Global Stability Analysis for a Delayed HIV Infection Model with General Incidence Rate and Cell Immunity

Chengjun Kang, Hui Miao and Xing Chen *

***Abstract*—In this paper, the global dynamical behaviors for a four-dimensional HIV infection model with intracellular delay and production delay which describes the interactions of cytotoxic T-lymphocyte (CTL) immune responses and general incidence rate are investigated. By using suitable Lyapunov functionals and LaSalle's invariance principle, the global stability of infection-free equilibrium, CTL-absent infection equilibrium and CTL-present infection equilibrium are established, respectively. These results can be applied to a variety of viral infection diseases that would make it possible to devise optimal treatment strategies. Numerical simulations are presented to verify the analytical results.**

***Index Terms*—HIV infection model; Cytotoxic T-lymphocyte; delay; Lyapunov functional; global asymptotical stability.**

I. Introduction

MANY viral infection models have been studied recently (see[1-12,15-22]). As well known, the HIV (human immunodeficiency virus) has been extensively studied in [1,6,9,19] and became a global problem. HIV is a retrovirus that can infect $CD4^+$ T lymphocytes, which are the most abundant white blood cells of the human immune system. It destroys $CD4^+$ T cells directly or indirectly, the body's immune system is impaired and eventually loses its ability to fight other diseases. Therefore, the immune response after HIV infection is universal and necessary to eliminate or control the diseases.

Mathematical models have been proven to be valuable in understanding the dynamics of viral population in vivo and these provide insights in our understanding of HIV and other viruses, such as HBV (hepatitis B virus) [3,7], HCV (hepatitis C virus) [2] and HTLV (human T cell leukemia virus) [4] are formulated and studied. Most of them use ordinary (delayed) differential equations to describe different aspects of the dynamics of the host-parasite interaction [1-12,15-22]. These models used different forms of incidence rate. For example, in forms as mass action process βxv [5,8,9], standard incidence function $\frac{\beta xv}{x+y}$ [3,7], saturated incidence function $\frac{\beta xv}{1+bv}$ [10,17,20], Beddington-DeAngelis functional response $\frac{\beta xv}{1+a_1x+bv}$ [15,16,22] and Crowley-Martin functional response $\frac{\beta xv}{1+a_1x+bv+a_1bxv}$ [21]. To cover the above incidence functions, Hattaf et al. [18] proposed the viral infection model with general incidence rate $f(x,v)v$ by the following nonlinear system of differential equation

$$\begin{cases} \dfrac{dx}{dt} = \lambda - dx(t) - f(x(t),v(t))v(t), \\ \dfrac{dy}{dt} = f(x(t),v(t))v(t) - ay(t), \\ \dfrac{dv}{dt} = ky(t) - uv(t), \end{cases} \tag{1.1}$$

where $x(t)$, $y(t)$ and $v(t)$ denote the uninfected target cells, productively infected cells and free virus, respectively. The parameter λ represents the rate at which new target cells are created, d is the death rate of uninfected target cells, a is the death rate of productively infected cells, k is the rate of the virus particles produced by infected cells, u is the viral clearance rate.

The salient features of the mechanism of the immune response during viral infection are as follows. First, the free virus enters its target, a susceptible cell. Inside this cell it replicates itself. And this susceptible cell becomes an infected cell. Then the infected cell dies and releases new viruses; these viruses begin to infect other susceptible cells. During the process of viral infection, the immune response is common and necessary to eliminate or control the disease. Antibodies, cytokines, natural killer cells and T cells are essential components of a normal immune response to viruses. In most viral infections, CTLs play a critical role in antiviral defense by attacking infected cells. It is believed that they are the main host immune factor that limits the extent of virus replication in vivo and thus determines virus load. Therefore, the interactions of HIV virus and CTL response have recently drawn much attentions of researchers in the related areas.

We noted that in model (1.1), time delays are always considered for the purpose of accurate representations of the phenomena. In order to incorporate the intracellular phase of the virus life-cycle, we assume that virus production occurs after the virus entry by the intracellular delay τ_1 [5,6,11,17,19,22]. The recruitment of virus-producing cells at time t is given by the number of the uninfected $CD4^+$ T cells that were newly infected at time $t-\tau_1$ and are still alive at time t. The constant m is assumed to be the death rate for newly infected cells during time period $[t-\tau_1, t]$. $e^{-m\tau_1}$ denotes the surviving rate of infected cells during the delay period. Virus replication delay τ_2 represents the time necessary for the newly produced viruses to become mature and then infectious, that is, the maturation time of the newly produced viruses [6,11,22]. $e^{-n\tau_2}$ accounts for

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Chengjun Kang is with Xinjiang Institute of Engineering, Urumqi, Xinjiang, P.C. 830091 China e-mail: chengjun0102@126.com.

Hui Miao is with College of Mathematics and System Sciences, Xinjiang University, Urumqi, Xinjiang, P.C. 830046 China.

Corresponding author: Xing Chen is with Xinjiang Institute of Engineering, Urumqi, Xinjiang, P.C. 830091 China e-mail: chenxingxjnu@163.com.(X. Chen)

the probability of survival of immature viruses.

