A delay-dependent model with HIV drug resistance during therapy

ARTICLE *in* JOURNAL OF MATHEMATICAL ANALYSIS AND APPLICATIONS · JUNE 2014

Impact Factor: 1.12 · DOI: 10.1016/j.jmaa.2013.12.064

4 AUTHORS:

Yan Wang
China University of Petroleum,China,…
6 PUBLICATIONS **64** CITATIONS
SEE PROFILE

Fred Brauer
University of British Columbia - Vanco…
102 PUBLICATIONS **1,561** CITATIONS
SEE PROFILE

Jianhong Wu
York University
380 PUBLICATIONS **7,200** CITATIONS
SEE PROFILE

Jane M Heffernan
York University
32 PUBLICATIONS **577** CITATIONS
SEE PROFILE

J. Math. Anal. Appl. 414 (2014) 514–531

Contents lists available at ScienceDirect

Journal of Mathematical Analysis and Applications

www.elsevier.com/locate/jmaa

A delay-dependent model with HIV drug resistance during therapy

Yan Wang [a,*], Fred Brauer [b], Jianhong Wu [c], Jane M. Heffernan [c,*]

[a] College of Science, China University of Petroleum, Qingdao, Shandong 266580, China
[b] Department of Mathematics, University of British Columbia, Vancouver, BC V6T 1Z2, Canada
[c] Centre for Disease Modelling, York Institute for Health Research, Department of Mathematics and Statistics, York University, Toronto, ON M3J 1P3, Canada

ARTICLE INFO

Article history:
Received 25 April 2013
Available online 7 January 2014
Submitted by J. Shi

Keywords:
HIV
Drug resistance
Antiretroviral therapy
Intracellular delay
Asymptotic stability
Hopf bifurcation

ABSTRACT

The use of combination antiretroviral therapy has proven remarkably effective in controlling HIV disease progression and prolonging survival. However, the emergence of drug resistance can occur. It is necessary that we gain a greater understanding of the evolution of drug resistance. Here, we consider an HIV viral dynamical model with general form of target cell density, drug resistance and intracellular delay incorporating antiretroviral therapy. The model includes two strains: wild-type and drug-resistant. The basic reproductive ratio for each strain is obtained for the existence of steady states. Qualitative analysis of the model such as the well-posedness of the solutions and the equilibrium stability is provided. Global asymptotic stability of the disease-free and drug-resistant steady states is shown by constructing Lyapunov functions. Furthermore, sufficient conditions related to the properties of the target cell density are obtained for the local asymptotic stability of the positive steady state. Numerical simulations are conducted to study the impact of target cell density and intracellular delay focusing on the stability of the positive steady state. The occurrence of Hopf bifurcation of periodic solutions is shown to depend on the target cell density.

1. Introduction

Human immunodeficiency virus (HIV) is a retrovirus that targets cells with $CD4^+$ receptors in the human body, including $CD4^+$ T-cells, the main driver of the immune response. When the number of the $CD4^+$ T-cells falls below a critical threshold an HIV patient is diagnosed with AIDS. Progression to AIDS can be controlled with the use of highly active antiretroviral therapy (HAART), combining reverse transcriptase inhibitors (RTIs) and protease inhibitors (PI) [49] which block the infection of target T-cells and cause infected cells to produce noninfectious virus particles respectively. HIV is a controllable infection, for the most part, in countries where a wide range of antiviral drugs are available. Unfortunately, the effectiveness

* Corresponding authors.
E-mail addresses: wangyan@upc.edu.cn (Y. Wang), brauer@math.ubc.ca (F. Brauer), wujh@mathstat.yorku.ca (J. Wu), jmheffer@mathstat.yorku.ca (J.M. Heffernan).

0022-247X/$ – see front matter
http://dx.doi.org/10.1016/j.jmaa.2013.12.064

of antiretroviral therapy (ART) can be remarkably reduced by the emergence of drug resistance [4,46]. With the high replication rate (on average 10^{10} particles per day [33]) and the high mutation rate (3×10^{-5} per base per replication cycle [24]) of HIV, coupled with poor adherence to the treatment protocol, poor absorption and pharmacokinetics, drug resistant mutations are likely to appear in most patients [17,41], which will lead to a diagnosis of AIDS if new drug therapy regimens cannot be prescribed. It is imperative that the conditions that favor the evolution of drug resistance under HAART be uncovered and understood, so that HIV progression can be controlled.

Mathematical models have been used to study HIV dynamics in-host, including the emergence of drug resistant mutations [1,2,8,23,30,36,37,40,44]. A limitation of these previous studies however, is that the effects of the viral eclipse phase on the viral life cycle (the intracellular delay between initial infection and release of new virus particles) have been ignored. Previous studies of the viral eclipse phase not including the emergence of drug resistance, have shown that the half-life of free virus can be reduced considerably [14] and that the infected cell loss rate may be increased [29] if a discrete intracellular delay is included in the model. Furthermore, it has been shown that the predicted rate of decline in plasma virus concentration depends on three factors: the death rate of virus producing cells, the efficacy of therapy, and the length of the intracellular delay, which can be anywhere from a few hours to 2 days depending on the drugs [10]. Thus, it is necessary to include an intracellular delay in models of the evolution of drug resistance.

A further limitation of previous models is that target cell dynamics are mainly described using a linear growth rate, ignoring the effects of proliferation and density dependence in the T-cell population [1,2,8–10,14,16,18,21–23,29,31,33,34,36,37,40,44,50]. However, the proliferation rate of T-cells is density-dependent, with the rate of proliferation slowing as T-cell count increases [15,38]. Some studies have assumed a logistic growth term including proliferation [6,9,18,19,22,32,33,42,43,48]. With the exception of [22], which found that the underlying mechanism for sustained oscillations in within-host viral models is the target cell proliferation rather than intracellular delay [22], the combined effects of intracellular delay and logistic growth have not been studied. Such oscillations may have a profound impact of the evolution of drug resistance.

We have developed a system of delay differential equations incorporating an intracellular delay, logistic growth and antiretroviral therapy. This model is used to study the effects of cell density and time delay on the evolution of drug resistance under antiretroviral therapy. The paper is organized as follows. In Section 2, we construct our model and show the well-posedness of the model solutions (a disease-free equilibrium, a drug-resistant strain only equilibrium and a positive equilibrium where both strains exist). Two basic reproductive ratios with drug-sensitive and drug-resistant strain are given to ensure the existence of positive steady state. We employ Lyapunov functions to prove the global stability of disease-free steady state and drug-resistant strain steady state in Section 3. Moreover, we investigate the local asymptotic stability of the positive steady state for the time delay and we extend our stability analysis of drug-resistant strain and positive steady states respectively. Numerical simulations are used to demonstrate the effect of the target cell density and the intracellular delay on the model dynamics. Finally, we conclude our work and identify future avenues of study.

