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ORIGINAL PAPER

Optimal control therapy and vaccination for special HIV-1 model with delay

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Abstract In this paper, we consider a four dimensional model of the human immunodeficiency virus-1 (HIV-1) with delay, which is an extension of some three dimensional models. We approach the treatment problem by adding two controllers to the system for inhibiting viral production. The optimal controller u_1 is considered for vaccine and u_2 for the drug. The Pontryagin maximum principle with delay is used to characterize these optimal controls. At the end, numerical results are presented to illustrate the optimal solutions. The validity of the model was confirmed by proper semi-quantitative simulation of some clinical data. The model was used to predict the possible beneficial effects of vaccine and anti-retroviral drug administration in HIV-1 disease.

Keywords CTL response · HIV-1 infection · Pontryagin maximum principle with delay · Optimal control

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Introduction

An abundance of mathematical models has been developed to understand the dynamics and control of infectious diseases. Many of them have been proposed to obtain the stable region of immune response and virus spread (Balasubramaniam et al. 2015; Tian and Xu 2014; Kwon 2007; Shamsara et al. 2016b; Elaiw 2010). HIV-1 is a widespread viral infection without cure. Drug treatment can transform HIV-1 disease into a treatable long-term infection. There are now 17 drugs in common use for HIV-1 treatment (Volberding and Deeks 2010). Reducing viral population and improving the immune response is the purpose of new treatments. Using optimal control techniques is one of the main strategies for such treatments (Grigorieva et al. 2014; Joshi 2002; Laarabi et al. 2015). In fact, optimal chemotherapy to avoid the excessive use of drugs is the aim of many mathematical models (Karrakchou et al. 2006; Shamsara et al. 2016a). Indeed, when these drugs are administered in high dose they are toxic to the human body and cause damages. Moreover, mathematical modelling with delay differential equations (DDEs) is widely used for analysis and predictions in various areas of the life sciences. The time delays in these models take into account a dependence of the present state of the modelled system on its past history. For example, the activation rate of cytotoxic T lymphocyte (CTL) response at time t may depend on the population of antigen at a previous time. In HIV-1, the period of contacting the HIV-1 with a target cell until producing new viruses from infected cell needs the following stages:

(i) The period between the viral entry of a target cell and integration of viral Deoxyribonucleic acid (DNA) into the host genome, (ii) the period from the integration of viral DNA to the transcription of viral Ribonucleic acid (RNA)

and translation of viral proteins such as reverse transcriptase, integrate, and protease, (iii) the period between the transcription of viral RNA for the release and maturation of virus. In more realistic HIV-1 infection models for studying the virus dynamics and Hopf bifurcation, time delay have been considered (Balasubramaniam et al. 2015; Tian and Xu 2014; Elaiw 2010; Shu et al. 2013; Shamsara et al. 2016c).

Many scientists, consider a three dimensional model for HIV-1 such as (Grigorieva et al. 2014; Wang et al. 2015). In addition, the dynamics of four dimensional models with considering different variables and parameters is investigated (with or without delay) (Laarabi et al. 2015; Shamsara et al. 2016a).

In this paper, first we define a four dimensional model with two controls and one delay. This contribution is an extension of three dimensional models, specially (Grigorieva et al. 2014). The three dimensional model with one controller in Grigorieva et al. (2014) is:

$$\begin{cases} \dot{x}(t) = \lambda - \dfrac{\beta x(t) y(t)}{1 + p z(t)} - \mu_1 x(t), \\ \dot{y}(t) = \dfrac{\beta x(t) y(t)}{1 + p z(t)} - \mu_2 y(t), \\ \dot{z}(t) = -\mu_4 z(t) + v(t). \end{cases} \tag{1.1}$$

where $x(t)$ and $y(t)$ are concentrations of the uninfected and infected target cells (which are T helper cells in case of HIV-1 infection) at moment t respectively. $z(t)$ is the immune response and concentration of an antiviral drug. In the model the uninfected cells are activated at a constant rate λ and die at a rate μ_1. The infected cells die at a rate μ_2 which includes the deaths caused by both cytopathicity of virus and cell-mediated immune response (cytotoxic T lymphocytes). Drug is introduced to a patient at a rate $v(t)$ and is removed at a rate $\mu_4 z(t)$.

In this paper, we used modelling of Wodarz (2014) for CTL immune response to extend the above three dimensional system as a four dimensional model. In fact, based on Wodarz (2014) for CTL modelling the population of CTL is divided into two subpopulations: CTL precursors (CTLp) and CTL effectors (CTLe). CTLp do not have any antiviral activity, while CTLe do have antiviral activity. Thus, the model includes two populations: the memory precursors $w(t)$ and the effector CTL $z(t)$. In this case, we assume that an initial number of CTL is present that has just been activated for the early stage of the disease. The new model has advantage that can show the different mechanisms of CTL. Furthermore, we add the delay parameter to show the time between the initial viral entry into a target cell and subsequent viral production.

Our extended model with CTL immune response and intracellular delay is as follows:

$$\begin{cases} \dot{x}(t) = \lambda - \dfrac{\beta x(t) y(t)}{1 + p z(t)} - \mu_1 x(t), \\ \dot{y}(t) = \dfrac{\beta x(t-\tau) y(t-\tau)}{1 + p z(t)} - \mu_2 y(t), \\ \dot{w}(t) = c(1-q) y(t) w(t) - \mu_3 w(t), \\ \dot{z}(t) = -\mu_4 z(t) + cqy(t) w(t). \end{cases} \tag{1.2}$$

In (1.2), upon contact with antigen, CTLp proliferate is described by the term $c(1-q)y(t)w(t)$. Differentiation into effectors is described by $cqy(t)w(t)$. The parameter c describes the rate of CTL expansion. The parameter q is the probability that the precursor CTL will differentiate into an effector CTL. CTL precursors die at a rate μ_3 and effectors die at a rate μ_4.

For simplifying of the analysis, one can substitute a variable $s(t) = \beta(1 + pz(t))^{-1}$ in (1.2). In the denominator of $s(t)$, from the biological point of view, the parameter p and the variable $z(t)$ cannot be negative. Consequently, the system (1.2) will be taken the form:

$$\begin{cases} \dot{x}(t) = \lambda - s(t) x(t) y(t) - \mu_1 x(t), \\ \dot{y}(t) = s(t) x(t-\tau) y(t-\tau) - \mu_2 y(t), \\ \dot{w}(t) = c(1-q) y(t) w(t) - \mu_3 w(t), \\ \dot{s}(t) = \mu_4 s(t) - \dfrac{cqp}{\beta} s^2(t) y(t) w(t) - \dfrac{\mu_4}{\beta} s^2(t). \end{cases} \tag{1.3}$$

The initial condition for the above system is

$$\begin{cases} x(\theta) = \phi_1(\theta) \geq 0 \\ y(\theta) = \phi_2(\theta) \geq 0 \\ w(\theta) = \phi_3(\theta) \geq 0 \\ s(\theta) = \phi_4(\theta) \geq 0 \end{cases} \tag{1.4}$$

where $\theta \in [-\tau, 0]$, $\phi = (\phi_1, \phi_2, \phi_3, \phi_4)^T \in C$. Here $C = C\left([-\tau, 0]; \mathbb{R}^4_+\right)$ is the Banach space of continuous functions from $[-\tau, 0]$ to $\mathbb{R}^4_+$ equipped with the sup-norm, where

$$\mathbb{R}^4_+ = \{(x_1, x_2, x_3, x_4) \mid x_i \geq 0, i = 1, 2, 3, 4\}.$$

The boundedness, positiveness and continuity of solutions of system (1.3) are given by the following lemma.

Lemma 1 *The corresponding solution* $(x(t), y(t), w(t), s(t))$ *of system* (1.3) *is defined on the biggest semi-interval* Δ *and are bounded.*

Proof Since the right hand side of system (1.3) is completely continuous and locally Lipschitz on C , the solution $(x(t), y(t), w(t), s(t))$ with initial conditions (1.4) exists and is unique on the biggest semi-interval $\Delta = [0, T]$, where $0 < T < +\infty$ (Hale and Lunel 2013). The forth equation of the system (1.3) is the Bernoulli equation, integrating yields

$$s(t) = s(0) e^{\mu_4 t} \left(1 + s(0) \int_0^t e^{\mu_4 s} \frac{cqp}{\beta} y(s) w(s) \mathrm{d}s\right)^{-1} \tag{1.5}$$

