Optimal treatment strategies to control acute HIV infection

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ABSTRACT

Various antiretroviral therapies (ART) are administered to symptomatic human immunodeficiency virus (HIV) infected individuals to improve their health. The treatment effectiveness may depend on suppressing development of drug resistance, reduce evolution of new viral strains, minimize serious side effects and the costs of drugs. This paper deals with some results concerning optimal drug administration scheme successful in improving patients' health especially in poorly resourced settings. The model under consideration describes the interaction between the uninfected cells, the latently infected cells, the productively infected cells, and the free viruses. Generally, in viral infection, the drug strategy aspects either the virus infectivity or reduce the virion production. The mathematical model proposed here, deals with both situations with the objective function based on a combination of maximizing benefit relied on T cells count (the white cells that coordinate activities of the immune system) and minimizing the systemic cost. The existence of the optimal control pair is established and the Pontryagin's minimum principle is used to characterize these two optimal controls. The optimality system is derived and solved numerically using the forward and backward sweep method (FBSM). Our results indicate that early initiation of treatment makes a profound impact in both improving the quality of life and reducing the economic costs of therapy.

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1. Introduction

Human immunodeficiency virus (HIV) continues to be one of the biggest burdens in human health with about 38 million people living with the virus around the world, 1.8 million people becoming newly infected with HIV and neatly 1 million deaths due to AIDS related illness (WHO, 2018). The HIV replicates within a host by infecting activated CD4$^+$T cells or T cells, which then produce additional copies of the virus. Many studies (Chun et al., 1997; NOE et al., 2005) have determined that upon infection and transcription of viral RNA into cell DNA, a fraction of CD4$^+$T cells fail to actively produce virus until they are activated, possibly years after their initial infection. Such cells may possess a much longer lifespan than their counterparts and are termed latently infected cells. Upon activation, latently infected cells do become actively productive, and hence begin to increase the viral load through viral replication despite immune surveillance or antiretroviral therapy (ART). The clinical data

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shows that latent *T* cell infection is established during early HIV infection (Chun et al., 1998). A study (Archin et al., 2012) on HIV patients treated early in infection showed that latently infected cells are mainly generated during primary infection from initiation of infection up to the time of ART, and once ART is initiated, there are many fewer infections generating fewer latently infected cells. This encouraging result suggests that the initiation of ART very early during infection can limit or possibly eradicate the virus. However, an experiment (Whitney et al., 2014) with simian immunodeficiency virus (SIV) infected monkeys showed that even the monkeys that were treated on day 3 post infection suffer from virus rebound after discontinuation of ART following 24 weeks of fully suppressive therapy. Many mathematical models have provided great insights into the dynamics of latently infected cells (Kim & Perelson, 2006; Perelson et al., 1993; Rong & Perelson, 2009). Kim and Perelson (Kim & Perelson, 2006) studied viral persistence during therapy with the effect of latent reservoir, Rong and Perelson (Rong & Perelson, 2009) modeled viral blips and showed that a latent reservoir could produce viral transients when activated by infection, while Perelson et al. (Perelson et al., 1993) employed the latent reservoir to show that its stability was unlikely to depend on a critical value. In each of these studies, the mathematical analysis was performed and the parameter was used for the chronic stage (infection after years) of HIV, some nonlinear behavior of the associated model was also fully elucidated.

Optimal treatment strategies can decrease the possibility of virus mutation, pharmaceutical side effects, and expensive medication burden. Since too large dosage may not be desirable for patients while too small dosage may be ineffective as therapy for the recommended therapeutic agents. Hence, mathematical modelling of optimal control theory has been considered important in a long-standing application in HIV treatment strategies (Adams et al., 2005; Ahmed et al., 2018; Butler et al., 1997; Hattaf & Yousfi, 2012; Joshi, 2002; Kirschner et al., 1997; Ogunlaran & Oukouomi Noutchie, 2016; Zhou et al., 2014). The basic viral infection model consists of three dynamical components including the uninfected cells, the infected cells, and the free viruses was first studied in (Nowak & May 2000). In a recent work, the model describing HIV viral dynamics incorporating the latent infected cells is formulated and studied in (Pankavich, 2016). The authors study the global stability of the endemic states and illustrate the numerical simulations in order to show the numerical stability for each problem steady state. This paper will be focused on studying optimal control for the HIV infection model given in (Pankavich, 2016). For this purpose, we will consider the following nonlinear differential equations:

$$
\begin{cases}
\dfrac{dT(t)}{dt} = \lambda - (1-u_1)kT(t)V(t) - d_T T(t), \\[2mm]
\dfrac{dI(t)}{dt} = (1-u_1)(1-f)kT(t)V(t) - d_I I(t) + \alpha L(t), \\[2mm]
\dfrac{dL(t)}{dt} = (1-u_1)fkT(t)V(t) - d_L L(t) - \alpha L(t), \\[2mm]
\dfrac{dV(t)}{dt} = (1-u_2)Nd_I I(t) - d_V V(t).
\end{cases}
\tag{1}
$$

with initial conditions $T(0) = T_0$, $I(0) = I_0$, $L(0) = L_0$, and $V(0) = V_0$ and $0 \le u_1, u_2 \le 1$. The values, $u_i = 0$ and $u_i = 1$ ($i = 1, 2$), reflect completely ineffective and perfectly effective treatment respectively. In the model (1), $T(t)$ is the concentration of uninfected *T* cells, $L(t)$ denotes the concentration of latently infected *T* cells, $I(t)$ is the concentration of productively infected cells, and $V(t)$ represents the concentration of virions in plasma at *t*. The parameter λ is the generate rate of uninfected *T* cells, d_T is the per capita death rate of uninfected cells, and k is the infection rate of the target cell by a virus. A small fraction f of infected cells are assumed to result in latency and the remaining become productively infected cells. Latently infected cells die at a rate constant d_L per cell and productively infected cells die at a rate constant d_I per cell. N is the viral burst size, which is the total number of virions released by one infected cell in its lifespan, and d_V is the viral clearance rate. Latently infected cells can be activated by their relevant antigens to become productively infected cells at a rate constant α. The two constants u_1 and u_2 stand for the efficiency of treatment in blocking new infection and in inhibiting viral production, respectively. So far, there is no individual effective treatment that eradicates the HIV virus; However, there are some combined therapies known as "cocktail drug therapy" that reduce HIV infection (Orellana, 2011). Two classes of antiretroviral drugs are mostly used to reduce the viral load and limit the infected *T* cell population. One class u_1, is known as Reverse Transcriptase Inhibitors (RTIs), which can block new HIV infections by disrupting the conversion of viral RNA into DNA. The other category u_2 is Protease Inhibitors (PIs), which prevents the assembly of key viral proteins after they have been mistakenly produced by infected host cells. We note that 62% of infected adults and 52% of infected children are receiving lifelong antiretroviral therapy (ART) (World Health Organization). Our work is dedicated to the question of optimizing treatment scheduling, i.e. when and how the treatment should be initiated assuming that treatment can be used only for a finite period of time due to both the adverse effects induced by the medications and the resistance developed by the virus at the prescribed drugs. We note that the effects of viral mutation, which may continuously change model and parameter values, and the possible spatial dependence of parameters can be ignored during primary stage of the disease.

The paper is structured as follows: The next section is dedicated to the qualitative analysis of the model, followed in section 3 by the optimal control problem with an objective functional that maximizes CD4$^+$T cells and minimizes systemic costs. In section 4, we construct an appropriate numerical algorithm and give some numerical simulations. Some concluding remarks are drawn in the last section.

2. Qualitative study of the model

In order to retain the biological validity of the model (1), we must prove that solutions to the system of differential equations exist and they are positive and bounded for all values of time.

Theorem 2.1. *(Existence of Solution). Let $T_0, I_0, L_0, V_0 \in \mathbb{R}$ be given. There exists $t_0 > 0$ and continuously differentiable functions $\{T, I, L, V : [0, t_0) \to \mathbb{R}\}$ such that the ordered quadruple (T, I, L, V) satisfies (1) and $(T, I, L, V)(0) = (T_0, I_0, L_0, V_0)$.*

