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Global dynamics of a class of HIV-1 infection models with latently infected cells*

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Abstract. In this paper, the global dynamics of a class of HIV-1 infection models with different infection rates and latently infected cells are investigated. We first modify the basic virus infection model and propose two models with bilinear infection rate and saturation infection rate, respectively, which take HIV-1 latency into consideration, and then study a model with a general nonlinear infection rate. By using proper Lyapunov functions and LaSalle's invariance principle, it is proved that in the first two models, if the basic reproduction ratio is less than unity, each of the infection-free equilibria is globally asymptotically stable; if the basic reproduction ratio is greater than unity, each of the chronic-infection equilibria is globally asymptotically stable. For the last model with general nonlinear infection rate, we obtain sufficient conditions for the global stability of both the infection-free and chronic-infection equilibria of the model.

Keywords: HIV-1 infection model, nonlinear infection rate, global stability, LaSalle's invariance principle.

1 Introduction

Mathematical and computational models of the human immune response under viral infection combined with experimental measurements has yielded important insights into HIV-1 pathogenesis and has enhanced progress in the understanding of HIV-1 infection. Hence, it is a useful tool to formulate meaningful mathematical models to help us better understand the disease dynamics, make prediction of disease outbreak and evaluate the prevention and drug therapy strategies used against HIV-1 infection.

It is well known that when HIV-1 enters the body, it targets cells with CD4 receptors, including the CD4+ T-cells, the main driver of the immune response. Recent studies have shown that a significant proportion of CD4+ T-cells are infected by the virus, and that this

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specific population of T-cells might be preferentially infected [5]. It is important and has become a hot topic to formulate models to explain the exhaustion of the CD4+ T-cells. Such models involve the concentrations of uninfected CD4+ T-cells, x, infected CD4+ T-cells that are producing virus, y, and free virus, v. A basic mathematical model describing HIV-1 infection dynamics that has been studied in [9, 16, 17, 19] is of the form

$$\begin{aligned} \dot{x}(t) &= \lambda - dx(t) - \beta x(t)v(t), \\ \dot{y}(t) &= \beta x(t)v(t) - ay(t), \\ \dot{v}(t) &= ky(t) - uv(t), \end{aligned} \tag{1}$$

where uninfected, susceptible CD4+ T-cells are created from sources within the body at a rate λ, uninfected CD4+ T-cells die at rate d, and become infected at rate βxv, where β is the rate constant describing the infection process; infected cells are produced at rate βxv and die at rate ay; free virus are produced from infected cells at rate ky and are removed at rate uv. Korobeinikov in [9] gave a complete global analysis of this basic virus infection model. After that, many authors modified the model and proposed many models with more complicated infection rates based on scientific research, for example, the saturation infection rate $\beta xv/(1 + \alpha v)$, where $\alpha > 0$ in [21], nonlinear infection rate $\beta x^q v$, where $q > 0$ in [22] and general nonlinear infection rate with the form of an unspecified function $f(x, v)$ in [10].

However, in all previous works mentioned above, they all neglected the fact that once in the cells not all virus initiate active virus production. An asymptomatic period of "clinical latency" can intervene between infection and the development of the acquired immune deficiency syndrome(AIDS) [15]. A large proportion of CD4+ T-cells are latently infected following the integration of pro-viral DNA into the host cell genome, some of which can remain quiescent for long periods of time before becoming activated [2]. In [18], such cells are defined as latently infected cells, i.e., cells that contain integrated pro-viral DNA and are transcriptionally silent, but upon activation are capable of producing infectious virus. Latently infected cells became a subject of great interest when they were subsequently shown to persist even in individuals on highly active antiretroviral therapy (HAART) who no longer had clinically detectable viremia [14]. *"The capability of the HIV-1 to persist latent inside CD4+ T-cells is currently regarded as a barrier to recovery from infection"* [3]. But till now, as far as we know, only a few works(see, e.g., [3, 12]) concern the effects that latently infected cells expected to have on HIV-1 infection process. In this paper, motivated by the works of [3, 12, 16], we modify the basic virus infection model and add a further state variable, ω, which represents the population of latently infected cells and propose a class of HIV-1 infection models with latently infected cells.

Our primary goal is to propose a class of HIV-1 infection models with different infection rates which take HIV-1 latency into consideration and carry out the global dynamics of these models. The organization of this paper is as follows. In the next section, we introduce an HIV-1 model with the simple mass-action infection rate and latently infected cells based on the basic virus infection model and discuss the global stability of the infection-free equilibrium and the chronic-infection equilibrium by means of constructing suitable Lyapunov functions and LaSalle's invariance principle, respectively. In Section 3,

we modify the model in Section 2 and study the global properties of an HIV-1 model of which the infection rate is given by saturation functional response. The infection rates in both models of Sections 2 and 3 have specific forms. An HIV-1 infection model with general nonlinear infection rate of unspecific form and latently infected cells is given in Section 4. A brief remark is given in Section 5 to conclude our work.

2 HIV-1 infection model with the mass-action infection rate and latency cells

In the rest of this paper, we suppose that infected CD4+ T-cells are either active or latent. From the loss of healthy T-cells due to infection, one fraction of these cells become active, or productively infected, while the rest remain latent. Both classes of infected cells are assumed to die with exponentially distributed waiting time. With the simple mass-action infection term, we first study the following system of differential equations:

$$\begin{aligned} \dot{x}(t) &= \lambda - dx - \beta xv, \\ \dot{\omega}(t) &= (1-q)\beta xv - e\omega - \delta\omega, \\ \dot{y}(t) &= q\beta xv - ay + \delta\omega, \\ \dot{v}(t) &= ky - uv, \end{aligned} \tag{2}$$

where the parameters λ, d, β, a, k, u are the same as that defined in model (1). Free virus interact with the uninfected cells to produce actively infected cells at a rate $q\beta xv$ and latently infected cells at a rate $(1-q)\beta xv$, where the parameter q: $0 < q < 1$. Latently infected cells containing pro-viral DNA die at a rate $e\omega$ and become activated at rate $\delta\omega$.