2. Model

Here, we derive a two-strain model with antiretroviral therapy. The model includes uninfected $CD4^+$ T-cells (T), productively infected $CD4^+$ T-cells (T^*) and infectious virus (V). To include drug resistance, we divide the infectious virus and productively infected cell classes into drug-sensitive infectious virus (V_s), drug-resistant infectious virus (V_r), drug-sensitive infected $CD4^+$ T-cells (T_s^*) and drug-resistant infected $CD4^+$ T-cells (T_r^*), respectively, where the subscripts s and r denote drug-sensitive and drug-resistant types. The transmission diagram without the intracellular delay is given in Fig. 1. Introducing the effects of the intracellular delay τ, we obtain the following delay-dependent HIV viral dynamical model with drug resistance during ART:

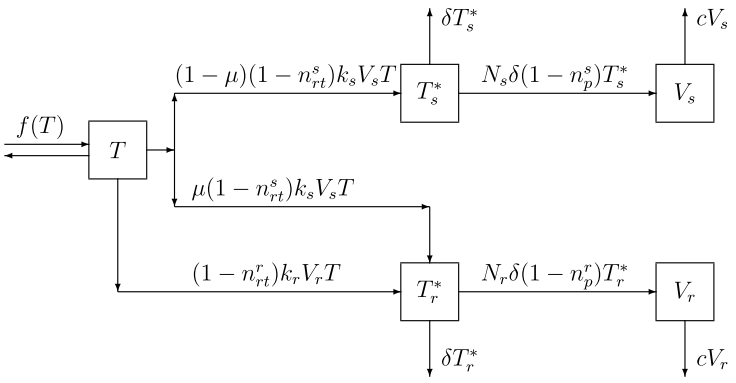


Fig. 1. Model schematic. The schematic diagram of HIV transmission with drug-sensitive and drug-resistant strains during ART (without the intracellular delay).

$$
\begin{aligned}
\dot{T}(t) &= f\big(T(t)\big) - k_s\big(1-n_{rt}^s\big)V_s(t)T(t) - k_r\big(1-n_{rt}^r\big)V_r(t)T(t),\\
\dot{T}_s^*(t) &= (1-u)k_se^{-m\tau}\big(1-n_{rt}^s\big)V_s(t-\tau)T(t-\tau) - \delta T_s^*(t),\\
\dot{V}_s(t) &= N_s\delta\big(1-n_p^s\big)T_s^*(t) - cV_s(t),\\
\dot{T}_r^*(t) &= uk_se^{-m\tau}\big(1-n_{rt}^s\big)V_s(t-\tau)T(t-\tau) + k_re^{-m\tau}\big(1-n_{rt}^r\big)V_r(t-\tau)T(t-\tau) - \delta T_r^*(t),\\
\dot{V}_r(t) &= N_r\delta\big(1-n_p^r\big)T_r^*(t) - cV_r(t),
\end{aligned}
\tag{1}
$$

with initial values

$$
\begin{aligned}
T(\theta) &= \psi_1(\theta), \qquad T_s^*(0) = \psi_2, \qquad V_s(\theta) = \psi_3(\theta),\\
T_r^*(0) &= \psi_4, \qquad V_r(\theta) = \psi_5(\theta) \quad \text{for } \theta\in[-\tau,0],
\end{aligned}
\tag{2}
$$

where, ψ_2 and ψ_4 are given non-negative constants, $\psi_1(\theta)$, $\psi_3(\theta)$, $\psi_5(\theta)\in C([-\tau,0],\mathbb{R}_+)$ with $\mathbb{R}_+=[0,+\infty)$, and $\psi=(\psi_1,\psi_2,\psi_3,\psi_4,\psi_5)\in C\times\mathbb{R}_+\times C\times\mathbb{R}_+\times C$.

The model is described as follows: uninfected CD4$^+$ T-cells have a proliferation dependent growth rate $f(T(t))$ (see the following assumptions (A1)–(A3) for detail). It is assumed that the infection rates k_s and k_r, representing the infection of uninfected CD4$^+$ T-cells by drug-sensitive and drug-resistant virus, may differ. When infection occurs an infected CD4$^+$ T-cell is produced after τ time. Here, τ represents a time delay between initial virus entry into a cell and subsequent viral production and the factor $e^{-m\tau}$ is the probability that an infected CD4$^+$ T cell survives the interval τ [10,14,16,18,21,47,50], where $1/m$ is the average lifetime of infected CD4$^+$ T-cells before they become productive. During the initial stages of infection, mutation from the drug-sensitive to the drug-resistant strain may occur with probability u $(0<u<1)$. Back mutation from the drug-resistant to the drug-sensitive strain is ignored similar to [2,30,36,44]. Infected CD4$^+$ T-cells die with rate δ. Drug-sensitive and drug-resistant virus particles are produced by the corresponding infected CD4$^+$ T-cell populations where N_s and N_r describe the burst sizes. Virus particles are cleared with rate c and are inhibited by RTIs and PIs with rates n_{rt}^s and n_{rt}^r, and n_p^s and n_p^r respectively.

We assume that the growth rate of the uninfected CD4$^+$ T-cells $f:\mathbb{R}_+\to\mathbb{R}$, is a smooth function and satisfies the following properties:

(A1) $\exists T_0$, such that $f(T_0)=0$ and $f'(T_0)<0$;
(A2) $f(T)>0$, $T\in(0,T_0)$ and $f(T)<0$, $T>T_0$;
(A3) $(f(T)-f(\bar{T}))(T-\bar{T})<0$, $T\neq\bar{T}$,

where $\bar{T}$ denotes the number of the healthy CD4$^+$ T-cells at each steady state. Assumptions (A1) and (A2) imply that the disease-free system $\dot{T}(t) = f(T(t))$ has a globally asymptotically stable steady state T_0, and (A3) assumes that the local or global asymptotic stability of each steady state of system (1). These assumptions are needed to properly reflect the disease states in individuals i.e. individuals that are disease free are in a stable state, and individuals infected with HIV are chronically infected.

3. Results

For convenience of notation in the following analysis let

$$\eta_s = 1 - \big(1 - n_{rt}^s\big)\big(1 - n_p^s\big), \qquad \eta_r = 1 - \big(1 - n_{rt}^r\big)\big(1 - n_p^r\big),$$
$$\bar{k}_s = k_s\big(1 - n_{rt}^s\big), \qquad \bar{k}_r = k_r\big(1 - n_{rt}^r\big), \qquad \bar{N}_s = N_s\big(1 - n_p^s\big), \qquad \bar{N}_r = N_r\big(1 - n_p^r\big).$$

So,

$$N_s k_s(1 - \eta_s) = \bar{N}_s \bar{k}_s, \qquad N_r k_r(1 - \eta_r) = \bar{N}_r \bar{k}_r.$$

By the basic theory of functional differential equations (see Theorem 2.3 in [12]), there is a unique solution $X(t) = (T(t), T_s^*(t), V_s(t), T_r^*(t), V_r(t))$ satisfying the initial conditions (2). The following theorem establishes the positivity and boundedness of solutions of system (1) with initial values satisfying (2).

Theorem 3.1. *If (2) holds, system (1) has a non-negative solution $X(t)$ with the initial values (2). Furthermore, the solution is ultimately bounded.*

Proof. From the first equation of system (1), $\dot{T}(t)|_{T=0} = f(0) > 0$. By Theorem 5.2.1 of [39], $T(t) \geqslant 0$ for all $t \geqslant 0$.

By the second and fourth equations in (1)

$$T_s^*(t) = T_s^*(0)e^{-\delta t} + \int_0^t e^{-\delta(t-a)}(1-u)\bar{k}_s e^{-m\tau} V_s(a-\tau)T(a-\tau)\,da$$

and

$$T_r^*(t) = T_r^*(0)e^{-\delta t} + \int_0^t e^{-\delta(t-a)} e^{-m\tau} T(a-\tau)\big(u\bar{k}_s V_s(a-\tau) + \bar{k}_r V_r(a-\tau)\big)\,da,$$

establishing $T_s^*(t) \geqslant 0$, $T_r^*(t) \geqslant 0$ for $t \in [0, \tau]$. Similarly, from the third and fifth equations in (1), $\dot{V}_s(t)|_{V_s=0} = \bar{N}_s \delta T_s^*(t) > 0$, $\dot{V}_r(t)|_{V_r=0} = \bar{N}_r \delta T_r^*(t) > 0$. By Theorem 5.2.1 of [39], we confirm that $V_s(t) \geqslant 0, V_r(t) \geqslant 0$ for all $t \in [0, \tau]$. By a recursive argument on $[\tau, 2\tau], [2\tau, 3\tau], \ldots$ we can then obtain the non-negativeness of solutions for all $t \geqslant 0$.

