Thresholds and bistability in HIV infection models with oxidative stress✩

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Abstract

Oxidative stress, a reaction caused by the imbalance between the reactive oxygen species of human organism and its ability to detoxify reactive intermediates and to repair the resulting damage plays an important role in HIV-infections. On one hand, HIV infection is responsible for the chronic oxidative stress of the patients. On the other hand, the oxidative stress contributions to the HIV disease pathogenesis. In this paper, we integrate oxidative stress into an HIV infection model to investigate its effects on the virus dynamics. Through mathematical analysis, we obtain the basic reproduction number $R_0$ of the model which describes the persistence of viruses. In particular, we show that for $R_0 > 1$, the model has a bistable interval with virus rebound threshold and elite control threshold. Numerical simulations and bifurcation analysis are presented to illustrate the viral dynamics under oxidative stress. Our investigation reveals the interplay between viruses and the reaction of human organism including immune response and oxidative stress, and their effects on the health of human being.

Keywords: Oxidative stress; Immune impairment; Post-treatment immune control; Elite control; Saddle-node bifurcation

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1. Introduction

Combination antiretroviral therapy gives patients long-term suppression of HIV with undetectable viral levels. Recent investigations show that for patients with undetectable viral levels, there exists a reservoir in which viruses remain alive in a long-lived latent state. With the termination of receiving combination antiretroviral therapy, after an average time period of 18 days, plasma viremia rebounds to detectable level. In the literature, medical cases of HIV rebound were reported. Medical examinations for the ‘Mississippi baby’ at the age of nearly 4 years old displayed a rebounded HIV level in blood (16,750 copies/ml) [1]. The ‘Mississippi baby’ case implies that there exists a time delay for the viral rebound [1, 2]. Researches had been carried to explain such phenomena [2, 3].

Conway and Perelson [3] developed a mathematical system to model to study the dynamics of HIV infection. Their investigation captures the interplay between viral dynamics and the response of the host and brings insight into the evolution of the disease infection process. By evaluating the designed model, the authors predicted that the strength of immune response and the initial size of the latent reservoir could affect the dynamics. Their results on post-treatment control provide guidance for future studies. Investigations implies that after HIV infection, patients who receive antiretroviral therapy early have a higher chance of getting post-treatment control, a situation where the amount of plasma virus remains undetectable after the termination of the medical treatment. However, clinically, only a small proportion of such patients that receive early treatment attain post-treatment control. Further investigations are to be carried out to reveal the mechanism behind the post-treatment control.

As a highly reactive oxygen species (ROS), oxidants are continuously produced during normal biochemical reactions in the human body. Most cells are able to detoxify physiologic levels of ROS in the human body using antioxidants such as enzymes. The processes of producing oxidants and detoxication may reach an equilibrium state. When the balance between the two processes disturbed, a condition called oxidative stress occurs [4]. Antioxidants play an important role in regulating the reactions that release free radicals. Cells need to reach certain level of antioxidant defenses to counteract the detrimental effects caused by an excessive production of ROS to protect the immune system [5]. Investigations suggest the existence of interactions between HIV-infection and oxidative stress. On one hand, the HIV-infection process contributes to the disturbance of the balance between the generation of free radicals and antioxidant defenses. On the other hand, oxidative stress is beneficial to HIV disease pathogenesis by promoting the replication of viruses, decreasing the proliferation of
immune cells, and increasing the sensitivity to drug toxicities etc [6].

After HIV infection, the initial reaction of the host is rapid and nonspecific by activating natural killer cells, macrophage cells, etc. The host develops delayed and specific reactions by activating CTLs and antibody cells. During most viral infections, CTLs attack infected cells and antibody cells attack viruses. These attacks against the viruses act as an antiviral defense for the host. Dynamics of viral infection with CTL response have been investigated in the literature. [7] introduced a mathematical system to model the interplay between activated CD4\(^+\) T cells, infected CD4\(^+\) T cells, viruses and immune cells. [8] and [9] performed investigation on the HIV infection and concluded that the turnover of free virus is much faster than that of infected cells. Based on these results, they proposed the quasi-steady state assumption, i.e., the load of free virus is proportional to the amount of infected cells. Thus we can estimate the viral load by evaluating the number of infected cells.

Investigations demonstrated that HIV mutates into new forms that escape from specific immune responses or immune exhaustion during virus evolution [10–17]. HIV infection may modulate dendritic cells, which are responsible for the viral evasion from immunity [18]. During the first stage of HIV infection, the viruses moderately decrease the amount of CD4\(^+\) T cells within the host. Then, the level of CD4\(^+\) T cell remains almost constant for several years due to the inhibition provided by the immune response. [19] modeled the interrelationship among timing, efficiency and success of antiviral drug therapy. [18] performed investigations on a variety of HIV models with immune impairment. The authors show that when the impairment rate of HIV overwhelms the threshold value, immune system of the host may collapse. [20, 21] constructed mathematical models to study the infection of HIV and carried out analysis to obtain a ‘risky threshold’ and an ‘immunodeficiency threshold’ for the impairment rate. Their investigations implies that when the impairment rate is greater than a threshold value, the immune system of the host always collapses.

