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PERMANENCE AND EXTINCTION OF A NON-AUTONOMOUS HIV-1 MODEL WITH TIME DELAYS

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Abstract. The environment of HIV-1 infection and treatment could be non-periodically time-varying. The purposes of this paper are to investigate the effects of time-dependent coefficients on the dynamics of a non-autonomous and non-periodic HIV-1 infection model with two delays, and to provide explicit estimates of the lower and upper bounds of the viral load. We established sufficient conditions for the permanence and extinction of the non-autonomous system based on two positive constants R^* and R_* ($R^* \geq R_*$) that could be precisely expressed by the coefficients of the system: (i) If $R^* < 1$, then the infection-free steady state is globally attracting; (ii) if $R_* > 1$, then the system is permanent. When the system is permanent, we further obtained detailed estimates of both the lower and upper bounds of the viral load. The results show that both R^* and R_* reduce to the basic reproduction ratio of the corresponding autonomous model when all the coefficients become constants. Numerical simulations have been performed to verify/extend our analytical results. We also provided some numerical results showing that both permanence and extinction are possible when $R_* < 1 < R^*$ holds.

1. Introduction.

Mathematical modeling of virus infections such as human immunodeficiency virus type 1 (HIV-1) has improved our understanding of the virus dynamics (see for example [6, 10, 11, 17, 18, 19, 20, 21, 22, 23, 24, 34]). Most of the HIV models have used constant coefficients for the infection rate, death rate of infected cells, viral production rate, viral clearance rate, and the effectiveness

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of antiretroviral therapy. However, the environment of HIV-1 infection and treatment may not be time-invariant. For example, the drug efficacy of antiretroviral agents can be oscillating because of dosing. No progeny virus is generated during the eclipse phase of the viral life cycle, after which the viral production rate increases [8]. A recent experiment in rhesus macaque monkeys infected with simian immunodeficiency virus (SIV, which infects macaques and leads to a clinical immunodeficiency syndrome similar to AIDS in HIV-infected humans) suggested that the infectivity of virus changes over time during infection [15]. A new model with time-dependent infectivity was shown to fit the data significantly better than the model with constant infectivity [31].

A number of non-autonomous epidemiological models [2, 7, 12, 13, 16, 28, 29, 30, 33, 36] have been proposed to account for the effects of seasonal (or periodic) changes such as contact rates [3, 4, 7], birth rates of populations, and periodic vaccinations [5]. In many of these non-autonomous epidemic models with (or without) delay, uniform persistence was either considered or studied by the persistence theory of discrete dynamical systems. Recently, a few non-autonomous HIV-1 viral infection models have been studied such as [1, 4, 9, 14, 25, 27, 32, 35], where time-varying coefficients (especially periodic coefficients) were used in within-host infection or epidemic HIV models. For example, Rong et al. [25] employed a two-strain model to study the emergence of drug resistance during antiretroviral therapy. Lou et al. [14] extended the model by including impulsive antiretroviral drug effects to investigate emergence of drug resistance during the course of different treatment programs. In [35], Yang et al. considered an HIV model with periodic regimen and obtained threshold conditions for the extinction and uniform persistence of the disease using the basic reproduction ratio for a periodic system. These models have investigated how time-varying drug efficacy due to the drug dosing schedule affects the dynamics of HIV infection. In addition, Samanta [27] considered a non-autonomous stage-structured HIV/AIDS epidemic model, established sufficient conditions for the permanence and extinction of the disease, and provided an estimate for the eventual lower bound of infected persons.

Although within-host HIV-1 models including periodic drug effectiveness have been studied [1, 4, 14, 25, 32, 35], up to now, a general non-autonomous HIV-1 model (not necessarily periodic) with time delays has not been considered. Since the popular techniques to address the periodic model, such as the basic reproduction ratio derivation and the persistence theory of periodic epidemic systems, are not applicable to the time-varying model of non-periodic type, analysis of such a model is not trivial. So far, no criteria for the extinction and permanence of the non-autonomous within-host viral dynamic model have been proposed. The relationship of the conditions for extinction or uniform persistence of the general non-autonomous delayed HIV model and the system with periodic drug effectiveness remains unclear. We also lack an explicit estimate of the viral load using lower or upper bounds of model parameters. Our study seems to be the first attempt to studying the dynamics of a general non-autonomous HIV-1 dynamics with time delays, and to addressing the explicit estimates of the lower and upper bounds of the viral load when the system is permanent.

In this paper, using the oscillation theory for differential equations, we provide sufficient conditions for the permanence and extinction of the non-autonomous system. These conditions are expressed in terms of two positive threshold values which can be explicitly estimated from the range of time-varying coefficients. The two values will become the basic reproductive ratio of the corresponding autonomous system when all the coefficients become constants. We also obtain explicit estimate of the viral load using the lower and upper bounds of coefficients.

The paper is organized as follows. In the next section, we introduce our main model, and give some Lemmas and definitions there. In section 3, we study the permanence and extinction of the main model. In the following section, we perform numerical simulations to verify/extend our analytical results. At the end of the paper, we give a brief summary of the results.

2. Model and preliminary results.

2.1. The non-autonomous model with delays. The general model given by the following system of integro-differential equations was originally proposed by Nelson and Perelson (see [19], Eq. (23)):

$$\begin{cases} \dot{x}(t) = \lambda - \mu x(t) - (1-n_{rt})kx(t)v(t), \\ \dot{y}(t) = (1-n_{rt})k\int_0^{\infty} G_1(\xi)x(t-\xi)v(t-\xi)d\xi - \delta y(t), \\ \dot{v}(t) = (1-n_p)N\delta\int_0^{\infty} G_2(\xi)y(t-\xi)d\xi - cv(t), \end{cases} \tag{1}$$

where x, y and v are the concentrations of uninfected target cells, infected cells, and free virus, respectively. The positive constant λ is the rate at which new target cells are generated. $\mu > 0,\ \delta > 0$ are the death rates of uninfected target cells and infected cells, respectively. $k > 0$ denotes the constant rate at which uninfected cells become infected cells by contacting with virus particles. $N > 0$ is the total number of new virus particles produced by each infected cell during its life time $\frac{1}{\delta}$. So, the virus is produced at the rate δN. $c \geq 0$ denotes the rate at which the virus is cleared from the blood. The constants $n_{rt},\ n_p \in [0,1]$ are the efficacies of reverse transcriptase inhibitors (RTs) and protease inhibitors (PIs), respectively. As mentioned in Nelson and Perelson [19], the two functions $G_1(\xi)$ and $G_2(\xi)$ are delay kernels. If $G_1(\xi) = e^{-\delta_1\tau_1}\delta(\xi-\tau_1)$ and $G_2(\xi) = e^{-\delta\tau_2}\delta(\xi-\tau_2)$, where $\delta(\cdot)$ is the Dirac delta function, then system (1) reduces to

$$\begin{cases} \dot{x}(t) = \lambda - \mu x(t) - (1-n_{rt})kx(t)v(t), \\ \dot{y}(t) = (1-n_{rt})ke^{-\delta_1\tau_1}x(t-\tau_1)v(t-\tau_1) - \delta y(t), \\ \dot{v}(t) = (1-n_p)N\delta e^{-\delta\tau_2}y(t-\tau_2) - cv(t), \end{cases} \tag{2}$$

where τ_1 can be regarded as the time needed for the infected cell to finish the reverse transcription (RT) after viral entry and τ_2 is the time needed for the infected cell (that has finished RT) to go through the rest processes and produce new virions. Here, δ_1 is the death rate of infected cells that have not finished RT, and it is less than δ because of low virion expression, and thus less immune attack during the early stage of infection.