As for boundedness of the solution, assumptions (A1) and (A2) and the first equation of system (1) imply that $\limsup T(t) \leqslant T_0$, $t \to +\infty$. We define

$$G(t) = e^{-m\tau}T(t) + T_s^*(t+\tau) + \frac{1}{2\bar{N}_s}V_s(t+\tau) + T_r^*(t+\tau) + \frac{1}{2\bar{N}_r}V_r(t+\tau)$$

and $h = \min\{1, \delta/2, c\}$. Calculating the derivative of $G(t)$ along the solution of system (1), we obtain

$$\begin{aligned}\dot{G}(t) &= e^{-m\tau} f\big(T(t)\big) - \frac{1}{2}\delta T_s^*(t+\tau) - \frac{1}{2\bar{N}_s} cV_s(t+\tau) - \frac{1}{2}\delta T_r^*(t+\tau) - \frac{1}{2\bar{N}_r} cV_r(t+\tau)\\ &\leqslant e^{-m\tau}\big[f\big(T(t)\big) + T(t)\big]\\ &\quad - \left[e^{-m\tau}T(t) + \frac{1}{2}\delta T_s^*(t+\tau) + \frac{1}{2\bar{N}_s} cV_s(t+\tau) + \frac{1}{2}\delta T_r^*(t+\tau) + \frac{1}{2\bar{N}_r} cV_r(t+\tau)\right]\\ &\leqslant e^{-m\tau}(\bar{\lambda} + T_0) - hG(t),\end{aligned}$$

where $\bar{\lambda} = \sup_{T\in[0,T_0]} f(T(t))$, which shows that $G(t) \leqslant M + \varepsilon$ for large t, $M = e^{-m\tau}(\bar{\lambda} + T_0)/h$ and $\varepsilon > 0$. Let $\rho = \min\{e^{-m\tau}, 1/(2\bar{N}_s), 1/(2\bar{N}_r)\}$. Then T_s^*, V_s, T_r^* and $V_r \leqslant M/\rho$ for large t. This implies that the solution $X(t)$ is ultimately bounded, completing the proof of the theorem. □

The dynamics of system (1) will be analyzed in the following bounded feasible region

$$\Gamma = \big\{X = \big(T, T_s^*, V_s, T_r^*, V_r\big) \in C \times \mathbb{R}_+ \times C \times \mathbb{R}_+ \times C\colon\ T \leqslant T_0, T_s^*, V_s, T_r^* \text{ and } V_r \leqslant M/\rho\big\}.$$

The argument in Theorem 3.1 shows that Γ is attractive. Moreover, since $\dot{T}(t) \leqslant 0$ when $T(t) = T_0$ the solution remains in Γ with $t \leqslant \bar{t}$. Similarly, $\dot{T}_s^*(\tilde{t}) \leqslant 0$ when $\dot{T}_s^*(\tilde{t}) = M/\rho$ and the solution remains in Γ with $t \leqslant \tilde{t}$. In the same manner it can be shown for all populations that the solution remains in Γ. Therefore, we conclude that Γ is positively invariant with respect to system (1).

3.1. Basic reproductive ratio

We use the survival method [13] to find the basic reproductive ratio, which is defined as the total number of newly infected cells produced by a single infected cell when introduced into a population of healthy T-cells [13,31]. Let $\mathcal{R}_s$ and $\mathcal{R}_r$ denote the basic reproductive ratios of only drug-sensitive and only drug-resistant strains with drug therapy, respectively, where

$$\mathcal{R}_s = \frac{(1-u)\bar{N}_s\bar{k}_s T_0}{c} e^{-m\tau}, \qquad \mathcal{R}_r = \frac{\bar{N}_r\bar{k}_r T_0}{c} e^{-m\tau}$$

and T_0 denotes the uninfected T-cell population when there is no virus in the system. We define

$$\sigma = \frac{\mathcal{R}_s}{\mathcal{R}_r}.$$

Biologically, if $\sigma < 1$, the drug-resistant strain dominates, while the drug-sensitive dominates if $\sigma > 1$. If there is no intracellular delay ($\tau = 0$), $\mathcal{R}_s$ and $\mathcal{R}_r$ reduce to the basic reproductive ratios of model [30,36] if term $1-u$ is included in their $\mathcal{R}_s$. It is obvious that an intracellular delay decreases $\mathcal{R}_s$ and $\mathcal{R}_r$. This implies that ignoring the intracellular delay τ in a viral model will overestimate $\mathcal{R}_s$ and $\mathcal{R}_r$, however, the delay (τ) has no effect on determining which strain dominates.

3.2. Steady states

System (1) always has one disease-free steady state $E_0(T_0, 0, 0, 0, 0)$, where $f(T_0) = 0$.

Note that, if $\mathcal{R}_r > 1$, then $T_0/\mathcal{R}_r \in (0, T_0)$. From assumption (A2), $f(T_0/\mathcal{R}_r) > 0$ is equivalent to $\mathcal{R}_r > 1$. Similarly, $f(T_0/\mathcal{R}_s) > 0$ is equivalent to $\mathcal{R}_s > 1$.

System (1) also has a boundary steady state $E_r(T_r, 0, 0, T_{rr}^*, V_{rr})$ (only the drug-resistant strain is present) if $\mathcal{R}_r > 1$, where

$$T_r = \frac{T_0}{\mathcal{R}_r}, \qquad T^*_{rr} = \frac{cV_{rr}}{\bar{N}_r\delta}, \qquad V_{rr} = \frac{f(T_0/\mathcal{R}_r)}{\bar{k}_r T_r}.$$

A positive steady state $E_e(T_e, T^*_{se}, V_{se}, T^*_{re}, V_{re})$ where both strains are present, exists if $\mathcal{R}_s > 1$ and $\sigma > 1$. Here,

$$T_e = \frac{T_0}{\mathcal{R}_s}, \qquad T^*_{se} = \frac{cV_{se}}{\bar{N}_s\delta}, \qquad T^*_{re} = \frac{cV_{re}}{\bar{N}_r\delta}, \qquad V_{se} = \frac{(\sigma-1)\bar{k}_r V_{re}}{u\bar{k}_s}, \qquad V_{re} = \frac{uf(T_0/\mathcal{R}_s)}{(\sigma-1+u)\bar{k}_r T_e}.$$

Note that, if $u = 0$ (no mutation from wild-type to mutant), the positive steady state E_e reduces to another boundary steady state $E_s(T_s, T^*_{ss}, V_{ss}, 0, 0)$ where only the drug-sensitive strain is present. Here, $\mathcal{R}_s > 1$ and

$$T_s = \frac{T_0}{\mathcal{R}_s}, \qquad T^*_{ss} = \frac{cV_{ss}}{\bar{N}_r\delta}, \qquad V_{ss} = \frac{f(T_0/\mathcal{R}_s)}{\bar{k}_s T_s}.$$

E_0 and E_r are unchanged when $u = 0$.