We note that model (2) is biologically acceptable in the sense that no population goes negative. Denote $N(t) = x(t) + \omega(t) + y(t)$, then we get

$$\dot{N}(t) = \dot{x}(t) + \dot{\omega}(t) + \dot{y}(t) \leqslant \lambda - \sigma\dot{N}(t),$$

where $\sigma = \min\{d, e, a\}$. Hence, $0 \leqslant N(t) \leqslant \lambda/\sigma$ for all $t \geqslant 0$ if $N(0) \leqslant \lambda/\sigma$. It follows that $0 \leqslant x(t), \omega(t), y(t) \leqslant \lambda/\sigma$ for all $t \geqslant 0$ if $x(0) + \omega(0) + y(0) \leqslant \lambda/\sigma$. On the other hand,

$$\dot{v}(t) \leqslant \frac{k\lambda}{\sigma} - uv,$$

then $0 \leqslant v(t) \leqslant k\lambda/(\sigma u)$ for all $t \geqslant 0$ if $v(0) \leqslant k\lambda/(\sigma u)$. Mathematical properties of the solutions lead us to studying system (2) in the closed set:

$$D = \left\{(x, \omega, y, v) \in R_4^+\colon\ x + \omega + y \leqslant \frac{\lambda}{\sigma},\ v(t) \leqslant \frac{k\lambda}{\sigma u}\right\},$$

which is usually considered as the phase space of the system. It is easy to show that D is positively invariant with respect to (2).

2.1 The existence of feasible equilibria

Clearly, system (2) always has an infection-free equilibrium $E_0(x_0, 0, 0, 0)$, where $x_0 = \lambda/d$.

Following the next generation matrix method formulated in [6], we define

$$R_0 = \frac{k\lambda\beta(eq+\delta)}{adu(e+\delta)}. \tag{3}$$

Here R_0 is called the basic reproduction ratio of system (2). This ratio describes the average number of newly infected cells generated from one infected cell at the beginning of the infectious process. Thus, it is a fundamental measure, which determines whether a virus spreads within the host or becomes extinct.

It is easy to show that if $R_0 > 1$, system (2) admits a unique chronic-infection equilibrium $E^*(x^*, \omega^*, y^*, v^*)$, where

$$x^* = \frac{au(e+\delta)}{k\beta(eq+\delta)}, \qquad \omega^* = \frac{(1-q)adu}{\beta k(eq+\delta)}(R_0-1),$$
$$y^* = \frac{du}{\beta k}(R_0-1), \qquad v^* = \frac{d}{\beta}(R_0-1).$$

2.2 Global stability

In this part, we study the global stability of each of feasible equilibria of system (2). The strategy of proofs is to use suitable Lyapunov functions and LaSalle's invariance principle in [13].

Define

$$F(x) = x - 1 - \ln x. \tag{4}$$

Clearly, for $x \in (0, +\infty)$, $F(x)$ is non-negative and has the global minimum at $x = 1$ and $F(1) = 0$.

We first state and prove our result on the global stability of the infection-free equilibrium $E_0(\lambda/d, 0, 0, 0)$.

Theorem 1. *The infection-free equilibrium $E_0(x_0, 0, 0, 0)$ of system* (2) *is globally asymptotically stable if $R_0 \leqslant 1$.*

Proof. Define a Lyapunov function of the form

$$W_0(t) = x_0 F\left(\frac{x}{x_0}\right) + \frac{\delta}{eq+\delta}\omega + \frac{e+\delta}{eq+\delta}y + \frac{a(e+\delta)}{k(eq+\delta)}v. \tag{5}$$

Calculating the derivative of $W_0(t)$ along positive solutions of system (2), it follows that

$$\dot{W}_0(t) = \left(1 - \frac{x_0}{x}\right)(\lambda - dx - \beta xv) + \frac{\delta}{eq+\delta}\big[(1-q)\beta xv - e\omega - \delta\omega\big]$$
$$+ \frac{e+\delta}{eq+\delta}(q\beta xv - ay + \delta\omega) + \frac{a(e+\delta)}{k(eq+\delta)}(ky - uv). \tag{6}$$

Since $\lambda = dx_0$ holds, we derive that

$$\dot{W}_0(t) = dx_0\left(2 - \frac{x_0}{x} - \frac{x}{x_0}\right) + \frac{\beta\lambda}{d}\left(1 - \frac{1}{R_0}\right)v. \tag{7}$$

Since the arithmetical mean is greater than or equal to the geometrical mean, then the first term of (7) is less than or equal to zero. Noting that $1 - 1/R_0 \leqslant 0$ if $R_0 \leqslant 1$, it follows from (7) that $\dot{W}_0(t) \leqslant 0$ for all $(x, \omega, y, v) > 0$. Also, it is easy to verify that $\dot{W}_0(t) = 0$ if and only if $x = x_0$, $\omega = y = v = 0$. The maximal compact invariant set in $\{(x, \omega, y, v) \in D\colon\ \dot{W}_0(t) = 0\}$ is the singleton $\{E_0\}$ if $R_0 \leqslant 1$. Accordingly, the global asymptotic stability of E_0 follows from LaSalle's invariance principle. This completes the proof. □

We are now in a position to establish the global stability of the chronic-infection equilibrium E^* of system (2). The form of Lyapunov function used here is motivated by the work in [23].

Theorem 2. *If $R_0 > 1$, then the chronic-infection equilibrium $E^*(x^*, \omega^*, y^*, v^*)$ of system* (2) *is globally asymptotically stable.*

Proof. Define a Lyapunov function of the form

$$W_1(t) = x^* F\left(\frac{x}{x^*}\right) + k_1\omega^* F\left(\frac{\omega}{\omega^*}\right) + k_2 y^* F\left(\frac{y}{y^*}\right) + k_3 v^* F\left(\frac{v}{v^*}\right), \tag{8}$$

where k_1, k_2 and k_3 are positive constants to be determined later.

Calculating the derivative of $W_1(t)$ along positive solutions of system (2), we derive that

$$\begin{aligned}\dot{W}_1(t) = {}& \left(1 - \frac{x^*}{x}\right)(\lambda - dx - \beta xv) + k_1\left(1 - \frac{\omega^*}{\omega}\right)\left[(1-q)\beta xv - e\omega - \delta\omega\right] \\ & + k_2\left(1 - \frac{y^*}{y}\right)(q\beta xv - ay + \delta\omega) + k_3\left(1 - \frac{v^*}{v}\right)(ky - uv).\end{aligned} \tag{9}$$

By substituting $\lambda = dx^* + \beta x^* v^*$, $ky^* = uv^*$ into (9), it follows that

$$\begin{aligned}\dot{W}_1(t) = {}& \left(1 - \frac{x^*}{x}\right)\left[-d(x - x^*) + \beta x^* v^*\right] - \beta xv + \beta x^* v \\ & + k_1\left[(1-q)\beta xv - e\omega - \delta\omega\right] + k_1\left[-(1-q)\beta xv\frac{\omega^*}{\omega} + (e+\delta)\omega^*\right] \\ & + k_2\left[q\beta xv - ay + \delta\omega\right] + k_2\left[-q\beta xv\frac{y^*}{y} + ay^* - \delta\omega\frac{y^*}{y}\right] \\ & + k_3\left(ky - uv - ky\frac{v^*}{v} + ky^*\right).\end{aligned} \tag{10}$$

