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An optimal strategy for HIV multitherapy

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ABSTRACT

The purpose of the paper is to use numerical analysis and optimization tools to suggest improved therapies to try and cure HIV infection. A HIV model of an ordinary differential equation, which includes immune response, neutralizing antibodies and multi-drug effects, is improved. For a fixed time, two drugs treatment strategies are explored based on Pontryagin's Maximum Principle. Four types of treatments are used, and existence and uniqueness results for the optimal control fair are established. The optimality system is derived and then solved numerically using Gradient Projection Method. On the basis of weight factors for controls, we find a well treatment strategy with steady lower dosage of RTIs and PIs during the main part of treatment, almost unchanged higher population of uninfected $CD4^+T$ cells and few increase of active virus throughout the duration.

1. Introduction

Mathematical models are often used to study disease spread and have become essential tools to make assumptions, suggest new experiments or help one explaining easily complex processes. Many important papers investigate dynamic models of host–drug–virus interactions [1,2]. Most of the models are deterministic prey–predator systems of nonlinear differential equations. Sometimes stochastic terms are included to address the random behavior of features of the disease process. Typically, dynamic changes are modeled considering cell numbers progression of $CD4^+T$ cells, infected cells and virus population under drugs effects [2–7]. At the same time, optimal control has received much attention. The main idea is to use optimization techniques and theories to propose an alternative treatment based on administrating continually adjustable antiviral drug doses once a proper model is obtained. We refer to [4–7] for studies of the HIV model based on optimal control that maximizes/minimizes a prescribed objective function.

In 2011, an optimal control problem including immune response and multi-drug effects for HIV multitherapy enhancement

$$\min J = \frac{c}{2}V^2(t_f) + \int_{t_0}^{t_f}\left[\frac{c}{2}V^2 + \frac{b}{2}\dot{V}^2 + \frac{\varepsilon}{2}(u_1^2 + u_2^2)\right]dt \tag{1}$$

s.t.

$$\dot{T} = rT\left(1 - \frac{T+L+I}{T_m}\right) - \mu_T T - (1-u_1)k_1 VT + s_1, \tag{2}$$

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$$\dot{L} = \omega(1-u_1)k_1VT - \mu_T L - k_2 I, \tag{3}$$

$$\dot{I} = (1-\omega)(1-u_1)k_1VT + k_2 I - \mu_I I - k_3 IE, \tag{4}$$

$$\dot{V} = a(1-u_2)I - k_1VT - \mu_V V, \tag{5}$$

$$\dot{E} = k_4 ITE - \mu_E E + s_2, \tag{6}$$

$$T(t_0), L(t_0), I(t_0), V(t_0), E(t_0) \geq 0, \quad 0 \leq u_1,\ u_2 \leq 1$$

was studied by Orellana [5]. For a fixed time, a two drugs treatment strategy was obtained based on Pontryagin's Minimum Principle. Basically, the method studied can be considered as an optimal control one where drug doses are regarded as control inputs. The quadratic objective function considered takes into account three contributions: the viral load, the transient evolution of infection and the quantities of drug used. Simulations were carried out using an indirect optimization method. At each step the differential system was solved using the Runge–Kutta five order scheme. Results highlighted that a progressive reduction of Reverse Transcriptase Inhibitor (RTI) drug dose on the one hand along with on the other hand a progressive increase of Protease Inhibitor (PI) one was needed for optimality.

Orellana [5] takes the Cytotoxic T Lymphocytes (CTL) into account, however, ignores the neutralizing antibodies. The antibodies can combine with the virus such that the virus cannot get into target cells, yet HIV-1 can mutate very quickly, so the antibodies' periods of validity is short. The antibodies can protect a host against the infection by HIV-1. The antibodies can be induced several weeks after infection [8,9]. The facts imply that the neutralizing antibodies may be important in the early stage of the infection. Because the concentration of antibodies is secreted by effector B cells, we add a term $B(t)$, which represents the concentration of effector B cells, to the control system. Because the differentiation and proliferation of B-cells to effector B-cells need the help of $CD4^+T$-cells, we assume the generation rate is k_5VT, where k_5 is a positive constant. Since HIV-1 mutates very fast, the average term of validity of effector B-cells is shorter than normal, therefore we multiply the death rate, μ_B, by a positive constant β, which is bigger than 1. And so, the term $B(t)$ should satisfy the following equation.

$$\dot{B} = k_5VT - \beta\mu_B B. \tag{7}$$

Owing to the assumption that the antibodies' concentration is proportional to effector B cells' concentration, the neutralizing rate should be expressed by qBV and the Eq. (5) should be modified to the following equation.

$$\dot{V} = a(1-u_2)I - k_1VI - \mu_V V - qBV. \tag{8}$$

Further more, due to the fact that latently infected cells could be aroused while the actively infected cells' concentration is quite low [10], we advise the arousing rate is not proportional to $I(t)$, but to its own concentration. As a result, Eqs. (3) and (4) should be modified to the following two equations respectively.

$$\dot{L} = \omega(1-u_1)k_1VT - \mu_T L - k_2 L, \tag{9}$$

$$\dot{I} = (1-\omega)(1-u_1)k_1VT + k_2 L - \mu_I I - k_3 IE. \tag{10}$$

In this paper, a new HIV treatment system is established as the following system (11).

$$\begin{cases} \dot{T} = rT\left(1 - \dfrac{T+L+I}{T_m}\right) - \mu_T T - (1-u_1)k_1VT + s_1, \\ \dot{L} = \omega(1-u_1)k_1VT - \mu_T L - k_2 L, \\ \dot{I} = (1-\omega)(1-u_1)k_1VT + k_2 L - \mu_I I - k_3 IE, \\ \dot{V} = a(1-u_2)I - k_1VT - \mu_V V - qBV, \\ \dot{E} = k_4 ITE - \mu_E E + s_2, \\ \dot{B} = k_5VT - \beta\mu_B B, \\ T(t_0), L(t_0), I(t_0), V(t_0), E(t_0), B(t_0) \geq 0, \\ 0 \leq u_1 \leq b_1, \qquad 0 \leq u_2 \leq b_2, \qquad 0 \leq b_1, b_2 \leq 1 \end{cases} \tag{11}$$

where T, L, I, V, E, B denote the concentration of uninfected $CD4^+T$ cells, latently infected T cells, actively infected cells, infectious viruses, cytotoxic lymphocytes effector and B cells respectively. Drugs efficiency is represented by the controls u_1 and u_2 which accounts respectively for reverse transcriptase and protease inhibitors actions.

It is worth pointing out that our model could be valid in a well mixed sample of blood, but by no means in all the body.

Table 1
Definitions and values of the parameters used in the HIV model.

