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Analysis and control of an age-structured HIV-1 epidemic model with different transmission mechanisms

Xiaoyan Wang[1*], Junyuan Yang[2] and Fei Xu[3]

*Correspondence:
xywang00@126.com
[1]School of Information Management, Shanxi University of Finance and Economics, Taiyuan, Shanxi 030006, P.R. China
Full list of author information is available at the end of the article

Abstract

In this paper, we propose a within-host HIV-1 epidemic model with cell-to-virus and cell-to-cell transmission. By mathematical analysis, we obtain the basic reproduction number $\mathcal{R}_0$, which determines the viral persistence and the basic reproduction number $\mathcal{R}_0^{cc}$ with respect to cell-to-cell transmission which is not strong enough, *i.e.*, it is less than 1. If the basic reproduction number is less than 1, then the viral-free steady state E_0 is globally asymptotically stable, which is proved by fluctuation lemma and comparison method; if $\mathcal{R}_0 > 1$ is greater than 1, the endemic steady state E^* is globally asymptotically stable, which is proved by constructing the Lyapunov functional. Antiretroviral therapy is implemented to suppress the viral replication. Protease inhibitors for cell-to-cell transmission play an important role in controlling cell-to-cell infection. Under some circumstances, the effects of the cell-to-cell infection process are more sensitive than those of cell-to-virus transmission.

Keywords: infection age; antiretroviral therapy; cell-to-cell transmission; Lyapunov functional

1 Introduction

Since the discovery of the first case of acquired immunodeficiency syndrome (AIDS), the disease has been in a major concern in global health. Nearly 43 million peopled are infected by human immunodeficiency virus (HIV) and about 29 million people died due to AIDS. Such accumulative cases are still increasing each year. Many infected individuals are receiving highly active antiretroviral therapy (HAART), an effective treatment that suppresses HIV-1 replication and progression. Even though the treatment does not lead to permanent cure of HIV infection, it extends the life of HIV-1-infected individuals and individuals under such treatment survive in asymptomatic chronic stages with low viral load. In particular, HAART is able to suppress viral replication to undetectable levels (<50 HIV-1 RNA copies/ml) in adherent patients [1, 2]. The process of in-host HIV infection is as follows. After entering the $CD4^+$ T cells, HIV viruses reversely transcribe from RNA to DNA and integrate viral DNA into the hosts DNA. Then infected $CD4^+$ T cells release viruses through transcription and translation. Because of the comprehensive infection process for HIV, applying antiretroviral drugs at different infection stages may have different treatment effects.

Mathematical models [3–9] have been used to investigate the within-host viral dynamics to explore the effects of drug treatment. In order to discover the effects of drug treatment applied to the infectives at different infection stages, Lloyd [3] proposed a within-host model with multiple infection stages and find that treatment at initial infection stage is much more sensitive than treatment at other stages. The model is described as follows:

$$\begin{cases} \frac{dx(t)}{dt} = \lambda_x - \mu x(t) - \beta x(t)v(t), \\ \frac{dy_1(t)}{dt} = \beta x(t)v(t) - \delta_1 y_1(t), \\ \frac{dy_2(t)}{dt} = q_1\delta_1 y_1(t) - \delta_2 y_2(t), \\ \vdots \\ \frac{dy_n(t)}{dt} = q_{n-1}\delta_{n-1} y_{n-1}(t) - \delta_n y_n(t), \\ \frac{dv(t)}{dt} = \sum_{i=1}^{n} p_i y_j(t) - \mu v(t). \end{cases} \tag{1.1}$$

Here $x(t)$ denotes the number of target cells, $y_i(t)$, $i = 1, 2, \ldots, n$ denote the number of productively infected cells at different infection phases and $v(t)$ denotes the number of free virus particles. $CD4^+$ T lymphoblasts have birth rate λ. Viruses are released from HIV infected cells at rate p_j, and cleared at rate μ; δ_j is the transfer rate from the jth stage to the $j + 1$th stage and q_j is the chance that a cell leaves the jth stage and enters the $j + 1$ stage. The model focuses on single target cell-lymphoblasts. Recent investigations show that macrophages are another type of target cells during the viral attack. Sedaghat *et al.* in [4] constructed a mathematical model with two targets and two transmission phases to investigate the decay dynamics of HIV-1. They focused on the effects of drug treatment applied to the patient at the last infectious stage. The authors show that drug applied at the last stage has better effects than that applied at other stages. Such a conclusion is in good agreement with results from clinical experiment. Then Wang *et al.* [5] proposed a mathematical model to study viral decay dynamics with multiple stages and analyze its long-term dynamical behaviors. The model is given by

$$\begin{cases} \frac{dx_i(t)}{dt} = \lambda_i - \mu_i x_i(t) - \beta_i x_i(t)v(t), \\ \frac{\partial y_i(t,a)}{\partial t} + \frac{\partial y_i(t,a)}{\partial a} = -\delta_i(a)y_i(t,a), \\ y_i(t,a) = h_i(x_i(t), v(t)), \\ \frac{dv(t)}{dt} = \sum_{i=1}^{n} \int_0^\infty p_i(a)y_i(t,a)\,da - cv(t). \end{cases} \tag{1.2}$$

All parameters in (1.2) have the same biological meaning as those in (1.1). (Parameters in system (1.1) and (1.2) may have different subscripts.) Here $x_i(t)$ and $y_i(t,a)$ denote the amount of target uninfected $CD4^+$ cells and infected cells, respectively. h_i is the incidence rate function satisfying some conditions (see assumptions from (H1) to (H4) [5]). The authors showed that if the therapy is 100% effective, then applying the drug at late infectious stage results in a faster decay of viremia.

Dixit and Perelson [10] studied the decay of viral load of individuals infected with HIV under monotherapy. They showed that such scenario can exhibit complicated dynamical behaviors depending on the relative magnitudes of the pharmacokinetic, intracellular, and intrinsic viral dynamic time-scales. The investigation indicated that exponential decay dynamics can be considered as a special case of HAART. Dixit *et al.* [11] constructed a mathematical model with increased accuracy to investigate HIV dynamics when the drug

is not 100% effective. Mathematical models have also been proposed to consider the life cycle of virus [12–14] and immune effects [15–17]. The authors compared therapeutic efficacy of medications applied at different infectious stages on the reduction of viremia. They showed that multiple stages, intracellular delay and different target cells have significant effects on viral dynamics.

Motivated by these works, we propose a mathematical model incorporating the three factors mentioned above to investigate the dynamics of life cycle of virus. We assume the multiple stages don't satisfy the Markov process. This indicates that their distributions are not exponential and they satisfy a general distribution. The mathematical model is proposed as follows:

$$\begin{cases} \frac{dx_i(t)}{dt} = \lambda_i - \mu_i x_i(t) - \beta_i x_i(t)v(t) - x_i(t)\int_0^\infty q_i(a)y_i(t,a)\,da, \\ \frac{\partial y_i(t,\tau)}{\partial t} + \frac{\partial y_i(t,\tau)}{\partial \tau} = -\delta_i(\tau)y_i(t,\tau), \\ y_i(t,0) = \beta_i x_i(t)v(t) + x_i(t)\int_0^\infty q_i(a)y_i(t,a)\,da, \\ \frac{dv(t)}{dt} = \sum_{i=1}^n \int_0^\infty p_i(\tau)y_i(t,\tau)\,d\tau - cv, \end{cases} \tag{1.3}$$

with initial condition

$$x_i(0) = x_{i0} \geq 0, \qquad y_i(0,\tau) = y_{i0}(\tau) \in L^1_+, \qquad v(0) = v_0 \geq 0,$$

where L^1_+ is the set of integrable functions from $(0,\infty)$ into $\mathbb{R}_+ = (0,\infty)$. Here $y_i(t,\tau)$ is the density of target cells at time t with infection age τ, respectively. The disease-related death rate $\delta_i(\tau)$ is a function of the infection age τ and all other disease parameters have the same meaning as those in (1.2).

Define the phase space for system (1.3) as $X = (\mathbb{R}_+)^n \times (L^1_+)^n \times \mathbb{R}_+$ with the norm given by

$$\left\| \left(x_i(t), y_i(t,\cdot), v(t)\right) \right\|_X = \sum_{i=1}^n \left(\left|x_i(t)\right| + \int_0^\infty y_i(t,a)\,da \right) + \left|v(t)\right|.$$

It follows from [18–20] that we can define a solution semi-flow $\Phi : (\mathbb{R}_+)^n \times (L^1_+)^n \times \mathbb{R}_+ \to X$ of (1.3) for $t \in \mathbb{R}_+$ and $(x_{i0}, y_{i0}, v_0) \in X$ as

$$\Phi\left(t, \left(x_{i0}, y_{i0}(\cdot), v_0\right)\right) = \left(x_i(t), y_i(t,\cdot), v(t)\right). \tag{1.4}$$

Actually, standard existence and uniqueness results follows from a similar process in Theorem 1.1 in [21].

For the continuability of the semi-flow $\Phi(t, (x_{i0}, y_{i0}(\cdot), v_0))$, we assume that the initial condition satisfies the compatibility condition

$$y_{i0}(0) = \beta_i x_{i0} v_0 + x_{i0} \int_0^\infty q_i(a)y_{i0}(a)\,da.$$

In order to get some theoretical results, we make the following assumptions.

Assumption 1.1 For all $i \in \mathbb{N}_n = \{1, 2, \ldots, n\}$

(1) $\lambda_i, \mu_i, \beta_i, c > 0$;

(2) $q_i(a), p_i(a) \in L_+^\infty$, that is, there exist essential upper bounds q_i^+ and p_i^+ such that

$$q_i^+ = \operatorname{ess.}\sup_{a\in[0,\infty)} q_i(a), \qquad p_i^+ = \operatorname{ess.}\sup_{a\in[0,\infty)} p_i(a);$$

(3) $q_i(a)$ is bounded and uniformly continuous from $[0,\infty)$ to $[0,+\infty)$;
(4) there exists $\underline{\delta_i} > 0$ such that $\delta_i(\tau) \geq \underline{\delta_i}$ for $\tau \in \mathbb{R}_+$ and $i \in \mathbb{N}_n$.

Under Assumption 1.1, we can obtain the nonnegativity of system (1.3).