Integrating the first, second and third equations of system (1.3) yields

$$x(t) = x(0)e^{\int_0^t (s(\delta)y(\delta)+\mu_1)\mathrm{d}\delta} + \lambda \int_0^t e^{-\int_0^t (\mu_1+s(\delta)y(\delta))d\delta}\mathrm{d}r \tag{1.6}$$

$$y(t) = y(0)e^{\int_0^t (s(\gamma)x(\gamma-\tau)y(\gamma-\tau)-\mu_2)\mathrm{d}\gamma} \tag{1.7}$$

$$w(t) = w(0)e^{\int_0^t (c(1-q)y(\xi)-\mu_3)\mathrm{d}\xi} \tag{1.8}$$

Thus, by (1.5)–(1.8), $x(t) > 0$, $y(t) > 0$, $w(t) > 0$ and $s(t) > 0$ hold for all $t \in \Delta$. Next we show that positive solutions of (1.3) are ultimately uniformly bounded for $t \geq 0$. The forth equation of (1.3) gives

$$\dot{s}(t) \leq \mu_4 s(t) - \frac{\mu_4}{\beta} s^2(t)$$

thus, $s(t) \leq \frac{\beta}{1+\beta c_0 e^{-\mu_4 t}}$ and $\limsup_{t\to\infty} s(t) \leq \beta$. Therefore, the solution $s(t)$ of system (1.3) is bounded. Let M denotes this upper bound. Also in (1.3)

$$\dot{x}(t) \leq \lambda - \mu_1 x(t)$$

so, $\limsup_{t\to\infty} x(t) \leq \frac{\lambda}{\mu_1}$. Now

$$\begin{aligned}\dot{x}(t) + \dot{y}(t+\tau) &= \lambda - s(t)x(t)y(t) - \mu_1 x(t) + s(t+\tau)x(t)y(t) \\ &\quad - \mu_2 y(t+\tau) \\ &\leq \lambda - Mx(t)y(t) - \mu_1 x(t) + Mx(t)y(t) \\ &\quad - \mu_2 y(t+\tau) = \lambda - \mu_1 x(t) - \mu_2 y(t+\tau) \\ &\leq \lambda - \mu(x(t) + y(t+\tau))\end{aligned}$$

where $\mu = \min\{\mu_1, \mu_2\}$ and $\limsup_{t\to\infty} (x(t) + y(t+\tau)) \leq \frac{\lambda}{\mu}$. Moreover,

$$\begin{aligned}\dot{x}(t) + \dot{w}(t) + \frac{c(q-1)\beta}{M^2 cqp}\dot{s}(t) &\leq \lambda - \mu_1 x(t) - c(q-1)y(t)w(t) \\ &\quad - \mu_3 w(t) - \frac{c(q-1)\beta\mu_4}{M^2 cqp}s(t) + \frac{c(q-1)}{M^2}s^2(t)y(t)w(t) \\ &\leq \lambda - \mu_1 x(t) - c(q-1)y(t)w(t) - \mu_3 w(t) \\ &\quad - \frac{c(q-1)\beta\mu_4}{M^2 cqp}s(t) + \frac{c(q-1)}{M^2}M^2 y(t)w(t) \\ &\leq \lambda - \mu_1 x(t) - \mu_3 w(t) - \frac{c(q-1)\beta\mu_4}{M^2 cqp}s(t) \\ &\leq \lambda - \delta(x(t) + w(t) + \frac{c(q-1)\beta}{M^2 cqp}s(t))\end{aligned}$$

where $\delta = \min\{\mu_1, \mu_3, \mu_4\}$ and $\limsup_{t\to\infty} (x(t) + w(t) + \frac{c(q-1)\beta}{M^2 cqp}s(t)) \leq \frac{\lambda}{\delta}$. As a consequence, $x(t)$, $y(t)$, $w(t)$ and $s(t)$ of system (1.3) are ultimately uniformly bounded. □

This paper is organized as follows:

In "The optimal control problem with delay" section, the Pontryagin maximum principle with delay for characterizing the optimal control and some preliminaries of optimal control with delay are stated. Section "Characterization of an optimal control for system (1.3)" is devoted to determine the optimal control problem to minimize the level of infection for system (3.1). Section "Numerical simulation" is illustrated some examples (simulations) which numerically shows the result of optimality of the system. In "Results and discussion" section, we compare our results with clinical data.

The optimal control problem with delay

This section is devoted to some preliminaries of optimal control problem with delay, which is necessary in the next sections. For more details, one can see (Göllmann et al. 2009).

Pontryagin maximum principle The Pontryagin maximum (or minimum) principle is used in optimal control theory to find the best possible control for taking a dynamical system from one state to another, especially in the presence of constraints for the state or input controls.

A quite general optimal control problem governed by a delay differential system can be formulated in the following form,

$$\text{minimize } L(u, x^u) = \int_0^T G(t, u(t), x^u(t), x^u(t-\tau))\mathrm{d}t + \varphi(x^u(T)) \tag{2.1}$$

subject to $u \in K \subset L^\infty(0, T; \mathbb{R}^m)$ $(T > 0)$, where x^u is the solution to

$$\begin{cases} x'(t) = f(t, u(t), x(t), x(t-\tau)), \ t \in (0, T) \\ x(0) = x_0 \end{cases} \tag{2.2}$$

Here

$$\begin{aligned} &G : [0, T] \times \mathbb{R}^m \times \mathbb{R}^N \times \mathbb{R}^N \to \mathbb{R}, \\ &\varphi : \mathbb{R}^N \to \mathbb{R}, \\ &f : [0, T] \times \mathbb{R}^m \times \mathbb{R}^N \times \mathbb{R}^N \to \mathbb{R}^N \end{aligned}$$

$x_0 \in \mathbb{R}^N, m, N \in \mathbb{N}$ and $K \subset L^\infty(0, T; \mathbb{R}^m)$ is a closed convex subset.

We assume here that for any $u \in L^\infty(0, T; \mathbb{R}^m)$, problem (2.2) admits a unique solution denoted by x^u. Equation (2.2) is called the state problem.

1. $u \in K$ is called the control (or controller). This is a constrained control because $u \in K$ and K is a subset of $L^\infty(0, T; \mathbb{R}^m)$.
2. x^u is the state corresponding to the control u and the mapping.

3. $u \mapsto L(u, x^u) = \phi(u)$ is the cost functional (the function that should be minimized).

We say that $u^* \in K$ is an optimal control for Problem (2.1) if

$$L(u^*, x^{u^*}) \leq L(u, x^u)$$

for any $u \in K$. The pair (u^*, x^{u^*}) is called an optimal pair and $L(u^*, x^{u^*})$ is the optimal value of the cost functional.

Pontryagin function with delay is given by:

$$H(t, u(t), x(t), x(t-\tau), p(t)) = G(t, u(t), x(t), x(t-\tau)) + f(t, u(t), x(t), x(t-\tau))p(t)$$

This function is Hamiltonian, if satisfies in the following relations

$$x'(t) = H_p$$

and

$$p'(t) = -H_x$$

$p(t)$ is defined as the adjoint function.

Since we are going to use optimal control, we state the following theorem which one can find the proof in Göllmann et al. (2009).

Theorem 1 (maximum principle for the optimal control problem (OCP)). *If $u^*(t)$ and $x^*(t)$ are optimal for problem (2.1) with delay, then there exists a piecewise differentiable costate (adjoint) function $p(t)$ such that*

$$\begin{aligned} &H(t, x^*(t), x^*(t-\tau), u^*(t), p(t)) \\ &\quad \leq H(t, x^*(t), x^*(t-\tau), u(t), p(t)) \end{aligned} \tag{2.3}$$

for all controls u at each time t, where H is the Hamiltonian previously defined and

$$p'(t) = -\frac{\partial H}{\partial x}(t, x(t), x(t-\tau), u(t), p(t)) - \chi_{[0, t_f - \tau]}(t) \frac{\partial H}{\partial x_\tau}(t+\tau, x(t+\tau), x(t), u(t+\tau), p(t+\tau)) \tag{2.14}$$

where $x_\tau = x(t-\tau)$.

$$p(t_f) = 0 \ \text{(transversality condition)} \tag{2.5}$$

the OCP must satisfy (optimality condition):

$$\frac{\partial H}{\partial u} = 0 \tag{2.6}$$

i.e., the minimization is over all admissible controls.

Characterization of an optimal control for system (1.3)

In this section, we determine the optimal control for our system (1.3).

There are some antiretroviral (ARV) drugs which help the immune system in preventing the HIV-1 infection, although it is not possible to cure it. Reverse Transcriptase Inhibitors (RTIs) is one of the chemotherapies, another group of antiretoviral drug is the Protease Inhibitors (PIs) which prevent the production of viruses from the actively infected CD4$^+$ T cells. In this study, u_1 shows the effect of different vaccines that is proposed for HIV-1 infection treatment such as DNA vaccines, mucosal vaccines and an HIV-1-lipopeptide vaccine (de Goede et al. 2015; Herasimtschuk et al. 2014; Launay et al. 2013). u_2 is devoted for the drug known as Reverse Transcriptase Inhibitor (RTI). This drug inhibits the virus from infecting new cells by preventing the reverse transcription (Shim et al. 2003). Hence, (1.3) becomes

$$\begin{cases} \dot{x}(t) = \lambda - s(t)x(t)y(t) - \mu_1 x(t), \\ \dot{y}(t) = s(t)x(t-\tau)y(t-\tau) - \mu_2 y(t) - u_2(t)y(t), \\ \dot{w}(t) = c(1-q)y(t)w(t) - \mu_3 w(t), \\ \dot{s}(t) = \mu_4 s(t) - \dfrac{cqp}{\beta} s^2(t)y(t)w(t) - \dfrac{\mu_4}{\beta} s^2(t) \\ \qquad + u_1(t)x(t) + u_2(t)y(t). \end{cases} \tag{3.1}$$

Our aim is to look for protocols of administration, which are as much as drugs and vaccine efficient as possible and not too toxic. So, we restrict the amount of drugs and vaccine administered to the patient (Lenhart and Workman 2007). Thus, we consider a biological bound for each of the controllers, as

$$0 \leq u_i(t) \leq u_{i_{\max}}, \quad i = 1, 2$$

The lower bounds for u_1 and u_2 correspond to no therapy. Next, we characterize the optimal control pair (u_1^*, u_2^*), which gives the optimal drug dosage for patient recovery (Laubenbacher 2007). Consider the closed convex set, K, which is defined in "The optimal control problem with delay" section. Let $K \subset L^\infty(0, t_f; \mathbb{R}^m)$ and $m = 2$ then, $K = U$ (see Roy 2016; Aniţa et al. 2011), where

$$U = \left\{ \begin{array}{l} u(t) = (u_1(t), u_2(t)) \mid u_1, u_2 \text{ are Lebesgue measurable,} \\ 0 \leq u_i(t) \leq u_{i\max},\ t \in [0, t_f], \quad i = 1, 2 \end{array} \right\}. \tag{3.2}$$

Our problem is to minimize the objective functional

$$\min_{u(.) \in U} \left\{ J = \int_0^{t_f} \left[A_1 x(t) + A_2 y(t) + \frac{1}{2} B_1 u_1^2(t) + \frac{1}{2} B_2 u_2^2(t) \right] \mathrm{d}t \right\} \tag{3.3}$$

$x(t)$ and $y(t)$ are the solutions of system (3.1) and the parameters $A_1 > 0$, $A_2 > 0$, $B_1 > 0$ and $B_2 > 0$ represent the weights on the benefit and cost functional.

