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ANALYSIS AND OPTIMAL CONTROL OF AN HIV MODEL WITH LOGISTIC GROWTH AND INFECTED CELLS IN ECLIPSE PHASE

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Abstract. A mathematical model of the human immunodeficiency virus infection with logistic growth, infected cells in eclipse phase and therapy is investigated. The model includes four nonlinear differential equations describing the evolution of uninfected $CD4^+$ T cells, infected $CD4^+$ T cells in latent stage, productively infected $CD4^+$ T cells and free virus. Two types of treatments are incorporated into the model; the purpose of the first one consists to block the viral proliferation while the role of the second is to prevent new infections. The positivity and boundedness of solutions are established. The local stability of the disease free steady state and the infection steady states are studied. An optimal control problem is proposed and investigated. Numerical simulations are performed, confirming stability of the free and endemic equilibria and illustrating the effectiveness of the two incorporated treatments via an efficient optimal control.

1. Introduction

Human immunodeficiency virus (HIV) is a virus that progressively weakens the immune system. It is known as the main cause of several deadly infections after the resulting acquired immunodeficiency syndrome (AIDS) is reached. Without treatment of the HIV infection, HIV advances in stages getting worse over time [1]. The most powerful antiretrovirals can not completely eliminate the virus because it remains dormant in some cells [2]. Individuals infected with HIV who are under treatment maintain their viral load below the detection limit [3, 4]. Currently, there exist two main kinds of antiretroviral drugs; Reverse Transcriptase Inhibitors (RTIs) and Protease Inhibitors (PIs) [5]. Many mathematical models have proved their usefulness for describing and understanding the dynamics of HIV infection

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[6, 5, 7, 8, 9, 10, 11, 12]. The basic of them was suggested in [6]:

$$\begin{cases} \dot{x} = \lambda - d_1 x(t) - k_1 x(t) v(t), \\ \dot{s} = k_1 x(t) v(t) - d_3 s(t), \\ \dot{v} = a s(t) - d_4 v(t), \end{cases} \tag{1}$$

where x, s and v denote the concentration of uninfected CD4$^+$ T cells, infected CD4$^+$ T cells and free virus, respectively. Susceptible host cells CD4$^+$ T cells are produced at a rate λ, die at a rate d_1 and become infected by virus at a rate $k_1 xv$. Infected cells die at a rate d_3. Finally, the free virus is produced by infected cells at a rate a and decays at a rate d_4. In these last two decades, some HIV mathematical models decompose the infect class into two classes that represent the infected cells in latent stage and others in active stage. For example in [10], this scenario is represented as follows:

$$\begin{cases} \dot{x} = \lambda - d_1 x(t) - k_1 x(t) v(t) + p y(t), \\ \dot{y} = k_1 x(t) v(t) - (d_2 + k_2 + p) y(t), \\ \dot{s} = k_2 y(t) - d_3 s(t), \\ \dot{v} = a s(t) - d_4 v(t), \end{cases} \tag{2}$$

here y denotes the concentration of infected CD4$^+$ T cells in latent stage. Latently infected cells die at a rate d_2, and become infected cells by a rate k_2. The infected cells become uninfected at rate p. More recently a modified model of (2) considering a saturated infection rate $\dfrac{k_1 x(t) v(t)}{x(t) + v(t)}$ was studied in [11]:

$$\begin{cases} \dot{x} = \lambda - d_1 x(t) - \dfrac{k_1 (1-\eta) x(t) v(t)}{x(t) + v(t)}, \\ \dot{y} = \dfrac{k_1 (1-\eta) x(t) v(t)}{x(t) + v(t)} - d_2 y(t) - k_2 y(t), \\ \dot{s} = k_2 y(t) - d_3 s(t), \\ \dot{v} = a(1-\epsilon) s(t) - d_4 v(t), \end{cases} \tag{3}$$

with the two constant η and ϵ stand for the efficiency of treatment in blocking new infection and in inhibiting viral production, respectively. Until now, there is no effective treatment that eradicates HIV virus; However there are some therapies that reduce HIV viral replication including reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs) [13]. Different works extend the basic model by including a logistic growth term that describes the growth rate of healty CD4$^+$ T cells [14, 15, 16, 17]. In this paper, we include into the model (3) the logistic growth function and the fraction of infection. To this end, we consider the following model

$$\begin{cases} \dot{x} = rx(1 - \dfrac{T}{T_m}) - d_1 x - \dfrac{(1-\eta)k_1 xv}{x+v}, \\ \dot{y} = \dfrac{\alpha(1-\eta)k_1 xv}{x+v} - (d_2 + k_2)y, \\ \dot{s} = \dfrac{(1-\alpha)(1-\eta)k_1 xv}{x+v} + k_2 y - d_3 s, \\ \dot{v} = (1-\epsilon)as - d_4 v, \end{cases} \tag{4}$$

With

$$T = x + y + s.$$

The initial data are

$$x(0) = x_0 \geq 0, y(0) = y_0 \geq 0, s(0) = s_0 \geq 0, v(0) = v_0 \geq 0. \tag{5}$$

