



Research article

Threshold dynamics of an HIV-1 model with both viral and cellular infections, cell-mediated and humoral immune responses

Jiazhe Lin¹, Rui Xu^{2,3,*} and Xiaohong Tian^{2,3}

¹ Institute of Applied Mathematics, Army Engineering University, Shijiazhuang 050003, Hebei, P.R. China

² Complex Systems Research Center, Shanxi University, Taiyuan 030006, Shanxi, P.R. China

³ Shanxi Key Laboratory of Mathematical Techniques and Big Data Analysis on Disease Control and Prevention, Shanxi University, Taiyuan 030006, Shanxi, P.R. China

* **Correspondence:** Email: xur2020meu@163.com; rxu88@163.com.

Abstract: Human specific immunity consists of two branches: humoral immunity and cellular immunity. To protect us from pathogens, cell-mediated and humoral immune responses work together to provide the strongest degree of efficacy. In this paper, we propose an HIV-1 model with cell-mediated and humoral immune responses, in which both virus-to-cell infection and cell-to-cell transmission are considered. Five reproduction ratios, namely, immunity-inactivated reproduction ratio, cell-mediated immunity-activated reproduction ratio, humoral immunity-activated reproduction ratio, cell-mediated immunity-competed reproduction ratio and humoral immunity-competed reproduction ratio, are calculated and verified to be sharp thresholds determining the local and global properties of the virus model. Numerical simulations are carried out to illustrate the corresponding theoretical results and reveal the effects of some key parameters on viral dynamics.

Keywords: HIV-1 infection; virus-to-cell infection; cell-to-cell transmission; cell-mediated immunity; humoral immunity; threshold dynamics

1. Introduction

The human immunodeficiency virus (HIV) is a lentivirus that causes HIV infection and over time acquired immunodeficiency syndrome (AIDS). AIDS leads to progressive failure of the immune system, which allows life-threatening opportunistic infections and cancers to thrive. In the past decades, within host virus models have been investigated in some literatures, which helps us understand the biological interactions between viruses and host cells. Nowak et al. [20] designed a mathematical model including uninfected cells $x(t)$, infected cells $y(t)$ and free virus $v(t)$ to describe

the viral dynamics in HIV-1 infection:

$$\begin{aligned}\dot{x}(t) &= s - dx(t) - \beta_1 x(t)v(t), \\ \dot{y}(t) &= \beta_1 x(t)v(t) - ay(t), \\ \dot{v}(t) &= ky(t) - uv(t),\end{aligned}\tag{1.1}$$

where uninfected cells $x(t)$ are produced at rate s and die at rate d ; β_1 is the infection rate of virus-to-cell infection; a is the death rate of infected cells; k denotes the number of free virus particles produced by per infected cell; u is the remove rate of virus. System (1.1) has been further investigated by Perelson and Nelson [21] and Cangelosi et al. [1].

Faced with different virus infections, immunity system protects us against pathogens. Human specific immunity can be classified into cell-mediated immunity, for which the protective function is associated with cells and humoral immunity, where the protective function exists in the humor [2]. As for cell-mediated immunity, activated effector T cells can detect peptide antigens originating from various types of pathogens and remove virus-infected cells. Some HIV-1 infection models have been proposed to describe the virus dynamics with cell-mediated immune response (see, for example, [15, 19, 24, 26, 34]). While, in humoral immunity, matured B cells migrate from bone marrow to lymph nodes or other lymphatic organs, where they begin to eliminate pathogens [23]. There have been several works on virus models with humoral immune response (see, for example, [4, 14, 28–30]). In [6], Fouts et al. pointed out that a guiding principle for HIV vaccine design has been that cellular and humoral immunities work together to provide the strongest degree of efficacy. In [33], Yan and Wang considered both cell-mediated and humoral immune responses and put forward an HIV-1 infection model including both T cells and B cells, which only involves virus-to-cell infection mechanism.

It is mentioned in [17] that cell-to-cell transmission is a more potent and efficient means of virus propagation than the virus-to-cell infection mechanism. Cell-to-cell spread not only facilitates rapid viral dissemination but also reduce the effectiveness of neutralizing antibodies and viral inhibitors by immune evasion. In [25], Sigal et al. proved that cell-to-cell spread of HIV-1 does reduce the efficacy of antiretroviral therapy, since cell-to-cell transmission can cause multiple infections of target cells, which can in turn reduce the sensitivity to the antiretroviral drugs. In view of this, some mathematical analysis of virus models with cell-to-cell transmission has been performed. For instance, Li and Wang [13] dealt with the global dynamics of an HIV infection model which incorporated direct cell-to-cell transmission. Meanwhile, Lai and Zou [11, 12] studied the effect of cell-to-cell transfer of HIV-1 on the virus dynamics.

It was assumed in system (1.1) that the infection process is governed by the mass-action principle, namely, the infection rate per host or per virus is a constant. In [22], Regoes et al. illustrated that the infection rate is often found to be a sigmoidal rather than a linear function of the parasite dose to which it is exposed, and presented a dose-dependent infection rate $(v/ID_{50})^\kappa/[1 + (v/ID_{50})^\kappa]$, where ID_{50} denotes the infectious dose at which 50% of the hosts are infected and κ measures the slope of the sigmoidal curve at ID_{50} . In [10], Huang et al. indicated that the bilinear incidence rate is insufficient to describe the infection process in detail and proposed a class of nonlinear incidence. Besides, to place the model on more sound biological grounds, Xu [31] and Elaiw et al. [5] incorporated a saturation incidence $\beta_1 v(t)/(1 + \alpha v(t))$ to replace the mass-action infection rate.

Motivated by the works of Fouts et al. [6], Yan and Wang [33], Sigal et al. [25] and Regoes et al. [22],

in the present paper, we are concerned with the effects of cell-to-cell transmission, saturation incidence, both cell-mediated and humoral immune responses on the global dynamics of HIV-1 infection model. To this end, we consider the following delay differential equations:

$$\begin{aligned}
 \dot{x}(t) &= s - dx(t) - \frac{\beta_1 x(t)v(t)}{1 + \alpha v(t)} - \beta_2 x(t)y(t), \\
 \dot{y}(t) &= \frac{\beta_1 e^{-m\tau} x(t-\tau)v(t-\tau)}{1 + \alpha v(t-\tau)} + \beta_2 e^{-m\tau} x(t-\tau)y(t-\tau) - ay(t) - p_1 y(t)z(t), \\
 \dot{v}(t) &= ky(t) - uv(t) - p_2 v(t)w(t), \\
 \dot{z}(t) &= c_1 y(t)z(t) - b_1 z(t), \\
 \dot{w}(t) &= c_2 v(t)w(t) - b_2 w(t),
 \end{aligned}
 \tag{1.2}$$

where $x(t)$, $y(t)$, $v(t)$, $z(t)$, $w(t)$ denote the concentration of uninfected cells, infected cells, virus, T cells and B cells at time t , respectively, and other parameters are described in Table 1. A simple schematic diagram for the virus infection corresponding to system (1.2) is shown in Figure 1.

The initial condition for system (1.2) takes the form

$$x(\theta) = \phi_1(\theta), \quad y(\theta) = \phi_2(\theta), \quad v(\theta) = \phi_3(\theta), \quad z(\theta) = \phi_4(\theta), \quad w(\theta) = \phi_5(\theta),
 \tag{1.3}$$

where it satisfies that $\phi_i(\theta) \geq 0$, $\theta \in [-\tau, 0)$, $\phi_i(0) > 0$, where $\phi_i \in C([-\tau, 0], \mathbb{R}_{+0}^5)$, $i = 1, 2, 3, 4, 5$, the Banach space of continuous functions mapping the interval $[-\tau, 0]$ into \mathbb{R}_{+0}^5 , where $\mathbb{R}_{+0}^5 = \{(x_1, x_2, x_3, x_4, x_5) : x_i \geq 0, i = 1, 2, 3, 4, 5\}$.

It can be proved by the fundamental theory of functional differential equations [7] that system (1.2) has a unique solution $(x(t), y(t), v(t), z(t), w(t))$ satisfying the initial condition (1.3). It is easy to show that all solutions of system (1.2) with initial condition (1.3) are defined on $[0, +\infty)$ and remain positive for all $t \geq 0$.

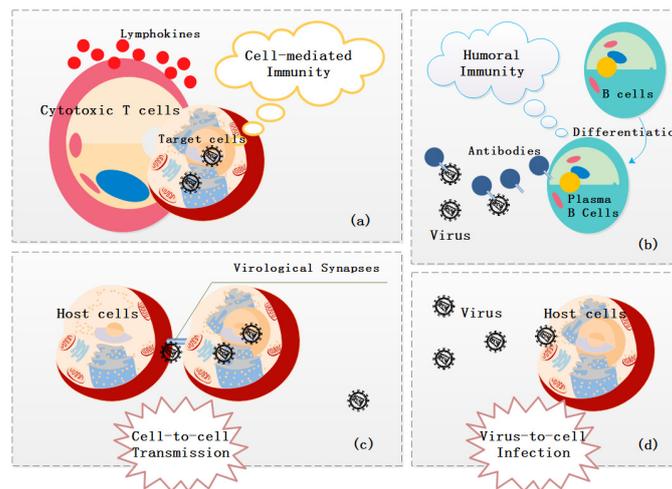


Figure 1. Simple schematic diagram of the HIV-1 infection model. (a), (b), (c) and (d) depict the process of cell-mediated immunity, humoral immunity, cell-to-cell infection and virus-to-cell transmission, respectively.

Table 1. Definitions of frequently used symbols

Symbols	Description
s	recruitment rate of uninfected cells
d	death rate of uninfected cells
β_1	infection rate of virus-to-cell infection
β_2	transmission rate of cell-to-cell transmission
α	saturation infection rate coefficient
τ	the time between viral entry into a cell and the production of new free virus or the time between infected cells spreading virus into uninfected cells and the production of new free virus [8]
$e^{-m\tau}$	the probability of surviving the time period from $t - \tau$ to t
a	death rate of infected cells
u	removal rate of virus
k	average number of free virus particles produced by per infected cell
p_1	kill ratio of infected cells by T cells
p_2	kill ratio of virus by B cells
b_1	death rate of T cells
b_2	death rate of B cells
c_1	maturing rate of new T cells from thymocytes in the thymus
c_2	production rate of new B cells by antigenic stimulation

This paper is organized as follows. In Section 2, we calculate the reproduction ratios to system (1.2) and establish the existence of feasible equilibria. In Section 3, the local asymptotic stability of each of feasible equilibria is studied. In Section 4, we investigate the global asymptotic stability of each of feasible equilibria. In Section 5, we present numerical simulations to illustrate the theoretical results and study the effects of cell-to-cell transmission, viral production rate, death rate of infected cells and viral removal rate on viral dynamics, respectively. Besides, we perform a sensitivity analysis of reproduction ratios. The paper ends with a conclusion in Section 6.

2. Reproduction ratios and feasible equilibria

Clearly, system (1.2) always has an infection-free equilibrium $E_0(s/d, 0, 0, 0, 0)$. Denote

$$\mathcal{R}_0 = \frac{(\beta_1 k + \beta_2 u) s e^{-m\tau}}{aud},$$

where \mathcal{R}_0 is called immunity-inactivated reproduction ratio of system (1.2), which represents the number of newly infected cells produced by one infected cell during its lifespan [3]. It is easy to show that if $\mathcal{R}_0 > 1$, system (1.2) has an immunity-inactivated equilibrium $E_1(x_1, y_1, v_1, 0, 0)$, where

$$x_1 = \frac{s(u + \alpha ky_1)}{(d + \beta_2 y_1)(u + \alpha ky_1) + \beta_1 ky_1}, \quad v_1 = \frac{ky_1}{u},$$

and

$$y_1 = \frac{-(\beta_1 ak + \beta_2 au + \alpha adk - \alpha \beta_2 k s e^{-m\tau}) + \sqrt{\Delta}}{2\alpha \beta_2 ak},$$

in which,

$$\Delta = (\beta_1 ak + \beta_2 au + \alpha adk - \alpha \beta_2 k se^{-m\tau})^2 - 4\alpha \beta_2 ak (adu - \beta_1 k se^{-m\tau} - \beta_2 sue^{-m\tau}).$$

Denote

$$\mathcal{R}_1 = \frac{c_1 se^{-m\tau} [\beta_2 (c_1 u + \alpha b_1 k) + \beta_1 c_1 k]}{a [(c_1 d + \beta_2 b_1) (c_1 u + \alpha b_1 k) + \beta_1 b_1 c_1 k]} = \frac{\mathcal{R}_0}{1 + X_1 \mathcal{R}_0},$$

where

$$X_1 = \frac{ab_1 (\beta_1 k + \beta_2 u) [c_1 (\beta_1 k + \beta_2 u) + \alpha \beta_2 b_1 k] + \alpha \beta_1 ab_1 c_1 dk^2}{c_1 se^{-m\tau} (\beta_1 k + \beta_2 u) [c_1 (\beta_1 k + \beta_2 u) + \alpha \beta_2 b_1 k]} > 0.$$

\mathcal{R}_1 is called cell-mediated immunity-activated reproduction ratio, which denotes the average number of T cells activated by infectious cells when virus infection is successful and humoral immune response has not been established. If $\mathcal{R}_1 > 1$, in addition to E_0 and E_1 , system (1.2) has a cell-mediated immunity-activated equilibrium $E_2(x_2, y_2, v_2, z_2, 0)$, where

$$x_2 = \frac{c_1 s (c_1 u + \alpha b_1 k)}{(c_1 d + \beta_2 b_1) (c_1 u + \alpha b_1 k) + \beta_1 b_1 c_1 k}, \quad y_2 = \frac{b_1}{c_1}, \quad v_2 = \frac{b_1 k}{c_1 u},$$

and

$$z_2 = \frac{c_1 se^{-m\tau} [\beta_2 b_1 (c_1 u + \alpha b_1 k) + \beta_1 b_1 c_1 k]}{b_1 p_1 [(c_1 d + \beta_2 b_1) (c_1 u + \alpha b_1 k) + \beta_1 b_1 c_1 k]} - \frac{ab_1}{b_1 p_1}.$$

We further denote

$$\mathcal{R}_2 = \frac{c_2 k se^{-m\tau} [\beta_2 u (c_2 + \alpha b_2) + \beta_1 c_2 k]}{au (c_2 + \alpha b_2) (\beta_2 b_2 u + c_2 dk) + \beta_1 ab_2 c_2 ku} = \frac{\mathcal{R}_0}{1 + X_2 \mathcal{R}_0},$$

in which

$$X_2 = \frac{ab_2 u (\beta_1 k + \beta_2 u) [\beta_2 u (c_2 + \alpha b_2) + \beta_1 c_2 k] + \alpha \beta_1 ab_2 c_2 dk^2 u}{c_2 k se^{-m\tau} (\beta_1 k + \beta_2 u) [\beta_2 u (c_2 + \alpha b_2) + \beta_1 c_2 k]}.$$

