Analysis of HIV models with multiple target cell populations and general nonlinear rates of viral infection and cell death

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Abstract

HIV can infect different cell populations such as CD4+ T cells and macrophages. In this paper, we study the global property of the solution of an HIV model with two target cell populations. The model includes general nonlinear rates of viral infection and cell death. For each class of target cells, the time delay between viral entry into cells and viral production is included in the model. We obtain the basic reproductive number of the model, which is shown to provide a threshold condition determining the long-term behavior of the solution of the model. Specifically, we show that the infection-free equilibrium is globally asymptotically stable when the basic reproductive number is less than or equal to 1, and that the infected equilibrium is globally asymptotically stable when the basic reproductive number is greater than 1. We also extend the model with two target cell populations to a general model with n populations. Similar global properties are obtained for the general model. Numerical simulations are performed to illustrate the stability results and to evaluate the relative contribution to viral production from the two cell populations.

Key words: Virus dynamics; Delay; Multiple target cells; Global stability; Lyapunov functional.

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1 Introduction

It is well known that mathematical modeling and analysis plays an important role in the study of epidemiology [1,2,15,17,20,25]. For example, Anderson and May constructed epidemic models embodying the essentials of the interaction between invertebrate hosts and their directly transmitted microparasites to study the dynamical behavior of conventional epidemiology [2]. Mathematical models have also been developed to study within-host dynamics of HIV infection, i.e., the interaction between cells, virus, and immune responses [4,22–24,26,31,36,39,40,42,50]. In [26], McLean and Kirkwood developed a mathematical model of the activation and proliferation of a clone of T helper cells in response to a replicating antigen and investigated the circumstance under which HIV can destabilize persistent infection and destroy immune memory. Rong and Perelson [39] reviewed mathematical models used to study HIV dynamics under antiretroviral therapy, low viral load persistence, the stability of latently infected cells, and the emergence of transient viral load measurements above the detection limit (so-called “viral blips”). A basic viral dynamic model of HIV infection is given below.

$$\begin{cases} \dot{x}(t) = \lambda - dx(t) - \beta x(t)v(t), \\ \dot{y}(t) = \beta x(t)v(t) - ay(t), \\ \dot{v}(t) = py(t) - \delta v(t), \end{cases} \quad (1)$$

where x, y and v represent the densities of uninfected target cells, infected cells and virus, respectively, in blood at time t . Uninfected cells are assumed to be generated at a constant rate λ , die at a per capita rate d , and become infected at a rate βxv , where β is the infection rate. Infected cells are produced at a rate βxv and die at a per capita rate a . Virus is assumed to be produced by productively infected cells at a rate p per cell, and is removed from blood at a per capita rate δ .

The mass action term βxv is used in model (1) to describe viral infection. However, the infection may not be strictly linear in each variable over the entire range of virions v and target cells x . Nonlinear contact rate has been used in some mathematical models [9,17,18,48]. For example, Wang et al. [48] used a virus infection rate with the Beddington-DeAngelis functional response $xv/(1+kx+cv)$. Georgescu and Hsieh [9] considered a nonlinear infection rate with $c(x)f(v)$, where $c(x)$ is the contact rate function depending on susceptible cells x and $f(v)$ represents the force of infection by virus at density v . Huang et al. [14] and Korobeinikov [17,18] assumed the incidence rate to be a nonlinear function $\varphi(x, v)$. In addition, there exists a time delay between viral entry into a target cell and viral production. This intracellular time delay has been studied in many models [6,10,12,14,21,27–30,46,47,49]. In this paper, we will include a time delay τ in the general incidence of viral infection, i.e. $\varphi(x(t-\tau), v(t-\tau))$.

The death rate of productively infected cells may not follow the exponential decay described by $-ay(t)$ in model (1). Productively infected cells are mainly cleared by the immune response, which is stimulated by infected cells [5]. Thus, the death rate

of productively infected cells may depend on the density of infected cells [39]. Holte et al. [13] assumed the death rate to be $a(y) = ay^\omega$, where ω governs the effect of the immune response on the death rate. In this paper, we will use a general nonlinear function $aG(y)$ to describe the death rate of productively infected cells.

All of the above-mentioned HIV infection models study the interaction between HIV and $CD4^+$ T cells. In addition to $CD4^+$ T cells, other cells such as macrophages [16] and dendritic cells [35] are known to be susceptible to HIV infection. HIV can infect macrophages through binding of gp120 to CD4 and CCR5 receptors, and were identified to be a highly productive source of HIV during the latter stage of viral infection [32]. Two-compartment models [5,34,39] are needed to study the interaction between HIV and two target cell populations. Elaiw and his collaborators have investigated the global asymptotic stability of the steady states of HIV models with two classes of target cells [7,8,45].

In the present paper, we study the global property of the solution of an HIV model with two target cell populations. The model includes general nonlinear rates of viral infection and cell death. Time delays between viral entry into each population of target cells and viral production are incorporated into the model. We analyze the model by deriving the basic reproductive number and proving the global stability of steady states. We also extend the model by including n target cell populations. Similar global properties are obtained for the general model and numerical simulations are performed to illustrate the theoretical results.

2 A model with two target cell populations

In this section, we introduce the following mathematical model of HIV infection with two time delays and two classes of target cells, $CD4^+$ T cells and macrophages.

$$\begin{cases} \dot{x}_1(t) = \lambda_1 - d_1x_1(t) - \varphi_1(x_1(t), v(t)), \\ \dot{x}_2(t) = \lambda_2 - d_2x_2(t) - \varphi_2(x_2(t), v(t)), \\ \dot{y}_1(t) = e^{-\mu_1\tau_1}\varphi_1(x_1(t-\tau_1), v(t-\tau_1)) - a_1G_1(y_1), \\ \dot{y}_2(t) = e^{-\mu_2\tau_2}\varphi_2(x_2(t-\tau_2), v(t-\tau_2)) - a_2G_2(y_2), \\ \dot{v}(t) = p_1G_1(y_1(t)) + p_2G_2(y_2(t)) - \delta v(t). \end{cases} \quad (2)$$

In the model, $x_1(t)$ and $x_2(t)$ are the populations of two classes of uninfected target cells, $CD4^+$ T cells and macrophages, respectively. $y_1(t)$ and $y_2(t)$ represent the populations of productively infected cells that can produce virions. λ_1 and λ_2 are the rates at which target cells are generated, d_1 and d_2 are their death rates, and the functions $\varphi_1(x_1, v)$, $\varphi_2(x_2, v)$ are the rates at which two target cell populations are infected by virus. For each population, a time delay (τ_1 or τ_2) is incorporated to describe the time between initial viral entry and viral production. $e^{-\mu_1\tau_1}$ (or $e^{-\mu_2\tau_2}$) is the probability of infected $CD4^+$ T cells (or macrophages) surviving to

produce virions, where μ_1 (or μ_2) is a constant death rate of infected $CD4^+$ T cells (or macrophages) that have not began to produce virions.

As addressed in the Introduction, we use nonlinear functions $a_1G(y_1)$ and $a_2G(y_2)$ to represent the death rates of infected cells, where a_1, a_2 are positive constants. We assume that an infected cell releases the same number of virions when it dies. Thus, the viral production rate is proportional to the death rate ($a_1G(y_1)$ or $a_2G(y_2)$) of infected cells, i.e., the viral production rates are $p_1G_1(y_1)$ and $p_2G_2(y_2)$, respectively, for the two populations. Virus is assumed to be cleared at a rate δ .