This optimal control is defined based on (Laarabi et al. 2015; Grigorieva et al. 2014). The aim is to find an optimal control for minimizing the objective functional defined in (3.3) subject to the state system (3.1). In other words, we are seeking optimal control pair (u_1^*, u_2^*) such that

$$J(u_1^*, u_2^*) = \min\{ J(u_1, u_2),\ (u_1, u_2) \in U \}. \tag{3.4}$$

Let the initial conditions be

$$\begin{cases} x(0) = x_0 \\ y(0) = y_0 \\ w(0) = w_0 \\ s(0) = s_0. \end{cases} \tag{3.5}$$

In addition, for biological reasons, we assume that the initial data for system (3.1) satisfy

$$x_0 \geq 0, \quad y_0 \geq 0, \quad w_0 \geq 0, \quad s_0 \geq 0, \quad t \in [-\tau, 0].$$

In the following by using Collins et al. (2010) in relation to our problem, we show the existence and uniqueness solution of system (3.1) in entire interval $[-\tau, t_f]$. First, we introduce the following notations

$$f(X(t)) = \begin{pmatrix} \lambda - s(t)x(t)y(t) - \mu_1 x(t) \\ s(t)x(t-\tau)y(t-\tau) - \mu_2 y(t) - u_2(t)y(t) \\ c(1-q)y(t)w(t) - \mu_3 w(t) \\ \mu_4 s(t) - \dfrac{cqp}{\beta} s^2(t)y(t)w(t) - \dfrac{\mu_4}{\beta} s^2(t) + u_1(t)x(t) + u_2(t)y(t) \end{pmatrix}$$

where $X(t) = (x(t), y(t), w(t), s(t))^T$. Let $\Theta : [t-\tau, t] \to \mathbb{R}$ be a function, then one can define a new function on $\Theta_t : [\tau, 0] \to \mathbb{R}$ by

$$\Theta_t(\sigma) = \Theta(t + \sigma)$$

for $-\tau \leq \sigma \leq 0$. Thus, system (3.1) can be rewritten as

$$X'(t) = F(t, x_t(\sigma), y_t(\sigma), w(t), s(t))$$

where $F : [0, \alpha) \times C([-\tau, 0], \mathbb{R}^2) \times \mathbb{R}^2 \to \mathbb{R}^5$ for $\alpha \in [0, t_f]$. In other words, for each $(t, \psi, \varphi, w, s) \in [0, \alpha) \times C([-\tau, 0], \mathbb{R}^2) \times \mathbb{R}^2$, $F(t, \psi, \varphi, w, s)$ should be a well defined point in $\mathbb{R}^5$. Also, we consider $x_t(t - \tau - t) = x(t + t - \tau - t) = x(t - \tau)$, hence, $x_t(-\tau) = x(t - \tau)$ and similarly $y_t(-\tau) = y(t - \tau)$. Furthermore,

$$F(t, x_t(-\tau), y_t(-\tau), w(t), s(t)) = f(t, x(t-\tau), y(t-\tau), w(t), s(t)) \tag{3.6}$$

From (3.6), one can see

$$x_0 = \phi_1(0), \quad y_0 = \phi_2(0)$$

where ϕ is defined in (1.4). We can further consider a solution to our problem in terms of an integral equation. We see that

$$x(t) = \begin{cases} \phi_1(t) & \text{if } -\tau \leq t \leq 0 \\ \phi_1(0) + \int_0^t F(r, x_r(-\tau), y_r(-\tau), w(r), s(r))\mathrm{d}r & \text{if } 0 \leq t \leq t_f \end{cases}$$

and

$$y(t) = \begin{cases} \phi_2(t) & \text{if } -\tau \leq t \leq 0 \\ \phi_2(0) + \int_0^t F(\gamma, x_\gamma(-\tau), y_\gamma(-\tau), w(\gamma), s(\gamma), u_2(\gamma))\mathrm{d}\gamma & \text{if } 0 \leq t \leq t_f \end{cases}$$

Now, we state the following Lemma

Lemma 2 *If $f(X(t))$ has continuous first partial derivatives with respect to all but its first argument, then $f(X(t))$ is locally Lipschitz.*

Proof Since all the partial in the Jacobian matrix of $f(X(t))$ with respect to $X(t)$ is continuous, thus $f(X(t))$ is locally Lipschitz. □

Moreover, since f is locally Lipschitz on $[0, \alpha] \times \mathbb{R}^4 \to \mathbb{R}^5$, then function F mapping $[0, \alpha) \times C([-\tau, 0], \mathbb{R}^2) \times \mathbb{R}^2 \to \mathbb{R}^5$ is locally Lipschitz.

Theorem 2 *Let $F(t, x_t, y_t, w, s) : [0, t_f) \times C([-\tau, 0], \mathbb{R}^2) \times \mathbb{R}^2 \to \mathbb{R}^5$ be continuous and be locally Lipschitz. If*

$$\|F(t, \rho)\| \leq M(t) + N(t)\|\rho\|$$

on $[0, t_f) \times C([-\tau, 0], \mathbb{R}^2) \times \mathbb{R}^2$, where $M(t)$ and $N(t)$ are continuous positive function on $[0, t_f]$ and $\rho = (x_t, y_t, w, s)^T$, the unique noncontinuable solution exists on the entire interval $[-\tau, t_f]$.

Proof $F(t, x_t, y_t, w, s)$ has already been shown to be locally Lipschitz. Also, with $g_1(t) = t - \tau$ and the right hand side of our differential equation system (3.1) being continuous, then $F(t, x(t-\tau), y(t-\tau), w(t), s(t))$ is a composition of continuous functions and hence is continuous on $[0, t_f)$. So, that's enough to show $\|F(t, \rho)\| \leq M(t) + N(t)\|\rho\|$ is satisfied. By neglecting the negative terms in the system (3.1), we have

$$\begin{cases} x'(t) \leq \lambda \\ y'(t) \leq s(t)x(t-\tau)y(t-\tau) \\ w'(t) \leq c(1-q)w(t)y(t) \\ s'(t) \leq \mu_4 s(t) + u_1(t)x(t) + u_2 y(t) \end{cases} \tag{3.7}$$

From first term of (3.7), $x(t)$ is bounded on the entire interval $[-\tau, t_f]$. By Lemma 1, the second and third terms of (3.7) indicate that $y(t)$ and $w(t)$ are also bounded on $[-\tau, t_f]$. The right hand side of the forth term of (3.7) is a first order linear differential equation with respect to $s(t)$. Since, $x(t)$ and $y(t)$ are bounded on $[-\tau, t_f]$ so solution, $s(t)$ is bound, if the admissible controls $u_i(t), i = 1, 2$ to be bounded on $[-\tau, t_f]$. Now, we can define Q and R as the upper bounds for the right hand side of the second and third terms of (3.7). As a consequence

$$\begin{pmatrix} x(t) \\ y(t) \\ w(t) \\ s(t) \end{pmatrix}' \leq \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ u_1(t) & u_2(t) & 0 & \mu_4 \end{pmatrix} \begin{pmatrix} x(t) \\ y(t) \\ w(t) \\ s(t) \end{pmatrix} + \begin{pmatrix} \lambda \\ Q \\ R \\ 0 \end{pmatrix} \tag{3.8}$$

We see that via our transformation in Eq. (3.6) that $\|F(t,\rho)\| \le \|f(t,x(t-\tau),y(t-\tau),w(t),s(t))\|$. Therefore, $\|F(t,\rho)\| \le M + N\|\rho\|$ where

$$M = \begin{pmatrix} \lambda \\ Q \\ R \\ 0 \end{pmatrix} \quad N = \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ u_1(t) & u_2(t) & 0 & \mu_4 \end{pmatrix}$$

Now, by application of this theorem and with the assumption of boundedness of admissible controls, we have the uniqueness of a solution on $[-\tau, t_f)$. □

Theorem 3 *There exists an optimal control pair* $(u_1^*, u_2^*) \in U$ *which minimizes the objective functional* $J(u_1, u_2)$.