In this paper, we investigate a non-autonomous HIV-1 infection model with two time delays as follows:

$$\begin{cases} \dot{x}(t) = \lambda(t) - \mu(t)x(t) - (1-n_{rt}(t))k(t)x(t)v(t), \\ \dot{y}(t) = (1-n_{rt}(t))k(t)e^{-\int_0^{\tau_1}\delta_1(s)ds}x(t-\tau_1)v(t-\tau_1) - \delta(t)y(t), \\ \dot{v}(t) = (1-n_p(t))N(t)\delta(t)e^{-\int_0^{\tau_2}\delta(s)ds}y(t-\tau_2) - c(t)v(t), \end{cases} \tag{3}$$

where functions $\lambda(t), \mu(t), k(t), \delta(t), \delta_1(t), N(t), c(t), n_{rt}(t)$ and $n_p(t)$ correspond to parameters $\lambda, \mu, k, \delta, \delta_1, N, c, n_{rt}$ and n_p in model (2), respectively.

For convenience of notations, we set

$$\begin{aligned}&\beta(t) = (1 - n_{rt}(t))k(t), \ \ \beta_1(t) = \beta(t)e^{-\int_0^{\tau_1} \delta_1(s)ds},\\ &\gamma(t) = (1 - n_p(t))N(t)\delta(t)e^{-\int_0^{\tau_2} \delta(s)ds},\end{aligned} \tag{4}$$

which simplify (3) to the following system:

$$\begin{cases} \dot{x}(t) = \lambda(t) - \mu(t)x(t) - \beta(t)x(t)v(t), \\ \dot{y}(t) = \beta_1(t)x(t-\tau_1)v(t-\tau_1) - \delta(t)y(t), \\ \dot{v}(t) = \gamma(t)y(t-\tau_2) - c(t)v(t). \end{cases} \tag{5}$$

2.2. **Preliminary results of (5).** In the following, we will introduce some assumptions and notations for system (5):

(H_1) Functions $\lambda(t), \mu(t), \beta(t), \beta_1(t), \delta(t), \delta_1(t), \gamma(t), c(t)$ are positive continuous bounded and have positive lower bounds.

(H_2) If $f(t)$ is a continuous bounded function defined on $[0, +\infty)$, then we set

$$f^l = \liminf_{t\to+\infty} f(t), \quad f^u = \limsup_{t\to+\infty} f(t).$$

The initial condition of (5) is given as

$$x(\theta) = \varphi_1(\theta),\ y(\theta) = \varphi_2(\theta),\ v(\theta) = \varphi_3(\theta),\ -\tau \le \theta \le 0,\ \varphi_i(0) > 0,\ i = 1, 2, 3, \tag{6}$$

where $\varphi = (\varphi_1, \varphi_2, \varphi_3)^T$ such that $\varphi_i(\theta) \ge 0$ $(i = 1, 2, 3)$ 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 is equipped with the norm of an element φ in C by

$$\|\varphi\| = \sup_{-\tau\le\theta\le0} \{|\varphi_1(\theta)|, |\varphi_2(\theta)|, |\varphi_3(\theta)|\}.$$

In order to investigate the persistence and extinction for the system (5), we introduce the following definition.

Definition 2.1. The system (5) is said to be permanent if there are positive constants $q,\ \widetilde{q_i}$ and $L,\ \widetilde{L_i}(i = 1, 2)$ such that

$$\begin{aligned} &q \le \liminf_{t\to+\infty} x(t) \le \limsup_{t\to+\infty} x(t) \le L, \\ &\widetilde{q_1} \le \liminf_{t\to+\infty} y(t) \le \limsup_{t\to+\infty} y(t) \le \widetilde{L_1}, \\ &\widetilde{q_2} \le \liminf_{t\to+\infty} v(t) \le \limsup_{t\to+\infty} v(t) \le \widetilde{L_2}, \end{aligned}$$

hold for any solution $(x(t), y(t), v(t))$ of (5) with initial condition (6). Here $q,\ \widetilde{q_i}$ and $L,\ \widetilde{L_i}$ $(i = 1, 2)$ are independent of (6).

Lemma 2.2. *(see [36]) Consider the following non-autonomous linear equation*

$$\dot{z}(t) = \lambda(t) - \mu(t)z(t). \tag{7}$$

Suppose that assumptions (H_1) *and* (H_2) *hold, then we have the following results:*
(1) *Denote the ultimate limit of all the solutions of Eq. (7) with the initial value* $z(0) > 0$ *by* $z^*(t)$. $z^*(t)$ *is bounded and globally uniformly attractive on* $R_+ = (0, +\infty)$.
(2) *There exist* $m, M > 0$, *such that* $m < \liminf_{t\to+\infty} z(t) \le \limsup_{t\to+\infty} z(t) < M$.
(3) *When Eq. (7) is* ω*-periodic, then Eq. (7) has a unique nonnegative* ω*-periodic solution* $z^*(t)$ *which is globally uniformly attractive.*

(4) *If* $\mu(t) > 0$ *for all* $t \geq 0$ *and*

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

then for any solution $z(t)$ *of Eq. (7) with the initial value* $z(0) > 0$*, we have*

$$\Big(\frac{\lambda(t)}{\mu(t)}\Big)^l < \liminf_{t\to+\infty} z(t) \leq \limsup_{t\to+\infty} z(t) < \Big(\frac{\lambda(t)}{\mu(t)}\Big)^u,$$

where

$$\Big(\frac{\lambda(t)}{\mu(t)}\Big)^l = \liminf_{t\to+\infty} \frac{\lambda(t)}{\mu(t)}, \quad \Big(\frac{\lambda(t)}{\mu(t)}\Big)^u = \limsup_{t\to+\infty} \frac{\lambda(t)}{\mu(t)}.$$

Lemma 2.3. *The solution* $(x(t), y(t), v(t))$ *of system (5) with (6) is positive and bounded for all* $t \geq 0$*.*

Proof. Since the right hand side of system (5) is completely continuous, the solution $(x(t), y(t), v(t))$ of system (5) with initial condition (6) exists and is unique. Clearly, from system (5), we have

$$\begin{aligned} x(t) &= x(0)e^{-\int_0^t(\mu(s)+\beta(s)v(s))ds} + \int_0^t \lambda(s)e^{\int_t^s(\mu(\theta)+\beta(\theta)v(\theta))d\theta}ds, \\ y(t) &= y(0)e^{-\int_0^t \delta(s)ds} + \int_0^t \beta_1(s)x(s-\tau_1)v(s-\tau_1)e^{\int_t^s \delta(\theta)d\theta}ds, \\ v(t) &= v(0)e^{-\int_0^t c(s)ds} + \int_0^t \gamma(s)y(s-\tau_2)e^{\int_t^s c(\theta)d\theta}ds. \end{aligned} \tag{8}$$

It is evident that $x(t) > 0$ for all $t \geq 0$ since $x(0) > 0$.

