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GLOBAL STABILITY OF AN HIV-1 MODEL WITH DISTRIBUTED INTRACELLULAR DELAYS AND A COMBINATION THERAPY

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Abstract. Global stability is analyzed for a general mathematical model of HIV-1 pathogenesis proposed by Nelson and Perelson [11]. The general model include two distributed intracellular delays and a combination therapy with a reverse transcriptase inhibitor and a protease inhibitor. It is shown that the model exhibits a threshold dynamics: if the basic reproduction number is less than or equal to one, then the HIV-1 infection is cleared from the T-cell population; whereas if the basic reproduction number is larger than one, then the HIV-1 infection persists and the viral concentration maintains at a constant level.

1. **Introduction.** It is well known that local stability and global stability are not equivalent and it is much more challenging to test for global stability than for local stability in dynamical systems ([5]). Local stability can be tested by linearzing the model about its equilibrium and checking the eigenvalues of the corresponding characteristic equation ([2]). While there is no standard procedure to test global stability, the commonly used method is to construct a Lyapunov function (for ordinary differential equation systems) or functional (for delay differential equation systems) ([2]), which sometimes is very difficult if not impossible. The aim of this paper is to establish global stability for a delay differential equation model of HIV-1 infection. The model was initially proposed by Nelson and Perelson [11, Eq.(23)]

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and is given by the following system of integro-differential equations

$$\begin{aligned}
\frac{dx(t)}{dt} &= s - d_T x(t) - (1-n_{rt})kx(t)v(t),\\
\frac{dy(t)}{dt} &= (1-n_{rt})k\int_0^\infty G_1(\tau)x(t-\tau)v(t-\tau)d\tau - \delta y(t),\\
\frac{dv(t)}{dt} &= (1-n_p)N\delta\int_0^\infty G_2(\tau)y(t-\tau)d\tau - cv(t),
\end{aligned} \tag{1}$$

where x, y and v are the concentrations of uninfected target cells (T-cells), productively infected cells, and infectious virus, respectively; The positive constant s is the rate at which new target cells are generated; $d_T > 0$ is the death rate of T-cells; $k > 0$ is the constant rate at which a $T-$cell becomes infected via contacting with virus; $\delta > 0$ is the death rate of productively infected cells; $N > 0$ is total number of new virus particles produced by each infected cell during its life time, which on average is $\frac{1}{\delta}$. Thus, virus is produced at rate δN; $c \geq 0$ is the rate at which the infectious virus to be cleared out. A combination therapy that employs both reverse transcriptase (RT) inhibitors and protease inhibitors is included in this model, where $n_{rt} \in [0,1]$ is the effectiveness of the RT inhibitor, thus $(1-n_{rt})k_1$ is the infection rate; $n_p \in [0,1]$ is the efficacy of the protease inhibitor. To account for the time lag between viral entry into a target cell and the production of new virus particles, two distributed intracellular delays are introduced with kernel functions given by $G_i(\tau) = f_i(\tau)\cdot e^{-m_i\tau}$, $(i = 1, 2)$. $G_1(\tau)$ is the probability that target cells contacted by the virus particles at time $t-\tau$ survived τ time units and become infected at time t and $G_2(\tau)$ is the probability that a cell infected at time $t-\tau$ starts to yield new infectious virus at time t. For HIV-1 infection, the delay differential equation model is shown to fit data more accurate than a non-delayed model does (see, for example, Fig. 2, [11]).

An equilibrium $E = (x^*, y^*, v^*)$ of (1) is *locally stable* if for some neighborhood of E, the solution of (1) approaches E for all initial values in the neighborhood. Such an equilibrium E is said to be *globally stable* in a set D if for all initial values in D, the solution approaches E as time t increases.

Note that system (1) includes many special cases. For example, when $f_1(\tau) = f_2(\tau) = \delta(\tau - 0)$ with $\delta(\cdot)$ being the Dirac delta function, $n_{rt} = n_p = 0$, system (1) reduces to the classical ordinary differential equation (ODE) model that has been widely studied in literature (see [12, 13] and references therein). When either $f_1(\tau) = \delta(\tau - \bar{\tau}), f_2(\tau) = \delta(\tau - 0)$ or $f_1(\tau) = \delta(\tau - 0), f_2(\tau) = \delta(\tau - \bar{\tau})$, system (1) reduces to a model with a single delay which is studied in [10, 11]. Nelson and Perelson [11] showed that the delay model and the corresponding ODE model share the same stability at the equilibrium as long as the delay is very small or very large ([11, Theorem 1]). Zhu and Zou [14] considered the case with two discrete delays as $G_1(\tau) = e^{-\mu_1\tau_1}\delta(\tau - \tau_1), G_2(\tau) = e^{-\mu_2\tau_2}\delta(\tau - \tau_2)$, and they obtained the global stability of the infection free equilibrium and local stability of the positive interior equilibrium.

