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Analysis of global stability and bifurcation for an HIV infection model with cell to cell transmission

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Abstract

Cell-to-cell infection cannot be ignored in the development of HIV in the host. The mathematical difficulty in (Wang et al. in J. Biol. Dyn. 11:455–483, 2016) is mainly due to the assumption of the equality of two parameters, in which they are the proportions of infection that lead to latency caused by virus-to-cell infection and cell-to-cell transmission, respectively. To overcome the restricted condition, we propose a more general HIV development model with virus-to-cell and cell-to-cell infection patterns with logistic growth and saturation incidence. By constructing a proper Lyapunov function we obtain the global stability of the disease-free equilibrium without this restricted condition, thereby the main result in (Wang et al. in J. Biol. Dyn. 11:455–483, 2016) removing the restricted condition is proved by using our method even if two parameters are not equal. We also investigate the existence of Hopf bifurcation of diseased equilibrium in four cases.

Keywords: HIV infection model; Delay differential equation; Global stability; Hopf bifurcation; Basic reproduction number

1 Introduction

Human immunodeficiency virus (HIV) attacks the immune system of a human body. The major target of HIV infection is a class of lymphocytes, or white blood cells, known as CD4+ T cells. Because of the central role of CD4+ T cells in immune regulation, their depletion has widespread detrimental effects on the functioning of the entire immune system and results in the immunodeficiency that characterizes AIDS [1].

To understand the HIV infection mechanism in hosts, various mathematical models have been formulated and extensively studied, some of which focus on infection between viruses and cells [2–6]. However, HIV can be transmitted efficiently through viral synapses (VSs) in lymphocytes [7–16]. It is more effective to spread the virus directly between cells than from virus to cell [14]. Although the cell-to-cell transmission is the main mode of rapid viral development [17], the underlying mechanism is not completely clear and attracts the attention of many researchers.

For the models with two transmission modes, Li [18] studied the cell-to-cell propagation model and analyzed the global dynamic properties and the existence of Hopf bifurcation.

A differential equation model of an HIV-1 infection with logistic growth for target cells, time delay, the classical cell-free infection, and the direct cell-to-cell transfer infection modes was put forward by Hu et al. [19]. A within-host viral infection delay model with two transmission modes was investigated in [20], and results showed that delay may destabilize the infected steady state and lead to Hopf bifurcation. Zhang and Liu [21] also put forward an age-structured HIV infection model with cell-to-cell transmissions and found that the model has a nontrivial periodic solution bifurcating from the positive equilibrium. Lai and Zou [22, 23] developed some models that incorporate two models of viral spreading with and without the logistic target cell growth and obtained the existence of Hopf bifurcation. Yang et al. [24] also studied a within-host viral infection model with two transmission modes and obtained some results on global stability of the equilibrium point. Especially, Wang, Tang, et al. [25] put forward an HIV latent infection model incorporating both the cell-free virus infection and cell-to-cell transmission. Their model is as follows:

$$\left\{\begin{aligned} \frac{dT(t)}{dt} &= s - d_T T(t) - \beta T(t)V(t) - kT(t)I(t), \\ \frac{dL(t)}{dt} &= f\beta T(t-\tau_1)V(t-\tau_1)e^{-\delta_1\tau_1} + \eta kT(t-\tau_1)I(t-\tau_1)e^{-\delta_1\tau_1} \\ &\quad -(\alpha+\delta_L)L(t), \\ \frac{dI(t)}{dt} &= (1-f)\beta T(t-\tau_2)V(t-\tau_2)e^{-\delta_1\tau_2} + (1-\eta)kT(t-\tau_2)I(t-\tau_2) \\ &\quad \times e^{-\delta_1\tau_2} - \delta I(t) + \alpha L(t), \\ \frac{dV(t)}{dt} &= N\delta I(t) - cV(t). \end{aligned}\right. \tag{1}$$

They obtained the global stability of the disease-free and disease equilibrium under the condition $f = \eta$ and consistent persistent results. However, in reality, the constants f and η may be not equal. In addition, the actual incidence rates are probably not strictly linear. For example, the following viral model took into account the nonlinear incidence, that is, the saturated mass action $\frac{\beta TV}{1+\alpha V}$ [26]:

$$\left\{\begin{aligned} \frac{dT(t)}{dt} &= s - d_T T(t) + aT\Big(1-\frac{T}{T_{\max}}\Big) - \frac{\beta T(t)V(t)}{1+bV(t)}, \\ \frac{dL(t)}{dt} &= \frac{f\beta T(t-\tau_1)V(t-\tau_1)e^{-\delta_1\tau_1}}{1+bV(t-\tau_1)} - (\alpha+\delta_L)L(t), \\ \frac{dI(t)}{dt} &= \frac{(1-f)\beta T(t-\tau_2)V(t-\tau_2)e^{-\delta_1\tau_2}}{1+bV(t-\tau_2)} - \delta I(t) + \alpha L(t), \\ \frac{dV(t)}{dt} &= N\delta I(t) - cV(t). \end{aligned}\right. \tag{2}$$

The symbols have the same meanings as in system (1). Obviously, model (2) does not reflect the phenomenon of cell-to-cell transmission.

To obtain the stability of disease-free equilibrium and endemic equilibrium without the restriction condition $f = \eta$ by constructing a proper Lyapunov function, in this paper, we propose the following more general HIV infection model (3) with both virus-to-cell infection and cell-to-cell transmission inspired by the saturation incidence and logistic growth terms to model (2):

$$\left\{\begin{aligned} \frac{dT(t)}{dt} &= s + aT\Big(1-\frac{T}{T_{\max}}\Big) - d_T T(t) - \frac{\beta T(t)V(t)}{1+bV(t)} - \frac{kT(t)I(t)}{1+nI(t)}, \\ \frac{dL(t)}{dt} &= \frac{f\beta T(t-\tau_1)V(t-\tau_1)e^{-\delta_1\tau_1}}{1+bV(t-\tau_1)} + \frac{\eta kT(t-\tau_1)I(t-\tau_1)e^{-\delta_1\tau_1}}{1+nI(t-\tau_1)} - (\alpha+\delta_L)L(t), \\ \frac{dI(t)}{dt} &= \frac{(1-f)\beta T(t-\tau_2)V(t-\tau_2)e^{-\delta_1\tau_2}}{1+bV(t-\tau_2)} + \frac{(1-\eta)kT(t-\tau_2)I(t-\tau_2)e^{-\delta_1\tau_2}}{1+nI(t-\tau_2)} - \delta I(t) \\ &\quad +\alpha L(t), \\ \frac{dV(t)}{dt} &= N\delta I(t) - cV(t), \end{aligned}\right. \tag{3}$$

where $T(t)$ denotes the concentration of uninfected CD4+ T cells at time t, $L(t)$ represents the concentration of latently infected T cells at time t, $I(t)$ is the concentration of productively infected T cells, and $V(t)$ denotes the concentration of virions in plasma. The model assumes that uninfected CD4+ T cells are produced at a rate s, and they are infected by free virus at a rate β or by direct cell-to-cell transmission at a rate k. The parameter a is a logistic growth rate of the CD4+ T-cells, $T_{\max}$ is the carrying capacity of the T-cell population, and d_T is the per capita death rate of uninfected CD4+ T cells. The constants f, $\eta \in (0,1)$ are the proportions of infection that lead to latency. Latently infected cells die at a rate δ_L per cell, and productively infected cells die at a rate δ per cell. Latently infected cells can be activated by their relevant antigens to become productively infected cells at a rate α. The factor N is the viral burst size, representing the total number of virus released by one infected cell during its lifespan, and c is the viral clearance rate. The parameter δ_1 is the death rate of infected cells in which viral DNA has not integrated into the DNA of the host cell. The time τ_1 represents the time from viral entry to viral DNA integrating into the host cell DNA, and τ_2 represents the time from viral entry to viral production. It was clear that $\tau_1 < \tau_2$ according to the viral life cycle. Thus $e^{-\delta_1\tau_1}$ and $e^{-\delta_1\tau_2}$ represent the probabilities of an infected cell will survive τ_1 and τ_2 ages, respectively.