During the early stage of an HIV infection, latent HIV reservoirs will be formed in the host. Latent reservoirs survive the antiretroviral therapy (ART) and remain alive even when the level of HIV in the blood is undetectable. Thus, the existence of such reservoir is a barrier to the elimination of HIV. HIV infection dynamics with latent reservoirs have been investigated in the literature[22–25]. [25] investigated the HIV infection with latent reservoirs by constructing a stochastic model. The authors showed that the latent reservoir has relatively stable size and cells can be activated to produce virions. [22] investigated influence of ongoing viral replication on the evolution of latent reservoirs and revealed the influences of a variety of viral and host factors on the dynamics of the latent reservoirs. [24] established a
mathematical model to investigate the activation of latently infected cells and revealed the mechanism behind the replenishment of the latent reservoirs.

In this article, we integrate oxidative stress into HIV infection model to consider the interplay between viruses and corresponding oxidative stress, and their combined effects on the host. The within host model is given by

\[
\begin{align*}
\frac{dx(t)}{dt} &= s - dx(t) - (1 - \epsilon)x(t)y(t), \\
\frac{dL(t)}{dt} &= \alpha_L(1 - \epsilon)x(t)y(t) + (\rho - a - d_L)L(t), \\
\frac{dy(t)}{dt} &= (1 - \alpha_L)(1 - \epsilon)x(t)y(t) + aL(t) - \delta y(t) - py(t)z(t), \\
\frac{dz(t)}{dt} &= cy(t)z(t)\frac{1}{1 + \eta y(t)} K(y) - bz(t),
\end{align*}
\]

where \(x\) denotes activated CD4\(^+\) T cells, \(L\) viral latent reservoir, \(y\) infected CD4\(^+\) T cells and \(z\) immune cells. Since HIV dynamics are known to be more rapid than infected cell dynamics, we make the quasi-steady assumption. Thus, the HIV cells are in proportion to the infected cells. Here we use the overall treatment effectiveness, denoted by \(\epsilon\), for \(0 \leq \epsilon \leq 1\), to describe their combined treatment effectiveness. In particular, when \(\epsilon = 1\), the therapy is 100\% effective. On the other hand, if the treatment is terminated, \(\epsilon = 0\) [3, 23].

The relationship between the ROS and antioxidant can be evaluated using the method proposed in [26]. [27–29] investigated the role of ROS in HIV infection. In this article, we are particularly interested in the effects of the oxidative stress on the process of viral infection. Since oxidative stress slows down the activation of the immune system, we hereby introduce the expression \(K(y) = \frac{1 + h}{\beta y}\) to model the influence of the oxidative stress. Since reactive oxygen species (ROS) are responsible for the oxidative stress, here use \(\rho(y) = k_0 + \frac{k_1}{y + y_0}\) to model oxidative stress in the HIV infection model. Here, \(k_0, k_1\) and \(y_0\) are constants. We notice that \(\rho(y)\) is a saturating, increasing function of \(y\). In order to simplify the analysis, we linearize the expression of \(\rho(y)\) to obtain \(\rho(y) = k_0 + \frac{k_1}{y_0}\). Letting \(k_0 = k\) and \(\frac{k_1}{y_0} = r\), we obtain \(\rho(y) = k + ry\). It thus follows that

\[K(y) = \frac{1 + h}{k + ry}.\]

ROS damage, the immune term is modeled using the expression \(\frac{cy}{1 + \eta y} K(y) - bz\). We notice that such immune term is different from the widely used immune and immune impairment function \(\frac{cy}{1 + \eta y} - bz - myz\) [19, 30–32] (\(m\) is the rate of immune impairment). Here constant \(h\) represents the influence of antioxidant on the immune response, \(k\) is the influence of naturally
produced oxidant, and \( r \) is the influence of oxidant produced by infected CD4\(^+\) T cells or HIV viral load \( y \).

The rest of this article is organized as follows. In, Section 2, we present some preliminary results on the structure of the equilibria of the model. We then, in Section 3, perform stability analysis on the equilibria. In Section 4, based on our stability analysis, we present sensitive analysis and numerical simulations. Finally, in Section 5, we conclude the paper with discussions and a summary.

2. Preparation

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 and nonnegative solution with the initial condition \((x(0), L(0), y(0), z(0)) \in \mathbb{R}_{+}^4\), 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.** By the fundamental theory of ordinary differential equations, system (1.1), with nonnegative initial conditions, has a unique solution. For any nonnegative initial data, let \( t_1 > 0 \) be the first time that \( x(t_1) = 0 \). The first equation of (1.1) implies that \( \dot{x}(t_1) = s > 0 \). That is to say, \( x(t) < 0 \) for \( t \in (t_1 - \epsilon_1, t_1) \), where \( \epsilon_1 \) is an arbitrarily small positive constant.

The above discussion leads to a contradiction. It thus follows that \( x(t) \) is always positive. Because \( z = 0 \) 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 that at time \( t_2 > 0 \), \( y(t_2)z(t_2) \) reaches 0 for the first time. Thus, 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), because \( x(t) \) 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 with \( L(t_2) = 0 \).

For case (ii), the third equation of system (1.1) implies that

\[
y(t_2) = y(0) + e^{\int_0^{t_2} (1 - \alpha L)(1 - \epsilon) \beta x(\xi) d\xi} \int_0^{t_2} a L(\xi) d\xi > 0,
\]

which contradicts \( y(t_2) = 0 \).

Thus, \( L(t) \) and \( y(t) \) are always positive.

