal control pair. In Section 5 we will provide numerical illustration of the optimal solutions for the RTI and PI treatment regimens as well as the corresponding CD4+ T-cell count and viral load over a fixed time interval. Finally, in Section 6 we will discuss the limitations and caveats of this approach to modeling HIV treatment as well as the limits of HAART treatment itself.

2. MATHEMATICAL MODEL

The infectious disease model for HIV given in a paper by J. Guedj, et. al. [10] uses a first-order system of ordinary differential equations with five variables. Descriptions of the variables and constants used are given in the following tables.

The rate of change of Q, the un-activated CD4+ T-Cell population, is given by the following equation:

$$\frac{dQ}{dt} = \zeta + \rho T - \alpha Q - \mu_Q Q$$

The first term, ζ, represents the supply on new cells from the thymus, which as previously noted, is constant. The next two terms represent the rates of activation of the CD4+ T-Cells and the reversion from an activated state, which depend on the

TABLE 1. Description of Variables used in the HIV model

Symbol	Description	Units
Q	Un-activated CD4+ T-cells	cells mm^{-3}
T	Activated CD4+ T-cells (Non-infected)	cells mm^{-3}
T_I	Activated CD4+ T-cells (Infected)	cells mm^{-3}
V_I	Infectious HIV Virus	copies mm^{-3}
V_{NI}	Non-infectious HIV Virus	copies mm^{-3}

TABLE 2. Description and Values of Parameters used in the HIV model

Symbol	Description	Value	Units
ζ	Rate of Q cell production	13.73	mm^{-3}day^{-1}
α	Activation rate of Q cells	0.042	day^{-1}
ρ	Reversion rate of T cells	0.017	day^{-1}
μ_Q	Death rate of Q cells	0.00014	day^{-1}
μ_T	Death rate of T cells	0.12	day^{-1}
μ_{T_I}	Death rate of T_I cells	0.67	day^{-1}
μ_V	Clearance rate of Virus	30.00	day^{-1}
γ	Infection rate of T cells per virion	0.050	mm^{-3}day^{-1}
π	Number of virions per T_I cell	104.00	N/A
η	Efficiency of treatment with RTI (proportion)	0.96	N/A
ω	Proportion of infectious virions	0.20	N/A

size of the populations of Q and T respectively. The last term is to account for the natural death rate of the cells.

The rate of change of T, the activated CD4+ T-Cell population, is given by:

$$\frac{dT}{dt} = \alpha Q - (1-\eta)\gamma T V_I - \rho T - \mu_T T$$

Here again, in the first and third terms, we see a representation of the activation of CD4+ T-Cells as well as their reversion to un-activated states. Of course these have opposite signs from the terms in last equation, as a cell's activation adds to the population of T and subtracts from the population of Q and so on. The second term represents the rate of infection of healthy, activated CD4+ T-Cells by the HIV virus. The rate of infection will increase in proportion to the amount of virus in the bloodstream and the amount of T-Cells available to be preyed upon. The η in this term represents the "efficiency of treatment with RTI", which is given experimentally at 0.96 or 96%. Later, we will replace this constant with a variable representing the

treatment. We can see that if the value of η were 1, this would represent new infection completely stopping, while the closer the value is to zero, the more healthy, activated CD4+ T-Cells we would lose to infection. The last term again is a natural death rate of these cells.

The rate of change of T_I, the population of activated CD4+ T-Cells that have been infected by the HIV virus, is given by:

$$\frac{dT_I}{dt} = (1-\eta)\gamma T V_I - \mu_{T_I} T_I$$

Here we see the infection term from the last equation again, but with a positive sign this time because it is adding to the population of infected T-Cells. The next term is simply the death rate for the infected CD4+ T-Cells. Note that the death rate for the infected cells is over five times the death rate of the un-infected cells, which is in turn almost one thousand times the death rate of the un-activated CD4+ T-Cells.

We distinguish between "infectious" and "non-infectious" HIV virus because, even without treatment, a significant of proportion of the copies that the HIV makes of itself have some type of error that renders them ineffective for infecting further CD4+ T-Cells. This proportion can be raised even higher by the use of a protease inhibitor, which we will introduce into our model later.

