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# Optimal control of an HIV infection model with the adaptive immune response and two saturated rates

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**Abstract**

The dynamics of a model describing the human immunodeficiency virus (HIV) infection with cytotoxic T-lymphocyte (CTL), antibodies and two saturated rates is investigated and studied in this paper. The model includes five nonlinear differential equations describing the evolution of uninfected cells, infected ones, free HIV viruses, CTL immune response and antibodies. This model includes also two treatments that represent the efficiency of drug treatment in inhibiting viral production and preventing new infections. Existence, positivity and boundedness of solutions are given. Existence of the optimal control pair is established and the Pontryagin's maximum principle is

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used to find an optimal treatment strategy that maximizes the number of uninfected CD4$^+$ T cells as well as cytotoxic T-lymphocyte and antibody immune responses. Finally, the optimality system is derived and solved numerically. Results show that administrating good therapy maximizes the amount of healthy CD4$^+$ T cells and deceases considerably the viral load and the infected cells.

# 1 Introduction

Human immunodeficiency virus (HIV) is a lentivirus (a subgroup of retrovirus) which damages cells in the immune system and causes the well known acquired immunodeficiency syndrome (AIDS). Currently, there is no cure or vaccine for HIV [1]. However, antiretroviral (ART) treatment are used to treat HIV. There are two kinds of these antiretroviral medications licensed for treatment of infected individuals with HIV: reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs). Reverse transcriptase inhibitors (RTIs) oppose the conversion of RNA of the virus to DNA (reverse transcription), consequently the viral population will be minimum and the CD4$^+$ T cells count remains higher. Protease inhibitors (PIs) prevents the production of viruses from the actively infected CD4$^+$ T cells. Over the last decades, many mathematical models have proved their usefulness for describing and understanding the dynamics of HIV infection [2, 3]. More recently, a modified model considering two saturated rates, CTL and antibody immune responses have been carried out in [4]:

$$\begin{cases} \dfrac{dT}{dt} = s - dT(t) - \dfrac{\beta V(t)T(t)}{1+aV(t)} + \rho I(t), \\ \dfrac{dI}{dt} = \dfrac{\beta V(t)T(t)}{1+aV(t)} - (\delta+\rho)I(t) - pI(t)Z(t), \\ \dfrac{dV}{dt} = N\delta I(t) - \mu V(t) - qV(t)W(t), \\ \dfrac{dW}{dt} = gV(t)W(t) - hW(t), \\ \dfrac{dZ}{dt} = \dfrac{cI(t)Z(t)}{1+\alpha I(t)} - bZ(t). \end{cases} \tag{1.1}$$

where $T$, $I$, $V$, $Z$ and $W$ denote the concentration of uninfected cells, infected cells, free virus, CTL cells and antibodies, respectively. Susceptible host cells CD4$^+$ T cells are produced at a rate $s$, die at a rate $dT$ and become

infected by virus at a rate $\frac{\beta VT}{1+aV}$. Infected cells die at a rate $\delta I$ and are killed by the CTL response at a rate $pIZ$. $\rho I$ is the cure rate of the infected cells to the susceptible host cells due to the noncytolytic processes [5, 6]. Free virus is produced by infected cells at a rate $N\delta I$, decays at a rate $\mu V$ and neutralized in the presence of antibodies at a rate $qVW$; where $N$ is the number of free virus produced by each actively infected cell during its life time. CTLs expand in response to viral antigen derived from infected cells at a rate $\frac{cIZ}{1+\alpha I}$ and decay in the absence of antigenic stimulation at a rate $bZ$. Antibodies develop in response to free virus at a rate $gVW$ and decay at a rate $hW$. The model contains also two saturated rate, the first is the saturated mass action which describe better the rate of viral infection while the second is the saturated function describing CTL proliferation when it is reduced by the presence of immune impairment effects caused by HIV infection [7]. The rate of infection in most HIV models is bilinear in the virus $V$ and the uninfected target cells $T$, actual incidence rates are probably not strictly linear in each variable over the entire range of $V$ and $T$. For example, a less than linear response in $V$ could occur due to saturation at high virus concentration, where the infectious fraction is high so that exposure is very likely. Thus, it is reasonable for us to assume that the infection rate of modelling HIV, HBV and HCV infection in saturated mass action [8, 9]. In recent work [10], two types of treatment are introduced into the system (1.1) and were considered constants. So, the model whose the transfer diagram shown in Figure 1 becomes as follows:

$$\begin{cases} \dfrac{dT}{dt} = s - dT(t) - \dfrac{(1-\eta)\beta V(t)T(t)}{1+aV(t)} + \rho I(t), \\ \dfrac{dI}{dt} = \dfrac{(1-\eta)\beta V(t)T(t)}{1+aV(t)} - (\delta+\rho)I(t) - pI(t)Z(t), \\ \dfrac{dV}{dt} = (1-\epsilon)N\delta I(t) - \mu V(t) - qV(t)W(t), \\ \dfrac{dW}{dt} = gV(t)W(t) - hW(t), \\ \dfrac{dZ}{dt} = \dfrac{cI(t)Z(t)}{1+\alpha I(t)} - bZ(t). \end{cases} \tag{1.2}$$

where the constants $\eta$ and $\epsilon$ represent the efficiency of drug therapy in blocking new infection and inhibiting viral production respectively.This article aspires to find an efficient treatment strategy for HIV infection using