2.1 Preliminaries

We assume that the functions $\varphi_i(x_i, v)$ and $G_i(y_i)$ in system (2) are always positive, differentiable, and monotonically increasing for all $x_i > 0$, $y_i > 0$ and $v > 0$. We also assume that $\varphi_i(x_i, v)$ is concave downward with respect to v , $i = 1, 2$. That is, they satisfy the following assumptions:

$$(H_1) \quad \varphi_i(0, v) = \varphi(x_i, 0) = 0, \quad \frac{\partial \varphi_i(x_i, 0)}{\partial v} > 0 \text{ for } x_i > 0 \text{ and } v > 0, \quad G_i(0) = 0, \quad G_i'(y_i) > 0 \text{ for } y_i > 0, \quad i = 1, 2.$$

$$(H_2) \quad \varphi_i(x_i, v) > 0, \quad \frac{\partial \varphi_i(x_i, v)}{\partial x_i} > 0, \quad \frac{\partial \varphi_i(x_i, v)}{\partial v} > 0 \text{ for any } x_i > 0 \text{ and } v > 0, \quad i = 1, 2.$$

(H₃) $\varphi_i(x_i, v)$ is concave downward with respect to v . This ensures that

$$\varphi_i(x_i, v) \leq v \frac{\partial \varphi_i(x_i, 0)}{\partial v}.$$

The initial condition of system (2) is given by

$$x_1(\theta) = \psi_1(\theta), \quad x_2(\theta) = \psi_2(\theta), \quad y_1(\theta) = \psi_3(\theta), \quad y_2(\theta) = \psi_4(\theta), \quad v(\theta) = \psi_5(\theta). \quad (3)$$

Here $\psi = (\psi_1, \psi_2, \psi_3, \psi_4, \psi_5)^T \in C([-\tau, 0], R^5)$, which is the Banach space of continuous functions from $[-\tau, 0]$ to R^5 equipped with the following sup-norm

$$\|\psi_j\| = \sup_{\theta \in [-\tau, 0]} \psi_j(\theta), \quad \tau = \max\{\tau_1, \tau_2\}, \quad j = 1, 2, \dots, 5.$$

By the fundamental theory of functional differential equations [19], any solution $(x_1(t), x_2(t), y_1(t), y_2(t), v(t))^T$ of system (2) exists and is differentiable for all $t > 0$. Furthermore, the state space $X = C^+ = C([-\tau, 0], R_+^5)$ is positively invariant for system (2).

Lemma 2.1 Under the above initial conditions (3), $x_1(t), y_1(t), x_2(t), y_2(t)$ and $v(t)$ are all nonnegative and bounded in X .

Proof. A similar argument as in the proof of Theorem 1 in [14] can show that any solution of system (2) with initial conditions (3) are nonnegative and bounded in X .

According to Lemma 2.1, we know that the following bounded feasible region

$$\Omega = \{(x_1, y_1, x_2, y_2, v) \in C^+ : \|x_i\| \leq x_i^0, \|y_i\| \leq M, \|v\| \leq M, \\ M > 0 \text{ is a constant}\} \subseteq X$$

is positively invariant with respect to system (2).

2.2 Equilibria and basic reproduction number

System (2) has an infection-free equilibrium point $E^0 = (x_1^0, x_2^0, 0, 0, 0)$, where $x_i^0 = \lambda_i/d_i$, $i = 1, 2$. If an infected equilibrium point $E^* = (x_1^*, x_2^*, y_1^*, y_2^*, v^*)$ exists, it must satisfy $x_i^*, y_i^*, v^* > 0$ for $i = 1, 2$, and

$$\begin{cases} 0 = \lambda_1 - d_1 x_1^* - \varphi_1(x_1^*, v^*), \\ 0 = \lambda_2 - d_2 x_2^* - \varphi_2(x_2^*, v^*), \\ 0 = e^{-\mu_1 \tau_1} \varphi_1(x_1^*, v^*) - a_1 G_1(y_1^*), \\ 0 = e^{-\mu_2 \tau_2} \varphi_2(x_2^*, v^*) - a_2 G_2(y_2^*), \\ 0 = p_1 G_1(y_1^*) + p_2 G_2(y_2^*) - \delta v^*. \end{cases} \quad (4)$$

We can show that system (2) is uniformly persistent by a similar argument as in the proof of Proposition 3.3 in ref. [20]. Together with the boundedness of the solution in the interior of the set Ω , denoted by $\text{int}\Omega$, we know that there exists a positive equilibrium point E^* of system (2) in $\text{int}\Omega$.

The dynamics of the virus infection model (2) depend on the basic reproduction number R_0 . Using the next generation method for ordinary differential equation systems in van den Driessche and Watmough [43] and for delay differential equation systems (see [14,21]), the basic reproduction number of our system is obtained as follows:

$$R_0 = \sum_{i=1}^2 \frac{p_i}{a_i \delta} \cdot \frac{\partial \varphi_i(x_i^0, 0)}{\partial v} e^{-\mu_i \tau_i}, \quad (5)$$

where $x_i^0 = \lambda_i/d_i$, $i = 1, 2$. The term p_i/a_i represents the number of virions produced by one virus-producing cell. $1/\delta$ is the lifespan of a virion. The term $\frac{\partial \varphi_i(x_i^0, 0)}{\partial v}$ denotes the maximal number of target cells that one virion can infect per unit time, and $e^{-\mu_i \tau_i}$ represents the probability of infected cells surviving to produce new virions. If there is only one population of target cells, then R_0 in (5) becomes the basic reproduction number in ref. [14].

3 Main results

In this section, we will construct Lyapunov functionals to study the global dynamics of system (2). We need the following assumptions for the nonlinear functions $\varphi(x, v)$ and $G(y)$.

(H₄) $\frac{\partial \varphi_i(x_i, 0)}{\partial v}$ is increasing with respect to $x_i > 0$, $i = 1, 2$.

(H₅) $x_i - x_i^0 - \int_{x_i^0}^{x_i} \lim_{v \rightarrow 0^+} \frac{\varphi_i(x_i^0, v)}{\varphi_i(\sigma, v)} d\sigma \rightarrow +\infty$ as $x_i \rightarrow 0^+$;

$$x_i - x_i^* - \int_{x_i^*}^{x_i} \frac{\varphi_i(x_i^*, v^*)}{\varphi_i(\sigma, v^*)} d\sigma \rightarrow +\infty \text{ as } x_i \rightarrow 0^+ \text{ or } x_i \rightarrow +\infty;$$

$$y_i - y_i^* - \int_{y_i^*}^{y_i} \frac{G_i(y_i^*)}{G_i(\sigma)} d\sigma \rightarrow +\infty \text{ as } y_i \rightarrow 0^+ \text{ or } y_i \rightarrow +\infty.$$

Theorem 3.1 Suppose that conditions (H₁) – (H₅) are satisfied. If $R_0 \leq 1$, then the infection-free equilibrium E^0 of system (2) is globally asymptotically stable.

Proof. Define a Lyapunov functional

$$L_1(t) = W_1(x_{1t}, x_{2t}, y_{1t}, y_{2t}, v_t) + W_+, \quad (6)$$

where

$$\begin{aligned} W_1 &= e^{-\mu_1 \tau_1} \left[x_1(t) - x_1^0 - \int_{x_1^0}^{x_1(t)} \lim_{v \rightarrow 0^+} \frac{\varphi_1(x_1^0, v)}{\varphi_1(\sigma, v)} d\sigma \right] + y_1(t) \\ &\quad + \alpha e^{-\mu_2 \tau_2} \left[x_2(t) - x_2^0 - \int_{x_2^0}^{x_2(t)} \lim_{v \rightarrow 0^+} \frac{\varphi_2(x_2^0, v)}{\varphi_2(\sigma, v)} d\sigma \right] + \alpha y_2(t) + \frac{a_1}{p_1} v(t), \\ W_+ &= e^{-\mu_1 \tau_1} \int_0^{\tau_1} \varphi_1(x_1(t-\theta), v(t-\theta)) d\theta + \alpha e^{-\mu_2 \tau_2} \int_0^{\tau_2} \varphi_2(x_2(t-\theta), v(t-\theta)) d\theta, \end{aligned}$$

where $\alpha = \frac{a_1 p_2}{a_1 p_1}$.