Our equation for the rate of change of V_I, the population of "infectious" HIV virus, is given by:

$$\frac{dV_I}{dt} = \omega \mu_{T_I} \pi T_I - \mu_V V_I$$

The first term represents the new copies of the virus being made by an infected CD4+ T-Cell, since the virus can not replicate itself. Since this represents the rate of change for only the "infectious" virus, this term is multiplied by ω, "proportion of infectious virus". The second term represents the clearance rate of the virus (essentially the death rate, but the virus is never actually alive).

The last equation, the rate of change of V_{NI}, the population of "non-infectious" HIV virus, is given by:

$$\frac{dV_{NI}}{dt} = (1-\omega)\mu_{T_I} \pi T_I - \mu_V V_{NI}$$

The first term here is the same as the term in the last equation, except multiplied by $(1-\omega)$ instead of ω since we are describing the rate of change of the "non-infectious" virus. The second term is for the clearance rate again, which is the same (μ_V) for both infectious and non-infectious virus.

All together, the system of equations is:

$$
\begin{aligned}
\frac{dQ}{dt} &= \zeta + \rho T - \alpha Q - \mu_Q Q \\
\frac{dT}{dt} &= \alpha Q - (1-\eta)\gamma T V_I - \rho T - \mu_T T \\
\frac{dT_I}{dt} &= (1-\eta)\gamma T V_I - \mu_{T_I} T_I \\
\frac{dV_I}{dt} &= \omega \mu_{T_I} \pi T_I - \mu_V V_I \\
\frac{dV_{NI}}{dt} &= (1-\omega)\mu_{T_I} \pi T_I - \mu_V V_{NI}
\end{aligned}
\tag{2.1}
$$

with initial conditions $Q(0) = Q_0$, $T(0) = T_0$, $T_I(0) = T_{I0}$, $V_I(0) = V_{I0}$, and $V_{NI}(0) = V_{NI0}$.

We will modify the set of ODEs given by Guedj et. al. [10] by inserting two variables into the equations: one variable, $n_{RTI}(t)$, which we let represent the dosage of a reverse-transcriptase inhibitor drug as a function over time, and another variable $n_{PI}(t)$, which we similarly let represent the dosage of a protease inhibitor drug as a function over time. $n_{RTI}(t)$ is substituted directly for η, the constant that is meant to represent the "effectiveness of treatment with a reverse transcriptase inhibitor" in the second and third equations.

To insert the second drug variable, $n_{PI}(t)$, we look at the constant ω representing "proportion of infectious virus". Without treatment using a protease inhibitor, this constant is given at 0.20, meaning that only approximately 20% of new virus copies are "infectious", while the rest have some type of error that prohibits them from infecting new cells. Although this may seem low, because of the massive amount of virus copies that infected T-Cells produce, this still allows the virus to propagate efficiently. Treatment with a protease inhibitor causes further disfunction in this process, causing the proportion of infectious virus to decrease significantly. Thus, we substitute $(1 - n_{PI}(t))\omega$ for ω in the fourth and fifth equations so that this quantity, representing the proportion of infectious virus particles, remains at 0.20 with no treatment and decreases toward 0 as the amount of treatment with a protease inhibitor increases.

Hence the state equation system becomes:

$$
\begin{aligned}
\frac{dQ}{dt} &= \zeta + \rho T - \alpha Q - \mu_Q Q \\
\frac{dT}{dt} &= \alpha Q - (1 - n_{RTI})\gamma T V_I - \rho T - \mu_T T \\
\frac{dT_I}{dt} &= (1 - n_{RTI})\gamma T V_I - \mu_{T_I} T_I \\
\frac{dV_I}{dt} &= (1 - n_{PI})\omega \mu_{T_I} \pi T_I - \mu_V V_I \\
\frac{dV_{NI}}{dt} &= (1 - \omega + \omega n_{PI})\mu_{T_I} \pi T_I - \mu_V V_{NI}.
\end{aligned} \tag{2.2}
$$

Now that we have our state system of ODEs with our control variables n_{RTI} (decreases rate of new T-cell infection) and n_{PI} (decreases rate of infectious virus production), we can define our objective functional to be maximized as

$$
J(n_{RTI}, n_{PI}) = \int_0^{t_f} \left[T(t) - \left(\frac{A_1}{2} n_{RTI}^2(t) + \frac{A_2}{2} n_{PI}^2(t) \right) \right] dt. \tag{2.3}
$$

