Bull Math Biol (2011) 73:2408–2429
DOI 10.1007/s11538-011-9630-z

ORIGINAL ARTICLE

Free Terminal Time Optimal Control Problem of an HIV Model Based on a Conjugate Gradient Method

Taesoo Jang · Hee-Dae Kwon · Jeehyun Lee

Received: 1 June 2010 / Accepted: 10 January 2011 / Published online: 27 January 2011

Abstract The minimum duration of treatment periods and the optimal multidrug therapy for human immunodeficiency virus (HIV) type 1 infection are considered. We formulate an optimal tracking problem, attempting to drive the states of the model to a "healthy" steady state in which the viral load is low and the immune response is strong. We study an optimal time frame as well as HIV therapeutic strategies by analyzing the free terminal time optimal tracking control problem. The minimum duration of treatment periods and the optimal multidrug therapy are found by solving the corresponding optimality systems with the additional transversality condition for the terminal time. We demonstrate by numerical simulations that the optimal dynamic multidrug therapy can lead to the long-term control of HIV by the strong immune response after discontinuation of therapy.

Keywords HIV dynamics · Optimal control · Free terminal time · Conjugate gradient method

1 Introduction

Human immunodeficiency virus (HIV) is the causative agent for acquired immune deficiency syndrome (AIDS). HIV infects $CD4^+$ T cells (and other target cells),

T. Jang · H.-D. Kwon (✉)
Department of Mathematics, Inha University, Yonghyundong, Namgu, Incheon 402-751, Republic of Korea
e-mail: hdkwon@inha.ac.kr

T. Jang
e-mail: iamnumber2@inha.ac.kr

J. Lee
Department of Computational Science and Engineering, Yonsei University, Shinchondong, Seodaemungu, Seoul 120-749, Republic of Korea
e-mail: ezhyun@yonsei.ac.kr

which are the fundamental components of the human immune response system. Since the first description of AIDS in 1981, the HIV/AIDS epidemic has continued to grow, but antiviral therapy for HIV-positive patients has greatly improved. The prevailing drug therapy is the highly active antiretroviral therapy (HAART), which consists of the concurrent administration of at least three antiretroviral drugs, commonly two nucleoside-analog reverse transcriptase inhibitors (RTI) and either a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor. Reverse transcriptase inhibitors lessen the HIV infection by blocking the integration of the viral code into the target cell. On the other hand, protease inhibitors are highly efficient at decreasing viral replication. Thus, HAART can reduce and maintain the viral load below detectable levels in many patients. However, the long-term use of HAART entails substantial complications. Patients taking these drugs suffer from many common and some critical side effects, such as cardiovascular problems, lactic acidosis, and mitochondrial damage. In addition, drug resistance, which reduces the effectiveness of the drugs in improving the symptoms of patients undergoing treatment, arises by natural selection; that is, mutant HIV strains are selected for viral replication in sublimiting drug concentrations. In addition, many patients in developing countries are burdened with high drug costs, and some do not have adequate access to anti-HIV drugs. For these reasons, some HIV-positive individuals refuse treatment, and an increasing number of patients discontinue the prescribed drug therapy for short or long periods. Consequently, there has been an urgent need for optimal treatment strategies that could reduce drug side effects and ease economic burdens associated with expensive drugs.

A number of studies have examined the role of cytotoxic T-lymphocytes (CD8 immune effector cells) (Ogg et al. 1998; Wodarz and Nowak 1999), which are considered to be key players in controlling the viral load. The present study investigates the treatment strategies that could boost adaptive cellular immune responses. One such strategy is structured treatment interruptions (STI), which involves alternating the on-and-off cycles of HAART to enhance the utility of therapy (Lisziewicz and Lori 2002; Ruiz et al. 2000). During treatment interruptions, the virus is free to replicate, consequently stimulating or reactivating HIV-specific immune responses. It has been reported that repeated treatment interruptions may enable patients to maintain immune control over the virus without any drug treatment (Lisziewicz and Lori 2002). In addition, STI has received considerable attention because it might reduce the risk of HIV mutating into strains resistant to current drug regimens. A concise summary of clinical STI studies, including protocols and results, is presented in Bajaria et al. (2004). Although the immune mechanisms corresponding to HIV are not clear, a number of mathematical models incorporating immune responses have been proposed. The model we use to demonstrate the optimal treatment of HIV infection is adapted from the model used in Adams et al. (2004, 2005), which includes the key compartments observed in clinical data sets. Our model choice is motivated by its admission of multiple stable steady states or equilibrium points. This feature enables us to more accurately model patients who interrupted treatment such that viral infection was controlled without further need for drugs. We consider the optimal strategies for effecting a transfer between these steady states in the minimum duration of treatment periods. Recently, the model

and an improved model including a compartment for $CD4^+$ memory cells have been validated with clinical data and have been shown to possess significant predictive capabilities with data at the individual patient level (Adams et al. 2007; Banks et al. 2008). The models in these reports have multiple locally asymptotically stable off-treatment equilibria. These off-treatment equilibria suggest that a treatment that moves a patient from a high virus load equilibrium to lower virus load equilibrium with strong immune effector is not always possible.

A number of researchers have used the control theoretic approach to derive an optimal drug administration scheme for controlling HIV infection. The open loop control problems of HIV infection in different types of models and objective functionals have been discussed in Adams et al. (2004, 2005), Fister et al. (1998), Kirschner et al. (1997). Feedback control problems have been explored and presented (Alvarez-Ramirez et al. 2000; Banks et al. 2006; Brandt and Chen 2001; Shim et al. 2003). Brandt and Chen (2001) consider some stable control methods for the HIV population by using an external feedback control term. Optimal feedback control problems with full state as well as with partial state measurements based on the state-dependent Riccati equation (SDRE) approach for HIV infection have been considered in Banks et al. (2006). Numerical simulations have demonstrated that the immune response would be stimulated and augmented sufficiently through optimal multidrug strategies to the point at which patients could control their infection without needing cumbersome treatment regimens (Adams et al. 2004, 2005; Banks et al. 2006). In the present paper, we propose an optimal control problem of HIV infection involving a free terminal condition, which has been applied mostly to economic and engineering-type problems. In addition, we suggest the minimum durations of treatment as well as the optimal treatment schedules for HIV patients to reach to a healthy state (i.e., immune control of viral infection).

The remainder of this paper proceeds as follows. In Sect. 2, we describe the HIV model suggested by Adams et al. (2004, 2005). In Sect. 3, we formulate a free terminal time optimal control problem with an objective functional that minimizes the duration of treatment and the systemic cost of chemotherapy. We also derive a corresponding optimality system, from which the optimal time and control may be obtained. In Sect. 4, we discuss a conjugate gradient method to solve the optimality system and present the numerical results of the optimal therapy and terminal time. We briefly summarize our efforts and findings in Sect. 5.

2 HIV Model

We introduce a nonlinear ordinary differential equation model that includes modeling for the immune response. As suggested by Callaways and Perelson (2001), our model has two target cells. In addition, the model contains an immune response component with Michaelis–Menten-type saturation nonlinearity (Adams et al. 2004, 2005). The

system of ODEs describing the compartmental infection dynamics is given by

$$\begin{aligned}
&\text{Type 1 target:} && \dot{S}_1 = \lambda_1 - d_1 S_1 - (1-\varepsilon_1) k_1 V S_1,\\
&\text{Type 2 target:} && \dot{S}_2 = \lambda_2 - d_2 S_2 - (1-f\varepsilon_1) k_2 V S_2,\\
&\text{Type 1 infected:} && \dot{I}_1 = (1-\varepsilon_1) k_1 V S_1 - \delta I_1 - m_1 E I_1,\\
&\text{Type 2 infected:} && \dot{I}_2 = (1-f\varepsilon_1) k_2 V S_2 - \delta I_2 - m_2 E I_2,\\
&\text{Virus:} && \dot{V} = (1-\varepsilon_2) N_T \delta (I_1 + I_2) - cV\\
&&&\qquad - \big[(1-\varepsilon_1)\rho_1 k_1 S_1 + (1-f\varepsilon_1)\rho_2 k_2 S_2\big] V,\\
&\text{Immune effectors:} && \dot{E} = \lambda_E + \frac{b_E (I_1+I_2)}{(I_1+I_2)+K_b} E - \frac{d_E (I_1+I_2)}{(I_1+I_2)+K_d} E - \delta_E E,
\end{aligned} \tag{1}$$

together with an initial condition

$$\big[S_1(0), S_2(0), I_1(0), I_2(0), V(0), E(0)\big].$$

This model includes six key compartments: two uninfected target cells (S_i, cells/ml), two infected cells (I_i, cells/ml), the free virus (V, copies/ml), and the immune response, CTLs (E, cells/ml). The model describes two co-circulating populations of target cells, potentially representing CD4$^+$ T-lymphocytes (S_1) and macrophages (S_2) (or perhaps activated and resting CD4$^+$ T cells; see Banks et al. 2008). We refer the reader to Adams et al. (2004, 2005), for an explanation of the source and death rates for these cell populations and focus our discussion on the interactions particularly relevant to drug treatment and STI scenarios. We discuss the model in the context of its representations of two methods for controlling infection: reverse transcriptase inhibitors and protease inhibitors.

