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Research article

Threshold dynamics of a general delayed HIV model with double transmission modes and latent viral infection

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Abstract: In this paper, a general HIV model incorporating intracellular time delay is investigated. Taking the latent virus infection, both virus-to-cell and cell-to-cell transmissions into consideration, the model exhibits threshold dynamics with respect to the basic reproduction number $\Re_0$. If $\Re_0 < 1$, then there exists a unique infection-free equilibrium E_0, which is globally asymptotically stable. If $\Re_0 > 1$, then there exists E_0 and a globally asymptotically stable infected equilibrium E^*. When $\Re_0 = 1$, E_0 is linearly neutrally stable and a forward bifurcation takes place without time delay around $\Re_0 = 1$. The theoretical results and corresponding numerical simulations show that the existence of latently infected cells and the intracellular time delay have vital effect on the global dynamics of the general virus model.

Keywords: threshold dynamics; time delay; double transmission modes; latent viral infection
Mathematics Subject Classification: 92D30, 34K20

1. Introduction

Human immunodeficiency virus (HIV), the causative agent of AIDS, remains one of the biggest causes of morbidity and mortality, infecting around 37.7 million people worldwide and bringing about nearly 0.68 million AIDS-related death in 2020 [42]. HIV attacks cells of the immune system, primarily macrophages and CD4+T cells, leading to immunodeficiency of individual. If untreated, individual has more difficulty fighting againt some opportunistic diseases and eventually results to death. Considerable efforts on immunity to HIV and drug development have been taken since the discovery of AIDS, which have brought about quite a few approved antiretroviral drugs [43]. Antiretroviral drugs, which can prevent the replication of HIV and restrain the transmission and progression to AIDS, are currently the only approved therapies specifically targeting HIV, and there were 27.5 million or so patients receiving antiretroviral therapies (ART) in 2020 [42]. However, ATR can not clear HIV due to the persistence of low-level viraemia from virus reservoirs which are

insensitive to ATR [33]. Despite intensive research and tremendous progress, there is still not an explicit explanation for the pathogenesis of HIV infection. Effective vaccines and permanent cure therapies for HIV have not been obtained and thus life-long treatment is necessary.

In the past decades, based on ongoing technology development and extensive clinical trials, a new research field, viral dynamics, arose. Various mathematical models on HIV are common and applicable to interpret and predict the time-course of viral levels during HIV infection process. Understanding threshold dynamics of virus models can be significant to design preventive measures, intervention means and treatment strategies for the infectious disease control and help to take more effective drug therapies in clinical practice [2, 6, 12, 21]. A basic within-host virus dynamics model consists of three compartments: uninfected target cells $T(t)$, infected cells $I(t)$ and free virus $V(t)$, constituting the following virus model [2, 13]:

$$\begin{cases} \dfrac{\mathrm{d}T}{\mathrm{d}t} = \Lambda - dT(t) - \beta T(t)V(t), \\ \dfrac{\mathrm{d}I}{\mathrm{d}t} = \beta T(t)V(t) - \delta_I I(t), \\ \dfrac{\mathrm{d}V}{\mathrm{d}t} = N\delta_I I(t) - kV(t), \end{cases} \tag{1.1}$$

where the target cells are produced at the constant rate Λ and lost to intrinsic mortality rate d. The viral infection on susceptible cells is modelled by a bilinear incidence function $\beta T(t)V(t)$. δ_I and k denote the corresponding death rates of infected cells and free virus, respectively. Per infected cell releases N particles in its lifespan.

In virus model (1.1), uninfected healthy cells are assumed to be infected only directly by free viruses, that is, through the virus-to-cell transmission in the bloodstream, in which virions are released from infected cells and then move randomly around to find a new uninfected target cell to infect. For decades it was believed that the spreading of HIV-1 within a host was mainly through free circulation of the viral particles, with a repeated process consisting of attachment of viruses to T cells, fusion of viruses into the T cells, replication and assembling of viruses inside the infected T cells, release of newly produced viral particles from the infected cells, and diffusion of the released viral particles to catch other T cells. However, recent studies have revealed that the cell-to-cell transmission also has a significant impact on the virus infection [31] and cell-to-cell spread mode may be more effective than virus-to-cell spread model in transmitting HIV-1 [7, 8, 24, 30]. A large number of viral particles can also be simultaneously translocated from infected cells to uninfected cells through the structures termed virological synapses [4, 11]. Sigal et al. [33] investigated that despite ART, cell-to-cell transmission of HIV permits ongoing replication.

Besides, it is not instantaneous to produce new virus particles in the process of viral spread. It is delayed by the time for virions entering into cells and the replication of new virions, including the process of the transcription and integration of RNA and the production of the capsid proteins. Since the maturation time of a virus (0.3 days for HIV) is much shorter than the life-span of infected cell [10, 23], researchers usually ignored the virus maturation time in viral infection dynamics. Recently, researchers have constructed and analyzed delayed intra-host viral infection models incorporating both virus-to-cell and cell-to-cell transmissions of virions [18, 32, 34, 40]. Spatial diffusion is also significant to describe viral transmission. In Wang and Wang [36], a model incorporating the random movement of viruses was proposed and analyzed while the motion of

corresponding cells was ignored, based on which McCluskey and Yang [20] and Sun and Wang [34] further considered general incidence rates and two transmission routes. In Teng et al. [35], a reaction-diffusion virus infection model with nonlinear incidence and humoral immunity was proposed, in which the random movement of individuals was also denoted by Fickian diffusions. In Wang et al. [37], extinction and persistence for a spatially heterogeneous HIV model and the global stability of steady states for corresponding spatially homogeneous model were explored. Further, in view of the propagation mechanism for the virus, age structure is a helpful tool to optimize the model [14, 41].

In addition, effective medical therapies can limit viral replication to a low level while virus particles cannot be eliminated. A critical factor is the existence of latently infected cells, which can not be ignored in clinic treatment and mathematical modelling. The latent reservoir persists mainly as proviruses integrated into the genomes of infected resting memory CD4+ T cells [5, 39]. Latently infected CD4+ T cells live long and can not be affected by antiretroviral drugs or immune responses, while they can be activated by relevant antigens to produce virus. Latently infected cells have been a topic of great interest since they were subsequently shown to persist even in individuals on highly active antiretroviral therapy (HAART) [17].

Motivated by above works, in this paper, we focus on the following delayed virus model with general functions, incorporating latent viral infection, both virus-to-cell transmission and cell-to-cell transmission

$$\begin{cases} \dfrac{\mathrm{d}T}{\mathrm{d}t} = \Lambda - dT(t) - f(T(t), V(t)) - g(T(t), I(t)), \\ \dfrac{\mathrm{d}L}{\mathrm{d}t} = \xi e^{-m_1\tau_1} f(T(t-\tau_1), V(t-\tau_1)) + \xi e^{-m_1\tau_1} g(T(t-\tau_1), I(t-\tau_1)) - (\alpha + \delta_L)L(t), \\ \dfrac{\mathrm{d}I}{\mathrm{d}t} = (1-\xi)e^{-m_2\tau_2} f(T(t-\tau_2), V(t-\tau_2)) + (1-\xi)e^{-m_2\tau_2} g(T(t-\tau_2), I(t-\tau_2)) - \delta_I I(t) + \alpha L, \\ \dfrac{\mathrm{d}V}{\mathrm{d}t} = N\delta_I I(t) - cV(t). \end{cases} \tag{1.2}$$

In model (1.2), $L(t)$ represents the concentration of latently infected cells at time t with the mortality rate δ_L. Latently infected cells can be activated by relevant antigens to become productively infected cells at the rate α. Here we introduce the constant $\xi \in (0, 1)$ to specify the proportion of infection that lead target cells into latency stage. The parameter $\tau_1 \geq 0$ and $\tau_2 \geq 0$ represent the intracellular latency for the virus-to-cell infection and the cell-to-cell infection. m_1 and m_2 denote the constant death rates of latently infected cells and infected cells which have not produced viruses. Then $e^{-m_i\tau_i}$ is the probability for infected cells to survive from time $t - \tau_i$ to t, $i = 1, 2$. In system (1.2), the virus-to-cell spread and the cell-to-cell spread are expressed by the incidence functions $f(T, V)$ and $g(T, I)$, which are assumed to satisfy the following assumptions:

(i) $f, g \in C^1(\mathbb{R}^2_+, \mathbb{R}_+)$ are differentiable; $f(T, 0) = f(0, V) = g(T, 0) = g(0, I) = 0$ for all $T, I, V \geq 0$, $f(T, V) > 0$ and $g(T, I) > 0$ for all $T, I, V > 0$.

(ii) $\frac{\partial f(T,V)}{\partial T} > 0$ and $\frac{\partial g(T,I)}{\partial T} > 0$ for all $T \geq 0$ and $V, I > 0$; $\frac{\partial f(T,V)}{\partial V} \geq 0$ and $\frac{\partial g(T,I)}{\partial I} \geq 0$ for all $T, V, I \geq 0$.

(iii) $\frac{\partial^2 f(T,V)}{\partial T \partial V} \geq 0$, $\frac{\partial^2 g(T,I)}{\partial T \partial I} \geq 0$, $\frac{\partial f(T,V)}{\partial V} \leq \frac{f(T,V)}{V}$ and $\frac{\partial g(T,I)}{\partial I} \leq \frac{g(T,I)}{I}$ for all $T, V, I \geq 0$. This indicates that $\frac{\partial}{\partial V}\left(\frac{f(T,V)}{V}\right) \leq 0$ and $\frac{\partial}{\partial I}\left(\frac{g(T,I)}{I}\right) \leq 0$.

Here, we are concerned with the general interaction functions to express the two modes of virus

transmission. That is, the contribution of the interaction between uninfected target cells T and free viruses V (infected cells I) to the growth rate of the infected cells is represented by a general functional response term $f(T, V)$ $(g(T, I))$, no longer accounted for by some specific function. Through this approach, we establish a unified theoretical framework to describe the HIV propagation process.

