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ORIGINAL RESEARCH

Mathematical analysis of a delayed HIV infection model with saturated CTL immune response and immune impairment

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Abstract

In this paper, we develop an HIV infection model with intracellular delay, Beddington–DeAngelis incidence rate, saturated CTL immune response and immune impairment. We begin model analysis with proving the positivity and boundedness of solutions of the model. By calculations, we derive immunity-inactivated and immunity-activated reproduction ratios. By analyzing corresponding characteristic equations, the local stabilities of feasible equilibria are addressed. With the help of suitable Lyapunov functionals and LaSalle's invariance principle, it is proven that the global dynamics of the system is completely determined by the immunity-inactivated and immunity-activated reproduction ratios: if the immunity-inactivated reproduction ratio is less than unity, the infection-free equilibrium is globally asymptotically stable; if the immunity-inactivated reproduction ratio is greater than unity, while the immunity-activated reproduction ratio is less than unity, the immunity-inactivated equilibrium is globally asymptotically stable; if the immunity-activated reproduction ratio is greater than unity, the immunity-activated equilibrium is globally asymptotically stable. Furthermore, sensitivity analysis is carried out to illustrate the effects of parameter values on the two thresholds.

Keywords HIV infection · Intracellular delay · Saturated CTL immune response · Immune impairment · Basic reproduction ratios

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1 Introduction

Virus dynamics has attracted worldwide attention in the academic field [1–3]. During the past decades, a large number of mathematical models have been employed to quantitatively or qualitatively analyze the transmission and treatment of HIV [2–5]. Nowak and Bangham [1] proposed the following model to describe virus dynamics:

$$\begin{aligned} \dot{x}(t) &= s - dx(t) - \beta x(t) v(t), \\ \dot{y}(t) &= \beta x(t) v(t) - ay(t), \\ \dot{v}(t) &= ky(t) - uv(t). \end{aligned} \tag{1.1}$$

Here $x(t)$, $y(t)$, $v(t)$ represent the concentrations of uninfected CD4$^+$T cells, infected CD4$^+$T cells and free virus particles at time t, respectively. The constant s represents the rate at which uninfected CD4$^+$T cells are produced. Free viruses infect the uninfected cells at rate βxv. Uninfected cells, infected cells and virus particles die at rate dx, ay and uv, respectively. Infected cells produce free virus at rate ky. However, the immune system is necessary to control the disease. In most virus infections, cytotoxic T lymphocytes (CTLs) could reduce viral load by attacking infected cells, which plays a vital role in protecting infected individuals against virus-related diseases. As a consequence, much attention has been paid to the dynamics of HIV-1 infection with CTLs response (see, for example, [1,6–9]). In addition, we notice that system (1.1) assumes the rate of infection to be bilinear. Nevertheless, during the process of virus infecting target cells, the actual incidence rate is probably not linear. Hence, it is more reasonable to consider the nonlinear infection rate, such as Beddington–DeAngelis type incidence (see, for example, [4,10–12]). Based on system (1.1), to consider the joint effects of CTL immune response and Beddington–DeAngelis type incidence on the HIV infection, Wang et al. [11] investigated the following system:

$$\begin{aligned} \dot{x}(t) &= s - dx(t) - \frac{\beta x(t) v(t)}{1 + a_1 x(t) + a_2 v(t)}, \\ \dot{y}(t) &= \frac{\beta x(t) v(t)}{1 + a_1 x(t) + a_2 v(t)} - ay(t) - py(t) z(t), \\ \dot{v}(t) &= ky(t) - uv(t), \\ \dot{z}(t) &= cy(t) z(t) - bz(t), \end{aligned} \tag{1.2}$$

where the state variable $z(t)$ represents the concentration of CTL cells at time t. The rate for infected cells to be killed by CTLs is chosen as pyz. CTL cells are activated by infected CD4$^+$T cells at rate cyz and die at rate bz. The infection rate is denoted by Beddington–DeAngelis function $\beta xv/(1 + a_1 x + a_2 v)$, which was proposed by Beddington [13] and DeAngelis et al. [14]. The Beddington–DeAngelis incidence rate reduces to a saturation response [15,16] when $a_1 = 0$, $a_2 > 0$. It is supposed in systems (1.1) and (1.2) that as long as free viruses enter the target cells, target cells are immediately infected and new free viruses are produced simultaneously. Herz et al. [17] introduced the intracellular phase of the life-cycle into the virus dynamics model first. There is a fixed time delay τ between infection of a cell and production of new free

viruses. Scholars have incorporated time delay into HIV infection models and analyzed the effect of the intracellular delay on HIV infection dynamics (see, for instance, [5,12,16,17]). Usually, the rate of CTL cells production stops increasing and reaches a saturation state when the concentration of infected cells reaches some level. Thus, De Boer [18] stated that the bilinear rate cannot model several immune responses that are together controlling a chronic infection and proposed an immune response function based on a competitive saturation term. While Wang and Li [19] chose $z/(1+\varepsilon z)$ as the CTL response function, where ε is a positive constant. Moreover, it is often supposed that the presence of antigen could only simulate the immune response and ignore the immune impairment. As a matter of fact, immune responses could be suppressed by several human pathogens. Thereby, Iwami et al. [20] reported that HIV could cause the impairment in CTL cells during the HIV infection. Further researches have been carried out on HIV infection with immune impairment [20–23], which helped us to better understand the biological interactions between virus and immune system. In [22], Wang et al. discussed a viral infection model with immune impairment denoted by the term nyz.