Letting

$$k_1 = \frac{\delta}{eq + \delta}, \qquad k_2 = \frac{e + \delta}{eq + \delta}, \qquad k_3 = \frac{a(e+\delta)}{k(eq+\delta)},$$

it is easy to verify that

$$k_1(1-q)+k_2q=1, \qquad k_1(e+\delta)=k_2\delta, \qquad k_2a=k_3k.$$

Then from (10) we can get

$$\begin{aligned}\dot{W}_1(t)={}&\left(1-\frac{x^*}{x}\right)\left[-d(x-x^*)+\beta x^*v^*\right]+\beta x^*v-k_1(1-q)\beta xv\frac{\omega^*}{\omega}\\&+k_1(e+\delta)\omega^*-k_2q\beta xv\frac{y^*}{y}+k_2ay^*-k_2\delta\omega\frac{y^*}{y}-k_3uv\\&-k_3ky\frac{v^*}{v}+k_3ky^*. \end{aligned}\tag{11}$$

Noting that

$$ay^*=q\beta x^*v^*+\delta\omega^*, \qquad (e+\delta)\omega^*=(1-q)\beta x^*v^*,$$

(11) can be rewritten as

$$\begin{aligned}\dot{W}_1(t)={}&\left(1-\frac{x^*}{x}\right)\left[-d(x-x^*)+\beta x^*v^*\right]+\beta x^*v^*\frac{v}{v^*}+k_1(e+\delta)\omega^*\\&-k_1(1-q)\beta x^*v^*\frac{xv}{x^*v^*}\frac{\omega^*}{\omega}-k_2q\beta x^*v^*\frac{xv}{x^*v^*}\frac{y^*}{y}+k_2(q\beta x^*v^*+\delta\omega^*)\\&-k_2\delta\omega^*\frac{\omega}{\omega^*}\frac{y^*}{y}-k_2(q\beta x^*v^*+\delta\omega^*)\frac{v}{v^*}-k_2(q\beta x^*v^*+\delta\omega^*)\frac{y}{y^*}\frac{v^*}{v}\\&+k_2(q\beta x^*v^*+\delta\omega^*)\\={}&\left(1-\frac{x^*}{x}\right)\left[-d(x-x^*)+\beta x^*v^*\right]+\beta x^*v^*\frac{v}{v^*}+3k_1(1-q)\beta x^*v^*\\&+2k_2q\beta x^*v^*-k_1(1-q)\beta x^*v^*\frac{xv}{x^*v^*}\frac{\omega^*}{\omega}-k_2q\beta x^*v^*\frac{xv}{x^*v^*}\frac{y^*}{y}\\&-k_1(1-q)\beta x^*v^*\frac{\omega}{\omega^*}\frac{y^*}{y}-k_1(1-q)\beta x^*v^*\frac{v}{v^*}-k_2q\beta x^*v^*\frac{v}{v^*}\\&-k_2q\beta x^*v^*\frac{y}{y^*}\frac{v^*}{v}-k_1(1-q)\beta x^*v^*\frac{y}{y^*}\frac{v^*}{v}\\={}&-\frac{d(x-x^*)^2}{x}+\frac{\delta(1-q)}{eq+\delta}\beta x^*v^*\left(4-\frac{x^*}{x}-\frac{xv}{x^*v^*}\frac{\omega^*}{\omega}-\frac{\omega}{\omega^*}\frac{y^*}{y}-\frac{y}{y^*}\frac{v^*}{v}\right)\\&+\frac{q(e+\delta)}{eq+\delta}\beta x^*v^*\left(3-\frac{x^*}{x}-\frac{xv}{x^*v^*}\frac{y^*}{y}-\frac{y}{y^*}\frac{v^*}{v}\right). \end{aligned}\tag{12}$$

Noting that x^*, ω^*, y^*, $v^*>0$, and the arithmetical mean is greater than or equal to the geometrical mean, then the last two terms of (12) are less than or equal to zero. Then we have $\dot{W}_1(t)\leqslant 0$, where the equality holds if and only if $(x,\omega,y,v)=(x^*,\omega^*,y^*,v^*)$. Using a similar argument as that in the proof of Theorem 1 and by LaSalle's invariance principle, the global asymptotic stability of E^* follows. This completes the proof. □

3 HIV-1 infection model with saturation infection rate and latency cells

It is assumed in model (2) that the rate of infection is bilinear in the uninfected CD4+ T-cells and free virus, i.e., the infection rate per host and per virus is a constant. However, *"actual incidence rates are probably not strictly linear in each variable over the entire range of CD4+ T-cells and virus"* [21]. The basic virus infection model with infection rate of the bilinear term needs modification. Experiments reported in [7] strongly suggested that the infection rate of microparasitic infections is an increasing function of the parasite dose, and is usually sigmoidal in shape (see, for example, [20]). In [20], to place the basic virus infection model on more sound biological grounds, Regoes et al. replaced the bilinear infection rate with a saturation infection rate. In this section, we modify model (2) and propose a new model taking into account the saturation infection rate and investigate its global dynamics. The model is given by

$$\begin{aligned}
\dot{x}(t) &= \lambda - dx - \frac{\beta x v}{1+\alpha v},\\
\dot{\omega}(t) &= \frac{(1-q)\beta x v}{1+\alpha v} - e\omega - \delta\omega,\\
\dot{y}(t) &= \frac{q\beta x v}{1+\alpha v} - ay + \delta\omega,\\
\dot{v}(t) &= ky - uv.
\end{aligned} \tag{13}$$

The parameters λ, d, β, q, e, δ, a, k, u are the same as that defined in model (2) and $\alpha > 0$. We note that the closed set D defined in Section 2 is positively invariant with respect to system (13).

3.1 The existence of feasible equilibria

It is easy to verify that system (13) always has an infection-free equilibrium $E_0(x_0, 0, 0, 0)$, where $x_0 = \lambda/d$.

