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Analysis of the dynamics of a delayed HIV pathogenesis model☆

Zhixing Hu*, Xiangdong Liu, Hui Wang, Wanbiao Ma

Department of Applied Mathematics and Mechanics, University of Science and Technology Beijing, Beijing, 100083, PR China

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ABSTRACT

In this paper, considering full Logistic proliferation of $CD4^+$ T cells, we study an HIV pathogenesis model with antiretroviral therapy and HIV replication time. We first analyze the existence and stability of the equilibrium, and then investigate the effect of the time delay on the stability of the infected steady state. Sufficient conditions are given to ensure that the infected steady state is asymptotically stable for all delay. Furthermore, we apply the Nyquist criterion to estimate the length of delay for which stability continues to hold, and investigate the existence of Hopf bifurcation by using a delay τ as a bifurcation parameter. Finally, numerical simulations are presented to illustrate the main results.

1. Introduction and the establishment of the model

It is well known that HIV mainly targets a host's $CD4^+$ T cells, the main driver of the immune response. Chronic HIV infection causes gradual depletion of the $CD4^+$ T cell pool, and thus progressively compromises the host's immune response, leading to humoral and cellular immune function loss (the marker of the on set of AIDS), making the host susceptible to opportunistic infections. The fact that HIV replicates rapidly, producing on average 10^{10} viral particles per day, led to the realization that HIV evolves so rapidly that treatment with a single drug is bound to fail [1]. The best current therapy for HIV involves the simultaneous administration of two or more anti-viral drugs, potential inhibitors of HIV replication in vivo. These drug cocktails generally consist of reverse transcriptase inhibitors (RTIs) that block the infection of $CD4^+$ T cells by infectious virus and protease inhibitors (PIs) that prevent HIV protease from cleaving HIV polyprotein into functional units, causing infected cells to produce virus particles that are non-infectious.

Many mathematical models, used extensively in research into HIV virus dynamics, help to improve our understanding of the disease development progress in the host. The basic mathematical model of HIV pathogenesis in the host describes interactions of the immune system and the virus by including healthy and infected $CD4^+$ T cells and HIV virion [2–6]. Much has been learned regarding the pathogenesis of HIV in the host using this basic model. Taking drug therapy into consideration, some scholars incorporate constant terms describing drug efficacy in the basic models [1,7–9]. In addition, researchers extend the basic models by adding $CD4^+$ T cells' simple Logistic proliferation term $rT\left(1-\frac{T}{T_{\max}}\right)$ [1,7,10–12] or $CD4^+$ T cells' full Logistic proliferation term $rT\left(1-\frac{T+I}{T_{\max}}\right)$ [13–15], where r is the maximum proliferation rate of $CD4^+$ T cells, T, I respectively represent the concentration of susceptible $CD4^+$ T cells, infected $CD4^+$ T cells, and $T_{\max}$ is the maximum level of $CD4^+$ T cell concentration in the body.

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* Corresponding author.
E-mail addresses: bkdhzhx@163.com (Z. Hu), liuxiangdong216@163.com (X. Liu).

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Perelson et al. [1] built on the biology of the HIV life cycle, including an intracellular delay. The intracellular delay describes the amount of time from initial infection of a $CD4^+$ T cell by HIV to the release of new virion. This work inspired several modeling studies (see [16,15,17–19]). Herz et al. [16] used a discrete delay to model the intracellular delay in the basic HIV pathogenesis model and demonstrated that the incorporation of a delay would substantially shorten the estimate for the half-life of free virus. After that there were also many authors who investigated delayed HIV pathogenesis models incorporating the Logistic proliferation term of $CD4^+$ T cells or cure rate [15,17–19].

Wang et al. investigate an HIV pathogenesis model including a simple Logistic growth term of $CD4^+$ T cells, intracellular delay and antiretroviral therapy [20]. However, note that the model of literature [20] neglect the full Logistic proliferation of healthy and infected $CD4^+$ T cells. In literature [21–23], they argue that all $CD4^+$ T cells (healthy and infected) divide and increase in population once stimulated by antigen or mitogen. Inspired by their work, we assume that $CD4^+$ T cells (healthy and infected) are governed by a full Logistic growth term. Therefore, we shall establish a mathematical model as follows

$$\begin{cases} T' = s - \alpha T + rT\left(1 - \dfrac{T+I}{T_{\max}}\right) - k_1(1-n_r)TV, \\ I' = k_2(1-n_r)T(t-\tau)V(t-\tau) + rI\left(1 - \dfrac{T+I}{T_{\max}}\right) - \beta I, \\ V' = (1-n_p)N\beta I - dV, \\ V_N' = n_p N\beta I - dV_N, \end{cases} \tag{1.1}$$

where T, I, V, V_N represent the concentration of susceptible $CD4^+$ T cells, infected $CD4^+$ T cells, infectious HIV virus particles and non-infectious HIV virus in the blood, respectively. s denotes the rate at which new $CD4^+$ T cells are created from precursors in the bone marrow and thymus, and new $CD4^+$ T cells is susceptible. Parameters α, β and d are the natural death rates of uninfected $CD4^+$ T cells and infected $CD4^+$ T cells, and the clearance rate of HIV virus particles, respectively. Because of the viral burden on the HIV infected $CD4^+$ T cells, we assume that $\beta \geq \alpha$. $T_{\max}$ is the maximum level of $CD4^+$ T cells concentration in the body. If the population ever reaches $T_{\max}$, it should decrease, thus we impose the constraint $\alpha T_{\max} > s$. $CD4^+$ T cells can also be created by proliferation of existing $CD4^+$ T cells. r denotes the maximum proliferation rate of $CD4^+$ T cells. The parameter k_1 represents the rate of infection of $CD4^+$ T cells with free virus, k_2 is the rate at which infected cells become actively infected (the ratio $0 \leq k_2/k_1 \leq 1$ is the proportion of $CD4^+$ T cells, which become actively infected (proportion of infected cells surviving incubation)). $CD4^+$ T cells can also be created by proliferation of existing $CD4^+$ T cells. r denotes the maximum proliferation rate of $CD4^+$ T cells, and the Logistic functions $rT\left(1 - \frac{T+I}{T_{\max}}\right)$ and $rI\left(1 - \frac{T+I}{T_{\max}}\right)$ represent the proliferation of healthy and infected $CD4^+$ T cells, respectively. HIV viruses are created by infected $CD4^+$ T cells, and each infected $CD4^+$ T cell is assumed to produce N virus particles during its life time, including any of its daughter cells. Protease inhibitors, with efficacy $0 \leq n_p < 1$, cause infected cells to produce non-infectious virus with rate n_pN. Reverse transcriptase inhibitors prevent the production of infected cells with efficacy $0 \leq n_r < 1$. The time lag τ is considered the amount of time from initial infection of a $CD4^+$ T cell by HIV to the release of new virion. We assume that all parameters are non-negative constant.

The initial conditions of system (1.1) are

$$T(\theta) = \varphi_1(\theta) > 0, \qquad I(\theta) = \varphi_2(\theta) > 0, \qquad V(\theta) = \varphi_3(\theta) > 0, \qquad V_N(\theta) = \varphi_4(\theta) > 0, \quad \theta \in [-\tau, 0],$$

where functions $\varphi_i \in C([-\tau, 0], R_+)$, $i = 1, 2, 3, 4$, and $C([-\tau, 0], R_+)$ is the Banach space of continuous functions mapping the interval $[-\tau, 0]$ into R_+, where $R_+ = (0, +\infty)$.

Note that the non-infectious HIV virus V_N does not appear in the first three equations. Therefore, we can consider the following subsystem of system (1.1)

$$\begin{cases} T' = s - \alpha T + rT\left(1 - \dfrac{T+I}{T_{\max}}\right) - k_1(1-n_r)TV, \\ I' = k_2(1-n_r)T(t-\tau)V(t-\tau) + rI\left(1 - \dfrac{T+I}{T_{\max}}\right) - \beta I, \\ V' = (1-n_p)N\beta I - dV, \end{cases} \tag{1.2}$$

with initial conditions

$$T(\theta) = \varphi_1(\theta) > 0, \qquad I(\theta) = \varphi_2(\theta) > 0, \qquad V(\theta) = \varphi_3(\theta) > 0, \quad \theta \in [-\tau, 0], \tag{1.3}$$

where $\varphi_i \in C([-\tau, 0], R_+)$, $i = 1, 2, 3$, $R_+ = (0, +\infty)$.

The paper is organized as follows. In the next section, the existence of equilibrium and stability of the model are studied. The estimation of the length of delay to preserve stability is presented in Section 3. In Section 4, the existence of Hopf bifurcation is discussed. In Section 5, some numerical simulations are performed to illustrate the main analytical results. The paper ends with a brief discussion.

2. The existence and stability of equilibria

In the following, we first show that all solutions of the system (1.2) with initial conditions (1.3) are positive and ultimately bounded.

Theorem 2.1. *For sufficiently large t, all solutions of system (1.2) with initial conditions (1.3) are positive and ultimately bounded.*

Proof. Suppose $T(t)$ is not always positive. Then, let $t_0 > 0$ be the first time such that $T(t_0) = 0$, that is $t_0 = \inf\{t|t > 0, T(t) = 0\}$. By the first equation of (1.2), we have $T'(t_0) = s > 0$. This means $T(t) < 0$ for $t \in (t_0 - \varepsilon, t_0)$, where $\varepsilon > 0$ is an arbitrarily small positive constant. This is a contradiction. It follows that $T(t)$ is always positive.

