SIAM J. APPL. MATH.
Vol. 74, No. 3, pp. 898–917

MODELING HIV-1 VIRUS DYNAMICS WITH BOTH VIRUS-TO-CELL INFECTION AND CELL-TO-CELL TRANSMISSION*

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Abstract. Direct cell-to-cell transfer of HIV-1 is found to be a more potent and efficient means of virus propagation than virus-to-cell infection. In this paper we propose a mathematical model to consider these two modes of viral infection and spread, in which infection age is also incorporated. By a rigorous analysis of the model, we show that the model demonstrates a global threshold dynamics, fully described by the basic reproduction number, which is identified explicitly. The formula for the basic reproduction number of our model reveals that the basic reproduction number of a model that neglects either cell-to-cell spread or virus-to-cell infection might be underevaluated.

Key words. cell-to-cell, virus-to-cell, distributed delay, basic reproduction number, local stability, global stability, efficacy, threshold

AMS subject classifications. 34K20, 34K25, 92B05, 92D25

DOI. 10.1137/130930145

1. Introduction.

It is known that the primary target cell for human immunodeficiency virus type 1 (HIV-1) infection is the $CD4^+$ T cell. For decades it was believed that the spreading of HIV-1 within a host was mainly through free circulation of the viral particles, with a repeated process consisting of attachment of viruses to T cells, fusion of viruses into the T cells, replication and assembling of viruses inside the infected T cells, release of newly produced viral particles from the infected cells, and diffusion of the released viral particles to catch other T cells. However, recent studies have revealed that a large number of viral particles can also be transferred from infected cells to uninfected cells through the formation of virally induced structures termed virological synapses [13].

Indeed, the direct cell-to-cell transmission of HIV-1 is found to be a more potent and efficient means of virus propagation than the virus-to-cell infection mechanism. Cell-to-cell spread not only facilitates rapid viral dissemination but may also promote immune invasion and, thereby, influence the disease [23]. Cell-to-cell spread of HIV-1 may reduce the effectiveness of neutralizing antibodies and viral inhibitors. However, it is unclear whether this mechanism of HIV-1 viral spread is susceptible or resistant to inhibition (by neutralizing antibodies) and to entry inhibition, causing some controversy in this field of study [2, 24]. Despite the controversies, it is commonly agreed that the high efficiency of infection by large numbers of virions is likely to result in a transfer of multiple virions to a target cell [6, 14]. In particular, a recent study published in *Nature* [38] shows that cell-to-cell spread of HIV-1 does reduce the efficacy of antiretroviral therapy, because cell-to-cell infection can cause multiple infections of target cells, which can in turn reduce the sensitivity to the antiretroviral drugs.

While HIV-1 can pass directly from an infected T cell to an uninfected and receptor-bearing T cell via virological synapses or membrane nanotubes, many other

*Received by the editors July 22, 2013; accepted for publication (in revised form) April 23, 2014; published electronically June 24, 2014. This research was supported by CSC Overseas Doctoral Scholarship (China) and NSERC (Canada).
http://www.siam.org/journals/siap/74-3/93014.html
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viruses also have some mechanisms to support their cell-to-cell transmissions [34, 35, 36]. For example, murine leukemia virus (MLV) moves between fibroblasts either by polarized assembly and budding at intact intercellular junctions [27] or by crossing adhesive bridges formed by filopodia [37]. Herpes simplex virus type-1 (HSV-1) can spread between a fibroblast and a T cell via a virological synapse, while it can also move between fibroblasts by assembly and budding at basolateral intercellular junctions [36]. In fact, the cell-to-cell spread mode has been adopted by a variety of animal virus families, including *Asfar, Flavi, Herpes, Paramyxo, Pox, Rhabdo*, and *Retroviridae*.

To compare the two transmission modes, Dimitrov et al. [7] studied the kinetics of HIV-1 accumulation in cell culture supernatants during multiple rounds of infections by viral production models. They found that the infection rate constant is the critical parameter that affects the kinetics of HIV-1 infection, and furthermore the infectivity of HIV-1 during cell-to-cell transmission is greater than the infectivity of cell-free viruses. Dixit and Perelson [8] studied the kinetics of HIV-1 infection by exploring the mechanisms of multiple infections. They found that multiple infections can be caused by both cell-free infection mode and cell-to-cell transmission mode. In cell-to-cell transfer mode, by contact of a target cell, an infectious cell can transfer multiple virions or genomes. However, in cell-free mode, multiple genomes are acquired one by one in a series of infectious contacts of a target cell with free virions.

Dynamical system models have been widely and effectively used to model viral infection dynamics. Most existing models consider only the virus-to-cell infection mechanism. Among such models is the following classic and basic model proposed in [1, 29, 30, 31], which describes the virus dynamics within a host by a system of ordinary differential equations:

$$\begin{cases} \frac{dT(t)}{dt} = h - d_T T(t) - \beta V(t) T(t), \\ \frac{dT^*(t)}{dt} = \beta V(t) T(t) - \delta T^*(t), \\ \frac{dV(t)}{dt} = bT^*(t) - cV(t), \end{cases} \tag{1.1}$$

where $T(t)$, $T^*(t)$, and $V(t)$ are the concentrations of uninfected T cells, infected T cells, and free viral particles at time t, respectively. The model assumes that uninfected T cells are produced at a constant rate h and infected by free virions at a rate $\beta V(t)T(t)$. The free virions are produced from the infected cells at a rate $bT^*(t)$. Uninfected T cells, infected T cells, and free virions are lost at rates $d_T T(t)$, $\delta T^*(t)$, and $cV(t)$, respectively. For this model, the virus dynamics are fully determined by an important parameter, called the basic reproduction number and given by $\mathcal{R}_0 = \beta hb/c\delta d_T$, in the following sense: if $\mathcal{R}_0 < 1$, then $V(t) \to 0$ and $T^*(t) \to 0$ as $t \to \infty$, implying infection cannot persist; while if $\mathcal{R}_0 > 1$, the virus will persist in the host [21].

Based on (1.1), there have been a variety of modifications/generalizations of (1.1) that have resulted from incorporating into (1.1) various factors/effects, such as immune responses (CTLs), nonlinear infection rate, latencies in virus infection and replications, and drug therapies. For details see, e.g., [16, 28, 40, 41, 42, 43, 44] and the references cited therein. Among these generalizations is the following model proposed

and studied by Nelson and Perelson [28]:

$$\begin{cases} \frac{dT}{dt} = h - d_T T - (1 - n_{rt})\beta V_I T, \\ \frac{dT^*}{dt} = \int_0^\infty f(s)e^{-\mu s}(1 - n_{rt})\beta V_I(t - s)T(t - s)d\tau - \delta T^*, \\ \frac{dV_I}{dt} = (1 - n_p)N\delta T^* - cV_I, \\ \frac{dV_{NI}}{dt} = n_p N\delta T^* - cV_{NI}, \end{cases} \tag{1.2}$$

where n_{rt} and n_p are the efficacy of reverse transcriptase (RT) inhibitor and protease inhibitor, respectively, and V_I and V_{NI} are the populations of infectious and noninfectious virions, respectively. Here, a time delay, s, from the time of initial infection until the production of new virions, is considered and assumed to vary according to a probability distribution $f(s)$. The term e^{-ms} accounts for the survival rates of cells that are infected at time t and become productively infected s time units later. Note that the V_{NI} equation in (1.2) is decoupled from the other three equations, which, by renaming the parameters, constitute the model system of the form investigated in Zhu and Zou [43]. We point out that, as in (1.1), all those variations in [16, 28, 40, 41, 42, 43, 44] have assumed that uninfected T cells can only be infected by the attachment of free virions, while the mechanism of cell-to-cell transmission has been neglected.

As far as cell-to-cell infection is concerned, much less has been done in mathematical modeling. Culshaw, Ruan, and Webb [3] studied the cell-to-cell spread of HIV-1 by the model

$$\begin{cases} \frac{dT}{dt} = rT(t)\left(1 - \frac{T(t)+T^*(t)}{K}\right) - \beta T(t)T^*(t), \\ \frac{dT^*}{dt} = \beta' \int_{-\infty}^{t} T(s)T^*(s)f(t - s)e^{-ms}ds - \delta T^*(t). \end{cases} \tag{1.3}$$

Here, a logistic growth for the uninfected cells is assumed, with r being the intrinsic growth rate of uninfected cells and K being the effective carrying capacity of the host. Assuming that $f(u)$ is a probability distribution, the integral in (1.3) reflects the variance of productivity of virions by infected cells at different infection ages. We see that in this model, only cell-to-cell infection is considered (at rate $\beta T(t)T^*(t)$), while virus-to-cell infection mechanism is neglected, in contrast to (1.1) and its variations/modifications.

