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DYNAMICS OF A NON-AUTONOMOUS HIV-1 INFECTION MODEL WITH DELAYS

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In this paper, following a previous paper ([32] Permanence and extinction of a non-autonomous HIV-1 model with two time delays, preprint) on the permanence and extinction of a delayed non-autonomous HIV-1 within-host model, we introduce and investigate a delayed HIV-1 model including maximum homeostatic proliferation rate of CD4$^+$ T-cells and varying coefficients. By applying the asymptotic analysis theory and oscillation theory, we show: (i) the system will be permanent when the threshold value $R_* > 1$, and for this case we also obtain the explicit estimate of the eventual lower bound of the HIV-1 virus load; (ii) the threshold value $R^* < 1$ implies the extinction of the virus. Furthermore, we obtain that the threshold dynamics is in agreement with that of the corresponding autonomous system, which extends the classic results for the system with constant coefficients. Numerical simulations are also given to illustrate our main results, and in particular, some sensitivity test of R_* is established.

Keywords: Non-autonomous; HIV-1 infection; delay; permanence and extinction; oscillation theory.

1. Introduction

In recent years, viral infection models consist of ordinary differential equations for the populations of uninfected CD4$^+$ T-cells, infected CD4$^+$ T-cells and free virus particles have been received with great attention and studied by many scholars (see [1–4, 8, 13, 15, 25, 24, 27, 33]). We know that many mathematical models of within-host viral infections have played an important role understanding the population dynamics of HIV-1 infection including drug treatment and drug resistance such as Perelson *et al.* [23, 26], De Boer and Doucher [7], Perelson [22], Wodarz and Nowak [35], Wodarz *et al.* [36]. A basic mathematical model describing HIV-1 infection dynamics with the simple mass-action infection is given by (see [25]):

$$\begin{cases} \dot{x}(t) = \lambda + ax(t)\left(1 - \dfrac{x(t)}{K}\right) - \mu x(t) - (1 - n_{\mathrm{rt}})kx(t)v(t), \\ \dot{y}(t) = (1 - n_{\mathrm{rt}})kx(t)v(t) - \delta y(t), \\ \dot{v}(t) = N\delta y(t) - cv(t), \end{cases} \tag{1.1}$$

where the variables and parameters are described in Table 1.

In general, time delay can arise for various practical dynamics behaviors in epidemiology. From the study of autonomous models with delay (see [6, 11, 14, 19, 20, 34]), we can find that the delay differential equations (DDEs) exhibit much more complicated dynamics than ODEs. The first model introduced the time between viral entry into a target cell and the production of new virus particles was developed by Herz *et al.* [12] and assumed that cells became productively infected τ time units after initial infection. Culshaw and Ruan [5] used the time delay between the infection CD4$^+$ T-cells and the emission of viral particles to study the effect of the time delay on the stability of the infected equilibrium. Song *et al.* [29] studied

Table 1. Descriptions of variables and parameters in (1.1).

	Description (unit)
Variables	
$x(t)$	Density of uninfected CD4$^+$ T-cells (mm^{-3})
$y(t)$	Density of infected T-cells (mm^{-3})
$v(t)$	Density of virus particles (mm^{-3})
Parameters	
λ	Rate at which new CD4$^+$ T-cells are created from sources (day^{-1}mm^{-3})
a	Maximum proliferation rate
K	T-cell population density at which proliferation shuts off (mm^{-3})
μ	Death rate of per CD4$^+$ T-cell (day^{-1})
k	Rate at which CD4$^+$ T-cells become infected with virus (mm^{3}day^{-1})
δ	Death rate of per uninfected cell (day^{-1})
N	Total number of new virus particles produced by each infected cell during its lifetime $\frac{1}{\delta}$
c	Rate at which the infectious virus is cleared out (day^{-1})
n_{rt}	Effectiveness of the reverse transcriptase inhibitor

the viral models with time delay as follows:

$$\begin{cases} \dot{x}(t) = \lambda + ax(t)\left(1 - \dfrac{x(t)}{K}\right) - \mu x(t) - kx(t)v(t), \\ \dot{y}(t) = kx(t-\tau)v(t-\tau) - \delta y(t), \\ \dot{v}(t) = N\delta y(t) - cv(t). \end{cases} \tag{1.2}$$

All parameters are the same as in system (1.1) except that the positive constant τ represents the length of the delay in days.

According to the model in [21], Liu and Wang [16] studied the following system:

$$\begin{cases} \dot{x}(t) = \lambda - \mu x(t) - (1-n_{\rm rt})kx(t)v(t), \\ \dot{y}(t) = (1-n_{\rm rt})ke^{-\delta_1\tau_1}x(t-\tau_1)v(t-\tau_1) - \delta y(t), \\ \dot{v}(t) = (1-n_p)N\delta e^{-\delta\tau_2}y(t-\tau_2) - cv(t), \end{cases} \tag{1.3}$$

where n_p denotes the effectiveness of the protease inhibitor, the terms $e^{-\delta_1\tau_1}, e^{-\delta\tau_2}$ account for the portion of cells infected at time t that is able to survive at least τ_1 time units and the portion of productively infected cells that can survive τ_2 time units to produce newly infectious virus (see [16], $\delta_1 = \mu + c$).

On the other hand, the non-autonomous phenomenon often occurs in many realistic epidemic models since biological and environmental parameters of the system are naturally subject to fluctuate in time. Many diseases show seasonal behaviors such as varying infection rates, fluctuations in birth rates and so on (see [17, 9, 10, 13, 30, 31, 37, 38, 18]). Rong *et al.* [28] considered the mechanisms underlying the emergence of drug-resistant variants during antiretroviral therapy (ART) and studied the effect of antiretroviral drugs on the evolution of drug-resistant HIV mutants by using a mathematical model. To investigate the non-autonomous phenomenon in the model, the coefficients should be periodic functions. Therefore, the purpose of our current paper is to establish the threshold values for a non-autonomous HIV-1 infection model with two delays and show that the disease will be permanent when the threshold value R_* is larger than unit, and the disease will go to extinction when the threshold value R^* is smaller than unit.

2. Model Formulation and Preliminary Lemmas

In this paper, we consider the following non-autonomous HIV-1 infection model with two delays:

$$\begin{cases} \dot{x}(t) = \lambda(t) + a(t)x(t)\left(1 - \dfrac{x(t)}{K(t)}\right) - \mu(t)x(t) - (1-n_{\rm rt}(t))k(t)x(t)v(t), \\ \dot{y}(t) = (1-n_{\rm rt}(t))k_1(t)e^{-\int_{t-\tau_1}^{t}\delta_1(s)ds}x(t-\tau_1)v(t-\tau_1) - \delta(t)y(t), \\ \dot{v}(t) = (1-n_p(t))N(t)\delta(t)e^{-\int_{t-\tau_2}^{t}\delta(s)ds}y(t-\tau_2) - c(t)v(t), \end{cases} \tag{2.1}$$

where the meanings of functions $\lambda(t)$, $a(t)$, $\mu(t)$, $K(t)$, $k(t)$, $k_1(t)$, $\delta(t)$, $N(t)$, $c(t)$, $n_{\rm rt}(t)$ and $n_p(t)$ appeared in (2.1) remain the same as the corresponding parameters $\lambda, a, \mu, K, k, k_1, \delta, N, c, n_{\rm rt}$ and n_p in models (1.2) and (1.3), respectively.

For convenience of notations, we denote

$$\begin{aligned}\beta(t) &= (1 - n_{\rm rt}(t))k(t),\\ \beta_1(t) &= (1 - n_{\rm rt}(t))k_1(t)e^{-\int_{t-\tau_1}^{t} \delta_1(s)ds},\\ \gamma(t) &= (1 - n_p(t))N(t)\delta(t)e^{-\int_{t-\tau_2}^{t} \delta(s)ds},\end{aligned}$$

then we can rewrite system (2.1) as follows:

$$\begin{cases}\dot{x}(t) = \lambda(t) + a(t)x(t)\left(1 - \dfrac{x(t)}{K(t)}\right) - \mu(t)x(t) - \beta(t)x(t)v(t),\\ \dot{y}(t) = \beta_1(t)x(t-\tau_1)v(t-\tau_1) - \delta(t)y(t),\\ \dot{v}(t) = \gamma(t)y(t-\tau_2) - c(t)v(t).\end{cases} \tag{2.2}$$

In the following, we will give some assumptions and notations for system (2.2).

(A_1) Functions $\lambda(t), \mu(t), \beta(t), \beta_1(t), \delta(t), \gamma(t), c(t)$ are positive continuous bounded and have positive lower bounds.

(A_2) If $f(t)$ is a continuous bounded function defined on $[0, +\infty)$, then we set

$$f^l = \inf_{t\geq 0} f(t), \quad f^u = \sup_{t\geq 0} f(t).$$

The initial condition of (2.2) is given by

$$x(\theta) = \varphi_1(\theta), \quad y(\theta) = \varphi_2(\theta), \quad v(\theta) = \varphi_3(\theta), \quad -\tau \leq \theta \leq 0, \quad \varphi_i(0) > 0, \quad i = 1, 2, 3, \tag{2.3}$$

where $\varphi = (\varphi_1, \varphi_2, \varphi_3)^{\rm T}$ such that $\varphi_i(\theta) \geq 0$ $(i = 1, 2, 3)$ for all $\theta \in [-\tau, 0]$, $\tau = \max\{\tau_1, \tau_2\}$, and C denotes the Banach space $C([-\tau, 0], R^3)$ of continuous functions mapping the interval $[-\tau, 0]$ into R^3 and designates the sup-norm of an element φ in C by

$$\|\varphi\| = \sup_{-\tau\leq\theta\leq 0}\{|\varphi_1(\theta)|, |\varphi_2(\theta)|, |\varphi_3(\theta)|\}.$$

Definition 2.1. The system (2.2) is said to be permanent if there exist positive constants $\widetilde{q}, \widetilde{q_1}, \widetilde{q_2}$ and $\widetilde{L}, \widetilde{L_1}, \widetilde{L_2}$ such that the following inequalities,

$$\widetilde{q} \leq \liminf_{t\to+\infty} x(t) \leq \limsup_{t\to+\infty} x(t) \leq \widetilde{L},$$

$$\widetilde{q_1} \leq \liminf_{t\to+\infty} y(t) \leq \limsup_{t\to+\infty} y(t) \leq \widetilde{L_1},$$

$$\widetilde{q_2} \leq \liminf_{t\to+\infty} v(t) \leq \limsup_{t\to+\infty} v(t) \leq \widetilde{L_2},$$

hold for any solution $(x(t), y(t), v(t))$ of system (2.2) with initial condition (2.3). Here $\widetilde{q}, \widetilde{q_1}, \widetilde{q_2}, \widetilde{L}, \widetilde{L_1}, \widetilde{L_2}$ are independent of (2.3).