Proof Let $(u_{1_n}(.), u_{2_n}(.))_{n\ge 1}$ be a minimizing sequence and $P_n(.) = (x_n, y_n, w_n, s_n)$ be the state trajectory corresponding to $(u_{1_n}(.), u_{2_n}(.))$. Since $P_n(.)$ and $P_n^{'}(.)$ are both bounded in L^∞, then $P_n(.)$ is a uniformly bounded and equicontinuous sequence. Therefore, by the Arzela-Ascoli Theorem, there exists P^* and (u_1^*, u_2^*) such that

$$P_n(.) \to P^*(.) \text{ uniformly on } [0, t_f].$$

Also, since $\{J(u_1,u_2); (u_1,u_2) \in U\}$ is bounded by zero by below and there exists a sequence (u_{1_n}, u_{2_n}) in U such that

$$\lim_{n\to\infty} J(u_{1_n}, u_{2_n}) = \lim_{n\to\infty} \int_0^{t_f} A_1 x_n(t) + A_2 y_n(t) + \frac{1}{2} B_1 u_{1_n}^2(t) + \frac{1}{2} B_2 u_{2_n}^2(t) = \inf_{(u_1,u_2)\in U} J(u_1,u_2)$$

since $x_n \to x^*$, $y_n \to y^*$ uniformly and $(u_{1_n}, u_{2_n}) \to (u_1^*, u_2^*)$ weakly in $L^\infty[0, t_f]$ on a subsequence due to the bounds on the controls. Passing to the limit in the state DDE system, we obtain that P^* is the state vector corresponding to control (u_1^*, u_2^*). Thus, we obtain

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

Therefore, (u_1^*, u_2^*) is an optimal control pair. □

The function

$$\begin{aligned} H = {} & H(x_*(t), y_*(t), w_*(t), s_*(t), \psi_1(t), \psi_2(t), \psi_3(t), \\ & \psi_4(t), u_1^*(t), u_2^*(t)) \\ = {} & (\lambda - s_*(t)x_*(t)y_*(t) - \mu_1 x_*(t))\psi_1(t) \\ & + (s_*(t)x_*(t-\tau)y_*(t-\tau) - \mu_2 y_*(t) - u_2^*(t)y_*(t))\psi_2(t) \\ & + (cy_*(t)w_*(t)(1-q) - \mu_3 w_*(t))\psi_3(t) \\ & + (-\frac{\mu_4}{\beta} s_*^2(t) + \mu_4 s_*(t) - \frac{cqp}{\beta} s_*^2(t) y_*(t) w_*(t) \\ & + u_1^*(t)x_*(t) + u_2^*(t)y_*(t))\psi_4(t) \\ & - \left[A_1 x_*(t) + A_2 y_*(t) + \frac{1}{2} B_1 (u_1^*(t))^2 + \frac{1}{2} B_2 (u_2^*(t))^2 \right], \end{aligned} \tag{3.9}$$

with the optimality condition

$$\frac{\partial H}{\partial u^*} = 0 \Rightarrow \begin{cases} \dfrac{\partial H}{\partial u_1^*} = 0 \\ \dfrac{\partial H}{\partial u_2^*} = 0 \end{cases} \tag{3.10}$$

and the adjoint equation

$$\begin{cases} \dot{\psi}_1 = -\dfrac{\partial H}{\partial x} - \chi_{[0,t_f-\tau]}(t) \dfrac{\partial H}{\partial x_\tau}(t+\tau) \\ \dot{\psi}_2 = -\dfrac{\partial H}{\partial y} - \chi_{[0,t_f-\tau]}(t) \dfrac{\partial H}{\partial y_\tau}(t+\tau) \\ \dot{\psi}_3 = -\dfrac{\partial H}{\partial w} \\ \dot{\psi}_4 = -\dfrac{\partial H}{\partial s} \end{cases} \tag{3.11}$$

with transversality conditions $\psi_i(t_f) = 0$, $i = 1,2,3,4$ is a Hamiltonian function. Now we apply the necessary conditions to the Hamiltonian function H in (3.9).

Theorem 4 *Let* $(x_*(t), y_*(t), w_*(t), s_*(t))$ *be optimal state solutions associated with the optimal control* $(u_1^*(t), u_2^*(t))$ *for the optimal control problem* (3.3)–(3.5). *Then by* (3.11), *the adjoint system can be obtained by with transversality conditions*

$$\begin{cases} \dot{\psi}_1(t) = -\dfrac{\partial H}{\partial x_*} - \chi_{[0,t_f-\tau]}(t) \dfrac{\partial H}{\partial x_{*_\tau}}(t+\tau) = (s_*(t)y_*(t) + \mu_1)\psi_1(t) - u_1^*(t)\psi_4(t) + A_1 - \chi_{[0,t_f-\tau]}(t) y_*(t) s_*(t+\tau)\psi_2(t+\tau) \\ \dot{\psi}_2(t) = -\dfrac{\partial H}{\partial y_*} - \chi_{[0,t_f-\tau]}(t) \dfrac{\partial H}{\partial y_{*_\tau}}(t+\tau) = s_*(t)x_*(t)\psi_1(t) + (\mu_2 + u_2^*(t))\psi_2(t) - c(1-q)w_*(t)\psi_3(t) + \\ \dfrac{cqp}{\beta} s_*^2(t) w_*(t)\psi_4(t) - u_2^*(t)\psi_4(t) + A_2 - \chi_{[0,t_f-\tau]}(t) x_*(t) s_*(t+\tau)\psi_2(t+\tau) \\ \dot{\psi}_3(t) = -\dfrac{\partial H}{\partial w_*} = -cy_*(t)(1-q)\psi_3(t) + \mu_3\psi_3(t) + \dfrac{cqp}{\beta} s_*^2(t) y_*(t)\psi_4(t) \\ \dot{\psi}_4(t) = -\dfrac{\partial H}{\partial s_*} = x_*(t)y_*(t)\psi_1(t) + \dfrac{2\mu_4}{\beta} s_*(t)\psi_4(t) - \mu_4\psi_4(t) + \dfrac{2cqp}{\beta} s_*(t) y_*(t) w_*(t)\psi_4(t) \end{cases} \tag{3.12}$$

$$\psi_i(t_f) = 0, \quad i = 1, \ldots, 4. \tag{3.13}$$

Furthermore, the optimal control is given as follows:

$$\begin{cases} u_1^* = \max\left(\min\left(\dfrac{x_*\psi_4}{B_1}, u_{1_{\max}}\right), 0\right) \\ u_2^* = \max\left(\min\left(\dfrac{y_*(\psi_2 - \psi_4)}{B_2}, u_{2_{\max}}\right), 0\right). \end{cases} \tag{3.14}$$

Proof By the theorem of existence and uniqueness in differential equation Hale and Lunel (2013) and the Pontryagin maximum principle with delay given in Göllmann et al. (2009), for the pair $(u_1^*(t), u_2^*(t))$ and the corresponding trajectory $(x_*(t), y_*(t), w_*(t), s_*(t))$, there exists a nontrivial solution $(\psi_1(t), \psi_2(t), \psi_3(t), \psi_4(t))$ of the adjoint system (3.12). Now by condition (3.10), one can have

$$\begin{cases} \dfrac{\partial H}{\partial u_1^*} = B_1 u_1^* + x_*\psi_4 = 0, \\ \dfrac{\partial H}{\partial u_2^*} = B_2 u_2^* - y_*\psi_2 + y_*\psi_4 = 0. \end{cases} \Rightarrow \begin{cases} u_1^* = -\dfrac{x_*\psi_4}{B_1}, \\ u_2^* = -\dfrac{y_*(\psi_2 - \psi_4)}{B_2}. \end{cases} \tag{3.15}$$

Control $(u_1^*(t), u_2^*(t))$ satisfies the relationships

$$u_1^* = \begin{cases} 0 & \text{if} \quad \dfrac{x_*\psi_4}{B_1} \le 0 \\ \dfrac{x_*\psi_4}{B_1} & \text{if} \quad 0 < \dfrac{x_*\psi_4}{B_1} < u_{1_{\max}} \\ u_{1_{\max}} & \text{if} \quad \dfrac{x_*\psi_4}{B_1} \ge 0 \end{cases} \tag{3.16}$$

and

$$u_2^* = \begin{cases} 0 & \text{if} \quad \dfrac{y_*(\psi_2 - \psi_4)}{B_2} \le 0 \\ \dfrac{y_*(\psi_2 - \psi_4)}{B_2} & \text{if} \quad 0 < \dfrac{y_*(\psi_2 - \psi_4)}{B_2} < u_{2_{\max}} \\ u_{2_{\max}} & \text{if} \quad \dfrac{y_*(\psi_2 - \psi_4)}{B_2} \ge 0 \end{cases} \tag{3.17}$$

Since $(\psi_1(t), \psi_2(t), \psi_3(t), \psi_4(t))$ is a solution of (3.12), then $(u_1^*(t), u_2^*(t))$ can be calculated as the optimal control (3.14). □

Numerical simulation

In this section, first we indicate the equilibria and the Jacobian matrix of system (1.2). We are going to use the result of the subsection (4.1) for other subsections, to determine the stable and unstable regions for the treated disease. Furthermore, in other subsections we will show different behaviours of system (3.1) by the figures.

Untreated model

Equilibria of system (1.2) at $\tau = 0$ are

$$E_0 = \left(\frac{\lambda}{\mu_1}, 0, 0, 0\right), \quad E_1 = \left(\frac{\mu_2}{\beta}, -\frac{\mu_1\mu_2 - \beta\lambda}{\mu_2\beta}, 0, 0\right),$$
$$E_2 = (x^*, y^*, w^*, z^*).$$

where at E_2

$$x^* = -\frac{\mu_2\mu_3 - \lambda c(1-q)}{\mu_1 c(1-q)}, \tag{4.1}$$

$$y^* = \frac{\mu_3}{c(1-q)}, \tag{4.2}$$

$$w^* = -\frac{\mu_4(\mu_1\mu_2 c(1-q) + \mu_2\mu_3\beta - \lambda c(1-q)\beta)}{\mu_1\mu_2\mu_3 pcq}, \tag{4.3}$$

$$z^* = -\frac{\mu_1\mu_2 c(1-q) + \mu_2\mu_3\beta - \lambda c(1-q)\beta}{\mu_1\mu_2 pc(1-q)}. \tag{4.4}$$

In the interior equilibria E_2 from biological point all four components, healthy and infected CD4 $^+$ T cells and both CTLs, $w(t)$ and $z(t)$ should be positive. Hence, from (4.2) and (4.1) one should have

$$(1-q) > 0 \tag{4.5}$$

$$\lambda c(1-q) > \mu_2\mu_3 \tag{4.6}$$

The Jacobian matrix of system (1.2) is

$$P(\Lambda) = \begin{bmatrix} \Lambda + \dfrac{\beta y}{pz+1} + \mu_1 & \dfrac{\beta x}{pz+1} & 0 & -\dfrac{\beta xyp}{(pz+1)^2} \\ -\dfrac{e^{-\Lambda\tau}\beta y}{pz+1} & \Lambda + \mu_2 - \dfrac{e^{-\Lambda\tau}\beta x}{pz+1} & 0 & \dfrac{e^{-\Lambda\tau}\beta xyp}{(pz+1)^2} \\ 0 & -c(1-q)w & \Lambda - c(1-q)y + \mu_3 & 0 \\ 0 & -cqw & -cqy & \Lambda + \mu_4 \end{bmatrix}. \tag{4.7}$$

Table 1 Parameters taken from Wang et al. (2015)

Parameter	Value	Unit
λ	180	$\text{day}^{-1}\ \text{mm}^{-3}$
β	0.002	$\text{day}^{-1}\ \text{mm}^{-3}$
μ_1	0.16	day^{-1}
μ_2	1.85	day^{-1}
μ_3	0.8	day^{-1}
μ_4	0.5	day^{-1}
c	2	day^{-1}
q	0.6	day^{-1}
p	0.2	day^{-1}

Numerical Hopf bifurcation for untreated model

Parameters are chosen as same as Wang et al. (2015):

Note that in Table 1, the parameters values are based on clinical data.

