Mathematics in Applied Sciences and Engineering
Volume **1**, Number **3**, September **2020**, pp.**236-248**
https://ojs.lib.uwo.ca/mase
https://doi.org/10.5206/mase/10828

GLOBAL DYNAMICS OF A TWO-STRAIN HIV INFECTION MODEL WITH INTRACELLULAR DELAY

JIN XU

Abstract. In this paper, we formulate a mathematical model to describe the interaction of two strains of HIV virus and the target cells within a host. The model is in the form of delay differential equations with two discrete delays to account for the average time for replication for the two strains. The model dynamic turns to be generically determined by two composite parameters R_1 and R_2, the basic reproduction numbers for strain 1 and strain 2, respectively in the absence of the other strain, in the sense that except for the critical case $R_1 = R_2 > 1$, the solutions are proved to converge to the corresponding equilibrium globally. The method used is Lyapunov functionals.

1. Introduction

It has been realized that mathematical modelling can provide valuable insight into HIV-1 pathogenesis. These mathematical models are formulated by using differential equations to explore the mechanisms and dynamical behaviors of the viral infection process [3, 8, 17, 18, 19]. Such understanding may offer guidance for developing efficient anti-viral drug therapies [14, 15, 10].

Most existing mathematical models for HIV virus dynamics are by systems of ordinary differential equations. A standard and classic differential equation model for HIV infection is the following system of ODEs [16, 14, 18]:

$$\begin{cases} \dot{T} = \lambda - dT - kTV, \\ \dot{T^*} = kTV - \mu T^*, \\ \dot{V} = pT^* - cV, \end{cases} \tag{1.1}$$

where $T(t), T^*(t)$ and $V(t)$ are the population sizes of uninfected target cells, infected cells and the free virus particles, respectively, at time t. The assumption is that uninfected cells are generated at a constant rate, λ, and die at a rate d. Free virus particles infect uninfected target cells at a rate proportional to the product of their abundances, kTV. The rate constant, k, describes the efficacy of this process. Infected cells produce free virus particles at a rate proportional to their abundance, pT^*. Infected cells die at a rate μT^* either due to the natural death or the action of the virus and free virus particles are removed from the system at rate cV by the immune system or natural decay. Therefore, the average life-time of an infected cell, a free virus particle and an uninfected cell are $1/\mu$, $1/c$ and $1/d$ respectively. The model well predicts the primary phase of HIV infection, showing that during the first weeks of infection there is a peak in viral load with a subsequent decline to a relatively stable steady-state.

Received by the editors 29 June 2020; accepted 24 August 2020; online first 6 September, 2020.
2000 *Mathematics Subject Classification.* 34K20, 34K25, 92B05, 92D25.
Key words and phrases. HIV, virus dynamics, intracellular delay, global stability, Lyapunov functional.

Now, we assume there is an another subtype of virus in within a host which competes with the original virus for host cell resource. Assuming that super infection is negligible, an ordinary differential equations can be formulate along the line of (1.1) to describe the interaction between the two subtype viruses and host cells, as given below.

$$\begin{cases} \dot{T} = \lambda - dT - k_1 T V_1 - k_2 T V_2, \\ \dot{T_1} = k_1 T V_1 - \mu_1 T_1, \\ \dot{T_2} = k_2 T V_2 - \mu_2 T_2, \\ \dot{V_1} = p_1 T_1 - c_1 V_1, \\ \dot{V_2} = p_2 T_2 - c_2 V_2, \end{cases} \tag{1.2}$$

where $T_1(t)$ denotes the population size of cells productively infected by strain-1 virus, whereas $T_2(t)$ denotes the population size of cells productively infected by strain-2 virus at time t; $V_1(t)$ and $V_2(t)$ represent the respective population sizes of subtype-1 and subtype-2 viruses; k_1 and k_2 represent the rate constants at which uninfected target cells are infected by subtype-1 and subtype-2 viruses, respectively. The two subtypes of infected cells are assumed to have two different death rate μ_1 and μ_2. Once uninfected target cells are infected by subtype-1 (subtype-2) viruses, new subtype-1 (subtype-2) virus particles are produced with constant rate p_1 (p_2). The new subtypes of virus have the respective clearance rate c_1 and c_2. All the parameters of the model are assumed to be positive. Here we omit the super-infection in host cells.

However, in reality, there is a lag between the time target cells are contacted by virus particles and the time the contacted cells become actively affected meaning that the virions have enter cells and started producing new virions [23]. This can be explained by the initial phase of the virus life cycle, which include all stages from viral attachment until the time that the host cell contains the infectious viral particles in its cytoplasm. To account for this lag, models that include time delays have been developed and investigated [8, 15, 23]. One distinct feature of delay differential equation models is that a delay typically destabilizes an stable equilibrium and causes sustained oscillation through Hopf bifurctions. By rigorously establishing the global dynamics of the two-strain competitive viral model with intracellular delays, we show that no sustained oscillations are possible in our model.

To incorporate the intracellular phase of the virus life-cycle, we assume that subtype-1 virus and subtype-2 virus production occur in average, τ_1 and τ_2 time units later, after the respective virus enter the host cells. The recruitment of subtype-1 virus producing cells at time t is given by the number of cells that were newly infected by strain-1 at time $t-\tau_1$ and are still alive at time t. In the same way, the recruitment of subtype-2 virus producing cells at time t is given by the number of cells that were newly infected by strain-2 at time $t-\tau_2$ and are still alive at time t. If we assume two constant death rates s_1 and s_2 for infected but not yet virus-producing cells for subtype-1 and subtype-2, the probability of subtype-1 surviving the time period from $t-\tau_1$ to t is $e^{-s_1\tau_1}$, the probability of subtype-2 surviving the time period from $t-\tau_2$ to t is $e^{-s_2\tau_2}$. The transfer diagram for the transmission of viral infection under such a scenario is shown in Figure 1. Thus the following delay differential equations model is proposed:

$$\begin{cases} \dot{T} = \lambda - dT(t) - k_1 T(t) V_1(t) - k_2 T(t) V_2(t), \\ \dot{T_1} = k_1 T(t-\tau_1) V_1(t-\tau_1) e^{-s_1\tau_1} - \mu_1 T_1(t), \\ \dot{T_2} = k_2 T(t-\tau_2) V_2(t-\tau_2) e^{-s_2\tau_2} - \mu_2 T_2(t), \\ \dot{V_1} = p_1 T_1(t) - c_1 V_1(t), \\ \dot{V_2} = p_2 T_2(t) - c_2 V_2(t), \end{cases} \tag{1.3}$$