Proof. To prove the result, first we use the classical Cauchy-Lipschitz Theorem (Kelley & Peterson, 2010). Since the system of ODEs is autonomous, it suffices to show that the function $\mathbf{f} : \mathbb{R}^4 \to \mathbb{R}^4$ defined by

$$\mathbf{f}(\mathbf{y}) = \begin{pmatrix} \lambda - (1-u_1)kTV - d_T T \\ (1-u_1)(1-f)kTV - d_I I + \alpha L \\ (1-u_1)fkTV - d_L L - \alpha L \\ (1-u_2)Nd_I I - d_V V \end{pmatrix}$$

is locally Lipschitz in its $\mathbf{y}$ argument. Note that the Jacobian matrix

$$\nabla \mathbf{f}(\mathbf{y}) = \begin{pmatrix} -(1-u_1)kV - d_T & 0 & 0 & -(1-u_1)kT \\ (1-u_1)(1-f)kV & -d_I & \alpha & (1-u_1)(1-f)kT \\ (1-u_1)fkV & 0 & -(d_L + \alpha) & (1-u_1)fkT \\ 0 & (1-u_2)Nd_I & 0 & -d_V \end{pmatrix}$$

is linear in $\mathbf{y} \in \mathbb{R}^4$. Thus, $\nabla \mathbf{f}(\mathbf{y})$ is continuous on a closed interval and differentiable on an open interval $I \in \mathbb{R}^4$. By the Mean Value Theorem, we know

$$\frac{|\mathbf{f}(\mathbf{y_1}) - \mathbf{f}(\mathbf{y_2})|}{|\mathbf{y_1} - \mathbf{y_2}|} \leq |\nabla \mathbf{f}(\mathbf{y}^*)|$$

for some $\mathbf{y}^* \in I$. By letting $|\nabla \mathbf{f}(\mathbf{y}^*)| = K$, we obtain $|\mathbf{f}(\mathbf{y_1}) - \mathbf{f}(\mathbf{y_2})| \leq K|\mathbf{y_1} - \mathbf{y_2}|$ for all $\mathbf{y_1}, \mathbf{y_2} \in I$ and therefore $\mathbf{f}(\mathbf{y})$ is locally bounded for every $\mathbf{y} \in \mathbb{R}^4$. Hence, $\mathbf{f}$ has a continuous, bounded derivative on any compact subset of $\mathbb{R}^4$ and so $\mathbf{f}$ is locally Lipschitz in $\mathbf{y}$. By the Picard-Lindelöf Theorem (Kelley & Peterson, 2010), there exists a unique solution, $y(t)$, to the ordinary differential equation $y'(t) = f(y(t))$ with initial value $y(0) = y_0$ on $[0, t_0]$ for some time $t_0 > 0$.

Theorem 2.2. *(Positivity and Boundedness). Assume the initial conditions of (1) satisfy $T_0 > 0$, $I_0 > 0$, $L_0 > 0$ and $V_0 > 0$. If the unique solution provided by Theorem 2.1 exists on the interval $[0, t_0]$ for some $t_0 > 0$, then the functions $T(t), I(t), L(t)$ and $V(t)$ will be bounded and remain positive for all $t \in [0, t_0]$.*

Proof. The state variables we consider here represent supersolutions for given problems (1). From the given equations we have

$$(T + I + L)'(t) = \lambda - d_T T - d_I I - d_L L.$$

Now, using $X(t) = T(t) + I(t) + L(t)$ and $d \geq \max\{d_T, d_I, d_L\}$, we get

$$X'(t) = \lambda - d_T T - d_I I - d_L L \leq \lambda - dX,$$

which implies that

$$\limsup_{t \to \infty} X(t) \leq \frac{\lambda}{d} \in \mathbb{R}_+, \quad \text{for all } t \in [0, t_0].$$

where $\mathbb{R}_+$, is the set of non-negative real numbers. The upper bound for X is also the upper bound for T, I, and L. Lastly

$$V'(t) = (1-u_2)Nd_I I(t) - d_V V(t) \leq Nd_I I(t) - d_V V(t) \leq \frac{Nd_I \lambda}{d} - d_V V(t),$$

which also leads to

$$\limsup_{t \to \infty} V(t) \leq \frac{Nd_I \lambda}{dd_V} \in \mathbb{R}_+$$

Since all of the parameters used in the system are positive, we can place lower bounds on the following equations such as

$$X'(t) = \lambda - d_T T - d_I I - d_L L \geq -dX,$$
$$V'(t) = (1 - u_2)Nd_I I - d_V V \geq -d_V V.$$

Using Gronwall's inequality (Gronwall, 1919) method for basic differential equations, we can resolve above inequalities and produce:

$$X(t) \geq X(0)e^{-dt} > 0,$$
$$V(t) \geq V(0)e^{-d_V t} > 0.$$

Since $0 \leq u_1, u_2 \leq 1$, then, $T(t)$, $I(t)$, $L(t)$ and $V(t)$ are bounded above with values elements of $\mathbb{R}_+$. Via a maximum principle (Protter & Weinberger, 1999) theory for first-order nonlinear differential equations, we obtain the solutions to the problems (1) bounded for all $t \in [0, t_0]$ and lies in the compact set

$$\mathbb{D} = \left\{ (T, I, L, V) \in \mathbb{R}_+^4 : T, I, L \leq \frac{\lambda}{d}, V \leq \frac{Nd_I \lambda}{dd_V} \right\},$$

where the quadruple set $\mathbb{R}_+^4$ defines as $\mathbb{R}_+^4 = \{(T, I, L, V) : T \geq 0, I \geq 0, L \geq 0, V \geq 0\}$.

2.1. Steady states

The model (1) admits two steady states which are biologically meaningful.

1. The non-infective (viral extinction) steady states as

$$E^0 = \left(T^0, I^0, L^0, V^0 \right) = \left(\frac{\lambda}{d_T}, 0, 0, 0 \right)$$

2. The infective (viral persistence) steady states as

$$E^* = (T^*, I^*, L^*, V^*) = \left\{ q, \frac{d_T d_V}{(1 - u_1)(1 - u_2)kNd_I} \left(\frac{\lambda}{d_T q} - 1 \right), \frac{f\lambda}{d_L + \alpha} \left(1 - \frac{d_T q}{\lambda} \right), \frac{d_T}{(1 - u_1)k} \left(\frac{\lambda}{d_T q} - 1 \right) \right\}.$$

where

$$q = \frac{d_V(\alpha + d_L)}{(1 - u_1)(1 - u_2)kN(\alpha + (1 - f)d_L)}$$

2.2. Basic reproduction number

Using the next-generation method (Diekmann et al., 1990; Heffernan et al., 2005), the infection and viral production term in the model (1) defined by matrices $\mathbb{F}$ and $\mathbb{V}$ as follows

$$\mathbb{F} = \begin{pmatrix} 0 & 0 & (1 - u_1)(1 - f)k\frac{\lambda}{d_T} \\ 0 & 0 & (1 - u_1)fk\frac{\lambda}{d_T} \\ 0 & 0 & 0 \end{pmatrix}, \quad \mathbb{V} = \begin{pmatrix} d_I & -\alpha & 0 \\ 0 & \alpha + d_L & 0 \\ -(1 - u_2)Nd_I & 0 & d_V \end{pmatrix}$$

the basic reproductive number R_L, can be defined as the spectral radius of the next generation operator $\mathbb{F}\mathbb{V}^{-1}$, straightforward calculation yields

$$R_L = \rho\left[\mathbb{F}\mathbb{V}^{-1} \right] = \frac{(1 - u_1)(1 - u_2)k\lambda N(\alpha + (1 - f)d_L)}{d_T d_V(\alpha + d_L)} \tag{2}$$

The basic reproduction number R_L is the average number of secondary infections produced when one single virus cell is introduced into a host where every T cell is susceptible.

Remark 1. Using basic reproduction number R_L the infected equilibrium point $E^* = (T^*, I^*, L^*, V^*)$ becomes

$$E^* = \left\{ \frac{\lambda}{d_T R_L}, \frac{d_T d_V}{(1 - u_1)(1 - u_2)kNd_I}(R_L - 1), \frac{f\lambda}{R_L(d_L + \alpha)}(R_L - 1), \frac{d_T}{(1 - u_1)k}(R_L - 1) \right\}.$$

From the components of E^*, it is clear that when $R_L > 1$ this endemic point exists. The following theorem summarizes the important properties of the model (1), it's Proof is given in (Ahmed et al.2020).

Theorem 2.3.

1. *If $R_L < 1$, then the non-infective equilibrium is locally asymptotically stable. If $R_L > 1$ then the non-infective equilibrium is an unstable saddle point, and the endemic equilibrium is locally asymptotically stable.*
2. *If $R_L \leq 1$, then the non-infective equilibrium (E^0) is globally asymptotically stable and the disease dies out. If $R_L > 1$, then the endemic equilibrium (E^*) is globally asymptotically stable and the disease persists.*

2.3. Critical drug efficacy

In the system (1), the efficacies of two drugs RTIs and PIs are combined to obtain a new term to reflects the overall efficacy for this combination treatment and is given by $1 - \theta = (1 - u_1)(1 - u_2)$. Motivated by the stability criterion (see Theorem 2.3) for E^0 and E^*, there is a transcritical point given by $R_L = 1$, that is

$$\frac{(1 - \theta_c)k\lambda N(\alpha + (1 - f)d_L)}{d_T d_V(\alpha + d_L)} = 1$$

thus,

$$\theta_c = 1 - \frac{(\alpha + d_L)d_T d_V}{k\lambda N(\alpha + (1 - f)d_L)}.$$

In order to achieve a successful treatment by way of elimination of virus persistence, we need $\theta > \theta_c$. On the other hand, whenever $\theta < \theta_c$, the infected steady state E^* remains stable and the infection persists.