Recently, Komarova et al. [17] studied the relative contribution of free-virus and synaptic transmission to the spread of HIV-1 using a dynamical system model. With data fitting they determined that the two transmission pathways contribute approximately equally to the growth of the virus population. Komarova, Levy, and Wodarz [18] and Komarova and Wodarz [19] further investigated the effect of synaptic transmission on virus dynamics and viral fitness in HIV infection. More specifically, using dynamical system models, they discussed the cell-to-cell transmission in different contexts such as multiple infection and different viral synaptic strategies and explored the effect of different strategies of the virus on the basic reproductive ratio of the virus. In a more recent paper [20], using a virus infection dynamical model with multiple infections, Komarova, Levy, and Wodarz explored the role of synaptic transmission in susceptibility of HIV infection to antiretroviral drugs. They found that multiple infections via synapses do not simply reduce susceptibility to treatment, which depends on the relative probability of individual virions to infect a cell during cell-free virus and synaptic transmission.

In this paper, we propose a dynamical system model that incorporates both the cell-to-cell infection mechanism and the virus-to-cell infection mode. As in [3, 28, 43], we also consider infection age. But we will adopt the simpler production mechanism for uninfected cells, as in (1.1) and (1.2). We also consider a well-mixed situation and no multiple infection for both modes of transmission. All these considerations lead to the following model:

$$
\begin{cases}
\frac{dT(t)}{dt} = h - d_T T(t) - \beta_1 T(t) V(t) - \beta_2 T(t) T^*(t), \\
\frac{dT^*(t)}{dt} = \int_0^\infty [\beta_1 T(t-s) V(t-s) + \beta_2 T(t-s) T^*(t-s)] e^{-\mu s} f(s) ds \\
\qquad\qquad -\delta T^*(t), \\
\frac{dV(t)}{dt} = bT^*(t) - cV(t),
\end{cases}
\tag{1.4}
$$

where β_1 is the infection rate of free virus and β_2 is the infection rate of productively infected cells. The infected cells may die or be cleared at rate μ before becoming productively infected, and thus, after a time period of length s, only a proportion $e^{-\mu s}$ survives. The time for infected cells to become productively infected may vary from individual to individual, and hence, a distribution function $f(s)$ is introduced to account for such variance. For mathematical tractability, yet without losing the major biological feature, we assume that $f : [0, \infty) \to [0, \infty)$ has compact support, $f(s) \geq 0$, and $\int_0^\infty f(s)\, ds = 1$. Other parameters in (1.4) are as in (1.1) and are self-explanatory.

In the rest of this paper, we will analyze the model (1.4). In section 2, we address the well-posedness of (1.4) by verifying the positivity and boundedness of solutions of system (1.4) with reasonable initial data. In section 3, we identify the basic reproduction number $\mathcal{R}_0$ of the model, in terms of which we discuss local stability of the infection-free equilibrium and the positive equilibrium. In section 4, we prove the persistence of infection under $\mathcal{R}_0 > 1$, and in section 5, we further explore the global stability of the two equilibria. Our theoretical results show that the virus dynamics governed by (1.4) are fully determined by $\mathcal{R}_0$. Thus, the dependence of $\mathcal{R}_0$ on the model's parameters may reveal some insights into the virus spread in the presence of both infection modes, and we discuss this in section 5.

We conclude this introduction by pointing out the main difference of this work from [17, 18, 19, 20]. The dynamical system models in [17, 18, 19, 20] are all given by ordinary differential equations. Such ordinary differential equation models have neglected the effect of infection ages, which correspond to various stages during the complicated process of virus replication (see, e.g., [3, 28, 43]), and the survival rate of infected cells before they become productive. Our model (1.4) incorporates not only both cell-to-cell infection mechanism and virus-to-cell infection mode, but also an infinite intracellular delay, which reflects the fact that an infected cell may remain latent forever. Moreover, while [17, 18, 19, 20] contain some analysis on the basic reproduction number $\mathcal{R}_0$ and offer some interesting insights into virus replication as well as some supportive numeric results, in this work, in addition to the mathematical derivation of $\mathcal{R}_0$, the global dynamics of the model are completely determined analytically.

2. Positivity and boundedness of solutions. The model (1.4) is a system of integro-differential equations with infinite delays. For such a system, the phase space needs to be equipped with some norm that accounts for fading memory. In other words, we need to specify a continuous and nondecreasing function $g : (-\infty, 0) \to$

$[1,\infty)$ satisfying (i) $g(0)=1$; (ii) $g(s+t)/g(s)\to 1$ uniformly on $(-\infty,0]$ as $t\to 0^-$; and (iii) $g(s)\to\infty$ as $s\to-\infty$. For details on this topic, see, e.g., [9, 12, 22]. For the purposes of this paper, we choose $g(s)=e^{-\Delta s}$ with $\Delta\in(0,\mu/2)$. Accordingly, the phase space is given by

$$C_\Delta := \left\{ \phi\in C((-\infty,0],\mathbb{R}) : \begin{array}{l} \phi(\theta)e^{\Delta\theta} \text{ is uniformly continuous on} \\ (-\infty,0] \text{ and } \sup_{\theta\le 0}\{|\phi(\theta)|e^{\Delta\theta}\}<\infty \end{array} \right\}, \tag{2.1}$$

equipped with the norm $\|\phi\|=\sup_{\theta\le 0}\{|\phi(\theta)|e^{\Delta\theta}\}$.

For a given function $u(t)=(x(t),y(t),z(t)):(\infty,\tau]\to\mathbb{R}^3$ $(\tau>0)$, we follow the standard notation to define $u_t\in C_\Delta\times C_\Delta\times C_\Delta$ by $u_t(\theta)=(x_t(\theta),y_t(\theta),z_t(\theta))=u(t+\theta)=(x(t+\theta),y(t+\theta),z(t+\theta))$, respectively, for $\theta\in(-\infty,0]$. By the fundamental theory of functional differential equations [9, 12, 22], we know that for any initial function $\phi\in C_\Delta\times C_\Delta\times C_\Delta$, (1.4) has a unique solution $(T(t),T^*(t),V(t))$ satisfying $(T_0,T_0^*,V_0)=\phi$.

The fact that all unknown variables in the model are populations suggests that we need only consider nonnegative initial functions, i.e., initial functions taken from the natural positive cone of this phase space given by $X:=C_\Delta^+\times C_\Delta^+\times C_\Delta^+$ where $C_\Delta^+=\{\phi\in C_\Delta:\ \phi(\theta)\ge 0 \text{ for } \theta\in(-\infty,0]\}$.

For an initial function $\phi=(\phi_1,\phi_2,\phi_3)\in X$, if $\phi_2(\theta)=0=\phi_3(\theta)$ for all $\theta\in(-\infty,0]$ (i.e, there is no initial inoculation/invasion of both viruses and infectious cells), one easily sees (e.g., by uniqueness of solution) that the $T^*(t)$ and $V(t)$ components of the corresponding solution remain zero for all $t\ge 0$. However, if either $\phi_2(\theta)>0$ or $\phi_3(\theta)>0$ for some $\theta\in(-\infty,0]$, these two components of the corresponding solution should remain positive for all $t>0$. It is also reasonable to expect that a solution should remain bounded. The following theorem establishes these properties of well-posedness for the model (1.4).

THEOREM 2.1. *Let $(T(t),T^*(t),V(t))$ be the solution of the system* (1.4) *with initial conditions*

$$\phi\in X^0 := \left\{ \phi=(\phi_1,\phi_2,\phi_3)\in X : \begin{array}{l} \textit{either } \phi_2(\theta)>0 \textit{ or } \phi_3(\theta)>0 \\ \textit{for some } \theta\in(-\infty,0] \end{array} \right\}. \tag{2.2}$$

Then $T(t)$, $T^*(t)$, and $V(t)$ are all positive and bounded for $t>0$.

Proof. Let $a(t)=d_T+\beta_1T^*(t)+\beta_2V(t)$. From the first equation in (1.4), we then have

$$T(t)=e^{\int_0^t a(\xi)\,d\xi}T(0)+\int_0^t e^{\int_\xi^t a(\theta)\,d\theta}h\,d\xi>0 \text{ for } t\ge 0.$$

Next, we prove the positivity of $T^*(t)$ and $V(t)$. Denote by $r(t)$ the integral term in the second equation of (1.4). From the second and the third equations in (1.4), one obtains

$$T^*(t)=e^{-\delta t}T^*(0)+\int_0^t e^{-\delta(t-\xi)}r(\xi)\,d\xi,\quad V(t)=e^{-ct}V(0)+\int_0^t e^{-c(t-\xi)}\,bT^*(\xi)\,d\xi,$$

which together with $\phi\in X^0$ implies that $T^*(t)>0$ and $V(t)>0$ for small $t>0$. We now show $T^*(t)>0$ and $V(t)>0$ for all $t>0$. Otherwise, there exists $t_2>0$ such that $\min\{T(t_2),V(t_2)\}=0$ for the first time. If $T^*(t_2)=0$, $T^*(t)>0$ for $0\le t<t_2$, and $V(t)>0$ for $0\le t\le t_2$, then

$$\frac{dT^*(t_2)}{dt}=\int_0^\infty[\beta_1T(t_2-s)V(t_2-s)+\beta_2T(t_2-s)T^*(t_2-s)]e^{-\mu s}f(s)ds>0,$$

which is a contradiction to $T^*(t_2) = 0$, $T^*(t) > 0$ for $0 \le t < t_2$. If $V(t_2) = 0$, $V(t) > 0$ for $0 \le t < t_2$, and $T^*(t) > 0$ for $0 \le t \le t_2$, then

$$\frac{dV(t_2)}{dt} = bT^*(t_2) > 0,$$

which is also a contradiction. Therefore, $T^*(t) > 0$ and $V(t) > 0$ for all $t > 0$.

