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Constant Drug Dose Leading Long-Term Non-Progressor for HIV-Infected Patients with RTI and PI

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Abstract— **This paper proposes a therapy that uses a constant dosage of Reverse Transcription Inhibitor (RTI) and Protease Inhibitor (PI) to help an HIV-infected patient achieve Long-Term Non-Progressor (LTNP) status. Based on the analysis of the Cytotoxic T Lymphocyte precursor (CTLp) concentration at the equilibrium point and the bifurcation of the equilibrium points, we found that therapy with a drug whose efficacy was below a certain level produced a higher CTLp concentration at the equilibrium point. We found that it is possible for a less-than-full constant dosage treatment to induce LTNP status. In fact, the treatment with an efficacy less than that of a full treatment proved to be more efficient when considering controllability.**

I. INTRODUCTION

The Human Immuno-deficiency Virus (HIV), which causes Acquired Immune Deficiency Syndrome (AIDS), destroys the immune system by infecting CD4 T-helper cells that assist in immune responses and macrophages that play an important role in phagocytosis [1], [2]. When the CD4 T-helper cell count reaches $200mm^{-3}$ or below in an HIV-infected patient, the patient is classified as having AIDS and will likely to die from an opportunistic infection. Moreover, a monotherapy is likely to fail because HIV can easily develop resistance to monotherapies [3], [4]. To avoid this problem, Highly Active Anti-Retroviral Therapy (HAART) is widely used to treat HIV-infected patients. HAART, which is known as a 'cocktail,' is effective in the prolonged reduction of the viral load. HAART uses a combination of two types of drugs. These drugs can be classified as Reverse Transcriptase Inhibitors (RTIs), which block the reverse transcription of HIV from RNA to DNA, and Protease Inhibitors (PIs), which inhibit the production of new composition components of HIV (such as enzymes) by cutting protein chains. Although prolonged treatment is needed because the viral load rebounds after cease HAART, the long-term use HAART is not recommended due to its serious side effects [5]. Therefore, a therapy that enables an HIV-infected patient to become a Long-Term Non-Progressor (LTNP) is needed. An LTNP is a patient who has been infected with HIV but does not progress to the status of AIDS for at least seven years by sustained immune responses without medication. It has been reported that the concentration of Cytotoxic T Lymphocyte precursor (CTLp), which can differentiate into Cytotoxic T Lymphocyte effector (CTLe) and plays a role in killing infected CD4 T-helper cells, should be maintained to help a patient become an LTNP [6], [7].

Recently, several methods that induce LTNP status by using the optimal control theory for efficient drug therapy have been studied [8], [9]. Shim et al. suggested a gradual reduction in the drug dosage and treatment using the Model-based Predictive Control (MPC) method under model parameter uncertainties [8]. Additionally, a Structured Treatment Interruption (STI) method has been introduced; this method intentionally provides interruptions in medication to help the immune system control HIV or reduce side effects [10]–[12]. It is reported that STI can induce LTNP [6]. However, medication using the optimal control method, continuously varying medications, and using repeated cessation of medications are all likely to result in the emergence of a highly drug-resistant virus and are hard to adopt in a treatment. Thus, these methods are not viable in clinical treatment [5], [13].

In this paper, we present a therapy that uses a constant and time-limited drug dosage to induces LTNP status in HIV-infected patients by increasing the CTLp concentration. This therapy is more clinically applicable than therapy using the optimal control method or STI, which are likely to cause the emergence of a mutant virus. To evaluate constant drug dosage, we examined the bifurcation phenomenon [14] and variations in the concentration of CTLp at stable equilibrium points in order to determine various drug efficacies. During the bifurcation analysis, it was observed that using a highly active RTI monotherapy produces a CTLp concentration of zero at a stable equilibrium point, while less effective therapy can result in inducing LTNP status by producing a sustained increase in CTLp. We added PI to RTI monotherapy for HAART to protect against monotherapy failure, and we set the efficacy of PI according to the efficacy of RTI in order to induce LTNP status. We also observed that treatment with RTIs and PIs, which have a lower efficacy, resulted in a lower probability of relative mutant emergence. In addition, we estimated that a treatment with an efficacy below a specific bifurcation point controls the immune system more efficiently than a treatment with a higher efficacy [15].

II. HIV DYNAMIC MODEL AND BIFURCATION

A. HIV DYNAMIC MODEL

CTLp plays an important role in inducing LTNP status. Therefore, in this study we used a modified Kubiak model,

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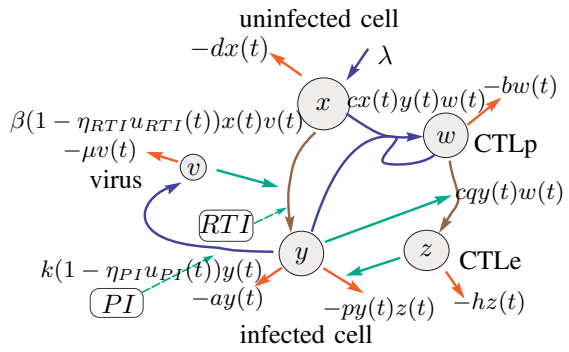


Fig. 1. HIV-immune system dynamics.

which is a 5^{th} order model that considers CTLp [16]. The model is given as follows, and dynamics of the model are depicted in Fig. 1.

