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Research article

Dynamics of a diffusive and delayed HIV infection model with impaired immunity and latent cell-to-cell transmission

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Abstract: Viral concentrations in plasma can be suppressed by antiviral drugs, yet reactivation of latently infected cells is the main obstacle to total human immunodeficiency virus (HIV) elimination. In this paper, to characterize the within-host dynamics of HIV with impaired immunity, we formulated and analyzed a general HIV infection model involving diffusion and three delays. Uninfected $CD4^+T$ cells were at risk of infection when they came into contact with three viral transmission routes, namely virus-to-cell infection, latent cell-to-cell transmission, and cell-to-cell transmission, all characterized by general incidence functions. Viral infection reproduction number was calculated, and the global properties were demonstrated. Numerical simulations were carried out to illustrate the corresponding theoretical results.

Keywords: viral infection model; latent cell-to-cell transmission; diffusion; general incidence function; global stability
Mathematics Subject Classification: 34D40, 35K57, 92D30

1. Introduction

Human immunodeficiency virus (HIV) mainly attacks $CD4^+T$ cells and immune response, which is the body's defense against viral infections. Mathematical models that take into account the time delay can not only provide better representation of the biological problem but can also exhibit much more complicated dynamical behavior. Nowak et al. [1] put forward a host-virus model. Based on this model, Perelson and Nelson [2] carried out in-depth follow-up research and elucidated the interplay between viruses and host biological mechanisms. Throughout viral infection, cellular immune responses and humoral immune responses act synergistically to combat invading pathogens, generating maximal protective effects as a combined system. These mathematical models have been used to study the dynamics of HIV infection, including the impact of cytotoxic T lymphocyte (CTL) response [3–5],

humoral response [6–8], and both CTL and humoral responses [9–11]. In addition, there are numerous biological factors, such as tumors, gene mutations, aging, etc., that can inhibit or disrupt the simulation of immune responses [12–14]. Lin et al. [9] have developed an HIV infection model with immune responses, virus-to-cell, and cell-to-cell infection modes. The model proposed in [9] fails to account for latently infected cells as well as immune impairment.

Although antiviral drugs can inhibit the production of viruses, they cannot clear the virus. One important reason is that the HIV provirus can exist in latent infection cells, but these cells do not generate viruses until they are activated [15, 16]. Beyond accelerating the rapid dissemination of viruses, latent cell-to-cell transmission enables immune evasion, thereby reducing the effectiveness of neutralizing antibodies and antiviral inhibitors. Yan et al. [4] have considered an HIV model with cell-to-cell transmission and CTL immune response. The model presented in [4] has neglected the latently infected cells. In [6], Miao et al. have proposed a virus infection model with humoral immune response, but the latently infected cells and spatial diffusion have been ignored. Meanwhile, Elaiw and AlShamrani [10], and Boukhouima et al. [11] have studied viral infection models with adaptive immune response. The models considered above all ignore latent cell-to-cell transmission.

It is worth pointing out that the aforementioned model makes an implicit assumption that cells and viruses are fully mixed, failing to account for the spatial migration features of both populations. As a matter of fact, the studied populations within numerous biological systems undergo temporal evolution alongside spatial diffusion [17]. Based on the model in [18], spatial diffusion is considered in viral models [19, 20]. McCluskey and Yang [21], Hattaf and Yousfi [22], Zhang et al. [23], Wu et al. [24, 25], and Miao and Feng [26] have studied the global dynamics of diffusive virus dynamic models. However, the above existing diffusion models have not taken into account immune impairment and latent cell-to-cell transmission. Therefore, it is more reasonable to study a diffusive virus model incorporating the virus-to-cell infection, cell-to-cell transmission, and latently cell-to-cell.

Motivated by the works of Guo et al. [3], Elaiw et al. [10], Sun et al. [27], and AlShamrani et al. [37], a spatially diffusive HIV infection model is developed to govern the concentration dynamics of six compartments with respect to space x and time t: uninfected cells $J(x,t)$, latently infected cells $P(x,t)$, infected cells $K(x,t)$, HIV particles $V(x,t)$, CTL immune cells $L(x,t)$, and antibody cells $U(x,t)$, respectively. Our proposed model is given by the following partial differential equations:

$$\begin{aligned}
\frac{\partial J}{\partial t} &= D_1\Delta J + \lambda - d_1 J(x,t) - \psi_1(J(x,t),V(x,t)) - \psi_2(J(x,t),P(x,t)) \\
&\quad -\psi_3(J(x,t),K(x,t)), \\
\frac{\partial P}{\partial t} &= D_2\Delta P + e^{-m_1\tau_1}[\psi_1(J(x,t-\tau_1),V(x,t-\tau_1)) + \psi_2(J(x,t-\tau_1),P(x,t-\tau_1)) \\
&\quad +\psi_3(J(x,t-\tau_1),K(x,t-\tau_1))] - (\alpha+d_2)P(x,t), \\
\frac{\partial K}{\partial t} &= D_3\Delta K + \alpha e^{-m_2\tau_2}P(x,t-\tau_2) - d_3K(x,t) - \eta L(x,t)K(x,t), \\
\frac{\partial V}{\partial t} &= D_4\Delta V + be^{-m_3\tau_3}K(x,t-\tau_3) - d_4V(x,t) - cU(x,t)V(x,t), \\
\frac{\partial L}{\partial t} &= D_5\Delta L + \omega K(x,t) - d_5L(x,t) - \sigma L(x,t)K(x,t), \\
\frac{\partial U}{\partial t} &= D_6\Delta U + hV(x,t) - d_6U(x,t) - \varepsilon U(x,t)V(x,t),
\end{aligned} \tag{1.1}$$

for any $t \geq 0$ and $x \in \Omega$. Other parameters are described in Table 1.

Table 1. Definition of parameters in model (1.1).

Parameter	Description
$D_i(i = 1 - 6)$	diffusion coefficients
λ	production rate of uninfected cells
d_1	death rate of uninfected cells
α	transmission rate of latent infected cells that become infected cells
d_2	death rate of latently infected cells
d_3	death rate of infected cells
η	kill rate of infected cells by CTL immune cells
b	the rate of the virus particles produced by infected cells
d_4	removal rate of virus
c	kill rate of virus by antibody cells
ω	production rate of new CTL immune response
h	production rate of new antibody cells by antigenic stimulation
d_5	death rate of CTL immune cells
d_6	death rate of antibody cells
σ	CTL impairment coefficient
ε	antibody impairment coefficient
$e^{-m_1\tau_1}$	probability of surviving of latently infected cells during $[t - \tau_1, t]$
$e^{-m_2\tau_2}$	probability of surviving of infected cells during $[t - \tau_2, t]$
$e^{-m_3\tau_3}$	probability of surviving of newly produced viruses during $[t - \tau_3, t]$

We assume that the incidence functions $\psi_1(J, V)$, $\psi_2(J, P)$, and $\psi_3(J, K)$, are satisfied by the following conditions:
Define

$$\begin{aligned}
\widetilde{\psi}_1(J) &= \lim_{V\to 0^+} \frac{\psi_1(J,V)}{V} = \frac{\partial \psi_1(J,0)}{\partial V},\\
\widetilde{\psi}_2(J) &= \lim_{P\to 0^+} \frac{\psi_2(J,P)}{P} = \frac{\partial \psi_2(J,0)}{\partial P},\\
\widetilde{\psi}_3(J) &= \lim_{K\to 0^+} \frac{\psi_3(J,K)}{K} = \frac{\partial \psi_3(J,0)}{\partial K}.
\end{aligned}$$

(H_1) $\psi_i(J, \theta)$ is continuously differentiable; $\psi_i(J, \theta) > 0$, $\psi_i(J, \theta) = 0$ if and only if $J = 0$ or $\theta = 0$; $\frac{\partial \psi_i(J,\theta)}{\partial J} > 0$, $\frac{\partial \psi_i(J,\theta)}{\partial \theta} > 0, i = 1, 2, 3$. (H_2) $\widetilde{\psi}_i(J) > 0$ and $\widetilde{\psi}_i'(J) > 0$ for all $J \geq 0$; $\frac{\psi_i(J,\theta)}{\theta}$ is non-increasing with respect to θ for all $\theta > 0$.

Assumption (H_1) implies that positive values are obtained for virus-to-cell infection, latent cell-to-cell transmission, and cell-to-cell transmission rates when uninfected cells, virions, latently infected cells, and infected cells exist at non-zero concentrations. In addition, no transmission events occur if uninfected cells are absent. What is more, all three transmission rates drop to zero without virions, latently infected cells, and infected cells. Meanwhile, elevated levels of virions, latently infected cells, infected cells, or uninfected cells accelerate the infection progression rate. Assumption (H_2) refers to the maximum average quantities of uninfected cells infected per particle, per latently infected cell, and

per infected cell at the initial stage of infection. Moreover, the infective efficacy of virions, latently infected cells, and infected cells does not rise with increases in their respective concentrations.