Therefore, motivated by the above works, in this paper we consider the following delayed HIV infection model with a general incidence rate and CTL immune response

$$\begin{cases} \frac{dx}{dt} = & \lambda - dx(t) - f(x(t), v(t))v(t), \\ \frac{dy}{dt} = & e^{-m\tau_1} f(x(t-\tau_1), v(t-\tau_1))v(t-\tau_1) \\ & -ay(t) - py(t)z(t), \\ \frac{dv}{dt} = & ke^{-n\tau_2} y(t-\tau_2) - uv(t), \\ \frac{dz}{dt} = & cy(t)z(t) - bz(t), \end{cases} \tag{1.2}$$

where $z(t)$ is the population of CTL response cells, p represents the killing rate of infected cells by CTL response cells, c is the rate at which the CTL response are produced, b is the death rate of the CTL response. $f(x,v)v$ is general incidence rate. $f \in C^1([0,+\infty) \times [0,+\infty), R)$ denotes the average number of cells which are infected by each virus in unite time and satisfies the following hypotheses.

(H_1) $f(x,v) \geq 0$, $f(x,v) = 0$ if and only if $x = 0$.

(H_2) $\frac{\partial f(x,v)}{\partial x} \geq 0$ for all $x \geq 0$ and $v \geq 0$.

(H_3) $\frac{\partial f(x,v)}{\partial v} \leq 0$ for all $x \geq 0$ and $v \geq 0$.

(H_4) $\frac{\partial f(x,v)v}{\partial v} \geq 0$ for all $x \geq 0$ and $v \geq 0$.

In this paper, our purpose is to investigate the dynamical properties of model (1.2), expressly the stability of equilibria. By constructing suitable Lyapunov functionals and using LaSalle's invariance principle, we will establish the global asymptotic stability of equilibria for infection-free, CTL-absent and CTL-present, respectively. Furthermore, the numerical simulations are performed in order to illustrate the dynamical behavior of the model.

The organization of this paper is as follows. In the next section, the basic properties of model (1.2) for the positivity and boundedness of solutions, the threshold values and the existence of equilibria are discussed. In Section 3, the threshold conditions on the global stability of infection-free equilibrium, CTL-absent infection equilibrium and CTL-present infection equilibrium are stated and proved. In Section 4, the numerical simulations are given to explain the results. In the last section, we offer a brief conclusion.

II. Basic results

Let $\tau = \max\{\tau_1, \tau_2\}$, $R^4_+ = \{(x_1, x_2, x_3, x_4) : x_i \geq 0, i = 1,2,3,4\}$. $C([-\tau, 0], R^4_+)$ denotes the space of continuous functions mapping the interval $[-\tau, 0]$ into R^4_+ with the norm $\|\phi\| = \sup_{-\tau \leq t \leq 0}\{|\phi(t)|\}$ for any $\phi \in C([-\tau, 0], R^4_+)$.

The initial conditions for model (1.2) are given as follows

$$\begin{cases} x(\theta) = \phi_1(\theta),\ y(\theta) = \phi_2(\theta), \\ v(\theta) = \phi_3(\theta),\ z(\theta) = \phi_4(\theta), \\ \phi_i(\theta) \geq 0,\ \theta \in [-\tau, 0], \\ \phi_i(0) \geq 0\ (i = 1,2,3,4), \end{cases} \tag{2.1}$$

where $(\phi_1(\theta), \phi_2(\theta), \phi_3(\theta), \phi_4(\theta)) \in C([-\tau, 0], R^4_+)$. It is well known by the fundamental theory of functional differential equation [13], model (1.2) admits a unique solution $(x(t), y(t), v(t), z(t))$ satisfying initial conditions (2.1).

Firstly, we have the following result on the positivity and boundedness of solutions for model (1.2).

Theorem 2.1 *Let $(x(t), y(t), v(t), z(t))$ be the solution of model (1.2) satisfying initial condition (2.1), then $x(t), y(t), v(t)$ and $z(t)$ are positive and ultimately bounded.*

Proof: It is easy to show that all solutions of model (1.2) with initial conditions (2.1) are defined on R^4_+ and remain positive for all $t \geq 0$. Denote

$$N(t) = e^{-m\tau_1} x(t-\tau_1) + y(t) + \frac{ae^{n\tau_2}}{2k} v(t+\tau_2) + \frac{p}{c} z(t).$$

Calculating the derivative of $N(t)$ along solutions of model (1.2) and by the positivity of solutions, we have

$$\begin{aligned} \dot{N}(t) = & \lambda e^{-m\tau_1} - de^{-m\tau_1} x(t-\tau_1) - \frac{a}{2} y(t) \\ & - \frac{aue^{n\tau_2}}{2k} v(t+\tau_2) - \frac{pb}{c} z(t) \\ \leq & \lambda e^{-m\tau_1} - sN(t), \end{aligned}$$

where $s = \min\{d, \frac{a}{2}, u, b\}$. This implies that $N(t)$ is ultimately bounded for large t. So, $x(t), y(t), v(t)$ and $z(t)$ also are ultimately bounded.