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

where $\lambda = 1$, $d = 0.1$, $\beta = 0.02$, $a = 0.2$, $p = 1$, $c = 0.027$, $q = 0.5$, $b = 0.001$, $h = 0.1$, $k = 25$, and $\mu = 1$ [16]. Each state is a concentration of uninfected CD4 T-helper cell (x), infected CD4 T-helper cell (y), free virus (v), CTLp (w), and CTLe (z). η_{RTI} and η_{PI} represent the drug efficacy of RTI and PI, respectively. $u_{RTI}(t)$ and $u_{PI}(t)$ indicate RTI and PI inputs. $\eta_{RTI} = 1$ or $\eta_{PI} = 1$ in a treatment ($u_{RTI} = 1$ or $u_{PI} = 1$) indicates that RTI or PI blocks HIV-infection perfectly, while $u_{RTI} = 0$ or $u_{PI} = 0$ means no medication (RTI or PI). Uninfected CD4 T-helper cells are replenished at a rate of λ, die at a rate of $dx(t)$, and become infected by free virus at a rate of $\beta(1-\eta_{RTI})xv$ when RTI therapy is being administered. Infected CD4 T-helper cells die at a rate of ay and are eliminated by CTL effectors at a rate of pyz. Free viruses are produced at a rate of $k(1-\eta_{PI})y$ when PI therapy is being given, and they are cleared by the immune system at a rate of μv. CTL precursors are produced by the help of uninfected cells, the stimulation of infected cells, and by CTL precursors themselves ($cxyw$), and they die at a rate of bw. CTL precursors proliferate into CTL effectors at a rate of $cqyw$, and CTL effectors die at a rate of hz.

Four equilibrium points of HIV model (1) are illustrated as follows, and numerical values without medication ($\eta_{RTI} = \eta_{PI} = 0$) are shown in Table I.

Point A:

$$x^{(A)} = \tfrac{\lambda}{d}, y^{(A)} = 0, v^{(A)} = 0, w^{(A)} = 0, z^{(A)} = 0.$$

This point is for an uninfected person who does not have HIV. It is unstable when there no medication is being administered. Therefore, it is impossible for HIV-infected patients to achieve uninfected status if medication is ceased.

TABLE I
EQUILIBRIUM POINTS

Equilibrium points	$X = [x, y, v, w, z]^T$
Point A	$[10, 0, 0, 0, 0]^T$
Point B	$[0.4, 4.8, 120, 0, 0]^T$
Point C	$[9.8, 0.0004, 0.1, 8751, 4.7]^T$
Point D	Not in our interest

Point B:

$$\begin{aligned}
&x^{(B)} = \tfrac{a\mu}{\beta k(1-\eta_{RTI})(1-\eta_{PI})}, y^{(B)} = \tfrac{\mu v^{(B)}}{k(1-\eta_{PI})},\\
&v^{(B)} = \tfrac{\lambda - dx^{(B)}}{\beta x^{(B)}(1-\eta_{RTI})}, w^{(B)} = 0, z^{(B)} = 0.
\end{aligned}$$

This state indicates HIV dominance and immune response failure, and is stable before the initiation of treatment.

Point C:

$$\begin{aligned}
&x^{(C)} = \tfrac{c\mu(\lambda+dq) - kb\beta\tau + \sqrt{[c\mu(\lambda+dq) - kb\beta\tau]^2 - 4c^2dq\lambda\mu^2}}{2cd\mu},\\
&y^{(C)} = \tfrac{b}{c(x^{(C)}-q)}, v^{(C)} = \tfrac{ky^{(C)}}{\mu(1-\eta_{PI})}, w^{(C)} = \tfrac{hz^{(C)}}{cqy^{(C)}},\\
&z^{(C)} = \tfrac{\beta x^{(C)}v^{(C)}(1-\eta_{RTI}) - ay^{(C)}}{py^{(C)}},\\
&where\ \tau = (1-\eta_{RTI})(1-\eta_{PI}).
\end{aligned}$$

This point represents LTNP status. The concentration of infected cells and viral loads are low while the concentration of CTL precursors is high. This combination is desirable for a sustained immune response, and this point is locally stable when no medication is used.

Point D:

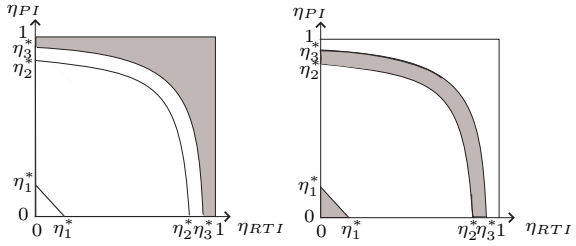
$$\begin{aligned}
&x^{(D)} = \tfrac{c\mu(\lambda+dq) - kb\beta\tau - \sqrt{[c\mu(\lambda+dq) - kb\beta\tau]^2 - 4c^2dq\lambda\mu^2}}{2cd\mu},\\
&y^{(D)} = \tfrac{b}{c(x^{(D)}-q)}, v^{(D)} = \tfrac{ky}{\mu(1-\eta_{PI})}, w^{(D)} = \tfrac{hz^{(D)}}{cqy^{(D)}},\\
&z^{(D)} = \tfrac{\beta x^{(D)}v^{(D)}(1-\eta_{RTI}) - ay^{(D)}}{py^{(D)}},\\
&where\ \tau = (1-\eta_{RTI})(1-\eta_{PI}).
\end{aligned}$$

This point is unstable and is not within our treatment interest.

B. BIFURCATION

Model (1) is a nonlinear dynamic equation whose equilibrium points and stability vary according to the efficacies of RTI and PI. The variation in the stability of each equilibrium point is illustrated in Fig. 2. Bifurcation lines are given in (2). Bifurcation diagrams are symmetric for both η_{RTI} and η_{PI} because η_{PI} has the same form of equation as η_{RTI} in (2). η_1^*, η_2^*, and η_3^* represent bifurcation points when η_{RTI} or η_{PI} in (2) equals zero, and these values are denoted in parentheses.

$$\begin{aligned}
&\eta_{RTI} = 1 - \tfrac{ac\mu(\lambda+dq) + \sqrt{a^2c^2\mu^2(\lambda+dq)^2 - 4a^2cd\mu^2(ab+cq\lambda)}}{2\beta k(ab+cq\lambda)(1-\eta_{PI})}\\
&(\eta_1^* = 0.2123),\\
&\eta_{RTI} = 1 - \tfrac{ac\mu(\lambda+dq) - \sqrt{a^2c^2\mu^2(\lambda+dq)^2 - 4a^2cd\mu^2(ab+cq\lambda)}}{2\beta k(ab+cq\lambda)(1-\eta_{PI})}\\
&(\eta_2^* = 0.9599),\\
&\eta_{RTI} = 1 - \tfrac{da\mu}{\beta\lambda k(1-\eta_{PI})}\ (\eta_3^* = 0.9600).
\end{aligned} \tag{2}$$



(a) point A (b) point B

(c) point C (d) point D

Fig. 2. Bifurcation diagrams of equilibrium points at various efficacies of RTI and PI. The stable and positive-value equilibrium regions of points A, B, C, and D are shaded.