In this model, $x(t)$, $y(t)$, $s(t)$, $v(t)$ represent the concentration of uninfected $CD4^+$ T cells, infected $CD4^+$ T cells in latent stage, productively infected $CD4^+$ T cells and free virus (HIV), respectively. Susceptible host cells $CD4^+$ cells grow at a rate r, die at a rate $d_1 x$ and become infectious by free virus a rate $\frac{(1-\eta)k_1 xv}{x+v}$. T_m is the carrying capacity of the T-cell population. Infected $CD4^+$ T cells in latent stage are produced at a rate $\frac{\alpha(1-\eta)k_1 xv}{x+v}$, die at a rate $d_2 y$ and become productively infected cells at a rate $k_2 y$. Productively infected $CD4^+$ T cells are produced at a rate $\frac{(1-\alpha)(1-\eta)k_1 xv}{x+v}$ and die at a rate $d_3 s$. Free virus (HIV) is produced from infected cells at a rate $(1-\epsilon)as$ and die a rate $d_4 v$. η and ϵ measure the efficacy of reverse transcriptase inhibitor and protease inhibitor, respectively. α is the fraction of infection leading to proviral latency.

The paper is organized as follows. Section 2 is devoted to the proof of existence, positivity and boundedness of solutions. The analysis of the model is described in Section 3. Then, in Section 4, we perform an optimization analysis of the viral infection model. Results obtained by numerical simulations are given in Section 5 and we conclude in the last section.

2. Positivity and Boundedness of solutions

For the problem deal with cell population evolution, the cell densities should remain non-negative and bounded. In this subsection, we will establish the positivity and boundedness of solutions of the model (4). First of all, for biological reasons, the parameters x_0, y_0, s_0 and v_0 must be larger than or equal to 0. Hence, we have the following result

Proposition 1. *The solutions of the problem* (4) *exist. Moreover, they are bounded and nonnegative for all* $t > 0$.

Proof. Notice that system (4) is locally lipschitzian at $t = 0$. Hence the solution of this system exists and is unique on $[0, b)$ for some $b > 0$. Observe that if $x(0) = 0$,

then $x \equiv 0$ for all $t > 0$. Hence we assume below that $x(0) > 0$. We also have the following:

$\dot{y} \mid_{y=0} = \dfrac{\alpha(1-\eta)k_1xv}{x+v} \geq 0$, $\dot{s} \mid_{s=0} = \dfrac{(1-\alpha)(1-\eta)k_1xv}{x+v} + k_2y \geq 0$ and $\dot{v} \mid_{v=0} = (1-\epsilon)as \geq 0$. This shows that $x(0) = x_0 > 0, y(0) = y_0 \geq 0, s(0) = s_0 \geq 0$ and $v(0) = v_0 \geq 0$ for all $t \in [0, b)$.

On the other hand, for the boundedness of the solutions, we have the following:

$$\frac{dT(t)}{dt} = rx(t)(1 - \frac{T(t)}{T_m}) - d_1x(t) - d_2y(t) - d_3s(t),$$

since

$$T(t) \leq T_m \text{ and } x(t) \leq T(t),$$

we obtain

$$\frac{dT(t)}{dt} \leq rT(t)(1 - \frac{T(t)}{T_m}) \leq rT(t),$$

thus

$$T(t) \leq T_0e^{-rt},$$

with $T_0 = x_0 + y_0 + s_0$.

We conclude that T is bounded, which means also that x, y and s are bounded.

From the last equation of (4), we have

$$v(t) \leq v(0)e^{-d_4t} + (1-\epsilon)a \int_0^t s(t)e^{(\xi - t)d_4} d\xi,$$

therefore

$$v(t) \leq v(0) + \frac{(1-\epsilon)a}{d_4} \|s\|_\infty (1 - e^{-d_4t}).$$

Since $(1 - e^{-d_4t}) \leq 1$, we conclude that v is bounded. □

3. Analysis of the model

A straightforward calculation by using the next generation matrix method [18] gives the following expression for the basic reproductive number of the model (4):

$$R_0 = \frac{ak_1(d_2 + k_2)(1-\alpha)(1-\theta) + \alpha ak_1k_2(1-\theta)}{d_3d_4(d_2 + k_2)}.$$

For simplicity, let's denote by $\theta = \eta + \epsilon - \eta\epsilon$ the efficacy combination of the two drugs. Then $1 - \theta = (1-\eta)(1-\epsilon)$ which means that each drug acts independently.

3.1. **Steady states.** There exist two steady states: the infection-free equilibrium $E_f = (\frac{T_m(r-d_1)}{r}, 0, 0, 0)$ which represent the disease free equilibrium that correspond to the maximal level of healthy CD4$^+$ T cells and $E^* = (x^*, y^*, s^*, v^*)$ is a state of persistent, chronic HIV infection. Explicitly, E^* requires

$$x^* = \frac{T_m a k_1 k_2 (1-\theta)(R_0-1)(R_2-1)}{r[ak_2R_0(1-\epsilon) + d_4k_2R_0(R_0-1) + ak_1(1-\alpha)(1-\theta)(R_0-1)(R_3-1)]},$$

$$y^* = \frac{T_m a k_1^2 (1-\alpha)(1-\eta)(1-\theta)(R_0-1)^2(R_2-1)(R_3-1)}{rR_0[ak_2R_0(1-\epsilon) + d_4k_2R_0(R_0-1) + ak_1(1-\alpha)(1-\theta)(R_0-1)(R_3-1)]},$$

$$s^* = \frac{T_m d_4 k_1 k_2 (1-\eta)(R_0-1)^2(R_2-1)}{r[ak_2R_0(1-\epsilon) + d_4k_2R_0(R_0-1) + ak_1(1-\alpha)(1-\theta)(R_0-1)(R_3-1)]},$$

$$v^* = \frac{T_m a k_1 k_2 (1-\theta)(R_0-1)^2(R_2-1)}{r[ak_2R_0(1-\epsilon) + d_4k_2R_0(R_0-1) + ak_1(1-\alpha)(1-\theta)(R_0-1)(R_3-1)]},$$