Inspired by the above works, in this paper, we consider the joint effects of intracellular delay, Beddington–DeAngelis incidence rate, saturated CTL immune response and immune impairment on the dynamics of HIV infection. For this purpose, we study the following delay differential equations:

$$\begin{aligned}
\dot{x}(t) &= s - dx(t) - \frac{\beta x(t) v(t)}{1 + a_1 x(t) + a_2 v(t)}, \\
\dot{y}(t) &= \frac{\mathrm{e}^{-m\tau} \beta x(t-\tau) v(t-\tau)}{1 + a_1 x(t-\tau) + a_2 v(t-\tau)} - ay(t) - py(t) z(t), \\
\dot{v}(t) &= ky(t) - uv(t), \\
\dot{z}(t) &= \frac{cy(t) z(t)}{1 + \varepsilon z(t)} - bz(t) - ny(t) z(t),
\end{aligned} \tag{1.3}$$

where the parameters have the same meanings as in systems (1.1) and (1.2). The parameter τ is the lag between viral entry into the target cells and the production of new virus particles. Assume that the generation of virus producing cells at time t is related to the infection of target cells at time $t-\tau$. The term $e^{-m\tau}$ represents the surviving rate of infected cells before it becomes productively infected. The term $cyz/(1+\varepsilon z)$ denotes the rate of saturated CTL immune response activated by infected cells. nyz is assumed to be the immune impairment rate. It is supposed that $c > n$. All parameters of system (1.3) are positive.

Let $\mathbb{C} = \mathbb{C}\left([-\tau, 0], \mathbb{R}_+^4\right)$ be the Banach space of continuous mapping the interval $[-\tau, 0]$ into $\mathbb{R}_+^4$ with the sup-norm, where $\mathbb{R}_+^4 = \{(x, y, v, z) : x \geq 0, y \geq 0, v \geq 0, z \geq 0\}$. It is biologically reasonable to assume the initial condition of system (1.3) having the following form:

$$\begin{aligned}
&x(\theta) = \varphi_1(\theta), y(\theta) = \varphi_2(\theta), v(\theta) = \varphi_3(\theta), z(\theta) = \varphi_4(\theta); \\
&\varphi_i(\theta) \geq 0, \theta \in [-\tau, 0], \varphi_i(0) > 0 \, (i = 1, 2, 3, 4).
\end{aligned} \tag{1.4}$$

In the light of the fundamental theory of functional differential equations [24], system (1.3) has a unique solution $(x(t), y(t), v(t), z(t))$ satisfying the initial condition (1.4).

The organization of the paper is as follows. In the next section, the positivity and boundedness of solutions of system (1.3) with the initial condition (1.4) are proved. In Sect. 3, we derive two reproduction ratios of system (1.3) and investigate the existence of the feasible equilibria. In Sect. 4, the local asymptotic stabilities of feasible equilibria are discussed by analyzing the corresponding characteristic equations. In Sect. 5, the global asymptotic stabilities of feasible equilibria are studied by constructing proper Lyapunov functionals and using LaSalle's invariance principle. In Sect. 6, we perform a sensitivity analysis to show the effects of parameter values on the immunity-inactivated and the immunity-activated reproduction ratios. Finally, we make a conclusion on our work.

2 Preliminaries

In this section, we verify that system (1.3) with the initial condition (1.4) is well-posed.

Theorem 1 *All solutions of system* (1.3) *with the initial condition* (1.4) *are positive for all* $t \geq 0$.

Proof We prove that $x(t) > 0$ for all $t \geq 0$ first. Assume the contrary and let $t_1 > 0$ be some time such that $x(t_1) = 0$, and $x(t) > 0$, if $t \in [0, t_1)$, we have

$$\dot{x}(t) \geq -dx(t) - \frac{\beta x(t) v(t)}{1 + a_1 x(t) + a_2 v(t)}.$$

It then follows that

$$x(t_1) \geq x(0) \exp\left[\int_0^{t_1} \left(-d - \frac{\beta v(t)}{1 + a_1 x(t) + a_2 v(t)}\right) dt\right] > 0.$$

It is a contradiction with $x(t_1) = 0$. Hence, we obtain that $x(t) > 0$.
As for the second equation of system (1.3), for $t \in [0, \tau]$, namely, $t - \tau \in [-\tau, 0]$, according to the initial condition (1.4), we have

$$\begin{aligned}\dot{y}(t) &= \frac{\beta e^{-m\tau} x(t-\tau) v(t-\tau)}{1 + a_1 x(t-\tau) + a_2 v(t-\tau)} - ay(t) - py(t) z(t) \\ &\geq -ay(t) - py(t) z(t).\end{aligned}$$

It yields that $y(t) \geq y(0) e^{-\int_0^t (a + pz(\theta)) d\theta} > 0$, for all $t \in [0, \tau]$. By the method of induction, we make a recursive argument on $[\tau, 2\tau]$, $[2\tau, 3\tau], \cdots$, and then obtain that $y(t) > 0$ for all $t \geq 0$. As for the third and fourth equations of system (1.3), by calculations, we have that

$$v(t) = v(0) e^{-ut} + \int_0^t my(\theta) e^{-u(t-\theta)} d\theta,$$

$$z(t) = z(0)\, e^{\int_0^t \left(\frac{cy(\theta)}{1+\varepsilon z(\theta)} - b - ny(\theta)\right) d\theta}.$$

It is apparent that $v(t) > 0$ and $z(t) > 0$ for all $t \geq 0$. This completes the proof. □

Theorem 2 *All solutions of system* (1.3) *satisfying the initial condition* (1.4) *are ultimately bounded for all* $t \geq 0$.

