OPTIMAL SWITCHING IN STRUCTURED TREATMENT INTERRUPTION FOR HIV THERAPY

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ABSTRACT

This paper proposes 'optimal switching control during structured treatment interruption,' which switches RTI and PI to reduce medication and establish long-term immune response against HIV. The proposed method is compared with 'optimized STI' through numerical simulation. The proposed method results in a more rapid increase of CTLp, and thus total drug intake and the therapy period are reduced. HIV treatment simulation results are analyzed in terms of controllability. Due to the effect of PI, 'optimal switching control during STI' can achieve greater controllability more quickly than 'optimized STI.'

KeyWords: STI, AIDS, LTNP, optimal control, RTI, PI.

I. INTRODUCTION

The Human Immunodeficiency Virus (HIV) destroys the immune system by infecting CD4 T-helper cells and macrophages. Recently, numerous drugs to treat HIV have been developed. Rapid progress in the approval of reverse transcriptase inhibitors (RTI: AZT, ddI, ddC, D4T, 3TC, delavirdine, nevirapine, abacavir, succinate, and efavirenz) and protease inhibitors (PI: ritonavir, saquinivir, indinavir, and nelfinavir) has been made. These drugs inhibit viral replication and lead to a rapid decline in viral abundance within days [1-3]. However, single therapy may result in virus emergence [4]. Therefore, inhibitor therapy is combined with antiretroviral therapy, where three or more different drugs are administered. In practice, HAART (highly active antiretroviral therapy) is the most effective combination therapy for treatment-naive patients infected with HIV [5,6]. The clinical results of various combination drugs are summarized in [7].

Despite its benefits, HAART treatment has many side effects [8-11]. Specifically, many HIV-infected patients have died of fatal liver failure due to the adverse effects of HAART. Furthermore, prolonged HAART may have the negative effect of decreasing HIV-specific cellular immune response [12,13], and HAART treatment is not able to eradicate HIV due to chronic virus latency [9]. Therefore HIV-infected patients must undergo continuous HAART therapy to suppress HIV, which may lead to liver failure and nerve damage [9,14,15].

In response to the adverse effects of HAART, recent advances in antiretroviral therapy have focused on enhancing immune response to HIV to achieve patient LTNP (Long-term non-progressor: HIV-infected patient without symptoms of AIDS for more than seven years in the absence of therapy) status [16,17]. Memory CTL (CTLp: Cytotoxic T Lymphocyte precursor) is a long-lived CTL and the key effector in establishing protective immunity against HIV. Thus it is important that any immune response enhancement treatment increases CTLp [16]. Many optimal control methods for achieving patient LTNP status during dosage reduction have been proposed. Model-based predictive control (MPC) methods have been used to construct treatment schedules that emphasize CTLp increase [18-20]. Zurakowski *et al.* suggested using MPC methods for cases involving modeling error or uncertainty [18], but due to the long sampling time of their study, one week, the virus load and CD4 T-helper cell count could not be kept within baseline ranges. Alternatively, optimal control problems can be solved by continuously varying drug levels [19]. The CD4 T-helper cell count and virus load can be kept within base-

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lines by adjusting the cost function. However, continuous variation of input levels increases regimen difficulty and drug resistance [16,18]. Ko *et al.* proposed that a shorter sampling time is needed to remain within baseline ranges [20]. They solved constrained optimal control problems, *i.e.* optimized STI by dynamic programming, using a one day sampling time. The shorter sampling time allowed the CD4 T-helper cell count and virus load to be kept within baseline ranges.

Ko *et al.* used a model in which the effect of HAART is represented by combinations of RTI. However, the reduction of total drug intake is limited if only RTI is used. In addition, the use of RTI alone may increase the risk of the emergence of drug resistant viral strains and other side effects [21]. Antiretroviral therapy that switches classes of drugs has been recently proposed as a potential strategy for treating metabolic complications [22-24]. In [23], many clinical data were used to consider a therapy that switches drugs between RTI and PI in STI. The model proposed in [25] was modified by adding PI efficacy.