Calculating the time derivative of W_1 along the solution of system (2), we obtain

$$\begin{aligned} \dot{W}_1 \Big|_{(2)} &= e^{-\mu_1 \tau_1} \left(1 - \lim_{v \rightarrow 0^+} \frac{\varphi_1(x_1^0, v)}{\varphi_1(x_1, v)} \right) (\lambda_1 - d_1 x_1 - \varphi_1(x_1, v)) \\ &\quad + e^{-\mu_1 \tau_1} \varphi_1(x_1(t-\tau_1), v(t-\tau_1)) - a_1 G_1(y_1) \\ &\quad + \alpha e^{-\mu_2 \tau_2} \left(1 - \lim_{v \rightarrow 0^+} \frac{\varphi_2(x_2^0, v)}{\varphi_2(x_2, v)} \right) (\lambda_2 - d_2 x_2 - \varphi_2(x_2, v)) \\ &\quad + \alpha (e^{-\mu_2 \tau_2} \varphi_2(x_2(t-\tau_2), v(t-\tau_2)) - a_2 G_2(y_2)) \\ &\quad + \frac{a_1}{p_1} (p_1 G_1(y_1(t)) + p_2 G_2(y_2(t)) - \delta v(t)). \end{aligned} \quad (7)$$

Similarly,

$$\begin{aligned}
\dot{W}_+ \Big|_{(2)} &= \frac{d}{dt} \left[e^{-\mu_1 \tau_1} \int_0^{\tau_1} \varphi_1(x_1(t-\theta), v(t-\theta)) d\theta \right. \\
&\quad \left. + \alpha e^{-\mu_2 \tau_2} \int_0^{\tau_2} \varphi_2(x_2(t-\theta), v(t-\theta)) d\theta \right] \\
&= e^{-\mu_1 \tau_1} \int_0^{\tau_1} \frac{d}{dt} \varphi_1(x_1(t-\theta), v(t-\theta)) d\theta \\
&\quad + \alpha e^{-\mu_2 \tau_2} \int_0^{\tau_2} \frac{d}{dt} \varphi_2(x_2(t-\theta), v(t-\theta)) d\theta \\
&= -e^{-\mu_1 \tau_1} \int_0^{\tau_1} \frac{d}{d\theta} \varphi_1(x_1(t-\theta), v(t-\theta)) d\theta \\
&\quad - \alpha e^{-\mu_2 \tau_2} \int_0^{\tau_2} \frac{d}{d\theta} \varphi_2(x_2(t-\theta), v(t-\theta)) d\theta \\
&= e^{-\mu_1 \tau_1} (\varphi_1(x_1, v) - \varphi_1(x_1(t-\tau_1), v(t-\tau_1))) \\
&\quad + \alpha e^{-\mu_2 \tau_2} (\varphi_2(x_2, v) - \varphi_2(x_2(t-\tau_2), v(t-\tau_2))). \tag{8}
\end{aligned}$$

Using $\lambda_i = d_i x_i^0$ and $\alpha = a_1 p_2 / (a_2 p_1)$, from (7)-(8) we have

$$\begin{aligned}
\dot{L}_1(t) \Big|_{(2)} &= \dot{W}_1 + \dot{W}_+ \\
&= e^{-\mu_1 \tau_1} d_1 x_1(t) \left(\frac{x_1^0}{x_1(t)} - 1 \right) \left(1 - \lim_{v \rightarrow 0^+} \frac{\varphi_1(x_1^0, v)}{\varphi_1(x_1, v)} \right) \\
&\quad + \alpha e^{-\mu_2 \tau_2} d_2 x_2(t) \left(\frac{x_2^0}{x_2(t)} - 1 \right) \left(1 - \lim_{v \rightarrow 0^+} \frac{\varphi_2(x_2^0, v)}{\varphi_2(x_2, v)} \right) \\
&\quad + e^{-\mu_1 \tau_1} \varphi_1(x_1, v) \lim_{v \rightarrow 0^+} \frac{\varphi_1(x_1^0, v)}{\varphi_1(x_1, v)} \\
&\quad + \alpha e^{-\mu_2 \tau_2} \varphi_2(x_2, v) \lim_{v \rightarrow 0^+} \frac{\varphi_2(x_2^0, v)}{\varphi_2(x_2, v)} - \frac{\delta a_1}{p_1} v(t) \\
&= e^{-\mu_1 \tau_1} d_1 x_1(t) \left(\frac{x_1^0}{x_1(t)} - 1 \right) \left(1 - \lim_{v \rightarrow 0^+} \frac{\varphi_1(x_1^0, v)}{\varphi_1(x_1, v)} \right) \\
&\quad + \alpha e^{-\mu_2 \tau_2} d_2 x_2(t) \left(\frac{x_2^0}{x_2(t)} - 1 \right) \left(1 - \lim_{v \rightarrow 0^+} \frac{\varphi_2(x_2^0, v)}{\varphi_2(x_2, v)} \right) \\
&\quad + \frac{\delta a_1}{p_1} v(t) \left[\frac{p_1 e^{-\mu_1 \tau_1}}{\delta a_1} \frac{\varphi_1(x_1, v)}{v} \lim_{v \rightarrow 0^+} \frac{\varphi_1(x_1^0, v)}{\varphi_1(x_1, v)} \right. \\
&\quad \left. + \frac{\alpha p_1 e^{-\mu_2 \tau_2}}{\delta a_1} \frac{\varphi_2(x_2, v)}{v} \lim_{v \rightarrow 0^+} \frac{\varphi_2(x_2^0, v)}{\varphi_2(x_2, v)} - 1 \right] \tag{9}
\end{aligned}$$

The condition (H_4) is equivalent to

$$\left(\frac{x_i^0}{x_i(t)} - 1 \right) \left(1 - \frac{\frac{\partial \varphi_i(x_i^0, 0)}{\partial v}}{\frac{\partial \varphi_i(x_i, 0)}{\partial v}} \right) \leq 0, \quad i = 1, 2. \tag{10}$$

Therefore,

$$\left(\frac{x_i^0}{x_i(t)} - 1 \right) \left(1 - \lim_{v \rightarrow 0^+} \frac{\varphi_i(x_i^0, v)}{\varphi_i(x_i, v)} \right) = \left(\frac{x_i^0}{x_i(t)} - 1 \right) \left(1 - \frac{\frac{\partial \varphi_i(x_i^0, 0)}{\partial v}}{\frac{\partial \varphi_i(x_i, 0)}{\partial v}} \right) \leq 0. \tag{11}$$

Furthermore, by the concavity of $\varphi_i(x_i, v)$ with respect to v in (H_3) , we have

$$\varphi_i(x_i, v) \leq v \frac{\partial \varphi_i(x_i, 0)}{\partial v}. \quad (12)$$

Thus,

$$\begin{aligned} & \frac{p_1 e^{-\mu_1 \tau_1}}{\delta a_1} \frac{\varphi_1(x_1, v)}{v} \lim_{v \rightarrow 0^+} \frac{\varphi_1(x_1^0, v)}{\varphi_1(x_1, v)} + \frac{\alpha p_1 e^{-\mu_2 \tau_2}}{\delta a_1} \frac{\varphi_2(x_2, v)}{v} \lim_{v \rightarrow 0^+} \frac{\varphi_2(x_2^0, v)}{\varphi_2(x_2, v)} - 1 \\ &= \sum_{i=1}^2 \frac{p_i}{\delta a_i} \cdot e^{-\mu_i \tau_i} \cdot \frac{\varphi_i(x_i, v)}{v} \cdot \frac{\frac{\partial \varphi_i(x_i^0, 0)}{\partial v}}{\frac{\partial \varphi_i(x_i, 0)}{\partial v}} - 1 \\ &\leq \sum_{i=1}^2 \frac{p_i}{\delta a_i} \cdot e^{-\mu_i \tau_i} \cdot \frac{\partial \varphi_i(x_i^0, 0)}{\partial v} - 1 = R_0 - 1. \end{aligned} \quad (13)$$

From (9), (11) and (13), we obtain

$$\begin{aligned} \dot{L}_1(t) \Big|_{(2)} &\leq e^{-\mu_1 \tau_1} d_1 x_1(t) \left(\frac{x_1^0}{x_1(t)} - 1 \right) \left(1 - \lim_{v \rightarrow 0^+} \frac{\varphi_1(x_1^0, v)}{\varphi_1(x_1, v)} \right) \\ &\quad + \alpha e^{-\mu_2 \tau_2} d_2 x_2(t) \left(\frac{x_2^0}{x_2(t)} - 1 \right) \left(1 - \lim_{v \rightarrow 0^+} \frac{\varphi_2(x_2^0, v)}{\varphi_2(x_2, v)} \right) \\ &\quad + \frac{\delta a_1}{p_1} v(t) (R_0 - 1) \\ &\leq \frac{\delta a_1}{p_1} v(t) (R_0 - 1), \end{aligned} \quad (14)$$

and $\dot{L}_1 \Big|_{(2)} = 0$ if and only if $v(t) \equiv 0$ or $R_0 \equiv 1$ and $x = x_i^0$. Therefore, the maximal compact invariant set in $\{\dot{L}_1 \Big|_{(2)} = 0\}$ is the singleton $\{E^0\}$. By LaSalle Invariance Principle for delay differential equations (see [11,44]), E^0 is globally attractive. It can be further shown that E^0 is locally stable using the similar method as in Corollary 5.3.1 of ref. [11]. Therefore, E^0 is globally asymptotically stable in X .