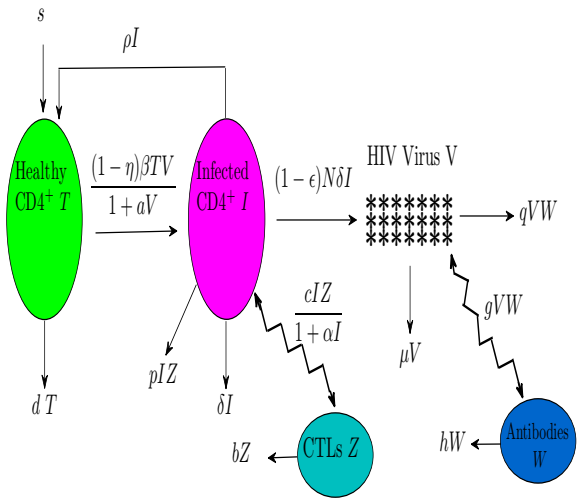


Figure 1: Schematic of the model under consideration.

similar optimal control techniques. It is worthy to notice that the optimal control of an hepatitis B virus model with the adaptive immunity is tackled in [11]. In the recent work [10], the mathematical analysis of an HIV model with two saturated rates and constant therapies is studied. In this present paper, we will study the optimal control of the same model (1.2) presented in [10]. To this end, we will vary the two considered treatments. Therefore, we will replace $\eta$ and $\epsilon$ by a pair of control $u = (u_1(t), u_2(t))$ to the above model representing an antiviral therapy time dependent. The first control $u_1(t)$ represents the efficiency of drug therapy in blocking new infection; while the second one $u_2(t)$ stands for the efficiency of drug therapy in inhibiting viral production. Our purpose is to find an optimal control that will minimize the viral load and maximize healthy cells. Moreover, several mathematical models prove the usefulness of the used controls [12, 13].

The paper is organized as follows. Section 2 is devoted to the proof of existence, positivity and boundedness of solutions. Mathematical analysis of the model is given in section 3, followed in Section 4 by an optimization analysis. In Section 5, we construct an appropriate numerical algorithm and give some simulations. Finally, the conclusion is summarized in Section 6.

## 2 Positivity and boundedness of solutions

In our model we will take into account two controls $u_1(t)$ and $u_2(t)$ describing the efficiency of the drug therapy and the model is the following

$$\begin{cases} \dfrac{dT}{dt} = s - dT(t) - \dfrac{(1-u_1(t))\beta V(t)T(t)}{1+aV(t)} + \rho I(t), \\ \dfrac{dI}{dt} = \dfrac{(1-u_1(t))\beta V(t)T(t)}{1+aV(t)} - (\delta+\rho)I(t) - pI(t)Z(t), \\ \dfrac{dV}{dt} = (1-u_2(t))N\delta I(t) - \mu V(t) - qV(t)W(t), \\ \dfrac{dW}{dt} = gV(t)W(t) - hW(t), \\ \dfrac{dZ}{dt} = \dfrac{cI(t)Z(t)}{1+\alpha I(t)} - bZ(t). \end{cases} \tag{2.1}$$

In this section, we will establish the positivity and boundedness of solutions of the model (2.1). First of all, for biological reasons, the parameters $T_0$, $I_0$, $V_0$, $W_0$ and $Z_0$ must be larger than or equal to 0. Hence, we have the following result:

**Proposition 2.1.** *The solutions of the problem* (2.1) *are nonnegative and bounded. Moreover we have:*

**i)** $T_1(t) \leq T_1(0) + \dfrac{s}{\delta_1}$,

**ii)** $V(t) \leq V(0) + \dfrac{N\delta}{\mu} \|I\|_\infty$,

**iii)** $W(t) \leq W(0) + \dfrac{g}{q}[\max(1; 2 - \dfrac{\mu}{h})V(0) + (\dfrac{N\delta}{\mu} + \dfrac{N\delta}{h}) \|I\|_\infty]$,

**iv)** $Z(t) \leq Z(0) + \dfrac{c}{p}[\max(1; 2 - \dfrac{d}{b})T(0) + I(0) + \max(\dfrac{s}{b}; \dfrac{s}{d}) + \max(0; 1 - \dfrac{\delta}{b}) \|I\|_\infty]$,

*where* $T_1(t) = T(t) + I(t)$ *and* $\delta_1 = \min(d; \delta)$.

*Proof.* First, we will show that the nonnegative orthant $\mathbb{R}^6_+ = \{(T, I, V, W, Z) \in \mathbb{R}^5 : T \geq 0, I \geq 0, V \geq 0, W \geq 0 \text{ and } Z \geq 0\}$ is positively invariant. Indeed, for $(T(t), I(t), V(t), W(t), Z(t)) \in \mathbb{R}^5_+$ we have:

$\dot{T} \mid_{T=0} = s + \rho I(t) \geq 0$, $\dot{I} \mid_{I=0} = \dfrac{(1-u_1)\beta VT}{1+aV} \geq 0$, $\dot{V} \mid_{V=0} = (1-u_2)N\delta I \geq 0$, $\dot{W} \mid_{W=0} = 0 \geq 0$ and $\dot{Z} \mid_{Z=0} = 0 \geq 0$. Therefore, all solutions initiating in $\mathbb{R}^5_+$ are positive.