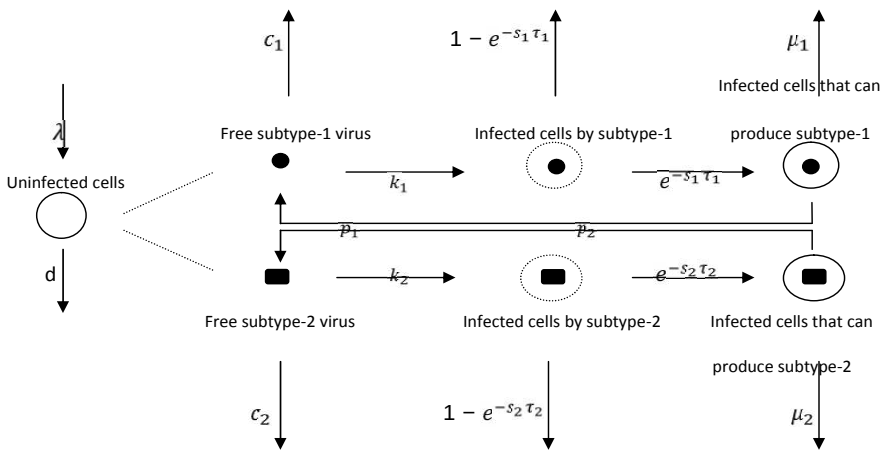

FIGURE 1. Transfer diagram for model (1.3)

Delays have been incorporated into virus dynamics models in [8, 23, 12], but only for single strain models. Here we consider two strains. Many previous in-host models also considered the effects of anti-viral drug therapies such as HAART [15, 1, 21], but only local stability were analysed in these works. We note that by renaming the coeffiicients due to the effect of reverse transcriptase inhibitors and protease inhibitors, the model in [15, 1, 21] can be transformed into the form of (1.3). Our results on the global dynamics of model (1.3) can apply to these models with anti-viral therapies, and hence can rule out the exitence of periodic solutions. This shows novelty of this work and should benefit other researchers working on similar models.

In the present section we analyse model (1.3) including intracellular delays. We establish global asymptotic stability of the infected-free, and single-infected by constructing Lyapunov functionals. To this end, we first establishes the well-posedness of (1.3) in section 3.2. Then we discuss the existence of equilibria in the feasible region and derive the basic reproductive number R_0. It turns out that R_1 is a decreasing function of the delay τ_1 and R_2 is a decreasing function of the delay τ_2. These imply that ignoring the intracellular delays will overestimate the basic reproduction number. We show that the basic reproductive number R_0 generically determines the global dynamics of model (1.3). More specifically, if $R_0 \leq 1$, the infection-free equilibrium E_0 is globally asymptotically stable, and two subtype viruses will be cleared; if $R_0 > 1$ and $R_1 \neq R_2$, the single-infected equilibrium arising from the greater basic reproduction number is globally asymptotically stable. The proof utilizes a global Lyapunov functional that is motivated by the work in [11, 12]. The global stability of single-infected equlibira rule out any possibility of sustained oscillations. In addition, numerical simulations are also conducted to demonstrate global dynamics of system (1.3).

2. Well-posedness

In the same way as in the previous section, the system (1.3) is biologically acceptable in the sense that no population goes negative. We expect that starting from non-negative initial values, the corresponding solution remains non-negative. To proceed, we follow the convention to denote by $C_1 = C([-\tau_1, 0], \mathbb{R})$ and $C_2 = C([-\tau_2, 0], \mathbb{R})$ the Banach spaces of continuous functions mapping the interval $[-\tau_i, 0]$ into $\mathbb{R}$, $i = 1, 2$, with norm $\|\Phi_i\| = sup_{-\tau_i \leq \theta \leq 0} |\Phi_i(\theta)|$ for $\Phi_i \in C_i$. Let $\tau = max\{\tau_1, \tau_2\}$, denote by

$C = C([-\tau, 0], \mathbb{R})$ the Banach space of continuous functions mapping the interval $[-\tau, 0]$ into $\mathbb{R}$, with norm $\|\Phi\| = sup_{-\tau \le \theta \le 0} |\Phi(\theta)|$ for $\theta \in C$. The nonnegative cone of C, C_1 and C_2 are defined as $C^+ = C([-\tau, 0], \mathbb{R}_+), C_1^+ = C([-\tau_1, 0], \mathbb{R}_+)$ and $C_2^+ = C([-\tau_2, 0], \mathbb{R}_+)$. The initial conditions for system (1.3) are chosen at $t = 0$ as $\varphi \in C^+ \times \mathbb{R}_+ \times \mathbb{R}_+ \times C_1^+ \times C_2^+$. The well-posedness for our delay differential equation model (1.3) is established by the following theorem.

Theorem 2.1. *Under the above initial conditions, all solutions of system* (1.3) *are positive and ultimately bounded in* $C \times \mathbb{R} \times \mathbb{R} \times C_1 \times C_2$

Proof. First, we prove that $T(t)$ is positive for all $t \ge 0$. Assuming the opposite, let $t_1 > 0$ be the first time such that $T(t_1) = 0$, which means $T(t) > 0$ as $t \in [0, t_1)$. Since

$$\dot{T} = \lambda - dT(t) - k_1 T(t) V_1(t) - k_2 T(t) V_2(t),$$

we get $\dot{T}(t_1) = \lambda > 0$,and hence $T(t) < 0$ for $t \in (t_1 - \epsilon, t_1)$ where $\epsilon > 0$ is sufficiently small. This contradicts $T(t) > 0$ for $t \in [0, t_1)$. It follows that $T(t) > 0$ for $t > 0$. Next, we show $V_1(t) \ge 0$ for all $t \ge 0$. Assume the opposite and let $t_2 > 0$ be the first time such that $V_1(t_2) = 0$. Since

$$\dot{V_1}(t) = p_1 T_1(t) - c_1 V_1(t),$$

we have $\dot{V_1}(t_2) = p_1 T_1(t_2)$. On the other hand, solving $T_1(t)$ by the second equation of (1.3) gives

$$T_1(t_2) = (T_1(0) + \int_0^{t_2} k_1 T(\theta - \tau_1) V_1(\theta - \tau_1) e^{-s_1 \tau_1} e^{\mu_1 \theta} d\theta) e^{-\mu_1 t_2} > 0$$

Hence $\dot{V_1}(t_2) = p_1 T_1(t_2) > 0$ implying $V_1(t)$ is positive for all $t \ge 0$.

The positiveness of $T(t)$ and $V_1(t)$ and the following formula

$$T_1(t) = (T_1(0) + \int_0^{t} k_1 T(\theta - \tau_1) V_1(\theta - \tau_1) e^{-s_1 \tau_1} e^{\mu_1 \theta} d\theta) e^{-\mu_1 t} > 0.$$

in turn leads to the positiveness of $T_1(t)$ for all $t \ge 0$. Similarly, we can show that $V_2(t)$ and $T_2(t)$ are positive for $t \ge 0$ under positive initial conditions.