To the best of our knowledge, no global stability result has been established for system (1) and local stability does not necessarily imply global stability. Therefore, in this paper we are concerned with global stability of system (1) and show that the dynamics of (1) is completely determined by a threshold parameter, $\Re_0$ (will be defined in (3)), which turns out to be the basic reproduction number. If $\Re_0 \leq 1$,

then all solutions approach the viral free steady state implying the HIV infection is cleared from the T-cell population; whereas if $\Re_0 > 1$, then all solutions tend to the infected steady state indicating that the HIV infection persists and the viral load maintains at a constant level. Our main approach is the method of Lyapunov functionals, which has been recently successfully employed to obtain global stability in [6, 8, 9].

The rest of the paper is organized as follows. In Section 2, we state our main results on the well-posedness and global stability of model (1), whose proofs are postponed to Section 4. In Section 3, we apply our main results to the models studied in [11, 14] and establish corresponding global stability results. A discussion is given to conclude this paper in Section 5.

2. Main results.

Assume the kernel functions G_1 and G_2 satisfy

$$\text{(A) } G_i(\tau) \geq 0, \quad \text{for } \tau \geq 0, \text{ and } 0 < \int_0^\infty G_i(\tau)d\tau < 1, \ i = 1, 2.$$

For any given initial condition

$$\phi(\theta) = (x(\theta), y(\theta), v(\theta)) \in UC_g((-\infty, 0], R^3_+), \tag{2}$$

system (1) satisfies the hypotheses that are sufficient to ensure the existence, uniqueness and continuity of solutions [1, Theorems 2.1-2.3], for the notation of UC_g, see [4, page 46].

Theorem 2.1. *Let $(x(t), y(t), v(t))^T$ be the unique solution to system (1) and (2) with $x(0) > 0, y(0) > 0, v(0) > 0$. Then $x(t), y(t)$ and $v(t)$ are positive for all $t > 0$. Moreover, the solution is bounded and thus exists globally.*

Denote $\alpha_i = \int_0^\infty G_i(\tau)d\tau$ and

$$\Re_0 = \frac{sk(1 - n_{rt})(1 - n_p)N\alpha_1\alpha_2}{d_T c}. \tag{3}$$

It is straightforward to show that if $\Re_0 \leq 1$, then (1) has only one nonnegative equilibrium, the infection free equilibrium, $E_0 = (\frac{s}{d_T}, 0, 0)$ and if $\Re_0 > 1$, in addition to E_0, there is an endemic equilibrium $E_1 = (x^*, y^*, v^*)$ with

$$x^* = \frac{s}{d_T \cdot \Re_0}, \ v^* = \frac{d_T}{1 - n_{rt}} \cdot (\Re_0 - 1), \ y^* = \frac{cv^*}{(1 - n_p)N\delta\alpha_2}... \tag{4}$$

The parameter $\Re_0$ indeed is the basic reproduction number as it can be rewritten as the product of three terms

$$\Re_0 = \frac{s}{d_T} \cdot \frac{(1 - n_{rt})k\alpha_1}{\delta} \cdot \frac{(1 - n_p)N\delta\alpha_2}{c}, \tag{5}$$

where the first term is the average number of healthy cells available for infection, the second term is the average number of cells that each virion can infect, and the last term accounts for the average number of virions that an infected cell can produce.

Theorem 2.2. *If $\Re_0 \leq 1$, then E_0 is globally stable, i.e. $\lim_{t\to\infty}(x(t), y(t), v(t)) = E_0$.*

Theorem 2.3. *If $\Re_0 > 1$, then E_1 is globally stable in $D = \mathbb{R}^3_+ \setminus \{E_0\}$.*

Remark 1. Theorems 2.2 and 2.3 show that the intracellular delays do not cause instability of equilibria. But the values of $\Re_0$ and E_1 are indeed delay dependent. This implies that the magnitude of delays does have an effect on the final steady state of the system. For instance, as seen in Section 3.2, $\Re_0$ is decreasing with respect to time delays. Thus (i) sufficiently large delays can reduce $\Re_0$ to be lower than 1 and hence the virus load in an HIV-1 patient can be eliminated if a treatment can cause sufficiently large delays in the T-cell infection process and virus production process; (ii) as seen from (4), even when a treatment cannot bring down $\Re_0$ to below 1, via increasing the delays, the therapy still has a positive effect on lowering the virus load to help prolong the patient's life.

3. Special cases of (1).

In this section we reconsider the models whose local stability is established in [11, 14] and we show that those models are indeed globally stable.