Proof Let $(x(t), y(t), v(t), z(t))$ be any positive solution of system (1.3) with the initial condition (1.4). Define

$$G(t) = x(t) + \mathrm{e}^{m\tau} y(t+\tau).$$

Differentiating $G(t)$ along positive solutions of system (1.3) with the initial condition (1.4), we have

$$\begin{aligned} \dot{G}(t) &\leq s - dx(t) - \mathrm{e}^{m\tau} a y(t+\tau) \\ &\leq s - \sigma G(t), \end{aligned}$$

yielding that $\limsup_{t\to\infty} G(t) \leq s/\sigma$, where $\sigma = \min\{a, d\}$. Thereby, for $\delta > 0$ sufficiently small, there is a $T > 0$ such that if $t > T$, we have

$$G(t) \leq \frac{s}{\sigma} + \delta.$$

Further, we derive from the third and fourth equations of system (1.3) that for $t > T$,

$$\begin{aligned} \dot{v}(t) &\leq k e^{-m\tau} \left(\frac{s}{\sigma} + \delta\right) - uv(t), \\ \dot{z}(t) &\leq e^{-m\tau} \frac{c}{\varepsilon} \left(\frac{s}{\sigma} + \delta\right) - bz(t). \end{aligned}$$

Since $\delta > 0$ is arbitrarily sufficiently small, we conclude that

$$\limsup_{t\to\infty} v(t) \leq \frac{ks}{\sigma u} e^{-m\tau}, \quad \limsup_{t\to\infty} z(t) \leq \frac{cs}{\varepsilon\sigma b} e^{-m\tau}.$$

Hence, $x(t)$, $y(t)$, $v(t)$, $z(t)$ are ultimately bounded for all $t \geq 0$, and the following set

$$\Omega = \left\{(x, y, v, z) : x \leq \frac{s}{\sigma}, y \leq \frac{s}{\sigma} e^{-m\tau}, v \leq \frac{ks}{\sigma u} e^{-m\tau}, z \leq \frac{cs}{b\varepsilon\sigma} e^{-m\tau}\right\}$$

is positively invariant for system (1.3). □

3 Feasible equilibria and reproduction ratios

It is easy to see that system (1.3) always has an infection-free equilibrium $E_0(s/d, 0, 0, 0)$.

We now calculate the immunity-inactivated reproduction ratio of system (1.3). Using the method of next generation matrix proposed by van den Driessche and Watmough [25], we obtain

$$\mathscr{F} = \begin{pmatrix} \frac{e^{-m\tau}\beta x(t-\tau)v(t-\tau)}{1+a_1x(t-\tau)+a_2v(t-\tau)} \\ 0 \end{pmatrix}, \mathscr{V} = \begin{pmatrix} ay(t) + py(t)z(t) \\ -ky(t) + uv(t) \end{pmatrix}.$$

Then, we have

$$F = \begin{pmatrix} 0 & \frac{e^{-m\tau}\beta s}{a_1 s+d} \\ 0 & 0 \end{pmatrix}, \ V = \begin{pmatrix} a & 0 \\ -k & u \end{pmatrix}.$$

So the next generation matrix is given as follows:

$$FV^{-1} = \begin{pmatrix} \frac{k\beta s e^{-m\tau}}{au(a_1 s+d)} & \frac{\beta s e^{-m\tau}}{u(a_1 s+d)} \\ 0 & 0 \end{pmatrix}.$$

Thus, the immunity-inactivated reproduction ratio has the following form:

$$\mathfrak{R}_0 = \rho(FV^{-1}) = \frac{k\beta s e^{-m\tau}}{au(a_1 s + d)}.$$

$\mathfrak{R}_0$ represents the expected number of secondary infectious produced by an infective cell in a totally susceptible population. It is easy to prove that if $\mathfrak{R}_0 > 1$, system (1.3) has a unique immunity-inactivated equilibrium $E_1\,(x_1, y_1, v_1, 0)$, where

$$x_1 = \frac{s - ae^{m\tau}y_1}{d}, v_1 = \frac{ky_1}{u}, y_1 = \frac{u\,(a_1 s + d)\,(\mathfrak{R}_0 - 1)}{k\beta - aa_1 ue^{m\tau} + ka_2 d}.$$

Denote

$$\mathfrak{R}_1 = \frac{(c-n)\,y_1}{b} = \frac{(c-n)\,u\,(a_1 s + d)\,(\mathfrak{R}_0 - 1)}{b\,(k\beta - aa_1 ue^{m\tau} + ka_2 d)},$$

where $\mathfrak{R}_1$ is called immunity-activated reproduction ratio of system (1.3). In the following, we show that if $\mathfrak{R}_1 > 1$, besides E_0 and E_1, system (1.3) has an immunity-activated equilibrium $E_2\,(x_2, y_2, v_2, z_2)$ satisfying the following system:

$$s - dx - \frac{\beta xv}{1 + a_1 x + a_2 v} = 0,$$
$$\frac{\beta e^{-m\tau} xv}{1 + a_1 x + a_2 v} - ay - pyz = 0,$$

$$\begin{aligned} ky - uv &= 0, \\ \frac{cyz}{1+\varepsilon z} - bz - nyz &= 0. \end{aligned} \tag{3.1}$$

Denote

$$f_1(y) \triangleq z = \frac{1}{\varepsilon}\left(\frac{cy}{b+ny} - 1\right), \tag{3.2}$$

$$f_2(z) \triangleq y = \frac{k\beta s e^{-m\tau} - u(a+pz)(a_1 s + d)}{[k\beta - a_1 u e^{m\tau}(a+pz) + ka_2 d](a+pz)}. \tag{3.3}$$

As is shown in Eq. (3.2), z is an increasing function of the variable y. By calculations, we obtain that $z = 0$ when $y = b/(c-n)$, and $z = -1/\varepsilon$ when $y = 0$. Moreover, $cy/(b+ny) \to c/n$ as $y \to \infty$. Hence, the graph of function $f_1(y)$ has an asymptote $f_1 = z = (c-n)/(\varepsilon n)$.