3.3. Global stability of E_0 and E_r steady states

To study the stability at the steady state $\bar{E}(\bar{T}, \bar{T}^*_s, \bar{V}_s, \bar{T}^*_r, \bar{V}_r)$, we let $y_1(t) = T(t) - \bar{T}$, $y_2(t) = T^*_s(t) - \bar{T}^*_s$, $y_3(t) = V_s(t) - \bar{V}_s$, $y_4(t) = T^*_r(t) - \bar{T}^*_r$, $y_5(t) = V_r(t) - \bar{V}_r$, and $Y(t) = (y_1(t), y_2(t), y_3(t), y_4(t), y_5(t))$. Then, system (1) can be written as

$$\dot{Y}(t) = AY(t) + BY(t-\tau) \tag{3}$$

where

$$A = \begin{pmatrix} -\bar{\alpha} & 0 & -\bar{k}_s\bar{T} & 0 & -\bar{k}_r\bar{T} \\ 0 & -\delta & 0 & 0 & 0 \\ 0 & \bar{N}_s\delta & -c & 0 & 0 \\ 0 & 0 & 0 & -\delta & 0 \\ 0 & 0 & 0 & \bar{N}_r\delta & -c \end{pmatrix},$$

$\bar{\alpha} := \bar{k}_s\bar{V}_s + \bar{k}_r\bar{V}_r - f'(\bar{T}) = f(\bar{T})/\bar{T} - f'(\bar{T})$, and

$$B = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 \\ (1-u)\bar{k}_s e^{-m\tau}\bar{V}_s & 0 & (1-u)\bar{k}_s e^{-m\tau}\bar{T} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ u\bar{k}_s e^{-m\tau}\bar{V}_s + \bar{k}_r e^{-m\tau}\bar{V}_r & 0 & u\bar{k}_s e^{-m\tau}\bar{T} & 0 & \bar{k}_r e^{-m\tau}\bar{T} \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}.$$

The linearization of system (1) at $\bar{E}(\bar{T}, \bar{T}^*_s, \bar{V}_s, \bar{T}^*_r, \bar{V}_r)$ becomes

$$\begin{aligned}
\dot{y}_1(t) &= -\bar{\alpha}y_1(t) - \bar{k}_s\bar{T}y_3(t) - \bar{k}_r\bar{T}y_5(t), \\
\dot{y}_2(t) &= (1-u)\bar{k}_s e^{-m\tau}\big(\bar{V}_s y_1(t-\tau) + \bar{T}y_3(t-\tau)\big) - \delta y_2(t), \\
\dot{y}_3(t) &= \bar{N}_s\delta y_2(t) - cy_3(t), \\
\dot{y}_4(t) &= \big(u\bar{k}_s e^{-m\tau}\bar{V}_s + \bar{k}_r e^{-m\tau}\bar{V}_r\big)y_1(t-\tau) + u\bar{k}_s e^{-m\tau}\bar{T}y_3(t-\tau) + \bar{k}_r e^{-m\tau}\bar{T}y_5(t-\tau) - \delta y_4(t), \\
\dot{y}_5(t) &= \bar{N}_r\delta y_4(t) - cy_5(t).
\end{aligned} \tag{4}$$

Let $Y = e^{\xi t}$ be a solution of Eq. (3). Then, we obtain,

$$A + Be^{-\xi\tau} - \xi I = 0$$

where I is the identity matrix. The characteristic equation of linearized system (4) at a steady state $\bar{E}$ then becomes:

$$\begin{vmatrix} -\bar{\alpha}-\xi & 0 & -\bar{k}_s\bar{T} & 0 & -\bar{k}_r\bar{T} \\ (1-u)\bar{k}_s e^{-(m+\xi)\tau}\bar{V}_s & \delta-\xi & (1-u)\bar{k}_s e^{-(m+\xi)\tau}\bar{T} & 0 & 0 \\ 0 & \bar{N}_s\delta & -c-\xi & 0 & 0 \\ (u\bar{k}_s\bar{V}_s + \bar{k}_r\bar{V}_r)e^{-(m+\xi)\tau} & 0 & u\bar{k}_s e^{-(m+\xi)\tau}\bar{T}e^{-\xi\tau} & -\delta-\xi & \bar{k}_r e^{-(m+\xi)\tau}\bar{T} \\ 0 & 0 & 0 & \bar{N}_r\delta & -c-\xi \end{vmatrix} = 0$$

where $\bar{\alpha} := \bar{k}_s\bar{V}_s + \bar{k}_r\bar{V}_r - f'(\bar{T}) = f(\bar{T})/\bar{T} - f'(\bar{T})$.

Theorem 3.2. *If $\mathcal{R}_s < 1$ and $\mathcal{R}_r < 1$, then the disease-free steady state E_0 is locally asymptotically stable for all $\tau \geqslant 0$ and unstable if $\mathcal{R}_s > 1$ or $\mathcal{R}_r > 1$.*

Proof. The characteristic equation of the linearized system (4) at the disease-free steady state E_0 is

$$(\xi+\alpha_0)\left[\xi^2 + (c+\delta)\xi + c\delta - (1-u)\bar{N}_s\bar{k}_s T_0\delta e^{-m\tau}e^{-\xi\tau}\right]\left[\xi^2 + (c+\delta)\xi + c\delta - \bar{N}_r\bar{k}_r T_0\delta e^{-m\tau}e^{-\xi\tau}\right] = 0. \tag{5}$$

Clearly, $\xi = -\alpha_0 = f'(T_0) < 0$ (assumption (A1)) is a negative root of Eq. (5). The remaining roots of Eq. (5) are determined by the following transcendental equation

$$\left[\xi^2 + (c+\delta)\xi + c\delta - (1-u)\bar{N}_s\bar{k}_s T_0\delta e^{-m\tau}e^{-\xi\tau}\right]\left[\xi^2 + (c+\delta)\xi + c\delta - \bar{N}_r\bar{k}_r T_0\delta e^{-m\tau}e^{-\xi\tau}\right] = 0. \tag{6}$$

Substituting $\tau = 0$ into Eq. (6) we obtain the following quartic equation:

$$\left[\xi^2 + (c+\delta)\xi + c\delta - (1-u)\bar{N}_s\bar{k}_s T_0\delta\right]\left[\xi^2 + (c+\delta)\xi + c\delta - \bar{N}_r\bar{k}_r T_0\delta\right] = 0. \tag{7}$$

Using the Descartes' rule of signs, it is obvious that the quartic equation (7) with $\tau = 0$ has four negative real roots if $\mathcal{R}_s < 1$ and $\mathcal{R}_r < 1$.

If $\tau > 0$, let $\xi = i\omega(\tau)$, $\omega(\tau) > 0$. Separating the real and imaginary parts of Eq. (6), and squaring and adding, we obtain two equations related with $\omega(\tau)$:

$$\begin{aligned} F_1\big(\omega(\tau)\big) &:= \omega^4(\tau) + \big(c^2+\delta^2\big)\omega^2(\tau) + (c\delta)^2 - \big((1-u)\bar{N}_s\bar{k}_s T_0\delta e^{-m\tau}\big)^2 = 0, \\ F_2\big(\omega(\tau)\big) &:= \omega^4(\tau) + \big(c^2+\delta^2\big)\omega^2(\tau) + (c\delta)^2 - \big(\bar{N}_r\bar{k}_r T_0\delta e^{-m\tau}\big)^2 = 0. \end{aligned} \tag{8}$$

Notice that $c > (1-u)\bar{N}_s\bar{k}_s T_0 e^{-m\tau}$ and $c > \bar{N}_r\bar{k}_r T_0 e^{-m\tau}$ when $\mathcal{R}_s < 1$ and $\mathcal{R}_r < 1$, respectively. Clearly, Eqs. (8) have no positive roots. That is to say, there is no root that can across the imaginary axis of Eq. (5). Therefore, the disease-free steady state is locally asymptotically stable for $\tau \geqslant 0$.