Now let us explain each item on the right side of model (3) in a biological sense. Since the concentration of uninfected T cells at time is $T(t)$, so $s + aT(1 - \frac{T}{T_{max}})$ is the growth rate including natural production and cell division. Since CD4+ T cells can be infected by HIV virions, the fourth term on the right-hand side of the first equation means that CD4+ T cells decrease at rate $-\frac{\beta T(t)V(t)}{1+bV(t)}$, then leading to become latency cells at a proportion f and infected T cells at a proportion $1-f$, respectively. Thus the first terms on the right-hand sides of the second and third equations are formed according to the probabilities $e^{-\delta_1\tau_1}$ and $e^{-\delta_1\tau_2}$, respectively. Similarly, CD4+ T cells can be also directly transmitted by infected T cells with transmission rate $-\frac{\beta T(t)V(t)}{1+bV(t)}$ (the fifth term on the right-hand side of the first equation), then becoming latency cells at proportion η and infected T cells at proportion $1 - \eta$, respectively. Hence the second terms on the right-hand sides of the second and third equations are formed according to the above two probabilities. Because latently infected cells can be converted to productively infected cells at a rate α, the last terms on the right-hand sides of the second and third equations are determined by $\alpha L(t)$. The first term $N\delta I(t)$ on the right-hand side of the fourth equation represents the virus release rate by infected cells. The last terms on the right-hand sides of the last three equations represent the mortality rate of the corresponding cells.

This paper is organized as follows. In the next section, we give the derivation of the nonnegativity, boundedness, the basic reproductive number, and positive equilibrium point of the proposed model. By constructing a Lyapunov function the results of the local and global stability of the disease-free equilibrium without condition $f = \eta$ will be proved in Sect. 4. We study the Hopf bifurcation from the endemic equilibrium in Sect. 5. The last section contains the conclusions.

2 Invariance

We denote the Banach space of continuous function $\varphi : [-\max\{\tau_1,\tau_2\}, 0] \to R^4$ with norm

$$\|\varphi\| = \sup\{|\varphi_1(\theta)|, |\varphi_2(\theta)|, |\varphi_3(\theta)|, |\varphi_4(\theta)|\}$$

by C, where $\varphi = (\varphi_1, \varphi_2, \varphi_3, \varphi_4)$. Further, let

$$C_+ = \{\varphi = (\varphi_1(\theta), \varphi_2(\theta), \varphi_3(\theta), \varphi_4(\theta)) : \varphi_i > 0, \forall\theta \in [-\max\{\tau_1, \tau_2\}, 0], i = 1, 2, 3, 4\}.$$

The initial condition for system (3) is given by

$$(T^0, L^0, I^0, V^0) \in C_+. \tag{4}$$

The local existence and uniqueness of solution to system (3) with the initial condition (4) follow from the standard result in the theory of delay differential equations [27]. The global existence of the solution on $[-\max\{\tau_1, \tau_2\}, \infty)$ follows from Theorem 1.

System (3) is an autonomous differential equation system with constant time delays. It always has an infection-free steady state $E_0 = (T_0, 0, 0, 0)$, where $T_0 = \frac{T_{\max}}{2a}\Big[a - d_T + \sqrt{(a - d_T)^2 + \frac{4as}{T_{\max}}}\Big]$.

We have the following result on the positivity and boundedness of solution of system (3).

Theorem 1 *Suppose that* $(T(t), L(t), I(t), V(t))$ *is a solution of system* (3) *with initial condition* (4). *Then it is positive and ultimately bounded for* $t > 0$.

Proof The proof is divided into two steps. In the first step, we prove that the solution of system (3) is positive. We state that $T(t) > 0$ for all $t > 0$. Otherwise, assume that there exists $t_1 > 0$ such that $T(t_1) = 0$ and $T(t) > 0$, $t \in [0, t_1)$, and thus $T'(t_1) \leq 0$. From the first equation of system (3) we have $T'(t_1) = s + aT(t_1)(1 - \frac{T(t_1)}{T_{max}}) - d_T T(t_1) - \frac{\beta T(t_1)V(t_1)}{1+bV(t_1)} - \frac{kT(t_1)I(t_1)}{1+nI(t_1)} = s > 0$. The contradiction implies that $T(t) > 0$ for all $t > 0$.

By the last three equations of system (3) and the variation-of-constants formula for nonhomogeneous linear differential equations we have

$$\begin{aligned}
L(t) =& L(0)e^{-(\alpha+\delta_L)t} + \int_0^t \Big[\frac{f\beta e^{-\delta_1\tau_1} T(\xi - \tau_1)V(\xi - \tau_1)}{1 + bV(\xi - \tau_1)} \\
&+ \frac{\eta k e^{-\delta_1\tau_1} T(\xi - \tau_1)I(\xi - \tau_1)}{1 + nI(\xi - \tau_1)}\Big] e^{-(\alpha+\delta_L)(t-\xi)} d\xi, \\
I(t) =& I(0)e^{-\delta t} + \int_0^t \Big[\frac{(1-f)\beta e^{-\delta_1\tau_2} T(\xi - \tau_2)V(\xi - \tau_2)}{1 + bV(\xi - \tau_2)} \\
&+ \frac{(1-\eta)k e^{-\delta_1\tau_2} T(\xi - \tau_2)I(\xi - \tau_2)}{1 + nI(\xi - \tau_2)} + \alpha L(\xi)\Big] e^{-\delta(t-\xi)} d\xi, \\
V(t) =& V(0)e^{-ct} + \int_0^t N\delta I(\xi) e^{-(t-\xi)} d\xi.
\end{aligned}$$

It is obvious that $L(t) > 0$, $I(t) > 0$, and $V(t) > 0$ for small $t > 0$. Next, we show that $L(t) > 0$, $I(t) > 0$, and $V(t) > 0$ for all $t > 0$. Assume that $t_2 > 0$ is the first time such that

$$\min\{L(t_2), I(t_2), V(t_2)\} = 0.$$

If $L(t_2) = 0$, $L(t) > 0$, $I(t) > 0$, and $V(t) > 0$ for $t \in [0, t_2)$, then we have $L'(t_2) \leq 0$. However, from the second equation of (3) we have

$$L'(t_2) = \frac{f\beta T(t_2-\tau_1)V(t_2-\tau_1)e^{-\delta_1\tau_1}}{1+bV(t_2-\tau_1)} + \frac{\eta kT(t_2-\tau_1)I(t_2-\tau_1)e^{-\delta_1\tau_1}}{1+nI(t_2-\tau_1)} > 0,$$

which is a contradiction.

By a similar proof we can obtain that $I(t_2) = 0$ and $V(t_2) = 0$ are impossible. Thus $L(t) > 0$, $I(t) > 0$, and $V(t) > 0$ for all $t > 0$.

In the second step, we prove the ultimate boundedness of the solution of system (3). From the positivity of the solution and the first equation of (3) we obtain that

$$\frac{dT}{dt} \leq s + aT(1 - \frac{T}{T_{\max}}) - d_T T(t),$$

which yields [28]

$$\limsup_{t\to+\infty} T(t) \leq T_0.$$

From the second equation of system (3) we get

$$\begin{aligned}\frac{dL(t)}{dt} \leq & \frac{f\beta T(t-\tau_1)V(t-\tau_1)e^{-\delta_1\tau_1}}{bV(t-\tau_1)} + \frac{\eta kT(t-\tau_1)I(t-\tau_1)e^{-\delta_1\tau_1}}{nI(t-\tau_1)} \\ & - (\alpha+\delta_L)L(t) \\ = & \frac{f\beta T(t-\tau_1)e^{-\delta_1\tau_1}}{b} + \frac{\eta kT(t-\tau_1)e^{-\delta_1\tau_1}}{n} - (\alpha+\delta_L)L(t) \\ \leq & (\frac{f\beta e^{-\delta_1\tau_1}}{b} + \frac{\eta ke^{-\delta_1\tau_1}}{n})T_0 - (\alpha+\delta_L)L(t).\end{aligned}$$

Then we have

$$\limsup_{t\to+\infty} L(t) \leq \Big(\frac{f\beta e^{-\delta_1\tau_1}}{b} + \frac{\eta ke^{-\delta_1\tau_1}}{n}\Big)\frac{T_0}{\alpha+\delta_L} \triangleq M_1.$$

Similarly, we can get

$$\begin{aligned}\limsup_{t\to+\infty} I(t) \leq & \frac{T_0\beta}{b\delta}\Big((1-f)e^{-\delta_1\tau_2} + \frac{\alpha fe^{-\delta_1\tau_1}}{\alpha+\delta_L}\Big) \\ & + \frac{T_0 k}{n\delta}\Big((1-\xi)e^{-\delta_1\tau_2} + \frac{\alpha\xi e^{-\delta_1\tau_1}}{\alpha+\delta_L}\Big) \triangleq M_2,\end{aligned}$$

and thus

$$\limsup_{t\to+\infty} V(t) \leq \frac{N\delta M_2}{c}.$$

Let $M = \max\{T_0, M_1, M_2, \frac{N\delta M_2}{c}\}$. Then $T(t)$, $L(t)$, $I(t)$, and $V(t)$ are ultimately uniformly bounded, and their upper bound is M. This completes the proof of the theorem. ☐

Denote

$$\Omega = \{(T,L,I,V) \in C_+ : \|T(t)\| \le T_0, \|L(t)\| \le M_1, \|I(t)\| \le M_2, \|V(t)\| \le \frac{N\delta M_2}{c}\}.$$

Then it follows from Theorem 1 that the region Ω is positive invariant with respect to system (3). This shows that system (3) is dissipative, i.e., the positivity of system may imply that HIV virus and all the CD4+ T cells including uninfected, latently infected, and infected T cells may survive. Because of availability of limited resources or spaces, the boundedness of the system may be viewed as the natural barrier to unrestricted expansion.