With the above parameters values and (4.7) at E_2, one can obtain the characteristic polynomial:

$$\begin{aligned}&\Lambda^4 + \left(2.510743438 - 1.850000000\,\mathrm{e}^{-\Lambda\tau}\right)\Lambda^3\\&\quad + \left(1.302747080 - 1.155600653\,\mathrm{e}^{-\Lambda\tau}\right)\Lambda^2\\&\quad + \left(-0.08521662687\,\mathrm{e}^{-\Lambda\tau} + 0.1486876805\right)\Lambda\\&\quad + 0.008371116414\,\mathrm{e}^{-\Lambda\tau} = 0\end{aligned} \tag{4.8}$$

Substituting $\Lambda = i\omega$ and separating the real and imaginary parts, one has

$$\begin{aligned}&\omega^4 + 1.850000000\,\sin(\omega\tau)\omega^3\\&\quad + (-1.302747080 + 1.155600653\,\cos(\omega\tau))\omega^2\\&\quad - 0.08521662687\,\sin(\omega\tau)\omega\\&\quad + 0.008371116414\,\cos(\omega\tau) = 0\end{aligned} \tag{4.9}$$

$$\begin{aligned}&(-2.510743438 + 1.850000000\,\cos(\omega\tau))\omega^3\\&- 1.155600653\,\sin(\omega\tau)\omega^2\\&+ (-0.08521662687\,\cos(\omega\tau) + 0.1486876805)\omega\\&- 0.008371116414\,\sin(\omega\tau) = 0\end{aligned} \tag{4.10}$$

Adding up the squares of the Eqs. (4.9) and (4.10), leads to

$$\begin{aligned}&\omega^8 + 0.275838451\,\omega^6 - 0.3848961513\,\omega^4\\&+ 0.01484615284\,\omega^2 - 0.00007007559002 = 0\end{aligned} \tag{4.11}$$

let ω_0 be a positive solution of (4.11). By (4.9) and (4.10), τ will obtain from

$$\begin{aligned}\tau_0 = \frac{1}{\omega_0}\Bigg(&\frac{(-\omega_0^4 + 1.302747080\omega_0^2)(1.155600653\omega_0^2 + 0.00837111641)}{(1.155600653\omega_0^2 + 0.008371116414)^2 + (1.85\omega_0^2 - 0.08521662687)^2}\\&+ \frac{(1.85\omega_0^3 - 0.08521662687)(2.510743438\omega_0^3 - .1486876805)}{(1.155600653\omega_0^2 + 0.008371116414)^2 + (1.85\omega_0^2 - 0.08521662687)^2}\Bigg)\end{aligned} \tag{4.12}$$

Note that, at $\tau = \tau_0$ the system (1.2) undergoes Hopf bifurcation (Balasubramaniam et al. 2015; Yu and Cao 2007). From Figs. 1, 2, one can see, as the delay parameter τ increases and $\tau > \tau_0$ oscillatory dynamics will return to the stable state form. But if the time delay is reduced, $\tau < \tau_0$, transient oscillations induced by unstable periodic solutions is appeared. This shows the sensitivity of the model dynamics on the time delay τ.

In Figs. 1, 2, the parameter τ is defined such that system (1.2) undergoes Hopf bifurcation as the parameter is varried. Hence, in Fig. 1, one can observe sustained periodic oscillations induced by stable periodic solutions.

In Fig. 2, transient oscillations induced by unstable periodic solutions are illustrated.

The Table 2 is corresponding with clinical information (Margolis 2014), see Figs. 3, 4, 5, 6, 7, 8, 9.

Figure 3 shows the unstable trajectories without treatment, by using the parameters value in Table 2.

Both $CD4^+$ and virus counts have large fluctuations and average counts of $CD4^+$ decreases while average virus counts increases by time.

Only Treatment Control ($u_1 = 0$)

In Fig. 4, only the treatment control u_2 is used to optimize the objective function $J(u)$ while the vaccination control u_1 is set to zero.

The graph of $CD4^+$ and virus counts demonstrated that the progression of HIV-1 can be simulated by the model. The Fig. 5 shows that high and frequent doses of antiretroviral drug were needed to achieve optimal control of HIV-1.

Only vaccination control ($u_2 = 0$)

In Fig. 6, only the vaccination, control u_1, is used to optimize the objective function $J(u)$ while the treatment control u_2 is set to zero (Fig. 7).

Combined vaccination and treatment strategy

In this case, the combination of vaccine and drug is considered.

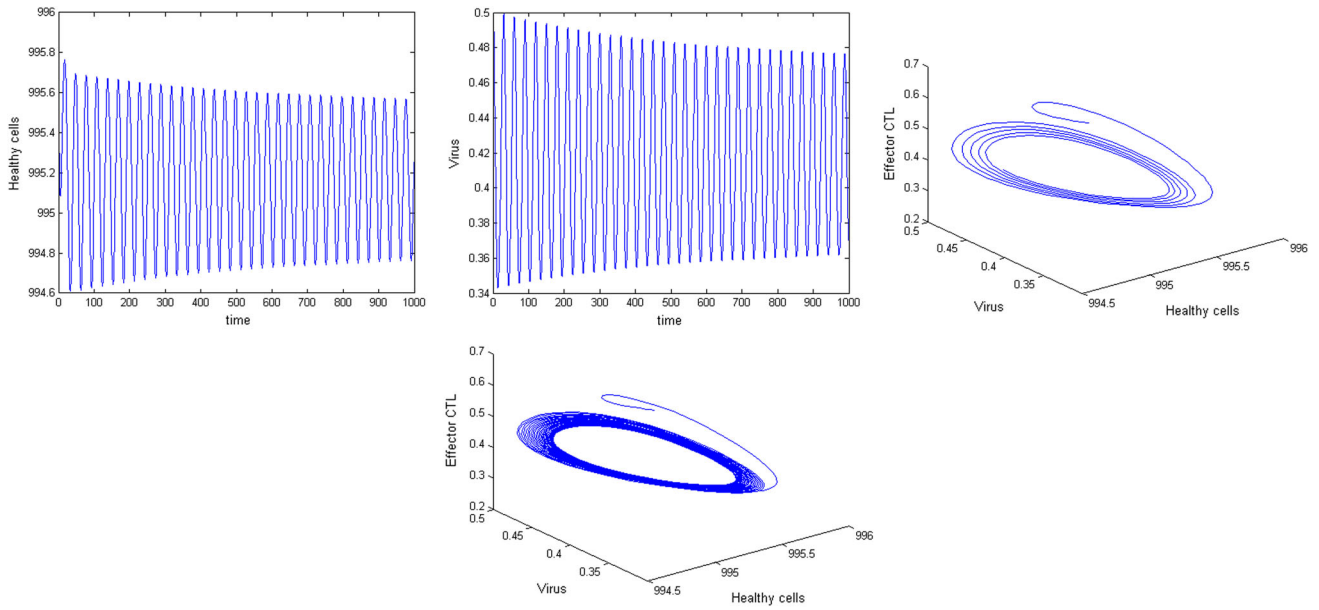


Fig. 1 Graphs of stable solutions $x(t)$ ($CD4^+$ T cells) and $y(t)$ (viral load), with initial value $(x_0, y_0, w_0, z_0) = (995.7, 0.5, 0.3962556306, 0.3804054055)$, and $\tau > \tau_0 = 1.454520056$