Parameter	Constants	Values with unit
r	Rate growth of uninfected CD4^+T	0.03 d^{-1}
μ_T	Death rate of uninfected CD4^+T	0.02 d^{-1}
μ_I	Death rate of infected CD4^+T	0.26 d^{-1}
μ_V	Death rate of virus	2.4 d^{-1}
μ_E	Death rate of CTL	0.1 d^{-1}
μ_B	Death rate of antibodies	0.0025 d^{-1}
q	Rate virus deleted by CTL	2.3e−2 mm^3 d^{-1}
k_1	Rate CD4^+T becomes infected by virus	2.4e−5 mm^3 d^{-1}
k_2	Rate latently infected convert to actively infected	3e−3 mm^3 d^{-1}
k_3	Rate actively infected cells deleted by CTL	2e−3 mm^3 d^{-1}
k_4	Rate growth of CTL	1e−5 mm^3 d^{-1}
k_5	Rate growth of antibody	1.8e−4 mm^3 d^{-1}
T_m	Maximum CD4^+T population	1500 mm^3
a	Number of virus produced by cell lysis	312 d^{-1}
s_1	Source term for uninfected CD4^+T	10 mm^3 d^{-1}
s_2	Source term for CTL	5 mm^3 d^{-1}
ω	Fraction of latently/infected CD4^+T	0.5
β	Multiple of death rate of antibodies	10

Using the method in [11] combined with the least square estimation, we fit the parameters q, k_5, β, μ_B keeping the rest of parameters in [5] unchanged, the fitting data comes from the literature [12]. We employ the data of patient 7 and patient 9 in [12] to estimate the parameters and get the range of the parameters $q : 0.0039 - 0.0234$, $k_5 : 0.0018 - 0.000182$, $\beta\mu_B = 0.2204 - 0.0256$.

Thus, definitions of the parameters used in this model is given in Table 1 (see also [5] with references).

Unlike [5], our objective functional is defined as

$$J(u_1, u_2) = \int_{t_0}^{t_f} [T - (\alpha_1 u_1^2 + \alpha_2 u_2^2)]dt. \tag{12}$$

The first term represents the benefit of T cells and other terms are systemic costs of drug treatments. The positive constants α_1 and α_2 balance the size of the terms, and u_1^2, u_2^2 reflect the severity of the side effects of the drugs. Our goal is maximizing the benefit based on the T cells and minimizing the systemic cost to the body (see also [6,7]). We seek an optimal control pair, u_1^*, u_2^* such that

$$J(u_1^*, u_2^*) = \max_{0 \le u_1 \le b_1, 0 \le u_2 \le b_2} J(u_1, u_2).$$

In Section 2, we investigate the existence of an optimal control pair. In Section 3, we derive the optimal control pair using Pontryagin's Maximum Principle [13–16]. In the same section we also derive the optimality system which characterizes the optimal control pair. The uniqueness of the optimality system is proved in Section 4, and some numerical results are illustrated in Section 5. In Section 6, we conclude by discussing the results of the numerical simulations based on different weight coefficients of controls.

2. Existence of an optimal control pair

There are certain parameter restrictions that are imposed to ensure that the model (11) is realistic (see also [1,6]):

$$r > \mu_T, \qquad \mu_I > \mu_T, \qquad \varepsilon := \mu_T T_m - s_1 > 0. \tag{13}$$

Theorem 2.1. *Consider control problem (11). Under assumption (13), there exists an optimal control pair* (u_1^*, u_2^*) *that maximizes the objective functional* $J(u_1, u_2)$.

Proof. To use an existence result, Theorem III.4.1 from [16], we must check the following properties:

1. The set of controls and corresponding state variables is nonempty.
2. The control U set is convex and closed.
3. The right hand side of the state system is bounded by a linear function in the state and control variables.
4. The integrand of the objective functional is concave on U.
5. There exist constants $c_1, c_2 > 0$ and $b > 1$ such that the integrand of the objective functional is bounded above by

$$c_2 - c_1(|u_1|^2 + |u_2|^2)^{\frac{b}{2}}.$$

First, an existence result in Lukes [17, Theorem 9.2.1] for the control system (11) for bounded coefficients is invoked, which gives condition 1. The control set is closed and convex by definition. Since the control system is bilinear in u_1, u_2, the right hand side of (11) satisfies condition 3, using the boundedness of the solutions obtained by the analytical method in [1]. Note that the integrand of the objective functional is concave on the admissible control set U. Also we have the last condition needed

$$T - (\alpha_1 u_1^2 + \alpha_2 u_2^2) \le c_2 - c_1(|u_1|^2 + |u_2|^2)^{\frac{b}{2}},$$

where c_2 depends on the upper bound on T, and $c_1 > 0$ since $\alpha_1, \alpha_2 > 0$. We conclude there exists an optimal control pair. This completes the proof.

3. Optimality system

Denote Hamiltonian $H(T, L, I, V, E, B; u_1, u_2; \lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5, \lambda_6)$ as

$$\begin{aligned} H &= T - (\alpha_1 u_1^2 + \alpha_2 u_2^2) + \lambda_1 \left(rT \left(1 - \frac{T + L + I}{T_m} \right) - \mu_T T - (1 - u_1) k_1 V T + s_1 \right) \\ &\quad + \lambda_2(\omega(1 - u_1)k_1 V T - \mu_T L - k_2 L) + \lambda_3((1 - \omega)(1 - u_1)k_1 V T + k_2 L - \mu_I I - k_3 I E) \\ &\quad + \lambda_4((1 - u_2)aI - k_1 V T - \mu_V V - qBV) + \lambda_5(k_4 I T E - \mu_E E + s_2) + \lambda_6(k_5 V T - \beta \mu_B B), \end{aligned}$$

where λ_i $(i = 1, 2, \ldots, 6)$ are co-state variables. By Pontryagin's Maximum Principle, we have the following Theorem 3.1.

Theorem 3.1. *If u_1^*, u_2^* are optimal controls of the optimal control problem ((11)–(12)), $T^*, L^*, I^*, V^*, E^*, B^*$ are the corresponding optimal paths, then there exist co-state variables λ_i $(i = 1, 2, \ldots, 6)$ such that, besides the control system (11) is satisfied, the following conditions are satisfied:*

(i) *co-state equations:*

$$\begin{cases} \dot{\lambda}_1 = -1 + \lambda_1 \left[\mu_T + \dfrac{rT}{T_m} + (1 - u_1)k_1 V - r \left(1 - \dfrac{T + L + I}{T_m} \right) \right] \\ \qquad - \lambda_2 \omega (1 - u_1) k_1 V - \lambda_3 (1 - \omega)(1 - u_1) k_1 V + \lambda_4 k_1 V - \lambda_5 k_4 I E - \lambda_6 k_5 V, \\ \dot{\lambda}_2 = \lambda_1 \dfrac{rT}{T_m} + \lambda_2(\mu_T + k_2) - \lambda_3 k_2, \\ \dot{\lambda}_3 = \lambda_1 \dfrac{rT}{T_m} + \lambda_3(\mu_I + k_3 E) - \lambda_4 a(1 - u_2) - \lambda_5 k_4 T E, \\ \dot{\lambda}_4 = \lambda_1(1 - u_1)k_1 T - \lambda_2 \omega (1 - u_1) k_1 T - \lambda_3 (1 - \omega)(1 - u_1) k_1 T + \lambda_4(k_1 T + \mu_V + qB) - \lambda_6 k_5 T, \\ \dot{\lambda}_5 = \lambda_3 k_3 I + \lambda_5(\mu_E - k_4 I T), \\ \dot{\lambda}_6 = \lambda_4 q V + \lambda_6 \beta \mu_B; \end{cases} \tag{14}$$

(ii) *optimality conditions:*

$$\begin{aligned} &H(T^*, L^*, I^*, V^*, E^*, B^*; u_1^*, u_2^*; \lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5, \lambda_6) \\ &\quad = \max_{0 \le u_i \le b_i, i = 1,2} H(T^*, L^*, I^*, V^*, E^*, B^*; u_1, u_2; \lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5, \lambda_6), \end{aligned}$$

which implies that

$$u_1^* = \min \left\{ b_1, \max \left\{ \frac{k_1 V^* T^* (\lambda_1 - \lambda_2 \omega - \lambda_3 (1 - \omega))}{2\alpha_1}, 0 \right\} \right\}, \tag{15}$$

$$u_2^* = \min \left\{ b_2, \max \left\{ -\frac{\lambda_4 a I^*}{2\alpha_2}, 0 \right\} \right\}; \tag{16}$$

(iii) *transversality conditions:*

$$\lambda_i(t_f) = 0, \quad i = 1, 2, \ldots, 6.$$

The optimality system consists of the control system (11) coupled with the co-state equation (14) with the initial conditions and transversality conditions together with the characterization of the optimal control pair (15) and (16).

