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ANALYSIS OF AN HIV MODEL WITH POST-TREATMENT CONTROL

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Abstract Recent investigation indicated that latent reservoir and immune impairment are responsible for the post-treatment control of HIV infection. In this paper, we simplify the disease model with latent reservoir and immune impairment and perform a series of mathematical analysis. We obtain the basic infection reproductive number R_0 to characterize the viral dynamics. We prove that when $R_0 < 1$, the uninfected equilibrium of the proposed model is globally asymptotically stable. When $R_0 > 1$, we obtain two thresholds, the post-treatment immune control threshold and the elite control threshold. The model has bistable behaviors in the interval between the two thresholds. If the proliferation rate of CTLs is less than the post-treatment immune control threshold, the model does not have positive equilibria. In this case, the immune free equilibrium is stable and the system will have virus rebound. On the other hand, when the proliferation rate of CTLs is greater than the elite control threshold, the system has stable positive immune equilibrium and unstable immune free equilibrium. Thus, the system is under elite control.

Keywords HIV infection, mathematical model, bistable behavior, post-treatment immune control, elite control.

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1. Introduction

In 2010, an HIV-infected mother gave birth to a baby prematurely in a Mississippi clinic. The infant was known as the 'Mississippi baby'. Before delivery, the mother was not diagnosed with HIV infection did not receive antiretroviral treatment [1]. At the age of 30 hours, the baby received liquid, triple-drug antiretroviral treatment. Such treatment was terminated at the age of 18 months and since then, the virus level in the baby remains undetectable. Though it was thought that the baby was cured of HIV, a routine clinical test on July 10, 2014 showed that the level of virus in the 'Mississippi baby' became detectable (16,750 copies/ml) [1].

Antiretroviral therapy (ART) is effective in inhibiting the HIV infection and prolongs the life of infected individuals. However, due to the existence of latent reservoirs, it is unable to totally eliminate the virus infection [10, 11, 14, 15, 51]. The time it takes the virus to rebound varies. For example, the virus level of the

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Mississippi baby remains undetectable for years before the virus rebound [1, 31]. Sometimes, a host may have low virus load after antiretroviral therapy. Investigations have been carried out to reveal the causes of low virus level and virus rebound [12, 31, 39].

Conway and Perelson constructed a mathematical model to investigate the dynamics of virus rebound [12]. Their investigation reveals the interplay between immune response and latent reservoir, and shows that post-treatment control may appear. Recent investigations indicated that early antiretroviral therapy may be responsible for the development of post-treatment control with plasma virus remaining undetectable after the cessation of treatment. However, only a small proportion of patients receiving early antiretroviral therapy developed post-treatment control. Further investigations are to be carried out to reveal the reasons behind this.

Treasure et al investigated the HIV rebound in patients who terminated the antiretroviral therapy. They showed that a patient who discontinued the antiretroviral therapy may or may not undergo immediate HIV rebound [39].

As an important approach to investigate disease transmission, mathematical modeling provides insights into interactions between viral and host factors. System of differential equations have been used to model the behavior of ecological systems [9] as well as within-host virus systems [2]. Evaluating the behaviors of the viral models yields a better understanding of the disease and is beneficial to the development of appropriate therapy strategies. In the literature, mathematical models of within-host viral dynamics have been designed [2, 4, 8, 13, 17, 28–30, 43, 44, 46, 48, 49]. Immune response has also been integrated into within host models to investigate the combined effects of viral dynamics and immune process of the host [7, 18, 25, 37, 41–45, 52].

Regoes et al. [33] incorporated immune impairment into viral models to consider the effects that target cell limitation and immune responses have on the evolution of virus. Their investigations indicated that the immune system of the host may collapse when the impairment rate of HIV surpasses its threshold value. Iwami et al. [19,20] investigated the HIV dynamics with immune impairment using mathematical models. The authors got the 'risky threshold' and 'immunodeficiency threshold' by performing analysis. The results implied that the immune system always collapses when the impairment rate is greater than the threshold value. Immune impairment in within-host virus models have received much attention in the literature [3,38,47].

HIV latent reservoir is responsible for the rebound in HIV viral load. As a major barrier to the eradication of HIV-1 virus, latent reservoir poses persistent risks to the hosts. The infected cells in the latent reservoir remain undetectable to the immune system and can be reactivated to produce virions with the termination of drug therapy [21, 22, 34, 35, 40]. Investigations showed that the size of the virus reservoir is relatively stable [40]. For a patient under sufficient antiretroviral therapy (ART), ongoing viral replication rate in the reservoir remains low [22]. However, for infected individuals under ART of lower efficiency, there might be coexistence of latent reservoir and virus. Rong and Perelson [35] performed a thorough study on the replenishment of the latent reservoir induced by latently infected cells that are occasionally reactivated. The authors indicated that such scenario corresponds to the half-life of the latent reservoir.

Post-treatment control of HIV attracted the attention of researchers. Conway and Perelson integrated the post treatment into an HIV model and performed anal-

ysis [12]. Here, we simplify the model proposed in [12] to obtain

$$\begin{cases} \frac{dx(t)}{dt} = s - dx(t) - (1-\epsilon)\beta x(t)y(t), \\ \frac{dL(t)}{dt} = \alpha_L(1-\epsilon)\beta x(t)y(t) + (\rho - a - d_L)L(t), \\ \frac{dy(t)}{dt} = (1-\alpha_L)(1-\epsilon)\beta x(t)y(t) + aL(t) \\ \qquad\quad -\delta y(t) - py(t)z(t), \\ \frac{dz(t)}{dt} = \frac{cy(t)z(t)}{1+\eta y(t)} - bz(t) - my(t)z(t), \end{cases} \tag{1.1}$$

where x denotes the concentration of activated CD4$^+$ T cells, L latently infected cells, y productively infected CD4$^+$ T cells and z the immune cells. Here, $0 < \alpha_L < 1$. The effectiveness of both drug classes is represented by $\epsilon \in [0, 1]$. Here ϵ is also known as the overall treatment effectiveness of HIV. If the treatment is terminated, $\epsilon = 0$. If the therapy is 100% effective, we have $\epsilon = 1$ [12, 34]. The default parameters for system (1.1) is listed in Table 5.