\mathcal{R}_2 is called humoral immunity-activated reproduction ratio, which denotes the average number of B cells activated by viruses when virus infection is successful and cell-mediated response has not been established. When $\mathcal{R}_2 > 1$, system (1.2) has a humoral immunity-activated equilibrium $E_3(x_3, y_3, v_3, 0, w_3)$, where

$$x_3 = \frac{c_2 ks (c_2 + \alpha b_2)}{(c_2 + \alpha b_2) (\beta_2 b_2 p_2 w_3 + \beta_2 b_2 u + c_2 kd) + \beta_1 b_2 c_2 k}, \quad y_3 = \frac{b_2 p_2}{c_2 k} w_3 + \frac{b_2 u}{c_2 k}, \quad v_3 = \frac{b_2}{c_2},$$

where w_3 is the positive real root of the following quadratic equation:

$$w_3^2 + \frac{(c_2 + \alpha b_2) (2\beta_2 ab_2 u + ac_2 dk - \beta_2 c_2 k se^{-m\tau}) + \beta_1 ab_2 c_2 k}{\beta_2 ab_2 p_2 (c_2 + \alpha b_2)} w_3 + \frac{au (c_2 + \alpha b_2) (\beta_2 b_2 u + c_2 dk) + \beta_1 ab_2 c_2 ku}{\beta_2 ab_2 p_2^2 (c_2 + \alpha b_2)} (1 - \mathcal{R}_2) = 0.$$

Denote

$$\mathcal{R}_3 = \frac{b_1 c_2 k}{b_2 c_1 u}, \quad \mathcal{R}_4 = \frac{c_1 se^{-m\tau} [\beta_2 b_1 (c_2 + \alpha b_2) + \beta_1 b_2 c_1]}{ab_1 [(c_1 d + \beta_2 b_1) (c_2 + \alpha b_2) + \beta_1 b_2 c_1]},$$

where \mathcal{R}_3 is called humoral immunity-competed reproduction ratio and represents the average number of B cells activated by viruses under the condition that cell-mediated immune response has been established, while, \mathcal{R}_4 is called cell-mediated immunity-competed reproduction ratio and represents the average number of T cells activated by infectious cells under the condition that humoral immune response has been established. If $\mathcal{R}_3 > 1$ and $\mathcal{R}_4 > 1$, system (1.2) has an immunity-activated equilibrium $E^*(x^*, y^*, v^*, z^*, w^*)$, where

$$x^* = \frac{c_1 s (c_2 + \alpha b_2)}{(c_1 d + \beta_2 b_1) (c_2 + \alpha b_2) + \beta_1 b_2 c_1}, \quad y^* = \frac{b_1}{c_1}, \quad v^* = \frac{b_2}{c_2}, \quad w^* = \frac{b_1 c_2 k - b_2 c_1 u}{b_2 c_1 p_2},$$

and

$$z^* = \frac{c_1 s e^{-m\tau} [\beta_2 b_1 (c_2 + \alpha b_2) + \beta_1 b_2 c_1] - a b_1 [(c_1 d + \beta_2 b_1) (c_2 + \alpha b_2) + \beta_1 b_2 c_1]}{b_1 p_1 [(c_1 d + \beta_2 b_1) (c_2 + \alpha b_2) + \beta_1 b_2 c_1]},$$

in which cell-mediated and humoral immune responses take effect simultaneously.

3. Local asymptotic stability

In this section, we are concerned with the local asymptotic stability of each of feasible equilibria to system (1.2) by analyzing the distribution of roots of corresponding characteristic equations .

Theorem 3.1. *If $\mathcal{R}_0 < 1$, the infection-free equilibrium $E_0(s/d, 0, 0, 0, 0)$ of system (1.2) is locally asymptotically stable; if $\mathcal{R}_0 > 1$, E_0 is unstable.*

Proof. The characteristic equation of system (1.2) at E_0 is

$$(\lambda + b_1) (\lambda + b_2) (\lambda + d) (\lambda + a) (\lambda + u) - \frac{s}{d} e^{-(\lambda+m)\tau} (\lambda + b_1) (\lambda + b_2) (\lambda + d) (\beta_2 \lambda + \beta_1 k + \beta_2 u) = 0. \tag{3.1}$$

It is clear that (3.1) has negative real roots $\lambda = -b_1$, $\lambda = -b_2$, $\lambda = -d$ and other roots are determined by the following equation:

$$(\lambda + a) (\lambda + u) - \frac{s}{d} (\beta_2 \lambda + \beta_1 k + \beta_2 u) e^{-(\lambda+m)\tau} = 0. \tag{3.2}$$

Denote $\mathcal{R}_0 = \mathcal{R}_{01} + \mathcal{R}_{02}$, where

$$\mathcal{R}_{01} = \frac{\beta_1 k s e^{-m\tau}}{a u d} \quad \text{and} \quad \mathcal{R}_{02} = \frac{\beta_2 s e^{-m\tau}}{a d}.$$

Substituting \mathcal{R}_0 and \mathcal{R}_{02} into (3.2) yields

$$\left(\frac{\lambda}{a} + 1\right) \left(\frac{\lambda}{u} + 1\right) = e^{-\lambda\tau} \left(\frac{\lambda}{u} \mathcal{R}_{02} + \mathcal{R}_0\right). \tag{3.3}$$

Now, we claim that all roots of (3.3) have negative real parts. Otherwise, there exists a root $\lambda_1 = \text{Re}\lambda_1 + i\text{Im}\lambda_1$ with $\text{Re}\lambda_1 \geq 0$. In this case, if $\mathcal{R}_0 < 1$, it is easy to see that

$$\left|\frac{\lambda_1}{a} + 1\right| \geq |e^{-\lambda_1\tau}|, \quad \left|\frac{\lambda_1}{u} + 1\right| > \left|\frac{\lambda_1}{u} \mathcal{R}_{02} + \mathcal{R}_0\right|.$$

It follows that

$$\left|\left(\frac{\lambda_1}{a} + 1\right) \left(\frac{\lambda_1}{u} + 1\right)\right| > \left|e^{-\lambda_1\tau} \left(\frac{\lambda_1}{u} \mathcal{R}_{02} + \mathcal{R}_0\right)\right|,$$

which contradicts to (3.3). Therefore, if $\mathcal{R}_0 < 1$, all roots of (3.1) have negative real parts and E_0 is locally asymptotically stable. If $\mathcal{R}_0 > 1$, we denote the left side of (3.2) by $G(\lambda)$:

$$G(\lambda) = (\lambda + a)(\lambda + u) - e^{-(\lambda+m)\tau} \frac{S}{d} (\beta_2 \lambda + \beta_1 k + \beta_2 u), \tag{3.4}$$

where $G(0) = au(1 - \mathcal{R}_0) < 0$ and $G(\lambda) \rightarrow \infty$ as $\lambda \rightarrow \infty$. Noting that $G(\lambda)$ is a continuous function in respect to λ , if $\mathcal{R}_0 > 1$, Eq. (3.1) has a positive real root, then E_0 is unstable. \square

Theorem 3.2. *If $\mathcal{R}_0 > 1$, $\mathcal{R}_1 < 1$ and $\mathcal{R}_2 < 1$, the immunity-inactivated equilibrium $E_1(x_1, y_1, v_1, 0, 0)$ of system (1.2) is locally asymptotically stable.*

Proof. The characteristic equation of system (1.2) at E_1 is

$$\begin{aligned} & (\lambda + a)(\lambda + u) [\lambda - (c_1 y_1 - b_1)] [\lambda - (c_2 v_1 - b_2)] \left(\lambda + d + \frac{\beta_1 v_1}{1 + \alpha v_1} + \beta_2 y_1 \right) \\ & = e^{-(\lambda+m)\tau} \beta_2 x_1 (\lambda + u) (\lambda + d) [\lambda - (c_1 y_1 - b_1)] [\lambda - (c_2 v_1 - b_2)] \\ & \quad + e^{-(\lambda+m)\tau} (\lambda + d) [\lambda - (c_1 y_1 - b_1)] [\lambda - (c_2 v_1 - b_2)] \frac{\beta_1 k x_1}{(1 + \alpha v_1)^2}. \end{aligned} \tag{3.5}$$

Note that

$$\mathcal{R}_1 = H_1 (c_1 y_1 - b_1) + 1 < 1, \tag{3.6}$$

in which

$$H_1 = \frac{y_1 (1 + \alpha v_1) [\beta_2 a (c_1 u + \alpha b_1 k) + \beta_1 a c_1 k] + \alpha \beta_1 c_1 d k x_1 v_1 e^{-m\tau}}{\alpha y_1 (1 + \alpha v_1) [(c_1 d + \beta_2 b_1) (c_1 u + \alpha b_1 k) + \beta_1 b_1 c_1 k]},$$

and

$$\mathcal{R}_2 = H_2 (c_2 v_1 - b_2) + 1 < 1, \tag{3.7}$$

where

$$H_2 = \frac{y_1 (1 + \alpha v_1) [\beta_2 a u^2 (c_2 + \alpha b_2) + \beta_1 a c_2 k u] + \alpha \beta_1 c_2 d k u x_1 v_1 e^{-m\tau}}{y_1 (1 + \alpha v_1) [a u (c_2 + \alpha b_2) (\beta_2 b_2 u + c_2 d k) + \beta_1 a b_2 c_2 k u]}.$$

It is clear that (3.5) has negative real roots $\lambda = c_1 y_1 - b_1$ and $\lambda = c_2 v_1 - b_2$, and other roots are determined by the following equation:

$$(\lambda + a)(\lambda + u) \left(\lambda + d + \frac{\beta_1 v_1}{1 + \alpha v_1} + \beta_2 y_1 \right) - e^{-(\lambda+m)\tau} (\lambda + d) \left[\beta_2 x_1 (\lambda + u) + \frac{\beta_1 k x_1}{(1 + \alpha v_1)^2} \right] = 0. \tag{3.8}$$

For the sake of contradiction, let $\lambda_2 = \text{Re} \lambda_2 + i \text{Im} \lambda_2$ with $\text{Re} \lambda_2 \geq 0$. In this case, it is easy to see that

$$\left| \lambda_2 + d + \frac{\beta_1 v_1}{1 + \alpha v_1} + \beta_2 y_1 \right| > \left| e^{-\lambda_2 \tau} (\lambda_2 + d) \right|.$$

Direct calculation shows that

$$\begin{aligned} & \left| (\lambda_2 + a)(\lambda_2 + u) \right| - \left| \beta_2 e^{-m\tau} x_1 (\lambda_2 + u) + \frac{\beta_1 e^{-m\tau} k x_1}{(1 + \alpha v_1)^2} \right| \\ & = \lambda_2 \left[\lambda_2 + u + \frac{\beta_1 e^{-m\tau} k x_1}{u (1 + \alpha v_1)} \right] + \frac{\beta_1 e^{-m\tau} k x_1}{1 + \alpha v_1} - \frac{\beta_1 e^{-m\tau} k x_1}{(1 + \alpha v_1)^2} \end{aligned}$$

$$> \lambda_2 \left[\lambda_2 + u + \frac{\beta_1 e^{-m\tau} k x_1}{u(1 + \alpha v_1)} \right] > 0,$$

which contradicts to (3.8). Thus, if $\mathcal{R}_0 > 1$, $\mathcal{R}_1 < 1$ and $\mathcal{R}_2 < 1$, all roots of Eq. (3.5) have negative real parts, and E_1 is locally asymptotically stable. \square

Theorem 3.3. *If $\mathcal{R}_1 > 1$ and $\mathcal{R}_3 < 1$, the cell-mediated immunity-activated equilibrium $E_2(x_2, y_2, v_2, z_2, 0)$ of system (1.2) is locally asymptotically stable.*

Proof. The characteristic equation of system (1.2) at E_2 is

$$\begin{aligned} & (\lambda + u) [\lambda - (c_2 v_2 - b_2)] [\lambda (\lambda + a + p_1 z_2) + c_1 p_1 y_2 z_2] \left(\lambda + d + \frac{\beta_1 v_2}{1 + \alpha v_2} + \beta_2 y_2 \right) \\ & = e^{-(\lambda+m)\tau} (\lambda + d) [\lambda - (c_2 v_2 - b_2)] \left[\beta_2 x_2 \lambda (\lambda + u) + \frac{\beta_1 k x_2}{(1 + \alpha v_2)^2} \lambda \right]. \end{aligned} \tag{3.9}$$

Note that $\mathcal{R}_3 = (c_2 v_2 - b_2) / b_2 + 1 < 1$. It is clear that (3.9) has negative real root $\lambda = c_2 v_2 - b_2$, and other roots are determined by the following equation:

$$\begin{aligned} & (\lambda + u) [\lambda (\lambda + a + p_1 z_2) + c_1 p_1 y_2 z_2] \left(\lambda + d + \frac{\beta_1 v_2}{1 + \alpha v_2} + \beta_2 y_2 \right) \\ & = e^{-(\lambda+m)\tau} (\lambda + d) \left[\beta_2 x_2 \lambda (\lambda + u) + \frac{\beta_1 k x_2}{(1 + \alpha v_2)^2} \lambda \right]. \end{aligned} \tag{3.10}$$

Similarly, we claim that all roots of (3.10) have negative real parts. Otherwise, there exists a root $\lambda_3 = \text{Re}\lambda_3 + i\text{Im}\lambda_3$ with $\text{Re}\lambda_3 \geq 0$. In this case, it is obvious that

$$\left| \lambda_3 + d + \frac{\beta_1 v_2}{1 + \alpha v_2} + \beta_2 y_2 \right| > \left| e^{-\lambda_3 \tau} (\lambda_3 + d) \right|.$$

It follows that

$$\begin{aligned} & \left| (\lambda_3 + u) [\lambda_3 (\lambda_3 + a + p_1 z_2) + c_1 p_1 y_2 z_2] \right| - \left| \beta_2 e^{-m\tau} x_2 \lambda_3 (\lambda_3 + u) + \frac{\beta_1 e^{-m\tau} k x_2}{(1 + \alpha v_2)^2} \lambda_3 \right| \\ & = \lambda_3^2 \left[\lambda_3 + u + \frac{\beta_1 e^{-m\tau} x_2 v_2}{y_2 (1 + \alpha v_2)} \right] + p_1 c_1 y_2 z_2 (\lambda_3 + u) + \frac{\beta_1 e^{-m\tau} k x_2}{1 + \alpha v_2} \lambda_3 - \frac{\beta_1 e^{-m\tau} k x_2}{(1 + \alpha v_2)^2} \lambda_3 \\ & > \lambda_3^2 \left[\lambda_3 + u + \frac{\beta_1 e^{-m\tau} x_2 v_2}{y_2 (1 + \alpha v_2)} \right] + p_1 c_1 y_2 z_2 (\lambda_3 + u) > 0, \end{aligned}$$

which contradicts to (3.10). Hence, if $\mathcal{R}_1 > 1$ and $\mathcal{R}_3 < 1$, all roots of Eq. (3.9) have negative real parts, and E_2 is locally asymptotically stable. \square

