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ANALYSIS OF HIV-1 MODEL: WITHIN HOST CELL TO CELL VIRAL TRANSMISSION WITH ART

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Abstract. Mathematical model for the effect of antiretroviral therapy on the dynamics of HIV-1 infection model with three distributed delays are proposed and analyzed. The effect of time delay on stability of the equilibria of the system has been studied and sufficient condition for local asymptotic stability infection free and chronic infected equilibrium. 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 under evaluated.

1. Introduction

Mathematical modeling of within host virus models has flourished over the past few decades. These models have been used to describe the dynamics inside the host of various infectious diseases such as HIV, HCV, HTLV, as well as the flu or even the malaria parasite. However, recent studies have revealed that a large number of viral particles can also be transformed from infected cells to uninfected cell through the formation of virally induced structure termed virological synapses [6]. Indeed, the direct cell to cell transmission of HIV-I is found to be more potent and efficient means of virus propagation than the virus to cell transmission mechanism. Cell to cell spread of HIV-I may educe

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the effectiveness of neutralizing antibodies and viral inhibitors. However, it is unclear whether this mechanism of HIV-I viral spread is susceptible or resistant to inhibition (by neutralizing antibodies) and to entry inhibition, causing some controversy in this field of study [2, 10].

On the other hand, great attention has also been paid to the study of in *vitro* cell to cell spread of virus since many features are easier to determine experimentally in tissue cultures than in the blood stream. For example, HIV is thought to be active in areas such as lymphnodes and the brain where cell to cell spread would be much more important mode of infection than virus to cell spread [3, 16]. Nowadays, a large number of deterministic models have been developed to describe the immune system and its interaction with HIV as well as the effects of drug therapy [11, 13].

Antiretroviral therapy slows the clinical progression of HIV infection at the beginning of the therapy. However drug resistance due to viral mutation typically occurs after some time and poses a challenging problem for long-term treatments. Some studies have speculated that alternating between drug regimens on a fixed schedule might forestall therapeutic failure. Early stages of the virus evolution are assumed to be mutation free. During further stages, the virus mutation can no longer be ignored. This is considered for instance in [5] in which the mutation of the virus is modeled using switching systems, which include 64 virus strains and three drug combinations. This issue remains the topic of ongoing research. Motivated by the works [12], recently, many authors discussed HIV-I virus dynamics for both virus to cell and cell to cell transmissions models in [8, 18].

Here we consider $x_1(t), x_2(t), x_3(t)$ and $x_4(t)$ are the concentration of uninfected target cells, infected cells that are producing virus, after protease inhibitors are given, virus is classified as either infectious, x_3 , i.e., not influenced by the protease inhibitor, or as non-infectious, x_4, due to the action of the protease inhibitor which prevents virion maturation into infectious particles at time t, respectively. The infected cells may die or be cleared at rate γ_1, before become productively infected and thus after a time period of length τ_1, only a proportion $e^{-\gamma_1\tau_1}$ survives. The infectious and non-infectious virion cells may be die or be cleared at rate γ_2 and γ_3, before generating new virus cells, and thus after a time period of length τ_2 and τ_3, only a proportion $e^{-\gamma_i\tau_i},\ i = 2, 3$ survives. The time for infected cells to become productively infected may vary from individual to individual, and hence a distribution function $f_1(\tau_1)$ is introduced to account for such variance. Similarly for generation of new virus cells may vary from individual to individual, and hence a distribution function $f_i(\tau_i)\ i = 2, 3$. Note that $\tau_1,\ \tau_2$ and τ_3 are all integration variables, withoutloss of generality they all will represented as τ. Now, we

present the following DDE model for antiretroviral therapy for both virus to cell and cell to cell transmission model is given by

$$\begin{aligned}
\dot{x_1}(t) &= h - dx_1(t) - (1-\eta_1)\beta_1 x_1(t)x_3(t) - (1-\eta_2)\beta_2 x_1(t)x_2(t),\\
\dot{x_2}(t) &= \int_0^\infty \{(1-\eta_1)\beta_1 x_1(t-\tau)x_3(t-\tau) + (1-\eta_2)\beta_2 x_1(t-\tau)x_2(t-\tau)\}\\
&\quad \times e^{-\gamma_1\tau} f_1(\tau)d\tau - \mu_1 x_2(t),\\
\dot{x_3}(t) &= \int_0^\infty (1-\eta_3) b x_2(t-\tau) e^{-\gamma_2\tau} f_2(\tau)d\tau - cx_3(t),\\
\dot{x_4}(t) &= \int_0^\infty \eta_3 b x_2(t-\tau) e^{-\gamma_3\tau} f_3(\tau)d\tau - cx_4(t), \qquad (1.1)
\end{aligned}$$

where η_1 and η_2 are the effectiveness of the RTI in preventing new infections from virus to cell and cell to cell transmission mode. η_3 is the efficacy of the protease inhibitor. Thus, $\eta_1,\ \eta_2,\ \eta_3 = 1$ corresponds to a completely effective drug therapy while $\eta_1,\ \eta_2,\ \eta_3 = 0$ represents a null therapy.