For the case $\mathcal{R}_s > 1$ or $\mathcal{R}_r > 1$, Eq. (6) has at least one positive root with $\tau = 0$. So, E_0 is unstable for $\tau = 0$. When $\tau > 0$, $\frac{\partial F_1}{\partial\omega} = \frac{\partial F_2}{\partial\omega} = 3\omega^3(\tau) + 2(c^2+\delta^2)\omega(\tau) > 0$, and thus from Cooke and van den Driessche [5] and Freedman and Kuang [11], E_0 is unstable for $\tau > 0$. This completes the proof. □

Theorem 3.3. *If $\mathcal{R}_s < 1-u$ and $\mathcal{R}_r < 1$, then the disease-free steady state E_0 is globally asymptotically stable for every given $\tau \geqslant 0$.*

Proof. Define a Lyapunov function $W_1 : C \times \mathbb{R}_+ \times C \times \mathbb{R}_+ \times C \to \mathbb{R}$

$$W_1 = T_s^*(t) + T_r^*(t) + \frac{1}{\bar{N}_s} V_s(t) + \frac{1}{\bar{N}_r} V_r(t) + e^{-m\tau}\bar{k}_s \int_{-\tau}^{0} \psi_1(t+s)\psi_3(t+s)\,ds + e^{-m\tau}\bar{k}_r \int_{-\tau}^{0} \psi_1(t+s)\psi_5(t+s)\,ds$$

The derivative of W_1 along solutions of system (1) is

$$\begin{aligned}\dot{W}_1 &= \big(\bar{N}_s\bar{k}_s e^{-m\tau}T(t) - c\big)\frac{V_s(t)}{\bar{N}_s} + \big(\bar{N}_r\bar{k}_r e^{-m\tau}T(t) - c\big)\frac{V_r(t)}{\bar{N}_r} \\ &\leqslant \big(\bar{N}_s\bar{k}_s T_0 e^{-m\tau} - c\big)\frac{V_s(t)}{\bar{N}_s} + \big(\bar{N}_r\bar{k}_r T_0 e^{-m\tau} - c\big)\frac{V_r(t)}{\bar{N}_r} \\ &= \left(\frac{\mathcal{R}_s}{1-u} - 1\right)\frac{cV_s(t)}{\bar{N}_s} + (\mathcal{R}_r - 1)\frac{cV_r(t)}{\bar{N}_r}.\end{aligned}$$

If $\mathcal{R}_s < 1-u$ and $\mathcal{R}_r < 1$, we obtain $\dot{W}_1 \leqslant 0$. Thus $\dot{W}_1 = 0$ if and only if $V_s(t) = V_r(t) = 0$. The maximum invariant set in $\{\psi \in \Gamma \mid \dot{W}_1 = 0\}$ is the singleton E_0. The LaSalle's invariance principle [20] implies that all solutions converge to E_0. This and the local stability of E_0 established in Theorem 3.2 imply the global asymptotic stability of E_0. □

Theorem 3.4. *If $\mathcal{R}_r > 1$ and $\sigma < 1$, E_r is locally asymptotically stable for every $\tau \geqslant 0$ under assumption* (A3).

Proof. The characteristic equation of the linearized system (4) at the steady state with the only drug-resistant virus E_r is

$$\big[(\xi+c)(\xi+\delta) - c\delta\sigma e^{-\xi\tau}\big]\left[(\xi+c)(\xi+\delta)\left(\xi + \frac{f(T_r)}{T_r} - f'(T_r)\right) - \big(\xi - f'(T_r)\big)c\delta e^{-\xi\tau}\right] = 0. \tag{9}$$

Clearly, the characteristic equation (9) is determined by the following two equations

$$\xi^2 + a_1\xi + a_0 + b_0 e^{-\xi\tau} = 0, \qquad \xi^3 + c_2(\tau)\xi^2 + c_1(\tau)\xi + c_0(\tau) + \big(d_1\xi + d_0(\tau)\big)e^{-\xi\tau} = 0, \tag{10}$$

where,

$$\begin{gathered}a_1 = c + \delta > 0, \qquad a_0 = c\delta, \qquad b_0 = -c\delta\sigma, \\ c_2(\tau) = c + \delta + \frac{f(T_r)}{T_r} - f'(T_r), \qquad c_1(\tau) = c\delta + (c+\delta)\left(\frac{f(T_r)}{T_r} - f'(T_r)\right), \\ c_0(\tau) = c\delta\left(\frac{f(T_r)}{T_r} - f'(T_r)\right), \\ d_1 = -c\delta, \qquad d_0(\tau) = c\delta f'(T_r).\end{gathered}$$

Notice that part of the coefficients are dependent on the delay τ in characteristic equation (6), since T_r includes τ.

We first consider the above equations with $\tau = 0$, then

$$\xi^2 + a_1\xi + a_0 + b_0 = 0, \qquad \xi^3 + c_2(0)\xi^2 + \big(c_1(0) + d_1\big)\xi + c_0(0) + d_0(0) = 0.$$

Using Routh–Hurwitz criterion, we easily get E_r is locally asymptotically stable with $\tau = 0$ since

$$a_0 + b_0 = c\delta(1-\sigma) > 0, \qquad c_0(0) + d_0(0) = c\delta\frac{f(T_r)}{T_r} > 0,$$

$$\begin{aligned} &c_2(0)\big(c_1(0) + d_1\big) - \big(c_0(0) + d_0(0)\big) \\ &\quad = (c+\delta)\left(\frac{f(T_r)}{T_r} - f'(T_r)\right)^2 + \big(c^2+\delta^2\big)\left(\frac{f(T_r)}{T_r} - f'(T_r)\right) + c\delta\left(\frac{f(T_r)}{T_r} - 2f'(T_r)\right) > 0, \end{aligned}$$

and assumption (A3) implies that $f'(T_r) < 0$.

If $\tau > 0$, let $\xi = iw(\tau)$ with $w(\tau) > 0$. Substituting ξ with $iw(\tau)$ into Eqs. (10), by simplification, we obtain the following

$$\begin{aligned} J_1\big(\omega(\tau)\big) &:= \omega^4(\tau) + \big(a_1^2 - 2a_0\big)\omega^2(\tau) + \big(a_0^2 - b_0^2\big) = 0, \\ J_2\big(\omega(\tau)\big) &:= \omega^6(\tau) + \big(c_2^2(\tau) - 2c_1(\tau)\big)\omega^4(\tau) \\ &\quad + \big(c_1^2(\tau) - 2c_0(\tau)c_2(\tau) - d_1^2\big)\omega^2(\tau) + \big(c_0^2(\tau) - d_0^2(\tau)\big) = 0, \end{aligned} \tag{11}$$

where,

$$\begin{aligned} a_1^2 - 2a_0 &= c^2 + \delta^2 > 0, \qquad a_0^2 - b_0^2 = c^2\delta^2\big(1-\sigma^2\big), \\ c_0^2(\tau) - d_0^2(\tau) &= c^2\delta^2\frac{f(T_r)}{T_r}\left(\frac{f(T_r)}{T_r} - 2f'(T_r)\right) > 0, \\ c_2^2(\tau) - 2c_1(\tau) &= c^2 + \delta^2 + \left(\frac{f(T_r)}{T_r} - f'(T_r)\right)^2 > 0, \\ c_1^2(\tau) - 2c_0(\tau)c_2(\tau) - d_1^2 &= \big(c^2+\delta^2\big)\left(\frac{f(T_r)}{T_r} - f'(T_r)\right)^2 > 0. \end{aligned}$$