In Eq. (3.3), we know that y is a decreasing function of the variable z. It is easy to get that $y = y_1$ when $z = 0$, and $y = 0$ when $z = a(\Re_0 - 1)/p$. When $\Re_1 > 1$, we have $y_1 > b/(c-n)$. Besides, by calculations, we get that $f_2(z) \to 0$ as $z \to \infty$. So the graph of function $f_2(z)$ has an asymptote $f_2 = y = 0$. Then, the curves of two functions defined in (3.2) and (3.3) have only one intersection (z_2, y_2) when $z \in (0, (c-n)/\varepsilon n)$ (see Figure 1).

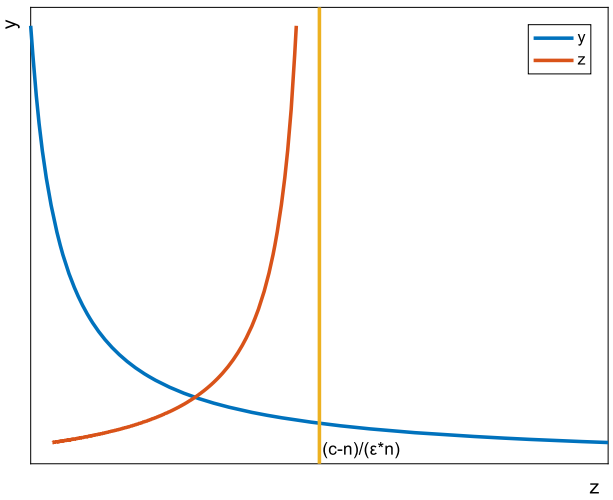

Fig. 1 The curves of functions y and z

Thus, $y_2 > 0, z_2 > 0, v_2 = ky_2/u > 0$. In addition, deriving from the first equation of system (3.1) at E_2, we have

$$(s - dx)(1 + a_1x + a_2v_2) - \beta x v_2 = 0. \tag{3.4}$$

For the fixed v_2, solving (3.4) yields that

$$x_2 = \frac{-[d(1 + a_2v_2) + \beta v_2 - a_1 s] + \sqrt{\Delta}}{2a_1 d},$$

where $\Delta = [d(1 + a_2v_2) + \beta v_2 - a_1 s]^2 + 4a_1 ds(1 + a_2v_2)$. Noting that

$$\begin{aligned}\sqrt{\Delta} - [d(1 + a_2v_2) + \beta v_2 - a_1 s] &\geq \sqrt{\Delta} - |d(1 + a_2v_2) + \beta v_2 - a_1 s| \\ &= \frac{4a_1 ds(1 + a_2v_2)}{\sqrt{\Delta} + |d(1 + a_2v_2) + \beta v_2 - a_1 s|},\end{aligned}$$

we therefore have $x_2 > 0$.

4 Local asymptotic stability

We are now in a position to study the local dynamics of system (1.3).

Theorem 3 *If $\Re_0 < 1$, the infection-free equilibrium $E_0(s/d, 0, 0, 0)$ of system (1.3) is locally asymptotically stable; if $\Re_0 > 1$, E_0 is unstable.*

Proof By calculation, we have the following characteristic equation of system (1.3) at E_0:

$$(\lambda + d)(\lambda + b)\left[(\lambda + a)(\lambda + u) - e^{-(\lambda+m)\tau}\frac{k\beta s}{a_1 s + d}\right] = 0. \tag{4.1}$$

Obviously, Eq. (4.1) has negative real roots $\lambda_0^* = -d$ and $\lambda_0^{**} = -b$, and other roots depend on the following equation:

$$\left(\frac{\lambda}{a} + 1\right)\left(\frac{\lambda}{u} + 1\right) = \Re_0 e^{-\lambda\tau}. \tag{4.2}$$

We now claim that all roots of Eq. (4.2) have negative real parts. Otherwise, Eq. (4.2) has a root $\lambda_0 = \mathrm{Re}\lambda_0 + \mathrm{i}\mathrm{Im}\lambda_0$ with $\mathrm{Re}\lambda_0 \geq 0$, then it is easy to see that $|\lambda_0/a + 1| \geq 1 > \Re_0$ and $|\lambda_0/u + 1| \geq \left|e^{-\lambda_0\tau}\right|$.
Thus, it follows that

$$\left|\left(\frac{\lambda_0}{a} + 1\right)\left(\frac{\lambda_0}{u} + 1\right)\right| > \left|\Re_0 e^{-\lambda_0\tau}\right|,$$

which contradicts Eq. (4.2). Therefore, all roots of Eq. (4.1) have negative real parts if $\Re_0 < 1$. Accordingly, $E_0(s/d, 0, 0, 0)$ of system (1.3) is locally asymptotically stable.
Define

$$H(\lambda) = (a_1 s + d)(\lambda + a)(\lambda + u) - k\beta s e^{-(\lambda+m)\tau}. \tag{4.3}$$