From the first equation of (1.3), we obtain $\dot{T(t)} \le \lambda - dT(t)$. Hence $limsup_{t \to \infty} T(t) \le \frac{\lambda}{d}$. Adding the first three equations of (1.3), it follows

$$\begin{aligned}(T(t) + T_1(t + \tau_1) + T_2(t + \tau_2))' &= \lambda - dT(t) - \mu_1 T_1(t + \tau_1) - \mu_2 T_2(t + \tau_2) \\ &\quad + k_1 T(t) V_1(t)(e^{-s_1 \tau_1} - 1) + k_2 T(t) V_2(t)(e^{-s_2 \tau_2} - 1) \\ &\le \lambda - \tilde{r}(T(t) + T_1(t + \tau_1) + T_2(t + \tau_2))\end{aligned}$$

where $\tilde{r} = min\{d, \mu_1, \mu_2\}$. Thus, $limsup_{t \to \infty}(T(t) + T_1(t + \tau_1) + T_2(t + \tau_2)) \le \frac{\lambda}{\tilde{r}}$. For any $\epsilon > 0, \exists t^* > 0$, such that $T(t) + T_1(t + \tau_1) + T_2(t + \tau_2) \le \frac{\lambda}{\tilde{r}} + \epsilon$ for all $t \ge t^*$. Thus, $T(t), T_1(t)$ and $T_2(t)$ are all ultimately bounded by $\frac{\lambda}{\tilde{r}}$. The fourth equation of (1.3) implies

$$\dot{V_1} = p_1 T_1(t) - c_1 V_1(t) \le p_1 (\frac{\lambda}{\tilde{r}} + \epsilon) - c_1 V_1(t), t \ge t^*$$

This implies $limsup_{t \to \infty} V_1 \le \frac{p_1}{c_1}(\frac{\lambda}{\tilde{r}} + \epsilon)$. Since $\epsilon > 0$ is arbitrary, we attain $limsup_{t \to \infty} V_1(t) \le \frac{p_1 \lambda}{c_1 \tilde{r}}$. Similarly, we can obtain $limsup_{t \to \infty} V_2(t) \le \frac{p_2 \lambda}{c_2 \tilde{r}}$. Therefore, $T(t), T_1(t), T_2(t), V_1(t)$ and $V_2(t)$ are ultimately bounded in $C \times \mathbb{R} \times \mathbb{R} \times C_1 \times C_2$.

3. Equilibria and basic reproduction numbers

In system (1.3), without infection $(T_1, T_2, V_1, V_2) = (0, 0, 0, 0)$, uninfected target cells stabilizes at the equilibrium $T = \frac{\lambda}{d}$. The basic reproductive number R_1 for in-host models [17, 12, 16] measures the average number virus-producing target cells produced by a single subtype-1 virus-producing target cell during its entire infectious period in an entirely uninfected target-cell population. As illustrated in Figure 2, the basic reproduction number R_1 for strain-1 is given by

$$R_1 = \frac{p_1}{\mu_1} \cdot \frac{k_1 e^{-s_1 \tau_1}}{c_1} \cdot \frac{\lambda}{d}. \tag{3.1}$$

Similarly, the basic reproduction number R_2 for strain-2 which is the average number virus-producing target cells produced by a single subtype-2 virus producing target cell during its entire infectious period in an entirely uninfected target-cell population is obtained by

$$R_2 = \frac{p_2}{\mu_2} \cdot \frac{k_2 e^{-s_2 \tau_2}}{c_2} \cdot \frac{\lambda}{d}. \tag{3.2}$$

When no intracellular delay is considered, $\tau_1 = \tau_2 = 0$, our R_1 and R_2 reduce to the respective basic reproduction number for our previous model (3.1) (i.e. (2.21)). If $s > 0$, R_1 and R_2 is the decreasing functions of the delay τ_1 and τ_2. It shows that the intracellular delays decrease R_1 and R_2 if cells die during the delay periods. Thus, ignoring the intracellular delay in a viral model will overestimate the basic reproduction number.

From our system (1.3) and our result (3.1) (3.2), we define the system basic reproduction number

$$R_0 = max\left\{R_1, R_2\right\}. \tag{3.3}$$

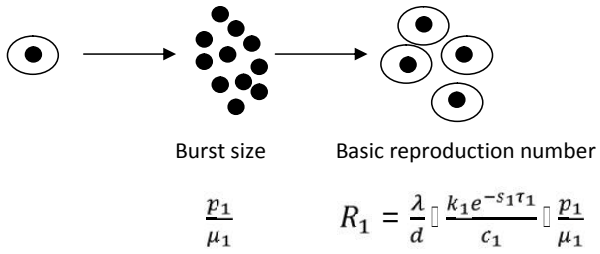

Figure 2. An illustration of the basic reproduction number of model(1.3)

Model system (1.3) always has the infection-free equilibrium $E_0 = \left(\frac{\lambda}{d}, 0, 0, 0, 0\right)$. There are two possible single-infection equilibria $E_1 = \left(\bar{T}, \bar{T_1}, 0, \bar{V_1}, 0\right)$ and $E_2 = \left(\tilde{T}, 0, \tilde{T_2}, 0, \tilde{V_2}\right)$, where

$$\bar{T} = \frac{\lambda}{d}\frac{1}{R_1},\ \bar{T_1} = \frac{dc_1}{k_1 p_1}(R_1 - 1),\ \bar{V_1} = \frac{d}{k_1}(R_1 - 1). \tag{3.4}$$

and

$$\tilde{T} = \frac{\lambda}{d}\frac{1}{R_2},\ \tilde{T_2} = \frac{dc_2}{k_2 p_2}(R_2 - 1),\ \tilde{V_2} = \frac{d}{k_2}(R_2 - 1). \tag{3.5}$$

It turns out that the values of R_1 and R_2 determine the existence of the single-infection equilibria: E_1 exists if and only if $R_1 > 1$ and E_2 exists if and only if $R_2 > 1$. Obviously, E_1 and E_2 are biologically meaningful under the conditions.

It is also possible for our model (1.3) to obtain the double-infection equilibrium which means a equilibrium with all components being positive. Denote such a possible equilibrium by $E_3 = (T^*, T_1^*, T_2^*, V_1^*, V_2^*)$, then calculation shows that the components in E_3 must satisfy

$$\begin{cases} T^* = \dfrac{\mu_1 c_1 e^{s_1\tau_1}}{k_1 p_1} (i.e. \dfrac{d}{\lambda R_1}) = \dfrac{\mu_2 c_2 e^{s_2\tau_2}}{k_2 p_2} \ \ (i.e. \dfrac{d}{\lambda R_2}), \\ T_1^* = \dfrac{c_1 V_1^*}{p_1}, \\ T_2^* = \dfrac{c_2 V_2^*}{p_2}, \\ d(R_1 - 1) = k_1 V_1^* + k_2 V_2^*, \\ d(R_2 - 1) = k_1 V_1^* + k_2 V_2^*. \end{cases} \tag{3.6}$$

By the last two equation in (3.6), it is clear that E_3 exists if and only if

$$R_1 = R_2 > 1. \tag{3.7}$$

If (3.7) holds, there are actually infinitely many co-existence equilibria.