Next, we will prove that $y(t), v(t) > 0$ for all $t \geq 0$. If they are not true, then there exists $t_0 > 0$ such that

$$\min\{y(t),\ v(t)\}_{t=t_0} = 0 \ \text{ and } \ \min\{y(t),\ v(t)\}_{t\in[0,t_0)} > 0.$$

If $y(t_0) \leq 0$, by (8), we get

$$\begin{aligned} y(t_0) &= y(0)e^{-\int_0^{t_0} \delta(s)ds} + \int_0^{t_0} \beta_1(s)x(s-\tau_1)v(s-\tau_1)e^{\int_{t_0}^s \delta(\theta)d\theta}ds \\ &\geq y(0)e^{-\int_0^{t_0} \delta(s)ds} > 0, \end{aligned}$$

which leads to a contradiction. Thus, $y(t) > 0$, for all $t \geq 0$.

Similarly, by (8), $v(t) > 0$, for all $t \geq 0$. Thus, we obtain $x(t) > 0, y(t) > 0, v(t) > 0$ for all $t \geq 0$ since $x(0), y(0), v(0) > 0$.

In the following, we will show that $x(t) > 0, y(t) > 0, v(t) > 0$ are bounded for all $t \geq 0$.

Let $H(t) = x(t) + \frac{\beta^l}{\beta_1^u}y(t+\tau_1) + \frac{\beta^l\delta^l}{2\beta_1^u\gamma^u}v(t+\tau_1+\tau_2)$, and $\sigma = \min\{\mu^l, \frac{\delta^l}{2}, c^l\}$, then we get

$$\begin{aligned} \dot{H}(t) &= \lambda(t) - \mu(t)x(t) + \Big(\frac{\beta^l}{\beta_1^u}\Big(\beta_1(t+\tau_1) - \beta(t)\Big)x(t)v(t) \\ &\quad + \Big(\frac{\beta^l\delta^l}{2\beta_1^u\gamma^u}\gamma(t+\tau_1+\tau_2) - \frac{\beta^l}{\beta_1^u}\delta(t+\tau_1)\Big)y(t+\tau_1) \end{aligned}$$

$$
\begin{aligned}
&-\frac{\beta^l\delta^l}{2\beta_1^u\gamma^u}c(t+\tau_1+\tau_2)v(t+\tau_1+\tau_2)\\
&\le \lambda(t)-\mu^l x(t)-\frac{\beta^l}{\beta_1^u}\cdot\frac{\delta^l}{2}y(t+\tau_1)-\frac{\beta^l\delta^l c^l}{2\beta_1^u\gamma^u}v(t+\tau_1+\tau_2)\\
&\le \lambda^u-\sigma H(t),
\end{aligned}
$$

which implies that

$$\limsup_{t\to+\infty} H(t)\le\frac{\lambda^u}{\sigma}. \tag{9}$$

Thus, we easily have that

$$\limsup_{t\to+\infty} y(t)\le\frac{\beta_1^u\lambda^u}{\beta^l\sigma}\triangleq\widetilde{L_1},\quad \limsup_{t\to+\infty} v(t)\le\frac{2\beta_1^u\gamma^u\lambda^u}{\beta^l\delta^l\sigma}\triangleq\widetilde{L_2},$$

where Δ means "is defined as". According to the first equation of system (5), we have $\dot{x}(t)\le\lambda^u-\mu^l x(t)$. By Lemma 2.2, we have $\limsup\limits_{t\to+\infty} x(t)\le\dfrac{\lambda^u}{\mu^l}\triangleq L$. This completes the proof of Lemma 2.3. □

Lemma 2.4. *For any monotonic increasing* $\{t_n\}_{n=1}^{\infty}$ *large enough, there exist* $c_1>0,\ c_2>0$ *such that*

$$y(t_n-s)\le c_1y(t_n),\quad v(t_n-s)\le c_2v(t_n),\quad 0\le s\le\tau,\quad \tau=\max\{\tau_1,\ \tau_2\}.$$

Proof. According to the second equation of (5), we can obtain

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

Integrating the above inequality from t_n-s to t_n, we have

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

So $y(t_n-s)\le e^{\delta^u\tau}y(t_n)\triangleq c_1y(t_n)$. Similarly, from the third equation of (5), we can obtain $\dot{v}(t)\ge-c(t)v(t)\ge-c^u v(t)$. Integrating this inequality from t_n-s to t_n, we obtain $v(t_n-s)\le e^{c^u\tau}v(t_n)\triangleq c_2v(t_n)$. □

Lemma 2.5. *The solution* $(x(t),y(t),v(t))$ *of system (5) with initial condition (6) satisfies*

$$\liminf_{t\to+\infty} x(t)\ge\left(\frac{\lambda(t)}{\mu(t)+2\beta(t)\frac{\beta_1^u\gamma^u\lambda^u}{\beta^l\delta^l\sigma}}\right)^l\triangleq q.$$

Proof. By Lemma 2.3, $H(t)\ge\frac{\beta^l\delta^l}{2\beta_1^u\gamma^u}v(t+\tau_1+\tau_2)$. From (9), for any $\varepsilon>0$, there exists a large enough $t_0>0$ such that

$$v(t)\le 2\frac{\beta_1^u\gamma^u\lambda^u}{\beta^l\delta^l\sigma}+\varepsilon,\qquad t\ge t_0.$$

Thus, from the first equation of system (5), when $t\ge t_0$, we have

$$\dot{x}(t)\ge\lambda(t)-\Big[\mu(t)+\beta(t)(2\frac{\beta_1^u\gamma^u\lambda^u}{\beta^l\delta^l\sigma}+\varepsilon)\Big]x(t),$$

which implies that

$$\liminf_{t\to+\infty} x(t)\ge\left(\frac{\lambda(t)}{\mu(t)+2\beta(t)\frac{\beta_1^u\gamma^u\lambda^u}{\beta^l\delta^l\sigma}}\right)^l\triangleq q. \tag{10}$$

□

Next, we derive the conditions for the permanence and extinction of system (5). We define two functions as follows:

$$w(t) = y(t) + \frac{\delta^u}{\gamma^l}v(t) + \int_{t-\tau_1}^{t} \beta_1(s+\tau_1)x(s)v(s)ds + \frac{\delta^u}{\gamma^l}\int_{t-\tau_2}^{t} \gamma(s+\tau_2)y(s)ds, \quad (11)$$

and

$$G(t) = y(t) + \frac{\delta^l}{\gamma^u}v(t) + \int_{t-\tau_1}^{t} \beta_1(\tau_1+\xi)x(\xi)v(\xi)d\xi + \frac{\delta^l}{\gamma^u}\int_{t-\tau_2}^{t} \gamma(\tau_2+\xi)y(\xi)d\xi. \quad (12)$$

For these two functions, we have the following results.