Utilizing (15) and (16), we have the following optimality system:

$$\begin{cases}
\dot{T} = rT\left(1-\dfrac{T+L+I}{T_m}\right) - \mu_T T - (1-u_1)k_1VT + s_1,\\
\dot{L} = \omega(1-u_1)k_1VT - \mu_T L - k_2L,\\
\dot{I} = (1-\omega)(1-u_1)k_1VT + k_2L - \mu_I I - k_3IE,\\
\dot{V} = a(1-u_2)I - k_1VT - \mu_V V - qBV,\\
\dot{E} = k_4ITE - \mu_E E + s_2,\\
\dot{B} = k_5VT - \beta\mu_B B,\\
\dot{\lambda}_1 = -1 + \lambda_1\left[\mu_T + \dfrac{rT}{T_m} + (1-u_1)k_1V - r\left(1-\dfrac{T+L+I}{T_m}\right)\right]\\
\qquad -\lambda_2\omega(1-u_1)k_1V - \lambda_3(1-\omega)(1-u_1)k_1V + \lambda_4k_1V - \lambda_5k_4IE - \lambda_6k_5V,\\
\dot{\lambda}_2 = \lambda_1\dfrac{rT}{T_m} + \lambda_2(\mu_T + k_2) - \lambda_3k_2,\\
\dot{\lambda}_3 = \lambda_1\dfrac{rT}{T_m} + \lambda_3(\mu_I + k_3E) - \lambda_4a(1-u_2) - \lambda_5k_4TE,\\
\dot{\lambda}_4 = \lambda_1(1-u_1)k_1T - \lambda_2\omega(1-u_1)k_1T - \lambda_3(1-\omega)(1-u_1)k_1T + \lambda_4(k_1T + \mu_V + qB) - \lambda_6k_5T,\\
\dot{\lambda}_5 = \lambda_3k_3I + \lambda_5(\mu_E - k_4IT),\\
\dot{\lambda}_6 = \lambda_4qV + \lambda_6\beta\mu_B;\\
T(t_0), L(t_0), I(t_0), V(t_0), E(t_0), B(t_0) \geq 0,\\
\lambda_i(t_f) = 0, \quad i = 1, 2, \ldots, 6,
\end{cases} \tag{17}$$

where

$$u_1 = \min\left\{b_1, \max\left\{\frac{k_1VT(\lambda_1 - \lambda_2\omega - \lambda_3(1-\omega))}{2\alpha_1}, 0\right\}\right\},$$
$$u_2 = \min\left\{b_2, \max\left\{-\frac{\lambda_4aI}{2\alpha_2}, 0\right\}\right\}.$$

4. Uniqueness of the optimality system

Theorem 4.1. *For sufficiently small t_f, the solution to the optimality system (17) is unique.*

Proof. Suppose $(T, L, I, V, E, B, \lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5, \lambda_6)$ and $(\bar{T}, \bar{L}, \bar{I}, \bar{V}, \bar{E}, \bar{B}, \bar{\lambda}_1, \bar{\lambda}_2, \bar{\lambda}_3, \bar{\lambda}_4, \bar{\lambda}_5, \bar{\lambda}_6)$ are two solutions of the optimality system (17). Let $T = e^{\lambda t}x_1, L = e^{\lambda t}x_2, I = e^{\lambda t}x_3, V = e^{\lambda t}x_4, E = e^{\lambda t}x_5, B = e^{\lambda t}x_6$; $\lambda_1 = e^{-\lambda t}y_1, \lambda_2 = e^{-\lambda t}y_2, \lambda_3 = e^{-\lambda t}y_3, \lambda_4 = e^{-\lambda t}y_4, \lambda_5 = e^{-\lambda t}y_5, \lambda_6 = e^{-\lambda t}y_6$; $\bar{T} = e^{\lambda t}\bar{x}_1, \bar{L} = e^{\lambda t}\bar{x}_2, \bar{I} = e^{\lambda t}\bar{x}_3, \bar{V} = e^{\lambda t}\bar{x}_4, \bar{E} = e^{\lambda t}\bar{x}_5, \bar{B} = e^{\lambda t}\bar{x}_6, \bar{\lambda}_1 = e^{-\lambda t}\bar{y}_1, \bar{\lambda}_2 = e^{-\lambda t}\bar{y}_2, \bar{\lambda}_3 = e^{-\lambda t}\bar{y}_3, \bar{\lambda}_4 = e^{-\lambda t}\bar{y}_4, \bar{\lambda}_5 = e^{-\lambda t}\bar{y}_5, \bar{\lambda}_6 = e^{-\lambda t}\bar{y}_6$, where λ is to be chosen. Further we let

$$u_1 = \min\left\{b_1, \max\left\{\frac{k_1x_1x_4e^{\lambda t}(y_1 - y_2\omega - y_3(1-\omega))}{2\alpha_1}, 0\right\}\right\},$$
$$u_2 = \min\left\{b_2, \max\left\{-\frac{ax_3y_4}{2\alpha_2}, 0\right\}\right\};$$
$$\bar{u}_1 = \min\left\{b_1, \max\left\{\frac{k_1\bar{x}_1\bar{x}_4e^{\lambda t}(\bar{y}_1 - \bar{y}_2\omega - \bar{y}_3(1-\omega))}{2\alpha_1}, 0\right\}\right\},$$
$$\bar{u}_2 = \min\left\{b_2, \max\left\{-\frac{a\bar{x}_3\bar{y}_4}{2\alpha_2}, 0\right\}\right\}.$$

From the first equation of (17), we get

$$\dot{x}_1 + \lambda x_1 = rx_1\left(1 - \frac{x_1 + x_2 + x_3}{T_m}e^{\lambda t}\right) - \mu_T x_1 - (1-u_1)k_1e^{\lambda t}x_1x_4 + s_1e^{-\lambda t},$$
$$\dot{\bar{x}}_1 + \lambda \bar{x}_1 = r\bar{x}_1\left(1 - \frac{\bar{x}_1 + \bar{x}_2 + \bar{x}_3}{T_m}e^{\lambda t}\right) - \mu_T \bar{x}_1 - (1-\bar{u}_1)k_1e^{\lambda t}\bar{x}_1\bar{x}_4 + s_1e^{-\lambda t}.$$

By subtracting and integrating from t_0 to t_f for the above two equations, we get

$$\begin{aligned}
&\frac{1}{2}(x_1(t_f)-\bar{x}_1(t_f))^2+(\lambda-r+\mu_T)\int_{t_0}^{t_f}(x_1-\bar{x}_1)^2dt\\
&=-\frac{r}{T_m}\int_{t_0}^{t_f}e^{\lambda t}[(x_1^2-\bar{x}_1^2)+(x_1x_2-\bar{x}_1\bar{x}_2)+(x_1x_3-\bar{x}_1\bar{x}_3)](x_1-\bar{x}_1)dt\\
&\quad-k_1\int_{t_0}^{t_f}e^{\lambda t}[(1-u_1)x_1x_4-(1-\bar{u}_1)\bar{x}_1\bar{x}_4](x_1-\bar{x}_1)dt. \qquad (18)
\end{aligned}$$

