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Viral dynamics of an HIV model with latent infection incorporating antiretroviral therapy

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Abstract

In this paper, we construct an HIV infection model which includes latent infection, logistic growth for healthy $CD4^+$ T-cells, and antiretroviral therapy. We obtain the global asymptotic stability of the uninfected equilibrium by constructing a Lyapunov function, and we give a sufficient condition for the local asymptotic stability of the infected equilibrium. We also use the latin hypercube sampling technique to identify the key parameters in determining the stability of the infected equilibrium. By numerical simulations, we observe that the model without logistic growth would underestimate the number of infectious virions, while the model without latent infection would overestimate the number of infectious virions.

Keywords: HIV; $CD4^+$ T-cells; latent infected T-cells; antiretroviral therapy; asymptotic stability

1 Introduction

Acquired immune deficiency syndrome (AIDS) is caused by human immunodeficiency virus (HIV), and it has become a very serious threat to the health of the people all over the world since it was first found in 1981. HIV-1 infects CD4 lymphocytes with CD4 molecules in the human body selectively, especially $CD4^+$ T-cells. When individuals are infected with HIV-1 over a long period of time (5-10 years), the body's $CD4^+$ T-cell count will gradually decline to 200 cells/mm^3, and the viral load will increase sharply. Finally, the body's immune system will be severely damaged and the human body will be much more vulnerable to a series of opportunistic infections. Fortunately, the virus replication can be suppressed through the use of highly active antiretroviral therapy (HAART). HAART is commonly composed of reverse transcriptase inhibitors (RTI) and protease inhibitors (PI). RTI can prevent the formation of HIV RNA and DNA in the $CD4^+$ T-cell host, so that the virus infection could not form provirus, and PI can restrain the virus protease hydrolysis and inhibit infected T-cells to produce mature infectious virions. However, people living with HIV-1 cannot recover in the process of long-time use of antiretroviral therapy, and the HIV-1 virus cannot be eradicated thoroughly [1–4]. Due to the existence of the latent reservoir, some HIV-1 virus particles can escape the immune clearance by hiding in the static memory CD4 T-cells [1]. Consequently, the latent infection is a major barrier to the elimination of HIV-1 virus [1, 4–6].

Mathematical models including the latent infection have been formulated to study HIV dynamics in-host in recent years [4, 7–12]. Banks *et al.* investigated that the model with

HIV latent infection was in accordance with the actual measured patient data especially when the viral load was lower than the detectable level, and their model could better predict the trend of the virus [8]. Rong and Perelson [4, 11, 12] developed a kind of mathematical models with latent infection and antiretroviral therapy, examined the relationships among combination drug therapy, viral blips, and the number of latent infected T-cells, and showed that the viral replication from the latent reservoir might result in low-level persistence of viraemia during combination drug therapy. However, in each of these studies, a linear growth rate for healthy $CD4^+$ T-cells with latent infection models was performed. In fact, Ho *et al.* in [13] and Sachsenberg *et al.* in [14] indicated that the mitosis for $CD4^+$ T-cells was density-dependent on the number of T-cells, and the mitosis would decrease if the number of T-cells increased to a certain value. Recently, mitosis in healthy $CD4^+$ T-cells was represented by a logistic growth term in within-host HIV-1 models [15–20], but these studies ignored the effect of latent infection. Also, Chomont *et al.* showed that T-cell survival and homeostatic mitosis could drive the number of latently infected T-cells [6]. Therefore, the inclusion of both a logistic growth term and latent infection in-host model is more reasonable, and the model would have further influence on the model progression.

The paper is organized as follows. In the next section, we will formulate an HIV infection model including latent infection, drug therapy, and logistic growth for healthy $CD4^+$ T-cells, and we will address the positivity and boundedness of the model solutions. In Section 3, the basic reproduction number is derived by the next generation method. Stability analyses of the uninfected equilibrium and the infected equilibrium are given. In Section 4, sensitivity analyses with the latin hypercube sampling method are conducted. Numerical simulations with realistic parameter values are illustrated to demonstrate model behaviors in Section 5. Finally, we conclude our work and mention future work.

2 Model and well-posedness

In this section, we will extend the basic HIV latent infection model with logistic growth for healthy $CD4^+$ T-cells and drug therapy. The model includes healthy $CD4^+$ T-cells (T), latently infected $CD4^+$ T-cells (L), productively infected $CD4^+$ T-cells (T^*), and free virus (V). Because of the use of protease inhibitors, we divide the free virus into infectious virus (V_I) and noninfectious virus (V_{NI}). The model can be described as

$$\begin{aligned}
&\frac{d}{dt}T(t) = \lambda - d_T T + rT\left(1 - \frac{T}{T_{\max}}\right) - (1-n_{rt})kV_I T,\\
&\frac{d}{dt}L(t) = \eta(1-n_{rt})kV_I T - d_L L - aL,\\
&\frac{d}{dt}T^*(t) = (1-\eta)(1-n_{rt})kV_I T - \delta T^* + aL,\\
&\frac{d}{dt}V_I(t) = (1-n_p)N\delta T^* - cV_I,\\
&\frac{d}{dt}V_{NI}(t) = n_p N\delta T^* - cV_{NI}.
\end{aligned} \tag{1}$$

Here, healthy $CD4^+$ T-cells are produced from precursors at a constant rate λ, the parameter d_T is the natural death rate of $CD4^+$ T-cells, r denotes the logistic growth rate, and $T_{\max}$ represents the carrying capacity of the $CD4^+$ T-cells population. The parameter k

denotes the rate of infection between T-cells and infectious virus, and η is the fraction of infections leading to latency. d_L and δ are the death rates of latently infected T-cells and productively infected T-cells, respectively. The parameter a is the activated rate from latently infected cells to productively infected T-cells. We assume a productively infected T-cell can release on average N viral particles during its lifespan with the mean period $1/\delta$, and the clearance rate of the HIV virus is c. n_{rt} and n_p represent the drug efficacy of RTI and PI ($0 \le n_{rt} < 1$ and $0 \le n_p < 1$), respectively.