Lemma 2.2 ([37]). *Consider the following non-autonomous linear equation*

$$\dot{w}(t) = \lambda(t) - \mu(t)w(t). \tag{2.4}$$

Suppose that assumptions (A_1) *and* (A_2) *hold, then*:

(i) *Each fixed solution $w^*(t)$ of Eq.* (2.4) *with initial value $w(0) > 0$ is bounded and globally uniformly attractive on R_+.*
(ii) *There exist $m, M > 0$, such that $m < \liminf_{t\to+\infty} w(t) \le \limsup_{t\to+\infty} w(t) < M$.*
(iii) *When Eq.* (2.4) *is T-periodic, then we obtain that Eq.* (2.4) *has a unique non-negative T-periodic solution $w^*(t)$ which is globally uniformly attractive.*
(iv) *If $\mu(t) > 0$ for all $t \ge 0$ and*

$$0 < \liminf_{t\to+\infty} \frac{\lambda(t)}{\mu(t)} \le \limsup_{t\to+\infty} \frac{\lambda(t)}{\mu(t)} < +\infty,$$

then for any solution $w(t)$ of Eq. (2.4) *with the initial condition $w(0) > 0$, we have*

$$\liminf_{t\to+\infty} \frac{\lambda(t)}{\mu(t)} = \left(\frac{\lambda}{\mu}\right)^l < \liminf_{t\to+\infty} w(t) \le \limsup_{t\to+\infty} w(t) < \left(\frac{\lambda}{\mu}\right)^u = \limsup_{t\to+\infty} \frac{\lambda(t)}{\mu(t)}.$$

Lemma 2.3. *The solution $(x(t), y(t), v(t))$ of system* (2.2) *with initial condition* (2.3) *is positive and bounded for all $t \ge 0$.*

Proof. Since the right-hand side of system (2.2) is completely continuous, then the solution $(x(t), y(t), v(t))$ of system (2.2) with initial condition (2.3) exists and is unique. Obviously, we can easily obtain $x(t) > 0$, $y(t) > 0$, $v(t) > 0$ for all $t \ge 0$.

Next, we only prove that $x(t), y(t), v(t)$ are positive bounded for all $t \ge 0$.

According to the first equation of (2.2), we get

$$\dot{x}(t) \le \lambda^u + (a^u - \mu^l)x(t) - \frac{a^l}{K^u}x^2(t),$$

then we have

$$\limsup_{t\to+\infty} x(t) \le \frac{K^u}{2a^l}\left(a^u - \mu^l + \sqrt{(a^u - \mu^l)^2 + \frac{4\lambda^u a^l}{K^u}}\right) \triangleq L.$$

Denote

$$U(t) = x(t) + \frac{\beta^l}{\beta_1^u}y(t+\tau_1) + \frac{\beta^l\delta^l}{2\beta_1^u\gamma^u}v(t+\tau_1+\tau_2),$$

then we can calculate the time derivative of $U(t)$:

$$\begin{aligned}\dot{U}(t) &\le \lambda^u + a^u x(t) - \frac{a^l}{K^u}x^2(t) - \sigma U(t)\\ &= -\frac{a^l}{K^u}\left(x(t) - \frac{K^u a^u}{2a^l}\right)^2 + \lambda^u + \frac{K^u(a^u)^2}{4a^l} - \sigma U(t)\\ &\le \lambda^u + \frac{K^u(a^u)^2}{4a^l} - \sigma U(t), \quad \sigma = \left\{\mu^l, \frac{\delta^l}{2}, c^l\right\},\end{aligned}$$

by Lemma 2.2, which implies that

$$\limsup_{t\to+\infty} U(t) \le \frac{4a^l\lambda^u + K^u(a^u)^2}{4a^l\sigma}. \tag{2.5}$$

□

Lemma 2.4. *If time series* $\{t_n\}_{n=1}^{\infty}$ *is large enough, then* $y(t), v(t)$ *satisfy*

$$y(t_n - s) \le c_1 y(t_n), \quad v(t_n - s) \le c_2 v(t_n), \quad c_1 = e^{\delta^u\tau}, \quad c_2 = e^{c^u\tau}, \quad s \in [0,\tau].$$

Proof. From the second equation of (2.2), we have

$$\dot{y}(t) \ge -\delta(t)y(t) \ge -\delta^u y(t),$$

then integrating from $t_n - s$ to t_n, we obtain

$$y(t_n) \ge y(t_n - s)\exp\left(-\int_{t_n-s}^{t_n}\delta^u d\theta\right) = e^{-\delta^u s}y(t_n - s) \ge e^{-\delta^u\tau}y(t_n - s).$$

Thus, $y(t_n - s) \le e^{\delta^u\tau}y(t_n) \triangleq c_1 y(t_n)$. Similarly, from the third equation of (2.2), we have $v(t_n - s) \le e^{c^u\tau}v(t_n) \triangleq c_2 v(t_n)$. □

Lemma 2.5. *The solution* $(x(t), y(t), v(t))$ *of system* (2.2) *with initial condition* (2.3) *satisfies*

$$\liminf_{t\to+\infty} x(t) \ge \frac{K^l}{2a^u}\left[\Lambda + \sqrt{\Lambda^2 + \frac{4a^u\lambda^l}{K^l}}\right] \triangleq q, \tag{2.6}$$

where $\Lambda = a^l - \mu^u - \frac{\beta^u\beta_1^u\gamma^u}{\beta^l\delta^l} \cdot \frac{4a^l\lambda^u + K^u(a^u)^2}{2a^l\sigma}$.

Proof. From Lemma 2.3, for any $\varepsilon > 0$, there exists a large enough T_0 such that

$$v(t) < \frac{2\beta_1^u\gamma^u}{\beta^l\delta^l} \cdot \frac{4a^l\lambda^u + K^u(a^u)^2}{4a^l\sigma} + \varepsilon, \quad \forall\, t \ge T_0.$$

Thus, by the first equation of system (2.2),

$$\begin{aligned}\dot{x}(t) &\geq \lambda(t) + a(t)x(t)\left(1 - \frac{x(t)}{K(t)}\right) - \mu(t)x(t)\\ &\qquad - \beta(t)\left(\frac{\beta_1^u\gamma^u}{\beta^l\delta^l}\cdot\frac{4a^l\lambda^u + K^u(a^u)^2}{2a^l\sigma} + \varepsilon\right)x(t)\\ &\geq \lambda^l - \left[\mu^u - a^l + \beta^u\left(\frac{\beta_1^u\gamma^u}{\beta^l\delta^l}\cdot\frac{4a^l\lambda^u + K^u(a^u)^2}{2a^l\sigma} + \varepsilon\right)\right]x(t) - \frac{a^u}{K^l}x^2(t)\end{aligned}$$

and hence, we have

$$\liminf_{t\to+\infty} x(t) \geq \frac{K^l}{2a^u}\left[\Lambda + \sqrt{\Lambda^2 + \frac{4a^u\lambda^l}{K^l}}\right]. \tag{2.7}$$

□

Set

$$W(t) = y(t) + \frac{\delta^u}{\gamma^l}v(t) + \int_{t-\tau_1}^t \beta_1(s+\tau_1)x(s)v(s)ds + \frac{\delta^u}{\gamma^l}\int_{t-\tau_2}^t \gamma(s+\tau_2)y(s)ds \tag{2.8}$$

and

$$G(t) = y(t) + \frac{\delta^l}{\gamma^u}v(t) + \int_{t-\tau_1}^t \beta_1(\xi+\tau_1)x(\xi)v(\xi)d\xi + \frac{\delta^l}{\gamma^u}\int_{t-\tau_2}^t \gamma(\xi+\tau_2)y(\xi)d\xi, \tag{2.9}$$

then we have the following lemma.

Lemma 2.6. *For any t large enough, then we have the following results*:

(i)

$$W(t) \leq k_1y(t) + k_2v(t), \tag{2.10}$$

where $k_1 = 1 + \frac{\delta^u\gamma^u}{\gamma^l}c_1\tau$ *and* $k_2 = \frac{\delta^u}{\gamma^l} + \frac{\beta_1^u\lambda^u}{\mu^l}c_2\tau.$

(ii)

$$G(t) \leq k_1'y(t) + k_2'v(t) \leq W(t), \tag{2.11}$$

where $k_1' = 1 + \delta^lc_1\tau$ *and* $k_2' = \frac{\delta^l}{\gamma^u} + \frac{\beta_1^u\lambda^u}{\mu^l}c_2\tau.$

Proof. It follows from (2.8) and Lemmas 2.3 and 2.4 that

$$\begin{aligned}W(t) &\leq y(t) + \frac{\delta^u}{\gamma^l}v(t) + \frac{\beta_1^u\lambda^u}{\mu^l}c_2\tau v(t) + \frac{\delta^u\gamma^u}{\gamma^l}c_1\tau y(t)\\ &= \left(1 + \frac{\delta^u\gamma^u}{\gamma^l}c_1\tau\right)y(t) + \left(\frac{\delta^u}{\gamma^l} + \frac{\beta_1^u\lambda^u}{\mu^l}c_2\tau\right)v(t)\\ &\triangleq k_1y(t) + k_2y(t).\end{aligned}$$

Similarly, from (2.9) and Lemmas 2.3 and 2.4, we easily obtain

$$G(t) \leq k_1'y(t) + k_2'v(t) \leq W(t).$$

□

3. Permanence and Extinction

In this section, we will establish sufficient conditions for the persistence of (2.2).

Denote

$$\begin{aligned} R_* &= \frac{K^l\beta_1^l\gamma^l}{2a^u\delta^u c^u}\left[a^l-\mu^u+\sqrt{(a^l-\mu^u)^2+\frac{4\lambda^l a^u}{K^l}}\right],\\ R^* &= \frac{K^u\beta_1^u\gamma^u}{2a^l\delta^l c^l}\left[a^u-\mu^l+\sqrt{(a^u-\mu^l)^2+\frac{4\lambda^u a^l}{K^u}}\right]. \end{aligned} \tag{3.1}$$

Theorem 3.1. *The system* (2.2) *with initial condition* (2.3) *is permanent if* $R_* > 1$.

Proof. We will give the propositions to complete the proof of this theorem. □

Proposition 3.2. *If* $R_* > 1$ *holds, for any positive solution* $(x(t), y(t), v(t))$ *of system* (2.2) *with initial condition* (2.3), *then we have*

$$\liminf_{t\to+\infty} y(t) \geq \widetilde{q}_1, \quad \liminf_{t\to+\infty} v(t) \geq \widetilde{q}_2, \tag{3.2}$$

where $\widetilde{q}_1 = \frac{1}{2}\frac{\beta_1^l q}{\delta^u}\frac{\gamma^l e^{-c^u(\tau+2p)}}{\gamma^l k_2 c_2 + k_1 c^u} q_1$, *where* q, q_1, p *and* $\widetilde{q}_2$ *are defined in* (2.6), (3.3), (3.6) *and* (3.16), *respectively.*

Proof. Here we will show that it holds by following four steps.