The initial conditions of model (1.1) are

$$\begin{aligned} &J(x,\theta) = \phi_1(x,\theta) \geq 0,\ P(x,\theta) = \phi_2(x,\theta) \geq 0,\\ &K(x,\theta) = \phi_3(x,\theta) \geq 0,\ V(x,\theta) = \phi_4(x,\theta) \geq 0,\\ &L(x,\theta) = \phi_5(x,\theta) \geq 0,\ U(x,\theta) = \phi_6(x,\theta) \geq 0,\ x \in \bar{\Omega},\ \theta \in [-\tau, 0], \end{aligned} \tag{1.2}$$

and the homogeneous Neumann boundary conditions are

$$\frac{\partial J}{\partial \vec{n}} = \frac{\partial P}{\partial \vec{n}} = \frac{\partial K}{\partial \vec{n}} = \frac{\partial V}{\partial \vec{n}} = \frac{\partial L}{\partial \vec{n}} = \frac{\partial U}{\partial \vec{n}} = 0,\ t > 0,\ x \in \partial\Omega, \tag{1.3}$$

where $\tau = \max\{\tau_1,\ \tau_2,\ \tau_3\}$, Ω is a connected, bounded domain in $\mathbb{R}^n$ with smooth boundary $\partial\Omega$. $\frac{\partial}{\partial \vec{n}}$ denotes the outward normal derivative on $\partial\Omega$. $\phi_i(x,\theta)(i = 1,2,3,4,5,6)$ is Hölder continuous in $\bar{\Omega} \times [-\tau, 0]$.

In this paper, our purpose is to investigate the global dynamics of model (1.1). The organization of this paper is as follows. In the next section, the basic properties of solutions and the existence of equilibria are discussed. In Section 3, under the assumptions (H_1) and (H_2), sufficient conditions for global stability are established. In Section 4, the numerical simulations are given to further illustrate the dynamical behavior of the model. In the last section, we will give a conclusion.

2. Positivity, boundedness, and equilibrium

In this section, we prove the existence, positivity, and boundedness of solutions to model (1.1)–(1.3), where these solutions correspond to the densities of uninfected cells, latently infected cells, infected cells, HIV particles, CTL immune cells, and antibody cells, respectively. Further, we discuss the existence of equilibria of model (1.1).

Let $C = C([-\tau, 0], \mathbb{X})$ be the Banach space of continuous functions from $[-\tau, 0]$ into $\mathbb{X}$ with the norm $\| \phi \| = \max_{\theta\in[-\tau,0]} \| \phi(\theta) \|_{\mathbb{X}}$. In our case, $\mathbb{X}$ is the Banach space $C(\overline{\Omega}, R^6)$. For convenience, we identify an element $\phi \in C$ as a function from $\overline{\Omega} \times [-\tau, 0]$ into R^6 defined by $\phi(x,s) = \phi(s)(x)$. For any continuous function $W(\cdot) : [-\tau, b) \to \mathbb{X}$ for $b > 0$, we define $W_t \in C$ by $W_t(s) = W(t+s),\ s \in [-\tau, 0]$. It is not hard to see that $t \to W_t$ is a continuous function from $[0, b)$ to C.

Theorem 2.1. *For any given initial condition $\phi \in C$ satisfying* (1.2)*, models* (1.1)–(1.3) *has a unique nonnegative solution. When $D_1 = D_2$, $D_3 = D_5$, and $D_4 = D_6$, this solution is defined on* $[0, +\infty)$ *and remains nonnegative and bounded for all $t \geq 0$.*

Proof. For any $\phi = (\phi_1, \phi_2, \phi_3, \phi_4, \phi_5, \phi_6)^T \in C$ and $x \in \overline{\Omega}$, we define $F = (F_1, F_2, F_3, F_4, F_5, F_6) : C \to \mathbb{X}$ by

$$\begin{aligned} F_1(\phi)(x) = \ & \lambda - d_1\phi_1(x,0) - \psi_1(\phi_1(x,0), \phi_4(x,0)) - \psi_2(\phi_1(x,0), \phi_2(x,0))\\ & -\psi_3(\phi_1(x,0), \phi_3(x,0)), \end{aligned} \tag{2.1}$$

$$\begin{aligned}
F_2(\phi)(x) = \; & e^{-m_1\tau_1}[\psi_1(\phi_1(x,-\tau_1),\phi_4(x,-\tau_1)) + \psi_2(\phi_1(x,-\tau_1),\phi_2(x,-\tau_1)) \\
& +\psi_3(\phi_1(x,-\tau_1),\phi_3(x,-\tau_1))] - (\alpha+d_2)\phi_2(x,0), \\
F_3(\phi)(x) = \; & \alpha e^{-m_2\tau_2}\phi_2(x,-\tau_2) - d_3\phi_3(x,0) - \eta\phi_5(x,0)\phi_3(x,0), \\
F_4(\phi)(x) = \; & be^{-m_3\tau_3}\phi_3(x,-\tau_3) - d_4\phi_4(x,0) - c\phi_6(x,0)\phi_4(x,0), \\
F_5(\phi)(x) = \; & \omega\phi_3(x,0) - d_5\phi_5(x,0) - \sigma\phi_5(x,0)\phi_3(x,0), \\
F_6(\phi)(x) = \; & h\phi_4(x,0) - d_6\phi_6(x,0) - \varepsilon\phi_6(x,0)\phi_4(x,0).
\end{aligned}$$

Then, model (1.1)–(1.3) can be rewritten as the following abstract functional differential equation:

$$\begin{aligned}
W'(t) = \; & AW + F(W_t),\ t > 0, \\
W(0) = \; & \phi \in \mathbb{X},
\end{aligned} \tag{2.2}$$

where $W = (J,\ P,\ K,\ V,\ L,\ U)^T, \phi = (\phi_1,\ \phi_2,\ \phi_3,\ \phi_4,\ \phi_5,\ \phi_6)^T$, and $AW = (D_1\Delta J,\ D_2\Delta P,\ D_3\Delta K,\ D_4\Delta V\ D_5\Delta L, D_6\Delta U)^T$. It is clear that F is locally Lipschitz in $\mathbb{X}$. From [28–30], we deduce that model (2.2) admits a unique local solution on $[0, T_{max})$, where T_{max} is the maximal existence time for a solution of model (2.2).

Therefore, we have $J(x,t) \geq 0,\ P(x,t) \geq 0,\ K(x,t) \geq 0,\ V(x,t) \geq 0,\ L(x,t) \geq 0$, and $U(x,t) \geq 0$ because 0 is a sub-solution of each equation of the model (1.1).

Next, we prove the boundedness of solutions. Denote

$$N_1(x,t) = J(x,t) + e^{m_1\tau_1}P(x,t+\tau_1).$$

So, we have

$$\begin{aligned}
\frac{\partial N_1(x,t)}{\partial t} = \; & D_1\Delta J + D_2e^{m_1\tau_1}\Delta P(x,t+\tau_1) + \lambda - d_1J - (\alpha+d_2)e^{m_1\tau_1}P(x,t+\tau_1) \\
\leq \; & D_1\Delta N_1 + \lambda - \xi_1N_1(x,t),
\end{aligned}$$

when $D_1 = D_2,\ \xi_1 = \min\{d_1, \alpha+d_2\}$. Hence,

$$N_1(x,t) \leq \max\left\{\frac{\lambda}{\xi_1}, \max_{x\in\overline{\Omega}}\{\phi_1(x,0) + e^{m_1\tau_1}\phi_2(x,\tau_1)\}\right\} = \varsigma_1.$$

This implies that J and P are bounded for large t.

Denote

$$N_2(x,t) = K(x,t) + \frac{d_3}{2\omega}L(x,t).$$

So, we can get

$$\begin{aligned}
\frac{\partial N_2(x,t)}{\partial t} = \; & D_3\Delta K + \frac{d_3D_5}{2\omega}\Delta L + \alpha e^{-m_2\tau_2}P(x,t-\tau_2) - \frac{d_3}{2}K - \frac{d_3d_5}{2\omega}L(x,t) \\
& -(\eta + \frac{d_3\sigma}{2\omega})L(x,t)K(x,t) \\
\leq \; & D_3\Delta N_2 + \alpha e^{-m_2\tau_2}\varsigma_1 - \xi_2N_2(x,t),
\end{aligned}$$

when $D_3 = D_5,\ \xi_2 = \min\{\frac{d_3}{2}, d_5\}$. Hence,

$$N_2 \leq \max\left\{\frac{\alpha e^{-m_2\tau_2}\varsigma_1}{\xi_2}, \max_{x\in\overline{\Omega}}\{\phi_3(x,0) + \frac{d_3}{2\omega}\phi_5(x,0)\}\right\} = \varsigma_2.$$

Denote

$$N_3(x,t) = V(x,t) + \frac{d_4}{2h}U(x,t).$$

So, we can get

$$\begin{aligned}\frac{\partial N_3(x,t)}{\partial t} &= D_4\Delta V + \frac{d_4D_6}{2h}\Delta U + be^{-m_3\tau_3}K(x,t-\tau_3) - \frac{d_4}{2}V - \frac{d_4d_6}{2h}U(x,t)\\ &\quad -(c+\frac{d_4\varepsilon}{2h})U(x,t)V(x,t)\\ &\leq D_4\Delta N_3 + be^{-m_3\tau_3}\varsigma_2 - \xi_3 N_3(x,t),\end{aligned}$$

when $D_4 = D_6,\ \xi_3 = \min\{\frac{d_4}{2}, d_6\}$. Hence,

$$N_3 \leq \max\left\{\frac{be^{-m_3\tau_3}\varsigma_2}{\xi_3}, \max_{x\in\overline{\Omega}}\{\phi_4(x,0) + \frac{d_4}{2h}\phi_6(x,0)\}\right\}.$$

From the above, we have proved that $J(x,t)$, $P(x,t)$, $K(x,t)$, $V(x,t)$, $L(x,t)$, and $U(x,t)$ are bounded on $\overline{\Omega}\times[0,T_{max})$. Therefore, it follows from the standard theory for semilinear parabolic systems [31–33] that $T_{max} = +\infty$. This completes the proof.