It should be noted that the fifth equation is independent from the first four equations in system (1). Therefore, the stability analysis of system (1) is equivalent to the following subsystem:

$$\begin{aligned}
&\frac{d}{dt}T(t) = \lambda - d_T T + rT\left(1 - \frac{T}{T_{\max}}\right) - (1-n_{rt})kV_I T,\\
&\frac{d}{dt}L(t) = \eta(1-n_{rt})kV_I T - d_L L - aL,\\
&\frac{d}{dt}T^*(t) = (1-\eta)(1-n_{rt})kV_I T - \delta T^* + aL,\\
&\frac{d}{dt}V_I(t) = (1-n_p)N\delta T^* - cV_I.
\end{aligned} \tag{2}$$

For simplicity, we denote

$$\bar{k} := (1-n_{rt})k, \qquad \bar{N} := (1-n_p)N, \qquad \epsilon = 1-(1-n_{rt})(1-n_p).$$

The following theorem illustrates that the solutions of system (2) are positive and bounded.

Theorem 2.1 *Let* $(T(t), L(t), T^*(t), V_I(t))$ *be the solution of system* (2) *with the initial values* $(T(0), L(0), T^*(0), V_I(0)) \in \mathbf{R}^4_+$, *where* $\mathbf{R}^4_+ = \{(x_1, x_2, x_3, x_4) | x_j \ge 0, j = 1, 2, 3, 4\}$, *Then* $T(t), L(t), T^*(t)$, *and* $V_I(t)$ *are all unique non-negative and ultimately bounded*.

Proof The right hand side functions of system (2) are continuous and satisfy the Lipschitz condition; by the existence and uniqueness of solutions for ordinary differential equations [21], we see that system (2) has a unique solution $(T(t), L(t), T^*(t), V_I(t)) \in \mathbf{C}([0, +\infty), \mathbf{R}^4_+)$ with non-negative initial values.

By the first equation of system (2), we obtain $\dot{T}|_{T=0} = \lambda > 0$. Then we see that $T(t) \ge 0$ for every $t \ge 0$ [22].

By the second equation of system (2), we get $\dot{L}|_{L=0} = \eta\bar{k}V_I T \ge 0$. Thus, we derive that $L(t) \ge 0$ is established. In the following, we will use reduction *ad absurdum* to prove the correctness of this statement.

Assume there is a $t_1 > 0$ with $t_1 = \inf\{t | L(t) = 0, t > 0\}$, such that $\dot{L}(t_1)|_{L(t_1)=0} = \eta\bar{k}V_I(t_1) \times T(t_1) < 0$. That is to say, $L(t_1) = 0$, $L(t) > 0$ with $t \in [0, t_1)$ and $V_I(t_1) < 0$. As $V_I(0) \ge 0$, there exists a $t_2 > 0$ with $t_2 = \inf\{t | V_I(t) = 0, t \in [0, t_1)\}$, and thus $\dot{V}_I(t_2) \le 0$. Moreover, we get $\dot{V}_I(t_2) = \bar{N}\delta T^*(t_2) \le 0$ from the fourth equation of system (2). Therefore, we can deduce that $T^*(t_2) \le 0$. Since $T^*(0) \ge 0$, there exists a $t_3 > 0$ with $t_3 = \inf\{t | T^*(t) = 0, t \in [0, t_2)\}$, and thus $\dot{T}^*(t_3) \le 0$. On the other hand, from the third equation of system (2), $\dot{T}^*(t_3) =$

$(1-\eta)\bar{k}V_I(t_3)T(t_3) + aL(t_3) > 0$ $(0 < t_3 < t_2 < t_1)$, which is a contradictory to the hypothesis. Similarly, we can verify that $T^*(t) \geq 0$ for every $t \geq 0$.

From the last equation of system (2), we get $\dot{V}_I|_{V_I=0} = \bar{N}\delta T^* \geq 0$, so we have $V_I(t) \geq 0, t \geq 0$ [22].

Now, we show the boundedness of solutions. From the first equation of (2), we have

$$\dot{T} \leq \lambda - d_T T + rT\left(1 - \frac{T}{T_{\max}}\right),$$

so

$$\lim_{t\to+\infty} \sup T(t) \leq T_0, \tag{3}$$

where

$$T_0 = \frac{T_{\max}}{2r}\left[r - d_T + \sqrt{(r-d_T)^2 + \frac{4r\lambda}{T_{\max}}}\right]. \tag{4}$$

We define $F = T + L + T^*$, and computing the derivative of F along the trajectories yields

$$\begin{aligned}\dot{F} &= \lambda - d_T T + rT\left(1 - \frac{T}{T_{\max}}\right) - \delta T^* - d_L L \\ &\leq -d_T T - d_L L - \delta T^* + \lambda + rT \\ &\leq -hF + M_0,\end{aligned}$$

where $M_0 = \lambda + rT_0$, $h = \min\{d_T, d_L, \delta\}$. Therefore, we see that F is ultimately bounded. From (3), we know that $T(t)$ has an ultimate bound T_0, therefore, $L(t)$ and $T^*(t)$ are ultimately bounded with some M_1. From the fourth equation of system (2), we can easily see that $V_I(t)$ is ultimately bounded with some M_2. □

Denote $M = \max\{M_1, M_2\}$. It follows that $T(t) \leq T_0, L(t) \leq M, T^*(t) \leq M$ and $V_I(t) \leq M$, for sufficiently large time t.

Next, we will analyze the dynamics of system (2) in the following bounded feasible region:

$$\Gamma = \left\{\left(T, L, T^*, V_I\right) \in \mathbf{R}^4_+ : T \leq T_0, L, T^* \text{ and } V_I \leq M\right\}.$$

It can be observed that all solutions of (2) eventually enter and stay within Γ, and Γ is a positive invariant set.