Next, we discuss the existence of equilibria of model (1.2). Firstly, we directly obtain that model (1.2) always has a unique infection-free equilibrium $E_0 = (x_0, 0, 0, 0)$ with $x_0 = \frac{\lambda}{d}$.

If $z = 0$ and $v \neq 0$, then we get the following equation

$$f(x, \frac{k(\lambda - dx)}{aue^{m\tau_1 + n\tau_2}}) - \frac{aue^{m\tau_1 + n\tau_2}}{k} = 0, \tag{2.2}$$

$$y = \frac{\lambda - dx}{ae^{m\tau_1}} \quad \text{and} \quad v = \frac{k(\lambda - dx)}{aue^{m\tau_1 + n\tau_2}}. \tag{2.3}$$

Since $v > 0$, the existence of equilibrium requires that equation (2.2) has a solution on the interval $(0, \frac{\lambda}{d})$. Denote

$$F(x) = f(x, \frac{k(\lambda - dx)}{aue^{m\tau_1 + n\tau_2}}) - \frac{aue^{m\tau_1 + n\tau_2}}{k}.$$

Because of (H_2) and (H_3), we know that the function $F(x)$ is strictly monotonically increasing with respect to x.

The basic reproductive number of virus which describes the average number of newly infected cells generated from one infected cell at the beginning of the infectious process is given by $R_0 = \frac{kf(\frac{\lambda}{d}, 0)}{aue^{m\tau_1 + n\tau_2}}$.

We have

$$F(0) = -\frac{aue^{m\tau_1 + n\tau_2}}{k} < 0$$

and

$$F(\frac{\lambda}{d}) = \frac{aue^{m\tau_1 + n\tau_2}}{k}(R_0 - 1).$$

If and only if $R_0 > 1$, there exists a unique $x_1 \in (0, \frac{\lambda}{d})$ such that $F(x_1) = 0$. Then by computing (2.3), we get a unique CTL-absent infection equilibrium $E_1 = (x_1, y_1, v_1, 0)$.

If $z \neq 0$, we get $y_2 = \frac{b}{c}$,

$$f(x, \frac{kb}{uce^{n\tau_2}}) \frac{kb}{uce^{n\tau_2}} - \lambda + dx = 0, \tag{2.4}$$

$$v_2 = \frac{ke^{-n\tau_2} y_2}{u} = \frac{kbe^{-n\tau_2}}{uc}, \tag{2.5}$$

and

$$z = \frac{c(\lambda - dx)}{pbe^{m\tau_1}} - \frac{a}{p}. \tag{2.6}$$

Since $z > 0$, we have $x < x^*$, where $x^* = \frac{\lambda}{d} - \frac{abe^{m\tau_1}}{cd}$.

The existence of equilibrium requires $x^* > 0$ and that equation (2.4) has a solution on the interval $(0, x^*)$.
Denote

$$R_{10} = \frac{\lambda c}{abe^{m\tau_1}}.$$

So, $R_{10} > 1$ is a necessary condition for the existence of equilibrium.
Denote

$$G(x) = f(x, \frac{kb}{uce^{n\tau_2}})\frac{kb}{uce^{n\tau_2}} - \lambda + dx.$$

We know that $G(x)$ is strictly monotonically increasing with respect to x from (H_2). Clearly, $G(0) = -\lambda < 0$, and

$$\begin{aligned} G(x^*) = & f(x^*, \frac{kb}{uce^{n\tau_2}})\frac{kb}{uce^{n\tau_2}} - \lambda + dx^* \\ = & f(x^*, \frac{kb}{uce^{n\tau_2}})\frac{kb}{uce^{n\tau_2}} - \lambda + d(\frac{\lambda}{d} - \frac{abe^{m\tau_1}}{cd}) \\ = & f(x^*, \frac{kb}{uce^{n\tau_2}})\frac{kb}{uce^{n\tau_2}} - \frac{abe^{m\tau_1}}{c} \\ = & \frac{abe^{m\tau_1}}{c}(R_{11} - 1), \end{aligned}$$

where $R_{11} = \frac{kf(x^*, \frac{kb}{uce^{n\tau_2}})}{aue^{m\tau_1 + n\tau_2}}$.

Therefore, if and only if $R_{10} > 1$ and $R_{11} > 1$, there exists a unique real value $x_2 \in (0, x^*)$ such that $G(x_2) = 0$. Then we can compute z_2 by equation (2.6). Define a quantity represents the basic reproduction number for immune cells response as $R_1 = \min\{R_{10}, R_{11}\}$. So, if $R_1 > 1$, then there exists the unique CTL-present infection equilibrium $E_2 = (x_2, y_2, v_2, z_2)$. From the above analysis the following theorem is hold.

Theorem 2.2 *The model (1.2) always has the infection-free equilibrium E_0; the CTL-absent infection equilibrium E_1 exists if and only if $R_0 > 1$; the CTL-present infection equilibrium E_2 exists if and only if $R_1 > 1$.*

Notice that the hypotheses (H_2) and (H_3) imply

$$f(x^*, \frac{kb}{uce^{n\tau_2}}) < f(\frac{\lambda}{d}, \frac{kb}{uce^{n\tau_2}}) < f(\frac{\lambda}{d}, 0).$$

Then we have $R_{11} < R_0$. Therefore $R_1 < R_0$. Clearly, $R_1 = 1$ is equivalent to $\frac{c}{b}y_1 = 1$. Now we show that $R_1 > 1$ is equivalent to $\frac{c}{b}y_1 > 1$.