This equilibrium exits only if $R_0 > 1$ and $R_2 > 1$ with

$$R_2 = \frac{R_0(r-d_1)}{k_1(1-\eta)(R_0-1)},$$

$$R_3 = 1 + \frac{a\alpha k_1 k_2 (1-\theta)}{d_3 d_4 (d_2+k_2)}.$$

3.2. **The stability analysis.** First, the jacobian matrix of the system (4) is given by

$$J = \begin{pmatrix} r(1-\frac{2x+y+s}{T_m}) - \frac{k_1(1-\eta)v^2}{(x+v)^2} - d_1 & -\frac{rx}{T_m} & -\frac{rx}{T_m} & -\frac{k_1(1-\eta)x^2}{(x+v)^2} \\ \frac{\alpha k_1(1-\eta)v^2}{(x+v)^2} & -(d_2+k_2) & 0 & \frac{\alpha k_1(1-\eta)x^2}{(x+v)^2} \\ \frac{k_1(1-\alpha)(1-\eta)v^2}{(x+v)^2} & k_2 & -d_3 & \frac{k_1(1-\alpha)(1-\eta)x^2}{(x+v)^2} \\ 0 & 0 & (1-\epsilon)a & -d_4 \end{pmatrix} \tag{6}$$

3.2.1. *Stability of the infection-free equilibrium point E_f.* Here, we will analyze locally asymptotical stability of the disease-free equilibrium E_f.

Proposition 2. *The free equilibrium point E_f is locally asymptotically stable when $R_0 < 1$ and unstable if $R_0 > 1$.*

Proof. The Jacobian matrix at E_f is given by

$$J_{E_f} = \begin{pmatrix} -(r-d_1) & -(r-d_1) & -(r-d_1) & -k_1(1-\eta) \\ 0 & -(d_2+k_2) & 0 & \alpha k_1(1-\eta) \\ 0 & k_2 & -d_3 & k_1(1-\alpha)(1-\eta) \\ 0 & 0 & a & -d_4 \end{pmatrix}$$

The characteristic polynomial of J_{E_f} is

$$P_{E_f}(\xi) = (\xi + (r-d_1))[\xi^3 + a_1\xi^2 + a_2\xi + a_3],$$

Where

$$\begin{aligned} a_1 &= d_2 + d_3 + d_4 + k_2, \\ a_2 &= (d_3+d_4)(d_2+k_2) + d_3d_4(1-R_1), \\ a_3 &= d_3d_4(d_2+k_2)(1-R_0). \end{aligned}$$

and

$$R_1 = \frac{ak_1(1-\alpha)(1-\theta)}{d_3d_4}.$$

While $\xi_1 = -(r-d_1)$ is a negative eigenvalue, the other three eigenvalues are given by the solution of the following cubic equation,

$$\xi^3 + a_1\xi^2 + a_2\xi + a_3 = 0.$$

First we remark that

$$R_0 = R_1 + \frac{\alpha a k_1 k_2(1-\theta)}{d_3d_4(d_2+k_2)},$$

since $R_0 < 1$ then $R_1 < 1$.

It is clear that, $a_1 > 0$. $a_2 > 0$ and $a_1a_2 - a_3 = (d_3+d_4)[(d_2+k_2)(d_2+d_3+d_4+k_2) + d_3d_4(1-R_1)] > 0$ when $R_0 < 1$. If $R_0 < 1$, then $a_3 > 0$. From the Routh-Hurwitz Theorem given in [16], all roots of this equation have negative real parts. Then E_f is locally asymptotically stable when $R_0 < 1$. □

3.2.2. *Stability of the endemic equilibrium point E^*.* In this part, we discuss the local stability of the endemic infection equilibrium point E^*.

Proposition 3. (1) *If $R_0 < 1$ or $R_2 < 1$ then the point E^* does not exist.*
(2) *If $R_0 = 1$, then $E^* = E_f$.*
(3) *The endemic equilibrium point E^* is locally asymptotically stable when $R_0 > 1$ and $R_2 > 1$.*

Proof. From the expression of E^* we observe that this point exists when $R_0 > 1$ and $R_2 > 1$, it becomes E_f when $R_0 = 1$.
We assume that $R_0 > 1$ and $R_2 > 1$.
The Jacobian matrix at the endemic equilibrium point E^* is given by

$$J = \begin{pmatrix} r(1 - \frac{2x^* + y^* + s^*}{T_m}) - \frac{k_1(1-\eta)v^{*2}}{(x^*+v^*)^2} - d_1 & -\frac{rx^*}{T_m} & -\frac{rx^*}{T_m} & -\frac{k_1(1-\eta)x^{*2}}{(x^*+v^*)^2} \\ \frac{\alpha k_1(1-\eta)v^{*2}}{(x^*+v^*)^2} & -(d_2 + k_2) & 0 & \frac{\alpha k_1(1-\eta)x^{*2}}{(x^*+v^*)^2} \\ \frac{k_1(1-\alpha)(1-\eta)v^{*2}}{(x^*+v^*)^2} & k_2 & -d_3 & \frac{k_1(1-\alpha)(1-\eta)x^{*2}}{(x^*+v^*)^2} \\ 0 & 0 & (1-\epsilon)a & -d_4 \end{pmatrix} \tag{7}$$