3.1. Distributed time lag in infection process.

Consider model (1) with $G_1(\tau) = \frac{\tau^{n-1}}{(n-1)!b^n}e^{-\frac{\tau}{b}} \cdot e^{-m\tau}$ and $G_2(\tau) = \delta(\tau - 0)$, then (1) reduces to

$$\begin{aligned} \tfrac{dx}{dt} &= s - d_T x - (1 - n_{rt})kxv, \\ \tfrac{dy}{dt} &= (1 - n_{rt})k \textstyle\int_0^\infty g_{n,b}(\tau)e^{-m\tau}x(t-\tau)v(t-\tau)d\tau - \delta y, \\ \tfrac{dv}{dt} &= (1 - n_p)N\delta y - cv. \end{aligned} \tag{6}$$

where $g_{n,b} = \frac{\tau^{n-1}}{(n-1)!b^n}e^{-\frac{\tau}{b}}$ is a gamma distribution function. Re-scaling system (6) gives

$$\begin{aligned} \tfrac{dx}{dt} &= s - d_T x - (1 - n_{rt})kxv, \\ \tfrac{dy}{dt} &= (1 - n_{rt})\bar{k} \textstyle\int_0^\infty g_{n,b'}(\tau)x(t-\tau)v(t-\tau)d\tau - \delta y, \\ \tfrac{dv}{dt} &= (1 - n_p)N\delta y - cv, \end{aligned} \tag{7}$$

where $g_{n,b'}(\tau) = \frac{\tau^{n-1}}{(n-1)!(b')^n}e^{-\frac{\tau}{b'}}$, $b' = \frac{b}{1+mb}$, $\bar{k} = \frac{k}{(1+mb)^n}$ and $\int_0^\infty g_{n,b'}(\tau)d\tau = 1$.

Note that the above system is proposed in [11, Eq. (11)] to explore the effects of the antiretroviral therapy (In [11], there is one more equation for the noninfectious virus V_{NI}, which is not included here since V_{NI} is decoupled from the above three equations).

It is shown [11, Lemmas 2,3] that (7) has a positive infected steady state $(\overline{x}, \overline{y}, \overline{v})$ if and only if

$$\eta_c = 1 - (1 - n_{rt})(1 - n_p) < 1 - \frac{d_T c}{sN\bar{k}} = \eta_{critical}, \tag{8}$$

which is locally stable in the absence of a delay. Note that $\eta_c < \eta_{critical}$ is equivalent to $\Re_0 = \frac{sN\bar{k}(1-n_p)(1-n_{rt})}{d_T c} > 1$. Applying Theorems 2.2 and 2.3 to system (7), we have the following global result.

Theorem 3.1. *If $\eta_c \geq \eta_{critical}$, then the only steady state is the viral free steady state $(\frac{s}{d_T}, 0, 0)$, which attracts all solutions implying that the combination therapy will eliminate the virus completely. If $\eta_c < \eta_{critical}$, then there is additional positive steady state, which is globally stable implying that the infection persists and the virus load will eventually be controlled at a constant level due to treatment.*

3.2. **Fixed time lags in infection process and viral production process.** A special case of system (1) with two discrete delays is considered in [14], where G_1 and G_2 in (1) take the form of $G_1(\tau) = e^{-d\tau_1}\delta(\tau - \tau_1)$ with $d = d_T + c$ and $G_2(\tau) = e^{-\delta\tau_2}\delta(\tau - \tau_2)$. Here the term $e^{-d_T\tau_1}$ accounts for the portion of cells infected at time t that is able to survive at least τ_1 time units. The term $e^{-c\tau_1}$ accounts for the virus that are produced at time t but is not cleared out during τ_1 time units, and thus at time $t+\tau_1$, the newly produced productively infected cell y is $(1-n_{rt})ke^{-d\tau_1}x(t)v(t)$. The term $e^{-\delta\tau_2}$ accounts for the portion of productively infected cells that can survive τ_2 units of time to produce newly infectious virus. The model (1) then becomes

$$\begin{aligned}
\tfrac{dx}{dt} &= s - d_T x - (1-n_{rt})kxv,\\
\tfrac{dy}{dt} &= (1-n_{rt})ke^{-d\tau_1}x(t-\tau_1)v(t-\tau_1) - \delta y,\\
\tfrac{dv}{dt} &= (1-n_p)N\delta e^{-\delta\tau_2}y(t-\tau_2) - cv
\end{aligned} \tag{9}$$

and the initial condition is $(x(\theta), y(\theta), v(\theta)) \in C([-max(\tau_1,\tau_2), 0], \mathbb{R}^3_+)$ with $x(0) > 0, y(0) > 0, v(0) > 0$. Applying Theorems 2.2 and 2.3 to system (9) yields the following global property.