Now, we discuss the existence of equilibria of model (1.1). It is easy to know that any equilibrium $E = (J,P,K,V,L,U)$ of model (1.1) satisfies

$$\begin{aligned}&\lambda - d_1J - \psi_1(J,V) - \psi_2(J,P) - \psi_3(J,K) = 0,\\ &e^{-m_1\tau_1}[\psi_1(J,V) + \psi_2(J,P) + \psi_3(J,K)] - (\alpha+d_2)P = 0,\\ &\alpha e^{-m_2\tau_2}P - d_3K - \eta LK = 0,\\ &be^{-m_3\tau_3}K - d_4V - cUV = 0,\\ &\omega K - d_5L - \sigma LK = 0,\\ &hV - d_6U - \varepsilon UV = 0.\end{aligned} \tag{2.3}$$

It is clear from (2.3) that model (1.1) always has a unique infection-free equilibrium $E_0 = (J_0,0,0,0,0,0)$ with $J_0 = \frac{\lambda}{d_1}$, which is the level of uninfected cells in the absence of infection. Inspired by the method in [34], we consider the infection and viral production, and define matrices $\mathbb{F}$ and $\mathbb{V}$ as

$$\mathbb{F} = \begin{pmatrix} e^{-m_1\tau_1}\cdot\frac{\partial\psi_2(\frac{\lambda}{d_1},0)}{\partial P} & e^{-m_1\tau_1}\cdot\frac{\partial\psi_3(\frac{\lambda}{d_1},0)}{\partial K} & e^{-m_1\tau_1}\cdot\frac{\partial\psi_1(\frac{\lambda}{d_1},0)}{\partial V}\\ 0 & 0 & 0\\ 0 & 0 & 0\end{pmatrix},$$

and

$$\mathbb{V} = \begin{pmatrix} \alpha+d_2 & 0 & 0\\ -\alpha e^{-m_2\tau_2} & d_3 & 0\\ 0 & -be^{-m_3\tau_3} & d_4\end{pmatrix}.$$

Thus, the basic reproductive number R_0 can be defined as the spectral radius of the next generation operator $\mathbb{F}\mathbb{V}^{-1}$, where

$$\mathbb{F}\mathbb{V}^{-1} = \begin{pmatrix} a_{11} & a_{12} & a_{13} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix},$$

where

$$\begin{aligned} a_{11} &= \frac{\alpha b e^{-m_1\tau_1-m_2\tau_2-m_3\tau_3}}{(\alpha+d_2)d_3d_4} \cdot \frac{\partial\psi_1(\frac{\lambda}{d_1},0)}{\partial V} + \frac{e^{-m_1\tau_1}}{\alpha+d_2} \cdot \frac{\partial\psi_2(\frac{\lambda}{d_1},0)}{\partial P} + \frac{\alpha e^{-m_1\tau_1-m_2\tau_2}}{(\alpha+d_2)d_3} \cdot \frac{\partial\psi_3(\frac{\lambda}{d_1},0)}{\partial K}, \\ a_{12} &= \frac{e^{-m_1\tau_1}}{d_3} \cdot \frac{\partial\psi_3(\frac{\lambda}{d_1},0)}{\partial K} + \frac{b e^{-m_1\tau_1-m_3\tau_3}}{d_3d_4} \cdot \frac{\partial\psi_1(\frac{\lambda}{d_1},0)}{\partial V}, \\ a_{13} &= \frac{e^{-m_1\tau_1}}{d_4} \cdot \frac{\partial\psi_1(\frac{\lambda}{d_1},0)}{\partial V}. \end{aligned}$$

Therefore,

$$\begin{aligned} R_0 = \; & \frac{\alpha b e^{-m_1\tau_1-m_2\tau_2-m_3\tau_3}}{(\alpha+d_2)d_3d_4} \cdot \frac{\partial\psi_1(\frac{\lambda}{d_1},0)}{\partial V} + \frac{e^{-m_1\tau_1}}{\alpha+d_2} \cdot \frac{\partial\psi_2(\frac{\lambda}{d_1},0)}{\partial P} \\ & + \frac{\alpha e^{-m_1\tau_1-m_2\tau_2}}{(\alpha+d_2)d_3} \cdot \frac{\partial\psi_3(\frac{\lambda}{d_1},0)}{\partial K}, \end{aligned}$$

which biologically describes the average number of secondary infections produced by one infected cell at the beginning of infection. In the above expression of R_0, divided into parts as $R_0 = R_{01} + R_{02} + R_{03}$, where $R_{01} = \frac{\alpha b e^{-m_1\tau_1-m_2\tau_2-m_3\tau_3}}{(\alpha+d_2)d_3d_4} \cdot \frac{\partial\psi_1(\frac{\lambda}{d_1},0)}{\partial V}$ is the basic reproduction number through the virus-to-cell infection, $R_{02} = \frac{e^{-m_1\tau_1}}{\alpha+d_2} \cdot \frac{\partial\psi_2(\frac{\lambda}{d_1},0)}{\partial P}$ is the basic reproduction number through the latent cell-to-cell transmission, and $R_{03} = \frac{\alpha e^{-m_1\tau_1-m_2\tau_2}}{(\alpha+d_2)d_3} \cdot \frac{\partial\psi_3(\frac{\lambda}{d_1},0)}{\partial K}$ is the basic reproduction number through the cell-to-cell transmission, respectively.

When $V \neq 0$, from the third, fifth, and sixth equation of (2.3), we get

$$P = \frac{(d_3+\eta L)K}{\alpha e^{-m_2\tau_2}}, \; L = \frac{\omega K}{d_5+\sigma K}, \; U = \frac{hV}{d_6+\varepsilon V}, \tag{2.4}$$

and from the fourth equation of (2.3), we obtain

$$K = \frac{\varepsilon d_4 V^2 + (ch+d_4d_6)V}{(d_6+\varepsilon V)be^{-m_3\tau_3}} = F_1(V), \tag{2.5}$$

where $F_1(0) = 0$. From (2.4) and (2.5), we have

$$L = \frac{\omega(ch+\varepsilon d_4)V^2 + \omega d_4d_6V}{d_5(d_6+\varepsilon V)be^{-m_3\tau_3} + \sigma[(ch+\varepsilon d_4)V^2 + d_4d_6V]} = F_2(V), \tag{2.6}$$

where $F_2(0) = 0$. Due to (2.4)–(2.6), we have

$$P = \frac{[(ch+\varepsilon d_4)V^2 + d_4d_6V]A(V)}{\alpha b e^{-m_2\tau_2-m_3\tau_3}(d_6+\varepsilon V)B(V)} = F_3(V), \tag{2.7}$$

where

$$\begin{aligned} A(V) &= (\sigma d_3+\omega\eta)[(ch+\varepsilon d_4)V^2 + d_4d_6V] + d_3d_5(d_6+\varepsilon V)be^{-m_3\tau_3}, \\ B(V) &= d_5(d_6+\varepsilon V)be^{-m_3\tau_3} + \sigma[(ch+\varepsilon d_4)V^2 + d_4d_6V], \end{aligned}$$

and $F_3(0) = 0$. From the first and second equation of (2.3), we get

$$d_1 J = \lambda - (\alpha + d_2)e^{m_1\tau_1} P. \tag{2.8}$$

From (2.7) and (2.8), we have

$$J = \frac{1}{d_1}\Big\{\lambda - \frac{(\alpha + d_2)e^{m_1\tau_1}[(ch + \varepsilon d_4)V^2 + d_4 d_6 V]A(V)}{\alpha b e^{-m_2\tau_2 - m_3\tau_3}(d_6 + \varepsilon V)B(V)}\Big\} = F_4(V), \tag{2.9}$$

where $F_4(0) = \dfrac{\lambda}{d_1} = J_0$. From the second equation of (2.3), we have

$$\begin{aligned} &\psi_1(F_4(V), V) + \psi_2(F_4(V), F_3(V)) + \psi_3(F_4(V), F_1(V)) \\ &-\frac{(\alpha + d_2)[(ch + \varepsilon d_4)V^2 + d_4 d_6 V]A(V)}{\alpha b e^{-m_1\tau_1 - m_2\tau_2 - m_3\tau_3}(d_6 + \varepsilon V)B(V)} = 0. \end{aligned} \tag{2.10}$$