3. The optimal control problem

Let $u_1(t)$ represent the normalized RTIs dosage as a function of time, then k in the model (1) will be modified to become $(1 - u_1(t))k$ and also let $u_2(t)$ be the normalized PIs dosage as a function of time, then the parameter N will be modified to become $(1 - u_2(t))N$. Hence the state system (1) becomes

$$\begin{cases} \dfrac{dT(t)}{dt} = \lambda - (1 - u_1(t))kT(t)V(t) - d_T T(t), \\[2mm] \dfrac{dI(t)}{dt} = (1 - u_1(t))(1 - f)kT(t)V(t) - d_I I(t) + \alpha L(t), \\[2mm] \dfrac{dL(t)}{dt} = (1 - u_1(t))fkT(t)V(t) - d_L L(t) - \alpha L(t), \\[2mm] \dfrac{dV(t)}{dt} = (1 - u_2(t))Nd_I I(t) - d_V V(t). \end{cases} \tag{3}$$

With initial conditions

$$T(0) = T_0, \ I(0) = I_0, \ L(0) = L_0, \ V(0) = V_0, \text{ and } T(t), \ I(t), \ L(t), \ V(t) \text{ are free at final time } T_f. \tag{4}$$

Our main objective is to maximize the benefit based on the CD4$^+$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). The objective functional is defined as,

$$J(u_1, u_2) = \int_0^{T_f} \left[T(t) - \left(\frac{A_1}{2} u_1^2(t) + \frac{A_2}{2} u_2^2(t) \right) \right] dt, \tag{5}$$

where T(t) is the benefit based on T cells count during treatment and the other terms are systemic costs of the drug treatments. The positive constants A_1 and A_2 represent desired weight on the benefit and cost, and u_1^2, u_2^2 reflect the severity of the side effects of the drugs (Joshi, 2002). The cost function is assumed to be nonlinear, basing on the fact that there is no linear relationship between the effects of treatment on T cells or viral load, hence the choice of a quadratic cost function (Kirschner et al., 1997). We impose a condition for treatment time, $t \in [0, T_f]$, limited treatment window (Butler et al., 1997), 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 control set U is defined as

$$U = \left\{ u_1, u_2 \text{ are Lebesgue measurable, } 0 \le u_1(t), u_2(t) \le 1, t \in \left[0, T_f \right] \right\}.$$

So we seek an optimal control pair, u_1^*, u_2^* such that

$$J(u_1^*, u_2^*) = \max_{u_1, u_2 \in U} J(u_1, u_2), \tag{6}$$

subject to state constraints (3—4). The basic framework of this problem is to prove the existence of the optimal control, characterize the optimal control and establish uniqueness of the optimality system.

3.1. Existence of an optimal control pair

Using the fact that the solution to each state equation is bounded (see Theorem 2.2). Now, the existence of an optimal control for the state system is analyzed using the theory developed by Fleming and Rishel in (Fleming & Rishel, 1975).

Theorem 3.1. *Given the objective functional*

$$J(u_1, u_2) = \int_0^{T_f} \left[T(t) - \left(\frac{A_1}{2} u_1^2(t) + \frac{A_2}{2} u_2^2(t) \right) \right] dt,$$

where $U = (u_2(t), u_2(t))$, piecewise continuous such that $0 \le u_1(t), u_2(t) \le 1$ for all $t \in [0, T_f]$ subject to equations of system (3—4) with $T(0) = T_0$, $I(0) = I_0$, $L(0) = L_0$ and $V(0) = V_0$, then there exists an optimal control pair u_1^* and u_2^*, such that

$$J(u_1^*, u_2^*) = \max\{J(u_1, u_2) | (u_1, u_2) \in U\}.$$

Proof. To prove this theorem, we follow the requirements from Theorem 4.1 and Corollary 4.1 developed by Fleming and Rishel in (Fleming & Rishel, 1975) and verify them. Let $\mathbf{f}(t, \mathbf{X}, \mathbf{u})$ be the right-hand side of (3-4) for $0 \le t \le T_f$, where $\mathbf{X} = (T, I, L, V) \in \mathbb{R}^4$, and $\mathbf{u} = (u_1, u_2) \in \mathbb{R}^2$. According to (Fleming & Rishel, 1975), the following conditions are need to satisfy for the existence:

1. The class of all initial conditions with an optimal control pair u_1, u_2 in the admissible control set along with each state equation being satisfied is not empty and is of class $\mathbb{C}^1$. That is

$$|\mathbf{f}(t, 0, 0)| \le C, \quad |\mathbf{f_X}(t, \mathbf{X}, \mathbf{u})| \le C(1 + |\mathbf{u}|) \text{ and } |\mathbf{f_u}(t, \mathbf{X}, \mathbf{u})| \le C.$$

2. The admissible control set U is closed and convex.
3. Each right hand side of equations of system (3—4) is continuous, is bounded above by a sum of the bounded control and the state, and can be written as a linear function of an optimal control pair u_1, u_2 with coefficients depending on time and the state variables. That is

$$\mathbf{f}(t, \mathbf{X}, \mathbf{u}) = \boldsymbol{\alpha}(t, \mathbf{X}) + \boldsymbol{\gamma}(t, \mathbf{X})\mathbf{u} \text{ and } |\mathbf{f}(t, \mathbf{X}, \mathbf{u})| \leq C_1(1 + |\mathbf{X}| + |\mathbf{u}|).$$

4. The integrand of the functional $J(u_1, u_2)$ is concave on the admissible control set and is bounded above by $C_2 - C_1|\mathbf{u}|^{\beta}$, where C_1, C_2 are positive constants and $\beta > 1$.

In order to verify the theorem, we write the right hand side of equations of system (3−4) as

$$\mathbf{f}(t, \mathbf{X}, \mathbf{u}) = \begin{pmatrix} \lambda - (1-u_1)kTV - d_T T \\ (1-u_1)(1-f)kTV - d_I I + \alpha L \\ (1-u_1)fkTV - d_L L - \alpha L \\ (1-u_2)Nd_I I - d_V V \end{pmatrix}$$

It is easy to see that $\mathbf{f}(t, \mathbf{X}, \mathbf{u})$ is of class $\mathbb{C}^1$ (continuously differentiable functions) and $|\mathbf{f}(t, 0, 0)| = \lambda$ and we have

$$|\mathbf{f}_\mathbf{X}(t, \mathbf{X}, \mathbf{u})| = \begin{pmatrix} a_{11} & 0 & 0 & a_{14} \\ a_{21} & -d_I & \alpha & a_{24} \\ a_{31} & 0 & -(d_L + \alpha) & a_{34} \\ 0 & Nd_I(1-u_2) & 0 & -d_V \end{pmatrix}$$

where
$a_{11} = -(1-u_1)kV - d_T$, $a_{14} = -(1-u_1)kT$, $a_{21} = (1-u_1)(1-f)kV$, $a_{24} = (1-u_1)(1-f)kT$, $a_{31} = (1-u_1)fkV$, $a_{34} = (1-u_1)fkT$ and

$$|\mathbf{f}_\mathbf{u}(t, \mathbf{X}, \mathbf{u})| = \left| \begin{pmatrix} kTV & 0 \\ -(1-f)kTV & 0 \\ -fkTV & 0 \\ 0 & -Nd_I I \end{pmatrix} \right|$$

Since T, I, L and V are bounded, then there exits a constant C such that

$$|\mathbf{f}(t, 0, 0)| \leq C, \quad |\mathbf{f}_\mathbf{X}(t, \mathbf{X}, \mathbf{u})| \leq C(1 + |\mathbf{u}|) \text{ and } |\mathbf{f}_\mathbf{u}(t, \mathbf{X}, \mathbf{u})| \leq C.$$

By definition, U is closed. Take any controls $u_1, u_2 \in U$ and $\theta \in [0, 1]$. Then

$$\theta u_1 + (1 - \theta)u_2 \geq 0,$$

with $\theta u_1 \leq \theta$ and $(1 - \theta)u_2 \leq (1 - \theta)$. Then

$$\theta u_1 + (1 - \theta)u_2 \leq \theta + (1 - \theta) = 1,$$

i.e $0 \leq \theta u_1 + (1 - \theta)u_2 \leq 1$, for all $u_1, u_2 \in U$ and $\theta \in [0, 1]$. Therefore, U is convex and condition (ii) is satisfied. The right hand side of system (3−4) is continuous, bilinear in the control and it can be written as:

$$\mathbf{f}(t, \mathbf{X}, \mathbf{u}) = \boldsymbol{\alpha}(t, \mathbf{X}) + \boldsymbol{\gamma}(t, \mathbf{X}).\mathbf{u}.$$

Where

$$\boldsymbol{\alpha}(t, \mathbf{X}) = \begin{pmatrix} \lambda - kTV - d_T T \\ (1-f)kTV - d_I I(t) + \alpha L \\ fkTV - d_L L - \alpha L \\ Nd_I I - d_V V \end{pmatrix}, \quad \boldsymbol{\gamma}(t, \mathbf{X}) = \begin{pmatrix} kTV & 0 \\ -(1-f)kTV & 0 \\ -fkTV & 0 \\ 0 & -Nd_I I \end{pmatrix}, \text{ and } \boldsymbol{u} = \begin{pmatrix} u_1 \\ u_2 \end{pmatrix},$$

are vector-valued functions of **X**. and the boundedness of solutions gives

$$|\mathbf{f}(t, \mathbf{X}, \mathbf{u})| \leq C_1(1 + |\mathbf{X}| + |\mathbf{u}|),$$

where C_1 depends on the coefficients of the system. Hence, satisfies condition (iii). In order to verify the convexity of the integrand of our objective functional J, we show that