Following the method in [6], the basic reproduction ratio of system (13) can be defined as

$$R_0 = \frac{k\lambda\beta(eq+\delta)}{adu(e+\delta)}. \tag{14}$$

Then if $R_0 > 1$, in addition to the infection-free equilibrium, system (13) also admits a unique chronic-infection equilibrium $E^*(x^*, \omega^*, y^*, v^*)$, where

$$\begin{aligned}
x^* &= \frac{\lambda(1+\alpha v^*)}{d(1+\alpha v^*)+\beta v^*}, \qquad & \omega^* &= \frac{\beta\lambda(1-q)v^*}{(e+\delta)[d(1+\alpha v^*)+\beta v^*]},\\
y^* &= \frac{uv^*}{k}, & v^* &= \frac{d}{\alpha d+\beta}(R_0-1).
\end{aligned}$$

3.2 Global stability

In this part, we study the global stability of each of feasible equilibria of system (13). The strategy of proofs is also to use suitable Lyapunov functions and LaSalle's invariance principle.

Theorem 3. *The infection-free equilibrium $E_0(x_0, 0, 0, 0)$ of system* (13) *is globally asymptotically stable if $R_0 \leqslant 1$.*

Proof. Define

$$W_0(t) = x_0 F\left(\frac{x}{x_0}\right) + \frac{k\beta\lambda\delta}{adu(e+\delta)}\omega + \frac{k\beta\lambda}{adu}y + \frac{\beta\lambda}{du}v, \tag{15}$$

where the function $F(x)$ is defined in (4). The time derivative of $W_0(t)$ along positive solutions of system (13) is given by

$$\begin{aligned}\dot{W}_0(t) = {} & \left(1 - \frac{x_0}{x}\right)\left(\lambda - dx - \frac{\beta x v}{1+\alpha v}\right) \\ & + \frac{k\beta\lambda\delta}{adu(e+\delta)}\left[\frac{(1-q)\beta x v}{1+\alpha v} - e\omega - \delta\omega\right] \\ & + \frac{k\beta\lambda}{adu}\left(\frac{q\beta x v}{1+\alpha v} - ay + \delta\omega\right) + \frac{\beta\lambda}{du}(ky - uv).\end{aligned} \tag{16}$$

Since $\lambda = dx_0$, from (16) we can get that

$$\dot{W}_0(t) = dx_0\left(2 - \frac{x_0}{x} - \frac{x}{x_0}\right) + (R_0 - 1)\frac{\beta x v}{1+\alpha v} - \frac{\alpha\beta x_0 v^2}{1+\alpha v}. \tag{17}$$

Since the arithmetical mean is greater than or equal to the geometrical mean, then the first term of (17) is less than or equal to zero. Noting that $R_0 \leqslant 1$, by (17) we have that $\dot{W}_0(t) \leqslant 0$, where the equality holds if and only if $(x, \omega, y, v) = E_0(x_0, 0, 0, 0)$. Using a similar argument as that in the proof of Theorem 1 and by LaSalle's invariance principle, the global asymptotic stability of E_0 follows. This completes the proof. □

We are now in a position to establish the global stability of the chronic-infection equilibrium E^* of system (13).

Theorem 4. *If $R_0 > 1$, then the chronic-infection equilibrium $E^*(x^*, \omega^*, y^*, v^*)$ of system* (13) *is globally asymptotically stable.*

Proof. Define

$$W_1(t) = x^* F\left(\frac{x}{x^*}\right) + k_1\omega^* F\left(\frac{\omega}{\omega^*}\right) + k_2 y^* F\left(\frac{y}{y^*}\right) + k_3 v^* F\left(\frac{v}{v^*}\right), \tag{18}$$

where the parameters k_1, k_2 and k_3 are defined in (8) in Section 2.

Calculation of the derivative of $W_1(t)$ along positive solutions shows that

$$\begin{aligned}\dot{W}_1(t) = {} & \left(1-\frac{x^*}{x}\right)\left[\lambda - dx - \frac{\beta xv}{1+\alpha v}\right] \\ & + k_1\left(1-\frac{\omega^*}{\omega}\right)\left[\frac{(1-q)\beta xv}{1+\alpha v} - e\omega - \delta\omega\right] \\ & + k_2\left(1-\frac{y^*}{y}\right)\left[\frac{q\beta xv}{1+\alpha v} - ay + \delta\omega\right] + k_3\left(1-\frac{v^*}{v}\right)(ky-uv). \end{aligned} \tag{19}$$

By substituting $\lambda = dx^* + \beta x^* v^*/(1+\alpha v^*)$, $ky^* = uv^*$ into (19), we get that

$$\begin{aligned}\dot{W}_1(t) = {} & \left(1-\frac{x^*}{x}\right)\left[-d(x-x^*) + \frac{\beta x^* v^*}{1+\alpha v^*}\right] - \frac{\beta xv}{1+\alpha v} + \frac{\beta x^* v}{1+\alpha v} \\ & + k_1\left[\frac{(1-q)\beta xv}{1+\alpha v} - e\omega - \delta\omega\right] + k_1\left[-\frac{(1-q)\beta xv}{1+\alpha v}\frac{\omega^*}{\omega} + (e+\delta)\omega^*\right] \\ & + k_2\left[\frac{q\beta xv}{1+\alpha v} - ay + \delta\omega\right] + k_2\left[-\frac{q\beta xv}{1+\alpha v}\frac{y^*}{y} + ay^* - \delta\omega\frac{y^*}{y}\right] \\ & + k_3\left(ky - uv - ky\frac{v^*}{v} + ky^*\right). \end{aligned} \tag{20}$$

Noting that

$$k_1(1-q) + k_2 q = 1, \qquad k_1(e+\delta) = k_2\delta, \qquad k_2 a = k_3 k,$$

we derive from (20) that

$$\begin{aligned}\dot{W}_1(t) = {} & \left(1-\frac{x^*}{x}\right)\left[-d(x-x^*) + \frac{\beta x^* v^*}{1+\alpha v^*}\right] + \frac{\beta x^* v}{1+\alpha v} \\ & - k_1(1-q)\frac{\beta xv}{1+\alpha v}\frac{\omega^*}{\omega} + k_1(e+\delta)\omega^* - k_2 q\frac{\beta xv}{1+\alpha v}\frac{y^*}{y} \\ & + k_2 a y^* - k_2\delta\omega\frac{y^*}{y} - k_3 uv - k_3 ky\frac{v^*}{v} + k_3 ky^*. \end{aligned} \tag{21}$$