3 The basic reproductive number and the existence of endemic equilibrium

Obviously, system (3) has a disease-free equilibrium point $E_0 = (T_0, 0, 0, 0)$. We define the matrices

$$\mathcal{F} = \begin{pmatrix} \frac{f\beta T(t-\tau_1)V(t-\tau_1)e^{-\delta_1\tau_1}}{1+bV(t-\tau_1)} + \frac{\eta k T(t-\tau_1)I(t-\tau_1)e^{-\delta_1\tau_1}}{1+nI(t-\tau_1)} \\ \frac{(1-f)\beta T(t-\tau_2)V(t-\tau_2)e^{-\delta_1\tau_2}}{1+bV(t-\tau_2)} + \frac{(1-\eta)kT(t-\tau_2)I(t-\tau_2)e^{-\delta_1\tau_2}}{1+nI(t-\tau_2)} \\ 0 \end{pmatrix}$$

and

$$\mathcal{V} = \begin{pmatrix} (\alpha + \delta_L)L(t) \\ \delta I(t) - \alpha L(t) \\ -N\delta I(t) + cV(t) \end{pmatrix}.$$

Then we have

$$\mathbb{F} = \frac{\partial \mathcal{F}(E_0)}{\partial(L,I,V)} = \begin{pmatrix} 0 & \eta k e^{-\delta_1\tau_1} T_0 & f\beta e^{-\delta_1\tau_1} T_0 \\ 0 & (1-\eta)k e^{-\delta_1\tau_1} T_0 & (1-f)\beta e^{-\delta_1\tau_1} T_0 \\ 0 & 0 & 0 \end{pmatrix}$$

and

$$\mathbb{V} = \frac{\partial \mathcal{V}(E_0)}{\partial(L,I,V)} = \begin{pmatrix} \alpha + \delta_L & 0 & 0 \\ -\alpha & \delta & 0 \\ 0 & -N\delta & c \end{pmatrix}.$$

Thus the basic reproductive number R_0 is the spectral radius of the next generation operator $\mathbb{F}\mathbb{V}^{-1}$ [29], that is,

$$\begin{aligned} R_0 =& \rho(\mathbb{F}\mathbb{V}^{-1}) = \frac{N\beta T_0}{c}\left(\frac{\alpha f}{\alpha + \delta_L} e^{-\delta_1\tau_1} + (1-f)e^{-\delta_1\tau_2}\right) \\ &+ \frac{kT_0}{\delta}\left(\frac{\alpha\eta}{\alpha + \delta_L} e^{-\delta_1\tau_1} + (1-\eta)e^{-\delta_1\tau_2}\right) \\ &\overset{\triangle}{=} R_{01} + R_{02}. \end{aligned}$$

Similarly to [25], R_{01} and R_{02} represent the contributions to R_0 from the virus-to-cell infection and cell-to-cell transmission, respectively.

Next, we show that the threshold condition guaranteeing the existence of the endemic equilibrium is $R_0 > 1$. An endemic equilibrium $E^* = (T^*, L^*, I^*, V^*)$ is a positive solution of the equation system

$$\begin{cases} s + aT^*(1 - \frac{T^*}{T_{max}}) - d_T T^* - \frac{\beta T^* V^*}{1+bV^*} - \frac{kT^* I^*}{1+nI^*} = 0, \\ \frac{f\beta T^* V^* e^{-\delta_1 \tau_1}}{1+bV^*} + \frac{\eta k T^* I^* e^{-\delta_1 \tau_1}}{1+nI^*} - (\alpha + \delta_L)L^* = 0, \\ \frac{(1-f)\beta T^* V^* e^{-\delta_1 \tau_2}}{1+bV^*} + \frac{(1-\eta)kT^* I^* e^{-\delta_1 \tau_2}}{1+nI^*} - \delta I^* + \alpha L^* = 0, \\ N\delta I^* - cV^* = 0. \end{cases} \tag{5}$$

After some calculations, we obtain that

$$\begin{aligned} T^* &= \frac{T_0(1 + bV^*)(N\delta + cnV^*)}{R_{01}(N\delta + cnV^*) + N\delta R_{02}(1 + bV^*)}, \\ I^* &= \frac{cV^*}{N\delta}, \\ L^* &= \frac{1}{\alpha + \delta_L}\left(\frac{f\beta T^* V^* e^{-\delta_1 \tau_1}}{1 + bV^*} + \frac{\eta k T^* I^* e^{-\delta_1 \tau_1}}{1 + nI^*}\right), \end{aligned}$$

and V^* satisfies the equation

$$A_4 x^4 + A_3 x^3 + A_2 x^2 + A_1 x + A_0 = 0,$$

where

$$\begin{aligned} A_4 &= \frac{-aT_0^2}{T_{\max}} b^2 n^2 c^2, \\ A_3 &= \frac{-aT_0^2}{T_{\max}}(2bn^2c^2 + 2N\delta b^2 nc) + T_0((a - d_T)bnc)(R_{01}nc + R_{02}N\delta b) \\ &\quad - T_0 R_{01}\beta n^2 c^2 - T_0 R_{01} kcbnc - T_0 N\delta\beta R_{02} bnc - T_0 kcR_{02} N\delta b^2, \\ A_2 &= \frac{-aT_0^2}{T_{\max}}(n^2c^2 + 4N\delta bnc + N^2\delta^2 b^2) + T_0 R_{01}(a - d_T)(n^2c^2 + 2N\delta bnc) \\ &\quad + T_0 R_{02} N\delta(a - d_T)(N\delta b^2 + 2bnc) + sR_{01}^2 n^2 c^2 + 2sR_{01}R_{02}N\delta bnc \\ &\quad + sR_{02}^2 N^2\delta^2 b^2 - 2T_0 R_{01} N\delta\beta nc + T_0(nc + N\delta b)(-kcR_{01} - N\delta\beta R_{02}) \\ &\quad - 2T_0 R_{02} kcN\delta b, \\ A_1 &= \frac{-aT_0^2}{T_{\max}} 2N\delta(nc + N\delta b) + T_0(a - d_T)[R_{01}(2N\delta nc + N^2\delta^2 b) + R_{02}N\delta(2N\delta b \\ &\quad + nc)] + 2sN\delta[{R_{01}}^2 nc + R_{01}R_{02}(N\delta b + nc) + R_{02}^2 N\delta b] + T_0 N\delta[-R_{01}\beta N\delta \\ &\quad - kcR_{01} - N\delta\beta R_{02} - kcR_{02}], \\ A_0 &= N^2\delta^2 R_0^2\left[\frac{-a}{T_{\max}}\left(\frac{T_0}{R_0}\right)^2 + (a - d_T)\left(\frac{T_0}{R_0}\right) + s\right]. \end{aligned}$$

When $R_0 > 1$, there must be at least one positive root for this quartic equation. In fact, we define the function $g(x) = A_4 x^4 + A_3 x^3 + A_2 x^2 + A_1 x + A_0$. Noticing that $0 < \frac{T_0}{R_0} < T_0$ and

$s + aT_0(1 - \frac{T_0}{T_{\max}}) - d_T T_0 = 0$, we get that $g(0) = A_0 > 0$. From $A_4 < 0$ we have that $g(x) \to -\infty$ as $x \to +\infty$. Thus the equation $g(x) = 0$ has at least one positive real root, denoted by V^*.

Based on the above analysis, we get that when $R_0 > 1$, there is an endemic equilibrium $E^* = (T^*, L^*, I^*, V^*)$ for system (3).

4 Stability of the disease-free equilibrium

In this section, we study the local and global stability of the disease-free equilibrium. The following results show that the basic reproductive number provides a threshold value determining the local and global stability.

4.1 The local stability of the disease-free equilibrium

Next, we give the locally asymptotic stability of the disease-free equilibrium.

Theorem 2 *For system* (3), *if* $R_0 < 1$, *then the disease-free equilibrium* E_0 *is locally asymptotically stable, and if* $R_0 > 1$, *then it is unstable for all time delays* $\tau_1, \tau_2 \geq 0$.