If

$$\frac{c}{b}y_1 = \frac{c}{b} \cdot \frac{\lambda - dx_1}{ae^{m\tau_1}} > 1,$$

we have $x_1 < x^*$ which is equivalent to

$$x^* > 0 \quad \text{and} \quad F(x^*) > 0. \tag{2.7}$$

Easy computations yield (2.6) and $R_1 > 1$ are equivalent. Therefore, we also have $R_1 < 1$ is equivalent to $\frac{c}{b}y_1 < 1$.

III. Stability analysis

A. Stability of equilibrium E_0

Theorem 3.1 *If $R_0 \le 1$, then infection-free equilibrium E_0 of model (1.2) is globally asymptotically stable.*

Proof. Define a Lyapunov functional $V_1(t)$ as follows

$$\begin{aligned} V_1(t) = & x(t) - x_0 - \int_{x_0}^{x(t)} \frac{f(x_0, 0)}{f(s, 0)}\,\mathrm{d}s + e^{m\tau_1}y(t) \\ & + \frac{ae^{m\tau_1 + n\tau_2}}{k}v(t) + \frac{pe^{m\tau_1}}{c}z(t) + U^-(t), \end{aligned}$$

where

$$\begin{aligned} U^-(t) = & \int_{t-\tau_1}^{t} f(x(\theta_1), v(\theta_1))v(\theta_1)\,\mathrm{d}\theta_1 \\ & + ae^{m\tau_1}\int_{t-\tau_2}^{t} y(\theta_2)\,\mathrm{d}\theta_2. \end{aligned}$$

Calculating the time derivative of $V_1(t)$ along any positive solution of model (1.2) and noticing that $x_0 = \frac{\lambda}{d}$, we can obtain

$$\begin{aligned} \frac{dV_1(t)}{dt} = & d(1 - \frac{f(x_0, 0)}{f(x, 0)})(x_0 - x) + \frac{f(x_0, 0)}{f(x, 0)}f(x, v)v \\ & - \frac{aue^{m\tau_1 + n\tau_2}}{k}v - \frac{pbe^{m\tau_1}}{c}z \\ = & d(1 - \frac{f(x_0, 0)}{f(x, 0)})(x_0 - x) - \frac{pbe^{m\tau_1}}{c}z \\ & - \frac{aue^{m\tau_1 + n\tau_2}}{k}v(1 - R_0\frac{f(x, v)}{f(x, 0)}). \end{aligned}$$

Since $f(x, v)$ is monotonically decreasing with respect to v and $R_0 < 1$, we have

$$(1 - R_0\frac{f(x, v)}{f(x, 0)}) \ge 0.$$

As $f(x, v)$ is strictly monotonically increasing with respect to x, we have

$$d(1 - \frac{f(x_0, 0)}{f(x, 0)})(x_0 - x) \le 0.$$

Therefore, $\frac{dV_1(t)}{dt} \le 0$ if $R_0 \le 1$. It is easy to show that $\frac{dV_1(t)}{dt} = 0$ if and only if $x = x_0, v = 0$ and $z = 0$. It follows from Lasalle's invariance principle [13] that E_0 is globally asymptotically stable when $R_0 \le 1$.

B. Stability of equilibrium E_1

Theorem 3.2 *If $R_0 > 1$ and $R_1 \le 1$, then CTL-absent infection equilibrium E_1 of model (1.2) is globally asymptotically stable.*

Proof: Denote $g(\xi) = \xi - 1 - \ln\xi$ with $\xi \in R_+$. Define a Lyapunov functional $V_2(t)$ as follows

$$\begin{aligned} V_2(t) = & x(t) - x_1 - \int_{x_1}^{x(t)} \frac{f(x_1, v_1)}{f(s, v_1)}\,\mathrm{d}s \\ & + e^{m\tau_1}y_1 g(\frac{y(t)}{y_1}) + \frac{pe^{m\tau_1}}{c}z(t) \\ & + \frac{ae^{m\tau_1 + n\tau_2}v_1}{k}g(\frac{v(t)}{v_1}) \\ & + f(x_1, v_1)v_1\int_{t-\tau_1}^{t} g(\frac{f(x(\theta), v(\theta))v(\theta)}{f(x_1, v_1)v_1})\mathrm{d}\theta \\ & + ae^{m\tau_1}y_1\int_{t-\tau_2}^{t} g(\frac{y(\theta)}{y_1})\mathrm{d}\theta. \end{aligned}$$