The characteristic polynomial of J_{E^*} is

$$P_{E^*}(\xi) = \xi^4 + b_1\xi^3 + b_2\xi^2 + b_3\xi + b_4,$$

Where

$$b_1 = d_1 + d_2 + d_3 + d_4 + k_2 + \frac{k_1(1-\eta)v^{*2}}{(x^*+v^*)^2} + \frac{r(2x^* + y^* + s^*)}{T_m} - r,$$

$$b_2 = (d_2 + d_3 + d_4 + k_2)(\frac{r(2x^* + y^* + s^*)}{T_m} + \frac{k_1(1-\eta)v^{*2}}{(x^*+v^*)^2} + d_1 - r) + d_3d_4$$
$$+ (d_2 + k_2)(d_3 + d_4) + \frac{k_1(1-\eta)rx^*v^{*2}}{T_m(x^*+v^*)^2} - \frac{ak_1(1-\alpha)(1-\theta)x^{*2}}{(x^*+v^*)^2},$$

$$b_3 = (d_3(d_2 + k_2) + d_4(d_2 + k_2) + d_3d_4)(\frac{k_1(1-\eta)v^{*2}}{(x^*+v^*)^2} + \frac{r(2x^* + y^* + s^*)}{T_m} + d_1$$
$$- r) + \frac{\alpha rk_1(1-\eta)x^*v^{*2}}{T_m(x^*+v^*)^2}(d_4 + d_3 + k_2) + \frac{rk_1(1-\alpha)(1-\eta)x^*v^{*2}}{T_m(x^*+v^*)^2}(d_4 + d_2 + k_2)$$
$$+ (d_2 + k_2)d_3d_4 - \frac{ark_1(1-\alpha)(1-\theta)x^{*3}}{T_m(x^*+v^*)^2} - \frac{\alpha ak_1k_2(1-\theta)x^{*2}}{(x^*+v^*)^2}$$
$$- \frac{ak_1(1-\alpha)(1-\theta)x^{*2}}{(x^*+v^*)^2}(d_1 + d_2 + k_2),$$

$$b_4 = d_3d_4(d_2 + k_2)(\frac{r(2x^* + y^* + s^*)}{T_m} + \frac{k_1(1-\eta)v^{*2}}{(x^*+v^*)^2} + d_1 - r)$$
$$+ \frac{r\alpha k_1(1-\eta)x^*v^{*2}(d_3d_4 + d_4k_2)}{T_m(x^*+v^*)^2} - ((d_2 + k_2)(1-\alpha) + \alpha k_2)(\frac{ak_1d_1(1-\theta)x^{*2}}{(x^*+v^*)^2}$$
$$+ \frac{ark_1(1-\theta)x^{*3}}{T_m(x^*+v^*)^2}) + \frac{rk_1d_4(d_2 + k_2)(1-\alpha)(1-\eta)x^*v^{*2}}{T_m(x^*+v^*)^2}.$$

From the Routh-Hurwitz theorem applied to the fourth order polynomial, the eigenvalues of the jacobian matrix (7) have negative real parts since we have $b_1b_2 >$

b_3 and $b_1b_2b_3 > b_3^2 + b_1^2b_4$. Consequently, we obtain the asymptotic local stability of the endemic point E^*. □

4. Optimal control

In this section, we study an optimal control problem by introducing drug therapy into the model (4) and we assume that treatment reduces the viral replication. Our purpose is to find a treatment strategy $u(t) = (u_1(t), u_2(t))$ that maximizes the number of $CD4^+$ T cells, keeping the cost, measured in terms of chemotherapy strength and a combination of duration and intensity, as low as possible.

4.1. **The optimization problem.**

To study the optimal control problem, we suggest the following control system with two control variables:

$$\begin{cases} \dfrac{dx}{dt} = rx(t)(1 - \dfrac{T(t)}{T_m}) - d_1x(t) - \dfrac{k_1(1-u_1(t))x(t)v(t)}{x(t)+v(t)}, \\ \dfrac{dy}{dt} = \dfrac{\alpha k_1(1-u_1(t))x(t)v(t)}{x(t)+v(t)} - (d_2+k_2)y(t), \\ \dfrac{ds}{dt} = \dfrac{k_1(1-\alpha)(1-u_1(t))x(t)v(t)}{x(t)+v(t)} + k_2y(t) - d_3s(t), \\ \dfrac{dv}{dt} = a(1-u_2(t))s(t) - d_4v(t), \end{cases} \tag{8}$$

Here, u_1 represents the efficiency of drug therapy in blocking new infection, so that infection rate in the presence of drug is $(1 - u_1)$; while u_2 stands for the efficiency of drug therapy in inhibiting viral production, such that the virion production rate under therapy is $(1 - u_2)$.