Apparently, $H(\lambda)$ is a continuous function in terms of λ. And $H(0) = au(a_1 s + d)(1 - \Re_0) < 0$. Moreover, $H(\lambda) \to +\infty$ as $\lambda \to \infty$. Hence, Eq. (4.3) has a positive root λ^* such that $H(\lambda^*) = 0$ if $\Re_0 > 1$. That is to say, E_0 is unstable if $\Re_0 > 1$. □

Theorem 4 *If $\Re_1 < 1 < \Re_0$, the immunity-inactivated equilibrium $E_1(x_1, y_1, v_1, 0)$ of system (1.3) is locally asymptotically stable.*

Proof The corresponding characteristic equation of system (1.3) at E_1 has the following form:

$$[\lambda - (c - n) y_1 + b] g(\lambda) = 0, \tag{4.4}$$

where

$$g(\lambda) = (\lambda + a)(\lambda + u)\left(\lambda + d + \frac{\beta v_1 (1 + a_2 v_1)}{(1 + a_1 x_1 + a_2 v_1)^2}\right) - \frac{k\beta x_1 (1 + a_1 x_1)}{(1 + a_1 x_1 + a_2 v_1)^2}(\lambda + d) e^{-(\lambda+m)\tau}. \tag{4.5}$$

Since $\Re_1 = (c - n) y_1 / b < 1$, Eq. (4.4) always has a negative root $\lambda_1^* = (c - n) y_1 - b$, other roots are determined by

$$g(\lambda) = 0. \tag{4.6}$$

Next, we verify that all roots of Eq. (4.6) have negative real parts. Otherwise, Eq. (4.6) has a root $\lambda_1 = \mathrm{Re}\lambda_1 + \mathrm{iIm}\lambda_1$ with $\mathrm{Re}\lambda_1 \geq 0$. Then it is easy to obtain

$$|(\lambda_1 + a)(\lambda_1 + u)| = \left| \frac{\lambda_1 + d}{\lambda_1 + d + \frac{\beta v_1 (1 + a_2 v_1)}{(1 + a_1 x_1 + a_2 v_1)^2}} \frac{k\beta x_1 (1 + a_1 x_1)}{(1 + a_1 x_1 + a_2 v_1)^2} e^{-(m+\lambda_1)\tau} \right| < \frac{k\beta x_1 e^{-m\tau}}{1 + a_1 x_1 + a_2 v_1} = au.$$

Nevertheless, it is obvious that $|(\lambda_1 + a)(\lambda_1 + u)| \geq au$, which leads to a contradiction. As a result, if $\Re_1 < 1 < \Re_0$, E_1 is locally asymptotically stable. □

Theorem 5 *If $\Re_1 > 1$, the immunity-activated equilibrium $E_2(x_2, y_2, v_2, z_2)$ of system (1.3) is locally asymptotically stable.*

Proof The characteristic equation at E_2 is given as follows:

$$\begin{aligned}&\left[\left(\lambda-\frac{cy_2}{(1+\varepsilon z_2)^2}+b+ny_2\right)(\lambda+a+pz_2)+\frac{(c-n)-\varepsilon nz_2}{1+\varepsilon z_2}py_2z_2\right]\\&\quad\times\left[\lambda+d+\frac{\beta v_2(1+a_2v_2)}{(1+a_1x_2+a_2v_2)^2}\right](\lambda+u)\\&=(\lambda+d)\left[\lambda-\frac{cy_2}{(1+\varepsilon z_2)^2}+b+ny_2\right]\frac{k\beta x_2(1+a_1x_2)}{(1+a_1x_2+a_2v_2)^2}e^{-(\lambda+m)\tau}.\end{aligned}\tag{4.7}$$

We now claim that all roots of Eq. (4.7) have negative real parts. If not, Eq. (4.7) has a root $\lambda_2=\mathrm{Re}\,\lambda_2+\mathrm{iIm}\,\lambda_2$ with $\mathrm{Re}\,\lambda_2\geq 0$, then we get

$$\begin{aligned}&\left|\frac{\lambda_2+d}{\lambda_2+d+\frac{\beta v_2(1+a_2v_2)}{(1+a_1x_2+a_2v_2)^2}}\left(\lambda_2-\frac{cy_2}{(1+\varepsilon z_2)^2}+b+ny_2\right)\frac{k\beta x_2(1+a_1x_2)}{(1+a_1x_2+a_2v_2)^2}e^{-(m+\lambda_2)\tau}\right|\\&<\left|\lambda_2-\frac{cy_2}{(1+\varepsilon z_2)^2}+b+ny_2\right|\frac{k\beta x_2(1+a_1x_2)}{(1+a_1x_2+a_2v_2)^2}e^{-m\tau}.\end{aligned}\tag{4.8}$$

At the same time, it follows from system (3.1) that

$$\frac{\beta x_2v_2}{1+a_1x_2+a_2v_2}e^{-m\tau}=(a+pz_2)y_2,\quad v_2=\frac{ky_2}{u}.\tag{4.9}$$

Substituting Eq. (4.9) into Eq. (4.8), we obtain

$$\begin{aligned}&\left|(\lambda_2+u)\left[\left(\lambda_2-\frac{cy_2}{(1+\varepsilon z_2)^2}+b+ny_2\right)(\lambda_2+a+pz_2)+\frac{(c-n)-\varepsilon z_2}{1+\varepsilon z_2}py_2z_2\right]\right|\\&\quad>\left|\lambda_2-\frac{cy_2}{(1+\varepsilon z_2)^2}+b+ny_2\right|\frac{k\beta x_2(1+a_1x_2)}{(1+a_1x_2+a_2v_2)^2}e^{-m\tau}.\end{aligned}$$

It results in a contradiction. Consequently, if $\Re_1>1$, all roots of Eq. (4.7) have negative real parts. That is, E_2 is locally asymptotically stable. □

5 Global asymptotic stability

In this section, we are ready to study the global asymptotic stability of each feasible equilibrium of system (1.3) with the help of proper Lyapunov functionals and LaSalle's invariance principle.