Step I. We first prove that there exists

$$q_1 = \frac{1}{2}(R_*-1)\left(\frac{a^u\delta^u c^u}{K^l\beta_1^l\gamma^l}+\frac{\lambda^l\beta_1^l\gamma^l}{R_*\delta^u c^u}\right)\min\left\{\frac{c^l}{\beta^u\gamma^u},\frac{\delta^u}{\beta^u\gamma^l}\right\} > 0, \tag{3.3}$$

such that $\limsup_{t\to+\infty} y(t) \geq q_1$, for any solution of system (2.2). Suppose that it is not true, then $\limsup_{t\to+\infty} y(t) < q_1$, by the third equation of system (2.2), we get

$$\dot{v}(t) = \gamma(t)y(t-\tau_2) - c(t)v(t) \leq \gamma^u q_1 - c^l\gamma(t),$$

from Lemma 2.2, we have $\limsup_{t\to+\infty} v(t) < \frac{\gamma^u q_1}{c^l}$. Thus, from the first equation of system (2.2), we get $\dot{x}(t) \geq \lambda^l - (\mu^u - a^l + \frac{\beta^u\gamma^u}{c^l}q_1)x(t) - \frac{a^u}{K^l}x^2(t)$.

Then we obtain

$$\liminf_{t\to+\infty} x(t) \geq \frac{K^l}{2a^u}\left[\Lambda_1+\sqrt{\Lambda_1^2+\frac{4\lambda^l a^u}{K^l}}\right] \triangleq h(q_1), \tag{3.4}$$

where $\Lambda_1 = a^l - \mu^u - \frac{\beta^u\gamma^u}{c^l}q_1$.

Noting that the definition of $W(t)$ in (2.8), then we have

$$\dot{W}(t) \geq \left(\beta_1^l h(q_1) - \frac{\delta^u c^u}{\gamma^l}\right)v(t) > 0, \quad \text{if } R_* > 1, \tag{3.5}$$

for all t large enough, which means that $W(t)$ is increasing. From Lemma 2.4, $W(t)$ is positive and bounded, so there exists a constant $W^* > 0$ such that

$W(t) \to W^*$ as $t \to +\infty$, which implies that $\dot{W}(t) \to 0$ as $t \to +\infty$, this reduces that $v(t) \to 0$, and then $y(t) \to 0$ as $t \to +\infty$, which means a contradiction. Thus, $\limsup_{t\to+\infty} y(t) \geq q_1$.

Step II. Next, we will prove that there exists $c_0 = q_1 e^{-(\tau+2p)c^u}$ such that $W(t) \geq c_0$.

From (2.8) and Step I, we obtain that for any $\widehat{t}_0 \geq 0$, $W(t) < q_1$ is impossible for all $t \geq \widehat{t}_0$. Hence, we will consider the following two possibilities:

(a) $W(t) \geq q_1$ for all t large enough.
(b) $W(t)$ oscillates about q_1 for all t large enough.

Here, we only need to consider the second case. Let t_1 and t_2 be sufficiently large satisfying:

$$W(t_1) = W(t_2) = q_1, \quad W(t) < q_1, \ \forall\, t \in (t_1, t_2).$$

If $t_2 - t_1 \leq \tau + 2p$, where

$$p = \frac{1}{2}\sqrt{\frac{K^l}{a^u\lambda^l + \frac{K^l}{4}\left(\mu^u - a^l + \frac{\beta^u\gamma^l q_1}{\delta^u}\right)^2}}\ \ln \frac{2K^l\left(\lambda^l + \dfrac{K^l\left(\mu^u - a^l + \frac{\beta^u\gamma^l q_1}{\delta^u}\right)^2}{4a^u}\right)}{a^u L\varepsilon_0} > 0, \tag{3.6}$$

where ε_0 is defined in (3.12). From (2.8), we have

$$\frac{\delta^u}{\gamma^l}v(t) \leq W(t) < q_1, \quad v(t) \leq \frac{q_1\gamma^l}{\delta^u}, \quad \forall\, t \in (t_1 + \tau, t_2).$$

By the first equation of system (2.2), for all t large enough, we have

$$\begin{aligned}\dot{x}(t) &\geq \lambda^l - \left(\mu^u - a^l + \frac{\beta^u\gamma^l q_1}{\delta^u}\right)x(t) - \frac{a^u}{K^l}x^2(t)\\ &= -\frac{a^u}{K^l}\left(x(t) + \frac{K^l}{2a^u}\left(\mu^u - a^l + \frac{\beta^u\gamma^l q_1}{\delta^u}\right)\right)^2 + \lambda^l\\ &\quad + \frac{K^l}{4a^u}\left(\mu^u - a^l + \frac{\beta^u\gamma^l q_1}{\delta^u}\right)^2.\end{aligned} \tag{3.7}$$

Let

$$\begin{aligned} z(t) &= x(t) + \frac{K^l}{2a^u}\left(\mu^u - a^l + \frac{\beta^u\gamma^l q_1}{\delta^u}\right),\\ b &= \lambda^l + \frac{K^l}{4a^u}\left(\mu^u - a^l + \frac{\beta^u\gamma^l q_1}{\delta^u}\right)^2.\end{aligned} \tag{3.8}$$

Then the inequality (3.7) can be rewritten as

$$\dot{z}(t) \geq -\frac{a^u}{K^l}z^2(t) + b = \left(\sqrt{b} + \sqrt{\frac{a^u}{K^l}}z(t)\right)\left(\sqrt{b} - \sqrt{\frac{a^u}{K^l}}z(t)\right),$$

which implies that

$$\frac{1}{2\sqrt{b}}\left(\frac{1}{\sqrt{\frac{a^u}{K^l}}z(t)+\sqrt{b}}+\frac{1}{-\sqrt{\frac{a^u}{K^l}}z(t)+\sqrt{b}}\right)dz(t)\geq dt, \tag{3.9}$$

for any $t\in(t_1+\tau,t_2)$; we may integrate (3.9) from $t_1+\tau$ to t, then

$$\begin{aligned}
z(t) &\geq \sqrt{\frac{bK^l}{a^u}}-\frac{2\sqrt{\frac{bK^l}{a^u}}}{\frac{\sqrt{b}+\sqrt{\frac{a^u}{K^l}}z(t_1+\tau)}{\sqrt{b}-\sqrt{\frac{a^u}{K^l}}z(t_1+\tau)}\exp\left(2\sqrt{\frac{ba^u}{K^l}}(t-t_1-\tau)\right)+1}\\
&\geq \sqrt{\frac{bK^l}{a^u}}-\frac{2\sqrt{\frac{K^l}{a^u}}\left(\sqrt{b}-\sqrt{\frac{a^u}{K^l}}z(t_1+\tau)\right)\exp\left(-2\sqrt{\frac{ba^u}{K^l}}(t-t_1-\tau)\right)}{\sqrt{b}+\sqrt{\frac{a^u}{K^l}}z(t_1+\tau)}\\
&= \sqrt{\frac{bK^l}{a^u}}+\frac{2\sqrt{b}z(t_1+\tau)\exp\left(-2\sqrt{\frac{ba^u}{K^l}}(t-t_1-\tau)\right)}{\sqrt{b}+\sqrt{\frac{a^u}{K^l}}z(t_1+\tau)}\\
&\quad -\frac{2b\sqrt{\frac{K^l}{a^u}}\exp\left(-2\sqrt{\frac{ba^u}{K^l}}(t-t_1-\tau)\right)}{\sqrt{b}+\sqrt{\frac{a^u}{K^l}}z(t_1+\tau)}\\
&\geq \sqrt{\frac{bK^l}{a^u}}-\frac{2b\sqrt{\frac{K^l}{a^u}}\exp\left(-2\sqrt{\frac{ba^u}{K^l}}(t-t_1-\tau)\right)}{\sqrt{b}+\sqrt{\frac{a^u}{K^l}}z(t_1+\tau)}.
\end{aligned} \tag{3.10}$$

By (3.10), we get

$$\begin{aligned}
x(t) &\geq \sqrt{\frac{bK^l}{a^u}}-\frac{K^l}{2a^u}\left(\mu^u-a^l+\frac{\beta^u\gamma^l q_1}{\delta^u}\right)\\
&\quad -\frac{2b\sqrt{\frac{K^l}{a^u}}\exp\left(-2\sqrt{\frac{ba^u}{K^l}}(t-t_1-\tau)\right)}{\sqrt{b}+\sqrt{\frac{a^u}{K^l}}\left(x(t_1+\tau)+\frac{K^l}{2a^u}\left(\mu^u-a^l+\frac{\beta^u\gamma^l q_1}{\delta^u}\right)\right)}\\
&\geq \sqrt{\frac{\lambda^l K^l}{a^u}+\left(\frac{K^l}{2a^u}\left(\mu^u-a^l+\frac{\beta^u\gamma^l q_1}{\delta^u}\right)\right)^2}-\frac{K^l}{2a^u}\left(\mu^u-a^l+\frac{\beta^u\gamma^l q_1}{\delta^u}\right)\\
&\quad -2\sqrt{\frac{K^l}{a^u}}\left(\lambda^l+\frac{K^l}{4a^u}\left(\mu^u-a^l+\frac{\beta^u\gamma^l q_1}{\delta^u}\right)^2\right)\\
&\quad \times\frac{\exp\left(-2\sqrt{\frac{\lambda^l a^u}{K^l}+4\left(\mu^u-a^l+\frac{\beta^u\gamma^l q_1}{\delta^u}\right)^2}(t-t_1-\tau)\right)}{\sqrt{\frac{a^u}{K^l}}x(t_1+\tau)}
\end{aligned}$$

$$
\begin{aligned}
&\geq \sqrt{\frac{\lambda^l K^l}{a^u} + \left(\frac{K^l}{2a^u}\left(\mu^u - a^l + \frac{\beta^u\gamma^l q_1}{\delta^u}\right)\right)^2} \\
&\quad - \frac{K^l}{2a^u}\left(\mu^u - a^l + \frac{\beta^u\gamma^l q_1}{\delta^u}\right) - \varepsilon_0 \\
&\triangleq x_\Delta,
\end{aligned} \tag{3.11}
$$

for any $t \in (t_1 + \tau + p, t_2)$, where

$$
\varepsilon_0 = \frac{1}{2}\left\{\sqrt{\frac{\lambda^l K^l}{a^u} + \Theta_1^2} - \Theta_1 - \frac{\delta^u c^u}{\beta_1^l \gamma^l}\right\} > 0, \tag{3.12}
$$

where $\Theta_1 = \frac{K^l}{2a^u}\left(\mu^u - a^l + \frac{\beta^u\gamma^l q_1}{\delta^u}\right)$.