Proposition 1.1 *If $x_{i0} \geq 0$, $y_{i0}(a) \in L_+^1$, $v_0 \geq 0$, system* (1.3) *has nonnegative solution.*

Proof Suppose $(x_i(t), y_i(t,\tau), v(t)) \in X$ is a solution of system (1.3) with nonnegative initial condition. For convenience, define $z_i(t) = y_i(t,0)$. Integrating the second and third equations of (1.3) with initial condition yields

$$y_i(t,\tau) = \begin{cases} z_i(t-\tau)\pi_i(\tau), & t \geq \tau, \\ y_{i0}(\tau - t)\frac{\pi_i(\tau)}{\pi_i(\tau - t)}, & t < \tau. \end{cases} \tag{1.5}$$

Substituting $y_i(t,\tau)$ into $z_i(t)$, we have

$$\begin{aligned} z_i(t) = {} & \beta x_i(t) v(t) + x_i(t)\int_0^t q_i(a) z_i(t-a)\pi_i(a)\,da \\ & + x_i(t)\int_t^\infty q_i(a) y_{i0}(a-t)\frac{\pi_i(a)}{\pi_i(a-t)}\,da. \end{aligned} \tag{1.6}$$

Solving the first equation of system (1.3), we obtain

$$x_i(t) = x_{i0} e^{-\mu_i t - \int_0^t z_i(s)\,ds} + \lambda_i \int_0^t e^{-\mu_i(t-s) - \int_s^t z_i(\xi)\,d\xi}\,ds. \tag{1.7}$$

By the nonnegativity of the initial condition and Assumption 1.1, $x_i(t)$ is nonnegative.

Next, we will show that $z_i(t)$ and $v(t)$ are nonnegative for all $t \in \mathbb{R}_+$. To achieve this goal, we define

$$s = \min\left\{\inf\left\{t \in \mathbb{R}_+ | z_i(t) < 0\right\}, \inf\left\{t \in \mathbb{R}_+ | v(t) < 0, \text{for some } i \in \mathbb{N}_n\right\}\right\}.$$

Suppose

$$s = \inf\left\{t \in \mathbb{R}_+ | z_i(t) < 0, \text{for some } i \in \mathbb{N}_n\right\}.$$

It follows from (1.6) that $v(s) < 0$, which results in a contradiction with $v(s) \geq 0$ since $s < \inf\{t \in \mathbb{R}_+ | v(t) < 0\}$. Hence, $z_i(t)$ is nonnegative for all $t \in \mathbb{R}_+$. Otherwise,

$$s = \inf\left\{t \in \mathbb{R}_+ | v(t) < 0\right\}.$$

This implies that, for all $t \in (0,s)$ $v(t) > 0$, $z_i(s) > 0$, $v(s) = 0$ and $v'(s) \leq 0$. From the last equation of system (1.3), it follows that

$$v'(s) = \sum_{i=1}^n \int_0^\infty p_i(a) z_i(s-a)\pi(a)\,da \geq 0.$$

This implies that $s > \inf\{t \in \mathbb{R}_+ | \nu(t) < 0\}$, which is in contradiction to the definition of s. Therefore, $\nu(t)$ is also nonnegative for all $t \in \mathbb{R}_+$. □

Let $L(t) = \sum_{i=1}^{n}(x_i(t) + \int_0^\infty y_i(t,a)\,da)$. Then

$$L'(t) = \sum_{i=1}^{n}\lambda_i - \sum_{i=1}^{n}\left[\mu_i x_i + \int_0^\infty \delta_i(a)y_i(t,a)\,da\right].$$

This implies that $L(t) \le \sum_{i=1}^{n}\frac{\lambda_i}{\mu}$, $\mu = \min_{i\in\mathbb{N}}\{\mu_i, \underline{\delta}_i\}$. Then by the last equation of (1.3), $\nu(t) \le \sum_{i=1}^{n}\frac{p_i^+\lambda_i}{c\mu}$. Therefore, we can define the following set:

$$\Gamma = \left\{(x_i, y_i(\cdot), \nu) \in X : \sum_{i=1}^{n}\left(x_i(t) + \int_0^\infty y_i(t,a)\,da\right) \le \sum_{i=1}^{n}\frac{\lambda_i}{\mu}, \nu(t) \le \sum_{i=1}^{n}\frac{p_i^+\lambda_i}{c\mu}\right\}. \quad (1.8)$$

It is easy to verify that Γ is positively invariant, *i.e.*, $\Phi(t, (x_{i0}, y_{i0}(\cdot), \nu_0)) \in \Gamma$ for all $t > 0$ if $(x_{i0}, y_{i0}(\cdot), \nu_0) \in \Gamma$. This also means that Φ is point dissipative and hence there is a bounded set attracting all solutions in Γ.

For convenience, define

$$\Lambda \triangleq \max\left\{\sum_{i=1}^{n}\frac{\lambda_i}{\mu}, \sum_{i=1}^{n}\frac{p_i^+\lambda_i}{c\mu}\right\},$$
$$Q_i(t) = \int_0^\infty q_i(a)y_i(t,a)\,da, \qquad P_i(t) = \int_0^\infty p_i(a)y_i(t,a).$$

From what has been discussed, we have the following prior estimates.

Lemma 1.2 *Let Assumption* 1.1 *hold. For* $t \ge 0$ *and* $(x_{i0}, y_{i0}(\cdot), \nu_0) \in \Gamma$, *the following estimates hold*:

(1) $x_i(t) \le \Lambda$, $\int_0^\infty y_i(t,a)\,da \le \Lambda$, $\nu(t) \le \Lambda$.
(2) $Q_i(t) \le q_i^+\Lambda$, $P_i(t) \le p_i^+\Lambda$.
(3) $z_i(t) \le \bar{\beta}\Lambda^2$, $\bar{\beta}_i = \beta + q_i^+$.

Obviously, system (1.3) is an infinite system. Based on Theorem 4.2 of Chapter IV in [22], we need to show the relative compactness of the orbit $\{\Phi(t, (x_{i0}, y_{i0}(\cdot), \nu_0)) | t \in \mathbb{R}_+\}$ in Γ. From Proposition 3.13 in [23], $\Phi(t, (x_{i0}, y_{i0}(\cdot), \nu_0)) : \mathbb{R}_+ \times \Gamma \to \Gamma$ can be decomposed into two operators defined by

$$\begin{aligned}\hat{\Phi}\big(t, (x_{i0}, y_{i0}(\cdot), \nu_0)\big) &= \big(0, \hat{y}_i(t,\cdot), 0\big),\\ \tilde{\Phi}\big(t, (x_{i0}, y_{i0}(\cdot), \nu_0)\big) &= \big(x_i(t), \tilde{y}_i(t,\cdot), \nu(t)\big),\end{aligned} \quad (1.9)$$

where

$$\begin{aligned}\tilde{y}_i(t,\tau) &= \begin{cases} y_i(t,\tau) & \text{for } 0 \le \tau \le t,\\ 0 & \text{for } t < \tau,\end{cases}\\ &= \begin{cases} z_i(t)\pi_i(\tau) & \text{for } 0 \le \tau \le t,\\ 0 & \text{for } t < \tau,\end{cases}\end{aligned} \quad (1.10)$$

and

$$\hat{y}_i(t,\tau) = y_i(t,\tau) - \tilde{y}_i(t,\tau) = \begin{cases} 0 & \text{for } 0 \le \tau \le t, \\ y_{i0}(\tau - t)\frac{\pi_i(\tau)}{\pi_i(\tau - t)} & \text{for } t < \tau. \end{cases} \tag{1.11}$$

Then $\Phi = \hat{\Phi} + \tilde{\Phi}$.

Lemma 1.3 (Proposition 3.13, [23]) *Let* Φ, Γ, $\tilde{\Phi}$, $\hat{\Phi}$ *be defined by* (1.4), (1.8) *and* (1.9), *respectively. Suppose* $\tilde{\Phi}$ *and* $\hat{\Phi}$ *satisfy the following properties*:

(1) *For any* $(x_{i0}, y_{i0}(\cdot), \nu_0) \in \Gamma$, *there exists a function* $\theta : \mathbb{R}_+ \times \mathbb{R}_+ \to \mathbb{R}_+$ *such that for any* $r > 0$ $\lim_{t\to+\infty} \theta(t, r) = 0$ *with* $\|(x_{i0}, y_{i0}(\cdot), \nu_0)\|_\Gamma \le r$, *then* $\|\Phi(t, (x_{i0}, y_{i0}(\cdot), \nu_0))\|_\Gamma \le \theta(t, r)$.

(2) *For* $t \ge 0$ *and* $(x_{i0}, y_{i0}(\cdot), \nu_0) \in \Gamma$, $\hat{\Phi}(t, (x_{i0}, y_{i0}(\cdot), \nu_0))$ *maps any bounded set of* Γ *into compact closure in* Γ.

Then Φ *has a compact closure in* Γ.

From (2) and (3) of Assumption 1.1 and Lemma 1.2, it follows that $x_i(t)$ and $\nu(t)$ have Lipschitz features with Lipschitz coefficients denoted by L_{x_i} and L_ν. With the assistance of Proposition 5 in [24] and Proposition 2.3 in [25], $Q_i(t)$ and $P_i(t)$ are Lipschitz continuous with Lipschitz coefficients denoted by L_{P_i} and L_{Q_i}. Combining these Lipschitz characters with Lemma 3.2.3 in [26], we can show that the semi-flow Φ is asymptotically smooth.

Proposition 1.4 *Let* $\Phi(t, (x_{i0}, y_{i0}(\cdot), \nu_0))$ *be defined by* (1.4). *The solution semi-flow* Φ *of* (1.3) *in* Γ *is asymptotically smooth.*

Proof Let C be any bounded set in Γ. For all $(x_{i0}, y_{i0}(\cdot), \nu_0) \in C$, $\Phi(t, (x_{i0}, y_{i0}(\cdot), \nu_0)) = (x_i(t), y_i(t, \cdot), \nu(t))$ is a solution of system (1.3). Using (1.11), we obtain

$$\begin{aligned} \left\|\hat{\Phi}\left(t, (x_{i0}, y_{i0}, \nu_0)\right)\right\|_\Gamma &= \sum_{i=1}^{n} \left\|\hat{y}_i(t, \cdot)\right\|_1 \\ &= \sum_{i=1}^{n} \int_t^\infty y_{i0}(a - t)\frac{\pi_i(a)}{\pi_i(a - t)}\, da \\ &= \sum_{i=1}^{n} \int_0^\infty y_{i0}(a)\frac{\pi_i(a + t)}{\pi_i(a)}\, da \\ &\le \sum_{i=1}^{n} e^{-\delta t} \int_0^\infty y_{i0}(a)\, da \\ &= \sum_{i=1}^{n} e^{-\delta t} \|y_{i0}\|_1 \\ &\le \sum_{i=1}^{n} e^{-\delta t} \left\|(x_{i0}, y_{i0}, \nu_0)\right\|_\Gamma, \end{aligned}$$

where $\delta = \min_{i\in\mathbb{N}}\{\underline{\delta}_i\}$ and $\|\cdot\|$ is the standard norm on L^1. We note that if $\|(x_{i0}, y_{i0}, \nu_0)\|_\Gamma < r$ then $\|\hat{\Phi}(t, (x_{i0}, y_{i0}, \nu_0))\|_\Gamma \le \theta(t, r) \to 0$ as $t \to +\infty$. This implies that (1) of Lemma 1.3 holds.