Next, we will prove that these solutions remain bounded. By adding the first and second equation in (2.1), we have $\dot{T}_1 = s - dT - \delta I - pIZ$, thus

$$T_1(t) \leq T_1(0)e^{-\delta_1 t} + \frac{s}{\delta_1}(1 - e^{-\delta_1 t}),$$

with $\delta_1 = \min(d; \delta)$. Since $0 \leq e^{-\delta_1 t} \leq 1$ and $1 - e^{-\delta_1 t} \leq 1$, we deduce $(i)$. Therefore $T$ and $I$ are bounded.

From the equation $\dot{V} = (1-u_2)N\delta I - \mu V - qVW$, we have

$$V(t) \leq V(0)e^{-\mu t} + N\delta \int_0^t (1 - u_2(t))I(\xi)e^{(\xi - t)\mu} d\xi.$$

Since $(1 - u_2(t)) \leq 1$, we have

$$V(t) \leq V(0) + \frac{N\delta}{\mu} \|I\|_\infty (1 - e^{-\mu t}).$$

Since $1 - e^{-\mu t} \leq 1$, we deduce $(ii)$.

The two equations $\dot{V} = (1-u_2(t))N\delta I - \mu V - qVW$ and $\dot{W} = gVW - hW$ imply

$$\dot{W} + hW = gVW = \frac{g}{q}\left((1 - u_2(t))N\delta I - (\dot{V} + \mu V)\right),$$

then,

$$W(t) = W_0 e^{-ht} + \frac{g}{q}\left\{\int_0^t [(1-u_2)N\delta I(\xi) + (h-\mu)V(s)]e^{h(\xi - t)} d\xi - V(t) + V(0)e^{-ht}\right\}.$$

If $h - \mu \leq 0$, then we have

$$W(t) \leq W_0 + \frac{g}{q}\left\{\frac{N\delta}{h}\|I\|_\infty + V(0)\right\},$$

else, we will have

$$W(t) \leq W_0 + \frac{g}{q}\left\{(\frac{N\delta}{h} + \frac{N\delta}{\mu})\|I\|_\infty + (2 - \frac{\mu}{h})V(0)\right\}.$$

From the two last inequalities, we have $(iii)$.

Finally, from the equation $\dot{Z} = \dfrac{cIZ}{1+\alpha I} - bZ$ we have

$$\dot{Z} + bZ \leq cIZ.$$

Since $cIZ = \dfrac{c}{p}[s - (\dot{T} + dT) - (\dot{I} + \delta I)]$, we get

$$Z(t) \leq [\frac{c}{p}(T(0)+I(0)-\frac{s}{b})+Z(0)]e^{-bt}+\frac{c}{p}\{\frac{s}{b}+\int_0^t [(b-d)T(\xi)+(b-\delta)I(\xi)]e^{b(\xi-t)}d\xi-T(t)-I(t)\}.$$

Following the same reasoning as in the previous cases for each sign of the $(b-d)$ and $(b-\delta)$, we will deduce (iv).

□

# 3 Analysis of the model

This section shows the analysis of the model with fixed control value $u_1$ and $u_2$:

## 3.1 Stability of the disease-free equilibrium

The system (2.1) has an infection-free equilibrium $E_f = (\dfrac{s}{d}; 0; 0; 0; 0)$, corresponding to the maximal level of healthy $CD4^+$ T-cells. In this case, the disease cannot invade the cell population. By a simple calculation, the basic reproduction number of (2.1) is given by:

$$R_0 = \frac{(1-\theta)\beta N \delta s}{d\mu(\delta+\rho)}$$

with $\theta = u_1 + u_2 - u_1 u_2$. As proved in [10] we have the folowing proposition for the local stability of the $E_f$:

**Proposition 3.1.**

1. *The disease-free equilibrium, $E_f$, is locally asymptotically stable for $R_0 < 1$.*

2. *The disease-free equilibrium, $E_f$, is unstable for $R_0 > 1$.*

### 3.2 Stability of infection equilibrium points

The system (2.1) has four infection equilibrium points given by :

$E_1 = (T_1; I_1; V_1; 0; 0)$, where
$T_1 = \frac{s}{d}(\frac{a(1-u_2)Ns+\mu}{a(1-u_2)Ns+\mu R_0}), I_1 = \frac{s}{\delta}(\frac{\mu(R_0-1)}{a(1-u_2)Ns+\mu R_0}), V_1 = \frac{(1-u_2)Ns(R_0-1)}{a(1-u_2)Ns+\mu R_0}$

$E_2 = (T_2; I_2; V_2; W_2; 0)$, where

$$T_2 = \frac{(\rho+\delta)(g+ah)s}{d(\rho+\delta)(g+ah)+(1-u_1)\beta\delta h}, I_2 = \frac{(1-u_1)\beta hs}{d(\rho+\delta)(g+ah)+(1-u_1)\beta\delta h},$$
$$V_2 = \frac{h}{g}, W_2 = \frac{\mu}{q}(\frac{(1-\theta)N\delta\beta gs}{\mu(d(\rho+\delta)(g+ah)+(1-u_1)\beta\delta h)} - 1)$$