Thus, from (2.8) and (3.5), $\forall\, t \in (t_1, t_2)$, we obtain

$$
\dot{W}(t) \geq \left(\beta_1(t+\tau)x(t) - \frac{\delta^u}{\gamma^l}c(t)\right)v(t) \geq -\frac{\delta^u c^u}{\gamma^l}v(t) \geq -c^u W(t). \tag{3.13}
$$

Note that $t_2 - t_1 \leq \tau + 2p$, so we have

$$
W(t) \geq W(t_1)\exp\left(-\int_{t_1}^{t} c^u d\theta\right) \geq q_1 \exp(-(\tau+2p)c^u) \triangleq c_0. \tag{3.14}
$$

If $t_2 - t_1 > \tau + 2p$, obviously, $W(t) \geq c_0$ holds when $t \in [t_1, t_1 + \tau + 2p]$, by (3.5), when $t \in [t_1 + \tau + 2p, t_2]$,

$$
\dot{W}(t) \geq \left(\beta_1^l x_\Delta - \frac{\delta^u}{\gamma^l}c^u\right)v(t) > 0, \quad \text{if } R_* > 1,
$$

then we have $W(t) \geq W(t_1 + \tau + 2p) \geq c_0$, for all $t \in [t_1 + \tau + 2p, t_2]$. Hence, $W(t) \geq c_0 > 0$ for all t large enough when $R_* > 1$.

Step III. In this step, we will prove that

$$
\liminf_{t\to+\infty} v(t) \geq \widetilde{q}_2, \tag{3.15}
$$

where

$$
\widetilde{q}_2 = \frac{1}{2}\frac{\gamma^l c_0}{\gamma^l k_2 c_2 + k_1 c^u} = \frac{1}{2}\frac{\gamma^l q_1 \exp(-c^u(\tau+2p))}{\gamma^l k_2 c_2 + k_1 c^u} > 0, \tag{3.16}
$$

and c_2, k_1, k_2 and q_1 are defined in Lemmas 2.4 and 2.6 and (3.3).

Suppose (3.15) does not hold, then $\liminf_{t\to+\infty} v(t) < \widetilde{q}_2$, from the definition of inferior limit of $v(t)$, we can choose a sequence $\{t_n\}_{n=1}^{\infty}$ such that

$$
v(t_n) < \widetilde{q}_2, \quad t_n \to +\infty, \quad \text{as } n \to \infty.
$$

By Lemmas 2.3–2.6, we get

$$y(t_n-\tau_2)\ge\frac{c_0-k_2v(t_n-\tau_2)}{k_1}\ge\frac{c_0-k_2c_2v(t_n)}{k_1}. \tag{3.17}$$

It follows from the third equation of (2.2) that

$$\begin{aligned}\dot v(t_n)&\ge\gamma(t_n)\frac{c_0-k_2c_2v(t_n)}{k_1}-c(t_n)v(t_n)\\&\ge\frac{\gamma^lc_0}{k_1}-\left(c^u+\frac{\gamma^lk_2c_2}{k_1}\right)\widetilde{q}_2\\&=\frac{\gamma^lc_0}{k_1}-\frac{c^uk_1+\gamma^lk_2c_0}{k_1}\cdot\frac{1}{2}\frac{\gamma^lc_0}{\gamma^lk_2c_2+k_1c^u}\\&=\frac{\gamma^lc_0}{2k_1}>0.\end{aligned} \tag{3.18}$$

Next, we will consider the following three cases:

(i) If $v(t_n)$ oscillates about $\widetilde{q}_2$, obviously, there exists a subsequence $\{t_{n_j}\}$ such that $t_{n_j}\to+\infty$, as $j\to\infty$, and $\dot v(t_{n_j})=0$; this is a contradiction from $\dot v(t_n)>0$.

(ii) If $v(t_n)<\widetilde{q}_2$ and $v(t_n)$ is uniformly ultimately increasing, by $\dot v(t_n)>0$, then there exists $T_n>0$ such that $v(T_n)\to v^*(\text{constant})\le\widetilde{q}_2$ as $n\to\infty$, so $\dot v(T_n)\to0$. Noting that (3.18), $\lim_{n\to\infty}\dot v(T_n)>\frac{\gamma^lc_0}{2k_1}>0$; this reduces a contradiction.

(iii) If $v(t_n)<\widetilde{q}_2$ and $v(t_n)$ is not uniformly ultimately increasing, for any $T>0$, then there exists $t_T>T$ such that $\dot v(t_T)<0$ and $v(t_T)<\widetilde{q}_2$; this reduces a contradiction again.

Therefore, we have $\liminf_{t\to+\infty}v(t)\ge\widetilde{q}_2$.

Step IV. Lastly, we will prove that $\liminf_{t\to+\infty}y(t)\ge\widetilde{q}_1$, where $\widetilde{q}_1$ is defined in Proposition 3.2.

By the second equation of system (2.2) and Lemma 2.5, we get

$$\dot y(t)=\beta_1(t)x(t-\tau_1)v(t-\tau_1)-\delta(t)y(t)\ge\beta_1^lq\widetilde{q}_2-\delta^uy(t),$$

according to Lemma 2.2, which means that

$$\liminf_{t\to+\infty}y(t)\ge\frac{\beta_1^lq\widetilde{q}_2}{\delta^u}=\frac{1}{2}\frac{\beta_1^lq}{\delta^u}\frac{\gamma^le^{-c^u(\tau+2p)}}{\gamma^lk_2c_2+k_1c^u}q_1=\widetilde{q}_1. \tag{3.19}$$

□

Remark 3.3. In system (2.2), $\lambda(t)$, $a(t)$, $K(t)$, $\mu(t)$, $\beta(t)$, $\beta_1(t)$, $\delta(t)$, $\gamma(t)$ and $c(t)$ are replaced by positive constants, namely, system (2.2) becomes an autonomous

HIV-1 infection model with two delays. The basic reproduction number of this autonomous HIV-1 infection system is given by

$$R_0 = \frac{K\beta_1\gamma}{2a\delta c}\left[a-\mu+\sqrt{(a-\mu)^2+\frac{4\lambda a}{K}}\right].$$

Clearly, $R_* > 1$ implies $R_0 > 1$.

Proposition 3.4. *If $R_* > 1$, then for any positive solution $(x(t), y(t), v(t))$ of system* (2.2) *with* (2.3), *we have*

$$\limsup_{t\to+\infty} y(t) \le \widetilde{L_1}, \quad \limsup_{t\to+\infty} v(t) \le \widetilde{L_2}, \tag{3.20}$$

where $\widetilde{L_1} \le c^0$, $\widetilde{L_2} \le \frac{\gamma^u}{\delta^l}c^0$, c^0 are defined in (3.39).

Proof. Similar to the proof of Proposition 3.2, we also only consider the following steps.

Step I. We first prove that there exists

$$L_1 = 2\frac{c^u}{\beta^l\gamma^l}(R^*-1)\left(\frac{a^l\delta^l c^l}{K^u\beta_1^u\gamma^u}+\frac{\lambda^u\beta_1^u\gamma^u}{R^*\delta^l c^l}\right) > 0, \quad \text{if } R^* > R_* > 1, \tag{3.21}$$

such that

$$\liminf_{t\to+\infty} y(t) \le L_1. \tag{3.22}$$

If it is not true, then $\liminf_{t\to+\infty} y(t) > L_1$; by the third equation of system (2.2), for all t large enough, we have

$$\dot v(t) = \gamma(t)y(t-\tau_2) - c(t)v(t) \ge \gamma^l L_1 - c^u v(t),$$

according to Lemma 2.3, then $\liminf_{t\to+\infty} v(t) \ge \frac{\gamma^l}{c^u}L_1$. Thus, by the first equation of system (2.2), for all t large enough, we can obtain

$$\dot x(t) \le \lambda^u - \left(\mu^l - a^u + \frac{\beta^l\gamma^l}{c^u}L_1\right)x(t) - \frac{a^l}{K^u}x^2(t),$$

which implies that

$$\begin{aligned}\limsup_{t\to+\infty} x(t) &\le \frac{K^u}{2a^l}\left[a^u-\mu^l-\frac{\beta^l\gamma^l}{c^u}L_1+\sqrt{\left(a^u-\mu^l-\frac{\beta^l\gamma^l}{c^u}L_1\right)^2+\frac{4\lambda^u a^l}{K^u}}\right]\\ &\triangleq g(L_1).\end{aligned} \tag{3.23}$$

Note the definition of $G(t)$ in (2.9), then we get

$$\begin{aligned}\dot G(t) &\le \beta_1(t+\tau_1)x(t)v(t) - \frac{\delta^l}{\gamma^u}c(t)v(t)\\ &\le \left(\beta_1^u g(L_1) - \frac{\delta^l c^l}{\gamma^u}\right)v(t) < 0,\end{aligned} \tag{3.24}$$

which means that $G(t)$ is decreasing. By Lemmas 2.3 and 2.4, $G(t)$ is positive bounded. Therefore, $G(t) \to G^*$ (constant) as $t \to +\infty$; then $\dot G(t) \to 0$ as $t \to +\infty$;

this reduces that $v(t) \to 0, y(t) \to 0$ when $t \to +\infty$, which implies a contradiction since $G(t) > 0$, so we obtain $\liminf_{t\to+\infty} y(t) \le L_1$.