This integral represents the cumulative health benefits of a raised CD4+ T-cell count minus the health costs and side effects of the drugs used in the treatment. Both variables representing the drugs in the integrand are quadratic because of their extreme toxicity. The parameters A_1 and A_2 are "toxicity weights" used to differentiate the toxicity of the two drugs and they are divided by 2 because we will need to take the derivative of the integrand later on and this will make our equations nicer. We desire an optimal control pair, n^*_{RTI}, n^*_{PI} such that these cumulative health benefits are maximized:

$$
J(n^*_{RTI}, n^*_{PI}) = max\{J(n_{RTI}, n_{PI}) | J(n_{RTI}, n_{PI}) \in U\}, \tag{2.4}
$$

where $U = \{(n_{RTI}, n_{PI}) | n_{RTI}, n_{PI}$ measurable, $0 < L_1 \leq n_{RTI} \leq U_1 < 1$, and $0 < L_2 \leq n_{PI} \leq U_2 < 1$, with $t \in [0, t_f]\}$ is the set of all suitable controls. In order to solve this problem, we must establish the existence of an optimal control pair before we derive the solution for this optimal control pair.

3. EXISTENCE OF AN OPTIMAL CONTROL PAIR

Upper bounds on the solutions to the state variables are needed to establish the existence of an optimal control [5]. In order to make our model realistic, we may add the restriction that CD4+ T-Cells do not grow unbounded, meaning there exist constants such that $Q(t) < Q_{max}, T(t) < T_{max}$, and $T_I(t) < T_{Imax}$. Now consider the supersolutions of the remaining state equations:

$$\begin{aligned} \frac{d\bar{V_I}}{dt} &= \omega\mu_{T_I}\pi T_{Imax} \\ \frac{d\bar{V}_{NI}}{dt} &= \mu_{T_I}\pi T_{Imax} \end{aligned} \tag{3.1}$$

Since the above system is linear with bounded coefficients on a finite time interval, the supersolutions $\bar{V_I}$ and $\bar{V_{NI}}$ are uniformly bounded. Therefore, all of the solutions to the state variables are bounded.

Theorem 3.1. *Given the objective functional*

$$J(n_{RTI}, n_{PI}) = \int_0^{t_f} \left[T(t) - \left(\frac{A_1}{2} n_{RTI}^2(t) + \frac{A_2}{2} n_{PI}^2(t) \right) \right] dt, \tag{3.1}$$

where $U = \{(n_{RTI}, n_{PI}) | n_{RTI}, n_{PI}$ *measurable,* $0 < L_1 \leq n_{RTI} \leq U_1 < 1$ *and* $0 < L_2 \leq n_{PI} \leq U_2 < 1$, *with* $t \in [0, t_f]\}$ *subject to the state equations (2.2) and initial conditions* $Q(0) = Q_0$, $T(0) = T_0$, $T_I(0) = T_{I0}$, $V_I(0) = V_{I0}$, *and* $V_{NI}(0) = V_{NI0}$ *there exists an optimal control pair,* n^*_{RTI}, n^*_{PI}, *such that*

$$J(n^*_{RTI}, n^*_{PI}) = max\{J(n_{RTI}, n_{PI}) | J(n_{RTI}, n_{PI}) \in U\}. \tag{3.2}$$

Proof: The existence of the optimal control pair is established using results of Joshi [13] and Fister et. al. [5], based on a theorem of Fleming and Rishel [6]. Using Theorem III.4.1 from [6] the existence of an optimal control pair is proven if the following conditions are satisfied:

1. The set of controls and state variables is non-empty.
2. The control set U is convex and closed.
3. The RHS of the state system (2.2) is bounded by a linear function in the state and control variables.
4. The integrand of the objective functional $J(n_{RTI}, n_{PI})$ is concave on U.
5. There exist constants $C_1, C_2 > 0$ such that the integrand of the objective functional $J(n_{RTI}, n_{PI})$ is bounded above by $C_2 - C_1(|n_{RTI}|^2 + |n_{PI}|^2)$.