Theorem 3.4. *If $\mathcal{R}_2 > 1$ and $\mathcal{R}_4 < 1$, the humoral immunity-activated equilibrium $E_3(x_3, y_3, v_3, 0, w_3)$ of system (1.2) is locally asymptotically stable.*

Proof. The characteristic equation of system (1.2) at E_3 is

$$\begin{aligned} & (\lambda + a) [\lambda - (c_1 y_3 - b_1)] [\lambda (\lambda + u + p_2 w_3) + c_2 p_2 v_3 w_3] \left(\lambda + d + \frac{\beta_1 v_3}{1 + \alpha v_3} + \beta_2 y_3 \right) \\ & = e^{-(\lambda+m)\tau} x_3 (\lambda + d) [\lambda - (c_1 y_3 - b_1)] \left[\beta_2 \lambda (\lambda + u + p_2 w_3) + \beta_2 c_2 p_2 v_3 w_3 + \frac{\beta_1 k \lambda}{(1 + \alpha v_3)^2} \right]. \end{aligned} \tag{3.11}$$

Note that

$$\mathcal{R}_4 = (c_1y_3 - b_1) \frac{y_3 [\beta_2ab_1 (c_2 + \alpha b_2) + \beta_1ab_2c_1] + \beta_1e^{-m\tau}b_2c_1dx_3}{ab_1y_3 [(c_1d + \beta_2b_1)(c_2 + \alpha b_2) + \beta_1b_2c_1]} + 1 < 1. \tag{3.12}$$

It is obvious that (3.11) has negative real root $\lambda = c_1y_3 - b_1$, and other roots are determined by the following equation:

$$\begin{aligned} & (\lambda + a) [\lambda(\lambda + u + p_2w_3) + c_2p_2v_3w_3] \left(\lambda + d + \frac{\beta_1v_3}{1 + \alpha v_3} + \beta_2y_3 \right) \\ & = e^{-(\lambda+m)\tau} x_3 (\lambda + d) \left[\beta_2\lambda(\lambda + u + p_2w_3) + \beta_2c_2p_2v_3w_3 + \frac{\beta_1k\lambda}{(1 + \alpha v_3)^2} \right]. \end{aligned} \tag{3.13}$$

Similarly, we claim that all roots of (3.13) have negative real parts. If not, there exists a root $\lambda_4 = \text{Re}\lambda_4 + i\text{Im}\lambda_4$ with $\text{Re}\lambda_4 \geq 0$. In this case, it is easy to see that

$$\left| \lambda_4 + d + \frac{\beta_1v_3}{1 + \alpha v_3} + \beta_2y_3 \right| > |e^{-\lambda_4\tau} (\lambda_4 + d)|.$$

Direct calculation yields

$$\begin{aligned} & \left| (\lambda_4 + a) [\lambda_4(\lambda_4 + u + p_2w_3) + c_2p_2v_3w_3] \right| \\ & - \left| e^{-m\tau} x_3 \left[\beta_2\lambda_4(\lambda_4 + u + p_2w_3) + \beta_2c_2p_2v_3w_3 + \frac{\beta_1k\lambda_4}{(1 + \alpha v_3)^2} \right] \right| \\ & = \lambda_4 [\lambda_4(\lambda_4 + u + p_2w_3) + c_2p_2v_3w_3] + \frac{\beta_1e^{-m\tau}x_3v_3}{y_3(1 + \alpha v_3)} (\lambda_4^2 + c_2p_2v_3w_3) \\ & + \frac{\beta_1e^{-m\tau}x_3v_3}{y_3(1 + \alpha v_3)} (u + p_2w_3) \lambda_4 - \frac{\beta_1e^{-m\tau}kx_3}{(1 + \alpha v_3)^2} \lambda_4 \\ & > \lambda_4 [\lambda_4(\lambda_4 + u + p_2w_3) + c_2p_2v_3w_3] + \frac{\beta_1e^{-m\tau}x_3v_3}{y_3(1 + \alpha v_3)} (\lambda_4^2 + c_2p_2v_3w_3) > 0, \end{aligned}$$

which contradicts to (3.13). Therefore, if $\mathcal{R}_2 > 1$ and $\mathcal{R}_4 < 1$, all roots of Eq. (3.11) have negative real parts, and E_3 is locally asymptotically stable. \square

Theorem 3.5. *If $\mathcal{R}_3 > 1$ and $\mathcal{R}_4 > 1$, the immunity-activated equilibrium $E^*(x^*, y^*, v^*, z^*, w^*)$ of system (1.2) is locally asymptotically stable.*

Proof. The characteristic equation of system (1.2) at E^* is

$$\begin{aligned} & \left(\lambda + d + \frac{\beta_1v^*}{1 + \alpha v^*} + \beta_2y^* \right) [\lambda(\lambda + a + p_1z^*) + c_1p_1y^*z^*] [\lambda(\lambda + u + p_2w^*) + c_2p_2v^*w^*] \\ & = e^{-(\lambda+m)\tau} x^* (\lambda + d) \left\{ \beta_2\lambda [\lambda(\lambda + u + p_2w^*) + c_2p_2v^*w^*] + \frac{\beta_1k\lambda^2}{(1 + \alpha v^*)^2} \right\}. \end{aligned} \tag{3.14}$$

Similarly, we claim that all roots of (3.14) have negative real parts. Otherwise, there exists a root $\lambda_5 = \text{Re}\lambda_5 + i\text{Im}\lambda_5$ with $\text{Re}\lambda_5 \geq 0$. In this case, it is clear that

$$\left| \lambda_5 + d + \frac{\beta_1v^*}{1 + \alpha v^*} + \beta_2y^* \right| > |e^{-\lambda_5\tau} (\lambda_5 + d)|.$$

Direct calculation shows that

$$\begin{aligned}
 & \left| [\lambda_5 (\lambda_5 + a + p_1 z^*) + c_1 p_1 y^* z^*] [\lambda_5 (\lambda_5 + u + p_2 w^*) + c_2 p_2 v^* w^*] \right| \\
 & - \left| \beta_2 e^{-m\tau} x^* \lambda_5 [\lambda_5 (\lambda_5 + u + p_2 w^*) + c_2 p_2 v^* w^*] + \frac{\beta_1 e^{-m\tau} k x^* \lambda_5^2}{(1 + \alpha v^*)^2} \right| \\
 & = (\lambda_5^2 + c_1 p_1 y^* z^*) [\lambda_5 (\lambda_5 + u + p_2 w^*) + c_2 p_2 v^* w^*] \\
 & + \frac{\beta_1 e^{-m\tau} x^* v^*}{y^* (1 + \alpha v^*)} \lambda_5 (\lambda_5^2 + c_2 p_2 v^* w^*) + \frac{\beta_1 e^{-m\tau} x^* \lambda_5^2}{y^* (1 + \alpha v^*)} \left(uv^* + p_2 v^* w^* - \frac{ky^*}{1 + \alpha v^*} \right) \\
 & > (\lambda_5^2 + c_1 p_1 y^* z^*) [\lambda_5 (\lambda_5 + u + p_2 w^*) + c_2 p_2 v^* w^*] \\
 & + \frac{\beta_1 e^{-m\tau} x^* v^*}{y^* (1 + \alpha v^*)} \lambda_5 (\lambda_5^2 + c_2 p_2 v^* w^*) > 0,
 \end{aligned}$$

which contradicts to (3.14). Therefore, if $\mathcal{R}_3 > 1$ and $\mathcal{R}_4 > 1$, all roots of Eq. (3.14) have negative real parts, and E^* is locally asymptotically stable. \square

4. Global asymptotic stability

In this section, we study the global stability of each of feasible equilibria to system (1.2) by suitable Lyapunov functionals and LaSalle's invariance principle. First, we discuss the boundedness of solutions.

Lemma 4.1. *Any solution of system (1.2) with initial condition (1.3) is bounded for all $t \geq 0$.*

Proof. Let $(x(t), y(t), v(t), z(t), w(t))$ be any solution of system (1.2) with initial condition (1.3). Denote

$$B_1(t) = x(t - \tau) + e^{m\tau} y(t) + \frac{p_1}{c_1} e^{m\tau} z(t), \quad B_2(t) = v(t) + \frac{p_2}{c_2} w(t).$$

Calculating the derivatives of $B_1(t)$ and $B_2(t)$ in respect to t yields

$$\dot{B}_1(t) = s - dx(t - \tau) - ae^{m\tau} y(t) - b_1 \frac{p_1}{c_1} e^{m\tau} z(t) \leq s - \min\{a, b_1, d\} B_1(t),$$

and

$$\dot{B}_2(t) = y(t) - uv(t) - b_2 \frac{p_2}{c_2} w(t) \leq \frac{e^{-m\tau} s}{\min\{a, b_1, d\}} - \min\{b_2, u\} B_2(t).$$

Therefore, the following set is positively invariant set for system (1.2):

$$\Omega = \left\{ (x, y, v, z, w) \left| x + e^{m\tau} y + \frac{p_1}{c_1} e^{m\tau} z \leq \frac{s}{\min\{a, b_1, d\}}, v + \frac{p_2}{c_2} w \leq \frac{e^{-m\tau} s}{\min\{a, b_1, d\} \min\{b_2, u\}} \right. \right\}.$$

It is easy to see that $x(t), y(t), v(t), z(t)$ and $w(t)$ are bounded in the invariant set Ω . \square

Next, define a function $g(x) = x - 1 - \ln x$, which will be used in Lyapunov functionals of this section.

Theorem 4.2. *If $\mathcal{R}_0 < 1$, the infection-free equilibrium $E_0(s/d, 0, 0, 0, 0)$ of system (1.2) is globally asymptotically stable.*

Proof. Let $(x(t), y(t), v(t), z(t), w(t))$ be any positive solution of system (1.2) with initial condition (1.3). Define

$$V_1(t) = x_0 g\left(\frac{x(t)}{x_0}\right) + l_{11}y(t) + l_{12}v(t) + l_{13}z(t) + l_{14}w(t) + \int_{t-\tau}^t \left(\frac{\beta_1 x(s)v(s)}{1 + \alpha v(s)} + \beta_2 x(s)y(s)\right) ds,$$

where $x_0 = s/d$, and constants $l_{11}, l_{12}, l_{13}, l_{14}$ will be determined later. Calculating the derivative of $V_1(t)$ along positive solutions of system (1.2) yields

$$\begin{aligned} \dot{V}_1(t) = & \left(1 - \frac{x_0}{x(t)}\right) \left(s - dx(t) - \frac{\beta_1 x(t)v(t)}{1 + \alpha v(t)} - \beta_2 x(t)y(t)\right) \\ & + l_{11} \left(\frac{\beta_1 e^{-m\tau} x(t-\tau)v(t-\tau)}{1 + \alpha v(t-\tau)} + \beta_2 e^{-m\tau} x(t-\tau)y(t-\tau) - ay(t) - p_1 y(t)z(t)\right) \\ & + l_{12} (ky(t) - uv(t) - p_2 v(t)w(t)) + l_{13} (c_1 y(t)z(t) - b_1 z(t)) + l_{14} (c_2 v(t)w(t) - b_2 w(t)) \\ & + \frac{\beta_1 x(t)v(t)}{1 + \alpha v(t)} + \beta_2 x(t)y(t) - \frac{\beta_1 x(t-\tau)v(t-\tau)}{1 + \alpha v(t-\tau)} - \beta_2 x(t-\tau)y(t-\tau). \end{aligned}$$

Direct calculation yields

$$\begin{aligned} \dot{V}_1(t) = & dx_0 \left(2 - \frac{x_0}{x(t)} - \frac{x(t)}{x_0}\right) + \frac{\beta_1 x_0 v(t)}{1 + \alpha v(t)} - l_{12} uv(t) - l_{13} b_1 z(t) - l_{14} b_2 w(t) \\ & + (l_{11} e^{-m\tau} - 1) \left(\frac{\beta_1 x(t-\tau)v(t-\tau)}{1 + \alpha v(t-\tau)} + \beta_2 x(t-\tau)y(t-\tau)\right) \\ & + (\beta_2 x_0 + l_{12} k - l_{11} a) y(t) + (l_{13} c_1 - l_{11} p_1) y(t)z(t) + (l_{14} c_2 - l_{12} p_2) v(t)w(t). \end{aligned} \quad (4.1)$$

Choose

$$l_{11} = e^{m\tau}, \quad l_{12} = \frac{e^{m\tau} a - \beta_2 x_0}{k} > 0, \quad l_{13} = \frac{e^{m\tau} p_1}{c_1}, \quad l_{14} = p_2 \frac{e^{m\tau} a - \beta_2 x_0}{c_2 k} > 0. \quad (4.2)$$

Thus, we obtain from (4.1) and (4.2) that

$$\dot{V}_1(t) \leq dx_0 \left(2 - \frac{x_0}{x(t)} - \frac{x(t)}{x_0}\right) + (\mathcal{R}_0 - 1) \frac{e^{m\tau} au}{k} v(t) - l_{13} b_1 z(t) - l_{14} b_2 w(t).$$

It follows that $\dot{V}_1(t) \leq 0$ with equality holding if and only if $x = x_0, y = v = z = w = 0$. It can be verified that $M_0 = \{E_0\} \subset \Omega$ is the largest invariant subset of $\{(x(t), y(t), v(t), z(t), w(t)) : \dot{V}_1(t) = 0\}$. Noting that if $\mathcal{R}_0 < 1$, E_0 is locally asymptotically stable, thus we obtain the global asymptotic stability of E_0 from LaSalle's invariance principle. \square

Theorem 4.3. *If $\mathcal{R}_0 > 1$, $\mathcal{R}_1 < 1$ and $\mathcal{R}_2 < 1$, the immunity-inactivated equilibrium $E_1(x_1, y_1, v_1, 0, 0)$ of system (1.2) is globally asymptotically stable.*

