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Free terminal time optimal control problem for the treatment of HIV infection

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Abstract. In this work, an optimal control approach is presented in order to propose an optimal therapy for the treatment HIV infection using a combination of two appropriate treatment strategies. The optimal treatment duration and the optimal medications amount are considered. The main objective of this study is to be able to maximize the benefit based on number of healthy $CD4^+$ T-cells and CTL immune cells and to minimize the infection level and the overall treatment cost while optimizing the duration of therapy. The free terminal time optimal control problem is formulated and the Pontryagin's maximum principle is employed to provide the explicit formulations of the optimal controls. The corresponding optimality system with the additional transversality condition for the terminal time is derived and solved numerically using an adapted iterative method with a Runge-Kutta fourth order scheme and a gradient method routine.

Keywords: Interleukin-2 immunotherapy; Highly active antiretroviral therapy; Pontryagin's maximum principle; Free terminal time optimal tracking control problem, Forward backward sweep method.
AMS Classification: 34H05, 49J15.

1. Introduction

Recent data from the World Health Organization [19] show that approximately 34 million people worldwide are infected with HIV, more than 30 million people died of AIDS-related causes since twenty years. HIV/AIDS is the sixth leading cause of death overall, and the third leading cause of death in poor countries, where an estimated 3.4 million children are infected with HIV/AIDS. Mathematical modeling allows public health officials to compare, plan, implement, evaluate and optimize various programs for the detection, prevention, treatment and control of this disease. Mathematical modeling of infectious diseases at the molecular level is a relatively new science. If epidemiology has a long history, it is only recently that mathematicians and immunologists have begun to work together to create models to predict the evolution of a disease. Since the discovery of human immunodeficiency virus (HIV) and the assertion that it is the cause of the acquired immune deficiency syndrome (AIDS), many scientific studies have focused on the HIV infection [8, 9, 11, 12, 23, 31, 39] and various mathematical models have been developed in order to suggest possible optimal treatment strategies for HIV infection [6, 7, 13, 29, 30, 33, 49, 51].

The HIV infection [19, 36] affects the immune system and particularly the body's natural defenses against disease. If the infection is not treated, serious illnesses can occur. Normally, harmless infections like flu or bronchitis can get worse and become very difficult to

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treat sometimes involving even death of the infected patients. The human immunodeficiency virus (HIV) approaches the Antigen-presenting cells (APCs) [54], once entered by phagocytosis; it joined the molecular recognition system of the cell. The HIV virus is a retrovirus, the RNA of this virus is converted into DNA inside the $CD4^+$ T-cell. Thus, when the infected $CD4^+$ T-cells begin to multiply for fighting this pathogen, eventually more viruses are produced in parallel.

The scientific research continues for the development of an effective drug therapy hence the interest of optimal control theory [33] which is presented as an indispensable tool for a better understanding of the dynamics of immune system and the evolution of HIV infection in order to propose an appropriate treatment strategy [6, 13, 20, 29, 30].

The HIV infection is usually treated with highly active antiretroviral therapy (HAART) [1, 18] which commonly refers to the combination of antiretroviral treatments struggling against the HIV. The different classes of antiretroviral agents act by disrupting different stages of the HIV replication cycle. This has the effect of reducing the number of virions in the body. The HAART has proven to be very effective limiting significantly the progression of HIV in order to minimize the viral load and to reduce both morbidity and mortality. There are several classes of antiretroviral drugs including: Reverse transcriptase inhibitors [24], HIV fusion inhibitor [48], CCR5 receptor antagonist class [37] and Protease inhibitors [40].

The Interleukin-2 [32, 34] is one of the chemical signals used by immune cells to communicate. This cytokine plays a role in the activation and the proliferation of healthy $CD4^+$ T-cells that are the target cells for HIV virus. The Interleukin-2 is currently used in addition to the antiretroviral therapy (HAART) for increasing the natural immunity of HIV patients. Indeed, the HAART controls the replication of the virus in the blood and IL-2 helps to regenerate more healthy $CD4^+$ T-cells causing effectively the maturation and the proliferation of target immune cells.

In this work, an optimal control approach with free terminal time is proposed for the treatment of HIV infection during an optimal therapeutic period. This approach is based on the introduction of two optimal controls characterizing a combination treatment using both HAART and IL-2 immunotherapy. A free terminal time optimal tracking control problem [3, 27, 28, 41, 46, 47] is formulated by defining a suitable objective function that summarizes the main objectives of the adopted treatment strategy. The corresponding optimality system is expanded to include the necessary condition on free terminal time. However, the Pontryagin maximum principle [17, 44, 45] is used to characterize the formulation of optimal controls. Finally, for the numerical resolution of the optimality system with the additional transversality condition for the terminal time, an adapted iterative method known as the Forward backward sweep method (FBSM) [33, 38]is implemented using a Runge-Kutta [33] fourth order scheme and a gradient method routine [3].

This paper is organized as follows: Section 2 describes the mathematical control model of HIV treatment using a combination treatment of both HAART and IL-2 immunotherapy. The analysis of the free terminal time optimal tracking control problem is also presented in the same section. In section 3, the iterative method is introduced and the numerical simulations are discussed. Finally, the results of this therapeutic approach are explored in the conclusion in section 4.

2. Mathematical model

2.1. Presentation of the treatment model

In this section, a system of ordinary differential equations modeling the treatment of HIV infection is presented. The adopted therapeutic approach is based on the introduction of a treatment strategy using combination of both Highly active antiretroviral therapy (HAART) and IL-2 immunotherapy with tolerated doses. The basic HIV dynamics model was originally discussed by Roy et al. in [50] and the control model providing optimal treatment strategies has been studied in [20].

The HIV dynamics model [50] explores the possible interactions between immune cells and HIV-producing cells in the presence of appropriate therapeutic agents. The obtained biological results have provided a better understanding of dynamics and behavior of the immune system, especially after stimulation of CTL cells that are produced after a maximum proliferation of $CD4^+$ T-cells, which ultimately enables to design the biological reasons that led to such a reaction of the immune system [42, 43, 56, 57].

Note with interest that it has been proven that results from mathematical analysis of the model is fully compatible with clinical and experimental

observations. In addition, it was verified analytically that this system is globally asymptotically stable under specific conditions [50].

The main purpose of this work [50] is the development of an adequate mathematical framework which must be consistent with medical experiments and biological observations in order to provide thereafter a set of optimal therapeutic strategies for the treatment of HIV infection. Clinical findings from biological results of treatment strategies that exploit antiretroviral therapy using Lamivudine and Zidovudine show that these treatment strategies enable reducing the viral load (10 *to* 100 %) and allow increasing the concentration of healthy $CD4^+$ T-cells by almost 25 %, provided that the treatment duration must exceed one year [42, 43, 58].

Since this study is interested primarily in the possible biological changes resulting from the introduction of an appropriate treatment in the equilibrium state [50], the mathematical analysis shows that any state variable relating to the dynamics of HIV particles can be omitted [50], which explains the absence of any specific compartment that characterizes the evolution of HIV concentration in the studied model.

However, it should be noted that it was necessary to introduce in this same mathematical model, a new state variable $z(t)$ that describes the behavior and models the dynamics of CTL cells during HIV infection [50]. Three compartments characterizing the different biological populations are defined as follows: $x(t)$ the uninfected $CD4^+$ T-cells, $y(t)$ the infected $CD4^+$ T-cells and $z(t)$ the immune response measured by the rate of the cytotoxic T-cells (CTL). Therefore, the mathematical control model representing the immune system dynamics in presence of appropriate treatments is governed by the following equations:

$$\begin{aligned}
\frac{dx}{dt} &= \lambda + px(1-\frac{x}{T_m}) - dx - (1-u_1)\beta xy \\
&\quad +u_2 x, \\
\frac{dy}{dt} &= (1-u_1)\beta xy - ay - lyz, \\
\frac{dz}{dt} &= sy - bz.
\end{aligned} \tag{1}$$

where $X(t) = \begin{pmatrix} x(t) \\ y(t) \\ z(t) \end{pmatrix}$ is the state vector and $u(t)=(u_1(t),u_2(t))$ is the control function which describes the medication used for the treatment of HIV infection. For biological specificities characterizing the HIV infection at AIDS stage, the initial values estimations assigned to state variables of the system (1) are measured in units of cells $mm^{-3}day^{-1}$ [50] and verify [16, 26] at $t = 0$:

$$x_0 = 50, \quad y_0 = 50, \quad z_0 = 2. \tag{2}$$

Note that $u_1(t)$ represents the HAART control function which inhibits the viral production in order to reduce the number of infected $CD4^+$ T-cells. It is important to observe that the parameter β represents both rates of infection and viral replication, which explains the choice of introduction of control u_1. The values of $u_1(t)$ vary between 0 if no treatment is used and 1 if totally effective HAART therapy is exploited.