Table I:

Parameters description and Values

Parameter	**Description**
h	Rate at which new uninfected cells are generated
d	death rate of uninfected cells
β_1	infection rate of free virus
β_2	infection rate of productively infected cells
μ_1	death rate of infected cells
b	Rate at which new virus cells are generated
c	death rate of infected cells

2. Preliminaries

In ref [7], we consider, for each $\alpha > 0$, the Banach space of fading memory type,

$$\begin{aligned}
\mathcal{C} &= \{\phi \in C((-\infty,0],\mathbb{R}^4) : \ell \to \phi(\ell)e^{\rho\ell} \text{ is uniformly continuous on}\\
&\quad (-\infty,0] \text{ and } \sup_{\ell\le 0}|\phi(\ell)|e^{\rho\ell} < \infty\},
\end{aligned}$$

where ρ is a positive constant and endowed with the norm $||\phi|| = \sup_{\ell\le 0}|\phi(\ell)|e^{\rho\ell}$. The nonnegative cone of $\mathcal{C}$ is defined by $\mathcal{C}_+ = C((-\infty,0],\mathbb{R}^4_+)$. For $\phi \in \mathcal{C}$, let $\phi_t \in \mathcal{C}$ as $\phi_t(\theta) = \phi(t+\theta), \theta \in (-\infty,0]$. We consider solutions $x_1(t), x_2(t), x_3(t), x_4(t)$ of system (1.1) with initial conditions

$$(x_1(0), x_2(0), x_3(0), x_4(0)) \in {\mathcal{C}_+}^4 = \mathcal{C}_+ \times \mathcal{C}_+ \times \mathcal{C}_+ \times \mathcal{C}_+. \qquad (2.1)$$

i.e., initial functions taken from the natural positive cone of this phase space given by $Z := \mathcal{C}_+ \times \mathcal{C}_+ \times \mathcal{C}_+ \times \mathcal{C}_+$, denote $Z = Z^0 \bigcup Z_0 = \mathcal{C}_+$, Z^0 is open and dense set in Z, where $\mathcal{C}_+ = \{\phi \in \mathcal{C} : \phi(0) \geq 0 \text{ for } \theta \in (-\infty, 0]\}$. By the standard theory and functional differential equations [7, 4], we can obtain the existence of solutions for $t > 0$. Let

$$\delta_i = \int_0^\infty e^{-\gamma_i \tau} f_i(\tau) d\tau, \quad i = 1, 2, 3.$$

Theorem 2.1. *Let $x_1(t), x_2(t), x_3(t), x_4(t)$ be the solution of the system* (1.1) *with initial conditions* (2.1) *are ultimately uniformly bounded for $t > 0$.*

Proof. Note that from (1.1), we obtain

$$\begin{aligned}
x_1(t) &= x_1(0)e^{-dt} + \int_0^t h e^{-d(t-\xi)} d\xi - \int_0^t \{(1-\eta_1)\beta_1 x_1(\xi) x_3(\xi) \\
&\quad + (1-\eta_2)\beta_2 x_1(\xi) x_2(\xi)\} e^{-d(t-\xi)} d\xi, \\
x_2(t) &= x_2(0)e^{-\mu_1 t} + \int_0^t \int_0^\infty \{(1-\eta_1)\beta_1 x_1(\xi) x_3(\xi) \\
&\quad + (1-\eta_2)\beta_2 x_1(\xi) x_2(\xi)\} e^{-\gamma_1 \tau} f(\tau) d\tau e^{-\mu_1 (t-\xi)} d\xi, \\
x_3(t) &= x_3(0)e^{-ct} + \int_0^t \int_0^\infty (1-\eta_3) b f(\tau) e^{-\gamma_2 \tau} d\tau e^{-c(t-\xi)} d\xi, \\
x_4(t) &= x_3(0)e^{-ct} + \int_0^t \int_0^\infty \eta_3 b f(\tau) e^{-\gamma_3 \tau} d\tau e^{-c(t-\xi)} d\xi. \qquad (2.2)
\end{aligned}$$

Using (2.1), we have $x_1(t) \geq 0,\ x_2(t) \geq 0,\ x_3(t) \geq 0,\ x_4(t) \geq 0, \forall t \geq 0$. Hence for all $t \geq 0$, our solution $(x_1(t), x_2(t), x_3(t), x_4(t)) \in {\mathcal{C}_+}^4$ with all parameters in ${\mathcal{C}_+}^4$.

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

$$\dot{x_1}(t) \leq h - d x_1(t).$$

It follows that $\limsup_{t\to\infty} \leq \dfrac{h}{d}$, implying that $x_1(t)$ is bounded.

Next we prove the boundedness of $x_2(t)$. To this end, we define

$$G(t) = \int_0^\infty e^{-\gamma_1 \tau} f(\tau) x_1(t-\tau) d\tau + x_2(t).$$

Since $x_1(t)$ is bounded and $\int_0^\infty f(\tau) d\tau$ 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 differentiable and integration can be

switched. Thus, we have

$$\begin{aligned}
\dot{G}(t) &= h\int_0^\infty e^{-\gamma_1\tau}f(\tau)d\tau - d\int_0^\infty e^{-\gamma_1\tau}f(\tau)x_1(t-\tau)d\tau \\
&\quad -\int_0^\infty \{(1-\eta_1)\beta_1 x_1(t-\tau)x_3(t-\tau)+(1-\eta_2)\beta_2 x_1(t-\tau)x_2(t-\tau)\} \\
&\quad \times e^{-\gamma_1\tau}f(\tau)d\tau + \int_0^\infty \{(1-\eta_1)\beta_1 x_1(t-\tau)x_3(t-\tau) \\
&\quad +(1-\eta_2)\beta_2 x_1(t-\tau)x_2(t-\tau)\}\, e^{-\gamma_1\tau}f(\tau)d\tau - \mu_1 x_2(t) \\
&= h\int_0^\infty e^{-\gamma_1\tau}f(\tau)d\tau - d\int_0^\infty e^{-\gamma_1\tau}f(\tau)x_1(t-\tau)d\tau - \mu_1 x_2(t), \\
&\leq h\delta_1 - mG(t),
\end{aligned}$$

where

$$\delta_i = \int_0^\infty e^{-\gamma_i\tau}f(\tau)d\tau, \quad i=1,2,3, \quad m=\min\{d,\mu_1\}>0.$$

