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OPTIMAL CONTROL OF COMBINED THERAPY IN A SINGLE STRAIN HIV - 1 MODEL

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Abstract . Highly active antiretroviral therapy (HAART) is administered to symptomatic human immunodeficiency virus (HIV) infected individuals to im - prove their health . Various administration schemes are used to improve pa - t ients ' lives and at the same t ime suppressing development of drug resistance , reduce evolution of new viral strains , minimize serious side effects , improve pa - t ient adherence and also reduce the costs of drugs . We deduce an optimal drug administration scheme useful in improving patients ' health especially in poor resourced settings . In this paper we use the Pontryagin ' s Maximum Principle to derive optimal drug dosages based on a mathematical dynamical model . We use methods of optimal control to determine optimal controls analytically , and then use the Runge - Kutta scheme of order four to numerically simulate different therapy effects . We simulate the different effects of a drug regimen composed of a protease inhibitor and a nucleoside reverse transcriptase in - hibitor . Our results indicate that for highly toxic drugs , small dosage sizes and allowing drug holidays make a profound impact in both improving the quality of life and reducing economic costs of therapy . The results show that for drugs with less toxicity , continuous therapy is beneficial .

1 . Introduction

Recently , there has been a rollout of antiretroviral (ARV) therapies in many countries around the world , but availability of ARVs in poor resourced settings is a major concern . The cost of these drugs is beyond reach of many infected pa - tients , hence there is need to come up with a comprehensive drug administration scheme that makes a significant impact in conferring clinical benefits and cost ef - fectiveness . Clinical benefits of drug therapy for HIV infected individuals include restoration of CD 4+ T cells levels , suppressing viral levels below detection limits and minimizing detrimental side effects such as risk of cardiovascular , acute retrovi - ral syndrome , fat loss , lactic acidosis , abnormal fat distribution and mitochondrial damage [3] . There are more than twenty anti - HIV - 1 drugs available and these are administered in many different combinations of three or four drugs . The drugs fall into three main categories , that is , reverse transcriptase inhibitors (RTIs) (nucleo - side , nucleotide and nonnucleoside) , protease inhibitors (PIs) and fusion inhibitors (FIs) . RTIs prevent new HIV - 1 infections by disrupting the conversion of viral

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RNA into DNA that can be incorporated into the host cell ' s genome . PIs function by preventing the assembly of key viral proteins after they have been mistakenly produced by infected host cells [1 5] . FIs function by preventing the fusion of the virus and the host cells . HAART consists of combined drug regimens that in - cludes two or three nucleoside agents alone or two nucleoside agents combined with a protease inhibitor or a nonnucleoside reverse trancriptase inhibitor [3] . Exam - ples of such regimen combinations include EFV (Efavirenz) + (3 TC (Lamivudine) or FTC (Emtricitabine)) + (AZT (Zidovudine) or TDF (Tenofovir Disoproxil Fu - marate)) , a combination of a nonnucleoside reverse transcriptase inhibitor (EFV) and two nucleoside reverse transcriptase inhibitors (3 TC or FTC and AZT) and LPV / r (Lopinavir) + (3 TC or FTC)+ AZT , a combination of a protease inhibitor (LPV / r) and two nucleoside reverse trancriptase inhibitors (3 TC or FTC and AZT) and other options that are selected by government agencies , although these options are limited by generic formulations [7] . In this paper we explore the effects of a combination of a protease inhibitor and a nucleoside reverse transcriptase inhibitor , that is , we only look at effects of two types of drugs that are used in a HAART regimen . Suppression of viremia to less than detection limits or maintenance of even partial viremic suppression by selection of an optimal regimen remains the goal of therapy . The ultimate goal is to prevent further immune deterioration . The new chemotherapies offer added dosing convenience and improved safety profiles . Various chemotherapies for patients with HIV - 1 are being examined to determine the optimal scheme for treatment [6] .

The primary attention of this paper is to establish when and how treatment should be initiated , dosage size and means to continue clinical benefit in the face of challenges like antiretroviral drug failure and antiretroviral resistances . The optimal controls in this paper represent percentage effects chemotherapies have on the interaction of the CD 4+ T cells with the virus (infection of CD 4+ T cells) and the virions produced by infected cells (burst size) . Chemotherapy has side effects if administered in high dosage sizes or continuously , therefore the length of treatment is a limited time frame . The interval of treatment is necessary since a plausible assumption is made that chemotherapy only has a certain designated time for allowable treatment [1 0] ; [6] . After some finite t ime frame , HIV - 1 is able to build up resistance to the treatment due to its mutation ability . Therefore , in this paper we fix the length of treatment . In this paper we need to determine optimal methodology for administering anti - viral medication therapies to fight HIV - 1 infection . The main reasons for such an optimal therapy are minimization of drug toxicity or systemic cost , maximization of CD 4+ T cell count and minimize cost of drugs .

Optimal control methods have been applied to the derivation of optimal therapies for HIV infection . Butler *e t al .* [4] and Fister *e t al .* [1 1] explored an optimal chemotherapy strategy using Pontryagin ' s Maximum Principle , with a single control that represents the percentage effect it has on viral infectivity (simulating a drug such as AZT (zidovudine)) using dynamical HIV models . Kirschner *e t al .* [1 0] used an existing model which describes the interaction of the immune system with HIV . In Kirschner *e t al .* [1 0] the authors used a single control representing the percentage effect chemotherapy has on viral production (simulating effects of a protease inhibitor) . Kutch and Gufil [1 5] investigated the reasons underlying the development of drug - insensitive HIV - strains , and demonstrated that optimal drug

administration may be useful in increasing patient health by delaying the emergence of drug - resistant mutant viral strains . Kutch and Gufil [1 5] used two controls representing the percentage effect chemotherapy has on CD 4+ T cells infection and viral production and also incorporated drug efficacy . In the study by Kutch and Gufil [1 5] , an alternative approach to Pontryagin ' s Maximum Principle was adopted , that involves converting the st andard optimal control problem into a parameter optimization problem by discretizing the control input vector . An HIV immune dynamics model with three viral strains was used . Joshi [8] explored optimal control
of an ordinary differential equation model taken from [1 1] . In the paper [8] , Joshi considered two controls , one boosting the immune system and the other delaying HIV progression . The novel part of our work is that we explore optimal control of chemotherapy using an HIV dynamical model that incorporates explicit cellular immune response (lytic mechanism and two non - lytic mechanisms) . We use two controls , one simulating effect of RTIs and the other control simulating effect of PIs , incorporating drug efficacy . The paper is structured as follows : Firstly in section 2 we formulate a model of HIV immune dynamics , with explicit immune response (lytic and non - lytic components) . The model mimics virus and CD 4+ T cells dynamics in an infected individual . We modify the model to capture the effects of combined therapy and derive an optimal control problem with an objective functional that maximizes CD 4+ T cells and minimizes systemic costs . In section 3 we prove the existence of an optimal control pair and characterize the control pair in section 4 . In section 5 we state the optimality system , which is the state system coupled with the adjoint system . In section 6 , we prove the uniqueness of the optimality system and we present numerical illustrations for the optimality system in section 7 . We make some concluding remarks in section 8 .

2 . The Model

Let T denote the population density of uninfected CD 4+ T cells , T^* the density of infected CD 4+ T cells , V the density of free viral particles and C the density of HIV - 1 specific cytotoxic T lymphocytes (CTLs) . The rate of change of each of these is governed by a first order differential equation .T cell dynamics are governed by proliferation due to virus presence , apoptosis , natural death and thymus supply and viral infectivity inhibited by CTL chemokines . For T the equation is

$$\frac{dT(t)}{dt} = s_1 + \frac{rT(t)V(t)}{B_V + V(t)} - e^{-a_0 C(t)}\beta V(t)T(t) - \mu T^T(t) - \frac{kV(t)T(t)}{B_T + T(t)}. \tag{2.1}$$

Here the first term on the right - hand side , s_1, represents the source of new CD 4+ T cells from the thymus [9] . This is followed by the proliferation term of CD 4+ T cells in the presence of the virus : r is the proliferation rate and B_V is a parameter that determines the amount of antigen needed to generate half maximal stimulation [9] . The third term describes the infection of CD 4+ T cells by the virus . The presence of CTLs that release chemokines , such as $\beta-$ chemokines that block the entry of certain virions into target cells [1 6] ; [1 2] , prevent infection of new cells by a factor
$e^{-a_0 C}$(effectiveness of CTLs) , where a_0 is the efficiency of each CTL in reducing CD 4+ T cells infection . The hypothesis is that reduction of infection of CD 4+ T cells is enhanced by the number of HIV - specific CTLs available . The idea goes as
follows : as $C \to \infty, e^{-a_0 C} \to 0$ meaning that the availability of large quantities of CTLs reduce the rate of infection of CD 4+ T cells . The extent of reduction depends on the effectiveness of CTLs ($e^{-a_0 C}$). Conversely as $C \to 0, e^{-a_0 C} \to 1$

meaning that for low CTL count or zero CTL , the infection rate of CD 4+ T cells by virus is slightly reduced or not reduced at all . The effectiveness value of CTLs ranges from 0 to 1 . We assume that reduction in infection rate has an exponential effect . Here β is the rate of infection of CD 4+ T cells by the virus . The fourth term is a natural death term , since cells have a finite life span . On average the
life span is $1/\mu T$. The last term represents the destruction of CD 4+ T cells by the influence of toxic viral proteins . The idea is as follows : The parameter k is the rate of apoptosis . There is a limit to the rate of T cell mortality due to the induction of apoptosis . The limit is a function of variables such as presentation
of HIV - 1 Env gp 1 20 / gp 4 1 , receptors involved (especially chemokines CCR 5 and CXCR 4) and the complexity of target cell contact [1] . In other words , there is a saturation effect in which the virus can only present itself to so many T cells even when the CD 4+ T cell population is low . Conversely , there is an increase in the effect of apoptosis at low CD 4+ T cell densities . If T cell density is low , there are more virions per cell and this could lead to higher engagement of apoptosis receptors . On the other hand , if the T cell density is high , there are less virions per cell therefore the chances of virus presentation decreases . Thus presentation exhibits this switching phenomenon and it is this behaviour which is represented
by the Hollings Type II function [1 3] . The importance of the parameter B_T, is that it determines the scale at which engagement of apoptosis receptors begins to take effect .