However, $u_2(t)$ represents the IL-2 immunotherapy control function that stimulates immune cells and restores the immune response. The Interleukin-2 is administered to patients with HIV by daily injections following a continuous process for an optimal immunotherapy period where $u_2(t) = \alpha = 0.003$ is the maximum tolerated dose (MTD) [25, 30] producing the desired effect without unacceptable toxicity.

The descriptions of parameters used in the state system (1) are ranged in the table (1). Notice that the experimental observation period is fixed $T = 600$ days [50] and the main objective of this study is to find the optimal duration of treatment T^* which allows to reach all goals set in the optimal control problem.

Note with interest that the scientific works [15, 21] present results of an optimal control approach which aims to introduce a notion of isoperimetric constraint representing the exact total amount of immunotherapy that could be administered to the patient during the treatment period reducing subsequently the total cost of therapy. Furthermore, the biological results observed during the discontinuous administration of immunotherapeutic agents to patients, following a pulse vaccination process, are the subject of a recent study [52] presenting an optimal control problem with a view to suggesting optimal treatment strategies.

Finally, in the presence of an additional initial pathogen concentration, the enhancement of immune response via immunotherapy was adopted using a neighboring optimal control approach in order to restore the optimality conditions of control system [22].

Table 1. The parameters descriptions [50].

Parameters	Descriptions
λ	Production rate of healthy $CD4^+$ T cells
β	Infection rate and viral replication rate
d	Natural mortality rate of healthy $CD4^+$ T cells
p	Maximum proliferation rate of healthy $CD4^+$ T cell
a	Natural mortality rate of infected $CD4^+$ T cells
l	Mortality rate of virus-producing cells by CTL cells
s	Production rate of CTL cells
b	Natural mortality rate of CTL cells
T_m	Number of $CD4^+$ T cells after a maximum proliferation

2.2. The optimal control problem

A free terminal time optimal tracking control problem is formulated in order to propose an optimal therapeutic schedule for an optimal treatment duration. For that purpose, an objective function is defined as follows:

$$\begin{aligned} J(u_1,u_2,T) &= \frac{1}{2}\int_0^T x^2(t)+z^2(t)-y^2(t) \\ &\quad -A_1u_1^2(t)-A_2u_2^2(t)dt, \end{aligned} \tag{3}$$

where the positive parameters $A_1 \geq 0$ and $A_2 \geq 0$ balance the terms size and characterize weight factors which are based on benefits and costs of the treatment.

The principal aim of this therapeutic strategy suggested for the treatment of HIV infection is to maximize the benefit based on the count of healthy CD4$^+$ T-cells and CTL immune cells while minimizing the number of infected CD4$^+$ T-cells and the concentration of infectious HIV population allowing thereafter to minimize the harmful side effects and costs based on the percentage effect of HAART and IL-2 immunotherapy given (i.e. u_1^* and u_2^*).

All elements constituting the objective function (3) are quadratic to ensure a better homogeneity of optimal control problem. Note with interest that the optimal duration T^* of the treatment program is also considered. Mathematically, the optimal controls $(u_1^*, u_2^*) \in U$ are sought such that:

$$J(u_1^*,u_2^*,T^*) = \max J(u_1,u_2,T), \tag{4}$$

Over the control set U defined as follows: $U = U_1 \times U_2$ where

$$U_1 = \{u_1 \ continuous, 0 \leq u_1(t) \leq 1, t \in [0,T]\},$$

and

$$U_2 = \{u_2 \ continuous, 0 \leq u_2(t) \leq \alpha, t \in [0,T]\}.$$

Notice that the scientific work [14] dealing with an optimal control problem has outlined the study results of a same objective function $J(u)$, presenting initially a quadratic cost and subsequently a linear cost [14].

The control system (1) is rewritten implicitly as follows:

$$\begin{aligned} &X^{'}(t) = f(t,X(t),u_1(t),u_2(t)), \\ &X(0) = X_0 \quad given. \end{aligned} \tag{5}$$

where $X(t) = \begin{pmatrix} x(t) \\ y(t) \\ z(t) \end{pmatrix}$ is the state vector and $u(t) = (u_1(t), u_2(t))$ is the control pair. Thus, the objective function (3) is implicitly defined at control $u(t) = (u_1, u_2)$ as follows:

$$\begin{aligned} J(u_1,u_2,T) &= \int_0^T g(t,X(t),u_1(t),u_2(t))dt \\ &\quad +\theta(T,X(T)), \end{aligned} \tag{6}$$

Consider the optimal control problem:

$$\begin{aligned} &\max \int_0^T g(t,X(t),u_1(t),u_2(t))dt + \theta(T,X(T)), \\ &subject\ to\ X^{'}(t) = f(t,X(t),u_1(t),u_2(t)), \\ &where\ X(0) = X_0\ given, \end{aligned} \tag{7}$$

The corresponding adjoint system is expressed as follows:

$$\begin{aligned} \psi'(t) &= -g_X(t,X(t),u_1(t),u_2(t)) \\ &\quad -\psi f_X(t,X(t),u_1(t),u_2(t)), \\ &\quad where\ \psi(T^*) = \theta_X(T^*,X(T^*)), \\ &\quad and\ 0 \leq u_1(t) \leq 1\ and\ 0 \leq u_2(t) \leq \alpha. \end{aligned} \tag{8}$$

The Pontryagin's Maximum Principle [17, 44, 45] is used to determine the precise formulation of the optimal control pair $u^*(t) = (u_1^*(t), u_2^*(t))$.

In order to characterize the optimal control u^*, the Hamiltonian is defined from the formulation of cost function (3) as follows:

$$H(X,u,\psi) = g(t,X,u_1,u_2) + \psi f(t,X,u_1,u_2)$$

where $\psi(t) = \begin{pmatrix} \psi_1(t) \\ \psi_2(t) \\ \psi_3(t) \end{pmatrix}$ is the adjoint variable vector.

Explicitly:

$$\begin{aligned} H(X,u,\psi) &= \frac{1}{2} \times (x^2 + z^2 - y^2 \\ &\quad -A_1u_1^2 - A_2u_2^2) \\ &\quad +\psi_1[\lambda + px(1 - \frac{x}{T_m}) \\ &\quad -dx - (1-u_1)\beta xy + u_2x] \\ &\quad +\psi_2[(1-u_1)\beta xy - ay - lyz] \\ &\quad +\psi_3[sy - bz]. \end{aligned} \tag{9}$$

The existence of an optimal control solution is satisfied using a classical result of existence that was developed by Fleming in [17]. Indeed, the following properties have to be checked:

(1) The class of all initial conditions with controls u_1 and u_2 in the admissible control set $U = U_1 \times U_2$ along with state system equations (1) is not empty;

(2) The admissible control set U is convex and closed;

(3) The right-hand side of the state system is continuous, is bounded above by a sum of the bounded control and the state, and can be expressed as a linear function of controls u_1 and u_2 with coefficients depending on time and state.

(4) The integrand $g(t,X,u_1,u_2)$ of the objective functional $J(u,T)$ is concave on U;

(5) There exist positive constants $b_1,\ b_2 > 0$ and $\beta > 1$ such that the integrand of the objective functional $J(u,T)$ is bounded below by $g(t,X,u_1,u_2) \leq b_2 - b_1(|u_1|^2 + |u_2|^2)^{\frac{\beta}{2}}$;

(6) The payoff function $\theta(T,X(T))$ in the objective functional $J(u)$ is continuous at the terminal time T.

Proof. Since the system has bounded coefficients and any state system solution is bounded on a finite interval $[0,T]$ [5], a classical result established by Lukes [35] is used to prove the existence of solutions for the state system (1). The admissible control set U is convex and closed by definition.

The system (1) is bilinear in controls u_1 and u_2 and each right-hand side of this state system (1) is continuous since each term has a nonzero denominator and can be written as a linear function of controls u_1 and u_2 with coefficients depending on time and state.