$E_3 = (T_3; I_3; V_3; 0; Z_3)$, where

$$T_3 = \frac{(a(1-u_2)N\rho\delta)I_3^2+(a(1-u_2)N\rho\delta+\mu\rho)I_3+\mu s}{(1-u_2)N\delta(ad+(1-u_1)\beta)I_3+\mu d}, I_3 = \frac{b}{c-\alpha b}$$

$$V_3 = \frac{(1-u_2)N\delta I_3}{\mu}$$

$$Z_3 = \frac{-(1-u_2)N\delta\left[ad\rho+\delta(ad+(1-u_1)\beta)\right]I_3+((1-\theta)\beta Ns\delta-d\mu(\rho+\delta))}{p((1-u_2)N\delta(ad+(1-u_1)\beta)I_3+\mu d}$$

$E_4 = (T_4; I_4; V_4; W_4; Z_4)$, where

$$T_4 = \frac{(s+\rho I_4)(1+aV_4)}{d(1+aV_4)+(1-u_1)\beta V_4}, I_4 = \frac{b}{c-\alpha b}, V_4 = \frac{h}{g},$$
$$W_4 = \frac{1}{q}(\frac{(1-u_2)N\delta I_4}{V_4} - 1), Z_4 = \frac{1}{p}(\frac{s}{I_4} - \frac{dT_4}{I_4} - \delta).$$

Here the endemic equilibrium point $E_1$ represents the equilibrium case in the absence of the adaptive immune response (CTLs and antibody reponses). The endemic equilibria points $E_2$ and $E_3$ represent the equilibrium case in the presence of only one kind of the adaptive immune response antibody response and CTL response, respectively. While the last endemic equilibrium point $E_4$ represents the equilibrium case of chronic HIV infection with the presence of both kinds of adaptive immune response CTLs and antibody type.

The local stability of the the endemic equilibrium points was investigated in [10] and the following theorems have been proved :

**Theorem 3.2.**

1. *If $R_0 < 1$, then the point $E_1$ does not exist.*
2. *If $R_0 = 1$, then $E_1 = E_f$.*
3. *If $R_0 > 1$, then $E_1$ is locally asymptotically stable for $H_0^W < 1$, and $H_0^Z < 1$;*

   *however it is unstable for $H_0^W > 1$ or $H_0^Z > 1$.*

**Theorem 3.3.**

1. *If $H_0^W < 1$, then the point $E_2$ does not exist.*
2. *If $H_0^W = 1$ then $E_2 = E_1$.*
3. *If $H_0^W > 1$ then $E_2$ is locally asymptotically stable for $H_0^{W,Z} < 1$ and unstable for $H_0^{W,Z} > 1$.*

**Theorem 3.4.**

1. *If $\alpha > \frac{c}{b}$ or $H_0^Z < 1$, then the point $E_3$ does not exist and $E_3 = E_2$ when $H_0^Z = 1$.*
2. *If $\alpha < \frac{c}{b}$, $H_0^Z > 1$ and $D_0^W < (1 - \frac{\alpha b}{c}) D_0^Z$ , then $E_3$ is locally asymptotically stable.*
3. *If $\alpha < \frac{c}{b}$, $H_0^Z > 1$ and $D_0^W > (1 - \frac{\alpha b}{c}) D_0^Z$, then $E_3$ is unstable.*

**Theorem 3.5.**

1. *If $\alpha > \frac{c}{b}$ or $D_0^W < (1 - \frac{\alpha b}{c}) D_0^Z$ or $H_0^{W,Z} < 1$, then the point $E_4$ does not exist. Moreover $E_4 = E_2$ when $H_0^{W,Z} = 1$ and $E_4 = E_3$ when $D_0^W = D_0^Z$*
2. *If $\alpha < \frac{c}{b}$, $D_0^W > (1 - \frac{\alpha b}{c}) D_0^Z$ and $H_0^{W,Z} > 1$, then $E_4$ is locally asymptotically stable.*

With:

$$D_0^W = \frac{(1-u_2)gNs}{h\mu},\ \widetilde{D_0^W} = D_0^W \frac{\mu R_0}{(a(1-u_2)Ns+\mu R_0)},\ H_0^W = \frac{1}{\frac{1}{R_0}+\frac{1}{\widetilde{D_0^W}}},$$

$$D_0^Z = \frac{cs}{b\delta},\ \widetilde{D_0^Z} = D_0^Z \frac{\mu\delta R_0}{(a(1-u_2)Ns+\mu R_0)+\alpha\mu s(R_0-1)},\ H_0^Z = \frac{1}{\frac{1}{R_0}+\frac{1}{\widetilde{D_0^Z}}},$$

and

$$H_0^{W,Z} = \frac{D_0^Z R_0}{D_0^W(1+\frac{ah}{g})+R_0(1+\frac{\alpha s^2}{\delta})}.$$

Where $D_0^Z$ represents the CTL immune response reproduction number, $D_0^W$ represents the antibody immune response reproduction number, $H_0^W$ is the half harmonic mean of $R_0$ and $\widetilde{D_0^W}$ and $H_0^Z$ is the half harmonic mean of $R_0$ and $\widetilde{D_0^Z}$.