The rate of change of the infected CD 4+ T cells is governed by the equation

$$\frac{dT^*(t)}{dt} = e^{-a_0 C(t)}\beta V(t)T(t) - \alpha T^*(t) - hT^*(t)C(t). \tag{2.2}$$

The first term on the right - hand side is a gain term for infected cells . The third term is a direct killing of virus infected cells through perforin - granzyme and Fas - FasL pathways . Infected cells are lysed by CTLs at a rate h[14]. Infected cells are also lost by cytopathic effect of virus and natural death such that they have a finite life span that averages $1/\alpha$.

The third equation of the system

$$\frac{dV(t)}{dt} = N\alpha T^*(t)e^{-a_1 C(t)} - \mu V^V(t), \tag{2.3}$$

describes the rate of change of viral load . The first term on the right - hand side explains the source of the virus . Virions are released by a burst of infected cells [9] , where an average of N viral particles are released per infected cell . $N\alpha$ is the average rate of virus production per productively infected cell . CTLs release cytokines such as interferon $-\gamma$(INF $-\gamma$) that can suppress the rate of virus production by virus infected cells [2] ; [1 8] . Therefore , they reduce viral burst by a factor of
$e^{-a_1 C}$, where a_1 is the rate at which each CTL suppresses virus production . The last term describes natural loss of viral particles .

The fourth equation

$$\frac{dC(t)}{dt} = s_2 + p0^T(t)V(t)C(t) - \mu C^C(t), \tag{2.4}$$

describes the dynamics of CTLs during HIV - 1 infection . Naive CD 8+ T cells differ - entiate into CTLs when stimulated by helper cells (CD 4+ T Cells) . HIV - 1 specific CTLs decline with increased disease and decreased CD 4+ T cell numbers , which means that the CTL population proliferation depends on the stimulation of CD 4+

T cells . High numbers of CTLs are associated with low virus titers at equilib - rium and loss of CTLs results in an increase in viral load . The first term on the
right - hand side , s_2 models the production rate of HIV specific CD 8+ T cells from pre - cursors [1 4] and the second term accounts for the differentiation of naive CD 8+ T cells into CTLs in response to HIV . Differentiation of CD 8+ T cells depends on the help of CD 4+ T cells present where $p0$ is the rate of the process . Wodarz and Nowak [20] used a similar term to model the proliferation of HIV specific CTLs .
CTLs are cleared at a rate μC, a blanket term for death (natural and apoptotic) .

The model of HIV immune dynamics given by equations (2 . 1) , (2 . 2) , (2 . 3) and
(2 . 4) has two steady states in the presence of immune response . The first steady state is the uninfected state given by

$$(\bar{T}_{un} = \frac{s_1}{\mu T}, \quad \bar{T}^*_{un} = 0, \quad \bar{V}_{un} = 0, \quad \bar{C}_{un} = \frac{s_2}{\mu C}).$$

If infection persists the system converges to a second steady state , an immune controlled equilibrium given by :

$$\bar{T}_{in} = \frac{\mu V(\alpha + h\bar{C}_{in})e^{(a_0+a_1)^{\bar{C}}in}}{N\alpha\beta}, \quad \bar{T}^*_{in} = \frac{\mu V}{N\alpha}e^{a_1^{\bar{C}}{}_{in}}\bar{V}_{in}, \quad \bar{C}_{in} = \frac{s_2}{\mu C - p^{\bar{T}}in^{\bar{V}}in},$$

and

$$\bar{V}_{in} = \frac{(s_1 + (r-\mu T)^{\bar{T}}in - \beta B^{\bar{T}}_{V}in e^{-a_0^{\bar{C}}{}_{in}} - \frac{kB^{\bar{T}}_{V}in}{B_T + \bar{T}_{in}})}{2(\frac{k\bar{T}_{in}}{B_T+\bar{T}_{in}} + \beta^{\bar{T}}in^{e^{-a_0^{\bar{C}}{}_{in}}})}$$

$$+((\beta B^{\bar{T}}_{V}in e^{-a_0^{\bar{C}}{}_{in}} + \frac{kB^{\bar{T}}_{V}in}{B_T + \bar{T}_{in}} + (\mu T - r)^{\bar{T}}in - s_1)2$$

$$-4(\frac{k\bar{T}_{in}}{B_T + \bar{T}_{in}} + \beta^{\bar{T}}in^{e^{-a_0^{\bar{C}}{}_{in}}})(\mu T^B V^{\bar{T}}in - s_1 B_V))1/2$$

$$\div \quad (2(\frac{k\bar{T}_{in}}{B_T + \bar{T}_{in}} + \beta^{\bar{T}}in^{e^{-a_0^{\bar{C}}{}_{in}}})).$$

The virus reproductive number , R_0 which is the number of newly infected cells that arise from any one infected cell when almost all cells are uninfected , is given by

$$R_0 = \frac{N\beta\alpha s_1 e^{-(a_0+a_1)^{\bar{C}}_{un}}}{\mu V \mu T(\alpha + h\bar{C}_{un})}$$

where $\bar{C}_{un} = \frac{s_2}{\mu C}$. The reproductive number is governed by several factors including
the efficiency with which HIV infects CD 4+ T cells , β(infectivity constant) , number of virions produced by one infected cell (burst size , N), rate of virion clearance from the body , μV, death rate of uninfected CD 4+ T cells , μT, CD 4+ T cells production rate , s_1, effectiveness of CTLs in reducing infection and reducing burst
size ($e^{-(a_0+a_1)^{\bar{C}}_{un}}$), the effect of CTLs in killing virally infected cells , $h\bar{C}_{un}$ and the the cytopathic effect of the virus , α. Determination of stability of equilibrium states give us the following results : if $R_0 < 1$, uninfected equilibrium st ate is asymptotically stable , that is , infection is abortive . If $R_0 > 1$, the uninfected state is unstable and it converges to an immune controlled equilibrium st ate that is lo cally asymptotically stable . The virus will spread after infection and the abundance of uninfected cells , infected cells , free viruses and CTLs is given by equations in $\bar{T}_{in}$,

$\bar{T}^*_{in}, \bar{V}_{in}$ and $\bar{C}_{in}$ respectively . If $R_0 = 1$ the uninfected state and the infected state coincide . If $R_0 > 1$ infection persists , then it will eventually leads to the acquired immune deficiency syndrome (AIDS) st age , associated with a weakened immune system which has difficulty fighting off opportunistic infections [1 9] . It is at this stage when therapy is initiated to boost the health of infected individuals .

After initiation of combined chemotherapy , combination of RTIs and PIs , infec - tion rate of CD 4+ T cells is reduced and the number of viral particles produced by an actively infected CD 4+ T cell is reduced . If we let $u_{RTI}(t)$ represent the normalized RTI dosage as a function of time , then β will be modified to become $(1 - \frac{1}{2}u_{RTI}(t))\beta$ where $\frac{1}{2}$ models drug efficacy [1 5]) and it is meant to take into account the effectiveness of the delivery . If we also let $u_{PI}(t)$ be the normalized PI dosage , then the parameter N will be modified to become $(1 - \frac{1}{2}u_{PI}(t))N$[15]. Hence the state system becomes

$$\begin{aligned}
\frac{dT(t)}{dt} &= s_1 + \frac{rT(t)V(t)}{B_V + V(t)} - (1 - \frac{1}{2}u_{RTI}(t))\beta e^{-a_0 C(t)}V(t)T(t) \\
&\quad -\mu T^T(t) - \frac{kV(t)T(t)}{B_T + T(t)} \\
\frac{dT^*(t)}{dt} &= (1 - \frac{1}{2}u_{RTI}(t))\beta e^{-a_0 C(t)}V(t)T(t) - \alpha T^*(t) - hT^*(t)C(t) \qquad (2.5)\\
\frac{dV(t)}{dt} &= (1 - \frac{1}{2}u_{PI}(t))Ne^{-a}1^C(t)_{\alpha T} * (t) - \mu V^V(t) \\
\frac{dC(t)}{dt} &= s_2 + p0^T(t)V(t)C(t) - \mu C^C(t).
\end{aligned}$$

The controls $u_{RTI}(t)$ and $u_{PI}(t)$ represent the action of RTI (viral infectivity re - duction) and PI (viral replication suppression) drugs respectively . The objective functional is defined as ,

$$J(u_{RTI}, u_{PI}) = \int_0^{T_f} [T(t) - (\frac{A_1}{2}RTI_u^2(t) + \frac{A_2}{2}PI_u^2(t))]dt \qquad (2.6)$$

where $T(t)$ is the benefit based on CD 4+ T cells and the other terms are systemic costs of the drug treatments . The benefit of treatment is based on an increase of CD 4+ T cells and systemic costs of drugs are minimized . The positive constants A_1 and A_2 represent desired weight on the benefit and cost , and RTI_u^2, PI_u^2 reflect the severity of the side effects of the drugs [8] . The cost function is assumed to be nonlinear , basing on the fact that there is no linear relationship between the effects of treatment on CD 4+ T cells or viral load hence the choice of a quadratic cost function [1 0] . We impose a condition for treatment time , $t \in [0, T_f]$, limited treatment window [4] , that monitors global effects of these phenomena ; treatment lasts for a given period of time because HIV can mutate and develop resistance to treatment after some finite time frame and in addition treatment has potentially harmful side effects , and these side effects increase with duration of treatment . The time $t = 0$ is the time when treatment is initiated and time $t = T_f$ is the time when treatment is stopped . The main objective is to maximize the benefit based on the CD 4+ T cell count (increase in quality of life) and the systemic cost based on the percentage effect of the chemotherapy given (RTIs and PIs) is being minimized (toxic side effects being avoided as much as possible and not causing patient death) .

