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Global stability of a delayed HIV infection model with nonlinear incidence rate

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Abstract Under the assumption that the incidence rate of the infection and the removal rate of the infective by cytotoxic T lymphocytes are nonlinear, we study the global dynamics of a HIV infection model with the response of the immune system using characteristic equation, the Fluctuation lemma, and the direct Lyapunov method. The existence of a threshold parameter, i.e., the basic reproduction number or basic reproductive ratio is established and the global stability of the equilibria is discussed.

Keywords Nonlinear incidence rate · Delay · Stability · HIV · CTL

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1 Introduction

A large number of mathematical models have been proposed in [2, 3, 20–24] and have enhanced the progress in understanding the HIV infection since the identification of human immunodeficiency virus (HIV) over 20 years ago. These models have been used to explain different phenomena. For more references and some detailed mathematical analysis on such models, we refer to the survey papers by Kirschner [15] and Perelson and Nelson [22].

Most existing mathematical models for HIV infection are described by systems of ordinary differential equations (ODEs) (see, e.g. [2, 3, 14, 20, 22, 25]). Considering Cytotoxic T Lymphocytes (CTLs) are T cells which are capable of recognizing and killing cells infected with HIV and are usually not susceptible to infection since they generally lack the $CD4^+$ receptor, Cuipe et al. in [7] proposed an ODE modeling the effect of the CTL population on HIV-1 reproduction. The model includes the response of the immune system and it accounted for uninfected cells, infected cells, virus, and CTL dynamics

$$\begin{cases} x' = \mu - kx - \alpha xv, \\ y' = \alpha xv - ry - \beta yz, \\ v' = py - dv, \\ z' = \delta y - qz, \end{cases} \tag{1.1}$$

where x, y, v, and z represent $CD4^+$ cells that are susceptible to infection, productively infected cells, virus,

and the effector population of CTLs, respectively. The constant μ represents a source of susceptible cells, and k is their death rate; α is the infection rate constant and infection is assumed to occur at a rate proportional to the product of the concentration of virus and target cells, an assumption which is valid for a well-mixed system with relatively high concentrations of each product; r is the infected cell death rate, β determines the rate of killing of productively infected cells by CTLs; p is the rate of virus production by infected cells and d is the clearance rate of virus; effectors are generated in the presence of infected cells at rate δy and die at rate q per cell.

Based on system (1.1), low steady state viral load is checked in [5]. A Bayesian technique was used in [1] to estimate the parameters of the model (1.1) and the parameters are determined. The local stability of (1.1) is studied in [7] and some complex sufficient conditions ensuing the local stability of the noninfected equilibrium as well as the infected equilibrium are obtained by Routh–Hurwitz criterion.

Obviously, an underlying assumption in such an ODE model (1.1) is that infection of cells by virions is instantaneous. In fact, in a real situation, there may be a lag between the time target cells are contacted by the virus particles and the time the contacted cells become actively affected (the time that the contacting virions enter cells). In general, delay-differential equations exhibit much more complicated dynamics than ordinary differential equations since a time delay could cause a stable equilibrium to become unstable and cause the populations to fluctuate. Hence, time delays have been incorporated into HIV infection models by some authors [8, 11, 13, 16–19, 23, 26, 28].

In this paper, we introduce a time delay in the model (1.1) by assuming that there is a lag between the time target cells are contacted by the virus particles and the time the contacted cells become actively infected (including the steps of successful attachment of virus to the cell, and penetration of virus into the cell). Precisely, the contacted cells become actively infected at time t is generated by the infection of a cell y at time $t-\tau$, where $\tau>0$ is constant. We assume that there is a death rate factors of the form $e^{-m\tau}$ $(m>0)$ which is the surviving rate of each target cell to get infected. Instead of bilinear incidence rate, two nonlinear incidence rates are used in our model. The model then becomes

$$\begin{cases} x'(t) = \mu - kx(t) - \alpha x(t) f(v(t)), \\ y'(t) = \alpha e^{-m\tau} x(t-\tau) f(v(t-\tau)) - ry(t) \\ \qquad\quad - \beta y(t) h(z(t)), \\ v'(t) = py(t) - dv(t), \\ z'(t) = \delta y(t) - qz(t), \end{cases} \tag{1.2}$$

where all parameters are positive. The function $f(\xi)$ denotes the force of infection by the infective at density ξ, and $h(\xi)$ denotes the force of CTLs to kill infected cells at density ξ. The function $f(\xi)$ and $h(\xi)$ are locally Lipschitz on $[0,\infty)$ and satisfy