We now show that $I(t) > 0$ for all $t > 0$. Otherwise, if it is not valid, noting that $T(t) > 0$ and $I(t) > 0$ for $t \in [-\tau, 0]$, then there exists a t_1 such that $I(t_1) = 0$. Assume that t_1 is the first time such that $I(t_1) = 0$, that is, $t_1 = \inf\{t|t > 0, I(t) = 0\}$, then $t_1 > 0$. From system (1.2) with initial conditions (1.3), we get

$$I'(t_1) = \begin{cases} k_2(1-n_r)\varphi_1(t_1-\tau)\varphi_3(t_1-\tau) > 0, & t_1 \in [0, \tau], \\ k_2(1-n_r)T(t_1-\tau)V(t_1-\tau) > 0, & t_1 \in [\tau, +\infty]. \end{cases}$$

Thus $I'(t_1) > 0$. Hence, there exists sufficiently small $\varepsilon_1 > 0$ to make $I(t) < 0$ for $t \in (t_1 - \varepsilon, t_1)$. By the definition of t_1, this is a contradiction. Therefore, $I(t) > 0$ for all $t > 0$. Similarly, we easily show that $V(t)$ is always positive. Thus, we can conclude that all solutions of system (1.2) with initial conditions (1.3) remain positive for all $t > 0$.

Next, we shall discuss the boundedness of solutions of the system (1.2). In the absence of HIV infection, the dynamics of healthy CD4$^+$ T cells are governed by

$$T' = s - \alpha T + rT\left(1 - \frac{T}{T_{\max}}\right).$$

It can be shown that the CD4$^+$ T cell concentration stabilizes at a level T_0, which is given by

$$T_0 = \frac{T_{\max}}{2r}\left(r - \alpha + \sqrt{(r-\alpha)^2 + \frac{4rs}{T_{\max}}}\right),$$

and T_0 satisfy the following equation

$$s = \alpha T_0 - rT_0 + \frac{rT_0^2}{T_{\max}}. \tag{2.1}$$

By the first equation of system (1.2), we have

$$T' \le s - \alpha T + rT\left(1 - \frac{T}{T_{\max}}\right).$$

Thus, if $T(0) < T_0$, we obtain

$$\lim_{t\to+\infty} \sup T(t) \le T_0, \quad \text{for all } t \ge 0. \tag{2.2}$$

Let $W(t) = k_2T(t-\tau) + k_1I$, then

$$\begin{aligned} W'(t) &= sk_2 - \alpha k_2 T(t-\tau) + rk_2T(t-\tau)\left(1 - \frac{T(t-\tau)+I(t-\tau)}{T_{\max}}\right) + rk_1I\left(1 - \frac{T+I}{T_{\max}}\right) - \beta k_1 I \\ &\le sk_2 - \alpha k_2 T(t-\tau) + rk_2T(t-\tau)\left(1 - \frac{T(t-\tau)}{T_{\max}}\right) + rk_1I\left(1 - \frac{I}{T_{\max}}\right) - \beta k_1 I \\ &\le sk_2 - \alpha k_2 T(t-\tau) + \frac{rk_2T_{\max}}{4} + \frac{rk_1T_{\max}}{4} - \beta k_1 I \\ &\le sk_2 + \frac{r(k_1+k_2)T_{\max}}{4} - \alpha W(t). \end{aligned} \tag{2.3}$$

Let $M_1 = sk_2 + \frac{r(k_1+k_2)T_{\max}}{4}$, and solving Eq. (2.3), we obtain

$$W(t) \le \frac{M_1}{\alpha} + \left[W(0) - \frac{M_1}{\alpha}\right]e^{-\alpha t}. \tag{2.4}$$

According to inequality (2.4), we get $W(t) < 2M_1/\alpha$ for sufficiently large t. Recall that $T(t), I(t)$ stay positive. Combining with inequality (2.2), $T(t)$ and $I(t)$ have ultimately above bound $M_2 > 0$.

Similarly, from the third equation of system (1.2), we easily obtain

$$V' = (1-n_p)N\beta I - dV \le (1-n_p)N\beta M_2 - dV. \tag{2.5}$$

Solving inequality (2.5), we have

$$V(t) \le \frac{(1-n_p)N\beta M_2}{d} + \left[V(0) - \frac{(1-n_p)N\beta M_2}{d}\right] e^{-dt}. \tag{2.6}$$

It follows from inequality (2.6) that $V(t)$ has an ultimately above bound $M_3 > 0$, for sufficiently large t. Then the proof of Theorem 2.1 is completed. □

Let $\Omega = \{(T, I, V) | 0 < T \le T_0, 0 < I \le M_2, 0 < V \le M_3\}$, then Ω is the positive invariant set of system (1.2).

Now, we investigate the existence of equilibrium of system (1.2). The equilibrium of system (1.2) satisfies the following equation

$$\begin{cases} s - \alpha T + rT\left(1 - \dfrac{T+I}{T_{\max}}\right) - k_1(1-n_r)TV = 0, \\ k_2(1-n_r)TV + rI\left(1 - \dfrac{T+I}{T_{\max}}\right) - \beta I = 0, \\ (1-n_p)N\beta I - dV = 0. \end{cases} \tag{2.7}$$

Clearly, system (1.2) has always the uninfected equilibrium $E_0 = (T_0, 0, 0)$. From the third equation of (2.7), we have

$$I = \frac{dV}{(1-n_p)N\beta}. \tag{2.8}$$

Substitute (2.8) into the second equation of (2.7) and solution for T results in

$$T = \frac{(\beta - r)dT_{\max}}{(1-n_p)(1-n_r)k_2N\beta T_{\max} - rd} + \frac{rd^2}{(1-n_p)N\beta[(1-n_p)(1-n_r)k_2N\beta T_{\max} - rd]}V. \tag{2.9}$$

Rewriting the first equation of (2.7) as

$$s = T\left[\alpha - r\left(1 - \frac{T+I}{T_{\max}}\right) + k_1(1-n_r)V\right]. \tag{2.10}$$

Substituting (2.8) and (2.9) into (2.10), we have

$$s = (A + BV)(C + DV)$$

or

$$BDV^2 + (AD + BC)V + AC - s = 0, \tag{2.11}$$

where

$$\begin{aligned} A &= \frac{(\beta - r)dT_{\max}}{(1-n_p)(1-n_r)k_2N\beta T_{\max} - rd}, \\ B &= \frac{rd^2}{(1-n_p)N\beta[(1-n_p)(1-n_r)k_2N\beta T_{\max} - rd]}, \\ C &= \alpha - r + \frac{rd(\beta - r)}{(1-n_p)(1-n_r)k_2N\beta T_{\max} - rd}, \\ D &= \frac{(1-n_p)(1-n_r)^2k_1k_2N\beta T_{\max} - (1-n_r)(k_1 - k_2)rd}{(1-n_p)(1-n_r)k_2N\beta T_{\max} - rd}. \end{aligned} \tag{2.12}$$

System (1.2) has positive equilibrium if and only if Eq. (2.11) has a positive root V such that $A + BV > 0$.

For the sake of convenience, let

$$V_{\pm} = \frac{-(AD + BC) \pm \sqrt{(AD + BC)^2 - 4BD(AC - s)}}{2BD}, \tag{2.13}$$

where V_+ and V_- correspond to the expression of taking "+" and "−" on the right side "±" of (2.13), respectively.

If $\beta > r$, it is proved that $AC - s < 0$ is equivalent to

$$\begin{aligned} &s\left[(1-n_p)(1-n_r)k_2\beta NT_{\max} - rd\right]^2 - d(\beta - r)(\alpha - r)T_{\max}\left[(1-n_p)(1-n_r)k_2\beta NT_{\max} - rd\right] \\ &\quad - r(\beta - r)^2d^2T_{\max} > 0. \end{aligned}$$

The solutions of the above inequality are

$$N > \frac{(\beta - r)d}{(1-n_p)(1-n_r)k_2\beta T_0} + \frac{rd}{(1-n_p)(1-n_r)k_2\beta T_{\max}} \triangleq N_{\text{crit}} \tag{2.14}$$

or

$$N < \frac{rd}{(1-n_p)(1-n_r)k_2\beta T_{\max}}\left(1 - \frac{(\beta - r)T_0}{s}\right) \triangleq N_{\min}. \tag{2.15}$$

As

$$N_{\text{crit}} = \frac{d}{(1-n_p)(1-n_r)k_2\beta T_0}\left[\frac{s}{T_0} + \beta - \alpha\right] > 0,$$

if $N > N_{\text{crit}}$, then $A > 0$, $B > 0$, $D > 0$ and $AC - s < 0$, it follows that $BD > 0$. Therefore, Eq. (2.11) has an unique positive root V_+ and $A + BV_+ > 0$. Thus, we obtain $T^* = A + BV^*$, and $I^* = \frac{d}{(1-n_p)N\beta}V^* > 0$, where $V^* = V_+$. So system (1.2) has an unique positive equilibrium $E^*(T^*, I^*, V^*)$.

If $0 < N < \frac{rd}{(1-n_p)(1-n_r)k_2\beta T_{\max}}$, then $A < 0$ and $B < 0$, even if the equation $s = (A + BV)(C + DV)$ has positive roots V^*, but $A + BV^* < 0$. So system (1.2) has no positive equilibrium.