 We seek an optimal control pair , u^*RTI, u^*PI such that

$$J(u^*RTI, u^*_{PI}) = \max\{J(u_{RTI}, u_{PI}) \mid (u_{RTI}, u_{PI}) \in U\} \tag{2.7}$$

where

$$U = \{(u_{RTI}, u_{PI}), u_{RTI}, u_{PI} \text{measurable}, 0 \le a_{11} \le u_{RTI} \le b_{11} \le 1 \\ \text{and} 0 \le a_{22} \le u_{PI} \le b_{22} \le 1\}$$

is the control set where $t \in [0, T_f]$.

The basic framework of this problem is to characterize the optimal control and prove the existence of the optimal control and uniqueness of the optimality system .

3 . Existence of an Optimal Control Pair

The existence of the optimal control pair can be obtained using a result by Joshi [8] , Fister *e t al .* [6] , and other references quoted therein . **Theorem 3 . 1 .** *Given the o bjective functional*

$$J(u_{RTI}, u_{PI}) = \int_0^{T_f} [T(t) - (\frac{A_1}{2} RTI_u^2(t) + \frac{A_2}{2} PI_u^2(t))]dt,$$

where $U = \{(u_{RTI}(t), u_{PI}(t))$, *piecewise continuous such that* $0 < a_{11} \le u_{RTI}(t) \le b_{11} < 1, 0 < a_{22} \le u_{PI}(t) \le b_{22} < 1\}$ *for al l* $t \in [0, T_f]$ *subject to equations of system* (2 . 5) *with* $T(0) = T_0, T^*(0) = T_0^*, V(0) = V_0$ *and* $C(0) = C_0$, *then th ere exists an optimal control pair* u^*RTI, u^*PI *such that*

$$\max\{J(u_{RTI}, u_{PI}) \mid (u_{RTI}, u_{PI}) \in U\} = J(u^*_{RTI}, u^*_{PI})$$

if the following conditions are met :

(1) *The class of al l initial conditions with an optimal control pair* u_{RTI}, u_{PI} *in the admissible control s e t along with each s tate equation being satisfied is not empty .*

(2) *The admissible control s e t* U *is clos ed and convex .*

(3) *Each right hand s ide of equations of system (2 . 5) is continuous , is bounded above by a sum of th e bounded control and the state , and can be written as a lin ear function of an optimal control pair* u_{RTI}, u_{PI} *with coefficients depending on time and th e s tate .*

(4) *The integrand* $J(u_{RTI}, u_{PI})$ *is concave .*

(5) *The integrand* $J(u_{RTI}, u_{PI})$ *is bounded a bove by* $C_2 - C_1(\mid u_{RTI} \mid^2 + \mid u_{PI} \mid^2)$ *with* $C_1 > 0$.

Proof . Our definition of the control set satisfies conditions 1 and 2 . For the model to be realistic , we impose the restrictions that CD 4+ T cells and CD 8+ T cells do not grow unbounded , so we use $T(t) < T_{\max}$ and $C(t) < C_{\max}$ where $T_{\max}$ and $C_{\max}$ are the maximum numbers of CD 4+ T cells and CD 8+ T cells that can be found in an individual respectively . Using $T(t) < T_{\max}$ and $C(t) < C_{\max}$, upper bounds on the solutions of system (2 . 5) are found .

$$\frac{d\bar{T}^*}{dt} = \beta e^{-a_0 C_{\max}} T_{\max}^{\bar{V}}, \quad \bar{T}^*(0) = \bar{T}_0^*,$$

where $\beta > 0, T_{\max} > 0$ and $0 < e^{-a_0 C_{\max}} < 1$.

$$\frac{d\bar{V}}{dt} = N\alpha e^{-a_1 C_{\max}} \bar{T}^*, \quad \bar{V}(0) = \bar{T}_0,$$

where $N > 0, \alpha > 0$ and $0 < e^{-a_1 C_{\max}} < 1$. Since this system is linear in finite time with bounded coefficients , then the supersolutions $\bar{T}^*$ and $\bar{V}$ are uniformly bounded . Since our state system is bilinear in u_{RTI} and u_{PI}, the right hand side of equations of system (2 . 5) satisfies condition 3 .

The right hand side of system (2 . 5) is continuous and it can be written as :

$$\mathbf{f}\ (t, \mathbf{T}\ , \mathbf{u}\ ) = \alpha(t, \mathbf{T}\ ) + \gamma(t, \mathbf{T}\ )\ \mathbf{u}$$

and the boundedness of solutions gives
$|\ \mathbf{f}\ (t, \mathbf{T}\ , \mathbf{u}\ )| \leq C_1(1 + |\ \mathbf{T}\ | + |\ \mathbf{u}\ |)$ for $0 \leq t \leq T_f$ where $\mathbf{T}\ \in \Re^4$, $\mathbf{u}\ \in \Re^2$ where $\mathbf{T}\ = (T, T^*, V, C)$ and $\mathbf{u}\ = (u_{RTI}, u_{PI})$)
and C_1 depends on the coefficients of the system .

The vectors α and γ are vector - valued functions of $\mathbf{T}\ $. In order to verify the convexity of the integrand of our objective functional , J we show that

$J\ (t, \mathbf{T}\ , (1-\epsilon)\ \mathbf{u}\ + \epsilon\ \mathbf{v}\ ) \geq (1-\epsilon)\ J\ (t, \mathbf{T}\ , \mathbf{u}\ ) + \epsilon\ J\ (t, \mathbf{T}\ , \mathbf{v}\ )$ (3 . 1) for $0 < \epsilon < 1$ and $J\ (t, \mathbf{T}\ , \mathbf{u}\ ) = T - (\frac{A_1}{2} RTI_u^2 + \frac{A_2}{2} u_{PI}^2)$.

$$J\ (t, \mathbf{T}\ , (1-\epsilon)\ \mathbf{u}\ + \epsilon\ \mathbf{v}\ )$$

$$\begin{aligned}
= \quad & [T - \frac{A_1}{2}((1-\epsilon)u_{RTI} + \epsilon v_{RTI})^2 - \frac{A_2}{2}((1-\epsilon)u_{PI} + \epsilon v_{PI})^2] \\
= T - \frac{A_1}{2}[RTI_u^2 - 2\epsilon u_{RTI}^2 \epsilon^2 RTI_u^2 + 2(1-\epsilon)u_{RTI}\epsilon v_{RTI} + \epsilon^2 v_{RTI}^2] \\
& -\frac{A_2}{2}[PI_u^2 - 2\epsilon PI_u^2 + \epsilon^2 PI_u^2 + 2(1-\epsilon)u_{PI}\epsilon v_{PI} + \epsilon^2 v_{PI}^2] \\
& = T - (\frac{A_1}{2} RTI_u^2 + \frac{A_2}{2} u_{PI}^2) \\
& -\frac{A_1}{2}[(\epsilon^2 - 2\epsilon)RTI_u^2 + \epsilon^2 RTI_v^2 + 2\epsilon(1-\epsilon)u_{RTI}v_{RTI}] \\
& -\frac{A_2}{2}[(\epsilon^2 - 2\epsilon)PI_u^2 + \epsilon^2 PI_v^2 + 2\epsilon(1-\epsilon)u_{PI}v_{PI}].
\end{aligned}$$

$$(1-\epsilon)\ J\ (t, \mathbf{T}\ , \mathbf{u}\ ) + \epsilon\ J\ (t, \mathbf{T}\ , \mathbf{v}\ )$$

$$\begin{aligned}
& = (1-\epsilon)[T - (\frac{A_1}{2} RTI_u^2 + \frac{A_2}{2} u_{PI}^2)] + \epsilon[T - (\frac{A_1}{2} RTI_v^2 + \frac{A_2}{2} v_{PI}^2)] \\
& = T - (\frac{A_1}{2} RTI_u^2 + \frac{A_2}{2} u_{PI}^2) - \epsilon[T - (\frac{A_1}{2} RTI_u^2 + \frac{A_2}{2} u_{PI}^2)] \qquad (3.2) \\
& \quad + \epsilon[T - (\frac{A_1}{2} RTI_v^2 + \frac{A_2}{2} v_{PI}^2)] \\
= T - (\frac{A_1}{2} RTI_u^2 + \frac{A_2}{2} u_{PI}^2) - \frac{\epsilon}{2}(-A_1 RTI_u^2 - A_2 PI_u^2 + A_1 RTI_v^2 + A_2 v_{PI}^2).
\end{aligned}$$