Summarizing the above results, we have the following conclusion. When $R_0 \leq 1$, E_0 is the only equilibrium; when $R_1 > 1, R_2 \leq 1$, there are E_0 and E_1; when $R_2 > 1, R_1 \leq 1$, there are E_0 and E_2; when $R_1 > 1$ and $R_2 > 1$, in addition to E_0, E_1 and E_2, there are infinitely many co-exitence equilibria if $R_1 = R_2 > 1$. Considering the fact that there are ten model parameters in R_1 and R_2, the identity $R_1 = R_2$ is unlikely to hold in practice (or infeasible), and hence, E_3 will not be considered here in this thesis.

4. Global Stability of Equilibria

In this section we study the global stability of equilibria by using the Lyapunov functionals.

We apply Lyapunov functionals similar to those recently used by [11, 6, 20]. A useful function is used to construct our Lyapunov fuctionals:

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

This function attains the global minimum at $x = 1$, $g(1) = 0$, and remains positive for all other postitive values of x. Our Lyapunov functionals take advantage of these properties of $g(x)$. In the following theorems we show that the equilibria exhibit global stability under some threshold conditions.

Theorem 4.1. *If $R_0 \leq 1$, the infection free-equilibrium E_0 is globally asymptotically stable.*

Proof. Let $T_0 = \frac{\lambda}{d}$ and consider the Lyapunov functional

$$\begin{aligned} V(T, T_1, T_2, V_1, V_2) = \quad & T_0 g(T(t)/T_0) + e^{s_1\tau_1} T_1(t) + e^{s_2\tau_2} T_2(t) \\ & + \frac{\mu_1}{p_1} e^{s_1\tau_1} V_1(t) + \frac{\mu_2}{p_2} e^{s_2\tau_2} V_2(t) \\ & + k_1 \int_{-\tau_1}^{0} T(t+\theta) V_1(t+\theta)\, d\theta + k_2 \int_{-\tau_2}^{0} T(t+\theta) V_2(t+\theta)\, d\theta. \end{aligned}$$

Obviously, $V(T, T_1, T_2, V_1, V_2)$ is non-negative in the positive cone $C^+ \times \mathbb{R}_+ \times \mathbb{R}_+ \times C_1^+ \times C_2^+$ and attains zero at E_0. We will show that the derivative of V along the trajectories of our model (1.3) is negatively defininte. Differentiation gives

$$
\begin{aligned}
\dot{V} = \quad & \dot{T(t)} - \frac{T_0}{T(t)}\dot{T(t)} + e^{s_1\tau_1}\dot{T_1(t)} + e^{s_2\tau_2}\dot{T_2(t)} + \frac{\mu_1}{p_1}e^{s_1\tau_1}\dot{V_1(t)} + \frac{\mu_2}{p_2}e^{s_2\tau_2}\dot{V_2(t)} \\
& + k_1T(t)V_1(t) - k_1T(t-\tau_1)V_1(t-\tau_1) + k_2T(t)V_2(t) - k_2T(t-\tau_2)V_2(t-\tau_2) \\
= \quad & \lambda - dT(t) - k_1T(t)V_1(t) - k_2T(t)V_2(t) - \frac{T_0}{T(t)}(\lambda - dT - k_1T(t)V_1(t) - k_2T(t)V_2(t)) \\
& + e^{s_1\tau_1}\left(k_1T(t-\tau_1)V_1(t-\tau_1)e^{-s_1\tau_1} - \mu_1T_1\right) + e^{s_2\tau_2}(k_2T(t-\tau_2)V_2(t-\tau_2)e^{-s_2\tau_2} - \mu_2T_2) \\
& + \frac{\mu_1}{p_1}e^{s_1\tau_1}\left(p_1T_1(t) - c_1V_1(t)) + \frac{\mu_2}{p_2}e^{s_2\tau_2}(p_2T_2(t) - c_2V_2(t)\right) \\
& + k_1T(t)V_1(t) - k_1T(t-\tau_1)V_1(t-\tau_1) + k_2T(t)V_2(t) - k_2T(t-\tau_2)V_2(t-\tau_2)
\end{aligned}
$$

After cancelling terms, using $T_0 = \frac{\lambda}{d}$ and rearranging terms, we get

$$
\begin{aligned}
\dot{V} = \quad & \lambda - dT(t) - \frac{T_0}{T(t)}\lambda + dT_0 \\
& + \left(k_1T_0 - \frac{c_1\mu_1}{p_1}e^{s_1\tau_1}\right)V_1(t) + \left(k_2T_0 - \frac{c_2\mu_2}{p_2}e^{s_2\tau_2}\right)V_2(t) \\
= \quad & \lambda\left(2 - \frac{T(t)}{T_0} - \frac{T_0}{T(t)}\right) \\
& + \frac{c_1\mu_1}{p_1}e^{s_1\tau_1}\left(\frac{k_1p_1\lambda}{\mu_1c_1d}e^{s_1\tau_1} - 1\right)V_1(t) + \frac{c_2\mu_2}{p_2}e^{s_2\tau_2}\left(\frac{k_2p_2\lambda}{\mu_2c_2d}e^{s_2\tau_2} - 1\right)V_2(t) \\
= \quad & \lambda\left(2 - \frac{T(t)}{T_0} - \frac{T_0}{T(t)}\right) \\
& + \frac{\mu_1c_1}{p_1}e^{s_1\tau_1}(R_1 - 1)V_1(t) + \frac{\mu_2c_2}{p_2}e^{s_2\tau_2}(R_2 - 1)V_2(t).
\end{aligned}
$$

Since the arithmetic mean is greater than or equal to the geometric mean, if $R_0 = max\{R_1, R_2\} \leq 1$, each of the three terms on the right hand side is non-positive. Hence $\dot{V}(T, T_1, T_2, V_1, V_2) \leq 0$, and $\dot{V} = 0$ if and only if $(T, T_1, T_2, V_1, V_2) = \left(\frac{\lambda}{d}, 0, 0, 0, 0\right) = E_0$ Therefore, the globally asymptotical stability of E_0 follows from the Lyaunov-LaSalle invariance principle by [7].

When $R_0 > 1$, then E_0 becomes unstable and at least one of the E_1 and E_2 exists. We now investigate the global stability of these two possible single-strain equilibria.