Moreover, the fact that state variables x, y, z and controls u_1 and u_2 are bounded on time interval $[0,T]$ involves the rest of the third property. In order to verify that the integrand $g(t,X,u_1,u_2)$ in the objective functional (3) is concave on U, the following condition should be verified:

$$\begin{aligned} h(t,X,(1-\lambda)u_i + \lambda v_i) &\leq (1-\lambda)h(t,X,u_i) \\ &\quad +\lambda h(t,X,v_i) \end{aligned} \tag{10}$$

where

$$\begin{aligned} h(t,X(t),u_i(t)) &= -g(t,X(t),u_i(t)) \\ &= \frac{1}{2} \times (-x^2(t) - z^2(t) + y^2(t) \\ &\quad +A_iu_i^2(t)), \end{aligned} \tag{11}$$

This inequality (10) is rewritten in the following form:

$$\begin{aligned} \mathcal{A} &= h(t,X,(1-\lambda)u_i + \lambda v_i) - (1-\lambda)h(t,X,u_i) \\ &\quad -\lambda h(t,X,v_i) \leq 0 \end{aligned} \tag{12}$$

where $\lambda \in [0,1]$, $u_i, v_i \geq 0$ and with $i = 1,2$.

$$\begin{aligned}\mathcal{A} = \ & \frac{1}{2}A_i((1-\lambda)^2u_i^2-(1-\lambda)u_i^2+\lambda^2v_i^2-\lambda v_i^2\\ & +2\lambda(1-\lambda)u_iv_i)\\ & =\frac{1}{2}A_i(u_i^2((1-\lambda)^2-(1-\lambda))+v_i^2(\lambda^2-\lambda)\\ & +2\lambda(1-\lambda)u_iv_i)\\ & =\frac{1}{2}A_i(u_i^2(\lambda^2-\lambda)+v_i^2(\lambda^2-\lambda)\\ & -2(\lambda^2-\lambda)u_iv_i)\\ & =\frac{1}{2}A_i(\lambda^2-\lambda)(u_i^2+v_i^2-2u_iv_i)\\ & =\frac{1}{2}A_i(\lambda^2-\lambda)(u_i-v_i)^2\leq 0\end{aligned} \tag{13}$$

Since $\lambda \in [0,1]$, this implies that $\lambda \geq \lambda^2$. Thus, the inequality (10) is verified which proves that the integrand $g(t,X,u_1,u_2)$ is concave. Thus, since h is convex on $U \Longrightarrow g$ is concave on U. In addition, notice that there exists positive constants $b_1,\ b_2>0$ and $\beta>1$ satisfying:

$$\begin{aligned}g(t,X(t),u_1(t),u_2(t)) & \leq x^2(t)+z^2(t)-A_1u_1^2(t)\\ & -A_2u_2^2(t)\\ & \leq b_2-b_1(|u_1|^2+|u_2|^2)^{\frac{\beta}{2}}\end{aligned} \tag{14}$$

where the positive constant b_2 depends on the upper bounds on x and z and by analogy it would be appropriate to set b_1=$inf(A_1,A_2)$ and β=2.

If the control pair $u(t)=(u_1(t),u_2(t))$ and the corresponding state $X(t)$ are optimal, there exists an adjoint vector $\psi(t)$ such that the Hamiltonian $H(t,X,u_1,u_2,\psi)$ reaches its maximum on the set U at u^*,T^*. It ensues the following theorem:

Theorem 1. *Given an optimal control vector u^*=(u_1^*,u_2^*), an optimal terminal time T^*, and solutions of corresponding state system (1), there exists an adjoint vector ψ=[ψ_1, ψ_2, ψ_3] satisfying the following equations:*

$$\begin{aligned}\psi_1'(t) & =-x+\psi_1(\frac{2px^*}{T_m}+d-p-u_2^*)\\ & +\beta y^*(1-u_1^*)(\psi_1-\psi_2),\\ \psi_2'(t) & =y+\beta x^*(1-u_1^*)(\psi_1-\psi_2)\\ & +\psi_2(a+lz^*)-\psi_3 s,\\ \psi_3'(t) & =-z+\psi_2 l y^*+\psi_3 b.\end{aligned} \tag{15}$$

with final conditions

$$\psi_j(T)=0,\ j=1,2,3.$$

The transversality condition for the terminal time is defined as follows:

$$\begin{aligned}&\frac{1}{2}\times(x^2(t)+z^2(t)-y^2(t)-A_1u_1^2(t)\\ &-A_2u_2^2(t))=0\ at\ t=T^*\end{aligned} \tag{16}$$

Further, u_1^* and u_2^* are represented by:

$$\begin{aligned}&u_1^*(t)\\ &=\min(1,\max(0,\tfrac{\beta x^*(t)y^*(t)(\psi_1(t)-\psi_2(t))}{A_1})),\end{aligned} \tag{17}$$

and

$$u_2^*(t)=\min(\alpha,\max(0,\frac{x^*(t)\psi_1(t)}{A_2})). \tag{18}$$

Proof. Due to the existence of an optimal couple (X^*,u^*) which maximizes the objective function J subject to the state system (1), the adjoint equations can be obtained using Pontryagin's maximum principle [17, 44, 45] such that:

$$\begin{aligned}\psi_1' &= -\frac{\partial H}{\partial x},\\ \psi_2' &= -\frac{\partial H}{\partial y},\\ \psi_3' &= -\frac{\partial H}{\partial z}.\end{aligned} \tag{19}$$

The terminal time T variable of the objective function J (3) should be exploited to provide all necessary information concerning the optimal final time T^* [33]. For this, consider a real number $\sigma \geq -T^*$ in order that $T^*+\sigma$ is an admissible final time and $T^*+\sigma \in \mathbb{R}^+$.

Note that the corresponding state X^* and the control function u^* are considered on an interval larger than $[0,T^*]$ [33]. Suppose that u^* is

left-continuous at T^*, then set $u^*(t) = u^*(T^*)$ for all $t > T^*$ in order that u^* is continuous at T^*. Now, x^* and z^* are also defined for $t > T^*$. As $J(u_1, u_2, T)$ reaches its maximum at $u^* = (u_1^*, u_2^*)$,T^*, the following equality is established [33]:

$$0 = \lim_{\sigma \to 0} \frac{J(u^*, T^* + \sigma) - J(u^*, T^*)}{\sigma}, \tag{20}$$

Hence,

$$\begin{aligned} 0 &= \lim_{\sigma \to 0} [\int_0^{T^*+\sigma} g(t, X^*(t), u^*(t))dt \\ &+\theta(T^* + \sigma, X^*(T^* + \sigma)) \\ &- \int_0^{T^*} g(t, X^*(t), u^*(t))dt - \theta(T^*, X^*(T^*))]. \end{aligned} \tag{21}$$

$$\begin{aligned} 0 &= \lim_{\sigma \to 0} [\int_0^{T^*+\sigma} g(t, X^*(t), u^*(t))dt \\ &+\theta(T^* + \sigma, X^*(T^* + \sigma)) \\ &- \int_0^{T^*} g(t, X^*(t), u^*(t))dt - \theta(T^*, X^*(T^*))] \\ &= \lim_{\sigma \to 0} \int_{T^*}^{T^*+\sigma} g(t, X^*(t), u^*(t))dt \\ &+\frac{\theta(T^* + \sigma, X^*(T^* + \sigma)) - \theta(T^*, X^*(T^*))}{\sigma} \\ &= g(T^*, X^*(T^*), u^*(T^*)) + \theta_t(T^*, X^*(T^*)) \\ &+\theta_X(T^*, X^*(T^*))\frac{X^*}{dt}(T^*) \\ &= g(T^*, X^*(T^*), u^*(T^*)) \\ &+\psi(T^*)f(T^*, X^*(T^*), u^*(T^*)) \\ &+\theta_t(T^*, X^*(T^*)) \\ &= H(T^*, X^*(T^*), u^*(T^*), \psi(T^*)) \\ &+\theta_t(T^*, X^*(T^*)). \end{aligned} \tag{22}$$

Taking into account that $\theta_t(T^*, X^*(T^*)) = 0$ and $\psi_j(T) = 0 \; for \; j = 1, 2, 3$. Thus, the transversality condition (16) for the terminal time is obtained.