The terms involving $k_i T_i V$ represent the infection process wherein infected cells I_i result from encounters between uninfected target cells T_i and the free virus V. The key difference between the two cell populations is in the infectivity rates k_1 and k_2, which could represent the difference in activation requirements for these types of cells. The model allows for the possibility of multiple (ρ_i) virions infecting each target cell. In the infectivity terms, the drug efficacy $\varepsilon_1(t)$ models an RT inhibitor that blocks new infections and is potentially more effective in Population 1 (S_1, I_1) than in Population 2 (S_2, I_2), where the efficacy is $f\varepsilon_1(t)$. We consider $0 \le a_1 \le \varepsilon_1(t) \le b_1 < 1$ so that a_1 and b_1 represent the minimal and maximal drug efficacy, respectively, and $f \in [0, 1]$.

Both types of infected cells produce free virus particles. We assume that the both types produce the same number N_T of free viral particles during a typical T_i cell life span. The control term $\varepsilon_2(t)$ represents the efficacy of protease inhibitors. Thus, the productivity, N_T is reduced by $(1-\varepsilon_2)N_T$ where $0 \le a_2 \le \varepsilon_2(t) \le b_2 < 1$. We do not add a compartment to explicitly model the production of the virus rendered non-infectious by the PIs.

Finally, infected cells I_i may be cleared via the action of immune effector cells (cytotoxic T-lymphocytes—CTLs), denoted by E. While the majority of the model

Table 1 The values and descriptions of the parameters used in the HIV model (1)

Parameter	Value	Units	Description
λ_1	10000	$\frac{\text{cells}}{\text{mL}\cdot\text{day}}$	Target cell type 1 production (source) rate
d_1	0.01	$\frac{1}{\text{day}}$	Target cell type 1 death rate
ε_1	$\in [0, 1)$	–	Efficacy of reverse transcriptase inhibitor
ε_2	$\in [0, 1)$	–	Efficacy of protease inhibitor
k_1	8.0×10^{-7}	$\frac{\text{mL}}{\text{virions}\cdot\text{day}}$	Population 1 infection rate
λ_2	31.98	$\frac{\text{cells}}{\text{mL}\cdot\text{day}}$	Target cell type 2 production (source) rate
d_2	0.01	$\frac{1}{\text{day}}$	Target cell type 2 death rate
f	0.34 ($\in [0, 1]$)	–	Treatment efficacy reduction in Population 2
k_2	1×10^{-4}	$\frac{\text{mL}}{\text{virions}\cdot\text{day}}$	Population 2 infection rate
δ	0.7	$\frac{1}{\text{day}}$	Infected cell death rate
m_1	1.0×10^{-5}	$\frac{\text{mL}}{\text{cells}\cdot\text{day}}$	Immune-induced clearance rate for Population 1
m_2	1.0×10^{-5}	$\frac{\text{mL}}{\text{cells}\cdot\text{day}}$	Immune-induced clearance rate for Population 2
N_T	100	$\frac{\text{virions}}{\text{cell}}$	Virions produced per infected cell
c	13	$\frac{1}{\text{day}}$	Virus natural death rate
ρ_1	1	$\frac{\text{virions}}{\text{cell}}$	Average number virions infecting a type 1 cell
ρ_2	1	$\frac{\text{virions}}{\text{cell}}$	Average number virions infecting a type 2 cell
λ_E	1	$\frac{\text{cells}}{\text{mL}\cdot\text{day}}$	Immune effector production (source) rate
b_E	0.3	$\frac{1}{\text{day}}$	Maximum birth rate for immune effectors
K_b	100	$\frac{\text{cells}}{\text{mL}}$	Saturation constant for immune effector birth
d_E	0.25	$\frac{1}{\text{day}}$	Maximum death rate for immune effectors
K_d	500	$\frac{\text{cells}}{\text{mL}}$	Saturation constant for immune effector death
δ_E	0.1	$\frac{1}{\text{day}}$	Natural death rate for immune effectors

is adapted from Callaway and Perelson (2001), the dynamics $\dot{E}$ for the immune response are as suggested by Bonhoeffer et al. (2000). The joint presence of infected cells and existing immune effector cells stimulates the proliferation of additional immune effector cells. In addition, the third term in the equation represents immune impairment at a high load. CTLs detect and lyse infected cells, thus killing them; their action is represented by the terms $m_i E I_i$ (infected cells die at the rate $m_i E$, which is dependent on the density of immune effectors). The inclusion of immune effectors reflects the belief that they have a crucial role in the context of STIs; The treatment strategies that can boost them to the point of immune control are shown later.

The mathematical model (1) contains numerous parameters that must be assigned before numerical simulations can be performed. In specifying the model parameters, we maximize the use of the values similar to those reported or justified in prior research. The definitions and numerical values for the parameters are summarized in Table 1 and are principally extracted from Bonhoeffer et al. (2000), Callaway and Perelson (2001). In practice, patients may have multiple locally asymptotically stable steady states, which depend on the patient's parameter values. The corresponding

attraction regions also depend on the parameter values. During continuous or STI drug treatment, the patient's system may be moved from one attraction region to another. For more information on the parameters and the attraction regions, see Adams et al. (2004, 2005). Our model choice is motivated in part by its accommodation of multiple stable steady states, which enables the modeling of patients such as the one mentioned earlier who interrupted therapy and then maintained viral control without therapy. Given the specified parameters, the model (1) exhibits several stable steady states with the assumption of no medication ($\varepsilon_1 = \varepsilon_2 = 0$) (Adams et al. 2004, 2005). Among these steady states, there exist two locally stable steady states:

$$\text{“unhealthy”:}\quad \widehat{S}_1 = 163573,\ \widehat{S}_2 = 5,\ \widehat{I}_1 = 11945,\ \widehat{I}_2 = 46,\ \widehat{V} = 63919,\ \widehat{E} = 24;$$

$$\text{“healthy”:}\quad \widetilde{S}_1 = 967839,\ \widetilde{S}_2 = 621,\ \widetilde{I}_1 = 76,\ \widetilde{I}_2 = 6,\ \widetilde{V} = 415,\ \widetilde{E} = 353108.$$

Here the “unhealthy” steady state corresponds to a dangerously high viral set point (i.e., depleted $CD4^+$ T cells) and a minimal immune response and the “healthy” steady state exhibits a high target cell count, a low viral load, and a strong immune response. Adams et al. (2004) and Banks et al. (2006) have considered optimal treatment strategies with open loop control and feedback control for effecting the transfer between two attraction regions of the steady state. In the present paper, we adopt a free terminal time optimal tracking problem to find both the minimum duration of treatment and the optimal therapy that can move from the attraction region of the “unhealthy” equilibria to that of the “healthy” equilibria.

3 A Free Terminal Time Optimal Tracking Control Problem

We now formulate an optimal tracking control problem with free terminal time to derive the optimal duration of treatment and the treatment schedule. We first define the objective functional as follows:

$$J(\varepsilon_1, \varepsilon_2, T) = \frac{1}{2}\left\{\int_0^T \left(R_1\varepsilon_1^2(t) + R_2\varepsilon_2^2(t)\right)dt + Q\big(V(T) - \widetilde{V}\big)^2 + S\big(E(T) - \widetilde{E}\big)^2 + PT^2\right\} \tag{2}$$

where R_1, R_2, Q, S, and P are the weight constants of the two controls, the virus, immune effectors, and time, respectively. The first and second terms represent the systemic costs of drug treatments. Our goal is to minimize the duration of treatment and systemic costs of drug treatments attempting to drive the virus and immune effectors to a “healthy” steady state. We seek an optimal control pair $\varepsilon^* = (\varepsilon_1^*, \varepsilon_2^*)$ and the optimal terminal time T^* such that

$$J(\varepsilon_1^*, \varepsilon_2^*, T^*) = \min\big\{J(\varepsilon_1, \varepsilon_2, T) | (\varepsilon_1, \varepsilon_2) \in U \text{ and } T \in \mathbb{R}_+\big\}$$

subject to the system of ODEs (1), where $U = \{(\varepsilon_1, \varepsilon_2) | \varepsilon_i$ is measurable, $a_i \le \varepsilon_i \le b_i,\ t \in [0, T],$ for $i = 1, 2\}$ is the control set. The basic framework of an optimal control problem is to prove the existence of the optimal control and then characterize the optimal control.