The optimization problem under consideration is to maximize the following objective functional

$$J(u_1, u_2) = \int_0^{t_f} \Big\{ x(t) - \Big[\frac{A_1}{2} u_1^2(t) + \frac{A_2}{2} u_2^2(t) \Big] \Big\} dt, \tag{9}$$

where t_f is the time period of treatment and the positive constants A_1 and A_2 stand for the benefits and costs of the introduced treatment. The two control functions, $u_1(t)$ and $u_2(t)$ are assumed to be bounded and Lebesgue integrable.

$$J(u_1^*, u_2^*) = max\{J(u_1, u_2) : (u_1, u_2) \in U\}, \tag{10}$$

where U is the control set defined by

$$U = \{(u_1(t), u_2(t)) : u_i(t) \quad \text{measurable}, 0 \le u_i(t) \le 1, t \in [0, t_f], i = 1, 2\}.$$

4.2. **Existence of an optimal control pair.** The existence of the optimal control pair can be directly obtained using the results in [19, 20]. More precisely, we have the following theorem.

Theorem 4. *There exists an optimal control pair* $(u_1^*, u_2^*) \in U$ *solution of* (10).

Proof. To use the existence result in [19], we first need to check the following properties:

- (P_1) the set of controls and corresponding state variables is nonempty;
- (P_2) the control set U is convex and closed;
- (P_3) the right-hand side of the state system is bounded by a linear function in the state and control variables;
- (P_4) the integrand of the objective functional is concave on U;
- (P_5) there exist constants $c_1, c_2 > 0$ and $\beta > 1$ such that the integrand

$$L(x, u_1, u_2) = x - \left(\frac{A_1}{2}u_1^2 + \frac{A_2}{2}u_2^2\right)$$

of the objective functional (9) satisfies

$$L(x, u_1, u_2) \leq c_2 - c_1(\mid u_1 \mid^2 + \mid u_2 \mid^2)^{\frac{\beta}{2}}.$$

Using the result in [20], we obtain existence of solutions of system (8), which gives condition (P_1). The control set is convex and closed by definition, which gives condition (P_2). Since our state system is bilinear in u_1 and u_2, the right-hand side of system (8) satisfies condition (P_3), using the boundedness of solutions. Note that the integrand of our objective functional is concave. Also, we have the last needed condition:

$$L(x, u_1, u_2) \leq c_2 - c_1\left(\mid u_1 \mid^2 + \mid u_2 \mid^2\right),$$

where c_2 depends on the upper bound on x, and $c_1 > 0$ since $A_1 > 0$ and $A_2 > 0$. We conclude that there exists an optimal control pair $(u_1^*, u_2^*) \in U$ such that

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

□

4.3. **The optimality system.** Pontryagin's minimum principle provides the necessary conditions for such optimal control problem [21]. This principle transforms (8), (9) and (10) into a problem of maximizing an Hamiltonian, H, point wisely with respect to u_1 and u_2:

$$H(t, x, y, s, v, u_1, u_2, \lambda) = \tfrac{A_1}{2}u_1^2 + \tfrac{A_2}{2}u_2^2 - x + \sum_{i=0}^{4} \lambda_i f_i,$$

with

$$\begin{cases} f_1 = rx(1-\dfrac{T}{T_m}) - d_1 x - \dfrac{k_1(1-u_1)xv}{x+v}, \\ f_2 = \dfrac{\alpha k_1(1-u_1)xv}{x+v} - (d_2+k_2)y, \\ f_3 = \dfrac{k_1(1-\alpha)(1-u_1)xv}{x+v} + k_2 y - d_3 s, \\ f_4 = a(1-u_2)s - d_4 v. \end{cases}$$

By applying Pontryagin's minimum principle [21], we obtain the following result.

Theorem 5. *Given optimal controls u_1^*, u_2^* and solutions x^*, y^*, s^* and v^* of the corresponding state system (8), there exists adjoint variables $\lambda_1, \lambda_2, \lambda_3$ and λ_4 satisfying the equations*

$$\begin{cases} \lambda_1'(t) = 1 - \lambda_1(t)\big[-r + r\big(\frac{2x^*(t)+y^*(t)+s^*(t)}{T_m}\big) + d_1 + \frac{k_1(1-u_1^*(t))v^{*2}(t)}{(x^*(t)+v^*(t))^2}\big] \\ -\lambda_2(t)\frac{\alpha k_1(1-u_1^*(t))v^{*2}(t)}{(x^*(t)+v^*(t))^2} - \lambda_3(t)\frac{k_1(1-\alpha)(1-u_1^*(t))v^{*2}(t)}{(x^*(t)+v^*(t))^2}, \\ \lambda_2'(t) = \lambda_1(t)\frac{rx^*(t)}{T_m} + \lambda_2(t)(d_2+k_2) - \lambda_3(t)k_2, \\ \lambda_3'(t) = \lambda_1(t)\frac{rx^*(t)}{T_m} + \lambda_3(t)d_3 - \lambda_4(t)a(1-u_2^*(t)), \\ \lambda_4'(t) = \lambda_1(t)\frac{k_1(1-u_1^*(t))x^{*2}(t)}{(x^*(t)+v^*(t))^2} - \lambda_2(t)\frac{\alpha k_1(1-u_1^*(t))x^{*2}(t)}{(x^*(t)+v^*(t))^2} - \lambda_3(t)\frac{k_1(1-\alpha)(1-u_1^*(t))x^{*2}(t)}{(x^*(t)+v^*(t))^2} \\ +\lambda_4(t)d_4 \end{cases}$$

with transversality conditions

$$\lambda_i(t_f) = 0, \quad i = 1, \dots, 4.$$

Moreover, the optimal controls satisfy

$$\begin{aligned} u_1^*(t) &= \min\left(1, \max\left(0, \frac{1}{A_1}\left[\lambda_2(t)\frac{\alpha k_1 x^*(t)v^*(t)}{x^*(t)+v^*(t)} - \lambda_1(t)\frac{k_1 x^*(t)v^*(t)}{x^*(t)+v^*(t)}\right.\right.\right. \\ &\qquad \left.\left.\left. + \lambda_3(t)\frac{k_1(1-\alpha)x^*(t)v^*(t)}{x^*(t)+v^*(t)}\right]\right)\right), \qquad (11) \\ u_2^*(t) &= \min\left(1, \max\left(0, \frac{1}{A_2}\lambda_4(t)as^*(t)\right)\right). \end{aligned}$$