$(1 - \varepsilon)J(t, \mathbf{X}, \mathbf{u}) + \varepsilon J(t, \mathbf{X}, \mathbf{v}) \leq J(t, \mathbf{X}, (1 - \varepsilon)\mathbf{u} + \varepsilon \mathbf{v})$

for $0 < \varepsilon < 1$ and $J(t, \mathbf{X}, \mathbf{u}) = T - \left(\frac{A_1}{2}u_1^2 + \frac{A_2}{2}u_2^2\right)$.
    Now

$(1 - \varepsilon)J(t, \mathbf{X}, \mathbf{u}) + \varepsilon J(t, \mathbf{X}, \mathbf{v}) - J(t, \mathbf{X}, (1 - \varepsilon)\mathbf{u} + \varepsilon \mathbf{v})$

$= (1 - \varepsilon)\left[T - \left(\frac{A_1}{2}u_1^2 + \frac{A_2}{2}u_2^2\right)\right] + \varepsilon\left[T - \left(\frac{A_1}{2}v_1^2 + \frac{A_2}{2}v_2^2\right)\right] - T - \frac{A_1}{2}((1 - \varepsilon)u_1 + \varepsilon v_1)^2 - \frac{A_2}{2}((1 - \varepsilon)u_2 + \varepsilon v_2)^2$

$= -\frac{A_1}{2}\left[(1 - \varepsilon)u_1^2 + \varepsilon v_1^2 - ((1 - \varepsilon)u_1 + \varepsilon v_1)^2\right] - \frac{A_2}{2}\left[(1 - \varepsilon)u_2^2 + \varepsilon v_2^2 - ((1 - \varepsilon)u_2 + \varepsilon v_2)^2\right]$

$= -\frac{A_1}{2}\left(\sqrt{\varepsilon(1 - \varepsilon)}\, u_1 - \sqrt{\varepsilon(1 - \varepsilon)}\, v_1\right)^2 - \frac{A_2}{2}\left(\sqrt{\varepsilon(1 - \varepsilon)}\, u_2 - \sqrt{\varepsilon(1 - \varepsilon)}\, v_2\right)^2$

$= -\frac{A_1}{2}\varepsilon(1 - \varepsilon)(u_1 - v_1)^2 - \frac{A_2}{2}\varepsilon(1 - \varepsilon)(u_2 - v_2)^2 \leq 0.$

Since $A_1, A_2 > 0$, $J(t, \mathbf{X}, \mathbf{u})$ is concave in U. Finally we need to show that $J(t, \mathbf{X}, \mathbf{u}) \leq C_2 - C_1|\mathbf{u}|^\beta$, where $C_1 > 0$ and $\beta > 1$. For our case

$$J(t, \mathbf{X}, \mathbf{u}) = T - \left(\frac{A_1}{2}u_1^2 + \frac{A_2}{2}u_2^2\right) \leq C_2 - C_1|\mathbf{u}|^2,$$

where C_2 depends on the upper bound on CD4+T cells, $\beta = 2$, and $C_1 > 0$ since $C_1 = \min\{A_1, A_2\}$ with $A_1, A_2 > 0$. So we conclude that there exists an optimal control pair.

3.2. The optimality conditions

The Pontryagin's Maximum Principle (Pontryagin et al., 1962) provides necessary conditions for an optimal control problem. This principle converted the problem of finding a control which maximizes the objective function J defined in (5) subject to the state system (3–4) to the problem of maximizing the Hamiltonian H, point-wisely with respect to u_1 and u_2. So it is sufficient to derive the Hamiltonian H instead of deriving the objective function J in order to characterize the optimal controls u_1^* and u_2^*. The Hamiltonian is defined from the formulation of the objective function as follows:

$$H = T(t) - \left(\frac{A_1}{2}u_1^2(t) + \frac{A_2}{2}u_2^2(t)\right) + \sum_{i=1}^{4} \lambda_i(t)F_i,$$

where F_i is the right hand side of the differential equation of i-th state variable. By applying Pontryagin's Maximum Principle (Pontryagin et al., 1962), we obtain the following theorem.

Theorem 3.2. *There exists an optimal control $u^* = (u_1^*, u_2^*)$ and corresponding solution T(t), I(t), L(t) and V(t), that maximizes $J(u_1, u_2)$ over U. Furthermore, there exists adjoint functions $\lambda_1(t)$, $\lambda_2(t)$, $\lambda_3(t)$ and $\lambda_4(t)$ satisfying the equations*

$$\begin{cases} \lambda_1'(t) = -1 + (1 - u_1(t))kV(t)(\lambda_1(t) - (1 - f)\lambda_2(t) - f\lambda_3(t)) + \lambda_1(t)d_T, \\ \lambda_2'(t) = \lambda_2(t)d_I - \lambda_4(t)(1 - u_2(t))Nd_I, \\ \lambda_3'(t) = -\lambda_2(t)\alpha + \lambda_3(t)(d_L + \alpha), \\ \lambda_4'(t) = (1 - u_1(t))kT(t)(\lambda_1(t) - (1 - f)\lambda_2(t) - f\lambda_3(t)) + \lambda_4(t)d_V, \end{cases} \tag{7}$$

with transversality conditions

$$\lambda_i\left(T_f\right) = 0, \ i = 1, 2, ..., 4. \tag{8}$$

Moreover, the optimal control is given by

$$u_1^*(t) = \min\left(\max\left(0, \frac{1}{A_1}(\lambda_1(t) - (1 - f)\lambda_2(t) - f\lambda_3(t))kT(t)V(t)\right), 1\right) \tag{9}$$

and

$$u_2^*(t) = \min\left(\max\left(0, \frac{-1}{A_2}\lambda_4(t)Nd_lI\right), 1\right). \tag{10}$$

Proof. The adjoint equations and transversality conditions can be obtained by using Pontryagin's Maximum Principle, such that

$$\lambda_1'(t) = -\frac{\partial H}{\partial T}, \quad \lambda_1\left(T_f\right) = 0,$$

$$\lambda_2'(t) = -\frac{\partial H}{\partial I}, \quad \lambda_2\left(T_f\right) = 0,$$

$$\lambda_3'(t) = -\frac{\partial H}{\partial L}, \quad \lambda_3\left(T_f\right) = 0,$$

$$\lambda_4'(t) = -\frac{\partial H}{\partial V}, \quad \lambda_4\left(T_f\right) = 0.$$

Since $T(t)$, $I(t)$, $L(t)$ and $V(t)$ do not have fixed values at the final time T_f, the values of the associated adjoints $\lambda_1(t)$, $\lambda_2(t)$, $\lambda_3(t)$ and $\lambda_4(t)$ at the final time are zero. The optimal control u_1^* and u_2^* on the interior of the control set can be solved from the optimality conditions,

$$\frac{\partial H}{\partial u_1}\bigg|_{u_1=u_1^*} = 0, \quad \text{and} \quad \frac{\partial H}{\partial u_2}\bigg|_{u_2=u_2^*} = 0,$$

That is

$$\frac{\partial H}{\partial u_1} = -A_1 u_1 + (\lambda_1(t) - (1-f)\lambda_2(t) - f\lambda_3(t))kT(t)V(t) = 0,$$

and

$$\frac{\partial H}{\partial u_2} = -A_2 u_2 - \lambda_4(t)Nd_lI = 0,$$

By using the bounds on the controls, we get

$$u_1^* = \begin{cases} 0, & \text{if } \frac{\partial H}{\partial u_1^*} < 0 \\[2mm] \frac{1}{A_1}(\lambda_1(t) - (1-f)\lambda_2(t) - f\lambda_3(t))kT(t)V(t), & \text{if } \frac{\partial H}{\partial u_1^*} = 0 \\[2mm] 1 & \text{if } \frac{\partial H}{\partial u_1^*} > 0. \end{cases}$$

In compact notation

$$u_1^*(t) = \min\left(\max\left(0, \frac{1}{A_1}(\lambda_1(t) - (1-f)\lambda_2(t) - f\lambda_3(t))kT(t)V(t)\right), 1\right).$$

Again, we get

$$u_2^* = \begin{cases} 0 & \text{if } \frac{\partial H}{\partial u_2^*} < 0, \\[2mm] \frac{-1}{A_2}\lambda_4(t)Nd_lI, & \text{if } \frac{\partial H}{\partial u_2^*} = 0 \\[2mm] 1 & \text{if } \frac{\partial H}{\partial u_2^*} > 0. \end{cases}$$

In compact notation

$$u_2^*(t) = \min\left(\max\left(0, \frac{-1}{A_2}\lambda_4(t)Nd_II\right), 1\right).$$