Calculating the time derivative of $V_2(t)$ along solutions of model (1.2), we obtain

$$\begin{aligned} \frac{dV_2(t)}{dt} = & d(x_1 - x(t))(1 - \frac{f(x_1, v_1)}{f(x, v_1)}) + f(x_1, v_1)v_1 \\ & - \frac{f(x_1, v_1)}{f(x, v_1)}f(x_1, v_1)v_1 + \frac{f(x_1, v_1)}{f(x, v_1)}f(x, v)v \\ & - \frac{y_1}{y(t)}f(x(t - \tau_1), v(t - \tau_1))v(t - \tau_1) \\ & + pe^{m\tau_1}y_1 z(t) - \frac{aue^{m\tau_1 + n\tau_2}}{k}v(t) \end{aligned}$$

$$
\begin{aligned}
&-\frac{av_1e^{m\tau_1}}{v(t)}y(t-\tau_2)+\frac{auv_1e^{m\tau_1+n\tau_2}}{k}\\
&+ae^{m\tau_1}y_1\ln\frac{y(t-\tau_2)}{y(t)}+ae^{m\tau_1}y_1\\
&-\frac{pbe^{m\tau_1}}{c}z(t)+f(x_1,v_1)v_1\\
&\times\ln\frac{f(x(t-\tau_1),v(t-\tau_1))v(t-\tau_1)}{f(x,v)v}.
\end{aligned}
$$

Because $f(x_1,v_1)v_1=\frac{aue^{m\tau_1+n\tau_2}}{k}v_1=ae^{m\tau_1}y_1$, Then we have

$$
\begin{aligned}
\frac{dV_2(t)}{dt}= \;& d(x_1-x(t))(1-\frac{f(x_1,v_1)}{f(x,v_1)})\\
&-f(x_1,v_1)v_1(g(\frac{f(x_1,v_1)}{f(x,v_1)})\\
&+g(\frac{y(t-\tau_2)v_1}{y_1v(t)})+g(\frac{f(x,v_1)}{f(x,v)})\\
&+g(\frac{f(x(t-\tau_1),v(t-\tau_1))v(t-\tau_1)y_1}{f(x_1,v_1)v_1y(t)}))\\
&+f(x_1,v_1)v_1(-1+\frac{f(x,v)v}{f(x,v_1)v_1}-\frac{v(t)}{v_1}\\
&+\frac{f(x,v_1)}{f(x,v)})+\frac{pe^{m\tau_1}}{c}(cy_1-b)z(t).
\end{aligned}
$$

Notice that

$$
f(x_1,v_1)v_1(-1+\frac{f(x,v)v}{f(x,v_1)v_1}-\frac{v(t)}{v_1}+\frac{f(x,v_1)}{f(x,v)})
$$

$$
=\frac{f(x_1,v_1)}{f(x,v_1)f(x,v)}(f(x,v)-f(x,v_1))(f(x,v)v-f(x,v_1)v_1).
$$

Since $f(x,v)$ is strictly monotonically increasing with respect to x, we have

$$
d(x_1-x(t))(1-\frac{f(x_1,v_1)}{f(x,v_1)})\le 0.
$$

Because $f(x,v)$ is monotonically decreasing for v and $f(x,v)v$ is monotonically increasing for v, it implies $(f(x,v)-f(x,v_1))(f(x,v)v-f(x,v_1)v_1)\le 0$. On the other hand, the function $g(\xi)=\xi-1-\ln\xi$ is always nonpositive for any function $g(\xi)>0$, and $g(\xi)=0$ if and only if $g(\xi)=1$.

If $R_1\le 1$, we have $y_1\le\frac{b}{c}$. Therefore, it is easy to see that $\frac{dV_2(t)}{dt}\le 0$. And $\frac{dV_2(t)}{dt}=0$ if and only if $x(t)=x_1,y(t)=y_1,v(t)=v_1,z(t)=0$. From Lasalle's invariance principle [13], it shows that E_1 is globally asymptotically stable when $R_0>1$ and $R_1\le 1$. This completes the proof.

C. Stability of equilibrium E_2

Theorem 3.3 *If $R_1>1$, then CTL-present infection equilibrium E_2 of model (1.2) is globally asymptotically stable.*

Proof: Define a Lyapunov functional $V_3(t)$ as follows

$$
\begin{aligned}
V_3(t)= \;& x(t)-x_2-\int_{x_2}^{x(t)}\frac{f(x_2,v_2)}{f(s,v_2)}\,\mathrm{d}s\\
&+e^{m\tau_1}y_2g(\frac{y(t)}{y_2})+\frac{pe^{m\tau_1}z_2}{c}g(\frac{z(t)}{z_2})\\
&+\frac{(a+pz_2)v_2e^{m\tau_1+n\tau_2}}{k}g(\frac{v(t)}{v_2})\\
&+f(x_2,v_2)v_2\int_{t-\tau_1}^{t}g(\frac{f(x(\theta),v(\theta))v(\theta)}{f(x_2,v_2)v_2})\mathrm{d}\theta\\
&+(a+pz_2)e^{m\tau_1}y_2\int_{t-\tau_2}^{t}g(\frac{y(\theta)}{y_2})\mathrm{d}\theta.
\end{aligned}
$$