3.1 Existence of an Optimal Control Pair

The existence of a solution to the optimal control problem can be obtained by verifying sufficient conditions. We refer to the conditions in Theorem III.4.1 and its corresponding Corollary in Fleming and Rishel (1975). The boundedness of solutions of the system (1) for the finite time interval is needed to establish the conditions. Note that the quantities S_1, S_2, I_1, I_2, V, and E decrease only in proportional to their present sizes, respectively, and thus, all variables remain positive provided the initial values are positive. To establish the upper bounds on the solutions, we consider the supersolutions $\check{S}_1, \check{S}_2, \check{I}_1, \check{I}_2, \check{V}$ and $\check{E}$ satisfying

$$\frac{d\check{S}_1}{dt} = \lambda_1, \qquad \frac{d\check{S}_2}{dt} = \lambda_2, \qquad \frac{d\check{E}}{dt} = \lambda_E + b_E\check{E}$$

and

$$\frac{d\check{I}_1}{dt} = C_1 k_1 \check{V}, \qquad \frac{d\check{I}_2}{dt} = C_2 k_2 \check{V}, \qquad \frac{d\check{V}}{dt} = N_T \delta(\check{I}_1 + \check{I}_2).$$

The variables $\check{S}_1, \check{S}_2, \check{E}$ are uniformly bounded in finite time interval. The other variables $\check{I}_1, \check{I}_2, \check{V}$ are also uniformly bounded since they satisfy the linear system with bounded coefficients.

We list and check the requirements from the theorem as follows.
Let $f(t, \vec{x}, \vec{\varepsilon})$ be the right-hand side of (1) with $\vec{x} = [S_1, S_2, I_1, I_2, V, E]^t$ and $\vec{\varepsilon} = [\varepsilon_1, \varepsilon_2]^t$.

1. The function f is of class C^1 and there exists a constant C such that

$$\left|f(t, 0, 0)\right| \le C, \qquad \left|f_{\vec{x}}(t, \vec{x}, \vec{\varepsilon})\right| \le C\big(1 + |\vec{\varepsilon}|\big), \qquad \left|f_{\epsilon}(t, \vec{x}, \vec{\varepsilon})\right| \le C.$$

2. The set of controls and corresponding solutions to the system (1) is non-empty.
3. The control set U is convex and closed.
4. The function $f(t, \vec{x}, \vec{\varepsilon})$ is linear in control $\vec{\varepsilon}$ with coefficients dependent on time t and the state variable $\vec{x}$.
5. The integrand of the objective functional is convex on U and is bounded below by $c_1(|\varepsilon_1|^2 + |\varepsilon_2|^2)^{\frac{\beta}{2}} - c_2$, where c_1, $c_2 > 0$ and $\beta > 1$.
6. The payoff term at the terminal time in the objective functional $\phi(\vec{x}(T), T) = Q(V(T) - \widetilde{V})^2 + S(E(T) - \widetilde{E})^2 + PT^2$ is continuous.

The right-hand side of the system (1) satisfies condition 1 since the solutions to the state equations are a priori bounded. Condition 2 follows from an application of the existence result in Lukes (1982, Theorem 9.2.1) for the system with bounded coefficients. Conditions 3 and 4 are clear by definition. To verify condition 5, we note that the integrand of the functional, $R_1\varepsilon_1^2 + R_2\varepsilon_2^2$, is quadratic in the control, it is convex on U and

$$R_1\varepsilon_1^2 + R_2\varepsilon_2^2 \ge c_1\big(|\varepsilon_1|^2 + |\varepsilon_2|^2\big)^{\frac{\beta}{2}} - c_2,$$

where c_1, $c_2 > 0$, and $\beta > 1$. Finally, it is obvious that $\phi(x(T), T)$ is continuous.

3.2 Optimality System

Because an optimal control pair and an optimal terminal time exist, minimizing the functional (2) subject to (1), we now derive the necessary conditions for the optimal control pair and the terminal time by applying a version of Pontryagin's Maximum Principal (Fleming and Rishel 1975; Kamien and Schwartz 1991; Pontryagin et al. 1962).

Theorem 3.1 *Given an optimal control vector* $\varepsilon^* = (\varepsilon_1^*, \varepsilon_2^*)$, *an optimal terminal time* (T^*), *and solutions of the corresponding state system* (1), *there exists an adjoint vector* $\xi = [\xi_1, \xi_2, \xi_3, \xi_4, \xi_5, \xi_6]$ *satisfying*

$$\begin{cases}
\dot{\xi_1} = -\{\xi_1[-d_1 - (1-\varepsilon_1)k_1V] + \xi_3(1-\varepsilon_1)k_1V - \xi_5(1-\varepsilon_1)\rho_1k_1V\},\\
\dot{\xi_2} = -\{\xi_2[-d_2 - (1-f\varepsilon_1)k_2V] + \xi_4(1-f\varepsilon_1)k_2V - \xi_5(1-f\varepsilon_1)\rho_2k_2V\},\\
\dot{\xi_3} = -\{\xi_3(-\delta - m_1E) + \xi_5(1-\varepsilon_2)N_T\delta + \xi_6(\frac{b_EEK_b}{(I_1+I_2+K_b)^2} - \frac{d_EEK_d}{(I_1+I_2+K_d)^2})\},\\
\dot{\xi_4} = -\{\xi_4(-\delta - m_2E) + \xi_5(1-\varepsilon_2)N_T\delta + \xi_6(\frac{b_EEK_b}{(I_1+I_2+K_b)^2} - \frac{d_EEK_d}{(I_1+I_2+K_d)^2})\},\\
\dot{\xi_5} = -\{\xi_1(1-\varepsilon_1)k_1S_1 - \xi_2(1-f\varepsilon_1)k_2S_2 + \xi_3(1-\varepsilon_1)k_1S_1 + \xi_4(1-f\varepsilon_1)k_2S_2\\
\qquad - \xi_5(c + (1-\varepsilon_1)\rho_1k_1S_1 + (1-f\varepsilon_1)\rho_2k_2S_2)\},\\
\dot{\xi_6} = -\{-\xi_3m_1I_1 - \xi_4m_2I_2 + \xi_6(\frac{b_E(I_1+I_2)}{I_1+I_2+K_b} - \frac{d_E(I_1+I_2)}{I_1+I_2+K_d} - \delta_E)\},
\end{cases} \tag{3}$$

where $\xi(T^*) = [0, 0, 0, 0, Q(V(T^*) - \widetilde{V}), S(E(T^*) - \widetilde{E})]$

$$\begin{aligned}
&\frac{1}{2}\left(R_1{\varepsilon_1}^2 + R_2{\varepsilon_2}^2\right) + \xi_6\left[\lambda_E + \frac{b_E(I_1+I_2)}{(I_1+I_2)+K_b}E - \frac{d_E(I_1+I_2)}{(I_1+I_2)+K_d}E - \delta_E E\right]\\
&\quad + \xi_5\left[(1-\varepsilon_2)N_T\delta(I_1+I_2) - V\left[c + (1-\varepsilon_1)\rho_1k_1S_1 + (1-f\varepsilon_1)\rho_2k_2S_2\right]\right]\\
&\quad + Pt = 0 \quad \text{at } t = T^*.
\end{aligned} \tag{4}$$

Further, ε_1^* *and* ε_1^* *are represented by*

$$\begin{aligned}
\varepsilon_1^* &= \max\left(a_1, \min\left(b_1, \frac{-(\xi_1 - \xi_3 + \rho_1\xi_5)k_1VS_1 - (\xi_2 - \xi_4 + \rho_2\xi_5)fk_2VS_2}{R_1}\right)\right),\\
\varepsilon_2^* &= \max\left(a_2, \min\left(b_2, \frac{\xi_5N_T\delta(I_1+I_2)}{R_2}\right)\right).
\end{aligned} \tag{5}$$

Proof Define the Lagrangian (Hamiltonian augmented with penalty terms for the constraints) by

$$\begin{aligned}
&L(S_1, S_2, I_1, I_2, V, E, \varepsilon_1, \varepsilon_2, \xi_1, \xi_2, \xi_3, \xi_4, \xi_5, \xi_6)\\
&\quad = \frac{1}{2}\left(R_1\varepsilon_1^2(t) + R_2\varepsilon_2^2(t)\right) + \xi_1\left(\lambda_1 - d_1S_1 - \left(1-\epsilon_1(t)\right)k_1VS_1\right)\\
&\qquad + \xi_2\left(\lambda_2 - d_2S_2 - \left(1-f\epsilon_1(t)\right)k_2VS_2\right)
\end{aligned}$$

$$
\begin{aligned}
&+\xi_3\big(\big(1-\epsilon_1(t)\big)k_1VS_1-\delta I_1-m_1EI_1\big)\\
&+\xi_4\big(\big(1-f\epsilon_1(t)\big)k_2VS_2-\delta I_2-m_2EI_2\big)\\
&+\xi_5\big((1-\epsilon_2)N_T\delta(I_1+I_2)-cV-\big[\big(1-\epsilon_1(t)\big)\rho_1k_1S_1\\
&+\big(1-f\epsilon_1(t)\big)\rho_2k_2S_2\big]V\big)\\
&+\xi_6\left(\lambda_E+\frac{b_E(I_1+I_2)}{(I_1+I_2)+K_b}E-\frac{d_E(I_1+I_2)}{(I_1+I_2)+K_d}E-\delta_EE\right)\\
&-w_{11}(t)\big(\epsilon_1(t)-a_1\big)-w_{12}(t)\big(b_1-\epsilon_1(t)\big)-w_{21}(t)\big(\epsilon_2(t)-a_2\big)\\
&-w_{22}(t)\big(b_2-\epsilon_2(t)\big),
\end{aligned}
\tag{6}
$$

where $w_{ij}(t)\geq 0$ are the penalty multipliers satisfying

$$
\begin{aligned}
&w_{11}(t)\big(\varepsilon_1(t)-a_1\big)=w_{12}(t)\big(b_1-\varepsilon_1(t)\big)=0 \quad \text{at } \varepsilon_1=\varepsilon_1^* \quad \text{and}\\
&w_{21}(t)\big(\varepsilon_2(t)-a_2\big)=w_{22}(t)\big(b_2-\varepsilon_2(t)\big)=0 \quad \text{at } \varepsilon_2=\varepsilon_2^*.
\end{aligned}
$$