Proof Let $\widetilde{E} = (\widetilde{T}, \widetilde{L}, \widetilde{I}, \widetilde{V})$ be an arbitrary equilibrium of system (3). Then the characteristic equation of the linearized system of system (3) at the equilibrium $\widetilde{E}$ is

$$\begin{vmatrix} \lambda - a + d_T + \frac{2a\widetilde{T}}{T_{\max}} + \frac{\beta\widetilde{V}}{1+b\widetilde{V}} + \frac{k\widetilde{I}}{1+n\widetilde{I}} & 0 & \frac{k\widetilde{T}}{(1+n\widetilde{I})^2} & \frac{\beta\widetilde{T}}{(1+b\widetilde{V})^2} \\ -(\frac{f\beta e^{-\delta_1\tau_1}\widetilde{V}}{1+b\widetilde{V}} + \frac{\eta k e^{-\delta_1\tau_1}\widetilde{I}}{1+n\widetilde{I}})e^{-\lambda\tau_1} & \lambda + \alpha + \delta_L & \frac{-\eta k\widetilde{T}e^{-\delta_1\tau_1}e^{-\lambda\tau_1}}{(1+n\widetilde{I})^2} & \frac{-f\beta\widetilde{T}e^{-\delta_1\tau_1}e^{-\lambda\tau_1}}{(1+b\widetilde{V})^2} \\ -\left(\frac{(1-f)\beta e^{-\delta_1\tau_2}\widetilde{V}}{1+b\widetilde{V}} + \frac{(1-\eta)ke^{-\delta_1\tau_2}\widetilde{I}}{1+n\widetilde{I}}\right)e^{-\lambda\tau_2} & -\alpha & \lambda + \delta - \frac{(1-\eta)k\widetilde{T}e^{-\delta_1\tau_2}e^{-\lambda\tau_2}}{(1+n\widetilde{I})^2} & -\frac{(1-f)\beta\widetilde{T}e^{-\delta_1\tau_2}e^{-\lambda\tau_2}}{(1+b\widetilde{V})^2} \\ 0 & 0 & -N\delta & \lambda + c \end{vmatrix} = 0. \tag{6}$$

Substituting $E_0 = (T_0, 0, 0, 0)$ into Eq. (6) and expanding the determinant by the first column, we obtain $\lambda - a + d_T + \frac{2aT_0}{T_{\max}} = 0$ or

$$\begin{aligned} (\lambda + \alpha + \delta_L)(\lambda + c)(\lambda + \delta) &= (\lambda + \alpha + \delta_L)(\lambda + c)(1 - \eta)kT_0e^{-\delta_1\tau_2}e^{-\lambda\tau_2} \\ &\quad + (\lambda + \alpha + \delta_L)N\delta\beta T_0(1 - f)e^{-\delta_1\tau_2}e^{-\lambda\tau_2} + \alpha(\lambda + c)\eta kT_0e^{-\delta_1\tau_1}e^{-\lambda\tau_1} \\ &\quad + N\delta\beta T_0\alpha fe^{-\delta_1\tau_1}e^{-\lambda\tau_1}. \end{aligned} \tag{7}$$

Therefore one of the characteristic roots is

$$\lambda = a - d_T - \frac{2aT_0}{T_{\max}} = -\sqrt{(a - d_T)^2 + \frac{4as}{T_{max}}} < 0,$$

and the remaining roots are determined by Eq. (7). When $R_0 < 1$, we claim that if $\lambda = x + yi$ is the solution to Eq. (7), then the real part $x < 0$. Assume that $x \geq 0$. By dividing both sides by $(\lambda+\alpha+\delta_L)(\lambda+c)(\lambda+\delta)$ Eq. (7) becomes

$$\begin{aligned}1=&\frac{N\delta\beta T_0\alpha f e^{-\delta_1\tau_1}e^{-\lambda\tau_1}}{(\lambda+\alpha+\delta_L)(\lambda+c)(\lambda+\delta)}+\frac{N\delta\beta T_0(1-f)e^{-\delta_1\tau_2}e^{-\lambda\tau_2}}{(\lambda+c)(\lambda+\delta)}\\&+\frac{\alpha\eta kT_0e^{-\delta_1\tau_1}e^{-\lambda\tau_1}}{(\lambda+\alpha+\delta_L)(\lambda+\delta)}+\frac{(1-\eta)kT_0e^{-\delta_1\tau_2}e^{-\lambda\tau_2}}{\lambda+\delta}.\end{aligned}\tag{8}$$

Taking the modulus of the left-hand side of Eq. (8), we obtain

$$\begin{aligned}1=&\bigg|\frac{N\delta\beta T_0\alpha f e^{-\delta_1\tau_1}e^{-\lambda\tau_1}}{(\lambda+\alpha+\delta_L)(\lambda+c)(\lambda+\delta)}+\frac{N\delta\beta T_0(1-f)e^{-\delta_1\tau_2}e^{-\lambda\tau_2}}{(\lambda+c)(\lambda+\delta)}\\&+\frac{\alpha\eta kT_0e^{-\delta_1\tau_1}e^{-\lambda\tau_1}}{(\lambda+\alpha+\delta_L)(\lambda+\delta)}+\frac{(1-\eta)kT_0e^{-\delta_1\tau_2}e^{-\lambda\tau_2}}{\lambda+\delta}\bigg|\\\le&\bigg|\frac{N\delta\beta T_0\alpha f e^{-\delta_1\tau_1}e^{-\lambda\tau_1}}{(\lambda+\alpha+\delta_L)(\lambda+c)(\lambda+\delta)}\bigg|+\bigg|\frac{N\delta\beta T_0(1-f)e^{-\delta_1\tau_2}e^{-\lambda\tau_2}}{(\lambda+c)(\lambda+\delta)}\bigg|\\&+\bigg|\frac{\alpha\eta kT_0e^{-\delta_1\tau_1}e^{-\lambda\tau_1}}{(\lambda+\alpha+\delta_L)(\lambda+\delta)}\bigg|+\bigg|\frac{(1-\eta)kT_0e^{-\delta_1\tau_2}e^{-\lambda\tau_2}}{\lambda+\delta}\bigg|\\\le&\frac{N\delta\beta\alpha fT_0e^{-\delta_1\tau_1}}{c\delta(\alpha+\delta_L)}+\frac{N\delta\beta T_0(1-f)e^{-\delta_1\tau_2}}{c\delta}\\&+\frac{\alpha\eta kT_0e^{-\delta_1\tau_1}}{\delta(\alpha+\delta_L)}+\frac{(1-\eta)kT_0e^{-\delta_1\tau_2}}{\delta}\\=&\frac{N\beta T_0}{c}\left(\frac{\alpha fe^{-\delta_1\tau_1}}{\alpha+\delta_L}+(1-f)e^{-\delta_1\tau_2}\right)+\frac{kT_0}{\delta}\left(\frac{\alpha\eta e^{-\delta_1\tau_1}}{\alpha+\delta_L}+(1-\eta)e^{-\delta_1\tau_2}\right)\\\overset{\triangle}{=}&R_0.\end{aligned}$$

This contradicts $R_0<1$. Thus all the roots of the characteristic equation have negative real parts. Therefore the disease-free equilibrium is locally asymptotically stable when $R_0<1$.

Next, we turn to the case of $R_0>1$ with delays $\tau_1,\tau_2\ge 0$. The characteristic equation (7) can be written in the form

$$F(\lambda)\overset{\triangle}{=}\lambda^3+B_2\lambda^2+B_1\lambda+B_0=0,\tag{9}$$

where

$$\begin{aligned}B_2=&(\alpha+\delta_L+c+\delta)-(1-\eta)kT_0e^{-\delta_1\tau_2}e^{-\lambda\tau_2},\\B_1=&(\alpha+\delta_L)c+(\alpha+\delta_L)\delta+c\delta-(c+\alpha+\delta_L)(1-\eta)kT_0e^{-\delta_1\tau_2}e^{-\lambda\tau_2}\\&-N\delta\beta T_0(1-f)e^{-\delta_1\tau_2}e^{-\lambda\tau_2}-\alpha\eta kT_0e^{-\delta_1\tau_1}e^{-\lambda\tau_1},\\B_0=&(\alpha+\delta_L)c\delta-(\alpha+\delta_L)c(1-\eta)kT_0e^{-\delta_1\tau_2}e^{-\lambda\tau_2}-(\alpha+\delta_L)N\delta\beta T_0\\&\times(1-f)e^{-\delta_1\tau_2}e^{-\lambda\tau_2}-c\alpha\eta kT_0e^{-\delta_1\tau_1}e^{-\lambda\tau_2}-N\delta\beta T_0\alpha fe^{-\delta_1\tau_1}e^{-\lambda\tau_1}.\end{aligned}$$

Obviously, $F(0)=B_0=(\alpha+\delta_L)c\delta(1-R_0)<0$, and $\lim_{\lambda\to+\infty}F(\lambda)=+\infty$. It shows that Eq. (9) has at least one positive root. Therefore the disease-free equilibrium E_0 is unstable when $R_0>1$. This completes the proof of the theorem. □

4.2 The global stability of the disease-free equilibrium

We use the Lyapunov direct method to study the global stability of the disease-free equilibrium of system (3).