3 Model analysis

We will find the possible equilibria of system (2) and will analyze their stabilities. First of all, we find the equilibria of system (2) by solving the following algebraic equations:

$$\begin{cases} 0 = \lambda - d_T T + rT(1 - \frac{T}{T_{\max}}) - (1-n_{rt})kV_I T, \\ 0 = \eta(1-n_{rt})kV_I T - d_L L - aL, \\ 0 = (1-\eta)(1-n_{rt})kV_I T - \delta T^* + aL, \\ 0 = (1-n_p)N\delta T^* - cV_I, \end{cases} \tag{5}$$

for the unknown constants T, L, T^*, V_I. From equation (5), we can easily get an uninfected equilibrium $E_0(T_0, 0, 0, 0)$, where T_0 is given by the expression of (4). The other equilibrium is $\bar{E} = (\bar{T}, \bar{L}, \bar{T^*}, \bar{V_I})$, where

$$\begin{aligned}
&\bar{T} = \frac{c(a + d_L)}{\bar{k}\bar{N}[a + (1 - \eta)d_L]},\\
&\bar{L} = \frac{c\eta\bar{V_I}}{\bar{N}[a + (1 - \eta)d_L]},\\
&\bar{T^*} = \frac{c\bar{V_I}}{\bar{N}\delta},\\
&\bar{V_I} = \frac{\lambda - d_T\bar{T} + r\bar{T}(1 - \frac{\bar{T}}{T_{\max}})}{\bar{k}\bar{T}}.
\end{aligned}$$

There are some methods to determine the basic reproduction number $\mathcal{R}_0$ [23, 24]. By the next generation method of Van den Driessche and Watmough [24], we obtain

$$\mathcal{R}_0 = \frac{a + (1 - \eta)d_L}{c(a + d_L)}\bar{k}\bar{N}T_0. \tag{6}$$

For the detailed calculation process refer to [7] with $\tau_1 = \tau_2 = 0$. If $\eta = 0$, then the basic reproduction number is $\tilde{\mathcal{R}}_0 = \bar{k}\bar{N}T_0/c$, which is the same as that of the HIV model without latent infection [15–19]. Since $0 < \eta < 1$, we see that $\mathcal{R}_0 < \tilde{\mathcal{R}}_0$. Biologically, the model without latent infection would overestimate the average number of infected T-cells.

It turns out that the value of $\mathcal{R}_0$ determines the existence of the infected equilibrium, that is, $\bar{E}$ exists if and only if $\mathcal{R}_0 > 1$. In fact,

$$\lambda = d_T T_0 - rT_0\left(1 - \frac{T_0}{T_{\max}}\right),$$

then

$$\begin{aligned}
\bar{V_I} &= \frac{d_T T_0 - rT_0(1 - \frac{T_0}{T_{\max}}) - d_T\bar{T} + r\bar{T}(1 - \frac{\bar{T}}{T_{\max}})}{\bar{k}\bar{T}}\\
&= \frac{(T_0 - \bar{T})[d_T - r(1 - \frac{T_0}{T_{\max}}) + \frac{r\bar{T}}{T_{\max}}]}{\bar{k}\bar{T}}\\
&= \frac{(\frac{T_0}{\bar{T}} - 1)(\frac{\lambda}{T_0} + \frac{r\bar{T}}{T_{\max}})}{\bar{k}}\\
&= \frac{(\mathcal{R}_0 - 1)(\frac{\lambda}{T_0} + \frac{r\bar{T}}{T_{\max}})}{\bar{k}}\\
&> 0.
\end{aligned}$$

Through the expression of $\mathcal{R}_0$, we can also rewrite $\bar{T} = \frac{T_0}{\mathcal{R}_0}$.

To study the stability at the equilibrium $\bar{E}(\bar{T}, \bar{L}, \bar{T^*}, \bar{V_I})$, we let $y_1(t) = T(t) - \bar{T}, y_2(t) = L(t) - \bar{L}, y_3(t) = T^*(t) - \bar{T^*}, y_4(t) = V_I(t) - \bar{V_I}$. The linearized system of system (2) at $\bar{E}(\bar{T}, \bar{L}, \bar{T^*}, \bar{V_I})$ is

$$\frac{d}{dt}y_1(t) = \left(-d_T + r - \frac{2r\bar{T}}{T_{\max}}\right)y_1 - \bar{k}\bar{T}y_4,$$

$$\frac{d}{dt}y_2(t) = \eta\bar{k}\bar{V}_I y_1 - (d_L + a)y_2 + \eta\bar{k}\bar{T}y_4,$$
$$\frac{d}{dt}y_3(t) = (1-\eta)\bar{k}\bar{V}_I y_1 + ay_2 - \delta y_3 + (1-\eta)\bar{k}\bar{T}y_4,$$
$$\frac{d}{dt}y_4(t) = \bar{N}\delta y_3 - cy_4.$$

Theorem 3.1 *The uninfected equilibrium E_0 for system* (2) *is locally asymptotically stable if $\mathcal{R}_0 < 1$, and it is unstable if $\mathcal{R}_0 > 1$.*

Proof The characteristic equation for system (2) at the uninfected equilibrium E_0 is

$$\left(\xi + d_T - r + \frac{2rT_0}{T_{\max}}\right)\left(\xi^3 + a_1\xi^2 + a_2\xi + a_3\right) = 0, \tag{7}$$

where

$$\begin{aligned}
a_1 &= a + d_L + c + \delta,\\
a_2 &= (a + d_L)(c + \delta) + c\delta - (1-\eta)\delta\bar{k}\bar{N}T_0\\
&= (a + d_L)(c + \delta) + c\delta\left(1 - (1-\eta)\frac{\mathcal{R}_0(a + d_L)}{a + (1-\eta)d_L}\right)\\
&= (a + d_L)(c + \delta) + c\delta\left(1 - \mathcal{R}_0 + \frac{a\eta\mathcal{R}_0}{a + (1-\eta)d_L}\right),\\
a_3 &= (a + d_L)c\delta - a\eta\delta\bar{k}\bar{N}T_0 - (a + d_L)(1-\eta)\delta\bar{k}\bar{N}T_0\\
&= (a + d_L)c\delta - a\delta\bar{k}\bar{N}T_0 - (1-\eta)\delta d_L\bar{k}\bar{N}T_0\\
&= (a + d_L)c\delta - \mathcal{R}_0 c\delta(a + d_L)\\
&= (a + d_L)(1 - \mathcal{R}_0)c\delta.
\end{aligned}$$