Thus to show that $J\ (t, \mathbf{T}\ , .\ )$ is concave in U, we note that the following inequality holds

$$\begin{aligned}
& \frac{A_1}{2}[(\epsilon^2 - 2\epsilon)RTI_u^2 + \epsilon^2 RTI_v^2 + 2\epsilon(1-\epsilon)u_{RTI}v_{RTI}] \\
& \quad + \frac{A_2}{2}[(\epsilon^2 - 2\epsilon)PI_u^2 + \epsilon^2 PI_v^2 + 2\epsilon(1-\epsilon)u_{PI}v_{PI}] \qquad (3.3) \\
& \quad \leq \frac{\epsilon}{2}(-A_1 RTI_u^2 - A_2 PI_u^2 + A_1 RTI_v^2 + A_2 v_{PI}^2).
\end{aligned}$$

 This implies

$$\frac{A_1}{2}\epsilon^2 RTI_u^2 - A_1\epsilon RTI_u^2 + \frac{A_1}{2}\epsilon^2 RTI_v^2 + A_1\epsilon(1-\epsilon)u_{RTI}v_{PI} + \frac{A_2}{2}\epsilon^2 PI_u^2 - A_2\epsilon PI_u^2$$
$$+\frac{A_1}{2}\epsilon^2 PI_v^2 + A_2\epsilon(1-\epsilon)u_{PI}v_{PI} + \frac{A_1}{2}\epsilon RTI_u^2 + \frac{A_2}{2}\epsilon PI_u^2 - \frac{A_1}{2}\epsilon RTI_v^2 - \frac{A_2}{2}\epsilon PI_v^2 \le 0.$$

Finally this gives

$$\frac{A_1}{2}(\epsilon^2-\epsilon)(RTI_u^2 + v_{RTI}^2) + \frac{A_2}{2}(\epsilon^2-\epsilon)(PI_u^2 + v_{PI}^2)$$
$$+\epsilon(1-\epsilon)(A_1 u_{RTI}v_{RTI} + A_2 u_{PI}v_{PI}) \le 0,$$

which is equivalent to

$$\frac{A_1}{2}(\epsilon^2-\epsilon)(RTI_u^2 + v_{RTI}^2) + (\epsilon-\epsilon^2)A_1 u_{RTI}v_{RTI}$$
$$+\frac{A_2}{2}(\epsilon^2-\epsilon)(PI_u^2 + v_{PI}^2) + (\epsilon-\epsilon^2)A_2 u_{PI}v_{PI} \le 0$$

which can be written as

$$-_{-}\frac{\frac{A_1}{2A_2}}{2}2^{\le}{}_{(({}^{\sqrt{}}_{\sqrt{}}{}^{\epsilon(1-\epsilon)u_{RTI}}{}_{\epsilon(1-\epsilon)u_{PI}-\bar{}\sqrt{\epsilon 1-\epsilon}\sqrt{\epsilon(1-\epsilon)}({}^{v_{RTI}}_{)v_{PI}})^{)2}{}_{0.}} \tag{3.4}$$

This holds since $A_1, A_2 > 0$, hence equation 3 . 1 holds . Finally we need to show that $J\ (t, \mathbf{T}\ , \mathbf{u}\ ) \le C_2 - C_1 \mid \mathbf{u}\ \mid^{\beta}$, where $C_1 > 0$ and $\beta > 1$. For our case

$$J\ (t, \mathbf{T}\ , \mathbf{u}\ ) = T - (\tfrac{A_1}{2}RTI_u^2 + \tfrac{A_2}{2}u_{PI}^2) \le C_2 - C_1 \mid \mathbf{u}\ \mid^2$$

where C_2 depends on the upper bound on CD 4+ T cells , T, and $C_1 > 0$ since A_1, $A_2 > 0$. We conclude that there exists an optimal control pair . □

4 . Characterization

Since there exists an optimal control pair for maximizing the functional , equation (2 . 6) , subject to system (2 . 5) we derive necessary conditions on the optimal control pair [6] . We discuss the theorem that relates to the characterization of the optimal control . In order to derive the necessary conditions for this optimal control pair , we use Pontryagin ' s Maximum Principle [1 3] . The Lagrangian is defined as

$$L = T(t) - (\frac{A_1}{2}RTI_u^2(t) + \frac{A_2}{2}PI_u^2(t)) + \lambda_1[s_1 + \frac{rT(t)V(t)}{B_V + V(t)}$$
$$-(1 - \frac{1}{2}u_{RTI}(t))\beta e^{-a_0 C(t)}V(t)T(t) - \mu T^T(t) - \frac{kV(t)T(t)}{B_T + T(t)}]$$
$$+\lambda_2[(1 - \frac{1}{2}u_{RTI}(t))\beta e^{-a_0 C(t)}V(t)T(t) - \alpha T^*(t) - hT^*(t)C(t)]$$
$$+\lambda_3[(1 - \frac{1}{2}u_{PI}(t))Ne^{-a}1^C(t)_{\alpha T} * (t) - \mu V^V(t)]$$
$$+\lambda_4[s_2 + p0^T(t)V(t)C(t) - \mu C^C(t)]$$
$$+w_{11}(t)(b_{11} - u_{RTI}(t)) + w_{12}(t)(u_{RTI}(t) - a_{11})$$
$$+w_{21}(t)(b_{22} - u_{PI}(t)) + w_{22}(t)(u_{PI}(t) - a_{22}),$$

where $w_{11}(t) \geq 0$, $w_{12}(t) \geq 0$, $w_{21}(t) \geq 0$, $w_{22}(t) \geq 0$ are penalty multipliers satisfying $w_{11}(t)(b_{11} - u_{RTI}(t)) = 0$, $w_{12}(t)(u_{RTI}(t) - a_{11}) = 0$ at the optimal u^*RTI, and $w_{21}(t)(b_{22} - u_{PI}(t)) = 0, w_{22}(t)(u_{PI}(t) - a_{22}) = 0$ at the optimal u^*PI.

Theorem 4 . 1 . *Given a pair of optimal controls u^*RTI, u^*PI and s o lutio ns T, T^*, V, C of th e co rresponding s tate system (2 . 5) , th ere exists adjoint variables λ_i for $i = 1 , 2 , 3 , 4$ satisfying th e following canonical equations*

$$\frac{d\lambda_1}{dt} \quad \frac{\partial L}{\partial T}$$

$$= -[1 + \lambda_1(\frac{rV(t)}{B_V + V(t)} - (1 - \frac{1}{2}u_{RTI}(t))\beta e^{-a_0C(t)}V(t) - \mu T - \frac{kV(t)B_T}{(B_T + T(t))^2})]$$

$$-[\lambda_2((1 - \frac{1}{2}u_{RTI}(t))\beta e^{-a_0C(t)}V(t)) + \lambda_4 p0^V(t)C(t)]$$

$$\frac{d\lambda_2}{dt} = -\frac{\partial L}{\partial T*} = -[\lambda_2(-\alpha - hC(t)) + \lambda_3((1 - \frac{1}{2}u_{PI}(t))Ne^{-a}1^C(t)_{\alpha)}]$$

$$\frac{d\lambda_3}{dt} \quad \frac{\partial L}{\partial V}$$

$$= -[\lambda_1(\frac{rT(t)B_V}{(B_V + V(t))^2} - (1 - \frac{1}{2}u_{RTI}(t))\beta e^{-a_0C(t)}T(t) - \frac{kT(t)}{B_T + T(t)})]$$

$$-[\lambda_2((1 - \frac{1}{2}u_{RTI}(t))\beta e^{-a_0C(t)}T(t)) - \lambda_3\mu V]$$

$$\frac{d\lambda_4}{dt} \quad \frac{\partial L}{\partial C}$$

$$= -[\lambda_1(a_0(1 - \frac{1}{2}u_{RTI}(t))\beta e^{-a_0C(t)}V(t)T(t))]$$

$$+[\lambda_2(a_0(1 - \frac{1}{2}u_{RTI}(t))\beta e^{-a_0C(t)}V(t)T(t) + hT^*(t))]$$

$$+[\lambda_3(a_1(1 - \frac{1}{2}u_{PI}(t))Ne^{-a}1^C(t)_{\alpha T} * (t)) - \lambda_4(p0^T(t)V(t) - \mu C)]$$

with transversality conditions $\lambda_i(T_f) = 0$ for $i = 1, 2, 3, 4$. Further , th e following characterization ho lds :

$$u^*RTI(t) = \min\{\max\{a_{11}, \frac{1}{2A_1}(\lambda_1 - \lambda_2)\beta e^{-a_0C(t)}V(t)T(t)\}, b_{11}\},$$

$$u^*PI(t) = \min\{\max\{a_{22}, \frac{-\lambda_3}{2A_2}Ne^{-a}1^C(t)_{\alpha T} * (t)\}, b_{22}\}.$$

Proof . The form of the adjoint equations and transversality conditions are stan - dard results from Pontryagin ' s Maximum Principle [8] ; therefore , solutions to the adjoint system exists and are bounded . To determine the interior maximum of our Lagrangian , we take the partial derivatives of L with respect to u_{RTI} and u_{PI} and set it equal to zero . Thus

$$\frac{\partial L}{\partial u_{RTI}} = -A_1 u^*_{RTI}(t) + \frac{\lambda_1}{2}\beta e^{-a_0 C(t)} V(t)T(t) - \frac{\lambda_2}{2}\beta e^{-a_0 C(t)} V(t)T(t)$$
$$-w_{11}(t) + w_{12}(t) = 0 \quad @u^* RTI.$$
$$\frac{\partial L}{\partial u_{PI}} = -A_2 u^* PI(t) - \frac{\lambda_3}{2} N e^{-a} 1^C(t)_{\alpha T} * (t) - w_{21}(t) + w_{22}(t) = 0 \quad @u^* PI.$$

 Hence upon simplification , we obtain

$$u^*RTI(t) = \frac{\frac{(\lambda_1-\lambda_2)}{2}\beta e^{-a_0C(t)}V(t)T(t) - w_{11}(t) + w_{12}(t)}{A_1} \tag{4.1}$$

$$u^*PI(t) = \frac{\frac{-\lambda_3}{2}Ne^{-a}1^C(t)_{\alpha T} * (t) - w_{21}(t) + w_{22}(t)}{A_2} \tag{4.2}$$

4 . 1 . **Case** u^*RTI.