(A$_1$) $f(0)=0$, the derivatives $f'(\xi)>0$ and $(\frac{f(\xi)}{\xi})'\le 0$ in $(0,\infty)$;

(A$_2$) The derivative $h'(\xi)>0$ with $h(0)=0$ in $[0,\infty)$.

We note that our incidence rates are sufficiently general to encompass many forms of commonly used incidence rate, including simple mass action and saturation incident rate. In fact, some virus infection model with nonlinear incident rates have been introduced in [4, 9, 27].

The initial conditions associated with system (1.2) are

$$\begin{aligned} &x(\theta)=\phi_1(\theta), \quad y(\theta)=\phi_2(\theta), \quad v(\theta)=\phi_3(\theta), \\ &z(\theta)=\phi_4(\theta), \quad \phi_i(\theta)\ge 0, \quad \theta\in[-\tau,0], \\ &\quad i=1,2,3,4, \end{aligned} \tag{1.3}$$

where $\phi=(\phi_1,\phi_2,\phi_3,\phi_4)\in C([-\tau,0],\mathbb{R}^4_{0+})$, the Banach space of continuous functions mapping the interval $[-\tau,0]$ into $\mathbb{R}^4_{0+}$ equipped with the sup-norm. Here, $\mathbb{R}^4_{0+}=\{(x_1,x_2,x_3,x_4): x_i\ge 0, i=1,2,3,4\}$.

It is well known by the fundamental theory of functional differential equations [10] that system (1.2) has a unique solution $(x(t), y(t), v(t), z(t))$ satisfying the initial conditions (1.3). By a similar argument as in [28, 29], it is easy to show that all solutions of system (1.2) with initial conditions (1.3) are defined on $[0,+\infty)$ and have the following properties: (i) $x(t)$, $y(t)$, $v(t)$ and $z(t)$ are all non-negative for all $t\ge 0$; (ii) There exists an $M>0$ such that $x(t)<M$, $y(t)<M$, $v(t)<M$, and $z(t)<M$ for sufficiently large time t; (iii) $x(t)$, $y(t)$ and $v(t)$ are all positive for all $t\ge 0$ if $\phi_i(0)>0$ $(i=1,2,3)$.

The purpose of this study is to obtain the sufficient conditions ensuring the global stability of the noninfected equilibrium as well as the infected equilibrium

of system (1.2) and (1.3). The paper is organized as follows: in Sect. 2, we will study the stability of the noninfected equilibrium. In Sect. 3, we prove that the basic productive number $\mathcal{R}_0 > 1$ is a threshold value ensuring the global stability of the infected equilibrium. The conclusion and discussion are included in Sect. 4.

2 Stability of the noninfected equilibrium

Let

$$\mathcal{R}_0 = \frac{\alpha p \mu e^{-m\tau} f'(0)}{krd}. \tag{2.1}$$

$\mathcal{R}_0$ is called the basic reproductive number which explained as the average number of secondary virus produced from a single virus for system (1.2). For system (1.2), there exists a noninfected equilibrium $E_0 = (\frac{\mu}{k}, 0, 0, 0)$. Now we show that $\mathcal{R}_0 > 1$ is a sufficient condition ensuring the existence of the infected equilibrium (positive equilibrium) $E_1 = (x^*, y^*, v^*, z^*)$. By a simple calculation, we know that the existence of the infected equilibrium is equivalent to the function

$$L(v) = \frac{\alpha \mu e^{-m\tau} f(v)}{k + \alpha f(v)} - \frac{rd}{p} v - \frac{\beta d v}{p} h\left(\frac{\delta d v}{pq}\right) \tag{2.2}$$

has a positive zero point. In fact, since

$$L(0) = 0, \qquad L'(0) = \frac{rd}{p}(\mathcal{R}_0 - 1) > 0,$$
$$L(+\infty) = -\infty,$$

it follows from the continuity of the function $L(v)$ in $[0, \infty)$ that $L(v)$ has at least a positive zero point. Hence, we see that (1.2) at least has an infected equilibrium $E_1 = (x^*, y^*, v^*, z^*)$ when $\mathcal{R}_0 > 1$.