# 4 The optimal control problem

## 4.1 The optimization problem

The Previous sections shows the analysis of model with fixed control value, but in real situation this parameter should be time dependent. To study the optimal control problem, we suggest the following control system with two control variables:

$$\begin{cases} \dfrac{dT}{dt} = s - dT(t) - \dfrac{(1-u_1(t))\beta V(t)T(t)}{1+aV(t)} + \rho I(t), \\ \dfrac{dI}{dt} = \dfrac{(1-u_1(t))\beta V(t)T(t)}{1+aV(t)} - (\delta+\rho)I(t) - pI(t)Z(t), \\ \dfrac{dV}{dt} = (1-u_2(t))N\delta I(t) - \mu V(t) - qV(t)W(t), \\ \dfrac{dW}{dt} = gV(t)W(t) - hW(t), \\ \dfrac{dZ}{dt} = \dfrac{cI(t)Z(t)}{1+\alpha I(t)} - bZ(t). \end{cases} \tag{4.1}$$

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

$$J(u_1,u_2) = \int_0^{t_f} \Big\{ T(t) + W(t) + Z(t) - \Big[ \frac{A_1}{2}u_1^2(t) + \frac{A_2}{2}u_2^2(t) \Big] \Big\} dt, \tag{4.2}$$

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.

$$J(u_1^*,u_2^*) = max\{J(u_1,u_2) : (u_1,u_2) \in U\}, \tag{4.3}$$

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 [14, 15]. More precisely, we have the following theorem

**Theorem 4.1.** *There exists an optimal control pair* $(u_1^*, u_2^*) \in U$ *such that*

$$J(u_1^*, u_2^*) = \max_{(u_1,u_2)\in U} J(u_1, u_2). \tag{4.4}$$

*Proof.* To use the existence result in [14], we must check the following properties:

($P_1$) The set of controls and corresponding state variables is nonempty.

($P_2$) The control U set 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 exists constants $c_1, c_2 > 0$ , and $\beta > 1$ such that the integrand $L(T, W, Z, u_1, u_2)$ of the objective functional satisfies

$$L(T, W, Z, u_1, u_2) \leq c_2 - c_1(\mid u_1 \mid^2 + \mid u_2 \mid^2)^{\frac{\beta}{2}}. \tag{4.5}$$

In order to verify these conditions, we use a result by Lukes in [15] to give the existence of solutions of system (2.1), 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 $u_1$, $u_2$, the right hand side of system (2.1) satisfies condition ($P_3$), using the boundedness of the solutions. Note that the integrand of our objective functional is concave. Also, we have the last needed condition

$$L(T, W, Z, u_1, u_2) \leq c_2 - c_1(\mid u_1 \mid^2 + \mid u_2 \mid^2), \tag{4.6}$$

where $c_2$ depends on the upper bound on $T$, $W$, $Z$, 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

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

□

## 4.3 The optimality system

Pontryagin's maximum principle given in [16] provides the necessary conditions for an optimal control problem. This principle transforms (4.1), (4.2) and (4.3) into a problem of maximizing an Hamiltonian, $H$, pointwisely with respect to $u_1$ and $u_2$:

$$H(t,T,I,V,W,Z,u_1,u_2,\lambda) = [\tfrac{A_1}{2}u_1^2 + \tfrac{A_2}{2}u_2^2] - T - W - Z + \sum_{i=0}^{4}\lambda_i f_i,$$

where $f_i$ is the right hand side of the differential equation of i-th state variable.

and we have

$$\begin{cases} f_1 = s - dT - \dfrac{(1-u_1)\beta VT}{1+aV} + \rho I, \\ f_2 = \dfrac{(1-u_1)\beta VT}{1+aV} - (\delta+\rho)I - pIZ, \\ f_3 = (1-u_2)N\delta I - \mu V - qVW, \\ f_4 = gVW - hW, \\ f_5 = \dfrac{cIZ}{1+\alpha I} - bZ. \end{cases}$$

By applying Pontryagin's maximum principle we obtain the following theorem

**Theorem 4.2.** *For any optimal control $u_1^*, u_2^*$ and solutions $T^*, I^*, V^*, W^*$ and $Z^*$ of the corresponding state system (2.1), there exists adjoint variables, $\lambda_1, \lambda_2, \lambda_3, \lambda_4$ and $\lambda_5$, satisfying the equations*

$$\begin{cases} \lambda_1'(t) &= 1 + \lambda_1(t)d + (\lambda_1(t) - \lambda_2(t))\frac{(1-u_1^*(t))\beta V^*(t)}{1+aV^*(t)}, \\ \lambda_2'(t) &= -\lambda_1(t)\rho + \lambda_2(t)(\delta+\rho+pZ^*(t)) - \lambda_3(t)(1-u_2^*(t))N\delta - \lambda_5(t)\frac{cZ^*(t)}{(1+\alpha I^*(t))^2}, \\ \lambda_3'(t) &= (\lambda_1(t) - \lambda_2(t))\frac{(1-u_1^*(t))\beta T^*(t)}{(1+aV^*(t))^2} + \lambda_3(t)(\mu + qW^*(t)) - \lambda_4(t)gW^*(t), \\ \lambda_4'(t) &= 1 + \lambda_3(t)qV^*(t) + \lambda_4(t)(h - gV^*(t)), \\ \lambda_5'(t) &= 1 + \lambda_2(t)pI^*(t) - \lambda_5(t)(\frac{cI^*(t)}{(1+\alpha I^*(t))} - b) \end{cases}$$