In the literature, the immune and immune impairment function $\frac{cyz}{1+\eta y} - bz - myz$ has been applied to the viral models to characterize the interaction between the immune cells and the productively infected CD4$^+$ T cells [8, 32, 47]. Wang and Liu [47] constructed a within-host viral dynamics models to consider HIV infection with immune impairment. In this article, we consider the post-treatment immune control, the biological implication behind the 'Mississippi baby'. By mathematical analysis, we obtain the threshold of proliferation rate of CTLs, which determines the HIV infection status. We also perform bifurcation analysis and demonstrate the bistable behavior of the model, which is consistence with results from recent medical trial.

2. Preparation

In this section, we perform mathematical analysis for the model (1.1). We prove the positiveness and boundedness of the solutions to system (1.1) and calculate the equilibria of the model. We always assume $a + d_L > \rho$. That is to say, the sum of the activation rate and the death rate of the latently infected cell is greater than the proliferation rate of latently infected cells.

2.1. Positiveness and boundedness

In the following, we show that system (1.1) is well-posed.

Theorem 2.1. *System (1.1) has a unique nonnegative solution with initial values* $(x(0), L(0), y(0), z(0)) \in \mathbb{R}^4_+$, *where* $\mathbb{R}^4_+ = \{(x_1, x_2, x_3, x_4) | x_j \geq 0, j = 1, 2, 3, 4\}$. *Furthermore, the solution is bounded.*

Proof. It follows from the fundamental theory of ordinary differential equations [16] that there exists a unique solution to system (1.1) with nonnegative initial conditions.

For any nonnegative initial data, let $t_1 > 0$ be the first time when $x(t_1) = 0$. From the first equation of (1.1) we have that $\dot{x}(t_1) = s > 0$, which implies that $x(t) < 0$ for $t \in (t_1 - \varepsilon_1, t_1)$, where ε_1 is an arbitrarily small positive constant. This is a contradiction. Therefore, $x(t)$ is always positive. Since $z = 0$ is a constant

solution of the last equation of (1.1), it follows from the fundamental existence and uniqueness theorem that $z > 0$ for all $t > 0$.

Suppose there is a first time $t_2 > 0$ when $y(t_2)z(t_2) = 0$. Then we have

(i) $L(t_2) = 0, y(t) \geq 0$ for $t \in [0, t_2]$, or

(ii) $y(t_2) = 0, L(t) \geq 0$ for $t \in [0, t_2]$.

For case(i), since $x(t)$ is positive, it follows from the variation of constants formula that $L(t_2) = L(0) + e^{-\int_0^{t_2}(a+d_L-\rho)d\xi}\int_0^{t_2}\alpha_L(1-\epsilon)\beta x(\xi)y(\xi)d\xi > 0$, which is in contradiction to $L(t_2) = 0$.

For case (ii), the third equation of system (1.1) implies that $y(t_2) = y(0) + e^{\int_0^{t_2}[(1-\alpha_L)(1-\epsilon)\beta x(\xi)-\delta-pz(\xi)]d\xi}\int_0^{t_2} aL(\xi)d\xi > 0$, which is in contradiction to $y(t_2) = 0$. Thus, $L(t)$ and $y(t)$ are always positive.

Next, we expatiate upon the boundedness of solutions of (1.1). Let

$$K(t) = \sigma x(t) + aL(t) + (a + d_L - \rho)y(t) + \frac{p(a + d_L - \rho)z(t)}{c - m},$$

where $\sigma = a\alpha_L + (1 - \alpha_L)(a + d_L - \rho)$. Since all solutions of (1.1) are positive, we have

$$\begin{aligned}
\tfrac{dK}{dt} &= \sigma\Big[s - dx - (1-\epsilon)\beta xy\Big] \\
&\quad + a\Big[\alpha_L(1-\epsilon)\beta xy + (\rho - a - d_L)L\Big] \\
&\quad + (a + d_L - \rho)\Big[(1-\alpha_L)(1-\epsilon)\beta xy \\
&\quad + aL - \delta y - pyz\Big] \\
&\quad + \tfrac{p(a+d_L-\rho)}{c-m}\Big(\tfrac{cyz}{1+\eta y} - bz - myz\Big) \\
&\leq \sigma s - \sigma dx - (a + d_L - \rho)\delta y - \tfrac{p(a+d_L-\rho)}{c-m}bz \\
&< \sigma s - \sigma r K,
\end{aligned}$$

where $r = \min\left\{\frac{d}{\sigma}, \frac{\delta}{\sigma}, \frac{b}{\delta}\right\} > 0$. Let φ denote the solution to the following system

$$\begin{cases} \dfrac{d\varphi}{dt} = \sigma s - \sigma r\varphi, \\ \varphi_0 = \sigma x_0 + aL_0 + (a + d_L - \rho)y_0 + \dfrac{p(a + d_L - \rho)z_0}{c - m}, \end{cases}$$

where x_0, y_0 and z_0 are the initial values of system (1.1) and $\varphi_0 = K_0 > 0$. We then obtain $\lim_{t\to+\infty}\sup\varphi(t) = \frac{s}{r}$. By comparison theorem [36], we get $K(t) < \varphi(t)$. Therefore, $x(t)$, $L(t)$, $y(t)$ and $z(t)$ are bounded. □

2.2. Equilibria

In this section, we consider the existence of the equilibria to system (1.1).

(i) If $R_0 < 1$, system (1.1) only has an infection-free equilibrium $E_0 = (x_0, 0, 0, 0) = (\frac{s}{d}, 0, 0, 0)$, where

$$R_0 = \frac{s\beta(1-\epsilon)[a\alpha_L + (1-\alpha_L)(a + d_L - \rho)]}{d\delta(a + d_L - \rho)}$$

is the basic infection reproductive number. Here, R_0 is the expected number of newly infected cells generated from an infected cell at the beginning of the infectious process.

(ii) If $R_0 > 1$, system (1.1) also has an immune-free equilibrium $E_1 = (x_1, L_1, y_1, 0)$, where

$$\begin{aligned} x_1 &= \tfrac{\delta(a+d_L-\rho)}{\beta(1-\epsilon)[a\alpha_L+(1-\alpha_L)(a+d_L-\rho)]}, \\ L_1 &= \tfrac{\alpha_L\beta(1-\epsilon)x_1y_1}{a+d_L-\rho}, \\ y_1 &= \tfrac{d(R_0-1)}{\beta(1-\epsilon)}. \end{aligned}$$

Solving equation $\frac{cy}{1+\eta y} - b - my = 0$ yields two positive roots, given by $c_1 = m + b\eta - 2\sqrt{bm\eta}$ and $c_2 = m + b\eta + 2\sqrt{bm\eta}$. We then get the existence conditions for the positive equilibria.