The characteristic equation associates with the equilibrium E_0 is

$$(\lambda + k)(\lambda + q)\left(\lambda^2 + (r + d)\lambda + rd - \frac{\alpha p \mu f'(0) e^{-(\lambda+m)\tau}}{k}\right) = 0. \tag{2.3}$$

The stability of E_0 is determined by the sign of real parts of the roots of (2.3): if all roots of (2.3) have negative real parts, then E_0 is asymptotically stable; if there is at least one root of (2.3) has positive real part, then E_0 is unstable. Obviously, the stability of E_0 is totally determined by the roots of

$$\lambda^2 + (r + d)\lambda + rd - \frac{\alpha p \mu f'(0) e^{-(\lambda+m)\tau}}{k} = 0. \tag{2.4}$$

Note that (2.4) can be written as

$$\mathcal{R}_0 = e^{\lambda\tau}\left(\frac{\lambda}{r} + 1\right)\left(\frac{\lambda}{d} + 1\right). \tag{2.5}$$

We claim that all roots of (2.5) have negative real parts under the condition $\mathcal{R}_0 < 1$. By way of contradiction, if $\lambda = \sigma + i\omega$ ($\sigma > 0$) is a root of (2.5). Taking moduli in both sides of (2.5) gives

$$\mathcal{R}_0 = e^{\sigma\tau}\sqrt{\left[\left(\frac{\sigma}{r} + 1\right)^2 + \frac{\omega^2}{r^2}\right]\left[\left(\frac{\sigma}{d} + 1\right)^2 + \frac{\omega^2}{d^2}\right]}$$
$$> 1.$$

It contradicts the fact $\mathcal{R}_0 < 1$, showing that all roots of (2.4) remain in the left plane for all $\tau > 0$ as long as $\mathcal{R}_0 < 1$.

On the other hand, when $\mathcal{R}_0 > 1$, (2.4) has a positive root. This can be easily seen by looking at the function $H(u) = u^2 + (r + d)u + rd - \frac{\alpha p \mu f'(0) e^{-(u+m)\tau}}{k}$, which satisfies that $H(0) = rd(1 - \mathcal{R}_0) < 0$ and $H(+\infty) = +\infty$.

From the above analysis, we see that $\mathcal{R}_0 = 1$ plays a role of threshold: if $\mathcal{R}_0 < 1$, the non-infected equilibrium E_0 is locally asymptotically stable; if $\mathcal{R}_0 > 1$, the noninfected equilibrium E_0 is unstable. Indeed, we can show that if $\mathcal{R}_0 < 1$, the noninfected equilibrium is global asymptotically stable. To prove this, we only need to show that E_0 is also globally attractive if $\mathcal{R}_0 < 1$.

Following the convention, we use the following notations: for a continuous and bounded function $l(t)$ defined on $[0, \infty)$,

$$l^\infty \overset{\text{def}}{=} \limsup_{t\to\infty} l(t) \quad \text{and} \quad l_\infty \overset{\text{def}}{=} \liminf_{t\to\infty} l(t).$$

Now, let $(x(t), y(t), v(t), z(t))$ be any solution of (1.2) and (1.3). By the previous arguments, we know

$$\begin{aligned} &0 \le x_\infty \le x^\infty < \infty; \qquad 0 \le y_\infty \le y^\infty < \infty; \\ &0 \le v_\infty \le v^\infty < \infty; \quad \text{and} \quad 0 \le z_\infty \le z^\infty < \infty. \end{aligned} \tag{2.6}$$