If $\frac{rd}{(1-n_p)(1-n_r)k_2\beta T_{\max}} < N \le N_{\text{crit}}$, then $AC - s \ge 0$, $A > 0$, $B > 0$, $D > 0$ and $BD > 0$. If $\alpha \ge r$, then $C > 0$. If $\alpha < r$, it follows from $N \le N_{\text{crit}}$ that

$$(1-n_p)(1-n_r)k_2N\beta T_{\max} - rd \le (\beta - r)d\frac{T_{\max}}{T_0}.$$

So

$$(\alpha - r)\left[(1-n_p)(1-n_r)k_2N\beta T_{\max} - rd\right] \ge (\beta - r)(\alpha - r)d\frac{T_{\max}}{T_0}.$$

It follows from (2.1) that

$$(\alpha - r)\left[(1-n_p)(1-n_r)k_2N\beta T_{\max} - rd\right] + rd(\beta - r) \ge (\beta - r)d\left((\alpha - r)\frac{T_{\max}}{T_0} + r\right) = s\frac{T_{\max}}{T_0^2} > 0.$$

That is, $C > 0$ and $AD + BC > 0$. Therefore, Eq. (2.11) has no positive root. So system (1.2) has no positive equilibrium.

If $N = \frac{rd}{(1-n_p)(1-n_r)k_2\beta T_{\max}}$, it is known from (2.9) that the Eq. (2.9) has no positive solution. So system (1.2) has no positive equilibrium.

If $\beta = r$, it is easy to prove that system (1.2) has an unique positive equilibrium if $N > N_{\text{crit}}$, and no positive equilibrium if $N \le N_{\text{crit}}$.

If $\beta < r$, then

$$N_{\text{crit}} < \frac{rd}{(1-n_p)(1-n_r)k_2\beta T_{\max}} < N_{\min}.$$

It can also be proved that system (1.2) has an unique positive equilibrium if $N > N_{\text{crit}}$, and no positive equilibrium if $N \le N_{\text{crit}}$. In fact.

(i) If $N > N_{\min}$, then $AC - s < 0$, $B > 0$ and $D > 0$, so $BD > 0$. therefore, Eq. (2.11) has an unique positive root V_+. Because

$$A + BV_+ = \frac{AD - BC + \sqrt{(AD - BC)^2 + 4BDs}}{2D} > \frac{AD - BC + |AD - BC|}{2D} \ge 0,$$

so system (1.2) has an unique positive equilibrium $E^* = (T^*, I^*, V^*)$, where $V^* = V_+$.

(ii) If $\frac{rd}{(1-n_p)(1-n_r)k_2\beta T_{\max}} < N < N_{\min}$, then $AC - s > 0$, $B > 0$, $D > 0$, but $A < 0$, it follows that $C < 0$. So $AD + BC < 0$ and Eq. (2.11) has two positive roots V_+ and V_-. Because

$$A + BV_- = \frac{AD - BC - \sqrt{(AD - BC)^2 + 4BDs}}{2D} < \frac{AD - BC - |AD - BC|}{2D} \le 0,$$

and

$$A + BV_+ = \frac{AD - BC + \sqrt{(AD - BC)^2 + 4BDs}}{2D} > \frac{AD - BC + |AD - BC|}{2D} \ge 0,$$

so system (1.2) has an unique positive equilibrium $E^* = (T^*, I^*, V^*)$, where $V^* = V_+$.

(iii) If $N_{\text{crit}} < N < \frac{rd}{(1-n_p)(1-n_r)k_2\beta T_{\max}}$, then $AC - s > 0$, $A > 0$ and $B < 0$, it follows that $C > 0$. If $D > 0$, then $BD < 0$, if follows that $V_- < 0$ and $V_+ > 0$. Because

$$A + BV_+ = \frac{AD + (-B)C + \sqrt{(AD - BC)^2 + 4BDs}}{2D} > 0,$$

so system (1.2) has an unique positive equilibrium $E^* = (T^*, I^*, V^*)$, where $V^* = V_+$. If $D > 0$, then $BD > 0$ and $AD+BC < 0$. Similar to case (ii), system (1.2) has an unique positive equilibrium $E^* = (T^*, I^*, V^*)$, where $V^* = V_+$.

(iv) If $N < N_{\text{crit}}$, then $AC - s < 0$, $A > 0$ and $B < 0$.

(a) If $D < 0$, then $BD > 0$, there exists an unique positive root V_+, but it follows from $D < 0$ that

$$A + BV_+ = \frac{AD - BC + \sqrt{(AD - BC)^2 + 4BDs}}{2D} < \frac{AD - BC + |AD - BC|}{2D} \le 0,$$

so system (1.2) has no positive equilibrium.

(b) If $k_1 = k_2$, then $D < 0$. According to the above conclusion, system (1.2) has no positive equilibrium.

(c) If $k_1 > k_2$ and $D \le 0$. Similarly, system (1.2) has no positive equilibrium.

(d) Suppose $k_1 > k_2$ and $D > 0$ below. Let

$$N_D \triangleq \frac{(k_1 - k_2)rd}{(1 - n_p)(1 - n_r)k_1k_2\beta T_{\max}}. \tag{2.16}$$

It is easy to prove that $D > 0$ if and only if $N < N_D$. Let

$$N_{AD-BC} \triangleq \frac{(\beta - \alpha)rd}{(1 - n_p)(1 - n_r)k_1\beta(r - \beta)T_{\max}}. \tag{2.17}$$

It is easy to prove that $AD - BC < 0$ if and only if $N < N_{AD-BC}$, and $AD - BC > 0$ if and only if $N > N_{AD-BC}$.

(d1) If $k_2(\beta - \alpha) \ge (k_1 - k_2)(r - \beta)$, then $N_{AD-BC} \ge N_D$. As $N < N_D$, so $AD - BC < 0$. It follows from $BD < 0$ that either Eq. (2.11) has no positive root or there exist two positive roots V_- and V_+. But

$$A + BV_\pm = \frac{AD - BC \pm \sqrt{(AD - BC)^2 + 4BDs}}{2D} < 0.$$

So system (1.2) has no positive equilibrium.

(d2) If $k_2(\beta - \alpha) < (k_1 - k_2)(r - \beta)$, then $N_{AD-BC} < N_D$.

If $0 < N \le N_{AD-BC}$, then $AD - BC \le 0$, it follows from $BD < 0$ that either Eq. (2.11) has no real root or there exist two positive roots V_- and V_+ such that $A + BV_\pm < 0$. So system (1.2) has no positive equilibrium.

If $N_{AD-BC} < N < N_D$, then $AD - BC > 0$.

It is easy to prove that the sign of $(AD - BC)^2 + 4BDs$ is determined by

$$\begin{aligned} &d^2r^2(\alpha - \beta)^2 + 2rd(1 - n_p)(1 - n_r)\beta\,[2(k_2 - k_1)rs + k_1(r - \beta)(\alpha - \beta)T_{\max}]\,N \\ &\quad + \beta^2(1 - n_p)^2(1 - n_r)^2\left[4k_1k_2rsT_{\max} + k_1^2T_{\max}^2(r - \beta)^2\right]N^2. \end{aligned} \tag{2.18}$$

Let

$$\begin{aligned} \Delta_s \triangleq\ &[4d(k_1 - k_2)(1 - n_p)(1 - n_r)r^2s\beta]^2 \\ &+ 16d^2r^3(1 - n_p)^2(1 - n_r)^2k_1s\beta^2(\alpha - \beta)T_{\max}\,[(k_2 - k_1)(r - \beta) - k_2(\alpha - \beta)] \end{aligned} \tag{2.19}$$

and

$$N_\pm \triangleq \frac{2(1 - n_p)(1 - n_r)rd\beta\,[2(k_1 - k_2)rs + k_1T_{\max}(r - \beta)(\beta - \alpha)] \pm \sqrt{\Delta_s}}{2(1 - n_p)^2(1 - n_r)^2\beta^2k_1T_{\max}\left[4k_2rs + k_1T_{\max}(r - \beta)^2\right]}, \tag{2.20}$$

where N_+ and N_- correspond to the expression of taking "+" and "−" on the right side "±" of (2.20), respectively.

It is easy to prove that $(AD - BC)^2 + 4BDs < 0$ if and only if $N_- < N < N_+$.

By calculation, we have

$$\begin{aligned} N_- &< \frac{2(1 - n_p)(1 - n_r)rd\beta k_1T_{\max}(r - \beta)(\beta - \alpha)}{2(1 - n_p)^2(1 - n_r)^2\beta^2k_1T_{\max}\left[4k_2rs + k_1T_{\max}(r - \beta)^2\right]} \\ &< \frac{2(1 - n_p)(1 - n_r)rd\beta k_1T_{\max}(r - \beta)(\beta - \alpha)}{2(1 - n_p)^2(1 - n_r)^2\beta^2k_1^2T_{\max}^2(r - \beta)^2} \\ &= N_{AD-BC}, \end{aligned}$$

and

$$\begin{aligned} N_+ &> \frac{2(1-n_p)(1-n_r)rd\beta\,[4(k_1-k_2)rs+k_1T_{\max}(r-\beta)(\beta-\alpha)]}{2(1-n_p)^2(1-n_r)^2\beta^2k_1T_{\max}\left[4k_2rs+k_1T_{\max}(r-\beta)^2\right]} \\ &> \frac{2(1-n_p)(1-n_r)rd\beta k_1T_{\max}(r-\beta)(\beta-\alpha)}{2(1-n_p)^2(1-n_r)^2\beta^2k_1^2T_{\max}^2(r-\beta)^2} \\ &= N_{AD-BC}. \end{aligned}$$

That is, $0 < N_- < N_{AD-BC} < N_+$. Therefore, if $N_{AD-BC} < N < N_+$, then $(AD-BC)^2+4BDs < 0$, so Eq. (2.11) has no real root. If $N_+ \le N < N_D$, then $AD-BC > 0$ and $(AD-BC)^2+4BDs \ge 0$. It can be proved that $AD+BC < 0$, so Eq. (2.11) has no positive real root.