Next, we need to show that $\tilde{y}_i(t,a)$ remains in a pre-compact subset of L^1_+ that is independent of $(x_{i0}, y_{i0}(\cdot), \nu_0) \in \Gamma$. This can be proven by verifying the following four conditions of Lemma 3.2.3 in [26].

(i) The supremum of $\int_0^\infty \tilde{y}_i(t,a)\,da$ is finite;
(ii) $\lim_{u\to+\infty} \int_u^\infty \tilde{y}_i(a,t)\,da = 0$;
(iii) $\lim_{h\to 0^+} |\tilde{y}_i(t,a+h) - \tilde{y}_i(t,a)|\,da = 0$;
(iv) $\lim_{h\to 0^+} \int_0^h \tilde{y}_i(t,a)\,da = 0$.

It follows from (3) of Lemma 1.2 that

$$\tilde{z}_i(t) = \tilde{y}_i(t,0) \le \bar{\beta}_i \Lambda^2 \triangleq L_{y_i}.$$

Then $y_i(t,a) = z_i(t-a)\pi_i(a) \le L_{y_i} e^{-\delta_i a}$. Conditions (i), (ii) and (iv) immediately hold by the boundedness of $\tilde{y}_i(t,\cdot)$ for $t \in \mathbb{R}_+$. In what follows, we demonstrate that the condition (iii) is also satisfied. With the help of Proposition 6 in [24], $z_i(t)$ is also a Lipschitz function with Lipschitz coefficient L_{z_i}. For all $h \in (0,t)$,

$$\begin{aligned}
&\left\|\tilde{y}_i(t,\cdot) - \tilde{y}_i(t,\cdot+h)\right\|_1 \\
&= \int_0^\infty \left|\tilde{y}_i(t,a) - \tilde{y}_i(t,a+h)\right| da \\
&= \int_0^{t-h} \left|z_i(t-a-h)\pi_i(a+h) - z_i(t-a)\pi_i(a)\right| da + \int_{t-h}^{t} z_i(t-a)\pi_i(a)\,da \\
&\le \int_0^{t-h} z_i(t-a-h)\left|\pi_i(a+h) - \pi_i(a)\right| da + L_{y_i} h \\
&\quad + \int_0^{t-h} \left|z(t-a-h) - z(t-a)\right|\pi_i(a)\,da \\
&\le L_{y_i} \int_0^{t-h} \left|\pi_i(a+h) - \pi_i(a)\right| da + L_{y_i} h + L_{z_i} h \int_0^{t-h} \pi_i(a)\,da \\
&\le \left(2L_{y_i} + L_{z_i}(t-h)\right)h,
\end{aligned}$$

where we use the fact $\int_0^{t-h} |\pi_i(a+h) - \pi_i(a)|\,da \le h$. By the definitions of L_{y_i} and L_{z_i}, they depend on Λ, which is dependent on the set C, but not on $(x_{i0}, y_{i0}(\cdot), \nu_0)$. This inequality holds for any $(x_{i0}, y_{i0}(\cdot), \nu_0) \in C$, and hence condition (iii) holds directly. Therefore, $y_i(t,\cdot)$ remains in a pre-compact subset C^{y_i} of $L^1_+(0,+\infty)$. It follows that $\Phi(t,C) \subseteq [0,\Lambda] \times C^{y_i} \times [0,\Lambda]$ has a compact closure in Γ. From what has been discussed, it follows from Lemma 1.3 that $\Phi(t,(x_{i0}, y_{i0}(\cdot), \nu_0))$ is asymptotically smooth. This completes the proof. □

The rest of this paper is organized as follows. In Section 2, we establish the existence and local stability of the steady states of (1.3). Results on global dynamics of system (1.3) are presented in Section 3. Section 4 gives the numerical simulations to illustrate the theoretical results. Conclusions and discussions are presented in Section 5.

2 Existence and local stability of steady states

Before investigating the dynamics of system (1.3), we present some definitions. The survival probability of an infected cell at infection age τ during the infectious period is given

by

$$\pi_j(\tau) = e^{-\int_0^\tau \delta_j(s)\,ds}, \quad j \in \mathbb{N}_n.$$

The total size of the viral particles and the total transmission probability with respect to the jth target cells are defined by

$$K_j = \int_0^\infty p_j(a)\pi_j(a)\,da, \qquad M_j = \int_0^\infty q_j(a)\pi_j(a)\,da, \quad j \in \mathbb{N}_n.$$

In order to estimate the transmission route with respect to cell-to-cell infection, we define the basic reproduction number as

$$\mathcal{R}_{i0}^{\mathrm{cc}} = \frac{\lambda_i}{\mu_i} M_i, \quad i \in \mathbb{N}_n. \tag{2.1}$$

$\mathcal{R}_{i0}^{\mathrm{cc}}$ is used to evaluate the ability of the ith infected cell infecting the target cells during its infectious period.

In order to obtain the condition for the existence of an endemic steady state, we define the basic reproduction number as

$$\mathcal{R}_0 = \sum_{i=1}^{n} \frac{\beta_i \frac{\lambda_i}{\mu_i} K_i}{c(1 - \frac{\lambda_i}{\mu_i} M_i)}. \tag{2.2}$$

From the expression of (2.2), it follows that $\mathcal{R}_0^{\mathrm{cc}} = \max_{i\in\mathbb{N}_n}\{\mathcal{R}_{i0}^{\mathrm{cc}}\} < 1$, which implies that the transmission ability associated with cell-to-cell is not strong enough. In epidemiology, the basic reproduction number $\mathcal{R}_0$ gives the average number of cases that one typical free virus generates, if introduced into a susceptible population, over its whole infectious period.

Theorem 2.1 *Let $\mathcal{R}_0^{\mathrm{cc}} < 1$ hold. If $\mathcal{R}_0 < 1$, then the only steady state is the viral-free steady state E_0; if $\mathcal{R}_0 > 1$, then besides the virus-free steady state E_0, there exists an endemic steady state E^*.*

Proof Let $(\bar{x}_i, \bar{y}_i(\cdot), \bar{v})$ be a steady state of system (1.3), and then it satisfies the following equations:

$$\begin{cases} 0 = \lambda_i - \mu_i \bar{x}_i - \beta_i \bar{x}_i \bar{v} - x_i \int_0^\infty q_i(a)\overline{y_i(a)}\,da, \\ \frac{d\overline{y_i(\tau)}}{d\tau} = -\delta_i(\tau)\overline{y_i(\tau)}, \\ \overline{y_i(0)} = \beta_i \bar{x} \bar{v} + x_i \int_0^\infty q_i(a)\overline{y_i(a)}\,da, \\ 0 = \sum_{i=1}^n \int_0^\infty p_i(a)\overline{y_i(a)}\,da - c\bar{v}. \end{cases} \tag{2.3}$$

By the second and third equations of (2.3), one obtains

$$\overline{y_i(a)} = \overline{y_i(0)}\pi_i(a), \quad i \in \mathbb{N}_n.$$

It follows from the first equation of (2.3) that

$$\bar{x}_i = \frac{\lambda_i - \overline{y_i(0)}}{\mu_i}, \quad i \in \mathbb{N}_n.$$

By the third equation of (2.3), we obtain

$$\overline{y_i(0)} = \big(\beta_i \bar{v} + \overline{y_i(0)} M_i\big)\bar{x}_i, \tag{2.4}$$

indicating that

$$\overline{y_i(0)} = \frac{-(1 - \frac{\lambda_i}{\mu_i} M_i + \frac{\beta_i}{\mu_i}\bar{v}) \pm \sqrt{(1 - \frac{\lambda_i}{\mu_i} M_i + \frac{\beta_i}{\mu_i}\bar{v})^2 + \frac{4\beta_i\lambda_i}{\mu_i^2} M_i \bar{v}}}{\frac{2M_i}{\mu_i}}, \quad i \in \mathbb{N}_n.$$

It is easy to see that there is only one positive solution to (2.4). Substituting the positive solution into the last equation of (2.3) yields

$$g(\bar{v}) \triangleq \sum_{i=1}^{n} \overline{y_i(0)} K_i - c\bar{v}. \tag{2.5}$$

Note that $g(0) = 0$ and $g(+\infty) < 0$. Furthermore,

$$\left.\frac{dg(\bar{v})}{d\bar{v}}\right|_{\bar{v}=0} = \sum_{i=1}^{n} \frac{\beta_i \frac{\lambda_i}{\mu_i} K_i}{1 - \frac{\lambda_i}{\mu_i} M_i} - c.$$

Obviously, $g(\bar{v}) = 0$ has a unique positive solution if and only if $\mathcal{R}_0 > 1$. Then system (1.3) admits a unique endemic steady state $E^* = (\bar{x}_i, \overline{y_i(0)}\pi_i(\tau), \bar{v})$. □

In what follows, we study the local stability of the steady states. The steady state is locally (asymptotically) stable if all eigenvalues of the corresponding characteristic equations have negative real parts and it is unstable if at least one eigenvalue has a positive real part (see [18]).

Theorem 2.2 *Suppose $\mathcal{R}_0^{cc} < 1$. If $\mathcal{R}_0 < 1$, then the virus-free steady state E_0 is locally asymptotically stable and if $\mathcal{R}_0 > 1$, the unique endemic steady state E^* is locally asymptotically stable.*

Proof Linearizing system (1.3) at virus-free steady state E_0, we obtain the associated characteristic equation

$$\begin{cases} 0 = -(\lambda + \mu_i)x_i - \beta_i x_i^0 v - x_i^0 \int_0^\infty q_i(a) y_i(a)\,da, \\ \frac{dy_i(\tau)}{d\tau} = -(\lambda + \delta_i(\tau)) y_i(\tau), \\ y_i(0) = \beta_i x_i^0 v + x_i^0 \int_0^\infty q_i(a) y_i(a)\,da, \\ 0 = \sum_{i=1}^{n} \int_0^\infty p_i(a) y_i(a)\,da - cv. \end{cases} \tag{2.6}$$

For convenience, denote

$$\widehat{K_j(\lambda)} = \int_0^\infty p_j(a)\pi_j(a)e^{-\lambda a}\,da, \qquad \widehat{M_j(\lambda)} = \int_0^\infty q_j(a)\pi_j(a)e^{-\lambda a}\,da, \quad j \in \mathbb{N}.$$

It follows from the second and the third equations of (2.6) that $y_i(a) = y_i(0)\pi_i(a)e^{-\lambda a}$. By the first and the last equations of (2.6), we have

$$x_i^0 = \frac{-y_i(0)}{\lambda + \mu_i}, \qquad \nu = \frac{\sum_{i=1}^n y_i(0)\widehat{K_i(\lambda)}}{c}.$$

Then we substitute them into the third equation to obtain

$$y_i(0) = \frac{\beta_i x_i^0 \sum_{i=1}^n y_i(0)\widehat{K_i(\lambda)}}{c} + y_i(0)x_i^0\widehat{M_i(\lambda)}.$$