By the fluctuation lemma in [12], there is a sequence $\{t_n\}$ with $t_n \to \infty$ as $n \to \infty$ such that

$$x(t_n) \to x^\infty, \quad x'(t_n) \to 0 \quad \text{as } n \to \infty.$$

Substituting the sequence $\{t_n\}$ into the first equation of (1.2) and taking limit give

$$kx^\infty \le \mu. \tag{2.7}$$

Applying a similar argument to the second and third equations of (1.2), we have

$$ry^\infty \le \alpha e^{-m\tau} x^\infty f(v^\infty), \tag{2.8}$$

$$dv^\infty \le py^\infty, \tag{2.9}$$

and

$$qz^\infty \le \delta y^\infty. \tag{2.10}$$

Combining (2.7)–(2.9) with Assumption (A_1), we obtain

$$ry^\infty \le \frac{\alpha p \mu e^{-m\tau} f'(0) y^\infty}{kd}.$$

If $y^\infty > 0$, then the above inequality yields

$$r \le \frac{\alpha p \mu e^{-m\tau} f'(0)}{kd},$$

contradicting $\mathcal{R}_0 < 1$. Therefore, $y^\infty = 0$, implying $\lim_{t\to\infty} y(t) = y^\infty = y_\infty = 0$ by (2.6). By (2.9) and (2.10), this in turn implies $v^\infty = z^\infty = 0$, and $\lim_{t\to\infty} v(t) = v^\infty = v_\infty = 0$, $\lim_{t\to\infty} z(t) = z^\infty = z_\infty = 0$ by (2.6). Finally, applying the theory of asymptotically autonomous system in [6] to the first equation of (1.2), we conclude that $\lim_{t\to\infty} x(t) = \frac{\mu}{k}$.

Summarizing the above, we have proved the following theorem.

Theorem 2.1 *Let $\mathcal{R}_0$ be the basic reproduction number given by (2.1). The following two statements are true.*

(i) *If $\mathcal{R}_0 < 1$, then the noninfected equilibrium E_0 is globally asymptotically stable.*
(ii) *If $\mathcal{R}_0 > 1$, then the noninfected equilibrium E_0 is unstable.*

3 Stability of the infected equilibrium

Let

$$F(w) = \frac{f(v^* w)}{f(v^*)}$$

and

$$g(u) = u - 1 - \ln u.$$

We note that $g : \mathbb{R}_+ \mapsto \mathbb{R}_+$ has the strict global minimum $g(1) = 0$. In order to prove the globally asymptotical stability of the infected equilibrium, we need the following lemma.

Lemma 3.1 *If $f(\xi)$ satisfies Assumption (A_1), then*

$$g(F(w)) \le g(w) \qquad \text{for } w > 0$$

with equality only if $w = 1$.

Proof Since $F(1) = 1$ and the derivative of $g(w)$ has the same sign as $w - 1$ for $w > 0$, we only need to show that $w \le F(w) \le 1$ for $w \in (0, 1)$ and $1 \le F(w) \le w$ for $w \in [1, \infty)$. The proofs of both cases are similar so we only consider the case where $w \in (0, 1)$. Note that $w \le F(w) \le 1$ is equivalent to $\frac{f(v^*)}{v^*} \le \frac{f(v^* w)}{v^* w} \le \frac{f(v^*)}{v^* w}$ for $w \in (0, 1)$. This fact is easy to verify from Assumption (A_1) and we complete the proof. □

Theorem 3.1 *If $\mathcal{R}_0 > 1$, then E_1 is globally asymptotically stable if $\phi_i(0) > 0$ $(i = 1, 2, 3)$.*

Proof Note that

$$\mu = kx^* + \alpha x^* f(v^*), \tag{3.1}$$

$$\alpha e^{-m\tau} x^* f(v^*) = ry^* + \beta y^* h(z^*), \tag{3.2}$$

$$py^* = dv^* \tag{3.3}$$

and

$$\delta y^* = qz^*. \tag{3.4}$$

The solution of (1.2) associated with (1.3) and $\phi_i(0) > 0$ $(i = 1, 2, 3)$ are bounded above and x, y, v bounded away from zero implies the following functions:

$$\begin{aligned}
&V_1(t) = g\left(\frac{x(t)}{x^*}\right), \qquad V_2(t) = g\left(\frac{y(t)}{y^*}\right),\\
&V_3(t) = g\left(\frac{v(t)}{v^*}\right),\\
&V_4(t) = \int_{z^*}^{z(t)} [h(\xi) - h(z^*)]\,\mathrm{d}\xi,\\
&V_5(t) = \int_{t-\tau}^{t} g\left(\frac{x(s) f(v(s))}{x^* f(v^*)}\right)\mathrm{d}s
\end{aligned} \tag{3.5}$$

are defined for all $t \geq 0$.