Theorem 3.2 Suppose that conditions $(H_1) - (H_5)$ are satisfied. If $R_0 > 1$, then the infected equilibrium E^* is globally asymptotically stable.

Proof. Define a Lyapunov functional

$$L_2(t) = W_2(x_{1t}, x_{2t}, y_{1t}, y_{2t}, v_t) + W^+,$$

where

$$\begin{aligned} W_2 &= e^{-\mu_1 \tau_1} \left[x_1(t) - x_1^* - \int_{x_1^*}^{x_1(t)} \frac{\varphi_1(x_1^*, v^*)}{\varphi_1(\sigma, v^*)} d\sigma \right] + y_1(t) - y_1^* \\ &\quad - \int_{y_1^*}^{y_1(t)} \frac{G_1(y_1^*)}{G_1(\sigma)} d\sigma + \alpha e^{-\mu_2 \tau_2} \left[x_2(t) - x_2^* - \int_{x_2^*}^{x_2(t)} \frac{\varphi_2(x_2^*, v^*)}{\varphi_2(\sigma, v^*)} d\sigma \right] \\ &\quad + \alpha \left(y_2(t) - y_2^* - \int_{y_2^*}^{y_2(t)} \frac{G_2(y_2^*)}{G_2(\sigma)} d\sigma \right) + \frac{a_1}{p_1} (v(t) - v^* - v^* \ln \frac{v(t)}{v^*}) \end{aligned}$$

and

$$\begin{aligned}
W^+ &= \varphi_1(x_1^*, v^*) e^{-\mu_1 \tau_1} \int_0^{\tau_1} \left(\frac{\varphi_1(x_1(t-\theta), v(t-\theta))}{\varphi_1(x_1^*, v^*)} - 1 \right. \\
&\quad \left. - \ln \frac{\varphi_1(x_1(t-\theta), v(t-\theta))}{\varphi_1(x_1^*, v^*)} \right) d\theta \\
&\quad + \alpha \varphi_2(x_2^*, v^*) e^{-\mu_2 \tau_2} \int_0^{\tau_2} \left(\frac{\varphi_2(x_2(t-\theta), v(t-\theta))}{\varphi_2(x_2^*, v^*)} - 1 \right. \\
&\quad \left. - \ln \frac{\varphi_2(x_2(t-\theta), v(t-\theta))}{\varphi_2(x_2^*, v^*)} \right) d\theta.
\end{aligned}$$

The derivative of W_2 along the solution of system (2) is

$$\begin{aligned}
\dot{W}_2 \Big|_{(2)} &= e^{-\mu_1 \tau_1} \left(1 - \frac{\varphi_1(x_1^*, v^*)}{\varphi_1(x_1, v^*)} \right) (\lambda_1 - d_1 x_1 - \varphi_1(x_1, v)) \\
&\quad + \left(1 - \frac{G_1(y_1^*)}{G_1(y_1)} \right) (e^{-\mu_1 \tau_1} \varphi_1(x_1(t-\tau_1), v(t-\tau_1)) - a_1 G_1(y_1)) \\
&\quad + \alpha e^{-\mu_2 \tau_2} \left(1 - \frac{\varphi_2(x_2^*, v^*)}{\varphi_2(x_2, v^*)} \right) (\lambda_2 - d_2 x_2 - \varphi_2(x_2, v)) \\
&\quad + \alpha \left(1 - \frac{G_2(y_2^*)}{G_2(y_2)} \right) (e^{-\mu_2 \tau_2} \varphi_2(x_2(t-\tau_2), v(t-\tau_2)) - a_2 G_2(y_2)) \\
&\quad + a_1 G_1(y_1(t)) \left(1 - \frac{v^*}{v} \right) + \frac{a_1 p_2}{p_1} \left(1 - \frac{v^*}{v} \right) G_2(y_2(t)) \\
&\quad - \frac{a_1}{p_1} \left(1 - \frac{v^*}{v} \right) \delta v.
\end{aligned}$$

Similarly, we have

$$\begin{aligned}
\dot{W}^+ \Big|_{(2)} &= \varphi_1(x_1^*, v^*) e^{-\mu_1 \tau_1} \frac{d}{dt} \int_0^{\tau_1} \left(\frac{\varphi_1(x_1(t-\theta), v(t-\theta))}{\varphi_1(x_1^*, v^*)} - 1 \right. \\
&\quad \left. - \ln \frac{\varphi_1(x_1(t-\theta), v(t-\theta))}{\varphi_1(x_1^*, v^*)} \right) d\theta \\
&\quad + \alpha \varphi_2(x_2^*, v^*) e^{-\mu_2 \tau_2} \frac{d}{dt} \int_0^{\tau_2} \left(\frac{\varphi_2(x_2(t-\theta), v(t-\theta))}{\varphi_2(x_2^*, v^*)} - 1 \right. \\
&\quad \left. - \ln \frac{\varphi_2(x_2(t-\theta), v(t-\theta))}{\varphi_2(x_2^*, v^*)} \right) d\theta \\
&= -\varphi_1(x_1^*, v^*) e^{-\mu_1 \tau_1} \int_0^{\tau_1} \frac{d}{d\theta} \left(\frac{\varphi_1(x_1(t-\theta), v(t-\theta))}{\varphi_1(x_1^*, v^*)} - 1 \right. \\
&\quad \left. - \ln \frac{\varphi_1(x_1(t-\theta), v(t-\theta))}{\varphi_1(x_1^*, v^*)} \right) d\theta \\
&\quad - \alpha \varphi_2(x_2^*, v^*) e^{-\mu_2 \tau_2} \int_0^{\tau_2} \frac{d}{d\theta} \left(\frac{\varphi_2(x_2(t-\theta), v(t-\theta))}{\varphi_2(x_2^*, v^*)} - 1 \right. \\
&\quad \left. - \ln \frac{\varphi_2(x_2(t-\theta), v(t-\theta))}{\varphi_2(x_2^*, v^*)} \right) d\theta \\
&= e^{-\mu_1 \tau_1} (\varphi_1(x_1, v) - \varphi_1(x_1(t-\tau_1), v(t-\tau_1)))
\end{aligned}$$

$$\begin{aligned}
& + e^{-\mu_1 \tau_1} \varphi_1(x_1^*, v^*) \ln \frac{\varphi_1(x_1(t - \tau_1), v(t - \tau_1))}{\varphi_1(x_1, v)} \\
& + \alpha e^{-\mu_2 \tau_2} (\varphi_2(x_2, v) - \varphi_2(x_2(t - \tau_2), v(t - \tau_2))) \\
& + \alpha e^{-\mu_2 \tau_2} \varphi_2(x_2^*, v^*) \ln \frac{\varphi_2(x_2(t - \tau_2), v(t - \tau_2))}{\varphi_2(x_2, v)}.
\end{aligned}$$