According to the above discussions, we have the following conclusions.

Theorem 2.2. *If $N > N_{\text{cirt}}$, then system (1.2) has two equilibria, the uninfected steady state $E_0 = (T_0, 0, 0)$ and the infected equilibrium $E^* = (T^*, I^*, V^*)$; if $N \le N_{\text{cirt}}$, then system (1.2) has an unique equilibrium, the uninfected equilibrium $E_0 = (T_0, 0, 0)$.*

Let $\tilde{E} = (\tilde{T}, \tilde{I}, \tilde{V})$ be an arbitrary equilibrium. Thus, linearizing the system (1.2) at equilibrium $\tilde{E} = (\tilde{T}, \tilde{I}, \tilde{V})$, we obtain the characteristic equation of $\tilde{E}$ as follows

$$\begin{vmatrix} \lambda+Q_1 & \dfrac{r\tilde{T}}{T_{\max}} & k_1(1-n_r)\tilde{T} \\ \dfrac{r\tilde{I}}{T_{\max}}-k_2(1-n_r)\tilde{V}e^{-\lambda\tau} & \lambda+Q_2 & -k_2(1-n_r)\tilde{T}e^{-\lambda\tau} \\ 0 & -(1-n_p)N\beta & \lambda+d \end{vmatrix} = 0, \tag{2.21}$$

where

$$Q_1 = \alpha + \frac{2r\tilde{T}+r\tilde{I}}{T_{\max}} + (1-n_r)k_1\tilde{V} - r, \qquad Q_2 = \frac{r\tilde{T}+2r\tilde{I}}{T_{\max}} + \beta - r.$$

Thus, for uninfected equilibrium $E_0 = (T_0, 0, 0)$, the characteristic equation (2.21) reduces to

$$\left(\lambda+\alpha+\frac{2rT_0}{T_{\max}}-r\right)\left(\lambda^2+A_0\lambda+B_0-C_0e^{-\lambda\tau}\right) = 0, \tag{2.22}$$

where

$$\begin{aligned} A_0 &= \frac{rT_0}{T_{\max}}+\beta+d-r = \frac{s}{T_0}+d+\beta-\alpha > 0, \\ B_0 &= d\left(\frac{rT_0}{T_{\max}}+\beta-r\right) = d\left(\frac{s}{T_0}+\beta-\alpha\right) > 0, \\ C_0 &= (1-n_p)(1-n_r)k_2N\beta T_0 > 0. \end{aligned}$$

Clearly, Eq. (2.22) has a characteristic root $\lambda_1 = r-\alpha-\frac{2rT_0}{T_{\max}} = -\frac{s}{T_0}-\frac{rT_0}{T_{\max}} < 0$, and the rest characteristic roots of Eq. (2.22) satisfy following equation

$$\lambda^2+A_0\lambda+B_0-C_0e^{-\lambda\tau} = 0. \tag{2.23}$$

When $\tau = 0$, if $N < N_{\text{cirt}}$, then $B_0 - C_0e^{-\lambda\tau} = B_0 - C_0 > 0$. By Routh–Hurwitz criterion, E_0 is locally asymptotically stable. If $N > N_{\text{cirt}}$, then $B_0 - C_0e^{-\lambda\tau} < 0$. Thus, E_0 is a saddle point with $W^s(E_0) = 2$ and $W^u(E_0) = 1$.

For any time delay $\tau > 0$, we can show that Eq. (2.22) has no root with positive real part as $N < N_{\text{cirt}}$. In fact,assume that $\lambda = u_1 \pm v_1\mathrm{i}$, where $v_1 > 0$ and $\mathrm{i} = \sqrt{-1}$. Substituting $\lambda = u_1 + v_1\mathrm{i}$ into Eq. (2.23) and separating the real and imaginary parts, we obtain

$$\begin{cases} u_1^2 - v_1^2 + A_0u_1 + B_0 = C_0e^{-u_1\tau}\cos v_1\tau, \\ 2u_1v_1 + A_0v_1 = -C_0e^{-u_1\tau}\sin v_1\tau. \end{cases} \tag{2.24}$$

Squaring and adding both equations of (2.24), we have

$$v_1^2(v_1^2+2u_1^2+2A_0u_1+A_0^2-2B_0)+u_1^4+A_0^2u_1^2+2A_0B_0u_1+2A_0u_1^3+2B_0u_1^2 = C_0^2e^{-2u_1\tau}-B_0^2. \tag{2.25}$$

Since $A_0^2-2B_0 = \left(\frac{s}{T_0}+\beta-\alpha\right)^2+d^2 > 0$, the left side of Eq. (2.25) is larger than zero, while the right side of Eq. (2.25) is less than zero (since $u_1 \ge 0$, and if $N < N_{\text{cirt}}$, then $B_0 > C_0$). This results in contradiction. Therefore, $u_1 < 0$, and E_0 is

locally asymptotically stable. When $N > N_{\text{cirt}}$, let $F_1(\lambda) = \lambda^2 + A_0\lambda + B_0 - C_0 e^{-\lambda\tau}$, and note that $F_1(0) = B_0 - C_0 < 0$ and $\lim_{\lambda\to+\infty} F_1(\lambda) = +\infty$. It follows from the continuity of the function $F_1(\lambda)$ on $[0, +\infty)$ that the Eq. (2.23) has at least one positive real root. Hence, the characteristic equation (2.22) has at least one positive real root. Hence, E_0 is unstable. Thus, we obtain the following theorem.

Theorem 2.3. *If $N < N_{\text{cirt}}$, then E_0 is locally asymptotically stable; if $N > N_{\text{cirt}}$, then E_0 is unstable.*

For infected equilibrium $E^* = (T^*, V^*, I^*)$, the characteristic equation (2.21) reduces to

$$F(\lambda, \tau) = \lambda^3 + p_1\lambda^2 + p_2\lambda + p_3 e^{-\lambda\tau} + p_4\lambda e^{-\lambda\tau} + p_5 = 0 \tag{2.26}$$

where

$$\begin{aligned}
p_1 &= \frac{s}{T^*} + \frac{r(T^* + I^*)}{T_{\max}} + \frac{(1-n_r)k_2T^*V^*}{I^*} + d,\\
p_2 &= \frac{s}{T^*}\left(\frac{(1-n_r)k_2T^*V^*}{I^*} + \frac{rI^*}{T_{\max}} + d\right) + \frac{(1-n_r)dk_2T^*V^*}{I^*} + \frac{(1-n_r)rk_2(T^*)^2V^*}{I^*T_{\max}} + \frac{dr(T^* + I^*)}{T_{\max}},\\
p_3 &= \frac{(1-n_r)drk_2T^*V^*}{T_{\max}} + \frac{(1-n_r)^2dk_1k_2T^*(V^*)^2}{I^*} - \frac{(1-n_r)dk_2T^*V^*}{I^*}\left(\frac{s}{T^*} + \frac{rT^*}{T_{\max}}\right),\\
p_4 &= \frac{(1-n_r)rk_2T^*V^*}{T_{\max}} - \frac{(1-n_r)dk_2T^*V^*}{I^*},\\
p_5 &= \frac{(1-n_r)dk_2T^*V^*}{I^*}\left(\frac{s}{T^*} + \frac{rT^*}{T_{\max}}\right) + \frac{drsI^*}{T^*T_{\max}} - \frac{(1-n_r)drk_1T^*V^*}{T_{\max}}.
\end{aligned}$$

When $\tau = 0$, Eq. (2.6) can write as

$$\lambda^3 + p_1\lambda^2 + \bar{p}_2\lambda + \bar{p}_3 = 0,$$

where

$$\begin{aligned}
\bar{p}_2 &= p_2 + p_4 = \frac{s}{T^*}\left(\frac{(1-n_r)k_2T^*V^*}{I^*} + \frac{rI^*}{T_{\max}} + d\right) + \left(\frac{(1-n_r)rk_2T^*V^*}{I^*T_{\max}} + \frac{dr}{T_{\max}}\right)(T^* + I^*) > 0,\\
\bar{p}_3 &= p_3 + p_5 = \frac{drsI^*}{T^*T_{\max}} + (1-n_r)dk_1V^*\left[\beta - r\left(1 - \frac{(k_2/k_1)T^* + I^*}{T_{\max}}\right)\right].
\end{aligned}$$

Hence, by directly calculating, we obtain

$$\begin{aligned}
Q &= p_1\bar{p}_2 - \bar{p}_3\\
&= \frac{s}{T^*}\left(\frac{(1-n_r)k_2T^*V^*}{I^*} + \frac{rI^*}{T_{\max}} + d\right)\left(\frac{s}{T^*} + \frac{r(T^* + I^*)}{T_{\max}} + \frac{(1-n_r)k_2T^*V^*}{I^*}\right) + \frac{ds}{T^*}\left(\frac{(1-n_r)k_2T^*V^*}{I^*} + d\right)\\
&\quad + p_1\left(\frac{(1-n_r)rk_2T^*V^*}{I^*T_{\max}} + \frac{dr}{T_{\max}}\right)(T^* + I^*) - (1-n_r)dk_1V^*\left[\beta - r\left(1 - \frac{(k_2/k_1)T^* + I^*}{T_{\max}}\right)\right].
\end{aligned}$$

If $\tau = 0$, by Routh–Hurwitz criterion, we have the following theorem.