Thus, we have

$$y_i(0) = \frac{\beta_i x_i^0 \sum_{i=1}^n y_i(0)\widehat{K_i(\lambda)}}{c(1 - x_i^0\widehat{M_i(\lambda)})}. \tag{2.7}$$

Multiplying $\widehat{K_i(\lambda)}$ on both sides of (2.7) and summing up from 1 to n yield

$$\Theta(y) = \sum_{i=1}^n \frac{\beta_i x_i^0\widehat{K_i(\lambda)}}{c(1 - x_i^0\widehat{M_i(\lambda)})}\Theta(y), \tag{2.8}$$

where $\Theta(y) = \sum_{i=1}^n y_i(0)\widehat{K_i(\lambda)}$. If $\Theta(y) \neq 0$, then we cancel $\Theta(y)$ on both sides of (2.7) and obtain the following characteristic equation:

$$\sum_{i=1}^n \frac{\beta_i x_i^0\widehat{K_i(\lambda)}}{c(1 - x_i^0\widehat{M_i(\lambda)})} = 1. \tag{2.9}$$

Since $\mathcal{R}_0^{cc} < 1$ for all $i \in \mathbb{N}$, we claim that all roots of (2.9) have negative real parts. Otherwise, let λ_0 be a root of (2.9) with $\mathrm{Re}(\lambda_0) \geq 0$. We notice that the module of the left hand side of (2.9) is smaller than $\mathcal{R}_0$. This leads to a contradiction when $\mathcal{R}_0 < 1$. If $\Theta(y) = 0$, then it follows from (2.7) that $y_i(0) = 0$. Substituting it into the first equation of system (2.6), we obtain $\lambda = -\mu < 0$. Therefore, the virus-free steady state E_0 is locally asymptotically stable when $\mathcal{R}_0 < 1$.

Similarly, linearizing system (1.3) at the endemic steady state $\bar{E^*} = (x_i^*, y_i^*(\cdot), \nu^*(\cdot))$ yields the following characteristic equation:

$$\begin{vmatrix} b_1 & -\beta_1 x_1^*\frac{\widehat{K_2(\lambda)}}{c} & \cdots & -\beta_1 x_1^*\frac{\widehat{K_n(\lambda)}}{c} \\ -\beta_2 x_2^*\frac{\widehat{K_1(\lambda)}}{c} & b_2 & \cdots & -\beta_2 x_2^*\frac{\widehat{K_1(\lambda)}}{c} \\ -\beta_n x_n^*\frac{\widehat{K_1(\lambda)}}{c} & -\beta_n x_n^*\frac{\widehat{K_2(\lambda)}}{c} & \cdots & b_n \end{vmatrix} = 0, \tag{2.10}$$

where $b_i = 1 - \beta_i x_i^*\frac{\widehat{K_i(\lambda)}}{c} + \frac{y_i^*(0)}{x_i^*(\lambda+\mu_i)} - x_i^*\widehat{M_i(\lambda)}$. Equation (2.10) is equivalent to the following equation:

$$\left(1 + \frac{y_1^*(0)}{x_1^*(\lambda + \mu_1)} - x_1^*\widehat{M_1(\lambda)}\right)\left(1 - \sum_{i=1}^n \frac{\beta_i x_i^*\widehat{K_i(\lambda)}}{c(1 + \frac{y_i^*(0)}{x_i^*(\lambda+\mu_i)} - x_i^*\widehat{M_i(\lambda)})}\right) = 0. \tag{2.11}$$

The characteristic roots of (2.11) are determined by

$$1 + \frac{y_1^*(0)}{x_1^*(\lambda + \mu_1)} - x_1^* \widehat{M_1(\lambda)} = 0 \tag{2.12}$$

and

$$1 = \sum_{i=1}^{n} \frac{\beta_i x_i^* \widehat{K_i(\lambda)}}{c(1 + \frac{\tilde{y}_i(0)}{x_i^*(\lambda+\mu_i)} - x_i^* \widehat{M_i(\lambda)})}. \tag{2.13}$$

Next, we show that (2.12) and (2.13) have no eigenvalues with nonnegative real parts. By way of contradiction, we assume that (2.12) has one eigenvalue λ_0 with $\mathrm{Re}(\lambda_0) \geq 0$. Then it follows from the positivity of the endemic steady state E^* that

$$\left| 1 + \frac{y_1^*(0)}{x_1^*(\lambda_0 + \mu_1)} - x_1^* \widehat{M_1(\lambda_0)} \right| \geq \left| 1 - x_1^* \widehat{M_1(\lambda_0)} \right| > 0. \tag{2.14}$$

This implies that (2.9) has no characteristic roots with positive real parts.

On the other hand, the right hand side of (2.13) is

$$\left| \sum_{i=1}^{n} \frac{\beta_i x_i^* \widehat{K_i(\lambda_0)}}{c(1 + \frac{y_i^*(0)}{x_i^*(\lambda+\mu_i)} - x_i^* \widehat{M_i(\lambda_0)})} \right| < \left| \sum_{i=1}^{n} \frac{\beta_i x_i^* \widehat{K_i(\lambda_0)}}{c(1 - x_i^* \widehat{M_i(\lambda_0)})} \right| \leq \left| \sum_{i=1}^{n} \frac{\beta_i x_i^* K_i}{c(1 - x_i^* M_i)} \right| = 1,$$

which leads to a contradiction with (2.13). From what has been discussed, the endemic steady state E^* is locally asymptotically stable if $\mathcal{R}_0 > 1$ and $\mathcal{R}_0^{\mathrm{cc}} < 1$. □

3 Global stability analysis

In this section, we perform the global stability analysis of steady states. Such analysis characterizes the dynamical behaviors of system (1.3) and provides insight into the virus dynamics. This is helpful for us to develop reasonable antiviral therapy against the disease. The global dynamic of system (1.3) is established by employing the fluctuation lemma in [20] and constructing the Lyapunov functional. First, we will show the attractivity of the viral-free steady state E_0. For convenience, we denote

$$\limsup_{t \to +\infty} f(t) = f^{\infty}, \qquad \liminf_{t \to +\infty} f(t) = f_{\infty}.$$

Theorem 3.1 *Suppose $\mathcal{R}_0^{\mathrm{cc}} < 1$. If $\mathcal{R}_0 < 1$, then the virus-free steady state $E_0 = (x_i^0, 0, 0)$ is globally asymptotically stable.*

Proof With the help of the first equation of (1.3), together with the positivity of the solution of system (1.3), we obtain $x_i(t) \leq x_i^0$ for t large enough. Borrowing (1.5), together with the third equation of (1.3), we have

$$\begin{aligned} z_i(t) &= \beta_i x_i(t) v(t) + x_i \int_0^t q_i(a) z_i(t-a) \pi(a)\, da \\ &\quad + x_i \int_t^{\infty} q_i'(a) z_{i0}(a-t) \frac{\pi_i(a)}{\pi_i(a-t)}\, da. \end{aligned} \tag{3.1}$$

Then we take super limitation on both sides of (3.1) to obtain

$$z^\infty \le \beta_i x_i^0(t)v^\infty + x_i^0 \int_0^\infty q_i(a)\pi_i(a)\,da z^\infty.$$

It follows from $\mathcal{R}_0^{cc} < 1$ and (3) of Assumption 1.1 that

$$z^\infty \le \frac{\beta_i x_i^0(t)v^\infty}{1 - x_i^0 Q_i}. \tag{3.2}$$

From the last equation of (1.3) and the fluctuation lemma [20], we can take a time sequence t_n such that $v(t_n) = v^\infty$ and $v'(t_n) \to 0$ as $t_n \to \infty$ and obtain

$$\begin{aligned} v^\infty &\le \frac{\sum_{i=1}^n \int_0^\infty p_i(a) z^\infty \pi_i(a)\,da}{c} \\ &\le \frac{\sum_{i=1}^n \int_0^\infty p_i(a)\pi_i(a)\,da \frac{\beta_i x_i^0}{1 - x_i^0 M_i}}{c} v^\infty \\ &= \mathcal{R}_0 v^\infty. \end{aligned} \tag{3.3}$$

Inequality (3.3) implies that $v^\infty \to 0$ as $t \to \infty$ when $\mathcal{R}_0 < 1$. It follows from (3.2) that $z_i(t) \to 0$ as t goes to infinity. Using (1.5) again, we have $y_i(t,a) \to 0$, when t is large enough. By Fluctuate Lemma again, we can choose a time sequence $\{s_n\}$ such that $\liminf_{n\to\infty} x_i(s_n) = x_{i\infty}$ and $\lim_{n\to\infty} x_i'(s_n) = 0$. Then

$$0 \ge \lambda_i - \beta_i x_{i\infty} v_\infty - x_{i\infty}\|\beta_i'\| y_{i\infty} - \mu x_{i\infty} = \lambda_i - \mu x_{i\infty}.$$

This implies that $x_i^0 \le x_{i\infty} \le x_i^\infty \le x_i^0$. Therefore, $\lim_{t\to\infty} x_i(t) = x_i^0$. From what has been discussed, E_0 is a global attractor if $\mathcal{R}_0 < 1$ and $\mathcal{R}_0^{cc} < 1$. □

Second, we will give the persistence of system (1.3). It follows from Proposition 1.4 that the orbit $\Phi(t, (x_{i0}, y_{i0}(\cdot), v_0)) \in \Gamma$ is relative compact. Define $\rho : \Gamma \to \mathbb{R}_+$ as

$$\rho\big(x_i(t), y_i(t,\cdot), v(t)\big) = \beta_i v + \int_0^\infty q_i(a) y_i(t,a)\,da \quad \text{for } \big(x_i(t), y_i(t,\cdot), v(t)\big) \in \Gamma.$$

Let

$$\Gamma_0 = \big\{\big(x_{i0}, y_{i0}(\cdot), v_0\big) \in \Gamma : t_0 \in \mathbb{R}_+ \text{ s.t. } \rho\big(\Phi\big(t_0, \big(x_{i0}, y_{i0}(\cdot), v_0\big)\big)\big) > 0\big\}.$$

Obviously, if $(x_{i0}, y_{i0}(\cdot), v_0) \in \Gamma \setminus \Gamma_0$, then $(x_i(t), y_i(t,\cdot), v(t)) \to E_0$ as $t \to \infty$.

Definition 3.1 ([27]) For $(x_{i0}, y_{i0}, v_0) \in \Gamma_0$, if there exists an $\varepsilon > 0$, independent of the initial conditions, such that $\limsup_{t\to\infty} \rho(\Phi(t, (x_{i0}, y_{i0}(\cdot), v_0))) > \varepsilon$, then (1.3) is said to be uniformly weakly ρ-persistent; while if there exists a positive ε such that $\liminf_{t\to\infty} \rho(\Phi(t, (x_{i0}, y_{i0}(\cdot), v_0))) > \varepsilon$, then (1.3) is said to be uniformly strongly ρ-persistent.