Since the coordinates of the chronic-infection equilibrium E^* satisfy the equalities

$$ay^* = \frac{q\beta x^* v^*}{1+\alpha v^*} + \delta\omega^*, \qquad (e+\delta)\omega^* = \frac{(1-q)\beta x^* v^*}{1+\alpha v^*},$$

equation (21) can be rewritten as

$$\begin{aligned}\dot{W}_1(t) = {} & \left(1-\frac{x^*}{x}\right)\left[-d(x-x^*) + \frac{\beta x^* v^*}{1+\alpha v^*}\right] + \frac{\beta x^* v^*}{1+\alpha v^*}\frac{v(1+\alpha v^*)}{v^*(1+\alpha v)} + k_1(e+\delta)\omega^* \\ & - k_1(1-q)\frac{\beta x^* v^*}{1+\alpha v^*}\frac{xv(1+\alpha v^*)}{x^* v^*(1+\alpha v)}\frac{\omega^*}{\omega} - k_2 q\frac{\beta x^* v^*}{1+\alpha v^*}\frac{xv(1+\alpha v^*)}{x^* v^*(1+\alpha v)}\frac{y^*}{y} \end{aligned}$$

$$
\begin{aligned}
&+k_2q\frac{\beta x^*v^*}{1+\alpha v^*}+k_2\delta\omega^*-k_2\delta\omega^*\frac{\omega}{\omega^*}\frac{y^*}{y}-\left(k_2q\frac{\beta x^*v^*}{1+\alpha v^*}+k_2\delta\omega^*\right)\frac{v}{v^*}\\
&-\left(k_2q\frac{\beta x^*v^*}{1+\alpha v^*}+k_2\delta\omega^*\right)\frac{y}{y^*}\frac{v^*}{v}+k_2q\frac{\beta x^*v^*}{1+\alpha v^*}+k_2\delta\omega^*\\
=&\left(1-\frac{x^*}{x}\right)\left[-d(x-x^*)+\frac{\beta x^*v^*}{1+\alpha v^*}\right]+\frac{\beta x^*v^*}{1+\alpha v^*}\frac{v(1+\alpha v^*)}{v^*(1+\alpha v)}+2k_2q\frac{\beta x^*v^*}{1+\alpha v^*}\\
&-k_1(1-q)\frac{\beta x^*v^*}{1+\alpha v^*}\frac{xv(1+\alpha v^*)}{x^*v^*(1+\alpha v)}\frac{\omega^*}{\omega}-k_2q\frac{\beta x^*v^*}{1+\alpha v^*}\frac{xv(1+\alpha v^*)}{x^*v^*(1+\alpha v)}\frac{y^*}{y}\\
&-k_2q\frac{\beta x^*v^*}{1+\alpha v^*}\frac{v}{v^*}-k_1(1-q)\frac{\beta x^*v^*}{1+\alpha v^*}\frac{\omega}{\omega^*}\frac{y^*}{y}-k_1(1-q)\frac{\beta x^*v^*}{1+\alpha v^*}\frac{v}{v^*}\\
&-k_2q\frac{\beta x^*v^*}{1+\alpha v^*}\frac{y}{y^*}\frac{v^*}{v}+3k_1(1-q)\frac{\beta x^*v^*}{1+\alpha v^*}-k_1(1-q)\frac{\beta x^*v^*}{1+\alpha v^*}\frac{y}{y^*}\frac{v^*}{v}\\
=&-\frac{d(x-x^*)^2}{x}-\frac{\beta x^*v^*}{1+\alpha v^*}\frac{\alpha(v-v^*)^2}{v^*(1+\alpha v)(1+\alpha v^*)}\\
&+\frac{\delta(1-q)}{eq+\delta}\frac{\beta x^*v^*}{1+\alpha v^*}\left[5-\frac{x^*}{x}-\frac{xv(1+\alpha v^*)}{x^*v^*(1+\alpha v)}\frac{\omega^*}{\omega}-\frac{\omega}{\omega^*}\frac{y^*}{y}-\frac{y}{y^*}\frac{v^*}{v}-\frac{1+\alpha v}{1+\alpha v^*}\right]\\
&+\frac{q(e+\delta)}{eq+\delta}\frac{\beta x^*v^*}{1+\alpha v^*}\left[4-\frac{x^*}{x}-\frac{y}{y^*}\frac{v^*}{v}-\frac{xv(1+\alpha v^*)}{x^*v^*(1+\alpha v)}\frac{y^*}{y}-\frac{1+\alpha v}{1+\alpha v^*}\right].
\end{aligned}
\tag{22}
$$

Noting that $x^*,\omega^*,y^*,v^*>0$, and the arithmetical mean is greater than or equal to the geometrical mean, then the last two terms of (22) are less than or equal to zero. Hence, from (22) we derive that $\dot{W}_1(t)\leqslant 0$, where the equality holds if and only if $(x,\omega,y,v)=(x^*,\omega^*,y^*,v^*)$. Using a similar argument as that in the proof of Theorem 1, the global asymptotic stability of E^* follows from LaSalle's invariance principle. This completes the proof. □

4 HIV-1 infection model with general nonlinear infection rate and latency cells

In order to obtain a comprehensive form of mathematical model describing nonlinear phenomena of HIV-1 infection process, in this section, we propose an HIV-1 infection model with a general form of nonlinear infection rate, of which the infection rate is given by an unspecified function of the concentrations of the uninfected CD4+ T-cells and free virus. The model we discuss is of the following form:

$$
\begin{aligned}
\dot{x}&=\lambda-dx-f(x,v),\\
\dot{\omega}&=(1-q)f(x,v)-e\omega-\delta\omega,\\
\dot{y}&=qf(x,v)-ay+\delta\omega,\\
\dot{v}&=ky-uv,
\end{aligned}
\tag{23}
$$

where the function $f(x,v)$ represents the rate for the uninfected CD4+ T-cells to be infected by the virus. All the other parameters are the same as that defined in model (2).

We assume that the infection rate $f(x,v)$ is always positive, continuous and differentiable. From the discussion in [11] we further assume that $f(x,v)$ grows monotonically with respect to both its variables, x and v and satisfy the conditions

$$f(x,0) = f(0,v) = 0, \tag{24}$$

$$\frac{\partial f(x,v)}{\partial x} > 0, \qquad \frac{\partial f(x,v)}{\partial v} > 0 \tag{25}$$

for all $x > 0$, $v > 0$. Also, one can easily show that the closed set D defined in Section 2, is positively invariant with respect to system (23).

4.1 The existence of feasible equilibria

It is straightforward to show that condition (24) ensures the existence of the infection-free equilibrium $E_0(x_0, 0, 0, 0)$ of system (23), where $x_0 = \lambda/d$.