To prove boundedness, first by the positivity of solutions we have

$$\frac{dT(t)}{dt} < h - d_T T(t).$$

It follows that $\limsup_{t\to\infty} T(t) \le h/d_T$, implying $T(t)$ is bounded.

Next, we prove the boundedness of $T^*(t)$ and $V(t)$. To this end, we define

$$G(t) = \int_0^\infty e^{-\mu s} f(s) T(t-s) ds + T^*(t) + \frac{\delta}{2b} V(t).$$

Since $T(t)$ is bounded and $\int_0^\infty f(s)\, ds$ is convergent, the integral in $G(t)$ is well defined and differentiable with respect to t. Moreover, when taking the time derivative of $G(t)$, the order of the differentiation and integration can be switched. Thus, we have

$$\begin{aligned}
\frac{dG(t)}{dt} &= h\int_0^\infty e^{-\mu s} f(s) ds - d_T \int_0^\infty e^{-\mu s} f(s) T(t-s) ds \\
&\quad - \int_0^\infty e^{-\mu s} f(s) [\beta_1 T(t-s) V(t-s) + \beta_2 T(t-s) T^*(t-s)] ds \\
&\quad + \int_0^\infty e^{-\mu s} f(s) [\beta_1 T(t-s) V(t-s) + \beta_2 T(t-s) T^*(t-s)] ds - \delta T^*(t) \\
&\quad + \frac{\delta}{2} T^*(t) - c\frac{\delta}{2b} V(t) \\
&= h\int_0^\infty e^{-\mu s} f(s) ds - d_T \int_0^\infty e^{-\mu s} f(s) T(t-s) ds - \frac{\delta}{2} T^*(t) - c\frac{\delta}{2b} V(t) \\
&\le h\eta - dG(t),
\end{aligned}$$

where

$$\eta = \int_0^\infty e^{-\mu s} f(s) ds, \quad d = \min\left\{ d_T, \frac{\delta}{2}, c \right\} > 0. \tag{2.3}$$

Therefore, $\limsup_{t\to\infty} G(t) \le h\eta/d$, implying that $\limsup_{t\to\infty} T^*(t) \le h\eta/d$ and $\limsup_{t\to\infty} V(t) \le 2bh\eta/\delta d$. Hence $T^*(t)$ and $V(t)$ are also bounded. ∎

3. Local stability of equilibria and the basic reproduction number. System (1.4) has the infection-free equilibrium $E_0 = (h/d_T, 0, 0)$. In order to determine the stability of E_0, we consider the linearization of (1.4) at E_0:

$$\begin{cases}
\frac{du_1(t)}{dt} = -d_T u_1(t) - \beta_1 \frac{h}{d_T} u_3(t) - \beta_2 \frac{h}{d_T} u_2(t), \\
\frac{du_2(t)}{dt} = \int_0^\infty \left[\beta_1 \frac{h}{d_T} u_3(t-s) + \beta_2 \frac{h}{d_T} u_2(t-s) \right] e^{-\mu s} f(s) ds - \delta u_2(t), \\
\frac{du_3(t)}{dt} = b u_2(t) - c u_3(t).
\end{cases} \tag{3.1}$$

The characteristic equation of this linear system is given by

$$\begin{vmatrix}
\lambda + d_T & \beta_2 h/d_T & \beta_1 h/d_T \\
0 & \lambda + \delta - \bar{\eta}(\lambda)\beta_2 h/d_T & -\bar{\eta}(\lambda)\beta_1 h/d_T \\
0 & -b & \lambda + c
\end{vmatrix} = 0, \tag{3.2}$$

where

$$\bar{\eta}(\lambda) = \int_0^\infty e^{-(\mu+\lambda)s} f(s)ds.$$

We see that (3.2) has an eigenvalue $\lambda_1 = -d_T < 0$, and other eigenvalues are determined by

$$[\lambda + \delta - \bar{\eta}(\lambda)\beta_2 h/d_T](\lambda + c) - \bar{\eta}(\lambda)\beta_1 bh/d_T = 0.$$

That is,

$$\begin{aligned}(\lambda+\delta)(\lambda+c) &= (\lambda+c)\bar{\eta}(\lambda)\beta_2 h/d_T + \bar{\eta}(\lambda)\beta_1 bh/d_T \\ &= \bar{\eta}(\lambda)\left(\lambda\frac{h\beta_2}{d_T} + \mathcal{R}_0\frac{c\delta}{\eta}\right) = \frac{\delta\bar{\eta}(\lambda)}{\eta}(\lambda\mathcal{R}_{02} + c\mathcal{R}_0),\end{aligned}$$

or

$$\left(\frac{\lambda}{\delta}+1\right)(\lambda+c) = \mathcal{R}_0\frac{\bar{\eta}(\lambda)}{\eta}\left(\frac{\mathcal{R}_{02}}{\mathcal{R}_0}\lambda + c\right), \tag{3.3}$$

where $\eta = \bar{\eta}(0)$ and

$$\mathcal{R}_{01} = \frac{h\eta\beta_1 b}{d_T\delta c}, \quad \mathcal{R}_{02} = \frac{h\eta\beta_2}{d_T\delta}, \quad \mathcal{R}_0 = \mathcal{R}_{01} + \mathcal{R}_{02}. \tag{3.4}$$

We first consider the case $\mathcal{R}_0 < 1$. We show that if $\lambda = x + iy$ is a solution of (3.3), then $x < 0$. Otherwise, $x \geq 0$ would imply

$$\left|\frac{\lambda}{\delta}+1\right| \geq 1, \quad |\lambda + c| > \left|\frac{\mathcal{R}_{02}}{\mathcal{R}_0}\lambda + c\right|, \quad \left|\frac{\bar{\eta}(\lambda)}{\eta}\right| \leq 1,$$

and thus

$$\left|\left(\frac{\lambda}{\delta}+1\right)(\lambda+c)\right| > \left|\mathcal{R}_0\frac{\bar{\eta}(\lambda)}{\eta}\left(\frac{\mathcal{R}_{02}}{\mathcal{R}_0}\lambda + c\right)\right|,$$

which is a contradiction to (3.3). Therefore, all roots of (3.3) have negative real parts when $\mathcal{R}_0 < 1$, implying that E_0 is locally asymptotically stable.

Next we consider the case $\mathcal{R}_0 > 1$. Let

$$\psi(\lambda) := \left(\frac{\lambda}{\delta}+1\right)(\lambda+c) - \mathcal{R}_0\frac{\bar{\eta}(\lambda)}{\eta}\left(\frac{\mathcal{R}_{02}}{\mathcal{R}_0}\lambda + c\right).$$

Then $\psi(0) = c(1-\mathcal{R}_0) < 0$. On the other hand, note that

$$\bar{\eta}(\lambda) = \int_0^\infty e^{-(\mu+\lambda)s} f(s)ds \leq \int_0^\infty f(s)ds = 1.$$

Thus,

$$\begin{aligned}\psi(\lambda) &\geq \left(\frac{\lambda}{d_{T^*}}+1\right)(\lambda+c) - \mathcal{R}_0\frac{1}{\eta}\left(\frac{\mathcal{R}_{02}}{\mathcal{R}_0}\lambda + c\right) \\ &= \frac{1}{d_{T^*}}\lambda^2 + \left(\frac{c}{d_{T^*}} + 1 - \frac{\mathcal{R}_{02}}{\eta}\right)\lambda - \frac{\mathcal{R}_0 c}{\eta} \to \infty \text{ as } \lambda \to \infty,\end{aligned}$$

implying $\lim_{\lambda\to+\infty}\psi(\lambda)=+\infty$. Therefore, there exists a positive (real) number λ^* such that $\psi(\lambda^*)=0$. This means that if $\mathcal{R}_0>1$, then (3.3) has a positive eigenvalue, and hence E_0 is unstable.

Summarizing the above analysis, we have proven the following theorem on the local stability/instability of E_0.