Therefore, $\limsup_{t\to\infty} G(t) \leq \dfrac{h\delta_1}{m}$, implying that $\limsup_{t\to\infty} x_2(t) \leq \dfrac{h\delta_1}{m}$. So, $x_2(t)$ is bounded. Then from the third and fourth equation of system (1.1), we have

$$\begin{aligned}
\dot{x_3}(t)+\dot{x_4}(t) &\leq b\int_0^\infty (1-\eta_3)x_2(t-\tau)e^{-\gamma\tau}f(\tau)d\tau - c(x_3(t)+x_4(t)), \\
&\leq \frac{bh\delta_1}{m} - c(x_3(t)+x_4(t)),
\end{aligned}$$

where

$$\gamma=\gamma_2+\gamma_3, \quad X=x_3+x_4.$$

Thus, $\limsup_{t\to\infty} X(t) \leq \dfrac{bh\delta_1}{cm}$, which implies that $\limsup_{t\to\infty} x_3(t) \leq \dfrac{bh\delta_1}{cm}$ and $\limsup_{t\to\infty} x_4(t) \leq \dfrac{bh\delta_1}{cm}$. Therefore $x_1(t), x_2(t), x_3(t)$ and $x_4(t)$ are ultimately uniformly bounded. □

Remark 2.2. Theorem 2.1 implies that omega limit set of system (1.1) are contained in the following bounded feasible region:

$$\begin{aligned}
\Lambda &= \left\{(x_1(t),x_2(t),x_3(t),x_4(t)) \in C_+^4 : ||x_1(t)|| \leq x_1^0, ||x_2(t)|| \leq \frac{h\delta_1}{m},\right. \\
&\quad \left. ||x_3(t)|| \leq \frac{bh\delta_1}{cm}, ||x_4(t)|| \leq \frac{bh\delta_1}{cm}\right\}.
\end{aligned}$$

It can be verified that the region Λ is positively invariant with respect to the system (1.1) and the system is well posed.

System (1.1) has an infection free equilibrium $I_0 = (x_1^0, 0, 0, 0)$, where $x_1^0 = \dfrac{h}{d}$. We define the basic reproduction number as follows:

$$\begin{aligned} R_0 &= R_{01} + R_{02} \\ &= \frac{(1-\eta_1)\beta_1 x_1^0 \delta_1 (1-\eta_3) b \delta_2}{\mu_1 c} + \frac{(1-\eta_2)\beta_2 x_1^0 \delta_1}{\mu_1} \end{aligned}$$

which represents the average number of secondary infections. In fact, $\dfrac{(1-\eta_1)\beta_1 x_1^0 \delta_1 (1-\eta_3) b.\delta_2}{\mu_1 c}$ is the average number of secondary viruses caused by a virus, that is the basic reproduction number corresponding to virus to cell transmission mode, while $\dfrac{(1-\eta_2)\beta_2 x_1^0 \delta_1}{\mu_1}$ is the average number of secondary infected cells caused by an infected cell, that is the basic reproduction number corresponding to cell to cell transmission mode.

3. Local stability of equilibria

System (1.1) has the infection-free equilibrium $I_0 = (h/d, 0, 0, 0)$. In order to determine the stability of I_0, we consider the linearization (1.1) at I_0:

$$\begin{aligned} \dot{y_1}(t) &= -dy_1(t) - (1-\eta_1)\beta_1 \frac{h}{d} y_3(t) - (1-\eta_2)\beta_2 \frac{h}{d} y_2(t) \\ \dot{y_2}(t) &= \int_0^\infty \left\{ (1-\eta_1)\beta_1 \frac{h}{d} y_3(t-\tau) + (1-\eta_2)\beta_2 \frac{h}{d} y_2(t-\tau) \right\} e^{-\gamma_1 \tau} f(\tau) d\tau \\ & -\mu_1 y_2 \\ \dot{y_3}(t) &= \int_0^\infty (1-\eta_3) b y_2(t-\tau) e^{-\gamma_2 \tau} f(\tau) d\tau - c y_3, \\ \dot{y_4}(t) &= \int_0^\infty \eta_3 b y_2(t-\tau) e^{-\gamma_3 \tau} f(\tau) d\tau - c y_4. \end{aligned} \tag{3.1}$$

The characteristic equation of the above system (3.1) is given by

$$\begin{vmatrix} -d-\lambda & -(1-\eta_2)\beta_2 \dfrac{h}{d} & -(1-\eta_1)\beta_1 \dfrac{h}{d} & 0 \\ 0 & -\mu_1 + (1-\eta_2)\beta_2 \dfrac{h}{d}\alpha_1(\lambda) - \lambda & (1-\eta_1)\beta_1 \dfrac{h}{d}\alpha_1(\lambda) & 0 \\ 0 & (1-\eta_3) b \alpha_2(\lambda) & -c-\lambda & 0 \\ 0 & \eta_3 b \alpha_3(\lambda) & 0 & -c-\lambda \end{vmatrix} = 0,$$

where

$$\alpha_i(\lambda) = \int_0^\infty e^{-(\gamma_i+\lambda)\tau} f(\tau), \quad i = 1, 2, 3.$$

We obtain from the above the determinant the above system (3.1) has an eigenvalue $\lambda = -d, -c$, and other eigenvalues are determined by

$$\lambda^2 + \lambda\left(c + \mu_1 - (1-\eta_2)\beta_2\frac{h}{d}\alpha_1(\lambda)\right) + \mu_1 c\,(1 - R_0) \;\; = \;\; 0. \qquad (3.2)$$

Theorem 3.1. *The infection free steady state of model* (3.1) *is locally asymptotically stable when* $R_0 < 1$ *and unstable when* $R_0 > 1$.