Noted that

$$\begin{aligned}
\int_{t_0}^{t_f}(u_1-\bar{u}_1)^2dt &\le \left(\frac{k_1}{2\alpha_1}\right)^2 e^{2\lambda t_f}\int_{t_0}^{t_f}[x_1x_4(y_1-y_2\omega-y_3(1-\omega))-\bar{x}_1\bar{x}_4(\bar{y}_1-\bar{y}_2\omega-\bar{y}_3(1-\omega))]^2dt\\
&\le \left(\frac{k_1}{2\alpha_1}\right)^2 e^{2\lambda t_f}L_1\int_{t_0}^{t_f}[(x_1-\bar{x}_1)^2+(x_4-\bar{x}_4)^2+(y_1-\bar{y}_1)^2+(y_2-\bar{y}_2)^2+(y_3-\bar{y}_3)^2]dt,\\
\int_{t_0}^{t_f}(u_2-\bar{u}_2)^2dt &\le \left(\frac{a}{2\alpha_2}\right)^2\int_{x_0}^{t_f}(x_3y_4-\bar{x}_3\bar{y}_4)^2dt,\\
&\le \left(\frac{a}{2\alpha_2}\right)^2 L_2\int_{x_0}^{t_f}[(x_3-\bar{x}_3)^2+(y_4-\bar{y}_4)^2]dt,\\
\int_{t_0}^{t_f}(x_1^2-\bar{x}_1^2)(x_1-\bar{x}_1)dt &\le C_1\int_{t_0}^{t_f}(x_1-\bar{x}_1)^2dt,\\
\int_{t_0}^{t_f}(x_1x_2-\bar{x}_1\bar{x}_2)(x_1-\bar{x}_1)dt &= \int_{t_0}^{t_f}[(x_1-\bar{x}_1)^2x_2+\bar{x}_1(x_2-\bar{x}_2)(x_1-\bar{x}_1)]dt\\
&\le C_2\int_{t_0}^{t_f}[(x_1-\bar{x}_1)^2+(x_2-\bar{x}_2)^2]dt,\\
\int_{t_0}^{t_f}(x_1x_3-\bar{x}_1\bar{x}_3)(x_1-\bar{x}_1)dt &\le C_3\int_{t_0}^{t_f}[(x_1-\bar{x}_1)^2+(x_3-\bar{x}_3)^2]dt,
\end{aligned}$$

and

$$\begin{aligned}
&\int_{t_0}^{t_f}[(1-u_1)x_1x_4-(1-\bar{u}_1)\bar{x}_1\bar{x}_4](x_1-\bar{x}_1)dt\\
&=\int_{t_0}^{t_f}[(u_1-\bar{u}_1)(x_1-\bar{x}_1)x_1x_4+(1-\bar{u}_1)[(x_1-\bar{x}_1)^2x_4+\bar{x}_1(x_4-\bar{x}_4)(x_1-\bar{x}_1)]]dt\\
&\le C_4\int_{t_0}^{t_f}[(u_1-\bar{u}_1)^2+(x_1-\bar{x}_1)^2+(x_4-\bar{x}_4)^2]dt,
\end{aligned}$$

where C_1 depends on the bounds of $x_1, \bar{x}_1$, C_2 does the bounds of $\bar{x}_1, x_2$, C_3 does the bounds of $\bar{x}_1, x_3$, C_4 does the bounds of $\bar{u}_1, x_1, \bar{x}_1, x_4$. Thus, by (18), we have

$$\begin{aligned}
&\frac{1}{2}(x_1(t_f)-\bar{x}_1(t_f))^2+(\lambda-r+\mu_T)\int_{t_0}^{t_f}(x_1-\bar{x}_1)^2dt\\
&\le M_1e^{\lambda t_f}\int_{t_0}^{t_f}[(x_1-\bar{x}_1)^2+(x_2-\bar{x}_2)^2+(x_3-\bar{x}_3)^2+(x_4-\bar{x}_4)^2]dt\\
&\quad+N_1e^{3\lambda t_f}\int_{t_0}^{t_f}[(x_1-\bar{x}_1)^2+(x_4-\bar{x}_4)^2+(y_1-\bar{y}_1)^2+(y_2-\bar{y}_2)^2+(y_3-\bar{y}_3)^2]dt, \qquad (19)
\end{aligned}$$

where M_1 is an appropriate upper-bound. Similarly, we can get the following inequalities for $(x_i(t_f), \bar{x}_i(t_f))$ and $(y_j(t_0), \bar{y}_j(t_0))$ $(i = 2, 3, 4, 5, 6, j = 1, 2, 3, 4, 5, 6)$:

$$\begin{aligned}\frac{1}{2}(x_2(t_f)-\bar{x}_2(t_f))^2+(\lambda+k_2+\mu_T)\int_{t_0}^{t_f}(x_2-\bar{x}_2)^2dt \;\le\; & M_2e^{\lambda t_f}\int_{t_0}^{t_f}[(x_1-\bar{x}_1)^2+(x_2-\bar{x}_2)^2+(x_4-\bar{x}_4)^2]dt\\ & +N_2e^{3\lambda t_f}\int_{t_0}^{t_f}[(x_1-\bar{x}_1)^2+(x_4-\bar{x}_4)^2+(y_1-\bar{y}_1)^2\\ & +(y_2-\bar{y}_2)^2+(y_3-\bar{y}_3)^2]dt, \end{aligned} \tag{20}$$

$$\begin{aligned}&\frac{1}{2}(x_3(t_f)-\bar{x}_3(t_f))^2+(\lambda+\mu_I)\int_{t_0}^{t_f}(x_3-\bar{x}_3)^2dt\\ &\le M_3e^{\lambda t_f}\int_{t_0}^{t_f}[(x_1-\bar{x}_1)^2+(x_3-\bar{x}_3)^2+(x_4-\bar{x}_4)^2+(x_5-\bar{x}_5)^2]dt\\ &\quad+N_3e^{3\lambda t_f}\int_{t_0}^{t_f}[(x_1-\bar{x}_1)^2+(x_4-\bar{x}_4)^2+(y_1-\bar{y}_1)^2+(y_2-\bar{y}_2)^2+(y_3-\bar{y}_3)^2]dt\\ &\quad+K_1\int_{t_0}^{t_f}[(x_2-\bar{x}_2)^2+(x_3-\bar{x}_3)^2]dt, \end{aligned} \tag{21}$$

$$\begin{aligned}\frac{1}{2}(x_4(t_f)-\bar{x}_4(t_f))^2+(\lambda+\mu_V)\int_{t_0}^{t_f}(x_4-\bar{x}_4)^2dt \;\le\; & M_4e^{\lambda t_f}\int_{t_0}^{t_f}[(x_1-\bar{x}_1)^2+(x_4-\bar{x}_4)^2+(x_6-\bar{x}_6)^2]dt\\ & +K_2\int_{t_0}^{t_f}[(x_3-\bar{x}_3)^2+(x_4-\bar{x}_4)^2], \end{aligned} \tag{22}$$

