MATHEMATICAL BIOSCIENCES
AND ENGINEERING
Volume **10**, Number **2**, April **2013**

doi:10.3934/mbe.2013.10.483

pp. **483–498**

GLOBAL THRESHOLD DYNAMICS IN AN HIV VIRUS MODEL WITH NONLINEAR INFECTION RATE AND DISTRIBUTED INVASION AND PRODUCTION DELAYS

Zhaohui Yuan

College of Mathematics and Econometrics
Hunan University
Changsha, Hunan 410082, China

Xingfu Zou

Department of Applied Mathematics
University of Western Ontario
London, Ontario, N6A 5B7, Canada

(Communicated by Jia Li)

Abstract. We consider a mathematical model that describes the interactions of the HIV virus, CD4 cells and CTLs within host, which is a modification of some existing models by incorporating (i) two distributed kernels reflecting the variance of time for virus to invade into cells and the variance of time for invaded virions to reproduce within cells; (ii) a nonlinear incidence function f for virus infections, and (iii) a nonlinear removal rate function h for infected cells. By constructing Lyapunov functionals and subtle estimates of the derivatives of these Lyapunov functionals, we shown that the model has the threshold dynamics: if the basic reproduction number (BRN) is less than or equal to one, then the infection free equilibrium is globally asymptotically stable, meaning that HIV virus will be cleared; whereas if the BRN is larger than one, then there exist an infected equilibrium which is globally asymptotically stable, implying that the HIV-1 infection will persist in the host and the viral concentration will approach a positive constant level. This together with the dependence/independence of the BRN on f and h reveals the effect of the adoption of these nonlinear functions.

1. Introduction.

Recently there has been a substantial effort in the mathematical modeling of virus dynamics, primarily motivated the HIV and AIDS epidemic, see, e.g., [3, 4, 26, 30]. Those mathematical models can provide some insights into the dynamics of HIV viral load in vivo and may play a significant role in the development of a better understanding of HIV/AIDs and drug therapies. For example, they provided a quantitative understanding of the level of virus production during the long asymptomatic stage of HIV infection; see [8, 28, 29].

Note that the immune response after viral infection is common and is necessary for eliminating or controlling the disease. Antibodies, cytokines, natural killer cells, and T cells are essential components of a normal immune response to a virus. In most virus infections, cytotoxic T lymphocytes (CTLs) play a critical role in

2010 *Mathematics Subject Classification.* Primary: 92D30; Secondary: 34C23.
Key words and phrases. HIV, non-linear infection rate, delay, CTLs, global stability.
Research Supported by NNSF of China (61102035,11171098) and NSERC of Canada.

antiviral defense by attacking virus-infected cell. 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 interaction of HIV virions and CTLs response has recently drawn much attention of researchers in the related areas (see, e.g., [1, 2, 3, 5, 8, 10, 11, 17, 22, 25, 31, 32, 33, 37, 38] and the references therein).

Many existing mathematical models for HIV infection with CTLs response are given by systems of ordinary differential equation (ODE) (see, e. g. [2, 12, 13, 3, 15, 19, 25]). However, time delays can not be ignored when modeling immune response, since antigenic stimulation generating CTLs may need a period of time, that is, the activation rate of CTL response at time t may depend on the population of antigen at a previous time. Based on such a reality, in [5, 9, 10, 22, 27, 31, 33, 37, 38], a time delay was incorporated into HIV infection models with immune response. It has been found in [10, 31, 33, 38] that the delay in activating immune response could lead to very complicated dynamics including stable periodic solutions and chaos, and such complicated dynamical behaviors may well explain irregularity of real time series data for the immune state of a patient.

Besides the delay to immune response, it has been realized recently that there are also delays in the process of cell infection and virus production, and thus, delays should be incorporated into the infection equation and/or the virus production equation of a model. For example, a discrete delay was considered in [23] in an HIV infection model to account for the intracellular delay in the absence of immune responses. By comparing their results to those from the corresponding models without delay, the authors in [23] showed that the predicted rate of decline in plasma virus concentration depends on the length of the delay. Zhu and Zou [36] investigated a model with a discrete delay in the infection equation and another discrete delay in the virus production equation; by analyzing the two delay model, they found that large delays can help eliminate the virus. Zhu and Zou [37] added a discrete intracellular delay in HIV infection model with immune responses and their results show that larger intracellular delay may help eradicate the virus, while the activation of CTLs can only help reduce the virus load and increase the healthy $CD^{+}4$ cells population in the long term sense. Arguing that constant delays are not biologically realistic, [20, 21, 31, 34] provocated the use of distributed intracellular delays represented by general kernel functions. As a follow-up of [21], Liu and Wang [18, 24] investigated an HIV-1 infection model with a distributed intracellular delay in the infection equation and another distributed intracellular delay in the virus production equation (without considering the immune responses). Nakata [22] investigated the stability of an HIV-1 infection model with immunity mediated and two distributed intracellular delays incorporated.

In this paper, following the line of [3, 18, 22, 23, 24, 36, 37] in the context of delays, we incorporate a distributed delay into the cell infection equation and another distributed intracellular delay in the virus production equation in an HIV-1 infection model with mediated immunity. Moreover, we allow a nonlinear incidence rate and a nonlinear removal rate for the infected cells. That is, we propose the following model:

$$\begin{cases} x'(t) &=& \mu - kx(t) - \alpha x(t)f(v(t)), \\ y'(t) &=& \alpha \int_0^\infty G_1(\tau)x(t-\tau)f(v(t-\tau))\mathrm{d}\tau - ry(t) - \beta y(t)h(z(t)), \\ v'(t) &=& Nr\int_0^\infty G_2(\tau)y(t-\tau)\mathrm{d}\tau - dv(t), \\ z'(t) &=& \lambda y(t) - qz(t), \end{cases} \tag{1}$$

where x, y, v and z represent the concentrations of uninfected target cells, productively infected cells, free virus in the serum, and the effector cell of CTLs, respectively. The parameter μ is the rate at which new target cells are generated, k is the death rate of the susceptible cells and α is the constant characterizing the infection rate. The infected cells are assumed to die at a rate r (say, via lysis) due to the action of virus, each releasing N new virus particles as the lysis of infected cells occurs. Virus particles are cleared from the system at rate d. β accounts for the strength of the lytic component. Effectors are generated in the presence of infected cells at rate λ, and q is the death rate for CTLs. To account for the time lag between viral entry into a target cell and the production of new virus particles, two distributed intracellular delays are introduced with kernel functions given by $G_i(\tau) = f_i(\tau)e^{-m_i\tau}, (i = 1, 2)$. $G_1(\tau)$ is the probability that target cells contacted by the virus particles at time $t-\tau$ survived τ time units and become infected at time t and $G_2(\tau)$ is the probability that a cell infected at time $t-\tau$ starts to yield new infectious virus at time t. Since our focus here is on the virus production part and (1) already contains two distributed delays, we neglect the delays in activating CTLs in this work to avoid further complicating the model.

All parameters in (1) are assumed to be positive. The function $f(\xi)$ denotes the force of infection by virus 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 satisfying

(A1): $f(0) = 0$, $f'(\xi)$ exists and satisfies $f'(\xi) \geq 0$ and $\left(\frac{f(\xi)}{\xi}\right)' \leq 0$ in $(0, \infty)$;
(A2): $h(0) = 0$ and $h(\xi)$ is strictly increasing in $[0, \infty)$.

Assume the kernel functions G_1 and G_2 satisfy

(A3): $G_i(\tau) > 0$, for $\tau > 0$, and $0 < a_i := \int_0^\infty G_i(\xi)\mathrm{d}\xi \leq 1$, $i = 1, 2$.