In order to prove the persistence of system (1.3) (see [27, Theorem 4.2]), we divided the proof process into two steps: Step 1, we show that system (1.3) is uniformly weakly ρ-persistent; Step 2, by the relative compactness of the orbit $\Phi(t,(x_{i0},y_{i0}(\cdot),\nu_0))$, system (1.3) is uniformly strongly ρ-persistent.

Proposition 3.2 *Suppose* $\mathcal{R}_0^{cc} < 1$. *If* $\mathcal{R}_0 > 1$, *then system* (1.3) *is uniformly weakly* ρ-*persistent*.

Proof For any $\varepsilon_0 > 0$, define

$$x_i^{\varepsilon_0} = \frac{\lambda_i}{\mu_i + \varepsilon_0} - \varepsilon_0.$$

Since $\mathcal{R}_0 > 1$, there exists an $\varepsilon_0 > 0$ such that

$$\sum_{i=1}^{n} \frac{\beta_i x_i^{\varepsilon_0} K_i}{1 - x^{\varepsilon_0} M_i} > 1. \tag{3.4}$$

By way of contradiction, there exists $(x_{i0}, y_{i0}(\cdot), \nu_0) \in \Gamma_0$ with

$$\limsup_{t\to\infty} \rho\big(\Phi\big(t,\big(x_{i0},y_{i0}(\cdot),\nu_0\big)\big)\big) \le \frac{\varepsilon_0}{2}.$$

Thus there exists $t_0 \in \mathbb{R}_+$ such that

$$\rho\big(\Phi\big(t,\big(x_{i0},y_{i0}(\cdot),\nu_0\big)\big)\big) \le \varepsilon_0 \quad \text{for } t \ge t_0.$$

Without loss of generality, we can assume that $t_0 = 0$. Then, for $t \ge 0$, together with the definition of ρ-persistence, we have

$$\beta_i \nu(t) + \int_0^\infty q_i(a) y_i(t,a)\,da \le \varepsilon_0. \tag{3.5}$$

In view of the first equation of (1.3), together with (3.5), we have

$$x_i'(t) \ge \lambda_i - (\mu_i + \varepsilon_0) x_i(t),$$

which implies that $x_{i\infty} \ge \frac{\lambda_i}{\mu_i+\varepsilon_0}$. Thus, there exists a $t_1 > 0$ for all $t > t_1$ such that $x_i(t) \ge x_i^{\varepsilon_0}$. It follows from the third equation of (1.3) that for all $t > t_1$

$$z_i(t) \ge \beta_i x_i^{\varepsilon_0} \nu(t) + x_i^{\varepsilon_0} \int_0^t q_i(a) z_i(t-a) \pi_i(a)\,da. \tag{3.6}$$

Taking a Laplace transformation on both sides of (3.6), one has

$$\widehat{z_i(\lambda)} \ge x_i^{\varepsilon_0}\big(\beta_i \widehat{\nu(\lambda)} + \widehat{M_i(\lambda)}\widehat{z_i(\lambda)}\big), \tag{3.7}$$

which implies

$$\widehat{z_i(\lambda)} \ge \frac{\beta_i x_i^{\varepsilon_0} \widehat{\nu(\lambda)}}{1 - x_i^{\varepsilon_0} \widehat{M_i(\lambda)}}. \tag{3.8}$$

Substituting (1.5) into the last equation of (1.3) yields

$$v'(t) = \sum_{i=1}^{n} \int_0^t p_i(a) z_i(t-a) \pi_i(a)\, da + \sum_{i=1}^{n} F_i(t) - cv(t),$$

where $F_i(t) = \int_t^\infty p_i(a) y_i(a-t) \frac{\pi_j(a)}{\pi_j(a-t)}\, da$, $i \in \mathbb{N}_n$, and $\lim_{t\to\infty} F_i(t) = 0$. Therefore, the derivative of $v(t)$ is determined by

$$v'(t) \geq \sum_{i=1}^{n} \int_0^t p_i(a) z_i(t-a) \pi_i(a)\, da - cv(t). \tag{3.9}$$

Taking the Laplace transformation on both sides of (3.9) yields

$$\lambda \widehat{v(\lambda)} - v(0) \geq \widehat{K_i(\lambda)} \widehat{z(\lambda)} - c\widehat{z(\lambda)}. \tag{3.10}$$

Equation (3.10), together with (3.8) implies that

$$\widehat{v(\lambda)} \geq \sum_{i=1}^{n} \frac{\beta_i x_i^{\varepsilon_0} \widehat{v(\lambda)}}{(\lambda + c)[1 - x_i^{\varepsilon_0} \widehat{M_i(\lambda)}]}. \tag{3.11}$$

This inequality holds for any given $\varepsilon_0 > 0$ and $\lambda > 0$. This leads to a contradiction with (3.4). Hence the proof is complete. □

Combining Propositions 1.4 and Proposition 3.2 with Theorems 4.2 in [27] and Theorem 3.2 in [28], we immediately have the following theorem.

Theorem 3.3 *System* (1.3) *is uniformly strongly ρ-persistent if $\mathcal{R}_0 > 1$ and $\mathcal{R}_0^{cc} < 1$.*

Theorem 3.3 indicates that system (1.3) has a global attractor $\mathcal{A}$. A *total trajectory* of Φ is a function $X : \mathbb{R} \to \mathbb{R}_+ \times L_+^1 \times \mathbb{R}_+$ such that $\Phi(s, X(t)) = X(t+s)$ for all $t \in \mathbb{R}$ and all $s \in \mathbb{R}_+$. As in [29], for all $s \in \mathbb{R}$, the total trajectory of system (1.3) is defined as

$$\begin{cases} \frac{dx_i(s)}{ds} = \lambda_i - \mu_i x(s) - \beta_i x_i(s) v(s) - x_i(s) \int_0^\infty q_i(a) y_i(t,a)\, da, \\ \frac{\partial y_i(s,\tau)}{\partial s} + \frac{\partial y_i(s,\tau)}{\partial \tau} = -\delta_i(a) y_i(s,\tau), \\ y_i(s,0) = \beta_i x_i(s) v(s) + x_i(s) \int_0^\infty q_i(a) y_i(t,a)\, da, \\ \frac{dv(s)}{ds} = \sum_{i=1}^n \int_0^\infty p_i(a) y_i(s,a)\, da - cv(s). \end{cases} \tag{3.12}$$

Proposition 3.4 *For a total trajectory $X(\cdot)$ in Γ, $x_i(t)$ is strictly positive and either $Q_i(t)$ and $v(t)$ are identically zero or $Q_i(t)$ and $v(t)$ are strictly positive.*

Proof By the definition of the total trajectory, for any $s \in \mathbb{R}$ the function $X_s(t) = X(s+t)$ is a semi-trajectory of system (1.3) with initial condition $X_s(0) = X(s) \in \Gamma$.

If $x_i(s) = 0$ for some s, then the first equation of system (3.12) implies that $\frac{dx_i(s)}{ds} > 0$. From the continuity of the solution, for sufficiently small $\varepsilon > 0$, we have $x_i(s-\varepsilon) < 0$, which is a contradiction with $X(\cdot) \in \Gamma$.

If $y_i(s,\cdot)$ and $v(s)$ are both equal to zero for some $s \in \mathbb{R}$ and any $t < s$, we have $0 = y_i(s, s-t) = y_i(t,0)\pi_i(s-t) = x_i(t)(\beta_i v(t) + Q_i(t))\pi_i(s-t)$. By the Assumption 1.1, $\pi_i(s-t)$

remains positive for $t \in \mathbb{R}$, $i \in \mathbb{N}_n$. Thus, $v(t)$ and $Q_i(t)$ are identically zero for all $t < s$. For $t > s$, it follows from (3.1) and Gronwall inequality that $v(t)$ and $Q_i(t)$ are both equal to zero.

Now we assume that $y_i(s,\cdot)$ is non-zero for each $s \in \mathbb{R}$. Since $X(\cdot) \in \Gamma$, there exists a sequence $\{s_n\}$ such that $y_i(s_n,\cdot)$ is non-zero for each n. For each n, there exists a sequence $\{a_n\}$ such that $0 \neq y_i(s_n,a_n) = y_i(s_n - a_n, 0)\pi_i(a)$. This implies that $y_i(s_n - a_n, 0) \neq 0$ as s_n goes to $-\infty$. Solving the last equation of system (3.12), we obtain $v(s) \neq 0$ for all $s \in \mathbb{R}$. □

The alpha limit set of a total trajectory $f(t)$ passing through $f(0) = f_0$ is

$$\mathcal{A}_0 = \mathcal{A} \cap (\Gamma \backslash \Gamma_0).$$

The omega limit set of a total trajectory $f(t)$ is $\mathcal{A}_1 = \mathcal{A} \cap \Gamma_0$. Let $C \subset \mathcal{A}$ be the set consisting of $(x_{i0}, y_{i0}(\cdot), v_0) \in \mathcal{A}$ such that a total trajectory $X(\cdot)$ approaching $\mathcal{A}_0$ as $t \to -\infty$ and approaching $\mathcal{A}_1$ as $t \to +\infty$.

Corollary 3.5 *Suppose* $\mathcal{R}_0 > 1$ *and* $\mathcal{R}_0^{cc} < 1$. *Let* $(x_i(s), y_i(s,\cdot), v(s))$ *be a total trajectory in* $\mathcal{A}_1$. *Then there exists an* $\varepsilon_0 > 0$ *such that* $x_i(s), v(s) > \varepsilon_0$ *and* $y_i(s,\tau) > \varepsilon_0\pi_i(\tau)$, *for all* $s \in \mathbb{R}$.

Proof Note that $\beta_i v(s) + \int_0^\infty q_i(a) y_i(t,a)\,da \leq M + \beta_i'^{+} x_i^0 \triangleq M_i^1$ for all $s \in \mathbb{R}$. By the first equation of (3.12), we have

$$\frac{dx_i(s)}{ds} \geq \lambda_i - \mu_i x_i - M_i^1 x_i,$$

which implies that $x_i(s) \geq \frac{\lambda_i}{\mu_i + M_i^1} \triangleq \varepsilon_1$ for all $s \in \mathbb{R}$. It follows from Theorem 3.3 and the basic reproduction number $\mathcal{R}_0 > 1$ that $\beta_i v(s) + \int_0^\infty q_i(a) y_i(t,a)\,da \geq \varepsilon_2$. In view of the second and fourth equations, we have

$$y_i(s,\tau) \geq \varepsilon_1\varepsilon_2\pi_i(\tau) \triangleq \varepsilon_3\pi_i(\tau).$$

Then define

$$\varepsilon_0 = \min\{\varepsilon_1, \varepsilon_2, \varepsilon_3\}$$

and hence the proof is complete. □

In order to get the global stability of system (1.3), we recall an energy function $\varphi : (0,\infty) \to \mathbb{R}$ as

$$\varphi(x) = x - 1 - \ln x.$$

φ attains a global minimum only at 1 with $\varphi(1) = 0$ and $\varphi(x) > 0$ for $x \neq 1$. Next, we base on φ and construct a class of Lyapunov functionals to finish our goal, which implies that the endemic steady state E^* is a global attractor. Now we are in the position to prove the following result.