Proof. Let $(x(t), y(t), v(t), z(t), w(t))$ be any positive solution of system (1.2) with initial condition (1.3). Define

$$V_2(t) = x_1 g\left(\frac{x(t)}{x_1}\right) + l_{21} y_1 g\left(\frac{y(t)}{y_1}\right) + l_{22} v_1 g\left(\frac{v(t)}{v_1}\right) + l_{23} z(t) + l_{24} w(t)$$

$$+ \frac{\beta_1 x_1 v_1}{1 + \alpha v_1} \int_{t-\tau}^t g \left(\frac{x(s)v(s)(1 + \alpha v_1)}{x_1 v_1 (1 + \alpha v(s))} \right) ds + \beta_2 x_1 y_1 \int_{t-\tau}^t g \left(\frac{x(s)y(s)}{x_1 y_1} \right) ds,$$

where constants l_{21}, l_{22}, l_{23} and l_{24} will be determined later. Calculating the derivative of $V_2(t)$ along positive solutions of system (1.2), we have

$$\begin{aligned} \dot{V}_2(t) = & \left(1 - \frac{x_1}{x(t)} \right) \left(s - dx(t) - \frac{\beta_1 x(t)v(t)}{1 + \alpha v(t)} - \beta_2 x(t)y(t) \right) \\ & + l_{21} \left(1 - \frac{y_1}{y(t)} \right) \left(\frac{\beta_1 e^{-m\tau} x(t-\tau)v(t-\tau)}{1 + \alpha v(t-\tau)} + \beta_2 e^{-m\tau} x(t-\tau)y(t-\tau) - ay(t) - p_1 y(t)z(t) \right) \\ & + l_{22} \left(1 - \frac{v_1}{v(t)} \right) (ky(t) - uv(t) - p_2 v(t)w(t)) \\ & + l_{23} (c_1 y(t)z(t) - b_1 z(t)) + l_{24} (c_2 v(t)w(t) - b_2 w(t)) \\ & + \frac{\beta_1 x_1 v_1}{1 + \alpha v_1} \left[g \left(\frac{x(t)v(t)(1 + \alpha v_1)}{x_1 v_1 (1 + \alpha v(t))} \right) - g \left(\frac{x(t-\tau)v(t-\tau)(1 + \alpha v_1)}{x_1 v_1 (1 + \alpha v(t-\tau))} \right) \right] \\ & + \beta_2 x_1 y_1 \left[g \left(\frac{x(t)y(t)}{x_1 y_1} \right) - g \left(\frac{x(t-\tau)y(t-\tau)}{x_1 y_1} \right) \right]. \end{aligned} \tag{4.3}$$

Substituting $s = dx_1 + \beta_1 x_1 v_1 / (1 + \alpha v_1) + \beta_2 x_1 y_1, \beta_1 e^{-m\tau} x_1 v_1 / (1 + \alpha v_1) + \beta_2 e^{-m\tau} x_1 y_1 = ay_1, ky_1 = uv_1$ into (4.3) yields

$$\begin{aligned} \dot{V}_2(t) = & dx_1 \left(2 - \frac{x_1}{x(t)} - \frac{x(t)}{x_1} \right) + l_{21} ay_1 + l_{22} uv_1 - l_{22} v_1 \frac{uv_1 y(t)}{y_1 v(t)} - l_{22} uv(t) \\ & + \frac{\beta_1 x_1 v_1}{1 + \alpha v_1} \left[1 + \frac{v(t)(1 + \alpha v_1)}{v_1 (1 + \alpha v(t))} - \frac{x_1}{x(t)} \right] - l_{21} e^{-m\tau} \frac{\beta_1 x_1 v_1}{1 + \alpha v_1} \frac{x(t-\tau)v(t-\tau)(1 + \alpha v_1)y_1}{x_1 v_1 (1 + \alpha v(t-\tau))y(t)} \\ & + \frac{\beta_1 x_1 v_1}{1 + \alpha v_1} \ln \frac{x(t-\tau)v(t-\tau)(1 + \alpha v(t))}{x(t)v(t)(1 + \alpha v(t-\tau))} + \beta_2 x_1 y_1 \left(1 - \frac{x_1}{x(t)} - l_{21} e^{-m\tau} \frac{x(t-\tau)y(t-\tau)}{x_1 y(t)} \right) \\ & + \beta_2 x_1 y_1 \ln \frac{x(t-\tau)y(t-\tau)}{x(t)y(t)} + (l_{21} e^{-m\tau} - 1) \left(\frac{\beta_1 x(t-\tau)v(t-\tau)}{1 + \alpha v(t-\tau)} + \beta_2 x(t-\tau)y(t-\tau) \right) \\ & + (\beta_2 x_1 + l_{22}k - l_{21}a) y(t) + (l_{21}p_1 y_1 - l_{23}b_1) z(t) + (l_{22}p_2 v_1 - l_{24}b_2) w(t) \\ & + (l_{23}c_1 - l_{21}p_1) y(t)z(t) + (l_{24}c_2 - l_{22}p_2) v(t)w(t). \end{aligned} \tag{4.4}$$

Choose

$$l_{21} = e^{m\tau}, \quad l_{22} = \frac{\beta_1 x_1 v_1}{ky_1 (1 + \alpha v_1)}, \quad l_{23} = \frac{e^{m\tau} p_1}{c_1}, \quad l_{24} = \frac{\beta_1 p_2 x_1 v_1}{c_2 ky_1 (1 + \alpha v_1)}. \tag{4.5}$$

From (4.4) and (4.5), we obtain that

$$\begin{aligned} \dot{V}_2(t) = & dx_1 \left(2 - \frac{x_1}{x(t)} - \frac{x(t)}{x_1} \right) + e^{m\tau} p_1 \frac{c_1 y_1 - b_1}{c_1} z(t) + \frac{\beta_1 p_2 x_1 v_1}{ky_1 (1 + \alpha v_1)} \frac{c_2 v_1 - b_2}{c_2} w(t) \\ & - \frac{\alpha(v(t) - v_1)^2}{v_1 (1 + \alpha v_1) (1 + \alpha v(t))} - g \left(\frac{1 + \alpha v(t)}{1 + \alpha v_1} \right) - \frac{\beta_1 x_1 v_1}{1 + \alpha v_1} \left[g \left(\frac{x_1}{x(t)} \right) + g \left(\frac{y(t)v_1}{y_1 v(t)} \right) \right] \\ & - \frac{\beta_1 x_1 v_1}{1 + \alpha v_1} g \left(\frac{x(t-\tau)v(t-\tau)(1 + \alpha v_1)y_1}{x_1 v_1 (1 + \alpha v(t-\tau))y(t)} \right) - \beta_2 x_1 y_1 \left[g \left(\frac{x_1}{x(t)} \right) + g \left(\frac{x(t-\tau)y(t-\tau)}{x_1 y(t)} \right) \right]. \end{aligned} \tag{4.6}$$

From (3.6) and (3.7), we derive that $c_1y_1 < b_1$ and $c_2v_1 < b_2$. Since function $g(x) = x - 1 - \ln x$ is always positive except for $x = 1$ where $g(x) = 0$. It follows from (4.6) that $\dot{V}_2(t) \leq 0$ with equality holding if and only if $x = x_1, y = y_1, v = v_1, z = w = 0$. It can be proved that $M_1 = \{E_1\} \subset \Omega$ is the largest invariant subset of $\{(x(t), y(t), v(t), z(t), w(t)) : \dot{V}_2(t) = 0\}$. Noting that if $\mathcal{R}_0 > 1$, $\mathcal{R}_1 < 1$ and $\mathcal{R}_2 < 1$, E_1 is locally asymptotically stable, hence we obtain the global asymptotic stability of E_1 from LaSalle's invariance principle. \square

Theorem 4.4. *If $\mathcal{R}_1 > 1$ and $\mathcal{R}_3 < 1$, the cell-mediated immunity-activated equilibrium $E_2(x_2, y_2, v_2, z_2, 0)$ of system (1.2) is globally asymptotically stable.*

Proof. Let $(x(t), y(t), v(t), z(t), w(t))$ be any positive solution of system (1.2) with initial condition (1.3). Define

$$V_3(t) = x_2 g\left(\frac{x(t)}{x_2}\right) + l_{31} y_2 g\left(\frac{y(t)}{y_2}\right) + l_{32} v_2 g\left(\frac{v(t)}{v_2}\right) + l_{33} z_2 g\left(\frac{z(t)}{z_2}\right) + l_{34} w(t) \\ + \frac{\beta_1 x_2 v_2}{1 + \alpha v_2} \int_{t-\tau}^t g\left(\frac{x(s)v(s)(1 + \alpha v_2)}{x_2 v_2 (1 + \alpha v(s))}\right) ds + \beta_2 x_2 y_2 \int_{t-\tau}^t g\left(\frac{x(s)y(s)}{x_2 y_2}\right) ds,$$

where constants l_{31}, l_{32}, l_{33} and l_{34} will be determined later. Calculating the derivative of $V_3(t)$ along positive solutions of system (1.2), we obtain that

$$\begin{aligned} \dot{V}_3(t) = & \left(1 - \frac{x_2}{x(t)}\right) \left(s - dx(t) - \frac{\beta_1 x(t)v(t)}{1 + \alpha v(t)} - \beta_2 x(t)y(t)\right) \\ & + l_{31} \left(1 - \frac{y_2}{y(t)}\right) \left(\frac{\beta_1 e^{-m\tau} x(t-\tau)v(t-\tau)}{1 + \alpha v(t-\tau)} + \beta_2 e^{-m\tau} x(t-\tau)y(t-\tau) - ay(t) - p_1 y(t)z(t)\right) \\ & + l_{32} \left(1 - \frac{v_2}{v(t)}\right) (ky(t) - uv(t) - p_2 v(t)w(t)) \\ & + l_{33} \left(1 - \frac{z_2}{z(t)}\right) (c_1 y(t)z(t) - b_1 z(t)) + l_{34} (c_2 v(t)w(t) - b_2 w(t)) \\ & + \frac{\beta_1 x_2 v_2}{1 + \alpha v_2} \left[g\left(\frac{x(t)v(t)(1 + \alpha v_2)}{x_2 v_2 (1 + \alpha v(t))}\right) - g\left(\frac{x(t-\tau)v(t-\tau)(1 + \alpha v_2)}{x_2 v_2 (1 + \alpha v(t-\tau))}\right) \right] \\ & + \beta_2 x_2 y_2 \left[g\left(\frac{x(t)y(t)}{x_2 y_2}\right) - g\left(\frac{x(t-\tau)y(t-\tau)}{x_2 y_2}\right) \right]. \end{aligned} \quad (4.7)$$

Substituting $s = dx_2 + \beta_1 x_2 v_2 / (1 + \alpha v_2) + \beta_2 x_2 y_2$, $\beta_1 e^{-m\tau} x_2 v_2 / (1 + \alpha v_2) + \beta_2 e^{-m\tau} x_2 y_2 = ay_2 + p_1 y_2 z_2$, $ky_2 = uv_2$, $c_1 y_2 z_2 = b_1 z_2$ into (4.7) yields

$$\begin{aligned} \dot{V}_3(t) = & dx_2 \left(2 - \frac{x_2}{x(t)} - \frac{x(t)}{x_2}\right) + l_{31} ay_2 + l_{32} uv_2 + l_{33} b_1 z_2 - l_{32} v_2 \frac{uv_2 y(t)}{y_2 v(t)} - l_{32} uv(t) \\ & + \frac{\beta_1 x_2 v_2}{1 + \alpha v_2} \left[1 + \frac{v(t)(1 + \alpha v_2)}{v_2 (1 + \alpha v(t))} - \frac{x_2}{x(t)}\right] - l_{31} e^{-m\tau} \frac{\beta_1 x_2 v_2}{1 + \alpha v_2} \frac{x(t-\tau)v(t-\tau)(1 + \alpha v_2) y_2}{x_2 v_2 (1 + \alpha v(t-\tau)) y(t)} \\ & + \frac{\beta_1 x_2 v_2}{1 + \alpha v_2} \ln \frac{x(t-\tau)v(t-\tau)(1 + \alpha v(t))}{x(t)v(t)(1 + \alpha v(t-\tau))} + \beta_2 x_2 y_2 \left(1 - \frac{x_2}{x(t)} - l_{31} e^{-m\tau} \frac{x(t-\tau)y(t-\tau)}{x_2 y(t)}\right) \\ & + \beta_2 x_2 y_2 \ln \frac{x(t-\tau)y(t-\tau)}{x(t)y(t)} + (l_{31} e^{-m\tau} - 1) \left(\frac{\beta_1 x(t-\tau)v(t-\tau)}{1 + \alpha v(t-\tau)} + \beta_2 x(t-\tau)y(t-\tau)\right) \end{aligned} \quad (4.8)$$

$$\begin{aligned}
 &+ (\beta_2 x_2 + l_{32} k - l_{33} c_1 z_2 - l_{31} a) y(t) + (l_{32} p_2 v_2 - l_{34} b_2) w(t) \\
 &+ (l_{31} p_1 y_2 - l_{33} b_1) z(t) + (l_{33} c_1 - l_{31} p_1) y(t) z(t) + (l_{34} c_2 - l_{32} p_2) v(t) w(t).
 \end{aligned}$$

Choose

$$l_{31} = e^{m\tau}, \quad l_{32} = \frac{\beta_1 x_2 v_2}{k y_2 (1 + \alpha v_2)}, \quad l_{33} = \frac{e^{m\tau} p_1}{c_1}, \quad l_{34} = \frac{\beta_1 p_2 x_2 v_2}{c_2 k y_2 (1 + \alpha v_2)}. \tag{4.9}$$

From (4.8) and (4.9), we obtain that

$$\begin{aligned}
 \dot{V}_3(t) = & dx_2 \left(2 - \frac{x_2}{x(t)} - \frac{x(t)}{x_2} \right) + \frac{\beta_1 p_2 x_2 v_2}{k y_2 (1 + \alpha v_2)} \frac{c_2 v_2 - b_2}{c_2} w(t) \\
 & - \frac{\alpha (v(t) - v_2)^2}{v_2 (1 + \alpha v_2) (1 + \alpha v(t))} - g \left(\frac{1 + \alpha v(t)}{1 + \alpha v_2} \right) - \frac{\beta_1 x_2 v_2}{1 + \alpha v_2} \left[g \left(\frac{x_2}{x(t)} \right) + g \left(\frac{y(t) v_2}{y_2 v(t)} \right) \right] \\
 & - \frac{\beta_1 x_2 v_2}{1 + \alpha v_2} g \left(\frac{x(t - \tau) v(t - \tau) (1 + \alpha v_2) y_2}{x_2 v_2 (1 + \alpha v(t - \tau)) y(t)} \right) - \beta_2 x_2 y_2 \left[g \left(\frac{x_2}{x(t)} \right) + g \left(\frac{x(t - \tau) y(t - \tau)}{x_2 y(t)} \right) \right].
 \end{aligned} \tag{4.10}$$

Noting that $\mathcal{R}_3 = (c_2 v_2 - b_2) / b_2 + 1 < 1$, it is clear that $c_2 v_2 < b_2$. It follows from (4.10) that $\dot{V}_3(t) \leq 0$ with equality holding if and only if $x = x_2, y = y_2, v = v_2, z = z_2, w = 0$. It can be verified that $M_3 = \{E_2\} \subset \Omega$ is the largest invariant subset of $\{(x(t), y(t), v(t), z(t), w(t)) : \dot{V}_3(t) = 0\}$. Noting that if $\mathcal{R}_1 > 1$ and $\mathcal{R}_3 < 1$, E_2 is locally asymptotically stable, thus we obtain the global asymptotic stability of E_2 from LaSalle’s invariance principle. \square

Theorem 4.5. *If $\mathcal{R}_2 > 1$ and $\mathcal{R}_4 < 1$, the humoral immunity-activated equilibrium $E_3(x_3, y_3, v_3, 0, w_3)$ of system (1.2) is globally asymptotically stable.*