Proof. The proof of positivity and boundedness of solutions is similar to the one of Proposition 1. It is enough to use the fact that $u_i(t) \in U$, $i = 1, 2$, which means that $\|u_i(t)\|_{L^\infty} \leq 1$. For the rest of the proof, we remark that the adjoint equations and transversality conditions are obtained by using the Pontryagin minimum principle

with delays of [21], from which

$$\begin{cases} \lambda_1'(t) = -\frac{\partial H}{\partial x}(t) & \lambda_1(t_f) = 0, \\ \lambda_2'(t) = -\frac{\partial H}{\partial y}(t), & \lambda_2(t_f) = 0, \\ \lambda_3'(t) = -\frac{\partial H}{\partial s}(t) & \lambda_3(t_f) = 0, \\ \lambda_4'(t) = -\frac{\partial H}{\partial v}(t), & \lambda_4(t_f) = 0. \end{cases}$$

From the optimality conditions,

$$\frac{\partial H}{\partial u_1}(t) = 0, \qquad \frac{\partial H}{\partial u_2}(t) = 0,$$

that is,

$$\begin{aligned} A_1 u_1(t) + \lambda_1(t)\frac{k_1 x^*(t)v^*(t)}{x^*(t)+v^*(t)} - \lambda_2(t)\frac{\alpha k_1 x^*(t)v^*(t)}{x^*(t)+v^*(t)} \\ -\lambda_3(t)\frac{k_1(1-\alpha)x^*(t)v^*(t)}{x^*(t)+v^*(t)} = 0, \\ A_2 u_2(t) - a s^*(t)\lambda_3(t) = 0. \end{aligned}$$

Taking into account the bounds in U for the two controls, one obtains u_1^* and u_2^* in form (11).

The optimality system consists of the state system coupled with the adjoint equations, the initial conditions, transversality conditions, and the characterization of optimal controls (11). Precisely, if we substitute the expressions of u_1^* and u_2^* in (8), then we obtain the following optimality system:

$$\begin{cases} \dfrac{dx^*(t)}{dt} = rx^*(t)(1 - \dfrac{T^*(t)}{T_m}) - d_1 x^*(t) - \dfrac{k_1(1-u_1^*(t))x^*(t)v^*(t)}{x^*(t)+v^*(t)}, \\ \dfrac{dy^*(t)}{dt} = \dfrac{\alpha k_1(1-u_1^*(t))x^*(t)v^*(t)}{x^*(t)+v^*(t)} - (d_2+k_2)y^*(t), \\ \dfrac{ds^*(t)}{dt} = \dfrac{k_1(1-\alpha)(1-u_1^*(t))x^*(t)v^*(t)}{x^*(t)+v^*(t)} + k_2 y^*(t) - d_3 s^*(t), \\ \dfrac{dv^*(t)}{dt} = a(1-u_2^*(t))s^*(t) - d_4 v^*(t), \end{cases}$$

$$\begin{cases} \dfrac{d\lambda_1(t)}{dt} = 1 - \lambda_1(t)\big[-r + r\big(\dfrac{2x^*(t)+y^*(t)+s^*(t)}{T_m}\big) + d_1 + \dfrac{k_1(1-u_1^*(t))v^{*2}(t)}{(x^*(t)+v^*(t))^2}\big] \\ -\lambda_2(t)\frac{\alpha k_1(1-u_1^*(t))v^{*2}(t)}{(x^*(t)+v^*(t))^2} - \lambda_3(t)\frac{k_1(1-\alpha)(1-u_1^*(t))v^{*2}(t)}{(x^*(t)+v^*(t))^2}, \\ \dfrac{d\lambda_2(t)}{dt} = \lambda_1(t)\dfrac{rx^*(t)}{T_m} + \lambda_2(t)(d_2+k_2) - \lambda_3(t)k_2, \\ \dfrac{d\lambda_3(t)}{dt} = \lambda_1(t)\dfrac{rx^*(t)}{T_m} + \lambda_3(t)d_3 - \lambda_4(t)a(1-u_2^*(t)), \\ \dfrac{d\lambda_4(t)}{dt} = \lambda_1(t)\dfrac{k_1(1-u_1^*(t))x^{*2}(t)}{(x^*(t)+v^*(t))^2} - \lambda_2(t)\dfrac{\alpha k_1(1-u_1^*(t))x^{*2}(t)}{(x^*(t)+v^*(t))^2} \\ -\lambda_3(t)\frac{k_1(1-\alpha)(1-u_1^*(t))x^{*2}(t)}{(x^*(t)+v^*(t))^2} + \lambda_4(t)d_4, \\ \lambda_i(t_f) = 0, \quad i = 1,\dots,4 \end{cases}$$

$$\begin{cases} u_1^* = \min\left(1, \max\left(0, \frac{1}{A_1}\left[\lambda_2(t)\frac{\alpha k_1 x^*(t)v^*(t)}{x^*(t)+v^*(t)} - \lambda_1(t)\frac{k_1 x^*(t)v^*(t)}{x^*(t)+v^*(t)} + \lambda_3(t)\frac{k_1(1-\alpha)x^*(t)v^*(t)}{x^*(t)+v^*(t)}\right]\right)\right), \\ u_2^* = \min\left(1, \max\left(0, \frac{1}{A_2}\lambda_4(t)as^*(t)\right)\right). \end{cases}$$