By our definition of the control set and state equations, conditions 1 and 2 are satisfied. Since the state system (2.2) is bilinear in the controls, n_{RTI}, n_{PI}, it follows that the right hand side of each of the equations is bounded by a linear function of the state and control variables, satisfying condition 3. Note that the integrand of the

objective functional is concave, satisfying condition 4. Finally we have the fact that the integrand of $J(n_{RTI}, n_{PI})$ satisfies

$$\left[T(t) - \left(\frac{A_1}{2} n_{RTI}^2(t) + \frac{A_2}{2} n_{PI}^2(t)\right)\right] \leq C_2 - C_1(|n_{RTI}|^2 + |n_{PI}|^2)$$

if we take $C_2 > T_max$ and $0 < C_1 < \frac{A_1}{2}, \frac{A_2}{2}$. Thus, the five conditions are satisfied and we can conclude that there exists an optimal control pair n_{RTI}^*, n_{PI}^*. □

4. CHARACTERIZATION OF THE OPTIMALITY SYSTEM

Now we know that there exists an optimal control pair maximizing the objective functional subject to the state equations, we use Pontryagin's Maximum Principle [18] to define the Hamiltonian and derive the necessary conditions for the optimal control pair. The Hamiltonian is defined as the sum of the integrand of the objective functional and each state equation multiplied by a corresponding adjoint variable $\lambda_i(t)$ where $i \in \{Q, T, T_I, V_I, V_{NI}\}$:

(4.1)
$$\begin{aligned} H = &\left[T(t) - \left(\frac{A_1}{2} n_{RTI}^2(t) + \frac{A_2}{2} n_{PI}^2(t)\right)\right] \\ &+ \lambda_Q(t)\left[\frac{dQ}{dt}\right] + \lambda_T(t)\left[\frac{dT}{dt}\right] + \lambda_{T_I}(t)\left[\frac{dT_I}{dt}\right] + \lambda_{V_I}(t)\left[\frac{dV_I}{dt}\right] + \lambda_{V_{NI}}(t)\left[\frac{dV_{NI}}{dt}\right]. \end{aligned}$$

So with our state equation and optimality system, the Hamiltonian is

(4.2)
$$\begin{aligned} H = &\left[T - \left(\frac{A_1}{2} n_{RTI}^2 + \frac{A_2}{2} n_{PI}^2\right)\right] \\ &+ \lambda_Q\left[\zeta + \rho T - \alpha Q - \mu_Q Q\right] \\ &+ \lambda_T\left[\alpha Q - (1 - n_{RTI})\gamma T V_I - \rho T - \mu_T T\right] \\ &+ \lambda_{T_I}\left[(1 - n_{RTI})\gamma T V_I - \mu_{T_I} T_I\right] \\ &+ \lambda_{V_I}\left[(1 - n_{PI})\omega \mu_{T_I} \pi T_I - \mu_V V_I\right] \\ &+ \lambda_{V_{NI}}\left[(1 - \omega + \omega n_{PI})\mu_{T_I} \pi T_I - \mu_V V_{NI}\right]. \end{aligned}$$

Theorem 4.1. *Given our optimal control pair, n_{RTI}^*, n_{PI}^* and the solutions Q^*, T^*, T_I^*, V_I^*, V_{NI}^* to the corresponding state system (2.2), there exist adjoint variables λ_i*

for $i \in \{Q, T, T_I, V_I, V_{NI}\}$ satisfying the following equations

$$\begin{aligned}
\lambda_Q' &= -\frac{\partial H}{\partial Q} = \lambda_Q(\alpha + \mu_Q) - \alpha\lambda_T \\
\lambda_T' &= -\frac{\partial H}{\partial T} = \lambda_T[\rho + \mu_T + \gamma V_I(1 - n_{RTI})] - \lambda_{TI}[\gamma V_I(1 - n_{RTI})] - \rho\lambda_Q - 1 \\
\lambda_{T_I}' &= -\frac{\partial H}{\partial T_I} = \mu_{T_I}\lambda_{T_I} - \lambda_{V_I}[\omega\mu_{T_I}\pi(1 - n_{PI})] - \lambda_{V_{NI}}[\mu_{T_I}\pi(1 - \omega + \omega n_{PI})] \\
\lambda_{V_I}' &= -\frac{\partial H}{\partial V_I} = (\lambda_T - \lambda_{T_I})[\gamma T(1 - n_{RTI})] + \mu_V\lambda_{V_I} \\
\lambda_{V_{NI}}' &= -\frac{\partial H}{\partial V_{NI}} = \mu_V\lambda_{V_{NI}}
\end{aligned} \tag{4.3}$$

and the transversality conditions $\lambda_i(t_f) = 0$ for all $i \in \{Q, T, T_I, V_I, V_{NI}\}$. Furthermore, the optimal control pair can be characterized by:

$$\begin{aligned}
n_{RTI}^* &= min\ \left\{ max\ \left\{ L_1, \frac{(\lambda_T - \lambda_{T_I})\gamma T V_I}{A_1} \right\}, U_1 \right\} \\
n_{PI}^* &= min\ \left\{ max\ \left\{ L_2, \frac{(\lambda_{V_{NI}} - \lambda_{V_I})\omega\pi\mu_{T_I} T_I}{A_2} \right\}, U_2 \right\}.
\end{aligned} \tag{4.4}$$