Proof. We have to prove the local stability of model (3.1), when $R_0 < 1$. The characteristic equation (3.2) at the infected free steady state can be rewritten as,

$$\begin{aligned}&(\lambda + c)(\lambda + \mu_1)\\ &= (\lambda + c)\beta_2(1-\eta_2)\beta_2\frac{h}{d}\alpha_1(\lambda) + (1-\eta_1)\beta_1\frac{h}{d}\alpha_1(\lambda)(1-\eta_3)b\alpha_2(\lambda).\end{aligned}$$

After simplification we get

$$\begin{aligned}&(\lambda + c)\left(\frac{\lambda}{\mu_1} + 1\right)\\ &= R_0\left(\frac{\alpha_1(\lambda)R_{02}}{\delta_1 R_0}\lambda c\left(\frac{\alpha_1(\lambda)R_{02}}{\delta_1 R_0} + \frac{\alpha_1(\lambda)\alpha_2(\lambda)R_{01}}{\delta_1\delta_2 R_0}\right)\right). \qquad (3.3)\end{aligned}$$

We first consider the case $R_0 < 1$. We show that if $\lambda = x + iy$ is a solutions of (3.3), then $x > 0$. Otherwise $x \geq 0$ would imply that

$$\begin{aligned}&|(\lambda + c)| > \left|\left(\frac{\alpha_1(\lambda)R_{02}}{\delta_1 R_0}\lambda + c\left(\frac{\alpha_1(\lambda)R_{02}}{\delta_1 R_0} + \frac{\alpha_1(\lambda)\alpha_2(\lambda)R_{01}}{\delta_1\delta_2 R_0}\right)\right)\right|,\\ &\left|\left(\frac{\lambda}{\mu_1} + 1\right)\right| \geq 1, \left|\frac{\alpha_1(\lambda)}{\delta_1}\right| \leq 1, \quad \left|\frac{\alpha_2(\lambda)}{\delta_2}\right| \leq 1,\end{aligned}$$

and thus

$$\left|(\lambda + c)\left(\frac{\lambda}{\mu_1} + 1\right)\right| > \left|R_0\left(\frac{\alpha_1(\lambda)R_{02}}{\delta_1 R_0}\lambda + c\left(\frac{\alpha_1(\lambda)R_{02}}{\delta_1 R_0} + \frac{\alpha_1(\lambda)\alpha_2(\lambda)R_{01}}{\delta_1\delta_2 R_0}\right)\right)\right|,$$

which is a contradiction to (3.3). Therefore all roots of (3.3) have negative real parts and hence the infection free steady state of the model (3.1) is locally asymptotically stable when $R_0 < 1$.

For the case of $R_0 > 1$, then we obtain,

$$\begin{aligned}\psi(\lambda) &= (\lambda + c)\left(\frac{\lambda}{\mu_1} + 1\right) \\ &\quad -R_0\left(\frac{\alpha_1(\lambda)R_{02}}{\delta_1 R_0}\lambda + c\left(\frac{\alpha_1(\lambda)R_{02}}{\delta_1 R_0} + \frac{\alpha_1(\lambda)\alpha_2(\lambda)R_{01}}{\delta_1\delta_2 R_0}\right)\right). \quad (3.4)\end{aligned}$$

Thus, $\psi(0) = c(1 - R_0) < 0$. On the other hand, noticing that

$$\alpha_i(\lambda) = \int_0^\infty e^{-(\gamma_i+\lambda)\tau} f(\tau)d\tau \leq \int_0^\infty f(\tau)d\tau = 1, \quad i = 1, 2, 3.$$

Thus,

$$\psi(\lambda) \geq (\lambda+c)\left(\frac{\lambda}{\mu_1}+1\right) - R_0\left(\frac{R_{02}}{\delta_1 R_0}\lambda + c\left(\frac{R_{02}}{\delta_1 R_0} + \frac{R_{01}}{\delta_1\delta_2 R_0}\right)\right), \quad (3.5)$$

the above inequality (3.5) leads to $\psi(\lambda) \to \infty$, as $\lambda \to \infty$. Now, obtain form the equation (3.3), which it has atleast one positive root, therefore the infection free equilibrium I_0 is unstable if $R_0 > 1$. □

Theorem 3.2. *If $R_0 > 1$, then the system (1.1) has a chronic equilibrium $I^*(x_1^*, x_2^*, x_3^*, x_4^*)$ (i.e., $x_1^* > 0$, $x_2^* > 0$, $x_3^* > 0$, $x_4^* > 0$) where x_1^*, x_2^*, x_3^* and x_4^* are given in the proof.*

Proof. If $R_0 > 1$, then the system (1.1) becomes as follows:

$$\begin{aligned} h - dx_1^* - (1-\eta_1)\beta_1 x_1^* x_3^* - (1-\eta_2)\beta_2 x_1^* x_2^* &= 0, \\ (1-\eta_1)\beta_1 x_1^* x_3^* + (1-\eta_2)\beta_2 x_1^* x_2^* - \mu_1 x_2^* &= 0, \\ (1-\eta_3)bx_2^* - cx_3^* &= 0, \\ \eta_3 bx_2^* - cx_4^* &= 0. \end{aligned} \quad (3.6)$$

From the above system (3.6), we easily get

$$\begin{aligned} x_1^* &= \frac{h}{dR_0}, \\ x_2^* &= \frac{dc}{(1-\eta_1)\beta_1(1-\eta_3)b + (1-\eta_2)\beta_2}(R_0 - 1), \\ x_3^* &= \frac{(1-\eta_3)b}{c}x_2^*, \\ x_4^* &= \frac{\eta_3 b}{c}x_2^*. \end{aligned} \quad (3.7)$$