We remark that (A3) is typical for a delay kernel. For h we do not require smoothness, but for f we do for the sake of linearization of (1) at the disease free equilibrium. While the condition $f'(\xi) \geq 0$ in (A1) ensures monotonicity which is a standard requirement for an infection force, the condition $\left(\frac{f(\xi)}{\xi}\right)' \leq 0$ is a technical one required in Lemma 4.1 (hence in Theorem 4.1). We point out that assumptions (A1) and (A2) are sufficiently general to encompass many forms of commonly used incidence rates, including simple mass action and the saturation incident rate. For justifications for considering nonlinear incidence rate and nonlinear removal rate in virus dynamics models, see, e.g., [7, 14, 35]. When both f and h are linear and CTL activation term $\lambda y(t)$ is replaced by the bilinear function $\lambda y(t)z(t)$ in (1), one obtain the model studied in [22]. Here, we follow [2, 32] to use the linear function, and we will compare the results in the conclusion section.

System (1) includes many special cases. For example, when $f_1(\tau) = f_2(\tau) = \delta(\tau - 0)$ with $\delta(\cdot)$ being the Dirac delta function, the incidence rate of the infection $f(\xi) = \xi$ and the removal rate of the infection $h(\xi) = \xi$, system (1) reduces to an ODE model that has been widely studied in literature (see [1, 8, 10] and references therein). Applying the Routh-Hurwitz conditions for linear systems, the stability of such an ODE model has been studied in [10] and some complex sufficient conditions ensuring the local stability of the non-infected equilibrium as well as the infected equilibrium are obtained.

For a model describing virus dynamics, a challenge of the model analysis is to establish the *global* stability of the unique infected equilibrium. Local stability can be tested by linearizing the model at its equilibrium and checking the eigenvalues of the corresponding characteristic equation. While there is no standard procedure to test global stability, the commonly used method is to construct a Lyapunov function (for ordinary differential equation systems) or functional (for delay differential equation systems), which is often very challenging, if not impossible. The aim of this paper is to establish global stability for system (1).

The rest of the paper is organized as follows. In Section 2, we will consider well-posedness of the model by addressing the positivity and boundedness of solutions of the model, and identify the basic reproduction number $\mathcal{R}_0$ for the model. We show that $\mathcal{R}_0 \leq 1$, the infection free equilibrium E_0 is the only equilibrium, while when $\mathcal{R}_0 > 1$ there is an infected equilibrium E^* in addition to E^0. In Section 3, we show that the infection free equilibrium is globally asymptotically stable if $\mathcal{R}_0 \leq 1$; and in Section 4, we prove E^* is globally asymptotically stable if $\mathcal{R}_0 > 1$, confirming the threshold role of $\mathcal{R}_0$ at the value 1. These global stability results are obtained by constructing proper Lyapunov functionals and using some subtle estimates of the derivatives of the Lyapunov functionals. Conclusions and some discussion are included in Section 5.

2. **Well-posedness and basic reproduction number.**

For biologically reasons, we only consider non-negative initial functions:

$$\phi(\theta) = (\phi_1(\theta), \phi_2(\theta), \phi_3(\theta), \phi_4(\theta)) \in UC_g((-\infty, 0], \mathbb{R}^4_+), \tag{2}$$

here $\mathbb{R}^4_+ = \{(x_1, x_2, x_3, x_4) : x_i \geq 0, i = 1, 2, 3, 4\}$ and the notation of UC_g, see [16]. Note that (A1)-(A2) assumes that the nonlinear functions f and h are quite standard ones. By the fundamental theory for integral-differential equations (see, e.g.,[6]), we know that system (1) and (2) has an unique solution on maximal interval $t \in [0, T_\phi)$. The following theorem shows that for positive initial values, the solution remains positive and is bounded, implying $T_\phi = \infty$, that is, the solution exists globally.

Theorem 2.1. *Let $(x(t), y(t), v(t), z(t))^T$ be the unique solution to system (1) and (2) with $\phi_i(0) > 0$ $(i = 1, 2, 3, 4)$. Then $x(t), y(t), v(t)$ and $z(t)$ are positive for all $t > 0$. Moreover, the solution is bounded and thus exists globally.*

Proof. Using the variation-of-constants formula, we obtain from (1) that

$$\begin{aligned}
x(t) &= x(0)e^{-\int_0^t (k+\alpha f(v(s)))\mathrm{d}s} + \mu \int_0^\infty e^{-\int_s^t (m+\beta v(\xi))\mathrm{d}\xi}\mathrm{d}s, \\
y(t) &= y(0)e^{-\int_0^t (r+\int_0^t h(z(s)))\mathrm{d}s} \\
&\quad + \alpha \int_0^t e^{-\int_s^t (r+h(z(\zeta)))\mathrm{d}\zeta} \int_0^\infty G_1(\xi)x(s-\xi)f(v(s-\xi))\mathrm{d}\xi\mathrm{d}s, \\
v(t) &= v(0)e^{-dt} + Nr \int_0^t e^{-d(t-s)} \int_0^\infty G_2(\xi)y(s-\xi)\mathrm{d}\xi\mathrm{d}s, \\
z(t) &= z(0)e^{-qt} + \lambda \int_0^t e^{-q(t-s)}y(s)\mathrm{d}s,
\end{aligned}$$

which yields the positivity of $x(t), y(t), v(t)$ and $z(t)$.

Next we show that the solution is also bounded. It follows from the first equation of system (1) that $x'(t) \leq \mu - kx(t)$. This implies $\limsup_{t\to\infty} x(t) \leq \frac{\mu}{k}$. Let

$$U(t) = \int_0^\infty G_1(\xi)x(t-\xi)\mathrm{d}\xi + y(t).$$

Then

$$\begin{aligned} U'(t)|_{(1)} &= \int_0^\infty G_1(\xi)x'(t-\xi)\mathrm{d}\xi + y'(t) \\ &= \int_0^\infty G_1(\xi)\left(\mu - kx(t-\xi) - \alpha x(t-\xi)f(v(t-\xi))\right)\mathrm{d}\xi \\ &\quad +\alpha\int_0^\infty G_1(\xi)x(t-\xi)f(v(t-\xi))\mathrm{d}\xi - ry(t) - \beta y(t)h(z(t)) \\ &= \mu a_1 - k\int_0^\infty G_1(\xi)x(t-\xi)\mathrm{d}\xi - ry(t) - \beta y(t)h(z(t)) \\ &\leq \mu a_1 - pU(t), \end{aligned}$$

where $p = \min\{r, k\}$ and thus $\limsup_{t\to\infty} \leq \frac{\mu a_1}{p}$. This implies that $U(t)$ is eventually bounded and so is $y(t)$. Thus, there exists a $M > 0$ such that $y(t) \leq M$ for $t \in (-\infty, \infty)$. It follow from the third and fourth equations in (1) that

$$v'(t) \leq ra_2NM - dv(t), \quad z'(t) \leq \lambda M - qz(t), \quad \forall t \geq 0,$$

proving the boundedness of $v(t)$ and $z(t)$. Therefore, the system (1) is dissipative and hence the solution of (1) exists globally. □

Let

$$\mathcal{R}_0 = \frac{\mu}{k}\,\frac{a_1\alpha f'(0)}{r}\,\frac{Nra_2}{d} = \frac{\mu\alpha f'(0)Na_1a_2}{kd}, \tag{3}$$

which is called the basic reproductive number of system (1). For system (1), there exists an infection free equilibrium $E_0 = (\mu/k, 0, 0, 0)$. Now we show that $\mathcal{R}_0 > 1$ is a sufficient condition ensuring the existence of an infected equilibrium (positive equilibrium) $E^* = (x^*, y^*, v^*, z^*)$. By simple calculation, we know that the existence of an infected equilibrium is equivalent to the existence of a positive root of the equation $L(v) = 0$ where

$$L(v) = \frac{\alpha a_1\mu f(v)}{k + \alpha f(v)} - \frac{d}{Na_2}v - \frac{\beta dv}{Nra_2}h\left(\frac{\lambda dv}{Nrqa_2}\right). \tag{4}$$

Since

$$L(0) = 0, \quad L'(0) = \frac{d}{Na_2}(\mathcal{R}_0 - 1) > 0, \quad L(+\infty) = -\infty,$$

it follows from the continuity of the function $L(v)$ in $[0, \infty)$ that $L(v) = 0$ has at least one positive root. Hence, we see that (2) at least has one infected equilibrium $E^* = (x^*, y^*, v^*, z^*)$ when $\mathcal{R}_0 > 1$.