□

5. Numerical Simulations

In order to solve numerically our optimization system, we will use a numerical scheme based on forward and backward finite difference approximation. Thus, we will have the following numerical algorithm

Step 1:
Initial conditions: x_0, y_0, s_0, $T_0 = x_0 + y_0 + s_0$, v_0, $u_1^0 = 0$, $u_2^0 = 0$.
$\lambda_1^n = 0, \lambda_2^n = 0, \lambda_3^n = 0, \lambda_4^n = 0$.
end for
Step 2:
for i = 0, ... , n-1, do:

$$x_{i+1} = x_i + h[rx_i(1 - \tfrac{T_i}{T_m}) - d_1 x_i - \tfrac{k_1(1-u_1^i)x_i v_i}{x_i+v_i}],$$
$$y_{i+1} = y_i + h[\tfrac{\alpha k_1(1-u_1^i)x_i v_i}{x_i+v_i} - (d_2+k_2)y_i],$$
$$s_{i+1} = s_i + h[\tfrac{k_1(1-\alpha)(1-u_1^i)x_i v_i}{x_i+v_i} - k_2 y_i - d_3 s_i],$$
$$v_{i+1} = v_i + h[a(1-u_2^i)s_i - d_4 v_i],$$

$$\lambda_1^{n-i-1} = \lambda_1^{n-i} - h[1 + \lambda_1^{n-i}[-r + r(\tfrac{2x_{i+1}+y_{i+1}+s_{i+1}}{T_m}) + d_1 + \tfrac{k_1(1-u_1^i)v_{i+1}^2}{(x_{i+1}+v_{i+1})^2}] - \lambda_2^{n-i}\tfrac{\alpha k_1(1-u_1^i)v_{i+1}^2}{(x_{i+1}+v_{i+1})^2} - \lambda_3^{n-i}\tfrac{(1-\alpha)k_1(1-u_1^i)v_{i+1}^2}{(x_{i+1}+v_{i+1})^2}],$$

$$\lambda_2^{n-i-1} = \lambda_2^{n-i} - h[\lambda_1^{n-i}\tfrac{rx_{i+1}}{T_m} + \lambda_2^{n-i}(d_2+k_2) - \lambda_3^{n-i}k_2],$$

$$\lambda_3^{n-i-1} = \lambda_3^{n-i} - h\big[\lambda_1^{n-i}\tfrac{rx_{i+1}}{T_m} + \lambda_3^{n-i}d_3 - \lambda_4^{n-i}a(1-u_2^i)\big],$$

$$\lambda_4^{n-i-1} = \lambda_4^{n-i} - h[\lambda_1^{n-i}\tfrac{k_1(1-u_1^i)x_{i+1}^2}{(x_{i+1}+v_{i+1})^2} - \lambda_2^{n-i}\tfrac{\alpha k_1(1-u_1^i)x_{i+1}^2}{(x_{i+1}+v_{i+1})^2} - \lambda_3^{n-i}\tfrac{k_1(1-\alpha)(1-u_1^i)x_{i+1}^2}{(x_{i+1}+v_{i+1})^2} + \lambda_4^{n-i}d_4],$$

$$R_1^{i+1} = (1/A_1)(\lambda_2^{n-i-1}\tfrac{\alpha k_1 x_{i+1}v_{i+1}}{(x_{i+1}+v_{i+1})^2} - \lambda_1^{n-i-1}\tfrac{k_1 x_{i+1}v_{i+1}}{(x_{i+1}+v_{i+1})^2} - \lambda_3^{n-i-1}\tfrac{k_1(1-\alpha)x_{i+1}v_{i+1}}{(x_{i+1}+v_{i+1})^2})$$
$$R_2^{i+1} = (1/A_2)\lambda_4^{n-i-1}as_{i+1},$$
$$u_1^{i+1} = min(1, max(R_1^{i+1}, 0)),$$
$$u_2^{i+1} = min(1, max(R_2^{i+1}, 0)),$$

end for
Step 3:
for i = 0, ... , n, write
$x^*(t_i) = x_i, y^*(t_i) = y_i, s^*(t_i) = s_i, v^*(t_i) = v_i, u_1^*(t_i) = u_1^i, u_2^*(t_i) = u_2^i$.
end for

The numerical algorithm.