□

Theorem 3.3. *If $R_0 > 1$, then the system (1.1) has a chronic infection equilibrium $I^*(x_1^*, x_2^*, x_3^*, x_4^*)$ given by (3.7), which is locally asymptotically stable.*

Proof. Now, we have to ascertain the stability of $I^*(x_1^*, x_2^*, x_3^*, x_4^*)$ for the system (1.1) at I^*

$$\begin{aligned}
\dot{y_1}(t) &= -dy_1(t) - (1-\eta_1)\beta_1 x_1^* y_3(t) - (1-\eta_1)\beta_1 x_3^* y_1(t) \\
&\quad -(1-\eta_2)\beta_2 x_2^* y_1(t) - (1-\eta_2)\beta_2 x_1^* y_2(t), \\
\dot{y_2}(t) &= \int_0^\infty \{(1-\eta_1)\beta_1 x_1^* y_3(t-\tau) + (1-\eta_1)\beta_1 x_3^* y_1(t-\tau) \\
&\quad +(1-\eta_2)\beta_2 x_2^* y_1(t-\tau) + (1-\eta_2)\beta_2 x_1^* y_2(t-\tau)\} e^{-\gamma_1\tau} f(\tau) d\tau \\
&\quad -\mu_1 y_2(t), \\
\dot{y_3}(t) &= \int_0^\infty (1-\eta_3) b y_2(t-\tau) e^{-\gamma_2\tau} f(\tau) d\tau - c y_3(t), \\
\dot{y_4}(t) &= \int_0^\infty \eta_3 b y_2(t-\tau) e^{-\gamma_3\tau} f(\tau) d\tau - c y_4(t). \qquad (3.8)
\end{aligned}$$

The determinant of the above linear system (3.8) is given by,

$$\begin{vmatrix}
(d+(1-\eta_1)\beta_1 x_3^* + \\ (1-\eta_2)\beta_2 x_2^*) + \lambda & (1-\eta_2)\beta_2 x_1^* & (1-\eta_1)\beta_1 x_1^* & 0 \\
-\alpha_1(\lambda)((1-\eta_1)\beta_1 x_3^* \\ +(1-\eta_2)\beta_2 x_2^*) & -\alpha_1(\lambda)(1-\eta_2)\beta_2 x_2^* + \\ \mu_1 + \lambda & -\delta_1(1-\eta_1)\beta_1 x_1^* & 0 \\
0 & -\alpha_2(\lambda) b(1-\eta_3) & c+\lambda & 0 \\
0 & -\alpha_3(\lambda) b\eta_3 & 0 & c+\lambda
\end{vmatrix} = 0.$$

Noticing that $d + (1-\eta_1)\beta_1 x_3^* + (1-\eta_2)\beta_2 x_2^* = dR_0$, we have

$$\bar{J}(\lambda) = \begin{vmatrix}
\lambda + dR_0 & (1-\eta_2)\beta_2 x_1^* & (1-\eta_1)\beta_1 x_1^* & 0 \\
\alpha_1(\lambda)(\lambda+d) & \lambda+\mu_1 & 0 & 0 \\
0 & -\alpha_2(\lambda) b(1-\eta_3) & \lambda+c & 0 \\
0 & 0 & c+\lambda & \lambda+c
\end{vmatrix} = 0$$

or

$$\begin{aligned}
&(\lambda+dR_0)\{(\lambda+\mu_1)(\lambda+c)(\lambda+c)\} - (1-\eta_2)\beta_2 x_1^* \alpha_1(\lambda)(\lambda+d)(\lambda+c)(\lambda+c) \\
&-(1-\eta_1)\beta_1 x_1^* \{\alpha_1(\lambda)(\lambda+d)\alpha_2(\lambda) b(1-\eta_3)(\lambda+c)\} = 0.
\end{aligned}$$

Thus, one of the eigenvalue of the chronic infection steady state is $\lambda = -c$, then the remaining eigenvalues are calculated as follows:

$$\begin{aligned}(\lambda+dR_0)\{(\lambda+\mu_1)(\lambda+c)\} &= (1-\eta_2)\beta_2 x_1^*\alpha_1(\lambda)(\lambda+d)(\lambda+c)\\ &\quad +(1-\eta_1)\beta_1 x_1^*\alpha_1(\lambda)(\lambda+d)\alpha_2(\lambda)b(1-\eta_3)\\ &= (\lambda+d)\alpha_1(\lambda)\left(\frac{(1-\eta_2)\beta_2 h}{dR_0}\lambda+\frac{\mu_1 c}{\delta_1}(R_{02}+R_{01})\right)\\ &= (\lambda+d)\alpha_1(\lambda)\frac{\mu_1}{\delta_1}(\lambda R_{02}+cR_0)\end{aligned}$$

i.e.,

$$(\lambda+dR_0)\left\{\left(\frac{\lambda}{\mu_1}+1\right)(\lambda+c)\right\} = (\lambda+d)\frac{\alpha_1(\lambda)}{\delta_1}R_0\left(\lambda\frac{R_{02}}{R_0}+c\right). \quad (3.9)$$

Assume $\lambda = x+iy$ is a solution of (3.9), we show that $x<0$ is $R_0>1$. Otherwise $x\geq 0$ would imply,

$$|\lambda+dR_0|>|\lambda+d|;\ \left|\frac{\lambda}{\mu_1}+1\right|\geq 1;\ |\lambda+c|>\left|\lambda\frac{R_{02}}{R_0}+c\right|;\ \left|\frac{\alpha_1(\lambda)}{\delta_1}\right|\leq 1.$$

Thus,

$$\left|(\lambda+dR_0)\left(\frac{\lambda}{\mu_1}+1\right)(\lambda+c)\right| > \left|(\lambda+d)\frac{\alpha_1(\lambda)}{\delta_1}\left(\lambda\frac{R_{02}}{R_0}+c\right)\right|.$$

This leads to contradiction to (3.9). Therefore if $R_0>1$, then all the roots of (3.9) have negative real parts, implying that the chronic infection equilibrium $I^*(x_1^*,x_2^*,x_3^*,x_4^*)$ is locally asymptotically stable. □

Summarizing the above analysis, we've the following theorem.