Theorem 3.2. *If* $\Re_0 = \frac{skN}{d_T c}(1-n_{rt})(1-n_p)e^{-(d\tau_1+\delta\tau_2)} \le 1$, *then (9) has only one nonnegative steady state, which is the viral free steady state* $E_0 = (\frac{s}{d_T}, 0, 0)$, *to which all solution tend; whereas if* $\Re_0 > 1$, *then there is a unique positive infected steady state* $E_1 = \left(\frac{ce^{d\tau_1+\delta\tau_2}}{Nk(1-n_{rt})(1-n_p)}, \frac{d(\Re_0-1)}{k(1-n_{rt})}, \frac{cd(\Re_0-1)e^{\delta\tau_2}}{k(1-n_{rt})(1-n_p)N\delta}\right)$, *satisfying*

$$\lim_{t\to\infty}(x(t), y(t), v(t)) = E_1.$$

4. **Proof of main results.** For the purpose of convenience, we rewrite (1) as

$$\begin{aligned}
\frac{dx(t)}{dt} &= \lambda - mx(t) - \beta x(t)v(t),\\
\frac{dy(t)}{dt} &= \beta_1\int_0^\infty g_1(\xi)x(t-\xi)v(t-\xi)d\xi - ay(t),\\
\frac{dv(t)}{dt} &= k_1\int_0^\infty g_2(\xi)y(t-\xi)d\xi - \mu v(t),
\end{aligned} \tag{10}$$

where

$$\lambda = s,\ m = d_T,\ \beta = (1-n_{rt})k,\ a = \delta,\ c = \mu,\quad \beta_1 = (1-n_{rt})k\cdot\alpha_1,$$
$$k_1 = (1-n_p)N\delta\cdot\alpha_2,\quad g_i(\xi) = \frac{G_i(\xi)}{\alpha_i},\ i = 1, 2.$$

Recall $\alpha_i = \int_0^\infty G_i(\tau)d\tau$, thus $\int_0^\infty g_i(\xi)d\xi = 1$. Then the basic reproduction number $\Re_0$ defined in (3) can be rewritten as

$$\widehat{\Re}_0 = \frac{\lambda\beta_1 k_1}{ma\mu}$$

for system (10).

Proof of Theorem 2.1. Using the variation-of-constants formula, we obtain from (10) that

$$x(t) = x(0)e^{-\int_0^t(m+\beta v(\zeta))d\zeta} + \int_0^t \lambda e^{-\int_s^t(m+\beta v(\zeta))d\zeta}ds,$$

$$y(t) = y(0)e^{-at} + \beta_1 \int_0^t e^{-a(t-s)} \int_0^\infty g_1(\zeta)x(s-\zeta)v(s-\zeta)d\zeta ds,$$

and

$$v(t) = v(0)e^{-\mu t} + k_1 \int_0^t e^{-\mu(t-s)} \int_0^\infty g_2(\zeta)y(s-\zeta)d\zeta ds,$$

which yields the positivity of $x(t), y(t), v(t)$.

Next we show that every solution is also bounded. It follows from the first equation of system (10) that $\frac{dx(t)}{dt} < \lambda - mx(t)$. This implies $\overline{\lim_{t\to\infty}} x(t) \le \frac{\lambda}{m}$. Let $V(t) = \frac{\beta_1}{\beta}\int_0^\infty g_1(\xi)x(t-\xi)d\xi + y(t)$. Then

$$\begin{aligned}
\left.\frac{dV(t)}{dt}\right|_{(10)} &= \frac{\beta_1}{\beta}\int_0^\infty g_1(\xi)\frac{dx(t-\xi)}{dt}d\xi + \frac{dy(t)}{dt} \\
&= \frac{\beta_1}{\beta}\int_0^\infty g_1(\xi)\left[\lambda - mx(t-\xi) - \beta x(t-\xi)v(t-\xi)\right]d\xi \\
&\quad +\beta_1\int_0^\infty g_1(\xi)x(t-\xi)v(t-\xi)d\xi - ay(t) \qquad (11)\\
&= \frac{\beta_1\lambda}{\beta} - \frac{\beta_1 m}{\beta}\int_0^\infty g_1(\xi)x(t-\xi)d\xi - ay(t) \\
&= \frac{\beta_1\lambda}{\beta} + \frac{\beta_1(a-m)}{\beta}\int_0^\infty g_1(\xi)x(t-\xi)d\xi - aV(t).
\end{aligned}$$

Note that $\int_0^\infty g_1(\xi)x(t-\xi)d\xi$ is ultimately bounded, then there exist positive constants C and T_0 such that

$$\left.\frac{dV(t)}{dt}\right|_{(10)} \le \frac{\beta_1\lambda}{\beta} + C - aV(t), \quad \forall\, t \ge T_0.$$

This yields that $V(t)$ is eventually bounded and so is $y(t)$. By a similar argument, one can show that there exist positive constants C_1 and $T_1 > T_0$ such that

$$\left.\frac{dv(t)}{dt}\right|_{(10)} \le C_1 - \mu\cdot v(t), \quad \forall\, t \ge T_1,$$

proving the boundedness of $v(t)$. Therefore, the system (10) is point dissipative [2] and hence the solution of (10) exists globally. □

Proof of Theorem 2.2. Note that $\Re_0 \le 1$ implies $\widehat{\Re}_0 \le 1$.