The parameters of our numerical simulations are inspired from [11, 22, 23] i.e. $r = 0.1$, $T_m = 1000$, $d_1 = 0.0139$, $k_1 = 0.04$, $d_2 = 0.0495$, $k_2 = 1.1$, $d_3 = 0.5776$, $a = 100$, $d_4 = 0.6$ and $\alpha = 10^{-3}$. We chose as in [24] the two last parameters $A_1 = 5000$ and $A_2 = 5000$. The role of the positive constants A_1 and A_2 is to balance the terms size in the equations. Figure 1 shows that with control the amount of the uninfected cells population is higher than those observed for without control case. From Fig. 2, we observe that the latently infected cells

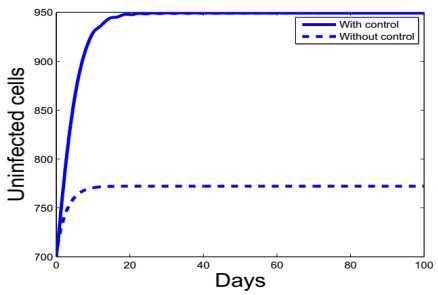

FIGURE 1. The uninfected cells as function of time.

under control converges towards 1.31, while without control it converges towards 47.69, which means that administrating the good therapy amounts can help the patient by significant reduction the exposed cells number. We notice that with control we observe a dumping oscillating regime and a significant reduce of the exposed cells. Figure 3 shows that with control the number of infected cells are

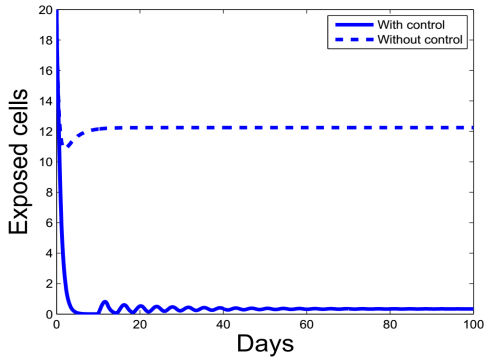

FIGURE 2. The exposed cells as function of time.

significantly reduced after the first days of therapy. However, without control this number remains much higher.

The goal of therapy control is also observed in Fig. 4. It was observed that with control, the number of HIV virus dies are reduced during the first days of therapy, while without control it stays equal to 7.94×10^3. This indicates the impact of the administrated therapy in controlling viral replication.

The two optimal controls u_1 and u_2 corresponding to blocking new infections and inhibiting viral production are represented in Fig. 5. The two curves present the drug administration schedule during the period of treatment. Both controls

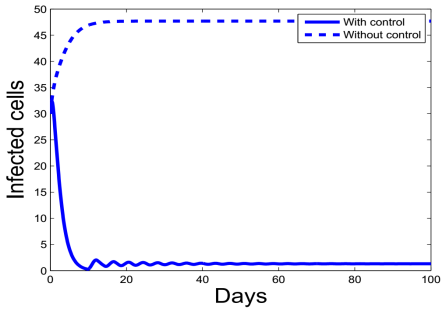

FIGURE 3. The infected cells as function of time.

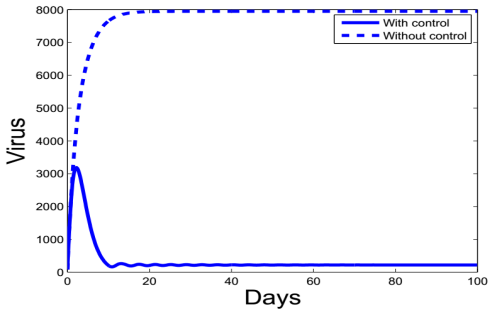

FIGURE 4. The virus as function of time.

start from zero and oscillate during the period of treatment. This figure shows that we should give more importance to the first drug (RTIs) than to the second one (PIs).

6. Conclusion

In this work, we have investigated a mathematical model describing the human immunodeficiency virus infection with logistic growth, infected cells in eclipse phase and therapy. Two types of treatments were incorporated into the model; the purpose of first one consists to block the viral proliferation while the role of the second is to prevent new infections. The positivity and boundedness of solutions were established and the local stability of the disease free steady state and the infection steady states were studied. An optimal control problem was proposed and investigated. Numerical simulations were performed, confirming the stability of the free and endemic equilibria and illustrating the effectiveness of the two incorporated

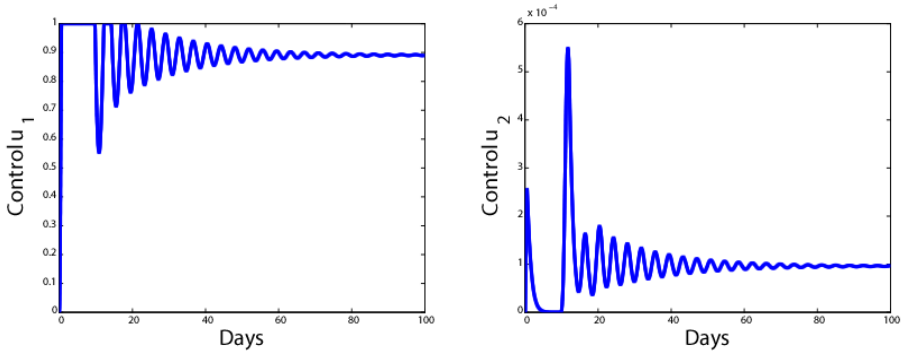

FIGURE 5. The optimal control u_1 (left) and the optimal control u_2 (right) versus time.

treatments via optimal control. It was shown that under optimal control the number of CD4+ cells increases while the viral load decreases significantly compared with the model without control, which will improve the life quality of the patient.

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