Since controls $u_1(t)$ and $u_2(t)$ are bounded, the optimal controls u_1^* and u_2^* can be solve from the following optimality conditions:

$$\frac{\partial L}{\partial u_1} = 0 \; and \; \frac{\partial L}{\partial u_2} = 0.$$

In order to find the characterization of optimal controls (17) and (18), the Lagrangian L is used and defined as follows:

$$L = H + \omega_{11}(1 - u_1) + \omega_{12}u_1 + \omega_{21}(\alpha - u_2) + \omega_{22}u_2 \tag{23}$$

where ω_{11}, ω_{12}, ω_{21}, $\omega_{22} \geqslant 0$ are the penalty multipliers which ensure the boundedness of controls $u_1(t)$ and $u_2(t)$ and satisfy the two following conditions [5, 27]:

$$\begin{aligned} \omega_{11}(1 - u_1^*) &= \omega_{12}u_1^* = 0 \; at \; u_1 = u_1^*, \\ \omega_{21}(\alpha - u_2^*) &= \omega_{22}u_2^* = 0 \; at \; u_2 = u_2^*. \end{aligned} \tag{24}$$

The maximization problem (4) is redefined as follows:

$$\begin{aligned} &L(T^*, X^*, u_1^*, u_2^*, \psi, \omega_{ij}) \\ &= \max L(T, X^*, u_1, u_2, \psi, \omega_{ij}) \end{aligned} \tag{25}$$

Differentiating the Lagrangian L with respect to u_1 on the set $U_1 : \{t \mid 0 \leq u_1(t) \leq 1\}$ allows to obtain the following optimality equation:

$$\frac{dL}{du_1} = -A_1u_1 + \beta xy(\psi_1 - \psi_2) - \omega_{11} + \omega_{12} = 0$$
at $u_1 = u_1^*$.

Thus, the control is expressed:

$$u_1^*(t) = \frac{\beta x^*(t)y^*(t)(\psi_1(t) - \psi_2(t)) - \omega_{11} + \omega_{12}}{A_1}$$

According to the conditions (24), three cases are distinguished:

$\star$ if $0 < u_1^*(t) < 1$ then $w_{11} = w_{12} = 0$. Therefore, the control is expressed as follows:

$$u_1^*(t) = \frac{\beta x^*(t)y^*(t)(\psi_1(t) - \psi_2(t))}{A_1}$$

$\star$ if $u_1^*(t) = 0$ then $w_{11} = 0$. Therefore, the control is expressed as follows:

$$u_1^* = \frac{\beta xy(\psi_1 - \psi_2) + \omega_{12}}{A_1} = 0$$
$$\Longrightarrow \omega_{12} = A_1u_1 - \beta xy(\psi_1 - \psi_2).$$

Knowing that $\omega_{12}(t) \geq 0$ and $A_1 > 0$, the control

is expressed as follows:

$$u_1^* = 0 \leq \beta xy(\psi_1 - \psi_2) \leq \frac{\beta xy(\psi_1 - \psi_2)}{A_1}$$

$\star$ if $u_1^*(t) = 1$ and $w_{12}(t) = 0$ then the control is expressed as follows:

$$u_1^* = \frac{\beta xy(\psi_1 - \psi_2) - \omega_{11}}{A_1} = 1$$
$$\Longrightarrow \omega_{11}(t) = -A_1 u_1 + \beta xy(\psi_1 - \psi_2).$$

Given that $w_{11}(t) \geq 0$ and $A_1 > 0$, the control is expressed as follows:

$$u_1^* = 1 \geq \frac{\beta xy(\psi_1 - \psi_2)}{A_1}$$

Combining these three results, the optimal control $u_1^*(t)$ is characterized as follows:

$$\begin{aligned} u_1^*(t) &= \frac{\beta xy(\psi_1 - \psi_2)}{A_1} \quad if\ 0 < \frac{\beta xy(\psi_1 - \psi_2)}{A_1} < 1, \\ u_1^*(t) &= 0 \qquad\qquad if\ \frac{\beta xy(\psi_1 - \psi_2)}{A_1} \leq 0, \\ u_1^*(t) &= 1 \qquad\qquad if\ \frac{\beta xy(\psi_1 - \psi_2)}{A_1} \geq 1. \end{aligned} \tag{26}$$

Thus, the optimal control $u_1^*(t)$ is formulated as follows:

$$u_1^*(t) = min(max(0, \frac{\beta x^*(t) y^*(t)(\psi_1(t) - \psi_2(t))}{A_1}, 1))$$

Differentiating the Lagrangian L with respect to u_2 on the set $U_2 : \{t \mid 0 \leq u_2(t) \leq \alpha\}$ allows to obtain the following optimality equation:

$$\frac{dL}{du_2} = -A_2 u_2 + \psi_1 x - \omega_{21} + \omega_{22} = 0 \text{ at } u_2 = u_2^*.$$

Thus, the control is expressed as follows:

$$u_2^*(t) = \frac{\psi_1 x - \omega_{21} + \omega_{22}}{A_2}$$

According to the conditions (24), three cases are distinguished:

$\star$ if $0 < u_2^*(t) < \alpha$ then $w_{11} = w_{12} = 0$. Therefore, the control is expressed as follows:

$$u_2^*(t) = \frac{\psi_1(t) x^*(t)}{A_2}$$

$\star$ if $u_2^*(t) = 0$ then $w_{11} = 0$. Therefore, the control is expressed as follows:

$$u_2^* = 0 = \frac{\psi_1 x + \omega_{22}}{A_2}$$
$$\Longrightarrow \omega_{22} = A_2 u_2 - \psi_1 x.$$

Knowing that $\omega_{22}(t) \geq 0$ and $A_2 > 0$, the control is expressed as follows:

$$u_2^* = 0 \leq \frac{\psi_1(t) x}{A_2}$$

$\star$ if $u_2^*(t) = \alpha$ and $w_{12}(t) = 0$, then the control is expressed as follows:

$$u_2^* = \alpha = \frac{\psi_1 x - \omega_{21}}{A_2}$$
$$\Longrightarrow \omega_{21}(t) = \psi_1 x - A_2 u_2.$$

Given that $w_{21}(t) \geq 0$ and $A_2 > 0$, the control is expressed as follows:

$$u_2^* = \alpha \geq \frac{\psi_1(t) x}{A_2}$$

Combining these three results, the optimal control $u_2^*(t)$ is characterized as follows:

$$\begin{aligned} u_2^*(t) &= \frac{\psi_1 x}{A_2} \quad if\ 0 < \frac{\psi_1 x}{A_2} < \alpha, \\ u_2^*(t) &= 0 \qquad if\ \frac{\psi_1 x}{A_2} \leq 0, \\ u_2^*(t) &= \alpha \qquad if\ \frac{\psi_1 x}{A_2} \geq \alpha. \end{aligned} \tag{27}$$

Thus, the optimal control $u_2^*(t)$ is formulated as follows:

$$u_2^*(t) = min(max(0, \frac{\psi_1 x^*(t)}{A_2}, \alpha))$$

3. Numerical simulations

3.1. Model parameters

The main purpose of the theoretical analysis developed by Roy et al. [50] was intended to explore the equilibrium of dynamical system and to study the various aspects of the stability of solutions in order to determine the threshold values of studied model parameters for which the disease can be controlled.

In this sense, any optimal control approach elaborated for the studied dynamical model and which aims to provide treatment strategies for

the HIV infection, should absolutely explore the equilibria and consider the theoretical results of stability analysis [50], which implies respecting the established conditions and constraints that characterize the different model parameters, thus allowing to define specific parametric regions where the equilibrium is locally or globally stable.

Indeed, the standard values of parameters [50] have been chosen in the context of this theoretical analysis in order to observe the particular dynamical behavior of state variables x, y and z with the threshold values that enable controlling the disease from a well-defined initial state ($x(0) = 50$, $y(0) = 50$, and $z(0) = 2$). Note with interest that analytical study and numerical resolution of the system have been developed entirely on the basis of these model parameters set to their standard values [50].

Subsequently, studying the influence of model parameters, allowed to observe the impact of these parameters on the dynamical behavior of state variables. The stability analysis shows that for the positive equilibrium of the dynamical system, the disease can only be controlled if the parameter p (Proliferation constant rate of $CD4^+$ T-cells) is greater than the parameter d (Death rate of Uninfected $CD4^+$ T-cells) [50].

Moreover, it is observed that if the parameter p increases, we note a considerable growth in the concentration of immune cells (Healthy $CD4^+$ T-cells and CTL immune cells) and we notice a significant decrease of oscillations characterizing the evolution of the state variables that manage to converge more quickly to their respective equilibrium states [50].