For convenience, we rewrite (1) as

$$\begin{cases} x'(t) &=& \mu - kx(t) - \alpha x(t) f(v(t)), \\ y'(t) &=& \alpha_1 \int_0^\infty g_1(\xi) x(t-\xi) f(v(t-\xi)) \mathrm{d}\xi - ry(t) - \beta y(t) h(z(t)), \\ v'(t) &=& \alpha_2 \int_0^\infty g_2(\xi) y(t-\xi) \mathrm{d}\xi - dv(t), \\ z'(t) &=& \lambda y(t) - qz(t), \end{cases} \tag{5}$$

where $\alpha_1 = \alpha a_1$, $\alpha_2 = Nra_2$ and $g_i(\xi) = \frac{G_i(\xi)}{a_i}$ for $i = 1, 2$. Recall that $a_i = \int_0^\infty G_i(\xi)\mathrm{d}\xi$, thus $\int_0^\infty g_i(\xi)\mathrm{d}\xi = 1$. Then the basic reproduction number $\mathcal{R}_0$ defined in (3) can be rewritten as

$$\mathcal{R}_0 = \frac{\mu \alpha_1 \alpha_2 f'(0)}{krd}$$

for system (5).

3. Stability of the infection-free equilibrium E_0.

Theorem 3.1. *If $\mathcal{R}_0 \leq 1$, then the infection free equilibrium E_0 of (2) is globally asymptotically stable.*

Proof. Let

$$H_i(t) = \int_t^\infty g_i(\xi)\mathrm{d}\xi, \quad i = 1, 2$$

and $W(t) = \sum_{i=1}^3 W_i(t)$ with

$$\begin{aligned} W_1(t) &= \frac{1}{2}\left(x(t) - \frac{\mu}{k}\right)^2 + \frac{\alpha\mu}{\alpha_1 k} y(t) + \frac{\alpha\mu r}{k\alpha_1\alpha_2} v(t) + \frac{\alpha\mu\beta}{k\lambda\alpha_1} \int_0^{z(t)} h(\xi)\mathrm{d}\xi, \\ W_2(t) &= \frac{\alpha\mu}{k} \int_0^\infty H_1(\xi) x(t-\xi) f(v(t-\xi))\mathrm{d}\xi, \\ W_3(t) &= \frac{\alpha\mu r}{k\alpha_1} \int_0^\infty H_2(\xi) y(t-\xi)\mathrm{d}\xi. \end{aligned}$$

It is clear that $W(t) \geq 0$ and $W(t) = 0$ if and only if $x(t) = \frac{\mu}{k}$, $y(t) = v(t) = z(t) = 0$. The derivative of W_1 along the solution of (5) is

$$\begin{aligned} W_1'(t) &= \left(x(t) - \frac{\mu}{k}\right)(\mu - kx(t) - \alpha x(t) f(v(t))) \\ &\quad + \frac{\alpha\mu}{k} \int_0^\infty g_1(\xi) x(t-\xi) f(v(t-\xi))\mathrm{d}\xi - \frac{\alpha\mu r}{k\alpha_1} y(t) - \frac{\alpha\mu\beta}{k\alpha_1} y(t) h(z(t)) \\ &\quad + \frac{\alpha\mu r}{k\alpha_1} \int_0^\infty g_2(\xi) y(t-\xi)\mathrm{d}\xi - \frac{\alpha\mu r d}{k\alpha_1\alpha_2} v(t) \\ &\quad + \frac{\alpha\mu\beta}{k\lambda\alpha_1} h(z(t))[\lambda y(t) - qz(t)]. \end{aligned}$$

Note that $H_1(0) = 1$, $H_1(\infty) = 0$, $\mathrm{d}H_1(t) = -g_1(t)\mathrm{d}t$. Using integration by parts, we calculate the derivative of W_2 as

$$\begin{aligned} W_2'(t) &= \frac{\alpha\mu}{k}\int_0^\infty H_1(\xi)\frac{\mathrm{d}(x(t-\xi)f(v(t-\xi)))}{\mathrm{d}t}\mathrm{d}\xi \\ &= -\frac{\alpha\mu}{k}\int_0^\infty H_1(\xi)\frac{\mathrm{d}(x(t-\xi)f(v(t-\xi)))}{\mathrm{d}\xi}\mathrm{d}\xi \\ &= -\frac{\alpha\mu}{k}H_1(\xi)x(t-\xi)f(v(t-\xi))\Big|_{\xi=0}^{\infty} + \frac{\alpha\mu}{k}\int_0^\infty x(t-\xi)f(v(t-\xi))\mathrm{d}H_1(\xi) \\ &= \frac{\alpha\mu}{k}x(t)f(v(t)) - \frac{\alpha\mu}{k}\int_0^\infty g_1(\xi)x(t-\xi)f(v(t-\xi))\mathrm{d}\xi. \end{aligned}$$

Similarly,

$$W_3'(t) = \frac{\alpha\mu r}{k\alpha_1}y(t) - \frac{\alpha\mu r}{k\alpha_1}\int_0^\infty g_2(\xi)y(t-\xi)\mathrm{d}\xi.$$

Thus

$$\begin{aligned} W'(t) &= -\frac{1}{k}\left(x(t)-\frac{\mu}{k}\right)^2 - \alpha x(t)f(v(t))\left(x(t)-\frac{\mu}{k}\right) \\ &\quad +\frac{\alpha\mu}{k}\int_0^\infty g_1(\xi)x(t-\xi)f(v(t-\xi))\mathrm{d}\xi - \frac{\alpha\mu r}{k\alpha_1}y(t) - \frac{\alpha\mu\beta}{k\alpha_1}y(t)h(z(t)) \\ &\quad +\frac{\alpha\mu r}{k\alpha_1}\int_0^\infty g_2(\xi)y(t-\xi)\mathrm{d}\xi - \frac{\alpha\mu r d}{k\alpha_1\alpha_2}v(t) + \frac{\alpha\mu\beta}{k\alpha_1}y(t)h(z(t)) \\ &\quad -\frac{\alpha\mu\beta q}{k\lambda\alpha_1}z(t)h(z(t)) + \frac{\alpha\mu}{k}x(t)f(v(t)) + \frac{\alpha\mu r}{k\alpha_1}y(t) \\ &\quad -\frac{\alpha\mu}{k}\int_0^\infty g_1(\xi)x(t-\xi)f(v(t-\xi))\mathrm{d}\xi - \frac{\alpha\mu r}{k\alpha_1}\int_0^\infty g_2(\xi)y(t-\xi)\mathrm{d}\xi \\ &= -\frac{1}{k}\left(x(t)-\frac{\mu}{k}\right)^2 - \alpha f(v(t))\left(x^2(t)-\frac{2\mu}{k}x(t)+\frac{\mu^2}{k^2}\right) \\ &\quad +\frac{\alpha\mu^2}{k^2}f(v(t)) - \frac{\alpha\mu r d}{k\alpha_1\alpha_2}v(t) - \frac{\alpha\mu\beta q}{k\lambda\alpha_1}z(t)h(z(t)) \\ &= \left[-\frac{1}{k}\left(x(t)-\frac{\mu}{k}\right)^2 - \alpha f(v(t))\left(x-\frac{\mu}{k}\right)^2 - \frac{\alpha\mu\beta q}{k\lambda\alpha_1}z(t)h(z(t))\right] \\ &\quad +\frac{\alpha\mu r d}{k\alpha_1\alpha_2}\left(\frac{\mu\alpha_1\alpha_2}{krd}\frac{f(v(t))}{v(t)}-1\right)v(t). \end{aligned} \tag{6}$$