Step II. Next, we show that there exists

$$\widehat{L}_1 = 2\frac{k_1c^u + \gamma^l k_2 c_2}{\beta^l\gamma^l}(R^* - 1)\left(\frac{a^l\delta^l c^l}{K^u\beta_1^u\gamma^u} + \frac{\lambda^u\beta_1^u\gamma^u}{R^*\delta^l c^l}\right) > 0, \tag{3.25}$$

where

$$k_1 = 1 + \frac{\delta^u\gamma^u}{\gamma^l}c_1\tau, \quad k_2 = \frac{\delta^u}{\gamma^l} + \frac{\beta_1 u\lambda^u c_2\tau}{\mu^l}, \quad c_1 = e^{\delta^u\tau}, \quad c_2 = e^{c^u\tau},$$

such that

$$\liminf_{t\to+\infty} G(t) \le \widehat{L}_1. \tag{3.26}$$

Otherwise, we have

$$\liminf_{t\to+\infty} G(t) > \widehat{L}_1,$$

using (2.8), (2.9) and Lemma 2.6, we obtain

$$\widehat{L}_1 < G(t) \le W(t) \le k_1 y(t) + k_2 v(t), \quad \text{for } t \text{ large enough.} \tag{3.27}$$

By the third equation of system (2.2), we get

$$\begin{aligned}\dot{v}(t) &\ge \gamma(t)\frac{\widehat{L}_1 - k_2 v(t-\tau_2)}{k_1} - c(t)v(t)\\ &\ge \frac{\gamma^l\widehat{L}_1}{k_1} - \left(c^u + \frac{\gamma^l k_2 c_2}{k_1}\right)v(t), \quad \text{for } t \text{ large enough,}\end{aligned} \tag{3.28}$$

then, from Lemma 2.2, we have

$$\liminf_{t\to+\infty} v(t) \ge \frac{\gamma^l\widehat{L}_1}{k_1c^u + \gamma^l k_2 c_2}.$$

According to the first equation of system (2.2), we have

$$\begin{aligned}\dot{x}(t) &= \lambda(t) + a(t)x(t)\left(1 - \frac{x(t)}{K(t)}\right) - \mu(t)x(t) - \beta(t)x(t)v(t)\\ &\le \lambda^u - \left(\mu^l - a^u + \frac{\beta^l\gamma^l\widehat{L}_1}{k_1c^u + \gamma^l k_2c_2}\right)x(t) - \frac{a^l}{K^u}x^2(t),\end{aligned}$$

which reduces that

$$\limsup_{t\to+\infty} x(t) \le \frac{K^u}{2a^l}\left[\Upsilon + \sqrt{\Upsilon + \frac{4\lambda^u a^l}{K^u}}\right] \triangleq \widehat{x}, \tag{3.29}$$

where $\Upsilon = \mu^l - a^u + \frac{\beta^l\gamma^l\widehat{L}_1}{k_1c^u + \gamma^l k_2c_2}$. By (2.9), we obtain

$$\begin{aligned}\dot{G}(t) &\le \beta_1(t+\tau_1)x(t)v(t) - \frac{\delta^l c(t)}{\gamma^u}v(t)\\ &\le \left(\beta_1^u\widehat{x} - \frac{\delta^l c^l}{\gamma^u}\right)v(t) < 0, \quad \text{if } R^* > 1,\end{aligned} \tag{3.30}$$

which implies a contradiction according to the same reason in Step I. Thus, we obtain $\liminf_{t\to+\infty} G(t) \le \widehat{L}_1$.

Step III. From (2.9) and Step II, we can find that $G(t) > \widehat{L}_1$ is impossible for all $t \ge t^0$, $\forall\, t^0 \ge 0$. Thus, we have the following two possibilities:

(a) $G(t) \le \widehat{L}_1$ for all t large enough.
(b) $G(t)$ oscillates about $\widehat{L}_1$ for all t large enough.

Similarly to the proof of Proposition 3.2, let t_1' and t_2' be large sufficiently such that

$$G(t_1') = G(t_2') = \widehat{L}_1, \quad G(t) > \widehat{L}_1, \quad \forall\, t \in (t_1', t_2').$$

If $t_2' - t_1' \le \tau + p_1 + p_2$, then here

$$\begin{aligned} p_1 &= \frac{k_1}{k_1c^u + k_2c_2\gamma^l}\ln 4 > 0, \quad \mu^l - a^u = \frac{\lambda^u\beta_1^u\gamma^u}{R^*\delta^l c^l} - \frac{R^*a^l\delta^l c^l}{K^u\beta_1^u\gamma^u}, \\ p_2 &= \frac{1}{2}\sqrt{\frac{K^u}{b_1a^l}}\ln\frac{2\left[L + \frac{K^u}{2a^l}\left(\frac{R^*-1}{2}\cdot\frac{a^l\delta^l c^l}{K^u\beta_1^u\gamma^u} + \frac{3R^*-1}{2}\cdot\frac{\lambda^u\beta_1^u\gamma^u}{R^*\delta^l c^l}\right)\right]}{\varepsilon_2}, \\ b_1 &= \lambda^u + \frac{K^u}{4a^l}\left(\mu^l - a^u + \frac{3}{4}\frac{\beta^l\gamma^l\widehat{L}_1}{k_1c^u + \gamma^l k_2c_2}\right)^2 \\ &= \lambda^u + \frac{K^u}{4a^l}\left[\mu^l - a^u + \frac{3}{2}(R^*-1)\left(\frac{a^l\delta^l c^l}{K^u\beta_1^u\gamma^u} + \frac{\lambda^u\beta_1^u\gamma^u}{R^*\delta^l c^l}\right)\right]^2, \\ \varepsilon_2 &= \frac{1}{2}\left\{\frac{\delta^l c^l}{\beta_1^u\gamma^u} + \frac{K^u}{2a^l}\left(\frac{R^*-1}{2}\cdot\frac{a^l\delta^l c^l}{K^u\beta_1^u\gamma^u} + \frac{3R^*-1}{2}\cdot\frac{\lambda^u\beta_1^u\gamma^u}{R^*\delta^l c^l}\right)\right. \\ &\quad \left. - \sqrt{\frac{b_1K^u}{a^l}}\right\}. \end{aligned} \tag{3.31}$$

Note that

$$\widehat{L}_1 < G(t) \le W(t) \le k_1y(t) + k_2v(t), \quad \forall\, t \in (t_1', t_1' + \tau + p_1),$$

then by the third equation of (2.2), we have

$$\begin{aligned} \dot{v}(t) &\ge \gamma^l\frac{\widehat{L}_1 - k_2v(t-\tau_2)}{k_1} - c(t)v(t) \\ &\ge \frac{\gamma^l\widehat{L}_1}{k_1} - \left(c^u + \frac{\gamma^lk_2c_2}{k_1}\right)v(t), \quad \forall\, t \in (t_1' + \tau, t_1' + \tau + p_1). \end{aligned} \tag{3.32}$$

Integrating the inequality (3.32) from $t_1' + \tau$ to t, we obtain

$$
\begin{aligned}
v(t) &\geq v(t_1'+\tau)\exp\left(-\int_{t_1'+\tau}^{t}\left(c^u + \frac{\gamma^l k_2 c_2}{k_1}\right)ds\right) \\
&\quad + \int_{t_1'+\tau}^{t} \frac{\gamma^l \widehat{L}_1}{k_1}\exp\left(-\int_{s}^{t}\left(c^u + \frac{\gamma^l k_2 c_2}{k_1}\right)d\theta\right)ds \\
&> \frac{\gamma^l \widehat{L}_1}{k_1 c^u + \gamma^l k_2 c_2}\left(1 - \exp\left(-\left(c^u + \frac{\gamma^l k_2 c_2}{k_1}\right)(t - t_1' - \tau)\right)\right), \qquad (3.33)
\end{aligned}
$$

then $v(t) \geq \frac{\gamma^l \widehat{L}_1}{k_1 c^u + \gamma^l k_2 c_2} - \varepsilon_1$, for all $t \in (t_1' + \tau + p_1, t_2')$, where

$$\varepsilon_1 = \frac{R^* - 1}{2\beta^l}\left(\frac{a^l \delta^l c^l}{K^u \beta_1^u \gamma^u} + \frac{\lambda^u \beta_1^u \gamma^u}{R^* \delta^l c^l}\right) > 0.$$

Using the first equation of system (2.2), we can obtain

$$
\begin{aligned}
\dot{x}(t) &\leq \lambda^u - \left(\mu^l - a^u + \beta^l \cdot \frac{3}{4}\frac{\gamma^l \widehat{L}_1}{k_1 c^u + \gamma^l k_2 c_2}\right)x(t) - \frac{a^l}{K^u}x^2(t) \\
&= \lambda^u - \left(\mu^l - a^u + \frac{3}{4}\frac{\beta^l \gamma^l \widehat{L}_1}{k_1 c^u + \gamma^l k_2 c_2}\right)x(t) - \frac{a^l}{K^u}x^2(t) \\
&= -\frac{a^l}{K^u}\left(x(t) + \frac{K^u}{2a^l}\left(\mu^l - a^u + \frac{3}{4}\frac{\beta^l \gamma^l \widehat{L}_1}{k_1 c^u + \gamma^l k_2 c_2}\right)\right)^2 \\
&\quad + \lambda^u + \frac{K^u}{4a^l}\left(\mu^l - a^u + \frac{3}{4}\frac{\beta^l \gamma^l \widehat{L}_1}{k_1 c^u + \gamma^l k_2 c_2}\right)^2, \qquad (3.34)
\end{aligned}
$$

for any $t \in (t_1' + \tau + p_1, t_2')$.

Denote

$$
\begin{aligned}
u(t) &= x(t) + \frac{K^u}{2a^l}\left(\mu^l - a^u + \frac{3}{4}\frac{\beta^l \gamma^l \widehat{L}_1}{k_1 c^u + \gamma^l k_2 c_2}\right), \\
b_1 &= \lambda^u + \frac{K^u}{4a^l}\left(\mu^l - a^u + \frac{3}{4}\frac{\beta^l \gamma^l \widehat{L}_1}{k_1 c^u + \gamma^l k_2 c_2}\right)^2,
\end{aligned}
$$

from (3.34), we have

$$\dot{u}(t) \leq -\frac{a^l}{K^u}u^2(t) + b_1 = \left(\sqrt{b_1} - \sqrt{\frac{a^l}{K^u}}u(t)\right)\left(\sqrt{b_1} + \sqrt{\frac{a^l}{K^u}}u(t)\right), \qquad (3.35)$$

we can integrate it from $t_1' + \tau + p_1$ to t, then

$$u(t) \leq \sqrt{\frac{b_1 K^u}{a^l}} \left(\frac{\frac{\sqrt{b_1}+\sqrt{\frac{a^l}{K^u}}u(t_1'+\tau+p_1)}{\sqrt{b_1}-\sqrt{\frac{a^l}{K^u}}u(t_1'+\tau+p_1)} \exp\left(2\sqrt{\frac{b_1 a^l}{K^u}}\left(t-t_1'-\tau-p_1\right)\right)-1}{\frac{\sqrt{b_1}+\sqrt{\frac{a^l}{K^u}}u(t_1'+\tau+p_1)}{\sqrt{b_1}-\sqrt{\frac{a^l}{K^u}}u(t_1'+\tau+p_1)} \exp\left(2\sqrt{\frac{b_1 a^l}{K^u}}(t-t_1'-\tau-p_1)\right)+1} \right)$$

$$= \sqrt{\frac{b_1 K^u}{a^l}} - \frac{2\sqrt{\frac{b_1 K^u}{a^l}}\left(\sqrt{b_1}-\sqrt{\frac{a^l}{K^u}}u(t_1'+\tau+p_1)\right)}{\Theta}$$

$$\leq \sqrt{\frac{b_1 K^u}{a^l}} - \frac{2\sqrt{\frac{b_1 K^u}{a^l}}\left(\sqrt{b_1}-\sqrt{\frac{a^l}{K^u}}u(t_1'+\tau+p_1)\right)}{\left(\sqrt{b_1}+\sqrt{\frac{a^l}{K^u}}u(t_1'+\tau+p_1)\right)\left(\exp\left(2\sqrt{\frac{b_1 a^l}{K^u}}(t-t_1'-\tau-p_1)\right)+1\right)}$$