The following lemma is used to cancel some terms in the proof of Theorem 3.7.

Lemma 3.6 *Suppose* $\mathcal{R}_0^{cc} < 1$. *If* $\mathcal{R}_0 > 1$, *the following equalities hold*:

$$y_i(t,0) = \frac{x_i^*\beta_i}{c}\sum_{i=1}^{n}\int_0^\infty p_i(a)y_i^*(a)\frac{x_i(t)v(t)}{x_i^*v^*}\,da + x_i^*\int_0^\infty q_i(a)y_i^*(a)\frac{x_i(t)y_i(t,a)}{x_i^*y_i^*(a)}\,da, \tag{3.13}$$

$$\begin{aligned} y_i^*(0) =& \frac{x_i^*\beta_i}{c}\sum_{i=1}^{n}\int_0^\infty p_i(a)y_i^*(a)\frac{x_i(t)v(t)y_i^*(0)}{x_i^*v^*y_i(t,0)}\,da \\ &+ x_i^*\int_0^\infty q_i(a)y_i^*(a)\frac{x_i(t)y_i(t,a)y_i^*(0)}{x_i^*y_i^*(a)y_i(t,0)}\,da. \end{aligned} \tag{3.14}$$

Proof By the fact that

$$cv^* = \sum_{i=1}^{n}\int_0^\infty p_i(a)y_i^*(a)\,da$$

and

$$y_i(t,0) = \beta_i x_i(t)v(t) + x_i(t)\int_0^\infty q_i(a)y_i(t,a)\,da,$$

we obtain

$$\begin{aligned} &\frac{x_i^*\beta_i}{c}\sum_{i=1}^{n}\int_0^\infty p_i(a)y_i^*(a)\frac{x_iv}{x_i^*v^*}\,da + x_i^*\int_0^\infty q_i(a)y_i^*(a)\frac{x_i(t)y_i(t,a)}{x_i^*y_i^*(a)}\,da \\ &\quad= \beta_i x_i(t)v(t) + x_i(t)\int_0^\infty q_i(a)y_i(t,a)\,da \\ &\quad= y_i(t,0). \end{aligned} \tag{3.15}$$

Similarly,

$$\begin{aligned} y_i^*(0) =& \frac{x_i^*\beta_i}{c}\sum_{i=1}^{n}\int_0^\infty p_i(a)y_i^*(a)\frac{x_i(t)v(t)y_i^*(0)}{x_i^*v^*y_i(t,0)}\,da \\ &+ x_i^*\int_0^\infty q_i(a)y_i^*(a)\frac{x_i(t)y_i(t,a)y_i^*(0)}{x_i^*y_i^*(a)y_i(t,0)}\,da \\ =& \frac{\beta_i}{c}\frac{x_i(t)v(t)y_i^*(0)}{v^*y_i(t,0)}\sum_{i=1}^{n}\int_0^\infty p_i(a)y_i^*(a)\,da \\ &+ \frac{x_i(t)y_i^*(0)}{y_i(t,0)}\int_0^\infty q_i(a)y_i(t,a)\,da \\ =& \left[\beta_i x_i(t)v(t) + x_i(t)\int_0^\infty q_i(a)y_i(t,a)\,da\right]\frac{y_i^*(0)}{y_i(t,0)} \\ =& y_i^*(0). \end{aligned} \tag{3.16}$$

□

Employing Lemma 3.6 and Lyapunov functional methods, we obtain the global stability of the endemic steady state E^*.

Theorem 3.7 *Suppose* $\mathcal{R}_0^{cc} < 1$. *If* $\mathcal{R}_0 > 1$, *then the endemic steady state* E^* *is globally asymptotically stable in* Γ_0.

Proof By Theorem 2.2 and Proposition 1.4, it suffices to show $\mathcal{A}_1 = \{E^*\}$. Let $X(t) = (x_i(t), y_i(t,\cdot), \nu(t))$ be a total trajectory in $\mathcal{A}$. By Corollary 3.5, there exists $\varepsilon_0 > 0$ for any $t \in \mathbb{R}$ and $\tau \in \mathbb{R}_+$ such that $0 \le \varphi(m) < \varepsilon_0$ for $m = \frac{x_i(t)}{x_i^*}$, $\frac{y_i(t,\tau)}{y_i^*(\tau)}$, and $\frac{\nu(t)}{\nu^*}$.

Let

$$\alpha_i(a) = \int_a^\infty \left[x_i^* \left(\beta_i \sum_{j=1}^n p_j(s) + q_i(s) \right) \right] y_i^*(s)\, ds, \quad i \in \mathbb{N}_n.$$

Then

$$\frac{d\alpha_i(a)}{da} = -x_i^* \left(\beta_i \sum_{j=1}^n p_j(s) + q_i(s) \right) y_i^*(a), \quad i \in \mathbb{N}_n.$$

Define

$$V_i(t) = V_{x_i}(t) + V_{y_i}(t) + V_\nu(t), \quad i \in \mathbb{N}_n,$$

where $V_{x_i}(t) = x_i^* \varphi(\frac{x_i(t)}{x_i^*})$, $V_{y_i}(t) = x_i^* \int_0^\infty \alpha_y(a) \varphi(\frac{y_i(t,a)}{y_i^*(a)})\, da$, and $V_\nu(t) = \frac{\beta_i x_i^* \nu^*}{c} \varphi(\frac{\nu(t)}{\nu^*})$. Thus $V(t)$ is bounded.

In what follows, we show that the derivative $V_i(t)$ along the solution of system (1.3) is non-positive. By the definition of $V_{x_i}(t)$, we have

$$\begin{aligned}
\frac{dV_{x_i}(t)}{dt} &= \left(1 - \frac{x_i^*}{x_i(t)}\right) \left[\lambda_i - \mu_i x_i(t) - \beta_i x_i(t) \nu(t) - x_i \int_0^\infty q_i(a) y_i(t,a)\, da \right] \\
&= -\mu_i x_i^* \left(\frac{x_i^*}{x_i(t)} + \frac{x_i(t)}{x_i^*} - 2 \right) + \beta_i x_i^* \nu^* \left[1 - \frac{x_i(t)\nu(t)}{x_i^* \nu^*} - \frac{x_i^*}{x_i} + \frac{\nu(t)}{\nu^*} \right] \\
&\quad + \int_0^\infty q_i(a) y_i^*(a) \left[1 - \frac{y_i(t,a)}{y_i^*(a)} - \frac{x_i^*}{x_i(t)} + \frac{x_i^* y_i(t,a)}{x_i(t) y_i^*(a)} \right] da \\
&= -\mu_i x_i^* \left(\frac{x_i^*}{x_i(t)} + \frac{x_i(t)}{x_i^*} - 2 \right) \\
&\quad + \frac{\beta_i x_i^*}{c} \sum_{i=1}^n \int_0^\infty p_i(a) y_i^*(a) \left[1 - \frac{x_i(t)\nu(t)}{x_i^* \nu^*} - \frac{x_i^*}{x_i(t)} + \frac{\nu(t)}{\nu^*} \right] da \\
&\quad + \int_0^\infty q_i(a) y_i^*(a) \left[1 - \frac{y_i(t,a)}{y_i^*(a)} - \frac{x_i^*}{x_i(t)} + \frac{x_i^* y_i(t,a)}{x_i(t) y_i^*(a)} \right] da.
\end{aligned}$$

By [19, Lemma 9.4], differentiating $V_{y_i}(t)$ with respect to t yields

$$\begin{aligned}
\frac{dV_{y_i}(t)}{dt} &= \int_0^\infty x_i^* \left(\beta_i \sum_{j=1}^n p_i(a) + q_i(a) \right) y_i^*(a) \left[\varphi\left(\frac{y_i(t,0)}{y_i^*(0)} \right) - \varphi\left(\frac{y_i(t,a)}{y_i^*(a)} \right) \right] da \\
&= \int_0^\infty x_i^* \left(\beta_i \sum_{j=1}^n p_i(a) + q_i(a) \right) y_i^*(a) \left[\frac{y_i(t,0)}{y_i^*(0)} - \frac{y_i(t,a)}{y_i^*(a)} + \ln \frac{y_i(t,a) y_i^*(0)}{y_i^*(a) y_i(t,0)} \right] da.
\end{aligned}$$

The derivative of $V_v(t)$ can be further calculated as

$$\begin{aligned}\frac{dV_v(t)}{dt} &= \frac{\beta_i x_i^*}{c}\left(1-\frac{v^*}{v(t)}\right)\left(\sum_{i=1}^{n}\int_0^\infty p_i(a)y_i(t,a)\,da - cv(t)\right)\\ &= \frac{\beta_i x_i^*}{c}\left(1-\frac{v^*}{v(t)}\right)\left(\sum_{i=1}^{n}\int_0^\infty p_i(a)y_i^*(a)\frac{y_i(t,a)}{y_i^*(a)}\,da - cv(t)\right)\\ &= \frac{\beta_i x_i^*}{c}\left[\sum_{i=1}^{n}\int_0^\infty p_i(a)y_i^*(a)\left(\frac{y_i(t,a)}{y_i^*(a)}-\frac{v^*}{v(t)}\frac{y_i(t,a)}{y_i^*(a)}\right) - cv(t) + cv^*\right]\\ &= \frac{\beta_i x_i^*}{c}\left[\sum_{i=1}^{n}\int_0^\infty p_i(a)y_i^*(a)\left(\frac{y_i(t,a)}{y_i^*(a)}-\frac{v^*}{v(t)}\frac{y_i(t,a)}{y_i^*(a)}\right) - \frac{v(t)}{v^*} + 1\right].\end{aligned}$$