It is clear that the square bracket term is non-positive, and is zero if and only $x(t) = \mu/k$ and $z(t) = 0$. For the last term in the above, (A1) implies

$$\begin{aligned} &\left(\frac{\mu\alpha_1\alpha_2}{krd}\frac{f(v(t))}{v(t)}-1\right)v(t) \\ &\le \left(\frac{\mu\alpha_1\alpha_2 f'(0)}{krd}-1\right)v(t) \\ &= (\mathcal{R}_0-1)\,v(t) \end{aligned} \tag{7}$$

which is zero if $\mathcal{R}_0 = 1$, and negative if $\mathcal{R}_0 < 1$ except at $v(t) = 0$ when it also becomes zero. Combining the signs in the bracket in (6) and that in (7), we know that $W'(t) \le 0$ and $\{E_0\}$ is the largest invariant subset of $\{W' = 0\}$. The global stability of E_0 follows from the classical Lyapunov-LaSalle invariance principle (see, for example, [16]). $\square$

4. **Stability of the infected equilibrium E^*.** Let

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

and

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

We note that $g : (0, \infty) \mapsto [0, \infty)$ has the global minimum $g(1) = 0$ and remains positive elsewhere for $\xi \in (0, \infty)$. In order to prove the globally asymptotical stability of the infected equilibrium, we need the following lemma.

Lemma 4.1. *If $f(\xi)$ satisfies Assumption (A1), then*

$$g(F(w)) \leq g(w), \quad \text{for} \quad w > 0$$

with the equality holding only at $w = 1$.

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 $w \leq F(w) \leq 1$ for $w \in (0, 1)$ and $1 \leq F(w) \leq w$ for $w \in [1, \infty)$. The proof of Case $w \in [1, \infty)$ is similar to that of Case $w \in (0, 1)$, so we only consider Case $w \in (0, 1)$. Note that $w \leq F(w) \leq 1$ is equivalent to $\frac{f(v^*)}{v^*} \leq \frac{f(v^*w)}{v^*w} \leq \frac{f(v^*)}{v^*w}$ for $w \in (0, 1)$, and the latter directly follows from assumption (A1). The proof is completed. $\square$

Theorem 4.2. *If $\mathcal{R}_0 > 1$, then E_1 is globally asymptotically stable if for all positive solutions.*

Proof. In order to simplify the expressions related to E^*, we will make use of the equations for E^*:

$$\mu = kx^* + \alpha x^* f(v^*), \tag{8}$$

$$\alpha_1 x^* f(v^*) = ry^* + \beta y^* h(z^*), \tag{9}$$

$$\alpha_2 y^* = dv^* \tag{10}$$

and

$$\lambda y^* = qz^*. \tag{11}$$

Let

$$\begin{aligned} V_1(t) &= g\left(\tfrac{x(t)}{x^*}\right), \qquad V_2(t) = \textstyle\int_0^\infty H_1(\xi) g\left(\tfrac{x(t-\xi)f(v(t-\xi))}{x^* f(v^*)}\right) \mathrm{d}\xi, \\ V_3(t) &= g\left(\tfrac{y(t)}{y^*}\right), \qquad V_4(t) = g(\tfrac{v(t)}{v^*}), \\ V_5(t) &= \textstyle\int_{z^*}^{z(t)} [h(\xi) - h(z^*)] \mathrm{d}\xi, \qquad V_6(t) = \textstyle\int_0^\infty H_2(\xi) g\left(\tfrac{y(s)}{y^*}\right) \mathrm{d}s. \end{aligned} \tag{12}$$

We will study the derivative of the Lyapunov functional

$$\begin{aligned} V(t) &= x^* V_1(t) + \alpha x^* f(v^*) V_2(t) + \tfrac{\alpha y^*}{\alpha_1} V_3(t) + \tfrac{\alpha r v^*}{\alpha_1 \alpha_2} V_4(t) \\ &\quad + \tfrac{\alpha\beta}{\lambda\alpha_1} V_5(t) + \tfrac{\alpha\beta y^* h(z^*)}{d\alpha_1} V_4(t) + \alpha x^* f(v^*) V_6(t). \end{aligned} \tag{13}$$

Obviously, V(t) is well defined and $V(t) \geq 0$ with the equality holding if and only if $x(t) = x^*, y(t) = y^*, v(t) = v^*, z(t) = z^*$ and $x(t - \xi) f(v(t - \xi)) = x^* f(v^*)$,

$y(t-\xi) = y^*$ for almost all $\xi \in [0, \infty)$. For clarity of evaluation $V'(t)$, we first calculate derivatives of $V_1, V_2, \cdots, V_6$ along the solution of (5) as below.

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

Using (8) to replace μ gives

$$\begin{aligned} V_1'(t) &= \frac{1}{x^*}\left(1 - \frac{x^*}{x(t)}\right)[k(x^* - x(t)) + \alpha(x^* f(v^*) - x(t) f(v(t)))]. \\ &= -\frac{k(x(t)-x^*)^2}{x^* x(t)} + \alpha f(v^*)\left(1 - \frac{x^*}{x(t)} - \frac{x(t) f(v(t))}{x^* f(v^*)} + \frac{f(v(t))}{f(v^*)}\right). \end{aligned} \tag{14}$$

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

$$\begin{aligned} V_2'(t) &= \int_0^\infty H_1(\xi) \frac{\mathrm{d}(g(\frac{x(t-\xi) f(v(t-\xi))}{x^* f(v^*)}))}{\mathrm{d}t} \mathrm{d}\xi \\ &= -\int_0^\infty H_1(\xi) \frac{\mathrm{d}(g(\frac{x(t-\xi) f(v(t-\xi))}{x^* f(v^*)}))}{\mathrm{d}\xi} \mathrm{d}\xi \\ &= -H_1(\xi) g\left(\frac{x(t-\xi) f(v(t-\xi))}{x^* f(v^*)}\right)\Bigg|_{\xi=0}^{\infty} \\ &\quad + \int_0^\infty g\left(\frac{x(t-\xi) f(v(t-\xi))}{x^* f(v^*)}\right) \mathrm{d}H_1(\xi) \\ &= g\left(\frac{x(t) f(v(t))}{x^* f(v^*)}\right) - \int_0^\infty g_1(\xi) g\left(\frac{x(t-\xi) f(v(t-\xi))}{x^* f(v^*)}\right) \mathrm{d}\xi \\ &= \frac{x(t) f(v(t))}{x^* f(v^*)} - \ln \frac{x(t) f(v(t))}{x^* f(v^*)} - \int_0^\infty g_1(\xi) \frac{x(t-\xi) f(v(t-\xi))}{x^* f(v^*)} \mathrm{d}\xi \\ &\quad + \int_0^\infty g_1(\xi) \ln \frac{x(t-\xi) f(v(t-\xi))}{x^* f(v^*)} \mathrm{d}\xi \\ &= \frac{x(t) f(v(t))}{x^* f(v^*)} - \int_0^\infty g_1(\xi) \frac{x(t-\xi) f(v(t-\xi))}{x^* f(v^*)} \mathrm{d}\xi \\ &\quad + \int_0^\infty g_1(\xi) \ln \frac{x(t-\xi) f(v(t-\xi))}{x(t) f(v(t))} \mathrm{d}\xi, \end{aligned}$$