Our goal is to find a control law for two input optimal control problems whose final state is LTNP. The proposed method is called 'optimal switching in STI' while the therapy proposed in [20] is called 'optimized STI.' We simulated two cases: patient A has been infected with HIV without therapy for a long time; patient B has undergone RTI for a long time. In case studies, the two patients each undergo two treatments: 'optimal switching in STI' and 'optimized STI'. In optimal switching in STI, both RTI and PI are used, but in optimized STI, only RTI is used. The proposed method was compared with the previous method in terms of treatment period and total drug intake. Optimal switching in STI administrated PI, if necessary, only during RTI interruption. As expected, the increase of CTLp improved due to the effects of PI. Consequently, the faster buildup of CTLp of the proposed method allows the use of fewer drugs to achieve LTNP status more rapidly than optimized STI.

This paper is organized as follows: modeling of the HIV-affected immune system is explained in section II. In section III, methodologies of optimal control are presented. Then, simulation results and analysis are presented in section IV. In section V, discussions and conclusions are given.

II. WORKING MODEL

To understand the role of CTLp in achieving LTNP, memory cells and effecter cells are distinguished in the dynamic model as in [25]. CTLp differentiate to Cytotoxic T Lymphocyte effectors (CTLe), which destroy infected cells [14,16]. It is proposed that switching classes of drugs in antiretroviral therapy is a potential strategy for treating metabolic complications [22-24]. Therefore, we need consider the effects of PI and RTI in the virus dynamic model. We modified the model proposed in [25] by adding PI efficacy. In [26], PI effectively reduces the reproduction rate of the virus. To achieve the effects of PI and RTI, we modified Kubiak's model, from [25], as follows:

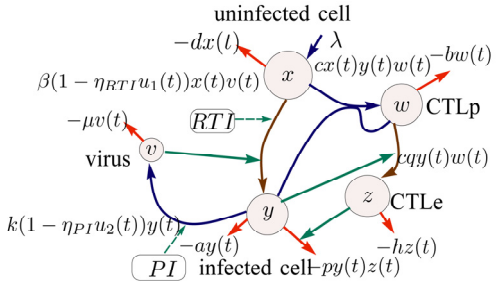

Fig. 1. Relationship between compartments in the model (1). RTI reduces infection rate of CD4T+ and PI decrease production rate of virus.

$$
\begin{aligned}
\dot{x}(t) &= \lambda - dx(t) - \beta(1-\eta_{RTI}\,u_1(t))\,x(t)\,v(t)\\
\dot{y}(t) &= \beta(1-\eta_{RTI}\,u_1(t))\,x(t)\,v(t) - ay(t) - py(t)\,z(t)\\
\dot{v}(t) &= k(1-\eta_{PI}\,u_2(t))\,y(t) - \mu v(t)\\
\dot{w}(t) &= cx(t)\,y(t)\,w(t) - cqy(t)\,w(t) - bw(t)\\
\dot{z}(t) &= cqy(t)\,w(t) - hz(t)
\end{aligned}
\tag{1}
$$

where $\lambda = 1$, $d = 0.1$, $\beta = 0.02$, $a = 0.2$, $p = 1$, $c = 0.027$, $q = 0.5$, $b = 0.001$, $h = 0.1$, $k = 25$, $\mu = 1$, and $\eta = 0.98$ derived from [25]. x, y, v, w, and z represent uninfected CD4 T-helper cells, infected CD4 T-helper cell, virus load, CTLp, and CTLe, respectively. λ is the uninfected CD4 T-helper cell production rate. dx, ay, bw, and hz are the natural death rates of x, y, w, and z, respectively. v is cleared at the rate of μv. β is the infection rate coefficient. Precursors are generated at the rate of $cxyw$, and are differentiated into effectors at the rate of $cqyw$. Effectors kill infected cells at the rate of pyz. The control inputs u_1 and u_2 are the RTI and PI doses ($0 \le u_1 \le 1$, $0 \le u_2 \le 1$). RTI reduces the infection rate by $1 - \eta_{RTI}\,u_1$, where η_{RTI} is the drug efficacy described in (1). PI reduces infection rate by $1 - \eta_{PI}\,u_2$, where η_{PI} is the drug efficacy described in (1). The proposed model (1) is depicted in detail in Fig. 1. The model (1) has four equilibrium points when no medication ($u_1 = u_2 = 0$) is administered. The numerical value of each equilibrium point is summarized in Table I. With given parameters, the equilibrium points are as follows:

Point 1.

$$x_1 = \frac{\lambda}{d},\ y_1 = 0,\ v_1 = 0,\ w_1 = 0,\ z_1 = 0$$

This is the status of an uninfected patient. This point is unstable.