Theorem 2.4. *Assume $N > N_{\text{cirt}}$, if $Q > 0$ and $\beta - r\left(1 - \frac{(k_2/k_1)T^* + I^*}{T_{\max}}\right) > 0$, then the infected equilibrium $E^* = (T^*, I^*, V^*)$ is locally asymptotically stable as $\tau = 0$.*

In order to show that the infected equilibrium $E^* = (T^*, I^*, V^*)$ is locally asymptotically stable for any time delay $\tau > 0$, we firstly introduce a lemma coming from literature [24].

Lemma 2.1. *A set of necessary and sufficient conditions for $E^* = (T^*, I^*, V^*)$ is locally asymptotically stable for all $\tau > 0$ if and only if the following conditions hold,*

(i) *The real parts of all the roots of the characteristic equation (2.26) $F(\lambda, 0) = 0$ are negative.*
(ii) *For all real ω and $\tau > 0$, $F(i\omega, \tau) \neq 0$, where $i = \sqrt{-1}$.*

Next, we apply Lemma 2.1 to show that the infected equilibrium $E^* = (T^*, I^*, V^*)$ is locally asymptotically stable for any time delay $\tau > 0$. By Theorem 2.4, the condition (i) of Lemma 2.1 is easily satisfied. Hence, we only need to verify the condition (ii) of Lemma 2.1.

In fact, if $\omega = 0$, then $F(0, \tau) = p_3 + p_5 \neq 0$ under the condition of Theorem 2.4.

If $\omega \neq 0$, we have

$$F(i\omega, \tau) = -i\omega^3 - p_1\omega^2 + ip_2\omega + p_3 e^{-i\omega\tau} + p_4 i\omega e^{-i\omega\tau} + p_5 = 0. \tag{2.27}$$

Separating the real and imaginary parts of (2.27), we obtain

$$\begin{cases} p_1\omega^2 - p_5 = p_3\cos\omega\tau + p_4\omega\sin\omega\tau, \\ \omega^3 - p_2\omega = -p_3\sin\omega\tau + p_4\omega\cos\omega\tau. \end{cases} \tag{2.28}$$

Squaring and adding both equations of (2.28), we have

$$\omega^6 + (p_1^2 - 2p_2)\omega^4 + (p_2^2 - 2p_1p_5 - p_4^2)\omega^2 + (p_5^2 - p_3^2) = 0. \tag{2.29}$$

Let

$$\eta = \omega^2, \qquad q_1 = p_1^2 - 2p_2, \qquad q_2 = p_2^2 - 2p_1p_5 - p_4^2, \qquad q_3 = p_5^2 - p_3^2. \tag{2.30}$$

Then Eq. (2.29) becomes

$$G_1(\eta) = \eta^3 + q_1\eta^2 + q_2\eta + q_3 = 0. \tag{2.31}$$

In the following, we prove that Eq. (2.31) has no positive root for $q_2 > 0$, $q_3 > 0$, and then equation $F(\mathrm{i}\omega, \tau) = 0$ has no root. In fact, note that $\frac{\mathrm{d}G_1(\eta)}{\mathrm{d}\eta} = 3\eta^2 + 2q_1\eta + q_2$.

Let

$$3\eta^2 + 2q_1\eta + q_2 = 0. \tag{2.32}$$

Then the solutions of Eq. (2.32) are given by

$$\eta_{1,2} = \frac{-q_1 \pm \sqrt{q_1^2 - 3q_2}}{3}.$$

If $q_2 > 0$, then $\sqrt{q_1^2 - 3q_2} < q_1$. Hence, η_1, η_2 are both negative, Eq. (2.32) has no positive root. Therefore, if $G_1(0) = q_3 > 0$, then Eq. (2.31) has no positive root. For any time delay $\tau > 0$, the infected equilibrium $E^* = (T^*, I^*, V^*)$ is locally asymptotically stable. Thus, we now can state the following theorem.

Theorem 2.5. *Assume $N > N_{\mathrm{cirt}}$, if* (i) $Q > 0$, $\beta - r\left(1 - \frac{(k_2/k_1)T^* + I^*}{T_{\max}}\right) > 0$, (ii) $q_2 > 0$, $q_3 > 0$, *then the infected equilibrium $E^* = (T^*, I^*, V^*)$ is locally asymptotically stable for any time delay $\tau > 0$.*

3. Estimates for the length of delay to preserve stability

In this section, we shall apply Nyquist criterion to get estimates on the length of delay for preserving stability of system (1.2).

Lemma 3.1 (*Nyquist Criterion*). *If L is the arc length of a curve encircling the right half-plane, the curve $\bar{P}_L(L)$ will encircle the origin a number of times equal to the difference between the number of poles and the number of zeroes of $\bar{P}_L(L)$ in the right half-plane.*

We consider the system (1.2) and the space of all real valued continuous functions defined on $[-\tau, +\infty]$ satisfying the initial conditions (1.3) on $[-\tau, 0]$. Let $X(t) = T(t) - T^*$, $Y(t) = I(t) - I^*$, $Z(t) = V(t) - V^*$, and we linearize the system (1.2) about its infected equilibrium $E^* = (T^*, I^*, V^*)$ and get

$$\begin{cases} X'(t) = A_1X(t) + A_2Y(t) + A_3Z(t), \\ Y'(t) = B_1X(t) + B_2X(t-\tau) + B_3Y(t) + B_4Z(t-\tau), \\ Z'(t) = C_1Y(t) + C_2Z(t), \end{cases} \tag{3.1}$$

where

$$A_1 = -\alpha - \frac{2rT^* + rI^*}{T_{\max}} - (1-n_r)k_1V^* + r, \qquad A_2 = -\frac{rT^*}{T_{\max}},$$
$$A_3 = -(1-n_r)k_1T^*, \qquad B_1 = -\frac{rI^*}{T_{\max}}, \qquad B_2 = (1-n_r)k_2V^*,$$
$$B_3 = r - \beta - \frac{rT^* + 2rI^*}{T_{\max}}, \qquad B_4 = (1-n_r)k_2T^*,$$
$$C_1 = (1-n_p)N\beta, \qquad C_2 = -d.$$

Let $\bar{X}(L)$, $\bar{Y}(L)$ and $\bar{Z}(L)$ be the Laplace transform of $X(t)$, $Y(t)$ and $Z(t)$, respectively. Then Laplace transform of system (3.1) yields

$$\begin{cases} (L-A_1)\bar{X}(L) = A_2\bar{Y}(L) + A_3\bar{Z}(L) + X(0), \\ (L-B_3)\bar{Y}(L) = B_1\bar{X}(L) + B_2\mathrm{e}^{-L\tau}\bar{X}(L) + B_4\mathrm{e}^{-L\tau}\bar{Z}(t-\tau) + B_2\mathrm{e}^{-L\tau}R_1(L) + B_4\mathrm{e}^{-L\tau}R_2(L) + Y(0), \\ (L-C_2)\bar{Y}(L) = C_1\bar{Y}(L) + Z(0), \end{cases}$$

where

$$R_1(L) = \int_{-\tau}^{0} \mathrm{e}^{-L\tau}X(t)\mathrm{d}t, \qquad R_2(L) = \int_{-\tau}^{0} \mathrm{e}^{-L\tau}Z(t)\mathrm{d}t.$$

Note that if $\bar{X}(L)$ has poles with positive real parts, then the inverse Laplace transform of $\bar{X}(L)$ will have terms which exponentially increase with time. Thus, if $E^* = (T^*, I^*, V^*)$ is locally asymptotically stable, then it is necessary and sufficient that all poles of $\bar{X}(L)$ have negative real parts. Following along the lines of [25] and using Nyquist criterion, it can be shown that the conditions for local asymptotic stability of $E^* = (T^*, I^*, V^*)$ are given by

$$\operatorname{Im} H(\mathrm{i}u_0) > 0, \tag{3.2}$$

$$\operatorname{Re} H(\mathrm{i}u_0) = 0, \tag{3.3}$$

where $H(s) = L^3 + p_1L^2 + p_2L + p_3\mathrm{e}^{-L\tau} + p_4L\mathrm{e}^{-L\tau} + p_5$, and u_0 is the smallest positive root of Eq. (3.3). Thus the conditions (3.2) and (3.3) in our case become

$$-p_1u_0^2 + p_5 = -p_3\cos u_0\tau - p_4u_0\sin u_0\tau, \tag{3.4}$$

$$-u_0^3 + p_2u_0 > p_3\sin u_0\tau - p_4u_0\cos u_0\tau. \tag{3.5}$$

To get further estimate of the length of delay, we need the following conditions, which are sufficient to guarantee stability.

$$-p_1u^2 + p_5 = -p_3\cos u\tau - p_4u\sin u\tau, \tag{3.6}$$

$$-u^3 + p_2u > p_3\sin u\tau - p_4u\cos u\tau. \tag{3.7}$$

Recall that E^* will be stable if the inequality (3.7) holds at $u = u_0$, where u_0 is the smallest positive root of the Eq. (3.7). Our aim will be to find an upper bound $\hat{u}$ of u_0, independent of τ, and then to estimate τ so that (3.8) holds for all values of $u \in [0, \hat{u}]$, and in particular at $u = u_0$.