Theorem 3 *If* $R_0 < 1$, *then the disease-free equilibrium* E_0 *of system* (3) *is globally asymptotically stable for all time delays* $\tau_1, \tau_2 \geq 0$.

Proof Let $G = \{(T, L, I, V) \in C_+ : T_0 \geq T \geq 0, L \geq 0, I \geq 0, V \geq 0\}$. From Theorem 1 we know that the region G attracts all solutions of system (3). Let $(T(t), L(t), I(t), V(t))$ be the solution of system (3) with any initial value (4). We claim that $T(t) \leq T_0$ for all $t \geq 0$. In fact, if there is $t_1 > 0$ such that $T(t_1) > T_0$ and $\frac{dT(t_1)}{dt} > 0$, then we have

$$\begin{aligned}\frac{dT(t_1)}{dt} &= s + aT(t_1)(1 - \frac{T(t_1)}{T_{\max}}) - d_T T(t_1) - \frac{\beta T(t_1)V(t_1)}{1 + bV(t_1)} - \frac{kT(t_1)I(t_1)}{1 + nI(t_1)} \\ &\leq -\frac{\beta T(t_1)V(t_1)}{1 + bV(t_1)} - \frac{kT(t_1)I(t_1)}{1 + nI(t_1)} \leq 0.\end{aligned}$$

Here we have used $T(t_1) > T_0$ and $s - d_T T_0 + aT_0(1 - \frac{T_0}{T_{\max}}) = 0$. This is a contradiction to $\frac{dT(t_1)}{dt} > 0$, so the claim is proved. Thus G is positively invariant with respect to system (3).

Define the function $W(t) = W_1(t) + W_2(t)$ on G, where

$$W_1(t) = \frac{\alpha}{\alpha + \delta_L} L(t) + I(t) + \frac{1 - R_{02}}{N} V(t),$$

and

$$\begin{aligned}W_2(t) =& \frac{\alpha f e^{-\delta_1 \tau_1}}{\alpha + \delta_L} \int_0^{\tau_1} \frac{\beta T(t-\theta)V(t-\theta)}{1 + bV(t-\theta)} d\theta \\ &+ \frac{\alpha \eta e^{-\delta_1 \tau_1}}{\alpha + \delta_L} \int_0^{\tau_1} \frac{kT(t-\theta)I(t-\theta)}{1 + nI(t-\theta)} d\theta \\ &+ (1-f)e^{-\delta_1 \tau_2} \int_0^{\tau_2} \frac{\beta T(t-\theta)V(t-\theta)}{1 + bV(t-\theta)} d\theta \\ &+ (1-\eta)e^{-\delta_1 \tau_2} \int_0^{\tau_2} \frac{kT(t-\theta)I(t-\theta)}{1 + nI(t-\theta)} d\theta.\end{aligned}$$

Calculating the derivatives of $W_1(t)$ and $W_2(t)$ along the solution of system (3), we obtain

$$\begin{aligned}\frac{dW_1(t)}{dt} &= \frac{\alpha e^{-\delta_1 \tau_1}}{\alpha + \delta_L} \left(\frac{f\beta T(t-\tau_1)V(t-\tau_1)}{1 + bV(t-\tau_1)} + \frac{\eta kT(t-\tau_1)I(t-\tau_1)}{1 + nI(t-\tau_1)} \right) \\ &+ \frac{(1-f)\beta T(t-\tau_2)V(t-\tau_2)e^{-\delta_1 \tau_2}}{1 + bV(t-\tau_2)} + \frac{(1-\eta)kT(t-\tau_2)I(t-\tau_2)e^{-\delta_1 \tau_2}}{1 + nI(t-\tau_2)} \\ &- \delta R_{02} I(t) - \frac{cV(t)}{N} + \frac{R_{02} cV(t)}{N}\end{aligned}$$

and

$$\frac{dW_2(t)}{dt} = e^{-\delta_1 \tau_1} \frac{\alpha f}{\alpha + \delta_L} \int_0^{\tau_1} \frac{d(\beta T(t-\theta)V(t-\theta))}{dt(1 + bV(t-\theta))} d\theta$$

$$
\begin{aligned}
&+ e^{-\delta_1\tau_1}\frac{\alpha\eta}{\alpha+\delta_L}\int_0^{\tau_1}\frac{d(kT(t-\theta)I(t-\theta))}{dt(1+nI(t-\theta))}d\theta\\
&+ e^{-\delta_1\tau_2}(1-f)\int_0^{\tau_2}\frac{d(\beta T(t-\theta)V(t-\theta))}{dt(1+bV(t-\theta))}d\theta\\
&+ e^{-\delta_1\tau_2}(1-\eta)\int_0^{\tau_2}\frac{d(kT(t-\theta)I(t-\theta))}{dt(1+nI(t-\theta))}d\theta\\
=&- e^{-\delta_1\tau_1}\frac{\alpha f}{\alpha+\delta_L}\int_0^{\tau_1}\frac{d(\beta T(t-\theta)V(t-\theta))}{d\theta(1+bV(t-\theta))}d\theta\\
&- e^{-\delta_1\tau_1}\frac{\alpha\eta}{\alpha+\delta_L}\int_0^{\tau_1}\frac{d(kT(t-\theta)I(t-\theta))}{d\theta(1+nI(t-\theta))}d\theta\\
&- (1-f)e^{-\delta_1\tau_2}\int_0^{\tau_2}\frac{d(\beta T(t-\theta)V(t-\theta))}{d\theta(1+bV(t-\theta))}d\theta\\
&- (1-\eta)e^{-\delta_1\tau_2}\int_0^{\tau_2}\frac{d(kT(t-\theta)I(t-\theta))}{d\theta(1+nI(t-\theta))}d\theta\\
=&e^{-\delta_1\tau_1}\frac{\alpha f}{\alpha+\delta_L}\frac{\beta T(t)V(t)}{1+bV(t)} - e^{-\delta_1\tau_1}\frac{\alpha f}{\alpha+\delta_L}\frac{\beta T(t-\tau_1)V(t-\tau_1)}{1+bV(t-\tau_1)}\\
&+ e^{-\delta_1\tau_1}\frac{\alpha\eta}{\alpha+\delta_L}\frac{kT(t)I(t)}{1+nI(t)} - e^{-\delta_1\tau_1}\frac{\alpha\eta}{\alpha+\delta_L}\frac{KT(t-\tau_1)I(t-\tau_1)}{1+nI(t-\tau_1)}\\
&+ (1-f)e^{-\delta_1\tau_2}\frac{\beta T(t)V(t)}{1+bV(t)} - (1-f)e^{-\delta_1\tau_2}\frac{\beta T(t-\tau_2)V(t-\tau_2)}{1+bV(t-\tau_2)}\\
&+ (1-\eta)e^{-\delta_1\tau_2}\frac{kT(t)I(t)}{1+nI(t)} - (1-\eta)e^{-\delta_1\tau_2}\frac{\beta T(t-\tau_2)I(t-\tau_2)}{1+nI(t-\tau_2)}.
\end{aligned}
$$