Note that

$$\begin{aligned}
\lambda_i &= d_i x_i^* + \varphi_i(x_i^*, v^*), \quad \varphi_i(x_i^*, v^*) = e^{\mu_i \tau_i} a_i G_i(y_i^*), \quad i = 1, 2, \\
\frac{\delta a_1}{p_1} v^* &= a_1 G_1(y_1^*) + \alpha a_2 G_2(y_2^*), \\
\frac{\delta a_1}{p_1} v &= (a_1 G_1(y_1^*) + \alpha a_2 G_2(y_2^*)) \frac{v}{v^*}, \\
\alpha &= \frac{a_1 p_2}{a_2 p_1},
\end{aligned}$$

we obtain

$$\begin{aligned}
\dot{L}_2 \Big|_{(2)} &= \dot{W}_2 + \dot{W}^+ \\
&= d_1 x_1^* e^{-\mu_1 \tau_1} \left(1 - \frac{\varphi_1(x_1^*, v^*)}{\varphi_1(x_1, v^*)} \right) \left(1 - \frac{x_1}{x_1^*} \right) + e^{-\mu_1 \tau_1} \varphi_1(x_1^*, v^*) \left(1 - \frac{\varphi_1(x_1^*, v^*)}{\varphi_1(x_1, v^*)} \right) \\
&\quad + \alpha d_2 x_2^* e^{-\mu_2 \tau_2} \left(1 - \frac{\varphi_2(x_2^*, v^*)}{\varphi_2(x_2, v^*)} \right) \left(1 - \frac{x_2}{x_2^*} \right) \\
&\quad + \alpha e^{-\mu_2 \tau_2} \varphi_2(x_2^*, v^*) \left(1 - \frac{\varphi_2(x_2^*, v^*)}{\varphi_2(x_2, v^*)} \right) \\
&\quad + e^{-\mu_1 \tau_1} \varphi_1(x_1^*, v^*) \frac{\varphi_1(x_1, v)}{\varphi_1(x_1, v^*)} + \alpha e^{-\mu_2 \tau_2} \varphi_2(x_2^*, v^*) \frac{\varphi_2(x_2, v)}{\varphi_2(x_2, v^*)} \\
&\quad - e^{-\mu_1 \tau_1} \varphi_1(x_1^*, v^*) \frac{G_1(y_1^*) \varphi_1(x_1(t - \tau_1), v(t - \tau_1))}{G_1(y_1) \varphi_1(x_1^*, v^*)} + a_1 G_1(y_1^*) \\
&\quad - \alpha e^{-\mu_2 \tau_2} \varphi_2(x_2^*, v^*) \frac{G_2(y_2^*) \varphi_2(x_2(t - \tau_2), v(t - \tau_2))}{G_2(y_2) \varphi_2(x_2^*, v^*)} + \alpha a_2 G_2(y_2^*) \\
&\quad - a_1 G_1(y_1(t)) \frac{v^*}{v} - \frac{\delta a_1}{p_1} v - \alpha a_2 G_2(y_2(t)) \frac{v^*}{v} + \frac{\delta a_1}{p_1} v^* \\
&\quad + e^{-\mu_1 \tau_1} \varphi_1(x_1^*, v^*) \ln \frac{\varphi_1(x_1(t - \tau_1), v(t - \tau_1))}{\varphi_1(x_1, v)} \\
&\quad + \alpha e^{-\mu_2 \tau_2} \varphi_2(x_2^*, v^*) \ln \frac{\varphi_2(x_2(t - \tau_2), v(t - \tau_2))}{\varphi_2(x_2, v)},
\end{aligned}$$

which is equal to

$$\begin{aligned}
& e^{-\mu_1 \tau_1} d_1 x_1^* \left(1 - \frac{\varphi_1(x_1^*, v^*)}{\varphi_1(x_1, v^*)}\right) \left(1 - \frac{x_1}{x_1^*}\right) \\
& + \alpha e^{-\mu_2 \tau_2} d_2 x_2^* \left(1 - \frac{\varphi_2(x_2^*, v^*)}{\varphi_2(x_2, v^*)}\right) \left(1 - \frac{x_2}{x_2^*}\right) \\
& + a_1 G_1(y_1^*) \left(1 - \frac{G_1(y_1^*) \varphi_1(x_1(t - \tau_1), v(t - \tau_1))}{G_1(y_1) \varphi_1(x_1^*, v^*)}\right) \\
& + \ln \frac{G_1(y_1^*) \varphi_1(x_1(t - \tau_1), v(t - \tau_1))}{G_1(y_1) \varphi_1(x_1^*, v^*)} \\
& + a_1 G_1(y_1^*) \left(1 - \frac{v^* G_1(y_1(t))}{v G_1(y_1^*)} + \ln \frac{v^* G_1(y_1(t))}{v G_1(y_1^*)}\right) \\
& + a_1 G_1(y_1^*) \left(1 - \frac{\varphi_1(x_1^*, v^*)}{\varphi_1(x_1, v^*)} + \ln \frac{\varphi_1(x_1^*, v^*)}{\varphi_1(x_1, v^*)}\right) \\
& + a_1 G_1(y_1^*) \left(1 - \frac{v \varphi_1(x_1, v^*)}{v^* \varphi_1(x_1, v)} + \ln \frac{v \varphi_1(x_1, v^*)}{v^* \varphi_1(x_1, v)}\right) \\
& + a_1 G_1(y_1^*) \left(-1 - \frac{v}{v^*} + \frac{v \varphi_1(x_1, v^*)}{v^* \varphi_1(x_1, v)} + \frac{\varphi_1(x_1, v)}{\varphi_1(x_1, v^*)}\right) \\
& + \alpha a_2 G_2(y_2^*) \left(1 - \frac{G_2(y_2^*) \varphi_2(x_2(t - \tau_2), v(t - \tau_2))}{G_2(y_2) \varphi_2(x_2^*, v^*)}\right) \\
& + \ln \frac{G_2(y_2^*) \varphi_2(x_2(t - \tau_2), v(t - \tau_2))}{G_2(y_2) \varphi_2(x_2^*, v^*)} \\
& + \alpha a_2 G_2(y_2^*) \left(1 - \frac{v^* G_2(y_2(t))}{v G_2(y_2^*)} + \ln \frac{v^* G_2(y_2(t))}{v G_2(y_2^*)}\right) \\
& + \alpha a_2 G_2(y_2^*) \left(1 - \frac{\varphi_2(x_2^*, v^*)}{\varphi_2(x_2, v^*)} + \ln \frac{\varphi_2(x_2^*, v^*)}{\varphi_2(x_2, v^*)}\right) \\
& + \alpha a_2 G_2(y_2^*) \left(1 - \frac{v \varphi_2(x_2, v^*)}{v^* \varphi_2(x_2, v)} + \ln \frac{v \varphi_2(x_2, v^*)}{v^* \varphi_2(x_2, v)}\right) \\
& + \alpha a_2 G_2(y_2^*) \left(-1 - \frac{v}{v^*} + \frac{v \varphi_2(x_2, v^*)}{v^* \varphi_2(x_2, v)} + \frac{\varphi_2(x_2, v)}{\varphi_2(x_2, v^*)}\right). \tag{15}
\end{aligned}$$

By the concavity and monotonicity of the function $\varphi_i(x_i, v)$ with respect to v , we have

$$\begin{aligned}
& -1 - \frac{v}{v^*} + \frac{v \varphi_i(x_i, v^*)}{v^* \varphi_i(x_i, v)} + \frac{\varphi_i(x_i, v)}{\varphi_i(x_i, v^*)} \\
& = \left(\frac{\varphi_i(x_i, v^*)}{\varphi_i(x_i, v)} - 1\right) \left(\frac{v}{v^*} - \frac{\varphi_i(x_i, v)}{\varphi_i(x_i, v^*)}\right) \\
& \leq 0. \quad i = 1, 2.
\end{aligned}$$

From the monotonicity of $\varphi_i(x_i, v)$ with respect to x_i , we have

$$\left(1 - \frac{x_i}{x_i^*}\right) \left(1 - \frac{\varphi_i(x_i^*, v^*)}{\varphi_i(x_i, v^*)}\right) \leq 0, \quad i = 1, 2.$$