The basic reproduction ratio describes the expected number of secondary cases produced by a typical infective individual in a completely susceptible population [4]. Following the result in [6], we can get the basic reproduction ratio of system (23)

$$R_0 = \frac{k(eq+\delta)}{au(e+\delta)} \frac{\partial f(x_0,0)}{\partial v}. \tag{26}$$

The system can also have a positive chronic-infection equilibrium $E^*(x^*, \omega^*, y^*, v^*)$, and, if it exists, the coordinates of the E^* satisfy the equalities

$$\lambda = dx^* + f(x^*, v^*), \tag{27}$$

$$(1-q)f(x^*, v^*) = (e+\delta)\omega^*, \tag{28}$$

$$qf(x^*, v^*) = ay^* - \delta\omega^*, \tag{29}$$

$$ky^* = uv^*. \tag{30}$$

4.2 Global stability

In this part, we constrain the function $f(x,v)$, so that it is sufficient to guarantee the global stability of the infection-free and chronic-infection equilibria of system (23). The Lyapunov functions that we construct in this part are partly inspired by Elaiw [8] and Ansari [1].

We first make two assumptions of the nonlinear infection rate $f(x,v)$.

(H1) The function $f(x,v)$ is concave with respect to the variable v, i.e.;

$$\frac{\partial^2 f(x,v)}{\partial v^2} \leqslant 0.$$

(H2) $\partial f(x,0)/\partial v$ is monotonically increasing with respect to x, i.e.,

$$\frac{\partial f(x_0,0)}{\partial v} > \frac{\partial f(x,0)}{\partial v} \quad \text{if } 0 < x < x_0,$$

$$\frac{\partial f(x_0,0)}{\partial v} < \frac{\partial f(x,0)}{\partial v} \quad \text{if } x > x_0.$$

Theorem 5. *Assume $R_0 \leqslant 1$. Then the infection-free equilibrium $E_0(x_0, 0, 0, 0)$ of system* (23) *is globally asymptotically stable if* (H1)–(H2) *hold.*

Proof. Define

$$W_0(t) = x - x_0 - \int_{x_0}^{x} \lim_{v\to 0^+} \frac{f(x_0, v)}{f(s, 0)}\,\mathrm{d}s + \frac{\delta}{eq+\delta}\omega + \frac{e+\delta}{eq+\delta}y + \frac{a(e+\delta)}{k(eq+\delta)}v. \quad (31)$$

It is easily seen that, for all $x, \omega, y, v > 0$, $W_0(t)$ is defined and continuous. Moreover, $W_0(t)$ reaches its global minimum at E_0 of system (23), and $W_0(E_0) = 0$. Therefore, $W_0(t)$ is a Lyapunov function. Calculation of the derivative of $W_0(t)$ along positive solutions shows that

$$\begin{aligned}\dot{W}_0(t) = {} & \left[1 - \lim_{v\to 0^+} \frac{f(x_0, v)}{f(x, 0)}\right]\big[\lambda - dx - f(x, v)\big] \\ & + \frac{\delta}{eq+\delta}\big[(1-q)f(x, v) - e\omega - \delta\omega\big] \\ & + \frac{e+\delta}{eq+\delta}\big[qf(x, v) - ay + \delta\omega\big] + \frac{a(e+\delta)}{k(eq+\delta)}(ky - uv). \end{aligned} \quad (32)$$

Noting that $\lambda = dx_0$,

$$\begin{aligned}\dot{W}_0(t) = {} & \lambda\left(1 - \frac{x}{x_0}\right)\left(1 - \frac{\partial f(x_0, 0)}{\partial v}\Big/\frac{\partial f(x, 0)}{\partial v}\right) \\ & + f(x, v)\frac{\partial f(x_0, 0)}{\partial v}\Big/\frac{\partial f(x, 0)}{\partial v} - \frac{au(e+\delta)}{k(eq+\delta)}v. \end{aligned} \quad (33)$$

The concavity of $f(x, v)$ with respect to v ensures that

$$f(x, v) \leqslant v\frac{\partial f(x, 0)}{\partial v} \quad (34)$$

holds for any $x > 0$, $v > 0$. Then from (33) and (34) we can show that

$$\begin{aligned}\dot{W}_0(t) &\leqslant \lambda\left(1 - \frac{x}{x_0}\right)\left(1 - \frac{\partial f(x_0, 0)}{\partial v}\Big/\frac{\partial f(x, 0)}{\partial v}\right) + v\frac{\partial f(x_0, 0)}{\partial v} - \frac{au(e+\delta)}{k(eq+\delta)}v \\ &= \lambda\left(1 - \frac{x}{x_0}\right)\left(1 - \frac{\partial f(x_0, 0)}{\partial v}\Big/\frac{\partial f(x, 0)}{\partial v}\right) + \frac{au(e+\delta)}{k(eq+\delta)}(R_0 - 1)v. \end{aligned} \quad (35)$$

Furthermore, by (H2), it is easy to get that

$$\left(1 - \frac{x}{x_0}\right)\left(1 - \frac{\partial f(x_0, 0)}{\partial v}\Big/\frac{\partial f(x, 0)}{\partial v}\right) \leqslant 0 \quad (36)$$

for all $x, v > 0$, and the equality holds only when $x = x_0$. Hence, if $R_0 \leqslant 1$, from (35) and (36), $\dot{W}_0(t) \leqslant 0$. It is easy to verify that $\dot{W}_0(t) = 0$ if and only if $x = x_0$, $\omega = y = v = 0$. Accordingly, using a similar argument as that in the proof of Theorem 1 and by LaSalle's invariance principle, the global asymptotic stability of E_0 follows. This completes the proof. □

We now state and prove our result on the global stability of the chronic-infection equilibrium E^* of system (23).

Theorem 6. *Assume that the chronic-infection equilibrium $E^*(x^*, \omega^*, y^*, v^*)$ of system* (23) *exists. If* (H1) *holds, then E^* is globally asymptotically stable.*

Proof. Define the Lyapunov function as

$$W_1(t) = x - x^* - \int_{x^*}^{x} \frac{f(x^*, v^*)}{f(s, v^*)}\,\mathrm{d}s + k_1\omega^* F\left(\frac{\omega}{\omega^*}\right) + k_2 y^* F\left(\frac{y}{y^*}\right) + k_3 v^* F\left(\frac{v}{v^*}\right), \quad (37)$$

where the function $F(x)$ is defined in (4) and the parameters k_1, k_2, k_3 are defined in (8).