Clearly, if $\sigma < 1$ then $J_1(0) = a_0^2 - b_0^2 > 0$. Thus, $\frac{\partial J_1}{\partial\omega} > 0$, $J_2(0) = c_0^2(\tau) - d_0^2(\tau) > 0$ and $\frac{\partial J_2}{\partial\omega} > 0$. It is obvious to see that there are no positive roots $\omega(\tau)$ existing in (11), and thus the characteristic equation (9) has no purely imaginary roots. Also, zero is not a root of Eq. (9). Therefore, E_r is locally asymptotically stable for all delay $\tau \geqslant 0$. This completes the proof. □

Next, we will establish a Lyapunov function to show the global stability of the drug-resistant steady state E_r.

Theorem 3.5. *If $\mathcal{R}_r > 1$ and $\sigma < 1 - u$, the drug-resistant steady state E_r is globally asymptotically stable for all $\tau \geqslant 0$ under assumption* (A3).

Proof. We first introduce a special function

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

similar to [21,22,26]. Then $g(x) > 0$ for all $x > 0$ and $g(x) = 0$ if and only if $x = 1$. We define a Lyapunov function $W_2 : C \times \mathbb{R}_+ \times C \times \mathbb{R}_+ \times C \to \mathbb{R}$

$$W_2 = T_r g\left(\frac{T(t)}{T_r}\right) + e^{m\tau}T_s^*(t) + \frac{e^{m\tau}}{\bar{N}_s}V_s(t) + e^{m\tau}T_{rr}^* g\left(\frac{T_r^*(t)}{T_{rr}^*}\right) + \frac{e^{m\tau}}{\bar{N}_r}V_{rr} g\left(\frac{V_r(t)}{V_{rr}}\right) + \bar{k}_s \int_{-\tau}^{0} \psi_1(t+s)\psi_3(t+s)\,ds + \bar{k}_r T_r V_{rr} \int_{-\tau}^{0} g\left(\frac{\psi_1(t+s)\psi_5(t+s)}{T_r V_{rr}}\right) ds.$$

Calculating the derivative of W_2 along with the solution of system (1), we obtain

$$\begin{aligned}\dot{W}_2 = {} & f\big(T(t)\big)\left(1 - \frac{T_r}{T(t)}\right) + \bar{k}_s T_r V_s(t) + \bar{k}_r T_r V_r(t) - \frac{ce^{m\tau}}{\bar{N}_s}V_s(t) \\ & - \big(u\bar{k}_s V_s(t-\tau) + \bar{k}_r V_r(t-\tau)\big)T(t-\tau)\frac{T_{rr}^*}{T_r^*(t)} + e^{m\tau}\delta T_{rr}^* - \frac{ce^{m\tau}}{\bar{N}_r}V_r(t) \\ & - e^{m\tau}\delta T_r^*(t)\frac{V_{rr}}{V_r(t)} + \frac{ce^{m\tau}}{\bar{N}_r}V_{rr} - \bar{k}_r T_r V_{rr} \ln\left(\frac{\psi_1(t)\psi_5(t)}{\psi_1(t-\tau)\psi_5(t-\tau)}\right).\end{aligned}$$

Using the equalities $f(T_r) = \bar{k}_r T_r V_{rr} = e^{m\tau}\delta T_{rr}^*$, $\bar{N}_r \delta T_{rr}^* = cV_{rr}$ at E_r into the above equation, by simplification, then

$$\begin{aligned}\dot{W}_2 = {} & \big(f\big(T(t)\big) - f(T_r)\big)\left(1 - \frac{T_r}{T(t)}\right) + e^{m\tau}\delta T_{rr}^*\left(1 - \frac{T_r}{T(t)}\right) \\ & - \left(1 - \frac{\sigma}{1-u}\right)\frac{ce^{m\tau}}{\bar{N}_s}V_s(t) - u\bar{k}_s T(t-\tau)V_s(t-\tau)\frac{T_{rr}^*}{T_r^*(t)} \\ & - e^{m\tau}\delta T_{rr}^*\frac{T(t-\tau)V_r(t-\tau)T_{rr}^*}{T_r V_{rr} T_r^*(t)} + e^{m\tau}\delta T_{rr}^* - e^{m\tau}\delta T_{rr}^*\frac{T_r^* V_{rr}}{T_{rr}^* V_r(t)} \\ & + e^{m\tau}\delta T_{rr}^* - e^{m\tau}\delta T_{rr}^* \ln\left(\frac{\psi_1(t)\psi_5(t)}{\psi_1(t-\tau)\psi_5(t-\tau)}\right) \\ = {} & \big(f\big(T(t)\big) - f(T_r)\big)\left(1 - \frac{T_r}{T(t)}\right) - \left(1 - \frac{\sigma}{1-u}\right)\frac{ce^{m\tau}}{\bar{N}_s}V_s(t) \\ & - e^{m\tau}\delta T_{rr}^*\left[g\left(\frac{T_r}{T(t)}\right) + g\left(\frac{T(t-\tau)V_r(t-\tau)T_{rr}^*}{T_r V_{rr} T_r^*(t)}\right) + g\left(\frac{V_{rr}T_r^*(t)}{T_{rr}^* V_r(t)}\right)\right] - u\bar{k}_s T(t-\tau)V_s(t-\tau)\frac{T_{rr}^*}{T_r^*(t)}.\end{aligned}$$

From assumption (A3), $(f(T(t)) - f(T_r))(1 - \frac{T_r}{T(t)}) < 0$. If $\sigma < 1 - u$, through the property of $g(x)$, then $\dot{W}_2 \leqslant 0$. $\dot{W}_2 = 0$ if and only if

$$\frac{T_r}{T(t)} = \frac{T(t-\tau)V_r(t-\tau)T_{rr}^*}{T_r V_{rr} T_r^*(t)} = \frac{V_{rr}T_r^*(t)}{T_{rr}^* V_r(t)} = 1 \quad \text{and} \quad V_s(t-\tau) = 0$$

are satisfied. Thus, the maximum invariant set in $\{\psi \in \Gamma \mid \dot{W}_2 = 0\}$ is the singleton E_r. Therefore, all solutions in Γ with non-negative initial values converge to E_r by the LaSalle's invariance principle [20]. This and the local stability of E_r established in Theorem 3.4 imply the global asymptotic stability of E_r for all given $\tau \geqslant 0$. This completes the proof. □

By Theorems 3.3 and 3.5, the global stability of the disease-free and drug-resistant only steady states have been obtained through constructing Lyapunov functions. These results imply that the intracellular delay has no effect on the occurrence of sustained oscillations for the well-defined growth rate $f(T)$. This conclusion is an extension of [16,21,22] that do not consider drug resistance.

3.4. Stability at E_e

Consider the interval $\tau \in [0, \tau_{max})$, where τ_{max} is the maximum value for the existence of positive steady state E_e and $\tau_{max} = \frac{1}{m}\ln(\frac{(1-u)\tilde{N}_s\tilde{k}_sT_0}{c})$.