Thus

$$
\begin{aligned}
\frac{dW(t)}{dt} =&\frac{dW_1(t)}{dt}+\frac{dW_2(t)}{dt}\\
=&e^{-\delta_1\tau_1}\frac{\alpha f}{\alpha+\delta_L}\frac{\beta T(t)V(t)}{1+bV(t)} + e^{-\delta_1\tau_1}\frac{\alpha\eta}{\alpha+\delta_L}\frac{kT(t)I(t)}{1+nI(t)}\\
&+ (1-f)e^{-\delta_1\tau_2}\frac{\beta T(t)V(t)}{1+bV(t)} + (1-\eta)e^{-\delta_1\tau_2}\frac{kT(t)I(t)}{1+nI(t)}\\
&- \delta R_{02}I(t) - \frac{cV(t)}{N} + \frac{R_{02}cV(t)}{N}\\
\le&\left(\frac{\alpha f}{\alpha+\delta_L}e^{-\delta_1\tau_1} + (1-f)e^{-\delta_1\tau_2}\right)\frac{\beta T_0V(t)}{1+bV(t)}\\
&+ \left(\frac{\alpha\eta}{\alpha+\delta_L}e^{-\delta_1\tau_1} + (1-\eta)e^{-\delta_1\tau_2}\right)\frac{kT_0I(t)}{1+nI(t)}\\
&- \delta R_{02}I(t) - \frac{cV(t)}{N} + \frac{R_{02}cV(t)}{N}\\
\le&\left(\frac{\alpha f}{\alpha+\delta_L}e^{-\delta_1\tau_1} + (1-f)e^{-\delta_1\tau_2}\right)\beta T_0V(t)\\
&+ \left(\frac{\alpha\eta}{\alpha+\delta_L}e^{-\delta_1\tau_1} + (1-\eta)e^{-\delta_1\tau_2}\right)kT_0I(t)\\
&- \delta R_{02}I(t) - \frac{cV(t)}{N} + \frac{R_{02}cV(t)}{N}
\end{aligned}
$$

$$
\begin{aligned}
&= \frac{c}{N}\left[\frac{N\beta T_0}{c}\left(\frac{\alpha f}{\alpha+\delta_L}e^{-\delta_1\tau_1}+(1-f)e^{-\delta_1\tau_2}\right)V(t)-V(t)\right] \\
&\quad + \delta\left[\frac{kT_0}{\delta}\left(\frac{\alpha\eta}{\alpha+\delta_L}e^{-\delta_1\tau_1}+(1-\eta)e^{-\delta_1\tau_2}\right)I(t)-R_{02}I(t)\right]+\frac{R_{02}cV(t)}{N} \\
&= \frac{c}{N}(R_{01}V(t)-V(t))+\delta(R_{02}I(t)-R_{02}I(t))+\frac{c}{N}R_{02}V(t) \\
&= \frac{c}{N}(R_{01}+R_{02}-1)V(t) \\
&= \frac{c}{N}(R_0-1)V(t).
\end{aligned}
$$

It is clear that $\frac{dW(t)}{dt} \leq 0$ when $R_0 < 1$. Moreover, $\frac{dW(t)}{dt} = 0$ if and only if $V(t) = 0$. The largest invariant set in $\{(T, L, I, V) : \frac{dW(t)}{dt} = 0\}$ is the singleton set $\{E_0\}$. Therefore by the Lyapunov-LaSalle invariance principle and Theorem 2 the disease-free equilibrium E_0 is globally asymptotically stable. □

Remark 1 Theorem 4.1 in [25] requires the condition $f = \eta$ to ensure the global stability of the disease-free equilibrium. However, in clinical practice, these two parameters may be not equal. Our Theorem 3 removes the condition $f = \eta$. Therefore our conclusion is more consistent with the actual situation. In fact, by using the method of proving Theorem 3, we can prove that Theorem 4.1 in [25] holds even if two parameters are not equal.

5 Hopf bifurcation from the endemic equilibrium

Once the system generates the Hopf bifurcation, the HIV viral load will fluctuate periodically in the hosts, which is not conducive to the prevention and control of AIDS. Therefore it is necessary to explore the existence conditions for the Hopf bifurcation in the system, so as to bring enlightenment to the prevention and control of AIDS. In this section, taking τ_1 and τ_2 as the bifurcation parameters, we consider the existence of Hopf bifurcation of system (3) from the endemic equilibrium $E^* = (T^*, L^*, I^*, V^*)$. We know that the endemic equilibrium E^* exists when $R_0 > 1$. Substituting E^* into Eq. (6), the characteristic equation of the linearized system of system (3) is

$$
P_0(\lambda) + P_1(\lambda)e^{-\lambda\tau_1} + P_2(\lambda)e^{-\lambda\tau_2} = 0, \tag{10}
$$

where

$$
\begin{aligned}
P_0(\lambda) &= \lambda^4 + a_3\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0, \\
P_1(\lambda) &= b_2\lambda^2 + b_1\lambda + b_0, \\
P_2(\lambda) &= c_3\lambda^3 + c_2\lambda^2 + c_1\lambda + c_0,
\end{aligned}
$$

and

$$
\begin{aligned}
a_3 &= -(a_{11}+a_{22}+a_{33}+a_{44}), \\
a_2 &= a_{11}a_{22}+a_{11}a_{33}+a_{11}a_{44}+a_{22}a_{33}+a_{22}a_{44}+a_{33}a_{44}, \\
a_1 &= -a_{11}a_{22}a_{33}-a_{11}a_{22}a_{44}-a_{11}a_{33}a_{44}-a_{22}a_{33}a_{44},
\end{aligned}
$$

$$\begin{aligned}
a_0 =& a_{11}a_{22}a_{33}a_{44},\\
b_2 =& -a_{32}b_{23},\\
b_1 =& -a_{32}a_{43}b_{24}-a_{13}a_{32}b_{21}+a_{32}b_{23}(a_{11}+a_{44}),\\
b_0 =& -a_{14}a_{32}a_{43}b_{21}+a_{11}a_{32}a_{43}b_{24}+a_{13}a_{32}a_{44}b_{21}-a_{11}a_{32}a_{44}b_{23},\\
c_3 =& -c_{33},\\
c_2 =& -a_{43}c_{34}+c_{33}(a_{11}+a_{22}+a_{44})-a_{13}c_{31},\\
c_1 =& (a_{11}+a_{22})a_{43}c_{34}-a_{14}a_{43}c_{31}-c_{33}(a_{11}a_{22}+a_{11}a_{44}+a_{22}a_{44})\\
&+a_{13}(a_{22}+a_{44})c_{31},\\
c_0 =& -a_{11}a_{22}a_{43}c_{34}+a_{14}a_{22}a_{43}c_{31}+a_{11}a_{22}a_{44}c_{33}-a_{13}a_{22}a_{44}c_{31}
\end{aligned}$$

with

$$\begin{aligned}
&a_{11}=a-d_T-\tfrac{2aT^*}{T_{\max}}-\tfrac{\beta V^*}{1+bV^*}-\tfrac{kI^*}{1+nI^*}, && a_{13}=-\tfrac{kT^*}{(1+nI^*)^2},\\
&a_{14}=-\tfrac{\beta T^*}{(1+bV^*)^2}, && a_{22}=-(\alpha+\delta_L),\\
&a_{32}=\alpha, && a_{33}=-\delta,\\
&a_{43}=N\delta, && a_{44}=-c,\\
&b_{21}=e^{-\delta_1\tau_1}\left(\tfrac{f\beta V^*}{1+bV^*}+\tfrac{\eta kI^*}{1+nI^*}\right), && b_{23}=\tfrac{\eta e^{-\delta_1\tau_1}kT^*}{(1+nI^*)^2},\\
&b_{24}=\tfrac{fe^{-\delta_1\tau_1}\beta T^*}{(1+bV^*)^2}, && c_{31}=e^{-\delta_1\tau_2}\left(\tfrac{(1-f)\beta V^*}{1+bV^*}+\tfrac{(1-\eta)kI^*}{1+nI^*}\right),\\
&c_{33}=\tfrac{(1-\eta)e^{-\delta_1\tau_2}kT^*}{(1+nI^*)^2}, && c_{34}=\tfrac{(1-f)e^{-\delta_1\tau_2}\beta T^*}{(1+bV^*)^2}.
\end{aligned}$$

Now we discuss the Hopf bifurcation of system (3) in three cases.

Case (1): when $\tau_1=\tau_2=0$, Eq. (10) is reduced to

$$\lambda^4+(\bar{a}_3+\bar{c}_3)\lambda^3+(\bar{a}_2+\bar{b}_2+\bar{c}_2)\lambda^2+(\bar{a}_1+\bar{b}_1+\bar{c}_1)\lambda+(\bar{a}_0+\bar{b}_0+\bar{c}_0)=0, \tag{11}$$

where $\bar{a}_i=a_i$, $\bar{b}_j=b_{j(\tau_1=0)}$, and $\bar{c}_k=c_{k(\tau_2=0)}$ $(i,k=0,1,2,3;j=0,1,2)$. By the Routh–Hurwitz criterion the roots of (11) must have negative real parts if the following condition is satisfied:

(H_1) $\bar{a}_3+\bar{c}_3>0, \bar{a}_1+\bar{b}_1+\bar{c}_1>0$, and $(\bar{a}_1+\bar{b}_1+\bar{c}_1)((\bar{a}_3+\bar{c}_3)(\bar{a}_2+\bar{b}_2+\bar{c}_2)-(\bar{a}_1+\bar{b}_1+\bar{c}_1))>(\bar{a}_3+\bar{c}_3)^2(\bar{a}_0+\bar{b}_0+\bar{c}_0)>0$.