Calculating the derivative of $W_1(t)$ along positive solutions, we derive that

$$\begin{aligned}\dot{W}_1(t) = {} & \left[1 - \frac{f(x^*, v^*)}{f(x, v^*)}\right]\big[\lambda - dx - f(x, v)\big] \\ & + k_1\left(1 - \frac{\omega^*}{\omega}\right)\big[(1-q)f(x, v) - e\omega - \delta\omega\big] \\ & + k_2\left(1 - \frac{y^*}{y}\right)\big[qf(x, v) - ay + \delta\omega\big] + k_3\left(1 - \frac{v^*}{v}\right)(ky - uv). \end{aligned} \quad (38)$$

By substituting $\lambda = dx^* + f(x^*, v^*)$, $ky^* = uv^*$ into (38), it follows that

$$\begin{aligned}\dot{W}_1(t) = {} & \left[1 - \frac{f(x^*, v^*)}{f(x, v^*)}\right]\big[dx^* + f(x^*, v^*) - dx - f(x, v)\big] \\ & + k_1\big[(1-q)f(x, v) - e\omega - \delta\omega\big] + k_1\left[-(1-q)f(x, v)\frac{\omega^*}{\omega} + (e+\delta)\omega^*\right] \\ & + k_2\big[qf(x, v) - ay + \delta\omega\big] + k_2\left[-qf(x, v)\frac{y^*}{y} + ay^* - \delta\omega\frac{y^*}{y}\right] \\ & + k_3\left(ky - uv - ky\frac{v^*}{v} + ky^*\right). \end{aligned} \quad (39)$$

Noting that

$$k_1(1-q) + k_2 q = 1, \qquad k_1(e+\delta) = k_2\delta, \qquad k_2 a = k_3 k,$$

we, therefore, derive from (39) that

$$\begin{aligned}\dot{W}_1(t) = {} & dx^* + f(x^*, v^*) - dx - dx^*\frac{f(x^*, v^*)}{f(x, v^*)} - f(x^*, v^*)\frac{f(x^*, v^*)}{f(x, v^*)} \\ & + dx\frac{f(x^*, v^*)}{f(x, v^*)} + f(x, v)\frac{f(x^*, v^*)}{f(x, v^*)} + k_1\left[-(1-q)f(x, v)\frac{\omega^*}{\omega} + (e+\delta)\omega^*\right] \\ & + k_2\left[-qf(x, v)\frac{y^*}{y} + ay^* - \delta\omega\frac{y^*}{y}\right] + k_3\left(-uv - ky\frac{v^*}{v} + ky^*\right). \end{aligned} \quad (40)$$

From (28) and (29) we can easily get that

$$k_2 a y^* = f(x^*, v^*), \qquad k_1(1-q)f(x^*, v^*) = k_1(e+\delta)\omega^* = k_2\delta\omega^*.$$

Then (40) can be rewritten as

$$\begin{aligned}
\dot{W}_1(t) &= dx^*\left(1-\frac{x}{x^*}\right)\left[1-\frac{f(x^*,v^*)}{f(x,v^*)}\right] + f(x^*,v^*) - f(x^*,v^*)\frac{f(x^*,v^*)}{f(x,v^*)} \\
&\quad + f(x^*,v^*)\frac{f(x,v)}{f(x,v^*)} - k_1(1-q)f(x^*,v^*)\frac{f(x,v)}{f(x^*,v^*)}\frac{\omega^*}{\omega} \\
&\quad + k_1(1-q)f(x^*,v^*) - k_2 q f(x^*,v^*)\frac{f(x,v)}{f(x^*,v^*)}\frac{y^*}{y} + 2f(x^*,v^*) \\
&\quad - k_1(1-q)f(x^*,v^*)\frac{\omega^*}{\omega}\frac{y^*}{y} - f(x^*,v^*)\frac{v}{v^*} - f(x^*,v^*)\frac{y}{y^*}\frac{v^*}{v} \\
&= dx^*\left(1-\frac{x}{x^*}\right)\left[1-\frac{f(x^*,v^*)}{f(x,v^*)}\right] + f(x^*,v^*)\frac{f(x,v)}{f(x,v^*)} - f(x^*,v^*)\frac{v}{v^*} \\
&\quad + 3f(x^*,v^*) - f(x^*,v^*)\frac{f(x^*,v^*)}{f(x,v^*)} - k_2 q f(x^*,v^*)\frac{f(x,v)}{f(x^*,v^*)}\frac{y^*}{y} \\
&\quad - k_1(1-q)f(x^*,v^*)\frac{\omega^*}{\omega}\frac{y^*}{y} - k_1(1-q)f(x^*,v^*)\frac{f(x,v)}{f(x^*,v^*)}\frac{\omega^*}{\omega} \\
&\quad + k_1(1-q)f(x^*,v^*) - f(x^*,v^*)\frac{y}{y^*}\frac{v^*}{v} \\
&= dx^*\left(1-\frac{x}{x^*}\right)\left[1-\frac{f(x^*,v^*)}{f(x,v^*)}\right] + \frac{\delta(1-q)}{eq+\delta}f(x^*,v^*) \\
&\quad \times\left[5 - \frac{f(x^*,v^*)}{f(x,v^*)} - \frac{\omega}{\omega^*}\frac{y^*}{y} - \frac{f(x,v)}{f(x^*,v^*)}\frac{\omega^*}{\omega} - \frac{y}{y^*}\frac{v^*}{v} - \frac{v}{v^*}\frac{f(x,v^*)}{f(x,v)}\right] \\
&\quad + \frac{q(e+\delta)}{eq+\delta}f(x^*,v^*)\left[4 - \frac{f(x^*,v^*)}{f(x,v^*)}\frac{f(x,v)}{f(x^*,v^*)}\frac{y^*}{y} - \frac{y}{y^*}\frac{v^*}{v} - \frac{v}{v^*}\frac{f(x,v^*)}{f(x,v)}\right] \\
&\quad + f(x^*,v^*)\left[1-\frac{f(x,v^*)}{f(x,v)}\right]\left[\frac{f(x,v)}{f(x,v^*)} - \frac{v}{v^*}\right]. \qquad (41)
\end{aligned}$$

We notice that $f(x,v)$ grows monotonically with respect to variable x, which ensures that

$$\left(1-\frac{x}{x^*}\right)\left[1-\frac{f(x^*,v^*)}{f(x,v^*)}\right] \leqslant 0.$$

By assumption (H1), we have that

$$\begin{aligned}
&\frac{f(x,v^*)}{f(x,v)} \geqslant \frac{v}{v^*} \quad \text{if } v \leqslant v^*, \\
&\frac{f(x,v^*)}{f(x,v)} \leqslant \frac{v}{v^*} \quad \text{if } v \geqslant v^*.
\end{aligned}$$