Clearly, $\xi = -d_T + r - \frac{2rT_0}{T_{\max}} = -\frac{\lambda}{T_0} - \frac{rT_0}{T_{\max}} < 0$ is a negative root of equation (7). The remaining roots of equation (7) are determined by the following equation:

$$\xi^3 + a_1\xi^2 + a_2\xi + a_3 = 0. \tag{8}$$

It is obvious that $a_1 = a + d_L + c + \delta > 0$, and $a_3 = (a + d_L)(1 - \mathcal{R}_0)c\delta > 0$ if $\mathcal{R}_0 < 1$ is satisfied. Furthermore,

$$\begin{aligned}
a_1a_2 - a_3 &= (a + d_L + c + \delta)\left[(a + d_L)(c + \delta) + c\delta\left(1 - \mathcal{R}_0 + \frac{a\eta\mathcal{R}_0}{a + (1-\eta)d_L}\right)\right]\\
&\quad - (a + d_L)(1 - \mathcal{R}_0)c\delta\\
&= (a + d_L)(c + \delta)(a + d_L + c + \delta) + (a + d_L)\frac{c\delta a\eta\mathcal{R}_0}{a + (1-\eta)d_L}\\
&\quad + (c + \delta)c\delta\left(1 - \mathcal{R}_0 + \frac{a\eta\mathcal{R}_0}{a + (1-\eta)d_L}\right),
\end{aligned}$$

and it follows that $a_1a_2 - a_3 > 0$ if $\mathcal{R}_0 < 1$ is satisfied. By the Routh-Hurwitz criterion, we know that equation (8) has negative real roots. Therefore, the uninfected equilibrium E_0 is locally asymptotically stable if $\mathcal{R}_0 < 1$.

If $\mathcal{R}_0 > 1$, it is easy to see that $a_3 < 0$. So, equation (8) has at least one positive root. Therefore, the uninfected equilibrium E_0 is unstable when $\mathcal{R}_0 > 1$. □

Theorem 3.2 *If $\mathcal{R}_0 < 1$, the uninfected equilibrium E_0 for system* (2) *is globally asymptotically stable.*

Proof Define a Lyapunov function $W_1 : R \times R \times R \times R \to R$

$$W_1 = \big[a + (1-\eta)d_L\big]\left(T - T_0 - T_0 \ln \frac{T}{T_0}\right) + aL + (a + d_L)T^* + \frac{a + d_L}{\bar{N}} V_I$$

for $T > 0, L \geq 0, T^* \geq 0, V_I \geq 0$, and it is obvious that $W_1 \geq 0$. By the calculus knowledge of a multi-variable function, we can derive that W_1 has a global minimum value attained at E_0 and thus, $W_1 = 0$ if and only if $(T, L, T^*, V_I) = (T_0, 0, 0, 0)$. Computing the derivatives of W_1 along the trajectories of system (2), and using the equalities $\lambda = d_T T_0 - rT_0(1 - \frac{T_0}{T_{\max}})$ and $\bar{k}\bar{N}T_0[a + (1-\eta)d_L] = c\mathcal{R}_0(a + d_L)$, we derive that

$$\begin{aligned}
\dot{W}_1 &= \big[a + (1-\eta)d_L\big]\left[\lambda - d_T T + rT\left(1 - \frac{T}{T_{\max}}\right) - \bar{k}V_I T\right]\left(1 - \frac{T_0}{T}\right) \\
&\quad + a(\eta\bar{k}V_I T - d_L L - aL) + (a + d_L)\big((1-\eta)\bar{k}V_I T - \delta T^* + aL\big) \\
&\quad + \frac{a + d_L}{\bar{N}}\big(\bar{N}\delta T^* - cV_I\big) \\
&= \big[a + (1-\eta)d_L\big]\left[(T_0 - T)\left(d_T - r + \frac{rT_0}{T_{\max}} + \frac{rT}{T_{\max}}\right) - \bar{k}V_I T\right]\left(1 - \frac{T_0}{T}\right) \\
&\quad + \big[a + (1-\eta)d_L\big]\bar{k}V_I T - \frac{c(a + d_L)}{\bar{N}} V_I \\
&= \big[a + (1-\eta)d_L\big]\left[(T_0 - T)\left(\frac{\lambda}{T_0} + \frac{rT}{T_{\max}}\right) - \bar{k}V_I T\right]\left(1 - \frac{T_0}{T}\right) \\
&\quad + \big[a + (1-\eta)d_L\big]\bar{k}V_I T - \frac{c(a + d_L)}{\bar{N}} V_I \\
&= \big[a + (1-\eta)d_L\big]\left[-\frac{(T - T_0)^2}{T}\left(\frac{\lambda}{T_0} + \frac{rT}{T_{\max}}\right) - \bar{k}V_I(T - T_0)\right] \\
&\quad + \big[a + (1-\eta)d_L\big]\bar{k}V_I T - \frac{c(a + d_L)}{\bar{N}} V_I \\
&= -\big[a + (1-\eta)d_L\big]\frac{(T - T_0)^2}{T}\left(\frac{\lambda}{T_0} + \frac{rT}{T_{\max}}\right) - \frac{c(a + d_L)}{\bar{N}}(1 - \mathcal{R}_0)V_I.
\end{aligned}$$

It is clear to see that $\dot{W}_1 < 0$ if $\mathcal{R}_0 < 1$. $\dot{W}_1 = 0$ if and only if

$$T = T_0, \qquad L = T^* = V_I = 0.$$

So, the maximum invariant set in $\{\psi \in \Gamma | \dot{W}_1 = 0\}$ is only the set $\{E_0\}$. By the LaSalle invariance principle [25], we get the global attraction of E_0. This and Theorem 3.1 indicate the global asymptotic stability of E_0. □