where again we use the fact that $H_1(0) = 1$, $H_1(\infty) = 0$, $\mathrm{d}H_1(t) = -g_1(t)\mathrm{d}t$ and integration by parts. We now calculate derivative of $V_3(t)$ along the solution of (5):

$$\begin{aligned} V_3'(t) =& \frac{1}{y^*}\left(1 - \frac{y^*}{y(t)}\right) y'(t) \\ =& \left(\frac{1}{y^*} - \frac{1}{y(t)}\right)\left(\alpha_1 \int_0^\infty g_1(\xi) x(t-\xi) f(v(t-\xi)) \mathrm{d}\xi - ry(t) - \beta y(t) h(z(t))\right) \\ =& \frac{\alpha_1 x^* f(v^*)}{y^*} \int_0^\infty g_1(\xi) \frac{x(t-\xi) f(v(t-\xi))}{x^* f(v^*)} \mathrm{d}\xi \\ & - \frac{\alpha_1 x^* f(v^*)}{y^*} \int_0^\infty g_1(\xi) \frac{x(t-\xi) y^* f(v(t-\xi))}{x^* y(t) f(v^*)} \mathrm{d}\xi \end{aligned}$$

$$-r\left(\frac{y(t)}{y^*}-1\right)-\beta h(z^*)\left(\frac{y(t)h(z(t))}{y^*h(z^*)}-\frac{h(z(t))}{h(z^*)}\right).$$

Using (9), we obtain

$$\begin{aligned}
V_3'(t) &= \frac{\alpha_1 x^* f(v^*)}{y^*}\int_0^\infty g_1(\xi)\frac{x(t-\xi)f(v(t-\xi))}{x^*f(v^*)}\mathrm{d}\xi \\
&\quad -\frac{\alpha_1 x^* f(v^*)}{y^*}\int_0^\infty g_1(\xi)\frac{x(t-\xi)y^*f(v(t-\xi))}{x^*y(t)f(v^*)}\mathrm{d}\xi \\
&\quad -r\left(\frac{y(t)}{y^*}-1\right)-\left(\frac{\alpha_1 x^* f(v^*)}{y^*}-r\right)\left(\frac{y(t)h(z(t))}{y^*h(z^*)}-\frac{h(z(t))}{h(z^*)}\right) \\
&= \frac{\alpha_1 x^* f(v^*)}{y^*}\int_0^\infty g_1(\xi)\frac{x(t-\xi)f(v(t-\xi))}{x^*f(v^*)}\mathrm{d}\xi \qquad (15)\\
&\quad -\frac{\alpha_1 x^* f(v^*)}{y^*}\int_0^\infty g_1(\xi)\frac{x(t-\xi)y^*f(v(t-\xi))}{x^*y(t)f(v^*)}\mathrm{d}\xi \\
&\quad -\frac{y(t)h(z(t))}{y^*h(z^*)}+\frac{h(z(t))}{h(z^*)}\Bigg]+r\left(1-\frac{y(t)}{y^*}+\frac{y(t)h(z(t))}{y^*h(z^*)}-\frac{h(z(t))}{h(z^*)}\right).
\end{aligned}$$

The derivatives of $V_4(t)$ and $V_5(t)$ are

$$\begin{aligned}
V_4'(t) &= \frac{1}{v^*}\left(1-\frac{v^*}{v(t)}\right)v'(t) \\
&= \frac{1}{v^*}\left(1-\frac{v^*}{v(t)}\right)\left(\alpha_2\int_0^\infty g_2(\xi)y(t-\xi)\mathrm{d}\xi-dv(t)\right) \\
&= d\left(1-\frac{v(t)}{v^*}+\int_0^\infty g_2(\xi)\frac{y(t-\xi)}{y^*}\mathrm{d}\xi-\int_0^\infty g_2(\xi)\frac{v^*y(t-\xi)}{v(t)y^*}\mathrm{d}\xi\right). \qquad (16)
\end{aligned}$$

$$\begin{aligned}
V_5'(t) &= [h(z(t))-h(z^*)][\lambda y(t)-qz(t)] \\
&= -q[z(t)-z^*][h(z(t))-h(z^*)] \\
&\quad +\lambda y^*h(z^*)\left(\frac{y(t)h(z(t))}{y^*h(z^*)}-\frac{y(t)}{y^*}-\frac{h(z(t))}{h(z^*)}+1\right). \qquad (17)
\end{aligned}$$

Similar to the derivative of $V_2'(t)$, differentiating $V_6(t)$ gives

$$V_6'(t) = \frac{y(t)}{y^*}-\int_0^\infty g_2(\xi)\frac{y(t-\xi)}{y^*}\mathrm{d}\xi+\int_0^\infty g_2(\xi)\ln\frac{y(t-\xi)}{y(t)}\mathrm{d}\xi. \qquad (18)$$

Multiplying the above derivative terms by the respective coefficients determined by (13), and adding the all resulting terms, we obtain

$$\begin{aligned}
V'(t) &= -\frac{k(x(t)-x^*)^2}{x(t)}+\alpha x^*f(v^*)\Bigg(1-\frac{x^*}{x(t)}+\frac{f(v(t))}{f(v^*)} \\
&\quad -\int_0^\infty g_1(\xi)\frac{x(t-\xi)f(v(t-\xi))}{x^*f(v^*)}\mathrm{d}\xi+\int_0^\infty g_1(\xi)\ln\frac{x(t-\xi)f(v(t-\xi))}{x(t)f(v(t))}\mathrm{d}\xi\Bigg)
\end{aligned}$$

$$
\begin{aligned}
&+\alpha x^*f(v^*)\int_0^\infty g_1(\xi)\frac{x(t-\xi)f(v(t-\xi))}{x^*f(v^*)}\mathrm{d}\xi\\
&-\alpha x^*f(v^*)\int_0^\infty g_1(\xi)\frac{x(t-\xi)y^*f(v(t-\xi))}{x^*y(t)f(v^*)}\mathrm{d}\xi\\
&-\alpha x^*f(v^*)\left(\frac{y(t)h(z(t))}{y^*h(z^*)}-\frac{h(z(t))}{h(z^*)}\right)\\
&+\frac{r\alpha y^*}{\alpha_1}\left(1-\frac{y(t)}{y^*}+\frac{y(t)h(z(t))}{y^*h(z^*)}-\frac{h(z(t))}{h(z^*)}\right)\\
&+\frac{\alpha r d v^*}{\alpha_1\alpha_2}\left(1-\frac{v(t)}{v^*}+\int_0^\infty g_2(\xi)\frac{y(t-\xi)}{y^*}\mathrm{d}\xi-\int_0^\infty g_2(\xi)\frac{v^*y(t-\xi)}{v(t)y^*}\mathrm{d}\xi\right)\\
&-\frac{q\alpha\beta}{\lambda\alpha_1}[z(t)-z^*][h(z(t))-h(z^*)]\\
&+\frac{\alpha\beta y^*h(z^*)}{\alpha_1}\left(\frac{y(t)h(z(t))}{y^*h(z^*)}-\frac{y(t)}{y^*}-\frac{h(z(t))}{h(z^*)}+1\right)\\
&+\frac{\alpha\beta y^*h(z^*)}{\alpha_1}\left(1-\frac{v(t)}{v^*}+\int_0^\infty g_2(\xi)\frac{y(t-\xi)}{y^*}\mathrm{d}\xi-\int_0^\infty g_2(\xi)\frac{v^*y(t-\xi)}{v(t)y^*}\mathrm{d}\xi\right)\\
&+\alpha x^*f(v^*)\left(\frac{y(t)}{y^*}-\int_0^\infty g_2(\xi)\frac{y(t-\xi)}{y^*}\mathrm{d}\xi+\int_0^\infty g_2(\xi)\ln\frac{y(t-\xi)}{y(t)}\mathrm{d}\xi\right)
\end{aligned}
$$