(1) On the set $\{t \mid a_{11} < u^*RTI(t) < b_{11}\}, w_{11}(t) = w_{12}(t) = 0$. From (4 . 1) we have

$$u^*RTI(t) = \frac{(\lambda_1 - \lambda_2)\beta e^{-a_0C(t)}V(t)T(t)}{2A_1}$$

(2) On the set $\{t \mid u^*RTI(t) = a_{11}\}, w_{11}(t) = 0$. Consequently ,

$$u^*RTI(t) = a_{11} = \frac{(\lambda_1 - \lambda_2)\beta e^{-a_0C(t)}V(t)T(t)}{2A_1} + \frac{w_{12}(t)}{A_1}$$

or

$$\frac{(\lambda_1 - \lambda_2)\beta e^{-a_0C(t)}V(t)T(t)}{2A_1} \le a_{11}, \quad \text{since} w_{12}(t) \ge 0.$$

(3) On the set $\{t \mid u^*RTI(t) = b_{11}\}, w_{12}(t) = 0$. Consequently ,

$$u^*_{RTI}(t) = b_{11} = \frac{(\lambda_1 - \lambda_2)\beta e^{-a_0C(t)}V(t)T(t)}{2A_1} - \frac{w_{11}(t)}{A_1}$$

or

$$\frac{(\lambda_1 - \lambda_2)\beta e^{-a_0C(t)}V(t)T(t)}{2A_1} \ge b_{11}, \quad \text{since} w_{11}(t) \ge 0.$$

Combining all the three cases in a compact form gives

$$u^*RTI(t) = \min\{\max\{a_{11}, \frac{1}{2A_1}(\lambda_1 - \lambda_2)\beta e^{-a_0C(t)}V(t)T(t)\}, b_{11}\}.$$

4 . 2 . **Case** u^*PI.

(1) On the set $\{t \mid a_{22} < u^*PI(t) < b_{22}\}, w_{21}(t) = w_{22}(t) = 0$. From (4 . 2) we have

$$u^*PI(t) = -\frac{\lambda_3 Ne^{-a}1^C(t)_{\alpha T} * (t)}{2A_2}.$$

(2) On the set $\{t \mid u^*PI(t) = a_{22}\}, w_{21}(t) = 0$. Consequently ,

$$u^*PI(t) = a_{22} = -\frac{\lambda_3 Ne^{-a}1^C(t)_{\alpha T} * (t)}{2A_2} + \frac{w_{22}(t)}{A_2}$$

or

$$-\frac{\lambda_3 Ne^{-a}1^C(t)_{\alpha T} * (t)}{2A_2} \le a_{22}, \quad \text{since} w_{22}(t) \ge 0.$$

(3) On the set $\{t \mid u^*PI(t) = b_{22}\}, w_{22}(t) = 0$. Consequently ,

$$u^*PI(t) = b_{22} = -\frac{\lambda_3 N e^{-a} 1^C(t)_{\alpha T} * (t)}{2A_2} - \frac{w_{21}(t)}{A_2}$$

or

$$-\frac{\lambda_3 N e^{-a} 1^C(t)_{\alpha T} * (t)}{2A_2} \geq b_{22}, \quad \text{since} w_{21}(t) \geq 0.$$

 Combining all the three cases in compact form gives

$$u^*PI(t) = \min\{\max\{a_{22}, \frac{-\lambda_3}{2A_2} Ne^{-a} 1^C(t)_{\alpha T} * (t)\}, b_{22}\}.$$

□

5 . Optimality System

Incorporating the presentation of the optimal treatment controls , we have the state system coupled with the adjoint system .

$$\begin{aligned}
\frac{dT(t)}{dt} &= s_1 + \frac{rT(t)V(t)}{(B_V + V(t))} - \mu T^T(t) - \frac{kV(t)T(t)}{(B_T + T(t))} \\
&-(1 - \frac{1}{2}\min\{\max\{a_{11}, \frac{1}{2A_1}(\lambda_1 - \lambda_2)\beta e^{-a_0 C(t)} V(t)T(t)\}, b_{11}\}) \\
&\times \beta e^{-a_0 C(t)} V(t)T(t) \\
\frac{dT^*(t)}{dt} &= (1 - \frac{1}{2}\min\{\max\{a_{11}, \frac{1}{2A_1}(\lambda_1 - \lambda_2)\beta e^{-a_0 C(t)} V(t)T(t)\}, b_{11}\}) \\
&\times \beta e^{-a_0 C(t)} V(t)T(t) - \alpha T^*(t) - hT(t)C(t) \\
\frac{dV(t)}{dt} &= (1 - \frac{1}{2}\min\{\max\{a_{22}, \frac{-\lambda_3}{2A_2} Ne^{-a} 1^C(t)_{\alpha T} * (t)\}, b_{22}\}) \\
&\times Ne^{-a} 1^C(t)_{\alpha T} * (t) - \mu V^V(t) \\
\frac{dC(t)}{dt} &= s_2 + p0^T(t)V(t)C(t) - \mu C^C(t) \\
\frac{d\lambda_1}{dt} &= -1 - \lambda_1(\frac{rV(t)}{(B_V + V(t))} - \mu T - \frac{kV(t)B_T}{(B_T + T(t))^2}) - \lambda_4 p0^C(t)V(t) \\
&+\lambda_1(1 - \frac{1}{2}\min\{\max\{a_{11}, \frac{1}{2A_1}(\lambda_1 - \lambda_2)\beta e^{-a_0 C(t)} V(t)T(t)\}, b_{11}\}) \\
&\times \beta e^{-a_0 C(t)} V(t) \\
&-\lambda_2((1 - \frac{1}{2}\min\{\max\{a_{11}, \frac{1}{2A_1}(\lambda_1 - \lambda_2)\beta e^{-a_0 C(t)} V(t)T(t)\}, b_{11}\}) \\
&\times \beta e^{-a_0 C(t)} V(t)) \\
\frac{d\lambda_2}{dt} &= \lambda_2(\alpha + hC(t)) \\
&-\lambda_3(1 - \frac{1}{2}\min\{\max\{a_{22}, \frac{-\lambda_3}{2A_2} Ne^{-a} 1^C(t)_{\alpha T} * (t)\}, b_{22}\}) Ne^{-a} 1^C(t)_{\alpha} \\
\frac{d\lambda_3}{dt} &= -\lambda_1(\frac{rT(t)B_V}{(B_V + V(t))^2} - \frac{kT(t)}{B_T + T(t)}^{)} + \lambda_3 \mu V \\
&+\lambda_1(1 - \frac{1}{2}\min\{\max\{a_{11}, \frac{1}{2A_1}(\lambda_1 - \lambda_2) \\
&\times \beta e^{-a_0 C(t)} V(t)T(t)\}, b_{11}\}\beta e^{-a_0 C(t)} T(t)) \\
&-\lambda_2((1 - \frac{1}{2}\min\{\max\{a_{11}, \frac{1}{2A_1}(\lambda_1 - \lambda_2)\beta e^{-a_0 C(t)} V(t)T(t)\}, b_{11}\}) \\
&\times \beta e^{-a_0 C(t)} T(t)) - \lambda_4 p0^T(t)C(t)
\end{aligned}$$

$$\frac{d\lambda_4}{dt} = -\lambda_1(a_0(1-\frac{1}{2}\min\{\max\{a_{11},\frac{1}{2A_1}(\lambda_1-\lambda_2)\beta e^{-a_0C(t)}V(t)T(t)\},b_{11}\}) \times\beta e^{-a_0C(t)}V(t)T(t)) +\lambda_2(a_0(1-\frac{1}{2}\min\{\max\{a_{11},\frac{1}{2A_1}(\lambda_1-\lambda_2)\beta e^{-a_0C(t)}V(t)T(t)\},b_{11}\}) \times\beta e^{-a_0C(t)}V(t)T(t)) +\lambda_3(a_1(1-\frac{1}{2}\min\{\max\{a_{22},\frac{-\lambda_3}{2A_2}Ne^{-a}1^C(t)_{\alpha T}*(t)\},b_{22}\}) \times Ne^{-a}1^C(t)_{\alpha T}*(t)) - \lambda_4(p0^T(t)V(t)-\mu C)+\lambda_2 hT^*(t) \tag{5.1}$$

$$\text{with} T(0)=T_0, T^*(0)=T_0^*, V(0)=V_0, C(0)=C_0, \lambda_i(T_f)=0 \text{for} i=1,2,3,4.$$

6. Uniqueness of the Optimality System

Since the state system moves forward in time and the adjoint system moves backward in time , we have a challenge with uniqueness . To prove uniqueness of solutions of the optimality system for the small time interval , we use the following theorems [8] .