Theorem 4.2. *Assume that E_1 exists (i.e. $R_1 > 1$), if $R_2 < R_1$, then, E_1 is globally asymptotically stable.*

Proof. Define a Lyapunov functional $V : C \times \mathbb{R} \times \mathbb{R} \times C_1 \times C_2 \to \mathbb{R}$ by

$$
\begin{aligned}
V(T, T_1, T_2, V_1, V_2) = \quad & \bar{T}g(\frac{T(t)}{\bar{T}}) + \bar{T_1}e^{s_1\tau_1}g(\frac{T_1(t)}{\bar{T_1}}) + e^{s_2\tau_2}T_2(t) + \frac{\mu_1}{p_1}\bar{V_1}e^{s_1\tau_1}g(\frac{V_1(t)}{\bar{V_1}}) \\
& + \frac{\mu_2}{p_2}e^{s_2\tau_2}V_2(t) + k_1\bar{T}\bar{V_1}\int_{-\tau_1}^{0} g(\frac{T(t+\theta)V_1(t+\theta)}{\bar{T}\bar{V_1}})\,d\theta \\
& + k_2\int_{-\tau_2}^{0} T(t+\theta)V_2(t+\theta)\,d\theta.
\end{aligned}
$$

By the properties of $g(x)$, the Lyapunov functional $V(T, T_1, T_2, V_1, V_2)$ is non-negative in the positive cone $C^+ \times \mathbb{R}_+ \times \mathbb{R}_+ \times C_1^+ \times C_2^+$ and attains zero at E_1. In order to show $\dot{V}$ is negatively definite, we differentiate $V(T, T_1, T_2, V_1, V_2)$ along the trajectories of (1.3) to get

$$\begin{aligned}\dot{V} = \quad & \dot{T}(t) + \frac{\bar{T}}{T(t)}\dot{T}(t) + e^{s_1\tau 1}\dot{T}_1(t) - e^{s_1\tau_1}\frac{\bar{T_1}}{T_1(t)}\dot{T}_1(t) + e^{s_2\tau_2}\dot{T}_2(t) \\ & + \frac{\mu_1}{p_1}e^{s_1\tau_1}\dot{V}_1(t) - \frac{\mu_1}{p_1}e^{s_1\tau_1}\frac{\bar{V_1}}{V_1(t)}\dot{V}_1(t) + \frac{\mu_2}{p_2}e^{s_2\tau 2}\dot{V}_2(t) \\ & + k_1\bar{T}\bar{V_1}\frac{\mathrm{d}}{\mathrm{dt}}\int_{-\tau_1}^{0} g(\frac{T(t+\theta)V_1(t+\theta)}{\bar{T}\bar{V_1}})\,d\theta \\ & + k_2T(t)V_2(t) - k_2T(t-\tau_2)V_2(t-\tau_2). \end{aligned} \tag{4.1}$$

Note that

$$\begin{aligned} & k_1\bar{T}\bar{V_1}\frac{\mathrm{d}}{\mathrm{dt}}\int_{-\tau_1}^{0} g(\frac{T(t+\theta)V_1(t+\theta)}{\bar{T}\bar{V_1}})\,d\theta \\ = \quad & k_1\bar{T}\bar{V_1}\int_{-\tau_1}^{0}\frac{\mathrm{d}}{\mathrm{dt}}g(\frac{T(t+\theta)V_1(t+\theta)}{\bar{T}\bar{V_1}})\,d\theta \\ = \quad & k_1\bar{T}\bar{V_1}\int_{-\tau_1}^{0}\frac{\mathrm{d}}{\mathrm{d}\theta}g(\frac{T(t+\theta)V_1(t+\theta)}{\bar{T}\bar{V_1}})\,d\theta \\ = \quad & k_1\bar{T}\bar{V_1}\left(g(\frac{T(t)V_1(t)}{\bar{T}\bar{V_1}}) - g(\frac{T(t-\tau_1)V_1(t-\tau_1)}{\bar{T}\bar{V_1}})\right) \\ = \quad & k_1\bar{T}\bar{V_1}\left(\frac{T(t)V_1(t)}{\bar{T}\bar{V_1}} - ln\frac{T(t)V_1(t)}{\bar{T}\bar{V_1}} - \frac{T(t-\tau_1)V_1(t-\tau_1)}{\bar{T}\bar{V_1}} + ln\frac{T(t-\tau_1)V_1(t-\tau 1))}{\bar{T}\bar{V_1}}\right) \\ = \quad & k_1T(t)V_1(t) - k_1\bar{T}\bar{V_1}lnT(t)V_1(t) + k_1\bar{T}\bar{V_1}ln\bar{T}\bar{V_1} - k_1T(t-\tau_1)V_1(t-\tau_1) \\ & + k_1\bar{T}\bar{V_1}lnT(t-\tau_1)V_1(t-\tau_1) - k_1\bar{T}\bar{V_1}ln\bar{T}\bar{V_1} \\ = \quad & k_1T(t)V_1(t) - k_1T(t-\tau_1)V_1(t-\tau_1) \\ & + k_1\bar{T}\bar{V_1}lnT(t-\tau_1)V_1(t-\tau_1) - k_1\bar{T}\bar{V_1}lnT(t)V_1(t) \end{aligned} \tag{4.2}$$

Plugging (4.2) and system of (1.3) into equation (4.1), we obtain

$$\begin{aligned}\dot{V} = & \lambda - dT(t) - k_1T(t)V_1(t) - k_2T(t)V_2(t) - \frac{\bar{T}}{T(t)}\lambda + d\bar{T} + k_1\bar{T}V_1(t) + k_2\bar{T}V_2(t) \\ & + k_1T(t-\tau 1)V_1(t-\tau_1) - \mu_1e^{s_1\tau_1}T_1(t) - \bar{T_1}\frac{k_1T(t-\tau_1)V_1(t-\tau_1)}{T_1(t)} + e^{s_1\tau_1}\mu_1\bar{T_1} \\ & + k_2T(t-\tau_2)V_2(t-\tau_2) - \mu_2e^{s_2\tau_2}T_2(t) + \mu_1e^{s_1\tau_1}T_1(t) - \frac{\mu_1c_1}{p_1}e^{s_1\tau_1}V_1(t) \\ & - \mu_1e^{s_1\tau_1}\bar{V_1}\frac{T_1(t)}{V_1(t)} + \frac{\mu_1c_1}{p_1}e^{s_1\tau_1}\bar{V_1} \\ & + \mu_2e^{s_2\tau_2}T_2(t) - \frac{\mu_2c_2}{p_2}e^{s_2\tau_2}V_2(t) \\ & + k_1T(t)V_1(t) - k_1T(t-\tau_1)V_1(t-\tau_1) \\ & - k_1\bar{T}\bar{V_1}lnT(t)V_1(t) + k_1\bar{T}\bar{V_1}lnT(t-\tau_1)V_1(t-\tau_1 \\ & + k_2T(t)V_2(t) - k_2T(t-\tau_2)V_2(t-\tau_2). \end{aligned} \tag{4.3}$$