Since

$$
\begin{aligned}
f(x_2,v_2)v_2= \;& \frac{(a+pz_2)ue^{m\tau_1+n\tau_2}}{k}v_1\\
= \;& (a+pz_2)e^{m\tau_1}y_2,
\end{aligned}
$$

$$
ke^{-n\tau_2}y_2=uv_2,\ cy_2=b.
$$

Calculating the time derivative of $V_3(t)$ along solutions of model (1.2) and using the similar method as that in the proof of Theorem 3.2, we have

$$
\begin{aligned}
\frac{dV_3(t)}{dt}= \;& d(x_2-x(t))(1-\frac{f(x_2,v_2)}{f(x,v_2)})\\
&-f(x_2,v_2)v_2(g(\frac{f(x_2,v_2)}{f(x,v_2)})\\
&+g(\frac{f(x(t-\tau_1),v(t-\tau_1))v(t-\tau_1)y_2}{f(x_2,v_2)v_2y(t)})\\
&+g(\frac{y(t-\tau_2)v_2}{y_2v(t)})+g(\frac{f(x,v_2)}{f(x,v)}))\\
&+f(x_2,v_2)v_2(-1+\frac{f(x,v)v}{f(x,v_2)v_2}\\
&-\frac{v}{v_2}+\frac{f(x,v_2)}{f(x,v)}).
\end{aligned}
$$

Notice that

$$
f(x_2,v_2)v_2(-1+\frac{f(x,v)v}{f(x,v_2)v_2}-\frac{v}{v_2}+\frac{f(x,v_2)}{f(x,v)})
$$

$$
=\frac{f(x_2,v_2)}{f(x,v_2)f(x,v)}(f(x,v)-f(x,v_2))(f(x,v)v-f(x,v_2)v_2).
$$

Since $f(x,v)$ is strictly monotonically increasing with respect to x, we have

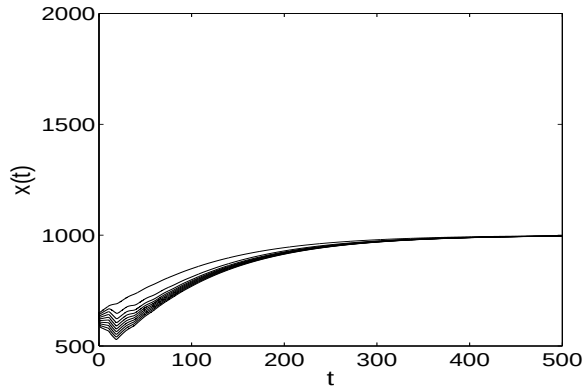
$$
d(x_2-x(t))(1-\frac{f(x_2,v_2)}{f(x,v_2)})\le 0.
$$

Because $f(x,v)$ is monotonically decreasing for v and $f(x,v)v$ is monotonically increasing for v, it implies $(f(x,v)-f(x,v_2))(f(x,v)v-f(x,v_2)v_2)\le 0$. On the other hand, the function $g(\xi)=\xi-1-\ln\xi$ is always nonpositive for any function $g(\xi)>0$, and $g(\xi)=0$ if and only if $g(\xi)=1$.

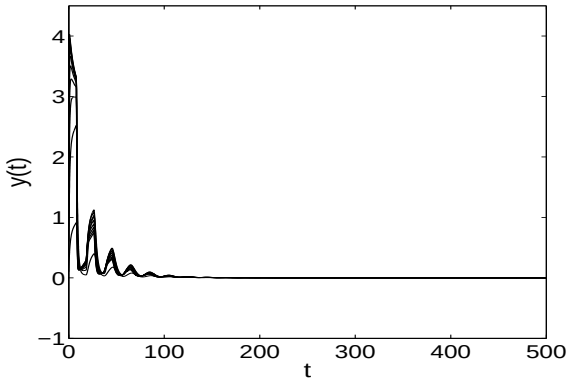
Therefore, $\frac{dV_3(t)}{dt}\le 0$. It is now easy to see that $\frac{dV_3(t)}{dt}=0$ if and only if $x(t)=x_2,y(t)=y_2,v(t)=v_2,z(t)=z_2$. From Lasalle's invariance principle [13], it shows that E_2 is globally asymptotically stable when $R_1>1$. This completes the proof.

IV. Numerical simulations

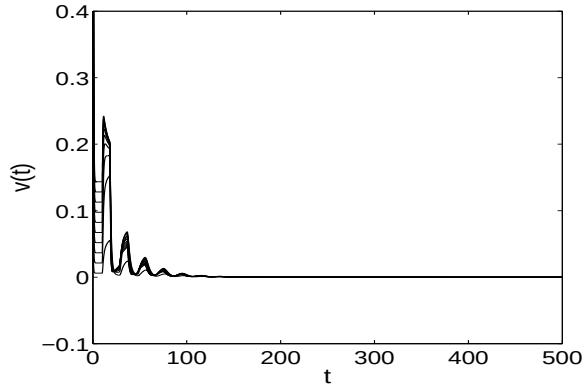
In the previous sections, we introduced the analytical tools proposed and used them for a qualitative analysis of the model obtaining some results about the dynamics of the model. In this section, we perform a numerical analysis of the model based on the section II. In model (1.2), we assume $f(x(t),v(t))=\frac{\beta x(t)}{1+a_1x(t)+b_1v(t)}$. It is easily verified that (H_1)-(H_4) hold. First we choose $c,\ k$ as free parameters. All other parameter values are the same as in Table I. In the following Figs.1-3, we denote figure (a): time-series of $x(t)$, figure (b): time-series of $y(t)$, figure (c): time-series of $v(t)$ and figure (d): time-series of $z(t)$.