*with the transversality conditions*

$$\lambda_i(t_f) = 0, i = 1, ..., 5.$$

*Moreover, the optimal control is given by*

$$\begin{aligned} u_1^* =& min\left(1, max\left(0, \frac{1}{A_1}(\lambda_2 - \lambda_1)\frac{\beta V^*(t)T^*(t)}{1 + aV^*(t)}\right)\right) \\ u_2^* =& min\left(1, max\left(0, \frac{1}{A_2}(\lambda_3 N\delta I^*(t))\right)\right) \end{aligned}$$

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

$$\begin{cases} \lambda_1'(t) = -\frac{\partial H}{\partial T}(t), & \lambda_1(t_f) = 0, \\ \lambda_2'(t) = -\frac{\partial H}{\partial I}(t), & \lambda_2(t_f) = 0, \\ \lambda_3'(t) = -\frac{\partial H}{\partial V}(t), & \lambda_3(t_f) = 0, \\ \lambda_4'(t) = -\frac{\partial H}{\partial W}(t), & \lambda_4(t_f) = 0, \\ \lambda_5'(t) = -\frac{\partial H}{\partial Z}(t), & \lambda_5(t_f) = 0, \end{cases} \tag{4.7}$$

The two optimal controls $u_1^*$ and $u_2^*$ can be solved from the optimality conditions,

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

That is,

$$\begin{aligned} \frac{\partial H}{\partial u_1}(t) =& A_1 u_1(t) + (\lambda_1 - \lambda_2)\frac{\beta V^*(t)T^*(t)}{1 + aV^*(t)} = 0, \\ \frac{\partial H}{\partial u_2}(t) =& A_2 u_2(t) - \lambda_3 N\delta I^*(t) = 0. \end{aligned} \tag{4.8}$$

By the bounds fact in $U$ of the two controls, it is easy to obtain $u_1^*$ and $u_2^*$ in the form of (4.2), respectively.

□

The optimality system consists of the state system coupled with the adjoint system with the initial conditions, the transversality conditions, and the characterization of the optimal control.

If we substitute the forms of $u_1^*$ and $u_2^*$ in the systems (4.1), we will obtain the following optimality system:

$$
\begin{cases}
\frac{dT^*(t)}{dt} = s - dT^*(t) - \frac{(1-u_1^*(t))\beta V^*(t)T^*(t)}{1+aV^*(t)} + \rho I^*(t), \\
\frac{dI^*(t)}{dt} = \frac{(1-u_1^*(t))\beta V^*(t)T^*(t)}{1+aV^*(t)} - (\delta+\rho)I^*(t) - pI^*(t)Z^*(t), \\
\frac{dV^*(t)}{dt} = (1-u_2^*(t))N\delta I^*(t) - \mu V^*(t) - qV^*(t)W^*(t), \\
\frac{dW^*(t)}{dt} = gV^*(t)W^*(t) - hW^*(t), \\
\frac{dZ^*(t)}{dt} = \frac{cI^*(t)Z^*(t)}{1+\alpha I^*(t)} - bZ^*(t), \\
\frac{d\lambda_1(t)}{dt} = 1 + \lambda_1(t)d + (\lambda_1(t)-\lambda_2(t))\frac{(1-u_1^*(t))\beta V^*(t)}{1+aV^*(t)}, \\
\frac{d\lambda_2(t)}{dt} = -\lambda_1(t)\rho + \lambda_2(t)(\delta+\rho+pZ^*(t)) - \lambda_3(t)(1-u_2^*(t))N\delta - \lambda_5(t)\frac{cZ^*(t)}{(1+\alpha I^*(t))^2}, \\
\frac{d\lambda_3(t)}{dt} = (\lambda_1(t)-\lambda_2(t))\frac{(1-u_1^*(t))\beta T^*(t)}{(1+aV^*(t))^2} + \lambda_3(t)(\mu+qW^*(t)) - \lambda_4(t)gW^*(t), \\
\frac{d\lambda_4(t)}{dt} = 1 + \lambda_3(t)qV^*(t) + \lambda_4(t)(h-gV^*(t)), \\
\frac{d\lambda_5(t)}{dt} = 1 + \lambda_2(t)pI^*(t) - \lambda_5(t)(\frac{cI^*(t)}{(1+\alpha I^*(t))} - b), \\
u_1^* = \min\left(1, max\left(0, \frac{1}{A_1}(\lambda_2-\lambda_1)\frac{\beta V^*(t)T^*(t)}{1+aV^*(t)}\right)\right), \\
u_2^* = \min\left(1, max\left(0, \frac{1}{A_2}(\lambda_3 N\delta I^*(t))\right)\right), \\
\lambda_i(t_f) = 0, \quad i = 1, \ldots, 5.
\end{cases}
$$