Point 2.

$$x_2 = \frac{a\mu}{\beta k},\ y_2 = \frac{\mu v_2}{k},\ v_2 = \frac{\lambda - dx_2}{\beta x_2},\ w_2 = 0,\ z_2 = 0$$

This is the status of a patient dominated by HIV with associated immune response failure. This point is locally stable.

Point 3.

$$x_3 = \frac{[c\mu(\lambda + dq) - kb\beta] + \sqrt{[c\mu(\lambda + dq) - kb\beta]^2 - 4c^2\, dq\lambda\mu^2}}{2cd\mu},$$

$$y_3 = \frac{b}{c(x_3 - q)},\ v_3 = \frac{ky_3}{\mu},\ w_3 = \frac{hz_3}{cqy_3},\ z_3 = \frac{\beta x_3\, v_3 - ay_3}{py_3}$$

This point is the status of a LTNP patient whose immune response is established. This point is also locally stable.

Point 4.

$$x_4 = \frac{[c\mu(\lambda + dq) - kb\beta] - \sqrt{[c\mu(\lambda + dq) - kb\beta]^2 - 4c^2\, dq\lambda\mu^2}}{2cd\mu},$$

$$y_4 = \frac{b}{c(x_4 - q)},\ v_4 = \frac{ky_4}{\mu},\ w_4 = \frac{hz_4}{cqy_4},\ z_4 = \frac{\beta x_4\, v_4 - ay_4}{py_4}$$

This point is unstable, thus we are not interested in point 4.

Table 1. Numerical values of equilibrium points.

Equilibrium points	$X = [x, y, v, w, z]^T$
Point 1	$[10, 0, 0, 0, 0]^T$
Point 2	$[0.4, 4.8, 120, 0, 0]^T$
Point 3	$[9.8, 0.004, 0.1, 8751, 4.7]^T$
Point 4	$[0.51, 3.72, 93.05, 0.11, 0.06]^T$

As the point 1 is unstable, it is impossible to return to the uninfected state after infection by and eradication of the virus. Therefore the goal of treatment is for the patient to achieve LTNP status. We consider two cases: patient A and patient B. The initial condition of patients A and *B* are X_A and X_B, respectively. Initial conditions are chosen such that

$$X_A := [x(0), y(0), v(0), w(0), z(0)]^T$$
$$= [0.4, 4.8, 119.9, 0.0001, 0.0001]^T$$

and

$$X_B := [x(0), y(0), v(0), w(0), z(0)]^T$$
$$= [9.94, 0.0069, 0.189, 0.0026, 8.43\times10^{-6}]^T$$

Due to infection and lack of treatment, virus and infected cells are dominant in patient A. The CTLp and CTLe numbers of patient B are low due to extensive treatment. Recall that our model (1) has five states, $X(t) = [x(t), y(t), v(t), w(t), z(t)]^T$ and two inputs, $U(t) = [u_1(t), u_2(t)]^T$. Therefore, we can be represented as

$$\dot{X}(t) = f(X(t), U(t)).$$

III. METHODOLOGY

Shim *et al.* proposed an optimal control method for continuous regimen HIV treatment [19]. However, continuously varying drug dosage may cause drug resistant mutants [18]. The optimal treatment problem was solved in [18] and [20] by making the input either 0 (no treatment) or 1 (full treatment). However, these works only considered the efficacy of RTI as the only control input. In this paper, we consider the effects of PI and RTI. The cost function for optimization is modified to include the second input such that

$$J = (X(t_f) - X_{eq})^T Q_f (X(t_f) - X_{eq}) + \int_0^{t_f} (R_1 u_1^2 + R_2 u_2^2)\, dt \tag{2}$$

subject to

$$\dot{X}(t) = f(X(t), U(t)),$$

$$x(t) > x^*,\ v(t) < v^*.$$

where both R_1 and R_2 are set to 1, and the terminal cost, Q_f is *diag* (500, 500, 500, 500, 500). X_{eq} is the status of the LTNP, which is represented as Point 3. The initial value for patients A and *B* is $X(0) = X_A$ and $X(0) = X_B$, respectively. The constraint $x(t) > x^*$, $v(t) < v^*$ means that the HIV infected person is not regarded as an AIDS patient during total therapy. That is, baselines for viral load and CD4 T-helper cells are well maintained during therapy. In [22-24], antiretroviral incorporating switching was purported to be more effective than therapy without switching. Therefore, we use a system with two inputs (RTI, PI).