Setting the first variations of the Lagrangian with respect to states S_1, S_2, I_1, I_2, V, and E equal to zero yields a system of adjoint equations

$$
\begin{aligned}
&\dot{\xi}_1=-\frac{\partial L}{\partial S_1}, \qquad \dot{\xi}_2=-\frac{\partial L}{\partial S_2}, \qquad \dot{\xi}_3=-\frac{\partial L}{\partial I_1}, \qquad \dot{\xi}_4=-\frac{\partial L}{\partial I_2},\\
&\dot{\xi}_5=-\frac{\partial L}{\partial V}, \quad \text{and} \quad \dot{\xi}_6=-\frac{\partial L}{\partial E},
\end{aligned}
$$

with the terminal conditions

$$
\xi_i(T)=\frac{\partial\phi}{\partial x_i}\big(x(T),T\big), \quad i=1,2,\ldots,6
$$

where $\phi(x(T),T)=Q(V(T)-\widetilde{V})^2+S(E(T)-\widetilde{E})^2+PT^2$ and $x=[S_1,S_2,I_1,I_2,V,E]$.

We now derive the other transversality condition (4). Consider a real number $\delta\geq -T^*$ so that $T^*+\delta\in\mathbb{R}_+$. We can assume that ε^* is left-continuous at T^* by simply reassigning its value there if necessary. Then set $\varepsilon^*(t)=\varepsilon^*(T^*)$ for all $t>T^*$ so that ε^* is continuous at T^*. Now, V^* and E^* are also defined for $t>T^*$. As $J(\varepsilon_1,\varepsilon_2,T)$ reaches its minimum at $(\varepsilon_1^*,\varepsilon_2^*)$ and T^*, we have

$$
\lim_{\delta\to 0}\frac{J(\varepsilon^*,T^*+\delta)-J(\varepsilon^*,T^*)}{\delta}=0.
$$

Hence,

$$
\begin{aligned}
\lim_{\delta\to 0}\frac{1}{2\delta}\Bigg[&\int_0^{T^*+\delta}\big(R_1\varepsilon_1^{*2}+R_2\varepsilon_2^{*2}\big)\,dt-\int_0^{T^*}\big(R_1\varepsilon_1^{*2}+R_2\varepsilon_2^{*2}\big)\,dt\\
&+Q\big(V^*(T^*+\delta)-\widetilde{V}\big)^2+S\big(E^*(T^*+\delta)-\widetilde{E}\big)^2+P(T^*+\delta)^2
\end{aligned}
$$

$$
\begin{aligned}
&- Q\big(V^*(T^*) - \widetilde{V}\big)^2 - S\big(E^*(T^*) - \widetilde{E}\big)^2 - P(T^*)^2\Big] \\
&= \lim_{\delta\to 0} \frac{1}{2\delta} \int_{T^*}^{T^*+\delta} \big(R_1\varepsilon_1^{*2} + R_2\varepsilon_2^{*2}\big)\, dt \\
&\quad + \lim_{\delta\to 0} \frac{Q(V^*(T^*+\delta) - \widetilde{V})^2 - Q(V^*(T^*) - \widetilde{V})^2}{2\delta} \\
&\quad + \lim_{\delta\to 0} \frac{S(E^*(T^*+\delta) - \widetilde{E})^2 - S(E^*(T^*) - \widetilde{E})^2}{2\delta} \\
&\quad + \lim_{\delta\to 0} \frac{P(T^*+\delta)^2 - P(T^*)^2}{2\delta} \\
&= \frac{1}{2}\big(R_1\varepsilon_1^{*2}(T^*) + R_2\varepsilon_2^{*2}(T^*)\big) + \xi_5(T^*)\dot{V}^*(T^*) + \xi_6(T^*)\dot{E}^*(T^*) + PT^* = 0.
\end{aligned}
$$

Thus, the transversality condition (4) for the terminal time is obtained.

Differentiating the Lagrangian L with respect to ε_1, we also have

$$
\begin{aligned}
\frac{\partial L}{\partial \varepsilon_1} &= R_1\varepsilon_1 + (\xi_1 - \xi_3 + \rho_1\xi_5)k_1VS_1 + (\xi_2 - \xi_4 + \rho_2\xi_5)fk_2VS_2 \\
&\quad - w_{11}(t) + w_{12}(t) = 0.
\end{aligned}
$$

Solving for the optimal control yields

$$
\varepsilon_1^* = \frac{-(\xi_1 - \xi_3 + \rho_1\xi_5)k_1VS_1 - (\xi_2 - \xi_4 + \rho_2\xi_5)fk_2VS_2 + w_{11}(t) - w_{12}(t)}{R_1}.
$$

To determine an explicit expression for the optimal control without w_{11} and w_{12}, a standard optimization technique is used. Consider the following three cases.

(i) On the set $\{t|a_1 < \varepsilon_1^*(t) < b_1\}$, we have $w_{11}(t) = w_{12}(t) = 0$. Hence, the optimal control is

$$
\varepsilon_1^* = \frac{-(\xi_1 - \xi_3 + \rho_1\xi_5)k_1VS_1 - (\xi_2 - \xi_4 + \rho_2\xi_5)fk_2VS_2}{R_1}.
$$

(ii) On the set $\{t|\,\varepsilon_1^*(t) = b_1\}$, we have $w_{11}(t) = 0$. Hence

$$
b_1 = \varepsilon_1^* = \frac{-(\xi_1 - \xi_3 + \rho_1\xi_5)k_1VS_1 - (\xi_2 - \xi_4 + \rho_2\xi_5)fk_2VS_2 - w_{12}(t)}{R_1}.
$$

This implies that

$$
\frac{-(\xi_1 - \xi_3 + \rho_1\xi_5)k_1VS_1 - (\xi_2 - \xi_4 + \rho_2\xi_5)fk_2VS_2}{R_1} \geq b_1 \quad \text{since } w_{12}(t) \geq 0.
$$

(iii) On the set $\{t|\,\varepsilon_1^*(t) = a_1\}$, we have $w_{12}(t) = 0$. Hence

$$
a_1 = \varepsilon_1^* = \frac{-(\xi_1 - \xi_3 + \rho_1\xi_5)k_1VS_1 - (\xi_2 - \xi_4 + \rho_2\xi_5)fk_2VS_2 + w_{11}(t)}{R_1}.
$$

This implies that

$$\frac{-(\xi_1-\xi_3+\rho_1\xi_5)k_1VS_1-(\xi_2-\xi_4+\rho_2\xi_5)fk_2VS_2}{R_1}\le a_1 \quad \text{because } w_{11}(t)\ge 0.$$

Combining these three cases, the optimal control is characterized as

$$\varepsilon_1^*=\max\left(a_1,\min\left(b_1,\frac{-(\xi_1-\xi_3+\rho_1\xi_5)k_1VS_1-(\xi_2-\xi_4+\rho_2\xi_5)fk_2VS_2}{R_1}\right)\right).$$

Similarly, we also obtain

$$\varepsilon_2^*=\max\left(a_2,\min\left(b_2,\frac{\xi_5N_T\delta(I_1+I_2)}{R_2}\right)\right). \qquad \square$$

4 Numerical Results

We consider a free terminal time optimal tracking control problem, which often presents convergence diculties because of the complex structure of Hamiltonian systems. In particular, many iterations are needed to solve a free terminal control problem due to the transversality condition (4) for the terminal time. We use a conjugate gradient-type iterative method to solve the optimality system which is a two point boundary value problem. The *Conjugate Gradient Algorithm* is a powerful scheme for solving large scale optimization problems (Dai et al. 2004; Gilbert and Nocedal 1992; Lasdon et al. 1967; Shi and Guo 2008). Using an initial guess for the control variables, the state system (1) with initial conditions is solved forward in time and then the adjoint system (3) with terminal conditions is solved backward in time. The controls are updated in each iteration by the conjugate gradient algorithm. Finally, the hybrid secant-bisection method has been employed to implement the transversality condition. The algorithm proceeds as follows:

- choose initial guess of terminal times, T_0 and T_1;
  - choose initial guess of controls;
  - solve the state system forward in time with initial conditions using initial guess of controls;
  - solve the adjoint system backward in time with terminal conditions;
  - update the controls using by the conjugate gradient method;
- update the terminal time by the hybrid secant-bisection method;
- continue the iterations until convergence is achieved.