To prove the stability of the infected equilibrium $\bar{E}$, we denote

$$B_1 := d_T - r + \frac{2r\bar{T}}{T_{\max}} + \bar{k}\bar{V}_I = \frac{\lambda}{\bar{T}} + \frac{r\bar{T}}{T_{\max}} > 0,$$

$$B_2 := c\delta - (1-\eta)\delta\bar{k}\bar{N}\bar{T} = c\delta\left(1 - \frac{(a+d_L)(1-\eta)}{a+(1-\eta)d_L}\right)$$

$$= \frac{c\delta\eta a}{a+(1-\eta)d_L} > 0.$$

Theorem 3.3 *When $\mathcal{R}_0 > 1$, the infected equilibrium $\bar{E}$ for system* (2) *is locally asymptotically stable if the condition $d_T - r + \frac{2r\bar{T}}{T_{\max}} > 0$ is satisfied.*

Proof The characteristic equation for system (2) at the infected equilibrium $\bar{E}$ is

$$\xi^4 + b_1\xi^3 + b_2\xi^2 + b_3\xi + b_4 = 0, \tag{9}$$

where

$$b_1 = B_1 + a + d_L + c + \delta > 0,$$

$$b_2 = B_1(a + d_L + c + \delta) + (a + d_L)(c + \delta) + B_2 > 0,$$

$$b_3 = B_1\big[(a + d_L)(c + \delta) + B_2\big] + (1-\eta)\delta\bar{k}^2\bar{N}\bar{V}_I\bar{T} > 0,$$

$$b_4 = c\delta\bar{k}\bar{V}_I(a + d_L) > 0.$$

In the following, we will use the Routh-Hurwitz criterion to verify the stability of the infected equilibrium. We have

$$H_1 = b_1 > 0,$$

$$\begin{aligned}
H_2 &= b_1b_2 - b_3 \\
&= (B_1 + a + d_L + c + \delta)\big[B_1(a + d_L + c + \delta) + (a + d_L)(c + \delta) + B_2\big] \\
&\quad - B_1\big[(a + d_L)(c + \delta) + B_2\big] - (1-\eta)\delta\bar{k}^2\bar{N}\bar{V}_I\bar{T} \\
&= B_1^2(a + d_L + c + \delta) + (a + d_L + c + \delta)\big[(a + d_L)(c + \delta) + B_2\big] \\
&\quad + B_1(a + d_L)(a + d_L + c + \delta) + B_1(a + d_L)(c + \delta) + B_1(c + \delta)^2 \\
&\quad - (1-\eta)\delta\bar{k}^2\bar{N}\bar{V}_I\bar{T} \\
&= (a + d_L + c + \delta)\big[B_1^2 + (a + d_L)(c + \delta) + B_2\big] + B_1(a + d_L)(a + d_L + 2c + 2\delta) \\
&\quad + B_1\big(c^2 + \delta^2\big) + \big(2c\delta B_1 - (1-\eta)\delta\bar{k}^2\bar{N}\bar{V}_I\bar{T}\big) \\
&= (a + d_L + c + \delta)\big[B_1^2 + (a + d_L)(c + \delta) + B_2\big] + B_1(a + d_L)(a + d_L + 2c + 2\delta) \\
&\quad + B_1\big(c^2 + \delta^2\big) + c\delta\left(2B_1 - \frac{(1-\eta)(a + d_L)}{a+(1-\eta)d_L}\bar{k}\bar{V}_I\right) \\
&> (a + d_L + c + \delta)\big[B_1^2 + B_2 + (a + d_L)(c + \delta)\big] + B_1(a + d_L)(a + d_L + 2c + 2\delta) \\
&\quad + B_1\big(c^2 + \delta^2\big) + c\delta(2B_1 - \bar{k}\bar{V}_I),
\end{aligned}$$

$$
\begin{aligned}
H_3 &= b_3H_2 - b_4b_1^2 \\
&> \left[B_1\left[(a+d_L)(c+\delta)+B_2\right]+(1-\eta)\delta\bar{k}^2\bar{N}\bar{V}_I\bar{T}\right]\left\{(a+d_L+c+\delta)\left[B_1^2+B_2\right.\right. \\
&\quad \left.\left.+(a+d_L)(c+\delta)\right]+B_1(a+d_L)(a+d_L+2c+2\delta)+B_1\left(c^2+\delta^2\right)+c\delta(2B_1-\bar{k}\bar{V}_I)\right\} \\
&\quad -c\delta\bar{k}\bar{V}_I(a+d_L)(B_1+a+d_L+c+\delta)^2 \\
&= D_1+D_2+D_3+D_4,
\end{aligned}
$$

where

$$
\begin{aligned}
D_1 &= \left[B_1B_2+(1-\eta)\delta\bar{k}^2\bar{N}\bar{V}_I\bar{T}-c\delta\bar{k}\bar{V}_I\right](a+d_L)(c+\delta+B_1)(a+d_L+c+\delta+B_1) \\
&= \left\{B_1B_2+\bar{k}\bar{V}_I\left[(1-\eta)\delta\bar{k}\bar{N}\bar{T}-c\delta\right]\right\}(a+d_L)(c+\delta+B_1)(a+d_L+c+\delta+B_1) \\
&= B_2(B_1-\bar{k}\bar{V}_I)(a+d_L)(c+\delta+B_1)(a+d_L+c+\delta+B_1), \\
D_2 &= \left(B_1B_2+(1-\eta)\delta\bar{k}^2\bar{N}\bar{V}_I\bar{T}\right)\left[B_2(a+d_L)+(c+\delta)\left(B_1^2+B_2\right)+B_1\left(c^2+\delta^2\right)\right. \\
&\quad \left.+c\delta\left(2B_1-\frac{(1-\eta)(a+d_L)}{a+(1-\eta)d_L}\bar{k}\bar{V}_I\right)\right] \\
&> \left(B_1B_2+(1-\eta)\delta\bar{k}^2\bar{N}\bar{V}_I\bar{T}\right)\left[B_2(a+d_L)+(c+\delta)\left(B_1^2+B_2\right)+B_1\left(c^2+\delta^2\right)\right. \\
&\quad \left.+c\delta(2B_1-\bar{k}\bar{V}_I)\right], \\
D_3 &= \left[B_1(c+\delta)^2-c\delta\bar{k}\bar{V}_I\right](a+d_L)^2(a+d_L+c+\delta+B_1)+B_1^2(c+\delta)^2(a+d_L)^2, \\
D_4 &= B_1(c+\delta)(a+d_L)\left[\left(B_1^2+B_2\right)(a+d_L+c+\delta)+B_1(a+d_L)^2\right. \\
&\quad \left.+B_1(c+\delta)^2-\frac{(1-\eta)(a+d_L)}{a+(1-\eta)d_L}c\delta\bar{k}\bar{V}_I\right] \\
&> B_1(c+\delta)(a+d_L)\left\{\left(B_1^2+B_2\right)(a+d_L+c+\delta)+B_1(a+d_L)^2\right. \\
&\quad \left.+\left[B_1(c+\delta)^2-c\delta\bar{k}\bar{V}_I\right]\right\}.
\end{aligned}
$$