Define

$$V(t) = x^* V_1(t) + e^{m\tau} y^* V_2(t) + \frac{\alpha x^* f(v^*)}{d} V_3(t) + \frac{\beta e^{m\tau}}{\delta} V_4 + \alpha x^* f(v^*) V_5(t). \tag{3.6}$$

Obviously, $V(t) \geq 0$ with equality if and only if $\frac{x(t)}{x^*} = \frac{y(t)}{y^*} = \frac{v(t)}{v^*} = \frac{z(t)}{z^*} = 1$ and $\frac{v(s)}{v^*} = 1$ for $s \in [t-\tau, t]$.

For clarity, the derivatives of V_1, V_2, V_3, V_4 and V_5, will be calculated separately and then combined to obtain $V'(t)$.

$$V_1'(t) = \frac{1}{x^*}\left(1 - \frac{x^*}{x(t)}\right) x'(t) = \frac{1}{x^*}\left(1 - \frac{x^*}{x(t)}\right)(\mu - kx(t) - \alpha x(t) f(v(t))).$$

Using (3.1) to replace μ gives

$$V_1'(t) = \frac{1}{x^*}\left(1 - \frac{x^*}{x(t)}\right)[k(x^* - x(t)) + \alpha(x^* f(v^*) - x(t) f(v(t)))]$$
$$= -\frac{k(x(t) - x^*)^2}{x^* x(t)} + \alpha f(v^*)\left(1 - \frac{x^*}{x(t)} - \frac{x(t) f(v(t))}{x^* f(v^*)} + \frac{f(v(t))}{f(v^*)}\right). \tag{3.7}$$

Next, we calculate $V_2'(t)$.

$$V_2'(t) = \frac{1}{y^*}\left(1 - \frac{y^*}{y(t)}\right) y'(t)$$
$$= \frac{1}{y^*}\left(1 - \frac{y^*}{y(t)}\right)(\alpha e^{-m\tau} x(t-\tau) f(v(t-\tau)) - r y(t) - \beta y(t) h(z(t)))$$
$$= \frac{\alpha e^{-m\tau} x^* f(v^*)}{y^*}\left[\frac{x(t-\tau) f(v(t-\tau))}{x^* f(v^*)} - \frac{x(t-\tau) y^* f(v(t-\tau))}{x^* y(t) f(v^*)}\right]$$
$$- r\left(\frac{y(t)}{y^*} - 1\right) - \beta h(z^*)\left(\frac{y(t) h(z(t))}{y^* h(z^*)} - \frac{h(z(t))}{h(z^*)}\right).$$

Using (3.2), we obtain

$$V_2'(t) = \frac{\alpha e^{-m\tau} x^* f(v^*)}{y^*}\left[\frac{x(t-\tau) f(v(t-\tau))}{x^* f(v^*)} - \frac{x(t-\tau) y^* f(v(t-\tau))}{x^* y(t) f(v^*)}\right]$$
$$- r\left(\frac{y(t)}{y^*} - 1\right) - \left(\frac{\alpha e^{-m\tau} x^* f(v^*)}{y^*} - r\right)\left(\frac{y(t) h(z(t))}{y^* h(z^*)} - \frac{h(z(t))}{h(z^*)}\right)$$
$$= \frac{\alpha e^{-m\tau} x^* f(v^*)}{y^*}\left[\frac{x(t-\tau) f(v(t-\tau))}{x^* f(v^*)} - \frac{x(t-\tau) y^* f(v(t-\tau))}{x^* y(t) f(v^*)} - \frac{y(t) h(z(t))}{y^* h(z^*)} + \frac{h(z(t))}{h(z^*)}\right]$$
$$+ r\left(1 - \frac{y(t)}{y^*} + \frac{y(t) h(z(t))}{y^* h(z^*)} - \frac{h(z(t))}{h(z^*)}\right). \tag{3.8}$$