First, we define a function

$$h(x)=x-1-\ln x.\tag{5.1}$$

It is readily seen that $h(1)=0$ and $h(x)$ attains its minimum at $x=1$.

Theorem 6 *If* $\Re_0 < 1$, *the infection-free equilibrium* $E_0 = (s/d, 0, 0, 0)$ *of system* (1.3) *is globally asymptotically stable.*

Proof Let $(x(t), y(t), v(t), z(t))$ be any positive solution of system (1.3) with the initial condition (1.4). Define

$$V_0(t) = \frac{1}{1+a_1x_0}\left(x(t) - x_0 - x_0 \ln \frac{x(t)}{x_0}\right) + e^{m\tau} y(t) + \frac{a}{k} e^{m\tau} v(t) + \frac{p}{c} e^{m\tau} z(t) + \int_{t-\tau}^{t} \frac{\beta x(\theta) v(\theta)}{1 + a_1 x(\theta) + a_2 v(\theta)} d\theta, \tag{5.2}$$

where $x_0 = s/d$. Calculating the derivative of $V_0(t)$ along positive solutions of system (1.3), we have

$$\dot{V}_0(t) = -\frac{d(x(t) - x_0)^2}{x(t)(1 + a_1x_0)} - e^{m\tau}(1 - \Re_0)\frac{au}{k}\frac{v(t)(1 + a_1x(t))}{1 + a_1x(t) + a_2v(t)} - e^{m\tau}\frac{aa_2u}{k}\frac{v^2(t)}{1 + a_1x(t) + a_2v(t)} - \frac{bp}{c}e^{m\tau} z(t) - \varepsilon p e^{m\tau}\frac{y(t) z^2(t)}{1 + \varepsilon z(t)} - \frac{np}{c} e^{m\tau} y(t) z(t). \tag{5.3}$$

Since $\Re_0 < 1$, we have $\dot{V}_0(t) \le 0$ and $\dot{V}_0(t) = 0$ if and only if $x = x_0$, $y = v = z = 0$. Obviously, the largest invariant subset of $\left\{(x(t), y(t), v(t), z(t)) : \dot{V}_0(t) = 0\right\}$ is $S_0 = \{E_0\} \subset \Omega$. Furthermore, based on Theorem 3, E_0 is locally asymptotically stable if $\Re_0 < 1$. Hence, it follows from LaSalle's invariance principle [24] that E_0 is globally asymptotically stable. □

Theorem 7 *If* $\Re_1 < 1 < \Re_0$, *the immunity-inactivated equilibrium* $E_1(x_1, y_1, v_1, 0)$ *of system* (1.3) *is globally asymptotically stable.*

Proof Let $(x(t), y(t), v(t), z(t))$ be any positive solution of system (1.3) with the initial condition (1.4). Define

$$V_1(t) = e^{m\tau}\left(x(t) - x_1 - \int_{x_1}^{x(t)} \frac{(1 + a_1\theta + a_2v_1)x_1}{(1 + a_1x_1 + a_2v_1)\theta} d\theta\right) + y_1 h\left(\frac{y(t)}{y_1}\right) + \frac{av_1}{k} h\left(\frac{v(t)}{v_1}\right) + \frac{py_1}{b} z(t) + ay_1 \int_{t-\tau}^{t} h\left(e^{-m\tau}\frac{\beta x(\theta) v(\theta)}{ay_1(1 + a_1x(\theta) + a_2v(\theta))}\right) d\theta, \tag{5.4}$$

where the function h is defined in (5.1).
Calculating the derivative of $V_1(t)$ along positive solutions of system (1.3), we have

$$\dot{V}_1(t) = -e^{-m\tau}\frac{d(1 + a_2v_1)(x(t) - x_1)^2}{x(t)(1 + a_1x_1 + a_2v_1)} - ay_1 h\left(\frac{(1 + a_1x(t) + a_2v_1)x_1}{(1 + a_1x_1 + a_2v_1)x(t)}\right)$$

$$
\begin{aligned}
&- a y_1 h\left(\frac{\left(1+a_1 x_1+a_2 v_1\right) x(t-\tau) v(t-\tau) y_1}{\left(1+a_1 x(t-\tau)+a_2 v(t-\tau)\right) x_1 v_1 y(t)}\right)-a y_1 h\left(\frac{v_1 y(t)}{v(t) y_1}\right) \\
&- a y_1 h\left(\frac{1+a_1 x(t)+a_2 v(t)}{1+a_1 x(t)+a_2 v_1}\right)+\frac{p y(t) z(t)}{1+\varepsilon z(t)}\left(\Re_1-1\right) \\
&- \frac{p \varepsilon(b+n y_1) y(t) z^2(t)}{b(1+\varepsilon z(t))}-\frac{a a_2 y_1\left(1+a_1 x(t)\right)\left(v(t)-v_1\right)^2}{v_1\left(1+a_1 x(t)+a_2 v(t)\right)\left(1+a_1 x(t)+a_2 v_1\right)}. \qquad (5.5)
\end{aligned}
$$