Note that (9) and (10) implies

$$\frac{rdv^*}{\alpha_2}=ry^*=\alpha_1x^*f(v^*)-\beta y^*h(z^*).$$

Thus, we can simplify the above as

$$
\begin{aligned}
&V'(t)\\
=\;&-\frac{k(x(t)-x^*)^2}{x(t)}-\frac{q\alpha\beta}{\lambda\alpha_1}[z(t)-z^*][h(z(t))-h(z^*)]\\
&+\alpha x^*f(v^*)\left(1-\frac{x^*}{x(t)}+\frac{f(v(t))}{f(v^*)}-\frac{y(t)h(z(t))}{y^*h(z^*)}+\frac{h(z(t))}{h(z^*)}\right)\\
&+\alpha x^*f(v^*)\int_0^\infty g_1(\xi)\ln\frac{x(t-\xi)f(v(t-\xi))}{x(t)f(v(t))}\mathrm{d}\xi\\
&-\alpha x^*f(v^*)\int_0^\infty g_1(\xi)\frac{x(t-\xi)y^*f(v(t-\xi))}{x^*y(t)f(v^*)}\mathrm{d}\xi\\
&+\frac{r\alpha y^*}{\alpha_1}\left(1-\frac{y(t)}{y^*}+\frac{y(t)h(z(t))}{y^*h(z^*)}-\frac{h(z(t))}{h(z^*)}\right)\\
&+\left(\alpha x^*f(v^*)-\frac{\alpha\beta y^*h(z^*)}{\alpha_1}\right)\left(1-\frac{v(t)}{v^*}\right.\\
&\left.+\int_0^\infty g_2(\xi)\frac{y(t-\xi)}{y^*}\mathrm{d}\xi-\int_0^\infty g_2(\xi)\frac{v^*y(t-\xi)}{v(t)y^*}\mathrm{d}\xi\right)\\
&+\frac{\alpha\beta y^*h(z^*)}{\alpha_1}\left(\frac{y(t)h(z(t))}{y^*h(z^*)}-\frac{y(t)}{y^*}-\frac{h(z(t))}{h(z^*)}+1\right)\\
&+\frac{\alpha\beta y^*h(z^*)}{\alpha_1}\left(1-\frac{v(t)}{v^*}+\int_0^\infty g_2(\xi)\frac{y(t-\xi)}{y^*}\mathrm{d}\xi-\int_0^\infty g_2(\xi)\frac{v^*y(t-\xi)}{v(t)y^*}\mathrm{d}\xi\right)
\end{aligned}
$$

$$
\begin{aligned}
& +\alpha x^* f(v^*)\left(\frac{y(t)}{y^*} - \int_0^\infty g_2(\xi)\frac{y(t-\xi)}{y^*}\mathrm{d}\xi + \int_0^\infty g_2(\xi)\ln\frac{y(t-\xi)}{y(t)}\mathrm{d}\xi\right)\\
= & -\frac{k(x(t)-x^*)^2}{x(t)} - \frac{q\alpha\beta}{\lambda\alpha_1}[z(t)-z^*][h(z(t))-h(z^*)] + \alpha x^* f(v^*)\left[2 - \frac{x^*}{x(t)}\right.\\
& + \frac{f(v(t))}{f(v^*)} - \frac{v(t)}{v^*} + \int_0^\infty g_1(\xi)\ln\frac{x(t-\xi)f(v(t-\xi))}{x(t)f(v(t))}\mathrm{d}\xi\\
& - \int_0^\infty g_1(\xi)\frac{x(t-\xi)y^* f(v(t-\xi))}{x^* y(t) f(v^*)}\mathrm{d}\xi - \frac{y(t)h(z(t))}{y^* h(z^*)} + \frac{h(z(t))}{h(z^*)}\\
& \left. + \int_0^\infty g_2(\xi)\frac{y(t-\xi)}{y^*}\mathrm{d}\xi - \int_0^\infty g_2(\xi)\frac{v^* y(t-\xi)}{v(t)y^*}\mathrm{d}\xi\right]\\
& + \frac{\alpha(ry^* + \beta y^* h(z^*))}{\alpha_1}\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{y(t)}{y^*} - \int_0^\infty g_2(\xi)\frac{y(t-\xi)}{y^*}\mathrm{d}\xi + \int_0^\infty g_2(\xi)\ln\frac{y(t-\xi)}{y(t)}\mathrm{d}\xi\right)\\
= & -\frac{k(x(t)-x^*)^2}{x(t)} - \frac{q\alpha\beta}{\lambda\alpha_1}[z(t)-z^*][h(z(t))-h(z^*)] + \alpha x^* f(v^*)\left[2 - \frac{x^*}{x(t)}\right.\\
& + \frac{f(v(t))}{f(v^*)} - \frac{v(t)}{v^*} + \int_0^\infty g_1(\xi)\ln\frac{x(t-\xi)f(v(t-\xi))}{x(t)f(v(t))}\mathrm{d}\xi\\
& - \int_0^\infty g_1(\xi)\frac{x(t-\xi)y^* f(v(t-\xi))}{x^* y(t) f(v^*)}\mathrm{d}\xi - \frac{y(t)h(z(t))}{y^* h(z^*)} + \frac{h(z(t))}{h(z^*)}\\
& \left. + \int_0^\infty g_2(\xi)\frac{y(t-\xi)}{y^*}\mathrm{d}\xi - \int_0^\infty g_2(\xi)\frac{v^* y(t-\xi)}{v(t)y^*}\mathrm{d}\xi\right]\\
& +\alpha x^* f(v^*)\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{y(t)}{y^*} - \int_0^\infty g_2(\xi)\frac{y(t-\xi)}{y^*}\mathrm{d}\xi + \int_0^\infty g_2(\xi)\ln\frac{y(t-\xi)}{y(t)}\mathrm{d}\xi\right)\\
= & -\frac{k(x(t)-x^*)^2}{x(t)} - \frac{q\alpha\beta}{\lambda\alpha_1}[z(t)-z^*][h(z(t))-h(z^*)]\\
& +\alpha x^* f(v^*)\left[3 - \frac{x^*}{x(t)} + \frac{f(v(t))}{f(v^*)} - \frac{v(t)}{v^*}\right.\\
& + \int_0^\infty g_1(\xi)\ln\frac{x(t-\xi)f(v(t-\xi))}{x(t)f(v(t))}\mathrm{d}\xi - \int_0^\infty g_1(\xi)\frac{x(t-\xi)y^* f(v(t-\xi))}{x^* y(t) f(v^*)}\mathrm{d}\xi\\
& \left. - \int_0^\infty g_2(\xi)\frac{v^* y(t-\xi)}{v(t)y^*}\mathrm{d}\xi + \int_0^\infty g_2(\xi)\ln\frac{y(t-\xi)}{y(t)}\mathrm{d}\xi\right].
\end{aligned}
$$