Lemma 2.6. *For any t large enough, we have*

(i)

$$w(t) \le k_1 y(t) + k_2 v(t), \quad (13)$$

where

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

(ii)

$$G(t) \le k_1' y(t) + k_2' v(t) \le w(t), \quad (14)$$

where

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

Proof. From (11) and Lemmas 2.3-2.5, we have

$$\begin{aligned} w(t) &= y(t) + \frac{\delta^u}{\gamma^l}v(t) + \int_{t-\tau_1}^{t} \beta_1(s+\tau_1)x(s)v(s)ds + \frac{\delta^u}{\gamma^l}\int_{t-\tau_2}^{t} \gamma(s+\tau_2)y(s)ds \\ &\le y(t) + \frac{\delta^u}{\gamma^l}\gamma^u c_1\tau y(t) + (\frac{\delta^u}{\gamma^l} + \beta_1^u\frac{\lambda^u}{\mu^l}c_2\tau)v(t) \\ &\triangleq k_1 y(t) + k_2 v(t). \end{aligned}$$

Similarly, from (12) and Lemmas 2.3-2.5, we have

$$G(t) \le k_1' y(t) + k_2' v(t) \le w(t).$$

□

3. Permanence and extinction.

3.1. Viral persistence.

Denote

$$R_* = \frac{\beta_1^l\gamma^l\lambda^l}{\delta^u c^u\mu^u}, \quad R^* = \frac{\beta_1^u\gamma^u\lambda^u}{\delta^l c^l\mu^l}. \quad (15)$$

We have the following Theorems.

Theorem 3.1. *Suppose that system (5) with initial condition (6) satisfies $R_* > 1$, then the system (5) is permanent. More specifically we have the following results:*

(I)

$$\liminf_{t\to+\infty} y(t) \ge \widetilde{q_1}, \quad \liminf_{t\to+\infty} v(t) \ge \widetilde{q_2}, \quad (16)$$

where

$$\widetilde{q_1} = \frac{1}{2}\frac{\beta_1^l q}{\delta^u}\frac{\gamma^l e^{-c^u(\tau+2p)}}{\gamma^l k_2 c_2 + k_1 c^u}q_1, \ \widetilde{q_2} = \frac{1}{2}\frac{\gamma^l q_1 e^{-c^u(\tau+2p)}}{\gamma^l k_2 c_2 + k_1 c^u}$$

with positive constants

$$p=\frac{1}{\mu^u(R_*+1)}\ln\frac{2R_*}{R_*-1},\ \ q_1=\frac{1}{2}\min\{\frac{c^l\mu^u}{\gamma^u\beta^u}(R_*-1),\quad \frac{\delta^u\mu^u}{\gamma^l\beta^u}(R_*-1)\} \tag{17}$$

and c_2, q, k_1 and k_2 are defined in Lemmas 2.4, 2.5 and 2.6, respectively.

(II)

$$\limsup_{t\to+\infty} y(t)\le \widetilde{L_1},\quad \limsup_{t\to+\infty} v(t)\le \widetilde{L_2}, \tag{18}$$

where $\widetilde{L_1}$, $\widetilde{L_2}$ are defined in Lemma 2.3.

We will use the following proposition in combination with Lemma 2.3 to complete the proof of this theorem.

Proposition 1. *Assume that $R_*>1$, then for any positive solution $(x(t),y(t),v(t))$ of system (5) with initial condition (6), we have $\liminf_{t\to+\infty} y(t)\ge\widetilde{q_1}$, and $\liminf_{t\to+\infty} v(t)\ge \widetilde{q_2}$, where $\widetilde{q_1}$ and $\widetilde{q_2}$ are defined in Theorem 3.1.*

Proof. we prove it using four steps:

Step 1. We will prove that there exists $q_1>0$ such that $\limsup_{t\to+\infty} y(t)\ge q_1$ for any solution of system (5). Suppose that it is not true, then we have $\limsup_{t\to+\infty} y(t)<q_1$. From the third equation of system (5), we get $\dot v(t)\le\gamma^u q_1-c^l v(t)$. By Lemma 2.2,

$$\limsup_{t\to+\infty} v(t)<q_1\frac{\gamma^u}{c^l}.$$

Thus, from the first equation of system (5), we obtain

$$\dot x(t)\ge\lambda^l-(\mu^u+\beta^u q_1\frac{\gamma^u}{c^l})x(t).$$

By Lemma 2.2 again, we have

$$\liminf_{t\to+\infty} x(t)\ge\frac{\lambda^l}{\mu^u+\beta^u q_1\frac{\gamma^u}{c^l}}\triangleq h(q_1).$$

According to the definition of $w(t)$ in (11), we have

$$\begin{aligned}\dot w(t)\ &=\beta_1(t)x(t-\tau_1)v(t-\tau_1)-\delta(t)y(t)+\frac{\delta^u}{\gamma^l}(\gamma(t)y(t-\tau_2)-c(t)v(t))\\ &\quad+\beta_1(t+\tau_1)x(t)v(t)-\beta_1(t)x(t-\tau_1)v(t-\tau_1)\\ &\quad+\frac{\delta^u}{\gamma^l}(\gamma(t+\tau_2)y(t)-\gamma(t)y(t-\tau_2))\\ &\ge[\beta_1(t+\tau_1)x(t)-\frac{\delta^u}{\gamma^l}c(t)]v(t)\\ &\ge[\beta_1^l h(q_1)-\frac{\delta^u}{\gamma^l}c^u]v(t).\end{aligned} \tag{19}$$

From (17), it follows that $q_1\le\frac{1}{2}\frac{c^l\mu^u}{\gamma^u\beta^u}(R_*-1)$. Thus,

$$\dot w(t)\ge\Big(\frac{\beta_1^l\lambda^l}{\mu^u[1+\frac{1}{2}(R_*-1)]}-\frac{\delta^u}{\gamma^l}c^u\Big)v(t)=\frac{\delta^u c^u}{\gamma^l}\frac{R_*-1}{R_*+1}v(t)>0,\ \text{if}\ R_*>1,$$

which means that $w(t)$ is increasing. By Lemma 2.3, $w(t)$ is positive bounded. There exists a constant $w^*>0$ such that $w(t)\to w^*$ as $t\to+\infty$. This shows that

$\dot{w}(t) \to 0$ as $t \to +\infty$. Thus, $v(t) \to 0$, and then $y(t) \to 0$ as $t \to +\infty$. Hence $w(t) \to 0$ as $t \to +\infty$. This generates a contradiction because $w(t) > w(0) > 0$. Thus, $\limsup_{t\to+\infty} y(t) \geq q_1$.

Step 2. We will show that there exists $c_0 = q_1 e^{-(\tau+2p)c^u} > 0$ such that $w(t) \geq c_0$.