Due to $\Re_1 < 1$, it is apparent to know $\dot{V}_1(t) \leq 0$ with equality if and only if $x = x_1$, $y = y_1$, $v = v_1$, $z = 0$. The largest invariant subset of $\left\{(x(t), y(t), v(t), z(t)) : \dot{V}_1(t) = 0\right\}$ is $S_1 = \{E_1\} \subset \Omega$. From Theorem 4, if $\Re_1 < 1 < \Re_0$, E_1 is locally asymptotically stable. Consequently, in light of LaSalle's invariance principle [24], we conclude that E_1 is globally asymptotically stable if $\Re_1 < 1 < \Re_0$. □

Theorem 8 *If $\Re_1 > 1$, the immunity-activated equilibrium $E_2(x_2, y_2, v_2, z_2)$ of system (1.3) is globally asymptotically stable.*

Proof Let $(x(t), y(t), v(t), z(t))$ be any positive solution of system (1.3) with the initial condition (1.4). Define

$$
\begin{aligned}
V_2(t) = & e^{-m\tau}\left(x(t)-x_2-\int_{x_2}^{x(t)} \frac{\left(1+a_1\theta+a_2 v_2\right) x_2}{\left(1+a_1 x_2+a_2 v_2\right)\theta} d\theta\right) \\
& + y_2 h\left(\frac{y(t)}{y_2}\right)+\frac{(a+p z_2) v_2}{k} h\left(\frac{v(t)}{v_2}\right)+\frac{p y_2 z_2}{b} h\left(\frac{z(t)}{z_2}\right) \\
& + (a+p z_2) y_2 \int_{t-\tau}^{t} h\left(e^{-m\tau} \frac{\beta x(\theta) v(\theta)}{(a+p z_2) y_2\left(1+a_1 x(\theta)+a_2 v(\theta)\right)}\right) d\theta, \qquad (5.6)
\end{aligned}
$$

where the function h is defined in (5.1).
Noting that E_2 is the equilibrium of system (1.3), we have the following expressions:

$$
\begin{aligned}
&\lambda = d x_2+\frac{\beta x_2 v_2}{1+a_1 x_2+a_2 v_2}, \quad (a+p z_2) y_2 = e^{-m\tau} \frac{\beta x_2 v_2}{1+a_1 x_2+a_2 v_2}, \\
&u = \frac{k y_2}{v_2}, \quad b = \frac{c y_2}{1+\varepsilon z_2}-n y_2. \qquad (5.7)
\end{aligned}
$$

Calculating the derivative of $V_2(t)$ along positive solutions of system (1.3), and substituting (5.7) into Eq. (5.6), we obtain

$$
\begin{aligned}
\dot{V}_2(t) = & -e^{-m\tau} \frac{d\left(1+a_2 v_2\right)\left(x(t)-x_2\right)^2}{x(t)\left(1+a_1 x_2+a_2 v_2\right)} \\
& - (a+p z_2) y_2\left[h\left(\frac{\left(1+a_1 x(t)+a_2 v_2\right) x_2}{\left(1+a_1 x_2+a_2 v_2\right) x(t)}\right)+h\left(\frac{1+a_1 x(t)+a_2 v(t)}{1+a_1 x(t)+a_2 v_2}\right)\right] \\
& - (a+p z_2) y_2\left[h\left(\frac{v_2 y(t)}{v(t) y_2}\right)+h\left(\frac{\left(1+a_1 x_2+a_2 v_2\right) x(t-\tau) v(t-\tau) y_2}{\left(1+a_1 x(t-\tau)+a_2 v(t-\tau)\right) x_2 v_2 y(t)}\right)\right]
\end{aligned}
$$

$$-\frac{a_2\left(a+pz_2\right)y_2\left(1+a_1x\left(t\right)\right)\left(v\left(t\right)-v_2\right)^2}{v_2\left(1+a_1x\left(t\right)+a_2v\left(t\right)\right)\left(1+a_1x\left(t\right)+a_2v_2\right)}-\frac{\varepsilon cpy_2y\left(t\right)\left(z\left(t\right)-z_2\right)^2}{b\left(1+\varepsilon z_2\right)\left(1+\varepsilon z\left(t\right)\right)}. \tag{5.8}$$

It is evident that $\dot{V}_2\left(t\right)\leq 0$. And we have $\dot{V}_2\left(t\right)=0$ iff $x=x_2, y=y_2, v=v_2, z=z_2$. Clearly, the largest invariant set in $\left\{\left(x\left(t\right),y\left(t\right),v\left(t\right),z\left(t\right)\right):\dot{V}_2\left(t\right)=0\right\}$ is the singleton $S_2=\{E_2\}$. Moreover, Theorem 5 implies that E_2 is locally asymptotically stable if $\Re_1>1$. On the basis of LaSalle's invariance principle [24], we claim that E_2 is globally asymptotically stable. □

6 Sensitivity analysis

In this section, the effects of parameter values on the immunity-inactivated reproduction ratio $\Re_0$ and the immunity-activated reproduction ratio $\Re_1$ will be shown by performing sensitivity analysis.
The parameter values are chosen as follows [26–28]:

$$\begin{aligned}&\lambda=46\ \text{cells ml}^{-1}\text{day}^{-1},\quad d=0.0046\ \text{day}^{-1},\quad \beta=4.8\times10^{-7}\ \text{ml virion}^{-1}\ \text{day}^{-1},\\&p=0.00094\ \text{ml cells}^{-1}\ \text{day}^{-1},\quad k=11.349\ \text{virion cells}^{-1}\ \text{day}^{-1},\quad u=0.25\ \text{day}^{-1},\\&m=1.39\ \text{day}^{-1},\quad \tau=0.5\ \text{day},\quad a=0.01\ \text{day}^{-1},\quad c=0.01\ \text{day}^{-1},\quad b=0.5\ \text{day}^{-1}.\end{aligned} \tag{6.1}$$