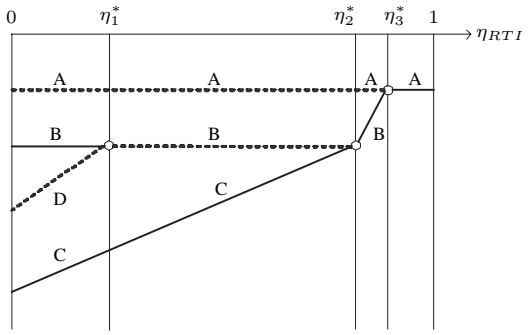


Fig. 3. Bifurcation diagram of the equilibrium points as the efficacy of RTI is varied. This bifurcation diagram is similar to the one in Fig. 2 except that $\eta_{PI} = 0$. The solid and dotted lines represent the stable and unstable equilibrium points, respectively.

Bifurcation diagram in the case of RTI monotherapy ($u_{RTI} = 1, u_{PI} = 0$) is given in Fig. 3. Both equilibrium points B and C are stable when $0 \leq \eta_{RTI} < \eta_1^*$. When $\eta_1^* < \eta_{RTI} < \eta_2^*$, point C is the only stable equilibrium point, and point B is the only one when $\eta_2^* < \eta_{RTI} < 1$. If $\eta_3^* < \eta_{RTI} < 1$ point A becomes stable [14]. However, if we consider HAART, which uses both RTI and PI in treatment, the bifurcation point is a function of the efficacies of RTI and PI, as seen in Fig. 2 and (2). Therefore, we should set the efficacy of PI in consideration of the efficacy of RTI used in RTI monotherapy.

In RTI monotherapy ($u_{PI} = 0$), if a patient is treated continuously with RTIs of $\eta_3^* < \eta_{RTI} < 1$, the patient maintains the status of an uninfected person. Here, we assume that there is no limit cycle. For systems whose order is over two, a method that identifies the existence of a limit cycle is unknown. However, if we stop medication ($\eta_{RTI} = 0$) point

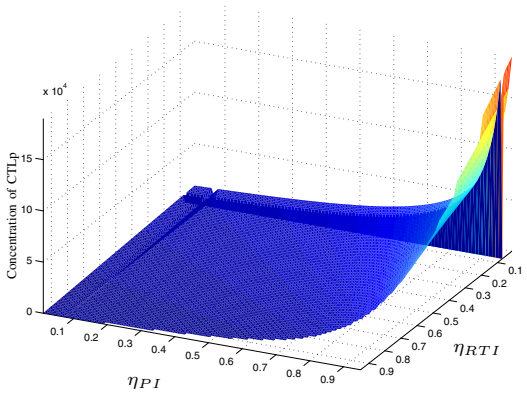


Fig. 4. The concentration of CTLp at the stable equilibrium point C as the efficacies of RTI and PI are varied.

A becomes unstable and points B and C stabilize. Because of this, the patient can no longer maintain an uninfected person's status. If the patient's status is close to point A, whose concentration of CTLp is zero, the patient's status usually converges to point B rather than point C. Few HIV-infected patients' statuses reach point C because it is difficult to converge to point C (LTNP status), which has a very high CTLp concentration [19]. This explains the phenomenon in which a patient's status returns to the pre-treatment status (which has a high viral load and concentration of infected CD4 T-helper cells) after ceasing a highly active treatment like HAART [13]. However, point C becomes stable and the concentration of CTLp increases to a higher level when $\eta_1^* < \eta_{RTI} < \eta_2^*$. Therefore, the patient would have a higher concentration of CTLp when the medication was ceased, which can then induce LTNP status (point C when $\eta_{RTI} = 0$).

However, if PIs are added as part of HAART, the efficacy of PI should be set based upon the efficacy of RTI, because the bifurcation point is a function of both RTI and PI. As shown in Fig. 2(c), an RTI less effective than η_2^* alone ensures a stable Equilibrium point C in RTI monotherapy. However, point C is no longer stable when the RTIs and PIs have the same efficacy such as $\eta_2^* - \epsilon$ for some $\epsilon > 0$ because that makes the efficacy exists outside of the shaded region.

The concentration of CTLp at the stable equilibrium points is depicted in Fig. 4. Either Equilibrium point A or B becomes stable if the efficacy is in the region above the curve joining η_2^*s on both axes in Fig. 2, except for the curve joining η_3^*s. The curve joining η_3^*s is excluded because we do not know stabilities of the bifurcation lines at which the eigenvalue is zero. The concentrations of CTLp at Equilibrium points A and B are zero. So the concentration of CTLp converges at zero when a patient is given a treatment with a drug with an efficacy higher than η_2^*, and the CTLp concentration becomes very low at the point when medication is ceased. For $0 \leq \eta_{RTI} < \eta_2^*$ and $0 \leq \eta_{PI} < \eta_2^*$, concentration of CTLp decreases as η_{RTI} increases, but it increases as η_{PI} increases. To induce LTNP