THEOREM 3.1. *Let $\mathcal{R}_0$ be as in* (3.4). *If $\mathcal{R}_0<1$, the infection-free equilibrium E_0 is locally asymptotically stable; if $\mathcal{R}_0>1$, E_0 is unstable.*

When $\mathcal{R}_0>1$, model system (1.4) has a unique positive equilibrium $\bar{E}=(\bar{T},\bar{T}^*,\bar{V})$ given by

$$\bar{T}=\frac{h}{d_T}\frac{1}{\mathcal{R}_0},\ \bar{T}^*=\frac{d_Tc}{\beta_1b+\beta_2c}(\mathcal{R}_0-1),\ \bar{V}=\frac{b}{c}\bar{T}^*=\frac{bd_T}{\beta_1b+\beta_2c}(\mathcal{R}_0-1). \tag{3.5}$$

Linearizing (1.4) at $\bar{E}$ yields

$$\begin{aligned}
\frac{du_1(t)}{dt}&=-d_Tu_1(t)-\beta_1\bar{V}u_1(t)-\beta_1\bar{T}u_3(t)-\beta_2\bar{T}^*u_1(t)-\beta_2\bar{T}u_2(t),\\
\frac{du_2(t)}{dt}&=\int_0^\infty\left[\beta_1\bar{T}u_3(t-s)+\beta_1\bar{V}u_1(t-s)+\beta_2\bar{T}u_2(t-s)\right.\\
&\quad\left.+\beta_2\bar{T}^*u_1(t-s)\right]e^{-\mu s}f(s)ds-\delta u_2(t),\\
\frac{du_3(t)}{dt}&=bu_2(t)-cu_3(t).
\end{aligned}$$

The characteristic equation of this linear system is given by

$$\bar{J}(\lambda)=\begin{vmatrix}\lambda+d_T+\beta_1\bar{V}+\beta_2\bar{T}^* & \beta_2\bar{T} & \beta_1\bar{T}\\ -\bar{\eta}(\lambda)(\beta_1\bar{V}+\beta_2\bar{T}^*) & \lambda+\delta-\bar{\eta}(\lambda)\beta_2\bar{T} & -\bar{\eta}(\lambda)\beta_1\bar{T}\\ 0 & -b & \lambda+c\end{vmatrix}=0.$$

Noticing that $d_T+\beta_1\bar{V}+\beta_2\bar{T}^*=d_T\mathcal{R}_0$, we have

$$\bar{J}(\lambda)=\begin{vmatrix}\lambda+d_T\mathcal{R}_0 & \beta_2\bar{T} & \beta_1\bar{T}\\ \bar{\eta}(\lambda)(\lambda+d_T) & \lambda+\delta & 0\\ 0 & -b & \lambda+c\end{vmatrix}=0,$$

or

$$(\lambda+d_T\mathcal{R}_0)(\lambda+\delta)(\lambda+c)-b\beta_1\bar{T}\bar{\eta}(\lambda)(\lambda+d_T)-\beta_2\bar{T}\bar{\eta}(\lambda)(\lambda+d_T)(\lambda+c)=0.$$

This equation is equivalent to

$$\begin{aligned}
(\lambda+d_T\mathcal{R}_0)(\lambda+\delta)(\lambda+c)&=b\beta_1\bar{T}\bar{\eta}(\lambda)(\lambda+d_T)+\beta_2\bar{T}\bar{\eta}(\lambda)(\lambda+d_T)(\lambda+c)\\
&=(\lambda+d_T)\bar{\eta}(\lambda)\bar{T}[b\beta_1+\beta_2(\lambda+c)]\\
&=(\lambda+d_T)\bar{\eta}(\lambda)\left(\lambda\frac{h\beta_2}{d_T\mathcal{R}_0}+\frac{c\delta}{\eta}\right)\\
&=(\lambda+d_T)\frac{\delta\bar{\eta}(\lambda)}{\eta}\left(\lambda\frac{\mathcal{R}_{02}}{\mathcal{R}_0}+c\right),
\end{aligned}$$

that is,

$$(\lambda+d_T\mathcal{R}_0)\left(\frac{\lambda}{\delta}+1\right)(\lambda+c)=(\lambda+d_T)\frac{\bar{\eta}(\lambda)}{\eta}\left(\lambda\frac{\mathcal{R}_{02}}{\mathcal{R}_0}+c\right). \tag{3.6}$$

Assume $\lambda = x + iy$ is a solution of (3.6). We show that $x < 0$ if $\mathcal{R}_0 > 1$. Otherwise, $x \geq 0$ would imply

$$|\lambda + d_T\mathcal{R}_0| > |\lambda + d_T|, \ \left|\frac{\lambda}{\delta} + 1\right| \geq 1, \ |\lambda + c| > \left|\lambda\frac{\mathcal{R}_{02}}{\mathcal{R}_0} + c\right|, \ \left|\frac{\bar{\eta}(\lambda)}{\eta}\right| \leq 1,$$

and thus

$$\left|(\lambda + d_T\mathcal{R}_0)\left(\frac{\lambda}{\delta} + 1\right)(\lambda + c)\right| > \left|(\lambda + d_T)\frac{\bar{\eta}(\lambda)}{\eta}\left(\lambda\frac{\mathcal{R}_{02}}{\mathcal{R}_0} + c\right)\right|.$$

This is a contradiction to (3.6). Therefore, if $\mathcal{R}_0 > 1$, then all roots of (3.6) have negative real parts, implying that $\bar{E}$ is locally asymptotically stable. Thus, we have proven the following theorem.

THEOREM 3.2. *Let $\mathcal{R}_0$ be as in* (3.4). *If $\mathcal{R}_0 > 1$, model system* (1.4) *has a positive equilibrium $\bar{E}$ given by* (3.5) *which is locally asymptotically stable.*

Theorems 3.1 and 3.2 show that $\mathcal{R}_0$ defined by (3.4) determines whether or not an infection caused by a small inoculation/invasion of virus can persist. Indeed, $\mathcal{R}_0$ is the basic reproduction number of the model (1.4).

We can justify $\mathcal{R}_{01}$ and $\mathcal{R}_{02}$ in (3.4) from a biological point of view. $\mathcal{R}_{01}$ can be rewritten as

$$\mathcal{R}_{01} = \beta_1\frac{h}{d_T}\cdot\frac{1}{\delta}\cdot\eta\cdot\frac{b}{c},$$

where h/d_T is the total number of uninfected cells when all cells are uninfected; β_1 is the infection rate by free viruses; $1/\delta$ is the life span of infected cells; η is the total survival rate of infected cells at all ages; b is the burst size of viruses; $1/c$ is the virus clearance rate; and b/c represents the total number of virus particles produced efficiently from one infected cell. Therefore, $\mathcal{R}_{01}$ means the total number of newly infected cells that arise from any one infected cell when almost all cells are uninfected, where the infection occurs by free-virus infection of cells, that is, the basic reproduction number corresponding to virus-to-cell infection mode. Similarly, we rewrite $\mathcal{R}_{02}$ as

$$\mathcal{R}_{02} = \beta_2\frac{h}{d_T}\cdot\frac{1}{\delta}\cdot\eta,$$

where β_2 is the infection rate by the cell-to-cell transfer; $1/\delta$ is the life span of infected cells; and η is the total survival rate of infected cells at all ages. Therefore, $\mathcal{R}_{02}$ means the total number of newly infected cells that arise from any one infected cell when almost all cells are uninfected, where the infection occurs by virus-to-cell transfer, that is, the basic reproduction number corresponding to cell-to-cell infection mode.

To see this mathematically, we just need to look at the linearization of (1.4) at the infection-free equilibrium E_0, that is, system (3.1), which carries all information of virus dynamics when the virus population is very small. Note that variables $u_2(t)$ and $u_3(t)$ correspond to $T^*(t)$ and $V(t)$, and at low densities these two variables are governed only by the last two equations (decoupled from the first one). Let $u(t) = (u_2(t), u_3(t))^T$; then the equations of u_2 and u_3 in (3.1) can be rewritten as

$$\frac{d}{dt}u(t) = \int_0^\infty Bu(t-s)e^{-\mu s}f(s)ds - Cu(t),$$

where

$$B = \begin{bmatrix} \beta_2 \frac{h}{d_T} & \beta_1 \frac{h}{d_T} \\ 0 & 0 \end{bmatrix}, \quad C = \begin{bmatrix} \delta & 0 \\ -b & c \end{bmatrix}.$$

We assume the initial distributions of $u_2(t)$ and $u_3(t)$ are $\psi(\theta) = (\psi_2(\theta), \psi_3(\theta))$; then without new infection these populations evolve as

$$S_0(t)\psi := e^{-Ct}\psi.$$

If new infection occurs at time $t = 0$, since there is a time delay s, from the time of initial infection until becoming productively infectious, the total distributions of the new infection populations are

$$\begin{aligned} L\psi : &= \int_0^\infty \int_s^\infty Be^{-C(t-s)}\psi e^{-\mu s} f(s)dtds \\ &= \int_0^\infty B \int_s^\infty e^{-C(t-s)}dt \cdot \psi e^{-\mu s} f(s)ds \\ &= \int_0^\infty BC^{-1}\psi e^{-\mu s} f(s)ds \\ &= BC^{-1}\psi \int_0^\infty e^{-\mu s} f(s)ds \\ &= BC^{-1}\eta\psi. \end{aligned}$$

Notice that

$$C^{-1} = \frac{1}{c\delta}\begin{bmatrix} c & 0 \\ b & \delta \end{bmatrix}, \quad BC^{-1} = \frac{1}{c\delta}\begin{bmatrix} c\beta_2 \frac{h}{d_T} + b\beta_1 \frac{h}{d_T} & \beta_1 \delta \frac{h}{d_T} \\ 0 & 0 \end{bmatrix}.$$

Therefore,

$$\mathcal{R}_0 = \rho(L) = \rho(BC^{-1})\eta = \frac{1}{c\delta}\left[\beta_2 c\frac{h}{d_T} + \beta_1 b\frac{h}{d_T}\right] = \frac{\beta_1 hb\eta}{d_T c\delta} + \frac{\beta_2 h\eta}{d_T \delta}.$$

Making use of the result and procedure on the basic reproduction number for structured models (here there is the structure in infection age) in [39], we confirm that $\mathcal{R}_0$ is the basic reproduction number.