Theorem 3.6. *With assumption* (A3)*, if* $\mathcal{R}_s > 1$ *and* $\sigma > 1$*, then the positive steady state* E_e *is locally asymptotically stable for all* $\tau \geqslant 0$.

Proof. The characteristic equation of the linearized system (4) at the positive steady state E_e is

$$\left[(\xi+c)(\xi+\delta) - \frac{c\delta}{\sigma}e^{-\xi\tau}\right]\left[(\xi+c)(\xi+\delta)\left(\xi + \frac{f(T_e)}{T_e} - f'(T_e)\right) - \big(\xi - f'(T_e)\big)c\delta e^{-\xi\tau}\right] = 0. \tag{12}$$

Clearly, the characteristic equation (12) is determined by the following two equations

$$\begin{gathered}\xi^2 + e_1\xi + e_0 + l_0e^{-\xi\tau} = 0,\\ \xi^3 + m_2(\tau)\xi^2 + m_1(\tau)\xi + m_0(\tau) + \big(n_1\xi + n_0(\tau)\big)e^{-\xi\tau} = 0,\end{gathered} \tag{13}$$

where,

$$\begin{gathered}e_1 = c+\delta > 0, \qquad e_0 = c\delta, \qquad l_0 = -c\delta/\sigma,\\ m_2(\tau) = c+\delta+\frac{f(T_e)}{T_e} - f'(T_e), \qquad m_1(\tau) = c\delta + (c+\delta)\left(\frac{f(T_e)}{T_e} - f'(T_e)\right),\\ m_0(\tau) = c\delta\left(\frac{f(T_e)}{T_e} - f'(T_e)\right),\\ n_1 = -c\delta, \qquad n_2(\tau) = c\delta f'(T_e).\end{gathered}$$

Notice that part of the coefficients are dependent on the delay τ in characteristic equation (13), since T_e includes τ.

Consider Eq. (13) with $\tau = 0$, then

$$\xi^2 + e_1\xi + e_0 + l_0 = 0, \qquad \xi^3 + m_2(0)\xi^2 + \big(m_1(0)+n_1\big)\xi + m_0(0) + n_2(0) = 0.$$

Assumption (A3) implies that $f'(T_e) < 0$. Therefore,

$$e_0 + l_0 = c\delta(1-1/\sigma) > 0, \qquad m_0(0) + n_0(0) = c\delta\frac{f(T_e)}{T_e} > 0,$$

$$\begin{aligned}&m_2(0)\big(m_1(0)+n_1\big) - \big(m_0(0)+n_0(0)\big)\\ &= (c+\delta)\left(\frac{f(T_e)}{T_e} - f'(T_e)\right)^2 + \big(c^2+\delta^2\big)\left(\frac{f(T_e)}{T_e} - f'(T_e)\right) + c\delta\left(\frac{f(T_e)}{T_e} - 2f'(T_e)\right) > 0.\end{aligned}$$

Using Routh–Hurwitz criterion, we easily obtain that E_e is locally asymptotically stable with $\tau = 0$.

Next, we investigate the existence of purely imaginary roots $\xi = iy$ with $y > 0$ if $\tau > 0$, noticing that y is related to τ. Substituting ξ with iy into Eq. (13), we obtain:

$$\begin{gathered}\mathcal{D}_1(y) := y^4 + \big(e_1^2 - 2e_0\big)y^2 + \big(e_0^2 - l_0^2\big) = 0,\\ \mathcal{D}_2(y) := y^6 + \big(m_2^2(\tau) - 2m_1(\tau)\big)y^4 + \big(m_1^2(\tau) - 2m_0(\tau)m_2(\tau) - n_1^2\big)y^2 + \big(m_0^2(\tau) - n_0^2(\tau)\big) = 0,\end{gathered} \tag{14}$$

where,

$$e_1^2 - 2e_0 = c^2 + \delta^2 > 0, \qquad e_0^2 - l_0^2 = c^2\delta^2\big(1 - 1/\sigma^2\big),$$
$$m_0^2(\tau) - n_0^2(\tau) = c^2\delta^2\frac{f(T_e)}{T_e}\left(\frac{f(T_e)}{T_e} - 2f'(T_e)\right) > 0,$$
$$m_2^2(\tau) - 2m_1(\tau) = c^2 + \delta^2 + \left(\frac{f(T_e)}{T_e} - f'(T_e)\right)^2 > 0,$$
$$m_1^2(\tau) - 2m_0(\tau)m_2(\tau) - n_1^2 = \big(c^2 + \delta^2\big)\left(\frac{f(T_e)}{T_e} - f'(T_e)\right)^2 > 0.$$

Obviously, if $\sigma > 1$ and assumption (A3) are satisfied, then $\mathcal{D}_1(0) = e_0^2 - l_0^2 > 0$ and $\mathcal{D}_2(0) = m_0^2(\tau) - n_0^2(\tau) > 0$. Thus, $\frac{\partial \mathcal{D}_1}{\partial y} > 0$ and $\frac{\partial \mathcal{D}_2}{\partial y} > 0$. It is obvious to see that there is no positive roots y existing in (14), and thus the characteristic equation (12) has no purely imaginary roots. Also, zero is not a root of Eq. (12). Therefore, E_e is locally asymptotically stable for all delay $\tau \geqslant 0$. This completes the proof. □

3.5. Extension of the stability results, when $u = 0$

Sections 3.3 and 3.4 discuss the stability of system (1) equilibria when $0 < u < 1$ of system. Now, we consider the stability results for the special case when $u = 0$.

When $u = 0$, the positive steady state E_e reduces to the drug-sensitive only strain steady state E_s if $\mathcal{R}_s > 1$ (see Section 3.2). By Theorems 3.2–3.5 and Theorem A.1 in Appendix A, we can easily obtain the corresponding stability results for the case $u = 0$.

Theorem 3.7. *For the case $u = 0$ of system (1). Then*

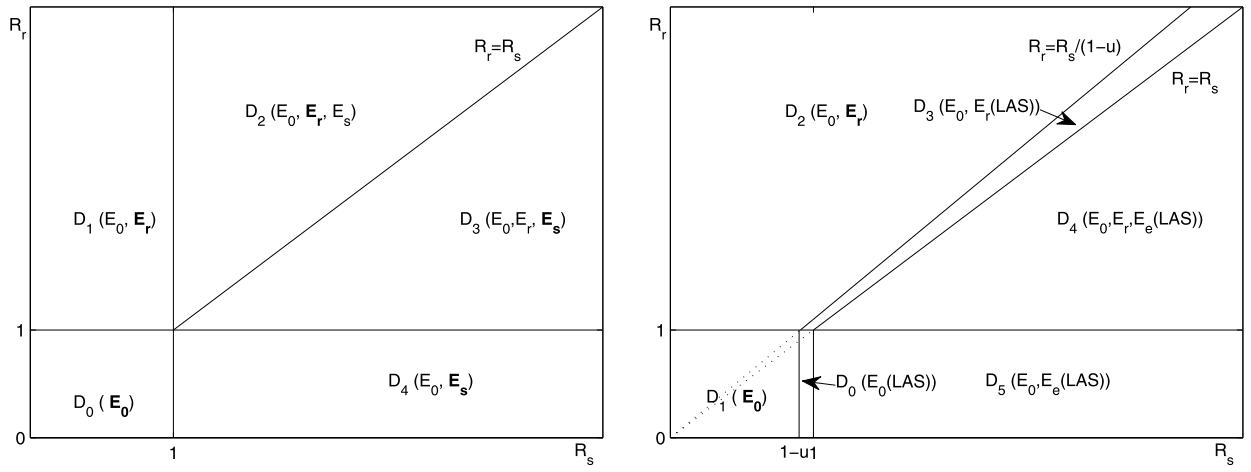
(a) *If $\mathcal{R}_s < 1$ and $\mathcal{R}_r < 1$, then the disease-free steady state E_0 is globally asymptotically stable for all $\tau \geqslant 0$; and it is unstable if $\mathcal{R}_s > 1$ or $\mathcal{R}_r > 1$.*
(b) *If $\mathcal{R}_r > 1$ and $\sigma < 1$, with assumption* (A3)*, the drug-resistant steady state E_r is globally asymptotically stable for all $\tau \geqslant 0$.*
(c) *If $\mathcal{R}_s > 1$ and $\sigma > 1$, with assumption* (A3)*, the drug-sensitive steady state E_s is globally asymptotically stable for all $\tau \geqslant 0$.*

All the stability results for system (1) are summarized in Fig. 2.