The study also allows to note that increasing of the parameter value β $(0,0008$ to $0,01)$ denoting the rate of infection, causes a development of the HIV infection followed by a rise in the number of CTLs and a substantial decline in the concentration of healthy $CD4^+$ T-cells [50].

However, we note that any increase of parameters k $(0,001$ to $0,005)$ and s $(0,01$ to $0,05)$ implies a significant growth in the count of active immune cells (Healthy $CD4^+$ T-cells and CTL immune cells) and an important decrease in the level of virus producing cells [50]. In addition, the theoretical analysis enables to determine a specific stability criteria of the equilibrium in the parametric space of β, p and k [50].

Finally, it is clear that the possibility of proposing a control approach for the treatment of HIV infection requires the exploitation of numerical results obtained in this analytical study.

Therefore, since the main purpose of this study is to use optimal control theory in the context of a free terminal time optimal tracking control problem which should be coherent and compatible with the parametric conditions obtained analytically in [50], in order to suggest an optimal strategy for the treatment of HIV infection during an optimal therapeutic period, the basic parameters set to their standard values and found in [4, 12, 42, 50, 56] are kept and it is stated that the stability properties [50] of the state system (1) are stored for these parameters which are rearranged in the table (2).

Table 2. The standard parameter values [50].

Parameters	Values
λ	10 $mm^{-3}day^{-1}$ [12, 42]
β	0.002 $mm^{-3}day^{-1}$ [4]
d	0.01 day^{-1} [42]
p	0.03 day^{-1} [42, 56]
a	0.024 day^{-1} [12]
l	0.001 $mm^{-3}day^{-1}$ [4]
s	0.2 day^{-1} [4]
b	0.02 day^{-1} [4]
T_m	1500 mm^{-3} [42, 56]

3.2. Numerical method

Various numerical methods are used to solve the optimality system and find an optimal solution for controls u_1 and u_2 [10, 55]. In this work, an iterative method known as the Forward-Backward sweep method (FBSM) [33, 38] is developed using a Runge-Kutta [33] fourth order scheme in order to characterize numerical solutions for the optimality system resulting from the studied free terminal time optimal tracking control problem (4).

The general principle of this numerical method is that from an initial guess for the control variables u_1 and u_2 and terminal time T, the state system (1) with initial conditions is solved forward in time and subsequently the adjoint system (15) with terminal conditions is solved backward in time. Taking into account the nature of the optimal control problem with free terminal time (4), a specific numerical technique is considered for the numerical resolution of the optimality system.

Indeed, an adapted iterative Forward backward sweep method is extended using a gradient algorithm with the Formulae of sensitivity to change of end-time [3] view to finding the optimal solutions u_1^*,u_2^* and T^* while considering the transversality condition for the terminal time (16).

This numerical resolution process comprises a number of numerical computation techniques summarized in the algorithm given below. Here the vector approximations for state variable $\vec{X}$=(X^1,...,X^{N+1}) and adjoint variable $\vec{\psi}$=(ψ^1,...,ψ^{N+1}).

Algorithm

Step 0:
. Make an initial guess for the terminal time T;
. Make an initial guess for the controls $\vec{u_1}$ and $\vec{u_2}$ over the time interval;

Step 1:
. Solve the state system (1) with initial conditions X^1=$X(0)$ forward in time using the stored values for the controls $\vec{u_1}$ and $\vec{u_2}$;

Step 2:
. Solve the adjoint system (15) with terminal conditions ψ^{N+1}=$\psi(T)$ backward in time using the stored values for the controls $\vec{u_1}$ and $\vec{u_2}$ and the state variable $\vec{X}$;

Step 3:
. Update the controls $\vec{u_1}$ and $\vec{u_2}$ using by the Forward backward sweep method;
. Update the terminal time by the gradient method defined as follows:

$$\begin{aligned} &T_{i+1} \\ &= T_i - h[H(T_i, X_i(T_i), \psi_i(T_i), u_{1_i}(T_i), u_{2_i}(T_i)) \\ &-\nabla J(T_i, X_i(T_i))], \end{aligned} \tag{28}$$

for $i = 1, .., n$ with h is a small positive constant,

. Test the convergence: If the difference of values of these variables in this iteration and the last iteration is sufficiently small, output the obtained current values as solutions. If the difference is not considerably small, go to Step 1.

3.3. Numerical results

The estimates of initial values assigned to the state variables at time $t = 0$ (2) and specifically the number of healthy CD4$^+$ T-cells which is far below than 200 cell units, indicate that the disease has reached the AIDS stage [16].

This biological phase of HIV infection is generally characterized by the progressive weakening of the immune system and the occurrence of various anomalies and opportunistic diseases [26]. Without therapeutic intervention, the state variables converge logically to their respective equilibrium points [20, 50]. The concentration of healthy CD4$^+$ T-cells after an observation period which lasts 600 days shows that the immune system is weak and defective and the general condition of the HIV patient is clearly deteriorated [20].

However, introducing a treatment strategy using both highly active antiretroviral therapy and IL-2 immunotherapy provides biological results which are satisfactory and especially promising (Figures 1, 2 and 3). Indeed, at the end of an observation therapeutic period of 600 days, the treatment effectively helps to maximize the number of healthy CD4$^+$ T-cells which reached 1400 cell units (Figure 1).

Similarly, the infection level has gradually decreased and the number of infected CD4$^+$ T-cells has achieved values lower than 5 units towards the end of the therapeutic period (Figure 3). Henceforth, the immune system makes full use of its defensive function and the immune response reacts actively to the evolution of the HIV infection: Any increase in the concentration of infected cells is followed immediately by a considerable proliferation of CTL immune cells (Figure 3).

However, it was observed that the count of immune cells which are stimulated for the immune response has naturally decreased after the minimization of the viral load thereby reducing the side effects resulting from a prolonged maximization of the immune cells level (Figure 3).

Considering the shape and the behavior of the optimal controls u_1^* and u_2^* (Figures 4 and 5) during the optimal duration of treatment, it is noted with interest that the therapeutic process has adopted an appropriate treatment approach which takes into consideration the progression of HIV infection and the development of infected cells in order to achieve the objectives of the optimal control problem (4).

Compared to the initial observation period lasting 600 days, this free terminal time optimal tracking control problem (4) situated within the

framework of a treatment strategy of HIV infection, has allowed to find an optimal terminal time T^* (Figure 6) satisfying the transversality condition (16) and has enabled to define an optimal treatment duration of 512 days, ensuring therefore a more consequent reduction of the overall cost of treatment and a minimization of the side effects resulting from the adopted therapy.

In fact, from the optimal terminal time T^*, it is observed that even after stopping the treatment process, the optimality conditions remain satisfied (Figures 1, 2 and 3), allowing subsequently to generate an important increase in the level of healthy $CD4^+$ T-cells (Figure 1) and a large reduction of infection level (Figure 2). Finally, for testing the effectiveness of the treatment approach which is adopted in this study, a new terminal time is fixed $T = 500$ days with the aim of finding a new optimal terminal time T^* able to further reduce the treatment duration and thereby allowing to further minimize the overall cost of treatment.

However, it is noticed that the obtained biological results (Figures 7, 8 and 9) show that this new therapeutic approach has not achieved the key objectives defined in the optimal control problem (4). Although the number of healthy $CD4^+$ T-cells is significantly important during the treatment period (Figure 7), the gradual reduction of the controls concentration in the last 30 days of the treatment period generates a substantial increase in the level of infected $CD4^+$ T-cells (Figure 8).

Moreover, despite a maximum stimulation of CTL immune cells (Figure 9), the HIV infection remains unstable and the concentration of infected $CD4^+$ T-cells increases abruptly just before the end of treatment, which explains the inability of the immune system that fails to limit the HIV infection progression and to restrict the action of the HIV particles. These recent observations prove the efficiency of the initial optimal control approach with free terminal time T^* for the treatment of HIV infection in an optimal duration which lasts 512 days.

Using standard parameter values given in table (2) [50], the behavior of the state variables has been observed in the presence of the natural immune response and without the intervention of any specific therapy. Indeed, the state variables converge respectively towards their equilibrium states [20, 50].

However, from a biological point of view, despite the weak growth in the level of immune cells and the limited reduction in viral load, this equilibrium state fails to reach the expected biological objectives since the concentration of healthy $CD4^+$ T-cells is still low and the general condition of the HIV patient remains critical [26]. By exploiting the different results of the study conducted by Roy et al. [50], the interest of adopting an appropriate therapeutic strategy for treatment of the HIV infection is well confirmed, thereby justifying the introduction of the control u_1 that limits the growth of the parameter β in order to reduce the level of infection and viral load and the control u_2 that stimulates the proliferation of active immune cells. Finally it is important to note that the effectiveness of drug used in the treatment process is assumed to be fully controlled by drug dose level.