Define

$$F(V) = \psi_1(F_4(V), V) + \psi_2(F_4(V), F_3(V)) + \psi_3(F_4(V), F_1(V)) - \frac{\alpha + d_2}{e^{-m_1\tau_1}} F_3(V),$$

where $F(0) = 0$. Thus, there exists a unique $\tilde{V}$ such that $F_4(\tilde{V}) = 0$, that is,

$$J^0 - \frac{(\alpha + d_2)[(ch + \varepsilon d_4)\tilde{V}^2 + d_4 d_6 \tilde{V}]A(\tilde{V})}{\alpha b d_1 e^{-m_1\tau_1 - m_2\tau_2 - m_3\tau_3}(d_6 + \varepsilon\tilde{V})B(\tilde{V})} = 0.$$

It follows that

$$G(\tilde{V}) = M_4\tilde{V}^4 + M_3\tilde{V}^3 + M_2\tilde{V}^2 + M_1\tilde{V} + M_0, \tag{2.11}$$

where

$$\begin{aligned} M_4 = \;& (\alpha + d_2)(\sigma d_3 + \omega\eta)(ch + \varepsilon d_4)^2, \\ M_3 = \;& (\alpha + d_2)(ch + \varepsilon d_4)[2d_4 d_6(\sigma d_3 + \omega\eta) + \varepsilon d_3 d_5 b e^{-m_3\tau_3}] \\ & -\alpha b\lambda e^{-m_1\tau_1 - m_2\tau_2 - m_3\tau_3}\varepsilon\sigma(ch + \varepsilon d_4), \\ M_2 = \;& (\alpha + d_2)\{(ch + \varepsilon d_4)d_3 d_5 d_6 b e^{-m_3\tau_3} + d_4 d_6[d_4 d_6(\sigma d_3 + \omega\eta) + \varepsilon d_3 d_5 b e^{-m_3\tau_3}]\} \\ & -\alpha b\lambda e^{-m_1\tau_1 - m_2\tau_2 - m_3\tau_3}[d_6\sigma(ch + \varepsilon d_4) + \varepsilon(d_5\varepsilon b e^{-m_3\tau_3} + \sigma d_4 d_6)], \\ M_1 = \;& (\alpha + d_2)d_3 d_4 d_5 d_6^2 b e^{-m_3\tau_3} - \alpha b\lambda(\varepsilon + d_6)d_5 d_6 b e^{-m_1\tau_1 - m_2\tau_2 - 2m_3\tau_3}, \\ M_0 = \;& -\alpha\lambda e^{-m_1\tau_1 - m_2\tau_2 - 2m_3\tau_3} b^2 d_5 d_6^2. \end{aligned}$$

Clearly, $\lim_{\tilde{V}\to+\infty} G(\tilde{V}) = +\infty$, $G(0) = -\alpha\lambda e^{-m_1\tau_1 - m_2\tau_2 - 2m_3\tau_3} b^2 d_5 d_6^2 < 0$. Then, there exists a unique $\tilde{V} \in (0, +\infty)$ such that $G(\tilde{V}) = 0$. Further, $F(\tilde{V}) = -(\alpha + d_2)e^{m_1\tau_1} F_3(\tilde{V}) < 0$. Moreover,

$$\begin{aligned} F'(V) = \;& F_4'(V)\cdot\frac{\partial\psi_1(F_4(V), V)}{\partial J} + \frac{\partial\psi_1(F_4(V), V)}{\partial V} + F_4'(V)\cdot\frac{\partial\psi_2(J, P)}{\partial J} \\ & + F_3'(V)\cdot\frac{\partial\psi_2(J, P)}{\partial P} + F_4'(V)\cdot\frac{\partial\psi_3(J, K)}{\partial J} + F_1'(V)\cdot\frac{\partial\psi_3(J, K)}{\partial K} \\ & -(\alpha + d_2)e^{m_1\tau_1} F_3'(V). \end{aligned}$$

Then, we have

$$\begin{aligned} F'(0) = & \frac{\partial \psi_1(J_0,0)}{\partial V} + F_3'(0)\cdot\frac{\partial \psi_2(J_0,0)}{\partial P} + F_1'(0)\cdot\frac{\partial \psi_3(J_0,0)}{\partial K} - (\alpha+d_2)e^{m_1\tau_1}F_3'(0) \\ = & \frac{(\alpha+d_2)d_3d_4}{\alpha b e^{-m_1\tau_1-m_2\tau_2-m_3\tau_3}}(R_0-1). \end{aligned}$$

Therefore, if $R_0 > 1$, then $F'(0) > 0$, and there exists $V^* \in (0, \tilde{V})$ such that $F(V^*) = 0$.

Define

$$N(J) = \lambda - d_1 J - \psi_1(J, V^*) - \psi_2(J, F_3(V^*)) - \psi_3(J, F_1(V^*)).$$

Clearly,

$$N(0) = \lambda > 0 \text{ and } N(J_0) = -[\psi_1(J_0, V^*) + \psi_2(J_0, F_3(V^*)) + \psi_3(J_0, F_1(V^*))] < 0.$$

According to (H_1), there is a unique $J^* \in (0, J_0)$ such that $N(J^*) = 0$. Hence, model (1.1) has a unique infected equilibrium $E_1 = (J^*, P^*, K^*, V^*, L^*, U^*)$, where

$$\begin{aligned} J^* \in & \ (0, J_0),\ U^* = \frac{hV^*}{d_6+\varepsilon V^*}, \\ P^* = & \frac{[(ch+\varepsilon d_4)V^{*2} + d_4 d_6 V^*]A(V^*)}{\alpha b e^{-m_2\tau_2-m_3\tau_3}(d_6+\varepsilon V^*)B(V^*)} = F_3(V^*), \\ K^* = & \frac{(ch+\varepsilon d_4)V^{*2} + d_4 d_6 V^*}{(d_4+\varepsilon V^*)be^{-m_3\tau_3}} = F_1(V^*), \\ L^* = & \frac{\omega(ch+\varepsilon d_4)V^{*2} + \omega d_4 d_6 V^*}{d_5(d_6+\varepsilon V^*)be^{-m_3\tau_3} + \sigma[(ch+\varepsilon d_4)V^{*2} + d_4 d_6 V^*]} = F_2(V^*). \end{aligned}$$

3. Stability analysis

In this section, we analyze the global stability of the above two equilibria E_0 and E_1 by means of the Lyapunov function method in [35–37].

3.1. Stability of equilibrium E_0

Theorem 3.1. *Let conditions (H_1) and (H_2) hold true and $R_0 \le 1$, then the infection-free equilibrium E_0 is globally asymptotically stable.*

Proof. Define a Lyapunov functional

$$\begin{aligned} G_1(t) = & \int_\Omega \Big\{ J - J_0 - \int_{J_0}^{J} \frac{\widetilde{\psi}_1(J_0)}{\widetilde{\psi}_1(\theta)}\,\mathrm{d}\theta + e^{m_1\tau_1}P + \frac{be^{m_1\tau_1}\widetilde{\psi}_1(J_0) + d_4\widetilde{\psi}_3(J_0)}{d_3d_4}K \\ & + \frac{\widetilde{\psi}_1(J_0)}{d_4}V + \frac{\eta(be^{m_1\tau_1}\widetilde{\psi}_1(J_0) + d_4\widetilde{\psi}_3(J_0))}{2\omega d_3 d_4}L^2 + \frac{c\widetilde{\psi}_1(J_0)}{2hd_4}U^2 \\ & + \int_{t-\tau_1}^{t} \Big(\psi_1(J(x,\theta),V(x,\theta)) + \psi_2(J(x,\theta),P(x,\theta)) \\ & + \psi_3(J(x,\theta),K(x,\theta))\Big)\,\mathrm{d}\theta + \frac{be^{-m_3\tau_3}\widetilde{\psi}_1(J_0)}{d_4}\int_{t-\tau_3}^{t} K(x,\theta)\,\mathrm{d}\theta \\ & + \frac{\alpha e^{-m_2\tau_2}(be^{m_1\tau_1}\widetilde{\psi}_1(J_0) + d_4\widetilde{\psi}_3(J_0))}{d_3d_4}\int_{t-\tau_2}^{t} P(x,\theta)\,\mathrm{d}\theta\Big\}. \end{aligned}$$