Theorem 6 . 1 . *The function* $u^*(c) = \min(\max(c,a),b)$ *is Lipschitz continuous in* c, *where* $a<b$ *are s ome fixed positive constants .*

Proof . Consider c_1, c_2 real numbers and a, b as fixed positive constants . We will show that the Lipschitz continuity holds in all possible cases for $\max(c,a)$. Similar arguments hold for $\min(\max(c,a),b)$ as well .

(1) $c_1 \geq a, c_2 \geq a$: $|\max(c_1,a)-\max(c_2,a)| = |c_1-c_2|$.
(2) $c_1 \geq a, c_2 \leq a$: $|\max(c_1,a)-\max(c_2,a)| = |c_1-a| \leq |c_1-c_2|$
(3) $c_1 \leq a, c_2 \geq a$: $|\max(c_1,a)-\max(c_2,a)| = |a-c_2| \leq |c_1-c_2|$
(4) $c_1 \leq a, c_2 \leq a$: $|\max(c_1,a)-\max(c_2,a)| = |a-a| = 0 \leq |c_1-c_2|$

Hence $|\max(c_1,a) - \max(c_2,a)| \leq |c_1-c_2|$ and we have Lipschitz continuity of u^* inc. □

Theorem 6 . 2 . *For sufficiently small final time* (T_f), *bounded s o lutions to the optimality system , 5 . 1 , are unique .*

Proof . Suppose $(T, T^*, V, C, \lambda_1, \lambda_2, \lambda_3, \lambda_4)$ and $(\bar{T}, \bar{T}^*, \bar{V}, \bar{C}, \bar{\lambda}_1, \bar{\lambda}_2, \bar{\lambda}_3, \bar{\lambda}_4)$ are two different solutions of our optimality system (5 . 1) . Let $T = e^{mt}p, T^* = e^{mt}p^*$,

$$V = e^{mt}q,\quad C = e^{mt}x,\quad \lambda_1 = e^{-mt}w,\quad \lambda_2 = e^{-mt}z,\quad \lambda_3 = e^{-mt}v,\quad \lambda_4 = e^{-mt}y$$
$$\text{and} \bar{T} = e^{mt}\bar{p}, \bar{T}^* = e^{mt}\bar{p}^*,\quad \bar{V} = e^{mt}\bar{q},\quad \bar{C} = e^{mt}\bar{x},\quad \bar{\lambda}_1 = e^{-mt}\bar{w},\quad \bar{\lambda}_2 = e^{-mt}\bar{z},$$

$\bar{\lambda}_3 = e^{-mt}\bar{v}, \bar{\lambda}_4 = e^{-mt}\bar{y},$ where $m>0$ is chosen . Further we let

$$u^*RTI(t) = \min\{\max\{a_{11}, \frac{1}{2A_1}(w-z)\beta e^{-a_0e^{mt}x}pq\}, b_{11}\},$$
$$u^*PI(t) = \min\{\max\{a_{22}, \frac{-\alpha N}{2A_2}e^{-a_1e^{-mt}x}vp^*\}, b_{22}\}$$

and

$$\bar{u}^*RTI(t) = \min\{\max\{a_{11}, \frac{1}{2A_1}(\bar{w}-\bar{z})\beta e^{\frac{-a_0e^{mt}\bar{x}}{\bar{p}\bar{q}}}\}, b_{11}\},$$

$$\bar{u}^* PI(t) = \min\{\max\{a_{22}, \frac{-\alpha N}{2A_2} e_{\bar{v}\bar{p}}^{-a_1 e^{-mt}\bar{x}} *\}, b_{22}\}.$$

For the first equation of system (5 . 1) we substitute $T = e^{mt}p$ and get

$$e^{mt}(\dot{p} + mp) = s_1 + \frac{re^{2mt}pq}{B_V + e^{mt}q} - \beta e^{-ae^{mt}x} e^{2mt}pq + \frac{1}{2}\beta e^{-a_0 e^{mt}x} e^{2mt}pqu^*_{RTI} - \mu T^{e^{mt}} p - \frac{ke^{2mt}pq}{B_T + e^{mt}p}$$

and for $\bar{T} = e^{mt}\bar{p}$ we have

$$e^{mt}(\dot{\bar{p}} + m\bar{p}) = s_1 + \frac{re^{2mt}\bar{p}\bar{q}}{B_V + e^{mt}\bar{q}} - \beta e^{-a_0 e^{mt}\bar{x}} e^{2mt}\bar{p}\bar{q} + \frac{1}{2}\beta e^{-a_0 e^{mt}\bar{x}} e^{2mt}\bar{p}\bar{q}\bar{u}^*_{RTI} - \mu T^{e^{mt}} \bar{p} - \frac{ke^{2mt}\bar{p}\bar{q}}{B_T + e^{mt}\bar{p}}.$$

Subtracting the expression for $\bar{T}$ from the expression for T we have

$$\begin{aligned}(\dot{p} - \dot{\bar{p}}) + m(p - \bar{p}) &= re^{mt}\Big(\frac{pq}{B_V + e^{mt}q} - \frac{\bar{p}\bar{q}}{B_V + e^{mt}\bar{q}}\Big) - \beta e^{mt}(e^{-a_0 e^{mt}x}pq - e_{\bar{p}\bar{q}}^{-a_0 e^{mt}\bar{x}}) \\ &\quad + \frac{1}{2}\beta e^{mt}(e^{-a_0 e^{mt}x}u^*_{RTI}pq - e_{\bar{u}_{RTI}}^{-a_0 e^{mt}\bar{x}*}\bar{p}\bar{q}) \\ &\quad - \mu T(p - \bar{p}) - ke^{mt}\Big(\frac{pq}{B_T + e^{mt}p} - \frac{\bar{p}\bar{q}}{B_T + e^{mt}\bar{p}}\Big).\end{aligned}$$

Multiplying by $(p - \bar{p})$ and integrating from $t = 0$ to $t = T_f$ we have

$$\begin{aligned}\frac{1}{2}(p - \bar{p})^2(T_f) + m\int_0^{T_f}(p - \bar{p})^2 dt &= r\int_0^{T_f} e^{mt}\Big(\frac{pq}{B_V + e^{mt}q} - \frac{\bar{p}\bar{q}}{B_V + e^{mt}\bar{q}}\Big)(p - \bar{p})dt - \mu T\int_0^{T_f}(p - \bar{p})^2 dt \\ &\quad - \beta\int_0^{T_f} e^{mt}(e^{-a_0 e^{mt}x}pq - e_{\bar{p}\bar{q}}^{-a_0 e^{mt}\bar{x}})(p - \bar{p})dt \\ &\quad - k\int_0^{T_f} e^{mt}\Big(\frac{pq}{B_T + e^{mt}p} - \frac{\bar{p}\bar{q}}{B_T + e^{mt}\bar{p}}\Big)(p - \bar{p})dt \\ &\quad + \frac{\beta}{2}\int_0^{T_f} e^{mt}(e^{-a_0 e^{mt}x}pqu^*_{RTI} - e_{\bar{p}\bar{q}^{\bar{u}}_{RTI}}^{-a_0 e^{mt}\bar{x}*})(p - \bar{p})dt.\end{aligned} \tag{6.1}$$

Similarly for $\lambda_1 = e^{-mt}w$ and $\bar{\lambda}_1 = e^{-mt}\bar{w}$ we have

$$-\dot{w} + mw = e^{mt} + \frac{rwqe^{mt}}{B_V + e^{mt}q} - w\beta qe^{-a_0 e^{mt}x}e^{mt} + \frac{1}{2}\beta we^{-a_0 e^{mt}x}e^{mt}qu^*_{RTI} - \mu T^w - \frac{kwqBT^{e^{mt}}}{(B_T + e^{mt}p)^2} + \beta zqe^{-a_0 e^{mt}x}e^{mt} - \frac{1}{2}\beta ze^{-a_0 e^{mt}x}e^{mt}quRTI - yp0^{x^2 e^{mt}}q$$

and

$$-\dot{\bar{w}} + m\bar{w}$$

$$= e^{mt} + \frac{r\bar{w}\bar{q}e^{mt}}{B_V + e^{mt}\bar{q}} - \beta\bar{w}\bar{q}e^{-a_0e^{mt}\bar{x}}e^{mt} + \frac{1}{2}\beta\bar{w}e^{-a_0e^{mt}\bar{x}}e^{mt}\bar{q}^{\bar{u}*}_{RTI} - \mu T^{\bar{w}}$$
$$-\frac{kB_Te^{mt}\bar{w}\bar{q}}{(B_T + e^{mt}\bar{p})^2} + \beta\bar{z}\bar{q}e^{-a_0e^{mt}\bar{x}}e^{mt} - \frac{1}{2}\beta\bar{z}e^{-a_0e^{mt}\bar{x}}e^{mt}\bar{q}^{\bar{u}}RTI - p0\bar{y}^{\bar{x}^2}e^{mt}\bar{q}$$