Proof: The form of the adjoint equations and the transversality conditions are standard results from Pontryagin's Maximum Principle [18], which is referenced in Joshi [13] and Garira et. al. [8]. Furthermore, it follows from the optimality condition of Pontryagin's Maximum Principle that the objective functional subject to the state equations is maximized when the partial derivative of the Hamiltonian with respect to the controls is equal to zero. In this way, we can solve for our optimal control pair n_{RTI}^*, n_{PI}^*. In our case, because our controls are bounded, when the partial derivative is less than zero we set the control equal to its lower bound and when it is greater than zero, we set the control equal to its upper bound in order to maximize the objective functional.

It follows that for n_{RTI} we have

$$\begin{aligned}
&\text{if } \frac{\partial H}{\partial n_{RTI}} < 0 \text{ then } n_{RTI}^* = L_1 \\
&\text{if } \frac{\partial H}{\partial n_{RTI}} > 0 \text{ then } n_{RTI}^* = U_1 \\
&\text{if } \frac{\partial H}{\partial n_{RTI}} = 0 \text{ then } \frac{\partial H}{\partial n_{RTI}} = (\lambda_T - \lambda_{T_I})\gamma T V_I - A_1 n_{RTI} = 0 \\
&\implies n_{RTI}^* = \frac{(\lambda_T - \lambda_{T_I})\gamma T V_I}{A_1}.
\end{aligned}$$

In compact form, this is written as

$$n_{RTI}^* = \min\ \left\{ \max\ \left\{ L_1, \frac{(\lambda_T - \lambda_{T_I})\gamma T V_I}{A_1} \right\}, U_1 \right\}. \tag{4.5}$$

Similarly, for n_{PI} we have

$$\text{if } \frac{\partial H}{\partial n_{PI}} < 0 \text{ then } n^*_{PI} = L_2$$
$$\text{if } \frac{\partial H}{\partial n_{PI}} > 0 \text{ then } n^*_{PI} = U_2$$
$$\text{if } \frac{\partial H}{\partial n_{PI}} = 0 \text{ then } \frac{\partial H}{\partial n_{PI}} = (\lambda_{V_{NI}} - \lambda_{V_I})\omega\pi\mu_{T_I}T_I - A_2 n_{PI} = 0$$
$$\implies n^*_{PI} = \frac{(\lambda_{V_{NI}} - \lambda_{V_I})\omega\pi\mu_{T_I}T_I}{A_2}.$$