Now define the following Banach space

$$C_+ = \{\phi \in C([-\tau, 0], \mathbb{R}_+) \mid \phi(\theta) \text{ is uniformly continuous for } \theta \in [-\tau, 0] \text{ and } \|\phi\| < \infty\},$$

with norm $\|\phi\| = \sup_{-\tau \le \theta \le 0} |\phi(\theta)|$. Then, we consider system (1.2) with the following initial conditions

$$T(\theta) = \phi_1(\theta),\ L(\theta) = \phi_2(\theta), I(\theta) = \phi_3(\theta),\ V(\theta) = \phi_4(\theta),\ \ \theta \in [-\tau, 0], \tag{1.3}$$

where $\phi_i(\theta) \in C_+$ satisfies $\phi_i(\theta) \geq, \not\equiv 0$ and $\phi_i(0) > 0,\ i = 1, 2, 3, 4$.

In this paper, we consider the existence, local and global asymptotical stability of the infection-free equilibrium and the infected equilibrium in terms of the basic reproduction number $\Re_0$. For each equilibrium, we first explore the local asymptotical stability by considering the corresponding characteristic equations, and then discuss their global attractiveness by constructing corresponding Liapunov functionals, arriving at the global asymptotical stability of the equilibria.

The paper is organized as follows. In Section 2, we study the boundedness and positivity of solutions and the existence of equilibria for system (1.2). In Section 3, we explore the dynamics of system without time delay. In Sections 4 and 5, we explore the corresponding local and global stability of infection-free equilibrium and infected equilibrium, respectively. In Section 6, some specific examples and applications are presented to illustrate the theoretical results. Conclusions and discussions can be found in Section 7.

2. Boundedness, positivity and the existence of equilibria

Through the fundamental theory analysis on functional differential equations [9], system (1.2) with initial conditions (1.3) admits one unique solution. In this section, we first explore the positivity and boundedness of the solutions of system (1.2).

Theorem 2.1. *Solutions of system (1.2) are positive and ultimately uniformly bounded for all $t > 0$.*

Proof. For $T(t)$, suppose that there exists $t_1 > 0$ such that $T(t_1) = 0$ and $T(t) > 0$ for $t \in [0, t_1)$. Then we have $T'(t_1) \leq 0$ while the first equation of (1.2) implies that $T'(t_1) = \Lambda > 0$. This is a contradiction. Thus, $T(t) > 0$ for $t > 0$.

Let $t_2 > 0$ be the first time such that $\min\{L(t_2), I(t_2), V(t_2)\} = 0$. In the following, we verify the non-existence of t_2 to ensure the positivity of $L(t)$, $I(t)$ and $V(t)$.

(I) If $L(t_2) = 0$ and $L(t) > 0$ for $t \in [0, t_2)$ $(I(t_2) \geq 0,\ V(t_2) \geq 0$ and $I(t) > 0,\ V(t) > 0$ for $t \in [0, t_2))$, then $L'(t_2) \leq 0$. From the second equation of (1.2), we have

$$L'(t_2) = \xi e^{-m_1\tau_1} f(T(t_2 - \tau_1), V(t_2 - \tau_1)) + \xi e^{-m_1\tau_1} g(T(t_2 - \tau_1), I(t_2 - \tau_1)) > 0,$$

which contradicts with $L'(t_2) \leq 0$. Thus, $L(t) > 0$ for $t > 0$.

(II) Similarly, if $I(t_2) = 0$ and $I(t) > 0$ for $t \in [0, t_2)$ ($L(t_2) \geq 0,\ V(t_2) \geq 0$ and $L(t) > 0,\ V(t) > 0$ for $t \in [0, t_2)$), then $I'(t_2) \leq 0$. From the third equation of (1.2), we have

$$I'(t_2) = (1-\xi)e^{-m_2\tau_2} f(T(t_2-\tau_2), V(t_2-\tau_2)) + (1-\xi)e^{-m_2\tau_2} g(T(t_2-\tau_2), I(t_2-\tau_2)) + \alpha L(t_2) > 0,$$

which contradicts with $I'(t_2) \leq 0$. Thus, $I(t) > 0$ for $t > 0$.

(III) Again, if $V(t_2) = 0$ and $V(t) > 0$ for $t \in [0, t_2)$ ($L(t_2) \geq 0,\ I(t_2) > 0$ and $L(t) > 0,\ I(t) > 0$ for $t \in [0, t_2)$), then $V'(t_2) \leq 0$. From the fourth equation of (1.2), we have

$$V'(t_2) = N\delta_I I(t_2) > 0,$$

which contradicts with $V'(t_2) \leq 0$. Thus, $V(t) > 0$ for $t > 0$.

Hence, from above discussion, $T(t) > 0,\ L(t) > 0,\ I(t) > 0$ and $V(t) > 0$ for all $t > 0$. In the following, we verify the boundedness.

From the first equation of (1.2), we obtain $T'(t) \leq \Lambda - dT(t)$. This implies that $\limsup_{t\to+\infty} T(t) \leq \frac{\Lambda}{d}$.

Let $W_1(t) = \xi e^{-m_1\tau_1} T(t-\tau_1) + L(t)$. Then

$$W_1'(t) \leq \Lambda\xi e^{-m_1\tau_1} - \min\{d, \alpha+\delta_L\} W_1.$$

This implies that $\limsup_{t\to+\infty} W_1(t) \leq \frac{\Lambda\xi e^{-m_1\tau_1}}{\min\{d,\alpha+\delta_L\}}$. Thus, we have $\limsup_{t\to+\infty} L(t) \leq \frac{\Lambda\xi e^{-m_1\tau_1}}{\min\{d,\alpha+\delta_L\}}$.

Let $W_2(t) = (1-\xi)e^{-m_2\tau_2} T(t-\tau_2) + I(t)$. Then

$$W_2'(t) \leq \left[\Lambda(1-\xi)e^{-m_2\tau_2} + \frac{\Lambda\xi e^{-m_1\tau_1}}{\min\{d, \alpha+\delta_L\}}\right] - \min\{d, \delta_I\} W_2.$$

This implies that $\limsup_{t\to+\infty} W_2(t) \leq \frac{\Lambda(1-\xi)e^{-m_2\tau_2}}{\min\{d,\delta_I\}} + \frac{\alpha\Lambda\xi e^{-m_1\tau_1}}{\min\{d,\delta_I\}\min\{d,\alpha+\delta_L\}} := \tilde{K}$. Thus, $\limsup_{t\to+\infty} I(t) \leq \tilde{K}$.

From the fourth equation of (1.2), we have $V'(t) \leq N\delta_I\tilde{K} - cV(t)$. Thus, we have $\limsup_{t\to+\infty} V(t) \leq \frac{N\delta_I\tilde{K}}{c}$.

Hence, solutions of system (1.2) are positive and ultimately uniformly bounded for all $t > 0$. □

Define the following bounded feasible region

$$\Omega = \left\{(T, L, I, V) \in C_+^4 \mid \|T\| \leq \frac{\Lambda}{d},\ \|L\| \leq \frac{\Lambda\xi e^{-m_1\tau_1}}{\min\{d, \alpha+\delta_L\}},\ \|I\| \leq \tilde{K},\ \|V\| \leq \frac{N\delta_I\tilde{K}}{c}\right\}.$$

Then from Theorem 2.1, Ω is a positively invariant set for system (1.2).

Secondly, we explore the existence of equilibria for system (1.2). To this end, we define

$$K := \frac{\alpha\xi}{\alpha+\delta_L} e^{-m_1\tau_1} + (1-\xi)e^{-m_2\tau_2}$$

and the following basic reproduction number

$$\Re_0 := K\left(\frac{N}{c}\frac{\partial f(\frac{\Lambda}{d}, 0)}{\partial V} + \frac{1}{\delta_I}\frac{\partial g(\frac{\Lambda}{d}, 0)}{\partial I}\right).$$

Then, the existence of equilibria of system (1.2) is determined by the sign of $\Re_0 - 1$.

Theorem 2.2. *If $\Re_0 \leq 1$, then system (1.2) only has an infection-free equilibrium E_0; whereas, if $\Re_0 > 1$, then there exist E_0 and an infected equilibrium E^*.*

Proof. The infection-free equilibrium $E_0 = (\frac{\Lambda}{d}, 0, 0, 0)$ always exists. In order to explore the existence of infected equilibrium $E^* = (T^*, L^*, I^*, V^*)$, we need to discuss the following equations

$$\begin{cases} \Lambda - dT - f(T,V) - g(T,I) = 0, \\ \xi f(T,V) + \xi g(T,I) - (\alpha + \delta_L)e^{m_1\tau_1}L = 0, \\ (1-\xi)f(T,V) + (1-\xi)g(T,I) - \delta_I e^{m_2\tau_2}I + \alpha e^{m_2\tau_2}L = 0, \\ N\delta_I I - cV = 0. \end{cases} \tag{2.1}$$

From the first and second equations of (2.1), we obtain

$$T = \frac{\Lambda}{d} - \frac{\alpha + \delta_L}{d\xi}e^{m_1\tau_1}L. \tag{2.2}$$

Let

$$J := \frac{1-\xi}{\xi}(\alpha + \delta_L)e^{m_1\tau_1 - m_2\tau_2} + \alpha = \frac{\alpha + \delta_L}{\xi}e^{m_1\tau_1}K. \tag{2.3}$$

Then, due to the second and third equations of (2.1), we have

$$I = \frac{J}{\delta_I}L. \tag{2.4}$$

The fourth equation of (2.1) yields

$$V = \frac{N\delta_I}{c}I = \frac{NJ}{c}L. \tag{2.5}$$

By substituting (2.2), (2.4) and (2.5) into the second and third equations of (2.1), we define the following auxiliary mapping:

$$\begin{aligned} \Phi(L) :=& f(T,V) + g(T,I) - \delta_I e^{m_2\tau_2}I + \alpha e^{m_2\tau_2}L - (\alpha + \delta_L)e^{m_1\tau_1}L \\ =& f(\frac{\Lambda}{d} - \frac{\alpha + \delta_L}{d\xi}e^{m_1\tau_1}L, \frac{NJ}{c}L) + g(\frac{\Lambda}{d} - \frac{\alpha + \delta_L}{d\xi}e^{m_1\tau_1}L, \frac{J}{\delta_I}L) - \frac{\alpha + \delta_L}{\xi}e^{m_1\tau_1}L. \end{aligned}$$

Clearly, $\Phi(0) = f(\frac{\Lambda}{d}, 0) + g(\frac{\Lambda}{d}, 0) = 0$ and $\Phi(\frac{\Lambda\xi}{\alpha+\delta_L}e^{-m_1\tau_1}) = -\Lambda < 0$. Besides, when $\Re_0 > 1$, we have

$$\begin{aligned} \Phi'(0) =& J\left(\frac{N}{c}\frac{\partial f(\frac{\Lambda}{d}, 0)}{\partial V} + \frac{1}{\delta_I}\frac{\partial g(\frac{\Lambda}{d}, 0)}{\partial I}\right) - \frac{\alpha + \delta_L}{\xi}e^{m_1\tau_1} \\ =& \frac{\alpha + \delta_L}{\xi}e^{m_1\tau_1}(\Re_0 - 1) > 0. \end{aligned}$$

Thus, there exists $L^* \in (0, \frac{\Lambda\xi}{\alpha+\delta_L}e^{-m_1\tau_1})$, such that $E^* = (T^*, L^*, I^*, V^*)$ exists.