It has been suggested that, when dosed together, RTI and PI have the same net effect as RTI only [27]. Thus we do not administer PI and RTI simultaneously. Instead, RTI is only administrated if either constraint $x(t) > x^*$ or $v(t) < v^*$ is violated. To avoid the risk of the emergence of drug resistant viral strains, we constrained inputs to either 0 or 1. A sampling time of one day was chosen to achieve baseline range (maintanance).

In [26,28], Jeffrey *et al.* proposed that controllability can be an estimate of drug efficiency within the patient, as a higher minimum singular value indicates a more controllable virus load. Thus the minimum S. V. (singular value) of a controllability matrix can approximate practical controllability. In [20], it was shown that higher controllability indicates more effective therapy. In this paper, we analyzed controllability to assess and compare the effectiveness of the optimal switching in STI method with the optimized STI method. To analyze controllability, system (1) can be linearized such that

$$\begin{aligned} \dot{X} &= AX + BU \\ &= AX + B_{RTI}\, u_1 + B_{PI}\, u_2 \end{aligned} \tag{3}$$

where

$$A=\begin{bmatrix} -d-\beta v & 0 & -\beta\varepsilon x & 0 & 0 \\ \beta\varepsilon v & -a-pz & \beta\varepsilon x & 0 & -py \\ 0 & k\varepsilon & -\mu & 0 & 0 \\ cyw & cxw-cqw & 0 & cxy-cqy-b & 0 \\ 0 & cqw & 0 & cqy & -h \end{bmatrix}, \quad (4)$$

$$B=\begin{bmatrix} \beta\eta_{RTI}xv & -\beta\eta_{RTI}xv & 0 & 0 & 0 \\ 0 & 0 & -k\eta_{PI}y & 0 & 0 \end{bmatrix}^T \quad (5)$$

$$B_{RTI}=[\beta\eta_{RTI}xv \quad -\beta\eta_{RTI}xv \quad 0 \quad 0 \quad 0]^T, \quad (6)$$

$$B_{PI}=[0 \quad 0 \quad -k\eta_{PI}y \quad 0 \quad 0]^T, \quad (7)$$

$$\varepsilon=(1-\eta_{RTI}u_1),$$

$$\varepsilon=(1-\eta_{PI}u_2).$$

From the linearized system (3), we computed the controllability matrix such that

$$C_{RTI\&PI}=[B \quad AB \quad A^2B \quad A^3B \quad A^4B],$$

$$C_{RTI}=[B_{RTI} \quad AB_{RTI} \quad A^2B_{RTI} \quad A^3B_{RTI} \quad A^4B_{RTI}],$$

$$C_{PI}=[B_{PI} \quad AB_{PI} \quad A^2B_{PI} \quad A^3B_{PI} \quad A^4B_{PI}].$$

We applied S. V. decomposition to the controllability matrix. Plotted minimum S. V. are shown in next section. Refer to [26,28] for detailed explanations of the controllability analysis.

IV. SIMULATION RESULTS AND ANALYSIS

System (1) was simulated for patients A and B with our proposed method, respectively. Figures 2 and 3 suggest that both methods were successful in yielding LTNP status for each patient. Figure 4 shows how CTLp increased for each case. (For easy visibility note that v and w are scaled by 0.1 and 0.01, respectively.) Figure 2 shows cases where patients A and B were treated with only RTI using the optimized STI method. LTNP status was successfully induced for each patient. Figure 3 shows the cases where both patients were treated by switching treatment in STI. From Fig. 3 we see that our proposed method also induces patient LTNP status. Figures 2 and 3 show that no great difference exists between the dosing schedule patterns of the two methods. Note that the first interruption for each case occurred on the same day. During the first interruption, the increase rate of CTLp is boosted. However, the virus load increased and CD4 decreased due to therapy interruption.