A detailed description of our conjugate gradient method is given below.

$$\begin{aligned}&\text{[Initialization]}\quad \varepsilon^0=\text{initial guess of controls},\\ &\qquad\qquad d^0=-g^0=-g\left(\varepsilon^0\right):=-\frac{\partial L}{\partial\varepsilon}\left(\varepsilon^0\right),\end{aligned} \tag{7}$$

$$\text{[Choose step size]}\quad \alpha^i:=\operatorname{Arg}\min_{\alpha} J\left(\varepsilon^i+\alpha d^i\right), \tag{8}$$

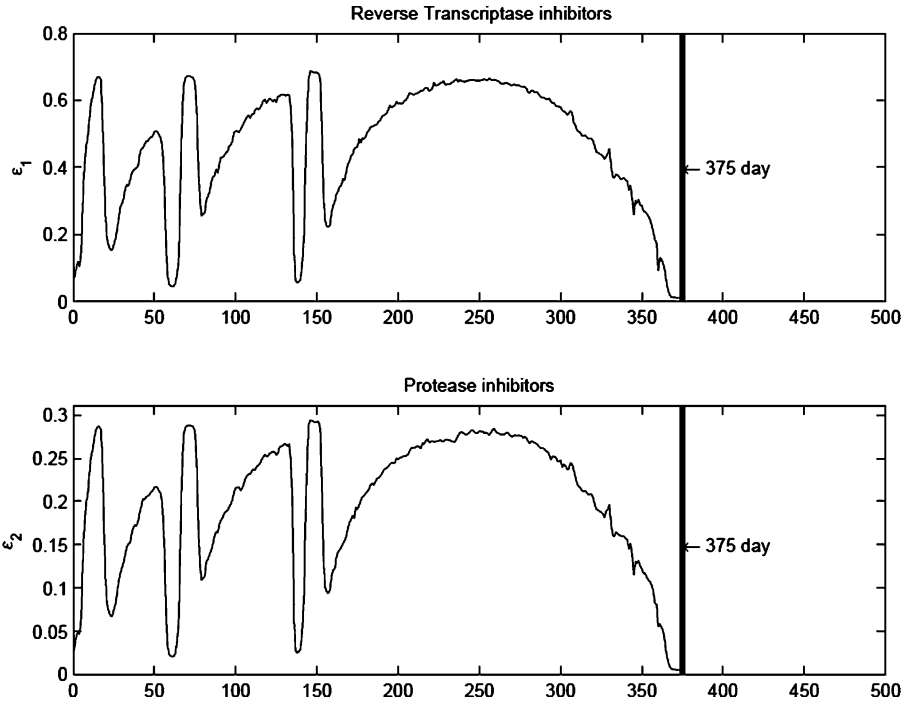

Fig. 1 Optimal control functions with $R_1 = 50000$, $R_2 = 50000$, $Q = 10^{-4}$, $S = 1$, and $P = 10^5$ in early infection. In this case, the optimal terminal time is $T^* = 375$ (day)

$$\text{[Update]} \quad \varepsilon^{i+1} = \varepsilon^i + \alpha^i d^i,$$

$$g^{i+1} = g\big(\varepsilon^{i+1}\big) := \frac{\partial L}{\partial \varepsilon}\big(\varepsilon^{i+1}\big), \tag{9}$$

$$\beta^i = \frac{(g^{i+1}, g^{i+1} - g^i)}{(g^i, g^i)},$$

$$d^{i+1} = -g^{i+1} + \beta^i d^i, \tag{10}$$

where

$$\big(g^i, g^j\big) = \int_0^T g^i(t) g^j(t)\, dt.$$

Let ε^i be the ith approximation to the optimal control ε^*. The corresponding gradient $g(\varepsilon^i)$ is computed by solving the state equation (1) forward with $\varepsilon = \varepsilon^i$, solving the adjoint equation (3) backward, and then computing $g(\varepsilon^i)$ from (9). The step size α is determined by solving the one dimensional minimization problem (8). For more information on this iterative method, we refer the interested reader to Lasdon et al. (1967). The parameters used in solving the optimality system are summarized in Table 1. We set the minimum efficacy at $a_1 = 0$ and $a_2 = 0$ and the maximum efficacy at $b_1 = 0.7$ and $b_2 = 0.3$. Because of differences in the magnitude of the cost of drug

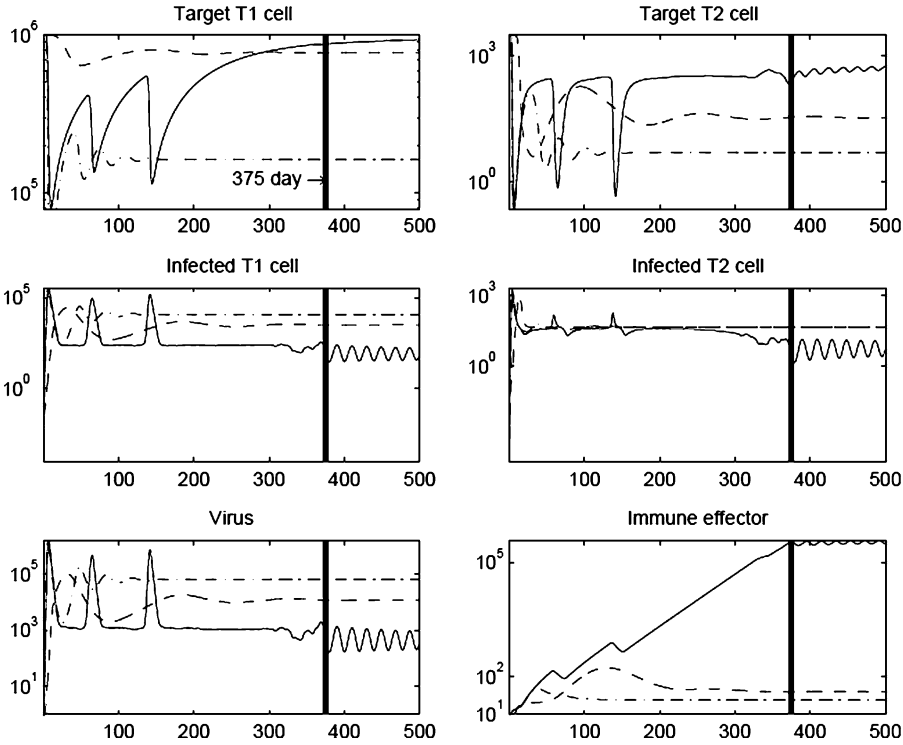

Fig. 2 Optimal solutions (*solid line*) with $R_1 = 50000$, $R_2 = 50000$, $Q = 10^{-4}$, $S = 1$, and $P = 10^5$; solutions (*dashed line*) with fully efficacious treatment using both drugs (i.e., $\varepsilon_1 \equiv 0.7$ and $\varepsilon_2 \equiv 0.3$); and solutions (*dashed and dotted line*) with no drug treatment (i.e., $\varepsilon_1 = \varepsilon_2 \equiv 0$) in early infection

treatment, the viral load, and immune effectors in the objective functional (2), the weight constants $R_1 = 50000$, $R_2 = 50000$, $Q = 10^{-4}$, $S = 1$ and $P = 10^5$ were selected to balance the units. On the other hand, in the numerical runs, we further varied the constants to place greater weight on the immune effectors and the terminal time.