Let

$$g(z) = z - 1 - \ln z, \quad z \in R^+.$$

It is nonnegative for any $z > 0$, and $g(z) = 0$ if and only if $z = 1$. Therefore, we

obtain

$$\begin{aligned}
\dot{L}_2 \Big|_{(2)} &= e^{-\mu_1 \tau_1} d_1 x_1^* \left(1 - \frac{\varphi_1(x_1^*, v^*)}{\varphi_1(x_1, v^*)} \right) \left(1 - \frac{x_1}{x_1^*} \right) \\
&\quad + \alpha e^{-\mu_2 \tau_2} d_2 x_2^* \left(1 - \frac{\varphi_2(x_2^*, v^*)}{\varphi_2(x_2, v^*)} \right) \left(1 - \frac{x_2}{x_2^*} \right) \\
&\quad - a_1 G_1(y_1^*) g \left(\frac{G_1(y_1^*) \varphi_1(x_1(t - \tau_1), v(t - \tau_1))}{G_1(y_1) \varphi_1(x_1^*, v^*)} \right) \\
&\quad - a_1 G_1(y_1^*) \left(g \left(\frac{v^* G_1(y_1)}{v G_1(y_1^*)} \right) + g \left(\frac{\varphi_1(x_1^*, v^*)}{\varphi_1(x_1, v^*)} \right) + g \left(\frac{v \varphi_1(x_1, v^*)}{v^* \varphi_1(x_1, v)} \right) \right) \\
&\quad + a_1 G_1(y_1^*) \left(\frac{\varphi_1(x_1, v^*)}{\varphi_1(x_1, v)} - 1 \right) \left(\frac{v}{v^*} - \frac{\varphi_1(x_1, v)}{\varphi_1(x_1, v^*)} \right) \\
&\quad - \alpha a_2 G_2(y_2^*) g \left(\frac{G_2(y_2^*) \varphi_2(x_2(t - \tau_2), v(t - \tau_2))}{G_2(y_2) \varphi_2(x_2^*, v^*)} \right) \\
&\quad - \alpha a_2 G_2(y_2^*) \left(g \left(\frac{v^* G_2(y_2)}{v G_2(y_2^*)} \right) + g \left(\frac{\varphi_2(x_2^*, v^*)}{\varphi_2(x_2, v^*)} \right) + g \left(\frac{v \varphi_2(x_2, v^*)}{v^* \varphi_2(x_2, v)} \right) \right) \\
&\quad + \alpha a_2 G_2(y_2^*) \left(\frac{\varphi_2(x_2, v^*)}{\varphi_2(x_2, v)} - 1 \right) \left(\frac{v}{v^*} - \frac{\varphi_2(x_2, v)}{\varphi_2(x_2, v^*)} \right). \tag{16}
\end{aligned}$$

Thus, $\dot{L}_2 \Big|_{(2)} \leq 0$ for all (x_1, x_2, y_1, y_2, v) . The largest invariant subset of $\{\dot{L}_2 \Big|_{(2)} = 0\}$ is $\{E^*\}$. By LaSalle Invariance Principle and a similar argument in the proof of Theorem 3.1, we show that E^* is globally asymptotically stable.

4 A general model with n target cell populations

In this section, we extend the model with two target cell populations to include n populations. The model becomes a $(2n + 1)$ -dimensional system with n time delays.

$$\begin{cases} \dot{x}_i(t) = \lambda_i - d_i x_i(t) - \varphi_i(x_i(t), v(t)), \\ \dot{y}_i(t) = e^{-\mu_i \tau_i} \varphi_i(x_i(t - \tau_i), v(t - \tau_i)) - a_i G_i(y_i), \quad i = 1, 2, \dots, n. \\ \dot{v}(t) = \sum_{i=1}^n p_i G_i(y_i(t)) - \delta v(t). \end{cases} \tag{17}$$

This system describes the interaction of virus with n classes of target cells. The state variables x_i, y_i, v and all the parameters of system (17) have the same biological meaning as those in Section 2.

The initial condition for system (17) is given by

$$x_i(\theta) = \varphi_i(\theta), \quad y_i(\theta) = \xi_i(\theta), \quad v(\theta) = \gamma(\theta), \quad i = 1, 2, \dots, n. \tag{18}$$

Here $\varphi = (\varphi_1, \dots, \varphi_n, \xi_1, \dots, \xi_n, \gamma)^T \in C([- \tau, 0], R_+^{2n+1})$, the Banach space of continuous functions from $[- \tau, 0]$ to R_+^{2n+1} , where $\tau = \max\{\tau_1, \dots, \tau_n\}$.

Similarly, the solutions of system (17) are all nonnegative and bounded. System (17) has an infection-free equilibrium

$$P^0 = (x_1^0, \dots, x_n^0, y_1^0, \dots, y_n^0, 0), \text{ where } x_i^0 = \frac{\lambda_i}{d_i}, y_i^0 = 0, i = 1, 2, \dots, n.$$

When $\tilde{R}_0 > 1$, it has an infected equilibrium $P^* = (\tilde{x}_1, \dots, \tilde{x}_n, \tilde{y}_1, \dots, \tilde{y}_n, \tilde{v})$, where

$$\tilde{R}_0 = \sum_{i=1}^n \frac{p_i}{\delta a_i} \cdot \frac{\partial \varphi_i(x_i^0, 0)}{\partial v} e^{-\mu_i \tau_i}. \quad (19)$$

For the general model, we have the following global stability results for the steady states P^0 and P^* by constructing Lyapunov functionals.

Theorem 4.1 Suppose that the conditions $(H_1) - (H_5)$ hold.

(i) If $\tilde{R}_0 \leq 1$, then the infection-free equilibrium P^0 of system (17) is globally asymptotically stable.

(ii) If $\tilde{R}_0 > 1$, then the infected equilibrium P^* of system (17) is globally asymptotically stable.

Proof. (i) Let

$$\tilde{L}_1(t) = U_1(x_{1t}, \dots, x_{nt}, y_{1t}, \dots, y_{nt}, v_t) + U_+,$$

where

$$U_1 = \sum_{i=1}^n \alpha_i e^{-\mu_i \tau_i} \left(x_i(t) - x_i^0 - \int_{x_i^0}^{x_i(t)} \lim_{v \rightarrow 0^+} \frac{\varphi_i(x_i^0, v)}{\varphi_i(\sigma, v)} d\sigma \right) + \sum_{i=1}^n \alpha_i y_i(t) + \frac{a_1}{p_1} e^{n_1 \omega_1} v(t), \quad (20)$$

$$U_+ = \sum_{i=1}^n \alpha_i e^{-\mu_i \tau_i} \int_0^{\tau_i} \varphi_i(x_i(t - \theta), v(t - \theta)) d\theta, \quad (21)$$

and $\alpha_i = \frac{a_1 p_i}{a_i p_1}$.

Using $\lambda_i = d_i x_i^0$ and the concavity of $\varphi_i(x_i, v)$ with respect to v , we have

$$\begin{aligned} & \frac{p_i e^{-\mu_i \tau_i}}{\delta a_i} \cdot \frac{\varphi_i(x_i, v)}{v} \cdot \lim_{v \rightarrow 0^+} \frac{\varphi_i(x_i^0, v)}{\varphi_i(x_i, v)} \\ &= \frac{p_i}{\delta a_i} \cdot \frac{\varphi_i(x_i, v)}{v} \cdot \frac{\frac{\partial \varphi_i(x_i^0, 0)}{\partial v}}{\frac{\partial \varphi_i(x_i, 0)}{\partial v}} \cdot e^{-\mu_i \tau_i} \\ &\leq \frac{p_i}{\delta a_i} \cdot \frac{\partial \varphi_i(x_i^0, 0)}{\partial v} \cdot e^{-\mu_i \tau_i}. \end{aligned} \quad (22)$$

From (H_4) , we get

$$\begin{aligned}
& \left(\frac{x_i^0}{x_i} - 1 \right) \left(1 - \lim_{v \rightarrow 0^+} \frac{\varphi_i(x_i^0, v)}{\varphi_i(x_i, v)} \right) \\
&= \left(\frac{x_i^0}{x_i} - 1 \right) \left(1 - \frac{\frac{\partial \varphi_i(x_i^0, 0)}{\partial v}}{\frac{\partial \varphi_i(x_i, 0)}{\partial v}} \right) \\
&\leq 0.
\end{aligned} \tag{23}$$