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

\[
M(t) = \sigma x(t) + a L(t) + (a + d_L - \rho) y(t) + \frac{pk(a + d_L - \rho)z(t)}{c(1 + h)}
\]
where \( \sigma = a \alpha_L + (1 - \alpha_L)(a + d_L - \rho) \). Since all solutions of (1.1) are positive, we have

\[
\frac{dM}{dt} = \sigma \left[ s - dx - (1 - \epsilon)\beta xy + a \left[ \alpha_L (1 - \epsilon) \beta xy + \rho(a + d_L - \rho)L \right] \right] + (a + d_L - \rho) \left[ (1 - \alpha_L)(1 - \epsilon)\beta xy + \rho(a + d_L - \rho)L - \delta y - pyz \right] + \frac{pk(a + d_L - \rho)\xi}{\epsilon(1 + h)} \leq \sigma s - \sigma dx - (a + d_L - \rho)y - \frac{b pk(a + d_L - \rho)\xi}{\epsilon(1 + h)} < \sigma s - \nu M.
\]

Here \( \nu = \min\{d, \delta, b\} \). Let \( \varphi \) be the solution of

\[
\begin{align*}
\frac{d\varphi}{dt} &= \sigma s - \nu \varphi, \\
\varphi_0 &= \sigma x_0 + a L_0 + (a + d_L - \rho)y_0 + \frac{pk(a + d_L - \rho)z_0}{\epsilon(1 + h)},
\end{align*}
\]

where \( x_0, y_0 \) and \( z_0 \) are initial values of system (1.1) and \( \varphi_0 = M_0 > 0 \). We then evaluate \( \lim_{t \to +\infty} \sup \varphi(t) = \frac{\alpha_L}{\nu} \). It follows from the comparison theorem \([33]\) that \( M(t) < \varphi(t) \). Thus, \( x(t), L(t), y(t) \) and \( z(t) \) are bounded.

### 2.2. Thresholds

In the following, we consider the threshold values of the model. Such threshold characterises the viral dynamics of model (1.1).

Let

\[
R_0 = (1 - \epsilon)\beta \left( 1 - \alpha_L \right) + \frac{\alpha_L}{a + d_L - \rho} \frac{1}{\delta} \sigma \left( \frac{1}{\sigma} \right)
\]

\[
= \frac{\beta(1 - \epsilon) \left( 1 - \alpha_L \right) + \frac{\alpha_L}{a + d_L - \rho}}{d \sigma}. \tag{2.2.1}
\]

Because \( (1 - \epsilon)\beta \frac{1}{\sigma} \left( \frac{1}{\sigma} \right) \) is the basic reproductive number of the model without viral latent reservoir, \( R_0 \) gives the basic reproductive number of model (1.1), which describes the average number of newly infected cells generated from an infected cell at the beginning of the infectious process.

Let

\[
R^*_\pm = \frac{\beta(1 - \epsilon) \left( 1 - \alpha_L \right) + \frac{\alpha_L}{a + d_L - \rho}}{d \sigma} \frac{1}{\beta(1 - \epsilon) \left( 1 - \alpha_L \right) + \frac{\alpha_L}{a + d_L - \rho}} \frac{1}{\beta(1 - \epsilon) \left( 1 - \alpha_L \right) + \frac{\alpha_L}{a + d_L - \rho}}
\]

\[
= \frac{2 B \eta \epsilon \beta(1 - \epsilon) \left( 1 - \alpha_L \right) + \frac{\alpha_L}{a + d_L - \rho}}{\delta(a + d_L - \rho) \left( 2 B \eta \epsilon \beta(1 - \epsilon) \left( 1 - \alpha_L \right) - B \eta \epsilon \beta(1 - \epsilon) \left( 1 - \alpha_L \right) \right)}
\]

where

\[
B = c + ch - br - b \eta.
\]
Because \( \frac{\beta(1-\epsilon)}{\eta(d+\eta(1-\epsilon))} \) is the basic immune reproductive number of the model with the bilinear immune incidence \((cyz)\) and without viral latent reservoir, \(R_0^*\) represent the two thresholds in addition to the basic reproductive ratio.

We also define the following thresholds

\[
h_1 = \frac{br + b\eta k}{c} - 2b\sqrt{\eta r k} - 1
\]

and

\[
h^* = \frac{br + b\eta k}{c} + \frac{2b\eta r y_1}{c} - 1.
\]

The post-treatment immune control threshold is then obtained as

\[
h_2 = \frac{br + b\eta k}{c} + \frac{2b\sqrt{\eta r k}}{c} - 1,
\]

and the elite control threshold is given by

\[
h^{**} = \frac{br + b\eta k}{c} + \frac{bk\beta(1-\epsilon)}{cd(R_0 - 1)} + \frac{bd\eta r (R_0 - 1)}{c\beta(1-\epsilon)} - 1.
\]

Denote \(R_c = 1 + \frac{\beta(1-\epsilon)\sqrt{\eta r k}}{d\eta}\), we have the following results.

**Lemma 2.1.** \(R_0 > R_c \Leftrightarrow h^* > h^{**}\).

**Lemma 2.2.** (i) If \(1 < R_0 < R_c\), then \(R_1^* < 1, h^* < h_2\) and \(R_0^* > 1 \Leftrightarrow h > h^{**}\).

(ii) If \(R_0 > R_c\), then \(h^* > h_2, R_1^* > 1 \Leftrightarrow h > h_2\) and \(R_0^* > 1 \Leftrightarrow h_2 < h < h^*\). □

### 2.3. Equilibria

In the following, we consider the existing conditions of equilibria of system (1.1).

System (1.1) always admits an uninfected equilibrium \(E_0 = (x_0, 0, 0, 0)\), where \(x_0 = \frac{\delta}{\beta}\).