Proof. Let $(x(t), y(t), v(t), z(t), w(t))$ be any positive solution of system (1.2) with initial condition (1.3). Define

$$\begin{aligned}
 V_4(t) = & x_3 g \left(\frac{x(t)}{x_3} \right) + l_{41} y_3 g \left(\frac{y(t)}{y_3} \right) + l_{42} v_3 g \left(\frac{v(t)}{v_3} \right) + l_{43} z(t) + l_{44} w_3 g \left(\frac{w(t)}{w_3} \right) \\
 & + \frac{\beta_1 x_3 v_3}{1 + \alpha v_3} \int_{t-\tau}^t g \left(\frac{x(s) v(s) (1 + \alpha v_3)}{x_3 v_3 (1 + \alpha v(s))} \right) ds + \beta_2 x_3 y_3 \int_{t-\tau}^t g \left(\frac{x(s) y(s)}{x_3 y_3} \right) ds,
 \end{aligned}$$

where constants l_{41}, l_{42}, l_{43} and l_{44} will be determined later. Calculating the derivative of $V_4(t)$ along positive solutions of system (1.2), we obtain that

$$\begin{aligned}
 \dot{V}_4(t) = & \left(1 - \frac{x_3}{x(t)} \right) \left(s - dx(t) - \frac{\beta_1 x(t) v(t)}{1 + \alpha v(t)} - \beta_2 x(t) y(t) \right) \\
 & + l_{41} \left(1 - \frac{y_3}{y(t)} \right) \left(\frac{\beta_1 e^{-m\tau} x(t - \tau) v(t - \tau)}{1 + \alpha v(t - \tau)} + \beta_2 e^{-m\tau} x(t - \tau) y(t - \tau) - ay(t) - p_1 y(t) z(t) \right) \\
 & + l_{42} \left(1 - \frac{v_3}{v(t)} \right) (ky(t) - uv(t) - p_2 v(t) w(t)) \\
 & + l_{43} (c_1 y(t) z(t) - b_1 z(t)) + l_{44} \left(1 - \frac{w_3}{w(t)} \right) (c_2 v(t) w(t) - b_2 w(t)) \\
 & + \frac{\beta_1 x_3 v_3}{1 + \alpha v_3} \left[g \left(\frac{x(t) v(t) (1 + \alpha v_3)}{x_3 v_3 (1 + \alpha v(t))} \right) - g \left(\frac{x(t - \tau) v(t - \tau) (1 + \alpha v_3)}{x_3 v_3 (1 + \alpha v(t - \tau))} \right) \right] \\
 & + \beta_2 x_3 y_3 \left[g \left(\frac{x(t) y(t)}{x_3 y_3} \right) - g \left(\frac{x(t - \tau) y(t - \tau)}{x_3 y_3} \right) \right].
 \end{aligned} \tag{4.11}$$

Substituting $s = dx_3 + \beta_1 x_3 v_3 / (1 + \alpha v_3) + \beta_2 x_3 y_3$, $\beta_1 e^{-m\tau} x_3 v_3 / (1 + \alpha v_3) + \beta_2 e^{-m\tau} x_3 y_3 = ay_3$, $ky_3 = uv_3 + p_2 v_3 w_3$, $c_2 v_3 w_3 = b_2 w_3$ into (4.11) yields

$$\begin{aligned} \dot{V}_4(t) = & dx_3 \left(2 - \frac{x_3}{x(t)} - \frac{x(t)}{x_3} \right) + l_{41} ay_3 + l_{42} uv_3 + l_{44} b_2 w_3 \\ & - l_{42} k v_3 \frac{y(t)}{v(t)} - (l_{42} u + l_{44} c_2 w_3) v(t) + \frac{\beta_1 x_3 v_3}{1 + \alpha v_3} \left[1 + \frac{v(t)(1 + \alpha v_3)}{v_3(1 + \alpha v(t))} - \frac{x_3}{x(t)} \right] \\ & - l_{41} e^{-m\tau} \frac{\beta_1 x_3 v_3}{1 + \alpha v_3} \frac{x(t - \tau) v(t - \tau)(1 + \alpha v_3) y_3}{x_3(1 + \alpha v(t - \tau)) v_3 y(t)} + \frac{\beta_1 x_3 v_3}{1 + \alpha v_3} \ln \frac{x(t - \tau) v(t - \tau)(1 + \alpha v(t))}{x(t) v(t)(1 + \alpha v(t - \tau))} \\ & + \beta_2 x_3 y_3 \left(1 - \frac{x_3}{x(t)} - l_{41} e^{-m\tau} \frac{x(t - \tau) y(t - \tau)}{x_3 y(t)} \right) + \beta_2 x_3 y_3 \ln \frac{x(t - \tau) y(t - \tau)}{x(t) y(t)} \\ & + (l_{41} e^{-m\tau} - 1) \left(\frac{\beta_1 x(t - \tau) v(t - \tau)}{1 + \alpha v(t - \tau)} + \beta_2 x(t - \tau) y(t - \tau) \right) \\ & + (\beta_2 x_3 + l_{42} k - l_{41} a) y(t) + (l_{41} p_1 y_3 - l_{43} b_1) z(t) + (l_{42} p_2 v_3 - l_{44} b_2) w(t) \\ & + (l_{43} c_1 - l_{41} p_1) y(t) z(t) + (l_{44} c_2 - l_{42} p_2) v(t) w(t). \end{aligned} \quad (4.12)$$

Choose

$$l_{41} = e^{m\tau}, \quad l_{42} = \frac{\beta_1 x_3 v_3}{k y_3 (1 + \alpha v_3)}, \quad l_{43} = \frac{e^{m\tau} p_1}{c_1}, \quad l_{44} = \frac{\beta_1 p_2 x_3 v_3}{c_2 k y_3 (1 + \alpha v_3)}. \quad (4.13)$$

It follows from (4.12) and (4.13) that

$$\begin{aligned} \dot{V}_4(t) = & dx_3 \left(2 - \frac{x_3}{x(t)} - \frac{x(t)}{x_3} \right) + e^{m\tau} p_1 \frac{c_1 y_3 - b_1}{c_1} z(t) - \frac{\alpha(v(t) - v_3)^2}{v_3(1 + \alpha v_3)(1 + \alpha v(t))} - g \left(\frac{1 + \alpha v(t)}{1 + \alpha v_3} \right) \\ & - \frac{\beta_1 x_3 v_3}{1 + \alpha v_3} \left[g \left(\frac{x_3}{x(t)} \right) + g \left(\frac{y(t) v_3}{y_3 v(t)} \right) + g \left(\frac{x(t - \tau) v(t - \tau)(1 + \alpha v_3) y_3}{x_3 v_3 (1 + \alpha v(t - \tau)) y(t)} \right) \right] \\ & - \beta_2 x_3 y_3 \left[g \left(\frac{x_3}{x(t)} \right) + g \left(\frac{x(t - \tau) y(t - \tau)}{x_3 y(t)} \right) \right]. \end{aligned} \quad (4.14)$$

According to (3.12), it is easy to see that $c_1 y_3 < b_1$. It follows from (4.14) that $\dot{V}_4(t) \leq 0$ with equality holding if and only if $x = x_3, y = y_3, v = v_3, z = 0, w = w_3$. It can be proved that $M_4 = \{E_3\} \subset \Omega$ is the largest invariant subset of $\{(x(t), y(t), v(t), z(t), w(t)) : \dot{V}_4(t) = 0\}$. Noting that if $\mathcal{R}_2 > 1$ and $\mathcal{R}_4 < 1$, E_3 is locally asymptotically stable, hence we obtain the global asymptotic stability of E_3 from LaSalle's invariance principle. \square

Theorem 4.6. *If $\mathcal{R}_3 > 1$ and $\mathcal{R}_4 > 1$, the immunity-activated equilibrium $E^*(x^*, y^*, v^*, z^*, w^*)$ of system (1.2) is globally asymptotically stable.*

Proof. Let $(x(t), y(t), v(t), z(t), w(t))$ be any positive solution of system (1.2) with initial condition (1.3). Define

$$\begin{aligned} V_5(t) = & x^* g \left(\frac{x(t)}{x^*} \right) + l_{51} y^* g \left(\frac{y(t)}{y^*} \right) + l_{52} v^* g \left(\frac{v(t)}{v^*} \right) + l_{53} z^* g \left(\frac{z(t)}{z^*} \right) + l_{54} w^* g \left(\frac{w(t)}{w^*} \right) \\ & + \frac{\beta_1 x^* v^*}{1 + \alpha v^*} \int_{t-\tau}^t g \left(\frac{x(s) v(s)(1 + \alpha v^*)}{x^* v^* (1 + \alpha v(s))} \right) ds + \beta_2 x^* y^* \int_{t-\tau}^t g \left(\frac{x(s) y(s)}{x^* y^*} \right) ds, \end{aligned}$$

where constants l_{51} , l_{52} , l_{53} and l_{54} will be determined later. Calculating the derivative of $V_5(t)$ along positive solutions of system (1.2), we have

$$\begin{aligned} \dot{V}_5(t) = & \left(1 - \frac{x^*}{x(t)}\right) \left(s - dx(t) - \frac{\beta_1 x(t)v(t)}{1 + \alpha v(t)} - \beta_2 x(t)y(t)\right) \\ & + l_{51} \left(1 - \frac{y^*}{y(t)}\right) \left(\frac{\beta_1 e^{-m\tau} x(t-\tau)v(t-\tau)}{1 + \alpha v(t-\tau)} + \beta_2 e^{-m\tau} x(t-\tau)y(t-\tau) - ay(t) - p_1 y(t)z(t)\right) \\ & + l_{52} \left(1 - \frac{v^*}{v(t)}\right) (ky(t) - uv(t) - p_2 v(t)w(t)) \\ & + l_{53} \left(1 - \frac{z^*}{z(t)}\right) (c_1 y(t)z(t) - b_1 z(t)) + l_{54} \left(1 - \frac{w^*}{w(t)}\right) (c_2 v(t)w(t) - b_2 w(t)) \\ & + \frac{\beta_1 x^* v^*}{1 + \alpha v^*} \left[g \left(\frac{x(t)v(t)(1 + \alpha v^*)}{x^* v^* (1 + \alpha v(t))} \right) - g \left(\frac{x(t-\tau)v(t-\tau)(1 + \alpha v^*)}{x^* v^* (1 + \alpha v(t-\tau))} \right) \right] \\ & + \beta_2 x^* y^* \left[g \left(\frac{x(t)y(t)}{x^* y^*} \right) - g \left(\frac{x(t-\tau)y(t-\tau)}{x^* y^*} \right) \right]. \end{aligned} \quad (4.15)$$

Substituting $s = dx^* + \beta_1 x^* v^* / (1 + \alpha v^*) + \beta_2 x^* y^*$, $\beta_1 e^{-m\tau} x^* v^* / (1 + \alpha v^*) + \beta_2 e^{-m\tau} x^* y^* = ay^* + p_1 y^* z^*$, $ky^* = uv^* + p_2 v^* w^*$, $c_1 y^* z^* = b_1 z^*$, $c_2 v^* w^* = b_2 w^*$ into (4.15) yields

$$\begin{aligned} \dot{V}_5(t) = & dx^* \left(2 - \frac{x^*}{x(t)} - \frac{x(t)}{x^*}\right) + \frac{\beta_1 x^* v^*}{1 + \alpha v^*} \left[1 + \frac{v(t)(1 + \alpha v^*)}{v^*(1 + \alpha v(t))} - \frac{x^*}{x(t)}\right] \\ & + \frac{\beta_1 x^* v^*}{1 + \alpha v^*} \left[\ln \frac{x(t-\tau)v(t-\tau)(1 + \alpha v(t))}{x(t)v(t)(1 + \alpha v(t-\tau))} - l_{51} e^{-m\tau} \frac{x(t-\tau)v(t-\tau)y^*(1 + \alpha v^*)}{x^* v^* y(t)(1 + \alpha v(t-\tau))} \right] \\ & + \beta_2 x^* y^* \left(1 - \frac{x^*}{x(t)} - l_{51} e^{-m\tau} \frac{x(t-\tau)y(t-\tau)}{x^* y(t)} + \ln \frac{x(t-\tau)y(t-\tau)}{x(t)y(t)}\right) \\ & + l_{51} ay^* + l_{52} uv^* + l_{53} c_1 y^* z^* + l_{54} c_2 v^* w^* - l_{52} v^* \frac{uv^* + p_2 v^* w^*}{y^*} \frac{y(t)}{v(t)} \\ & + (l_{51} e^{-m\tau} - 1) \left(\frac{\beta_1 x(t-\tau)v(t-\tau)}{1 + \alpha v(t-\tau)} + \beta_2 x(t-\tau)y(t-\tau)\right) \\ & + \left(\beta_2 x^* + l_{52} \frac{uv^* + p_2 v^* w^*}{y^*} - l_{51} a - l_{53} c_1 z^*\right) y(t) \\ & - (l_{54} c_2 w^* + l_{52} u) v(t) + (l_{51} p_1 - l_{53} c_1) y^* z(t) + (l_{52} p_2 - l_{54} c_2) v^* w(t) \\ & + (l_{53} c_1 - l_{51} p_1) y(t)z(t) + (l_{54} c_2 - l_{52} p_2) v(t)w(t). \end{aligned} \quad (4.16)$$

Choose

$$l_{51} = e^{m\tau}, \quad l_{52} = \frac{\beta_1 x^*}{(1 + \alpha v^*)(u + p_2 w^*)}, \quad l_{53} = \frac{p_1}{c_1} e^{m\tau}, \quad l_{54} = \frac{\beta_1 p_2 x^*}{c_2 (1 + \alpha v^*)(u + p_2 w^*)}. \quad (4.17)$$

From (4.16) and (4.17), we can obtain that

$$\begin{aligned} \dot{V}_5(t) = & dx^* \left(2 - \frac{x^*}{x(t)} - \frac{x(t)}{x^*}\right) - \frac{\alpha(v(t) - v^*)^2}{v^*(1 + \alpha v^*)(1 + \alpha v(t))} - g \left(\frac{1 + \alpha v(t)}{1 + \alpha v^*}\right) \\ & - \frac{\beta_1 x^* v^*}{1 + \alpha v^*} \left[g \left(\frac{x^*}{x(t)}\right) + g \left(\frac{y(t)v^*}{y^* v(t)}\right) + g \left(\frac{x(t-\tau)v(t-\tau)y^*(1 + \alpha v^*)}{x^* v^* y(t)(1 + \alpha v(t-\tau))}\right) \right] \end{aligned} \quad (4.18)$$

$$-\beta_2 x^* y^* \left[g \left(\frac{x^*}{x(t)} \right) + g \left(\frac{x(t-\tau)y(t-\tau)}{x^*y(t)} \right) \right].$$

It follows from (4.18) that $\dot{V}_5(t) \leq 0$ with equality holding if and only if $x = x^*, y = y^*, v = v^*, z = z^*, w = w^*$. It can be verified that $M_5 = \{E^*\} \subset \Omega$ is the largest invariant subset of $\{(x(t), y(t), v(t), z(t), w(t)) : \dot{V}_5(t) = 0\}$. Noting that if $\mathcal{R}_3 > 1$ and $\mathcal{R}_4 > 1$, E^* is locally asymptotically stable, we therefore obtain the global asymptotic stability of E^* from LaSalle's invariance principle. \square

5. Numerical simulations

In this section, we want to illustrate the theoretical results for system (1.2) by numerical simulations. Besides, we investigate the effects of cell-to-cell transmission, viral production rate, death rate of infected cells and viral remove rate on viral dynamics. Furthermore, sensitivity analysis is used to quantify the range of variables in reproduction ratios and identify the key factors giving rise to reproduction ratios, which can be helpful to design treatment strategies and provide insights on evaluating effective antiviral drug therapies.