Thus, it follows from (20) and (21) that

$$\begin{aligned}
\tilde{L}_1(t) \Big|_{(17)} &= \dot{U}_1 + \dot{U}_+ \\
&= \sum_{i=1}^n \alpha_i e^{-\mu_i \tau_i} d_i x_i \left(\frac{x_i^0}{x_i} - 1 \right) \left(1 - \lim_{v \rightarrow 0^+} \frac{\varphi_i(x_i^0, v)}{\varphi_i(x_i, v)} \right) \\
&\quad + \sum_{i=1}^n \alpha_i e^{-\mu_i \tau_i} \varphi_i(x_i, v) \lim_{v \rightarrow 0^+} \frac{\varphi_i(x_i^0, v)}{\varphi_i(x_i, v)} - \frac{\delta a_1}{p_1} v(t) \\
&= \sum_{i=1}^n \alpha_i e^{-\mu_i \tau_i} d_i x_i \left(\frac{x_i^0}{x_i} - 1 \right) \left(1 - \lim_{v \rightarrow 0^+} \frac{\varphi_i(x_i^0, v)}{\varphi_i(x_i, v)} \right) \\
&\quad + \frac{\delta a_1}{p_1} v(t) \left[\sum_{i=1}^n \frac{\alpha_i p_1 e^{-\mu_i \tau_i}}{\delta a_1} \cdot \frac{\varphi_i(x_i, v)}{v} \cdot \lim_{v \rightarrow 0^+} \frac{\varphi_i(x_i^0, v)}{\varphi_i(x_i, v)} - 1 \right] \\
&= \sum_{i=1}^n \alpha_i e^{-\mu_i \tau_i} d_i x_i \left(\frac{x_i^0}{x_i} - 1 \right) \left(1 - \lim_{v \rightarrow 0^+} \frac{\varphi_i(x_i^0, v)}{\varphi_i(x_i, v)} \right) \\
&\quad + \frac{\delta a_1}{p_1} v(t) \left[\sum_{i=1}^n \frac{p_i}{\delta a_i} \cdot \frac{\varphi_i(x_i, v)}{v} \cdot \frac{\frac{\partial \varphi_i(x_i^0, 0)}{\partial v}}{\frac{\partial \varphi_i(x_i, 0)}{\partial v}} \cdot e^{-\mu_i \tau_i} - 1 \right] \\
&\leq \sum_{i=1}^n \alpha_i e^{-\mu_i \tau_i} d_i x_i \left(\frac{x_i^0}{x_i} - 1 \right) \left(1 - \lim_{v \rightarrow 0^+} \frac{\varphi_i(x_i^0, v)}{\varphi_i(x_i, v)} \right) \\
&\quad + \frac{\delta a_1}{p_1} v(t) (\tilde{R}_0 - 1).
\end{aligned} \tag{24}$$

By LaSalle Invariance Principle and a similar argument in the proof Theorem 3.1, we show that the infection-free equilibrium P^0 is globally asymptotically stable.

(ii) Define

$$\tilde{L}_2(t) = U_2(x_{1t}, \dots, x_{nt}, y_{1t}, \dots, y_{nt}, v_t) + U^+,$$

where

$$\begin{aligned}
U_2 &= \sum_{i=1}^n \alpha_i e^{-\mu_i \tau_i} \left(x_i(t) - \tilde{x}_i - \int_{\tilde{x}_i}^{x_i(t)} \lim_{v \rightarrow 0^+} \frac{\varphi_i(\tilde{x}_i, \tilde{v})}{\varphi_i(\sigma, \tilde{v})} d\sigma \right) \\
&\quad + \sum_{i=1}^n \alpha_i \left(y_i(t) - \tilde{y}_i - \int_{\tilde{y}_i}^{y_i(t)} \frac{G_i(\tilde{y}_i)}{G_i(\sigma)} d\sigma \right) \\
&\quad + \frac{a_1}{p_1} \left(v(t) - \tilde{v} - \tilde{v} \ln \frac{v(t)}{\tilde{v}} \right),
\end{aligned} \tag{25}$$

$$U^+ = \sum_{i=1}^n \alpha_i \varphi_i(\tilde{x}_i, \tilde{v}) e^{-\mu_i \tau_i} \int_0^{\tau_i} \left(\frac{\varphi_i(x_i(t-\theta), v(t-\theta))}{\varphi_i(x_i, v)} - 1 - \ln \frac{\varphi_i(x_i(t-\theta), v(t-\theta))}{\varphi_i(x_i, v)} \right) d\theta. \tag{26}$$

The derivative of $\tilde{L}_2$ along the solution of system (17) is

$$\begin{aligned}
\dot{\tilde{L}}_2(t) \Big|_{(17)} &= \dot{U}_2 + \dot{U}^+ \\
&= \sum_{i=1}^n \alpha_i e^{-\mu_i \tau_i} d_i \tilde{x}_i \left(1 - \frac{\varphi_i(\tilde{x}_i, \tilde{v})}{\varphi_i(x_i, \tilde{v})} \right) \left(1 - \frac{x_i}{\tilde{x}_i} \right) \\
&\quad - \sum_{i=1}^n \alpha_i a_i G_i(\tilde{y}_i) g \left(\frac{G_i(\tilde{y}_i) \varphi_i(x_i(t - \tau_i), v(t - \tau_i))}{G_i(y_i) \varphi_i(\tilde{x}_i, \tilde{v})} \right) \\
&\quad - \sum_{i=1}^n \alpha_i a_i G_i(\tilde{y}_i) g \left(\frac{\tilde{v} g_i(y_i)}{v G_i(\tilde{y}_i)} \right) \\
&\quad - \sum_{i=1}^n \alpha_i a_i G_i(\tilde{y}_i) \left(g \left(\frac{\varphi_i(\tilde{x}_i, \tilde{v})}{\varphi_i(x_i, \tilde{v})} \right) + g \left(\frac{v \varphi_i(x_i, \tilde{v})}{\tilde{v} \varphi_i(x_i, v)} \right) \right) \\
&\quad + \sum_{i=1}^n \alpha_i a_i G_i(\tilde{y}_i) g \left(\frac{\varphi_i(x_i, \tilde{v})}{\varphi_i(x_i, v)} - 1 \right) \left(\frac{v}{\tilde{v}} - \frac{\varphi_i(x_i, v)}{\varphi_i(x_i, \tilde{v})} \right).
\end{aligned} \tag{27}$$

The following three conditions are satisfied.

(a)

$$\begin{aligned}
&-1 - \frac{v}{\tilde{v}} + \frac{v \varphi_i(x_i, \tilde{v})}{\tilde{v} \varphi_i(x_i, v)} + \frac{\varphi_i(x_i, v)}{\varphi_i(x_i, \tilde{v})} \\
&= \left(\frac{\varphi_i(x_i, \tilde{v})}{\varphi_i(x_i, v)} - 1 \right) \left(\frac{v}{\tilde{v}} - \frac{\varphi_i(x_i, v)}{\varphi_i(x_i, \tilde{v})} \right) \\
&\leq 0, \quad i = 1, 2, \dots, n.
\end{aligned} \tag{28}$$

(b) By the monotonicity of $\varphi_i(x_i, v)$ with respect to x_i , we have

$$\left(1 - \frac{x_i}{\tilde{x}_i} \right) \left(1 - \frac{\varphi_i(\tilde{x}_i, \tilde{v})}{\varphi_i(x_i, \tilde{v})} \right) \leq 0, \quad i = 1, 2, \dots, n. \tag{29}$$

(c) $g(z) = z - 1 - \ln z \geq 0$, $z \in R^+$ and $g(z) = 0$ if and only if $z = 1$.

It follows from (27)-(29) that $\dot{\tilde{L}}_2(t) \Big|_{(17)} \leq 0$ for all $x_1, \dots, x_n, y_1, \dots, y_n, v > 0$. Again by LaSalle Invariance Principle, we know that P^* is globally asymptotically stable.