Then the monotonicity of $f(x,v)$ with respect to variable v guarantees that

$$\frac{f(x,v^*)}{f(x,v)} \geqslant \frac{v}{v^*} \quad \text{if } f(x,v) \leqslant f(x,v^*),$$
$$\frac{f(x,v^*)}{f(x,v)} \leqslant \frac{v}{v^*} \quad \text{if } f(x,v) \geqslant f(x,v^*).$$

Therefore, it is easily seen that

$$\left[1 - \frac{f(x,v^*)}{f(x,v)}\right]\left[\frac{f(x,v)}{f(x,v^*)} - \frac{v}{v^*}\right] \leqslant 0$$

holds for any $x > 0$, $v > 0$. Then the first and the fourth two terms of (41) are non-positive. Noting that $x^*, \omega^*, y^*, v^* > 0$, $f(x,v) > 0$, and the arithmetical mean is greater than or equal to the geometrical mean, the second and the third two terms of (41) are also non-positive. From (41) we have that $\dot{W}_1(t) \leqslant 0$ for all $x, \omega, y, v > 0$, where the equality holds if and only if $(x, \omega, y, v) = (x^*, \omega^*, y^*, v^*)$. Using a similar argument as that in the proof of Theorem 1 and by LaSalle's invariance principle, the global asymptotic stability of E^* follows. This completes the proof. □

5 Conclusion

In this paper, we have investigated the global dynamics of a class of HIV-1 infection models with different infection rates and latently infected cells. The global stability of the infection-free equilibria and the chronic-infection equilibria have been completely established by using the Lyapunov–LaSalle type theorem. The basic reproduction ratio R_0 which determines the dynamics of the HIV-1 models was obtained. By Theorems 1 and 3, we see that, in the first two models, if the basic reproduction ratio $R_0 < 1$, each of the disease-free equilibria is a global attractor, and the infections cannot persist. In this case, the virus is cleared up. From Theorems 2 and 4 we see that if the basic reproduction ratio $R_0 > 1$, each of the chronic-infection equilibria becomes a global attractor, and the infections persist indefinitely. In the last model, we have used a general form of nonlinear infection rate to describe the nonlinear phenomena of HIV-1 infection process. By giving Theorems 5 and 6, we showed that assumption (H1) and (H2) ensure the global stability of the infection-free equilibrium of this model; under assumption (H1), i.e., the concavity of the infection rate $f(x,v)$, the chronic-infection equilibrium of this model is globally asymptotically stable whenever it exists.

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References

1. H. Ansari, M. Hesaaraki, Global properties of infections disease models with general incidence rate, *Canadian Journal on Science and Engineering Mathematics*, **2**:48–52, 2011.

2. O. Bagasra, R. Pomerantz, Human immunodeficiency virus type-1 provirus is demonstrated in peripheral blood monocytes in vivo: A study utilizing an in situ polymerase chain reaction, *AIDS Res. Hum. Retrov.*, **9**:69–76, 1993.

3. M.A. Capistrán, A study of latency, reactivation and apoptosis throughout HIV pathogenesis, *Math. Comput. Modelling*, **52**:1011–1015, 2010.

4. O. Diekmann, J.A.P. Heesterbeek, J.A.J. Metz, On the definition and the computation of the basic reproduction ratio R_0 in models for infectious diseases in heterogeneous populations, *J. Math. Biol.*, **28**:365–382, 1990.

5. D.C. Douek, J.M. Brenchley, M.R. Betts, D.R. Ambrozak, B.J. Hill, HIV preferentially infects HIV-specific CD4+T cells, *Nature*, **417**:95–98, 2002.

6. P.D. Driessche, J. Watmough, Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission, *Math. Biosci.*, **180**:29–48, 2002.

7. D. Ebert, C.D. Zschokke-Rohringer, H.J. Carius, Dose effects and density-dependent regulation of two microparasites of Daphnia magna, *Oecologia*, **122**:200–209, 2000.

8. A.M. Elaiw, Global properties of a class of virus infection models with multitarget cells, *Nonlinear Dyn.*, **69**:423–435, 2012.

9. A. Korobeinikov, Global properties of basic virus dynamics models, *Bull. Math. Biol.*, **66**:879–883, 2004.

10. A. Korobeinikov, Global properties of infectious disease models with nonlinear incidence, *Bull. Math. Biol.*, **69**:1871–1886, 2007.

11. A. Korobeinikov, P.K. Maini, Non-linear incidence and stability of infectious disease models, *Math. Med. Biol.*, **22**:113–128, 2005.

12. D.C. Krakauer, M. Nowak, T-cell induced pathogenesis in HIV: Bystander effects and latent infection, *Proc. R. Soc. Lond., Ser. B*, **266**:1069–1075, 1999.

13. J.P. LaSalle, *The stability of dynamical system*, CBMS-NSF Reg. Conf. Ser. Appl. Math., SIAM, Philadephia, PA, 1976.

14. K. Lassen, Y. Han, Y. Zhou, J. Siliciano, R. F. Siliciano, The multifactorial nature of HIV-1 latency, *Trends Mol. Med.*, **11**:525–531, 2004.

15. J.M. McCune, Viral latency in HIV disease, *Cell*, **82**:183–188, 1995.

16. M.A. Nowak, R. Anderson, M. Boerlijst, S. Bonhoeffer, R. May, A. McMichael, HIV-1 evolution and disease progression, *Science*, **274**:1008–1010, 1996.

17. M.A. Nowak, C.R.M. Bangham, Population dynamics of immune responses to persistent viruses, *Science*, **272**:74–79, 1996.

18. M.J. Pace, L.Agosto, E.H. Graf, U. O'Doherty, HIV reservoirs and latency models, *Virology*, **411**:344–354, 2011.

19. A.S. Perelson, P.W. Nelson, Mathematical analysis of HIV-1 dynamics in vivo, *SIAM Rev.*, **41**:3–44, 1999.

20. R.R. Regoes, D. Ebert, S. Bonhoeffer, Dose-dependent infection rates of parasites produce the Allee effect in epidemiology, *Proc. R. Soc. London, Ser. B*, **269**:271–279, 2002.

21. X. Song, A.U. Neumann, Global stability and periodic solution of the viral dynamics, *J. Math. Anal. Appl.*, **329**:281–297, 2007.

22. X. Wang, X. Song, Global stability and periodic solution of a model for HIV infection of CD4+ Tcells, *Appl. Math. Comput.*, **189**:1331–1340, 2007.

23. R. Xu, Global dynamics of a delayed epidemic model with latency and relapse, *Nonlinear Anal. Model. Control*, **13**:250–263, 2013.