$$\frac{1}{2}(x_5(t_f)-\bar{x}_5(t_f))^2+(\lambda+\mu_E)\int_{t_0}^{t_f}(x_5-\bar{x}_5)^2dt \le D_1e^{2\lambda t_f}\int_{t_0}^{t_f}[(x_1-\bar{x}_1)^2+(x_3-\bar{x}_3)^2+(x_5-\bar{x}_5)^2]dt, \tag{23}$$

$$\frac{1}{2}(x_6(t_f)-\bar{x}_6(t_f))^2+(\lambda+\beta\mu_B)\int_{t_0}^{t_f}(x_6-\bar{x}_6)^2dt \le M_5e^{\lambda t_f}\int_{t_0}^{t_f}[(x_1-\bar{x}_1)^2+(x_4-\bar{x}_4)^2+(x_6-\bar{x}_6)^2]dt, \tag{24}$$

$$\begin{aligned}&\frac{1}{2}(y_1(t_0)-\bar{y}_1(t_0))^2+(\lambda-r+\mu_T)\int_{t_0}^{t_f}(y_1-\bar{y}_1)^2dt \le M_6e^{\lambda t_f}\int_{t_0}^{t_f}[(x_1-\bar{x}_1)^2+(x_2-\bar{x}_2)^2+(x_3-\bar{x}_3)^2\\ &+(x_4-\bar{x}_4)^2+(y_1-\bar{y}_1)^2+(y_2-\bar{y}_2)^2+(y_3-\bar{y}_3)^2+(y_4-\bar{y}_4)^2+(y_6-\bar{y}_6)^2]dt\\ &+D_2e^{2\lambda t_f}\int_{t_0}^{t_f}[(x_3-\bar{x}_3)^2+(x_5-\bar{x}_5)^2+(y_1-\bar{y}_1)^2+(y_5-\bar{y}_5)^2]dt\\ &+N_4e^{3\lambda t_f}\int_{t_0}^{t_f}[(x_1-\bar{x}_1)^2+(x_4-\bar{x}_4)^2+(y_1-\bar{y}_1)^2+(y_2-\bar{y}_2)^2+(y_3-\bar{y}_3)^2]dt, \end{aligned} \tag{25}$$

$$\begin{aligned}\frac{1}{2}(y_2(t_0)-\bar{y}_2(t_0))^2+(\lambda+k_2+\mu_T)\int_{t_0}^{t_f}(y_2-\bar{y}_2)^2dt \;\le\; & M_7e^{\lambda t_f}\int_{t_0}^{t_f}[(x_1-\bar{x}_1)^2+(y_1-\bar{y}_1)^2+(y_2-\bar{y}_2)^2]dt\\ & +K_3\int_{t_0}^{t_f}[(y_2-\bar{y}_2)^2+(y_3-\bar{y}_3)^2]dt, \end{aligned} \tag{26}$$

$$\begin{aligned}&\frac{1}{2}(y_3(t_0)-\bar{y}_3(t_0))^2+(\lambda+\mu_I)\int_{t_0}^{t_f}(y_3-\bar{y}_3)^2dt\\ &\le M_8e^{\lambda t_f}\int_{t_0}^{t_f}[(x_1-\bar{x}_1)^2+(x_5-\bar{x}_5)^2+(y_1-\bar{y}_1)^2+(y_3-\bar{y}_3)^2]dt\\ &\quad+D_3e^{2\lambda t_f}\int_{t_0}^{t_f}[(x_1-\bar{x}_1)^2+(x_5-\bar{x}_5)^2+(y_3-\bar{y}_3)^2+(y_5-\bar{y}_5)^2]dt\\ &\quad+K_4\int_{t_0}^{t_f}[(x_3-\bar{x}_3)^2+(y_3-\bar{y}_3)^2+(y_4-\bar{y}_4)^2]dt, \end{aligned} \tag{27}$$

$$\begin{aligned}\frac{1}{2}(y_4(t_0)-\bar{y}_4(t_0))^2+(\lambda+\mu_V)\int_{t_0}^{t_f}(y_4-\bar{y}_4)^2dt \;\le\; & M_9e^{\lambda t_f}\int_{t_0}^{t_f}[(x_1-\bar{x}_1)^2+(x_6-\bar{x}_6)^2+(y_1-\bar{y}_1)^2\\ &+(y_2-\bar{y}_2)^2+(y_3-\bar{y}_3)^2+(y_4-\bar{y}_4)^2+(y_6-\bar{y}_6)^2]dt\\ &+N_5e^{3\lambda t_f}\int_{t_0}^{t_f}[(x_1-\bar{x}_1)^2+(x_4-\bar{x}_4)^2+(y_1-\bar{y}_1)^2\\ &+(y_2-\bar{y}_2)^2+(y_3-\bar{y}_3)^2]dt, \end{aligned}\tag{28}$$

$$\begin{aligned}\frac{1}{2}(y_5(t_0)-\bar{y}_5(t_0))^2+(\lambda+\mu_E)\int_{t_0}^{t_f}(y_5-\bar{y}_5)^2dt \;\le\; & M_{10}e^{\lambda t_f}\int_{t_0}^{t_f}[(x_3-\bar{x}_3)^2+(y_3-\bar{y}_3)^2+(y_5-\bar{y}_5)^2]dt\\ &+D_4e^{2\lambda t_f}\int_{t_0}^{t_f}[(x_1-\bar{x}_1)^2+(x_3-\bar{x}_3)^2+(y_5-\bar{y}_5)^2]dt \end{aligned}\tag{29}$$

$$\frac{1}{2}(y_6(t_0)-\bar{y}_6(t_0))^2+(\lambda+\beta\mu_B)\int_{t_0}^{t_f}(y_6-\bar{y}_6)^2dt\le M_{11}e^{\lambda t_f}\int_{t_0}^{t_f}[(x_4-\bar{x}_4)^2+(y_4-\bar{y}_4)^2+(y_6-\bar{y}_6)^2]dt,\tag{30}$$

where M_i $(i=1,2,\ldots,11)$, N_j $(j=1,2,\ldots,5)$, D_k $(k=1,2,3,4)$ and K_l $(l=1,2,3,4)$ depend on the coefficients and the bounds of the state variables and co-state variables. Combining form (19)–(30) gives