5 Numerical simulation

In this section, we perform computer simulation of system (2) with specific rates of viral infection and cell death. We choose $\varphi_i(x_i(t), v(t)) = \beta_i x_i(t) v(t)$ and $G_i(y_i) = y_i$, $i = 1, 2$, which are widely used in viral dynamic models. In Fig. 1, we showed a case in which viral infection is predicted to die out. We chose $\lambda_1 = \lambda_2 = 1.0 \times 10^4$ cells $\text{ml}^{-1} \text{day}^{-1}$, $d_1 = 0.01 \text{ day}^{-1}$, $d_2 = 0.01 \text{ day}^{-1}$, $\beta_1 = 2.4 \times 10^{-8} \text{ ml day}^{-1}$,

$\beta_2 = 2.4 \times 10^{-9}$ ml day $^{-1}$, $\delta = 23$ day $^{-1}$, $\mu_1 = 0.05$ day $^{-1}$, $\mu_2 = 0.02$ day $^{-1}$, $a_1 = 0.5$ day $^{-1}$, $a_2 = 0.1$ day $^{-1}$, $\tau_1 = 0.25$ days, $\tau_2 = 0.5$ days, $p_1 = 150$ per cell per day, and $p_2 = 50$ per cell per day. Most of them were chosen from existing literature [37,39,41]. The viral infection rate and viral production rate include the effect of antiretroviral therapy, which can block viral infection or production. With these parameters, the basic reproductive number is $R_0 \approx 0.361 < 1$. By Theorem 3.1, the infection-free equilibrium E^0 is globally asymptotically stable. Fig. 1(a) and (b) show the dynamics of cells and viral load, respectively. When we change some parameters to $\beta_1 = 2.4 \times 10^{-7}$ ml day $^{-1}$, $\beta_2 = 2.4 \times 10^{-8}$ ml day $^{-1}$, $p_2 = 8$ per cell per day, and let the other parameters remain unchanged, the basic reproductive number becomes $R_0 \approx 3.17 > 1$. It follows from Theorem 3.2 that the infected steady state E^* is globally asymptotically stable. The dynamics of cells and viral load are shown in Fig. 2.

To study the influence of time delays (τ_1 and τ_2) on the dynamics of viral load, we considered the following two cases. In Fig. 3(a), we increased τ_1 (i.e., $\tau_1 = 0.25, 1$, or 2 days) but fixed $\tau_2 = 1$ day and other parameter values as in Fig. 2. We found that increasing the time delay does not have a visible influence on the magnitude of the viral peak or the steady state, but postpones the time to reach the viral load peak. If we increased τ_2 (i.e., $\tau_2 = 1, 5$, or 10 days) but fixed $\tau_1 = 0.25$ days, we did not observe any change in the viral load (see Fig. 3(b)). This is because of the minor contribution from infected macrophages to the total viral load. We will further investigate the relative contribution to viral production from the two cell populations below.

To evaluate the relative contribution to viral load from infected CD4 $^+$ T cells and macrophages, we plotted two ratios

$$\frac{p_1 y_1(t)}{p_1 y_1(t) + p_2 y_2(t)} \text{ and } \frac{p_2 y_1(t)}{p_1 y_1(t) + p_2 y_2(t)},$$

which represent the proportion of viral production from productively infected CD4 $^+$ T cells and macrophages, respectively. Parameter values were chosen to be the same as those used in Fig. 3(b). In Fig. 4(a), τ_2 was fixed to be 1 day and τ_1 increased from 0.25 to 2 days. In Fig. 4(b), τ_1 was fixed to be 0.25 days and τ_2 increased from 0.5 to 5 days. In both cases, viral production from infected CD4 $^+$ T cells accounts for the majority of viral load. When τ_1 increases from 0.25 to 2 days, the contribution from infected CD4 $^+$ T cells becomes less. However, it is still much higher than the contribution from macrophages. Thus, the plot of relative contributions does not have a difference at the steady state level (Fig. 4(a)). When τ_2 increases from 0.5 to 5 days, the contribution from infected macrophages becomes less. This explains why a larger value of τ_2 leads to a lower contribution from macrophages and a higher contribution from CD4 $^+$ T cells (see Fig. 4(b)).

6 Conclusion and discussion

Most of existing mathematical models of HIV infection study the viral infection and production in $CD4^+$ T cells. However, HIV can also infect other cells such as macrophages. In this paper, we study the global stability of the equilibrium points of an HIV model with two target cell populations. The model includes general nonlinear rates of viral infection and cell death. Time delays between viral entry into cells and production of new virions are also included in the model. We derived the basic reproductive number of the model and performed the global stability analysis of the steady states. The infection-free steady state is globally asymptotically stable when the basic reproductive number is less than or equal to 1, and the infected steady state is globally asymptotically stable when the basic reproductive number is greater than 1. Our analysis extends some existing results in the literature. For example, the global stability was analyzed for a model with one target cell population [14]. If the general nonlinear rate of infected cell death is chosen to be $a_i G_i(y_i) = a_i y_i$ and the rate of viral infection is chosen to be $\varphi_i(x_i, v) = \beta_i x_i v$, $\beta_i x_i v / (1 + v)$, or $\beta_i x_i v / (1 + m_i x_i + b_i v)$, then the model studied here becomes those in refs. [7,8].

Mathematical analysis of the model suggests that the virus is predicted to be completely cleared from infected individuals if the basic reproductive number is reduced to below 1 by antiretroviral therapy (which can reduce the infection rate and viral production rate). However, current antiretroviral therapy cannot eradicate the virus. The major obstacle to viral elimination is the existence of latently infected $CD4^+$ T cells, which cannot be affected by treatment or the immune response but can be activated to produce new virions. Mathematical models have been constructed to study the dynamics of low-level viral load persistence and latently infected cells (see the review in ref. [39]). Models have also been developed to study the emergence of drug resistance during treatment [38] and HIV immune responses [3], which are not included here. The major goal of this paper is to study the dynamics of HIV infection in multiple target cell populations.

We also extend the model with two target cell populations to a general model with n populations. Similar global stability results are obtained for the general model. Numerical simulations are performed to illustrate the stability results. The simulation also shows that virus is mainly produced from infected $CD4^+$ T cells. Thus, the time delay between viral entry into macrophages and viral production does not have an influence in the dynamics of viral load. The delay between viral entry into $CD4^+$ T cells does not change the magnitude of the viral peak and the steady-state viral load, but postpones the time to reach the viral peak. This is consistent with the results in ref. [33] in which a model including two time delays (one is the intracellular delay and the other is the time for the adaptive immune response to emerge) was analyzed and fit to patient data during primary HIV infection.

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Fig. 1. Dynamics of system (2) with $\varphi_i(x_i(t), v(t)) = \beta_i x_i(t) v(t)$ and $G_i(y_i) = y_i$. The basic reproductive number is $R_0 \approx 0.361 < 1$. The virus is predicted to be cleared and uninfected cells increase to the pre-infection level.

Fig. 2. Dynamics of system (2) with $\varphi_i(x_i(t), v(t)) = \beta_i x_i(t)v(t)$ and $G_i(y_i) = y_i$. The basic reproductive number is $R_0 \approx 3.17 > 1$. Viral infection is established and the viral load converges to a steady state.

Fig. 3. Effect of time delays on the viral load change in model (2). (a) τ_2 is fixed at 1 day and τ_1 increases from 0.25 to 2 days. (b) τ_1 is fixed at 0.25 days and τ_2 increases from 1 to 10 days. Other parameters are the same as those in Fig. 2.

Fig. 4. The relative contribution to viral production from infected CD4+ T cells and macrophages. (a) $\tau_2 = 1$ day is fixed and τ_1 increases from 0.25 to 2 days (the thick line represents the case of $\tau_1 = 2$ days). (b) $\tau_1 = 0.25$ days is fixed and τ_2 increases from 0.5 to 5 days (the thick line is the case of $\tau_2 = 5$ days). Other parameters used are the same as those in Fig. 2.