$$= \sqrt{\frac{b_1 K^u}{a^l}} - \frac{2b_1\sqrt{\frac{K^u}{a^l}}}{\left(\sqrt{b_1}+\sqrt{\frac{a^l}{K^u}}u(t_1'+\tau+p_1)\right)\left(\exp\left(2\sqrt{\frac{b_1 a^l}{K^u}}(t-t_1'-\tau-p_1)\right)+1\right)}$$

$$+ \frac{2\sqrt{b_1}u(t_1'+\tau+p_1)}{\left(\sqrt{b_1}+\sqrt{\frac{a^l}{K^u}}u(t_1'+\tau+p_1)\right)\left(\exp\left(2\sqrt{\frac{b_1 a^l}{K^u}}(t-t_1'-\tau-p_1)\right)+1\right)}$$

$$\leq \sqrt{\frac{b_1 K^u}{a^l}} + \frac{2\sqrt{b_1}u(t_1'+\tau+p_1)}{\left(\sqrt{b_1}+\sqrt{\frac{a^l}{K^u}}u(t_1'+\tau+p_1)\right)\exp\left(2\sqrt{\frac{b_1 a^l}{K^u}}(t-t_1'-\tau-p_1)\right)}$$

$$\leq \sqrt{\frac{b_1 K^u}{a^l}} + 2u(t_1'+\tau+p_1)\exp\left(-2\sqrt{\frac{b_1 a^l}{K^u}}(t-t_1'-\tau-p_1)\right), \tag{3.36}$$

where

$$\Theta = \left(\sqrt{b_1}+\sqrt{\frac{a^l}{K^u}}u(t_1'+\tau+p_1)\right)\exp\left(2\sqrt{\frac{b_1 a^l}{K^u}}(t-t_1'-\tau-p_1)\right) + \sqrt{b_1} - \sqrt{\frac{a^l}{K^u}}u(t_1'+\tau+p_1).$$

Therefore,

$$x(t) \leq \sqrt{\frac{b_1 K^u}{a^l}} - \frac{K^u}{2a^l}\left(\mu^l - a^u + \frac{3}{4}\frac{\beta^l\gamma^l\widehat{L}_1}{k_1 c^u + \gamma^l k_2 c_2}\right) + 2\left(x(t_1'+\tau+p_1) + \frac{K^u}{2a^l}\left(\mu^l - a^u + \frac{3}{4}\frac{\beta^l\gamma^l\widehat{L}_1}{k_1 c^u + \gamma^l k_2 c_2}\right)\right)$$

$$\times \exp\left(-2\sqrt{\frac{b_1 a^l}{K^u}}(t - t_1' - \tau - p_1)\right)$$
$$\le \sqrt{\frac{b_1 K^u}{a^l}} - \frac{K^u}{2a^l}\left(\mu^l - a^u + \frac{3}{4}\frac{\beta^l\gamma^l\widehat{L}_1}{k_1 c^u + \gamma^l k_2 c_2}\right) + \varepsilon_2 \triangleq x^\Delta, \tag{3.37}$$

for any $t \in (t_1' + \tau + p_1, t_2')$, where

$$\varepsilon_2 = \frac{1}{2}\left\{\frac{\delta^l c^l}{\beta_1^u\gamma^u} + \frac{K^u}{2a^l}\left(\mu^l - a^u + \frac{3}{4}\frac{\beta^l\gamma^l\widehat{L}_1}{k_1 c^u + \gamma^l k_2 c_2}\right) - \sqrt{\frac{b_1 K^u}{a^l}}\right\}$$
$$= \frac{1}{2}\left\{\frac{\delta^l c^l}{\beta_1^u\gamma^u} + \frac{K^u}{2a^l}\left(\frac{R^* - 1}{2}\frac{a^l\delta^l c^l}{K^u\beta_1^u\gamma^u} + \frac{3R^* - 1}{2}\frac{\lambda^u\beta_1^u\gamma^u}{R^*\delta^l c^l}\right) - \sqrt{\frac{b_1 K^u}{a^l}}\right\} > 0.$$

Thus, from (2.9) and (3.34), we obtain

$$\begin{aligned}\dot{G}(t) &\le \beta_1(t+\tau_1)x(t)v(t) - \frac{\delta^l}{\gamma^u}c(t)v(t)\\ &\le \beta_1(t+\tau_1)x(t)v(t) \le \beta_1^u x^\Delta v(t)\\ &\le \frac{\beta_1^u\gamma^u}{\delta^l}x^\Delta G(t).\end{aligned} \tag{3.38}$$

So

$$\begin{aligned}G(t) &\le G(t_1')\exp\left(\int_{t_1'}^t \frac{\beta_1^u\gamma^u}{\delta^l}x^\Delta ds\right)\\ &= \widehat{L}_1\exp\left((t - t_1')\frac{\beta_1^u\gamma^u}{\delta^l}x^\Delta\right)\\ &\le \widehat{L}_1\exp\left((\tau + p_1 + p_2)\frac{\beta_1^u\gamma^u}{\delta^l}x^\Delta\right)\\ &\triangleq c^0.\end{aligned} \tag{3.39}$$

If $t_2' - t_1' > \tau + p_1 + p_2$, then $G(t) \le c^0$ for any $t \in [t_1', t_1' + \tau + p_1 + p_2]$. When $t \in [t_1' + \tau + p_1 + p_2, t_2')$, from (3.30) and (3.37),

$$\begin{aligned}\dot{G}(t) &\le \beta_1(t+\tau_1)x(t)v(t) - \frac{\delta^l}{\gamma^u}c(t)v(t)\\ &\le \left(\beta_1^u x^\Delta - \frac{\delta^l c^l}{\gamma^u}\right)v(t) < 0, \quad \text{if } R_* > 1,\end{aligned} \tag{3.40}$$

then we have

$$G(t) \le G\big(t_1' + \tau + p_1 + p_2\big) \le c^0.$$

Therefore, we have that if $R_* > 1$, then there exists a positive constant c^0 such that $G(t) \le c^0$ for all t large enough. We note that the expression of $G(t)$ defined in (2.9), then

$$y(t) \le G(t) \le c^0, \quad v(t) \le \frac{\gamma^u}{\delta^l} G(t) \le \frac{\gamma^u}{\delta^l} c^0, \quad \text{for all } t > 0.$$

Thus we obtain $\limsup_{t\to+\infty} y(t) \le \widetilde{L_1} \le c^0$, $\limsup_{t\to+\infty} v(t) \le \widetilde{L_2} = \frac{\gamma^u}{\delta^l} c^0$. □

Remark 3.5. From Propositions 3.2 and 3.4, we obtain

$$\widetilde{q} \le \liminf_{t\to+\infty} x(t) \le \limsup_{t\to+\infty} x(t) \le \frac{\lambda^u}{\mu^l},$$

$$\widetilde{q_1} \le \liminf_{t\to+\infty} y(t) \le \limsup_{t\to+\infty} y(t) \le \widetilde{L_1} \le c^0$$

and

$$\widetilde{q_2} \le \liminf_{t\to+\infty} v(t) \le \limsup_{t\to+\infty} v(t) \le \frac{\gamma^u}{\delta^l} c^0.$$

This completes the proof of Theorem 3.1.

Next we present the sufficient condition for the extinction of both virus and infected T-cells.

Theorem 3.6. *If* $R^* < 1$, *then any positive solution* $(x(t), y(t), v(t))$ *of system* (2.2) *with* (2.3) *satisfies* $\lim_{t\to+\infty} y(t) = 0$, $\lim_{t\to+\infty} v(t) = 0$, *that is, the disease in system* (2.2) *will go to extinction.*

Proof. From $R^* < 1$, there exists a small $\epsilon > 0$ such that $\frac{\beta_1^u \gamma^u}{\delta^l c^l}(L + \epsilon) < 1$, where L is defined in Lemma 2.3.

By Proposition 3.4, we obtain that there exists a $T^0 > 0$ satisfied as $t > T^0$, and

$$\begin{aligned} \dot{G}(t) &\le \beta_1(t+\tau_1)x(t)v(t) - \frac{\delta^l}{\gamma^u} c(t)v(t) \le \left(\beta_1^u(L+\epsilon) - \frac{\delta^l c^l}{\gamma^u}\right) v(t) \\ &= \frac{\delta^l c^l}{\gamma^u}\left(\frac{\beta_1^u \gamma^u}{\delta^l c^l}(L+\epsilon) - 1\right) v(t) \\ &\le c^l \left(\frac{\beta_1^u \gamma^u}{\delta^l c^l}\left(\frac{\lambda^u}{\mu^l} + \epsilon\right) - 1\right) G(t). \end{aligned}$$

Using $R^* < 1$, we obtain $\dot{G}(t) < 0$, and $\lim_{t\to+\infty} G(t) = 0$. Thus we have

$$\lim_{t\to+\infty} y(t) = 0, \quad \lim_{t\to+\infty} v(t) = 0.$$

□

4. Numerical Simulation and Sensitivity Test of R_*

In this section, we present computer simulation of some results of the system (2.1) using MATLAB 7.0. Most of the parameters' values are taken from Perelson and

Nelson [25], Rong *et al.* [28], or smaller changes according to the corresponding parameters of [5, 25, 28]. Consider the following system:

$$\begin{cases} \dot{x}(t) = \lambda - \mu x(t) + ax(t)\left(1 - \dfrac{x(t)}{K}\right) - k(1 - (0.2\sin(4t) + 0.3))x(t)v(t), \\ \dot{y}(t) = k(1 - (0.2\sin(4t) + 0.3)))e^{-\delta_1\tau_1}x(t - \tau_1)v(t - \tau_1) - \delta y(t), \\ \dot{v}(t) = N\delta(1 - (0.25\cos(4t) + 0.4))e^{-\delta\tau_2}y(t - \tau_2) - cv(t). \end{cases} \tag{4.1}$$

According to the expressions of R_*, R^* in (3.1), we have

$$R_* = \frac{0.175KNke^{-\delta_1\tau_1}e^{-\delta\tau_2}\left(a - \mu + \sqrt{(a-\mu)^2 + \frac{4\lambda a}{K}}\right)}{2ac}$$