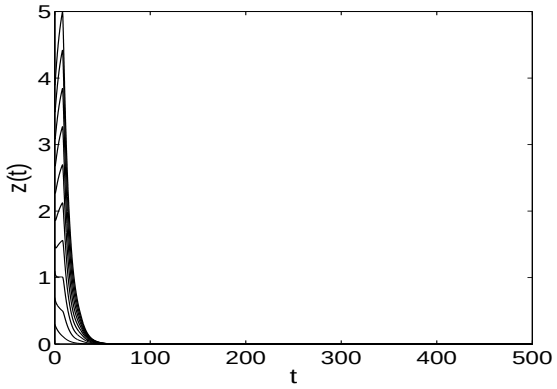
(a)



(b)

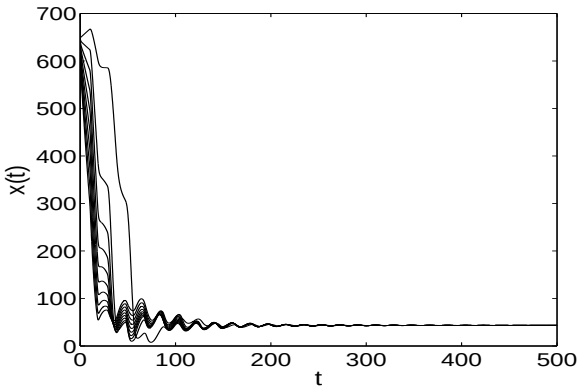


(c)

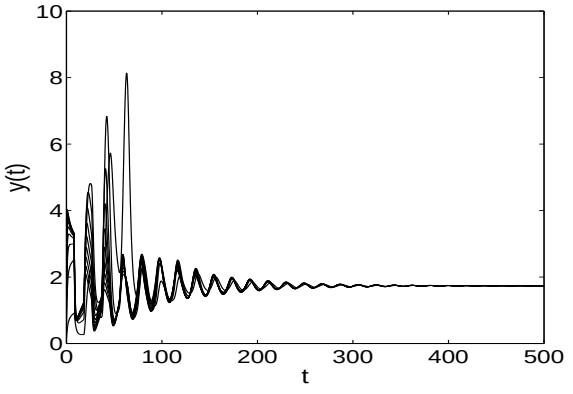


(d)

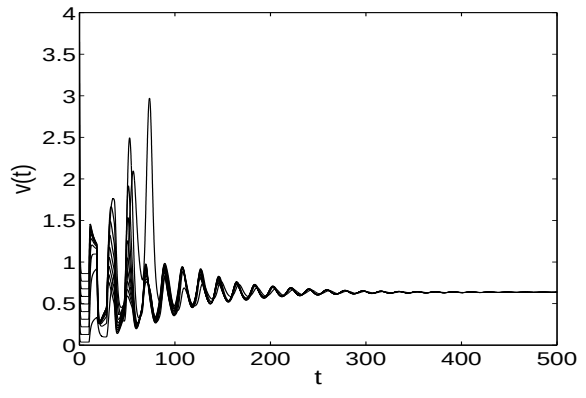
Fig.1. When $c = 0.05$ and $k = 10$, $R_0 = 0.5035 < 1$, the infection-free equilibrium E_0 is globally asymptotically stable.



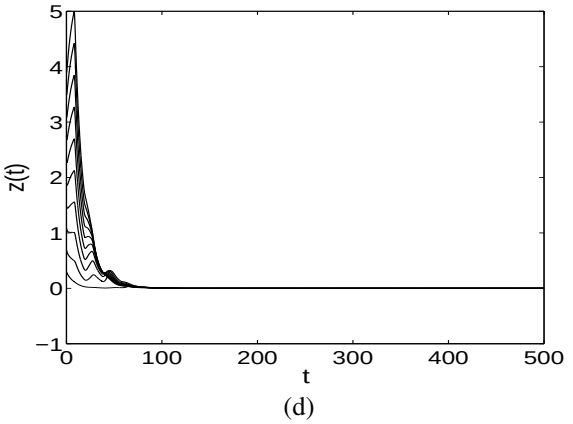
(a)



(b)



(c)



(d)

Fig.2. When $c = 0.05$ and $k = 60$, $R_0 = 3.0210 > 1$, $R_1 = -0.4772 < 1$, the CTL-absent infection equilibrium E_1 is globally asymptotically stable.