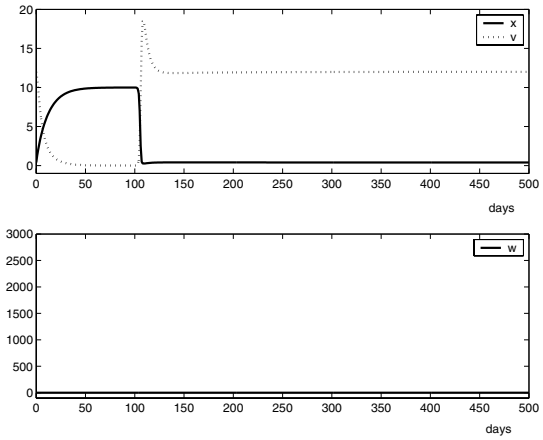
after ceasing medication, the CTLp concentration should be higher than a certain level on medication, which makes point C a stable equilibrium point [6]. For $\eta_1^* < \eta_{RTI} < \eta_2^*$ and $\eta_1^* < \eta_{PI} < \eta_2^*$, we noticed that a lower effective RTI treatment and a higher effective PI treatment narrowed the difference between the CTLp concentration at treatment cessation and the concentration when LTNP status was reached (point C where $\eta_{RTI} = \eta_{PI} = 0$). This is because the concentration of CTLp increases with therapy as the efficacy of RTI decreases and the efficacy of PI increases (Fig. 4). In addition, we observed that the probability of an opportunistic infection can be reduced with a highly effective treatment that causes the patient's state to converge more rapidly to the equilibrium point. Therefore, setting an appropriate effectiveness of therapy is important for the trade-off between the speed of convergence of a patient's state to the equilibrium point and the concentration of CTLp while on medication [20].

III. SIMULATION RESULTS AND CONTROLLABILITY

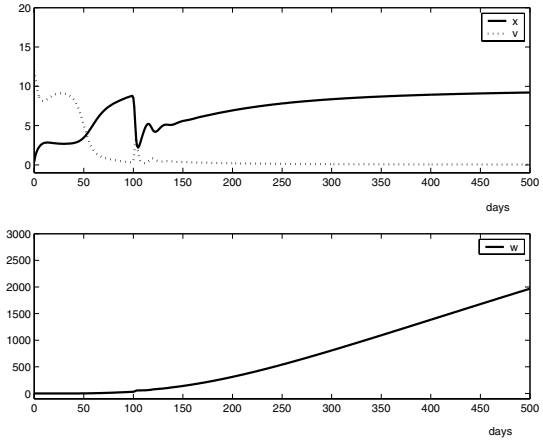
Two patients who had different initial conditions were considered for simulation. HIV-infected patient A represents a patient who has been infected with HIV for several years and, thus, the HIV population is dominant. HIV-infected patient B represents a patient who had undergone long-term RTI treatment after infection so this patient's concentration of uninfected CD4 T-helper cells is relatively high. patients A and B had initial conditions of $[0.4, 4.8, 119.9, 0.0001, 0.0001]^T$ and $[9.94, 0.0069, 0.189, 0.0026, 8.43 \times 10^{-6}]^T$ respectively. In this paper, we present the simulation results of the disease progression and controllability change in patients A and B with two treatment methods: RTI monotherapy and RTI & PI combination therapy (HAART), for 100 days. In simulations, we presented x (uninfected CD4 T-helper cell), v (virus), and w (CTLp), and v is scaled by 0.1 throughout the report.

A. RTI MONOTHERAPY

1) SIMULATION: Fig. 5 shows disease progression of patient A for 100 days of $\eta_{RTI} = 0.98$ and $\eta_{RTI} = 0.85$ which have values higher and lower than η_2^*, respectively. In Fig. 5(a), patient A maintained uninfected status (equilibrium point A) on medication with $\eta_{RTI} = 0.98$, and converged to concentrations of uninfected CD4 T-helper cell, infected CD4 T-helper cell, virus, CTLp, and CTLe to 10, 0, 0, 0, and 0, respectively. However, if medication ceased ($\eta_{RTI} = 0$), Equilibrium point A became unstable and low concentrations of CTLe and CTLp could not prevent the virus from rapidly rebounding. Thus, the concentration of uninfected cells declines drastically and the patient will likely die from an opportunistic infection because the patient's status reverts to AIDS [22]. In Fig. 5(b), patient A's viral load becomes very low as in the case of $\eta_{RTI} = 0.98$ but the concentration of CTLp increases somewhat when the patient is treated with $\eta_{RTI} = 0.85$. CTLp- and CTLe-related adaptive immune responses suppress HIV. Therefore, even if medication is stopped, the concentration of uninfected CD4 T-helper cells



(a) patient A with $\eta_{RTI} = 0.98$



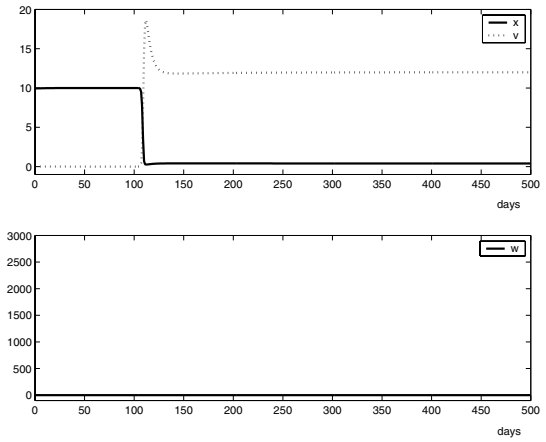
(b) patient A with $\eta_{RTI} = 0.85$

Fig. 5. Simulation results for patient A with $\eta_{RTI} = 0.98$ and $\eta_{RTI} = 0.85$ for 100 days.