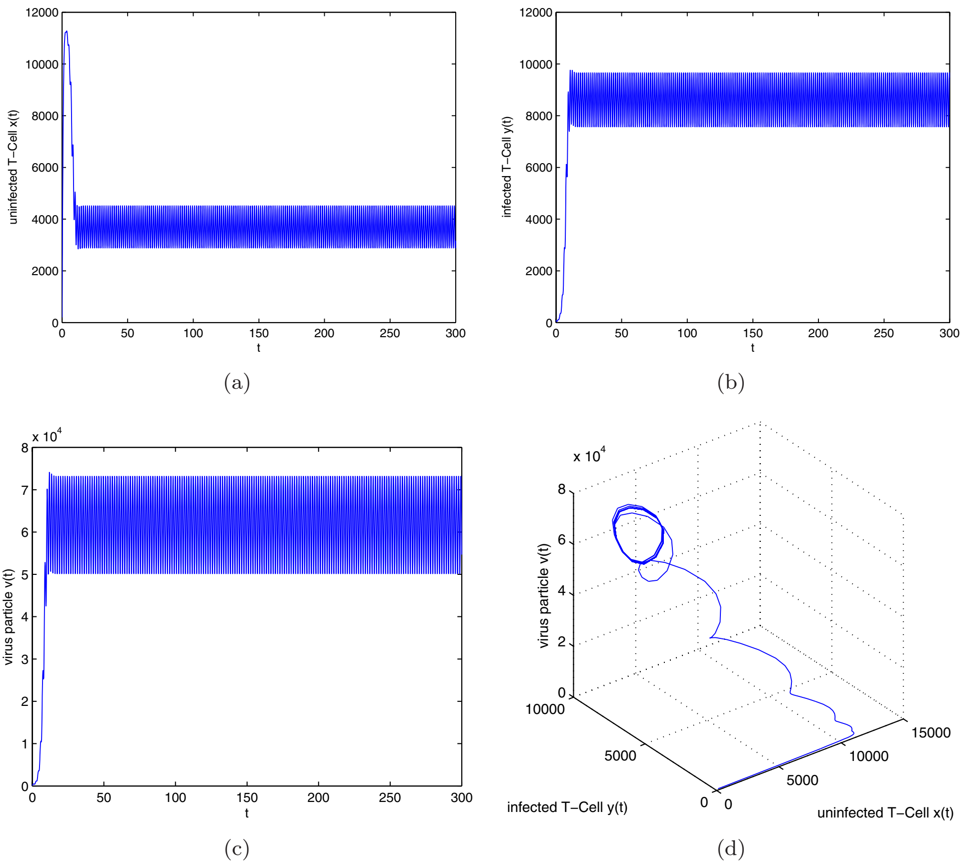


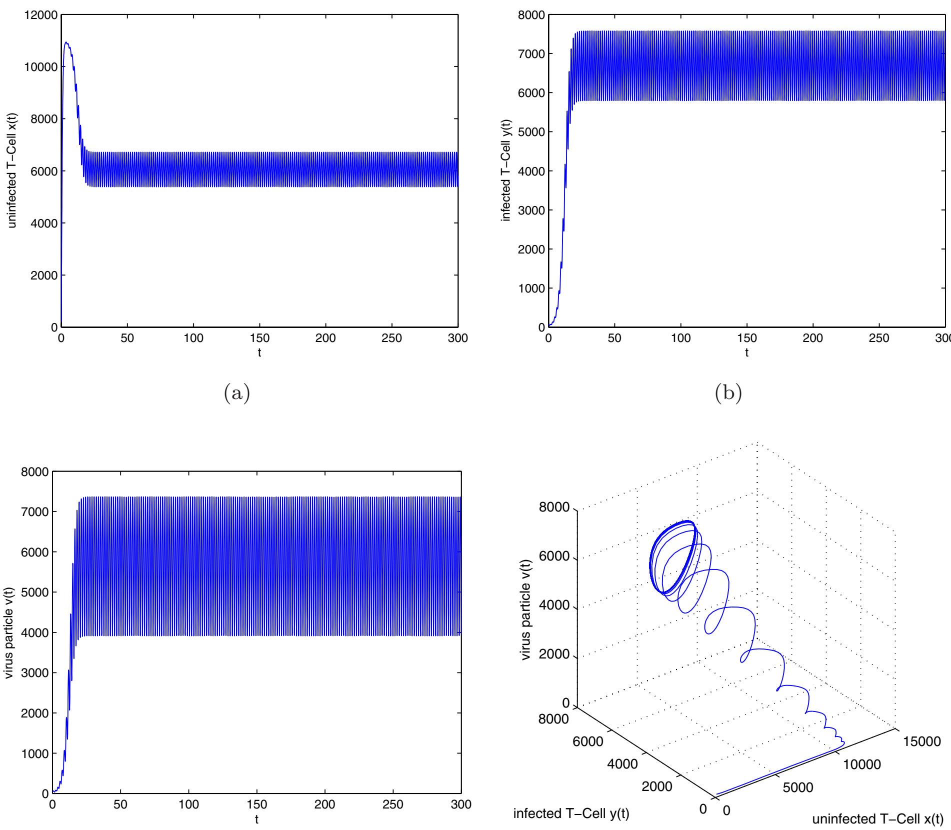
Fig. 1. Time series of uninfected T-cell $x(t)$ (see (a)), infected T-cell $y(t)$ (see (b)), virus particle $v(t)$ (see (c)) in (4.1) with $R^* \approx 5.75 > R_* \approx 1.32 > 1$, respectively; (d) phase diagram of a periodic solution of the model (4.1).

and

$$R^* = \frac{0.765KNke^{-\delta_1\tau_1}e^{-\delta\tau_2}\left(a-\mu+\sqrt{(a-\mu)^2+\frac{4\lambda a}{K}}\right)}{2ac}.$$

Case (I). If we choose the parameters that $\lambda = 10{,}000$, $\mu = 0.01$, $k = 0.00006$, $\delta_1 = 0.5$, $\delta = 1$, $a = 0.2$, $N = 100$, $K = 2200$, $c = 3$, $\tau_1 = 0.25$, $\tau_2 = 1$, from (3.1), we have $R^* \approx 5.75 > R_* \approx 1.32 > 1$; then, from Theorem 3.1 we know that the system (4.1) is permanent (see Fig. 1).

Case (II). If we choose the parameters that $\lambda = 10{,}000$, $\mu = 0.1$, $k = 0.0003$, $\delta_1 = 0.5$, $\delta = 1$, $a = 0.2$, $N = 100$, $K = 2200$, $c = 25$, $\tau_1 = 0.25$, $\tau_2 = 1$, we have $R_* \approx 0.75 < 1 < R^* \approx 3.29$; this example is to show that even if the conditions of Theorems 3.1 and 3.6 do not hold, system (4.1) still may be permanent (see Fig. 2).



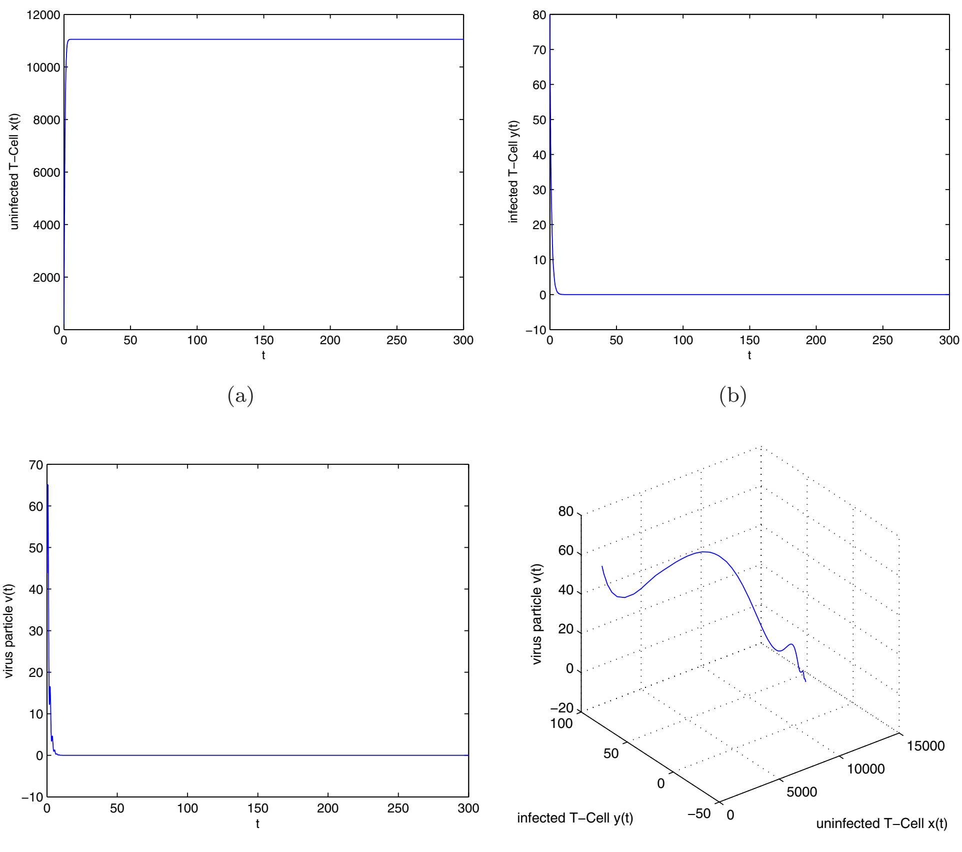
(a) (b)

(c) (d)

Fig. 2. Time series of uninfected T-cell $x(t)$ (see (a)), infected T-cell $y(t)$ (see (b)), virus particle $v(t)$ (see (c)) in (4.1) with $R^* \approx 3.29 > 1 > R_* \approx 0.75$, respectively; (d) phase diagram of a periodic solution of the model (4.1).

Case (III). If we choose the parameters that $\lambda = 10{,}000$, $\mu = 0.1$, $k = 0.00002$, $\delta_1 = 0.5$, $\delta = 1$, $a = 0.2$, $N = 100$, $K = 2200$, $c = 25$, $\tau_1 = 0.25$, $\tau_2 = 1$, from (3.1), we have $R^* \approx 0.22 < 1$, then, from Theorem 3.6 we know that the disease in the system (4.1) goes to extinction (see Fig. 3).

Obviously, $R^* \approx 4.37R_*$, thus, in the following, we will analyze the relationships between R_* and some coefficients in our model (4.1) with parameters in Case (I). By numerical analysis (see Fig. 4), we obtained a threshold value for some parameters in system (4.1) such that R_* is 1. Specifically, when $\lambda < \lambda^*$ or $k < k^*$ or $N < N^*$, R_* is less than 1 by plotting the change of R_* as a function of one parameter (all the other parameters were fixed). When a (or δ or τ_2) is greater than its corresponding threshold value, R_* is also less than 1. Thus, the virus is predicted to be cleared in these cases.



(a) (b) (c) (d)

Fig. 3. Time series of uninfected T-cell $x(t)$ (see (a)), infected T-cell $y(t)$ (see (b)), virus particle $v(t)$ (see (c)) in (4.1) with $R_* \approx 0.05 < R^* \approx 0.22 < 1$, respectively; (d) phase diagram of the extinction solutions of the model (4.1).