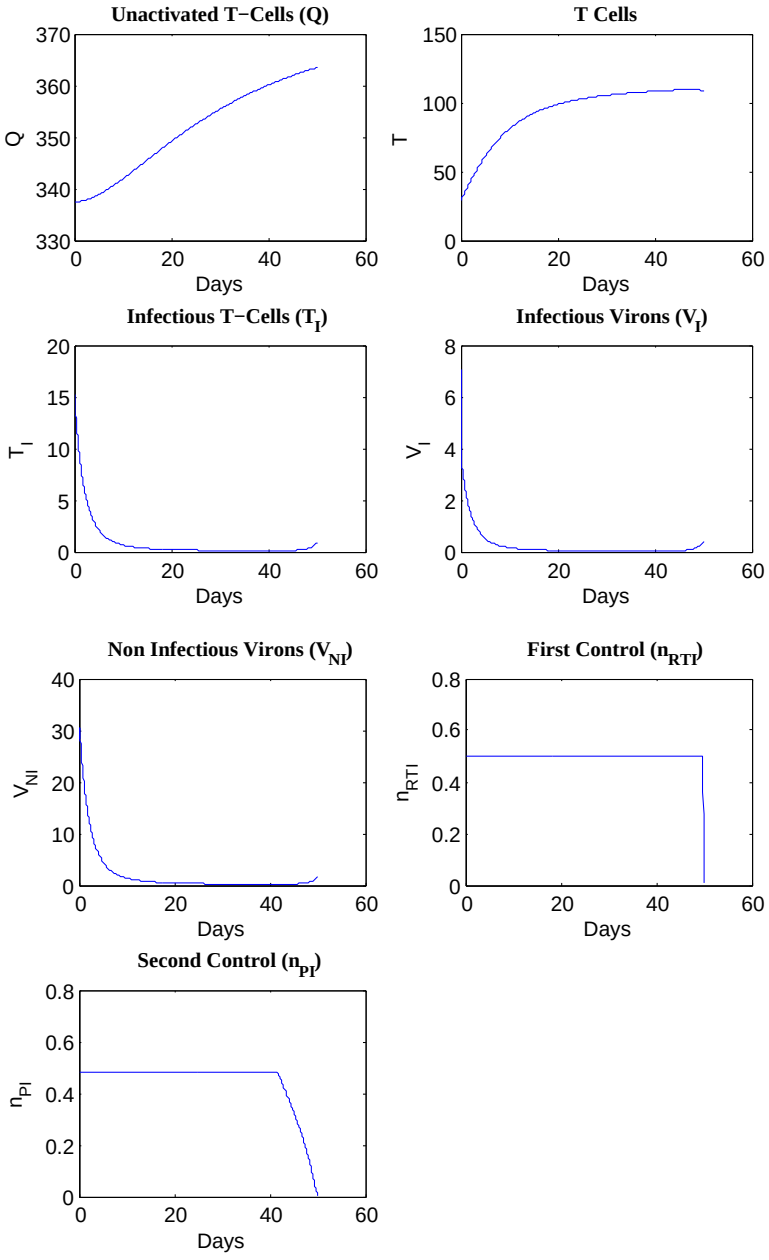
In compact form, this is notated

$$n^*_{PI} = \min\left\{\max\left\{L_2, \frac{(\lambda_{V_{NI}} - \lambda_{V_I})\omega\pi\mu_{T_I}T_I}{A_2}\right\}, U_2\right\}. \tag{4.6}$$

□

5. NUMERICAL ILLUSTRATION

This section shows our results after running the model simulation using MATLAB. The figures represent the un-activated CD4+ T-Cells (Q), activated (non-infected) CD4+ T-Cells (T), activated (infected) CD4+ T-Cells (T_I), infectious HIV virus (V_I), non-infectious HIV virus (V_{NI}), treatment with a reverse transcriptase inhibitor(n_{RTI}), and treatment with a protease inhibitor(n_{PI}) over a 50-day treatment cycle. Our numerical result suggests that the optimal course of treatment, in order to raise the patient's CD4+ T-Cell count as much as possible while taking into account the toxic side effects of the drugs, is that the reverse transcriptase inhibitors (n_{RTI}) be given in full dose during the entire treatment cycle and protease inhibitor (n_{PI}) be given in full dose for the first 40 days of the treatment and tapered down during the last 10 days. Our results show the populations of un-activated CD4+ T-Cells and activated, non-infected CD4+ T-Cells growing very fast in the beginning of the treatment, with growth slowing down towards the end of the treatment period. Similarly, activated, infected CD4+ T-Cells, infectious virus, and non-infectious virus populations decrease very quickly in the first couple of weeks into the treatment, but have a tendency to bounce back at the end of the treatment cycle.


Unactivated T−Cells (Q)
Q
Days
T Cells
T
Days
Infectious T−Cells (T_I)
T_I
Days
Infectious Virons (V_I)
V_I
Days
Non Infectious Virons (V_{NI})
V_{NI}
Days
First Control (n_{RTI})
n_{RTI}
Days
Second Control (n_{PI})
n_{PI}
Days

6. CONCLUSION AND DISCUSSION

This treatment for HIV is expensive and most of the people living in developing countries can not afford it without a large subsidy from developed countries or international organizations. Starting time for the treatment and when to switch regimens is very important, but access to treatment is equally important. We hope that more antiretroviral treatment is made available to patients in these countries so that they can be treated before their condition reaches the advanced stages of the disease.

Highly Active Antiretroviral Therapy (HAART) may develop resistance mutations and may limit treatment using a second line of drugs [25] . We should identify the best possible option for an infected individual and treat him or her as soon as we can.

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