Let

$$H_i(t) = \int_t^\infty g_i(\zeta)d\zeta, \quad i = 1, 2$$

and $L(t) = L_1(t) + L_2(t) + L_3(t)$ with

$$\begin{aligned}
L_1(t) &= \tfrac{1}{2}\left(x(t) - \tfrac{\lambda}{m}\right)^2 + \tfrac{\beta\lambda}{\beta_1 m}y(t) + \tfrac{\beta\lambda a}{\beta_1 m k_1}v(t), \\
L_2(t) &= \tfrac{\beta\lambda}{m}\int_0^\infty H_1(\zeta)x(t-\zeta)v(t-\zeta)d\zeta, \\
L_3(t) &= \tfrac{\beta\lambda a}{\beta_1 m}\int_0^\infty H_2(\zeta)y(t-\zeta)d\zeta.
\end{aligned}$$

It is clear that $L(t) \geq 0$ and $L(t) = 0$ if and only if $x(t) = \frac{\lambda}{m}, y(t) = v(t) = 0$. The derivative of L_1 along the solution of (10) is

$$\begin{aligned}\frac{dL_1}{dt} &= \left(x(t) - \frac{\lambda}{m}\right)(\lambda - mx(t) - \beta x(t)v(t)) \\ &\quad + \frac{\beta\lambda}{m}\int_0^\infty g_1(\zeta)x(t-\zeta)v(t-\zeta)d\zeta - \frac{\beta\lambda a}{\beta_1 m}y(t) \\ &\quad + \frac{\beta\lambda a}{\beta_1 m}\int_0^\infty g_2(\zeta)y(t-\zeta)d\zeta - \frac{\beta\lambda a\mu}{\beta_1 m k_1}v(t).\end{aligned}$$

Noticing that $H_1(0) = 1, H_1(\infty) = 0$, $dH_1(t) = -g_1(t)dt$, and using integration by parts, we calculate the derivative of L_2

$$\begin{aligned}\frac{dL_2}{dt} &= \frac{\beta\lambda}{m}\int_0^\infty H_1(\zeta)\frac{d(x(t-\zeta)v(t-\zeta))}{dt}d\zeta \\ &= -\frac{\beta\lambda}{m}\int_0^\infty H_1(\zeta)\frac{d(x(t-\zeta)v(t-\zeta))}{d\zeta}d\zeta \\ &= -\frac{\beta\lambda}{m}H_1(\zeta)x(t-\zeta)v(t-\zeta)\,\big|_{\zeta=0}^{\infty} + \frac{\beta\lambda}{m}\int_0^\infty x(t-\zeta)v(t-\zeta)dH_1(\zeta) \\ &= \frac{\beta\lambda}{m}x(t)v(t) - \frac{\beta\lambda}{m}\int_0^\infty g_1(\zeta)x(t-\zeta)v(t-\zeta)d\zeta.\end{aligned}$$

Similarly,

$$\frac{dL_3}{dt} = \frac{\beta\lambda a}{\beta_1 m}\left(y(t) - \int_0^\infty g_2(\zeta)y(t-\zeta)d\zeta\right).$$

Thus

$$\begin{aligned}\frac{dL}{dt} &= \frac{dL_1}{dt} + \frac{dL_2}{dt} + \frac{dL_3}{dt} \\ &= -m\left(x(t) - \frac{\lambda}{m}\right)^2 - \beta v(t)\left(x(t)^2 - 2\frac{\lambda}{m}x(t) + \left(\frac{\lambda}{m}\right)^2\right) - \frac{\beta\lambda a\mu}{\beta_1 m k_1}v(t) \\ &= -(m + \beta v(t))\left(x(t) - \frac{\lambda}{m}\right)^2 - \frac{\beta\lambda a\mu}{m\beta_1 k_1}(1 - \Re_0)v(t) \\ &\leq 0.\end{aligned}$$

Note that E_0 is the largest invariant subset of $\{\frac{dL}{dt} = 0\}$, then the global stability of E_0 follows from the classical Lyapunov-LaSalle invariance principle (see, for example, [4, Theorem 2.7.1]). □

Proof of Theorem 2.3. Note that $\Re_0 > 1$ is equivalent to $\widehat{\Re}_0 > 1$. Let $W(t) = W_1(x(t), y(t), v(t)) + W_2(x(t), y(t), v(t)) + W_3(x(t), y(t), v(t))$ with

$$W_1(x(t), y(t), v(t)) = F(x(t), x^*) + \tfrac{\beta}{\beta_1}F(y(t), y^*) + \tfrac{a\beta}{k_1\beta_1}F(v(t), v^*)$$

$$W_2(x(t), y(t), v(t)) = \beta\textstyle\int_0^\infty H_1(\zeta)F(x(t-\zeta)v(t-\zeta), x^*v^*)d\zeta$$

$$W_3(x(t), y(t), v(t)) = \tfrac{a\beta}{\beta_1}\textstyle\int_0^\infty H_2(\zeta)F(y(t-\zeta), y^*)d\zeta$$