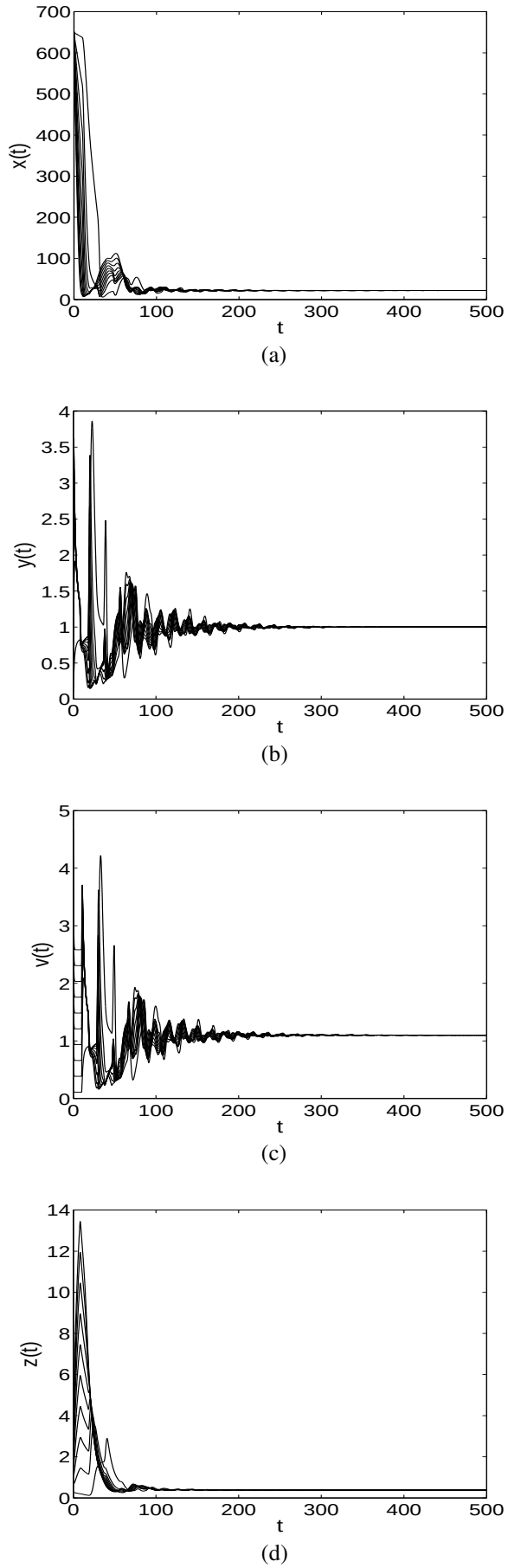


Fig.3. When $c = 0.15$ and $k = 150$, $R_1 = 1.8144 > 1$, the CTL-present infection equilibrium E_2 is globally asymptotically stable.

TABLE I
LIST OF PARAMETERS

Parameter	Value	Source
λ	10	References [23]
d	0.01	References [23]
β	0.5	References [24]
a_1	0.01	Assumed
b_1	0.01	Assumed
a	0.5	References [24]
p	1	References [9,23]
u	3	References [2,9]
τ_1	8	Assumed
τ_2	10	Assumed
m	0.3	Assumed
n	0.4	Assumed
b	0.15	References [2,9]

V. CONCLUSION

In this paper, we have discussed a delayed HIV infection model with a general incidence rate and CTL immune response. This nonlinear function $f(x, v)$ only satisfies hypotheses (H_1)-(H_4) which follow from obvious biological facts. During viral infection, the CTL immune response to HIV infection is observed in the first few weeks, coincident with the initial decline in the plasma viral load (see [25]). Wodarz et al. found that the turnover of free virus is much faster than that of infected cells, which allowed them to make a quasi-steady state assumption, that is, the amount of free virus is simply proportional to the number of infected cells in [26]. Hence, we assume that the production of CTL cells depends on the infected cells and CTL cells. We see that similar assumption is also given in [2,8,9,11,12]. In order to obtain a comprehensive view for the CTL immune dynamics in vivo, we investigate the global stability of model (1.2) by utilizing the method of constructing suitable Lyapunov functionals which are motivated by recent works of Li and Shu [4], Pawelek [9], Zhu [12], Olaniyi [14] and Huang et al. [15].

By the analysis, we have shown that when $R_0 < 1$, the infection-free equilibrium is globally asymptotically stable, which means that the viruses are cleared and the immune is not active. When $R_0 > 1$ and $R_1 < 1$, the CTL-absent infection equilibrium exists and is globally asymptotically stable, which means that the CTL immune response would not be activated and viral infection becomes vanished. When $R_1 > 1$, the CTL-present infection equilibrium is globally asymptotically stable. In this case, the virus persists. From the above analysis, we see that intracellular delay τ_1 and virus replication delay τ_2 do not affect the stability of the feasible equilibrium and therefore do not induce periodic oscillations and the possibility of Hopf bifurcations is therefore ruled out. Verifying the correctness of the conclusion is through the numerical simulation. From $R_0 = \frac{kf(\frac{\lambda}{d},0)}{aue^{m\tau_1+n\tau_2}}$, we see that the basic reproductive ratio R_0 is a decreasing function on two time delays τ_1 and τ_2. We foresee that the

endemic equilibrium disappears and the virus is cleared in the host. This can help to develop drug treatment strategies which would more effectively bring the infection under control.

As is well known, the immune response consists of both cellular response and humoral response in our body. The cellular response is that T cells kill the infected cells, the humoral response is that B cells produce an antibody to neutralize the virus. In this paper, we only consider the cellular response. In the future, our work will focus on the idea that the two kinds of immune response simultaneously play a role.

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