4. Persistence of infection. In this section, we will show that the model system is persistent when $\mathcal{R}_0 > 1$. Such a property itself is of some biological significance; in addition, it will be used in constructing the Lyapunov functional in section 5 to prove the global stability of the positive equilibrium.

Due to the infinite delay in the model, the solution semiflow of (1.4)–(2.2) may not be compact, and this brings in some mathematical challenge. In the following, just as in Röst and Wu [33], we will apply a theorem in Hale and Waltman [10] to achieve our goal. To this end, let $S(t)$, $t > 0$, be the solution semiflow of model system (1.4)–(2.2). Then, we shall make use of the following theorem on the semiflow $S(t)$ on X, which does not require $S(t)$ to be compact.

THEOREM 4.1 (Hale and Waltman [10, Theorem 4.2]). *Suppose we have the following:*

(i) X^0 *is an open and dense set in* X *with* $X^0 \cup X_0 = X$ *and* $X^0 \cap X_0 = \emptyset$*;*

(ii) $S(t)$ *satisfies* $S(t)X^0 \subset X^0$ *and* $S(t)X_0 \subset X_0$ *for* $t > 0$*;*

(iii) *$S(t)$ is point dissipative in X;*
(iv) *$\gamma^+(U)$ is bounded in X if U is bounded in X;*
(v) *$S(t)$ is asymptotically smooth;*
(vi) *$\mathcal{A} = \cup_{x\in A_b}\omega(x)$ is isolated and has an acyclic covering $Q = \cup_{i=1}^{k} Q_i$, where A_b is the global attractor of $S(t)$ restricted to X_0;*
(vii) *For each $Q_i \in Q$, $W^s(Q_i) \cap X^0 = \emptyset$, where W^s refers to the stable set.*
Then $S(t)$ is uniformly persistent; that is, there is a $\sigma > 0$ such that for any $x \in X^0$,

$$\liminf_{t\to\infty} d(S(t)x, X_0) \geq \sigma.$$

Applying the above theorem, we can prove the following persistence result for (1.4)–(2.2).

THEOREM 4.2. *For system* (1.4)*, if $\mathcal{R}_0 > 1$, then the solution semiflow $S(t)$ is uniformly persistent; that is, there exists a $\sigma > 0$ such that any solution of* (1.4)–(2.2) *satisfies*

$$\liminf_{t\to\infty} T(t) \geq \sigma, \quad \liminf_{t\to\infty} T^*(t) \geq \sigma, \quad \liminf_{t\to\infty} V(t) \geq \sigma.$$

Proof. Let X^0 be as in (2.2) and

$$X_0 = \{\phi = (\phi_1, \phi_2, \phi_3) \in X : \phi_2(\theta) = \phi_3(\theta) = 0 \text{ for all } \theta \in (-\infty, 0]\}.$$

We just need to verify the conditions in Theorem 4.1. (i) is obvious, and (ii) has been confirmed in section 2. We now prove (iii); that is, the solutions of (1.4)–(2.2) are ultimately bounded. By $\limsup_{t\to\infty} T(t) \leq h/d_T$, we know that there exists an $N_1 > 0$ such that $T(t) \leq h/d_T + 1$ for all $t > N_1$. Let M_1 be the maximum of $T(t)$ on $[0, N_1]$. Then, for any $0 < t \leq N_1$, we have

$$\begin{aligned}\|T_t\| &= \sup_{-\infty<\theta\leq 0} |T_t(\theta)|e^{\triangle\theta} = \sup_{-\infty<s\leq t} |T(s)|e^{\triangle s}e^{-\triangle t} \\ &\leq \max\left\{\|\phi_1\|e^{-\triangle t}, M_1 e^{\triangle t}e^{-\triangle t}\right\} \leq \max\left\{\|\phi_1\|, M_1\right\},\end{aligned}$$

and for $t > N_1$, we obtain

$$\begin{aligned}\|T_t\| &= \sup_{-\infty<\theta\leq 0} |T_t(\theta)|e^{\triangle\theta} = \sup_{-\infty<s\leq t} |T(s)|e^{\triangle s}e^{-\triangle t} \\ &\leq \max\left\{\|\phi_1\|e^{-\triangle t}, M_1 e^{\triangle N_1}e^{-\triangle t}, h/d_T + 1\right\}.\end{aligned}$$

Thus, there is an $N_2 > N_1$ such that

$$\|\phi_1\|e^{-\triangle t} \leq h/d_T + 1 \quad \text{and} \quad M_1 e^{\triangle N_1}e^{-\triangle t} \leq h/d_T + 1 \quad \text{for } t \geq N_2,$$

and therefore,

$$\|T_t\| \leq h/d_T + 1 =: T_M \text{ for } t \geq N_2. \tag{4.1}$$

Similarly, from $\limsup_{t\to\infty} T^*(t) \leq h\eta/d$ and $\limsup_{t\to\infty} V(t) \leq 2bh\eta/\delta d$ (see proof of Theorem 2.1), we know that there exist $N_3 > 0$ and $N_4 > 0$ such that

$$\|T_t^*\| \leq h\eta/d + 1 =: T_M^* \text{ for } t \geq N_3, \tag{4.2}$$

$$\|V_t\| \leq 2bh\eta/\delta d + 1 =: V_M \text{ for } t \geq N_4. \tag{4.3}$$

Thus, the solution $(T(t), T^*(t), V(t))$ is ultimately bounded; that is, $S(t)$ is point dissipative in X, proving (iii).

Noticing that the three bounds in (4.1), (4.2), and (4.3) are all independent of initial functions, condition (iv) is verified.

Next we verify condition (v): $S(t)$ is asymptotically smooth; that is, for any bounded subset U of X, for which $S(t)U \subset U$ for $t \geq 0$, there exists a compact set $\mathcal{M}$ such that $d(S(t)U, \mathcal{M}) \to 0$ as $t \to \infty$. Let U be an arbitrarily given bounded set in X, and let (T_t, T_t^*, V_t) be the segment of solution with initial condition $(\phi_1, \phi_2, \phi_3) \in U$. Set

$$\mathcal{M}_1 = \left\{ \phi \in C_\Delta^+ : \sup_{\theta \leq 0} \phi(\theta) e^{\frac{\Delta}{2}\theta} \leq T_M \right\},$$

$$\mathcal{M}_2 = \left\{ \phi \in C_\Delta^+ : \sup_{\theta \leq 0} \phi(\theta) e^{\frac{\Delta}{2}\theta} \leq T_M^* \right\},$$

$$\mathcal{M}_3 = \left\{ \phi \in C_\Delta^+ : \sup_{\theta \leq 0} \phi(\theta) e^{\frac{\Delta}{2}\theta} \leq V_M \right\},$$

and let $\mathcal{M} = \mathcal{M}_1 \times \mathcal{M}_2 \times \mathcal{M}_1$. It follows from Lemma 3.2 in Burton and Hutson [5] that $\mathcal{M}$ is compact in X. Then, by using exactly the same argument in proving $\lim_{t\to\infty} d(E_t, \mathcal{M}) = 0$ in the proof of Theorem 6.1 in Röst and Wu [33], we conclude that

$$\lim_{t\to\infty} d(T_t, \mathcal{M}_1) = 0, \quad \lim_{t\to\infty} d(T_t^*, \mathcal{M}_2) = 0, \quad \lim_{t\to\infty} d(V_t, \mathcal{M}_3) = 0.$$

Therefore, $S(t)$ is asymptotically smooth, proving (v).

For condition (vi), it is obvious that $\mathcal{A} = \{E_0\}$, and it is isolated, where $E_0 = (h/d_T, 0, 0)$. Thus the covering Q is simply $Q = \{E_0\}$, which is acyclic because there is no orbit connecting E_0 to itself in X_0.