Using the fact that 3 can be written as $3 = \int_0^\infty g_1(\xi)(1+1)\mathrm{d}\xi + \int_0^\infty g_2(\xi)\mathrm{d}\xi$ and $g(u) = u - 1 - \ln u \geq 0$ for $u > 0$, we further have

$$
\begin{aligned}
V'(t) = & -\frac{k(x(t)-x^*)^2}{x(t)} - \frac{q\alpha\beta}{\lambda\alpha_1}[z(t)-z^*][h(z(t))-h(z^*)]\\
& +\alpha x^* f(v^*)\left[\int_0^\infty g_1(\xi)\left(-g\left(\frac{x^*}{x(t)}\right) - g\left(\frac{x(t-\xi)y^* f(v(t-\xi))}{x^* y(t) f(v^*)}\right)\right.\right.\\
& \left. - \ln\frac{x^*}{x(t)} - \ln\frac{x(t-\xi)y^* f(v(t-\xi))}{x^* y(t) f(v^*)} + \ln\frac{x(t-\xi)f(v(t-\xi))}{x(t)f(v(t))}\right)\mathrm{d}\xi
\end{aligned}
$$

$$
\begin{aligned}
& +\int_0^\infty g_2(\xi)\left(-g\left(\frac{v^*y(t-\xi)}{v(t)y^*}\right)-\ln\frac{v^*y(t-\xi)}{v(t)y^*}+\ln\frac{y(t-\xi)}{y(t)}\right)\mathrm{d}\xi \\
& +\frac{f(v(t))}{f(v^*)}-\frac{v(t)}{v^*}\Bigg] \\
\leq\ & \alpha x^* f(v^*)\left[\frac{f(v(t))}{f(v^*)}-\ln\frac{f(v(t))}{f(v^*)}-\frac{v(t)}{v^*}+\ln\frac{v(t)}{v^*}\right] \\
=\ & \alpha x^* f(v^*)\left(g(F(w))-g(w)\right), \qquad (19)
\end{aligned}
$$

where $w=\frac{v(t)}{v^*}$ and $F(w)=\frac{f(v(t))}{f(v^*)}=\frac{f(v^*w)}{f(v^*)}$. Using the fact in Lemma 4.1, we see that $V'(t)\leq 0$ and $V'(t)=0$ if and only if $x(t)=x^*, z(t)=z^*, y^*f(v(t-\xi))=y(t)f(v^*), v^*y(t-\xi)=v(t)y^*$ and $v(t)=v^*$ for almost all $\xi\in[0,\infty)$. Again by the Lyapunov- LaSalle invariance principle, all solutions of (5) are attracted to B, which is the largest invariant subset of $\{W'=0\}$. Since B is invariant with respect to (5), it is ease to verify that $B=\{(x^*,y^*,v^*,z^*)\}=\{E^*\}$. This shows that

$$\lim_{t\to\infty}(x(t),y(t),v(t),z(t))=E^*,$$

completing the proof. □

Consider the special forms $G_1(\tau)=e^{-m\tau_1}\delta(\tau-\tau_1)$ with $m=k+d$ and $G_2(\tau)=e^{-r\tau_2}\delta(\tau-\tau_2)$, where $\delta(\cdot)$ is the Dirac delta function. When $f(\xi)=h(\xi)=\xi$, the model (1) reduces to

$$
\begin{cases}
x'(t) = \mu-kx(t)-\alpha x(t)v(t), \\
y'(t) = \alpha e^{-m\tau_1}x(t-\tau_1)v(t-\tau_1)-ry(t)-\beta y(t)z(t), \\
v'(t) = Nre^{-r\tau_2}y(t-\tau_2)-dv(t), \\
z'(t) = \lambda y(t)-qz(t),
\end{cases}
\qquad (20)
$$

for which, the initial functions are given as

$$(x(\theta),y(\theta),v(\theta)),z(\theta)\in C(-[\max(\tau_1,\tau_2),0],\mathbb{R}^4_+)$$

with $x(0)>0, y(0)>0, v(0)>0, z(0)>0$. Applying Theorems 3.1 and 4.2 to system (20) yields the following global property.

Theorem 4.3. *If $\mathcal{R}_0=\frac{\mu\alpha Ne^{-(m\tau_1+r\tau_2)}}{kd}\leq 1$, then (20) has only one nonnegative steady state, which is the viral free steady state $E_0=(\frac{\mu}{k},0,0,0)$, to which all solution tend; whereas if $\mathcal{R}_0>1$, then there is a unique positive infected steady state $E^*=(x^*,y^*,v^*,z^*)$, to which all positive solutions converge.*

If $\tau_1=\tau_2=0$, then system (20) further reduced an ODE system investigated in [10]. Applying the Routh-Hurwitz conditions to the linearized system of that ODE system, the stability of the equilibria has been studied in [10] and some sufficient conditions ensuring the *local stability* of the infection free equilibrium as well as the infected equilibrium are obtained. We point out that the conditions for the local stability of the infected equilibrium [10] are very complex, consisting of several inequalities. Comparing our results to those in [10], we have obtained *global stability* and our condition is in the form of threshold in terms of the basic reproductive number only, which is clinically more desirable and and theoretically explicit and simple.

5. **Conclusion and discussion.** In this paper, we propose a general model describing the interactions of HIV virus, cells and CTLs within host. In the model we allow general nonlinear incidence rate and removal rate, as well as two general distributed delays accounting for the variance of time for virions to invade into cells and the variance of time for invade virions to reproduce. We have confirmed the well-posedness of the model, identified the basic reproduction number $\mathcal{R}_0$ for the model, and analysed the stability of both infection free equilibrium E_0 and the infected equilibrium E^*. By constructing proper Lyapunov functionals and subtle estimates of the derivatives of the Lyapunov functionals, we have shown that $\mathcal{R}_0$ plays a global threhold role in the sense that when $\mathcal{R}_0 \leq 1$, then E_0 is globally asymptotically stable, and when $\mathcal{R}_0 > 1$, then E^* comes into existence and is globally asymptotically stable (hence E_0 becomes unstable). Thus, the dynamics of the model is fully determined by $\mathcal{R}_0$.

By the explicit expression of $\mathcal{R}_0$, we see $\mathcal{R}_0$ is proportional to $f'(0)$ and to the delay effect parameters a_1 and a_2, but it is independent of $h(y)$. This is because $\mathcal{R}_0$ measures the average number of new infections resulted from a single infected cell, and is thus determined by the linearization of the model system at the infection free equilibrium in which the term containing $h(z)$ disappears due to the assumption $h(0) = 0$. Intuitively, the basic reproduction number only governs local dynamics near the infection free equilibrium, but some times, it can also determines the global dynamics of a model, as in this work and some others, see, e.g., [17, 18, 22, 31, 32, 34, 35] and the reference therein.

Also note that the values of parameters β, λ and q have no impact on the value of $\mathcal{R}_0$ since $\mathcal{R}_0$ is independent of those parameters. This fact seems to suggest that CTLs do not play a role in *eliminating* the virus load. However, from the expression of L in (4), we see that v^* can be decreased by increasing β and λ or decreasing q. This suggests that CTLs can increase the healthy cells population and decrease viral load at the infected equilibrium. Similar conclusions are also obtained in [22] where considered is a model similar to (1), with f and h being linear functions, the CTL activation term $\lambda y(t)$ being replaced by $\lambda y(t)z(t)$ and the two delay integrals being on finite intervals only. However, there is an essential difference in the case when $\mathcal{R}_0 > 1$. In [22], beside $\mathcal{R}_0$, there is another combined parameter $\mathcal{R}_1 < \mathcal{R}_0$ taking care of the activation of the CTLs in the following sense: when $\mathcal{R}_1 \leq 1 < \mathcal{R}_0$, the model in [22] has an infection equilibrium E_1^* *without* CTLs which attracts all solutions with x, y components positive ($z(t)$ can remain 0); when $1 < \mathcal{R}_1$, in addition to E_1^*, there is another infection equilibrium E_2^* *with* a positive CTL component which attracts all those positive solutions. This is due to the adoption of the bilinear form for the CTLs activation term, leading to $z'(t) = \lambda y(t)z(t) - qz(t)$ in [22]. From this equation, one sees that if $z(0) = 0$, then $z(t) = 0$ for all $t \geq 0$, which does not seem to be the case in reality. The choice of linear term $\lambda y(t)$ can avoid this problem, and thus, seems to be more realistic in this context.

In reality, there are also delays in activating CTLs by infected cells. As we mentioned in the introduction, there have been quite a few works incorporating such delays into models. Some of these works have shown that the delay in activating immune response could lead to very complicated dynamics including stable periodic solutions and chaos (see, e.g., [9, 33]). Since our focus is on the virus production part and (1) already contains two distributed delays, we neglect the delays in activating CTLs in this work to avoid further complicating the model. One possible and natural way to incorporate the delay in immune response is to replace the term $\lambda y(t)$ in the fourth equation in (1) by $\lambda \int_0^\infty G_3(\tau)y(t-\tau)\,d\tau$ where G_3 is another kernel function similar to G_1 and G_2. We leave the analysis of such a modified model as a future project, which should be more interesting yet more challenging.