Calculating the time derivative of $G_1(t)$ along any positive solution of model (1.1) and noticing that $J_0 = \dfrac{\lambda}{d_1}$, we can obtain

$$\begin{aligned}\frac{dG_1(t)}{dt} = & \int_\Omega \Big\{\Big(1-\frac{\widetilde{\psi}_1(J_0)}{\widetilde{\psi}_1(J)}\Big)D_1\Delta J + D_2e^{m_1\tau_1}\Delta P + \frac{D_4\widetilde{\psi}_1(J_0)}{d_4}\Delta V + \frac{c\widetilde{\psi}_1(J_0)}{hd_4}D_6\Delta U\cdot U\\ & + \frac{be^{-m_3\tau_3}\widetilde{\psi}_1(J_0)+d_4\widetilde{\psi}_1(J_0)}{d_3d_4}D_3\Delta K + \frac{\eta(be^{-m_3\tau_3}\widetilde{\psi}_1(J_0)+d_4\widetilde{\psi}_1(J_0))}{\omega d_3d_4}D_5\Delta L\cdot L\\ & + \Big(1-\frac{\widetilde{\psi}_1(J_0)}{\widetilde{\psi}_1(J)}\Big)(\lambda-d_1J) + \Big(\frac{\widetilde{\psi}_1(J_0)\psi_1(J,V)}{\widetilde{\psi}_1(J)V} - \widetilde{\psi}_1(J_0)\Big)V\\ & + \Big[\frac{\widetilde{\psi}_1(J_0)\psi_2(J,P)}{\widetilde{\psi}_1(J)P} - (\alpha+d_2)e^{m_1\tau_1} + \frac{\alpha e^{-m_2\tau_2}(be^{-m_3\tau_3}\widetilde{\psi}_1(J_0)+d_4\widetilde{\psi}_1(J_0))}{d_3d_4}\Big]P\\ & + \Big(\frac{\widetilde{\psi}_1(J_0)\psi_3(J,K)}{\widetilde{\psi}_1(J)K} - \widetilde{\psi}_3(J_0)\Big)K - \frac{c\widetilde{\psi}_1(J_0)}{hd_4}(d_6+\varepsilon E)U^2\\ & - \frac{\eta(be^{-m_3\tau_3}\widetilde{\psi}_1(J_0)+d_4\widetilde{\psi}_1(J_0))}{\omega d_3d_4}(d_5+\sigma K)L^2\Big\}\,\mathrm{d}x,\end{aligned}$$

where

$$\begin{aligned}& \frac{\widetilde{\psi}_1(J_0)}{\widetilde{\psi}_1(J)}\cdot\frac{\psi_2(J,P)}{P} - (\alpha+d_2)e^{m_1\tau_1} + \frac{\alpha e^{-m_2\tau_2}(be^{-m_3\tau_3}\widetilde{\psi}_1(J_0)+d_4\widetilde{\psi}_1(J_0))}{d_3d_4}\\ \le\ & \frac{\widetilde{\psi}_1(J_0)}{\widetilde{\psi}_1(J)}\cdot\widetilde{\psi}_2(J) - (\alpha+d_2)e^{m_1\tau_1} + \frac{\alpha e^{-m_2\tau_2}(be^{-m_3\tau_3}\widetilde{\psi}_1(J_0)+d_4\widetilde{\psi}_1(J_0))}{d_3d_4}\\ \le\ & \frac{\widetilde{\psi}_1(J_0)}{\widetilde{\psi}_1(J_0)}\cdot\widetilde{\psi}_2(J_0) - (\alpha+d_2)e^{m_1\tau_1} + \frac{\alpha e^{-m_2\tau_2}(be^{-m_3\tau_3}\widetilde{\psi}_1(J_0)+d_4\widetilde{\psi}_1(J_0))}{d_3d_4}\\ =\ & (\alpha+d_2)e^{m_1\tau_1}(R_0-1),\end{aligned}$$

and

$$\frac{\widetilde{\psi}_1(J_0)}{\widetilde{\psi}_1(J)}\cdot\frac{\psi_3(J,K)}{K} - \widetilde{\psi}_3(J_0) \le \frac{\widetilde{\psi}_1(J_0)}{\widetilde{\psi}_1(J)}\cdot\widetilde{\psi}_3(J) - \widetilde{\psi}_3(J_0) = 0.$$

Similarly,

$$\frac{\widetilde{\psi}_1(J_0)}{\widetilde{\psi}_1(J)}\cdot\frac{\psi_1(J,V)}{V} - \widetilde{\psi}_1(J_0) \le \frac{\widetilde{\psi}_1(J_0)}{\widetilde{\psi}_1(J)}\cdot\widetilde{\psi}_1(J) - \widetilde{\psi}_1(J_0) = 0.$$

From (H_1), we have

$$\Big(1-\frac{\widetilde{\psi}_1(J_0)}{\widetilde{\psi}_1(J)}\Big)(\lambda-d_1J) \le 0.$$

Therefore, we obtain

$$\begin{aligned}\frac{dG_1(t)}{dt} = & \int_\Omega \Big\{\Big(1-\frac{\widetilde{\psi}_1(J_0)}{\widetilde{\psi}_1(J)}\Big)D_1\Delta J + D_2e^{m_1\tau_1}\Delta P + \frac{D_4\widetilde{\psi}_1(J_0)}{d_4}\Delta V\\ & + \frac{be^{-m_3\tau_3}\widetilde{\psi}_1(J_0)+d_4\widetilde{\psi}_1(J_0)}{d_3d_4}D_3\Delta K + (\alpha+d_2)e^{m_1\tau_1}(R_0-1)P\\ & + \frac{\eta(be^{-m_3\tau_3}\widetilde{\psi}_1(J_0)+d_4\widetilde{\psi}_1(J_0))}{\omega d_3d_4}D_5\Delta L\cdot L + \frac{c\widetilde{\psi}_1(J_0)}{hd_4}D_6\Delta U\cdot U\\ & - \frac{c\widetilde{\psi}_1(J_0)}{hd_4}(d_6+\varepsilon V)U^2 - \frac{\eta(be^{-m_3\tau_3}\widetilde{\psi}_1(J_0)+d_4\widetilde{\psi}_1(J_0))}{\omega d_3d_4}(d_5+\sigma K)L^2\Big\}\,\mathrm{d}x.\end{aligned}$$

Using the divergence theorem and the homogeneous Neumann boundary conditions, we get

$$\begin{aligned}
&\int_\Omega \Delta J \,\mathrm{d}x = \int_{\partial\Omega} \frac{\partial J}{\partial \vec{n}} \,\mathrm{d}x = 0, \ \int_\Omega \Delta P \,\mathrm{d}x = \int_{\partial\Omega} \frac{\partial P}{\partial \vec{n}} \,\mathrm{d}x = 0,\\
&\int_\Omega \Delta K \,\mathrm{d}x = \int_{\partial\Omega} \frac{\partial K}{\partial \vec{n}} \,\mathrm{d}x = 0, \ \int_\Omega \Delta V \,\mathrm{d}x = \int_{\partial\Omega} \frac{\partial V}{\partial \vec{n}} \,\mathrm{d}x = 0,\\
&\int_\Omega \Delta L \cdot L \,\mathrm{d}x = -\int_\Omega \| \nabla L \|^2 \ \mathrm{d}x, \ \int_\Omega \Delta U \cdot U \,\mathrm{d}x = -\int_\Omega \| \nabla U \|^2 \ \mathrm{d}x.\\
&\int_\Omega \frac{\Delta J}{\widetilde{\psi}_1(J)} \,\mathrm{d}x = \int_\Omega \frac{\| \nabla J \|^2}{\widetilde{\psi}_1^2(J)} \,\mathrm{d}x.
\end{aligned}$$

Thus,

$$\begin{aligned}
\frac{dG_1(t)}{dt} = \ & \int_\Omega \Big\{ -\frac{\widetilde{\psi}_1^2(J_0) \| \nabla J \|^2}{\widetilde{\psi}_1^2(J)} - \frac{\eta(be^{-m_3\tau_3}\widetilde{\psi}_1(J_0) + d_4\widetilde{\psi}_1(J_0))}{\omega d_3 d_4} D_5 \| \nabla L \|^2 \\
& - \frac{c\widetilde{\psi}_1(J_0)}{hd_4} D_6 \| \nabla U \|^2 + (\alpha + d_2)e^{m_1\tau_1}(R_0 - 1)P \\
& - \frac{c\widetilde{\psi}_1(J_0)}{hd_4}(d_6 + \varepsilon V)U^2 - \frac{\eta(be^{-m_3\tau_3}\widetilde{\psi}_1(J_0) + d_4\widetilde{\psi}_1(J_0))}{\omega d_3 d_4}(d_5 + \sigma K)L^2 \Big\} \,\mathrm{d}x.
\end{aligned}$$

Obviously, if $R_0 \le 1$, then $\frac{dG_1(t)}{dt} \le 0$. $\frac{dG_1(t)}{dt} = 0$ if and only if $P = 0$, $L = 0$, and $U = 0$. Let M be the largest invariant set of $\{(J, P, K, V, L, U) \in R_+^6 : \frac{dG_1(t)}{dt} = 0\}$. From the third equation of model (1.1), we easily obtain $M = \{E_0\}$. It follows from LaSalle's invariance principle that E_0 is globally asymptotically stable when $R_0 \le 1$.