Finally, we verify (vii). To show $W^s(E_0) \cap X^0 = \emptyset$, we suppose the opposite, that is, that there exists a solution $u_t \in X^0$ such that

$$\lim_{t\to\infty} T(t) = \frac{h}{d_T}, \quad \lim_{t\to\infty} T^*(t) = 0, \quad \lim_{t\to\infty} V(t) = 0.$$

Note that $\mathcal{R}_0 > 1$ is equivalent to

$$\frac{h}{d_T}\left(\frac{\beta_1 b}{c} + \beta_2\right) \int_0^\infty e^{-\mu s} f(s) ds > \delta.$$

Choose $\varepsilon > 0$ to be sufficiently small such that

$$\left(\frac{h}{d_T} - \varepsilon\right)\left(\frac{\beta_1 b}{c} + \beta_2\right) \int_0^\infty e^{-\mu s} f(s) ds > \delta. \tag{4.4}$$

For this ε, there exists a $\tau_0 > 0$ such that $T(t) > h/d_T - \varepsilon$ for all $t > \tau_0$. Truncating the integral in (4.4), there is another $\tau_1 > 0$ such that

$$\left(\frac{h}{d_T} - \varepsilon\right)\left(\frac{\beta_1 b}{c} + \beta_2\right) \int_0^{\tau_1} e^{-\mu s} f(s) ds > \delta. \tag{4.5}$$

Let $\tau_2 = \tau_0 + \tau_1$. Then, for $t \geq \tau_2$, we have

$$\begin{aligned}\frac{dT^*}{dt} &\geq \int_0^{\tau_1} [\beta_1 T(t-s)V(t-s) + \beta_2 T(t-s)T^*(t-s)]e^{-\mu s} f(s)ds - \delta T^*(t)\\ &= \int_{t-\tau_1}^{t} [\beta_1 T(\xi)V(\xi) + \beta_2 T(\xi)T^*(\xi)]e^{-\mu(t-\xi)} f(t-\xi)d\xi - \delta T^*(t)\\ &\geq \left(\frac{h}{d_T} - \varepsilon\right) \int_{t-\tau_1}^{t} [\beta_1 V(\xi) + \beta_2 T^*(\xi)]e^{-\mu(t-\xi)} f(t-\xi)d\xi - \delta T^*(t)\\ &= \left(\frac{h}{d_T} - \varepsilon\right) \int_0^{\tau_1} [\beta_1 V(t-s) + \beta_2 T^*(t-s)]e^{-\mu s} f(s)ds - \delta T^*(t).\end{aligned}$$

This suggests the following comparison system for $(T^*(t), V(t))$:

$$\begin{cases} n_1'(t) = \left(\dfrac{h}{d_T} - \epsilon\right) \displaystyle\int_0^{\tau_1} [\beta_1 n_2(t-s) + \beta_2 n_1(t-s)]e^{-\mu s} f(s)ds - \delta n_1(t),\\ n_2'(t) = bn_1(t) - cn_2(t)\end{cases} \tag{4.6}$$

for $t \geq \tau_2$. Notice that this is a monotone system, and hence, by the comparison theorem and the equations $\lim_{t\to\infty} T^*(t) = 0$ and $\lim_{t\to\infty} V(t) = 0$, one should have $\lim_{t\to\infty}(n_1(t), n_2(t)) = (0,0)$. On the other hand, the two equations for $n_1(t)$ and $n_2(t)$ are in the same forms of the second and third equations in (3.1), except the upper limit ∞ in the integral is replaced by τ_1 and the h/d_T is perturbed to $h/d_T - \varepsilon$. Repeating the same argument for proving the instability of E_0 in Theorem 3.1 and replacing the condition $\mathcal{R}_0 > 1$ by (4.5), we conclude that the characteristic equation of (4.6) has a positive real eigenvalue, which is a contradiction to $\lim_{t\to\infty}(n_1(t), n_2(t)) = (0,0)$. Thus, we have $W^s(E_0) \cap X^0 = \emptyset$, confirming condition (vii).

Now, by Theorem 4.1, there exists a $\sigma_1 > 0$ such that $\liminf_{t\to\infty} d(S(t)\phi, X_0) \geq \sigma_1$ for every $\phi \in X^0$, implying that the T^* and V components of the solution with initial function $\phi \in X^0$ satisfy

$$\liminf_{t\to\infty} \|T_t^*\| \geq \sigma_1 \ \text{ and } \ \liminf_{t\to\infty} \|V_t\| \geq \sigma_1.$$

By estimates similar to those in the proof of Theorem 2.1, we obtain

$$\liminf_{t\to\infty} T^*(t) > \sigma_1 \ \text{ and } \ \liminf_{t\to\infty} V(t) > \sigma_1. \tag{4.7}$$

It remains to show the persistence of $T(t)$. From (4.1) and (4.2), we have

$$\frac{dT(t)}{dt} > h - (d_T + \beta_1 T_M + \beta_2 T_M^*)T(t) \ \text{ for } \ t \geq N_5,$$

where $N_5 = \max\{N_3, N_4\}$. This means that whenever $T(t) < \sigma_2 := h/(d_T + \beta_1 T_M + \beta_2 T_M^*)$ with $t \geq N_5$, $T(t)$ will be increasing, which implies that $\liminf_{t\to\infty} T(t) > \sigma_2/2$. Taking $\sigma = \min\{\sigma_1, \sigma_2/2\}$, the proof of the theorem is completed. □

5. Global stability of equilibria. In this section, we prove that E_0 is actually *globally* asymptotically stable when $\mathcal{R}_0 < 1$, and so is $\bar{E}$ provided that $\mathcal{R}_0 > 1$. Therefore, the model (1.4) demonstrates global threshold dynamics. We shall achieve our goal by constructing an appropriate Lyapunov functional. The form of our Lyapunov functional is motivated by the Lyapunov function in [15], and similar functionals have

recently been applied to many other models, including some with infinite delays; see, e.g., [25, 26] and the references therein.

We first deal with the global asymptotic stability of E_0 under $\mathcal{R}_0 < 1$.

THEOREM 5.1. *If $\mathcal{R}_0 < 1$, the infection-free equilibrium E_0 is indeed globally asymptotically stable.*

Proof. Let $T_0 = h/d_T$, and let $(T(t), T^*(t), V(t))$ be a solution of system (1.4)–(2.2) satisfying $T(t) > 0$. Let

$$\Psi_{01}(T, T^*, V)(t) = T(t) - T_0 \ln \frac{T(t)}{T_0} + \frac{1}{\eta} T^*(t) + \frac{h\beta_1}{cd_T} V(t).$$

Calculating the time derivative of Ψ_{01} along (1.4), we have

$$\begin{aligned}
\tfrac{d}{dt}\Psi_{01}(t) = {} & \left(1 - \tfrac{T_0}{T(t)}\right)[h - d_T T(t) - \beta_1 T(t)V(t) - \beta_2 T(t)T^*(t)] \\
& + \tfrac{1}{\eta}\textstyle\int_0^\infty [\beta_1 T(t-s)V(t-s) + \beta_2 T(t-s)T^*(t-s)]e^{-\mu s} f(s)ds \\
& - \tfrac{\delta}{\eta} T^*(t) + \tfrac{h\beta_1}{d_T c}[bT^*(t) - cV(t)] \\
= {} & d_T T_0 \left(2 - \tfrac{T_0}{T(t)} - \tfrac{T(t)}{T_0}\right) - \beta_1 T(t)V(t) - \beta_2 T(t)T^*(t) \\
& + \beta_1 T_0 V(t) + \beta_2 T_0 T^*(t) \\
& + \tfrac{1}{\eta}\textstyle\int_0^\infty [\beta_1 T(t-s)V(t-s) + \beta_2 T(t-s)T^*(t-s)]e^{-\mu s} f(s)ds \\
& - \tfrac{\delta}{\eta} T^*(t) + \tfrac{h\beta_1}{d_T c}[bT^*(t) - cV(t)] \\
= {} & d_T T_0 \left(2 - \tfrac{T_0}{T(t)} - \tfrac{T(t)}{T_0}\right) + \beta_1 T_0 V(t) + \beta_2 T_0 T^*(t) - \tfrac{\delta}{\eta} T^*(t) \\
& + \tfrac{h\beta_1}{d_T c}[bT^*(t) - cV(t)] - \tfrac{1}{\eta}\textstyle\int_0^\infty f(s)e^{-\mu s}[\beta_1 T(t)V(t) \\
& + \beta_2 T(t)T^*(t) - \beta_1 T(t-s)V(t-s) - \beta_2 T(t-s)T^*(t-s)]ds \\
= {} & d_T T_0 \left(2 - \tfrac{T_0}{T(t)} - \tfrac{T(t)}{T_0}\right) + \tfrac{\delta}{\eta}(\mathcal{R}_0 - 1)T^*(t) \\
& - \tfrac{1}{\eta}\textstyle\int_0^\infty f(s)e^{-\mu s}[\beta_1 T(t)V(t) + \beta_2 T(t)T^*(t) \\
& - \beta_1 T(t-s)V(t-s) - \beta_2 T(t-s)T^*(t-s)]ds.
\end{aligned} \tag{5.1}$$

In light of the integral term in the last equation in (5.1), we define

$$\Psi_{02}(T, T^*, V)(t) = \int_0^\infty f(s)e^{-\mu s} \int_{t-s}^t [\beta_1 T(\tau)V(\tau) + \beta_2 T(\tau)T^*(\tau)]d\tau ds.$$