From (11) and Step 1, we obtain that $\forall\ t_0 \geq 0$, $w(t) < q_1$ is impossible for all $t \geq t_0$. Hence, we will consider the following two possibilities:

(i) $w(t) > q_1$ for all t large enough.

(ii) $w(t)$ oscillates about q_1 for all t large enough.

Obviously, we only need to consider the second case. Let t_1 and t_2 be sufficiently large such that

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

If $t_2 - t_1 \leq \tau + 2p$, where p is defined in Theorem 3.1, from (11), we have $w(t) \geq \frac{\delta^u}{\gamma^l} v(t)$. Thus,

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

From the first equation of system (5), we get

$$\dot{x}(t) \geq \lambda^l - (\mu^u + \frac{\beta^u \gamma^l q_1}{\delta^u}) x(t), \ \forall t \in (t_1 + \tau, t_2). \tag{20}$$

For any $t \in (t_1 + \tau, t_2)$, integrating the inequality (20) from $t_1 + \tau$ to t, we have

$$\begin{aligned} x(t) \ &\geq x(t_1+\tau) \exp\Big(-\int_{t_1+\tau}^{t} (\mu^u + \frac{\beta^u\gamma^l q_1}{\delta^u}) ds\Big) \\ &\quad + \int_{t_1+\tau}^{t} \lambda^l \exp\Big(-\int_{s}^{t} (\mu^u + \frac{\beta^u\gamma^l q_1}{\delta^u}) d\theta\Big) ds \\ &\geq \frac{\lambda^l}{\mu^u + \frac{\beta^u\gamma^l q_1}{\delta^u}} \Big(1 - \exp\Big(-(\mu^u + \frac{\beta^u\gamma^l q_1}{\delta^u})(t - t_1 - \tau)\Big)\Big). \end{aligned} \tag{21}$$

Thus, there exits

$$\varepsilon_0 = \frac{\lambda^l}{2\mu^u} \frac{R_* - 1}{R_*(R_*+1)} > 0, \tag{22}$$

such that

$$x(t) \geq \frac{\lambda^l}{\mu^u + \frac{\beta^u\gamma^l q_1}{\delta^u}} - \varepsilon_0 \triangleq x_\Delta \geq \frac{\lambda^l}{\mu^u(R_*+1)} \frac{3R_*+1}{2R_*}, \ \forall t \in (t_1 + \tau + p, t_2). \tag{23}$$

From (11) and (19), we further obtain

$$\dot{w}(t) \geq (\beta_1(t+\tau_1)x(t) - \frac{\delta^u}{\gamma^l} c(t)) v(t) \geq -\frac{\delta^u c^u}{\gamma^l} v(t) \geq -c^u w(t), \ \forall t \in (t_1, t_2). \tag{24}$$

Noting that $t_2 - t_1 \leq \tau + 2p$, where p is defined in Theorem 3.1, we get

$$w(t) \geq w(t_1) e^{-\int_{t_1}^{t} c^u ds} = q_1 e^{-(t-t_1)c^u} \geq q_1 e^{-(\tau+2p)c^u} \triangleq c_0. \tag{25}$$

If $t_2 - t_1 > \tau + 2p$ and $t \in [t_1, t_1 + \tau + 2p]$, then $w(t) \geq c_0$ is valid. When $t \in [t_1 + \tau + 2p, t_2]$, from (19) and (23), we have

$$\dot{w}(t) \geq \Big(\beta_1^l x_\Delta - \frac{\delta^u}{\gamma^l} c^u\Big) v(t) \geq \frac{\delta^u}{\gamma^l} c^u \frac{R_* - 1}{2(R_*+1)} v(t) > 0, \ \text{if } R_* > 1.$$

By the monotonicity of $w(t)$ in $t \in [t_1 + \tau + 2p, t_2]$, we have

$$w(t) \geq w(t_1 + \tau + 2p) \geq c_0, \quad \text{for all } t \in [t_1 + \tau + 2p, t_2].$$

Therefore, we have that if $R_* > 1$, then there exists a positive constant c_0 such that $w(t) \geq c_0 > 0$ for all t large enough.

Step 3. We will show that

$$\liminf_{t \to +\infty} v(t) \geq \widetilde{q}_2, \tag{26}$$

where

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

and c_2, k_1 and k_2 are defined in Lemmas 2.4 and 2.6.

If (26) is not true, then we have $\liminf_{t \to +\infty} v(t) < \widetilde{q}_2$. By the definition of inferior limit of $v(t)$, we obtain that there exists a time-sequence $\{t_n\}_{n=1}^{\infty}$ such that

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

From Lemmas 2.3-2.6, we have

$$v(t_n - s) \leq c_2 v(t_n), \quad 0 \leq s \leq \tau, \text{ and } c_0 \leq w(t_n) \leq k_1 y(t_n) + k_2 v(t_n).$$

Thus,

$$y(t_n - \tau_2) \geq \frac{c_0 - k_2 v(t_n - \tau_2)}{k_1} \geq \frac{c_0 - k_2 c_2 v(t_n)}{k_1}.$$

From the third equation of system (5), we can obtain

$$\begin{aligned} \dot{v}(t_n) \quad & \geq \gamma(t_n) \frac{c_0 - k_2 c_2 v(t_n)}{k_1} - c(t_n) v(t_n) \\ & \geq \frac{\gamma^l c_0}{k_1} - (c^u + \frac{\gamma^l k_2 c_2}{k_1}) v(t_n) \\ & \geq \frac{\gamma^l c_0}{k_1} - (c^u + \frac{\gamma^l k_2 c_2}{k_1}) \widetilde{q}_2 > \frac{\gamma^l c_0}{2k_1} > 0. \end{aligned} \tag{27}$$

Next, we 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 $\dot{v}(t_n) > 0$, there exists $T_n > 0$ such that $v(T_n) \to v^*(\text{constant}) \leq \widetilde{q}_2$ as $n \to \infty$. Thus, $\dot{v}(T_n) \to 0$. Noting (27), we have $\lim_{n \to \infty} \dot{v}(T_n) > \dfrac{\gamma^l c_0}{2k_1} > 0$. This leads to a contradiction.

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

Therefore, we have

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

Step 4. Lastly, we will prove that $\liminf_{t \to +\infty} y(t) \geq \widetilde{q}_1$, where $\widetilde{q}_1$ is defined in the following (28).

By the second equation of system (5) and Lemma 2.5, we get

$$\dot{y}(t) = \beta_1(t) x(t - \tau_1) v(t - \tau_1) - \delta(t) y(t) \geq \beta_1^l q \widetilde{q}_2 - \delta^u y(t).$$

According to Lemma 2.2, we have

$$\liminf_{t\to+\infty} y(t) \geq \frac{\beta_1^l q \widetilde{q_2}}{\delta^u} = \frac{1}{2}\frac{\beta_1^l q}{\delta^u}\frac{\gamma^l e^{-c^u(\tau+2p)}}{\gamma^l k_2 c_2 + k_1 c^u} q_1 = \widetilde{q_1}. \tag{28}$$

□

Remark 1. From Lemma 2.3 and Proposition 1, we obtain

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

and

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

and

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

This completes the proof of Theorem 3.1.