# 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:

$T_{i+1} = T_i + \Delta h[s - dT_i - \frac{(1-u_1^i)\beta V_i T_i}{1+aV_i} + \rho I_i]$,

$I_{i+1} = I_i + \Delta h[\frac{(1-u_1^i)\beta V_i T_i}{1+aV_i} - (\delta+\rho)I_i - pI_i Z_i]$,

$V_{i+1} = V_i + \Delta h[(1-u_2^i)N\delta I_i - \mu V_i - qV_i W_i]$,

$W_{i+1} = W_i + \Delta h[gV_i W_i - hW_i]$,

$Z_{i+1} = Z_i + \Delta h[\frac{cI_i Z_i}{1+\alpha I_i} - bZ_i]$,

$\lambda_1^{n-i-1} = \lambda_1^{n-i} - \Delta h[1 + \lambda_1^{n-i} d + (\lambda_1^{n-i} - \lambda_2^{n-i})\frac{(1-u_1^i)\beta V_{i+1}}{1+aV_{i+1}}]$,

$\lambda_2^{n-i-1} = \lambda_2^{n-i} - \Delta h[-\lambda_1^{n-i}\rho + \lambda_2^{n-i}(\delta+\rho+pZ_{i+1}) - \lambda_3^{n-i}(1-u_2^i)N\delta - \lambda_5^{n-i}\frac{cZ_{i+1}}{(1+\alpha I_{i+1})^2}]$,

$\lambda_3^{n-i-1} = \lambda_3^{n-i} - \Delta h\big[(\lambda_1^{n-i} - \lambda_2^{n-i})\frac{(1-u_1^i)\beta T_{i+1}}{(1+aV_{i+1})^2} + \lambda_3^{n-i}(\mu + qW_{i+1}) - \lambda_4^{n-i} gW_{i+1}\big]$,

$\lambda_4^{n-i-1} = \lambda_4^{n-i} - \Delta h[1 + \lambda_3^{n-i} qV_{i+1} + \lambda_4^{n-i}(h - gV_{i+1})]$,

$\lambda_5^{n-i-1} = \lambda_5^{n-i} - \Delta h[1 + \lambda_2^{n-i} pI_{i+1} - \lambda_5^{n-i}(\frac{cI_{i+1}}{(1+\alpha I_{i+1})} - b)]$,

$R_1^{i+1} = (1/A_1)(\lambda_2^{n-i-1} - \lambda_1^{n-i-1})\frac{\beta V_{i+1} T_{i+1}}{1+aV_{i+1}}$,

$R_2^{i+1} = (1/A_2)\lambda_3^{n-i-1} N\delta I_{i+1}$,

$u_1^{i+1} = min(1, max(R_1^{i+1}, 0))$,

$u_2^{i+1} = min(1, max(R_2^{i+1}, 0))$,

end for
Step 3:
for i = 0, ... , n, write
$T^*(t_i) = T_i, I^*(t_i) = I_i, V^*(t_i) = V_i, W^*(t_i) = W_i, Z^*(t_i) = Z_i, u_1^*(t_i) = u_1^i, u_2^*(t_i) = u_2^i$.
end for

The numerical algorithm.

The following parameters are used for the simulation which we have taken from ( [4], [10] and [13]): $s = 5$, $\beta = 0.000024$, $d = 0.02$, $\delta = 0.3$, $p = 0.001$, $N = 1100$, $\mu = 3$, $\rho = 0.01$, $a = 0.001$, $\alpha = 0.001$, $c = 0.03$, $b = 0.2$, $q = 0.01$, $g = 10^{-4}$, $h = 0.1$, $A_1 = 250$ and $A_2 = 2500$.

Moreover, besides the parameters we use the following initial conditions: $T_0 = 190, I_0 = 2, V_0 = 1000, W_0 = 20, Z_0 = 10$.

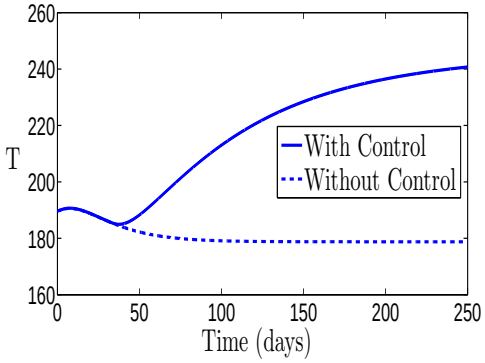


Figure 2: The evolution of the uninfected cells during time.

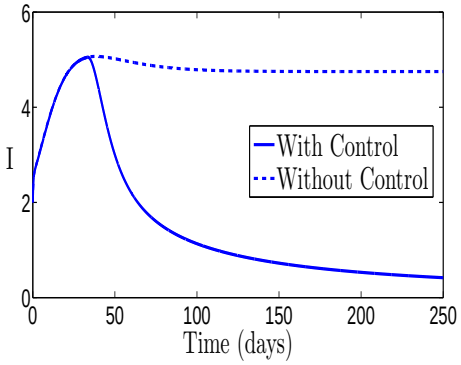


Figure 3: The evolution of the infected cells during time.