(iii) If $R^*_- > 1$ and $c > c_2$, system (1.1) has an immune equilibrium $E^*_- = (x^*_-, L^*_-, y^*_-, z^*_-)$. If $R^*_+ > 1$ and $c > c_2$, system (1.1) has an immune equilibrium $E^*_+ = (x^*_+, L^*_+, y^*_+, z^*_+)$ as well. Here

$$\begin{aligned} x^*_\pm &= \tfrac{s}{d+\beta(1-\epsilon)y^*_\pm}, \\ L^*_\pm &= \tfrac{\alpha_L(1-\epsilon)\beta x^*_\pm y^*_\pm}{a+d_L-\rho}, \\ y^*_\pm &= \tfrac{-B\mp\sqrt{B^2-4bm\eta}}{2m\eta}, \\ z^*_\pm &= \tfrac{\delta(R^*_\pm-1)}{p}, \\ B &= m + b\eta - c, \end{aligned}$$

$$R^*_- = \tfrac{2m\eta s\beta(1-\epsilon)}{\delta(a+d_L-\rho)} \tfrac{[a\alpha_L+(a+d_L-\rho)(1-\alpha_L)]}{\{2m\eta d+\beta(1-\epsilon)[c-m-b\eta-\sqrt{(c-m-b\eta)^2-4bm\eta}]\}},$$

and

$$R^*_+ = \tfrac{2m\eta s\beta(1-\epsilon)}{\delta(a+d_L-\rho)} \tfrac{[a\alpha_L+(a+d_L-\rho)(1-\alpha_L)]}{\{2m\eta d+\beta(1-\epsilon)[c-m-b\eta+\sqrt{(c-m-b\eta)^2-4bm\eta}]\}}.$$

Denote

$$c^* = m + b\eta + \frac{2dm\eta(R_0-1)}{\beta(1-\epsilon)},$$

$$c^{**} = m + b\eta + \frac{b\beta(1-\epsilon)}{d(R_0-1)} + \frac{dm\eta(R_0-1)}{\beta(1-\epsilon)}$$

and

$$R_c = 1 + \frac{\beta(1-\epsilon)\sqrt{bm\eta}}{dm\eta}.$$

We then have the following results.

Lemma 2.1. $R_0 > R_c > 1 \Leftrightarrow c^* > c^{**}$.

Proof.

$$\begin{aligned} c^* > c^{**} &\Leftrightarrow \tfrac{dm\eta(R_0-1)}{\beta(1-\epsilon)} > \tfrac{b\beta(1-\epsilon)}{d(R_0-1)}, \\ &\Leftrightarrow R_0 > 1 + \tfrac{\beta(1-\epsilon)\sqrt{bm\eta}}{dm\eta} = R_c. \end{aligned}$$

□

Lemma 2.2. *(i)* $R_0 > R_c > 1 \Leftrightarrow c^* > c_2$. *(ii)* $1 < R_0 < R_c \Leftrightarrow c^* < c_2$.

Proof.

$$\begin{aligned} c^* > c_2 &\Leftrightarrow \tfrac{dm\eta(R_0-1)}{\beta(1-\epsilon)} > \sqrt{bm\eta}, \\ &\Leftrightarrow R_0 > 1 + \tfrac{\beta(1-\epsilon)\sqrt{bm\eta}}{dm\eta} = R_c. \\ c^* < c_2 &\Leftrightarrow \tfrac{dm\eta(R_0-1)}{\beta(1-\epsilon)} < \sqrt{bm\eta}, \\ &\Leftrightarrow R_0 < 1 + \tfrac{\beta(1-\epsilon)\sqrt{bm\eta}}{dm\eta} = R_c. \end{aligned}$$

□

Lemma 2.3. *(i) Assume* $1 < R_0 < R_c$. *If* $R_-^* > 1$, *then* $c > c^{**}$. *(ii) Assume* $R_0 > R_c > 1$. *If* $R_-^* > 1$, *then* $c > c_2$.

Proof.

$$\begin{aligned} R_-^* > 1 \Leftrightarrow\ & \tfrac{s\beta(1-\epsilon)[a\alpha_L+(a+d_L-\rho)(1-\alpha_L)]}{\delta(a+d_L-\rho)} \\ & > d + \tfrac{\beta(1-\epsilon)}{2m\eta}[c-m-b\eta-\sqrt{(c-m-b\eta)^2-4bm\eta}], \\ \Leftrightarrow\ & \sqrt{(c-m-b\eta)^2-4bm\eta} > c-m-b\eta-\tfrac{2dm\eta}{\beta(1-\epsilon)}(R_0-1), \\ \Leftrightarrow\ & \sqrt{(c-m-b\eta)^2-4bm\eta} > c-c^*. \end{aligned}$$

If $c < c^*$ and one of the conditions $c < c_1$ or $c > c_2$ holds, then R_-^* is always greater than one. If $c > c^*$, solving $\sqrt{(c-m-b\eta)^2-4bm\eta} > c-c^*$ yields $c > c^{**}$.

(i) If $1 < R_0 < R_c$, then $c^* < c_2$. From $R_-^* > 1$, we can deduce that $c > c^{**}$.

(ii) If $R_0 > R_c > 1$, then $c^* > c_2$. From $R_-^* > 1$, we can deduce that $c > c_2$. □

Lemma 2.4. *(i) If* $1 < R_0 < R_c$, *then* $R_+^* > 1$ *has no solution. (ii) Assume that* $R_0 > R_c > 1$. *If* $R_+^* > 1$, *then* $c_2 < c < c^{**}$.