The continuous character [6, 13, 29, 30, 33] of optimal solutions u_1^* and u_2^* (Figures 4 and 5) is essentially acquired from the definition of the admissible control set U. This continuity aspect characterizing the controls u_1 and u_2 permits theoretically to find optimal solutions that achieve the objectives set in the optimal control problem, thus enabling to provide a general profile of therapeutic strategies to be adopted with a view to treating the HIV infection (Figures 4 and 5).

For clinical tests and trials, the treatment strategies relating to the optimal controls u_1^* and u_2^* that are represented by continuous functions would be difficult to implement from a practical point of view. As part of an optimal control problem presenting an objective function with linear control, the optimal control may just take the extreme constant values (The solution is of the bang-bang type) [33] provided that it is possible to prove the absence of singular arcs [33].

However, the problem studied in this work defines a quadratic objective function in order to ensure more consistency to the optimal control problem by minimizing the contributions of small variations [53]. Hence the interest to provide functions approaching the optimal solutions and which are much easier to prescribe practically in the context of the adopted treatment strategy.

At first, the curves illustrating the evolution of optimal controls u_1^* and u_2^* were fitted [2] with the aim of reducing the irregularities and the singularities characterizing these curves (Figures 10,11,20 and 21) and thus enabling to mitigate the observed disturbances. Then, on the basis of obtained results, piecewise constant functions are defined to characterize the control functions u_1 and u_2 (Figures 10,11,20 and 21).

The impact of applying these new treatment regimens $u_1^{'}$ and $u_2^{'}$ (Figures 10 and 11) on the behavior of the state variables is observed by illustrating graphically the evolution of the variables x, y and z using the two types of control functions (Figures 12,13 and 14). Over an observation period of 600 days, although the results of the optimal treatment strategy are better than those obtained with piecewise constant control functions, the treatments $u_1^{'}$ and $u_2^{'}$ (Figures 10 and 11) allow to obtain satisfactory biological results and manage to reach all objectives of optimal control problem.

Indeed, using constant control functions modeling the adopted treatment, the healthy $CD4^+$ T-cells follow an increasing evolution. The proliferation peak occurs around the 600^{th} day by reaching the count of 1320 cell units (Figure 12). Similarly, the immune response is active allowing the stimulation of immune cells thus generating a significant proliferation of the CTL immune cells (Figure 14) when the viral load is growing. The infection is reduced considerably and the concentration of virus producing cells reaches very low levels towards the end of the observation period (Figure 13).

A number of scientific works [29, 30, 33] show that the administration of a treatment strategy during early stages of the HIV infection is more beneficial for the therapeutic process. For example, the immunotherapy adopted in an earlier stage increases the levels of healthy $CD4^+$ T-cells [29, 30].

In this respect, we use numerical data suggested in the scientific work developed by Butler et al. [6] and which characterizes a new initial state corresponding to a clinical case presenting an infection appeared since only 74 days ($x(0) = 494.3$ and $y(0) = 0.04$) [6]. During this stage of the disease which is known as the Acute HIV syndrome that precedes the stage of clinical latency, we note a wide spread of the virus particles in the body and a replication of HIV in lymphoid organs.

Indeed, towards the 20^{th} day of treatment, a severe increase in the concentration of infected $CD4^+$ T-cells is observed due to the biological resistance of these virus producing cells to the introduction of therapeutic agents involved in the treatment process (Figure 16). The stimulation of cells involved in immune response (Figure 17) and the action of optimal controls (Figures 18 and 19), allow to reduce the viral load in the short term from the 23^{th} day (Figure 16). The level of infection is stabilizing from the 200^{th} day.

Furthermore, the count of infected $CD4^+$ T-cells reached values below 10 cell units from the 420^{th} day of treatment (optimal final time T^* (Figure 22)) and it eventually reached values below 2 cell units towards the end of the observation period (Figure 16). In addition, we note a gradual growth in the number of healthy $CD4^+$ T-cells from the 30^{th} day, thus enabling to reach a count of 1492 cell units by the end of the clinical observation period (Figure 15).

Finally, note with interest that the introduction of an appropriate treatment strategy at an early stage of HIV infection has achieved all the objectives set in the optimal control problem thereby allowing to further stimulating the immune cell proliferation (Figures 15 and 17) and reducing the viral load (Figure 16) while minimizing the optimal treatment duration (Figure 22).

Compared to the first studied case ($x(0) = 50$, $y(0) = 50$, $z(0) = 2$), the optimal treatment duration was considerably minimized (T^*=420 days) (Figure 22) and the concentration of controls used in the therapeutic process has decreased significantly (Figures 18,19,20 and 21).

The results obtained have helped to reduce side effects and overall costs of the adopted treatment leading to a marked improvement in the quality of life of HIV patients.

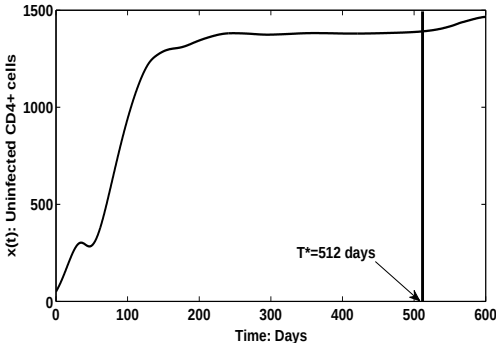

Figure 1. The state variable x with $x(0)$=50 units $mm^{-3}day^{-1}$, initial terminal time $T = 600$ days and optimal terminal time $T^* = 512$ days.

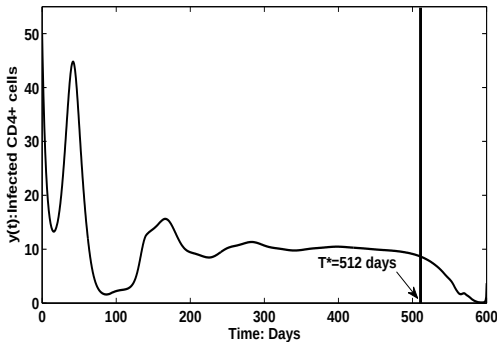

Figure 2. The state variable y with $y(0)$=50 units $mm^{-3}day^{-1}$, initial terminal time $T = 600$ days and optimal terminal time $T^* = 512$ days.

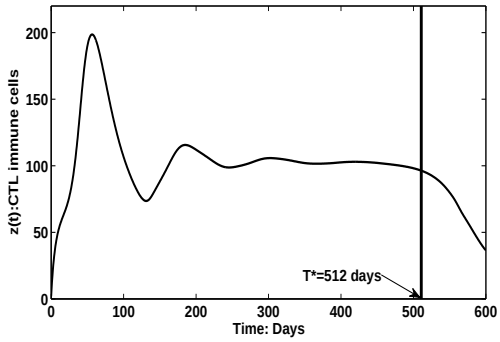

Figure 3. The state variable z with $z(0)$=2 units $mm^{-3}day^{-1}$, initial terminal time $T = 600$ days and optimal terminal time $T^* = 512$ days.

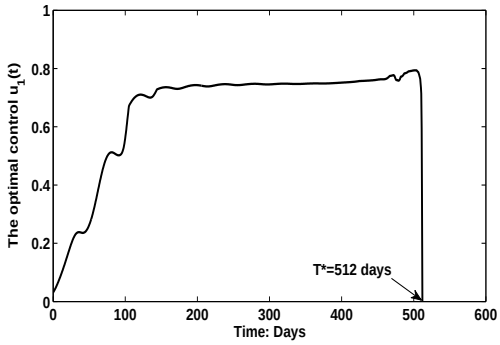

Figure 4. The optimal control $u_1^*(t)$ with $x(0)$=50 units $mm^{-3}day^{-1}$, $y(0)$=50 units $mm^{-3}day^{-1}$, $z(0)$=2 units $mm^{-3}day^{-1}$ and $T^* = 512$ days.