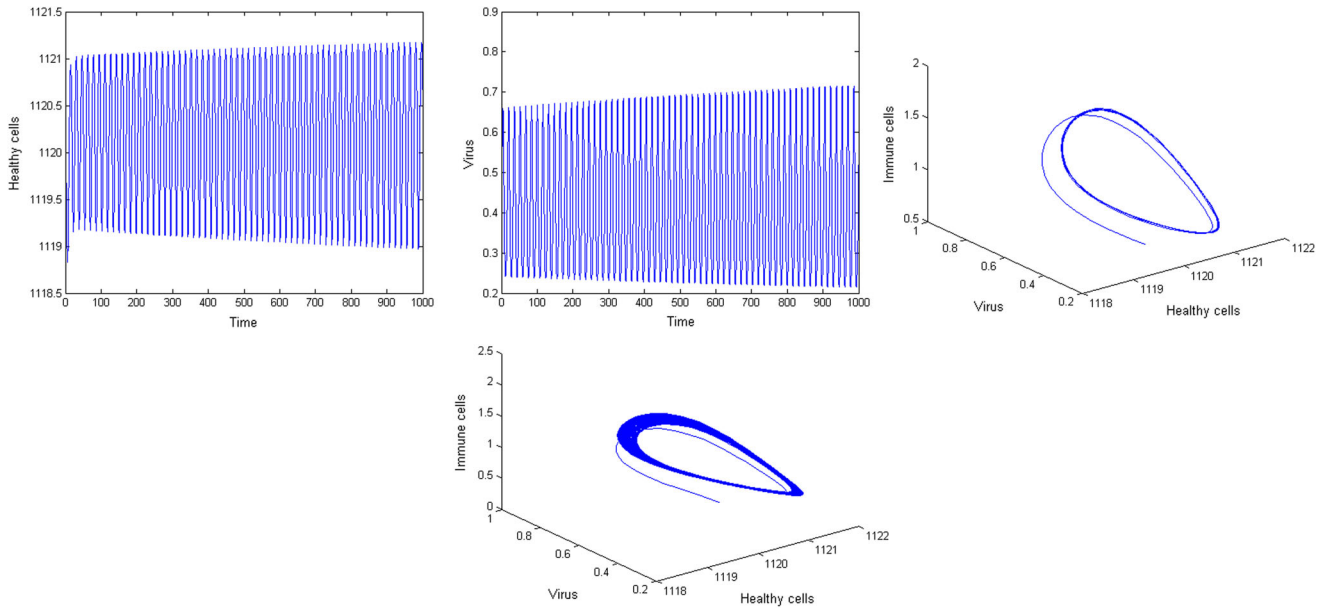


Fig. 2 Graphs of unstable solutions $x(t)$ ($CD4^+$ T cells) and $y(t)$ (viral load), with initial value $(x_0, y_0, w_0, z_0) = (1120, 0.4, 0.03962556306, 0.53804054055)$, and $\tau < \tau_0 = 1.454520056$

Explanations of the Figs. 3, 4, 5, 6, 7, 8, 9

Combination therapy controlled the disease progression better than treatment by vaccine or antiretroviral drug. There is less fluctuation in the level of $CD4^+$ and virus. Additionally, the proposed treatment regime for the antiretroviral drug had a more regular pattern. The total dose of administered drug in a same period was lower than mono therapy with antiretroviral drug. The AUC (area under the curve), of the ART graph in Fig. 9 is 388.8379 and it was lower than the one that calculated for Fig. 5 (AUC of Fig. 5 is 450.6702).

Remark 1 Although in Fig. 8 most of HIV-1-infected cells die, but a small proportion of them survive with HIV-

Table 2 Parameters are chosen such that the equilibrium point E_2 to be unstable

Parameter	Value	Unit
λ	10	$\text{day}^{-1}\ \text{mm}^{-3}$
β	5	$\text{day}^{-1}\ \text{mm}^{-3}$
μ_1	0.1	day^{-1}
μ_2	2	day^{-1}
μ_3	3	day^{-1}
μ_4	0.25	day^{-1}
c	0.75	day^{-1}
q	0.5	day^{-1}
p	100	day^{-1}
τ	7×10^{-8}	day^{-1}

1 DNA persistently integrated in their genome. Since these cells are some of the longest-lived cells in the body, HIV-1 infection can persist for decades in this latent cellular reservoir that is inaccessible to the immune system or present antiretroviral therapy (Palmisano and Vella 2011).

Furthermore, the initiation of antiretroviral therapy (ART) during primary infection may offer clinical benefits for HIV-1-infected individuals by reducing HIV-1 DNA reservoir size and chronic T-cell activation (Hey-Cunningham et al. 2015). So, it was attempted to find out if the beneficial effect of early retroviral therapy can be simulated by the proposed model. For this aim, the Fig. 10 is simulated with the initial value which is obtained after near 6 month, without any treatment (see Fig. 3).

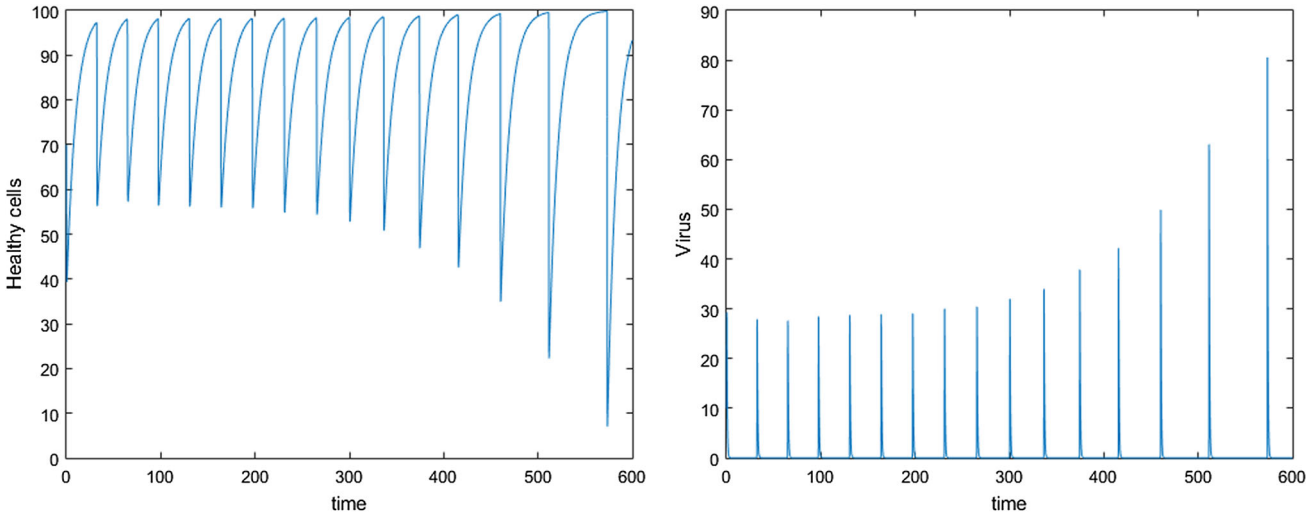


Fig. 3 Graphs of unstable solutions $x(t)$ ($CD4^+$ T cells) and $y(t)$ (viral load), with initial value $(x_0, y_0, w_0, z_0) = (70, 10, 0.081, 0.21)$

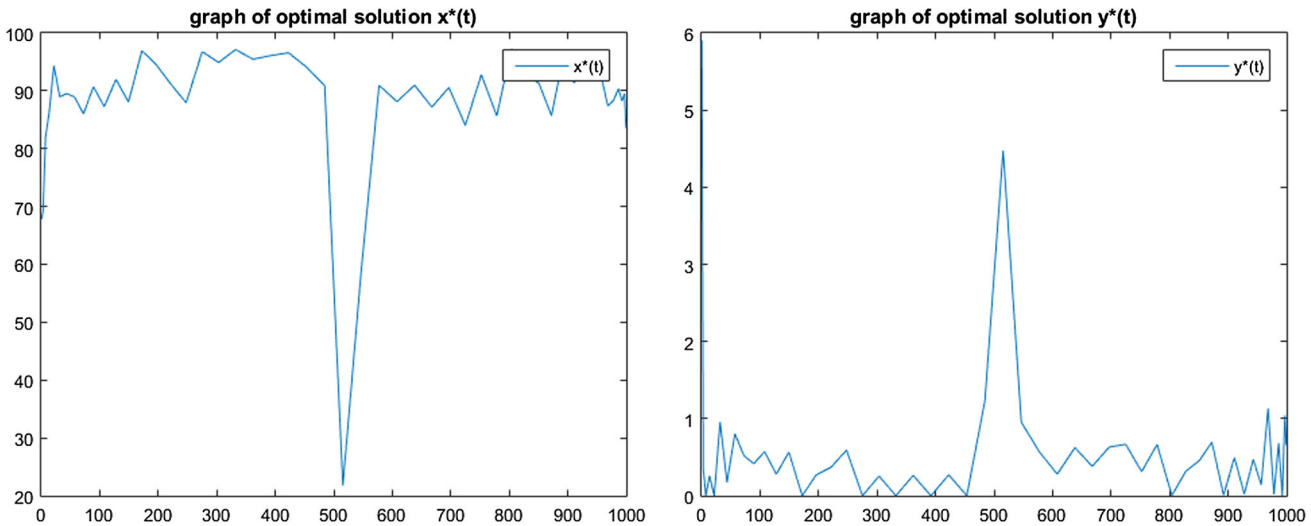


Fig. 4 Graphs of optimal solutions $x^*(t)$ (optimal $CD4^+$) and $y^*(t)$ (optimal viral load) with the same initial values and same parameter τ, as Fig. 3 and $u_1 = 0$

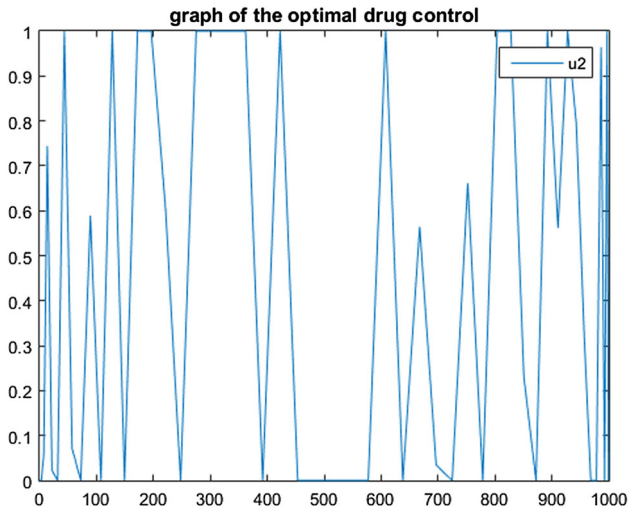


Fig. 5 Graphs of optimal control u_2, with $A_1 = A_2 = 100$ and $B_2 = 4$. The area under the curve u_2 is equal with 450.6702

As it was shown early ART (Fig. 4) accompanied with better control of $CD4^+$ level compared to 6-months delayed ART (Fig. 10) that was consistent with clinical results Le et al. (2013).