Since the right side of (3.6) is always less than or equal to $\sqrt{p_3^2 + p_4^2u^2}$, the unique positive solution of $-p_1u^2 + p_5 = \sqrt{p_3^2 + p_4^2u^2}$, denoted by $\hat{u}$, is clearly greater than or equal to u_0. By straightforward calculation, we obtain

$$\hat{u} = \begin{cases} \sqrt{\dfrac{(2p_1p_5 + p_4^2) + \sqrt{p_4^4 + 4p_1p_5p_4^2 + 4p_1^2p_3^2}}{2p_1^2}}, & p_3 \neq p_5, \\ \dfrac{\sqrt{2p_1p_5 + p_4^2}}{p_1}, & p_3 = p_5. \end{cases} \tag{3.8}$$

Note that $\hat{u}$ is independent of τ. We now need an estimate on τ so that Eq. (3.8) holds for all $u \in [0, \hat{u}]$. Rewriting (3.7) as

$$u^2 < p_2 - \frac{p_3\sin u\tau}{u} + p_4\cos u\tau. \tag{3.9}$$

Note that at $\tau = 0$, inequality (3.9) becomes $u^2 < p_2 + p_4$. Hence, (3.9) holds when $\tau = 0$ and $u = u_0$. Substituting u^2 from (3.6) into (3.9), we have

$$(p_3 - p_1p_4)\cos u\tau + \left(p_4u + \frac{p_1p_3}{u}\right)\sin u\tau < p_1p_2 - p_5. \tag{3.10}$$

Form (3.10), we obtain

$$(p_3 - p_1p_4)(\cos u\tau - 1) + \left(p_4u + \frac{p_1p_3}{u}\right)\sin u\tau < p_1(p_2 + p_4) - (p_5 + p_3) \triangleq \sigma. \tag{3.11}$$

Denote the left of (3.11) by $\Phi(\tau, u)$. Using the inequality $\sin\tau u \leq \tau u$ and $1 - \cos\tau u = 2\sin^2\frac{\tau u}{2} \leq \frac{\tau^2u^2}{2}$, we obtain

$$\Phi(\tau, u) \leq \psi(\tau, u) = \frac{1}{2}\left|p_3 - p_1p_4\right|\tau^2u^2 + (\left|p_4\right|u^2 + p_1\left|p_3\right|)\tau. \tag{3.12}$$

Noting that for $u \in [0, \hat{u}]$, we have $\Phi(\tau, u) \leq \psi(\tau, u) \leq \psi(\tau, \hat{u})$. Hence, if $\psi(\tau, \hat{u}) \leq \sigma$, then $\Phi(\tau, \hat{u}) \leq \sigma$. Let τ^* denote the unique positive root of $\psi(\tau, \hat{u}) = \sigma$, that is

$$\tau^* = \frac{1}{2a_1}\left(-a_2 + \sqrt{a_2^2 + 4a_1\sigma}\right), \tag{3.13}$$

where $a_1 = |p_3 - p_1p_4|\,\hat{u}^2$, $a_2 = |p_4|\,\hat{u}^2 + p_1\,|p_3|$. Then for $\tau < \tau^*$, the Nyquist criterion holds, and τ^* is the estimate for the length of delay for which stability is preserved. Thus, we obtain the following theorem.

Theorem 3.1. *Suppose that $N > N_{\text{cirt}}$, if there exists a delay τ^* satisfying (3.13), then for any τ with $0 \leq \tau \leq \tau^*$, $E^* = (T^*, I^*, V^*)$ is locally asymptotically stable.*

4. Hopf bifurcation analysis

In this section, we wish to obtain criteria for preservation of stability or instability. Furthermore, we shall determine criteria for Hopf bifurcation to occur using the time delay τ as the bifurcation parameter.

Note that it is the sign of the real parts of the solutions λ of Eq. (2.26) that determines the stability of the infected equilibrium $E^* = (T^*, I^*, V^*)$. Letting $\lambda = b + v\mathrm{i}$ and substituting into Eq. (2.26), gives the following equation

$$\begin{cases} b^3 - 3bv^2 + p_1(b^2 - v^2) + p_2b + p_5 = -[(p_3 + p_4b)\cos v\tau + p_4v\sin v\tau]\mathrm{e}^{-b\tau}, \\ -v^3 + 3b^2v + 2p_1bv + p_2v = [(p_3 + p_4b)\sin v\tau - p_4v\cos v\tau]\mathrm{e}^{-b\tau}. \end{cases} \tag{4.1}$$

We now investigate λ, and thus b and v are considered as functions of the delay τ. Since the change of stability of $E^* = (T^*, I^*, V^*)$ will occur at any values of τ for which $b(\tau) = 0$, we let $\hat{\tau}$ be such that $b(\tau) = 0$, that is, $b(\hat{\tau}) = 0$. Thus the Eq. (4.1) reduces to

$$\begin{cases} p_1\hat{v}^2 - p_5 = p_3\cos\hat{v}\hat{\tau} + p_4\hat{v}\sin\hat{v}\hat{\tau}, \\ \hat{v}^3 - p_2\hat{v} = p_4\hat{v}\cos\hat{v}\hat{\tau} - p_3\sin\hat{v}\hat{\tau}, \end{cases} \tag{4.2}$$

where $\hat{v} = v(\hat{\tau})$. Squaring and adding the equations of (4.2) and simplifying, we obtain an equation for $\hat{v}$ of the following form

$$\hat{v}^6 + (p_1^2 - 2p_2)\hat{v}^4 + (p_2^2 - 2p_1p_5 - p_4^2)\hat{v}^2 + (p_5^2 - p_3^2) = 0. \tag{4.3}$$

Differentiating (4.1) with respect to τ, and setting $\tau = \hat{\tau}$, $v = \hat{v}$, $b = 0$, we obtain

$$\begin{cases} g\dfrac{\mathrm{d}b(\hat{\tau})}{\mathrm{d}\tau} + h\dfrac{\mathrm{d}v(\hat{\tau})}{\mathrm{d}\tau} = m, \\ g\dfrac{\mathrm{d}v(\hat{\tau})}{\mathrm{d}\tau} - h\dfrac{\mathrm{d}b(\hat{\tau})}{\mathrm{d}\tau} = n, \end{cases} \tag{4.4}$$

where

$$\begin{cases} g = 3\hat{v}^2 - p_2 + p_4\hat{v}\hat{\tau}\sin\hat{v}\hat{\tau} + (p_3\hat{\tau} - p_4)\cos\hat{v}\hat{\tau}, \\ h = 2p_1\hat{v} + (p_3\hat{\tau} - p_4)\sin\hat{v}\hat{\tau} - p_4\hat{v}\hat{\tau}\cos\hat{v}\hat{\tau}, \\ m = p_4\hat{v}^2\cos\hat{v}\hat{\tau} - p_3\sin\hat{v}\hat{\tau}, \\ n = -p_4\hat{v}^2\sin\hat{v}\hat{\tau} - p_3\hat{v}\cos\hat{v}\hat{\tau}. \end{cases} \tag{4.5}$$

Solving (4.4), we have

$$\frac{\mathrm{d}b(\hat{\tau})}{\mathrm{d}\tau} = \frac{gm - hn}{g^2 + h^2}. \tag{4.6}$$

From (4.5), after some simplification, we obtain

$$gm - hn = [(2p_1p_4 - 3p_3) + p_2p_3\hat{v}]\sin\hat{v}\hat{\tau} + [(2p_1p_3 - p_2p_4) + 3p_4\hat{v}^4]\cos\hat{v}\hat{\tau} - p_2^2\hat{v}^2. \tag{4.7}$$

Substituting (4.2) into (4.7), we get

$$\begin{aligned} gm - hn &= 3\hat{v}^3(p_4\hat{v}\cos\hat{v}\hat{\tau} - p_3\sin\hat{v}\hat{\tau}) + 2p_1\hat{v}^2(p_3\cos\hat{v}\hat{\tau} + p_4\hat{v}\sin\hat{v}\hat{\tau}) - p_2\hat{v}(p_4\hat{v}\cos\hat{v}\hat{\tau} - p_3\sin\hat{v}\hat{\tau}) \\ &= 3\hat{v}^6 + 2(p_1^2 - 2p_2)\hat{v}^4 + (p_2^2 - 2p_1p_5 - p_4^2)\hat{v}^2 \\ &= \hat{v}^2\left(3(\hat{v}^2)^2 + 2q_1(\hat{v}^2) + q_2\right). \end{aligned} \tag{4.8}$$

Let

$$G(x) = x^3 + q_1x^2 + q_2x + q_3, \tag{4.9}$$

which is the left side of (4.3) with $x = \hat{v}^2$, where q_1, q_2, q_3 is defined in (2.30). Then $G(\hat{v}^2) = 0$, and from (4.8) and (4.9), we obtain

$$\frac{\mathrm{d}b(\hat{\tau})}{\mathrm{d}\tau} = \frac{\hat{v}^2}{g^2+h^2}\frac{\mathrm{d}G(\hat{v}^2)}{\mathrm{d}x}. \tag{4.10}$$

Clearly, $\frac{\mathrm{d}b(\hat{\tau})}{\mathrm{d}\tau}$ has the same sign as $\frac{\mathrm{d}G(\hat{v}^2)}{\mathrm{d}x}$. Hence, we can describe criteria for preservation of instability (stability) geometrically as follows:

(H_1) If the polynomial $G(x)$ has no positive roots, there can be no change of stability.