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

\[
x_1 = \frac{\delta(a+\alpha \gamma)}{\beta(1-\epsilon)[a\alpha + (1-\alpha)(a+\alpha \gamma)]},
\]

\[
L_1 = \frac{\alpha \gamma \beta(1-\epsilon) x_1 y_1}{a+\alpha \gamma},
\]

\[
y_1 = \frac{\delta(R_0 - 1)}{\beta \gamma(1-\epsilon)}.
\]

(ii) If \(R_0^* > 1\) and \(0 < h < h_1\) or \(h > h_2\), equation \(\frac{cyz}{1+ry} - \frac{1+h}{k+ry} - bz = 0\) has two positive roots.
If $R^* > 1$ and $h > h_2$, system (1.1) has an immune equilibrium $E^*_\pm = (x^*_\pm, L^*_\pm, y^*_\pm, z^*_\pm)$. If $R^*_+ > 1$ and $h > h_2$, system (1.1) also has an immune equilibrium $E^*_+ = (x^*_+, L^*_+, y^*_+, z^*_+)$. Here

\[
\begin{align*}
    x^*_\pm &= \frac{s}{a+\beta(1-\epsilon)x^*_\pm}, \\
    L^*_\pm &= \frac{\alpha L(1-\epsilon)x^*_\pm y^*_\pm}{a+d_l-p}, \\
    y^*_\pm &= \frac{R^\pm \sqrt{b^2-4bk\eta}}{2bk\eta}, \\
    z^*_\pm &= \frac{\delta(R^\pm-1)}{\rho}.
\end{align*}
\]

From Lemmas 2.1 and 2.2, summing up the above analysis yields the existing results of equilibria of system (1.1)

**Theorem 2.2.** (i) System (1.1) always admits an uninfected 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 $h > h^{**}$, system (1.1) has only one positive equilibrium $E^*_+$. If $R_0 > R_c$ and $h_2 < h < h^*$, system (1.1) has two positive equilibria $E^*_-$ and $E^*_+$. When $R_0 > R_c$ and $h > h^*$, system (1.1) has only one positive equilibrium $E^*_+$. (iv) If $R_0 > R_c$ and $h = h_2$, system (1.1) has only one positive equilibrium $E^*_+$. □

The existence results for positive equilibria are summarized in Tables 2.1 and 2.2.

|       | $h_2 < h < h^{**}$ | $h > h^{**}$ |
|-------|-------------------|--------------|
| $E^*_+$ | —                 | exist        |
| $E^*_-$ | —                 | —            |

Table 2.1: The existence of the positive equilibria when $1 < R_0 < R_c$.

|       | $h_2 < h < h^*$ | $h > h^*$ |
|-------|-----------------|----------|
| $E^*_+$ | exist           | exist    |
| $E^*_-$ | exist           | —        |

Table 2.2: The existence of the positive equilibria when $R_0 > R_c$.

3. Stability analysis

In this section, we consider the stabilities of equilibria for system (1.1).
Let \( \tilde{E} \) be any arbitrary equilibrium of system (1.1). Denote

\[
\mathcal{J} = \begin{bmatrix}
-d - \beta(1 - \epsilon)\tilde{y} & 0 & -\beta(1 - \epsilon)\tilde{x} & 0 \\
\alpha_L\beta(1 - \epsilon)\tilde{y} & \rho - a - d_L & \alpha_L(1 - \epsilon)\tilde{x} & 0 \\
(1 - \alpha_L)\beta(1 - \epsilon)\tilde{y} & a & (1 - \alpha_L)\beta(1 - \epsilon)\tilde{x} - \delta - p\tilde{z} & -p\tilde{y} \\
0 & 0 & \frac{c(1 + h)(k - \eta\tilde{y})}{(1 + \eta\tilde{y})(k + \eta\tilde{y})} & -b \\
\end{bmatrix}.
\]

The characteristic equation of the linearized system of (1.1) at \( \tilde{E} \) is then obtained as

\[
|\lambda I - \mathcal{J}| = 0. \quad (3.1)
\]

### 3.1 Stability analysis of Equilibrium \( E_0 \)

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

**Proof.** The characteristic equation (3.1) with respect to equilibrium \( E_0(x_0, 0, 0, 0) \) is

\[
\begin{vmatrix}
-d - \lambda & 0 & -\beta(1 - \epsilon)x_0 & 0 \\
0 & \rho - a - d_L - \lambda & \alpha_L(1 - \epsilon)x_0 & 0 \\
0 & a & (1 - \alpha_L)(1 - \epsilon)x_0 - \delta - \lambda & 0 \\
0 & 0 & 0 & -b - \lambda \\
\end{vmatrix} = 0. \quad (3.2)
\]

It is clear that equation (3.2) has two negative roots \(-d\) and \(-b\). The other two eigenvalues are solutions of

\[
\lambda^2 + a_1\lambda + a_2 = 0, \quad (3.3)
\]

where

\[
a_1 = a + d_L - \rho + \delta[1 - \frac{(1 - \alpha_L)(1 - \epsilon)x_0}{\delta}],
\]

\[
a_2 = (a + d_L - \rho) - a\beta(1 - \epsilon)[\delta - (1 - \alpha_L)(1 - \epsilon)x_0] - \frac{as\beta\alpha_L(1 - \epsilon)}{d}.
\]

It is easy to see that \( a_1 > 0 \) and \( a_2 > 0 \) for \( R_0 < 1 \). When \( R_0 < 1 \), equation (3.3) has two negative roots indicating that \( E_0 \) is locally stable. On the other hand, when \( R_0 > 1 \), then \( a_2 < 0 \), and \( E_0 \) is a saddle with \( \dim W^s(E_0) = 2 \) and \( \dim W^u(E_0) = 1 \), and hence unstable. This completes the proof of Theorem 3.1.