Results and discussion

Result

For numerical simulation first we considered the untreated model without any control. In this case, the parameter τ is chosen to show that system (1.2) with delay can have a complex dynamic and undergoes Hopf bifurcation. Thereafter, the effects of controllers on (1.3) have been investigated. Decline in uninfected $CD4^+$ cells and uncontrollable increase in virus counts are seen in acute phase of the HIV-1 disease (Hattaf and Yousfi 2012) that was simulated by the model (Fig. 3). It was shown clinically that ART can keep the virus count very low (Sáez-Cirión et al. 2013) and similar results were obtained by simulation (Fig. 4). The viral load can be controlled by current antiviral therapy regimes. However, they do not eliminate HIV-1 from latently infected reservoirs and lifelong antiviral therapy is necessary. Despite of this decline in virus level, reservoir of the virus was remained (Margolis 2014). It was proposed that concomitant vaccination can improve the results of ART (de Goede et al. 2015). In addition, there is a concern of adverse effects and even

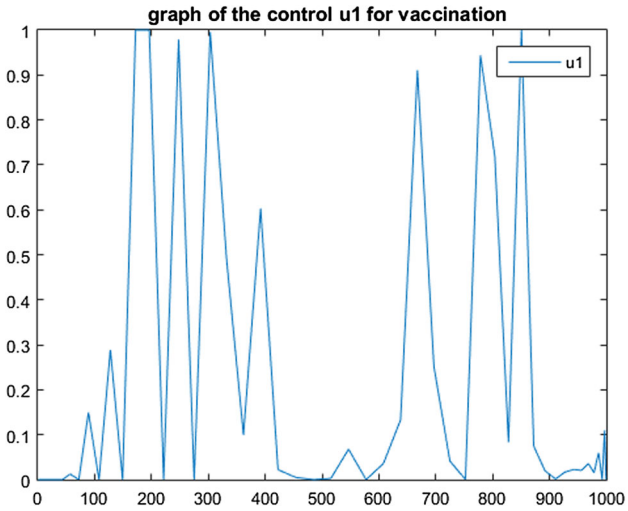
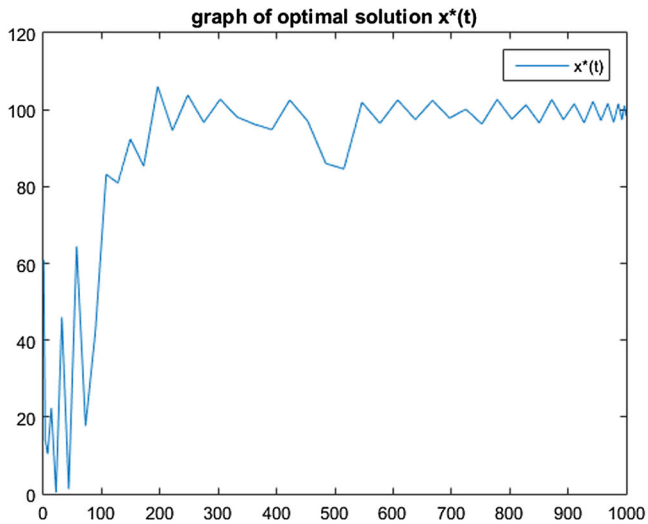


Fig. 7 Graphs of optimal control u_1, with $A_1 = A_2 = B_1 = 100$. The area under the curve u_1 is equal to 260.7155



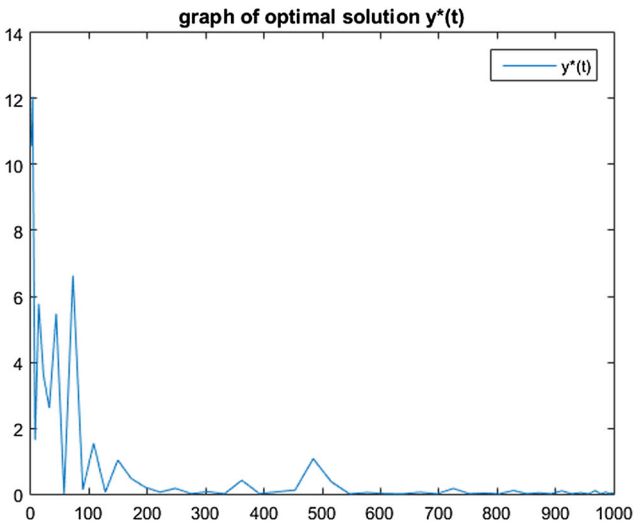


Fig. 6 Graphs of optimal solutions $x^*(t)$ (optimal $CD4^+$) and $y^*(t)$ (optimal viral load) with the same initial values and same parameter τ, as Fig. 3 and $u_2 = 0$

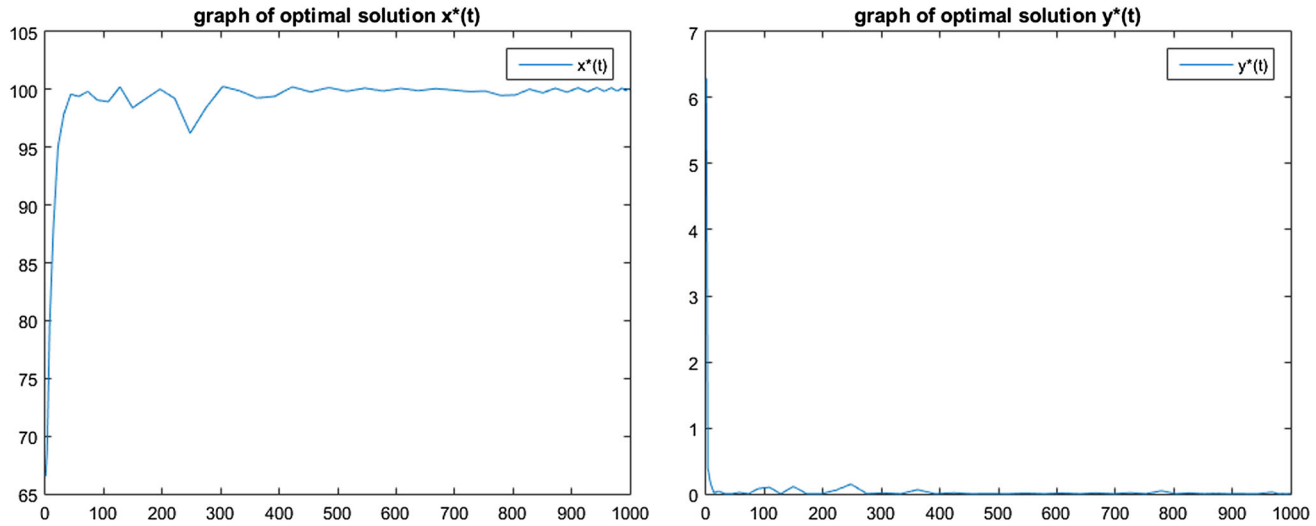


Fig. 8 Graphs of optimal solutions $x^*(t)$ (optimal CD4$^+$) and $y^*(t)$ (optimal viral load) with the same initial values and same parameter τ, as Fig. 3

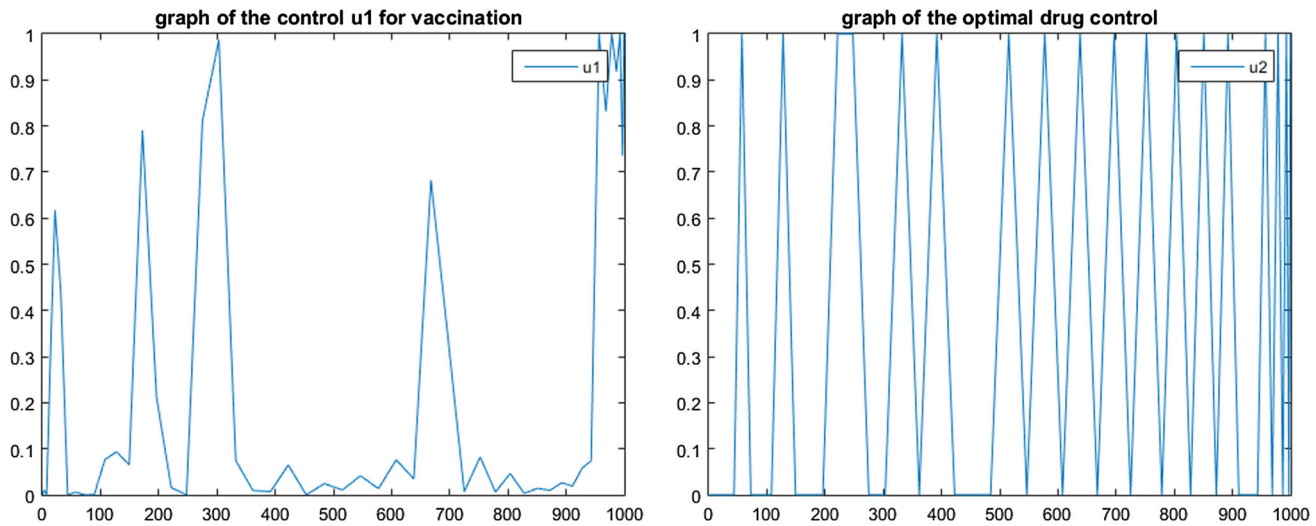


Fig. 9 Graphs of optimal controls u_1, and u_2, with $A_1 = A_2 = B_1 = 100$ and $B_2 = 4$. The area under the curve for u_1 is 186.4272 and the area under the curve for u_2 is 388.8379

toxicity of life-long therapy with the antiretroviral drugs (Margolis 2014).