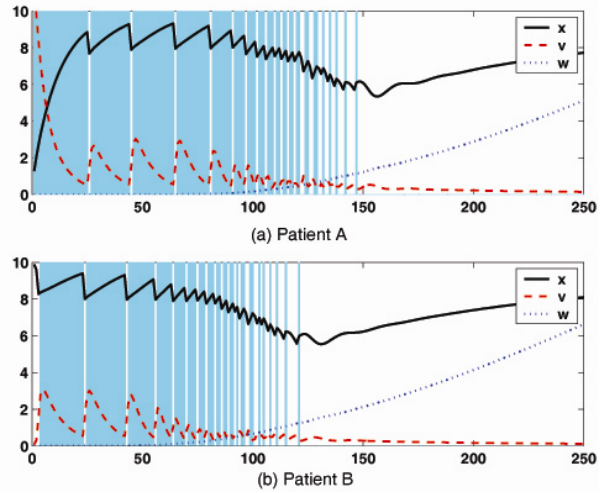

Fig. 2. Results of 'optimized STI.' Cyan shade indicates RTI input. (a) Therapy duration of patient A is 147 days. RTI was administered to patient A for 122 days (b) Therapy duration of patient B was 121 days. RTI was administered to patient B for 93 days. CTLp increased during interruption, while CD4 and virus levels remained within baseline ranges due to the one day sampling time. Consequently, both patients Achieved LTNP status.

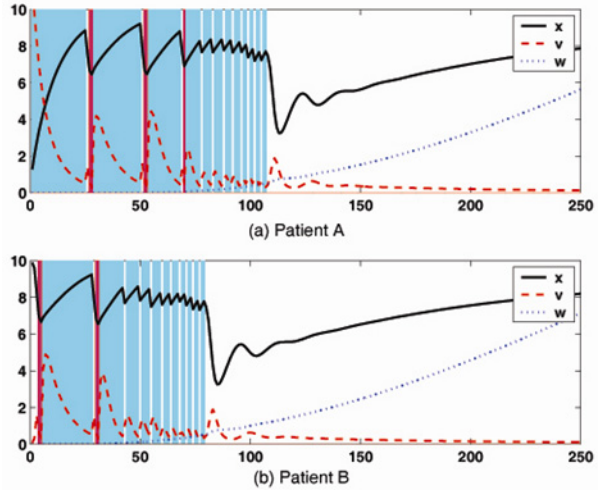

Fig. 3. Results of 'optimal switching in STI.' Each cyan shade and red shade indicates RTI input and PI input. (a) Therapy duration of patient A was 107 days. RTI was administered to patient A for 92 days and PI was given to patient A for 5 days. (b) Therapy duration of patient B was 79 days. RTI was administered to patient B for 63 days and PI was given to patient B for 4 days. CTLp increased and the immune system established more quickly due to PI administration during the interruptions. Therefore, the total drug intake and the therapy period were reduced. Note that PI was not always administrated during RTI interruption.

RTI is not as effective as PI on patients with a high viral load and a low CD4 T-helper cell count [24]. Therefore, in the proposed method, PI is administered to both patients during the first interruption. Figure 3 shows that treatment switches to PI from RTI when the viral load is relatively high and the CD4 T-helper cell count is relatively low. Taking PI during the interruption does not affect the overall pattern of the STI. However we observed that CTLp, which is the main factor affecting the immune system [16], increased more rapidly due to PI. Optimal control simulation results from [18-20] also show that CTLp increases gradually when control is successful. Figure 4 confirms that CTLp increased faster if PI is administered during RTI interruption. Therefore, the period of therapy and total drug intake were reduced while still achieving patient LTNP status. In [19], Shim *et al.* indicated that gradual drug dose reduction occurs under optimal control. Ko *et al.* suggested that gradual drug dose reduction also occurs under a discrete regimen [20]. The same gradual drug dose reduction can be observed in Figs. 2 and 3. Figures 5 and 6 compare controllability of optimal switching in STI with controllability of optimized STI. In [20], Ko *et al.* indicated that treatment interruption increases the minimum S. V. of the controllability matrix. For both methods, controllability increased during interruption. In Fig. 6, the minimum S.V. of $C_{RTI\&PI}$ is very close to that of C_{RTI}. RTI has a greater effect on HIV therapy than PI [27]. Although PI dose not greatly affect HIV therapy, PI contributes to the overall increase of controllability. Therefore, optimal switching in STI is able to achieve high controllability earlier in the treatment process than optimized STI, while still reducing the treatment period and the total drug intake. For patient A, optimal switching in STI was over on the 107th day, while optimized STI was finished on the 147th day. For patient B, optimal switching STI was over on the 79th day, while optimized STI was finished on the 121st day. Table 2 shows that the total drug intake and therapy period were reduced relative to the total input sum, when both switching methods were used. For patient A, total drug intake was reduced by 20 percent and the therapy period was reduced by 27 percent. For patient B, total drug intake was reduced by 27 percent and the therapy period was reduced by 35 percent.