The components of E_1 are related by the equilibrium equation, i.e.,

$$\begin{cases} \lambda = d\bar{T} + k_1\bar{T}\bar{V_1} \\ k_1\bar{T}\bar{V_1} = \mu_1\bar{T_1}e^{s_1\tau_1} \\ p_1\bar{T_1} = c_1\bar{V_1} \\ k_1\bar{T} = \dfrac{\mu_1\bar{T_1}e^{s_1\tau_1}}{\bar{V_1}} = \dfrac{\mu_1\bar{T_1}e^{s_1\tau_1}c_1}{p_1\bar{T_1}} = \dfrac{\mu_1 c_1}{p_1}e^{s_1\tau_1}. \end{cases} \tag{4.4}$$

Making use of these, we can rearrange and simplify the equation (4.3) as

$$\begin{aligned} \dot{V} = \quad & d\bar{T}\left(2 - \frac{Tt}{\bar{T}} - \frac{\bar{T}}{T(t)}\right) - \frac{k_1\bar{T}^2\bar{V_1}}{T(t)} \\ & + k_1\bar{T}\bar{V_1} + k_2\bar{T}V_2(t) - k_1\bar{T_1}\frac{T(t-\tau_1)V_1(t-\tau_1)}{T_1(t)} \\ & + k_1\bar{T}\bar{V_1} - \frac{k_1\bar{T}\bar{V_1}}{\bar{T_1}}\bar{V_1}\frac{T_1(t)}{V_1(t)} + k_1\bar{T}\bar{V_1} - \frac{\mu_2 c_2}{p_2}e^{s_2\tau_2}V_2(t) \\ & - k_1\bar{T}\bar{V_1}lnT(t)V_1(t) + k_1\bar{T}\bar{V_1}lnT(t-\tau_1)V_1(t-\tau_1) \\ = \quad & d\bar{T}\left(2 - \frac{Tt}{\bar{T}} - \frac{\bar{T}}{T(t)}\right) \\ & - k_1\bar{T}\bar{V_1}\left(g(\frac{\bar{T_1}T(t-\tau_1)V_1(t-\tau_1)}{\bar{T}\bar{V_1}T_1(t)}) - ln\frac{\bar{T_1}T(t-\tau_1)V_1(t-\tau_1)}{\bar{T}\bar{V_1}T_1(t)}\right) \\ & - k_1\bar{T}\bar{V_1}\left(g(\frac{\bar{T}}{T(t)}) - ln\frac{\bar{T}}{T(t)}\right) - k_1\bar{T}\bar{V_1}(g(\frac{\bar{V_1}T_1(t)}{\bar{T_1}V_1(t)}) - ln\frac{\bar{V_1}T_1(t)}{\bar{T_1}V_1(t)}\right) \\ & - k_1\bar{T}\bar{V_1}\left[lnT(t)V_1(t) - lnT(t-\tau_1)V_1(t-\tau_1)\right] \\ & + \left(k_2\bar{T} - \frac{\mu_2 c_2}{p_2}e^{s_2\tau_2}\right)V_2(t) \\ = \quad & d\bar{T}\left(2 - \frac{Tt}{\bar{T}} - \frac{\bar{T}}{T(t)}\right) \\ & - k_1\bar{T}\bar{V_1}g(\frac{\bar{T_1}T(t-\tau_1)V_1(t-\tau_1)}{\bar{T}\bar{V_1}T_1(t)}) \\ & - k_1\bar{T}\bar{V_1}g(\frac{\bar{T}}{T(t)}) - k_1\bar{T}\bar{V_1}g(\frac{\bar{V_1}T_1(t)}{\bar{T_1}V_1(t)}) \\ & + \frac{k_2\lambda}{d}\left(\frac{1}{R_1} - \frac{1}{R_2}\right)V_2(t). \end{aligned}$$

Therefore, by our assumptions, $\dot{V} \leq 0$ with equality holding only at E_1. From the Lyapunov- LaSalle inveriance principle [7], the equilibrium E_1 is globally asymptotically stable. The proof is completed.

Parallel to Theorem 4.2, we have the following theorem for E_2

Theorem 4.3. *Assume that E_2 exists (i.e. $R_2 > 1$), if $R_1 < R_2$, then E_2 is globally asymptotically stable.*

Proof. The proof of this theorem is symmetric to that of Theorem 4.2 by considering the following Lyapunov functional:$V : C \times \mathbb{R} \times \mathbb{R} \times C_1 \times C_2 \to \mathbb{R}$

$$V(T,T_1,T_2,V_1,V_2) = \tilde{T}g(\frac{T(t)}{\tilde{T}}) + e^{s_1\tau_1}T_1(t) + \tilde{T}_2e^{s_2\tau_2}g(\frac{T_2(t)}{\tilde{T}_2}) + \frac{\mu_1}{p_1}e^{s_1\tau_1}V_1(t)$$
$$+\frac{\mu_2}{p_2}\tilde{V}_2e^{s_2\tau_2}g(\frac{V_2(t)}{\tilde{V}_2}) + k_1\int_{-\tau_1}^{0} T(t+\theta)V_1(t+\theta)\,d\theta$$
$$k_2\tilde{T}\tilde{V}_2\int_{-\tau_2}^{0} g(\frac{T(t+\theta)V_2(t+\theta)}{\tilde{T}\tilde{V}_2})\,d\theta$$

We omit the details of the proof.

5. Numerical Simulations

In this section, we present some numeric simulations for the DDE model (3.2) to confirm and illustrate the theoretic results obtained in Section 3.4, which is not significantly different from those for the ODE model (2.2), except that some plottings are in logarithmic function for better and clearer displays.

First, we chose the following values for the model parameters: $\lambda = 6, d = 1, k_1 = 2, p_1 = 1, c_1 = 3, \mu_1 = 10, s_1 = 2, \tau_1 = 0.1, k_2 = 3, p_2 = 2, c_2 = 2.5, \mu_2 = 15, s_2 = 1.5, \tau_2 = 0.15$. This give the values two individual basic reproduction numbers $R_1 = 0.327$ and $R_2 = 0.767$. Three sets of initial values are used: (I) $T(0) = 80, T_1(0) = 50, T_2(0) = 40, V_1(0) = 45, V_2(0) = 35$; (II) $T(0) = 60, T_1(0) = 70, T_2(0) = 50, V_1(0) = 30, V_2(0) = 20$; (III) $T(0) = 50, T_1(0) = 60, T_2(0) = 30, V_1(0) = 20, V_2(0) = 45$. We used a base 10 logarithmic scale for target cells population. The corresponding solutions are presented in Figure 3.