With the condition $d_T - r + \frac{2r\bar{T}}{T_{\max}} > 0$, we have $B_1 > \bar{k}\bar{V}_I$, then

$$
\begin{aligned}
&B_1(c+\delta)^2 - c\delta\bar{k}\bar{V}_I = B_1\left(c^2+\delta^2\right)+c\delta(2B_1-\bar{k}\bar{V}_I) > 0, \\
&D_1 > 0, \qquad D_2 > 0, \qquad D_3 > 0, \qquad D_4 > 0.
\end{aligned}
$$

Thus,

$$
H_2 > 0 \quad \text{and} \quad H_3 > 0.
$$

It is clear to see that

$$
H_4 = b_4H_3 > 0.
$$

The Routh-Hurwitz criterion is satisfied, thus we see that equation (9) has negative real roots. Therefore, the infected equilibrium $\bar{E}$ is locally asymptotically stable with the condition $d_T - r + \frac{2r\bar{T}}{T_{\max}} > 0$. □

4 Sensitivity analysis

In Section 3, we have discussed the dynamics for system (2) at the uninfected and infected equilibria, respectively. It has been proved that the conditions $H_2 > 0$ and $H_3 > 0$ (they are more easily to satisfy than the condition $d_T - r + \frac{2r\bar{T}}{T_{\max}} > 0$ numerically) are sufficient to guarantee the local asymptotic stability of the infected equilibrium $\bar{E}$ if $\mathcal{R}_0 > 1$. From Table 1, we observe that some parameters have large variations in our model, which may affect the outcomes greatly. Therefore, it is necessary to do an uncertainty analysis and a sensitivity analysis, so that the key parameters which can impact the stability of the infected equilibrium can be discovered.

To examine the uncertainty analysis of the local stability of the infected equilibrium, we use the latin hypercube sampling (LHS) method to sample parameter ranges [26–28]. We choose the sample size $n = 1{,}000$, and we treat each input variable ($\lambda, d_T, r, k, \eta, d_L, a, \delta, N, c$, n_{rt}, and n_p) as a uniform distribution and treat each set of value of H_2, H_3, and $\mathcal{R}_0 - 1$ as the output variables. All the parameter ranges can be found in Table 1 in detail. A thousand data sets are generated from the 12 input variables distributions and 1,000 output data sets of the three output variables are obtained. Repeating the above procedure ten times, we investigate that there are a minimum of 855 and a maximum of 881 in 1,000 values satisfying $\mathcal{R}_0 > 1$ for determining the existence of the infected equilibrium, and we also observe that there are a minimum of 855 and a maximum of 881 in 1,000 values satisfying $H_2 > 0, H_3 > 0$, and $\mathcal{R}_0 > 1$ for identifying the local stability of the infected equilibrium. Therefore, we conclude that the probability of the local stability for the infected equilibrium is between 0.855 and 0.881, and thus the local stability for the infected equilibrium is likely to occur. This phenomenon is consistent with the actual situation. Moreover, we observe that the sufficient conditions $H_2 > 0$ and $H_3 > 0$ are always satisfied when the basic reproduction number $\mathcal{R}_0 > 1$. That is to say, there is no stability changes at the infected equilibrium if $\mathcal{R}_0 > 1$, numerically.

To detect the key parameters to impact the local stability of the infected equilibrium, we compute the partial rank correlation coefficients (PRCCs) between each input parameter and three corresponding outputs. Figure 1 shows the PRCCs results for each input parameters. The sign of the PRCCs indicates that the input parameter has a positive or negative

Table 1 List of parameters

Paras	Definition	Unit	Data1	Data2	Data3	Range	Source
λ	T-cells source term	μl^{-1} day^{-1}	10	10	10	1-10	[4, 11, 12, 20]
d_T	Death rate of healthy T-cells	day^{-1}	0.03	0.01	0.01	0.01-0.1	[4, 11, 12, 20]
r	Growth rate of T-cells	day^{-1}	0.1	0.03	0.1	0.03-0.1	[20]
$T_{\max}$	Carrying capacity of T-cells	μl^{-1}	1,500	1,500	1,500	1,500	[20]
k	Infection rate	μl day^{-1}	10^{-4}	10^{-4}	10^{-4}	10^{-5}-10^{-2}	[4, 11, 12, 16, 20]
η	Fraction of infections that result in latency		0.02	0.001	0.5	0.001-0.5	[4, 11, 12]
d_L	Death rate of latently infected T-cells	day^{-1}	0.001	0.004	0.2	0.001-0.2	[4, 11, 12]
a	Transition rate	day^{-1}	0.1	0.01	0.3	0.01-0.3	[4, 11, 12]
δ	Death rate of infected T-cells	day^{-1}	1	1	0.8	0.5-1.4	[4, 11, 12, 20]
N	Burst term	virions/cell	1,000	200	500	200-3,000	[4, 11, 12, 16, 20]
c	Clearance rate of virus	day^{-1}	20	3	15	3-36	[4, 11, 12, 20]
n_{rt}	RTI efficacy		0.4, 0.5, 0.7	0.4	0.3	0-1	-
n_p	PI efficacy		0.5, 0.6, 0.8	0.5	0.4	0-1	-