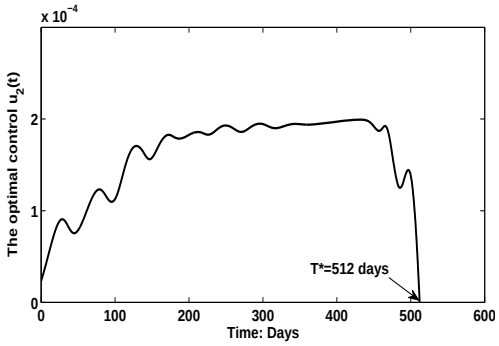

Figure 5. The optimal control $u_2^*(t)$ with $x(0)$=50 units $mm^{-3}day^{-1}$, $y(0)$=50 units $mm^{-3}day^{-1}$, $z(0)$=2 units $mm^{-3}day^{-1}$ and $T^* = 512$ days.

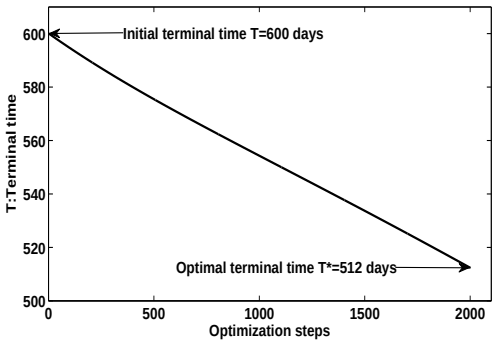

Figure 6. Estimation of optimal terminal time T^*, zero of ∇J with initial terminal time $T = 600$ days, $x(0)$=50 units $mm^{-3}day^{-1}$, $y(0)$=50 units $mm^{-3}day^{-1}$ and $z(0)$=2 units $mm^{-3}day^{-1}$.

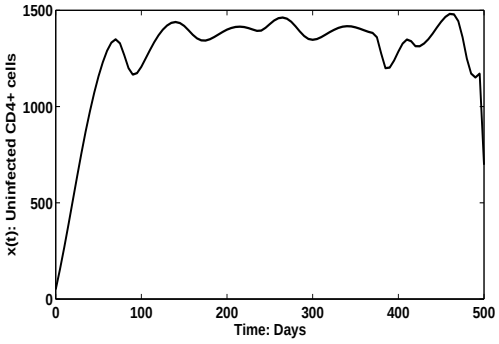

Figure 7. The state variable x with $x(0)$=50 units $mm^{-3}day^{-1}$ and terminal time $T = 500$ days.

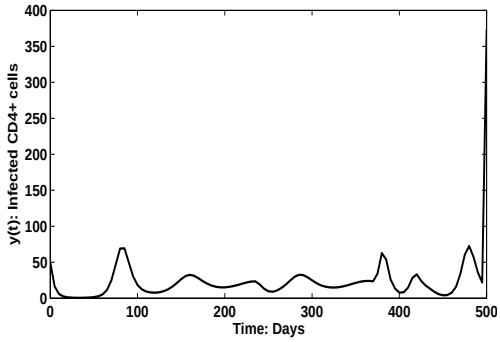

Figure 8. The state variable y with $y(0)$=50 units $mm^{-3}day^{-1}$ and terminal time $T = 500$ days.

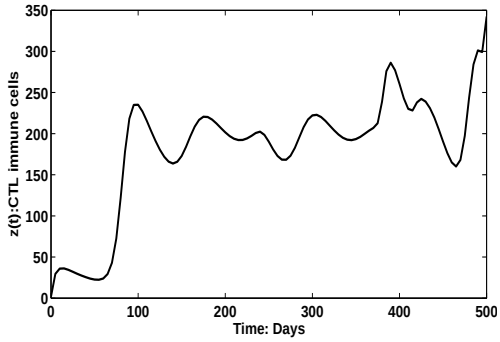

Figure 9. The state variable z with $z(0)$=2 units $mm^{-3}day^{-1}$ and terminal time $T = 500$ days.

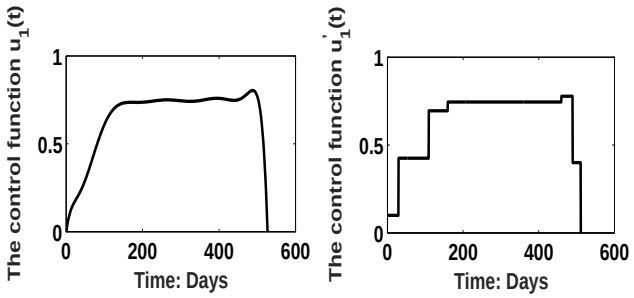

Figure 10. The profile fitting of the optimal control function $u_1^*(t)$ (Left) and the piecewise constant control function $u_1^{'}(t)$ (Right) with $x(0)$=50 units $mm^{-3}day^{-1}$, $y(0)$=50 units $mm^{-3}day^{-1}$, $z(0)$=2 units $mm^{-3}day^{-1}$ and $T^* = 512$ days.

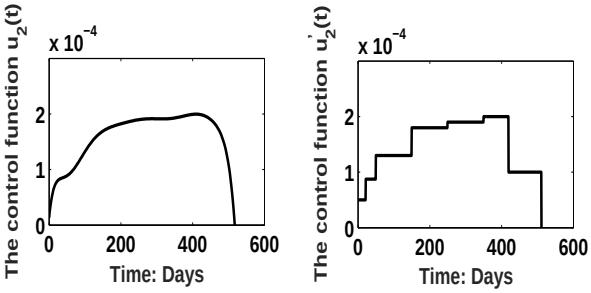

Figure 11. The profile fitting of the optimal control function $u_2^*(t)$ (Left) and the piecewise constant control function $u_2^{'}(t)$ (Right) with $x(0)$=50 units $mm^{-3}day^{-1}$, $y(0)$=50 units $mm^{-3}day^{-1}$, $z(0)$=2 units $mm^{-3}day^{-1}$ and $T^* = 512$ days.

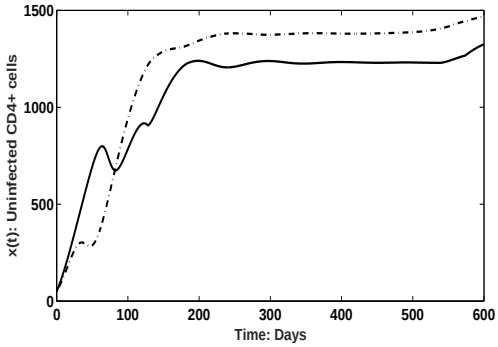

Figure 12. The state variable x using optimal controls $u_1^*(t)$ and $u_2^*(t)$ (DashDot) and using piecewise constant control functions $u_1^{'}(t)$ and $u_2^{'}(t)$ (Solid) with $x(0)$=50 units $mm^{-3}day^{-1}$, initial terminal time $T = 600$ days and optimal terminal time $T^* = 512$ days.

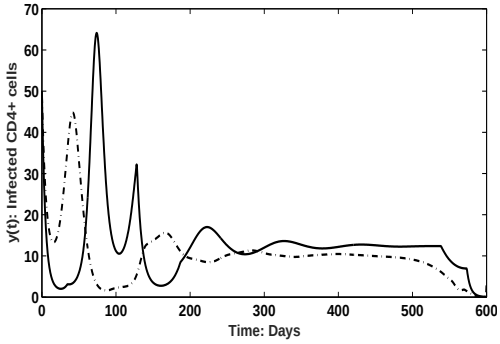

Figure 13. The state variable y using optimal controls $u_1^*(t)$ and $u_2^*(t)$ (DashDot) and using piecewise constant control functions $u_1^{'}(t)$ and $u_2^{'}(t)$ (Solid) with $y(0)$=50 units $mm^{-3}day^{-1}$, initial terminal time $T = 600$ days and optimal terminal time $T^* = 512$ days.

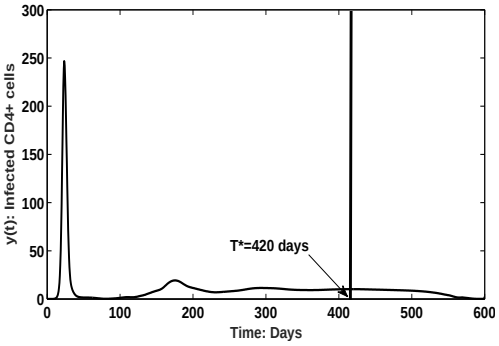

Figure 16. The state variable y with $y(0)$=0.04 units $mm^{-3}day^{-1}$, initial terminal time $T = 600$ days and optimal terminal time $T^* = 420$ days.