4.1 Optimal Treatment and Terminal Time in Early Infection

The first example is a case in which a patient is placed on medication immediately after HIV infection. For this, we simulated early infection by introducing one virus particle and very low levels of infected T cells as follows:

$$S_1(0) = 10^6, \qquad S_2(0) = 3198, \qquad I_1(0) = 10^{-4}, \qquad I_2(0) = 10^{-4},$$
$$V(0) = 1 \quad \text{and} \quad E(0) = 10.$$

As shown in Fig. 1, the numerical simulations suggest the minimum duration of drug treatment of 375 days and the optimal control function pair. In Fig. 2, we observed the corresponding system behavior by solving the model equations (1) under this optimal treatment regimen up to the 375th day and no treatment from the 376th

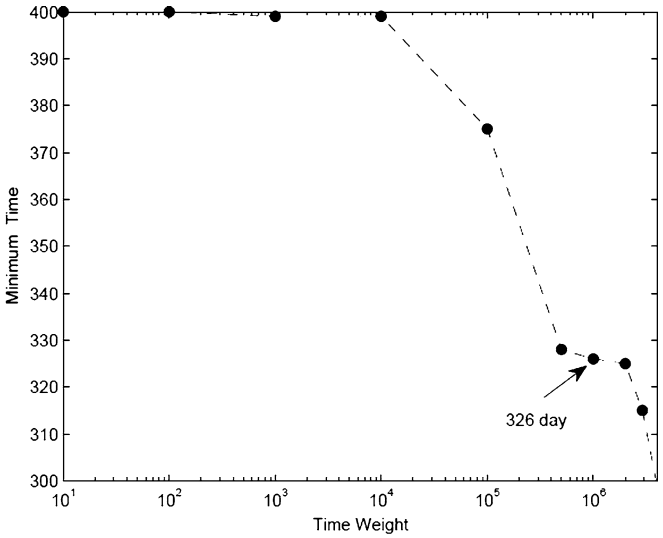

Fig. 3 The relationship between the weight constants for time P and the optimal time T^* with $R_1 = 50000$, $R_2 = 50000$, $Q = 10^{-4}$, and $S = 1$ in early infection

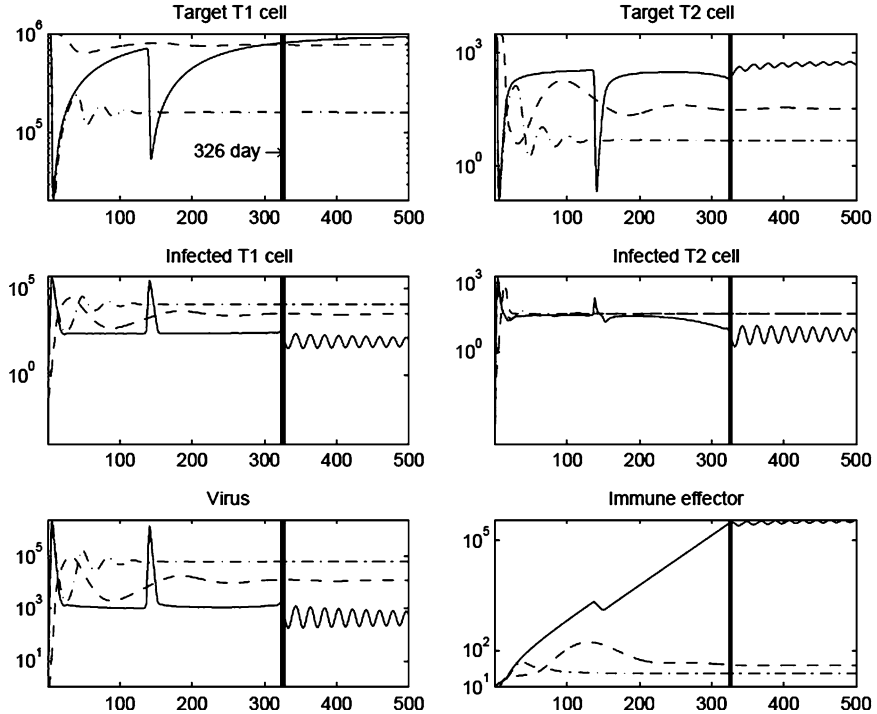

Fig. 4 Optimal solutions (*solid line*) for $T^* = 326$ (day); solutions (*dashed line*) with fully efficacious treatment; and solutions (*dashed and dotted line*) with no treatments in early infection

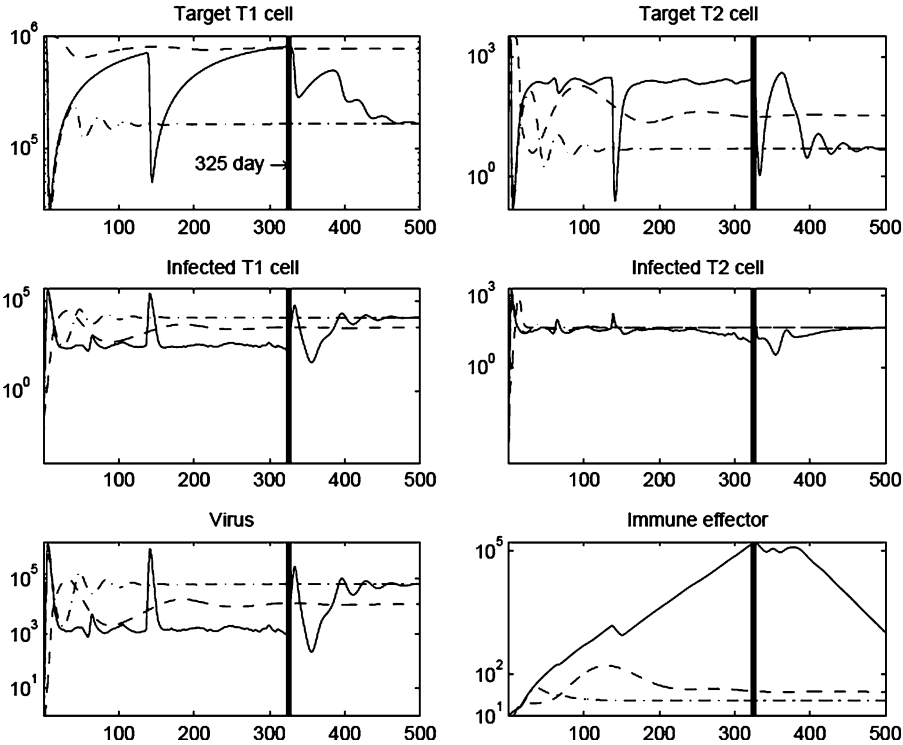

Fig. 5 Optimal solutions (*solid line*) for $T^* = 325$ (day); solutions (*dashed line*) with fully efficacious treatment; and solutions (*dashed and dotted line*) with no treatments in early infection

day to the 500th day. Figure 2 also compares the result of full treatment solutions (i.e., $\varepsilon_1 \equiv 0.7$ and $\varepsilon_2 \equiv 0.3$) with that of no treatment solutions (i.e., $\varepsilon_1 = \varepsilon_2 \equiv 0$) for 500 days.

The shapes of the two control functions are almost identical as depicted in Fig. 1. Noteworthy in Fig. 1 is the STI-like characteristics of the optimal dynamic therapy. In particular, both drugs tapered off around 20th, 60th, and 140th days. Because of the decreased controls, the populations of the virus (V) and the infected target cells (I_1 and I_2) grew to extremely high levels around those days (Fig. 2). In addition, high viral loads stimulated the immune effectors (E), boosting immune responses.

Note that the treatment schedule based on the optimal solutions was highly efficient. The population of uninfected S_1 cells with an optimal control pair approached that of uninfected S_1 cells with full treatment and mostly recovered from the effects of HIV at the end of the time period, even though both drugs were discontinued after 375th day. Moreover, the viral load with an optimal control pair was sustained at low levels except around the 20th, 60th, and 140th days because of the high concentration of immune effectors (E). The immune effector population with the optimal control pair at the 375th day was high enough to reach the "healthy" stable equilibrium, resulting in a strong immune response that successfully controlled the virus and consequently restored uninfected target cells (S_1 and S_2) with-

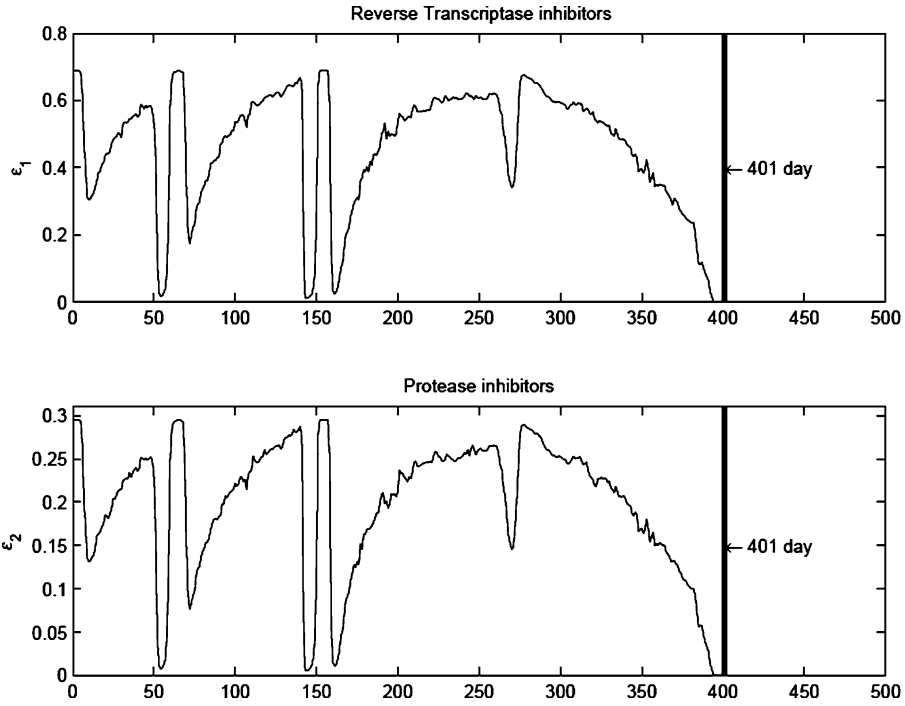

Fig. 6 Optimal control functions with $R_1 = 50000$, $R_2 = 50000$, $Q = 10^{-4}$, $S = 1$, and $P = 10^5$ in the unhealthy steady state. In this case, the optimal terminal time is $T^* = 401$ (day)

out the need for drugs. This scenario (i.e., the effective control of HIV after discontinuation of therapy because of a very strong immune response) is consistent with the findings of many previous studies (e.g., Adams et al. 2004; Banks et al. 2006; Lisziewicz and Lori 2002 and the references therein).