where

$$F(u, u^*) = u - u^*\ln u - (u^* - u^*\ln u^*) \geq F(u^*, u^*) = 0$$

for $u > 0$ and any positive constant u^*. By Theorem 2.1, all solutions are positive and bounded. Thus $W(t)$ is well defined and $W(t) \geq 0$, in which the equality holds

if and only if $x(t) = x^*, y(t) = y^*, v(t) = v^*$ and $x(t-\zeta)v(t-\zeta) = x^*v^*, y(t-\zeta) = y^*$ for almost all $\zeta \in [0, \infty)$. To find the derivative of W along the solution of (10), we first calculate the derivative of W_1 along the solution of (10)

$$\begin{aligned}\frac{dW_1}{dt} &= \frac{x(t)-x^*}{x(t)}(\lambda - mx(t) - \beta x(t)v(t)) \\ &\quad +\beta\frac{y(t)-y^*}{y(t)}\int_0^\infty g_1(\zeta)x(t-\zeta)v(t-\zeta)d\zeta - \frac{a\beta}{\beta_1}(y(t)-y^*) \\ &\quad +\frac{a\beta}{\beta_1}\frac{v(t)-v^*}{v(t)}\int_0^\infty g_2(\zeta)y(t-\zeta)d\zeta - \frac{a\beta\mu}{k_1\beta_1}(v(t)-v^*).\end{aligned}$$

That is

$$\begin{aligned}\frac{dW_1}{dt} &= \lambda - mx(t) - \beta x(t)v(t) + mx^* + \frac{a\beta}{\beta_1}y^* + \frac{a\beta\mu}{k_1\beta_1}v^* \\ &\quad -\frac{\lambda x^*}{x(t)} + \beta x^* v(t) - \frac{a\beta}{\beta_1}y(t) - \frac{a\beta\mu}{k_1\beta_1}v(t) \\ &\quad +\beta\left(1-\frac{y^*}{y(t)}\right)\int_0^\infty g_1(\zeta)x(t-\zeta)v(t-\zeta)d\zeta \\ &\quad +\frac{a\beta}{\beta_1}\left(1-\frac{v^*}{v(t)}\right)\int_0^\infty g_2(\zeta)y(t-\zeta)d\zeta.\end{aligned}$$

We now calculate the derivative of W_2 along the solution of (10)

$$\begin{aligned}\frac{dW_2}{dt} &= \beta\int_0^\infty H_1(\zeta)\frac{dF(x(t-\zeta)v(t-\zeta), x^*v^*)}{dt}d\zeta \\ &= -\beta\int_0^\infty H_1(\zeta)\frac{dF(x(t-\zeta)v(t-\zeta), x^*v^*)}{d\zeta}d\zeta \\ &= -\beta H_1(\zeta)F(x(t-\zeta)v(t-\zeta), x^*v^*)\,|_{\zeta=0}^{\infty} .. \\ &\quad +\beta\int_0^\infty F(x(t-\zeta)v(t-\zeta), x^*v^*)dH_1(\zeta) \\ &= F(x(t)v(t), x^*v^*) - \beta\int_0^\infty g_1(\zeta)F(x(t-\zeta)v(t-\zeta), x^*v^*)d\zeta \\ &= \beta[x(t)v(t) - x^*v^*\ln(x(t)v(t))] - \beta\int_0^\infty g_1(\zeta)x(t-\zeta)v(t-\zeta)d\zeta \\ &\quad +\beta x^*v^*\int_0^\infty g_1(\zeta)\ln\left(x(t-\zeta)v(t-\zeta)\right)d\zeta \\ &= \beta x(t)v(t) - \beta\int_0^\infty g_1(\zeta)x(t-\zeta)v(t-\zeta)d\zeta \\ &\quad +\beta x^*v^*\int_0^\infty g_1(\zeta)\ln\frac{x(t-\zeta)v(t-\zeta)}{x(t)v(t)}d\zeta,\end{aligned}$$

where again we use the fact that $H_1(0) = 1, H_1(\infty) = 0$, $dH_1(t) = -g_1(t)dt$ and integration by parts. In a similar way, using $H_2(0) = 1, H_2(\infty) = 0$, $dH_2(t) = -g_2(t)dt$, we calculate the derivative of W_3 to get

$$\frac{dW_3}{dt} = \frac{a\beta}{\beta_1}y(t) - \frac{a\beta}{\beta_1}\int_0^\infty g_1(\zeta)y(t-\zeta)d\zeta + \frac{ay^*\beta}{\beta_1}\int_0^\infty g_2(\zeta)\ln\frac{y(t-\zeta)}{y(t)}d\zeta.$$