In addition, the second derivative of the Hamiltonian H with respect to $u_1(t)$ and $u_2(t)$ are negative, indicating a maximum at $u^* = (u_1^*, u_2^*)$. That is flushleft

$$\frac{\partial^2 H}{\partial u_i^2} = -A_i \leq 0, \quad i = 1, 2 \quad \text{since} \quad A_i \geq 0$$

We point out that the optimality system consists of the state system (3) with the initial conditions (4), adjoint system (7) with transversality conditions (8), and optimality condition (9−10). Thus, we have the following optimality system at $u^*(t) = (u_1^*(t), u_2^*(t))$:

$$
\begin{cases}
\dfrac{dT(t)}{dt} = \lambda - (1 - u_1^*(t))kT(t)V(t) - d_TT(t) \\[2mm]
\dfrac{dI(t)}{dt} = (1 - u_1^*(t))(1 - f)kT(t)V(t) - d_II(t) + \alpha L(t) \\[2mm]
\dfrac{dL(t)}{dt} = (1 - u_1^*(t))fkT(t)V(t) - d_LL(t) - \alpha L(t) \\[2mm]
\dfrac{dV(t)}{dt} = (1 - u_2^*(t))Nd_II(t) - d_VV(t), \\[2mm]
\lambda_1'(t) = -1 + (1 - u_1^*(t))kV(t)(\lambda_1(t) - (1 - f)\lambda_2(t) - f\lambda_3(t)) + \lambda_1(t)d_T, \\[2mm]
\lambda_2'(t) = \lambda_2(t)d_I - \lambda_4(t)(1 - u_2^*(t))Nd_I, \\[2mm]
\lambda_3'(t) = -\lambda_2(t)\alpha + \lambda_3(t)(d_L + \alpha), \\[2mm]
\lambda_4'(t) = (1 - u_1^*(t))kT(t)(\lambda_1(t) - (1 - f)\lambda_2(t) - f\lambda_3(t)) + \lambda_4(t)d_V, \\[2mm]
\quad T(0), I(0), L(0), V(0) \geq 0, \\[2mm]
\quad \lambda_i(T_f) = 0, \; i = 1, 2, ..., 4,
\end{cases}
\tag{11}
$$

where the controls $u_1^*(t)$ and $u_2^*(t)$ are given by (9) and (10) respectively.

3.3. Uniqueness of the optimality system

To prove uniqueness of solutions of the optimality system for the small time interval, we use the following theorems (Joshi, 2002).

Theorem 3.3. *The function* $u^*(c) = \min(\max(c, a), b)$ *is Lipschitz continuous in* c, *where* a < b *are some 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^* in c.

Theorem 3.4. *For sufficiently small final time* (T_f), *bounded solutions to the optimality system* (11), *are unique.*
Proof. Suppose $(T, I, L, V, \lambda_1, \lambda_2, \lambda_3, \lambda_4)$ and $(\overline{T}, \overline{I}, \overline{L}, \overline{V}, \overline{\lambda_1}, \overline{\lambda_2}, \overline{\lambda_3}, \overline{\lambda_4})$ are two non-identical solutions of our optimality system (11). To show that the two solutions are equivalent, it is convenient to make a change of variables. Let

$$T = e^{mt}x_1, I = e^{mt}x_2, L = e^{mt}x_3, V = e^{mt}x_4, \; \lambda_1 = e^{-mt}y_1, \lambda_2 = e^{-mt}y_2, \lambda_3 = e^{-mt}y_3, \lambda_4 = e^{-mt}y_4,$$

$$\overline{T} = e^{mt}\overline{x_1}, \overline{I} = e^{mt}\overline{x_2}, \overline{L} = e^{mt}\overline{x_3}, \overline{V} = e^{mt}\overline{x_4}, \; \overline{\lambda_1} = e^{-mt}\overline{y_1}, \overline{\lambda_2} = e^{-mt}\overline{y_2}, \overline{\lambda_3} = e^{-mt}\overline{y_3}, \overline{\lambda_4} = e^{-mt}\overline{y_4}.$$

where m > 0 is a positive constant to be chosen later. With the new variables the optimality conditions become

$$u_1^* = \min\left(\max\left(0, \frac{(y_1 - (1-f)y_2 - fy_3)kx_1x_4e^{mt}}{A_1}\right), 1\right),$$

$$u_2^* = \min\left(\max\left(0, \frac{-Nd_ly_4x_2}{A_2}\right), 1\right),$$

$$\overline{u_1^*} = \min\left(\max\left(0, \frac{(\overline{y_1} - (1-f)\overline{y_2} - f\overline{y_3})k\overline{x_1}\ \overline{x_4}e^{mt}}{A_1}\right), 1\right),$$

$$\overline{u_2^*} = \min\left(\max\left(0, \frac{-Nd_l\overline{y_4}\ \overline{x_2}}{A_2}\right), 1\right).$$

For the first equation of system (11) we substitute $T = e^{mt}x_1$ and get

$$\dot{x}_1 + mx_1 = \lambda e^{-mt} - (1 - u_1^*)kx_1x_4e^{mt} - d_Tx_1$$

and for $\overline{T} = e^{mt}\overline{x_1}$ we have

$$\dot{\overline{x_1}} + m\overline{x_1} = \lambda e^{-mt} - (1 - \overline{u_1^*})k\overline{x_1}\ \overline{x_4}e^{mt} - d_T\overline{x_1}.$$

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

$$\dot{x}_1 - \dot{\overline{x_1}} + m(x_1 - \overline{x_1}) = -ke^{mt}\left[(1 - u_1^*)x_1x_4 - (1 - \overline{u_1^*})\overline{x_1}\ \overline{x_4}\right] - d_T(x_1 - \overline{x_1}).$$

Multiplying by $(x_1 - \overline{x_1})$ and integrating from $t = 0$ to $t = T_f$ we have

$$\frac{1}{2}(x_1 - \overline{x_1})^2\left(T_f\right) + m\int_0^{T_f}(x_1 - \overline{x_1})^2 dt = -k\int_0^{T_f}e^{mt}\left[(1 - u_1^*)x_1x_4 - (1 - \overline{u_1^*})\overline{x_1}\ \overline{x_4}\right](x_1 - \overline{x_1})dt - d_T\int_0^{T_f}(x_1 - \overline{x_1})^2 dt. \quad (12)$$

In order to simplify the right-hand expressions of (12), we need some elementary inequalities. By the elementary inequality $(a+b)^2 \le 2(a^2 + b^2)$, we have

$$(x_1y_1 - \overline{x_1}\ \overline{y_1})^2 = (x_1y_1 - x_1\overline{y_1} + x_1\overline{y_1} - \overline{x_1}\ \overline{y_1})^2 = [x_1(y_1 - \overline{y_1}) + \overline{y_1}(x_1 - \overline{x_1})]^2$$

$$\le \max\left\{2x_1^2, 2\overline{y_1}^2\right\}[(x_1 - \overline{x_1}) + (y_1 - \overline{y_1})]^2 \le C[(x_1 - \overline{x_1}) + (y_1 - \overline{y_1})]^2,$$

where C depends on bounds for $x_1, \overline{y_1}$. Another common expression can be used repeatedly,

$$(xy - \overline{x}\ \overline{y})(w - \overline{w}) = (xy - \overline{x}y + \overline{x}y - \overline{x}\ \overline{y})(w - \overline{w}) = y(x - \overline{x})(w - \overline{w}) + \overline{x}(y - \overline{y})(w - \overline{w})$$

$$\le y^2(x - \overline{x})^2 + \overline{x}^2(y - \overline{y})^2 + 2(w - \overline{w})^2 \le C\left[(x - \overline{x})^2 + (y - \overline{y})^2 + (w - \overline{w})^2\right],$$

where C depends on bounds for $\overline{x}, y$.

Based on the above arguments and Theorem 3.3, we find

$$\int_0^{T_f}(u_1^* - \overline{u_1^*})^2 dt = \frac{k^2}{A_1^2}\int_0^{T_f}\left[e^{mt}\{x_1x_4(y_1 - (1-f)y_2 - fy_3) - \overline{x_1}\ \overline{x_4}(\overline{y_1} - (1-f)\overline{y_2} - f\overline{y_3})\}\right]^2 dt$$

$$\le C_2\frac{k^2e^{2mT_f}}{A_1^2}\int_0^{T_f}\left[(y_1 - \overline{y_1})^2 + (y_2 - \overline{y_2})^2 + (y_3 - \overline{y_3})^2\right]dt.$$

Also,

$$k \int_0^{T_f} e^{mt} \left[(1-u_1^*)x_1 x_4 - (1-\overline{u_1^*})\overline{x_1}\,\overline{x_4} \right](x_1 - \overline{x_1})dt \leq C_3 e^{mT_f} \int_0^{T_f} \left[(x_1 - \overline{x_1})^2 + (x_4 - \overline{x_4})^2 \right.$$

$$+ (u_1^* - \overline{u_1^*})^2 \left. \right] dt \leq C_2' e^{3mT_f} \int_0^{T_f} \left[(x_1 - \overline{x_1})^2 + (x_4 - \overline{x_4})^2 + (y_1 - \overline{y_1})^2 + (y_2 - \overline{y_2})^2 + (y_3 - \overline{y_3})^2 \right] dt.$$

Substituting above relations in Eqn (12), it becomes

$$\frac{1}{2}(x_1 - \overline{x_1})^2 \left(T_f \right) + m \int_0^{T_f} (x_1 - \overline{x_1})^2 dt \leq C_1' \int_0^{T_f} (x_1 - \overline{x_1})^2 dt + C_2' e^{3mT_f} \int_0^{T_f} \left[(x_1 - \overline{x_1})^2 + (x_4 - \overline{x_4})^2 + (y_1 - \overline{y_1})^2 \right.$$

$$\left. + (y_2 - \overline{y_2})^2 + (y_3 - \overline{y_3})^2 \right] dt$$

where the constant C_2, C_1' and C_2' obtained above are dependent on the system coefficients as well as the bounds on the state and adjoint variables.