As shown in Fig. 3, we investigated the effect of the weight constant for time P to the optimal terminal time T^* by varying P from 10^1 to 10^7. Consequently, the optimal terminal time decreased as the weight constant for time increased. Of great interest then is the minimum duration of treatment for a patient to reach a "healthy" steady state. In this regard, we investigated the threshold quantity for the terminal time, which indicates whether it is possible to achieve the "healthy" equilibrium with any admissible control functions. As shown in Figs. 4 and 5, the patient's system stayed in the attraction region of the "healthy" equilibrium when the treatment was discontinued after 326 days, whereas the system returned to the "unhealthy" attraction region when the terminal time was less than or equal to 325 days. This suggests that a minimum duration of 326 days is required for a treatment strategy that can lead to the long-term control of HIV after discontinuation of therapy. On the other hand, the optimal terminal time T^* stayed around 400 days as the weight constant for time decreased (Fig. 3). This suggests that 400 days of treatment might be sufficient for a patient's system to move to a healthy state of immune control.

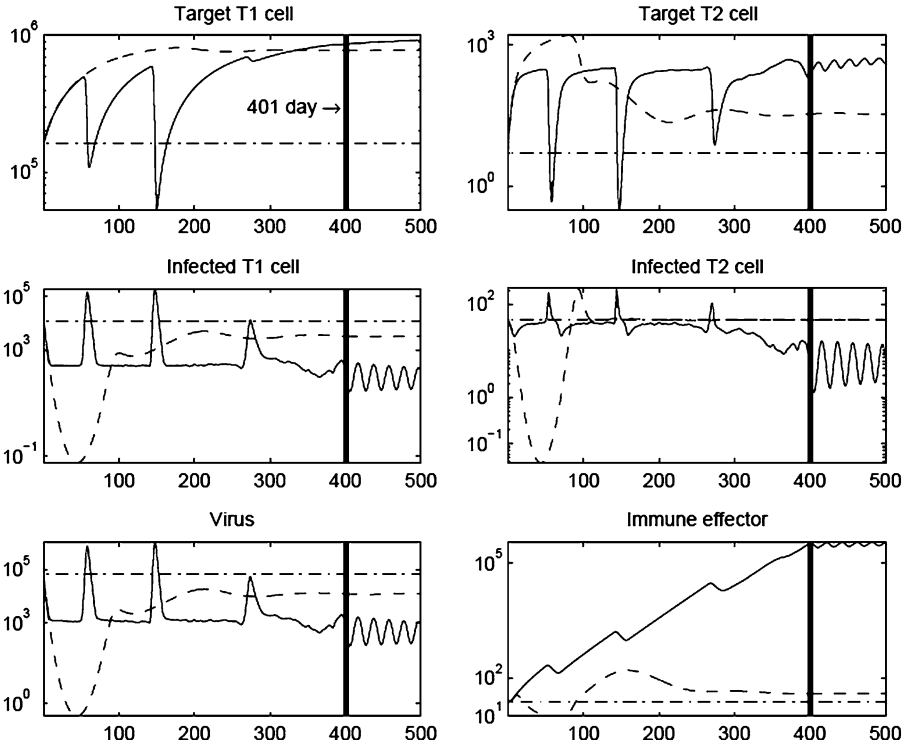

Fig. 7 Optimal solutions (*solid line*) with $R_1 = 50000$, $R_2 = 50000$, $Q = 10^{-4}$, $S = 1$, and $P = 10^5$; solutions (*dashed line*) with fully efficacious treatment using both drugs (i.e., $\varepsilon_1 \equiv 0.7$ and $\varepsilon_2 \equiv 0.3$); and solutions (*dashed and dotted line*) with no drug treatment (i.e., $\varepsilon_1 = \varepsilon_2 \equiv 0$) in the unhealthy steady state

4.2 Optimal Treatment and Terminal Time in the "Unhealthy" Steady State

We now consider the case of AIDS patients. For this, we ran the simulations under an initial condition reflecting the "unhealthy" steady states

$$T_1(0) = 163573, \qquad T_2(0) = 5, \qquad I_1(0) = 11945, \qquad I_2(0) = 46,$$
$$V(0) = 63919, \qquad E(0) = 24.$$

The same weight constants in the early infection case were used to compare the minimum durations of drug treatment and the optimal control function pairs. Figure 6 shows the optimal duration of drug treatment and the optimal control function pair. The treatment strategies were qualitatively similar to early infection. The optimal treatment in this case required 26 more days than the early infection case to reach a "healthy" steady state. The graphs shown in Fig. 7 show the system behavior under this optimal treatment regimen up to the 401st day and from the 402nd day to the 500th day with no treatment. Again, these corresponding solutions were compared with the full treatment (i.e., $\varepsilon_1 \equiv 0.7$ and $\varepsilon_2 \equiv 0.3$) and no treatment solutions (i.e., $\varepsilon_1 = \varepsilon_2 \equiv 0$) for 500 days. Similar to the previous example, the results suggest that

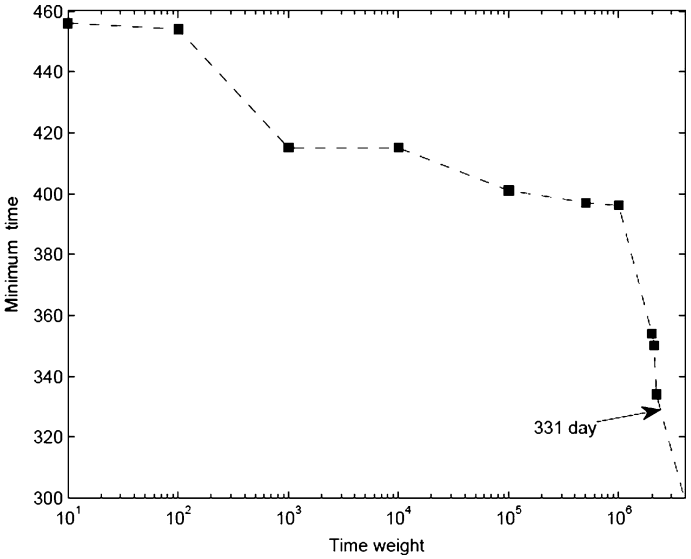

Fig. 8 The relationship between the weight constants for time P and the optimal time T^* with $R_1 = 50000$, $R_2 = 50000$, $Q = 10^{-4}$, and $S = 1$ in the unhealthy steady state

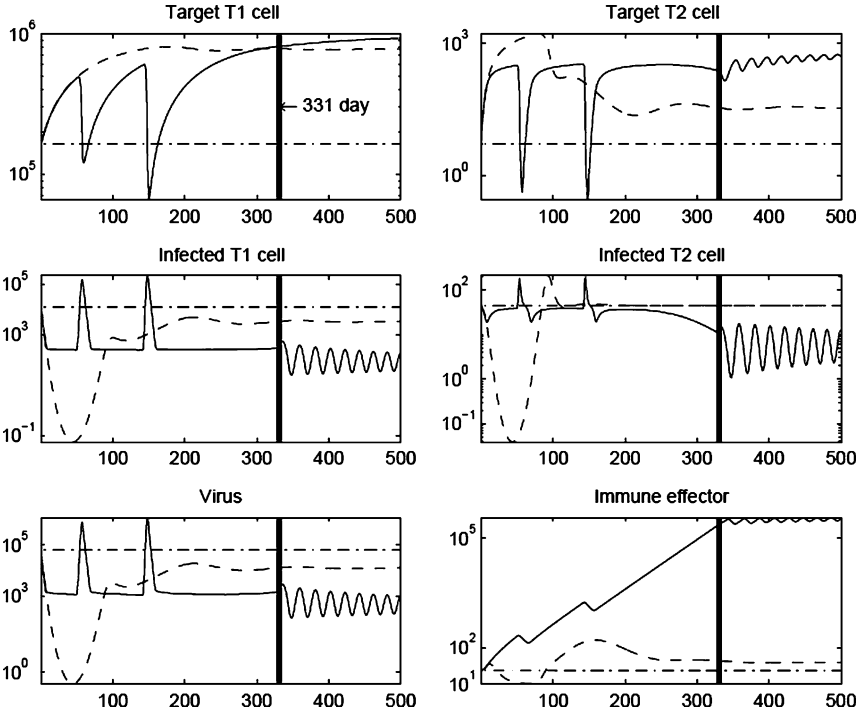

Fig. 9 Optimal solutions (*solid line*) for $T^* = 331$ (day); solutions (*dashed line*) with fully efficacious treatment; and solutions (*dashed and dotted line*) with no treatment in the unhealthy steady state