Moreover, we can verify that E^* is unique. On (T^*, L^*, I^*, V^*), due to the second equation of (2.1), (2.5) and (2.4), there holds

$$\frac{\alpha + \delta_L}{\xi}e^{m_1\tau_1} = \frac{f(T^*, V^*) + g(T^*, I^*)}{L^*} = J\left(\frac{N}{c}\frac{f(T^*, V^*)}{V^*} + \frac{1}{\delta_I}\frac{g(T^*, I^*)}{I^*}\right).$$

Then under Assumptions (ii) and (iii), we further have

$$\begin{aligned}\Phi'(L^*) =& -\frac{\alpha+\delta_L}{d\xi}e^{m_1\tau_1}\left(\frac{\partial f(T^*,V^*)}{\partial T}+\frac{\partial g(T^*,I^*)}{\partial T}\right)\\ &+J\left(\frac{N}{c}\frac{\partial f(T^*,V^*)}{\partial V}+\frac{1}{\delta_I}\frac{\partial g(T^*,I^*)}{\partial I}\right)-\frac{\alpha+\delta_L}{\xi}e^{m_1\tau_1}\\ =& -\frac{\alpha+\delta_L}{d\xi}e^{m_1\tau_1}\left(\frac{\partial f(T^*,V^*)}{\partial T}+\frac{\partial g(T^*,I^*)}{\partial T}\right)\\ &+\frac{NJ}{c}\left(\frac{\partial f(T^*,V^*)}{\partial V}-\frac{f(T^*,V^*)}{V^*}\right)+\frac{J}{\delta_I}\left(\frac{\partial g(T^*,I^*)}{\partial I}-\frac{g(T^*,I^*)}{I^*}\right)\\ <&0.\end{aligned}$$

Thus, when $\Re_0 > 1$, there exists a unique infected equilibrium $E^* = (T^*, L^*, I^*, V^*)$; when $\Re_0 < 1$, there exists no infected equilibrium. Whereas, when $\Re_0 = 1$, $\Phi'(0) = 0$ and $\Phi''(0) \le 0$. If $\Phi''(0) < 0$, then there exists no infected equilibrium. If $\Phi''(0) = 0$, then $\Phi^{(l)}(0) = 0,\ l = 3, 4, ...$, and due to Assumption (ii), for any $I \in (0, \frac{\Lambda K}{\delta_I})$,

$$\begin{aligned}\Phi'(I) =& -\frac{\delta_I}{Kd}\left(\frac{\partial f(\frac{\Lambda-\frac{\delta_I}{K}I}{d},\frac{N\delta_I}{c}I)}{\partial T}+\frac{\partial g(\frac{\Lambda-\frac{\delta_I}{K}I}{d},I)}{\partial T}\right)+\frac{N\delta_I}{c}\frac{\partial f(\frac{\Lambda-\frac{\delta_I}{K}I}{d},\frac{N\delta_I}{c}I)}{\partial V}+\frac{\partial g(\frac{\Lambda-\frac{\delta_I}{K}I}{d},I)}{\partial I}-\frac{\delta_I}{K}\\ <&\frac{N\delta_I}{c}\frac{\partial f(\frac{\Lambda}{d},0)}{\partial V}+\frac{\partial g(\frac{\Lambda}{d},0)}{\partial I}-\frac{\delta_I}{K}=\frac{\delta_I}{K}(\Re_0-1)=0.\end{aligned}$$

Thus, in this case, there exists no infected equilibrium. □

3. Dynamics of system without time delay

In this section, we consider system (1.2) without time delay. Let $T = \varsigma_1$, $L = \varsigma_2$, $I = \varsigma_3$, $V = \varsigma_4$, then we discuss the following ODE system:

$$\begin{cases}\dfrac{\mathrm{d}\varsigma_1}{\mathrm{d}t} = \Lambda - d\varsigma_1(t) - f(\varsigma_1(t),\varsigma_4(t)) - g(\varsigma_1(t),\varsigma_3(t)) := \chi_1,\\ \dfrac{\mathrm{d}\varsigma_2}{\mathrm{d}t} = \xi f(\varsigma_1(t),\varsigma_4(t)) + \xi g(\varsigma_1(t),\varsigma_3(t)) - (\alpha+\delta_L)\varsigma_2(t) := \chi_2,\\ \dfrac{\mathrm{d}\varsigma_3}{\mathrm{d}t} = (1-\xi) f(\varsigma_1(t),\varsigma_4(t)) + (1-\xi) g(\varsigma_1(t),\varsigma_3(t)) - \delta_I\varsigma_3(t) + \alpha\varsigma_2 := \chi_3,\\ \dfrac{\mathrm{d}\varsigma_4}{\mathrm{d}t} = N\delta_I\varsigma_3(t) - c\varsigma_4(t) := \chi_4.\end{cases} \tag{3.1}$$

Through similar analysis as in Section 2, for system (3.1), $\Re_0 := K\left(\frac{N}{c}\frac{\partial f(\frac{\Lambda}{d},0)}{\partial \varsigma_4}+\frac{1}{\delta_I}\frac{\partial g(\frac{\Lambda}{d},0)}{\partial \varsigma_3}\right)$ and we have the following result.

Theorem 3.1. *If $\Re_0 < 1$, then the infection-free equilibrium E_0 is locally asymptotically stable. If $\Re_0 > 1$, then E_0 is unstable. If $\Re_0 = 1$, then E_0 is linearly neutrally stable and there exists a forward bifurcation around E_0.*

Proof. The characteristic equation of the linearization for system (3.1) is $(\lambda + d)G_0(\lambda) = 0$, where

$$G_0(\lambda) = (\lambda + \alpha + \delta_L)(\lambda + c)(\lambda + \delta_I) - \left[N\delta_I \frac{\partial f(\frac{\Lambda}{d}, 0)}{\partial \varsigma_4} + (\lambda + c)\frac{\partial g(\frac{\Lambda}{d}, 0)}{\partial \varsigma_3}\right]\left[\alpha\xi + (\lambda + \alpha + \delta_L)(1 - \xi)\right].$$

Obviously, there is always a negative root $\lambda = -d$ and $G_0(\lambda) = 0$ can be written as

$$(\lambda + \alpha + \delta_L)(\lambda + c)(\lambda + \delta_I) = \left[N\delta_I \frac{\partial f(\frac{\Lambda}{d}, 0)}{\partial \varsigma_4} + (\lambda + c)\frac{\partial g(\frac{\Lambda}{d}, 0)}{\partial \varsigma_3}\right]\left[\alpha\xi + (\lambda + \alpha + \delta_L)(1 - \xi)\right]. \tag{3.2}$$

By dividing $(\lambda + \alpha + \delta_L)(\lambda + c)(\lambda + \delta_I)$ in both sides of (3.2), we obtain

$$1 = \left[\frac{N\delta_I}{(\lambda + c)(\lambda + \delta_I)}\frac{\partial f(\frac{\Lambda}{d}, 0)}{\partial \varsigma_4} + \frac{1}{\lambda + \delta_I}\frac{\partial g(\frac{\Lambda}{d}, 0)}{\partial \varsigma_3}\right]\left[\frac{\alpha\xi}{\lambda + \alpha + \delta_L} + (1 - \xi)\right]. \tag{3.3}$$

Suppose that there exists a eigenvalue $\lambda = \iota + \kappa i$ $(\iota \geq 0)$. Then the modulus of both sides of (3.3) satisfies

$$1 < \left(\frac{N}{c}\frac{\partial f(\frac{\Lambda}{d}, 0)}{\partial \varsigma_4} + \frac{1}{\delta_I}\frac{\partial g(\frac{\Lambda}{d}, 0)}{\partial \varsigma_3}\right)\left[\frac{\alpha\xi}{\alpha + \delta_L} + (1 - \xi)\right] = \Re_0.$$

This contradicts with $\Re_0 < 1$. Thus, all roots of (3.2) have negative real parts. Hence, when $\Re_0 < 1$, E_0 is locally asymptotically stable.

On the other hand, when $\Re_0 > 1$, there holds

$$\begin{aligned} G_0(0) =& c\delta_I(\alpha + \delta_L) - \left(N\delta_I \frac{\partial f(\frac{\Lambda}{d}, 0)}{\partial \varsigma_4} + c\frac{\partial g(\frac{\Lambda}{d}, 0)}{\partial \varsigma_3}\right)\left[\alpha\xi + (\alpha + \delta_L)(1 - \xi)\right] \\ =& c\delta_I(\alpha + \delta_L)(1 - \Re_0) < 0 \end{aligned}$$

and $G_0(+\infty) = +\infty$. Thus, there exists at least one real root $\lambda_0 > 0$, such that $G_0(\lambda_0) = 0$. Hence, if $\Re_0 > 1$, then E_0 is unstable.

When $\Re_0 = 1$, characteristic equation (3.2) has one simple zero root $\lambda = 0$ and two roots with negative real part. Thus E_0 is a linearly neutrally stable non-hyperbolic equilibrium as $\Re_0 = 1$. We can further verify that system (3.1) exhibits forward bifurcation around E_0 at $\xi^* := (\frac{\alpha}{\delta_L} + 1)(1 - \frac{1}{\hat{K}})$, where $\hat{K} = \frac{N}{c}\frac{\partial f(\frac{\Lambda}{d}, 0)}{\partial \varsigma_4} + \frac{1}{\delta_I}\frac{\partial g(\frac{\Lambda}{d}, 0)}{\partial \varsigma_3}$, that is, $\Re_0 = 1$.