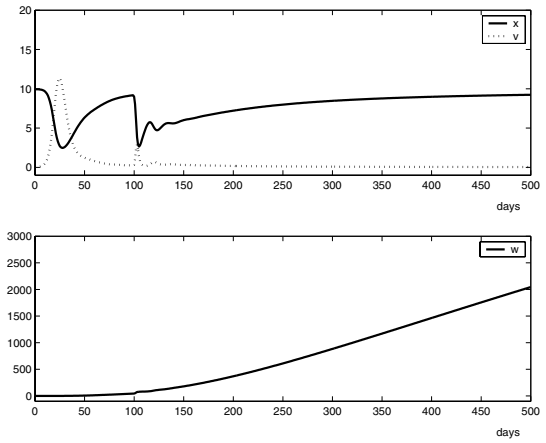
falls slightly right after cessation, but then it rebounds. Notice that a continuous increase in CTLp concentration levels is very important in inducing LTNP status [6].

Disease progression of HIV-infected patient B when $\eta_{RTI} = 0.98$ and $\eta_{RTI} = 0.85$ for 100 days is presented in Fig. 6. In Fig. 6(a), HIV-infected patient B's status converges to uninfected status, and then progresses to AIDS after treatment cessation as seen in patient A when $\eta_{RTI} = 0.98$. In Fig. 6(b), the concentration of uninfected CD4 T-helper cells declined at the initiation of treatment, but recovered soon after with medication. patient B was converted to an LTNP by the same mechanism as patient A, who was treated with $\eta_{RTI} = 0.85$.

A highly active treatment of RTI monotherapy induces the concentration of CTLp at a stable equilibrium point to zero. Therefore, CTLe cannot be produced. This prevents the immune system from adequately suppressing HIV-rebound after medication cessation. Excessive antiretroviral therapy, which is likely to destroy the immune system, is not appropriate for inducing LTNP [21]. As shown by the simulation results, the cessation of medication is needed to induce LTNP status through constant and time-limited drug



(a) patient B with $\eta_{RTI} = 0.98$



(b) patient B with $\eta_{RTI} = 0.85$

Fig. 6. Simulation results for patient B with $\eta_{RTI} = 0.98$ and $\eta_{RTI} = 0.85$ for 100 days.

dose after increasing the concentration of CTLp when using treatments that have an efficacy below a certain level.

2) CONTROLLABILITY: Controllability is an estimate of drug efficacy within a patient. By examining the minimum singular value decomposition of the controllability matrix, we can estimate how controllable the system is at a particular time during the disease progression [15]. For controllability analysis, we linearized the system (1) as (3).

$$\dot{X} = A_{RTI}X + B_{RTI}\eta_{RTI} \tag{3}$$

where

$$A_{RTI} = \begin{bmatrix} -d-\beta\eta^* v & 0 & -\beta\eta^* x & 0 & 0 \\ \beta\eta^* v & -a-pz & \beta\eta^* x & 0 & -py \\ 0 & k & -\mu & 0 & 0 \\ cyw & cxw-cqw & 0 & cxy-cqy-b & 0 \\ 0 & cqw & 0 & cqy & -h \end{bmatrix},$$

$$B_{RTI} = [\,\beta xv \;\; -\beta xv \;\; 0 \;\; 0 \;\; 0\,]^T,$$

$$\eta^* = 1 - \eta_{RTI}.$$

We computed the controllability matrix as

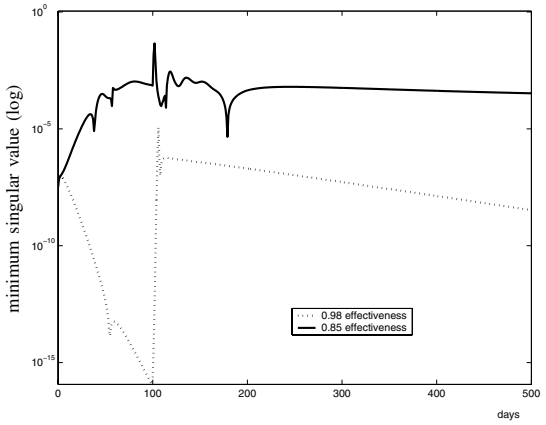
$$\mathcal{C}_{RTI} = \big[\, B_{RTI} \;\; A_{RTI}B_{RTI} \;\; A^2_{RTI}B_{RTI} \;\; A^3_{RTI}B_{RTI} \;\; A^4_{RTI}B_{RTI} \,\big]^T.$$

Then we applied singular value decomposition to the controllability matrix $\mathcal{C}$, and plotted the minimum singular values.

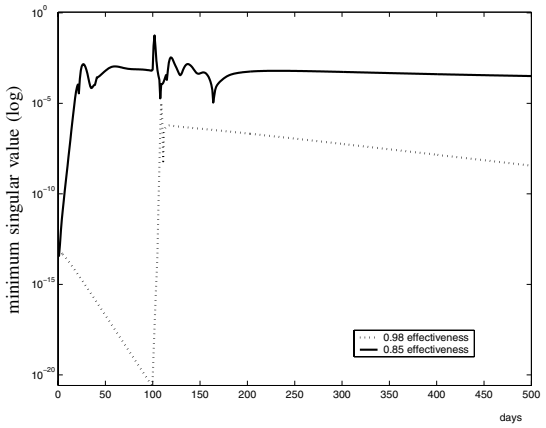
Fig. 7 indicates the minimum singular values of controllability matrices for patients A and B with $\eta_{RTI} = 0.98$ and $\eta_{RTI} = 0.85$. Figs. 5(a) and 6(a) show that treatments received by both patients A and B with $\eta_{RTI} = 0.98$ do not succeed in leading LTNP. In Fig. 7, controllability falls radically while on the medication of $\eta_{RTI} = 0.98$ for 100 days. This means that the treatment efficiency decreases as highly active antiretroviral therapy is continued. However, treatments with $\eta_{RTI} = 0.85$ induce LTNP status, as shown in Figs. 5(b) and 6(b). Fig. 7 shows that treatment with $\eta_{RTI} = 0.85$ for 100 days induces a rise in controllability and maintains the level achieved. Thus, the controllability is higher than either $\eta_{RTI} = 0.98$ for 100 days. This demonstrates that the immune system controls HIV or infected CD4 T-helper cells more efficiently with higher controllability. Therefore, it is desirable to use a therapy with an efficacy lower than a certain level (which may increase the concentration of CTLp and induce LTNP), instead of using therapies that suppress HIV and infected CD4 T-helper cells rapidly with high-efficacy drugs. We found that this lower efficacy treatment proves to have a higher relative efficiency in treatment of the immune system.