Proof.

$$\begin{aligned} R_+^* > 1 \Leftrightarrow\ & \tfrac{s\beta(1-\epsilon)[a\alpha_L+(a+d_L-\rho)(1-\alpha_L)]}{\delta(a+d_L-\rho)} \\ & > d + \tfrac{\beta(1-\epsilon)}{2m\eta}[c-m-b\eta+\sqrt{(c-m-b\eta)^2-4bm\eta}], \\ \Leftrightarrow\ & -(c-m-b\eta) + \tfrac{2dm\eta}{\beta(1-\epsilon)}(R_0-1) > \sqrt{(c-m-b\eta)^2-4bm\eta}, \\ \Leftrightarrow\ & c^*-c > \sqrt{(c-m-b\eta)^2-4bm\eta}. \end{aligned}$$

(i) If $1 < R_0 < R_c$, then $c^* < c_2$. Thus $R_+^* > 1$ has no solution. (ii) If $R_0 > R_c > 1$, then $c^* > c_2$. Solving $R_+^* > 1$, we have $c_2 < c < c^{**}$. □

By Lemmas 2.1∼2.4, summing up the above analysis yields the existence results of the equilibria of system (1.1)

Theorem 2.2. *(i) System (1.1) always has an infection-free equilibrium* E_0.

(ii) If $R_0 > 1$, *system (1.1) also has an immune-free equilibrium* E_1.

(iii) If $1 < R_0 < R_c$ *and* $c > c^{**}$, *system (1.1) has only one positive equilibrium* E_+^*.

(iv) If $R_0 > R_c > 1$ *and* $c_2 < c < c^{**}$, *system (1.1) has two positive equilibria* E_-^* *and* E_+^*. *While* $R_0 > R_c$ *and* $c > c^{**}$, *system (1.1) has only one positive equilibrium* E_+^*.

The existence of the positive equilibria of the model is summarized in Tables 1 and 2.

Table 1. The existence of the positive equilibria when $1 < R_0 < R_c$.

	$c_2 < c < c^{**}$	$c > c^{**}$
E_-^*	—	exist
E_+^*	—	—

Table 2. The existence of the positive equilibria when $R_0 > R_c > 1$.

	$c_2 < c < c^{**}$	$c > c^{**}$
E_-^*	exist	exist
E_+^*	exist	—

3. Stability analysis

In this section, we consider the stability of the equilibria of system (1.1).

Let $\tilde{E}$ be any arbitrary equilibrium of system (1.1). Its corresponding Jacobian matrix is obtained as

$$\mathcal{J} = \begin{bmatrix} J_{11} & 0 & J_{13} & 0 \\ J_{21} & J_{22} & J_{23} & 0 \\ J_{31} & J_{32} & J_{33} & J_{34} \\ 0 & 0 & J_{43} & J_{44} \end{bmatrix},$$

where

$$\begin{aligned}
J_{11} &= -d - \beta(1-\epsilon)\tilde{y}, \\
J_{13} &= -\beta(1-\epsilon)\tilde{x}, \\
J_{21} &= \alpha_L\beta(1-\epsilon)\tilde{y}, \\
J_{22} &= \rho - a - d_L, \\
J_{23} &= \alpha_L(1-\epsilon)\beta\tilde{x}, \\
J_{31} &= (1-\alpha_L)\beta(1-\epsilon)\tilde{y}, \\
J_{32} &= a, \\
J_{33} &= (1-\alpha_L)\beta(1-\epsilon)\tilde{x} - \delta - p\tilde{z}, \\
J_{34} &= -p\tilde{y}, \\
J_{43} &= \frac{c\tilde{z}}{(1+\eta\tilde{y})^2} - m\tilde{z}, \\
J_{44} &= \frac{c\tilde{y}}{1+\eta\tilde{y}} - b - m\tilde{y}.
\end{aligned}$$

The characteristic equation of the linearized system of (1.1) at $\tilde{E}$ is given by

$$|\lambda I - \mathcal{J}| = 0. \tag{3.1}$$

3.1. Stability analysis of Equilibrium E_0

Theorem 3.1. *If $R_0 < 1$, then the infection-free equilibrium E_0 of system (1.1) is locally asymptotically stable. If $R_0 > 1$, then E_0 is unstable.*

Proof. For equilibrium $E_0(x_0, 0, 0, 0)$, the characteristic equation (3.1) reduces to

$$(\lambda + d)(\lambda + b)(\lambda + a + d_L - \rho)[\lambda + \delta - (1 - \alpha_L)(1 - \epsilon)\beta x_0] = 0. \tag{3.2}$$

It is easy to see that equation (3.2) has two negative roots, obtained as

$$\lambda_1 = -d, \quad \lambda_2 = -b. \tag{3.3}$$

The other eigenvalues are determined by

$$\lambda^2 + a_1\lambda + a_2 = 0, \tag{3.4}$$

where

$$\begin{aligned} a_1 &= a + d_L - \rho + \delta[1 - \tfrac{(1-\alpha_L)(1-\epsilon)\beta x_0}{\delta}], \\ a_2 &= (a + d_L - \rho) - \tfrac{as\beta\alpha_L(1-\epsilon)}{d} \\ &\quad -a\beta(1 - \epsilon)[\delta - (1 - \alpha_L)(1 - \epsilon)\beta x_0] \\ &= \delta(a + d_L - \rho)(1 - R_0). \end{aligned} \tag{3.5}$$

If $R_0 < 1$, we have $a_1 > 0$ and $a_2 > 0$, and as such equation (3.4) has two negative roots. Thus, E_0 is locally stable for $R_0 < 1$.

If $R_0 > 1$, from (3.5) we know that E_0 is a saddle, and hence unstable. The proof of Theorem 3.1 is complete. □

Theorem 3.2. *If $R_0 < 1$, then the infection-free equilibrium E_0 of system (1.1) is globally asymptotically stable.*

Proof. Define a function

$$V = \frac{1}{2}(x - x_0)^2 + AL + By + \frac{pB}{c - m}z,$$

where A and B are undetermined positive coefficients. It is easy to see that V is a positive Lyapunov function. Evaluating the time derivative of V along the solution of system (1.1) yields

$$\begin{aligned} \dot{V}|_{(1.1)} =& (x - x_0)[s - dx - (1 - \epsilon)\beta xy] + A[\alpha_L(1 - \epsilon)\beta xy - (a + d_L - \rho)L] \\ &+ B[(1 - \alpha_L)(1 - \epsilon)\beta xy + aL - \delta y - pyz] + \frac{pB}{c - m}(\frac{cyz}{1 + \eta y} - bz - myz) \\ =& (x - x_0)[dx_0 - dx - (1 - \epsilon)\beta xy + (1 - \epsilon)\beta x_0 y - (1 - \epsilon)\beta x_0 y] \\ &+ A\alpha_L(1 - \epsilon)\beta xy - A(a + d_L - \rho)L + B(1 - \alpha_L)(1 - \epsilon)\beta xy \\ &+ BaL - B\delta y - Bpyz + \frac{pB}{c - m}\frac{cyz}{1 + \eta y(t)} - \frac{pB}{c - m}bz - \frac{pB}{c - m}myz \\ \le& -(d + (1 - \epsilon)\beta y)(x - x_0)^2 - [x_0 - A\alpha_L - B(1 - \alpha_L)](1 - \epsilon)\beta xy \\ &- [B\delta - (1 - \epsilon)\beta x_0^2]y - [A(a + d_L - \rho) - Ba]L \\ &- (Bp - Nc + Nm)yz - Nbz. \end{aligned}$$