Let $\mathcal{L}_0(E_0, \xi^*)$ be the Jacobian matrix of the system (3.1) at $\xi = \xi^*$. The left eigenvector $\mu = (\mu_1, \mu_2, \mu_3, \mu_4)$ of the Jacobian matrix $\mathcal{L}_0(E_0, \xi^*)$ is given by $\mu \cdot \mathcal{L}_0(E_0, \xi^*)$. We obtain

$$(\mu_1, \mu_2, \mu_3, \mu_4) = (0, \alpha, \alpha + \delta_L, \frac{\alpha + \delta_L}{c}\left[\frac{\alpha\xi}{\alpha + \delta_L} + (1 - \xi)\right]\frac{\partial f(\frac{\Lambda}{d}, 0)}{\partial \varsigma_4}).$$

The right eigenvector $\omega = (\omega_1, \omega_2, \omega_3, \omega_4)$ of the Jacobian matrix $\mathcal{L}_0(E_0, \xi^*)$ is given by $\mathcal{L}_0(E_0, \xi^*) \cdot \omega$. We obtain

$$(\omega_1, \omega_2, \omega_3, \omega_4)^T = (-\frac{1}{d}\left(N\delta_I \frac{\partial f(\frac{\Lambda}{d}, 0)}{\partial \varsigma_4} + c\frac{\partial g(\frac{\Lambda}{d}, 0)}{\partial \varsigma_3}\right), \frac{\xi}{\alpha + \delta_L}\left(N\delta_I \frac{\partial f(\frac{\Lambda}{d}, 0)}{\partial \varsigma_4} + c\frac{\partial g(\frac{\Lambda}{d}, 0)}{\partial \varsigma_3}\right), 0, N\delta_I)^T.$$

Let $\chi_i,\ i = 1, 2, 3, 4$, denotes the right-hand side of system (3.1). Then we obtain the following non-zero derivations

$$\begin{aligned}
&\left(\frac{\partial^2\chi_1}{\partial\varsigma_3^2}\right)_{E_0} = -\frac{\partial^2 g(\frac{\Lambda}{d},0)}{\partial\varsigma_3^2}, \quad \left(\frac{\partial^2\chi_1}{\partial\varsigma_4^2}\right)_{E_0} = -\frac{\partial^2 f(\frac{\Lambda}{d},0)}{\partial\varsigma_4^2},\\
&\left(\frac{\partial^2\chi_2}{\partial\varsigma_3^2}\right)_{E_0} = \xi\frac{\partial^2 g(\frac{\Lambda}{d},0)}{\partial\varsigma_3^2}, \quad \left(\frac{\partial^2\chi_2}{\partial\varsigma_4^2}\right)_{E_0} = \xi\frac{\partial^2 f(\frac{\Lambda}{d},0)}{\partial\varsigma_4^2},\\
&\left(\frac{\partial^2\chi_3}{\partial\varsigma_3^2}\right)_{E_0} = (1-\xi)\frac{\partial^2 g(\frac{\Lambda}{d},0)}{\partial\varsigma_3^2}, \quad \left(\frac{\partial^2\chi_3}{\partial\varsigma_4^2}\right)_{E_0} = (1-\xi)\frac{\partial^2 f(\frac{\Lambda}{d},0)}{\partial\varsigma_4^2},\\
&\left(\frac{\partial^2\chi_2}{\partial\varsigma_3\partial\xi^*}\right)_{E_0} = \frac{\partial g(\frac{\Lambda}{d},0)}{\partial\varsigma_3}, \quad \left(\frac{\partial^2\chi_2}{\partial\varsigma_4\partial\xi^*}\right)_{E_0} = \frac{\partial f(\frac{\Lambda}{d},0)}{\partial\varsigma_4},\\
&\left(\frac{\partial^2\chi_3}{\partial\varsigma_3\partial\xi^*}\right)_{E_0} = -\frac{\partial g(\frac{\Lambda}{d},0)}{\partial\varsigma_3}, \quad \left(\frac{\partial^2\chi_3}{\partial\varsigma_4\partial\xi^*}\right)_{E_0} = -\frac{\partial f(\frac{\Lambda}{d},0)}{\partial\varsigma_4}.
\end{aligned}$$

Due to [3], we yield the following bifurcation constants ϱ and σ:

$$\begin{aligned}
\varrho &= \sum_{i,j,k=1}^{4}\mu_k\omega_i\omega_j\left(\frac{\partial^2\chi_k}{\partial\varsigma_i\partial\varsigma_j}\right)_{E_0} = \left[\alpha\xi^2+(\alpha+\delta_L)(1-\xi)^2\right]\left(N^2\delta_I^2\frac{\partial^2 f(\frac{\Lambda}{d},0)}{\partial\varsigma_4^2}+c^2\frac{\partial^2 g(\frac{\Lambda}{d},0)}{\partial\varsigma_3^2}\right)\le 0,\\
\sigma &= \sum_{i,k=1}^{4}\mu_k\omega_i\left(\frac{\partial^2\chi_k}{\partial\varsigma_i\partial\xi^*}\right)_{E_0} = -\delta_L\left(N\delta_I\frac{\partial f(\frac{\Lambda}{d},0)}{\partial\varsigma_4}+c\frac{\partial g(\frac{\Lambda}{d},0)}{\partial\varsigma_3}\right)\le 0.
\end{aligned}$$

Under conditions $\frac{\partial^2 f(\frac{\Lambda}{d},0)}{\partial\varsigma_4^2}+\frac{\partial^2 g(\frac{\Lambda}{d},0)}{\partial\varsigma_3^2}\neq 0$ and $\frac{\partial f(\frac{\Lambda}{d},0)}{\partial\varsigma_4}+\frac{\partial g(\frac{\Lambda}{d},0)}{\partial\varsigma_3}\neq 0$, $a_1 < 0$ and $b_1 < 0$. Thus, due to Theorem 4.1 in [3], there exists a forward bifurcation. When $\xi < \xi^*$, that is, $\Re_0 > 1$, E_0 is unstable and there exists an locally asymptotically stable positive equilibrium E^*; when $\xi > \xi^*$, that is, $\Re_0 < 1$, E_0 is locally asymptotically stable. □

Note that the presence of forward bifurcation confirms the inhibition of the disease when $\Re_0 < 1$. From the forward bifurcation analysis, we know that if there is a stable coexistence equilibrium E^* bifurcating from E_0, E_0 changes its stability from stable to unstable.

4. Stability analysis of the infection-free equilibrium

In this section, we investigate the stability of the infection-free equilibrium E_0. We first focus on the local asymptotical stability of E_0 by discussing the distribution of the corresponding characteristic values.

Theorem 4.1. *If $\Re_0 < 1$, then the infection-free equilibrium E_0 is locally asymptotically stable. If $\Re_0 = 1$, then E_0 is linearly neutrally stable. If $\Re_0 > 1$, then E_0 is unstable.*

Proof. Let $\mathrm{X} = (T(t), L(t), I(t), V(t))$ and $\mathrm{X}_{\tau_i} = (T(t-\tau_i), L(t-\tau_i), I(t-\tau_i), V(t-\tau_i)),\ i = 1, 2$. Then the linearization of system (1.2) at E_0 can be expressed by

$$\frac{\mathrm{dX}}{\mathrm{d}t} = \mathcal{L}_0\mathrm{X} + \mathcal{M}_{01}\mathrm{X}_{\tau_1} + \mathcal{M}_{02}\mathrm{X}_{\tau_2},$$

where

$$\mathcal{L}_0 = \begin{pmatrix} -d & 0 & -\frac{\partial g(\frac{\Lambda}{d},0)}{\partial I} & -\frac{\partial f(\frac{\Lambda}{d},0)}{\partial V} \\ 0 & -(\alpha+\delta_L) & 0 & 0 \\ 0 & \alpha & -\delta_I & 0 \\ 0 & 0 & N\delta_I & -c \end{pmatrix},$$

$$\mathcal{M}_{01} = \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & \xi e^{-m_1\tau_1}\frac{\partial g(\frac{\Lambda}{d},0)}{\partial I} & \xi e^{-m_1\tau_1}\frac{\partial f(\frac{\Lambda}{d},0)}{\partial V} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

and

$$\mathcal{M}_{02} = \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & (1-\xi)e^{-m_2\tau_2}\frac{\partial g(\frac{\Lambda}{d},0)}{\partial I} & (1-\xi)e^{-m_2\tau_2}\frac{\partial f(\frac{\Lambda}{d},0)}{\partial V} \\ 0 & 0 & 0 & 0 \end{pmatrix}.$$

Then the characteristic equation is

$$det(\lambda I - \mathcal{L}_0 - \mathcal{M}_{01}e^{-\lambda\tau_1} - \mathcal{M}_{02}e^{-\lambda\tau_2}) = (\lambda+d)G_0(\lambda) = 0,$$

where

$$\begin{aligned} G_0(\lambda) =& (\lambda+\alpha+\delta_L)(\lambda+c)(\lambda+\delta_I) \\ & - \left[N\delta_I\frac{\partial f(\frac{\Lambda}{d},0)}{\partial V} + (\lambda+c)\frac{\partial g(\frac{\Lambda}{d},0)}{\partial I}\right]\left[\alpha\xi e^{-(m_1+\lambda)\tau_1} + (\lambda+\alpha+\delta_L)(1-\xi)e^{-(m_2+\lambda)\tau_2}\right]. \end{aligned}$$

Obviously, there is always a negative root $\lambda = -d$ and $G_0(\lambda) = 0$ can be written as

$$\begin{aligned} & (\lambda+\alpha+\delta_L)(\lambda+c)(\lambda+\delta_I) = \\ & \left[N\delta_I\frac{\partial f(\frac{\Lambda}{d},0)}{\partial V} + (\lambda+c)\frac{\partial g(\frac{\Lambda}{d},0)}{\partial I}\right]\left[\alpha\xi e^{-(m_1+\lambda)\tau_1} + (\lambda+\alpha+\delta_L)(1-\xi)e^{-(m_2+\lambda)\tau_2}\right]. \end{aligned} \tag{4.1}$$