We now calculate the derivatives of $V_3(t)$ and $V_4(t)$:

$$V_3'(t) = \frac{1}{v^*}\left(1 - \frac{v^*}{v(t)}\right) v'(t) = d\left(1 - \frac{v(t)}{v^*} + \frac{y(t)}{y^*} - \frac{v^* y(t)}{v(t) y^*}\right), \tag{3.9}$$

$$V_4'(t) = [h(z(t)) - h(z^*)][\delta y(t) - q z(t)]$$
$$= -q[z(t) - z^*][h(z(t)) - h(z^*)] + \delta y^* h(z^*)\left(1 - \frac{y(t)}{y^*} + \frac{y(t) h(z(t))}{y^* h(z^*)} - \frac{h(z(t))}{h(z^*)}\right). \tag{3.10}$$

The derivative of $V_5(t)$ is

$$V_5'(t) = g\left(\frac{x(t)f(v(t))}{x^*f(v^*)}\right) - g\left(\frac{x(t-\tau)v(t-\tau)}{x^*f(v^*)}\right)$$
$$= \frac{x(t)f(v(t))}{x^*f(v^*)} - \frac{x(t-\tau)f(v(t-\tau))}{x^*f(v^*)} - \ln\frac{x(t)f(v(t))}{x^*f(v^*)} + \ln\frac{x(t-\tau)f(v(t-\tau))}{x^*f(v^*)}. \tag{3.11}$$

Combining (3.7)–(3.11) and multiplying appropriately by coefficients determined by (3.6), we obtain

$$\begin{aligned}
V'(t) = &-\frac{k(x(t)-x^*)^2}{x(t)} - \frac{\beta q e^{m\tau}}{\delta}[z(t)-z^*][h(z(t))-h(z^*)]\\
&+\alpha x^* f(v^*)\left(1 - \frac{x^*}{x(t)} - \frac{x(t)f(v(t))}{x^*f(v^*)} + \frac{f(v(t))}{f(v^*)} + \frac{x(t-\tau)f(v(t-\tau))}{x^*f(v^*)}\right.\\
&\left.- \frac{x(t-\tau)y^*f(v(t-\tau))}{x^*y(t)f(v^*)} + \frac{h(z(t))}{h(z^*)} - \frac{y(t)h(z(t))}{y^*h(z^*)}\right)\\
&+re^{m\tau}y^*\left(1 - \frac{y(t)}{y^*} + \frac{y(t)h(z(t))}{y^*h(z^*)} - \frac{h(z(t))}{h(z^*)}\right) + \alpha x^* f(v^*)\left[1 - \frac{v(t)}{v^*} + \frac{y(t)}{y^*} - \frac{v^*y(t)}{v(t)y^*}\right]\\
&+\beta e^{m\tau}y^*h(z^*)\left[1 - \frac{y(t)}{y^*} + \frac{y(t)h(z(t))}{y^*h(z^*)} - \frac{h(z(t))}{h(z^*)}\right]\\
&+\alpha x^* f(v^*)\left[\frac{x(t)f(v(t))}{x^*f(v^*)} - \frac{x(t-\tau)f(v(t-\tau))}{x^*f(v^*)} - \ln\frac{x(t)f(v(t))}{x^*f(v^*)} + \ln\frac{x(t-\tau)f(v(t-\tau))}{x^*f(v^*)}\right],
\end{aligned}$$