Discussion

Our numerical simulations indicated that using two controllers (vaccine and drug) lead to better outcomes in comparison to vaccine or drug alone. Furthermore, administration of vaccine decreases the total dosage of drug (area under the curve of Figs. 9 and 5 for u_2). Thus, administration of vaccine decreases the dosage and possible side effects of long-term therapy by antiviral drugs. The beneficial effect of early ART were reported by several studies (Le et al. 2013; Macatangay and Rinaldo 2015; Hogan et al. 2012; Sáez-Cirión et al. 2013; Stöhr et al. 2013). The better improvement of CD4$^+$ using early ART was reported (Le et al. 2013). The simulation results were in consistence with this report and early treatment with antiretroviral drug (Fig. 4) showed more promising outcomes than a delayed treatment (Fig. 10).

For numerical simulating with controllers, the package TOMLAB and MATLAB software is used.

Conclusion

In this paper, we considered a problem of optimal control for HIV-1 infection model with delay. We have defined a four dimensional model which is equipped with two controls. Introducing controller u_2 in conjunction with

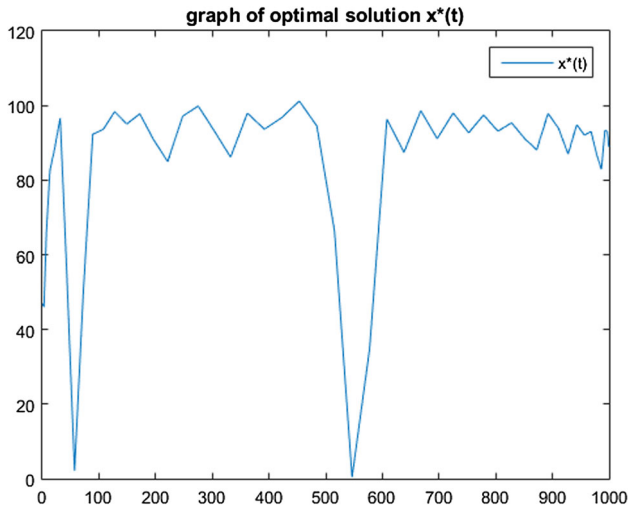


Fig. 10 Graphs of optimal control $x^*(t)$, with initial value $(x_0, y_0, w_0, z_0) = (58, 21, 0, 0.2)$, that is after 197 days without any treatment

controller u_1 improved the CTL response and inhibited the viral replication effectively. Introduced model in this study simulated some of the features of HIV-1 disease and predicted the beneficiary effects of combination therapy by vaccine and anti-retroviral therapy. Also, by the Figs. 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10, we have shown that our numerical solutions are corresponding with the clinical information.

References

Aniţa S, Arnăutu V, Capasso V (2011) An introduction to optimal control problems in life sciences and economics: from mathematical models to numerical simulation with MATLAB. Birkhäuser, Boston

Balasubramaniam P, Tamilalagan P, Prakash M (2015) Bifurcation analysis of HIV infection model with antibody and cytotoxic T-lymphocyte immune responses and beddington-deangelis functional response. Math Methods Appl Sci 38(7):1330–1341

Collins C, Fister K, Williams M (2010) Optimal control of a cancer cell model with delay. Math Model Nat Phenom 5(3):63–75

Elaiw A (2010) Global properties of a class of HIV models. Nonlinear Anal Real World Appl 11(4):2253–2263

de Goede AL, Vulto AG, Osterhaus ADME, Gruters RA (2015) Understanding HIV infection for the design of a therapeutic vaccine. Part II: vaccination strategies for HIV. In: Annales Pharmaceutiques Françaises, vol 73, no. 3. Elsevier, pp 169–179

Göllmann L, Kern D, Maurer H (2009) Optimal control problems with delays in state and control variables subject to mixed control-state constraints. Optim Control Appl Methods 30(4):341–365

Grigorieva EV, Khailov EN, Bondarenko NV, Korobeinikov A (2014) Modeling and optimal control for antiretroviral therapy. J Biol Syst 22(02):199–217

Hale JK, Lunel SMV (2013) Introduction to functional differential equations, vol 99. Springer, New York

Hattaf K, Yousfi N (2012) Optimal control of a delayed HIV infection model with immune response using an efficient numerical method. In: ISRN biomathematics

Herasimtschuk A, Downey J, Nelson M, Moyle G, Mandalia S, Sikut R, Adojaan M, Stanescu I, Gotch F, Imami N (2014) Therapeutic immunisation plus cytokine and hormone therapy improves CD4 T-cell counts, restores anti-HIV-1 responses and reduces immune activation in treated chronic HIV-1 infection. Vaccine 32(51):7005–7013

Hey-Cunningham WJ, Murray JM, Natarajan V, Amin J, Moore CL, Emery S, Cooper DA, Zaunders J, Kelleher AD, Koelsch KK et al (2015) Early antiretroviral therapy with raltegravir generates sustained reductions in HIV reservoirs but not lower T-cell activation levels. AIDS 29(8):911–919

Hogan CM, DeGruttola V, Sun X, Fiscus SA, Del Rio C, Hare CB, Markowitz M, Connick E, Macatangay B, Tashima KT et al (2012) The setpoint study (ACTG A5217): effect of immediate versus deferred antiretroviral therapy on virologic set point in recently HIV-1-infected individuals. J Infect Dis 205(1):87–96

Joshi HR (2002) Optimal control of an HIV immunology model. Optim Control Appl Methods 23(4):199–213

Karrakchou J, Rachik M, Gourari S (2006) Optimal control and infectiology: application to an HIV/AIDS model. Appl Math Comput 177(2):807–818

Kwon HD (2007) Optimal treatment strategies derived from a HIV model with drug-resistant mutants. Appl Math Comput 188(2):1193–1204

Laarabi H, Abta A, Hattaf K (2015) Optimal control of a delayed SIRS epidemic model with vaccination and treatment. Acta Biotheoretica 63(2):87–97

Laubenbacher R (2007) An introduction to optimal control applied to immunology problems. In: Modeling and simulation of biological networks, vol 64. American Mathematical Soc, pp 94–110

Launay O, Surenaud M, Desaint C, Hamouda NB, Pialoux G, Bonnet B, Poizot-Martin I, Gonzales G, Cuzin L, Bourgault-Villada I et al (2013) Long-term CD4+ and CD8+ T-cell responses induced in HIV-uninfected volunteers following intradermal or intramuscular administration of an HIV-lipopeptide vaccine (anrs vac16). Vaccine 31(40):4406–4415

Le T, Wright EJ, Smith DM, He W, Catano G, Okulicz JF, Young JA, Clark RA, Richman DD, Little SJ et al (2013) Enhanced CD4+ T-cell recovery with earlier HIV-1 antiretroviral therapy. N Engl J Med 368(3):218–230

Lenhart S, Workman JT (2007) Optimal control applied to biological models. CRC Press, Boca Raton

Macatangay BJ, Rinaldo CR (2015) Preserving hiv-specific t cell responses: does timing of antiretroviral therapy help? Curr Opin HIV AIDS 10(1):55–60

Margolis DM (2014) How might we cure HIV? Curr Infect Dis Rep 16(3):1–5

Palmisano L, Vella S (2011) A brief history of antiretroviral therapy of HIV infection: success and challenges. Annali dell'Istituto superiore di sanita 47(1):44–48

Roy PK (2016) Mathematical models for therapeutic approaches to control HIV disease transmission. Springer, New York

Sáez-Cirión A, Bacchus C, Hocqueloux L, Avettand-Fenoel V, Girault I, Lecuroux C, Potard V, Versmisse P, Melard A, Prazuck T et al (2013) Post-treatment HIV-1 controllers with a long-term virological remission after the interruption of early initiated antiretroviral therapy ANRS VISCONTI study. PLoS Pathog 9(3):E1003211

Shamsara E, Afsharnezhad Z, Efatti S (2016a) Optimal drug control of a four dimensional HIV infection model. Preprint

Shamsara E, Afsharnezhad Z, Mostolizadeh R (2016b) Hopf bifurcation for a discontinuous HTLV-1 model. Filomat. http://journal.pmf.ni.ac.rs/filomat/index.php/filomat/article/view/3401

Shamsara E, Javidmanesh E, Afsharnezhad Z (2016c) Stability and hopf bifurcation of a discontinuous HTLV-1 model with delayed CTL immune response. Preprint

Shim H, Han SJ, Chung CC, Nam SW, Seo JH (2003) Optimal scheduling of drug treatment for HIV infection: continuous dose control and receding horizon control. Int J Control Autom Syst 1:282–288

Shu H, Wang L, Watmough J (2013) Global stability of a nonlinear viral infection model with infinitely distributed intracellular delay and CTL immune responses. SIAM J Appl Math 73(3):1280–1302

Stöhr W, Fidler S, McClure M, Weber J, Cooper D, Ramjee G, Kaleebu P, Tambussi G, Schechter M, Babiker A et al (2013) Duration of HIV-1 viral suppression on cessation of antiretroviral therapy in primary infection correlates with time on therapy. PloS one 8(10):e78287

Tian X, Xu R (2014) Global stability and hopf bifurcation of an HIV-1 infection model with saturation incidence and delayed CTL immune response. Appl Math Comput 237:146–154

Volberding PA, Deeks SG (2010) Antiretroviral therapy and management of HIV infection. The Lancet 376(9734):49–62

Wang J, Wang K, Jiang Z (2015) Dynamical behaviors of an HTLV-I infection model with intracellular delay and immune activation delay. Adv Differ Equ 1:1–17

Wodarz D (2014) Modeling T cell responses to antigenic challenge. J Pharmacokin Pharmacodyn 41(5):415–429

Yu W, Cao J (2007) Stability and hopf bifurcation on a two-neuron system with time delay in the frequency domain. Int J Bifurcat Chaos 17(4):1355–1366