Table 2. List of parameters.

Parameters (units)	Case 1	Case 2	Case 3	Case4	Case5	Source
s (cells · ml/day)	50	23	100	23	100	Assumed
d (/day)	0.0046	0.0065	0.0046	0.0046	0.0046	[26]
β_1 (ml · virion/day)	4.8×10^{-7}	[26]				
β_2 (ml · virion/day)	4.7×10^{-7}	4.7×10^{-9}	4.7×10^{-7}	4.7×10^{-7}	4.7×10^{-7}	[26]
α	0.01	0.0001	0.01	0.01	0.01	Assumed
m	1.39	1.39	1.39	1.39	1.39	[26]
τ (day)	0.5	0.3	0.5	0.5	0.5	[26]
a (/day)	0.015	0.032	0.008	0.01	0.008	Assumed
p_1 (cells · ml/day)	0.005	0.005	0.001	0.005	0.001	[27]
k (cells · virion/day)	1.1349	7.3	1.1349	11.349	11.349	[26]
u (/day)	0.5	0.25	0.05	0.05	0.05	[26]
p_2 ($\mu\text{g}/\text{day}$)	0.01	0.01	0.01	0.01	0.01	[27]
c_1 (cells · ml/day)	0.002	0.021	0.002	0.002	0.002	Assumed
b_1 (/day)	0.12	0.25	0.02	0.12	0.02	Assumed
c_2 (cells · virion/day)	0.0006	0.0013	0.00013	0.0013	0.0013	[27]
b_2 (/day)	0.12	0.46	0.12	0.12	0.12	Assumed

Following [18,26,27,32], we choose appropriate parameters and simulate each of feasible equilibria, respectively.

Case 1: Corresponding parameters are listed in Case 1 of Table 2. The immunity-inactivated reproduction ratio is calculated as $\mathcal{R}_0 = 0.5640 < 1$. From Theorem 3.1, we derive that infection-free equilibrium E_0 is locally asymptotically stable, which is illustrated in Figure 2.

Case 2: Corresponding parameters are listed in Case 2 of Table 2. By simple computing, we obtain that $\mathcal{R}_0 = 1.0217 > 1$, $\mathcal{R}_1 = 0.9635 < 1$ and $\mathcal{R}_2 = 0.9625 < 1$. From Theorem 3.2, we derive that immunity-inactivated equilibrium E_1 is locally asymptotically stable, which is in accord with Figure 3.

Case 3: Corresponding parameters are listed in Case 3 of Table 2. Similarly, we obtain that $\mathcal{R}_1 = 5.1140 > 1$ and $\mathcal{R}_3 = 0.2459 < 1$. From Theorem 3.3, we derive that cell-mediated immunity-activated equilibrium E_2 is locally asymptotically stable, which is illustrated in Figure 4.

Case 4: Corresponding parameters are listed in Case 4 of Table 2. Likewise, we obtain that $\mathcal{R}_2 = 14.1830 > 1$ and $\mathcal{R}_4 = 0.2108 < 1$. From Theorem 3.4, we derive that humoral immunity-activated equilibrium E_3 is locally asymptotically stable, which is in keeping with in Figure 5.

Case 5: Corresponding parameters are listed in Case 5 of Table 2. By calculation, we obtain that $\mathcal{R}_3 = 24.5895 > 1$ and $\mathcal{R}_4 = 3.7395 > 1$. From Theorem 3.5, we derive that immunity-activated equilibrium E^* is locally asymptotically stable, which is consistent with observation in Figure 6.

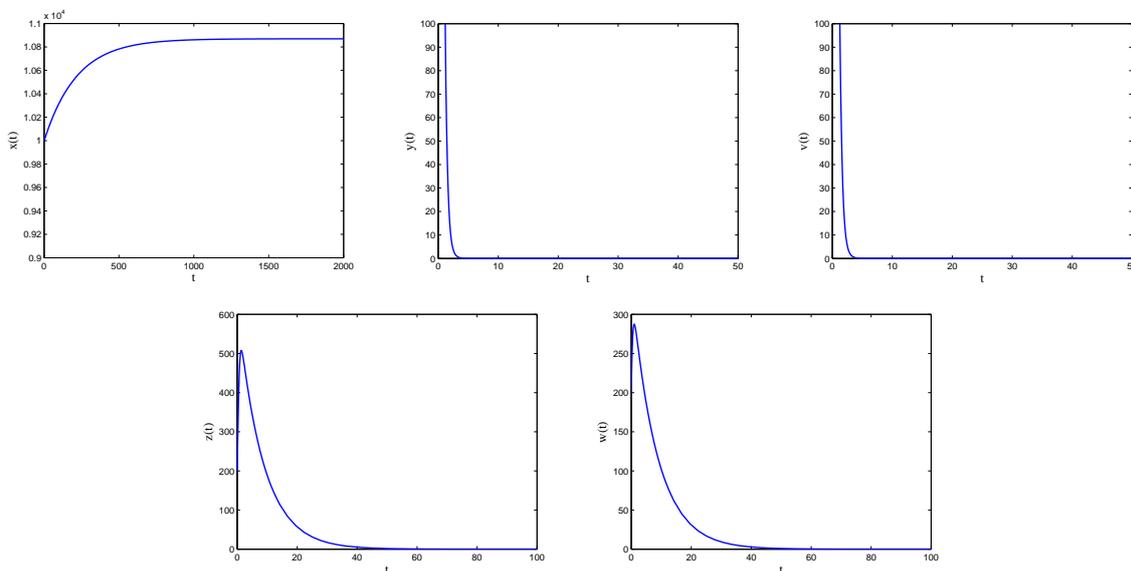


Figure 2. The temporal solutions of $x(t)$, $y(t)$, $v(t)$, $z(t)$ and $w(t)$ versus t of system (1.2) where $\mathcal{R}_0 = 0.5640 < 1$.

5.1. Effect of cell-to-cell transmission

In order to investigate the effect of cell-to-cell transmission, we carry out some numerical simulations to show the contribution of cell-to-cell transmission during the whole infection. First, we let β_2 as zero to compare the virus infection without cell-to-cell transmission with the infection which has both transmissions. Figure 7 ($\beta_2 = 0$, $\beta_2 = 4.7 \times 10^{-7}$) shows that cell-to-cell transmission is of benefit to HIV-1 transmission and the time to reach the peak level of virus is shorter. Then, we increase β_2 to study the change of the peak level of infected cells and virus, and the time to reach the peak level. Figure 7 ($\beta_2 = 4.7 \times 10^{-7}$, $\beta_2 = 4.7 \times 10^{-6}$, $\beta_2 = 4.7 \times 10^{-5}$) shows that infected cells and virus reach the peak level more quickly as β_2 increases, meanwhile, the peak level become larger as β_2 increases, too. Therefore, cell-to-cell transmission plays an important role in the whole virus infection.

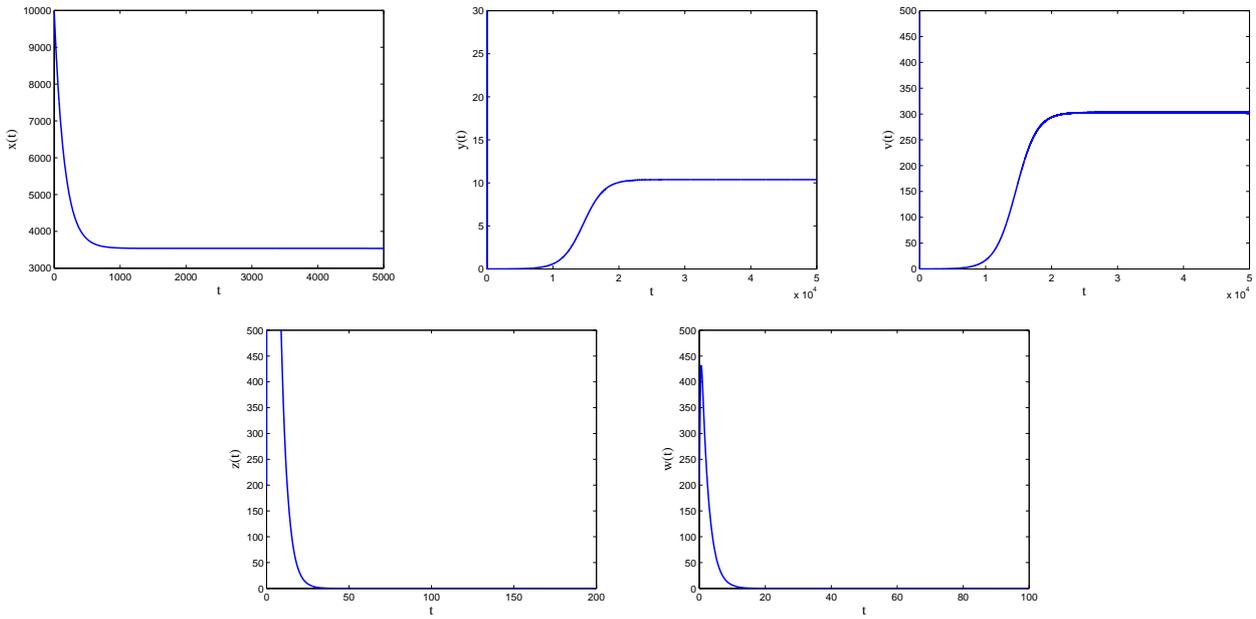


Figure 3. The temporal solutions of $x(t)$, $y(t)$, $v(t)$, $z(t)$ and $w(t)$ versus t of system (1.2) where $\mathcal{R}_0 = 1.0217 > 1$, $\mathcal{R}_1 = 0.9635 < 1$ and $\mathcal{R}_2 = 0.9625 < 1$.

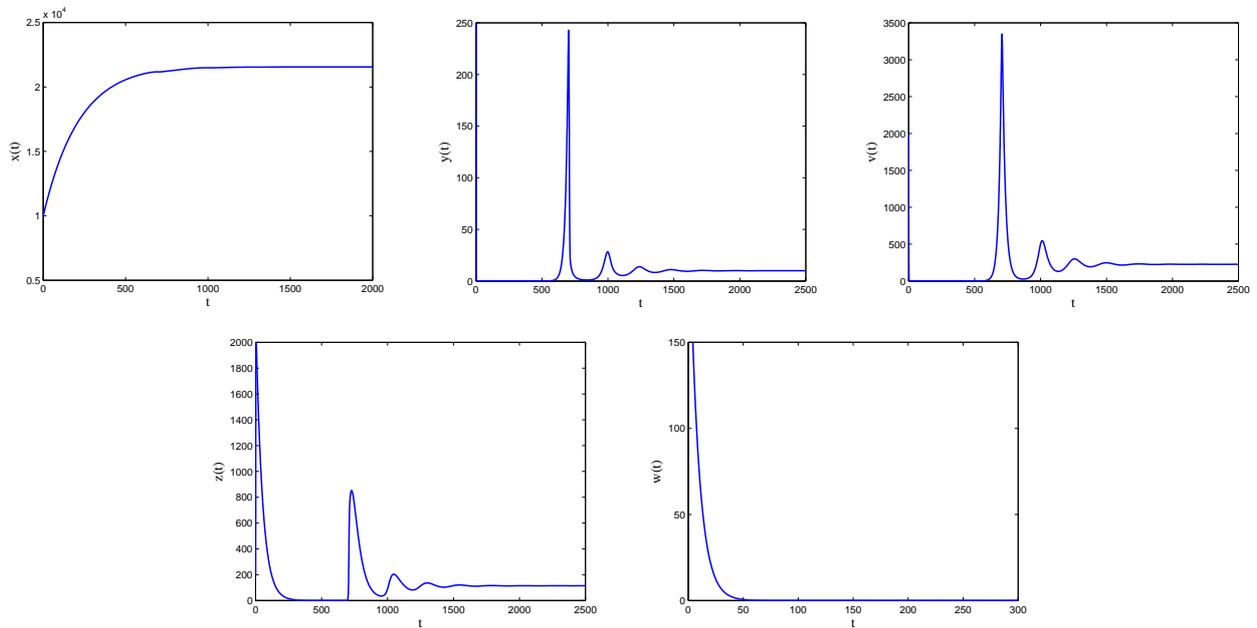


Figure 4. The temporal solutions of $x(t)$, $y(t)$, $v(t)$, $z(t)$ and $w(t)$ versus t of system (1.2) where $\mathcal{R}_1 = 5.1140 > 1$ and $\mathcal{R}_3 = 0.2459 < 1$.

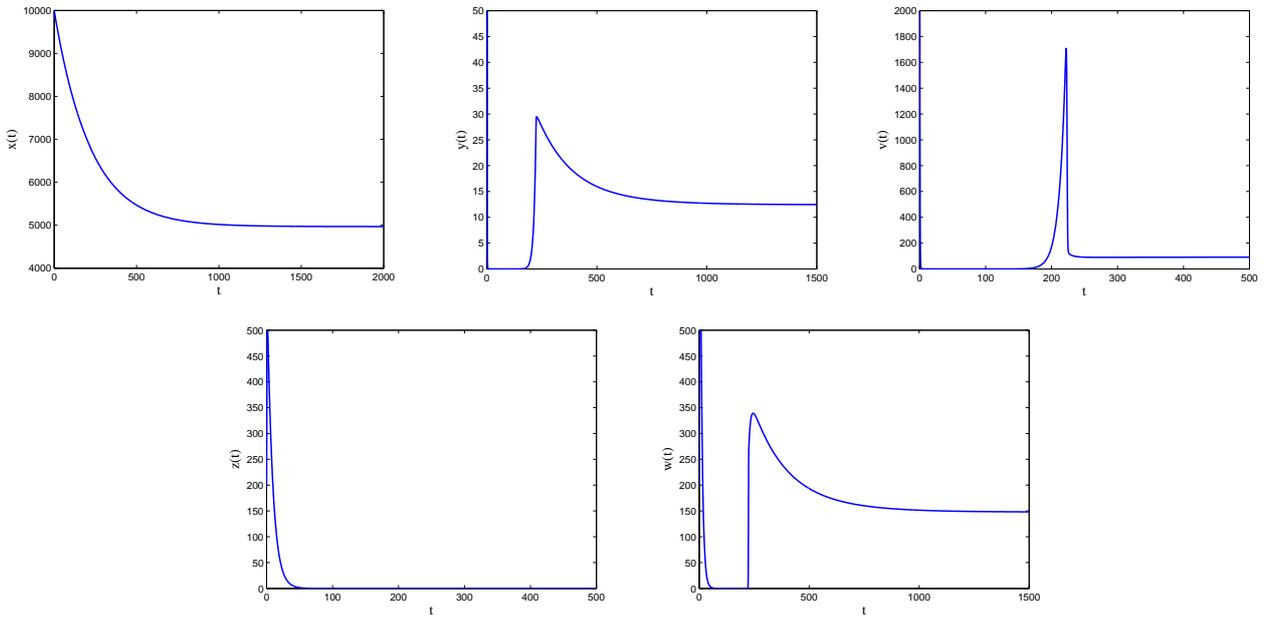


Figure 5. The temporal solutions of $x(t)$, $y(t)$, $v(t)$, $z(t)$ and $w(t)$ versus t of system (1.2) where $\mathcal{R}_2 = 14.1830 > 1$ and $\mathcal{R}_4 = 0.2108 < 1$.