**Theorem 3.2.** If \( R_0 < 1 \), then the uninfected equilibrium \( E_0 \) of system (1.1) is global asymptotically stable.
\textbf{Proof.} Define a function
\[ V = \frac{1}{2}(x - x_0)^2 + AL + By + \frac{pB}{c(1 + h)}z, \]
where \(A\) and \(B\) are positive coefficients to be undetermined. 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
\[
\dot{V}_{|_{(1.1)}} = (x - x_0)\left[ s - dx - (1 - \epsilon)\beta xy + A[\alpha L(1 - \epsilon)\beta xy - (a + dL - \rho)L] + B\left[(1 - \alpha L)(1 - \epsilon)\beta xy + aL - \delta y - pB\right] + \frac{pB}{c(1 + h)}\left(\frac{cyz}{1 + \eta y k + ry} - bz\right)\right]
\]
\[
= (x - x_0)\left[ dx_0 - dx - (1 - \epsilon)\beta xy + (1 - \epsilon)\beta x_0 y - (1 - \epsilon)\beta x_0 y + A\alpha L(1 - \epsilon)\beta xy - A(a + dL - \rho)L + B(1 - \alpha L)(1 - \epsilon)\beta xy + BaL - B\delta y - BpB + \frac{pB}{c(1 + h)}\left(\frac{cyz}{1 + \eta y k + ry} - bz\right)\right]
\]
\[
\leq -\left(d + (1 - \epsilon)\beta y\right)(x - x_0)^2 - \left[x_0 - A\alpha L - B(1 - \alpha L)\right](1 - \epsilon)\beta xy - \left[B\delta - (1 - \epsilon)\beta x_0^2\right]y - \left[A(a + dL - \rho) - Ba\right]L - \frac{pB}{c(1 + h)}bz.
\]
Choosing
\[
A = \frac{x_0}{(1 - \alpha L)\left[\frac{a + dL - \rho}{a} + \frac{\alpha L}{1 - \alpha L}\right]},
\]
\[
B = \frac{A(a + dL - \rho)}{a},
\]
we get
\[
x_0 - A\alpha L - B(1 - \alpha L) \geq 0,
\]
\[
B\delta - (1 - \epsilon)\beta x_0^2 \geq 0,
\]
\[
A(a + dL - \rho) - Ba \geq 0.
\]
Thus, if \(R_0 \leq 1\), we have \(\dot{V}_{|_{(1.1)}} \leq 0\). Since \(x, L, y, z\) are positive, we get \(V = 0\) if and only if \((x, L, y, z) = (x_0, 0, 0)\). It thus follows from the classical Krasovskii-LaSalle principle \([34, 35]\) that \(E_0\) is globally asymptotically stable. \(\square\)

The global asymptotic stability of the uninfected equilibrium \(E_0\) of system (1.1) biologically implies that the virus will die out in the host. Generally, with treatment strong enough, we have \(R_0 < 1\) which guarantees the elimination of the virus.
3.2. Stability analysis of Equilibrium $E_1$

**Theorem 3.3.** Assume $R_0 > 1$, if $h < h_1$, $h_1 < h < h_2$ or $h_2 < h < h^{*}$, then the immune free equilibrium $E_1$ of system (1.1) is locally asymptotically stable. If $h > h^{*}$, $E_1$ is unstable.

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

$$
\lambda^3 + b_1\lambda^2 + b_2\lambda + b_3 = 0,
$$

where

\begin{align*}
    b_1 &= d + (1 - \epsilon)\beta y_1 + a + d_L - \rho + \frac{a\alpha_L(1 - \epsilon)\beta x_1}{a + d_L - \rho} \\
    b_2 &= d(a + d_L - \rho + \frac{a\alpha_L}{y_1}) + (1 - \epsilon)\beta aL_1 + (1 - \epsilon)\beta y_1(a + d_L - \rho) \\
    &+ (1 - \epsilon)\beta x_1(1 - \alpha_L)(1 - \epsilon)\beta y_1 \\
    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.
\end{align*}

It is easy to see that

\[
(1) \times (4) + (2) \times (3) - b_3 = 0.
\]

Thus, $b_1b_2 - b_3 > 0$ holds true. Now, we discuss the sign of the eigenvalue

\[
\lambda_4 = \frac{c(1 + h)y_1}{(1 + \eta y_1)(k + ry_1)} - b
\]

\[
= \frac{-br\eta y_1^2 + (c + ch - br - bk\eta)y_1 - bk}{(1 + \eta y_1)(k + ry_1)},
\]

which is determined by

$$
\Delta = (c + ch - br - bk\eta)^2 - 4b^2kr\eta.
$$

(i) If $\Delta = 0$, then $h = h_1$ or $h = h_2$, which is a critical situation.

(ii) If $\Delta < 0$, then $h_1 < h < h_2$, we have $\lambda_4 < 0$.

(iii) If $\Delta > 0$, we have $h < h_1$ or $h > h_2$. To get $\lambda_4 < 0$, we need to ensure that $h < \frac{br+bnk \beta(1-\epsilon)}{c} - 1$, $R_0 < 1 + R_1$ or $R_0 > 1 + R_2$, from which we can obtain that $h < h^{*}$. Here $R_{1,2} = \frac{br+bnk \beta(1-\epsilon)}{2br\eta}$. Notice $h_2 < h^{*}$. It thus follows that if $h < \frac{br+bnk \beta(1-\epsilon)}{c} - 1$ or $h_2 < h < h^{*}$, then the eigenvalue $\lambda_4 < 0$. If $h > h^{*}$, we have $\lambda_4 > 0$.