3.2. **Viral clearance.** Next we provide the sufficient condition for the extinction of both virus and infected cells for model (5).

Theorem 3.2. *If $R^* < 1$, then any positive solution $(x(t), y(t), v(t))$ of system (5) with (6) satisfies $\lim_{t\to+\infty} y(t) = 0$, $\lim_{t\to+\infty} v(t) = 0$, and $\lim_{t\to+\infty} |x(t) - z^*(t)| = 0$, where $z^*(t)$ is the ultimate limit of all the solutions of Eq. (7) with the initial value $z(0) > 0$.*

Proof. From $R^* < 1$, there exists a small $\epsilon > 0$ such that

$$\frac{\beta_1^u \gamma^u}{\delta^l c^l}\left(\frac{\lambda^u}{\mu^l} + \epsilon\right) < 1.$$

By the definition of $G(t)$ in (12), we obtain

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

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

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

Next, we consider the globally attracting property of $x(t)$. Let $\tilde{z}(t) = x(t) - z^*(t)$, we have

$$\begin{aligned}
\dot{\tilde{z}}(t) &= \dot{x}(t) - \dot{z}^*(t)\\
&= -\mu(t)\tilde{z}(t) - \beta(t)x(t)v(t).
\end{aligned}$$

Thus we have

$$\begin{aligned}
|\tilde{z}(t)| &= \left|\tilde{z}(0)e^{-\int_0^t \mu(s)ds} - \int_0^t \beta(s)x(s)v(s)e^{-\int_s^t \mu(\theta)d\theta}ds\right|\\
&\leq |\tilde{z}(0)|e^{-\int_0^t \mu(s)ds} + \int_0^t \beta(s)x(s)v(s)e^{-\int_s^t \mu(\theta)d\theta}ds\\
&\leq |\tilde{z}(0)|e^{-\int_0^t \mu(s)ds} + \frac{\beta^u\lambda^u}{\mu^l}\int_0^t \frac{v(s)}{e^{\mu^l(t-s)}}ds.
\end{aligned} \tag{29}$$

From $v(t) > 0$, we know

$$A(t) = \int_0^t v(s)e^{\mu^l s}ds \tag{30}$$

is increasing with respect to t. Thus we obtain that $A(t)$ has the property: either $\lim_{t\to+\infty} A(t) = A^*$ (a positive constant), or $\lim_{t\to+\infty} A(t) = +\infty$, since $\lim_{t\to+\infty} v(t) = 0$ and a simple calculation shows that

$$\lim_{t\to+\infty} \frac{\beta^u\lambda^u}{\mu^l} \frac{\int_0^t v(s)e^{\mu^l s}ds}{e^{\mu^l t}} = \frac{\beta^u\lambda^u}{\mu^l} \lim_{t\to+\infty} \frac{A(t)}{e^{\mu^l t}} = 0. \tag{31}$$

Thus, we easily get $\lim_{t\to+\infty} |\tilde{z}(t)| = 0$, that is $\lim_{t\to+\infty} |x(t) - z^*(t)| = 0$. □

Remark 2. If we assume that all coefficients $\lambda(t), \mu(t), \beta(t), \beta_1(t), \delta(t), \gamma(t)$ and $c(t)$ are constant, then system (5) degenerates to the following autonomous system:

$$\begin{cases} \dot{x}(t) = \lambda - \mu x(t) - \beta x(t)v(t) \\ \dot{y}(t) = \beta_1 x(t-\tau_1)v(t-\tau_1) - \delta y(t) \\ \dot{v}(t) = \gamma y(t-\tau_2) - cv(t). \end{cases} \tag{32}$$

Evidently, we have

$$R_* = R^* = R_0 = \frac{\beta_1}{\delta} \cdot \frac{\lambda}{\mu} \cdot \frac{\gamma}{c},$$

where R_0 is the basic reproduction number of system (32). From Theorem 3.1, we easily find that the main results in Liu and Wang [11] are improved and extended in the present paper when $R_0 < 1$.

4. **Numerical example and sensitivity test of R_* and R^*.** Consider the following non-periodic time-varying HIV-1 system with delays:

$$\begin{cases} \dot{x}(t) = \lambda - \mu x(t) - (1 - a(0.5\sin(b(t^2+t)) + s))kx(t)v(t), \\ \dot{y}(t) = (1 - a(0.5\sin(b(t^2+t)) + s))ke^{-\delta_1\tau_1}x(t-\tau_1)v(t-\tau_1) - \delta y(t), \\ \dot{v}(t) = N\delta e^{-\delta\tau_2}y(t-\tau_2) - cv(t), \end{cases} \tag{33}$$

where all parameters are defined in Table 1.

From (15), we have

$$R_* = \frac{(1 - a(s+0.5))N\lambda e^{-\delta_1\tau_1}e^{-\delta\tau_2}}{c\mu},$$

and

$$R^* = \frac{(1 - a(s-0.5))N\lambda e^{-\delta_1\tau_1}e^{-\delta\tau_2}}{c\mu}.$$

We chose parameters $\lambda = 10000$ ml^{-1}day^{-1}, $\mu = 0.01$ day^{-1}, $k = 0.00002$ ml day^{-1}, $a = 0.5$, $b = 3.5$, $s = 0.6$, $\delta = 1$ day^{-1}, $\delta_1 = 0.3$ day^{-1}, $N = 20$, $c = 23$ day^{-1}, $\tau_1 = 0.25$ day, $\tau_2 = 1$ day. By Theorem 3.1, we have $R_* \approx 2.676 > 1$. Thus, the system (33) is permanent (see FIG. 1).

When we chose parameters $\lambda = 10000$ ml^{-1}day^{-1}, $\mu = 0.1$ day^{-1}, $k = 0.00002$ ml day^{-1}, $a = 0.5$, $b = 3.5$, $s = 0.9$, $\delta = 1$ day^{-1}, $\delta_1 = 0.5$ day^{-1}, $N = 20$, $c = 23$ day^{-1}, $\tau_1 = 0.25$ day, $\tau_2 = 1$ day, from Theorem 3.2, we have $R^* \approx 0.476 < 1$. Thus, the system (33) goes to extinction (see FIG. 2).

When the condition in neither Theorem 3.1 nor Theorem 3.2 is satisfied, we provide the simulations in FIGs. 3 and 4: If we chose parameters $\lambda = 10000$ ml^{-1}day^{-1}, $\mu = 0.03$ day^{-1}, $k = 0.00002$ ml day^{-1}, $a = 0.5$, $b = 3.5$, $s = 0.9$, $\delta = 1$ day^{-1}, $\delta_1 = 0.5$ day^{-1}, $N = 20$, $c = 23$ day^{-1}, $\tau_1 = 0.25$ day, $\tau_2 = 1$ day,

TABLE 1. Parameter values in numerical simulations for system (33).