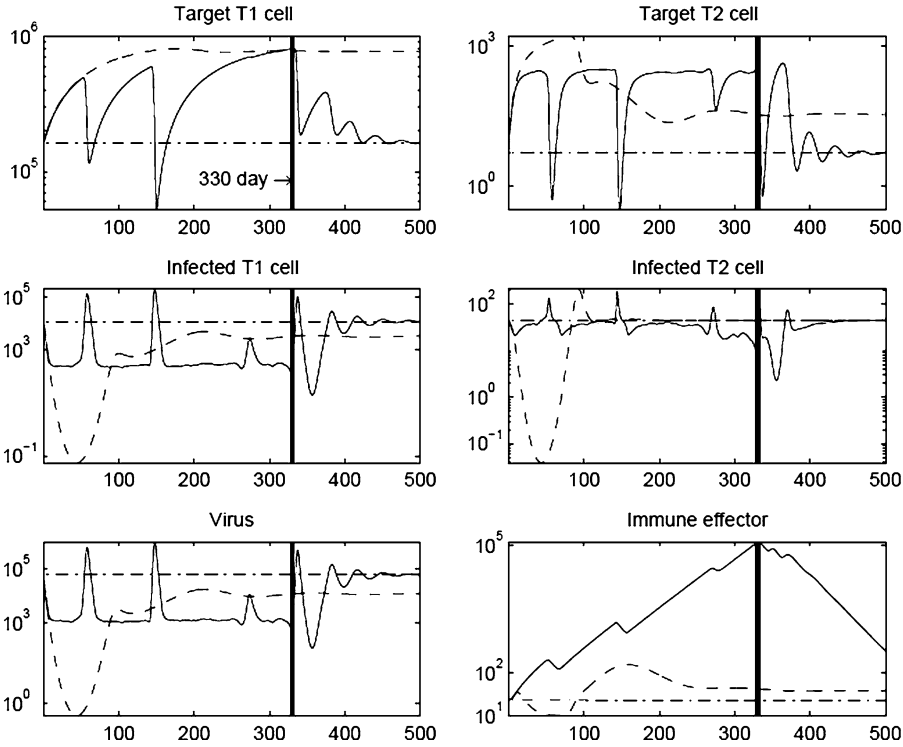

Fig. 10 Optimal solutions (*solid line*) for $T^* = 330$ (day); solutions (*dashed line*) with fully efficacious treatment; and solutions (*dashed and dotted line*) with no treatment in the unhealthy steady state

an "unhealthy" stable state (i.e., a high viral load and a low concentration of immune effectors) can be moved to a "healthy" one (i.e., a low viral load and a high concentration of immune effectors) with an optimal treatment regimen.

To investigate the optimal duration of treatment, we varied the weight constant for time P (Fig. 8). The threshold quantity for the terminal time was 331 days (Figs. 9 and 10). As shown in Fig. 8, the optimal control simulations indicated another upper bound for the treatment period: the maximum number of days recommended for treatment did not exceed 460 days.

Another observation is the influence of optimal terminal time on the systemic costs of the drug treatments which represent severity of unintended side effects as well as treatment costs. In general, one would expect that the costs of the treatments increase as the terminal time decreases. However, our numerical results show that the total drug use, $\int_0^T \varepsilon_1(t) + \varepsilon_2(t)\,dt$, decreases as the optimal terminal time decreases (Fig. 11). We believe that this is due to the tracking terms which derive the states of the system to the "healthy" steady state. Note that full treatment is not the best way for the states to approach the "healthy" steady state. The advice suggested by the various simulations is consistent to propose guidelines for therapy protocols including treatment period which could reduce the long-term pharmaceutical side effects.

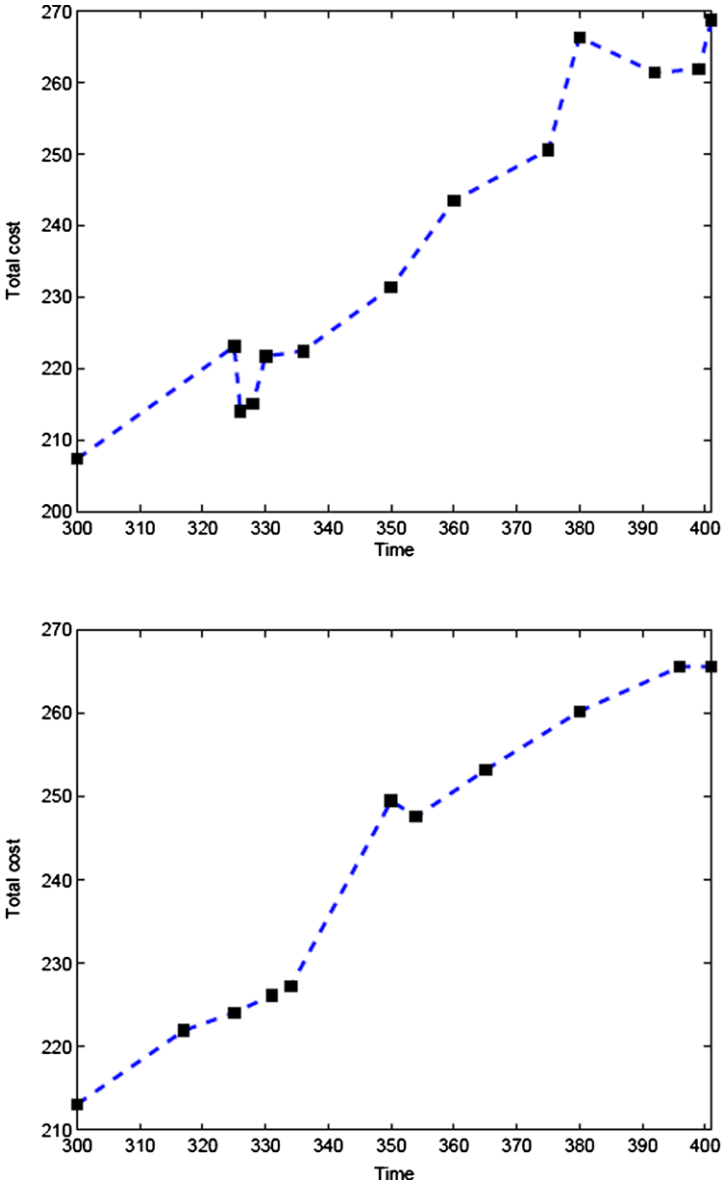

Fig. 11 The relationship between the terminal time and the systemic costs of both drug treatments, $\int_0^T \varepsilon_1(t) + \varepsilon_2(t)\,dt$. The *upper graph* is in early infection and *lower graph* is in the unhealthy steady state

5 Conclusions

We used techniques and ideas from control theory to derive the treatment strategies in HIV therapy. In particular, we considered a free terminal time optimal tracking control problem to incorporate the optimal duration of treatment in HIV therapy pro-

tocols. The mathematical model for HIV infection includes compartments for target cells, infected cells, virus, and immune response that are subjected to multiple (RTI- and PI-type) drug treatments as controllers. A conjugate gradient-type method was designed and implemented to address this problem, which often presents convergence difficulties because of the complex structure of Hamiltonian systems. We have demonstrated through numerical simulations that the optimal drug therapies with minimum duration can be designed to lead to a state in which a strong immune response can successfully control the virus without the need of drugs. So the possibility of treatment strategies that would shift patients from higher viral load equilibrium to lower viral load equilibrium is supported. We then investigated the effect of the weight constant for optimal terminal time. The threshold quantity and the upper bound for minimum duration of treatment to achieve the healthy equilibrium was estimated numerically. An interesting observation was that both the costs of the treatments and the terminal time could be reduced. Thus, this approach suggested guidelines for therapy protocols including treatment period which could reduce the long-term pharmaceutical side effects.

Acknowledgements The work of Hee-Dae Kwon was supported in part by the National Research Foundation of Korea (NRF) Grant funded by the Korean government (MEST) (2009-0065241) and in part by the Korea Research Foundation Grant funded by the Korean Government (KRF-2008-331-C00053). The work of Jeehyun Lee was supported by the Korea Research Foundation Grant funded by the Korean government (KRF-2008-531-C00012) and in part by the WCU program through NRF (R31-2008-000-10049-0).

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