Theorem 3.4.

(i) *The infection free steady state $I_0(x_1^0,0,0,0)$ is Locally asymptotically stable for all $\tau>0$, when $R_0<1$.*

(ii) *The chronic infection steady state $I^*(x_1^*,x_2^*,x_3^*,x_4^*)$ is Locally asymptotically stable for all $\tau>0$, when $R_0>1$.*

4. Persistence of infection

In this section, we will show that the model (1.1) is persistent when $R_0>1$. The methods and techniques, we are using have seen recently employed in [9] Theorem 2, [14] Theorem 6.1, [17] Theorem 3.1 for distributed and infinite delay systems and in [15] for a discrete delay system. To proceed, we introduce the following notation and terminology. Let $S(t)$ be the solution semiflow of model (1.1) with initial conditions (2.1). Then, we shall make use of the

following theorem on the semiflow $S(t)$ on Z, which does not require $S(t)$ to be compact.

Theorem 4.1. *Suppose we have the following:*

(i) Z^0 *is an open and dense set in* X *with* $Z^0 \cup Z_0 = Z$ *and* $Z^0 \cap Z_0 = \emptyset$;
(ii) $S(t)$ *satisfies* $S(t)Z^0 \subset Z^0$ *and* $S(t)Z_0 \subset Z_0$ *for* $t > 0$;
(iii) $S(t)$ *is dissipative in* Z;
(iv) $\kappa^+(N)$ *is bounded in* Z *if* N *is bounded in* Z;
(v) $S(t)$ *is asymptotically smooth;*
(vi) $\mathcal{A} = \cup_{x\in\mathcal{A}_b}\omega(x)$ *is isolated and has an acyclic covering* $Q = \cup_{i=1}^{k} Q_i$, *where* $\mathcal{A}_b$ *is the global attractor of* $S(t)$ *restricted to* Z_0;
(vii) *For each* $Q_i \in Q, W^s(Q_i) \cap Z^0 = \emptyset$, *where* W^s *refers to the stable set. Then* $S(t)$ *is uniformly persistent; i.e., there is a* $\sigma > 0$ *such that for any* $z \in Z^0$,

$$\liminf_{t\to\infty} d(S(t)x, Z_0) \geq \sigma.$$

Applying the above theorem, we can prove the following persistence result for the system (1.1).

Theorem 4.2. *For system* (1.1), *if* $R_0 > 1$, *then the solution semiflow* $S(t)$ *is uniformly persistent; i.e., there is a* $\sigma > 0$ *such that for any* $z \in Z^0$,

$$\liminf_{t\to\infty} x_1(t) \geq \sigma, \ \liminf_{t\to\infty} x_2(t) \geq \sigma, \ \liminf_{t\to\infty} x_3(t) \geq \sigma \ \text{ and } \ \liminf_{t\to\infty} x_4(t) \geq \sigma.$$

Proof. Let Z^0 be as in (2.1) and

$$Z_0 = \{\phi = (\phi_1, \phi_2, \phi_3, \phi_4) \in X : \phi_2(\theta) = \phi_3(\theta) = \phi_4(\theta) = 0, \ \forall\, \theta \in (-\infty, 0]\}.$$

As based on the above Theorem 4.1, the conditions (i) and (ii) are obvious. It has to be confirmed in Section 2. Now, we have to prove (iii), *i.e.*, the solutions of the system (1.1) with initial conditions (2.1) are ultimately bounded. By $\liminf_{t\to\infty} x_1(t) \leq \dfrac{h}{d}$, we know that there exists an $n_1 > 0$ such that $x_1(t) \leq \dfrac{h}{d} + 1$ for all $t > n_1$. Let n_1 be the maximum of $x_1(t)$ on $[0, n_1]$. Then for any $0 < t \leq n_1$, we have

$$\begin{aligned} \|x_1(t)\| &= \sup_{-\infty<\theta\leq 0} |x_1(\theta)|e^{\Delta\theta} = \sup_{-\infty<r\leq s} |x_1(\theta)|e^{\Delta r}e^{-\Delta s} \\ &\leq \max\left\{\|\phi_1\|e^{\Delta t}, n_1 e^{\Delta t}e^{-\Delta t}\right\} \\ &\leq \max\left\{\|\phi_1\|, n_1\right\} \end{aligned}$$

and for $t > r_1$, we obtain

$$\leq \max\left\{\|\phi_1\|e^{\Delta t}, n_1 e^{\Delta r_1}e^{-\Delta t}, \frac{h}{d} + 1\right\}.$$

Thus there is an $r_2 > r_1$ such that

$$\|\phi_1\|e^{\Delta t} \leq \frac{\lambda}{d_1} + 1 \text{ and } e^{\Delta r_1}e^{-\Delta t} \leq \frac{h}{d} + 1 \quad \text{for} \quad t \geq r_2$$

and therefore

$$\|x_1(t)\| \leq \frac{h}{d} + 1 := x_{1M} \quad \text{for} \quad t \geq r_2. \tag{4.1}$$