Parameters	Base values	Reference
λ : Recruitment rate of uninfected cells	10^4 cellsml^{-1}day^{-1}	[25]
μ : Death rate of uninfected cells	0.01 day^{-1}	[25]
k : Infection rate	2×10^{-5} ml day^{-1}	[23]
δ : Death rate of infected cells that have finished RT	1 day^{-1}	[25]
δ_1 : Death rate of infected cells that have not finished RT	0.5 day^{-1}	[25]
a : The constant used in time-varying drug efficacy	0.5	—
s : The constant used in time-varying drug efficacy	0.6 or 0.9	—
b : The constant used in time-varying drug efficacy	3.5	—
N : Number of virion produced by an infected cell	20	—
c : Clearance rate of free virus	23 day^{-1}	[25]
τ_1 : Time needed to complete RT	0.25 day	[26]
τ_2 : Time between RT and the release of new virions	1 day	—

we have $R_* \approx 0.892 < 1 < R^* \approx 1.883$, and the system (33) is permanent (see FIG. 3). If we let $\mu = 0.1$ day^{-1}, $N = 50$, and other parameters remain unchanged, then we have $R_* \approx 0.669 < 1 < R^* \approx 1.412$, and the system (33) goes to extinction (see FIG. 4). Thus, when $R_* < 1 < R^*$, both viral persistence and extinction are possible.

From the analysis we know that R_*, R^* are important values that determines whether the virus can be cleared. In FIG. 5, we plotted the change of R_* (or R^*) as a function of one parameter (all the other parameters were fixed). We obtained a threshold value for each parameter such that R_* (or R^*) is 1. Specifically, when $\lambda < \lambda_*$ (or $\lambda < \lambda^*$), or $N < N_*$ (or $N < N^*$), R_* (or R^*) is less than 1. When μ (or δ_1 or δ or τ_1 or τ_2 or c) is greater than its corresponding threshold value, R_* (or R^*) is also less than 1.

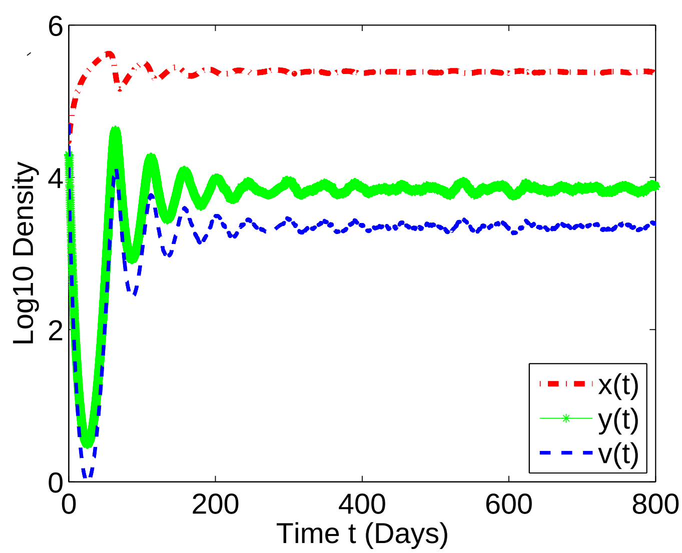

FIGURE 1. Dynamics of uninfected cells $x(t)$, infected cells $y(t)$, viral load $v(t)$ in (33) with initial value (30000,20000,50000) and $R_* \approx 2.676 > 1$.

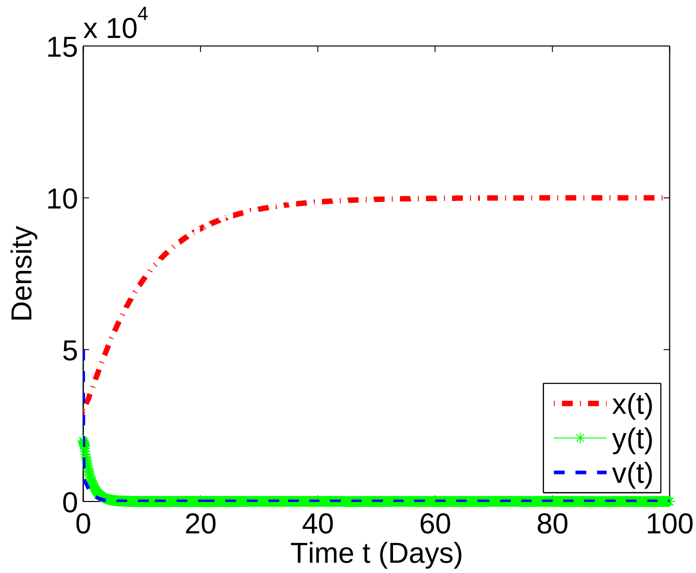

FIGURE 2. Dynamics of uninfected cells $x(t)$, infected cells $y(t)$, viral load $v(t)$ in (33) with initial value (30000,20000,50000) and $R^* \approx 0.476 < 1$.

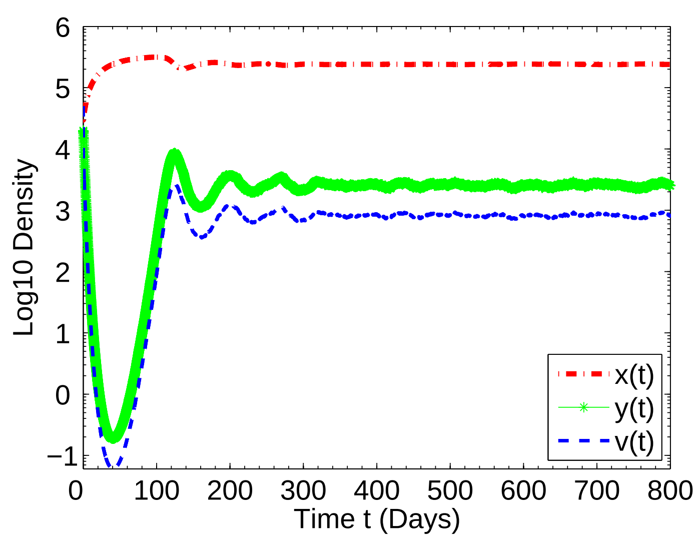

FIGURE 3. Dynamics of uninfected cells $x(t)$, infected cells $y(t)$, viral load $v(t)$ in (33) with initial value (30000,20000,50000) and $R_* \approx 0.892 < 1 < R^* \approx 1.883$.