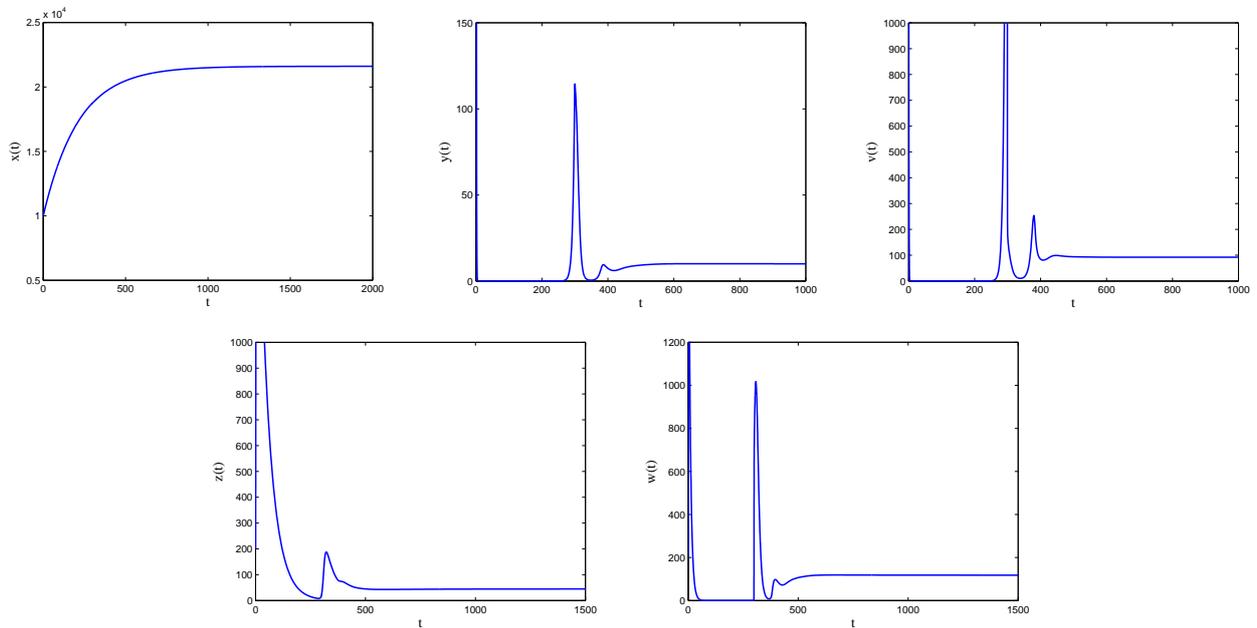


Figure 6. The temporal solutions of $x(t)$, $y(t)$, $v(t)$, $z(t)$ and $w(t)$ versus t of system (1.2) where $\mathcal{R}_3 = 24.5895 > 1$ and $\mathcal{R}_4 = 3.7395 > 1$.

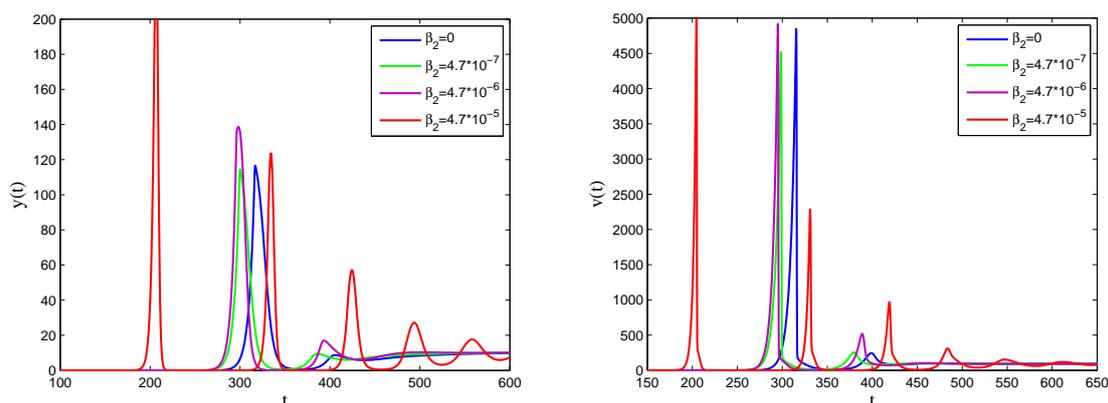


Figure 7. The effect of β_2 on the dynamical behavior of system (1.2).

5.2. Effect of viral production rate

Viral production rate also has great influence on the dynamical behavior of the model. We set the viral production rate k as 11.349, 34.047, 68.094. In Figure 8, we observe that the time to reach the peak level of infected cells and virus becomes shorter as k increases, which means that larger viral production rate contributes to the viral infection. Meanwhile, T cells and B cells increase more quickly as k increases, especially, larger viral production rate can stimulate more B cells. Hence, the peak level of infected cells and virus decreases as k increases. In terms of the prevention and treatment of HIV, it implies that antiretroviral therapies, such as, reverse transcriptase inhibitors and protease inhibitors are effective methods to decrease k , namely, to inhibit virus reproduction.

5.3. Effect of death rate of infected cells and viral remove rate

Usually, the death rate of infected cells is larger than the death rate of uninfected cells due to the fact that HIV infection can kill more host cells. We present some numerical simulations to study the effect of death rate of infected cells on the dynamical behavior of the model. We can observe from Figure 9 that, infected cells and virus increase more slowly as a increases, which indicates that increasing the death rate of infected cells can slow down the virus infection. Humoral immunity is mainly used to clear virus in our humor, so the viral remove rate has an effect on viral infection as well. Figure 10 implies that as the viral remove rate increases, infected cells and virus increase more slowly, which has the similar results to a . In the clinic treatment of HIV, promoting body's immune capacity contributes to increasing the death rate of infected cells and viral remove rate.

5.4. Sensitivity analysis

Sensitivity analysis is used to quantify the range of variables in reproduction ratios and to identify the key factors giving rise to reproduction ratios. In [9, 16], Latin hypercube sampling (LHS) is found to be a more efficient statistical sampling technique which has been introduced to the field of disease modelling.

LHS allows an un-biased estimate of the reproduction ratios, with the advantage that it requires fewer samples than simple random sampling to achieve the same accuracy. For each parameter of

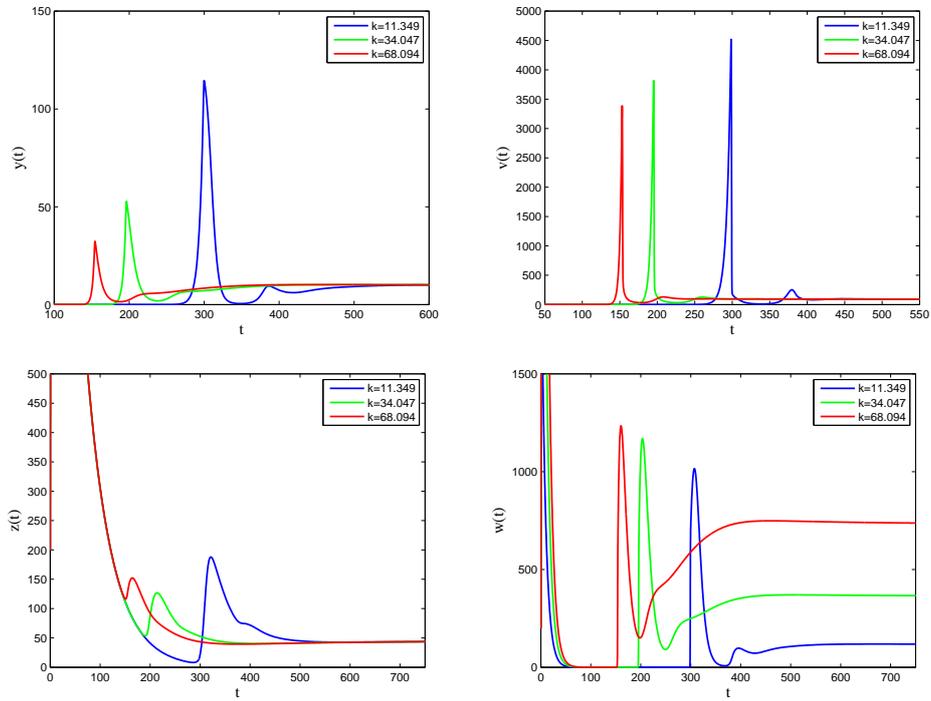


Figure 8. The effect of k on the dynamical behavior of system (1.2).

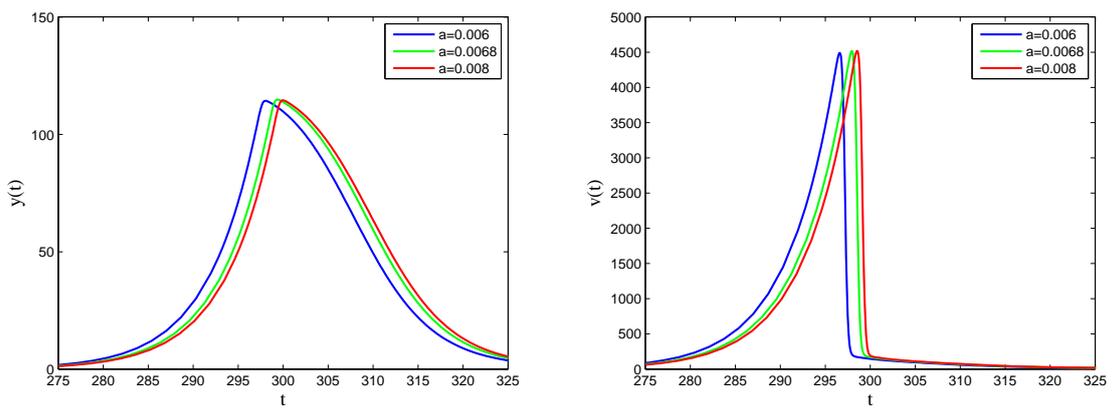


Figure 9. The effect of a on the dynamical behavior of system (1.2).

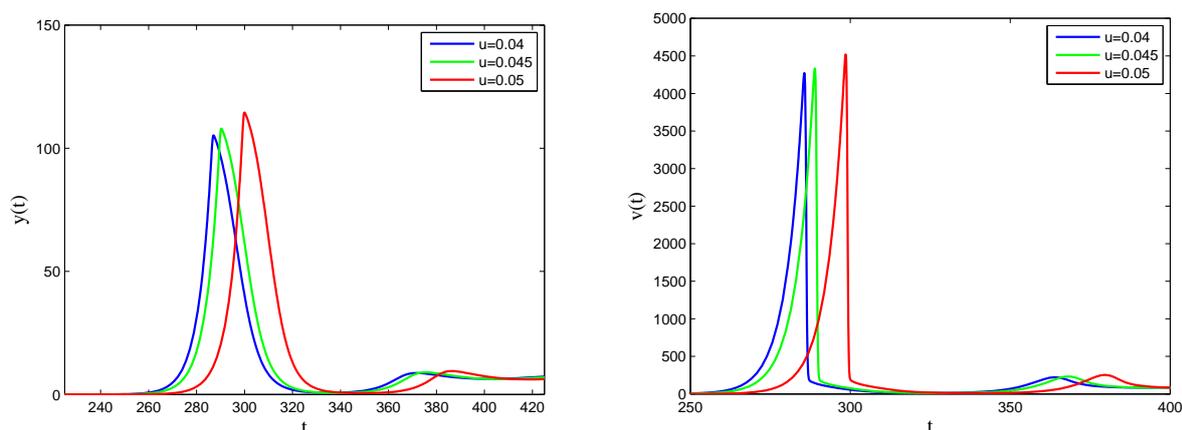


Figure 10. The effect of u on the dynamical behavior of system (1.2).

reproduction ratios, a probability density function is defined based on experimental data and stratified into N equiprobable serial intervals. A single value is then selected randomly from every interval and this is done for every parameter. In this way, a parameter value from each sampling interval is used only once in the analysis but the entire parameter space is equitably sampled in an efficient manner. Distributions of the reproduction ratios can then be derived directly by running the model N times with each of the sampled parameter sets.

In terms of the prevention and treatment of HIV, we pay more attention to antiretroviral therapies, which is directly related to viral production rate and viral remove rate. Figure 11 shows the scatter plots of \mathcal{R}_0 , \mathcal{R}_1 and \mathcal{R}_2 in respect to k and u , which implies that k is a positively correlative variable with \mathcal{R}_0 and \mathcal{R}_2 , while u is a negatively correlative variable. As for \mathcal{R}_1 , we find that the correlation between k and \mathcal{R}_1 or u and \mathcal{R}_1 is not clear.

In [16], Marino et al. mentioned that Partial Rank Correlation Coefficients (PRCCs) provide a measure of the strength of a linear association between the parameters and the reproduction ratios. Furthermore, PRCCs are useful for identifying the most important parameters. The positive or negative of PRCCs respectively denote the positive or negative correlation with the reproduction ratios, and the sizes of PRCCs measure the strength of the correlation. First, we investigate the immunity-inactivated reproduction ratio \mathcal{R}_0 , as we can see in Figure 12, β_1 and k are positively correlative variables with \mathcal{R}_0 while others are negatively correlative variables. In order of correlative strength, it goes: β_1 , d , a , k , u and β_2 . Similarly, we obtain the PRCCs of \mathcal{R}_1 and \mathcal{R}_2 (see Figure 13). Specially, we observe that k and u is weakly correlative in respect to \mathcal{R}_1 , which accords with the scatter plots of \mathcal{R}_1 .