In summary, if $h < h_2$ or $h_2 < h < h^{*}$, then $\lambda_4 < 0$. From the Routh-Hurwitz criterion [36, 37], with the assumption $R_0 > 1$, if $h < h_2$ or $h_2 < h < h^{*}$, the equilibrium $E_1$ of system (1.1) is locally asymptotically stable. On the other hand, when $h > h^{*}$, $E_1$ is unstable. □
**Remark 3.1.** (i) $h_1, h_2$ and $h^*$ are critical values.
(ii) If $R_0 > 1$ and $h > h^*$, then the equilibrium $E_1$ of system (1.1) is unstable.

Here, the elite control threshold $h^*$ determines whether a system is under elite control [3]. Biologically, if the proliferation rate of CTLs is greater than the critical value $h^*$, the virus may remain at high levels with no control.

### 3.3. Stability analysis of positive equilibria

We denote by $E^* = (x^*, L^*, y^*, z^*)$ an arbitrary positive equilibrium of system (1.1).

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

\[ A.1\] 1 < $R_0 < R_c$ and $h > h^*$, or

\[ A.2\] $R_0 > R_c$ and $h > h_2$,

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

(ii) If $R_0 > R_c$ and $h_2 < h < h^*$, system (1.1) also has an immune equilibrium $E^*$, which is an unstable saddle point.

**Proof.** The characteristic equation of the linearized system of (1.1) at the arbitrary positive equilibrium $E^*$ is obtained as

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

where

\[
A_1 = a + d_L - \rho + d + \beta(1 - \epsilon)y^* + \frac{\alpha L^*}{y^*},
\]

\[
A_2 = (a + d_L - \rho)[d + \beta(1 - \epsilon)y^*] + \frac{\alpha L^*}{y^*}[d + \beta(1 - \epsilon)y^*]
+ py^*\frac{\epsilon(1 + \beta y^*)^2}{(1 + g y^*)^2} + (1 - \alpha_L)(1 - \epsilon)\beta x^*(1 - \epsilon)\beta y^*,
\]

\[
A_3 = \frac{\alpha L^*}{y^*}(a + d_L - \rho)(1 - \epsilon)\beta y^* + py^*\frac{\epsilon(1 + \beta y^*)^2}{(1 + g y^*)^2}[a + d_L - \rho + d + \beta(1 - \epsilon)y^*]
+ (1 - \alpha_L)(1 - \epsilon)\beta x^*(1 - \epsilon)\beta y^*(a + d_L - \rho),
\]

\[
A_4 = py^*\frac{\epsilon(1 + \beta y^*)^2}{(1 + g y^*)^2}(a + d_L - \rho)[d + \beta(1 - \epsilon)y^*].
\]

Then we have

\[
A_1A_2 - A_3 = \frac{\alpha L^*}{y^*}d(a + d_L - \rho) + \frac{(\alpha L^*)^2}{y^*}[d + \beta(1 - \epsilon)y^*]
+ \frac{\alpha L^*}{y^*}py^*\frac{\epsilon(1 + \beta y^*)^2}{(1 + g y^*)^2} + \frac{\alpha L^*}{y^*}(1 - \alpha_L)(1 - \epsilon)\beta x^*(1 - \epsilon)\beta y^*
+ [a + d_L - \rho + d + \beta(1 - \epsilon)y^*][a + d_L - \rho][d + \beta(1 - \epsilon)y^*]
+ \frac{\alpha L^*}{y^*}[d + \beta(1 - \epsilon)y^*][a + d_L - \rho + d + \beta(1 - \epsilon)y^*]
+ (1 - \alpha_L)(1 - \epsilon)\beta x^*(1 - \epsilon)\beta y^*[a + d_L - \rho + d + \beta(1 - \epsilon)y^*],
\]

\[
A_2^2 - 4A_1A_3 = \frac{(\alpha L^*)^2}{y^*}[d + \beta(1 - \epsilon)y^*][a + d_L - \rho + d + \beta(1 - \epsilon)y^*]
+ \frac{\alpha L^*}{y^*}(1 - \alpha_L)(1 - \epsilon)\beta x^*(1 - \epsilon)\beta y^*[a + d_L - \rho + d + \beta(1 - \epsilon)y^*],
\]

\[
A_4^2 - 4A_1A_3 = \frac{(\alpha L^*)^2}{y^*}[d + \beta(1 - \epsilon)y^*][a + d_L - \rho + d + \beta(1 - \epsilon)y^*]
+ \frac{\alpha L^*}{y^*}(1 - \alpha_L)(1 - \epsilon)\beta x^*(1 - \epsilon)\beta y^*[a + d_L - \rho + d + \beta(1 - \epsilon)y^*].
\]
(i) For equilibrium $E^*_+$, we have

$$k - \eta r y^*_2 < 0 \iff h > h_2.$$ 

If $h > h_2$, then $A_4 < 0$. Clearly, $A_i > 0$, $i = 1, 2, 3$ and $A_1 A_2 - A_3 > 0$. If $A_3 (A_1 A_2 - A_3) - A_1^2 A_4 > 0$, from the Routh-Hurwitz criterion [36, 37], we know that the positive equilibrium $E^*_+$ is a stable node.