respectively . Subtracting the expression for $\bar{\lambda}_1$ from the expression for λ_1 and multiplying by $(w - \bar{w})$ and integrating from $t = 0$ to $t = T_f$ we have

$$\frac{1}{2}(w-\bar{w})^2(0) + m\int_0^{T_f}(w-\bar{w})^2dt$$
$$= r\int_0^{T_f} e^{mt}(\frac{wq}{B_V + e^{mt}q} - \frac{\bar{w}\bar{q}}{B_V + e^{mt}\bar{q}})(w-\bar{w})dt$$
$$-\beta\int_0^{T_f} e^{mt}(e^{-a_0e^{mt}x}wq - e^{-a_0e^{mt}\bar{x}}_{\bar{w}\bar{q}})(w-\bar{w})dt$$
$$+\frac{\beta}{2}\int_0^{T_f} e^{mt}(e^{-a_0e^{mt}x}wqu^*_{RTI} - e^{-a_0e^{mt}\bar{x}*}_{\bar{w}\bar{q}^{\bar{u}}_{RTI}})(w-\bar{w})dt$$
$$+\beta\int_0^{T_f} e^{mt}(e^{-a_0e^{mt}x}zq - e^{-a_0e^{mt}\bar{x}}_{\bar{z}\bar{q}})(w-\bar{w})dt - \mu T\int_0^{T_f}(w-\bar{w})^2dt$$
$$-\frac{\beta}{2}\int_0^{T_f} e^{mt}(e^{-a_0e^{mt}x}zqu^*_{RTI} - e^{-a_0e^{mt}\bar{x}*}_{\bar{z}\bar{q}^{\bar{u}}_{RTI}})(w-\bar{w})dt$$
$$-p0\int_0^{T_f} e^{mt}(yxq - \bar{y}^{\bar{x}}\bar{q})(w-\bar{w})dt$$
$$-kB_T\int_0^{T_f} e^{mt}(\frac{wq}{(B_T + e^{mt}p)^2} - \frac{\bar{w}\bar{q}}{(B_T + e^{mt}\bar{p})^2})(w-\bar{w})^2dt.$$

Similarly , the equations for T^* and $\bar{T}^*_{,}V$ and $\bar{V}_{,}C$ and $\bar{C}_{,}\lambda_2$ and $\bar{\lambda}_{2,}\lambda_3$ and $\bar{\lambda}_{3,}\lambda_4$ and $\bar{\lambda}_4$ are subtracted , then each expression is multiplied by an appropriate function and integrated from $t = 0$ to $t = T_f$. We obtain eight integral equations
and we use estimates to obtain the result . Several terms are estimated in these eight equations . For example the third term on the right - hand side of equation 6 . 1 ,

$$k\int_0^{T_f} e^{mt}(\frac{pq}{B_T + e^{mt}p} - \frac{\bar{p}\bar{q}}{B_T + e^{mt}\bar{p}})(p-\bar{p})dt$$
$$\leq C_1e^{mt}\int_0^{T_f}((p-\bar{p})^2 + (q-\bar{q})^2)dt,$$

utilizes upper bounds on the solutions . Other estimates can be presented by utiliz - ing upper bounds on solutions . They involve separating terms that involve squares , powers , several multiplied terms , and quotients . Also using Theorem 6 . 1 we have

$$\mid u^*RTI(t) - \bar{u}^*RTI(t) \mid$$
$$\leq \frac{\beta}{2A_1}|e^{-a_0e^{mt}x}pq(w-z) - e^{-a_0e^{mt}\bar{x}}_{\bar{p}\bar{q}}(\bar{w}-\bar{z})|$$
$$\leq \frac{\beta}{2A_1}|(e^{-a_0e^{mt}x}pqw - e^{-a_0e^{mt}\bar{x}}_{\bar{p}\bar{q}^{\bar{w}}}) - (e^{-a_0e^{mt}x}pqz - e^{-a_0e^{mt}\bar{x}}_{\bar{p}\bar{q}^{\bar{z}}})|$$

and

$$\mid u^*PI(t) - \bar{u}^*PI(t) \mid \leq \frac{\alpha N}{2A_2}|e^{-a_1e^{mt}x}vp^* - e^{-a_1e^{mt}\bar{x}}_{\bar{v}\bar{p}} * |.$$

 To show uniqueness , the integral equations are combined . Adding all the eight
estimates gives

$$\begin{aligned}
&\frac{1}{2}(p-\bar{p})^2(T_f)+\frac{1}{2}(p^*-*\bar{p})^2(T_f)+\frac{1}{2}(q-\bar{q})^2(T_f)+\frac{1}{2}(x-\bar{x})^2(T_f)\\
&\quad+\frac{1}{2}(w-\bar{w})^2(0)+\frac{1}{2}(z-\bar{z})^2(0)+\frac{1}{2}(v-\bar{v})^2(0)+\frac{1}{2}(y-\bar{y})^2(0)\\
&\quad+m\int_0^{T_f}[(p-\bar{p})^2+(p^*-*\bar{p})^2+(q-\bar{q})^2+(x-\bar{x})^2+(w-\bar{w})^2\\
&\qquad+(z-\bar{z})^2+(v-\bar{v})^2+(y-\bar{y})^2]dt\\
&\leq (\tilde{C}1+\tilde{C}_{2^e}^{3mT_f})\int_0^{T_f}[(p-\bar{p})^2+(p^*-*\bar{p})^2+(q-\bar{q})^2+(x-\bar{x})^2]dt\\
&\qquad+\int_0^{T_f}[(w-\bar{w})^2+(z-\bar{z})^2+(v-\bar{v})^2+(y-\bar{y})^2]dt.
\end{aligned}$$

Thus from the above expression , using the non - negativity of the variable expressions evaluated at the initial and the final time and simplifying , the inequality is reduced to

$$\begin{aligned}
&(m-\tilde{C}_1-\tilde{C}_{2^e}^{3mT_f})\int_0^{T_f}[(p-\bar{p})^2+(p^*-\bar{p}^*)^2+(q-\bar{q})^2+(x-\bar{x})^2+(w-\bar{w})^2\\
&\qquad+(z-\bar{z})^2+(v-\bar{v})^2+(y-\bar{y})^2]dt\leq 0
\end{aligned}$$

where $\tilde{C}_1$ and $\tilde{C}_2$ depend on the coefficients [6] ; [8] and the bounds on all solution variables p, p^*, q, x, w, z, v, y. If we choose m such that $m-\tilde{C}_1-\tilde{C}_{2^e}^{3mT}f \quad > 0$, the above inequality holds if the integrand is identically zero . Since the natural logarithm is an increasing function , then ln $(\frac{m-\tilde{C}_1}{\tilde{C}_2})^{} > 3mT_f$ if $m > \tilde{C}_1+\tilde{C}_2$. This gives that $T_f < \frac{1}{3m}$ ln $(\frac{m-\tilde{C}_1}{\tilde{C}_2})^{}$, then $p=\bar{p}, p^*=\bar{p}^*, q=\bar{q}, x=\bar{x}, w=\bar{w}, z=\bar{z}$,
$v=\bar{v}, y=\bar{y}$. Hence the solution is unique for small t ime . □

7 . Numerical S imulations

The optimality system in section 5 is solved using an iterative method with Runge - Kutta of order four scheme . The optimality system is a two - point bound - ary value problem , where initial conditions are specified for the state system and terminal conditions are specified for the adjoint system . The method of obtaining the optimal control is as follows [8] :

(1) Take a guess for the two controls .

(2) Solve the state system forward using those controls and using a Runge - kutta method of order four algorithm . Use state variables initial conditions .

(3) Using the new state values , solve the adjoint system backwards using the final time zero boundary conditions and Runge - Kutta of order four scheme . (4) Calculate the new control values from the characterization .

(5) Go to steps 2 , 3 again with new control from step 4 .

(6) Calculate other new control values from step 5 . Compare controls from last iteration to new iteration and compare states also . Keep repeating control updates and forward and backward solving until the iterates converge .

In the virtual simulations in this section we chose a set of parameters and initial values yielding approximately realistic population numbers . Our initial conditions

resemble clinical data for HIV infected individuals during symptomatic phase . Since therapy is initiated when patients are symptomatic , we consider cases when CD 4+ T cell count is less than or equal 250 cells μl^{-1}. The following parameter values have been used to generate the solutions in this section : $s_1 = 20$, $\mu T = 0.2$,

$$r = 0.01, N = 10[9], s_2 = 10, \beta = 2 \times 10^{-4}, B_T = 350, B_V = 400, h = 2 \times 10^{-3},$$
$$\mu C = 1.5, \mu V = 0.95[3], k = 2 \times 10^{-3}, a_0 = 0.01, a_1 = 0.75, p0 = 1 \times 10^{-5} \text{and}$$