If we choose

$$A = \frac{x_0}{(1-\alpha_L)[\frac{a+d_L-\rho}{a} + \frac{\alpha_L}{1-\alpha_L}]},$$
$$B = \frac{A(a+d_L-\rho)}{a},$$

then

$$x_0 - A\alpha_L - B(1-\alpha_L) \geq 0,$$
$$B\delta - (1-\epsilon)\beta x_0^2 \geq 0,$$
$$A(a+d_L-\rho) - Ba \geq 0.$$

Thus, if $R_0 \leq 1$, then $\dot{V}|_{(1.1)} \leq 0$. Since x, L, y, z are positive, we have $\dot{V} = 0$ if and only if $(x, L, y, z) = (x_0, 0, 0, 0)$. Therefore, it follows from the classical Krasovskii-LaSalle principle [23, 24] that E_0 is globally asymptotically stable. □

Biologically, the global asymptotic stability of the uninfected equilibrium E_0 of system (1.1) implies that the virus will die out in the host if the treatment is strong enough to ensure $R_0 < 1$.

3.2. Stability analysis of Equilibrium E_1

Now we consider the stability of equilibrium E_1.

Theorem 3.3. *Suppose that the immune-free equilibrium exists (i.e., $R_0 > 1$). When $0 < c < c^{**}$, E_1 is locally asymptotically stable. When $c > c^{**}$, E_1 is unstable.*

Proof. The characteristic equation of the linearized system of (1.1) at E_1 is given by

$$(\lambda^3 + b_1\lambda^2 + b_2\lambda + b_3)\Big(\lambda - \frac{cy_1}{1+\eta y_1} + b + my_1\Big) = 0,$$

where

$$b_1 = d + (1-\epsilon)\beta y_1 + \underbrace{a + d_L - \rho}_{①}$$
$$+ \underbrace{\frac{a\alpha_L(1-\epsilon)\beta x_1}{a+d_L-\rho}}_{②},$$
$$b_2 = d(a + d_L - \rho + \tfrac{aL_1}{y_1}) + (1-\epsilon)\beta a L_1$$
$$+ \underbrace{(1-\epsilon)\beta y_1(a+d_L-\rho)}_{③}$$
$$+ \underbrace{(1-\epsilon)\beta x_1(1-\alpha_L)(1-\epsilon)\beta y_1}_{④},$$
$$b_3 = a\alpha_L(1-\epsilon)\beta x_1(1-\epsilon)\beta y_1$$
$$+(a+d_L-\rho)(1-\epsilon)\beta x_1(1-a_L)(1-\epsilon)\beta y_1.$$

Clearly,

$$① \times ④ + ② \times ③ - b_3 = 0.$$

Thus, we have $b_1b_2 - b_3 > 0$. We then consider the sign of the eigenvalue

$$\begin{aligned}\lambda &= \frac{cy_1}{1+\eta y_1} - b - my_1 \\ &= \frac{-\frac{dm\eta}{\beta(1-\epsilon)}(R_0-1)^2 + (c-m-b\eta)(R_0-1) - \frac{b\beta(1-\epsilon)}{d}}{[\beta(1-\epsilon)+d\eta(R_0-1)]/d},\end{aligned}$$

which is determined by

$$\Delta = (c-m-b\eta)^2 - 4bm\eta.$$

Let $\Delta = 0$, we have $c = c_1$ or $c = c_2$.

(i) If $\Delta = 0$, then $c = c_1$ or $c = c_2$, which is a critical situation.

(ii) If $\Delta < 0$, then $c_1 < c < c_2$, and we have $\lambda < 0$.

(iii) If $\Delta > 0$, then $c < c_1$ or $c > c_2$. To get $\lambda < 0$, we must ensure $c < m+b\eta$ and $R_0 < 1 + R_1$, or $R_0 > 1 + R_2$. Meanwhile, from $R_0 < 1 + R_1$ and $R_0 > 1 + R_2$, we have $c < c^{**}$. Here $R_{1,2} = \frac{\beta(1-\epsilon)\left[(c-m-b\eta)\mp\sqrt{(c-m-b\eta)^2-4bm\eta}\right]}{2dm\eta}$. In view of $c_2 < c^{**}$, if $c < m + b\eta$ or $c_2 < c < c^{**}$, then the eigenvalue $\lambda < 0$. If $c > c^{**}$, we have $\lambda > 0$.

In summary, if $c < c_2$ or $c_2 < c < c^{**}$, then $\lambda < 0$. By the Routh-Hurartz criterion, for $R_0 > 1$, if $c < c_2$ or $c_2 < c < c^{**}$, the equilibrium E_1 of system (1.1) is locally asymptotically stable. If $c > c^{**}$, E_1 is unstable. □

Biologically, if the proliferation rate of CTLs is less than the critical value c^{**}, the viral load can be at high level.

3.3. Stability analysis of positive equilibria

In this subsection, we consider the stability of the positive equilibria. Here, we use $E^* = (x^*, L^*, y^*, z^*)$ to denote a positive equilibrium of system (1.1).

Theorem 3.4. *(i) Assume $A_3(A_1A_2 - A_3) - A_1^2A_4 > 0$. If*

*(**A**.**1**)* $1 < R_0 < R_c$ *and* $c > c^{**}$, *or*

*(**A**.**2**)* $R_0 > R_c > 1$ *and* $c > c_2$,

system (1.1) has an immune equilibrium E_-^*, which is a stable node.

(ii) If $R_0 > R_c > 1$ and $c_2 < c < c^{**}$, system (1.1) also has an immune equilibrium E_+^*, which is an unstable saddle.