By dividing $(\lambda+\alpha+\delta_L)(\lambda+c)(\lambda+\delta_I)$ in both sides of (4.1), we obtain

$$1 = \left[\frac{N\delta_I}{(\lambda+c)(\lambda+\delta_I)}\frac{\partial f(\frac{\Lambda}{d},0)}{\partial V} + \frac{1}{\lambda+\delta_I}\frac{\partial g(\frac{\Lambda}{d},0)}{\partial I}\right]\left[\frac{\alpha\xi}{\lambda+\alpha+\delta_L}e^{-(m_1+\lambda)\tau_1} + (1-\xi)e^{-(m_2+\lambda)\tau_2}\right]. \tag{4.2}$$

Suppose that there exists a eigenvalue $\lambda = \iota + \kappa i$ ($\iota \geq 0$). Then the modulus of both sides of (4.2) satisfies

$$1 < \left(\frac{N}{c}\frac{\partial f(\frac{\Lambda}{d},0)}{\partial V} + \frac{1}{\delta_I}\frac{\partial g(\frac{\Lambda}{d},0)}{\partial I}\right)\left[\frac{\alpha\xi}{\alpha+\delta_L}e^{-m_1\tau_1} + (1-\xi)e^{-m_2\tau_2}\right] = \Re_0.$$

This contradicts with $\Re_0 < 1$. Thus, all roots of (4.1) have negative real parts. Hence, when $\Re_0 < 1$, E_0 is locally asymptotically stable. Further, due to similar analysis, when $\Re_0 = 1$, any root of characteristic equation (4.1) has negative real part except a simple zero root $\lambda = 0$ and thus E_0 is linearly neutrally stable.

On the other hand, when $\Re_0 > 1$, there holds

$$\begin{aligned} G_0(0) =& c\delta_I(\alpha+\delta_L) - \left(N\delta_I\frac{\partial f(\frac{\Lambda}{d},0)}{\partial V} + c\frac{\partial g(\frac{\Lambda}{d},0)}{\partial I}\right)\left[\alpha\xi e^{-m_1\tau_1} + (\alpha+\delta_L)(1-\xi)e^{-m_2\tau_2}\right] \\ =& c\delta_I(\alpha+\delta_L)(1-\Re_0) < 0 \end{aligned}$$

and $G_0(+\infty) = +\infty$. Thus, there exists at least one real root $\lambda_0 > 0$, such that $G_0(\lambda_0) = 0$. Hence, if $\Re_0 > 1$, then E_0 is unstable. □

Based on the local asymptotical stability analysis, we construct a Lyapunov functional to verify the global asymptotical stability of E_0. Similar to the local asymptotical stability of E_0, the following theorem shows that the basic reproduction number $\Re_0$ acts as the threshold value for the global asymptotical stability of E_0.

Theorem 4.2. *If $\Re_0 < 1$, then the infection-free equilibrium E_0 is globally asymptotically stable; if $\Re_0 = 1$, then E_0 is globally attractive.*

Proof. Let

$$\Re_{01} = \frac{NK}{c}\frac{\partial f(\frac{\Lambda}{d},0)}{\partial V} \text{ and } \Re_{02} = \frac{K}{\delta_I}\frac{\partial g(\frac{\Lambda}{d},0)}{\partial I}.$$

Then $\Re_0 = \Re_{01} + \Re_{02}$. Define the following Liapunov functional

$$\begin{aligned} \mathcal{V}_0(t) =& \frac{\alpha}{\alpha+\delta_L}L + I + \frac{1-\Re_{02}}{N}V \\ &+ \frac{\alpha\xi}{\alpha+\delta_L}e^{-m_1\tau_1}\int_0^{\tau_1}(f(T(t-\theta),V(t-\theta)) + g(T(t-\theta),I(t-\theta)))\mathrm{d}\theta \\ &+ (1-\xi)e^{-m_2\tau_2}\int_0^{\tau_2}(f(T(t-\theta),V(t-\theta)) + g(T(t-\theta),I(t-\theta)))\mathrm{d}\theta. \end{aligned}$$

Calculating the time derivative of $\mathcal{V}_0(t)$ along (1.2) yields

$$\begin{aligned} \frac{\mathrm{d}\mathcal{V}_0}{\mathrm{d}t} =& K(f(T,V)+g(T,I)) - \delta_I\Re_{02}I - (1-\Re_{02})\frac{c}{N}V \\ =& \left[K\frac{f(T,V)}{V} - (1-\Re_{02})\frac{c}{N}\right]V + \left(K\frac{g(T,I)}{I} - \delta_I\Re_{02}\right)I. \end{aligned}$$

From Assumption (iii), we know $\frac{f(\frac{\Lambda}{d},V)}{V}$ is decreasing with respect to V and $\frac{g(\frac{\Lambda}{d},I)}{I}$ is decreasing with

respect to I. Thus, when $\Re_0 < 1$,

$$\begin{aligned}\frac{\mathrm{d}\mathcal{V}_0}{\mathrm{d}t} \leq & \left[K\lim_{V\to 0}\frac{f(\frac{\lambda}{d},V)}{V} - (1-\Re_{02})\frac{c}{N}\right]V + \left(K\lim_{I\to 0}\frac{g(\frac{\lambda}{d},I)}{I} - \delta_I\Re_{02}\right)I\\ =& \left[\frac{NK}{c}\frac{\partial f(\frac{\lambda}{d},0)}{\partial V} - (1-\Re_{02})\right]\frac{c}{N}V + \left(\frac{K}{\delta_I}\frac{\partial g(\frac{\lambda}{d},0)}{\partial I} - \Re_{02}\right)\delta_I I\\ =& [\Re_{01} - (1-\Re_{02})]\frac{c}{N}V + (\Re_{02}-\Re_{02})\delta_I I\\ =& (\Re_0 - 1)\frac{c}{N}V \leq 0.\end{aligned}$$

Let $\Theta_0 = \left\{(T, L, I, V) : \frac{\mathrm{d}\mathcal{V}_0}{\mathrm{d}t} = 0\right\}$. Then the largest invariant subset of Θ_0 just consists of E_0. Thus, due to the LaSalle's invariance principle [15], when $\Re_0 \leq 1$, E_0 is a global attractor. Further, combining the local asymptotical stability of E_0 under the condition $\Re_0 < 1$, E_0 is globally asymptotically stable. □

5. Stability analysis of the infected equilibrium

In this section, we analyze the stability of the infected equilibrium E^*. In order to explore the local asymptotical stability of E^*, we need to analyze the characteristic equation of system (1.2) on E^*. The linearization of system (1.2) at E^* can be expressed by

$$\frac{\mathrm{dX}}{\mathrm{d}t} = \mathcal{L}_1\mathrm{X} + \mathcal{M}_{11}\mathrm{X}_{\tau_1} + \mathcal{M}_{12}\mathrm{X}_{\tau_2},$$

where

$$\mathcal{L}_1 = \begin{pmatrix} -d - \frac{\partial g(T^*,I^*)}{\partial T} - \frac{\partial f(T^*,V^*)}{\partial T} & 0 & -\frac{\partial g(T^*,I^*)}{\partial I} & -\frac{\partial f(T^*,V^*)}{\partial V} \\ 0 & -(\alpha+\delta_L) & 0 & 0 \\ 0 & \alpha & -\delta_I & 0 \\ 0 & 0 & N\delta_I & -c \end{pmatrix},$$

$$\mathcal{M}_{11} = \begin{pmatrix} 0 & 0 & 0 & 0 \\ \xi e^{-m_1\tau_1}\left(\frac{\partial g(T^*,I^*)}{\partial T} + \frac{\partial f(T^*,V^*)}{\partial T}\right) & 0 & \xi e^{-m_1\tau_1}\frac{\partial g(T^*,I^*)}{\partial I} & \xi e^{-m_1\tau_1}\frac{\partial f(T^*,V^*)}{\partial V} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

and

$$\mathcal{M}_{12} = \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ (1-\xi)e^{-m_2\tau_2}\left(\frac{\partial g(T^*,I^*)}{\partial T} + \frac{\partial f(T^*,V^*)}{\partial T}\right) & 0 & (1-\xi)e^{-m_2\tau_2}\frac{\partial g(T^*,I^*)}{\partial I} & (1-\xi)e^{-m_2\tau_2}\frac{\partial f(T^*,V^*)}{\partial V} \\ 0 & 0 & 0 & 0 \end{pmatrix}.$$

Then the characteristic equation is

$$\begin{aligned}
&det(\lambda I - \mathcal{L}_1 - \mathcal{M}_{11}e^{-\lambda\tau_1} - \mathcal{M}_{12}e^{-\lambda\tau_2})\\
=&\left(\lambda + d + \frac{\partial g(T^*, I^*)}{\partial T} + \frac{\partial f(T^*, V^*)}{\partial T}\right)(\lambda + \alpha + \delta_L)(\lambda + c)(\lambda + \delta_I)\\
&- (\lambda + d)\left[N\delta_I\frac{\partial f(T^*, V^*)}{\partial V} + (\lambda + c)\frac{\partial g(T^*, I^*)}{\partial I}\right]\\
&\times\left[\alpha\xi e^{-(m_1+\lambda)\tau_1} + (\lambda + \alpha + \delta_L)(1 - \xi)e^{-(m_2+\lambda)\tau_2}\right]\\
=&0,
\end{aligned}$$

that is,

$$\begin{aligned}
&\left(\lambda + d + \frac{\partial g(T^*, I^*)}{\partial T} + \frac{\partial f(T^*, V^*)}{\partial T}\right)(\lambda + \alpha + \delta_L)(\lambda + c)(\lambda + \delta_I)\\
=&(\lambda + d)\left[N\delta_I\frac{\partial f(T^*, V^*)}{\partial V} + (\lambda + c)\frac{\partial g(T^*, I^*)}{\partial I}\right]\\
&\times\left[\alpha\xi e^{-(m_1+\lambda)\tau_1} + (\lambda + \alpha + \delta_L)(1 - \xi)e^{-(m_2+\lambda)\tau_2}\right].
\end{aligned} \tag{5.1}$$