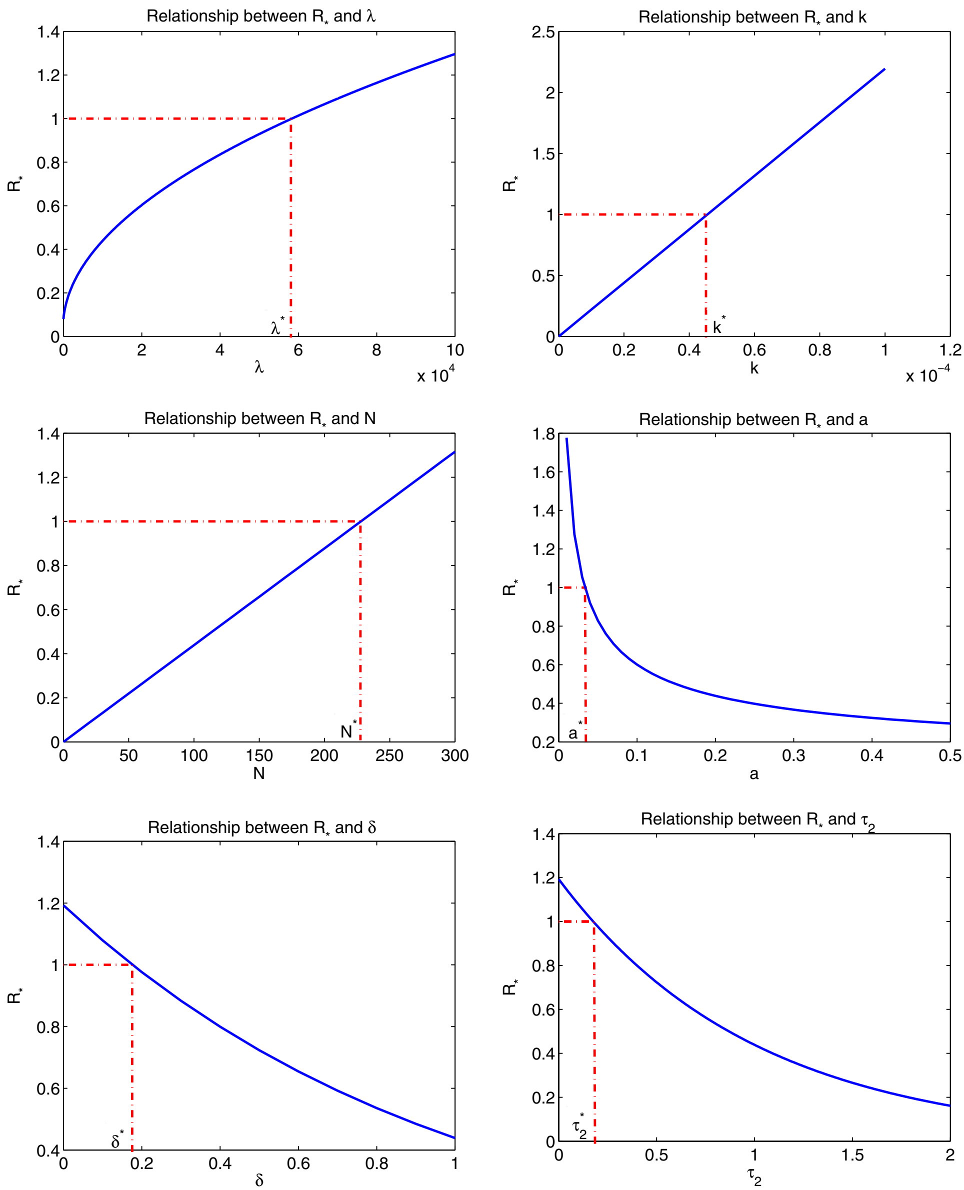


Fig. 4. The relationships between R_* and $\lambda, k, N, a, \delta, \tau_2$.

5. Conclusion

In this paper, a non-autonomous HIV-1 infection model with delays is investigated. Usually, the non-autonomous systems do not have any disease-free equilibrium and endemic equilibrium. Many methods to study autonomous systems may not be suitable to the non-autonomous cases. Therefore, the dynamical behaviors may be more difficult to study than autonomous system. In our present system, we have established some new threshold values R_* and R^*, and further obtained that the disease will be permanent when $R_* > 1$ and the disease will be going to extinct when $R^* < 1$ by introducing the persistence theory and oscillation theory. We also obtained threshold values for the parameters $\lambda, a, k, \delta, \tau_2, N$. These values are important in determining if the virus can be eradicated from infected individuals.

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References

[1] R. M. Anderson and R. M. May, Epidemiology parameters of HIV transmission, *Nature* **333** (1988) 514–519.
[2] S. Bonhoeffer, J. M. Coffin and M. A. Nowak, Human immunodeficiency virus drug therapy and virus load, *J. Virol.* **71** (1997) 3275–3278.
[3] 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.
[4] S. Bonhoeffer and M. A. Nowak, Pre-existence and emergence of drug resistance in HIV-1 infection, *Proc. Roy. Soc. London B* **264** (1997) 631–637.
[5] R. V. Culshaw and S. G. Ruan, A delay-differential equation model of HIV infection of $CD4^+$ T-cells, *Math. Biosci.* **165** (2000) 27–39.
[6] J. M. Cushing, *Integrodifferential Equations and Delay Models in Population Dynamics* (Springer, Heidelberg, 1977).
[7] R. J. De Boer and C. A. Boucher, Anti-CD4 therapy for AIDs suggested by mathematical models, *Proc. Roy. Soc. London B* **263** (1996) 899–905.
[8] R. J. De Boer and A. S. Perelson, Target cell limited and immune control models of HIV infection: A comparison, *J. Theor. Biol.* **190** (1998) 201–214.
[9] S. F. Dowell, Seasonal variation in host susceptibility and cycles of certain infectious diseases, *Emerg. Infect. Diseases* **7** (2001) 369–374.
[10] D. J. D. Earn, J. Dushoff and S. A. Levin, Ecology and evolution of the flu, *Trends Ecol. Evol.* **17** (2002) 334–340.
[11] K. Gopalsamy, *Stability and Oscillations in Delay-Differential Equations of Population Dynamics* (Kluwer, Dordrecht, 1992).
[12] A. V. M. Herz, S. Bonhoeffer, R. M. Anderson, R. M. May and M. A. Nowak, Viral dynamics *in vivo*: Limitations on estimates of intracellular delay and virus decay, *Proc. Natl. Acad. Sci. USA* **93** (1996) 7247–7251.

[13] Y. Huang, S. L. Rosenkranz and H. Wu, Modelling HIV dynamics and antiviral responses with consideration of time-varying drug exposures, sensitivities and adherence, *Math. Biosci.* **184** (2003) 165–186.

[14] Y. Kuang, *Delay-Differential Equations with Applications in Population Dynamics* (Academic Press, New York, 1993).

[15] S. J. Little, A. R. McLean, C. A. Spina, D. D. Richman and D. V. Havlir, Viral dynamics of acute HIV-1 infection, *J. Exp. Med.* **190** (1999) 841–850.

[16] S. Liu and L. Wang, Global stability of an HIV-1 model with distributed intracellular delays and a combination therapy, *Math. Biosci. Engrg.* **7** (2010) 677–687.

[17] W. London and J. A. Yorke, Recurrent outbreaks of measles, chickenpox and mumps: I. Seasonal variation in contact rates, *Amer. J. Epidemiol.* **98** (1973) 453–468.

[18] Y. J. Lou and X. Q. Zhao, A climate-based malaria transmission model with structured vector population, *SIAM J. Appl. Math.* **70** (2010) 2023–2044.

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

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

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

[22] A. S. Perelson, Modelling viral and immune system dynamics, *Nat. Rev.*: *Immunol.* **2** (2002) 28–36.

[23] A. S. Perelson, P. Essunger, Y. Cao, M. Vesanen, A. Hurley, K. Saksela, M. Markowitz and D. Ho, Decay characteristics of HIV-1-infected compartments during combination therapy, *Nature* **387** (1997) 188–191.

[24] A. S. Perelson, D. E. Kirschner and R. De Boer, Dynamics of HIV infection of $CD4^+$ T cells, *Math. Biosci.* **114** (1993) 81–125.

[25] A. S. Perelson and P. W. Nelson, Mathematical analysis of HIV-1 dynamics *in vivo*, *SIAM Rev.* **41** (1999) 3–44.

[26] A. S. Perelson, A. U. Neumann, M. Markowitz, J. M. Leonard and D. D. Ho, HIV-1 dynamics *in vivo*: Virion clearance rate, infected cell life-span, and viral generation time, *Science* **271** (1996) 1582–1585.

[27] A. N. Phillips, Reduction of HIV concentration during acute infection: Independence from a specific immune response, *Science* **71** (1996) 497–499.

[28] L. Rong, Z. Feng and A. S. Perelson, Emergence of HIV-1 drug resistance during anti-retroviral treatment, *Bull. Math. Biol.* **69** (2007) 2027–2060.

[29] X. Song and S. Cheng, A delay-differential equation model of HIV infection of $CD4^+$ T-cells, *J. Korean Math. Soc.* **42** (2005) 1071–1086.

[30] H. R. Thieme, Uniform weak implies uniform strong persistence also for non-autonomous semiflows, *Proc. Amer. Math. Soc.* **127** (1999) 2395–2403.

[31] H. R. Thieme, Uniform persistence and permanence for non-autonomous semiflows in population biology, *Math. Biosci.* **166** (2000) 173–201.

[32] X. Wang, S. Liu and L. Rong, Permanence and extinction of a non-autonomous HIV-1 model with two time delays, preprint.

[33] X. Wang and Y. Tao, Lyapunov function and global properties of virus dynamics with CTL immune response, *Int. J. Biomath.* **1** (2008) 443–448.

[34] X. Wang, Y. Tao and X. Song, A delayed HIV-1 infection model with Beddington–DeAngelis functional, *Nonlinear Dynam.* **62** (2010) 67–72.

[35] D. Wodarz and M. A. Nowak, Specific therapy regimes could lead to long-term immunological control of HIV, *Proc. Natl. Acad. Sci. USA* **96** (1999) 14,464–14,469.

[36] D. Wodarz, K. Page, R. Arnaout, A. R. Thomsen, J. D. Lifson and M. A. Nowak, A new theory of cytotoxic T-lymphocyte memory: Implications for HIV treatment, *Philos. Trans. Roy. Soc. London B* **355** (2000) 329–343.
[37] T. Zhang and Z. Teng, On a nonautonomous SEIRS model in epidemiology, *Bull. Math. Biol.* **69** (2007) 2537–2559.
[38] T. Zhang and Z. Teng, Permanence and extinction for a non-autonomous SIRS epidemic model with time delay, *Appl. Math. Model.* **33** (2009) 1058–1071.