Proof. The characteristic equation of the linearized system of (1.1) at an arbitrary positive equilibrium E^* is given by

$$\lambda^4 + A_1\lambda^3 + A_2\lambda^2 + A_3\lambda + A_4 = 0,$$

where

$$
\begin{aligned}
A_1 &= a + d_L - \rho + d + \beta(1-\epsilon)y^* + \tfrac{aL^*}{y^*},\\
A_2 &= (a + d_L - \rho)\Big[d + \beta(1-\epsilon)y^*\Big]\\
&\quad + \tfrac{aL^*}{y^*}\Big[d + \beta(1-\epsilon)y^*\Big] + py^*z^*\Big[\tfrac{c}{(1+\eta y^*)^2} - m\Big]\\
&\quad + (1-\alpha_L)(1-\epsilon)\beta x^*(1-\epsilon)\beta y^*,\\
A_3 &= \tfrac{aL^*}{y^*}(a + d_L - \rho)(1-\epsilon)\beta y^*\\
&\quad + py^*z^*\Big[\tfrac{c}{(1+\eta y^*)^2} - m\Big]\Big[a + d_L - \rho + d + \beta(1-\epsilon)y^*\Big]\\
&\quad + (1-\alpha_L)(1-\epsilon)\beta x^*(1-\epsilon)\beta y^*(a + d_L - \rho),\\
A_4 &= py^*z^*(a + d_L - \rho)\Big[\tfrac{c}{(1+\eta y^*)^2} - m\Big]\Big[d + \beta(1-\epsilon)y^*\Big].
\end{aligned}
$$

Then we have

$$
\begin{aligned}
A_1A_2 - A_3 &= \tfrac{aL^*}{y^*}d(a + d_L - \rho) + (\tfrac{aL^*}{y^*})^2\Big[d + \beta(1-\epsilon)y^*\Big]\\
&\quad + \tfrac{aL^*}{y^*}py^*z^*\Big[\tfrac{c}{(1+\eta y^*)^2} - m\Big]\\
&\quad + \tfrac{aL^*}{y^*}(1-\alpha_L)(1-\epsilon)\beta x^*(1-\epsilon)\beta y^*\\
&\quad + (a + d_L - \rho)\Big[a + d_L - \rho + d + \beta(1-\epsilon)y^*\Big]\\
&\quad \times\Big[d + \beta(1-\epsilon)y^*\Big] + \tfrac{aL^*}{y^*}\Big[d + \beta(1-\epsilon)y^*\Big]\\
&\quad \times\Big[a + d_L - \rho + d + \beta(1-\epsilon)y^*\Big]\\
&\quad + (1-\alpha_L)(1-\epsilon)\beta x^*(1-\epsilon)\beta y^*\\
&\quad \times\Big[a + d_L - \rho + d + \beta(1-\epsilon)y^*\Big].
\end{aligned}
$$

(i) For equilibrium E_-^*, if $c > c_2$, we have $m(\sqrt{\frac{c}{m}} - 1) > \frac{b\eta}{\sqrt{\frac{c}{m}} - 1}$. It thus follows that $\sqrt{(c - m - b\eta)^2 - 4bm\eta} > c - m - b\eta - 2m(\sqrt{\frac{c}{m}} - 1)$. Therefore, $\frac{c}{(1+\eta y_+^*)^2} - m > 0$. Clearly, $A_i > 0, i = 1, 2, 3$ and $A_1A_2 - A_3 > 0$. If $A_3(A_1A_2 - A_3) - A_1^2A_4 > 0$, by Routh-Hurwitz Criterion, we know that the positive equilibrium E_+^* is a stable node in this case.

(ii) For equilibrium E_+^*, if $R_0 > R_c > 1$ and $c_2 < c < c^{**}$, then $\frac{c}{(1+\eta y_+^*)^2} - m < 0$ and $A_4 < 0$. Thus, equilibrium E_+^* is an unstable saddle for $R_0 > R_c$ and $c_2 < c < c^{**}$. □

By Theorem 3.3 and Theorem 3.4, we have the following result.

Theorem 3.5. *If $R_0 > R_c > 1$ and $c = c_2$, the immune equilibrium E_+^* and E_-^* coincide with each other and a saddle-node bifurcation occurs when c passes through c_2.*

The stabilities of the equilibria and the behaviors of system (1.1) are summarized in Tables 3 and 4.

Table 3. The stabilities of the equilibria and the behaviors of system (1.1) in the case $1 < R_0 < R_c$. Here, c^{**} is the critical value, and we assume $A_3(A_1A_2 - A_3) - A_1^2A_4 > 0$.

	E_0	E_1	E_-^*	E_+^*	System (1.1)
$R_0 < 1$	GAS	—	—	—	Converges to E_0
$1 < R_0 < R_c$, $0 < c < c^{**}$	US	LAS	—	—	Converges to E_1
$1 < R_0 < R_c$, $c^{**} < c$	US	US	LAS	—	Converges to E_+^*

Table 4. The stabilities of the equilibria and the behaviors of system (1.1) in the case $R_0 > R_c > 1$. Here, c_2, c^* and c^{**} are critical values, and c_2 is a saddle-node bifurcation point. Here we assume $A_3(A_1A_2 - A_3) - A_1^2A_4 > 0$.

	E_0	E_1	E_-^*	E_+^*	System (1.1)
$R_0 < 1$	GAS	—	—	—	Converges to E_0
$R_0 > 1$, $0 < c < c_2$,	US	LAS	—	—	Converges to E_1
$R_0 > R_c > 1$, $c_2 < c < c^{**}$	US	LAS	LAS	US	Bistable
$R_0 > R_c > 1$, $c^{**} < c < c^*$	US	US	LAS	US	Converges to E_+^*
$R_0 > R_c > 1$, $c > c^{**}$	US	US	LAS	—	Converges to E_+^*

4. Sensitive analysis and numerical simulations

4.1. Sensitive analysis

Sensitive analysis provides insights into the basic infection reproductive number R_0 with respect to system parameters [50]. In this section, we use latin hypercube sampling (LHS) and partial rank correlation coefficients (PRCCs) [5, 26] to reveal the dependence of the basic infection reproduction number R_0 on a variety of system parameters. As a statistical sampling method, LHS provides efficient analysis of parameter variations across simultaneous uncertainty ranges in each parameter [5]. PRCC, which is obtained from the rank transformed LHS matrix and output matrix [26], indicates the parameters that have the most significant influences on the behaviors of the model. In this work, we perform 4000 simulations per run. We use a uniform distribution function to test the PRCCs for a variety of system parameters.