By dividing $(\lambda + \alpha + \delta_L)(\lambda + c)(\lambda + \delta_I)(\lambda + d)$ in two sides of system (5.1), we obtain

$$\begin{aligned}
&\frac{\lambda + d + \frac{\partial g(T^*, I^*)}{\partial T} + \frac{\partial f(T^*, V^*)}{\partial T}}{\lambda + d}\\
=&\left[\frac{N\delta_I\frac{\partial f(T^*, V^*)}{\partial V}}{(\lambda + c)(\lambda + \delta_I)} + \frac{\frac{\partial g(T^*, I^*)}{\partial I}}{\lambda + \delta_I}\right]\\
&\times\left[\frac{\alpha\xi}{\lambda + \alpha + \delta_L}e^{-(m_1+\lambda)\tau_1} + (1 - \xi)e^{-(m_2+\lambda)\tau_2}\right].
\end{aligned} \tag{5.2}$$

Suppose that there exists eigenvalue $\lambda = \iota + \kappa i$ ($\iota \geq 0$). Then, since Assumption (ii), the modulus of the left side of (5.2) is more than one. Note that from the second and third equations of (2.1), we have

$$\alpha L^* = \frac{\alpha\xi}{\alpha + \delta_L}e^{-m_1\tau_1}(f(T^*, V^*) + g(T^*, I^*)) \tag{5.3}$$

and

$$\delta I^* = (1 - \xi)e^{-m_2\tau_2}(f(T^*, V^*) + g(T^*, I^*)) + \alpha L^*. \tag{5.4}$$

Then it follows from (5.3) and (5.4) that

$$\delta I^* = K\left(f(T^*, V^*) + g(T^*, I^*)\right). \tag{5.5}$$

Due to Assumption (iii), $V^* = \frac{N\delta_I}{c}I^*$ and (5.5), the other side of (5.2) satisfies

$$\begin{aligned}
&\left[\frac{N\delta_I\frac{\partial f(T^*, V^*)}{\partial V}}{(\lambda + c)(\lambda + \delta_I)} + \frac{\frac{\partial g(T^*, I^*)}{\partial I}}{\lambda + \delta_I}\right]\left[\frac{\alpha\xi}{\lambda + \alpha + \delta_L}e^{-(m_1+\lambda)\tau_1} + (1 - \xi)e^{-(m_2+\lambda)\tau_2}\right]\\
\leq&K\left(\frac{N}{c}\frac{\partial f(T^*, V^*)}{\partial V} + \frac{1}{\delta_I}\frac{\partial g(T^*, I^*)}{\partial I}\right) \leq K\left(\frac{N}{c}\frac{f(T^*, V^*)}{V^*} + \frac{1}{\delta_I}\frac{g(T^*, I^*)}{I^*}\right)\\
\leq&K\left(\frac{N}{c}\frac{f(T^*, V^*)}{\frac{N\delta_I}{c}I^*} + \frac{1}{\delta_I}\frac{g(T^*, I^*)}{I^*}\right) = \frac{K}{\delta_I I^*}\left(f(T^*, V^*) + g(T^*, I^*)\right) = 1.
\end{aligned}$$

This is a contradiction. Thus, all roots of (5.2) have negative real parts.

Hence, we obtain the following theorem on local asymptotical stability of E^*.

Theorem 5.1. *If $\Re_0 > 1$, then the infected equilibrium E^* is locally asymptotically stable.*

Moreover, using the similar proof of Section 4 in [16] and Theorem 3.1 in [38], we have the following theorem on uniformly persistence.

Theorem 5.2. *If $\Re_0 > 1$, then system (1.2) is uniformly persistent, that is, there exists a constant $\varpi > 0$ such that $\limsup_{t\to+\infty} \min\{T(t), L(t), I(t), V(t)\} \geq \varpi$.*

Based on the local asymptotical stability of the infected equilibrium E^* and the uniformly persistence of system (1.2), we further investigate the global asymptotical stability of E^*. For this purpose, we also need to make the following hypothesises on $f(T, V)$ and $g(T, I)$:

(A1): $\Big(\frac{T^*f(T,V)}{Tf(T^*,V^*)} - 1\Big)\Big(\frac{V}{V^*} - \frac{T^*f(T,V)}{Tf(T^*,V^*)}\Big) \geq 0$ and $\Big(\frac{T^*g(T,I)}{Tg(T^*,I^*)} - 1\Big)\Big(\frac{I}{I^*} - \frac{T^*g(T,I)}{Tg(T^*,I^*)}\Big) \geq 0$.

Then, by virtue of the Volterra type function [19]

$$h(\zeta) = \zeta - 1 - \ln\zeta,\ \zeta > 0,$$

we can construct a Lyapunov functional to ensure E^* to be globally attractive with respect to all the solutions with non-negative initial values, arriving at the following results on global asymptotical stability.

Theorem 5.3. *Suppose that Assumption (A1) holds. If $\Re_0 > 1$, then the infected equilibrium E^* is globally asymptotically stable.*

Proof. Define the following Liapunov functional $\mathcal{V}_1(t) = \mathcal{V}_{11}(t) + \mathcal{V}_{12}(t)$, where

$$\mathcal{V}_{11}(t) = KT^*h(\frac{T(t)}{T^*}) + \frac{\alpha L^*}{\alpha+\delta_L}h(\frac{L(t)}{L^*}) + I^*h(\frac{I(t)}{I^*}) + \frac{K}{c}f(T^*, V^*)h(\frac{V(t)}{V^*})$$

and

$$\begin{aligned}
&\mathcal{V}_{12}(t)\\
=&\frac{\alpha\xi}{\alpha+\delta_L}e^{-m_1\tau_1}f(T^*, V^*)\int_0^{\tau_1} h(\frac{f(T(t-\theta), V(t-\theta))}{f(T^*, V^*)})\mathrm{d}\theta\\
&+ (1-\xi)e^{-m_2\tau_2}f(T^*, V^*)\int_0^{\tau_2} h(\frac{f(T(t-\theta), V(t-\theta))}{f(T^*, V^*)})\mathrm{d}\theta\\
&+ \frac{\alpha\xi}{\alpha+\delta_L}e^{-m_1\tau_1}g(T^*, I^*)\int_0^{\tau_1} h(\frac{g(T(t-\theta), I(t-\theta))}{g(T^*, I^*)})\mathrm{d}\theta\\
&+ (1-\xi)e^{-m_2\tau_2}g(T^*, I^*)\int_0^{\tau_2} h(\frac{g(T(t-\theta), I(t-\theta))}{g(T^*, I^*)})\mathrm{d}\theta.
\end{aligned}$$

Since $\Lambda = dT + f(T^*, V^*) + g(T^*, I^*)$ and $cV^* = N\delta_I I^*$, calculating the time derivative of $\mathcal{V}_{11}(t)$ along (1.2) yields

$$
\begin{aligned}
&\frac{\mathrm{d}\mathcal{V}_{11}}{\mathrm{d}t}\\
=&K\left(1-\frac{T^*}{T}\right)(\Lambda-dT-f(T,V)-g(T,I))\\
&+\frac{\alpha}{\alpha+\delta_L}\left(1-\frac{L^*}{L}\right)[\xi f(T(t-\tau_1),V(t-\tau_1))e^{-m_1\tau_1}\\
&+\xi g(T(t-\tau_1),I(t-\tau_1))e^{-m_1\tau_1}-(\alpha+\delta_L)L]\\
&+\left(1-\frac{I^*}{I}\right)[(1-\xi)f(T(t-\tau_2),V(t-\tau_2))e^{-m_2\tau_2}\\
&+(1-\xi)g(T(t-\tau_2),I(t-\tau_2))e^{-m_2\tau_2}-\delta_I I+\alpha L]\\
&+K\frac{f(T^*,V^*)}{cV^*}\left(1-\frac{V^*}{V}\right)(N\delta_I I-cV)\\
=&-K\frac{d}{T}(T-T^*)^2+K(-f(T^*,V^*)-g(T^*,I^*)+f(T,V)+g(T,I))\left(\frac{T^*}{T}-1\right)\\
&-\frac{\alpha\xi}{\alpha+\delta_L}e^{-m_1\tau_1}\left(\frac{L^*}{L}-1\right)(f(T(t-\tau_1),V(t-\tau_1))+g(T(t-\tau_1),I(t-\tau_1)))\\
&-(1-\xi)e^{-m_2\tau_2}\left(\frac{I^*}{I}-1\right)(f(T(t-\tau_2),V(t-\tau_2))+g(T(t-\tau_2),I(t-\tau_2)))\\
&+\alpha L^*+\delta_I(I^*-I)-\alpha L\frac{I^*}{I}+Kf(T^*,V^*)\left(1-\frac{V^*}{V}\right)\left(\frac{I}{I^*}-\frac{V}{V^*}\right).
\end{aligned}
\tag{5.6}
$$

Moreover, due to (5.3), $\delta_I I^* = JL^*$ and (2.3), we have

$$
\delta_I(I^*-I)=-K\left(\frac{I}{I^*}-1\right)(f(T^*,V^*)+g(T^*,I^*)). \tag{5.7}
$$