Therefore, if the conditions $(H1)$ and $R_0>1$ hold, then the endemic equilibrium E^* is locally asymptotically stable in the absence of delay.

Case (2): when $\tau_1=0$, $\tau_2>0$, Eq. (10) is reduced to

$$\lambda^4+m_3\lambda^3+m_2\lambda^2+m_1\lambda+m_0+(c_3\lambda^3+c_2\lambda^2+c_1\lambda+c_0)e^{-\lambda\tau_2}=0, \tag{12}$$

where $m_0=a_0+b_0$, $m_1=a_1+b_1$, $m_2=a_2+b_2$, and $m_3=a_3$.

Without loss of generality, we assume that Eq. (12) has a pair of simple and conjugate imaginary roots $\lambda=\pm i\omega(\tau_2)$, where $\omega(\tau_2)$ is a real and positive function of τ_2. It follows that

$$\begin{cases}(c_2\omega^2-c_0)\cos\omega\tau_2+(c_3\omega^3-c_1\omega)\sin\omega\tau_2=\omega^4-m_2\omega^2+m_0,\\ (c_0-c_2\omega^2)\sin\omega\tau_2+(c_3\omega^3-c_1\omega)\cos\omega\tau_2=-m_3\omega^3+m_1\omega.\end{cases} \tag{13}$$

Squaring and adding the equations of (13), we obtain that

$$\omega^8 + h_3\omega^6 + h_2\omega^4 + h_1\omega^2 + h_0 = 0, \tag{14}$$

where

$$\begin{aligned} h_3 &= m_3^2 - 2m_2 - c_3^2, \\ h_2 &= m_2^2 + 2m_0 - 2m_1m_3 - c_2^2 + 2c_1c_3, \\ h_1 &= m_1^2 - 2m_0m_2 + 2c_0c_2 - c_1^2, \\ h_0 &= m_0^2 - c_0^2. \end{aligned}$$

Taking $z = \omega^2$, (14) can be converted to

$$G_1(z) \overset{\triangle}{=} z^4 + h_3z^3 + h_2z^2 + h_1z + h_0 = 0. \tag{15}$$

Denote

$$p = \frac{8h_2 - 3h_3^2}{16}, q = \frac{h_3^3 - 2h_2h_3 + 8h_1}{32}, D_0 = \frac{q^2}{4} + \frac{p^3}{27}$$

and define

$$\begin{aligned} z_1^* &= -\frac{h_3}{4} + \sqrt[3]{-\frac{q}{2} + \sqrt{D_0}} + \sqrt[3]{-\frac{q}{2} - \sqrt{D_0}} \quad \text{if} \quad D_0 > 0, \\ z_2^* &= \max\left\{-\frac{h_3}{4} - 2\sqrt[3]{\frac{q}{2}}, -\frac{h_3}{4} + \sqrt[3]{\frac{q}{2}}\right\} \quad \text{if} \quad D_0 = 0, \\ z_3^* &= \max\left\{-\frac{h_3}{4} + 2Re\{\alpha\}, -\frac{h_3}{4} + 2Re\{\alpha\varepsilon\}, -\frac{h_3}{4} + 2Re\{\alpha\bar{\varepsilon}\}\right\} \quad \text{if} \quad D_0 < 0, \end{aligned}$$

where $\alpha = \sqrt[3]{-\frac{q}{2} + \sqrt{D_0}}$ and $\varepsilon = \frac{-1+\sqrt{3}i}{2}$.

By a similar argument as for Lemma 2.1 in [30], we have the following lemma.

Lemma 1 *For Eq. (15), we have:*

(H_2) *If $h_0 < 0$ or $h_0 \geq 0$ and one of the following conditions holds:*

(1) $D_0 > 0, z_1^* > 0,$ *and* $G_1(z_1^*) < 0,$

(2) $D_0 = 0, z_2^* > 0,$ *and* $G_1(z_2^*) < 0,$

(3) $D_0 < 0, z_3^* > 0,$ *and* $G_1(z_3^*) < 0,$

then Eq. (15) has at least one positive root.

(H_3) *If $h_0 \geq 0$ and one of the following conditions holds:*

(1) $D_0 > 0$ *and* $z_1^* < 0,$

(2) $D_0 = 0$ *and* $z_2^* < 0,$

(3) $D_0 < 0$ *and* $z_3^* < 0,$

then Eq. (15) has no positive root.

Without loss of generality, we assume that Eq. (15) has four positive roots, denoted by q_k. Then Eq. (14) also has positive roots $\omega_k = \sqrt{q_k}$ $(k = 1, 2, 3, 4)$. Furthermore, from Eq. (13)

we have

$$\tau_{2(k)}^{(j)} = \frac{1}{\omega_k} \arccos(\theta_1) + \frac{2j\pi}{\omega_k},$$

where

$$\theta_1 = \frac{(\omega_k^4 - m_2\omega_k^2 + m_0)(c_2\omega_k^2 - c_0) + (-m_3\omega_k^3 + m_1\omega_k)(c_3\omega_k^3 - c_1\omega)}{(c_3\omega_k^3 - c_1\omega_k)^2 + (c_2\omega_k^2 - c_0)^2},$$

$k = 1, 2, 3, 4$, $j = 0, 1, 2, \ldots$. Then $\pm i\omega_k$ is a pair of purely imaginary roots of Eq. (12) with $\tau_2 = \tau_{2k}^{(j)}$. Let $\tau_2^* = \min_{\{1,2,3,4\}}\{\tau_{2k}^{(0)}\}$ and $\omega_0 = \omega(\tau_2^*)$, where $\omega(\tau_2^*)$ is the value of ω when $t = t_2^*$.

Let $\lambda(\tau_2) = \xi_1(\tau_2) + i\omega(\tau_2)$ be a root of Eq. (12) satisfying $\xi_1(\tau_2^*) = 0$ and $\omega_0 = \omega(\tau_2^*)$.

Differentiating both sides of Eq. (12) with respect to τ_2, it follows that

$$\left(\frac{d\lambda}{d\tau_2}\right)^{-1} = \frac{3c_3\lambda^2 + 2c_2\lambda + c_1}{\lambda(c_3\lambda^3 + c_2\lambda^2 + c_1\lambda + c_0)} - \frac{4\lambda^3 + 3m_3\lambda^2 + 2m_2\lambda + m_1}{\lambda(\lambda^4 + m_3\lambda^3 + m_2\lambda^2 + m_1\lambda + m_0)} - \frac{\tau_2}{\lambda}.$$

Notice that

$$sign\left\{\frac{d(Re\lambda)}{d\tau_2}\right\}_{\tau_2=\tau_2^*} = sign\left\{Re\left(\frac{d\lambda}{d\tau_2}\right)^{-1}\right\}_{\tau_2=\tau_2^*}.$$

According to Eqs. (12), (13), (14), and (15), we have

$$\begin{aligned} sign\left\{\frac{d(Re\lambda)}{d\tau_2}\right\}_{\tau_2=\tau_2^*} &= sign\left\{\frac{G_1'(\omega_0)}{(c_3\omega_0^2 - c_1)^2\omega_0^2 + (c_0 - c_2\omega_0^2)^2}\right\} \\ &= sign\left\{G_1'(\omega_0)\right\}. \end{aligned}$$

Since $\omega_0 > 0$, we conclude that $\frac{dRe\lambda}{d\tau_2}|_{\tau_2=\tau_2^*}$ and $G_1'(\omega_0)$ have the same sign. By applying Lemma 1 to Eq. (15) and Hopf bifurcation theorem we get the following theorem about the existence of a Hopf bifurcation.

Theorem 4 *Suppose that* $\tau_1 = 0$, $\tau_2 > 0$, *and* $R_0 > 1$.

(I) *If* (H_1) *and* (H_3) *hold, then the endemic equilibrium* E^* *of system* (3) *is asymptotically stable for* $\tau_2 > 0$.

(II) *If* (H_1), (H_2), *and* $G_1'(\omega_0) \neq 0$ *hold, then the endemic equilibrium* E^* *of system* (3) *is locally asymptotically stable for* $\tau_2 \in [0, \tau_2^*)$. *In addition, Hopf bifurcation occurs when* $\tau_2 = \tau_2^*$, *and system* (3) *generates a cluster of bifurcated periodic solutions near* τ_2^*, *where*

$$\tau_2^* = \frac{1}{\omega_0} \arccos\left\{\frac{(\omega_0^4 - m_2\omega_0^2 + m_0)(c_2\omega_0^2 - c_0) + (-m_3\omega_0^3 + m_1\omega_0)(c_3\omega_0^3 - c_1\omega_0)}{(c_3\omega_0^3 - c_1\omega_0)^2 + (c_2\omega_0^2 - c_0)^2}\right\}.$$

Case (3): when $\tau_1 > 0$ and $\tau_2 = 0$, this is similar to Case (2).