The PRCC results of the model, Fig. 1, illustrate the dependence of R_0 on different system parameters. The estimations of the distributions for R_0 is approximately a normal distribution. We use |PRCC| as an index to test if the parameter has important correlation with the infection reproduction number R_0. If $|\text{PRCC}| > 0.4$, we say that the correlation is strong. If $0.4 \geq |\text{PRCC}| > 0.2$, we say that the correlation is moderate. For $0.2 \geq |\text{PRCC}| > 0$, there correlation is weak. As is shown in Fig. 1, the general rate of $CD4^+$ T cells s, the decay rate of $CD4^+$ T cells d, the infection rate of $CD4^+$ T cells β, the drug efficacy ϵ and the latently infected cell death rate d_L have significant influence on the infection reproduction number R_0.

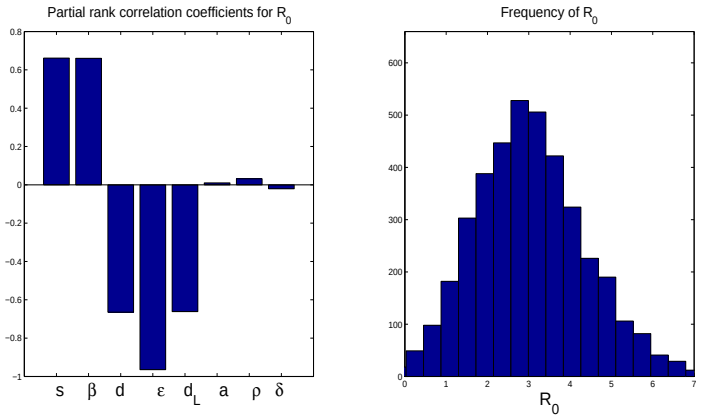

Figure 1. Partial rank correlation coefficients for R_0 and the frequency distribution of R_0. The parameters are shown in Table 5.

Table 5. Parameters for the model.

Symbol	Description	Value	Reference
s	Proliferation rate of $CD4^+$ T cells	10 cells /μ L/ day	[6]
d	Decay rate of $CD4^+$ T cells	0.01 day^{-1}	[6]
β	Infection rate of $CD4^+$ T cells	0.015 μ L / day	–
ϵ	Drug efficacy	0.8	–
α_L	Fraction of newly infected cells that become latently infected	0.001	–
ρ	Proliferation rate of latently infected cells	0.0045 day^{-1}	[12]
a	Activation rate	0.001 day^{-1}	[12]
d_L	Latently infected cell death rate	0.004 day^{-1}	[12]
δ	Infected cell death rate	1 day^{-1}	[27]
p	Killing rate of infected $CD4^+$ T cells	0.42 day^{-1}	–
c	Proliferation rate of CTLs	0.45 day^{-1}	–
η	Effector cell production Hill function scaling	1 cells/μ L	–
b	Decay rate of CTLs	0.1 day^{-1}	–
m	Immune impairment rate of viral	0.05 cells /μ L / day	–

4.2. Numerical simulations

In this section, we carry out numerical simulations to consider the HIV dynamics of our model. The parameter values are listed in Table 5. We then calculate the thresholds $R_0 \approx 3.0030 > 1$, $R_c \approx 1.4243$, $c_2 \approx 0.2914$ and $c^{**} \approx 0.4988$. Notice that $A_3(A_1A_2 - A_3) - A_1^2A_4 = 8.9125 \times 10^{-011} > 0$. We then get the bistable interval $(0.2914, 0.4988)$. In this case, when $c < c_2$, the immune-free equilibrium E_1 is stable. When $c_2 < c < c^{**}$, the immune-free equilibrium E_1 and the positive equilibrium E_+^* are stable. When $c > c^{**}$, only the positive equilibrium E_+^* is stable.

Fig.2 shows that there is no positive equilibrium if $c < 0.2914$ and a saddle-node bifurcation appear when c passes through 0.2914. The system display bistable behavior for $0.2914 < c < 0.4988$. As an example, we simulate the time history of the system for $c = 0.45 \in (0.2914, 0.4988)$ with different initial conditions (see Fig. 3). We find that, with the same parameter values and different initial conditions, the system may converge to different equilibriums. Such simulation result is consistent with recent clinic trial performed by Treasure et al [39].

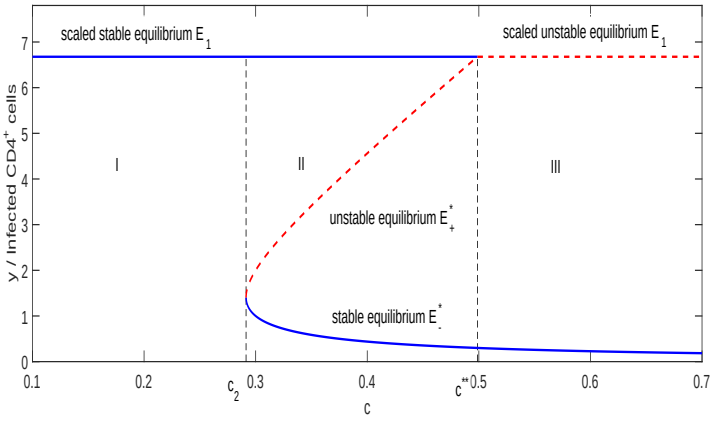

Figure 2. Bistability and saddle-node bifurcation diagram of system (1.1). Here $c = 0.2914$ is a saddle-node bifurcation (SN) point. The bistable interval is $(0.2914, 0.4988)$. The parameter values are shown in Table 5. There are three phases in this figure. In phase I ($0 < c < c_2$), the system has virus rebound. In phase II ($c_2 < c < c^{**}$), the system has bistable behavior. In phase III ($c > c^{**}$), the system is under elite control.