Table 2. Total drug intake and therapy period of different methods.

Patient	Method	Total drug intake	Therapy period
Patient A	Optimal switching during STI	RTI(92), PI(5)	107days
Patient A	Optimized STI	RTI(122)	147days
Patient B	Optimal switching during STI	RTI(64), PI(4)	79days
Patient B	Optimized STI	RTI(93)	121days

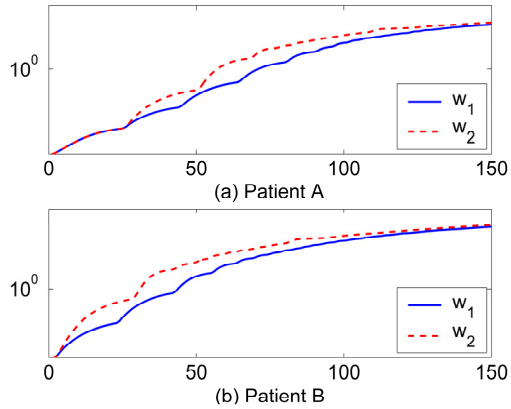

Fig. 4. Comparison of increasing CTLp of 'optimal switching in STI' with 'optimized STI.' w_1 indicates increasing CTLp of 'optimized STI' and w_2 indicates increasing CTLp of optimal switched STI. (a) Result of patient A, (b) Result of patient B. In 'optimal switching in STI', CTLp is increased more due to PI during RTI interruption. Consequently both patients Are led to LTNP faster.

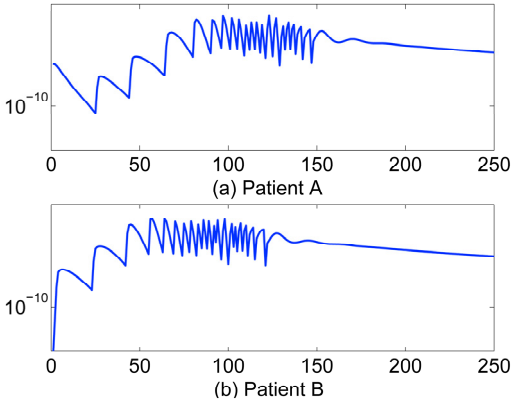

Fig. 5. Controllability of 'optimized STI' for (a) patient A and (b) patient B. Controllability increased during interruption.

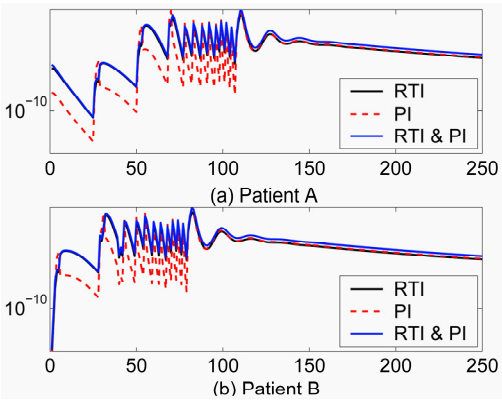

Fig. 6. Controllability of 'optimal switching in STI' for (a) patient A and (b) patient B. Controllability increased during PI administration and during interruption. Furthermore, PI dosage enhanced controllability.

V. DISCUSSION AND CONCLUSION

Our proposed method was able to establish immune response similarly to previous treatment methods. The treatment of HIV should take precedence over the potential benefits of antiretroviral switching. Therefore, it was proposed that RTI and PI be switched during treatment. We simulated two cases using our proposed method and a previous method and compared results. Constrained optimization problems for HIV treatment were solved using Dynamic Programming. The proposed method is able to reduce the total drug intake further while still achieving patient LTNP status more rapidly than previous methods. Additionally, our simulation results agree well with reported clinical data. Though PI was incorporated, the overall pattern of the therapy did not differ greatly from RTI monotherapy. However, PI helps increase CTLp, which is major factor in establishing the immune system. Therefore, we see a more rapid establishment of the immune system. Consequently, optimal switching in STI allows the reduction of total drug intake and the therapy period.

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