which, together with (3.3), implies that

$$\begin{aligned}
V'(t) = &-\frac{k(x(t)-x^*)^2}{x(t)} - \frac{\beta q e^{m\tau}}{\delta}[z(t)-z^*][h(z(t))-h(z^*)] + \alpha x^* f(v^*)\left(3 - \frac{x^*}{x(t)} + \frac{f(v(t))}{f(v^*)}\right.\\
&\left.- \frac{x(t-\tau)y^*f(v(t-\tau))}{x^*y(t)f(v^*)} - \frac{v(t)}{v^*} - \frac{v^*y(t)}{v(t)y^*} - \ln\frac{x(t)f(v(t))}{x^*f(v^*)} + \ln\frac{x(t-\tau)f(v(t-\tau))}{x^*f(v^*)}\right)\\
= &-\frac{k(x(t)-x^*)^2}{x(t)} - \frac{\beta q e^{m\tau}}{\delta}[z(t)-z^*][h(z(t))-h(z^*)]\\
&-\alpha x^* f(v^*)\left[g\left(\frac{x^*}{x(t)}\right) + g\left(\frac{x(t-\tau)y^*f(v(t-\tau))}{x^*y(t)f(v^*)}\right) + g\left(\frac{v^*y(t)}{v(t)y^*}\right)\right]\\
&+\alpha x^* f(v^*)\left[\frac{f(v(t))}{f(v^*)} - \ln\frac{f(v(t))}{f(v^*)} - \frac{v(t)}{v^*} + \ln\frac{v(t)}{v^*}\right]\\
\le &\,\alpha x^* f(v^*)(g(F(w)) - g(w)),
\end{aligned}$$

where $w = \frac{v(t)}{v^*}$. Using the fact in Lemma 3.1, we see that $V'(t) \le 0$ with equality only if the argument $\frac{x(t)}{x^*} = \frac{z(t)}{z^*} = \frac{y^*x(t-\tau)f(v(t-\tau))}{y(t)x^*f(v^*)} = \frac{v^*y(t)}{v(t)y^*} = \frac{v(t)}{v^*} = 1$. By Theorem 5.3.1 of [10], solutions limit to B, the largest invariant subset of $\{V'(t) = 0\}$. We note that $V'(t)$ is only zero if $x(t) = x^*, y(t) = y^*, v(t) = v^*, z(t) = z^*$ for all t, and so B consists of the single point E_1. Thus, the infected equilibrium E_1 is globally asymptotically stable. □

Remark 3.1 Applying the Routh–Hurwitz criterion of linearized system of (1.1), the stability of system (1.1) has been studied in [7] and some sufficient conditions ensuring the local stability of the noninfected equilib-

rium as well as the infected equilibrium are obtained. Compared our global stability to the local stability in [7], our condition is only determined by the basic reproductive number and it is very easy to verify. However, the condition for the local stability of the infected equilibrium [7] is very complex because it includes several inequalities. Furthermore, since a general nonlinear incident rate and a delay between the time target cells contacted by the virus particles and the time the contacted cells become actively affected is included in system (1.2), our results obtained in the paper improve and extend some existing ones.

4 Conclusion and discussion

In this paper, modeling the effect of the CTL, a delayed HIV infection model with nonlinear incidence rates is studied. We have identified the basic reproduction number $\mathcal{R}_0$ and proved that if $\mathcal{R}_0 < 1$, the noninfected equilibrium is global asymptotically stable; if $\mathcal{R}_0 > 1$, the noninfected equilibrium becomes unstable and there occurs an infected equilibrium which is global asymptotically stable. Thus, $\mathcal{R}_0 = 1$ plays a role of threshold value that determines whether or not the HIV virus in host will be persistent or will go to extinction.

From our results, we conclude that to control the concentrations of the virus and the infected cells, a strategy should aim to reduce the value of the basic reproduction number to below one. By the explicit expression of $\mathcal{R}_0$, we see the values of parameters β, δ, and q have no impact on the value of $\mathcal{R}_0$ since $\mathcal{R}_0$ is independent of those parameters. This fact indicates CTL does not play a role in eliminating the virus load. However, from the expression of L in (2.2), we see that v^* can be decreased by increasing β and δ or decreasing q. This suggests CTL can increase the healthy cells population and maintain low steady state viral load when $\mathcal{R}_0 > 1$.

Our results imply that the intracellular delay describing the time between viral entry into a target cell and the production of new virus particles does not affect the stability of the feasible equilibria and, therefore, does not induce periodic oscillations and the possibility of Hopf bifurcations is therefore ruled out. However, once a delay is introduced in CTL production, numerical simulations illustrate the solutions of (1.2) may oscillate around the infection equilibrium even if $\mathcal{R}_0 > 1$. It would be very interesting when a delay is incorporated into CTL production. Such modifications should more precisely describe the reality and give us more insights into the infection process, but would lead to much more challenging mathematical problems.

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