Summing up $\frac{dV_{x_i}(t)}{dt}$, $\frac{dV_{y_i}(t)}{dt}$, and $\frac{dV_v(t)}{dt}$ yields

$$\begin{aligned}\frac{dV_i(t)}{dt} &= -\mu_i x_i^*\left(\frac{x_i^*}{x_i(t)}+\frac{x_i(t)}{x_i^*}-2\right)\\ &\quad+\frac{\beta_i x_i^*}{c}\sum_{j=1}^{n}\int_0^\infty p_i(a)y_i^*(a)\left(2-\frac{x_i^*}{x_i(t)}-\frac{v^*y_i(t,a)}{v(t)y_i^*}-\frac{x_i(t)v(t)}{x_i^*v^*}+\frac{y_i(t,0)}{y_i^*(0)}\right.\\ &\quad\left.+\ln\frac{y_i(t,a)y_i^*(0)}{y_i^*(a)y_i(t,0)}\right)da\\ &\quad+x_i^*\int_0^\infty q_i(a)y_i^*(a)\left[1-\frac{x_i^*}{x_i(t)}+\frac{x_i(t)y_i(t,a)}{x_i^*y_i^*}+\frac{y_i(0)}{y_i^*(0)}+\ln\frac{y_i(t,a)y_i^*(0)}{y_i^*(a)y_i(0)}\right]da\\ &= -\mu_i x_i^*\left(\frac{x_i^*}{x_i(t)}+\frac{x_i(t)}{x_i^*}-2\right)\\ &\quad-\frac{\beta_i x_i^*}{c}\int_0^\infty p_i(a)y_i^*(a)\left[\varphi\left(\frac{v^*y_i(t,a)}{v(t)y_i^*(a)}\right)+\varphi\left(\frac{x_i^*}{x_i}\right)+\varphi\left(\frac{x_iv y_i^*(0)}{x_i^*(t)v^*(t)y_i(t,0)}\right)\right]da\\ &\quad-x_i^*\int_0^\infty q_i(a)y_i^*(a)\left[\varphi\left(\frac{x_i^*}{x_i(t)}\right)+\varphi\left(\frac{x_i(t)y_i^*(0)y_i(t,a)}{x_i^*y_i(t,0)y_i^*(a)}\right)\right]da\\ &\le 0.\end{aligned}$$

Therefore, $V_i(t)$ is nonincreasing with respect to time t. Since $V_i(t)$ is bounded on $X(\cdot)$, the ω-limit set of $X(\cdot)$ must be contained in $\mathcal{M}$, the largest invariant subset of $\{\frac{dV_i(t)}{dt}=0\}$. It follows from $\frac{dV_i(t)}{dt}=0$ that $x_i(t)=x_i^*$ and $v(t)y_i^*(0)=v^*y_i(t,0)$. Thus $\frac{dx_i(t)}{dt}=0$ in $\mathcal{M}$. This implies that

$$0=\lambda_i-\mu_i x_i^*-y_i(t,0)$$

for $t\in\mathbb{R}$, which yields $y_i^*(0)=y_i(t,0)$ for all $t\in\mathbb{R}$. This, together with the expression of $y_i(t,\tau)$ implies that $y_i(t,\tau)=y_i^*(\tau)$ and $v(t)=v^*$ for all t. Therefore, $\mathcal{M}=\{E^*\}$.

The above analysis indicates that the ω-limit set of $X(\cdot)$ consists of just the endemic steady state E^* and hence $V(X(t))\ge V(E^*)$ for all $t\in\mathbb{R}$. Thus $\mathcal{A}_1=\{E^*\}$. □

4 Numerical simulations

In this section, we present numerical simulations to illustrate the effects of different treatment strategies on the evolution of HIV infection. Our simulations also serve the purpose of verifying our theoretical results obtained in the previous sections. We perform the numerical analysis using Matlab. Here, we are particularly interested in two types of target cells, the $CD4^+$ lymphoblasts and macrophages. The maximum infectious period is assumed to be $a_{\max} = 15$ days. The cells-to-cells transmission rate is $q_j(a) = 0.00065$ in [12] and the death rate for lymphoblasts is defined as

$$\delta_1(a) = \begin{cases} \delta_0, & 0 \le a \le a_1, \\ \delta_0 + \delta_1(1 - e^{-\Theta(a-a_1)}), & a > a_1. \end{cases}$$

The viral production kernel is defined as

$$p_1(a) = \begin{cases} 0, & 0 \le a \le a_2, \\ p_{1\max}(1 - e^{-\gamma(a-a_1)}), & a > a_2, \end{cases}$$

where γ is the saturation rate and a_1 is the viral reproduction delay. The other parameters are obtained from the literature and are listed in Table 1.

We choose production rates of $CD4^+$ lymphoblasts and macrophages as $\lambda_i = 1$ ml/day, $i = 1, 2$, respectively and the viral production rate for macrophage as $p_2(a) = 0.1\exp(-3 \times 0.00028a)$ in [5]. The basic reproduction number is obtained, $\mathcal{R}_0 = 0.4417 < 1$, which implies that the virus-free steady state E_0 is globally asymptotically stable by Theorem 2.2 and Theorem 3.1 (see Figure 1). For increased the production rates for the two target cells $\lambda_i = 10$ ml/day, $i = 1, 2$, the basic reproduction number $\mathcal{R}_0 = 4.4173 > 1$. It follows from Theorem 2.1 and Theorem 3.7 that the endemic steady state E^* is globally asymptotically stable (see Figure 2).

4.1 Effects of drug inhibitors

The drugs play an important role in inhibiting the replication of virus. Two types of inhibitors are commonly used clinically in HAART regimens, including reverse-transcriptase inhibitors (RT), and protease inhibitors (PI). RT inhibitors restrain RT's enzymatic function and interdict viral replication from HIV-1 RNA to DNA. Such process can be modeled by reducing viral infection rate β_i with mathematical factor $1 - \varepsilon_i^{\mathrm{RT}}$. Protease inhibitors (PI) can effectively restrain HIV protease by cleaving the HIV polyproteins

Table 1 List of parameters

Parameters	Biological meaning	Values	Source
β_1	Transmission rate from virus-to-cell	4.6×10^{-6}	[5]
q_1	Transmission rate from cell-to-cell	8×10^{-5}	[30]
δ_0	Background death rate	0.05	[12]
δ_m	Extra death rate	0.35	[5]
c	Clearance rate of virus	23	[5]
μ_1	Death rate for lymphoblasts	0.01	[31]
μ_2	Death rate for macrophages	0.024	[31]
a_1	Age at which reverse transcription is completed	0.25	[12]
a_2	Window in viral reproduction	0.5	[12]
$p_{1\max}$	Maximum production rate for lymphoblasts	850	[12]

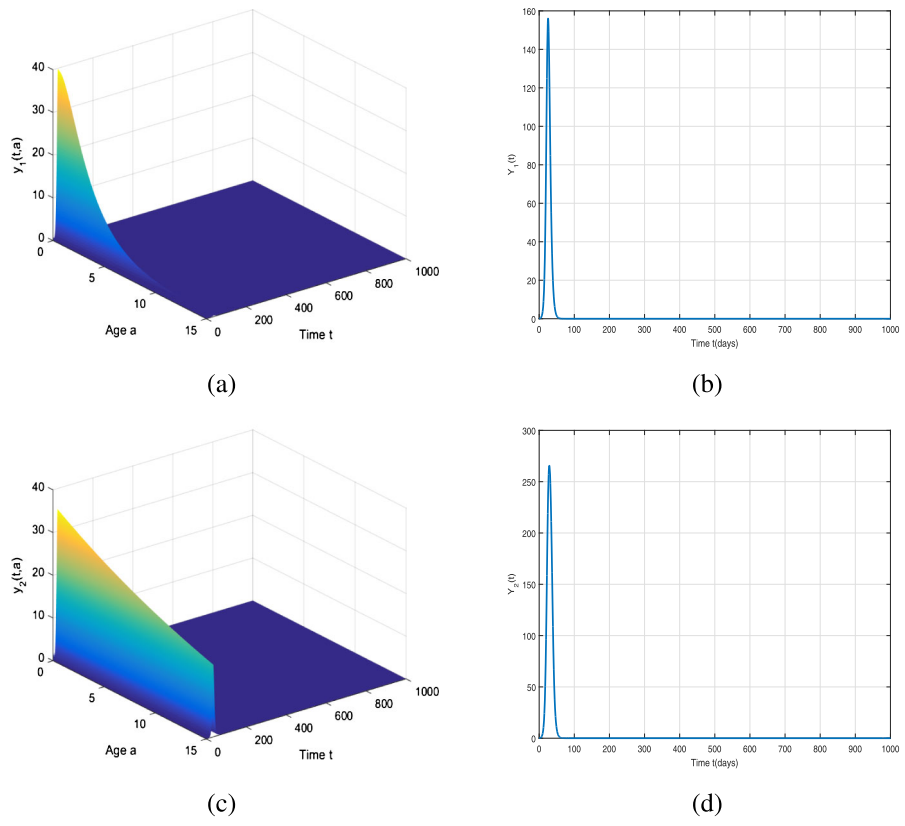

Figure 1 All the parameters are listed in Table 1 except $\lambda_i = 1$, $i = 1, 2$. Stability of equilibria of (1.3). The virus-free equilibrium is globally asymptotically stable when $\mathcal{R}_0 < 1$ and $\mathcal{R}_0^{cc} < 1$. The graph trajectories of $y_j(t, a)$, $j = 1, 2$ versus time t and age a are illustrated in (**a**) and (**b**). The graph trajectories of $Y_j(t)$, $j = 1, 2$ versus time t are illustrated in (**c**) and (**d**).

into functional sub-units resulting in producing immature noninfectious virus particles. This can be described as reducing cell-to-cell transmission rate and viral protease rate with factors $1 - \varepsilon_i^{\mathrm{PI}c}$ and $1 - \varepsilon_i^{\mathrm{PI}p}$, respectively. In order to reveal the antiretroviral therapy effects of RT inhibitors and PI inhibitors, we propose the following model:

$$\begin{cases} \frac{dx_i(t)}{dt} = \lambda_i - \mu_i x_i(t) - (1 - \varepsilon_i^{\mathrm{RT}})\beta_i x_i(t) v(t) \\ \qquad\qquad - x_i(t) \int_0^\infty (1 - \varepsilon_i^{\mathrm{PI}c}) q_i(a) y_i(t, a)\, da, \\ \frac{\partial y_i(t,\tau)}{\partial t} + \frac{\partial y_i(t,\tau)}{\partial \tau} = -\delta_i(\tau) y_i(t, \tau), \\ y_i(t, 0) = (1 - \varepsilon_i^{\mathrm{RT}})\beta_i x_i(t) v(t) + x_i(t) \int_0^\infty (1 - \varepsilon_i^{\mathrm{PI}c}) q_i(a) y_i(t, a)\, da, \\ \frac{dv(t)}{dt} = \sum_{i=1}^2 \int_0^\infty (1 - \varepsilon_i^{\mathrm{PI}p}) p_i(\tau) y_i(t, \tau)\, d\tau - cv. \end{cases} \tag{4.1}$$

In order to compare different antiretroviral therapy effects, we perform simulation using $\varepsilon_i^j = 0.11$, and $\varepsilon_i^j = 0.21$, $i = 1, 2$, $j = \mathrm{PI}c, \mathrm{PI}p, \mathrm{RT}$. From Figure 3, it is easy to say that Protease inhibitors are more effective on decreasing the load of particle virion than reverse-transcriptase inhibitors. Furthermore, protease inhibitors have significant influences on cell-to-cell transmission by preventing viral replication. Protease inhibitors decrease the peak magnitude of the disease and postpone the arrival of such peak. Investigating the cell-to-cell transmission is essential to developing optimal disease control strategies. Nu-