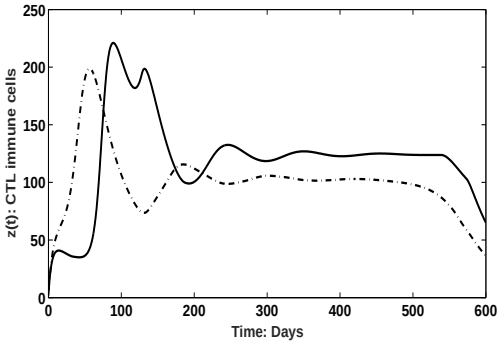

Figure 14. The state variable z using optimal controls $u_1^*(t)$ and $u_2^*(t)$ (DashDot) and using piecewise constant control functions $u_1^{'}(t)$ and $u_2^{'}(t)$ (Solid) with $z(0)$=2 units $mm^{-3}day^{-1}$, initial terminal time $T = 600$ days and optimal terminal time $T^* = 512$ days.

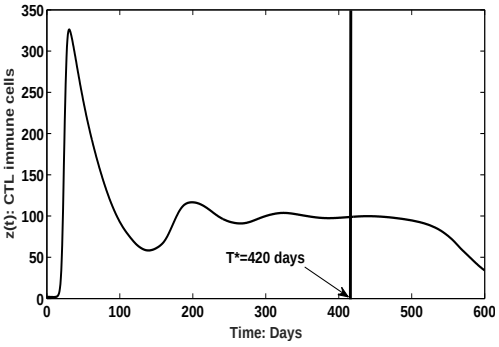

Figure 17. The state variable z with $z(0)$=2 units $mm^{-3}day^{-1}$, initial terminal time $T = 600$ days and optimal terminal time $T^* = 420$ days.

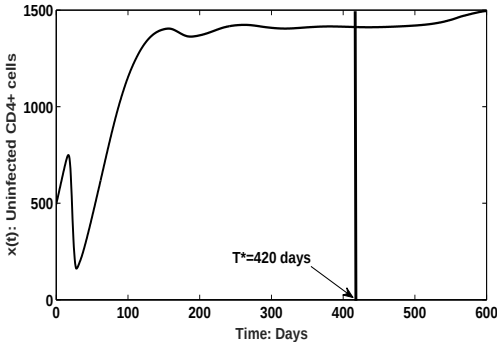

Figure 15. The state variable x with $x(0)$=494.3 units $mm^{-3}day^{-1}$, initial terminal time $T = 600$ days and optimal terminal time $T^* = 420$ days.

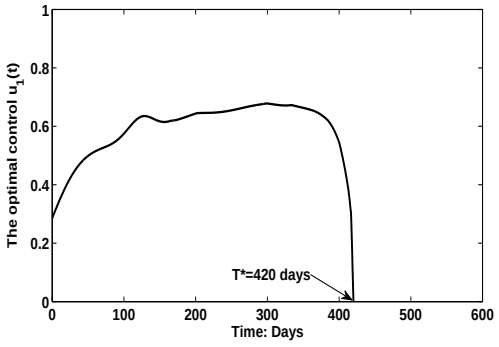

Figure 18. The optimal control $u_1^*(t)$ with $x(0)$=494.3 units $mm^{-3}day^{-1}$, $y(0)$=0.04 units $mm^{-3}day^{-1}$, $z(0)$=2 units $mm^{-3}day^{-1}$ and $T^* = 420$ days.

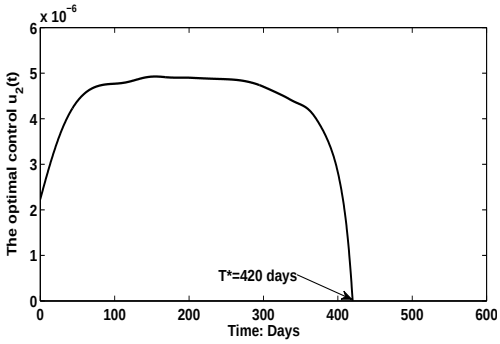

Figure 19. The optimal control $u_2^*(t)$ with $x(0)$=494.3 units $mm^{-3}day^{-1}$, $y(0)$=0.04 units $mm^{-3}day^{-1}$, $z(0)$=2 units $mm^{-3}day^{-1}$ and $T^* = 420$ days.

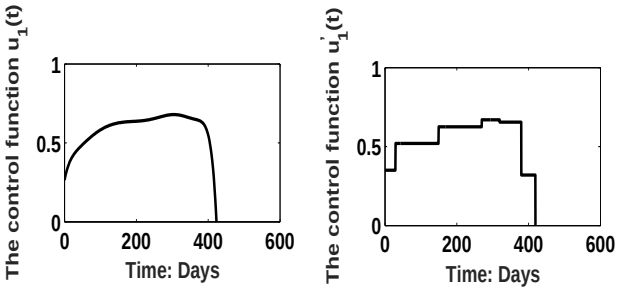

Figure 20. The profile fitting of the optimal control function $u_1^*(t)$ (Left) and the piecewise constant control function $u_1^{'}(t)$ (Right) with $x(0)$=494.3 units $mm^{-3}day^{-1}$, $y(0)$=0.04 units $mm^{-3}day^{-1}$, $z(0)$=2 units $mm^{-3}day^{-1}$ and $T^* = 420$ days.

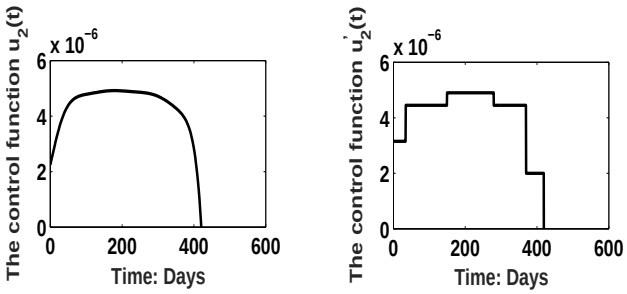

Figure 21. The profile fitting of the optimal control function $u_2^*(t)$ (Left) and the piecewise constant control function $u_2^{'}(t)$ (Right) with $x(0)$=494.3 units $mm^{-3}day^{-1}$, $y(0)$=0.04 units $mm^{-3}day^{-1}$, $z(0)$=2 units $mm^{-3}day^{-1}$ and $T^* = 420$ days.

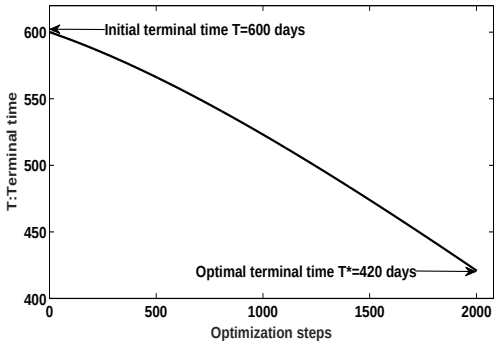

Figure 22. Estimation of optimal terminal time T^*, zero of ∇J with initial terminal time $T = 600$ days, $x(0)$=494.3 units $mm^{-3}day^{-1}$, $y(0)$=0.04 units $mm^{-3}day^{-1}$ and $z(0)$=2 units $mm^{-3}day^{-1}$.

4. Conclusion

In this work, a therapeutic approach has been suggested with the aim of treating the HIV infection by adopting a treatment strategy that uses both highly active antiretroviral therapy (HAART) to limit the virus evolution and an IL-2 immunotherapy to stimulate the active immune response.

In this sense, techniques of the optimal control theory have been used to develop an appropriate mathematical framework relating to this treatment approach. Indeed, a free terminal time optimal control problem was formulated by identifying a specific objective function that includes

all the main objectives of the adopted therapeutic strategy.

The Pontryagin's maximum principle is used to characterize the optimal controls related to the used treatments. An adapted forward backward sweep method is implemented using a Runge-Kutta fourth order scheme and a gradient method routine for numerical resolution of the optimality system with the additional transversality condition for the terminal time.

Taking into account all the theoretical and numerical techniques used in the context of this research work, the treatment strategy suggested for the treatment of HIV infection has achieved all the objectives defined in the optimal control problem. Indeed, the adopted treatments have led to maximize the healthy $CD4^+$ T-cells and to establish an active immune response while reducing both the infection concentration and the treatment duration.

Finally, this optimal control approach has enabled the minimization of side effects and therefore the overall cost of the medication treatment allowing a significant improvement of the quality of life of HIV patients.

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