(H_2) If the polynomial $G(x)$ is decreasing (increasing) at all of its positive roots, stability (instability) is preserved. Now we proceed to analyze $G(x)$. By directly calculating, we have

$$\begin{aligned} q_1 &= p_1^2 - 2p_2 \\ &= \left(\frac{s}{T^*}\right)^2 + \left(\frac{r(T^*+I^*)}{T_{\max}}\right)^2 + \left(\frac{(1-n_r)dk_2T^*V^*}{I^*}\right)^2 + d^2 + \frac{2rsT^*}{T^*T_{\max}} + \frac{2(1-n_r)rk_2I^*T^*V^*}{I^*T_{\max}} > 0. \end{aligned}$$

If $G(0) = q_3 > 0$, then $G(x)$ will either have two positive roots or no positive roots. We consider the following two cases in order that $G(x)$ may have no positive roots.

(i) If $q_2 > 0, q_3 > 0$, then $G'(x) > 0$ for all $x > 0$. Obviously, the above (H_1) holds. Namely, stability or instability will be preserved in this case.

(ii) Consider $q_2 < 0, q_3 > 0$. Let $G'(x_c) = 3x_c^2 + 2q_1x_c + q_2 = 0$ and $x_c > 0$, we have

$$x_c = \frac{-q_1 + \sqrt{q_1^2 - 3q_2}}{3}. \tag{4.11}$$

Substituting (4.11) into (4.9), we have

$$G(x_c) = \frac{2q_1^3 - 9q_1q_2 + 27q_3}{27} - \frac{2(q_1^2 - 9q_1q_2)^{3/2}}{27}. \tag{4.12}$$

Hence, $G(x_c) > 0$ if and only if

$$2q_1^3 - 9q_1q_2 + 27q_3 > 2(q_1^2 - 9q_1q_2)^{3/2}. \tag{4.13}$$

Thus, the polynomial $G(x)$ has also no positive roots in the case (ii) if (4.13) holds. Summarizing the above discussion, we have the following conclusions.

Theorem 4.1. *Assume that $N > N_{\mathrm{cirt}}$ holds, if either*

(i) $q_2 > 0, q_3 > 0$ *or*
(ii) $q_2 < 0, q_3 > 0$ *and* (4.13) *holds.*

Then E^* remains stable (unstable) for all $\tau > 0$ if the infected equilibrium E^* is stable (unstable) at $\tau = 0$.

If $G(0) = q_3 \le 0$, then $G(x)$ has at most one positive root. Note that if $G(x)$ has only one positive root, then $G(x)$ must be increasing at this positive root. Thus, we have the following theorem.

Theorem 4.2. *Assume that $N > N_{\mathrm{cirt}}$ and $G(0) = q_3 \le 0$ holds, if E^* is unstable at $\tau = \tau_0 > 0$, then E^* remains unstable for all $\tau > \tau_0$.*

Note that if the polynomial $G(x)$ have two or three distinct positive roots, the above criterion (H_2) cannot hold, since it is decreasing at one root and increasing at the other. Hence, stability cannot be preserved if $G(x_0) < 0$ for some $x_0 > 0$. In particular, a Hopf bifurcation may occur as τ passes through critical value τ_0.

Next, we assume that $Q > 0$, $\beta - r\left(1 - \frac{(k_2/k_1)T^*+I^*}{T_{\max}}\right) > 0$ and $q_3 < 0$. For $Q > 0$ and $\beta - r\left(1 - \frac{(k_2/k_1)T^*+I^*}{T_{\max}}\right) > 0$, by Theorem 2.3, we have shown that the infected equilibrium $E^* = (T^*, I^*, V^*)$ is stable at $\tau = 0$. The cubic equation (4.3) in $\hat{v}^2$ has one or more positive real roots $\hat{v}_0^2$, since when $\hat{v} = 0$, the left side of Eq. (4.3) $q_3 = p_5^2 - p_3^2 < 0$, and $\lim_{\hat{v}\to+\infty} G(x) > 0$. Namely, the characteristic equation (2.6) has a pair of purely imaginary roots, denoted by $\pm\mathrm{i}\hat{v}_0$. Thus from (4.2), we can solve for $\hat{\tau}$, which is of the form

$$\hat{\tau}_n = \frac{1}{\hat{v}_0}\arccos\frac{p_4\hat{v}_0^4 + (p_1p_3 - p_2p_4)\hat{v}_0^2 - p_3p_5}{p_3^2 + p_4^2\hat{v}_0^2} + \frac{2n\pi}{\hat{v}_0}, \quad n = 0, 1, 2, \ldots. \tag{4.14}$$

If $\hat{v}_0$ is the first positive root of Eq. (4.3), it follows from (4.10) that

$$\frac{\mathrm{d}b(\hat{\tau}_0)}{\mathrm{d}\tau} = \frac{\hat{v}_0^2}{g^2+h^2}\frac{\mathrm{d}G(\hat{v}_0^2)}{\mathrm{d}x} > 0.$$

By Butlers lemma [25] and the Hopf bifurcation theorem [26], we have the following conclusions.

Table 1
List of parameters.

Variables	Definition	Data 1 values	Data 2 values	Units
T	Uninfected T-cells concentration	900	900	cells mm^{-3}
I	Productively infected T-cells concentration	0.1	0.1	cells mm^{-3}
V	Infectious virus concentration	0.1	0.1	virions mm^{-3}
V_N	Non-infectious virus concentration			virions mm^{-3}
Parameters				
s	T-cells source term	10	0.1	cells day^{-1} mm^{-3}
α	Death rate of healthy T cells	0.02	0.2	day^{-1}
β	Death rate of infected T cells	0.26	1	day^{-1}
d	Clearance rate of virus	2.4	2.4	day^{-1}
r	Growth rate of T cells	0.03	0.95	day^{-1} mm^{-3}
$T_{\max}$	Carrying capacity of T cells	1500	1500	mm^{-3}
k_1	Viral infectivity rate	2.5×10^{-4}	2.5×10^{-4}	virions day^{-1} mm^{-3}
k_2	Rate infected cells becomes active	2×10^{-4}	2×10^{-4}	virions day^{-1} mm^{-3}
N	Bursting term for viral production after lysis	500	200	virions/cell
n_r	Reverse transcriptase inhibitor efficacy	0.6	0.6	
n_p	Protease inhibitor efficacy	0.7	0.7	

Theorem 4.3. *Assume that* $N > N_{\text{cirt}}$, *if* $Q > 0$, $\beta - r\left(1 - \frac{(k_2/k_1)T^* + I^*}{T_{\max}}\right) > 0$ *and* $q_3 < 0$ *hold, and* $\hat{v}_0$ *is the first positive root of Eq. (4.3), then the infected equilibrium* E^* *is locally asymptotically stable when* $\tau < \hat{\tau}_0$ *and unstable when* $\tau > \hat{\tau}_0$, *where*

$$\hat{\tau}_0 = \frac{1}{\hat{v}_0} \arccos \frac{p_4\hat{v}_0^4 + (p_1p_3 - p_2p_4)\hat{v}_0^2 - p_3p_5}{p_3^2 + p_4^2\hat{v}_0^2}. \tag{4.15}$$

Furthermore, when $\tau = \hat{\tau}_0$, *system (1.2) undergoes a Hopf bifurcation to periodic solutions at the infected state* E^*.

5. Numerical simulations

In order to check the main results of this paper, we use Matlab software to carry out some numerical simulations. For the simulations, we use a similar set of parameter values as those in [9–14,16,15,17–20].

Firstly, considering Data 1 values in Table 1, we find that $N_{\text{crit}} = 96.1538 < N, Q = 0.3904 > 0, \beta - r(1 - \frac{(k_2/k_1)T^* + I^*}{T_{\max}}) = 0.2336 > 0, q_2 = 0.02541 > 0$, and $q_3 = 0.001073 > 0$. If choose $\tau = 2$, which satisfies condition of Theorem 2.5, then the trajectories converge at the infected equilibrium $E^* = (180.2751, 37.6081, 611.1311)$. We obtain the time histories and the phase trajectories of system (1.2) as shown in Fig. 1. Under the condition of Theorem 2.5, the infected steady state is locally asymptotically stable independent of the size of the delay, though the time delay does cause transient oscillations in all components. Computer simulations confirm our analysis. Biologically, this implies that the intracellular delay can cause the cell and virus populations to fluctuate in the early stage of infection, in a longer term they will converge to the infected steady state values.

Furthermore, we numerically illustrate the change of the stability and the occurrence of a Hopf bifurcation by varying the time delay. We consider parameters listed in Data 2 of Table 1. Here $N_{\text{crit}} = 67.5551 < N, Q = 1.3812 > 0, \beta - r(1 - \frac{(k_2/k_1)T^* + I^*}{T_{\max}}) = 0.2529 > 0, q_1 = 5.9540 > 0, q_2 = 1.3734 > 0$ and $q_3 = -0.1379 < 0$, which satisfy conditions of Theorem 4.3. Hence, we shall utilize these values to work out the critical time delay preserving stability or not. For this, substituting these values into Eq. (4.3), we have

$$\hat{v}^6 + 5.9540\hat{v}^4 + 1.3734\hat{v}^2 - 0.1379 = 0. \tag{5.1}$$

Solving (5.1), we get one positive value of $\hat{v}_0 = 0.2747$. Substituting $\hat{v}_0 = 0.2747$ into (4.15), we obtain the critical time delay $\hat{\tau}_0 = 1.5663$. Hence, the infected equilibrium E^* remains stable for $\tau < \hat{\tau}_0$ (see Fig. 2), while E^* bifurcates into a periodic solution at $\hat{\tau}_0$ and remains unstable for $\tau > \hat{\tau}_0$ (see Fig. 3). Fig. 3 depict the bifurcation is supercritical and the bifurcating periodic solution is orbitally asymptotically stable.