Note that E_1 is an equilibrium, thus $\lambda = mx^* + \beta x^* v^*, \beta_1 x^* v^* = ay^*,\ ky^* = \mu v^*$ and $x^* = \frac{a\mu}{k_1\beta_1}$. We employ this relation together with the assumption (A) to obtain the derivative of W along the solution of (10)

$$\begin{aligned}\frac{dW}{dt} &= -\frac{m(x(t)-x^*)^2}{x(t)} + 3\beta x^* v^* - \beta x^* v^* \frac{x^*}{x(t)} \\ &\quad -\beta x^* v^* \frac{y^*}{x^* v^* y(t)} \int_0^\infty g_1(\zeta) x(t-\zeta) v(t-\zeta) d\zeta \\ &\quad -\beta x^* v^* \frac{v^*}{y^* v(t)} \int_0^\infty g_2(\zeta) y(t-\zeta) d\zeta \\ &\quad +\beta x^* v^* \int_0^\infty g_1(\zeta) \ln \frac{x(t-\zeta)v(t-\zeta)}{x(t)v(t)} d\zeta \\ &\quad +\beta x^* v^* \int_0^\infty g_2(\zeta) \ln \frac{y(t-\zeta)}{y(t)} d\zeta.\end{aligned}$$

Using the fact that 3 can be written as $3 = \int_0^\infty g_1(\zeta)(1+1)d\zeta + \int_0^\infty g_2(\zeta)d\zeta$ and $u - 1 - lnu \geq 0$ for $u > 0$, we further have

$$\begin{aligned}\frac{dW}{dt} &= -\frac{m(x(t)-x^*)^2}{x(t)} + \beta x^* v^* \int_0^\infty g_1(\zeta) \left(1 - \frac{x^*}{x(t)} + \ln \frac{x^*}{x(t)} - \ln \frac{x^*}{x(t)} + 1 \right. \\ &\quad \left. - \frac{y^* x(t-\zeta) v(t-\zeta)}{x^* v^* y(t)} + \ln \frac{y^* x(t-\zeta) v(t-\zeta)}{x^* v^* y(t)} - \ln \frac{y^* x(t-\zeta) v(t-\zeta)}{x^* v^* y(t)} \right) d\zeta \\ &\quad +\beta x^* v^* \int_0^\infty g_2(\zeta) \left(1 - \frac{v^* y(t-\zeta)}{y^* v(t)} + \ln \frac{v^* y(t-\zeta)}{y^* v(t)} - \ln \frac{v^* y(t-\zeta)}{y^* v(t)} \right) d\zeta \\ &\quad +\beta x^* v^* \left(\int_0^\infty g_1(\zeta) \ln \frac{x(t-\zeta)v(t-\zeta)}{x(t)v(t)} d\zeta + \int_0^\infty g_2(\zeta) \ln \frac{y(t-\zeta)}{y(t)} d\zeta \right).\end{aligned}$$

Thus

$$\begin{aligned}\frac{dW}{dt} &\leq \beta x^* v^* \int_0^\infty g_1(\zeta) \left(\ln \frac{x(t-\zeta)v(t-\zeta)}{x(t)v(t)} - \ln \frac{y^* x(t-\zeta)v(t-\zeta)}{v^* x(t) y(t)} \right) d\zeta \\ &\quad +\beta x^* v^* \int_0^\infty g_2(\zeta) \left(\ln \frac{y(t-\zeta)}{y(t)} - \ln \frac{v^* y(t-\zeta)}{y^* v(t)} \right) d\zeta \\ &= \beta x^* v^* \int_0^\infty \left(g_1(\zeta) \ln \frac{v^* y(t)}{y^* v(t)} + g_2(\zeta) \ln \frac{y^* v(t)}{v^* y(t)} \right) d\zeta \\ &= \beta x^* v^* \ln \left(\frac{v^* y(t)}{y^* v(t)} \cdot \frac{y^* v(t)}{v^* y(t)} \right) = 0.\end{aligned}$$

That is $\frac{dW}{dt} \leq 0$ and $\frac{dW}{dt} = 0$ if and only if $x(t) = x^*$ and $x(t-\zeta)v(t-\zeta)y^* = x^* v^* y(t), y(t-\zeta)v^* = y^* v(t)$ for almost all $\zeta \in [0, \infty)$. Again by the Lyapunov-LaSalle invariance principle, all solutions of (10) are attracted to M, which is the largest invariant subset of $\{\frac{dW}{dt} = 0\}$. Since M is invariant with respect to (10), it is ease to verify that $M = \{(x^*, y^*, v^*)\} = E_1$. This shows that

$$\lim_{t\to\infty} (x(t), y(t), v(t)) = E_1.$$

This completes the proof. □

5. **Discussion.** Global stability of a general delay differential equation model of HIV-1 infection, namely, system (1), has been established by the method of Lyapunov functionals. It has been shown that the basic reproduction number $\Re_0$ defined

in (3) is a sharp threshold value in the sense that if $\Re_0 \leq 1$, then all nonnegative solutions converge to the unique infection free equilibrium E_0; whereas if $\Re_0 > 1$, then all nonnegative solutions except E_0 approach to the unique endemic equilibrium E_1. Applying our result to models whose local stability was previously investigated in [11, 14] shows that the local stability does imply global stability.