Similarly, for $\lambda_1 = e^{-mt}y_1$ and $\overline{\lambda_1} = e^{-mt}\overline{y_1}$ we have

$$-\dot{y_1} + m y_1 = e^{mt} - d_T y_1 - k e^{mt} (1-u_1^*) x_4 [y_1 - (1-f)y_2 - fy_3]$$

and

$$-\dot{\overline{y_1}} + m\overline{y_1} = e^{mt} - d_T \overline{y_1} - k e^{mt} (1-\overline{u_1^*})\overline{x_4}[\overline{y_1} - (1-f)\overline{y_2} - f\overline{y_3}]$$

respectively. Subtracting the expression for $\overline{\lambda_1}$ from the expression for λ_1 and multiplying by $(y_1 - \overline{y_1})$ and integrating from $t = 0$ to $t = T_f$ we have

$$\frac{1}{2}(y_1 - \overline{y_1})^2(0) + m \int_0^{T_f}(y_1 - \overline{y_1})^2 dt = -d_T \int_0^{T_f}(y_1 - \overline{y_1})^2 dt - k \int_0^{T_f} e^{mt}(1-u_1^*)x_4(y_1 - (1-f)y_2 - fy_3) - (1-\overline{u_1^*})\overline{x_4}(\overline{y_1} - (1-f)\overline{y_2}$$

$$-f\overline{y_3})(y_1 - \overline{y_1})dt \leq C_3' \int_0^{T_f}(y_1 - \overline{y_1})^2 dt + C_4' e^{3mT_f} \int_0^{T_f} \left[(x_4 - \overline{x_4})^2 + (y_1 - \overline{y_1})^2 + (y_2 - \overline{y_2})^2 + (y_3 - \overline{y_3})^2 \right] dt$$

where the constant C_3' and C_4' obtained above are dependent on the system coefficients as well as the bounds on the state and adjoint variables.

Similarly, after appropriate substitutions the equations for I and $\overline{I}$, L and $\overline{L}$, V and $\overline{V}$, λ_2 and $\overline{\lambda_2}$, λ_3 and $\overline{\lambda_3}$, λ_4 and $\overline{\lambda_4}$ are subtracted, then each expression is multiplied by an appropriate function and integrated from $t = 0$ to $t = T_f$. We obtain total eight integral equations and to show uniqueness, the integral equations are combined. Adding all the eight estimates gives

$$\frac{1}{2}(x_1 - \overline{x_1})^2 \left(T_f \right) + \frac{1}{2}(x_2 - \overline{x_2})^2 \left(T_f \right) + \frac{1}{2}(x_3 - \overline{x_3})^2 \left(T_f \right) + \frac{1}{2}(x_4 - \overline{x_4})^2 \left(T_f \right) + \frac{1}{2}(y_1 - \overline{y_1})^2(0) + \frac{1}{2}(y_2 - \overline{y_2})^2(0) + \frac{1}{2}(y_3 - \overline{y_3})^2(0)$$

$$+ \frac{1}{2}(y_4 - \overline{y_4})^2(0) + m \int_0^{T_f} (x_1 - \overline{x_1})^2 + (x_2 - \overline{x_2})^2 + (x_3 - \overline{x_3})^2 + (x_4 - \overline{x_4})^2 + (y_1 - \overline{y_1})^2 + (y_2 - \overline{y_2})^2 + (y_3 - \overline{y_3})^2 + (y_4 - \overline{y_4})^2 dt$$

$$\leq \left(\tilde{C_1} + \tilde{C_2} e^{3mT_f} \right) \int_0^{T_f} (x_1 - \overline{x_1})^2 + (x_2 - \overline{x_2})^2 + (x_3 - \overline{x_3})^2 + (x_4 - \overline{x_4})^2 + (y_1 - \overline{y_1})^2 + (y_2 - \overline{y_2})^2 + (y_3 - \overline{y_3})^2 + (y_4 - \overline{y_4})^2 dt.$$

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

$$\left(m - \tilde{C}_1 - \tilde{C}_2 e^{3mT_f}\right) \int_0^{T_f} (x_1 - \overline{x_1})^2 + (x_2 - \overline{x_2})^2 + (x_3 - \overline{x_3})^2 + (x_4 - \overline{x_4})^2 + (y_1 - \overline{y_1})^2 + (y_2 - \overline{y_2})^2 + (y_3 - \overline{y_3})^2 + (y_4 - \overline{y_4})^2 dt \leq 0.$$

where $\tilde{C}_1$ and $\tilde{C}_2$ depend on the system coefficients as well as the bounds on state and adjoint variables. If we choose m such that $m - \tilde{C}_1 - \tilde{C}_2 e^{3mT_f} > 0$, the above inequality holds if the integrand is identically zero. Since the natural logarithm is an increasing function, then $\ln\left(\frac{m - \tilde{C}_1}{\tilde{C}_2}\right). > 3mT_f$ if $m > \tilde{C}_1 + \tilde{C}_2$. This gives that $T_f < \frac{1}{3m} \ln\left(\frac{m - \tilde{C}_1}{\tilde{C}_2}\right)$, then $x_1 = \overline{x_1}, x_2 = \overline{x_2}, x_3 = \overline{x_3}$, $x_4 = \overline{x_4}, y_1 = \overline{y_1}, y_2 = \overline{y_2}, y_3 = \overline{y_3}, y_4 = \overline{y_4}$. Hence the solution is unique for small time.

4. Numerical results

In this section, we explore the model (3) to study the effects of both RTIs and PIs on the proliferation of the viral and infected cells within the host. Since HIV symptoms are exposed during symptomatic phase (7−12 days after infection), so treatment was assumed to be given during this phase. Using various combinations of the two drugs, one at a time and combined, we investigate and compare the numerical results from simulations. In doing so, the model parameters $\Theta = (k, f, d_I, \alpha, d_L, N, d_V)$ are estimated under no treatments ($u_1 = u_2 = 0$) at the primary stage of HIV infection, rest of the parameters such as production rate λ, natural death rates d_T of T cells can be estimated directly from population data. Using the set of data gathered from plasma donor samples obtained in (Nowak & May 2000), and using Markov-chain Monte Carlo (MCMC) method to fit our model (3) under no treatments, our estimated parameters shown in Table A.6 and Fig. 1. The procedure of the MCMC method is carried out in Appendix A.

Now, we study the influence of efficiency u_1 and u_2 (RTIs and PIs respectively) on the basic reproduction number R_L. Recall that the infection die out (persists) whenever $R_L < 1 (>1)$, which is equivalent to $\theta > \theta_c (<\theta_c)$. By using values form Table A.6, prior to the initiation of treatment $R_L = 18.37 > 1$, and $u_1 = 0$, $u_2 = 0$. The goal is to keep increasing u_1 and u_2 such that R_L is driven to a value less than unity. In this case, u_1 and u_2 must be chosen such that $\theta > \theta_c = 0.95$. We illustrate this by a surface plot and a contour plot in Fig. 2. One can easily observe that for $u_1 = 0$ and $u_2 = 0$ the value of R_L reaches its maximum value of 18.37. By increasing u_1 and u_2 from 0 to 1, we observe that the value of R_L gradually decreases and tends towards 0 (corresponding to $u_1 = 1$, $u_2 = 1$). This clearly reflects how the efficacy of the drugs effect the level of infection in order to achieve viral clearance.