In the meantime, suppose that $a_1=0.1$ ml virion^{-1}, $a_2=0.0003$ ml virion^{-1}, $n=0.005$ cells^{-1}day^{-1}, $\varepsilon=0.01$ cells ml^{-1}. Firstly, we perform sensitivity analysis of the immune-inactivated reproduction ratio $\Re_0$ on the parameters τ, u, m, k, a_1, a and β with the method of Latin Hypercube Sampling and Partial Rank Correlation Coefficients (PRCCs) developed in [29] (see Fig. 2). In Fig. 2, it is clearly that β, k are positively related with $\Re_0$, and β contributes more to $\Re_0$ compared to k. However, τ, u, m, a_1 and a are negatively correlated with $\Re_0$, and m makes the least contribution to $\Re_0$ compared to τ, u, a_1 and a. It shows that we should reduce β or increase the intracellular delay τ to decrease the value of $\Re_0$.

Secondly, sensitivity analysis of the immune-activated reproduction ratio $\Re_1$ in regard to the parameters τ, u, m, k, b, n, c and β is carried out. As is shown in Fig. 3, it is obvious that $\Re_1$ is positively correlated with β, k and c, while $\Re_1$ is negatively correlated with τ, u, m, b and n. In addition, in order to more effectively reduce $\Re_1$, we can decrease the virus-to-cell infection rate and the activation rate of CTL immune response.

7 Conclusion

In this paper, we developed an HIV infection model for the interaction of HIV, host cells and CTL immune cells. In system (1.3), we used Beddington–DeAngelis type incidence to describe the rate of contact between the HIV and host cells. Moreover,

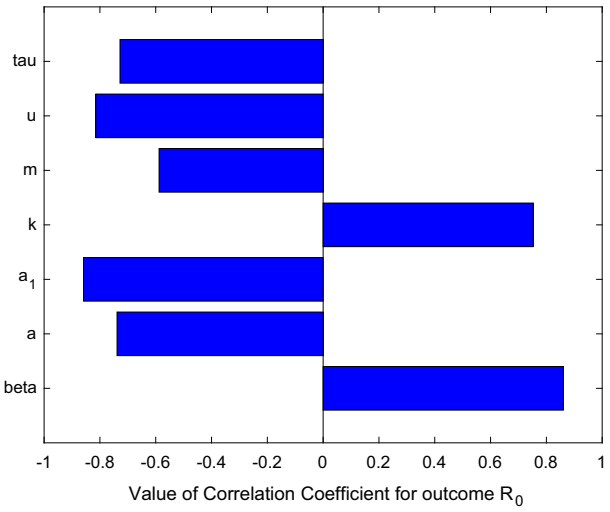

Fig. 2 Tornado plots of PRCCs in regard to $\mathfrak{R}_0$ with parameter values assumed in (6.1)

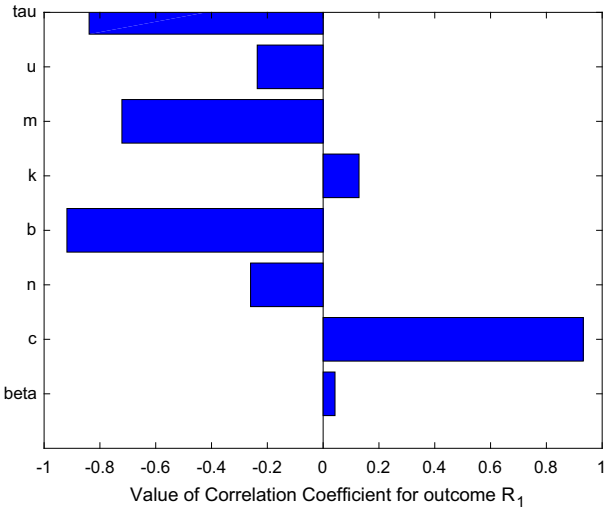

Fig. 3 Tornado plots of PRCCs in regard to $\mathfrak{R}_1$ with parameter values assumed in (6.1)

the intracellular delay, saturated CTL immune response and immune impairment were considered in system (1.3). We derived immunity-inactivated and immunity-activated reproduction ratios: $\mathfrak{R}_0$ and $\mathfrak{R}_1$. The expression of $\mathfrak{R}_1$ implies that $\mathfrak{R}_1$ is positively related to c and $\mathfrak{R}_0$, negatively correlated to n and b. The immune impairment has an effect on the immunity-activated equilibrium of system (1.3). Moreover, we studied the local asymptotic stability of feasible equilibria, and the global asymptotic stability was investigated with the help of constructing Lyapunov functionals and using LaSalle's

invariance principle. It is obvious that $\mathfrak{R}_0$ and $\mathfrak{R}_1$ play crucial roles in the stabilities of feasible equilibria of system (1.3).

Furthermore, intracellular delay does not affect the stabilities of equilibria, so it does not induce periodic solutions or Hopf bifurcation. As is shown in sensitivity analysis, the two thresholds $\mathfrak{R}_0$ and $\mathfrak{R}_1$ are positively associated to the parameter values β and k. The immunity-inactivated reproduction ratio and immunity-activated reproduction ratio gradually decrease as intracellular delay increases, which could help us to better control the viral load.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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