$\alpha = 0.25[16]$. The bounds for controls are $a_{11} = 0.0, a_{22} = 0.0, b_{11} = 0.2$ and

$$b_{22} = 0.9.$$

Figure 1 shows the graph of the solution to the optimality system , showing propagation of CD 4+ T cells , infected CD 4+ T cells , reverse transcriptase inhibitor and a protease inhibitor when treatment is administered for 50 days . Here we initiate treatment when CD 4+ T cell count , T (0) is 250 cells μl^{-1}, viral load , V (0) is 4000 copies ml^{-1}, infected CD 4+ T cells , $T^*(0)$ of 200 cells μl^{-1} and a CTL count , C (0) of $10\mu l^{-1}$. The value for the first weight factor is given by $A_1 = 250000$ and the second weight factor $A_2 = 250$ [8]. Figure 1 (a) shows the propagation of uninfected CD 4+ T cells after initiation of therapy . Initial decline of CD 4+ T cells for a day is due to pharmacokinetics and pharmacology delay , and thereafter T cell count start to increase for about 25 days , nearly an increase of 10% and thereafter CD 4+ T cells start to gradually decline . Within the first week of drug administration , viral load drops to zero , figure 1 (c) , followed by a sudden increase and oscillation at around 400 for another week and then stabilizes for the next 25 days and starts to slowly increase at day 40 . The CD 4+ T cell and viral kinetics are produced if the nucleoside RTI (figure 1 (b)) is administered in full scale for one day (normalised dosage size of 0 . 2) after 4 days , and the drug is stopped for 2 - 3 days . Drug administration resume with almost 10% of the initial dosage size and gradually increased up to day 30 and then tapered off up to day 50 . Therapy start with high doses (normalised dosage size of 0 . 9) of a protease inhibitor (figure 1 (d)) for the first day , then stopped for 5 days . The drug is administered at full scale (dosage size of 0 . 9) for a day and then stopped for one day or two days . Finally , 40% of the initial dosage is administered for 1 - 2 days and stopped for 30 - 35 days and resumed with $2\% - 5\%$ of the initial therapy for the last 3 days . The effect of the regimen , in a short term , managed to increase the CD 4+ T cells to nearly 450 cells in 25 days and level of viremia is suppressed to low levels (below 500 copies of RNA ml^{-1}) which is beneficial to the infected individual ' s health .

Figure 2 shows the graph of the solution to the optimality system , showing prop - agation of CD 4+ T cells , infected CD 4+ T cells , reverse transcriptase inhibitor and a protease inhibitor where CTL activity is decreased . Here we initiate treatment when CD 4+ T cell count , T (0) is 250 cells μl^{-1}, viral load , V (0) is 4000 copies ml^{-1}, infected CD 4+ T cells , $T^*(0)$ of 200 cells μl^{-1} and a CTL count , C (0) of $10\mu l^{-1}$, and treatment is administered for 50 days . The value for the first weight factor is given by $A_1 = 250000$ and the second weight factor $A_2 = 250$. A decrease in the effect of CTL activity , that is decrease in $a_0 = 0.01$ and $a_1 = 0.75$ with the same initial conditions leads to CD 4+ T cells decline for 1 - 2 days due to pharma - cology and pharmacokinetics (similar to Dixit and Perelson [5] results) j ust after initiation of therapy (figure 2 (a)) and build up for nearly 1 0 days before a decreas - ing tendency up to day 50 . Viral load sharply decreases to very low levels (figure 2 (c)) during the first 5 days of therapy initiation , sharply increase and sharply decrease before it starts to gradually increase . The kinetics of the CD 4+ T cells

(a) (b)
(c) (d)

FIGURE 1 . Graph of the numerical solution to the optimality sys - tem , showing propagation of CD 4+ T cells , infected CD 4+ T cells , reverse transcriptase inhibitor and a protease inhibitor when treat - ment is administered for 50 days . Here we initiate treatment when CD 4+ T cell count , T (0) is 250 cells μl^{-1}, viral load , V (0) is 4000 copies ml^{-1}, infected CD 4+ T cells , $T^*(0)$ of 200 cells μl^{-1} and a CTL count , C (0) of $10\mu l^{-1}$. The value for the first weight factor is given by $A_1 = 250000$ and the second weight factor $A_2 = 250$. (a) CD 4+ T cell kinetics (b) Reverse Transcriptase Inhibitor dosage sizes (c) Viral Load (d) Protease Inhibitor dosage sizes .

and viral load are given if the nucleoside reverse transcriptase inhibitor (normalised dosage size of 0 . 2) is administered for 1 day and then stopped for 4 days (figure 2 (b)) . The drug is given in small dosage sizes , increased daily to almost 10% of initial dosage at day 1 0 for 2 days . The dosage size is decreased to nearly 40%, then increased at day 1 5 and then tapered off up to day 50 . Protease inhibitor drug schedule is st arted at day 6 (figure 2 (d)) , increased to nearly 0 . 9 at day 9 and lowered to nearly zero at day 1 2 . Small quantities are given , nearly 10% of the initial dosage size and maintained up to day 50 . The scheme is effective during the first 1 0 days and thereafter the immune system is heavily compromised due to little activity of CTLs . Figure 3 shows the graph of the solution to the optimal - ity system , showing propagation of CD 4+ T cells , infected CD 4+ T cells , reverse transcriptase inhibitor and a protease inhibitor when treatment is administered for 50 days . Here we initiate treatment when CD 4+ T cell count T (0) is 250 cells

(a) (b)
(c) (d)

FIGURE 2 . Graph of the numerical solution to the optimality sys - tem , showing propagation of CD 4+ T cells , infected CD 4+ T cells , reverse transcriptase inhibitor and a protease inhibitor when treat - ment is administered for 50 days . Here we initiate treatment when CD 4+ T cell count , T (0) is 250 cells μl^{-1}, viral load , V (0) is 4000 copies ml^{-1}, infected CD 4+ T cells , $T^*(0)$ of 200 cells μl^{-1} and a CTL count , C (0) of $10\mu l^{-1}$. The value for the first weight factor is given by $A_1 = 250000$ and the second weight factor $A_2 = 250$. The activity CTL in reducing burst size and reducing infection has been decreased to $a_1 = 0.75$ and $a_0 = 0.01$ respectively . Here a_0 and a_1 are different from figure 1 . (a) CD 4+ T cell kinetics (b) Reverse Transcriptase Inhibitor dosage sizes (c) Viral Load (d) Protease Inhibitor dosage sizes .

μl^{-1}, viral load V (0) is 4000 copies ml^{-1}, infected CD 4+ T cells , $T^*(0)$ is 200 cells μl^{-1} and a CTL count , C (0) of $10\mu l^{-1}$. The value for the first weight factor is given by $A_1 = 250$ and the second weight factor $A_2 = 10$. Exploring the effects of drug toxicity , that is reducing the weight factors $A_1 = 250$ and $A_2 = 10$ and all the other parameters remain as in figure (2) . We have the following numerical results , given by figure (3) : Effect of reducing the weight factors simulate the effect of a decrease in drug toxicity , and therefore we observe that dosage sizes for both
drug types are increased . Since the efficacy of drugs is not changed , CD 4+ T cells and viral kinetics (figure 3 (a) and (c)) respectively) do not change . The nucleoside reverse transcriptase inhibitor (figure 3 (b)) is administered at full scale for 2 days

and stopped for 1 to 2 days . Therapy is given again at full scale up to day 50 . Protease inhibitor schedule (figure 3 (d)) is given at day 7 , increased to full scale for 4 - 5 days and decreased to nearly 11 % up to day 50 .

(a) (b)
(c) (d)

FIGURE 3 . Graph of the numerical solution to the optimality sys - tem , showing propagation of CD 4+ T cells , infected CD 4+ T cells , reverse transcriptase inhibitor and a protease inhibitor when treat - ment is administered for 50 days . Here we initiate treatment when CD 4+ T cell count , T (0) is 250 cells μl^{-1}, viral load , $V(0)$ is 4000 copies ml^{-1}, infected CD 4+ T cells , $T^*(0)$ of 200 cells μl^{-1} and a CTL count , C (0) of $10\mu l^{-1}$. The value for the first weight factor is given by $A_1 = 250$ and the second weight factor $A_2 = 10$. (a) CD 4+ T cell kinetics (b) Reverse Transcriptase Inhibitor dosage sizes (c) Viral Load (d) Protease Inhibitor dosage sizes .

8 . D ISCUSSION

The virtual combined therapy simulations in this paper are designed to provide insights of drug scheduling in short term therapy performance . Similar to Baj aria *e t al* . [3] , reduced dosage sizes and drug holidays can achieve goals of antiretroviral therapy (increase of CD 4+ T cells and suppression of viral load) . In poor resourced settings , an effective schedule should improve the patient ' s life , be affordable (small dosages sizes) and allowing drug holidays should relax the concept of strict patient adher- ence to treatment and compliance . The scheme should increase or restore the immuno- logical function (CD 4+ T cell increases) through less exposure to drugs . We

also observe that the weight factors in the objective functional model drug toxicity , therefore the more toxic the drugs are the less dosage sizes to be administered to reduce systemic costs . Figure 1 shows that if an individual ' s immune response is strong , virus can be effectively controlled during therapy whilst weak immune responses , figure 2 and figure 3 , lead to a short term control of the virus . We can conclude that effectiveness of therapy largely depends on the immune response of an individual , that is if the immune response is better , virus can be controlled effectively . Also an effective immune response leads to administration of small dosage sizes which are cost effective . We observe from numerical illustrations that if therapy can induce CTL activity , control of viremia is feasible and this can facilitate the implementation of drug holidays . During drug holiday periods , CTLs will be controlling viremia . Due to drug toxicity , allowing drug holidays can be beneficial in the short term implementation of HAART . If therapy has less toxic effects , continuous therapy is beneficial as there will be less harmful side effects . Our dynamical model did not take into account the effects of viral population mutation over time in response to drug therapy . These effects can become significant in the case of long term anti - HIV therapy .

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