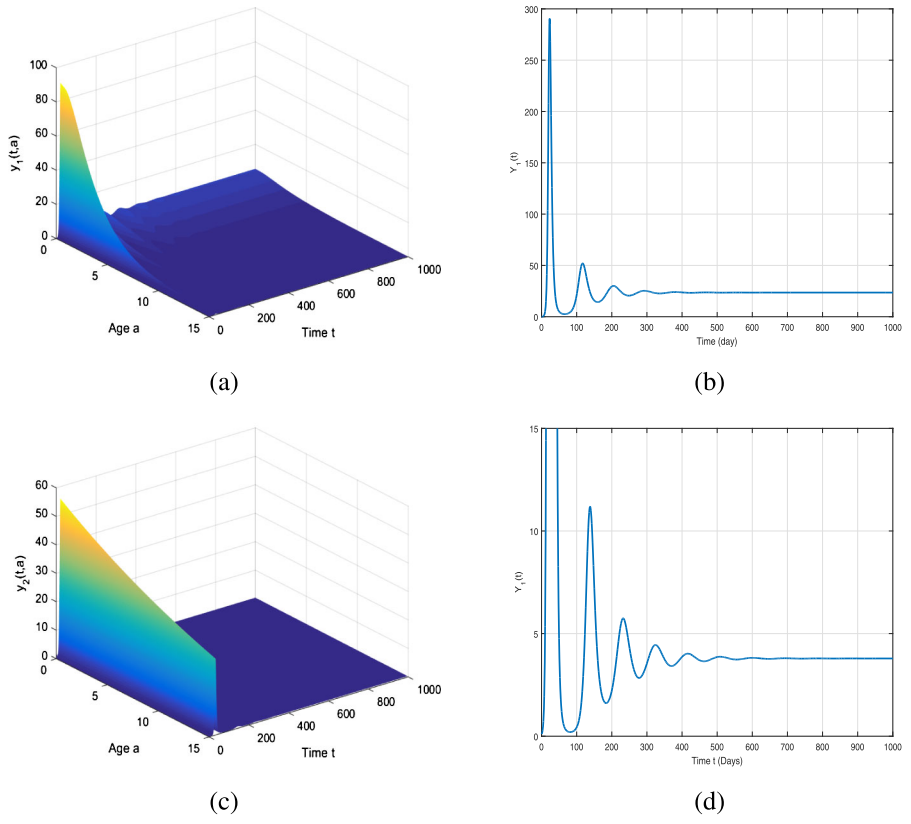

Figure 2 All the parameters are listed in Table 1 except $\lambda_i = 10$, $i = 1, 2$. The antiretroviral therapy effects for reverse-transcriptase inhibitors (RT) and protease inhibitors (PI).

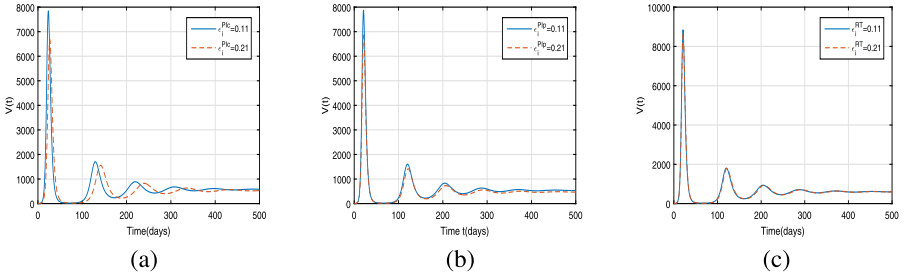

Figure 3 The effects of the different antiretroviral therapies with respect to time *t*. (**a**) $\varepsilon_1^{\mathrm{PI}c} = 0.11$, $\varepsilon_1^{\mathrm{PI}c} = 0.21$, (**b**) $\varepsilon_1^{\mathrm{PI}p} = 0.11$, $\varepsilon_1^{\mathrm{PI}p} = 0.21$, (**c**) $\varepsilon_1^{\mathrm{RT}} = 0.11$, $\varepsilon_1^{\mathrm{RT}} = 0.21$.

merical simulation indicates that decreasing the cell-to-cell transmission is more effective in disease control than the other two treatments.

When investigating the effects of multi-target cells on the evolution of virus, we assume the antiretroviral therapy for macrophages is more sensitive than the therapy for lymphoblasts. This implies that $\varepsilon_2^j = 1$ and $\varepsilon_1^{\mathrm{RT}} = 0.4$, $\varepsilon_1^{\mathrm{PI}c} = 0.2$, $\varepsilon_1^{\mathrm{PI}p} = 0.6$. As shown in Figure 4, the evolutions of virion for multi-target cells and single cell has some common properties. They increase as fast as possible and then reach the peak level, followed by a decay. However, the viruses for single target cell have slower decay rate than that for two

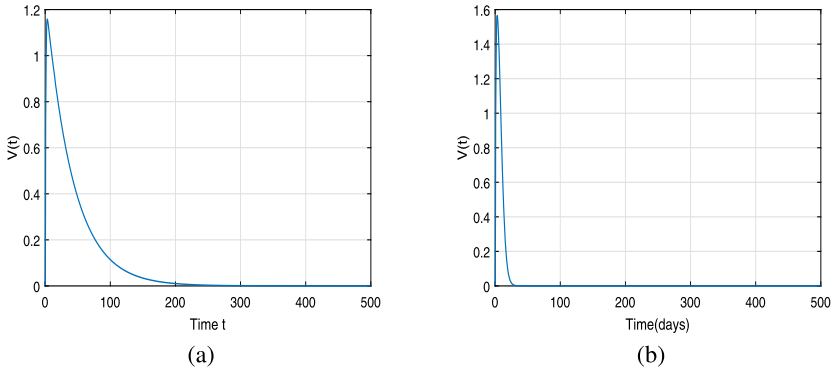

Figure 4 The virion evolves with respect to time. (**a**) Evolution of the virion for multi-target cell. (**b**) Evolution of the virion for single target cell.

target cells, indicating that multi-target cells contribute to slowing down the accumulation of virion and increase the difficulties of treatment.

4.2 Decay dynamics of the system

From initial HAART treatment, viremia decays and becomes undetectable (<50 HIV-1 RNA copies/ml) in adherent patients. During the first antiretroviral therapy period, the evolution of viremia strongly depends on the distributions of the infected target cells.

Now, we assume that reverse-transcriptase inhibitors totally suppress reverse-transcriptase's enzymatic function and prevent the synthesis of viral DNA from HIV-1 RNA. This means $\varepsilon_i^{\mathrm{RT}} = 1$. For convenience, we assume that $\varepsilon_i^{\mathrm{PI}c} = 1$ since the mechanism for cell-to-cell transmission is obscure. It follows from equation (1.3) that $y_i(t,\tau) = y_{i0}(\tau - t)\pi_i(t)$. Since the plasma viruses decay faster (lasting only $1/c \approx 1$ h) [4, 32, 33] than uninfected target cells and infected target cells. The time scale of decay rate for infected target cell is much lower than that for viremia. Therefore viremia reaches the quasisteady state relative to infected target cells and uninfected target cells. Then

$$v(t) = \sum_{i=1}^{2} \frac{\int_0^\infty p_i(a) y_i(t,a)\,da}{c} = \sum_{i=1}^{2} \frac{\int_0^\infty p_i(a) y_{i0}(a-t)\pi_i(t)\,da}{c}.$$

If we choose the initially infected target cells to be $y_{10} = e^{-ma}$ then

$$v(t) = \sum_{i=1}^{2} \frac{\int_0^\infty p_i(a) e^{-m(a-t)}\pi(t)\,da}{c} = \sum_{i=1}^{2} \pi_i(t) e^{mt} \int_0^\infty p_i(a) e^{-ma}\,da/c.$$

The trend of the disease depends on the relations between the survival rate π_i and the decay rate of the initial target cells m_i. If π_{i-} is greater than m then it decreases. Otherwise it increases.

Second, if protease inhibitors completely block the production of infected virion, *i.e.* $\varepsilon_i^{\mathrm{PI}p} = 100\%$, we then have $v(t) = v_0 e^{-ct}$. The decay of viremia is at the clearance rate.

5 Conclusion and discussion

As popular antireviral therapies, reverse-transcriptase (RT) inhibitor and protease inhibitor (PI) suppress the reproduction of virion particles. Recent investigations showed

that the persistence of latent viral reservoirs is responsible for viral rebound. Such a reservoir is insensitive to HAART and able to self-re-establish. It is necessary to evaluate the effects that the cell-to-cell infection has on viral dynamics. HIV viruses weaken and damage human immune systems, and invade many target cells. In this article, we propose a mathematical model with infection age to investigate the viral dynamics of HIV with different therapies. Cell-to-cell and multi-target-cell infections are both integrated into the model to consider their effects on the evolution of the virus under treatments. We obtain the basic reproduction number of the model, which determines the persistence of the disease. We show that when the basic reproduction number is less than one, the virus-free equilibrium is globally stable. On the other hand, if it is greater than one, then the endemic equilibrium is globally asymptotically stable. It follows from the expression of the basic reproduction number that multi-target-cell and cell-to-cell infections contribute positively to the value of the basic reproduction number. Such type of infections was underestimated. Revealing the consequences of multi-target-cell and cell-to-cell infections provides insights into the development of optimal therapy to control the disease.

We consider the decay dynamics of our model and analyze the effects of the reverse-transcriptase inhibitors and protease inhibitors. If the protease inhibitor is effective enough [4], the decay rate of the virus only depends on the clearance rate of the virion particles. On the other hand, if the reverse-transcriptase inhibitors are effective enough, the decay rate of the virus depends on the distribution of initially infected cells. Through the comparison with the two kinds of inhibitors, it is easy to show that protease inhibitors play a more effective role in controlling cell-to-cell transmission than other therapies.

In order to investigate global behaviors of our model with multi-target-cell and cell-to-cell transmissions, we simplified the input rate of uninfected target cells as a constant. In the literature, logistic growth [34] and mixed growth forms [35] have been used in modeling such input rate. We thus change the input mechanism in our model and the model may display complex dynamical behaviors. The drift phenomenon for free virus often happens in the virion disperse process. Fickian diffusion term models biologically meaningful scenario in virus dynamics and as such incorporating the diffusion into HIV model is necessary [36]. Therefore, we will incorporate such growth rates and diffusions into HIV disease model to investigate viral dynamics under various antiretroviral treatments.

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Competing interests
The authors declare that they have no competing interests.

Authors' contributions
XW designed the modeling process and analyzed theoretical results. JY carried out numerical algorithms and simulation parts. FX conceived of the study and helped to draft the manuscript. All the authors read and approved the final manuscript.

Author details
[1]School of Information Management, Shanxi University of Finance and Economics, Taiyuan, Shanxi 030006, P.R. China. [2]Complex Systems Research Center, Shanxi University, Taiyuan, Shanxi 030006, P.R. China. [3]Department of Mathematics, Wilfrid Laurier University, Waterloo, Ontario N2L 3C5, Canada.

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