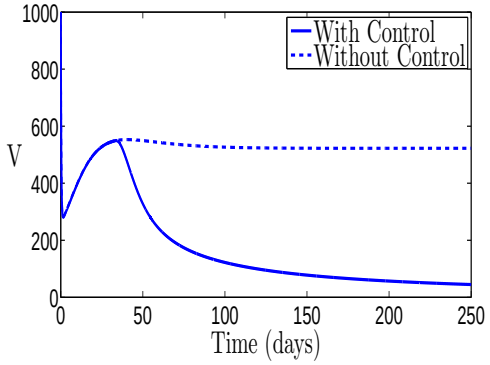


Figure 4: The evolution of the HIV virus during time.

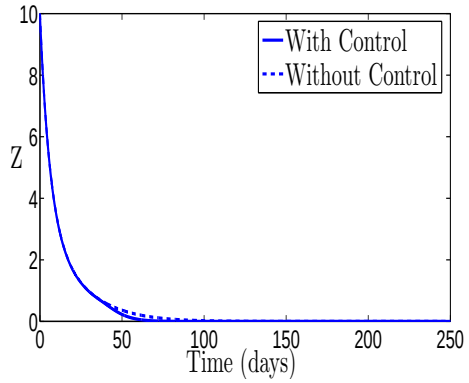


Figure 5: The evolution of the CTL cells during time.

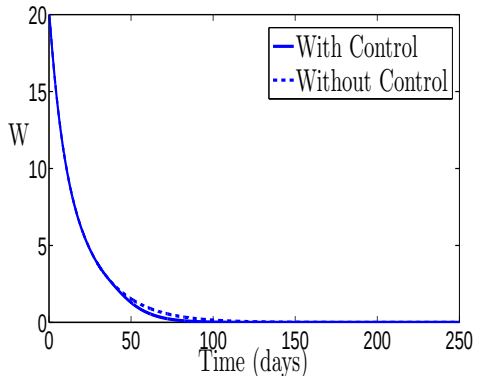


Figure 6: The evolution of the antibodies during time.

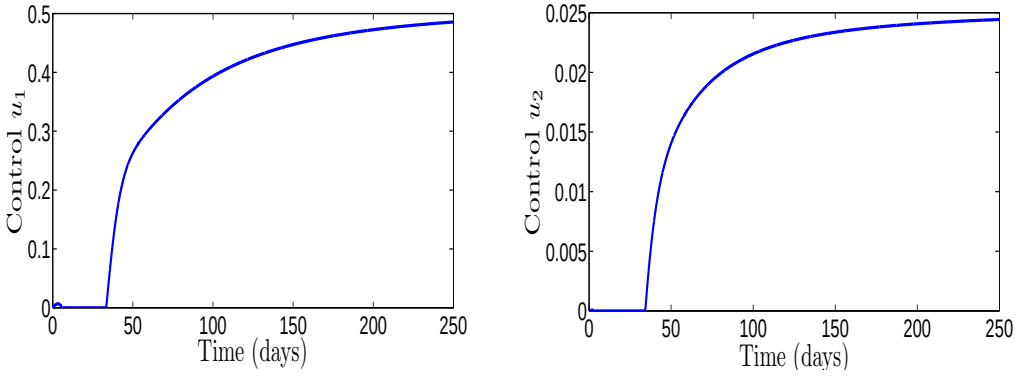


Figure 7: The behaviour of the optimal controls.

In Figure 2, it can be clearly seen that with control the uninfected cells population grows significantly comparing with those without control. Figure 3, shows that after introducing therapy, the number of infected cells decreases significantly and declines towards a very low level. The curve representing the infected cells under control converges toward 0.4, nevertheless, without control, it converges towards 4.92. This proves the role of control in reducing the number of infected cells which contributes in curing the disease. Figure 4, shows that with control, the viral load decreases significantly after the first days of therapy, whereas, without control, it stays equal to 580.11. This indicates the impact of the administrated drug in controlling the viral replication. Figure 5 and 6, show the adaptive immune response as function of time. It can be seen observed that without control, the two immune responses are maintained at a strictly positive level. We also note that an increase of infected cells or viral load corresponds to an increase in immune response. With control, the immune response tends toward zero when time increases. The two optimal controls $u_1$ and $u_2$, corresponding to blocking new infections and inhibiting viral production, are represented in Figure 7. The two curves present the drug administration schedule during the period of treatment. The plots show that patient should take the two treatments during the first days of therapy in increasing manner and both of the two treatments should be administrated for the lifetime period in a constant way.

# 6 Conclusion

In this work we have studied a mathematical model describing the human immunodeficiency virus with the adaptive immune response, two saturated rates and therapy. Two types of drug 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. Firstly, the positivity and boundedness of solutions were established. Next, an optimal control problem was proposed and investigated. Then, numerical simulations were performed, illustrating the effectiveness of the two incorporated treatments via optimal control. It was proved that under optimal control the amount of CD4+ cells increases while the viral load decreases significantly compared with the model without control.

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