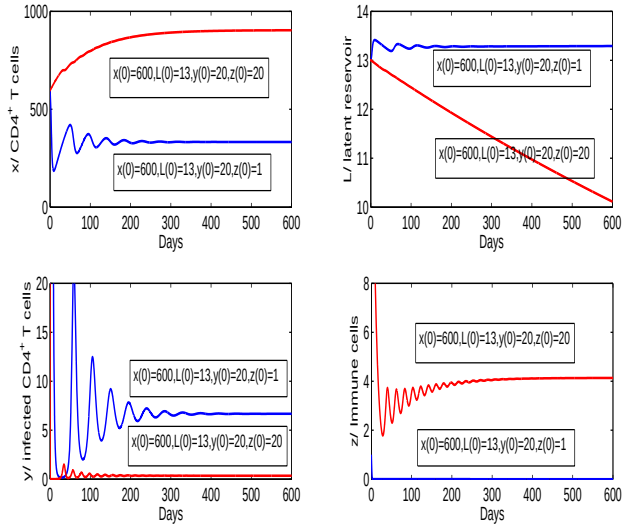

Figure 3. Time history of system (1.1) for $c = 0.45$ ($c_2 < c < c^{**}$). All the other parameter values are listed in Table 5. The trajectories of system (1.1) converge to different equilibria for different initial values, i.e., system (1.1) has bistable behavior. The initial values are $x(0) = 600$, $L(0) = 13$, $y(0) = 20$, $z(0) = 1$ (blue) and $x(0) = 600$, $L(0) = 13$, $y(0) = 20$, $z(0) = 20$ (red).

We also consider the influence of system parameters on the elite control threshold c^{**} by PRCCs. Fig.4 shows that the immune impairment rate of virus m and the proliferation rate of latently infected cells ρ are positively correlated with the elite control threshold c^{**}. On the other hand, the death rate of infected cells δ has negative correlation with the elite control threshold c^{**}. It thus follows that decreasing immune impairment rate m is beneficial for obtaining post-treatment immune control. Decrease the immune impairment rate m and the proliferation

rate of latently infected cells ρ, and increasing the death rate of infected cells δ are beneficial for the host to get elite control.

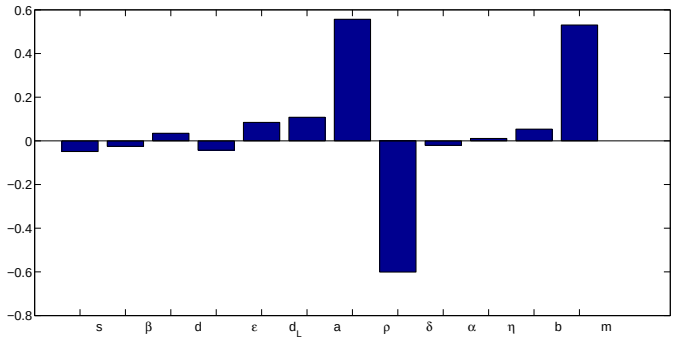

Figure 4. Partial rank correlation coefficients for c^{**}. The parameter values are shown in Table 5.

5. Discussion

In this paper, we investigate the viral dynamics of a simplified within host model. By performing mathematical analysis and numerical simulations, we obtain the post-treatment immune control threshold and the elite control threshold. We get conditions for the model to reach post-treatment immune control and elite control.

The expression of the post treatment control threshold implies that the immune impairment rate of virus m has positive correlation with the post treatment control threshold . Early initiation of ART after infection allows PTC by limiting the size of latent reservoir. A patient with latent HIV reservoir small enough may obtain adaptive immune response to prevent viral rebound (VR), and thus has controlled infection [12].

Sensitive analysis and numerical simulations imply that decreasing the immune impairment rate is beneficial for the host obtain post-treatment immune control and the elite control. A comprehensive HIV treatment involving decreasing the immune impairment rate of virus, decay rate of CTLs and effector cell production Hill function scaling allows the host to obtain elite control efficiently.

The proliferation rate of latently infected cells ρ plays an important role in the elite control. It is worth carrying out further investigation to reveal the viral dynamics of the within host model with logistic proliferation rate of latently infected cells, given by system (5.1).

$$\begin{cases} \frac{dx(t)}{dt} = s - dx(t) - (1-\epsilon)\beta x(t)y(t), \\ \frac{dL(t)}{dt} = \alpha_L(1-\epsilon)\beta x(t)y(t) - (a+d_L)L(t) + \rho L(t)(1-\frac{L(t)}{L_{max}}), \\ \frac{dy(t)}{dt} = (1-\alpha_L)(1-\epsilon)\beta x(t)y(t) + aL(t) - \delta y(t) - py(t)z(t), \\ \frac{dz(t)}{dt} = \frac{cy(t)z(t)}{1+\eta y(t)} - bz(t) - my(t)z(t), \end{cases} \tag{5.1}$$

Using the same method of analyzing system (1.1), we can get theoretical results. Here, we carry out numerical simulations to show its bistable behaviors. As shown

in Fig.5, if we choose parameters listed in Table 5 and $L_{max} = 50$, system (5.1) displays bistable behaviors.

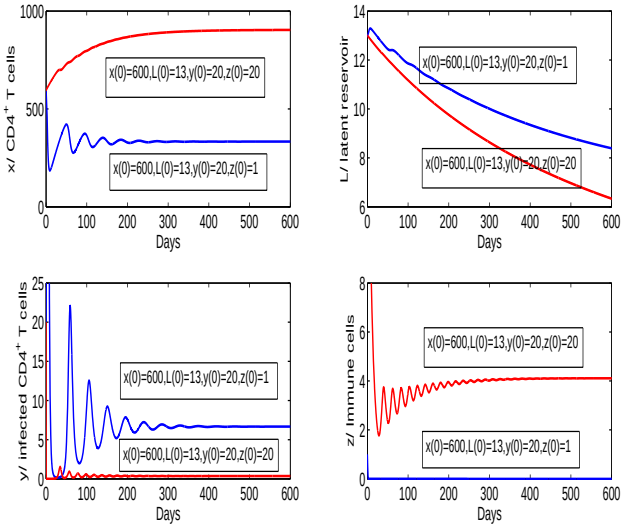

Figure 5. Time history of system (5.1). The trajectories of system (5.1) converge to different equilibria for different initial values, i.e., system (5.1) has bistable behavior. The initial values are $x(0) = 600$, $L(0) = 13$, $y(0) = 20$, $z(0) = 1$ (blue) and $x(0) = 600$, $L(0) = 13$, $y(0) = 20$, $z(0) = 20$ (red). The parameter values are shown in Table 5.

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