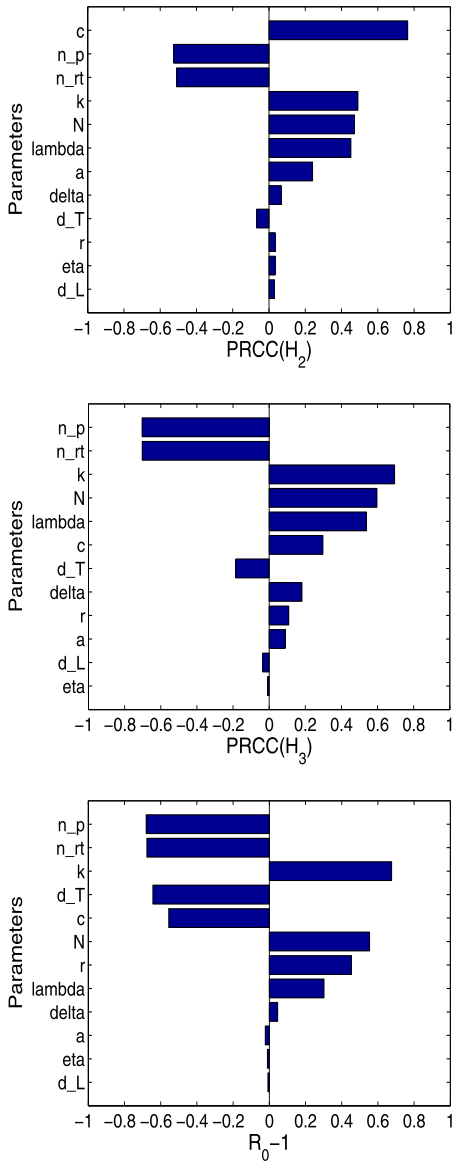

Figure 1 The PRCCs between input parameters and three outputs (H_2, H_3 and $\mathcal{R}_0 - 1$). The parameters k and N have a positive effect on the three outputs, while n_p and n_{rt} have a negative effect.

effect on the corresponding output. From Figure 1, we observe that parameters k, N, and λ have a positive effect on the size of H_2 and H_3 ($|\text{PRCC}| > 0.5$), while the parameters n_p and n_{rt} have a negative effect, and we also find that the parameters k, N, and r have a positive effect on the size of $\mathcal{R}_0 - 1$, while the parameters n_p, n_{rt}, d_T, and c have a negative effect. As we have seen, the local asymptotic stability of the infected equilibrium depends on the sign of these three outputs ($H_2 > 0, H_3 > 0$, and $\mathcal{R}_0 - 1 > 0$) from Section 3, Figure 1 further indicates that the parameters k and N have a positive effect on the three outputs, while n_p and n_{rt} have a negative effect.

5 Numerical simulations

In this section, we carry out numerical simulations to explore the cell and viral dynamics of system (2). Using Data1 values in Table 1 and computing, $\mathcal{R}_0 = 1.7657 > 1$ with $n_{rt} = 0.4, n_p = 0.5$ (combination drug efficacy $\epsilon = 0.70$), $\mathcal{R}_0 = 1.1772 > 1$ with

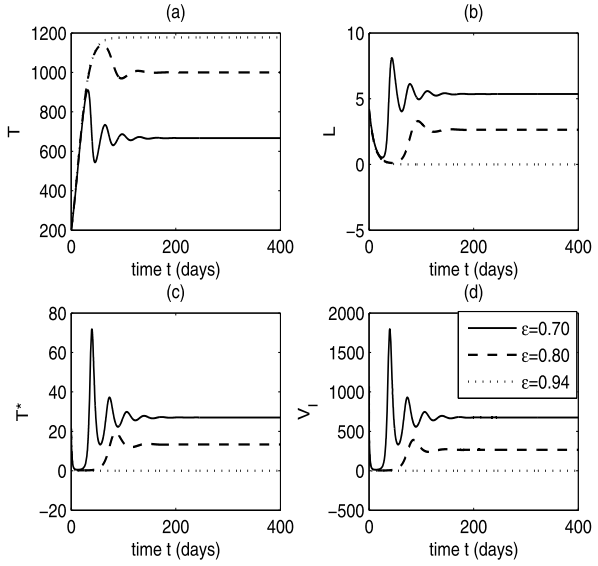

Figure 2 With the increase of the combination drug therapy ϵ, the number of the healthy CD4$^+$ T-cells becomes larger (a), while the number of the latently infected CD4$^+$ T-cells, productively infected CD4$^+$ T-cells and infectious virions (b), (c), (d) become smaller. The virus can be eliminated when $\epsilon = 0.94$. For the parameters see the Data1 values of Table 1.

$n_{rt} = 0.5, n_p = 0.6$ ($\epsilon = 0.80$), and $\mathcal{R}_0 = 0.3531 < 1$ with $n_{rt} = 0.7, n_p = 0.8$ ($\epsilon = 0.94$), respectively. To show how antiretroviral therapy impacts the T-cell count and viral load, we choose the infected equilibrium without drug therapy $(T(0), L(0), T^*(0), V_I(0)) = (200.0396, 4.2248, 21.3308, 1{,}066.5412)$ as the initial value. Figure 2 shows that the infected equilibrium is locally asymptotically stable when the combination drug efficacy $\epsilon = 0.70$ and $\epsilon = 0.80$, while the infected equilibrium does not exist and the uninfected equilibrium is globally asymptotically stable when the combination drug efficacy $\epsilon = 0.94$. With the increase of combination drug efficacy, the number of healthy CD4$^+$ T-cells becomes larger, while the number of latently infected CD4$^+$ T-cells, productively infected CD4$^+$ T-cells and infectious virions become smaller. Also, the influence of drug therapy on T-cell count and viral load changes dramatically. Figure 2 also demonstrates that the stability of the equilibrium changes as combination drug efficacy increases.