Then it follows from (5.3), (5.6) and (5.7) that

$$
\begin{aligned}
&\frac{\mathrm{d}\mathcal{V}_1}{\mathrm{d}t}\\
=&-K\frac{d}{T}(T-T^*)^2-K(f(T^*,V^*)+g(T^*,I^*))\left(\frac{T^*}{T}-1\right)\\
&+K(f(T,V)+g(T,I))\frac{T^*}{T}\\
&-\frac{\alpha\xi}{\alpha+\delta_L}e^{-m_1\tau_1}\frac{L^*}{L}(f(T(t-\tau_1),V(t-\tau_1))+g(T(t-\tau_1),I(t-\tau_1)))\\
&+\frac{\alpha\xi}{\alpha+\delta_L}e^{-m_1\tau_1}(f(T^*,V^*)+g(T^*,I^*))\\
&-(1-\xi)e^{-m_2\tau_2}\frac{I^*}{I}(f(T(t-\tau_2),V(t-\tau_2))+g(T(t-\tau_2),I(t-\tau_2)))\\
&-K\left(\frac{I}{I^*}-1\right)(f(T^*,V^*)+g(T^*,I^*))
\end{aligned}
$$

$$
\begin{aligned}
&- \frac{I^*L}{IL^*}\frac{\alpha\xi}{\alpha+\delta_L}e^{-m_1\tau_1}(f(T^*,V^*)+g(T^*,I^*)) + Kf(T^*,V^*)\left(\frac{I}{I^*}-\frac{V}{V^*}-\frac{V^*I}{VI^*}+1\right)\\
&+ \frac{\alpha\xi}{\alpha+\delta_L}e^{-m_1\tau_1}\left(f(T^*,V^*)\ln\frac{f(T(t-\tau_1),V(t-\tau_1))}{f(T,V)} + g(T^*,I^*)\ln\frac{g(T(t-\tau_1),I(t-\tau_1))}{g(T,I)}\right)\\
&+ (1-\xi)e^{-m_2\tau_2}\left(f(T^*,V^*)\ln\frac{f(T(t-\tau_2),V(t-\tau_2))}{f(T,V)} + g(T^*,I^*)\ln\frac{g(T(t-\tau_2),I(t-\tau_2))}{g(T,I)}\right),
\end{aligned}
$$

that is,

$$
\begin{aligned}
&\frac{\mathrm{d}\mathcal{V}_1}{\mathrm{d}t}\\
&= - K\frac{d}{T}(T-T^*)^2 - K(f(T^*,V^*)+g(T^*,I^*))\left(\frac{T^*}{T}-1\right)\\
&+K\left(\frac{T^*}{T}f(T,V) - \frac{I}{I^*}f(T^*,V^*) - \frac{V}{V^*}f(T^*,V^*) + \frac{I}{I^*}f(T^*,V^*)\right)\\
&+K\left(\frac{T^*}{T}g(T,I) - \frac{I}{I^*}g(T^*,I^*)\right)\\
&-\frac{\alpha\xi}{\alpha+\delta_L}e^{-m_1\tau_1}f(T^*,V^*)\left(\frac{f(T(t-\tau_1),V(t-\tau_1))L^*}{f(T^*,V^*)L}-1\right)\\
&-\frac{\alpha\xi}{\alpha+\delta_L}e^{-m_1\tau_1}g(T^*,I^*)\left(\frac{g(T(t-\tau_1),I(t-\tau_1))L^*}{g(T^*,I^*)L}-1\right)\\
&-(1-\xi)e^{-m_2\tau_2}f(T^*,V^*)\left(\frac{f(T(t-\tau_2),V(t-\tau_2))I^*}{f(T^*,V^*)I}-1\right)\\
&-(1-\xi)e^{-m_2\tau_2}g(T^*,I^*)\left(\frac{g(T(t-\tau_2),I(t-\tau_2))I^*}{g(T^*,I^*)I}-1\right)\\
&-\frac{\alpha\xi}{\alpha+\delta_L}e^{-m_1\tau_1}f(T^*,V^*)\left(\frac{I^*L}{IL^*}-1\right)\\
&-\frac{\alpha\xi}{\alpha+\delta_L}e^{-m_1\tau_1}g(T^*,I^*)\left(\frac{I^*L}{IL^*}-1\right) - Kf(T^*,V^*)\left(\frac{V^*I}{VI^*}-1\right)\\
&+\frac{\alpha\xi}{\alpha+\delta_L}e^{-m_1\tau_1}\left(f(T^*,V^*)\ln\frac{f(T(t-\tau_1),V(t-\tau_1))}{f(T,V)} + g(T^*,I^*)\ln\frac{g(T(t-\tau_1),I(t-\tau_1))}{g(T,I)}\right)\\
&+(1-\xi)e^{-m_2\tau_2}\left(f(T^*,V^*)\ln\frac{f(T(t-\tau_2),V(t-\tau_2))}{f(T,V)} + g(T^*,I^*)\ln\frac{g(T(t-\tau_2),I(t-\tau_2))}{g(T,I)}\right).
\end{aligned}
$$

Moreover, for simplification, let

$$
\begin{aligned}
&f := f(T,V), f^* := f(T^*,V^*), f_{\tau_1} := f(T_{\tau_1},V_{\tau_1}), f_{\tau_2} := f(T_{\tau_2},V_{\tau_2}),\\
&g := g(T,I), g^* := g(T^*,I^*), g_{\tau_1} := g(T_{\tau_1},I_{\tau_1}), g_{\tau_2} := g(T_{\tau_2},I_{\tau_2}).
\end{aligned}
$$

Then, $\frac{\mathrm{d}\mathcal{V}_1}{\mathrm{d}t}$ is converted to

$$\begin{aligned}
&\frac{\mathrm{d}\mathcal{V}_1}{\mathrm{d}t}\\
=&-K\frac{d}{T}(T-T^*)^2-K(f^*+g^*)h(\frac{T^*}{T})\\
&+Kf^*\left(h(\frac{T^*f}{Tf^*})-h(\frac{V}{V^*})\right)+Kg^*\left(h(\frac{T^*g}{Tg^*})-h(\frac{I}{I^*})\right)\\
&-\frac{\alpha\xi}{\alpha+\delta_L}e^{-m_1\tau_1}\left(f^*h(\frac{f_{\tau_1}L^*}{f^*L})+g^*h(\frac{g_{\tau_1}L^*}{g^*L})+f^*h(\frac{I^*L}{IL^*})+g^*h(\frac{I^*L}{IL^*})\right)\\
&-(1-\xi)e^{-m_2\tau_2}\left(f^*h(\frac{f_{\tau_2}I^*}{f^*I})+g^*h(\frac{g_{\tau_2}I^*}{g^*I})\right)-Kf^*h(\frac{V^*I}{VI^*}).
\end{aligned}$$

From Assumption (A1), $\frac{fT^*}{f^*T}$ lies between 1 and $\frac{V}{V^*}$, $\frac{gT^*}{g^*T}$ lies between 1 and $\frac{I}{I^*}$. Then, there holds that $h(\frac{fT^*}{f^*T})-h(\frac{V}{V^*})\le 0$ and $h(\frac{gT^*}{g^*T})-h(\frac{I}{I^*})\le 0$. Thus, when $\Re_0>1$ and Assumption (A1) holds, $\frac{\mathrm{d}\mathcal{V}_1}{\mathrm{d}t}\le 0$. Let $\Theta_1=\left\{(T,L,I,V):\frac{\mathrm{d}\mathcal{V}_1}{\mathrm{d}t}=0\right\}$ and the largest invariant subset of Θ_1 just consists of E^*. Thus, due to the LaSalle's invariance principle [15], E^* is a global attractor. Further, combining the local asymptotical stability of E^* under condition $\Re_0>1$, E^* is globally asymptotically stable. □

6. Numerical simulations

In this section, we perform some specific examples to support our main results, verifying the effect of $\Re_0$ on system (1.2).

Example 6.1. *In [38], X. Wang et al. considered model (1.2) with the virus-to-cell transmission and the cell-to-cell transmission functions as the mass-action infection rates, that is, $f(T,V)=\beta TV$ and $g(T,I)=kTI$ for $\beta,k>0$. Then system (1.2) becomes*

$$\begin{cases}
\frac{\mathrm{d}T}{\mathrm{d}t}=\Lambda-dT(t)-\beta T(t)V(t))-kT(t)I(t),\\
\frac{\mathrm{d}L}{\mathrm{d}t}=\xi e^{-m_1\tau_1}\beta T(t-\tau_1)V(t-\tau_1)+\xi e^{-m_1\tau_1}kT(t-\tau_1),I(t-\tau_1)-(\alpha+\delta_L)L(t),\\
\frac{\mathrm{d}I}{\mathrm{d}t}=(1-\xi)e^{-m_2\tau_2}\beta T(t-\tau_2),V(t-\tau_2)+(1-\xi)e^{-m_2\tau_2}kT(t-\tau_2),I(t-\tau_2)-\delta_I I(t)+\alpha L,\\
\frac{\mathrm{d}V}{\mathrm{d}t}=N\delta_I I(t)-cV(t).
\end{cases}\tag{6.1}$$

Based on the above analysis, we obtain

$$\Re_0=\left[\frac{\alpha\xi}{\alpha+\delta_L}e^{-m_1\tau_1}+(1-\xi)e^{-m_2\tau_2}\right]\left(\frac{N\beta\Lambda}{cd}+\frac{k\Lambda}{\delta_I d}\right).$$

If $\Re_0<1$, then model (6.1) only has an infection-free equilibrium E_0, which is globally asymptotically stable. If $\Re_0>1$, then there exist E_0 and an globally asymptotically stable infected equilibrium E^*. The results are the same as those in [38], in which X. Wang et al. analyzed the global dynamics of the HIV latent infection model (6.1).

Example 6.2. *Let* $f(T,V) = \frac{\beta_1 T(t)V(t)}{1+aV(t)}$ *and* $g(T,I) = \beta_2 T(t)I(t)$, *for* $\beta_1, \beta_2, a > 0$. *We consider the following system*

$$\begin{cases} \dfrac{\mathrm{d}T}{\mathrm{d}t} = \Lambda - dT(t) - \dfrac{\beta_1 T(t)V(t)}{1+aV(t)} - \beta_2 T(t)I(t), \\ \dfrac{\mathrm{d}L}{\mathrm{d}t} = \xi e^{-m_1\tau_1}\dfrac{\beta_1 T(t-\tau_1)V(t-\tau_1)}{1+aV(t-\tau_1)} + \xi e^{-m_1\tau_1}\beta_2 T(t-\tau_1), I(t-\tau_1) - (\alpha+\delta_L)L(t), \\ \dfrac{\mathrm{d}I}{\mathrm{d}t} = (1-\xi)e^{-m_2\tau_2}\dfrac{\beta_1 T(t-\tau_2)V(t-\tau_2)}{1+aV(t-\tau_2)} + (1-\xi)e^{-m_2\tau_2}\beta_2 T(t-\tau_2)I(t-\tau_2) - \delta_I I(t) + \alpha L(t), \\ \dfrac{\mathrm{d}V}{\mathrm{d}t} = N\delta_I I(t) - cV(t). \end{cases} \tag{6.2}$$

Through our analysis, for system (6.2),

$$\Re_0 = \left[\frac{\alpha\xi}{\alpha+\delta_L}e^{-m_1\tau_1} + (1-\xi)e^{-m_2\tau_2}\right]\left(\frac{N\beta_1\Lambda}{cd} + \frac{\beta_2\Lambda}{\delta_I d}\right).$$

The model (6.2) presents threshold dynamics with respect to $\Re_0$ *as shown in Theorem 4.2 and Theorem 5.3.*

Note that different values of τ_1 *and* τ_2 *can evaluate the effect of time delays on the virus dynamics. Through our analysis,* $\Re_0$ *is decreasing with respect to* τ_1 *and* τ_2. *Thus, extending the time delay with the aid of drug treatment can help to inhibit viruses. We take numerical simulations to show the effect of time delay* τ_i, $i = 1, 2$. *For system (6.2) with parameters listed in Table 1, the graph trajectories with respect to different values of* $\tau_1 = \tau_2 = \tau$ *are depicted in Figure 1.*

Through $\Re_0$, *different values of* ξ *also affect the virus dynamics. Thus, changing the the proportion of latent infection through the aid of drug treatment can help to reduce viruses. We take numerical simulations to show the effect of* ξ. *For system (6.2) with parameters* $\tau_1 = \tau_2 = 1.75$ *days. The graph trajectories of system (6.2) with respect to different values of* ξ *are depicted in Figure 2.*

Table 1. The parameters of system (6.2).