Case (4): when $\tau_1 > 0$ and $\tau_2 > 0$, let $\lambda = i\omega$ (notice that the ω here has nothing to do with the ω in Case (2); it is just an expression) be the root of Eq. (10)). Then we obtain

$$\omega^4 - a_3\omega^3 i - a_2\omega^2 + a_1\omega i + a_0 + (-b_2\omega^2 + b_1\omega i + b_0)e^{-i\omega\tau_1}$$

$$+ (-c_3\omega^3 i - c_2\omega^2 + c_1\omega i + c_0)e^{-i\omega\tau_2} = 0.$$

Separating the real and imaginary parts, we get

$$\begin{cases} (b_2\omega^2 - b_0)\cos\omega\tau_1 - b_1\omega\sin\omega\tau_1 = \omega^4 - a_2\omega^2 + a_0 + d_1, \\ (b_0 - b_2\omega^2)\sin\omega\tau_1 - b_1\omega\cos\omega\tau_1 = -a_3\omega^3 + a_1\omega + g_1, \end{cases} \tag{16}$$

where

$$\begin{aligned} d_1 &= - c_3\omega^3\sin\omega\tau_2 - c_2\omega^2\cos\omega\tau_2 + c_1\omega\sin\omega\tau_2 + c_0\cos\omega\tau_2, \\ g_1 &= - c_3\omega^3\cos\omega\tau_2 + c_2\omega^2\sin\omega\tau_2 + c_1\omega\cos\omega\tau_2 - c_0\sin\omega\tau_2. \end{aligned}$$

Squaring and adding the above equations, we obtain

$$\omega^8 + e_6\omega^6 + e_4\omega^4 + e_3\omega^3 + e_2\omega^2 + e_1\omega + e_0 = 0, \tag{17}$$

where

$$\begin{aligned} &e_6 = a_3^2 - 2a_3, && e_4 = a_2^2 + 2a_0 + 2d_1 - 2a_1a_3 - b_2^2, \\ &e_3 = -2a_3g_1, && e_2 = -2a_0a_2 - 2a_2d_1 + a_1^2 + 2b_0b_2 - b_1^2, \\ &e_1 = 2a_1g_1, && e_0 = a_0^2 + d_1^2 + 2a_0d_1 + g_1^2 - b_0^2. \end{aligned}$$

Suppose that

(H_4) *Eq. (17) has at least one positive real root.*

Then without loss of generality, we assume that Eq. (17) has eight positive real roots ω_k, $k = 1, 2, \dots, 8$, and from Eq. (16) we have

$$\tau_{1(k)}^{(j)} = \frac{1}{\omega_k}\arccos(\theta_2) + \frac{2j\pi}{\omega_k},$$

where $\theta_2 = \frac{(\omega_k^4 - a_2\omega_k^2 + a_0 + d_1)(b_2\omega_k^2 - b_0) + (a_3\omega_k^3 - a_1\omega_k - g_1)b_1\omega_k}{(b_2\omega_k^2 - b_0)^2 + b_1^2\omega_k^2}$, $j = 0, 1, 2, \dots$.

Let $\tau_1^* = \min_{\{k=1,2,\dots,8\}}\{\tau_{1(k)}^{(0)}\}$ and $\lambda(\tau_1) = \xi_2(\tau_1) + i\omega(\tau_1)$ be a root of Eq. (10) satisfying $\xi_2(\tau_1^*) = 0$, and let $\omega_0^* = \omega(\tau_1^*)$, where $\omega(\tau_1^*)$ is the value of ω when $\tau_1 = \tau_1^*$. Next, we consider the transversality condition. Taking the derivative of λ with respect to τ_1 in Eq. (10), it follows that

$$Re\left\{\left(\frac{d\lambda}{d\tau_1}\right)^{-1}\Bigg|_{\tau_1=\tau_1^*}\right\} = Re\frac{F_{23} + F_{24}i}{F_{21} + F_{22}i} = \frac{F_{21}F_{23} + F_{22}F_{24}}{F_{21}^2 + F_{22}^2},$$

where

$$\begin{aligned} F_{21} =& (b_0 - b_2(\omega_0^*)^2)\omega_0^*\sin\omega_0^*\tau_1^* - b_1(\omega_0^*)^2\cos\omega_0^*\tau_1^*, \\ F_{22} =& (b_0 - b_2(\omega_0^*)^2)\omega_0^*\cos\omega_0^*\tau_1^* + b_1(\omega_0^*)^2\sin\omega_0^*\tau_1^*, \\ F_{23} =& - 3a_2(\omega_0^*)^2 + 2b_2\omega_0^*\sin\omega_0^*\tau_1^* - \tau_1^*(b_0 - b_2(\omega_0^*)^2)\cos\omega_0^*\tau_1^* + b_1\cos\omega_0^*\tau_1^* \\ &+ a_1 - \tau_1^*b_1\omega_0^*\sin\omega_0^*\tau_1^* + (c_1 - 3c_3(\omega_0^*)^2)\cos\omega_0^*\tau_2 + 2c_2\omega_0^*\sin\omega_0^*\tau_2 \end{aligned}$$

$$
\begin{aligned}
&\quad - \tau_2(c_0 - c_2(\omega_0^*)^2)\cos\omega_0^*\tau_2 - \tau_2(c_1\omega_0^* - c_3(\omega_0^*)^3)\sin\omega_0^*\tau_2,\\
F_{24} ={}& - 4(\omega_0^*)^3 + 2a_2\omega_0^* + 2b_2\omega_0^*\cos\omega_0^*\tau_1^* - b_1\sin\omega_0^*\tau_1^* - \tau_1^* b_1\omega_0^*\cos\omega_0^*\tau_1^*\\
&\quad + \tau_1^*(b_0 - b_2(\omega_0^*)^2)\sin\omega_0^*\tau_1^* - (c_1 - 3c_3(\omega_0^*)^2)\sin\omega_0^*\tau_2 + 2c_2\omega_0^*\cos\omega_0^*\tau_2\\
&\quad - \tau_2(c_1\omega_0^* - c_3(\omega_0^*)^3)\cos\omega_0^*\tau_2 + \tau_2(c_0 - c_2(\omega_0^*)^2)\sin\omega_0^*\tau_2.
\end{aligned}
$$

If we suppose that $F_{21}F_{23} + F_{22}F_{24} \neq 0$, then $Re(\frac{d\lambda}{d\tau_1})^{-1}_{\tau_1=\tau_1^*} \neq 0$.

We obtain the following conclusion.

Theorem 5 *Suppose that* $\tau_1 > 0$, $\tau_2 > 0$, *and* $R_0 > 1$. *If* (H_1), (H_4), *and* $F_{21}F_{23} + F_{22}F_{24} \neq 0$ *hold, then the endemic equilibrium* E^* *of system* (3) *is asymptotically stable when* $\tau_1 \in [0, \tau_1^*)$, *and Hopf bifurcation occurs when* $\tau_1 = \tau_1^*$.

6 Conclusions

We constructed a latent HIV infection model (3) with virus-to-cell and cell-to-cell transmission modes. In addition, we added logistic growth terms and nonlinear incidence to model (3). According to [31], it is reasonable to assume that the infection rate of modeling HIV infection has $\frac{\beta TV}{1+bV}$ and $\frac{kTI}{1+nI}$ forms. Time delays between viral entry and the establishment of latent infection or virus production were also included in the model. We derived the basic reproductive number R_0. Our results show that R_0 is a threshold that affects the stability of the equilibrium point.

By constructing a proper Lyapunov function we obtained the global asymptotic stability of the disease-free equilibrium when $R_0 < 1$ without condition $f = \eta$ of Theorem (4.1) in [25]. This means that once drug treatment, such as antiretroviral therapy, makes $R_0 < 1$, the infection is expected to disappear. In addition, by using the method of Theorem 3 we can also obtain the global stability of the disease-free equilibrium point of system (1) without the condition $f = \eta$.

The analysis showed that the local stability of the disease-free equilibrium is independent of the size of the delay, but the size of the delay may affect the endemic equilibrium, leading to a Hopf bifurcation. We studied the existence of the Hopf bifurcation of system (3) at the endemic equilibrium and gave the conditions for the emergence of Hopf bifurcation of the system in four cases.

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Author contributions

ZL: Conceptualization, Methodology, Writing–Original draft preparation, Validation. TZ: Writing–Review and Editing, Supervision, Project administration. All authors read and approved the final manuscript.

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Data availability

Not applicable.

Declarations

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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