In order to examine the effect of the logistic term $rT(1 - \frac{T}{T_{\max}})$ in system (2), we choose the infected equilibrium without drug therapy when $r = 0$ (that is, the model in [10, 11]) $(T(0), L(0), T^*(0), V_I(0)) = (150.0429, 0.6071, 8.4971, 566.4762)$ as the initial value, and we use Data2 values in Table 1. We observe that the logistic term can cause transient oscillations at the beginning of the viral progression, and it has no effect on the stability of the infected equilibrium (see Figure 3). Figure 3 also demonstrates that the model without logistic term would underestimate the number of the latently infected CD4$^+$ T-cells, productively infected CD4$^+$ T-cells, and infectious virions, while it does not change the number of healthy CD4$^+$ T-cells obviously.

Researchers have done a lot of work about HIV model, and most of them did not consider latent infection. Here, we consider the model without latent infection which has been

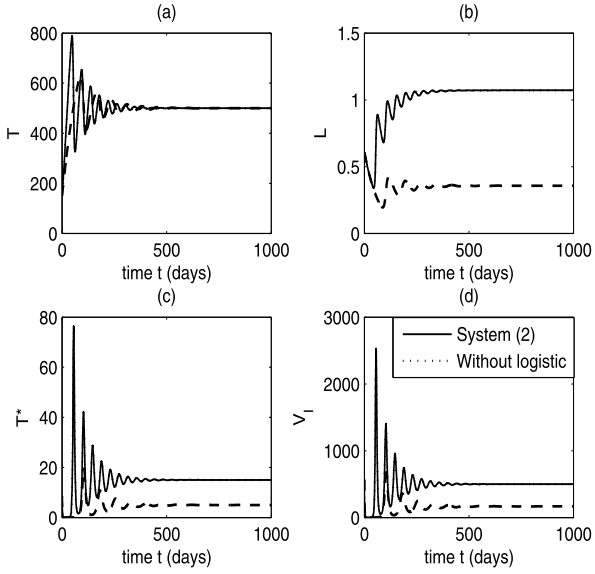

Figure 3 When $\mathcal{R}_0 > 1$, compared system (2) to the model without logistic term, the logistic term can cause transient oscillations to all populations at the beginning, and finally the model without logistic term may underestimate the number of the latently infected CD4$^+$ T-cells, productively infected CD4$^+$ T-cells, and infectious virions (b), (c), (d), while there is no too much difference with the number of healthy CD4$^+$ T-cells (a). For the parameters see the Data2 values of Table 1.

studied in [15–19]:

$$\begin{aligned}
&\frac{d}{dt}T(t) = \lambda - d_T T + rT\left(1 - \frac{T}{T_{\max}}\right) - (1 - n_{rt})kV_I T,\\
&\frac{d}{dt}T^*(t) = (1 - n_{rt})kV_I T - \delta T^*,\\
&\frac{d}{dt}V_I(t) = (1 - n_p)N\delta T^* - cV_I.
\end{aligned} \tag{10}$$

It is a special case of system (2) with $\eta = d_L = a = 0$. In order to observe the effect of latent infection of system (2), we choose the infected equilibrium of system (10) without drug therapy $((T(0), T^*(0), V_I(0)) = (300, 38.7500, 1{,}033.3333)$ with tiny latently infected T-cells 10^{-3}) as the initial value, and use Data3 values in Table 1. The dynamics of system (2) and system (10) is shown in Figure 4, which indicates that system (10) would underestimate the total number of CD4$^+$ T-cells and overestimate the number of infectious virions.

6 Conclusions

We have studied an HIV model including latent infection, antiretroviral therapy and a logistic growth for healthy CD4$^+$ T-cells. If the basic reproduction number is less than one, we obtained the global asymptotic stability of the uninfected equilibrium. If the basic reproduction number is greater than one, we proved local asymptotic stability of the infected equilibrium. Through latin hypercube sampling method, we investigate that, as long as the infected equilibrium exists, it should be locally asymptotically stable ultimately. Furthermore, we derive that the infection rate k and the burst size N have a positive ef-

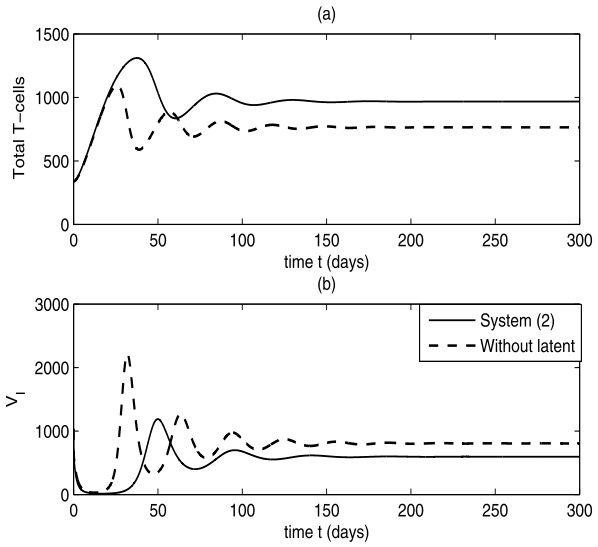

Figure 4 When $\mathcal{R}_0 > 1$, compared to system (2), system (10) may underestimate the total number of T-cells (a), and overestimate the number of infectious virions (b). For the parameters see the Data3 values of Table 1.

fect on the stability of the infected equilibrium, while the drug efficacy n_p and n_{rt} have a negative effect.

Comparing our model behaviors with those established in Perelson *et al.* [10] and Rong and Perelson [11] without logistic growth, we found that their models would underestimate the number of the latently infected $CD4^+$ T-cells, productively infected $CD4^+$ T-cells and infectious virions. Also, comparing our model with [15–19], which do not include latently infected T-cells, we observed that those models would underestimate the total number of T-cells, and overestimate the number of infectious virions. Our conclusion can be regarded as an extension of the work of Perelson *et al.* [10] and Rong and Perelson [11] when $r = 0$.

In fact, cytotoxic T lymphocyte (CTL) is closely related to the suppression of viral replication and disease progression, and it plays a major part in the control of viral infection [29]. A mathematical model including latent infection and the influence of CTLs will be our future research work.

Competing interests
The authors declare to have no competing interests.

Authors' contributions
YW and LL constructed the model, carried out the analysis, and contributed to writing the manuscript. JL performed the numerical simulations.

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