Then,

$$\begin{aligned}
\frac{d}{dt}\Psi_{02}(t) = & \int_0^\infty f(s)e^{-\mu s}[\beta_1 T(t)V(t) + \beta_2 T(t)T^*(t) \\
& - \beta_1 T(t-s)V(t-s) - \beta_2 T(t-s)T^*(t-s)]ds.
\end{aligned}$$

Using $\Psi_{01}(t)$ and $\Psi_{02}(t)$, we define the following functional:

$$\Psi_0(t) = \Psi_{01}(t) + \frac{1}{\eta}\Psi_{02}(t).$$

Then

$$\frac{d}{dt}\Psi_0(t) = d_T T_0 \left(2 - \frac{T_0}{T(t)} - \frac{T(t)}{T_0}\right) + \frac{\delta}{\eta}(\mathcal{R}_0 - 1)T^*(t). \tag{5.2}$$

Notice that

$$2-\frac{T_0}{T(t)}-\frac{T(t)}{T_0}\le 0$$

for all $T(t)>0$, and the equality holds if and only if $T(t)=T_0$. Hence if $\mathcal{R}_0<1$, then $\Psi_0'(t)\le 0$. Let $E=\{(T(t),T^*(t),V(t)):\Psi_0'(t)=0\}$ and M be the largest invariant set in E. By the LaSalle invariance principle (e.g., [11, Theorem 5.3.1] or [22, Theorem 2.5.3]), all nonnegative solutions tend to M. Note that $\Psi_0'(t)=0$ if and only if $T(t)=T_0$ and $T^*(t)=0$. Using this and the invariance of M, we easily see that M is indeed the singleton $M=\{E_0\}$, showing that every nonnegative solution with $T(t)>0$ indeed approaches E_0. Hence E_0 is globally attractive under $\mathcal{R}_0<1$, which, together with the local stability of E_0 established in section 3, confirms the global asymptotic stability of E_0 under $\mathcal{R}_0<1$. ∎

For $\bar{E}$, we also have the following theorem about its global stability.

THEOREM 5.2. *If $\mathcal{R}_0>1$, then any solution $u(t)=(T_t,T_t^*,V_t)$ of (1.4)–(2.2) converges to the positive equilibrium $\bar{E}$, that is,*

$$\lim_{t\to\infty}(T(t),T^*(t),V(t))=(\bar{T},\bar{T}^*,\bar{V}).$$

Proof. For convenience of notation, we denote $P(x)=x-1-\ln x$ and let

$$\begin{aligned}\Psi_1(T,T^*,V)(t)&=T(t)-\bar{T}\ln\frac{T}{\bar{T}}+\frac{1}{\eta}\left[T^*(t)-\bar{T}^*\ln\frac{T^*(t)}{\bar{T}^*}\right]\\&\quad+\frac{\beta_1\bar{T}\bar{V}}{\bar{T}^*b}\left[V(t)-\bar{V}\ln\frac{V(t)}{\bar{V}}\right],\\\Psi_{11}(T,V)(t)&=\int_0^\infty e^{-\mu s}f(s)\int_{t-s}^t P\left(\frac{T(\tau)V(\tau)}{\bar{T}\bar{V}}\right)d\tau ds,\\\Psi_{12}(T,T^*)(t)&=\int_0^\infty e^{-\mu s}f(s)\int_{t-s}^t P\left(\frac{T(\tau)T^*(\tau)}{\bar{T}\bar{T}^*}\right)d\tau ds.\end{aligned}$$

By the boundedness and persistence of solutions established in sections 2 and 4, and the assumption that $f(s)$ has compact support, we know that the above functions are well defined for large t. Let

$$\Psi_2(t)=\Psi_1(t)+\frac{\beta_1\bar{T}\bar{V}}{\eta}\Psi_{11}(t)+\frac{\beta_2\bar{T}\bar{T}^*}{\eta}\Psi_{12}(t).$$

Taking the derivative of $\Psi_2(t)$ and making use of the equations defining the positive equilibrium $\bar{E}$, we obtain, after simplifications, the following:

$$\begin{aligned}\frac{d}{dt}\Psi_2(t)&=\frac{d_T}{\bar{T}}\left(2-\frac{\bar{T}}{T(t)}-\frac{T(t)}{\bar{T}}\right)+\frac{\beta_1\bar{T}\bar{V}}{\eta}\int_0^\infty e^{-\mu s}f(s)\left[3-\frac{\bar{T}}{T(t)}\right.\\&\quad\left.-\frac{\bar{T}^*T(t-s)V(t-s)}{T^*(t)\bar{T}\bar{V}}-\frac{T^*(t)\bar{V}}{\bar{T}^*V(t)}+\ln\frac{T(t-s)V(t-s)}{T(t)V(t)}\right]ds\\&\quad+\frac{\beta_2\bar{T}\bar{T}^*}{\eta}\int_0^\infty\left[2-\frac{\bar{T}}{T(t)}-\frac{T(t-s)T^*(t-s)}{\bar{T}T^*(t)}+\ln\frac{T(t-s)T^*(t-s)}{T(t)T^*(t)}\right]ds.\end{aligned}$$

Notice that

$$2-\frac{\bar{T}}{T(t)}-\frac{T(t)}{\bar{T}}\le 0. \tag{5.3}$$

Also note that $P(x) \geq 0$ for all $x \in (0, \infty)$ and $P(x) = 0$ if and only if $x = 1$. Making use of this function $P(x)$, we have

$$3 - \frac{\bar{T}}{T(t)} - \frac{\bar{T}^* T(t-s)V(t-s)}{T^*(t)\bar{T}\bar{V}} - \frac{T^*(t)\bar{V}}{\bar{T}^* V(t)} + \ln \frac{T(t-s)V(t-s)}{T(t)V(t)} \tag{5.4}$$
$$= -P\left(\frac{\bar{T}}{T(t)}\right) - P\left(\frac{\bar{T}^* T(t-s)V(t-s)}{T^*(t)\bar{T}\bar{V}}\right) - P\left(\frac{T^*(t)\bar{V}}{\bar{T}^* V(t)}\right) \leq 0,$$

and

$$2 - \frac{\bar{T}}{T(t)} - \frac{T(t-s)T^*(t-s)}{\bar{T}T^*(t)} + \ln \frac{T(t-s)T^*(t-s)}{T(t)T^*(t)} \tag{5.5}$$
$$= -P\left(\frac{\bar{T}}{T(t)}\right) - P\left(\frac{T(t-s)T^*(t-s)}{\bar{T}T^*(t)}\right) \leq 0$$

for all $T(t)$, $T^*(t)$, $V(t) > 0$. Thus $\Psi_2'(t) \leq 0$. Let $E = \{(T(t), T^*(t), V(t)) : \Psi_2'(t) = 0\}$, and let M be the largest invariant set in E. By the LaSalle invariance principle (e.g., [11, Theorem 5.3.1] or [22, Theorem 2.5.3]) and Theorem 2.1, every positive solution tends to M.

It remains to show that $M = \{\bar{E}\}$. From (5.3), (5.4), and (5.5), we know that

$$\frac{d}{dt}\Psi_2(t) = 0,$$
$$\Leftrightarrow \begin{cases} T(t) = \bar{T}, \quad \bar{T}^* T(t-s)V(t-s) = T^*(t)\bar{T}\bar{V}, \quad T^*(t)\bar{V} = \bar{T}^* V(t), \\ T(t-s)V(t-s) = T(t)V(t), \ T(t-s)T^*(t-s) = \bar{T}T^*(t), \\ T(t-s)T^*(t-s) = T(t)T^*(t), \end{cases}$$
$$\Leftrightarrow \begin{cases} T(t) = \bar{T}, \quad T^*(t)\bar{V} = \bar{T}^* V(t), \\ T(t-s)V(t-s) = \bar{T}V(t), \quad T(t-s)T^*(t-s) = \bar{T}T^*(t). \end{cases}$$

Applying $T^*(t)\bar{V} = \bar{T}^* V(t)$ to the third equation in (1.4), we have $\frac{dV(t)}{dt} = 0$, meaning that $V(t)$ is a constant; this in turn implies that $T^*(t)$ is also a constant. Since $T(t) = \bar{T}$, by the uniqueness of the positive equilibrium, we then conclude that $T^*(t) = \bar{T}$ and $V(t) = \bar{V}$. Therefore, $M = \{\bar{E}\}$; that is, $\bar{E}$ is globally attractive for all positive solutions. The global attractivity and the local stability of $\bar{E}$ proved under $\mathcal{R}_0 > 1$ lead to the global asymptotic stability of $\bar{E}$, completing the proof. ∎

6. Conclusion and discussion. HIV-1 has two predominant infection modes: the classical virus-to-cell infection and cell-to-cell spread. In the classical virus-to-cell infection, viruses released from infected cells randomly move around to find a new target cell to infect. Recently, it was revealed that HIV-1 infection may also occur by the transfer of viruses through direct contact between infected cells and uninfected cells via certain structures, such as membrane nanotubes or macromolecular adhesive contacts termed virological synapses [36]. During this cell-to-cell transmission, many viral particles can be simultaneously transferred from infected to uninfected $CD4^+$ T cells.