$$\begin{aligned}&\left[(\lambda-r+\mu_T)-\left(\sum_{i=1}^{9}M_i\right)e^{\lambda t_f}-(D_1+D_3+D_4)e^{2\lambda t_f}-\left(\sum_{i=1}^{5}N_i\right)e^{3\lambda t_f}\right]\int_{t_0}^{t_f}(x_1-\bar{x}_1)^2dt\\ &+[(\lambda+K_2+\mu_T)-(M_1+M_2+M_6)e^{\lambda t_f}]\int_{t_0}^{t_f}(x_2-\bar{x}_2)^2dt\\ &+[(\lambda+\mu_I-K_2-K_4)-(M_1+M_3+M_6+M_{10})e^{\lambda t_f}-(D_1+D_2+D_4)e^{2\lambda t_f}]\int_{t_0}^{t_f}(x_3-\bar{x}_3)^2dt\\ &+\left[(\lambda+\mu_V-K_2)-\left(\sum_{i=1}^{6}M_i+M_{11}\right)e^{\lambda t_f}-\left(\sum_{i=1}^{5}N_i\right)e^{3\lambda t_f}\right]\int_{t_0}^{t_f}(x_4-\bar{x}_4)^2dt\\ &+[(\lambda+\mu_E)-(M_3+M_8)e^{\lambda t_f}-(D_1+D_2+D_3)e^{2\lambda t_f}]\int_{t_0}^{t_f}(x_5-\bar{x}_5)^2dt\\ &+[(\lambda+\beta\mu_B)-(M_4+M_5+M_9)e^{\lambda t_f}]\int_{t_0}^{t_f}(x_6-\bar{x}_6)^2dt\\ &+\left[(\lambda-r+\mu_T)-\left(\sum_{i=6}^{9}M_i\right)e^{\lambda t_f}-(D_1+D_2)e^{2\lambda t_f}-\left(\sum_{i=1}^{5}N_i\right)e^{3\lambda t_f}\right]\int_{t_0}^{t_f}(y_1-\bar{y}_1)^2dt\\ &+\left[(\lambda+K_2-K_3+\mu_T)-(M_6+M_7+M_9)e^{\lambda t_f}-\left(\sum_{i=1}^{5}N_i\right)e^{3\lambda t_f}\right]\int_{t_0}^{t_f}(y_2-\bar{y}_2)^2dt\\ &+\left[(\lambda+\mu_I-K_3-K_4)-\left(M_6+\sum_{i=8}^{10}M_i\right)e^{\lambda t_f}-D_3e^{2\lambda t_f}-\left(\sum_{i=1}^{5}N_i\right)e^{3\lambda t_f}\right]\int_{t_0}^{t_f}(y_3-\bar{y}_3)^2dt\\ &+[(\lambda+\mu_V-K_4)-(M_6+M_9+M_{11})e^{\lambda t_f}-N_4e^{3\lambda t_f}]\int_{t_0}^{t_f}(y_4-\bar{y}_4)^2dt+[(\lambda+\mu_E)-M_{10}e^{\lambda t_f}\\ &-(D_2+D_4)e^{2\lambda t_f}]\int_{t_0}^{t_f}(y_5-\bar{y}_5)^2dt+[(\lambda+\beta\mu_B)-(M_6+M_9+M_{11})e^{\lambda t_f}]\int_{t_0}^{t_f}(y_6-\bar{y}_6)^2dt\\ &\le 0. \end{aligned}\tag{31}$$

Notice that the coefficients of all of integrals in (31) are non-negative if we choose a sufficiently large λ and a sufficiently small t_f. For example, if we let $\lambda > r-\mu_T+\sum_{i=1}^{9}M_i+D_1+D_3+D_4+\sum_{i=1}^{5}N_i$ and $t_f < \frac{1}{3\lambda}\ln\frac{\lambda-r+\mu_T}{A_1}$, $A_1 := \sum_{i=1}^{9}M_i+D_1+D_3+D_4+\sum_{i=1}^{5}N_i$, then the coefficient $(\lambda-r+\mu_T)-(\sum_{i=1}^{9}M_i)e^{\lambda t_f}-(D_1+D_3+D_4)e^{2\lambda t_f}-(\sum_{i=1}^{5}N_i)e^{3\lambda t_f}\ge 0$ for the integral $\int_{t_0}^{t_f}(x_1-\bar{x}_1)^2dt$. Similarly, we can get all of the other λs and t_fs relative to the other integral terms. If we take the maximum of all of the λs obtained as λ and the minimum of the t_fs obtained as t_f, the coefficient of each integral in (31) is non-negative.

This implies that $x_1 = \bar{x}_1, x_2 = \bar{x}_2, x_3 = \bar{x}_3, x_4 = \bar{x}_4, x_5 = \bar{x}_5, x_6 = \bar{x}_6, y_1 = \bar{y}_1, y_2 = \bar{y}_2, y_3 = \bar{y}_3, y_4 = \bar{y}_4, y_5 = \bar{y}_5, y_6 = \bar{y}_6$, and $T = \bar{T}, L = \bar{L}, I = \bar{I}, V = \bar{V}, E = \bar{E}, B = \bar{B}, \lambda_1 = \bar{\lambda}_1, \lambda_2 = \bar{\lambda}_2, \lambda_3 = \bar{\lambda}_3, \lambda_4 = \bar{\lambda}_4, \lambda_5 = \bar{\lambda}_5, \lambda_6 = \bar{\lambda}_6$. Hence the solution of (17) is unique for small time. This completes the proof.

The unique optimal control pair (u_1^*, u_2^*) is characterized in terms of the unique solution of the optimality system. The above optimal control pair gives an optimal treatment strategy for the HIV infected patient under the scenario of these two types of drug treatment.

5. Numerical illustration

Analytical solution for optimal control is difficult to obtain since the system is non-linear. In this paper, the method we used to numerically solve the optimal control problem is Gradient Projection Method. The ODE is discrete with Euler discrete format, and the co-state equations of the recurrence equations produced by discretion is employed to calculate the gradient. The dynamic systems response is exactly computed with adjusted control history from one iteration to the next to increase objective function at each step. The iterations continue until convergence is achieved. The convergence criterion is the norm of the gradient projection on feasible control field. The convergence rate of this method is slow, but it is convergent in the problem of this paper.

Using different combinations of weight factors (α_1, α_2) and upper-bounds (b_1, b_2) for controls, one can generate several treatment schedules for various time periods. Here we illustrate four cases for different combinations of the pairs (α_1, α_2) for a 60-day treatment schedule. We choose a 60-day treatment period in keeping with what is in other literature on treatment of HIV/AIDS such as [5] with references. Similarly, we take the initial conditions $T(0) = 1000, L(0) = 0, I(0) = 0, V(0) = 0.1, E(0) = 50, B(0) = 0\ \text{mm}^{-3}$, because we concern mainly on how to blocking infection after occupational exposure to HIV which is possible to happen to health workers. Studies have shown that taking anti-HIV drugs immediately after the HIV exposure could significantly lowers the chance of infection.

Fig. 1 are plotted using $\alpha_1 \gg \alpha_2$ (for instance, $\alpha_1 = 100, \alpha_2 = 5$), $b_1 = 1, b_2 = 0.7$; Fig. 2 are plotted using sufficiently small $\alpha_1 \approx \alpha_2$ (especially $\alpha_1 = \alpha_2 = 5$) and keeping the rest of the parameters unchanged. Fig. 3 are plotted using sufficiently large $\alpha_1 \approx \alpha_2$ (especially $\alpha_1 = \alpha_2 = 100$) and keeping the rest of the parameters unchanged. Fig. 4 are plotted using $\alpha_1 \ll \alpha_2$(for instance $\alpha_1 = 5, \alpha_2 = 100$) and keeping the rest of the parameters unchanged. The first figure in Fig. 1 represents the number of T cells during our treatment period. After the T cell population maintains in almost full scale for a long time (about 50 days), it starts to decrease sharply but above a higher scale (greater than 998). The fourth figure in Fig. 1 represents the virus population during our treatment period. Just the opposite of the first figure, after the virus population keeps 0-value unchanged for a long time (about 50 days), it starts to increases sharply but under a lower scale (less than 46). The last two figures in Fig. 1 represent the controls u_1^*, u_2^* for drug administration schedule for the first set of parameters. For the reverse transcriptase inhibitor medication (u_1), we see a sharp decrease at the beginning and after few days it levels off under a lower scale (less than 0.024) during main part of treatment and is tapered off finally. For the protease inhibitor medication (u_2), after the treatment maintains in maximum effort for a long period (about 52 days), it starts to decrease sharply till no treatment. The rest figures in Fig. 1 represent the number of the latently infected cells L, actively infected cells I, immune response E and effector cells B respectively. They have similar profile with V (see Fig. 1). We omit them in the following discussion, because in the clinical practice we are more interested in the controls (u_1, u_2), the virus V and the uninfected cells T. In the next three figures, all of profiles for T are similar with one of the Fig. 1, and all of profiles for V are also similar with one of the Fig. 1, but there are different numbers of cells in different cases. In the Fig. 2, $T \geq 999$, $V \leq 19$, in the Fig. 3, $T \geq 899$, $V \leq 220$, and in the Fig. 4, $T \geq 999$, $V \leq 25$. In addition, all of profiles for each control of u_1 and u_2 are similar in the last three pictures. Each reverse transcriptase inhibitor medication (u_1) is administered in full case not less than 9 days at the beginning and after few days it levels off during main part of treatment and it is tapered off finally. And each protease inhibitor medication (u_2) is administered without any treatment not less than 8 days in the beginning and after few days it levels off during main part of treatment and it is tapered off finally. But, the doses used in different treatments are different during main part of treatment: $u_1 \leq 0.15, u_2 \leq 0.15$ in the Fig. 2, $u_1 \leq 0.14, u_2 \leq 0.13$ in the Fig. 3, and $u_1 \leq 0.19, u_2 \leq 0.0077$ in the Fig. 4.