6. Conclusion

In this paper, we have considered an HIV-1 infection model to describe cell-to-cell transmission, saturation incidence, both cell-mediated and humoral immune responses. By a complete mathematical analysis, the threshold dynamics of the model is established and it can be fully determined by reproduction ratios. If $\mathcal{R}_0 < 1$, the infection-free equilibrium E_0 is locally and globally asymptotically stable; if $\mathcal{R}_0 > 1$, $\mathcal{R}_1 < 1$ and $\mathcal{R}_2 < 1$, the immunity-inactivated equilibrium E_1 is locally and globally

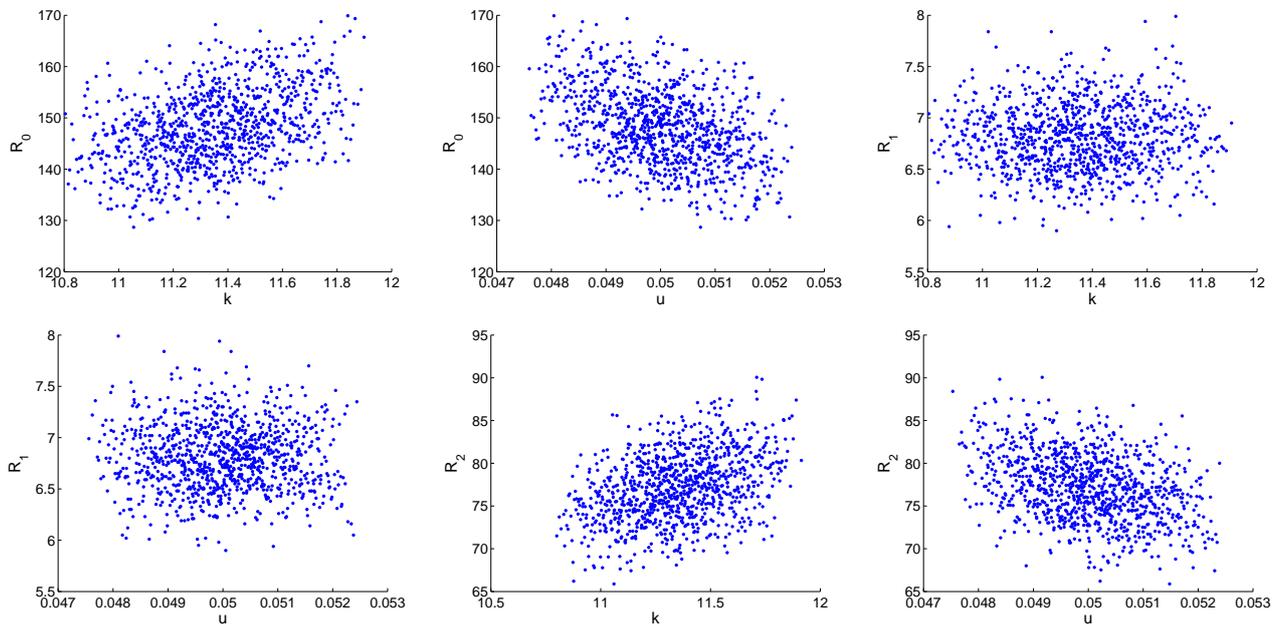


Figure 11. Scatter plots of \mathcal{R}_0 , \mathcal{R}_1 and \mathcal{R}_2 in respect to k and u .

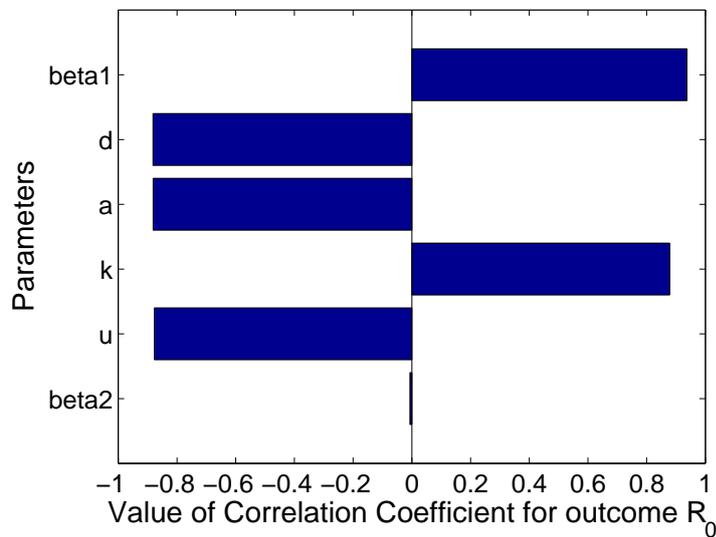


Figure 12. Tornado plot of PRCCs in regard to \mathcal{R}_0 .

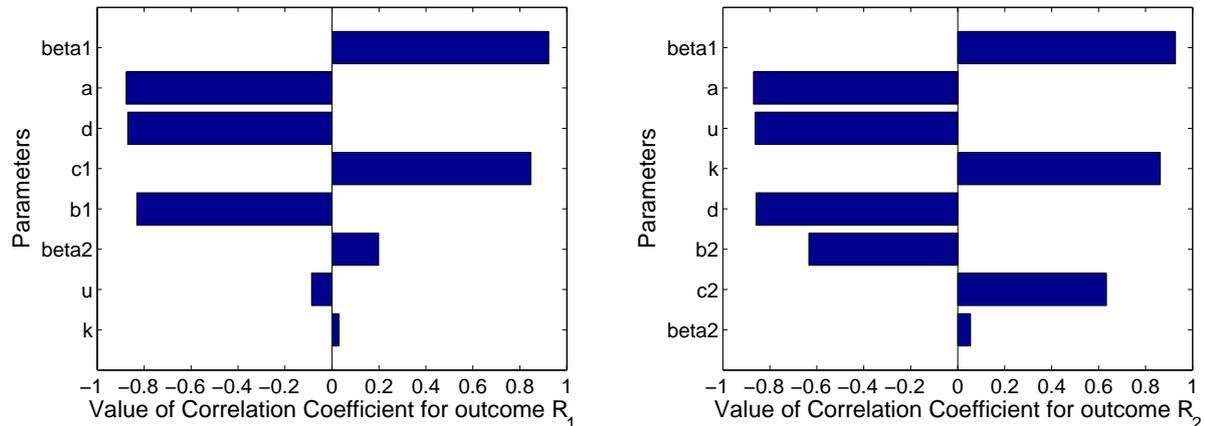


Figure 13. Tornado plots of PRCCs in regard to \mathcal{R}_1 and \mathcal{R}_2 .

asymptotically stable; if $\mathcal{R}_1 > 1$ and $\mathcal{R}_3 < 1$, the cell-mediated immunity-activated equilibrium E_2 is locally and globally asymptotically stable; if $\mathcal{R}_2 > 1$ and $\mathcal{R}_4 < 1$, the humoral immunity-activated equilibrium E_3 is locally and globally asymptotically stable; if $\mathcal{R}_3 > 1$ and $\mathcal{R}_4 > 1$, the immunity-activated equilibrium E^* is locally and globally asymptotically stable.

Numerical simulations vividly illustrate our main results of stability analysis for system (1.2). Besides, we have investigated the effects of cell-to-cell transmission, viral production rate, death rate of infected cells and viral remove rate on viral dynamics. It is worth mentioning that as the infection rate of cell-to-cell transmission β_2 increases, virus load rises quickly and largely, which implies that cell-to-cell transmission facilitates virus spread. Furthermore, we perform a sensitivity analysis of reproduction ratios, which implies some useful consequences on the prevention and treatment of HIV-1.

It is easy to see that immunity-inactivated reproduction ratios \mathcal{R}_0 is the sum of the reproduction ratio determined by virus-to-cell infection, \mathcal{R}_{01} , and that determined by cell-to-cell transmission, \mathcal{R}_{02} . In other words, immunity-inactivated reproduction ratio \mathcal{R}_0 becomes larger when the model includes cell-to-cell transmission. Meanwhile, we find that our research includes some existing work. When $\beta_2 = 0$ and $\alpha = 0$, our virus model is similar to the model in [33] and the immunity-inactivated reproduction ratio \mathcal{R}_0 reduces to \mathcal{R}_{01} . Based on the model in [33], Wang et al. [27] consider nonlinear incidence and continuous intracellular delay, which is similar to our model with $\beta_2 = 0$ only. Besides, when we only consider one of the immune responses, our model reduces to the models in [14] and [26].

Acknowledgments

This work was supported by the National Natural Science Foundation of China (Nos.11871316,11801340,11371368,11331009), Shanxi Scientific Data Sharing Platform for Animal Diseases (201605D121014), and the Science and Technology Innovation Team of Shanxi Province (201605D131044-06).

Conflict of interest

The authors declare there is no conflict of interest.

References

1. R. A. Cangelosi, E. J. Schwartz and D. J. Wollkind, A quasi-steady-state approximation to the basic target-cell-limited viral dynamics model with a non-cytopathic effect, *Front. Microbiol.*, **9** (2018), 54.
2. J. Charles, T. Paul and W. Mark, *Immunobiology*, 5th edition, Garland Science, New York, 2001.
3. P. van den Driessche and J. Watmough, Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission, *Math. Biosci.*, **180** (2002), 29–48.
4. A. M. Elaiw and N. H. AlShamrani, Global stability of humoral immunity virus dynamics models with nonlinear infection rate and removal, *Nonlinear Anal. RWA*, **26** (2015), 161–190.
5. A. M. Elaiw, A. A. Raezah and K. Hattaf, Stability of HIV-1 infection with saturated virus-target and infected-target incidences and CTL immune response, *Int. J. Biomath.*, **10** (2017), 1750070.
6. T. R. Fouts, K. Bagley, I. J. Prado, et al., Balance of cellular and humoral immunity determines the level of protection by HIV vaccines in rhesus macaque models of HIV infection, *Proc. Natl. Acad. Sci.*, **13** (2015), 992–999.
7. J. K. Hale and S. Verduyn Lunel, *Introduction to Functional Differential Equations*, Springer, New York, 1993.
8. K. Hattaf and N. Yousfi, A class of delayed viral infection models with general incidence rate and adaptive immune response, *Int. J. Dynam. Control*, **4** (2016), 254.
9. A. Hoare, D. G. Regan and D. P. Wilson, Sampling and sensitivity analyses tools (SaSAT) for computational modelling, *Theor. Biol. Med. Model.*, **5** (2008), 4.
10. G. Huang, Y. Takeuchi and W. Ma, Lyapunov functionals for delay differential equations model of viral infections, *SIAM J. Appl. Math.*, **70** (2010), 2693–2708.
11. X. Lai and X. Zou, Modeling cell-to-cell spread of HIV-1 with logistic target cell growth, *J. Math. Anal. Appl.*, **426** (2015), 563–584.
12. X. Lai and X. Zou, Modeling HIV-1 virus dynamics with both virus-to-cell infection and cell-to-cell transmission, *SIAM J. Appl. Math.*, **74** (2014), 898–917.
13. F. Li and J. Wang, Analysis of an HIV infection model with logistic target-cell growth and cell-to-cell transmission, *Chaos Soliton Fract.*, **81** (2015), 136–145.
14. J. Lin, R. Xu and X. Tian, Threshold dynamics of an HIV-1 virus model with both virus-to-cell and cell-to-cell transmissions, intracellular delay, and humoral immunity, *Appl. Math. Comput.*, **315** (2017), 516–530.
15. C. Lv, L. Huang and Z. Yuan, Global stability for an HIV-1 infection model with Beddington-DeAngelis incidence rate and CTL immune response, *Commun. Nonlinear Sci. Numer. Simulat.*, **19** (2014), 121–127.

16. S. Marino, I. B. Hogue and C. J. Ray, A methodology for performing global uncertainty and sensitivity analysis in systems biology, *J. Theor. Biol.*, **254** (2008), 178–196.
17. N. Martin and Q. Sattentau, Cell-to-cell HIV-1 spread and its implications for immune evasion, *Curr. Opin. HIV AIDS*, **4** (2009), 143–149.
18. A. Murase, T. Sasaki and T. Kajiwara, Stability analysis of pathogen-immune interaction dynamics, *J. Math. Biol.*, **51** (2005), 247–267.
19. Y. Nakata, Global dynamics of a cell mediated immunity in viral infection models with distributed delays, *J. Math. Anal. Appl.*, **375** (2011), 14–27.
20. M. Nowak, S. Bonhoeffer, G. Shaw and R. May, Anti-viral drug treatment: Dynamics of resistance in free virus and infected cell populations, *J. Theor. Biol.*, **184** (1997), 203–217.
21. A. S. Perelson and P. W. Nelson, Mathematical Analysis of HIV-1: Dynamics in Vivo, *SIAM Review*, **41** (1999), 3–44.
22. R. R. Regoes, D. Ebert and S. Bonhoeffer, Dose-dependent infection rates of parasites produce the Allee effect in epidemiology, *Proc. R. Soc. Lond. Ser. B*, **269** (2002), 271–279.
23. E. J. Schwartz, N. K. Vaidya, K. S. Dorman, S. Carpenter and R. H. Mealey, Dynamics of lentiviral infection in vivo in the absence of adaptive immune responses, *Virology*, **513** (2018), 108–113.
24. H. Shu, L. Wang and J. Watmough, Global stability of a nonlinear viral infection model with infinitely distributed intracellular delays and CTL immune responses, *SIAM J. Appl. Math.*, **73** (2013), 1280–1302.
25. A. Sigal, J. T. Kim, A. B. Balazs, E. Dekel, A. Mayo, R. Milo and D. Baltimore, Cell-to-cell spread of HIV permits ongoing replication despite antiretroviral therapy, *Nature*, **477** (2011), 95–98.
26. J. Wang, M. Guo, X. Liu and Z. Zhao, Threshold dynamics of HIV-1 virus model with cell-to-cell transmission, cell-mediated immune responses and distributed delay, *Appl. Math. Comput.*, **291** (2016), 149–161.
27. J. Wang, J. Pang, T. Kuniya and Y. Enatsu, Global threshold dynamics in a five-dimensional virus model with cell-mediated, humoral immune responses and distributed delays, *Appl. Math. Comput.*, **241** (2014), 298–316.
28. S. Wang and D. Zou, Global stability of in-host viral models with humoral immunity and intracellular delays, *Appl. Math. Model.*, **36** (2012), 1313–1322.
29. T. Wang, Z. Hu, F. Liao and W. Ma, Global stability analysis for delayed virus infection model with general incidence rate and humoral immunity, *Math. Comput. Simulat.*, **89** (2013), 13–22.
30. T. Wang, Z. Hu and F. Liao, Stability and Hopf bifurcation for a virus infection model with delayed humoral immunity response, *J. Math. Anal. Appl.*, **411** (2014), 63–74.
31. R. Xu, Global stability of an HIV-1 infection model with saturation infection and intracellular delay, *J. Math. Anal. Appl.*, **375** (2011), 75–81.
32. J. Xu, Y. Geng and Y. Zhou, Global dynamics for an age-structured HIV virus infection model with cellular infection and antiretroviral therapy, *Appl. Math. Comput.*, **305** (2017), 62–83.
33. Y. Yan and W. Wang, Global stability of a five-dimensional model with immune responses and delay, *Discrete and Continuous Dynamical Systems - Series B*, **17** (2012), 401–416.

-
34. H. Zhu and X. Zou, Dynamics of a HIV-1 infection model with cell-mediated immune response and intracellular delay, *Discrete and Continuous Dynamical Systems - Series B*, **12** (2009), 511–524.



AIMS Press

©2018 the Author(s), licensee AIMS Press. This is an open access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>)