B. RTI & PI COMBINATION THERAPY

1) SIMULATION: Fig. 8 shows the disease progression of HIV-infected patient A for 100 days when $\eta_{RTI} = 0.85$ & $\eta_{PI} = 0.85$, $\eta_{RTI} = 0.85$ & $\eta_{PI} = 0.65$, and $\eta_{RTI} = 0.85$ & $\eta_{PI} = 0.55$. The RTI monotherapy of $\eta_{RTI} = 0.85$ succeeded in inducing LTNP, so we fixed the efficacy of RTI of RTI & PI combination therapies at 0.85. In Fig. 8(a), patient A maintained uninfected status while on medication with $\eta_{RTI} = 0.85$ & $\eta_{RTI} = 0.85$ whose values are lower than η_2^*. However, if the medication is ceased, low CTLe and CTLp levels cannot prevent the virus from rapidly rebounding. The concentration of uninfected CD4 T-helper cells greatly decreases and patients are likely to die from an opportunistic infection due to the progression to AIDS, as in the case of RTI monotherapy [22]. Although $\eta_{RTI} = 0.85$ ensures that equilibrium point C stable in RTI monotherapy, $\eta_{RTI} = 0.85$ and $\eta_{PI} = 0.85$ together do not make equilibrium point C as stable as we estimated in Fig. 2(c). From (2), the efficacy of PI should be less than 0.7331 to make point C stable when $\eta_{RTI} = 0.85$. Because $\eta_{PI} = 0.85$ is higher than 0.7331 when $\eta_{RTI} = 0.85$, point A is stable but point C is not. In order for HAART and to induce LTNP status in patients, the efficacy of PI should be set to the value that stabilizes Equilibrium point C in consideration of the efficacy of RTI. In Fig. 8(b), patient A's viral load fell but the concentration of CTLp slightly increased when the patient was treated with $\eta_{RTI} = 0.85$ & $\eta_{PI} = 0.65$, whose efficacy of PI is less than 0.7331. CTLp and CTLe suppress HIV, so if medication is stopped, the concentration



(a) patient A with $\eta_{RTI} = 0.98$ and $\eta_{RTI} = 0.85$

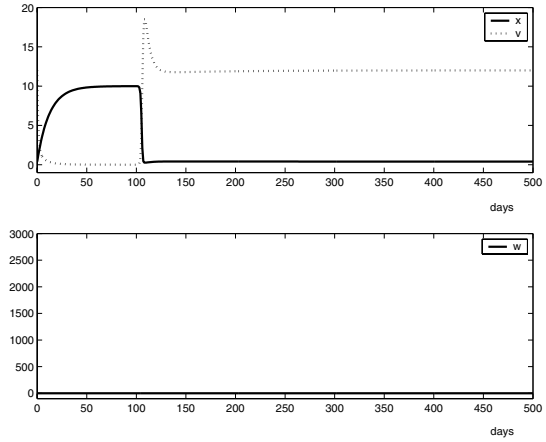


(b) patient B with $\eta_{RTI} = 0.98$ and $\eta_{RTI} = 0.85$

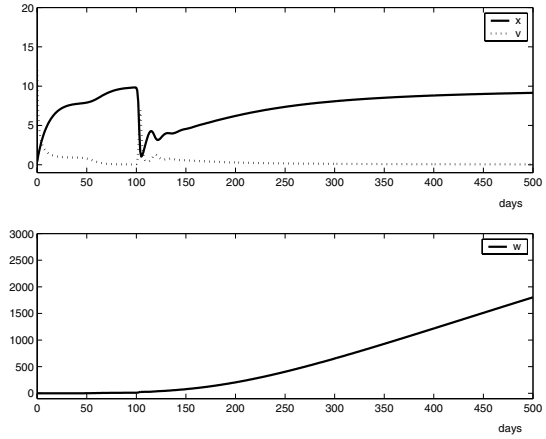
Fig. 7. Controllability for patients A and B when $\eta_{RTI} = 0.98$ and $\eta_{RTI} = 0.85$.

of uninfected CD4 T-helper cells falls and the patient reaches LTNP status immediately. In Fig. 8(c), we see that a less-effective PI resulted in lower peak of the viral load, and an increase in the concentration of CTLp while on medication.