3.2. Stability of equilibrium E_1

Theorem 3.2. *Assume that (H_1) and (H_2) hold. If $R_0 > 1$, then the chronic-infection equilibrium E_1 is globally asymptotically stable.*

Proof. Define the function $H(\xi) = \xi - 1 - \ln\xi$. Clearly, $H(\xi) \ge 0$ for $\xi > 0$ and $H(1) = 0$. Define a Lyapunov functional

$$\begin{aligned}
G_2(t) = \ & \int_\Omega \Big\{ J - J^* - \int_{J^*}^{J} \frac{\psi_1(J^*, V^*)}{\psi_1(\theta, V^*)} \,\mathrm{d}\theta + e^{m_1\tau_1} P^* H\Big(\frac{P}{P^*}\Big) + \frac{M}{V^*(d_3 + \eta L^*)(d_4 + cU^*)} H\Big(\frac{K}{K^*}\Big) \\
& + \frac{\psi_1(J^*, V^*)}{d_4 + cU^*} H\Big(\frac{V}{V^*}\Big) + \frac{\eta M}{2K^*V^*(d_3 + \eta L^*)(d_4 + cU^*)(\omega - \sigma L^*)}(L - L^*)^2 \\
& + \frac{c\psi_1(J^*, V^*)}{2V^*(d_4 + cU^*)(h - \varepsilon U^*)}(U - U^*)^2 + \psi_1(J^*, V^*) \int_{t-\tau_1}^{t} H\Big(\frac{\psi_1(J(\theta), V(\theta))}{\psi_1(J^*, V^*)}\Big) \,\mathrm{d}\theta \\
& + \psi_2(J^*, P^*) \int_{t-\tau_1}^{t} H\Big(\frac{\psi_2(J(\theta), P(\theta))}{\psi_2(J^*, P^*)}\Big) \,\mathrm{d}\theta + \psi_3(J^*, K^*) \int_{t-\tau_1}^{t} H\Big(\frac{\psi_3(J(\theta), K(\theta))}{\psi_3(J^*, K^*)}\Big) \,\mathrm{d}\theta \\
& + \frac{e^{-m_2\tau_2}\alpha P^* M}{K^*V^*(d_3 + \eta L^*)(d_4 + cU^*)} \int_{t-\tau_2}^{t} H\Big(\frac{P(\theta)}{P^*}\Big) \,\mathrm{d}\theta \\
& + \frac{bK^*\psi_1(J^*, V^*)e^{-m_3\tau_3}}{V^*(d_4 + cU^*)} \int_{t-\tau_3}^{t} H\Big(\frac{K(\theta)}{K^*}\Big) \,\mathrm{d}\theta \Big\},
\end{aligned}$$

where $M = be^{-m_3\tau_3}K^*\psi_1(J^*, V^*) + V^*(d_4 + cU^*)\psi_3(J^*, K^*)$.

Use

$$\lambda = d_1J^* + \psi_1(J^*, V^*) + \psi_2(J^*, P^*) + \psi_3(J^*, K^*),$$
$$\psi_1(J^*, V^*) + \psi_2(J^*, P^*) + \psi_3(J^*, K^*) = (\alpha + d_2)e^{m_1\tau_1}P^*,$$
$$\alpha e^{-m_2\tau_2}P^* = K^*(d_3 + \eta L^*),\ be^{-m_3\tau_3}K^* = V^*(d_4 + cU^*),$$
$$\omega K^* = d_5L^* + \sigma L^*K^*,\ hV^* = d_6U^* + \varepsilon U^*V^*.$$

Calculating the time derivative of $G_2(x, t)$ along any positive solution of model (1.1), we can obtain

$$\begin{aligned}
\frac{\mathrm{d}G_2(t)}{\mathrm{d}t} = \int_\Omega \Big\{ & \Big(1 - \frac{\psi_1(J^*, V^*)}{\psi_1(J, V^*)}\Big)D_1\Delta J + D_2e^{m_1\tau_1}\Big(1 - \frac{P^*}{P}\Big)\Delta P + \frac{\psi_1(J^*, V^*)}{V^*(d_4 + cU^*)}\Big(1 - \frac{V^*}{V}\Big)D_4\Delta V \\
& + \frac{M}{V^*(d_3 + \eta L^*)(d_4 + cU^*)}\Big(1 - \frac{K^*}{K}\Big)D_3\Delta K + \psi_1(J^*, V^*)\frac{\psi_1(J, V)}{\psi_1(J, V^*)} \\
& + \frac{\eta M}{K^*V^*(d_3 + \eta L^*)(d_4 + cU^*)(\omega - \sigma L^*)}(L - L^*)D_5\Delta L \\
& + \frac{c\psi_1(J^*, V^*)}{V^*(d_4 + cU^*)(h - \varepsilon U^*)}(U - U^*)D_6\Delta U + \Big(1 - \frac{\psi_1(J^*, V^*)}{\psi_1(J, V^*)}\Big)d_1J^*\Big(1 - \frac{J^*}{J}\Big) \\
& + \Big(2 - \frac{\psi_1(J^*, V^*)}{\psi_1(J, V^*)}\Big)(\psi_1(J^*, V^*) + \psi_2(J^*, P^*) + \psi_3(J^*, K^*)) \\
& + \psi_2(J^*, P^*)\frac{\psi_1(J^*, V^*)\psi_2(J, P)}{\psi_1(J, V^*)\psi_2(J^*, P^*)} + \psi_3(J^*, K^*)\frac{\psi_1(J^*, V^*)\psi_3(J, K)}{\psi_1(J, V^*)\psi_3(J^*, K^*)} \\
& - \psi_1(J^*, V^*)\frac{\psi_1(J(t - \tau_1), V(t - \tau_1))P^*}{\psi_1(J^*, V^*)P} - \psi_2(J^*, P^*)\frac{P}{P^*} - \psi_1(J^*, V^*)\frac{V}{V^*} \\
& - \psi_2(J^*, P^*)\frac{\psi_2(J(t - \tau_1), P(t - \tau_1))P^*}{\psi_2(J^*, P^*)P} - \psi_3(J^*, K^*)\frac{K}{K^*} \\
& - \psi_3(J^*, K^*)\frac{\psi_3(J(t - \tau_1), K(t - \tau_1))P^*}{\psi_3(J^*, K^*)P} + 2\psi_1(J^*, V^*) + \psi_3(J^*, K^*) \\
& - (\psi_1(J^*, V^*) + \psi_3(J^*, K^*))\frac{P(t - \tau_2)K^*}{P^*K} - \psi_1(J^*, V^*)\frac{K(t - \tau_3)V^*}{K^*V} \\
& - \frac{\eta M}{K^*V^*(d_3 + \eta L^*)(d_4 + cU^*)(\omega - \sigma L^*)}(d_5 + \sigma K)(L - L^*)^2 \\
& - \frac{c\psi_1(J^*, V^*)}{V^*(d_4 + cU^*)(h - \varepsilon U^*)}(d_6 + \varepsilon V)(U - U^*)^2 \\
& + \psi_1(J^*, V^*)\ln\Big(\frac{\psi_1(J(t - \tau_1), V(t - \tau_1))}{\psi_1(J, V)}\Big) + \psi_2(J^*, P^*)\ln\Big(\frac{\psi_2(J(t - \tau_1), P(t - \tau_1))}{\psi_2(J, P)}\Big) \\
& + \psi_3(J^*, K^*)\ln\Big(\frac{\psi_3(J(t - \tau_1), K(t - \tau_1))}{\psi_3(J, K)}\Big) + \psi_1(J^*, V^*)\ln\Big(\frac{K(t - \tau_3)}{K}\Big) \\
& + (\psi_1(J^*, V^*) + \psi_3(J^*, K^*))\ln\Big(\frac{P(t - \tau_2)}{P}\Big)\Big\}\,\mathrm{d}x.
\end{aligned}$$

Using the divergence theorem and the homogeneous Neumann boundary conditions, we get

$$\int_\Omega \Delta J \,\mathrm{d}x = \int_{\partial\Omega} \frac{\partial J}{\partial \vec{n}} \,\mathrm{d}x = 0, \ \int_\Omega \Delta P \,\mathrm{d}x = \int_{\partial\Omega} \frac{\partial P}{\partial \vec{n}} \,\mathrm{d}x = 0,$$
$$\int_\Omega \Delta K \,\mathrm{d}x = \int_{\partial\Omega} \frac{\partial K}{\partial \vec{n}} \,\mathrm{d}x = 0, \ \int_\Omega \Delta V \,\mathrm{d}x = \int_{\partial\Omega} \frac{\partial V}{\partial \vec{n}} \,\mathrm{d}x = 0,$$
$$\int_\Omega \Delta L \,\mathrm{d}x = \int_{\partial\Omega} \frac{\partial L}{\partial \vec{n}} \,\mathrm{d}x = 0, \ \int_\Omega \Delta U \,\mathrm{d}x = \int_{\partial\Omega} \frac{\partial U}{\partial \vec{n}} \,\mathrm{d}x = 0,$$
$$\int_\Omega \frac{\Delta J}{\psi_1(J, V^*)} \,\mathrm{d}x = \int_\Omega \frac{\| \nabla J \|^2}{\psi_1^2(J, V^*)} \,\mathrm{d}x, \ \int_\Omega \frac{\Delta P}{P} \,\mathrm{d}x = \int_\Omega \frac{\| \nabla P \|^2}{P^2} \,\mathrm{d}x,$$
$$\int_\Omega \frac{\Delta K}{K} \,\mathrm{d}x = \int_\Omega \frac{\| \nabla K \|^2}{K^2} \,\mathrm{d}x, \ \int_\Omega \frac{\Delta V}{V} \,\mathrm{d}x = \int_\Omega \frac{\| \nabla V \|^2}{V^2} \,\mathrm{d}x,$$
$$\int_\Omega \Delta L \cdot L \,\mathrm{d}x = -\int_\Omega \| \nabla L \|^2 \ \mathrm{d}x, \ \int_\Omega \Delta U \cdot U \,\mathrm{d}x = -\int_\Omega \| \nabla U \|^2 \ \mathrm{d}x.$$