Acknowledgments. The authors are grateful to the two anonymous referees for their valuable comments on our initial submission, which have led to an improvement in the presentation of the paper in this revised version.

REFERENCES

[1] L. K. Andrea and S. Ranjan, *Evaluation of HIV-1 kinetic models using quantitative discrimination analysis*, Bioinformatics, **21** (2005), 1668–1677.

[2] R. Arnaout, M. Nowak and D. Wodarz, *HIV-1 dynamics revisited: Biphasic decay by cytotoxic lymphocyte killing?*, Proc. Roy. Soc. Lond. B, **265** (2000), 1347–1354.

[3] S. Bonhoeffer, J. M. Coffin and M. A. Nowak, *Human immunodeficiency virus drug therapy and virus load*, J. Virol., **71** (1997), 3275–3278.

[4] S. Bonhoeffer, R. M. May, G. M. Shaw and M. A. Nowak, *Virus dynamics and drug therapy*, Proc. Natl. Acad. Sci. USA, **94** (1997), 6971–6976.

[5] N. Burić, M. Mudrinic and N. Vasović, *Time delay in a basic model of the immune response*, Chaos, Solitons and Fractals, **12** (2001), 483–489

[6] T. A. Burton, *Volterra integral and differential equations*, in "Mathematics In Science And Engineering" 2^{nd} edition, Elsevier, Amsterdam-Boston, **202** (2005).

[7] L. Cai and J. Wu, *Analysis of an HIV/AIDS treatment model with a nonlinear incidence*, Chaos, Solitons and Fractals, **41** (2009), 175–182.

[8] D. Callaway and A. S. Perelson, *HIV-1 infection and low steady state viral loads*, Bulletin of Mathematical Biology, **64** (2002), 29–64.

[9] A. A. Canabarro, I. M. Gléria and M. L. Lyra, *Periodic solutions and chaos in a non-linear model for the delayed cellular immune response*, Physica A, **342** (2004), 234–241.

[10] M. S. Ciupe, B. L. Bivort, D. M. Bortz and P. W. Nelson, *Estimating kinetic parameters from HIV primary infection data through the eyes of three different mathematical models*, Math. Biosci., **200** (2006), 1–27.

[11] R. Culshaw, S. Ruan and R. Spiteri, *Optimal HIV treatment by maximising immune response*, J. Math. Biol., **48** (2004), 545–562.

[12] R. J. De Boer and A. S. Perelson, *Towards a general function describing T cell proliferation*, J. Theoret. Biol., **175** (1995), 567–576.

[13] R. J. De Boer and A. S. Perelson, *Target cell limited and immune control models of HIV infection: A comparison*, J. Theoret. Biol., **190** (1998), 201–214.

[14] P. Georgescu and Y. Hsieh, *Global stability for a virus dynamics model with nonlinear incidence of infection and removal*, SIAM J. Appl. Math., **67** (2006), 337–353.

[15] T. Kajiwara and T. Sasaki, *A note on the stability analysis of pathogen-immune interaction dynamics*, Discrete Continuous Dynam. Systems-B, **4** (2004), 615–622.

[16] Y. Kuang, "Delay Differential Equations with Applications in Population Dynamics," Academic Press, San Diego, 1993.

[17] Y. Li, R. Xu, Z. Li and S. Mao, *Global dynamics of a delayed HIV-1 infection model with CTL immune response*, Discrete Dynamics in Nature and Society, **2011** (2011), Art. ID 673843, 13 pp.

[18] S. Liu and L. Wang, *Global stability of an HIV-1 model with dstributed intracellular delays and a combination therapy*, Math. Biosci. and Eng., **7** (2010), 675–685.

[19] W. Liu, *Nonlinear oscillation in models of immune response to persistent viruses*, Theor. Popul. Biol., **52** (1997), 224–230.

[20] C. Lv and Z. Yuan, *Stability analysis of delay differential equation models of HIV-1 therapy for fighting a virus with another virus*, J. Math. Anal. Appl., **352** (2009), 672–683.

[21] J. Mittler, B. Sulzer, A. Neumann and A. Perelson, *Influence of delayed viral production on viral dynamics in HIV-1 infected patients*, Math. Biosci., **152** (1998), 143–163.

[22] Y. Nakata, *Global dynamics of a cell mediated immunity in viral infection models with distributed delays*, J. Math. Anal. Appl., **375** (2011), 14–27.

[23] P. Nelson, J. Murray and A. S. Perelson, *A model of HIV-1 pathogenesis that includes an intracellular delay*, Math. Biosci., **163** (2000), 201–215.

[24] P. Nelson and A. S. Perelson, *Mathematica analysis of delay differential equation models of HIV-1 infection*, Math. Biosci., **179** (2002), 73–94.

[25] M. Nowak and C. Bangham, *Population dynamics of immune response to persistent viruses*, Science, **272** (1996), 74–79.

[26] M. A. Nowak, S. Bonhoeffer, G. M. Shaw and R. M. May, *Anti-viral drug treatment: Dynamics of resistance in free virus and infected cell populations*, J. Theor. Biol., **184** (1997), 203–217.

[27] K. A. Pawelek, S. Liu, F. Pahlevani and L. Rong, *A model of HIV-1 infection with two time delays: Mathematical analysis and comparison with patient data*, Math. Biosci., **235** (2012), 98–109.

[28] A. S. Perelson and P. Nelson, *Mathematical models of HIV dynamics in vivo*, SIAM Rev., **41** (1999), 3–44.

[29] A. S. Perelson, A. Neumann, M. Markowitz, J. Leonard and D. Ho, *HIV-1 dynamics in vivo: Virion clearance rate, infected cell life-span, and viral generation time*, Science, **271** (1996), 1582–1586.

[30] A. N. Phillips, *Reduction of HIV concentration during acute infection: Independence from a specific immune response*, Science, **271** (1996), 497–499.

[31] J. Wang, G. Huang and Y. Takeuchi, *Global asymptotic stability for HIV-1 dynamics with two distributed delays*, Mathematical Medicine and Biology, IMA.

[32] K. Wang, W. Wang and X. Liu, *Global Stability in a viral infection model with lytic and nonlytic immune response*, Comput. Math. Appl., **51** (2006), 1593–1610.

[33] K. Wang, W. Wang, H. Pang and X. Liu, *Complex dynamic behavior in a viral model with delayed immune response*, Physica D, **226** (2007), 197–208.

[34] R. Xu, *Global dynamics of an HIV-1 infection model with distributed intracellular delays*, Comput. Math. Appl., **61** (2011), 2799–2805.

[35] R. Xu, *Global stability of an HIV-1 infection model with saturation infection and intracellular delay*, J. Math. Anal. Appl., **375** (2011), 75–81.

[36] H. Zhu and X. Zou, *Impact of delays in cell infection and virus production on HIV-1 dynamics*, Mathematical Medicine and Biology, IMA, **25** (2008), 99–112.

[37] H. Zhu and X. Zou, *Dynamics of a HIV-1 infection model with cell-mediated immune response and intracellular delay*, Discrete Continuous Dynam. Systems-B, **12** (2009), 511–524.

[38] H. Zhu, Y. Luo and M. Chen, *Stability and Hopf bifurcation of a HIV infection model with CTL-response delay*, Comput. Math. Appl., **62** (2011), 3091–3102.

Received January 15, 2012; Accepted September 05, 2012.

E-mail address: yzhh312@tom.com
E-mail address: xzou@uwo.ca