Second, we chose the following values for the model parameters: $\lambda = 6, d = 1, k_1 = 5, p_1 = 6, c_1 = 4, \mu_1 = 3, s_1 = 2, \tau_1 = 0.1, k_2 = 1, p_2 = 4, c_2 = 3, \mu_2 = 4, s_2 = 1.5, \tau_2 = 0.15$. This give the values two individual basic reproduction numbers $R_1 = 12.28$ and $R_2 = 1.597$. Three sets of initial values are used: (I) $T(0) = 80, T_1(0) = 50, T_2(0) = 40, V_1(0) = 45, V_2(0) = 35$; (II) $T(0) = 60, T_1(0) = 70, T_2(0) = 50, V_1(0) = 30, V_2(0) = 20$; (III) $T(0) = 50, T_1(0) = 60, T_2(0) = 30, V_1(0) = 20, V_2(0) = 45$. A base 10 logarithmic scale for target cells population, subtype-1 infected cells and subtype-1 virus cells was employed in our figures. The corresponding solutions are presented in Figure 4.

Third, we chose the following values for the model parameters: $\lambda = 6, d = 1, k_1 = 4, p_1 = 8, c_1 = 8, \mu_1 = 5, s_1 = 2, \tau_1 = 0.1, k_2 = 3, p_2 = 10, c_2 = 5, \mu_2 = 4, , s_2 = 1.5, \tau_2 = 0.15$. This give the values two individual basic reproduction numbers $R_1 = 3.93$ and $R_2 = 7.19$. Three sets of initial values are used: (I) $T(0) = 80, T_1(0) = 50, T_2(0) = 40, V_1(0) = 45, V_2(0) = 35$; (II) $T(0) = 60, T_1(0) = 70, T_2(0) = 50, V_1(0) = 30, V_2(0) = 20$; (III) $T(0) = 50, T_1(0) = 60, T_2(0) = 30, V_1(0) = 20, V_2(0) = 45$. A base 10 logarithmic scale for target cells population, subtype-2 infected cells and subtype-2 virus cells was employed in our figures. The corresponding solutions are presented in Figure 5.

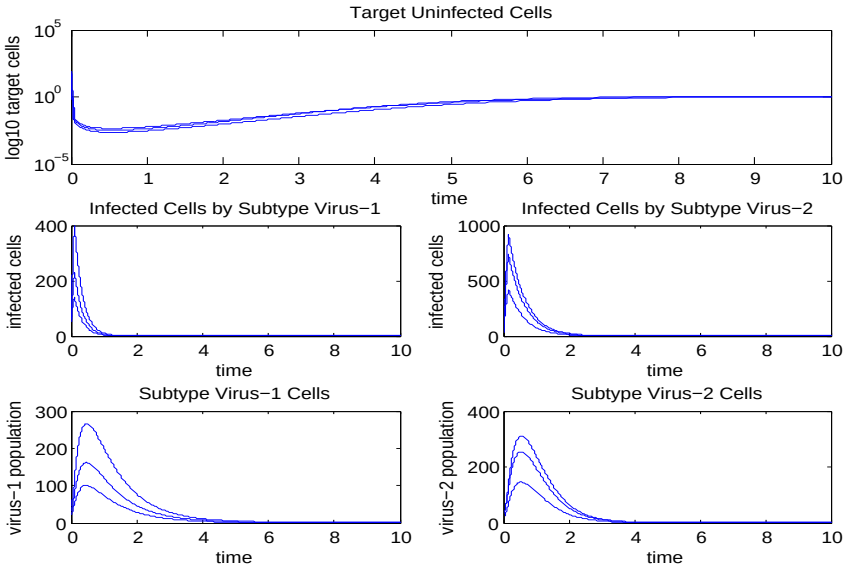

FIGURE 3. $R_1 < 1$ and $R_2 < 1$: viruses of both strains all die out

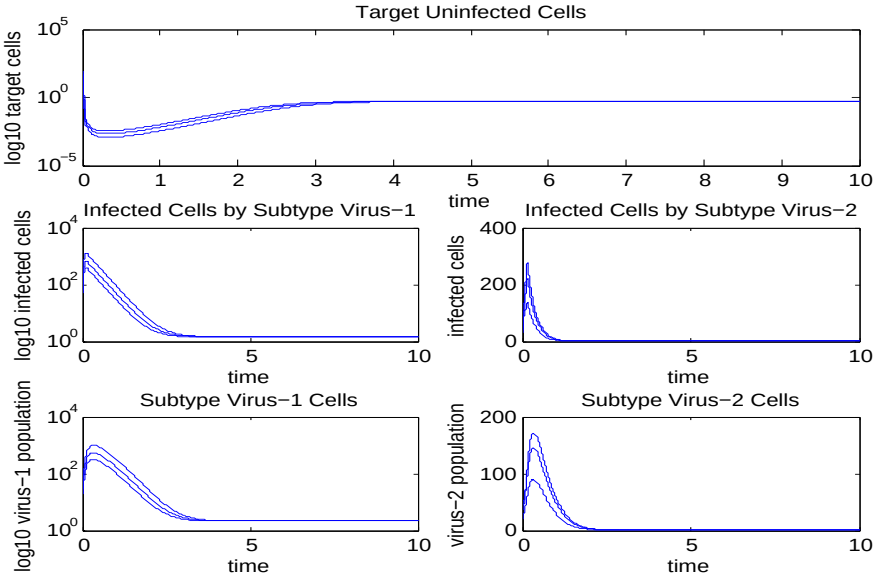

FIGURE 4. $R_1 > 1$ and $R_2 < R_1$: subtype-1 wins the competition

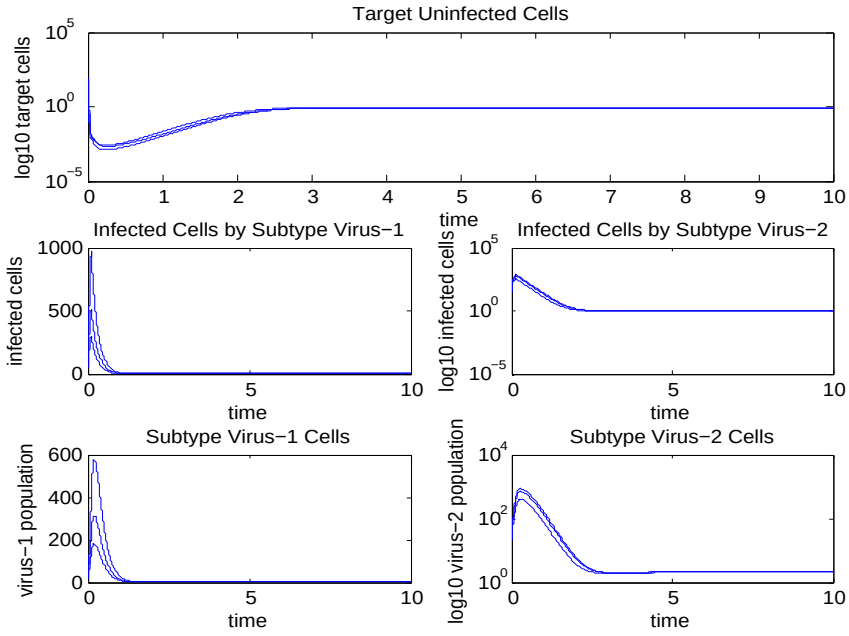

FIGURE 5. $R_2 > 1$ and $R_1 < R_2$: subtype-2 wins the competition

6. Discussion

It is widely recognized that time delays cause sustained oscillations in form of periodic solutions in in-host models with cell divisions and intracellular delays [2]. It is interesting to explore the dynamics of the viral load for two strains with intracellular delays both from mathematical and biological perspective [9].