Parameter	Description	Value	Source
Λ	Recruitment rate of target cells	10000 $cells\cdot ml^{-1}\cdot day^{-1}$	[1]
d	Death rate of uninfected cells	0.01 day^{-1}	[22]
β_1	Virus-to-cell infection rate	2.4×10^{-8} $ml\cdot day^{-1}$	[27]
β_2	Cell-to-cell infection rate	1×10^{-6} $ml\cdot day^{-1}$	[25]
α	Activation rate of infected cells	0.01 day^{-1}	[28]
δ_I	Death rate of activated infected cells	0.05 day^{-1}	[1]
δ_L	Death rate of latently infected cells	0.004 day^{-1}	[1]
ξ	Fraction of latency	0.001	[29]
N	Virus production rate of per infected cell	2000 *per cell per day*	[27]
c	Death rate of virus	23 day^{-1}	[26]
m_1	Death rate of latently infected cells which have not produced viruses	1 day^{-1}	Assume
m_2	Death rate of infected cells which have not produced viruses	1 day^{-1}	Assume
a	Inhibition taken by virus	0.01 $cells\cdot ml^{-1}$	Assume

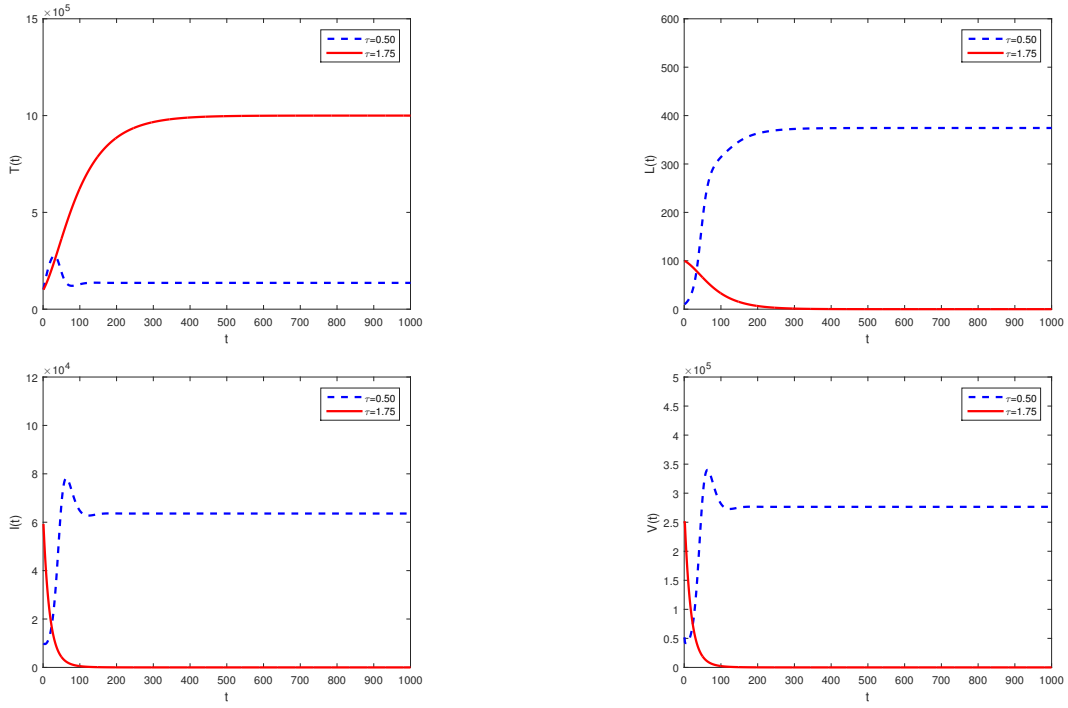

Figure 1. Graph trajectories of system (6.2) with respect to different values of $\tau_i = \tau,\ i = 1, 2$. The time delay τ is extended from 0.5 *day* ($\Re_0 = 8.1268$) to 1.75 *days* ($\Re_0 = 0.6690$).

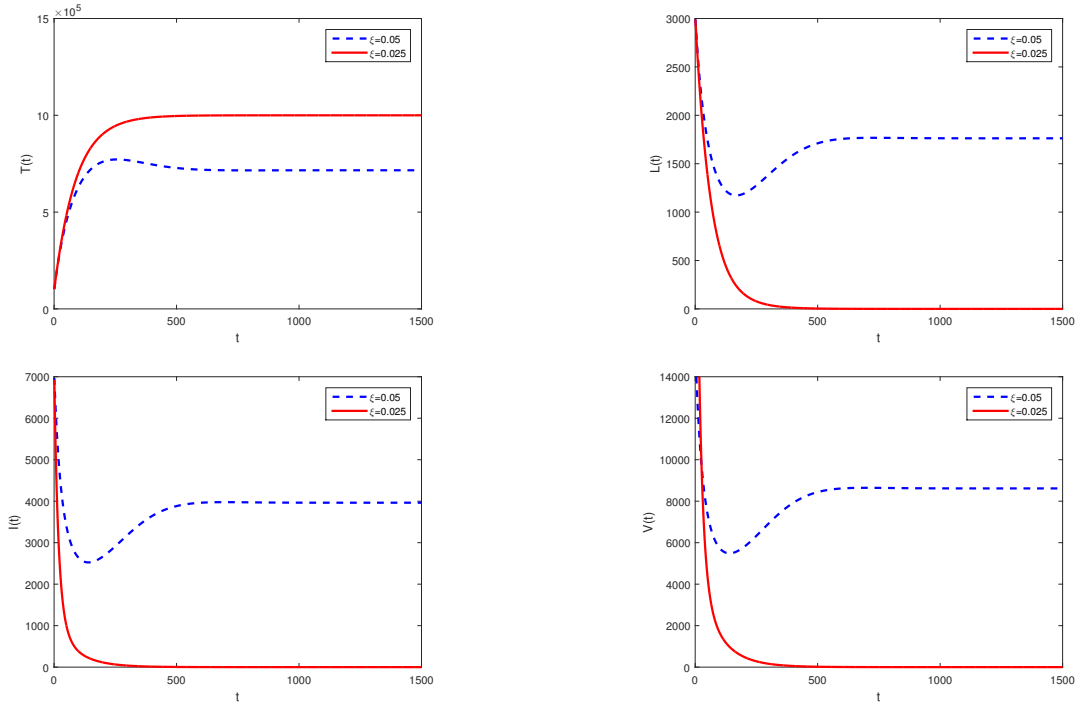

Figure 2. Graph trajectories of system (6.2) with respect to different values of ξ. The parameter ξ is decreased from 0.05 ($\Re_0 = 1.4686$) to 0.025 ($\Re_0 = 0.7188$).

7. Conclusions and discussion

In this paper, the global dynamic analysis of a general within-host latent viral infection model with intracellular delays was carried out. By introducing general transmission functions $f(T, V)$ and $g(T, I)$, which were assumed to satisfy several reasonable biological assumptions, we considered two virus predominant infection modes. The theoretical analysis showed that model (1.2) possesses two equilibria, relying on the basic reproductive number $\Re_0$, which consists of two parts: One is the contribution from the virus-to-cell infection and the other is the contribution from the cell-to-cell transmission. Afterwards, through local and global analysis, we verified that the model exhibits threshold dynamics with respect to $\Re_0$. When $\Re_0$ is less than unity, there exists a unique globally asymptotically stable infection-free equilibrium E_0. In this situation, the disease with virus is inhibited effectively. When $\Re_0$ is greater than one, E_0 is unstable and there exists a globally asymptotically stable infected equilibrium E^*. For the critical case when $\Re_0$ equals to one, E_0 is a linearly neutrally stable non-hyperbolic equilibrium. Center manifold theory should be applied to further explore the stability and bifurcation around E_0 when $\Re_0 = 1$.

In our model (1.2), we extend the existing research on HIV transmission process and take into account generalized incidence rates. This not only enables us to establish a unified theoretical framework that can be applied to numerous situations, but also provides deeper insight into the relationship among different transmission dynamics. By considering double virus spread routes, we found that the infection rate tends to increase with higher transmission rates. We also illustrated that the infection can be inhibited through proper drug block, while a proper treatment still needs to be further investigated. According to the results of theoretical analysis and numerical simulations, cellular time lags and latent infection cells have significant effect on the global asymptotical stability. By reducing the proportion of latent infection or extending the intracellular delay, it is possible to inhibit the secondary infection produced by each primary case and block the transmission of HIV.

Based on our generalized HIV transmission model, further research still need to be conducted. Despite the efforts to explore a general model, there exist several assumptions and some nonlinear incidence rates are not incorporated, such as Beddington-DeAngelis function. Hence, the results could be generalized by adopting more analytical techniques. Spatial diffusion and age structure are also useful to describe viral transmission, which are neglected in model (1.2). Based on the pattern and age structures, more effective strategies can be taken to inhibit the propagation of the virus. Combining the delay effect and PDE structure, it would be more challenging to explore the model, including the well-posedness of solutions, stability and bifurcation analysis, the existence of travelling wave solution. This is a significant work that we will take effort on in the future.

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Conflict of interest

The author declares that there are no conflicts of interest regarding the publication of this paper.

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