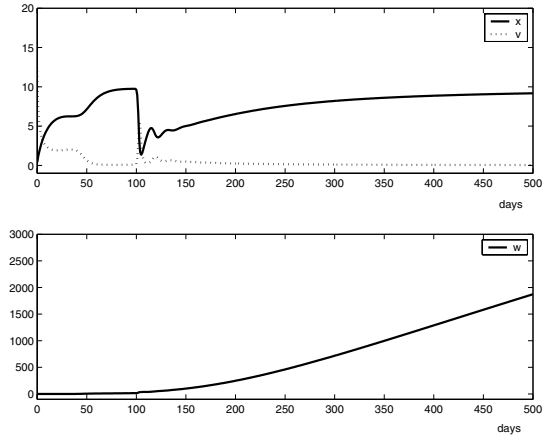
The disease progression of HIV-infected patient B for 100 days when $\eta_{RTI} = 0.85$ & $\eta_{PI} = 0.85$, $\eta_{RTI} = 0.85$ & $\eta_{PI} = 0.65$, and $\eta_{RTI} = 0.85$ & $\eta_{PI} = 0.55$ is presented in Fig. 9. patient B's status converges to an uninfected status (as does patient A) when $\eta_{RTI} = 0.85$ & $\eta_{PI} = 0.85$ in Fig. 9(a). However, the immune system fails to prevent the viral load from increasing rapidly, and the concentration of uninfected CD4 T-helper cells decreases after medication is stopped. After cessation, the patient's status progresses to AIDS. As was seen with patient A, $\eta_{PI} = 0.85$ makes point C unstable when $\eta_{RTI} = 0.85$, so the efficacy of PI should be lowered to induce LTNP status. In Fig. 9(b), patient B's CTLp increases while the viral load is maintained at a low level for $\eta_{RTI} = 0.85$ & $\eta_{PI} = 0.65$. CTLp and CTLe suppress HIV, so the concentration of uninfected CD4 T-helper cells increases. As a result, patient B was reached LTNP status in Fig. 9(b). In Fig. 9(c), a less-effective PI results in lower peak of the viral load and a rapid increase in the concentration of CTLp on medication when compared



(a) patient A with $\eta_{RTI} = 0.85$ & $\eta_{PI} = 0.85$



(b) patient A with $\eta_{RTI} = 0.85$ & $\eta_{PI} = 0.65$



(c) patient A with $\eta_{RTI} = 0.85$ & $\eta_{PI} = 0.55$

Fig. 8. Simulation results for patient A with $\eta_{RTI} = 0.85$ & $\eta_{PI} = 0.85$, $\eta_{RTI} = 0.85$ & $\eta_{PI} = 0.65$, and $\eta_{RTI} = 0.85$ & $\eta_{PI} = 0.55$ for 100 days.

to Fig. 9(b).

When we use RTI and PI combination therapy (HAART), PI (which has the same efficacy as RTI that stabilizes Equilibrium point C in RTI monotherapy) does not always ensure the induction of LTNP status. This is because the bifurcation point is a function of the efficacies of RTI and PI, and the bifurcation line, which determines the stability of point C, is a curve. Thus, the efficacy of PI should be selected based upon the efficacy of RTI for inducing LTNP status from Figs. 8 and 9.

2) CONTROLLABILITY: For the controllability analysis of RTI and PI combination therapy, we linearized system (1) as (4).

$$\dot{X} = A_{CO}X + B_{CO}\eta_{CO} \tag{4}$$

where

$$A_{CO} = \begin{bmatrix} -d-\beta\eta^* v & 0 & -\beta\eta^* x & 0 & 0 \\ \beta\eta^* v & -a-pz & \beta\eta^* x & 0 & -py \\ 0 & \eta^{**}k & -\mu & 0 & 0 \\ cyw & cxw-cqw & 0 & cxy-cqy-b & 0 \\ 0 & cqw & 0 & cqy & -h \end{bmatrix},$$

$$B_{CO} = \begin{bmatrix} \beta xv & -\beta xv & 0 & 0 & 0 \\ 0 & 0 & -ky & 0 & 0 \end{bmatrix}^T,$$

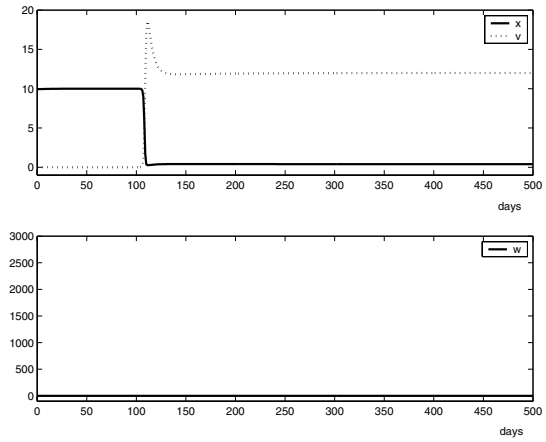
$$\eta^* = 1-\eta_{RTI}, \eta^{**} = 1-\eta_{PI}.$$

We computed the controllability matrix as

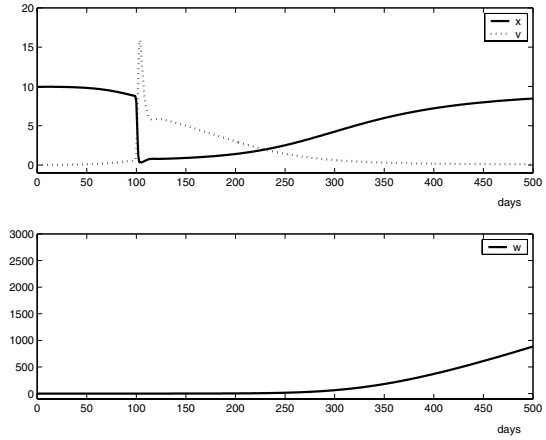
$$\mathcal{C}_{CO} = \begin{bmatrix} B_{CO} & A_{CO}B_{CO} & A_{CO}^2 B_{CO} & A_{CO}^3 B_{CO} & A_{CO}^4 B_{CO} \end{bmatrix}^T.$$

We then applied singular value decomposition to the controllability matrix.