In particular, comparing with the system in [20] only including simple Logistic proliferation term for healthy $CD4^+$ T cells, denoted by system $(*)$, if choose parameters listed in Data 2 of Table 1 and $\tau = 0.5$, we will find that the total number of $CD4^+$ T cells (healthy and infected) in system (1.2) is larger while the number of HIV virions in system (1.2) is smaller (see Fig. 4). Biologically, it suggests that the proliferation of infected $CD4^+$ T cells increases the possibility that HIV infection becomes persistent.

6. Discussion

In this paper, we analyze a HIV pathogenesis model including antiretroviral therapy, an intracellular delay and full Logistic proliferation term of $CD4^+$ T cells (healthy and infected). Similar to the analysis in [23], we obtain a critical number N_{crit} on

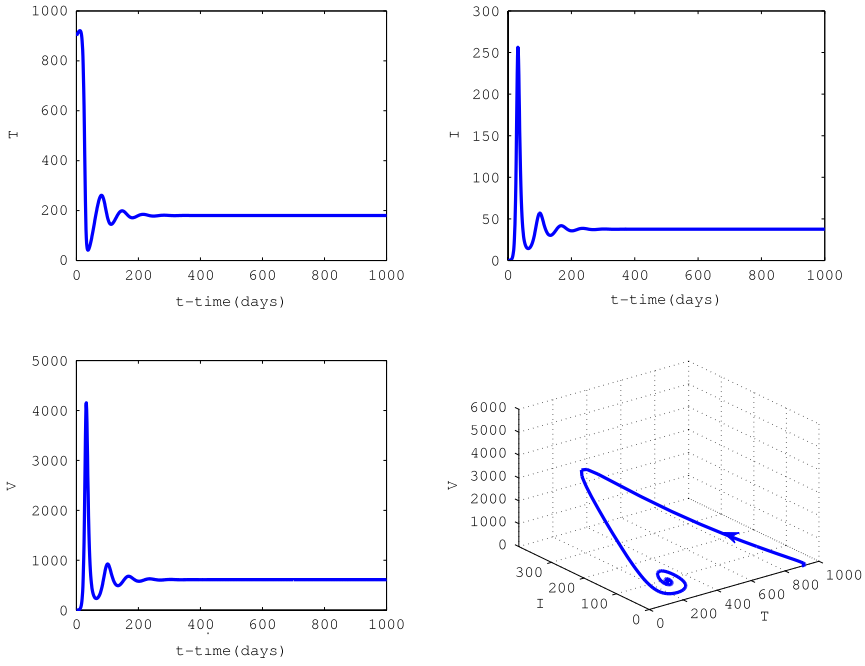

Fig. 1. The infected equilibrium E^* is asymptotically stable for $\tau = 2$.

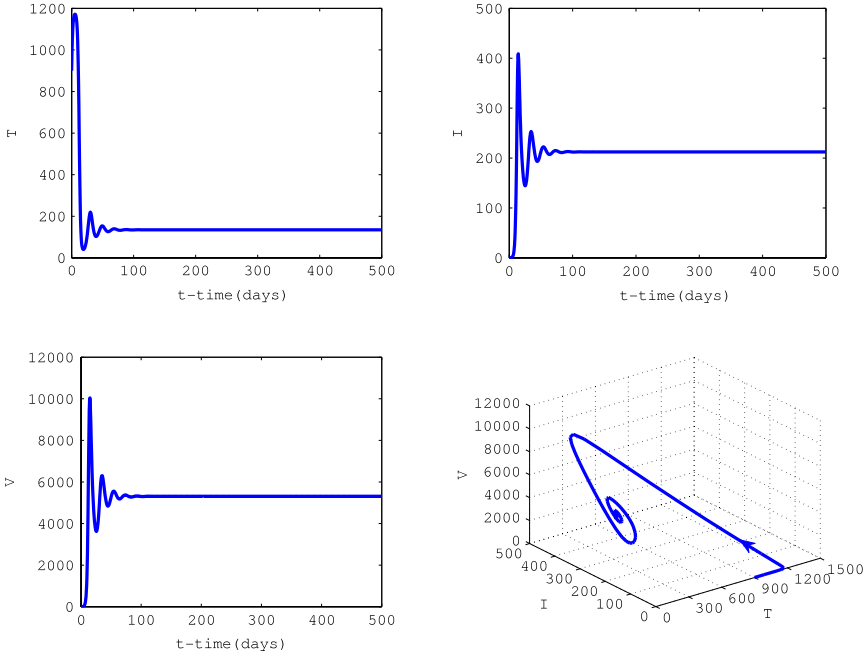

Fig. 2. The infected equilibrium E^* is asymptotically stable for $\tau = 0.2 < \hat{\tau}_0$.

the number of HIV virions released per infectious CD4$^+$ T cell in order for infection to be sustained. Analyzing the critical number in [20] for models only including simple Logistic proliferation term for healthy CD4$^+$ T cells, we obtain its critical number of HIV virions released per infection CD4$^+$ T cell during its life time is $N^*_{\text{crit}} = \frac{d}{(1-n_p)(1-n_r)k_2\beta T_0}$. If chosen data follow the clinically actual state, we will find $N^*_{\text{crit}} > N_{\text{crit}}$. Biologically, it suggests that the proliferation of infected CD4$^+$ T cells increases the possibility that HIV infection becomes persistent. Furthermore, the influence of the time delay on the stability of equilibrium states is discussed. We first show that the local stability of the uninfected steady state is independent of the size of the delay (see Theorem 2.3). We then obtain sufficient conditions for the stability of the infected equilibrium E^*, independent of the size of the delay (see Theorem 2.5). By utilizing the Nyquist criterion, we also obtain the maximum

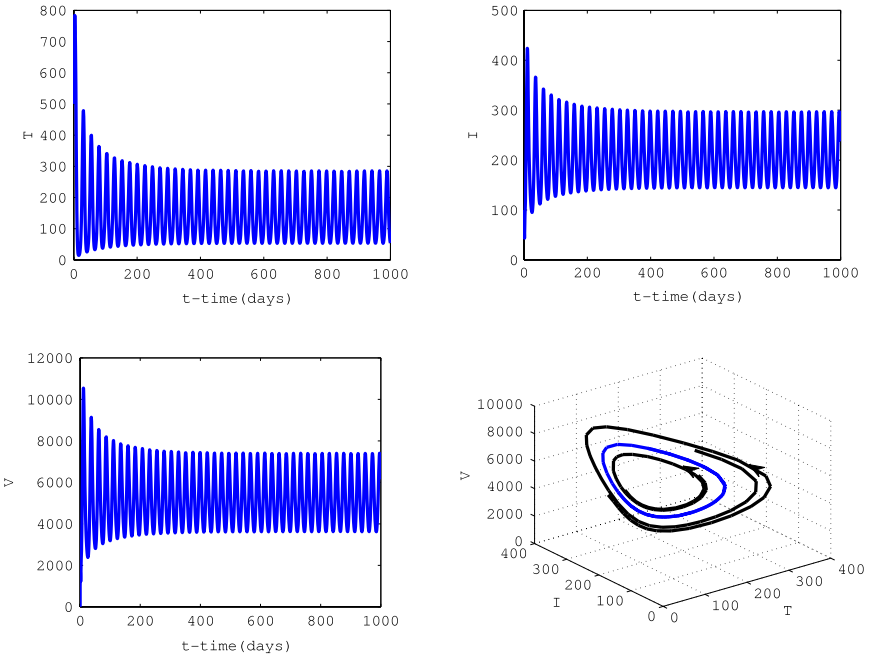

Fig. 3. The infected equilibrium E^* bifurcating into a periodic solution remains unstable for $\tau = 1.7 > \hat{\tau}_0$.

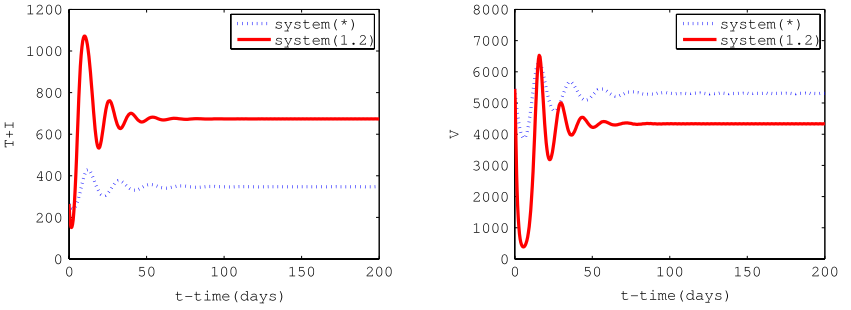

Fig. 4. The total number of CD4$^+$ T cells (healthy and infected) in system (1.2) is larger than system $(*)$ while the number of HIV virions in system (1.2) is smaller than system $(*)$.

value of delay length for which the infected equilibrium E^* will preserve asymptotically stable. Finally, we investigate the delay-induced oscillations that could occur via instability. Specially, the unstable infected equilibrium E^* bifurcates into a small amplitude periodic solution as τ passes through critical value $\hat{\tau}_0$, where $\hat{\tau}_0$ is given by Eq. (4.15). This clearly shows the importance of time delay on HIV dynamics under the influence of antiretroviral drug treatment.

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