In this paper, we employ a two-strain mathematical model to study the mechanistic basis of the emergence of the competitive viral strains in host cells. We have carried out complete analysis for two-strain in-host model with intracellular delays system (1.3). The analysis suggests that the basic reproductive ratio palys an important role in predicting viral persistence or eradication. The global dynamics of model (1.3) is rigorously established: if the basic reproduction number $R_0 \leq 1$, then all solutions converge to the infection-free equilibirum E_0; if $R_0 > 1$, then all positive solutions converge to the single chronic-infection equilibrium E_1 or E_2 which is determined by the relative magnitudes of R_1 and R_2. The stability results for E_0, E_1 and E_2 are obtained analytically, while the stability of the co-existence equilibrium E_3 via numerical simulations.

The intracellular delays can reduce the basic reproduction number R_0 if cell die during the delay period (3.1) (3.2). As a consequence, ignoring the delay will produce overestimation of R_0. Our result shows that no sustained oscillation regime exists without cell division even in the presence of intracellular delays. The two-strain HIV model with intracellular delays could provide worthwile information that potentially could allow the design of efficient individual strategies of HIV treatment.

References

[1] S. Bonhoeffer, R. M. May, G. M. Shaw and M. A. Nowak, *Virus dynamics and drug therapy*, Proc.Natl.Acad.Sci.USA, **94** (1997), 6971–6976.

[2] R. V. Culshaw and S. G. Ruan, *A delay-differential equation model of HIV infection of CD4+ T-cells*, Mathematical Biosciences, **165** (2000), 27–39.

[3] R. V. Culshaw, S. Ruan and G. Webb, *A mathematical model of cell-to-cell spread of HIV-1 that includes a time delay*, Journal of Mathematical Biology, **46** (2003), 425–444.

[4] E. Fanales-Belasio, M. Raimondo, B. Suligoi and S. Butto, *HIV virology and pathogenetic mechanisms of infection: a brief overview*, annali dell istituto superiore di sanita, **46**, (2010), 5–14.

[5] H. R. Gelderblom, M. Ozel and G. Pauli, *Morphogenesis and morphology of HIV structure-function relations*, Archives of Virology, **106** (1989), 1–13.

[6] H. Guo, M. Y. Li and Z. Shuai, *A graph-theoretic approach to the method of global Lyapunov functions*, Proc. Amer.Math.Soc, **136** (2008), 2793–2802.

[7] J. K. Hale and L. S. Verduyn, *Introduction to Functional Differential Equations*, Springer, New York, 1993.

[8] V. Herz, S. Bonhoeffer, R. Anderson, R. May and M. Nowak, *Viral dynamics in vivo: limitations on estimations on intracellular delay and virus decay*, Proc.Natl.Acad.Sci.USA, **93** (1996), 7247–7251.

[9] A. Jung, R. Maier, J. P. Vartanian, G. Bocharov, V. Jung, U. Fischer, E. Meese, S. Wain-Hobson and A. Meyerhans, *Mutiply infected spleen cells in HIV patients*, Nature, **418** (2002), 144.

[10] T. Kepler and A. Perelson, *Drug concentration heterogeneity facilitates the evolution of drug resistance*, Proc.Natl.Acad.Sci.USA, **95** (1998), 11514–11519.

[11] A. Korobeinikov and P. K. Maini, *A Lyapunov function and global properties for SIR and SEIR eidemiological models with nonlinear incidence*, Math. Biosci. Eng, **1** (2004), 57–60.

[12] M. Y. Li and H. Shu, *Global Dynamics of an In-host Viral Model with Intracellular Delay*, Bulletin of Mathematical Biology, **72** (2010), 1492–1505.

[13] K. Manavi, *A review on infection with human immunodeficiency virus*, Best Practic and Research Clinical Obsterics and Gynaecology, **20** (2006), 923–940.

[14] P. Nelson, J. Mittler and A. Perelson, *Effect of drug efficacy and the eclipse phase of the viral life cycle on estimates of HIV-1 viral dynamic parameters*, Journal of Acquired Immune Deficiency Syndromes, **26** (2001), 405–412.

[15] P. Nelson, J. Murray and A. Perelson, *A model of HIV-1 pathogenesis that includes an intracellular delay*, Mathematical Biosciences, **163** (2000), 201–215.

[16] M. A. Nowak and R. M. May, *Virus dynamics mathematical principles of immunology and virology*, Oxford University Press, 2000.

[17] A. Perelson, D. Kirschner and R. De Boer, *Dynamics of HIV infection of CD4+ T cells*, Mathematical Biosciences, **114** (1993), 81–125.

[18] A. Perelson and P. Nelson, *Mathematical models of HIV dynamics in vivo*, SIAM Review, **41** (1999), 3–44.

[19] A. Perelson, A. Neumann, M. Markowitz, J. Leonard and D. Ho, *HIV-1 dynamics in vivo: viron clearance rate, infected cell life-span, and viral generation time*, Science, **271** (1996), 1582–1586.

[20] S. M. A. Rahman and X. Zou, *Flu epidmics: A two strain flu model with a single vaccination*, Journal of Biological Dynamics, DOI:10.1080/17513758.2010.510213.

[21] L. Rong, Z. Feng and A. S. Perelson, *Emergence of HIV-1 Drug Resistance During Antiretroviral Treatment*, Bulletin of Mathematical Biology, **69** (2007), 2027–2060.

[22] J. H. Strauss and E. G. Strauss, *Viruses and Human Disease*, Academic Press, 2008.

[23] H. Zhu and X. Zou, *Impact of delays in cell infection and virus production on HIV-1 dynamics*, Mathematical Medicine and Biology, **25** (2008), 99–112.

School of Artificial Intelligence, Jianghan University, Wuhan 430056, P. R. China

E-mail address: jxu259@protonmail.com