Now we consider the optimal control problem which comprising of the optimality system in (11) is solved using an iterative method named forward and backward sweep method (FBSM). The optimality system is a two-point boundary 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 (Lenhart & Workman, 2007):

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 with state variables initial conditions.
3. Using the new state values, solve the adjoint system backwards using the final time zero boundary conditions with 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 iteration converges.
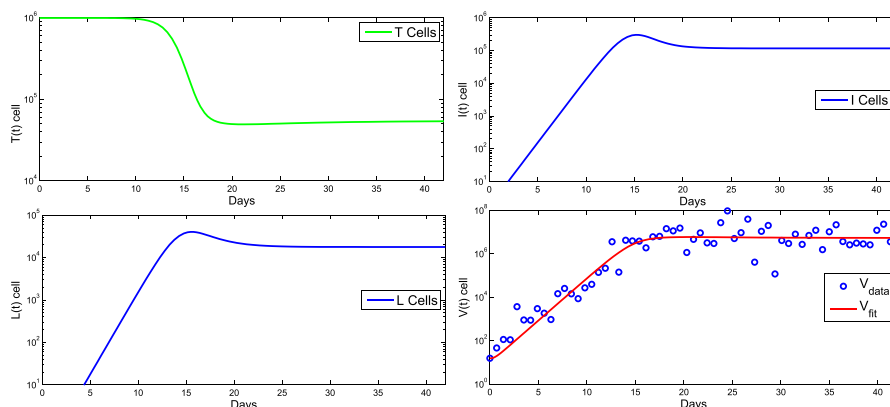

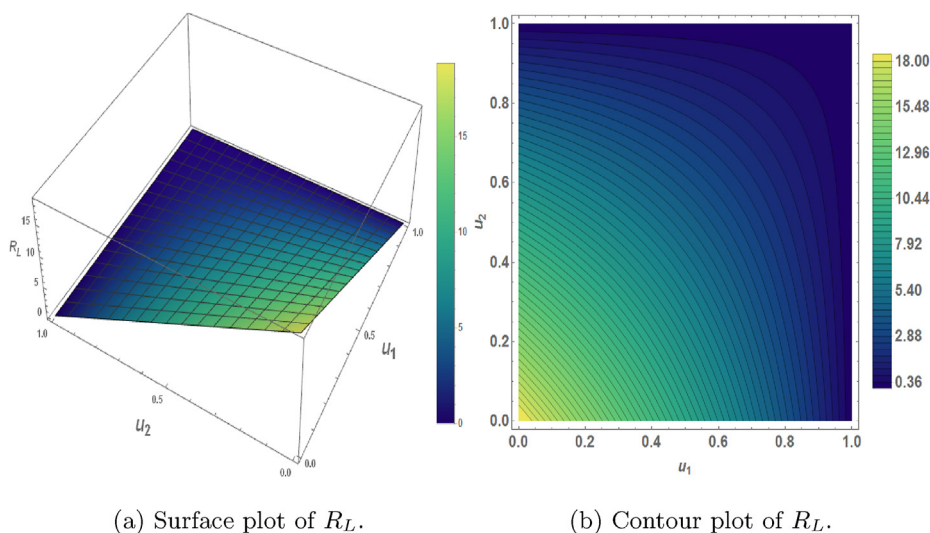**Fig. 1.** Dynamics and data fitting of model (3) under no treatments in Semi-log scale.

(a) Surface plot of R_L. (b) Contour plot of R_L.

Fig. 2. Surface and contour plot of R_L for various values of u_1 and u_2.
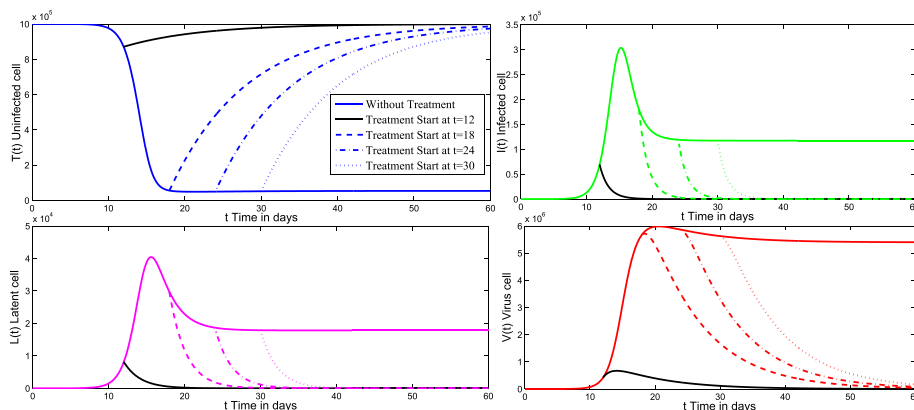

Fig. 3. The evolution of the immune cells in contact with HIV with and without optimal treatment. Here we initiate treatment at different days after infection.

Most individuals in the acute phase of HIV infection are highly infectious to others, primarily because of high HIV RNA levels, and often lack of awareness of their HIV status (Hollingsworth et al., 2008). Thus, accurate and timely detection of primary HIV infection is critical for the future health of the infected individual and for preventing forward transmission of HIV. In order to understand the impact of different treatment strategies, we look at different dynamics simultaneously. We vary initiation of treatment during later days of symptomatic phase with the following initial values:

For the purpose of the simulation we take the minimum and maximum control to be $0 \leq u_1, u_2 \leq 1$ and the cost coefficients that were introduced in the definition of the objective functional (5) were set at $A_1 = A_2 = 1$ (Joshi, 2002). Fig. 3 shows that without any preventive control the uninfected T cells continue to decrease, the number of infected cells (I & L) and virus V cells increases at the end of the time interval, these cells achieving a infected state at $t = 60$. By using therapy at any time we can alter the situation.

For better understanding the treatment dynamics starting at different time, we summarize the end state variables in the following tables:

According to Table 2, it signifies that treatment must be started immediately regardless the time elapsed since infection (see Table 1). We also notice the cases when the objective function values are larger, i.e., when initial T cell counts are higher. So, for the patients who are in the early stage of infection, the greatest effect does occur when treatment is initiated earlier which is end with a maximum value of T-cells adverted. This result resembles the clinical output given by D. Ho (Ho, 1995) which conferred as "Time to hit HIV, early and hard!". "The acute infection stage, when the viral load is very high is the easiest stage to control" results given by P. Paci et al. (Paci et al., 2009) also confirms our output. So by administering early

Table 1
The cell populations at different moments of time following the infection.

Days after infection	Initial T(t)	Initial I(t)	Initial L(t)	Initial V(t)
t = 12	870691	69466	8130	415083
t = 18	56088	179896	29738	5684380
t = 24	50148	119087	18679	5863112
t = 30	52185	117373	17888	5628812

Table 2
The cell populations at the end of time following the treatment.

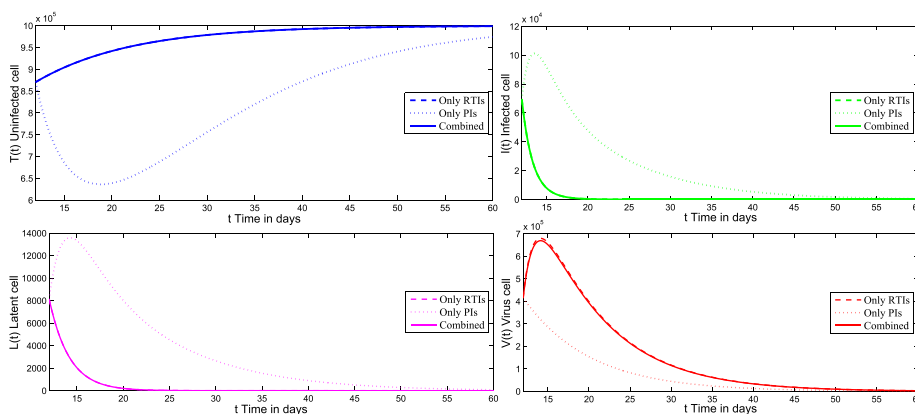| Treatment initiate at	End T(t)	End I(t)	End L(t)	End V(t)	J(u*)
t = 12	998936	2.5×10^{-6}	1.9×10^{-6}	2781	7.8×10^8
t = 18	985846	0.00015	0.00011	40462	5.5×10^8
t = 24	974047	0.0015	0.0011	80627	4.5×10^8
t = 30	952811	0.023	0.017	163588	3.5×10^8

Fig. 4. State dynamics in various optimal treatment strategy.

antiretroviral therapy can prevents the explosive burst of viremia during acute infection and thus may improve long-term health outcomes for the infected individuals and decrease the likelihood of viral transmission.

Now we turn our attention to why we use combined drug treatment strategy. Fig. 4 shows the graph of the solution to the optimality system when drugs (RTIs and PIs) are administered individually and combinedly for 60 days. The figure depicts that except administrating only PIs both combined and only RTIs show almost same result at the end. By covering different path during treatment period all treatment strategies attain optimal level at the end. Fig. 5 shows corresponding drug administration schedule during the period of treatment, which shows each drug have to use 100% dose to attain optimal level except PIs during combined therapy.

Again, for better understanding insight the treatment dynamics, we summarize the state variables at different time of the treatment in the following tables:

Regarding the question of optimizing treatment scheduling, i.e. which treatment should be given, whatever the stage of infection would be, the results from Tables 3–5 are conclusive. More or less each strategy is efficient to increase T cell but in contest of decrease virus cell only PIs treatment clearly dominate to others. However, when comparing the objective function values in case of different treatment strategy (only RTIs, only PIs and combined therapy) following the infection, we remark that the best result is obtained in the last situation.