Moreover, there are two different class of treatment strategies according to different combinations of the weight factors: $\alpha_1 \gg \alpha_2$ and the rest of their combinations, while there exist four choice of optimal treatment strategies. From the clinical practice, the optimal treatment strategy on the basis of the combination of $\alpha_1 \ll \alpha_2$ should be best among four strategies owing to few doses of PI during main part of treatment.

6. Conclusion

In this paper, a deterministic model including immune response, neutralizing antibodies and multi drug effects is introduced to model HIV infection evolution. We use optimization theories in order to derive optimal control solution and design improved treatments. We proved the existence and uniqueness of the optimal control pair. The optimality system is derived and then solved numerically using Gradient Projection Method. On the basis of combinations of weight factors for

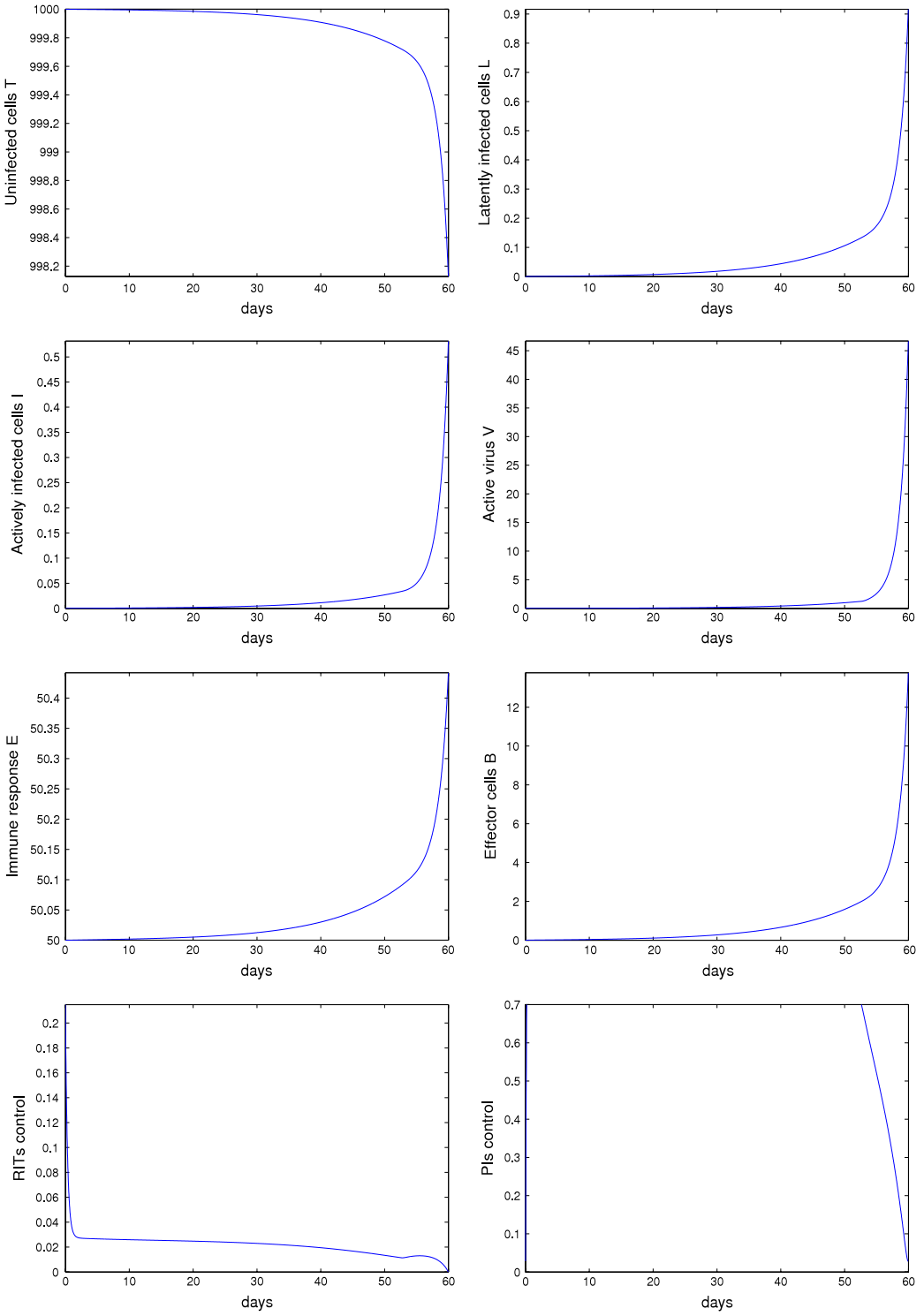

Fig. 1. Optimal solutions for 60 days, $\alpha_1 \gg \alpha_2$.

controls, we establish four types of optimal treatment strategies. Among these strategies, the one relative to the combination of $\alpha_1 \ll \alpha_2$ should be best clinical one owing to smaller steady dosage of RTIs (about 19%) and few dosage of PIs (about 0.77%) during main part of treatment (not less 40 days) and smaller numbers of the virus even throughout the last days (less than 25) and bigger numbers of the uninfected cells T even throughout the last days (greater than 999, i.e. almost un-decrease).