Thus, we have

$$\begin{aligned}
\frac{\mathrm{d}G_2(t)}{\mathrm{d}t} =& -\psi_1(J^*, V^*)D_1 \int_\Omega \frac{\| \nabla J \|^2}{\psi_1^2(J, V^*)} \,\mathrm{d}x - D_2 e^{m_1\tau_1} P^* \int_\Omega \frac{\| \nabla P \|^2}{P^2} \,\mathrm{d}x \\
&- \frac{MD_3K^*}{V^*(d_3 + \eta L^*)(d_4 + cU^*)} \int_\Omega \frac{\| \nabla K \|^2}{K^2} \,\mathrm{d}x - \frac{D_6 c\psi_1(J^*, V^*)}{V^*(d_4 + cU^*)(h - \varepsilon U^*)} \int_\Omega \| \nabla U \|^2 \ \mathrm{d}x \\
&- \frac{\psi_1(J^*, V^*)D_4}{d_4 + cU^*} \int_\Omega \frac{\| \nabla V \|^2}{V^2} \,\mathrm{d}x - \frac{D_5\eta M}{K^*V^*(d_3 + \eta L^*)(d_4 + cU^*)(\omega - \sigma L^*)} \int_\Omega \| \nabla L \|^2 \ \mathrm{d}x \\
&+ \int_\Omega \Big\{ d_1 J^* \Big(1 - \frac{\psi_1(J^*, V^*)}{\psi_1(J, V^*)}\Big)\Big(1 - \frac{J}{J^*}\Big) + \psi_1(J^*, V^*)\Big(\frac{\psi_1(J, V)}{\psi_1(J, V^*)} - \frac{V}{V^*}\Big)\Big(1 - \frac{\psi_1(J, V^*)}{\psi_1(J, V)}\Big) \\
&+ \psi_2(J^*, P^*)\Big(\frac{\psi_1(J^*, V^*)\psi_2(J, P)}{\psi_1(J, V^*)\psi_2(J^*, P^*)} - \frac{P}{P^*}\Big)\Big(1 - \frac{\psi_1(J, V^*)\psi_2(J^*, P^*)}{\psi_1(J^*, V^*)\psi_2(J, P)}\Big) \\
&+ \psi_3(J^*, K^*)\Big(\frac{\psi_1(J^*, V^*)\psi_3(J, K)}{\psi_1(J, V^*)\psi_3(J^*, K^*)} - \frac{K}{K^*}\Big)\Big(1 - \frac{\psi_1(J, V^*)\psi_3(J^*, K^*)}{\psi_1(J^*, V^*)\psi_3(J, K)}\Big) \\
&- \psi_1(J^*, V^*)\Big[H\Big(\frac{\psi_1(J^*, V^*)}{\psi_1(J, V^*)}\Big) + H\Big(\frac{\psi_1(J(t - \tau_1), V(t - \tau_1))P^*}{\psi_1(J^*, V^*)P}\Big) + H\Big(\frac{\psi_1(J, V^*)V}{\psi_1(J, V)V^*}\Big)\Big] \\
&- \psi_2(J^*, P^*)\Big[H\Big(\frac{\psi_1(J^*, V^*)}{\psi_1(J, V^*)}\Big) + H\Big(\frac{\psi_2(J(t - \tau_1), P(t - \tau_1))P^*}{\psi_2(J^*, P^*)P}\Big) + H\Big(\frac{\psi_1(J, V^*)\psi_2(J^*, P^*)P}{\psi_1(J^*, V^*)\psi_2(J, P)P^*}\Big)\Big] \\
&- \psi_3(J^*, K^*)\Big[H\Big(\frac{\psi_1(J^*, V^*)}{\psi_1(J, V^*)}\Big) + H\Big(\frac{\psi_3(J(t - \tau_1), K(t - \tau_1))P^*}{\psi_3(J^*, K^*)P}\Big) \\
&+ H\Big(\frac{\psi_1(J, V^*)\psi_3(J^*, K^*)K}{\psi_1(J^*, V^*)\psi_3(J, K)K^*}\Big)\Big] - \psi_1(J^*, V^*)H\Big(\frac{K(t - \tau_3)V^*}{K^*V}\Big) \\
&- (\psi_1(J^*, V^*) + \psi_3(J^*, K^*))H\Big(\frac{P(t - \tau_2)K^*}{P^*K}\Big)
\end{aligned}$$

$$- \frac{\eta(d_5 + \sigma K)(\psi_1(J^*, V^*) + \psi_3(J^*, K^*))}{K^*(d_3 + \eta L^*)(\omega - \sigma L^*)}(L - L^*)^2$$
$$- \frac{c\psi_1(J^*, V^*)}{V^*(d_4 + cU^*)(h - \varepsilon U^*)}(d_6 + \varepsilon V)(U - U^*)^2\Big\}\,\mathrm{d}x.$$

Obviously, we have $\frac{dG_2(t)}{dt} \leq 0$, and $\frac{dG_2(t)}{dt} = 0$ if and only if $J(t) = J^*, P(t) = P^*, K(t) = K^*, V(t) = V^*, L(t) = L^*$, and $U(t) = U^*$. From LaSalle's invariance principle, we finally have that E_1 is globally asymptotically stable when $R_0 > 1$.

4. Numerical simulations

In this section, we present several numerical examples to illustrate the results obtained in Section 3. We will use the finite difference scheme, which is proposed in [38–40] for the delayed reaction-diffusion epidemic models. For convenience, we consider model (1.1) under the one-dimensional spatial domain $\Omega = [0, 1]$. The grid sizes used in the spatial and temporal directions are $\Delta x = 0.1$, and $\Delta t = 0.1$, respectively. The homogeneous Neumann boundary conditions and the initial conditions are given by

$$\frac{\partial J}{\partial \vec{n}} = \frac{\partial P}{\partial \vec{n}} = \frac{\partial K}{\partial \vec{n}} = \frac{\partial V}{\partial \vec{n}} = \frac{\partial L}{\partial \vec{n}} = \frac{\partial U}{\partial \vec{n}} = 0,\ t > 0,\ x = 0,\ 1, \tag{4.1}$$

and

$$J(x, \theta) = 400,\ P(x, \theta) = 10,\ K(x, \theta) = 2,\ V(x, \theta) = 2,\ L(x, \theta) = 0.3,\ U(x, \theta) = 0.09,$$

for $0 \leq x \leq 1$ and $-\tau \leq \theta \leq 0$.

In model (1.1), we choose the nonlinear incidences $\psi_1(J, V) = \frac{\beta_1 JV}{(1 + a_1 J)(1 + c_1 V)}$, $\psi_2(J, P) = \frac{\beta_2 JP}{(1 + a_2 J)(1 + c_2 P)}$, and $\psi_3(J, K) = \frac{\beta_3 JK}{(1 + a_3 J)(1 + c_3 K)}$. Furthermore, we observe

$$\frac{\partial \psi_i(J, \theta)}{\partial J} = \frac{\beta_i \theta}{(1 + a_i J)^2(1 + c_i \theta)} > 0, \text{ for all } J,\ \theta > 0,$$
$$\frac{\partial \psi_i(J, \theta)}{\partial \theta} = \frac{\beta_i J}{(1 + a_i J)(1 + c_i \theta)^2} > 0, \text{ for all } J,\ \theta > 0,$$

where $\theta \in \{V, P, K\}$. Then assumption (H_1) is valid. It is obvious that

$$\widetilde{\psi}_i(J) = \frac{\partial \psi_i(J, 0)}{\partial \theta} = \frac{\beta_i J}{1 + a_i J} > 0, \text{ for all } J > 0,$$
$$\widetilde{\psi}_i'(J) = \frac{d}{dJ}\left(\frac{\partial \psi_i(J, 0)}{\partial \theta}\right) = \frac{\beta_i}{(1 + a_i J)^2} > 0, \text{ for all } J > 0,$$
$$\frac{\partial}{\partial \theta}\left(\frac{\partial \psi_i(J, \theta)}{\partial \theta}\right) = \frac{-c_i \beta_i J}{(1 + a_i J)(1 + c_i \theta)^2} < 0, \text{ for all } J,\ \theta > 0.$$

Hence, assumption (H_2) is verified. Select $D_1 = 0.1,\ D_2 = 0.1,\ D_3 = 0.1,\ D_4 = 0.1,\ D_5 = 0.1,\ D_6 = 0.1,\ \tau_1 = 10,\ \tau_2 = 5$, and $\tau_3 = 2$. Furthermore, β_1, β_2, and β_3 are chosen as free parameters. All other parameter values are the same as in Table 2.

Table 2. Definition of parameters in model (1.1).