In this paper, we have considered a mathematical model to describe the presence of both of these transmission modes. By a rigorous analysis, we have shown that the model has a threshold dynamics. Such a threshold dynamics is fully determined by the basic reproduction number $\mathcal{R}_0$ in the sense that the infection-free equilibrium E_0

is globally asymptotically stable if $\mathcal{R}_0 < 1$, and when $\mathcal{R}_0 > 1$, E_0 yields to a globally asymptotically stable positive equilibrium $\bar{E}$, implying the infection will persist.

Examining the formula for the basic reproduction number $\mathcal{R}_0$, we found that it is larger than that given in existing models that considered only one infection mode. Indeed, note that when $\beta_1 = 0$, meaning that infection is exclusively through cell-to-cell transmission, which is the scenario of the work in [3], the basic reproduction number $\mathcal{R}_0$ reduces to $\mathcal{R}_{02}$. This would be the basic reproduction number of the corresponding model that ignores the virus-to-cell infection mode. Similarly, when $\beta_2 = 0$, $\mathcal{R}_0$ reduces to $\mathcal{R}_{01}$, which is exactly the basic reproduction number for the corresponding model that neglects the cell-to-cell transmission mechanism. Therefore, we see that our model not only reveals that the basic reproduction number of the model that neglects either the cell-to-cell spread or virus-to-cell infection is underevaluated, but also tells us precisely by how much it is underevaluated, reflected by the relation $\mathcal{R}_0 = \mathcal{R}_{01} + \mathcal{R}_{02}$ and the formulas for $\mathcal{R}_{01}$ and $\mathcal{R}_{02}$ in (3.4). This formula also reflects the impact of the infection age through the distribution function $f(s)$.

Cell-to-cell spread not only facilitates rapid viral dissemination but may also promote immune invasion and influence disease [23]. Cell-to-cell spread of HIV-1 may also reduce the effectiveness of neutralizing antibodies and viral inhibitors. However, it is unclear whether this mode of viral spread is susceptible or resistant to inhibition by neutralizing antibodies and entry inhibition. There are ongoing controversies in this field of study [2, 24]. Considering the antiretroviral therapy of reverse transcriptase (RT) inhibitor and incorporating the efficacy of the RT inhibitor in same way as in [28] (see (1.2)), our model (1.4) now reads

$$
\begin{cases}
\frac{dT(t)}{dt} &= h - d_T T(t) - (1-n_1)\beta_1 V(t)T(t) - (1-n_2)\beta_2 T(t)T^*(t), \\
\frac{dT^*(t)}{dt} &= \int_0^\infty f(s)e^{-\mu s}[(1-n_1)\beta_1 T(t-s)V(t-s) \\
&\qquad +(1-n_2)\beta_2 T(t-s)T^*(t-s)]\,ds - \delta T^*(t), \\
\frac{dV(t)}{dt} &= bT^*(t) - cV(t),
\end{cases}
\tag{6.1}
$$

where n_1 denotes the efficacy of the RT inhibitor inhibiting the virus-to-cell infection and n_2 represents the efficacy of the RT inhibitor with respect to the cell-to-cell channel. Comparing (6.1) to (1.4), we see that the basic reproduction number for (6.1) is

$$
\hat{\mathcal{R}}_0 = \frac{(1-n_1)\beta_1 \eta h b}{d_T \delta c} + \frac{(1-n_2)\beta_2 \eta h}{d_T \delta} =: \hat{\mathcal{R}}_{01} + \hat{\mathcal{R}}_{02}.
$$

It follows that if the RT inhibitor is very effective for inhibition of virus-to-cell infection, then large n_1 would make $\hat{\mathcal{R}}_{01}$ less than one, meaning that the virus would be eliminated by the therapy in the absence of cell-to-cell transmission ($\beta_2 = 0$). However, if cell-to-cell transmission coexists ($\beta_2 > 0$) and is less sensitive to the RT inhibitor, then n_2 could be small, such that $\hat{\mathcal{R}}_{02} > 1$. Thus $\hat{\mathcal{R}}_0 > 1$, meaning the virus would persist. The virus can be cleared if and only if the RT inhibitor is effective for both modes of infections, such that $\hat{\mathcal{R}}_0 < 1$.

In our model, we do not consider multiple infection per cell which may occur by synaptic transmission. However, the high efficiency of infection by large numbers of virions is likely to result in a transfer of multiple virions to a target cell [6, 14]. Komarova, Levy, and Wodarz [18] and Komarova and Wodarz [19] considered multiple infection during the cell-to-cell transmission by mathematical modeling and explored

the effect of different strategies of the virus (that is, the number of viruses passed per synapse) on the basic reproductive ratio of the virus. They showed that the strategy of single virus transmission per synapse maximizes the reproductive ratio if the synapses can be formed quickly and the process of infection is independent of the number of resident viruses, while strategies with intermediate numbers of viruses transferred correspond to the highest values of the basic reproductive number if the synapse formation is slow or if the multiplicity of infection strongly influences the kinetics of virus production. Multiple infection of the same cell may waste a large number of viruses that could otherwise enter uninfected target cells; hence fewer newly infected cells are generated, and the infection eventually cannot be maintained for larger numbers of transferred viruses.

Multiple infections may reduce the sensitivity to antiretroviral therapies. Sigal et al. [38] showed that cell-to-cell spread of HIV-1 is sufficient to reduce the efficacy of antiretroviral therapy. A possible explanation is that the cell-to-cell transmission may play a significant role for multiple infections per target cell, which reduced sensitivity to drugs. They found that virus-to-cell infection was efficiently prevented by *tenofovir* and *efavirenz*. In the presence of *tenofovir*, virus-to-cell infection declined thirtyfold. But once infection becomes established, cell-to-cell transfer through direct contact between cells becomes possible (likely dominant), and the infection is much less affected by the presence of drugs. Sigal et al. [38] attempted to explain why highly potent regimens that target several different steps in the HIV-1 life cycle cannot shut down replication, despite reducing HIV-1 replication to very low levels, which could be due to cell-to-cell transfer of multiple virions and the drugs' inability to inhibit replication when virus levels are high.

However, Permanyer et al. [32] argued that the results of Sigal et al. depend on their particular experimental conditions and that the results therefore might not be correct. Permanyer et al. also pointed out that the conclusion of drug resistance of cell-to-cell transfer by Sigal et al. was obtained under the incorrect assumption that each virus transferred will lead to a productive infection. They found that antiretroviral drugs, such as the RT inhibitors *zidovudine* and *tenofovir*, and the attachment inhibitor IgGb120, are able to block virus replication with similar efficacy to cell-free virus infections. That indicates that cell-to-cell transmission may not allow for ongoing virus replication in the presence of antiretroviral therapy.

Komarova, Levy, and Wodarz [20] explored the role of synaptic transmission in susceptibility of HIV-1 infection to antiretroviral drugs using a virus infection dynamical model with multiple infections. They found that multiple infections via synapses do not simply reduce susceptibility to treatment, which depends on the relative probability of individual virions to infect a cell during cell-free virus and cell-to-cell virus transmission. If this probability is higher for cell-free virus transmission, then susceptibility to antiretroviral drugs is lowest when a single virus is transferred per synapse, which maximizes the release of free virus. On the other hand, if the infection probability is higher for synaptic transmission, then they found that the susceptibility to antiretroviral drugs is minimized for an intermediate number of virions transferred per synapse. Further experimental investigations are needed to determine whether the virus persists by synaptic transmission during antiretroviral therapy.

HIV-1 infection can be very effectively suppressed with antiretroviral therapy, a combination of drugs that block various steps in the HIV-1 lifecycle such as the ability of the virus to reversely transcribe its RNA genome to DNA (RT inhibitor), integrate DNA into the cell genome, or make viable new virions by the cleavage of

viral protein precursors (protease inhibitor). However, these antiretroviral therapies cannot completely eliminate HIV-1 infection, and the infection can re-establish itself within weeks after therapy interruption. The main reason is the existence of a reservoir of infected cells that are insensitive to drugs, which could be latently infected cells consisting of those that are quiescent in the genomically integrated form, long-lived infected cells, or those on ongoing transmission cycles called ongoing replication. It is believed that the reservoir of infected cells is enough to cause a huge rebound in viral load within weeks after stopping an antiretroviral treatment. Considering an antiretroviral therapy in the presence of both cell-free and cell-to-cell transmissions seems to be an interesting yet worthy project.

In our model (1.4), we have assumed that target cells $T(t)$ are produced at a constant rate h and have a constant death rate d_T. It would be more reasonable to consider the density dependent production rate. One possibility is to assume a logistic growth for the healthy cells in the absence of infection, as in [4]. We leave this as a future project.

Acknowledgment. The authors are grateful to the two anonymous referees for their valuable and helpful comments, which greatly improved the paper.

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