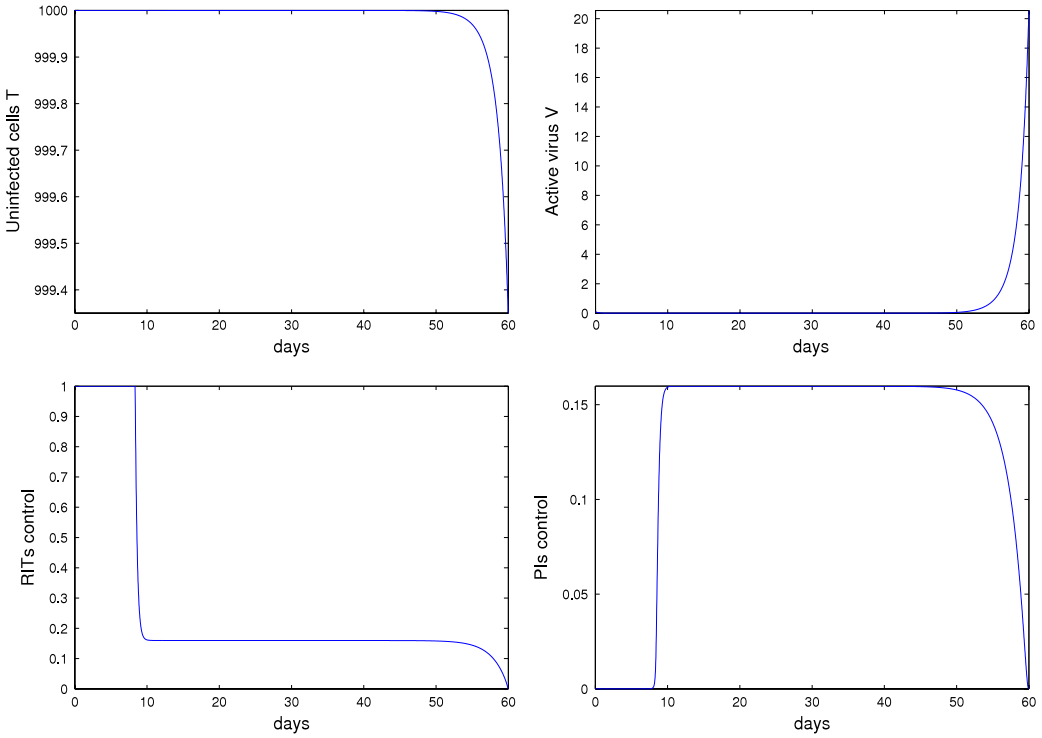

Fig. 2. Optimal solutions for 60 days, $\alpha_1 \approx \alpha_2$ sufficiently small.

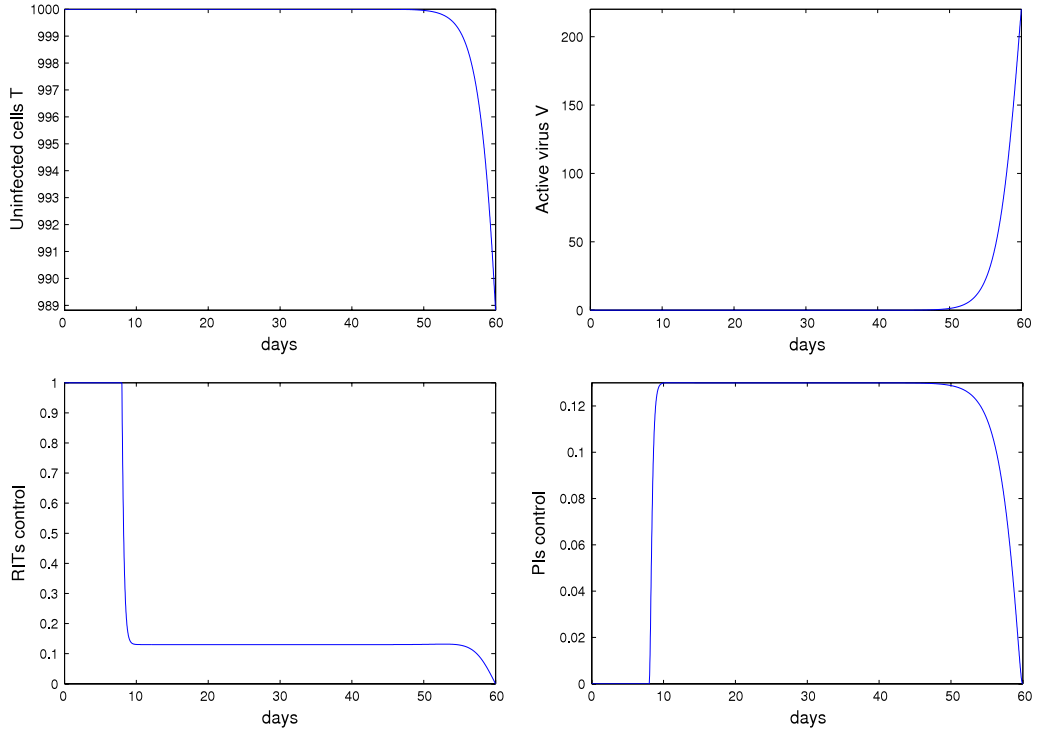

Fig. 3. Optimal solutions for 60 days, $\alpha_1 \approx \alpha_2$ sufficiently large.

Dynamic of infection is certainly far more complicated and varied than the one captured by this mathematical model, the numerical solution based on the model cannot be a recommendation for practical usage. But, it illustrate the role that mathematical methods can play in formulate treatment strategy.

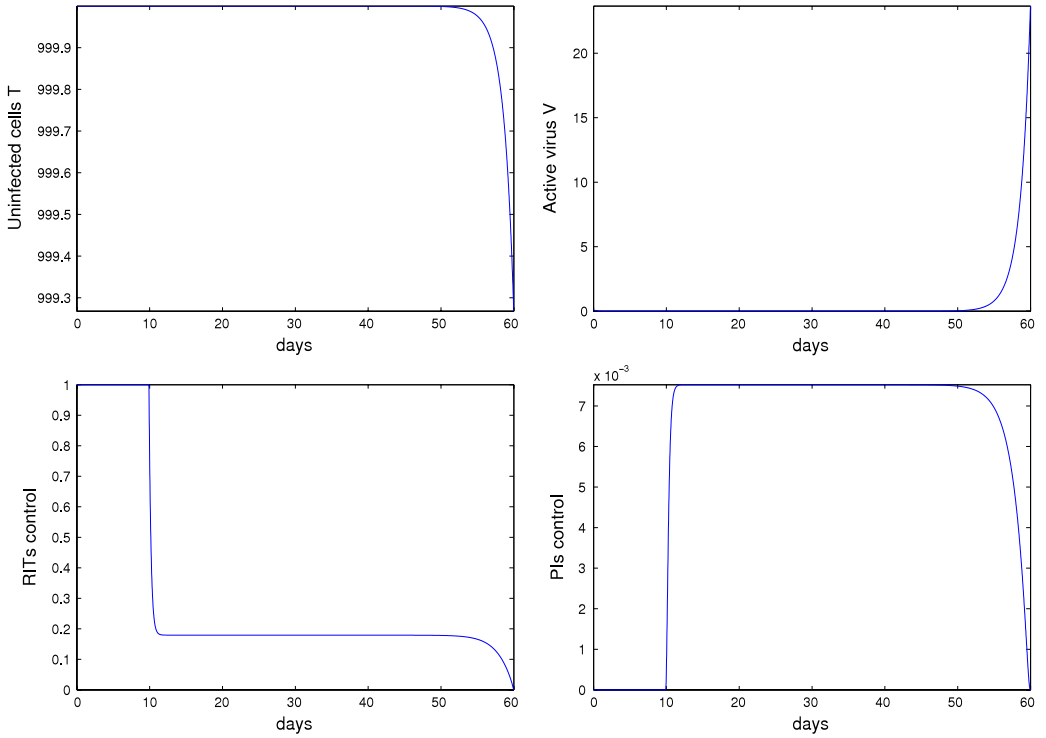

Fig. 4. Optimal solutions for 60 days, $\alpha_1 \ll \alpha_2$.

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