Similarly $\limsup_{t\to\infty} x_2(t) \leq \frac{h\delta_1}{m}$ and $\limsup_{t\to\infty} x_3(t) \leq \frac{bh\delta_1}{cm}$ and $\limsup_{t\to\infty} x_4(t) \leq \frac{bh\delta_1}{cm}$. We know that there exist $r_3 > 0$ and $r_4 > 0$ such that

$$\|x_2(t)\| \leq \frac{h\delta_1}{m} + 1 := x_{2M} \quad \text{for} \quad t \geq r_3, \tag{4.2}$$

$$\|x_3(t)\| \leq \frac{bh\delta_1}{cm} + 1 := x_{3M} \quad \text{for} \quad t \geq r_4, \tag{4.3}$$

$$\|x_4(t)\| \leq \frac{bh\delta_1}{cm} + 1 := x_{4M} \quad \text{for} \quad t \geq r_5. \tag{4.4}$$

Thus, the solution $(x_1(t), x_2(t), x_3(t), x_4(t))$ are ultimately bounded. *i.e.*, $S(t)$ is point dissipative in Z. Hence the condition (iii) proved.

Noticing that the above four bounds in (4.1), (4.2), (4.3) and (4.4) are all independent of initial functions, conditions (iv) is verified.

Next we verify the condition (v), $S(t)$ is asymptotically smooth; that is for any bounded subset N of Z, for which $S(t)N \subset N$, for $t \geq 0$, there exists a compact set $\mathcal{P}$ such that $d(S(t)N, \mathcal{P}) \to 0$ as $t \to \infty$. Let N be an arbitrarily given bounded set in X, and let (x_1, x_2, x_3, x_4) be the segment of solution with initial condition $(\phi_1, \phi_2, \phi_3, \phi_4) \in N$. Set

$$\mathcal{P}_1 = \left\{ \phi \in \mathcal{C}^+ : \sup_{\theta\leq 0} \phi_1(\theta)e^{\frac{\triangle}{2}\theta} \leq x_{1\mathcal{P}} \right\},$$

$$\mathcal{P}_2 = \left\{ \phi \in \mathcal{C}^+ : \sup_{\theta\leq 0} \phi_2(\theta)e^{\frac{\triangle}{2}\theta} \leq x_{2\mathcal{P}} \right\},$$

$$\mathcal{P}_3 = \left\{ \phi \in \mathcal{C}^+ : \sup_{\theta\leq 0} \phi_3(\theta)e^{\frac{\triangle}{2}\theta} \leq x_{3\mathcal{P}} \right\},$$

$$\mathcal{P}_4 = \left\{ \phi \in \mathcal{C}^+ : \sup_{\theta\leq 0} \phi_4(\theta)e^{\frac{\triangle}{2}\theta} \leq x_{4\mathcal{P}} \right\}$$

and let $\mathcal{P} = \mathcal{P}_1 \times \mathcal{P}_2 \times \mathcal{P}_3 \times \mathcal{P}_4$. It follows from Lemma 3.2 in [1] that $\mathcal{P}$ is compact in Z. 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 [14], we conclude that

$$\lim_{t\to\infty} d(x_1, \mathcal{P}_1) = 0, \lim_{t\to\infty} d(x_2, \mathcal{P}_2) = 0, \lim_{t\to\infty} d(x_3, \mathcal{P}_3) = 0, \lim_{t\to\infty} d(x_4, \mathcal{P}_4) = 0.$$

For condition (vi), it is obvious that $N = \{I_0\}$, and it is isolated, where $I_0 = (h/d, 0, 0, 0)$. Thus the covering $Q = \{I_0\}$, which is acyclic because there is no orbit connecting I_0 to itself in Z_0.

Finally we verify condition (vii), to show $W^s(I_0) \cap Z^0 = \emptyset$. We assume the contrary, that is there exists a solution $(x_1, x_2, x_3, x_4) \in Z^0$ such that $\lim_{t\to\infty} x_1(t) \leq \dfrac{h}{d}$; $\lim_{t\to\infty} x_2(t) = 0$; $\lim_{t\to\infty} x_3(t) = 0$ and $\lim_{t\to\infty} x_4(t) = 0$. Note that $R_0 > 1$ is equivalent to

$$(1-\eta_1)\beta_1 x_1^0 \delta_1 (1-\eta_3) b\delta_2\mu_1 c + (1-\eta_2)c\beta_2 x_1^0 \delta_1\mu_1 \int_0^\infty e^{-\gamma_1\tau} f(\tau)d\tau > \mu_1 c.$$

Choose $\epsilon_1 > 0$ be sufficiently small such that

$$\left(\frac{h}{d} - \epsilon_1\right)\left((1-\eta_1)\beta_1\delta_1(1-\eta_3)b\delta_2\mu_1 c + (1-\eta_2)c\beta_2\delta_1\mu_1\int_0^\infty e^{-\gamma_1\tau}f(\tau)d\tau\right) > \mu_1 c.$$

For this ϵ_1, there exists $\bar{\tau} > 0$ such that $x_1(t) > \dfrac{h}{d} - \epsilon_1$ for all $t \geq \bar{\tau}$. Truncating the above integral, there is another $\tau_1 > 0$ such that

$$\left(\frac{h}{d} - \epsilon_1\right)\left((1-\eta_1)\beta_1\delta_1(1-\eta_3)b\delta_2\mu_1 c + (1-\eta_2)c\beta_2\delta_1\mu_1\int_0^{\tau_1} e^{-\gamma_1\tau}f(\tau)d\tau\right) > \mu_1 c. \tag{4.5}$$