Our global analysis shows that the intracellular delays have no destabilizing effect on stability of steady states even when the initial viral load is not around the equilibrium level, and no sustained oscillations will appear for any value of delays. However, as seen in Theorem 3.2, the values of delays do have influence on the value of $\Re_0$ and thus the value of endemic steady state. For instance, if $\tau_1 + \tau_2$ is large enough, then it can bring down the value of $\Re_0$ to be lower than 1 and thus to clear the virus load in an HIV-1 patient.

Notice that global stability results of (1) ((7)(9)) are independent of initial conditions, this indicates that for HIV patients with different initial virus loads, a combination therapy with a reverse transcriptase inhibitor and a protease inhibitor would either completely clear out the virus if $\Re_0 \leq 1$ or drive the virus load eventually to a constant level if $\Re_0 > 1$. As expected it may takes longer to reach the equilibrium level if the initial virus load is much lower or higher than the equilibrium level. As local stability implies that if the initial virus load is very close to the equilibrium level, then the virus load will remain nearby and approach the equilibrium level as time increases. While in practice, it is very likely that the the equilibrium level is not known in advance, and thus it is not possible to know if a HIV patient's virus load is near the equilibrium level or not and thus it is not informative about the future of the treatment. Fortunately global stability guarantees that there is no need to concern about if the initial virus load is around the equilibrium level or not, as in the long-run, the virus load will approach the equilibrium level. In this sense, it is more desirable to accomplish global dynamics than to achieve local dynamics only.

Global stability results suggest that increasing the effectiveness of a combination therapy (i.e., increasing n_{rt} and n_p), prolonging the latent period, slowing down virus production processes (i.e., increasing τ_1 and /or τ_2) are desirable control strategies. Some of these strategies have been employed in treatment practice such as the most popular highly active antiretroviral therapy (HAART) for the treatment of HIV infection ([3, 7]).

We should point out, though a combination therapy may not be perfectly effective to completely eliminate the virus (i.e., $\Re_0$ remains above 1), the therapy still has a positive effect on lowering the virus load to help prolong the patient's life.

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REFERENCES

[1] J. K. Hale and J. Kato, *Phase space for retarded equation with infinite delay*, Funk. Ekv., **21** (1978), 11–41.

[2] J. K. Hale and S. M. Verduyn Lunel, "Introduction to Functional Differential Equations," Appl. Math. Sci., vol. **99**, Springer, New York, 1993.

[3] D. D. Ho, A. U. Neumann, A. S. Perelson, W. Chen, J. M. Leonard and M. Markowitz, *Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection*, Nature, **373** (1995), 123–126.
[4] Y. Kuang, "Delay Differential Equations with Applications in Population Dynamics," Academic Press, San Diego, 1993.
[5] J. P. LaSalle, "The Stability of Dynamical Systems," Reg. Conf. Ser. Appl. Math., SIAM, Philadelphia, 1976.
[6] M. Y. Li, Z. Shuai and C. Wang, *Global stability of multi-group epidemic models with distributed delays*, J. Math. Anal. Appl., **361** (2010), 38–47.
[7] M. T. May, J. A. Sterne, D. Costagliola, C. A. Sabin, A. N. Phillips, A. C. Justice, F. Dabis, J. Gill, J. Lundgren, R. S. Hogg, F. de Wolf, G. Fätkenheuer, S. Staszewski, A d'Arminio Monforte and M. Egger, *HIV treatment response and prognosis in Europe and North America in the first decade of highly active antiretroviral therapy: A collaborative analysis*, Lancet., **368** (2006), 451–458.
[8] C. C. McCluskey, *Global stability for an SEIR epidemiological model with varying infectivity and infinite delay*, Math. Biosci. and Eng., **6** (2009), 603–610.
[9] C. C. McCluskey, *Complete global stability for an SIR epidemic model with delay– Distributed or discrete*, Nonlinear Anal.: Real World Applications, **11** (2010), 55–59.
[10] P. W. Nelson and A. S. Perelson, *A model of HIV-1 pathogenesis that includes an intracellular delay*, Math. Biosci., **163** (2000), 201–215.
[11] P. W. Nelson and A. S. Perelson, *Mathematical analysis of delay differential equation models of HIV-1 infection*, Mathematical Biosciences, **179** (2002), 73–94.
[12] M. Nowak and R. May, "Virus Dynamics," Oxford University Press, Cambridge, 2000.
[13] A. S. Perelson and P. W. Nelson, *Mathematical analysis of HIV dynamics in vivo*, SIAM Rev., **41** (1999), 3–44.
[14] H. Zhu and X. Zou, *Impact of delays in cell infection and virus production on HIV-1 dynamics*, Mathematical Medicine and Biology, IMA, **25** (2008), 99–112.

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