Parameter	Value	Source	Parameter	Value	Source
λ	$10\mu l^{-1}day^{-1}$	[36]	b	$2.6day^{-1}$	[5,37]
d_1	$0.01day^{-1}$	[36]	c_1	0.01	assumed
α	$0.2day^{-1}$	[6,37]	c_2	0.01	assumed
a_1	0.01	assumed	c_3	0.01	assumed
a_2	0.01	assumed	c	$0.06\mu l^{-1}day^{-1}$	[37]
a_3	0.01	assumed	ω	$0.25day^{-1}$	[6]
d_2	$0.2day^{-1}$	[2,3]	d_5	$0.2day^{-1}$	[37]
d_3	$0.8day^{-1}$	[5,37]	m_1	0.001	assumed
d_4	$3day^{-1}$	[5]	m_2	0.001	assumed
η	$0.4\mu l^{-1}day^{-1}$	[37]	m_3	0.001	assumed
σ	$0.001\mu l^{-1}day^{-1}$	[8]	h	$0.1day^{-1}$	[5]
d_6	$0.1day^{-1}$	[36]	ε	$0.001\mu l^{-1}day^{-1}$	[7]

In the following, Figures 1 and 2 are denoted as time-series figures of $J(x,t)$, $P(x,t)$, $K(x,t)$, $V(x,t)$, $L(x,t)$, and $U(x,t)$.

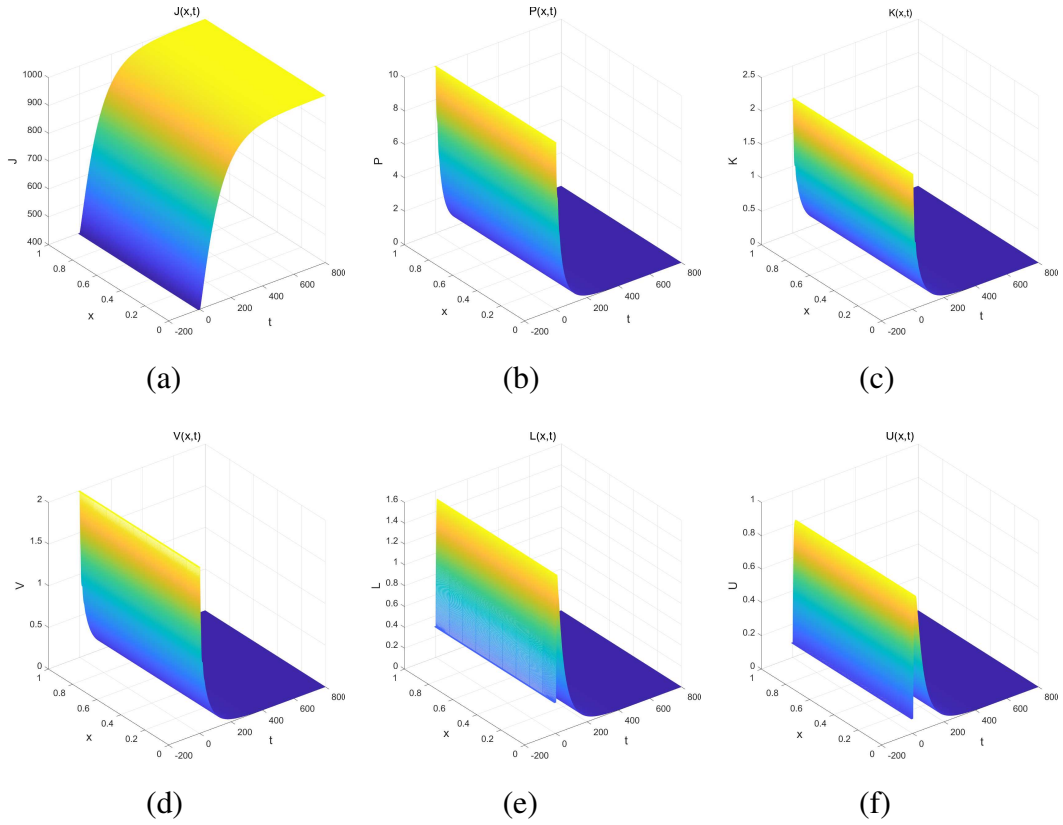

Figure 1. Taking $\beta_1 = 0.001$, $\beta_2 = 0.003$, and $\beta_3 = 0.002$, we have $R_0 = 0.8357 < 1$, and equilibrium $E_0 = (1000, 0, 0, 0, 0, 0)$ is globally asymptotically stable.

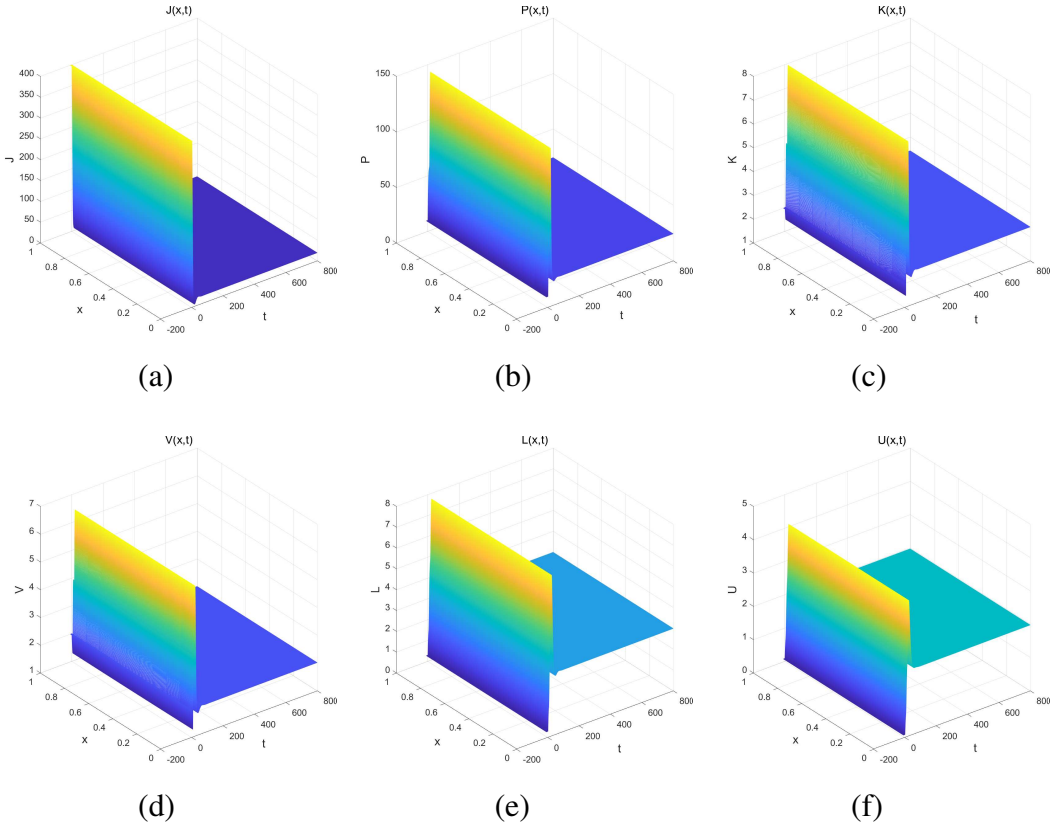

Figure 2. Taking $\beta_1 = 0.01$, $\beta_2 = 0.03$, and $\beta_3 = 0.002$, we have $R_0 = 7.3498 > 1$, and equilibrium $E_1 = (19.14, 24.28, 2.421, 2.014, 2.99, 1.974)$ is globally asymptotically stable.

5. Conclusions

In this paper, we have discussed a generalized delayed HIV infection model (1.1) with diffusion, immune impairment, and three modes of transmission, in which the virus-to-cell infection $\psi_1(J, V)$, the latent cell-to-cell transmission $\psi_2(J, P)$, and the cell-to-cell transmission $\psi_3(J, K)$ are considered. Assume that the incidence functions satisfy the biologically reasonable interpretations presented in (H_1)–(H_2). By the analysis, we have shown that when $R_0 < 1$, E_0 is globally asymptotically stable, which is illustrated in Figure 1. This implies viral clearance and infection extinction. When $R_0 > 1$, E_1 is globally asymptotically stable. It implies coexistence of virus and host with chronic infection, as confirmed in Theorem 3.2 by Figure 2. The novelty of the present work is the establishment of a suitable Lyapunov functional for a diffusive HIV model incorporating adaptive immune responses, three time delays, and three mechanisms of viral transmission, and the technique can be generalized to more sophisticated models.

One can readily observe that the reproduction ratio R_0 is the sum of three reproduction ratios: R_{01} determined by virus-to-cell infection, R_{02} governed by spread among latently infected cells, and R_{03} from cell-to-cell transmission. For one thing, the existence of time delays significantly lowers the basic reproduction number, which in turn suppresses HIV viral replication; for another, the existence of

latent cell-to-cell transmission raises R_0, exacerbating HIV infection progression and accelerating HIV disease progression. If latent spread is omitted from the HIV dynamical model, the basic reproduction number will be underestimated, and the therapeutic effect of anti-HIV drugs for viral eradication may be inadequate. The findings facilitate elucidation of virus-host cell interaction mechanisms and further uncover the dissemination dynamics of viruses within the host.

It would be worthwhile to improve model (1.1) by introducing memory-dependent effects and age structure. Furthermore, model (1.1) can be extended to characterize spatiotemporal dynamics involving two types of target cells or coinfection by multiple viruses. We will address these directions in future research.

Use of Generative-AI tools declaration

The author declares she has not used Artificial Intelligence (AI) tools in the creation of this paper.

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Conflict of interest

The author declares that there are no conflicts of interest.

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