(ii) For equilibrium $E^*_-$, we have

$$k - \eta r y^*_2 > 0 \iff B - 2b \sqrt{r \eta} < \sqrt{B^2 - 4b^2 r \eta}. \quad (3.4)$$

For any positive $h$, (3.4) holds true. Thus, equilibrium $E^*_-$ is unstable. □

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

**Theorem 3.5.** If $R_0 > R_c$ and $h = h_2$, the immune equilibrium $E^*_-$ and $E^*_+$ coincide with each other and a saddle-node bifurcation occurs when $h$ passes through $h_2$. □

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

Table 3.3: The stabilities of the equilibria and the behaviors of system (1.1). Here, $h^{**}$ is a critical value and we assume $A_3 (A_1 A_2 - A_3) - A_1^2 A_4 > 0$.

| $R_0$ | $E_0$ | $E_1$ | $E^*_+$ | $E^*_-$ | System (1.1) |
|-------|-------|-------|---------|---------|---------------|
| $< 1$ | GAS   | —     | —       | —       | Tends to $E_0$|
| $1 < R_0 < R_c$, $0 < h < h^{**}$ | US    | LAS   | —       | —       | Tends to $E_1$|
| $1 < R_0 < R_c$, $h^{**} < h$ | US    | US    | LAS     | —       | Tends to $E^*_+$|

4. Sensitive analysis and numerical simulations

4.1. Sensitive analysis

Sensitive analysis has been widely performed to investigate the basic reproductive number $R_0$ in epidemic models [38]. In the following, we carry out sensitive analysis with the aim of revealing the relationship between the basic infection reproductive number $R_0$ and the basic immune reproductive number $R^*_c$, and system parameters in our model. Here, we use latin hypercube sampling (LHS) and partial rank correlation coefficients (PRCCs) [39, 40] to test the dependence of the basic infection reproduction number $R_0$ and the basic immune
Table 3.4: The stabilities of the equilibria and the behaviors of system (1.1). Here, $h_2$, $h^*$ and $h^{**}$ are critical values, $h_2$ is a saddle-node bifurcation point and we assume $A_3(A_1A_2 - A_3) - A_1^2A_4 > 0$.

| $R_0 < 1$ | $E_0$ | $E_1$ | $E^*_+ | E^*_-$ | System (1.1) |
|-----------|-------|-------|-------------|-------------|
| $R_0 > 1, 0 < h < h_2,$ | US | LAS | — | — | Tends to $E_0$ |
| $R_0 > R_c, h_2 < h < h^{**}$ | US | LAS | LAS | US | Bistable |
| $R_0 > R_c, h^{**} < h < h^*$ | US | US | LAS | US | Tends to $E^*_+$ |
| $R_0 > R_c, h > h^*$ | US | US | LAS | — | Tends to $E^*_+$ |

reproduction number $R^*_-$. As a statistical sampling method, LHS provides an efficient analysis of parameter variations across simultaneous uncertainty ranges in each parameter [39]. PRCC, on the other hand, shows the level of significance for each parameter. The PRCC is obtained using the rank transformed LHS matrix and output matrix [40]. We performed 4000 simulations per run and used a uniform distribution function to test for the significance of PRCCs for all parameters with wide ranges.

PRCC results Figs. 1 and 2 illustrate the dependence of $R_0$ and $R^*_-$. When $|PRCC| > 0.4$, there is significant correlation between input parameters and output variables. For $|PRCC| \in (0.2, 0.4]$, the correlations are moderate. When $|PRCC| \in [0, 0.2]$, we have weak correlations. We notice that the proliferation rate of CD4$^+$ T cells $s$, the decay rate of CD4$^+$ T cells $d$, the infection rate of CD4$^+$ T cells $\beta$, the drug efficacy $\epsilon$ and the latently infected cell death rate $d_L$ have significant influences on the infection reproduction number $R_0$ and the immune reproduction number $R^*_-$.  

4.2. Numerical simulations

In the following, we perform some numerical simulations to verify our analysis results. The default parameter values are listed in Table 5.5.

Using these default parameters, we obtain the values of thresholds $R_0 \approx 3.0030$, $R_c \approx 1.4243$, $h_2 \approx 0.7325$, $h^* \approx 1.4353$ and $h^{**} \approx 0.9174$. The bistable interval is $(0.7325, 0.9174)$. Fig.3 indicates that there is no positive equilibrium for $h < 0.7325$, and a saddle-node bifurcation appears when $h$ passes through 0.7325.

We are also interested in the influences of system parameters on the virus rebound threshold $h_2$ and the elite control threshold $h^{**}$. From PRCCs. Fig.5, we can see that the decay rate
of CTLs $b$, the effector cell production Hill function scaling $\eta$, the natural oxidant content $k$ significantly positively correlated to the virus rebound threshold $h_2$. The proliferation rate of CTLs $c$ significantly negatively correlated to the virus rebound threshold $h_2$.

Fig. 6 indicates that the activation rate of viral latent reservoir $a$ is significantly positively correlated to the elite control threshold $h^{**}$. The proliferation rate of latently infected cells $\rho$ is significantly negatively correlated to the elite control threshold $h^{**}$.

Biologically, the increased decay rate of CTLs, the effector cell production Hill function scaling and the natural oxidant content make it difficult to treat the disease. While the increased proliferation rate of CTLs are beneficial to the disease treatment.