5. Conclusion

In this paper, we studied an optimal control problem, with the state equation describing the interaction of the immune system with HIV and the objective function based on a contribution of maximizing benefit relied on T cells count and minimizing the side effects of combined treatment. The controls represent the efficiency of drug treatment in inhibiting viral
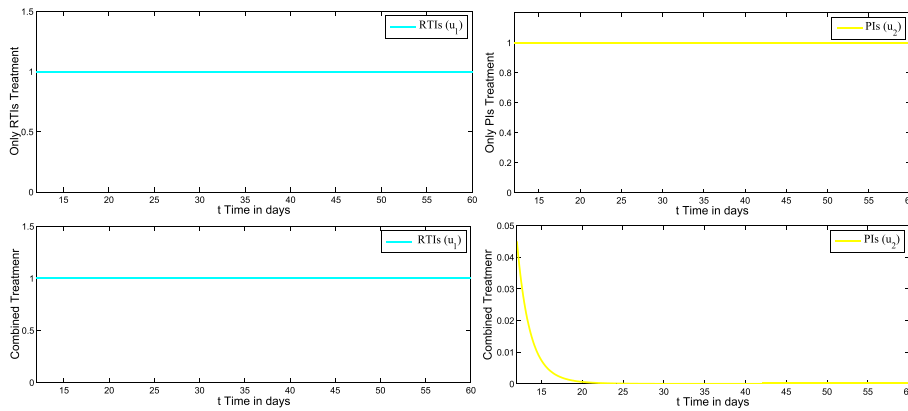
Fig. 5. Optimal drug profile during treatment.

Table 3
A summary of the cell populations at different moments of time administering only RTIs.

Time	Only RTIs			
	$T_R(t)$	$I_R(t)$	$L_R(t)$	$V_R(t)$
$t = 21$	9.5×10^5	213	127	3.5×10^5
$t = 45$	9.95×10^5	0.14	0.024	18159
$t = 60$	9.989×10^5	0.02	0.004	2824
$J(u^*)$		779554636		

Table 4
A summary of the cell populations at different moments of time administering only PIs.

Time	Only PIs			
	$T_P(t)$	$I_P(t)$	$L_P(t)$	$V_P(t)$
$t = 21$	6.4×10^5	42311	7125	1.3×10^5
$t = 45$	9.1×10^5	3023	509	6913
$t = 60$	9.7×10^5	508	86	1075
$J(u^*)$		655996592		

Table 5
A summary of the cell populations at different moments of time during combined treatment strategy.

Time	Combined Therapy			
	$T_C(t)$	$I_C(t)$	$L_C(t)$	$V_C(t)$
$t = 21$	9.5×10^5	210	127	3.5×10^5
$t = 45$	9.95×10^5	0.0026	0.0019	17893
$t = 60$	9.99×10^5	2.52×10^{-6}	1.9×10^{-6}	2781
$J(u^*)$		779560365		

production and preventing new infections; this combination efficacy was defined in such a way that the persistence or clearance of infection depend on a critical drug efficacy. Existence for the optimal control pair is established and the Pontryagin's maximum principle is used to uniquely characterized these optimal controls. Our results show that with preventive control the uninfected T cells continue to increase, the number of infected cells (I & L) and virus V cells decreases at the end of the time interval, which improves the quality of life of the patient. The key finding is that during acute infection earlier treatment with a better pharmacodynamics profile is always associated with more substantial suppression of the viral load

and latently infected cells and corresponds to the highest number of T cells. The model we consider in this paper is a basic model with HIV latency; further studies need to be done to incorporate a more accurate model of the immune system. For instance, taking multi-scale (within host and between hosts) and mutation of the virus into account in the model formulation will better reflect HIV dynamics over a longer time interval or when drug resistance emerges in patients. It would be interesting to compare the corresponding difference in optimal controls.

Appendix A. Appendix

Appendix A.1 Parameter Estimation

The Markov Chain Monte Carlo (MCMC) method has become more and more popular, which is widely used in actual research and data fitting. A brief introduce of the basic steps of MCMC using virus concentration data to estimate unknown parameters is given below.

Step 1. Collect sample observations
Suppose, we are fitting the given virions $\widehat{V}(t_i)$ at time t_i, with the given data

$$\{(t_1, \widehat{V}_1), (t_2, \widehat{V}_2), ..., (t_n, \widehat{V}_n)\}.$$

and $V(t_i, \Theta)$ represents the virus concentration at time t_i with parameter Θ.

Step 2. Determine the conditional density function
Consider $\widehat{V} = \{\widehat{V}_1, \widehat{V}_2, ..., \widehat{V}_n\}$, the conditional density function of parameter vector Θ is given by

$$P(\Theta|\widehat{V}) = \frac{P(\widehat{V}|\Theta)P(\Theta)}{P(\widehat{V})}.$$

Since $P(\widehat{V})$ is a constant relative to parameter vector Θ, the conditional density function is usually rewritten as follows

$$P(\Theta|\widehat{V}) \propto P(\widehat{V}|\Theta)P(\Theta).$$

Step 3. Construct the likelihood function
We assume that the viral load of day t_i follows a Poisson distribution with parameter $V(t_i, \Theta)$. Then the likelihood function is given by

$$L\left(\widehat{V}|\Theta\right) = \prod_{i=1}^{n} P(\widehat{V}_i|\Theta) = \prod_{i=1}^{n} \frac{V(t_i, \Theta)^{\widehat{V}_i} e^{-\sum_{i=1}^{n} V(t_i, \Theta)}}{(\widehat{V}_1, \widehat{V}_2, ..., \widehat{V}_n)!}.$$

Step 4. Establish the probability of joint posterior distribution
By selecting the non-informative prior distribution $P(\Theta) \propto$ constant, then the probability of joint posterior distribution is given by

$$P(\Theta|\widehat{V}) \propto L(\widehat{V}|\Theta)P(\Theta) \propto \prod_{i=1}^{n} P(\widehat{V}_i|\Theta) \propto \prod_{i=1}^{n} \frac{V(t_i, \Theta)^{\widehat{V}_i} e^{-V(t_i, \Theta)}}{\widehat{V}_i!}.$$

Step 5. Select the initial value of parameters
Here, we select the initial parameter vector Θ^0 based on previous studies and use the random walk method to generate candidate parameter $\Theta*$ and assume that the proposal distribution $q(\Theta*, \Theta)$, that satisfies

$$q(\Theta^*, \Theta) = q(\Theta, \Theta^*).$$

Step 6. Determine the acceptance probability
Since the proposal distribution is symmetric, the acceptance probability can be simplified as

$$\alpha(\Theta^*, \Theta) = \min\left\{1, \frac{q(\Theta, \Theta^*)P(\Theta^*|\widehat{V})}{q(\Theta^*, \Theta)P(\Theta|\widehat{V})}\right\} = \min\left\{1, \left(\frac{V(t_i, \Theta)}{V(t_i, \Theta^*)}\right)^{\widehat{V}_i} e^{V(t_i, \Theta) - V(t_i, \Theta^*)}\right\}$$

Select the random number ζ from the Uniform distribution $U(0, 1)$. When $\alpha(\Theta*, \Theta) \geq \zeta$ accept the candidate parameter $\Theta*$ and denoted by $\Theta^{t+1} = \Theta*$, otherwise reject $\Theta*$. Select a burn-in period of m times and a cycle of N times, calculate the mean value $\Theta*$ of the last $N - m$ times about unknown parameters and take them as the estimated values of Θ.

Appendix A.2 Results

Certain parameters such as production rate λ, natural death rates d_T of T cells can be estimated directly from population data as given in Table A.6. The rest of the parameters $\Theta = (k, f, d_I, \alpha, d_L, N, d_V)$ are estimated from the set of data gathered from plasma donor samples obtained in (Nowak & May 2000) at primary stage of HIV infection. We have taken most of our initial parameters from previous literature (Perelson et al., 1993) except the fraction of latent infection f. Since $f \in (0, 1)$, we take the initial guess as $\Theta^0 = (2 \times 10^{-7}, 0.1, 0.5, 0.4, 0.004, 50, 5)$ with initial conditions $(T_0, I_0, L_0, V_0) = (10^6, 0, 0, 15.8)$, under no treatments $(u_1 = u_2 = 0)$ we obtained estimated parameters of model (3) in Table A.6.

Table A.6
Description of parameter and values for model (3).

Parameter	Description	Value	Reference
λ	Production rate of T cells	10^5 cells ml^{-1} d^{-1}	Nowak and May (2000)
d_T	Death rate of T cell population	0.1 d^{-1}	Nowak and May (2000)
k	Rate of T cell become infected by free virus	3.22×10^{-7} ml d^{-1}	Estimated
f	Proportion of latent infection	0.087	Estimated
d_I	Death rate of Infected T cell population	0.80 d^{-1}	Estimated
α	Activation rate of latent cells	0.45d^{-1}	Estimated
d_L	Death rate of latently T cell population	0.008 d^{-1}	Estimated
N	Number of free virus produced by I cells	7	Estimated
d_V	Death rate of free virions	0.12 d^{-1}	Estimated

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