Let $\tau_2 = \bar{\tau} + \tau_1$. Then, for $t \geq \tau_2$, we have

$$\begin{aligned}
\dot{x_2}(t) &\geq \int_0^{\tau_1} \{(1-\eta_1)\beta_1 x_1(t-\tau)x_3(t-\tau) \\
&\quad +(1-\eta_2)\beta_2 x_1(t-\tau)x_2(t-\tau)\} e^{-\gamma_1\tau} f(\tau)d\tau - \mu_1 x_2(t), \\
&= \int_{t-\tau_1}^{t} \{(1-\eta_1)\beta_1 x_1(\zeta)x_3(\zeta) + (1-\eta_2)\beta_2 x_1(\zeta)x_2(\zeta)\} e^{-\gamma_1(t-\zeta)} f(t-\zeta)d\zeta \\
&\quad - \mu_1 x_2(t) \\
&\geq \left(\frac{h}{d} - \epsilon_1\right)\int_{t-\tau_1}^{t} \{(1-\eta_1)\beta_1 x_3(\zeta) + (1-\eta_2)\beta_2 x_2(\zeta)\} e^{-\gamma_1(t-\zeta)} f(t-\zeta)d\zeta \\
&\quad - \mu_1 x_2(t)
\end{aligned}$$

$$= \left(\frac{h}{d} - \epsilon_1\right) \int_0^{\tau_1} \{(1-\eta_1)\beta_1 x_3(t-\tau) + (1-\eta_2)\beta_2 x_2(t-\tau)\} e^{-\gamma_1\tau} f(\tau) d\tau - \mu_1 x_2(t).$$

This suggests that the following comparison system for $(x_2(t), x_3(t), x_4(t))$:

$$\begin{aligned} \dot{n_1}(t) &= \left(\frac{h}{d} - \epsilon_1\right) \int_0^{\tau_1} \{(1-\eta_1)\beta_1 n_2(t-\tau) + (1-\eta_2)\beta_2 n_1(t-\tau)\} \\ &\quad e^{-\gamma_1\tau} f(\tau) d\tau - \mu_1 n_1(t), \\ \dot{n_2}(t) &= \int_0^{\tau_1} (1-\eta_3) b n_1(t-\tau) e^{-\gamma_2\tau} f(\tau) d\tau - c n_2, \\ \dot{n_3}(t) &= \int_0^{\tau_1} \eta_3 b n_1(t-\tau) e^{-\gamma_3\tau} f(\tau) d\tau - c n_3. \end{aligned} \tag{4.6}$$

for $t \geq \tau_2$. Noticing that this is a monotone system and hence by the comparison theorem and the equations $\lim_{t\to\infty} x_2(t) = 0, \lim_{t\to\infty} x_3(t) = 0$ and $\lim_{t\to\infty} x_4(t) = 0$, one should have $\lim_{t\to\infty}(x_2(t), x_3(t), x_4(t)) = (0,0,0)$. On the other hand, the above system (4.6) are in the same forms of the system (3.1), except the upper limit ∞ in the integral is replaced by τ_1 and the $\frac{h}{d}$ is perturbed to $\frac{h}{d} - \epsilon_1$. Repeating the same argument for proving instability of I_0 in Theorem 3.1 and replacing the condition $R_0 > 1$ by (4.5), we conclude that the characteristic equation of (4.6) has a positive real eigenvalue, which is a contradiction to $\lim_{t\to\infty}(x_2(t), x_3(t), x_4(t)) = (0,0,0)$. Thus, we have $W^s(I_0) \bigcap Z^0 = \emptyset$. confirming the condition (vii).

Now, by Theorem 4.1, there exist $\sigma_1 > 0$ such that $\liminf_{t\to\infty} d(S(t)\phi, Z_0) \geq \sigma_1$ for every $\phi \in Z^0$, implying that $x_2(t), x_3(t)$ and $x_4(t)$ components of the solution with initial function $\phi \in Z^0$ satisfy

$$\liminf_{t\to\infty} \|x_2(t)\| \geq \sigma_1, \quad \liminf_{t\to\infty} \|x_3(t)\| \geq \sigma_1 \quad \text{and} \quad \liminf_{t\to\infty} \|x_4(t)\| \geq \sigma_1.$$

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

$$\liminf_{t\to\infty} x_2(t) \geq \sigma_1, \ \liminf_{t\to\infty} x_3(t) \geq \sigma_1 \quad \text{and} \quad \liminf_{t\to\infty} x_4(t) \geq \sigma_1.$$

It remains to show that the persistence of $x_1(t)$. From (4.1) and (4.2), we have

$$\dot{x_1}(t) \quad > \quad h - (d + (1-\eta_1)\beta_1 x_3 + (1-\eta_2)\beta_2 x_2)\, x_1(t) \quad \text{for} \quad t \geq r_6.$$

Where $r_6 = \max\{r_3, r_4, r_5\}$. This means that whenever

$$x_1(t) < \sigma_2 := h/(d + (1-\eta_1)\beta_1 x_3 + (1-\eta_2)\beta_2 x_2)$$

with $t \geq r_6$, $x_1(t)$ will be increasing which implies that $\liminf_{t\to\infty} x_1(t) > \sigma_2/2$, taking $\sigma = \min\{\sigma_1, \sigma_2/2\}$. Hence the proof. □

5. Conclusion

Mathematical analysis of HIV-1 viral dynamics and immune responses has led to a number of important insights about the dynamics and pathogenesis of HIV infection. Modeling plasma virus decay under therapy demonstrated the fast turnover of virus, explaining the potential for generation of mutants and the development of drug resistance Our article is focused on antiretroviral therapy for both virus to cell and cell to cell transmission mode. HIV-I infection can be very effectively 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 in virus to cell transmission mode. But our proposed model overcomes all the difficulties from the virus to cell infection mode.

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