5. Discussion

The bistability phenomenon can also appear in other HIV infection model with oxidative stress. For example, we investigate the HIV infection model (5.2) with logistic proliferation rate of latently infected cells, which can reveal the effects of proliferation rate of latently infected cells on HIV infection model. Instead of using similar method as analyzing system (1.1), we carry out simulations to show the existence of bistability. Fig. 7 shows that system (5.2) has bistable behaviors for different initial values when $L_{max} = 50$ (the values of other parameters are listed in Table 2).

\[
\begin{align*}
\frac{dx(t)}{dt} &= s - dx(t) - (1 - \epsilon)\beta x(t)y(t), \\
\frac{dL(t)}{dt} &= \alpha_L(1 - \epsilon)\beta x(t)y(t) - (a + d_L)L(t) + \rho L(t)(1 - \frac{L(t)}{L_{max}}), \\
\frac{dy(t)}{dt} &= (1 - \alpha_L)(1 - \epsilon)\beta x(t)y(t) + aL(t) - \delta y(t) - py(t)z(t), \\
\frac{dz(t)}{dt} &= \frac{cy(t)z(t)}{1 + \eta y(t)k + ry(t)} - bz(t).
\end{align*}
\]

(5.2)

In fact, the function $\frac{cy}{1 + \eta y} \frac{1 + h}{k + ry}$ is a Monod-Haldane function [42] about $y$. We show the predator-prey system with Monod-Haldane function or simplified Monod-Haldane function also has bistability appear [43]. In viral infection systems, the models with nonmonotonic immune responses has bistability appear. However, the model with monotonic immune responses has no bistability appear [44]. The bistability phenomenon also be discovered in a NK-tumor-immune system [45].

In this paper, we design a simplified within host model to investigate the post-treatment immune control and elite control of a disease. We obtain the model’s post-treatment immune
control threshold and the elite control threshold, and show that the model displays rich dynamical behaviors. By performing sensitive analysis and numerical simulations, we find that decreasing the immune impairment rate is beneficial for the host to obtain post-treatment immune control and the elite control. A therapeutic strategy that decreases the immune impairment rate of virus, decay rate of CTLs and effector cell production Hill function scaling is helpful for the host to obtain elite control efficiently. The results have potential applications in designing optimal treatment plan for corresponding diseases.

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Table 5.5: Parameters for model (1.1).

| Symbol | Description                                      | Value                  | Reference |
|--------|--------------------------------------------------|------------------------|-----------|
| $s$    | Proliferation rate of CD4$^+$ T cells            | 10 cells /µL/ day      | [41]      |
| $d$    | Decay rate of CD4$^+$ T cells                    | 0.01 day$^{-1}$        | [41]      |
| $\beta$| Infection rate of CD4$^+$ T cells                | 0.015 µL / day         | –         |
| $\epsilon$ | Drug efficacy                                        | 0.8                    | –         |
| $\alpha_L$ | Fraction of newly infected cells that become latently infected | 0.001                 | –         |
| $\rho$ | Proliferation rate of latently infected cells    | 0.0045 day$^{-1}$      | [3]       |
| $a$    | Activation rate                                  | 0.004 day$^{-1}$       | [3]       |
| $d_L$  | Latently infected cell death rate                | 0.004 day$^{-1}$       | [3]       |
| $\delta$ | Infected cell death rate                         | 1 day$^{-1}$           | [3]       |
| $p$    | Killing rate of infected CD4$^+$ T cells         | 0.1 day$^{-1}$         | –         |
| $c$    | Proliferation rate of CTLs                       | 0.1 day$^{-1}$         | –         |
| $\eta$ | Effector cell production Hill function scaling   | 1 cells/µL             | –         |
| $b$    | Decay rate of CTLs                               | 0.1 day$^{-1}$         | –         |
| $h$    | Antioxidant parameter                            | 0.8 day$^{-1}$         | –         |
| $k$    | The natural oxidant content                      | 1 cells /µL            | –         |
| $r$    | Oxidant content produced by HIV viral load       | 0.1 cells /µL          | –         |

Figure 1: Partial rank correlation coefficients illustrating the dependence of $R_0$ for the model (1.1) on each parameter and the frequency distribution of $R_0$. 
Figure 2: Partial rank correlation coefficients illustrating the dependence of $R^*_\text{b}$ for the model (1.1) on each parameter.

Figure 3: Bistability and saddle-node bifurcation diagram of system (1.1). The bistable interval is $(0.7325, 0.9174)$. When $h < 0.7325$, the model has a high viral load steady state, which corresponds to viral rebound. When $h > 0.9174$, the model shows a low viral load steady state, which means that patients are under elite control. When $h$ is between the two values, the model shows bistability depending on the initial conditions (population size of infected cells or immune cells at the time of treatment cessation). The parameter values are shown in Table 5.
Figure 4: The bistability of system (1.1). The initial values are $x(0) = 600$, $L(0) = 80$, $y(0) = 20$, $z(0) = 1$ (blue) and $x(0) = 600$, $L(0) = 80$, $y(0) = 20$, $z(0) = 20$ (red). The parameter values are listed in Table 5.

Figure 5: Partial rank correlation coefficients illustrating the dependence of $h_2$ on each parameter.
Figure 6: Partial rank correlation coefficients illustrating the dependence of $h^{**}$ on each parameter.

Figure 7: The bistability of system (1.1). Here, $L_{\text{max}} = 50$. The initial values are $x(0) = 600, L(0) = 20, y(0) = 20, z(0) = 1$ (blue) and $x(0) = 600, L(0) = 80, y(0) = 20, z(0) = 20$ (red). The parameter values are listed in Table 5.