5. **Conclusion.** In this paper, we have formulated a model of HIV infection incorporating non-periodic coefficients and two intracellular time delays. We have

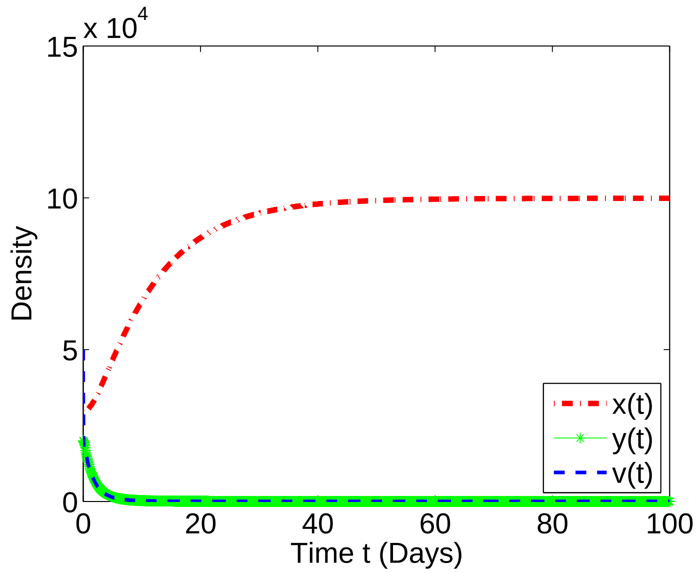

FIGURE 4. Dynamics of uninfected cells $x(t)$, infected cells $y(t)$, viral load $v(t)$ in (33) with initial value (30000,20000,50000) and $R_* \approx 0.669 < 1 < R^* \approx 1.412$.

developed a rigorous analysis of the model by applying the oscillation theory and the comparison theory of differential equations.

Our analysis yields two positive constants R^* and R_* (see (15)), both of which can be explicitly expressed by the parameters of the system, to obtain conditions for the permanence and extinction of the virus. We derived a sufficient condition ($R_* > 1$) for the permanence of this general system (see Theorem 3.1 and FIG. 1), and a sufficient condition ($R^* < 1$) for the clearance of the virus (see Theorem 3.2 and FIG. 2). From these results, we can obtain the complicated effects of the time-varying parameters on the sufficient conditions for the permanence and the extinction of the model.

When $R_* > 1$ (i.e., the system is permanent), based on the explicitly parameter-dependent values $\widetilde{q_2}$ and $\widetilde{L_2}$, we obtain estimates of the lower and upper bounds of the viral load and their dependence on the parameters. When all the coefficients are constant, the two values R_* and R^* reduce to the basic reproductive number of the corresponding autonomous system (see Remark 2), and thus our work improved some existing results of HIV models including time delays [11].

We performed numerical simulations using non-periodic drug effectiveness. The numerical results confirmed our theoretical analysis. We also obtained the corresponding permanence threshold values for all the parameters (see FIG. 5). These values are important in determining whether the virus can be eradicated from infected individuals. Moreover, our simulations suggest the significant differences in the sensitivities of R_* and R^* to the different coefficients of the model.

We remark that the dynamics of our model are still unclear for the case of $R_* < 1 < R^*$, in which the virus may be persistent (see FIG. 3) or cleared (see FIG. 4) under this condition. It remains an interesting future problem for a non-autonomous HIV model.

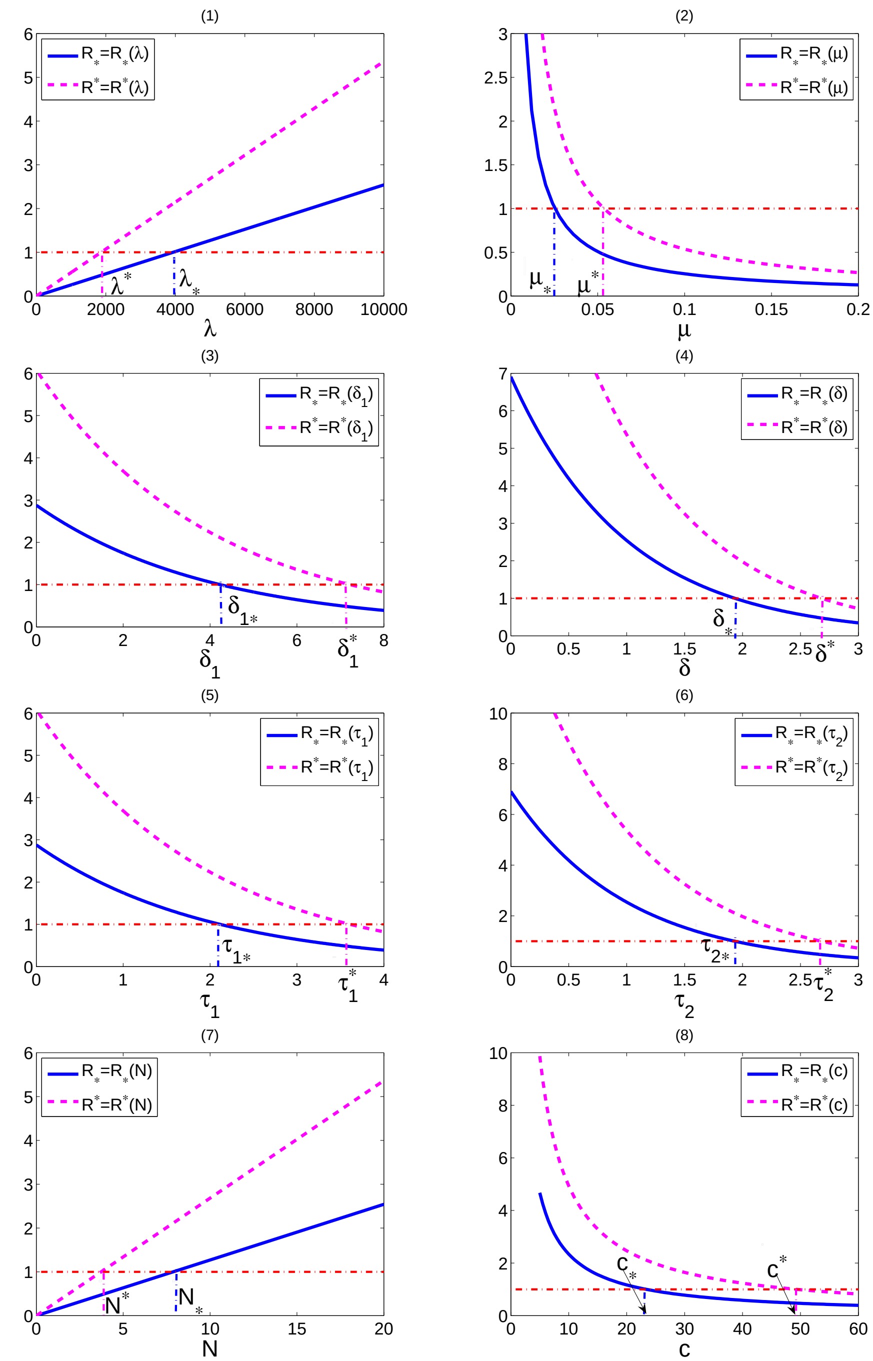

FIGURE 5. The relationships between R_*, R^* and parameters λ, μ, δ_1, δ, τ_1, τ_2, N and c, respectively.

In the previous works, by using the methods of persistence theory, threshold dynamics for periodic HIV-1 models were established [14, 35]. However, the methods used in these references are not applicable to our non-autonomous model (3) since the coefficients are not necessarily periodic. Our methods may be used in the analysis of permanence and extinction for other general time-varying mathematical models (with or without delay).

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