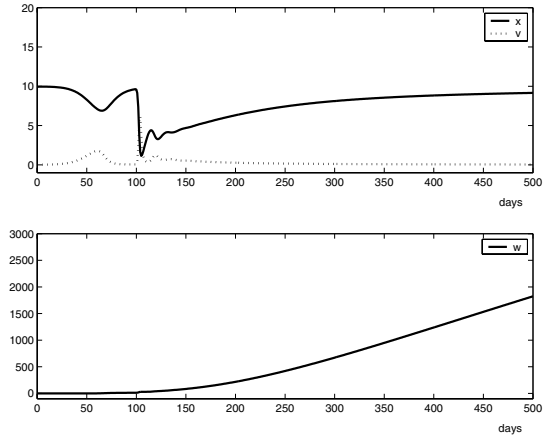
Fig. 10 contains the minimum singular values of the controllability matrices for patients A and B with $\eta_{RTI} = 0.85$ & $\eta_{PI} = 0.85$, $\eta_{RTI} = 0.85$ & $\eta_{PI} = 0.65$, and $\eta_{RTI} = 0.85$ & $\eta_{PI} = 0.55$. In Figs. 8(a) and 9(a), treatments with $\eta_{RTI} = 0.85$ & $\eta_{PI} = 0.85$ for both patients A and B were not successful in inducing LTNP status. In Fig. 10, controllability falls rapidly while on the medication of $\eta_{RTI} = 0.85$ & $\eta_{PI} = 0.85$ for 100 days. The treatment efficiency decreases rapidly as antiretroviral therapy with a very high efficacy is continued. However, treatments with $\eta_{RTI} = 0.85$ & $\eta_{PI} = 0.65$ induce LTNP status in the patients in Figs. 8(b) and 9(b). In contrast, Fig. 10 shows the treatments with $\eta_{RTI} = 0.85$ & $\eta_{PI} = 0.65$ for 100 days that made the controllability increase to greater than the controllability for $\eta_{RTI} = 0.85$ & $\eta_{PI} = 0.85$. This indicates that the immune system controls HIV or infected CD4 T-helper cells more efficiently with higher controllability. For $\eta_{RTI} = 0.85$ & $\eta_{PI} = 0.55$, the controllability increases more rapidly as CTLp increases in Fig. 9(c) and is higher than in the other cases. Therefore, a combination therapy needs to include RTIs and PIs, which together have efficacies lower than a certain level in order to increase the concentration of CTLp and induce LTNP. We discovered that a lower efficacy therapy results in a higher relative efficiency in treatment of the immune system.



(a) patient B with $\eta_{RTI} = 0.85$ & $\eta_{PI} = 0.85$

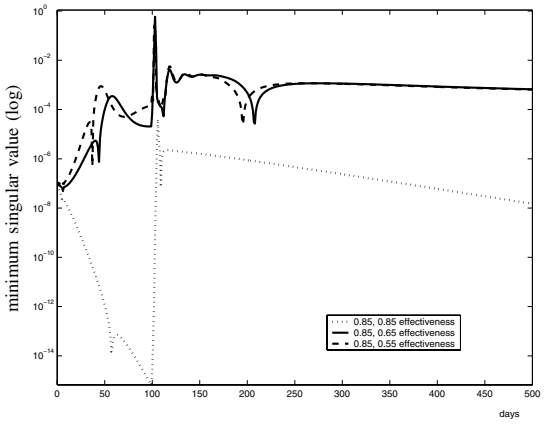


(b) patient B with $\eta_{RTI} = 0.85$ & $\eta_{PI} = 0.65$

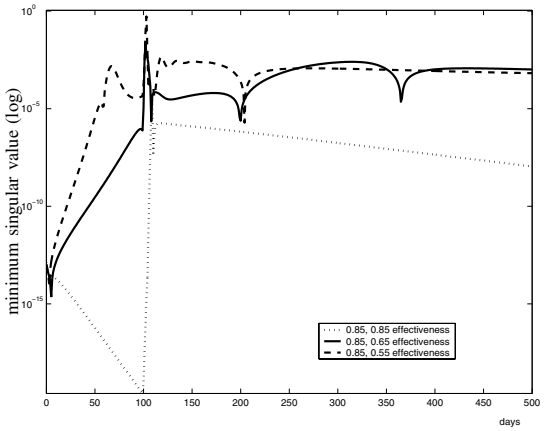


(c) patient B with $\eta_{RTI} = 0.85$ & $\eta_{PI} = 0.55$

Fig. 9. Simulation results for patient B with $\eta_{RTI} = 0.85$ & $\eta_{PI} = 0.85$, $\eta_{RTI} = 0.85$ & $\eta_{PI} = 0.65$, and $\eta_{RTI} = 0.85$ & $\eta_{PI} = 0.55$ for 100 days.



(a) patient A with $\eta_{RTI} = 0.85$ & $\eta_{PI} = 0.85$, $\eta_{RTI} = 0.85$ & $\eta_{PI} = 0.65$, and $\eta_{RTI} = 0.85$ & $\eta_{PI} = 0.55$



(b) patient B with $\eta_{RTI} = 0.85$ & $\eta_{PI} = 0.85$, $\eta_{RTI} = 0.85$ & $\eta_{PI} = 0.65$, and $\eta_{RTI} = 0.85$ & $\eta_{PI} = 0.55$

Fig. 10. Controllability of patients A and B when $\eta_{RTI} = 0.85$ & $\eta_{PI} = 0.85$, $\eta_{RTI} = 0.85$ & $\eta_{PI} = 0.65$, and $\eta_{RTI} = 0.85$ & $\eta_{PI} = 0.55$ for 100 days.

IV. CONCLUSION

Treatments whose efficacies are continuously varied are not viable for application in clinical treatment as they are likely to result in the emergence of a highly resistant virus. We presented a therapy that used a constant drug dosage of RTI and PI which could induce LTNP status in an HIV-infected patient. We observed the bifurcation phenomenon as the efficacy of therapy and the variation of the concentration of CTLp at a stable equilibrium point changed. In addition, we implemented simulations that explored the bifurcation phenomenon. From the simulation results, we determined that the patient's status does not progress to AIDS after cessation of medication if we use a therapy that had an efficacy lower than a certain level (η_2^*). This therapy stabilized Equilibrium point C, which has higher concentration of CTLp. The efficacy of PI should be selected while considering of the efficacy of RTI, especially for an RTI and PI combination therapy. By comparing minimum singular values of the controllability matrix as the disease progressed, we determined that therapy with a lower efficacy has a higher relative efficiency in HIV treatment.

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