Now, let us go back to the situation $0 < u < 1$ of system (1). In Section 1, we introduced two well-accepted forms of target-cell dynamics $f(T) = \lambda - dT$ with a linear growth rate and $f(T) = \lambda - dT + rT(1 - \frac{T}{T_{max}})$ with logistic growth proliferation, where λ is the recruitment rate, d is the natural death rate of healthy CD4$^+$ T-cells, r is the growth rate and T_{max} is the carrying capacity of the T-cell population. Obviously, the linear form with $f'(\bar{T}) = -d < 0$ satisfies assumption (A3), while the logistic growth form with $f'(\bar{T}) = r - d - 2\bar{T}/T_{max}$ does not always satisfy (A3). In our whole proof of Theorems 3.4 and 3.7, we assume (A3) $f'(\bar{T}) < 0$ is satisfied, however, we did not consider the case $f'(\bar{T}) > 0$. So, even if $f'(\bar{T}) > 0$ and $f(\bar{T})/\bar{T} - 2f'(\bar{T}) > 0$, then we can obtain the same results as Theorems 3.4 and 3.6.

Theorem 3.8. *When $f'(T_r) > 0$ and $f(T_r)/T_r - 2f'(T_r) > 0$, then the drug-resistant steady state E_r is locally asymptotically stable for all $\tau \geqslant 0$ if $\mathcal{R}_r > 1$ and $\sigma < 1$.*

Theorem 3.9. *When $f'(T_e) > 0$ and $f(T_e)/T_e - 2f'(T_e) > 0$, then the positive steady state E_e is locally asymptotically stable for all $\tau \geqslant 0$ if $\mathcal{R}_s > 1$ and $\sigma > 1$.*



(a) $u = 0$ (b) $0 < u < 1$

Fig. 2. Stability of steady states. Steady states and stability regions of system (1) under assumption (A3) when $u = 0$ (left) and $0 < u < 1$ (right). Steady states that are listed in the brackets exist in that region. Steady states listed in bold face are globally asymptotically stable in that region. LAS indicates the steady states that are locally asymptotically stable in specific regions.

3.6. Numerical simulation

We perform numerical simulations to study the effects of the target cell density and intracellular delay on the viral dynamics during drug therapy.

Analytically, in Section 3.4, we found that the interval of the intracellular delay $\tau \in (0, \tau_{max})$ where $\tau_{max} = \frac{1}{m} \ln(\frac{(1-u)\bar{N}_s \bar{k}_s T_0}{c})$. Biologically, the accepted maximum value of τ is 2 days under drug therapy [10]. Therefore, we conduct our simulations considering an interval $\tau \in (0, \bar{\tau})$, where $\bar{\tau} = \min(2, \tau_{max})$. The death rate of infected but not yet productive T-cells, m, is in general larger than the death rate of uninfected T-cells, d, since immune responses can target viral proteins presented on infected cells early on during the course of infection and effectively kill infected cells before they become productive. The precise value of m, however, remains unknown. For simplicity, we let $m = d$ [10] in the following simulations.

To compare the model with and without the intracellular delay we consider $f = \lambda - dT$ and the Data1 values ($r = 0$ and $T_{max} = 0$) in Table 1. Here, $f' = -d < 0$, $\mathcal{R}_s > 1$ and $\sigma > 1$ and the hypotheses of Theorem 3.6 are satisfied, therefore, the positive steady state E_e is always locally asymptotically stable on the interval $\tau \in (0, \bar{\tau})$. Fig. 3 demonstrates that the intracellular delay prolongs the time to peak for every population. It also shows that the delay has no effect on the stability of the positive steady state E_e.

To study the effects of proliferation on the model populations we consider the T-cell dynamics with and without proliferation, $f = \lambda - dT + rT(1 - T/T_{max})$ where $r = 0, 0.03, 0.3, 2$. Fig. 4 demonstrates that for some parameter values the positive equilibrium (except for the uninfected cell count, since it is not affected by the growth rate r), decreases as r decreases, but the stability of E_e is maintained (left column). However, for other sets of parameter values changes in r may induce periodic oscillations (right column). This is indicative of the existence of a Hopf bifurcation. Note that, when the proliferation rate r decreases, the average viral load and infected cell count decrease (Fig. 4, both columns). Thus, the viral load and infected cell count are underestimated when a value of $r = 0$ is assumed. Thus, the true level of drug resistant virus would be missed, which would greatly affect the success of any ART regimen.

Figs. 3 and 4 demonstrate that the stability of E_e depends on the target cell density, causing sustained oscillations as r increases, and not the intracellular delay. This agrees with Li and Shu [22] who studied the impact of intracellular delays and target-cell dynamics on *in vivo* viral infections.

Table 1
List of parameters values.

Param	Definition	Unit	Data1	Data2	Source
λ	T-cells source term	$\text{mm}^{-3}\,\text{day}^{-1}$	10	10	[32]
d	Death rate of healthy T-cells	day^{-1}	0.01	0.03	[27,28]
m	The death rate of infected but not yet productive cells	day^{-1}	0.01	0.03	see text
r	Growth rate of T-cells	day^{-1}	0.03	0.03	[32]
T_{max}	Carrying capacity of T-cells	mm^{-3}	1500	1500	[32]
k_s	Infection rate of healthy T-cells by wild type virus	$\text{mm}^3\,\text{day}^{-1}$	2.4×10^{-5}	0.0027	[9] [32]
k_r	Infection rate of healthy T-cells by drug-resistant virus	$\text{mm}^3\,\text{day}^{-1}$	2.0×10^{-5}	0.0020	[36,7]
u	Mutation rate from sensitive strain to resistant strain		3×10^{-5}	3×10^{-5}	[24]
δ	Death rate of infected T-cells	day^{-1}	1	1	[25]
N_s	Bursting size of drug-sensitive strain	virions/cell	3000	200	[36,7]
N_r	Bursting size of drug-resistant strain	virions/cell	2000	50	[36,43]
c	Clearance rate of virus	day^{-1}	23	23	[35]
τ	Virus replication time	days	1	1	[29,34]
n^s_{rt}	Efficacy of RTIs for wild type		0.4	0.6	see text
n^r_{rt}	Efficacy of RTIs for mutants		0.2	0.5	see text
n^s_p	Efficacy of PIs for wild type		0.1	0.3	see text
n^r_p	Efficacy of PIs for mutants		0.1	0.2	see text

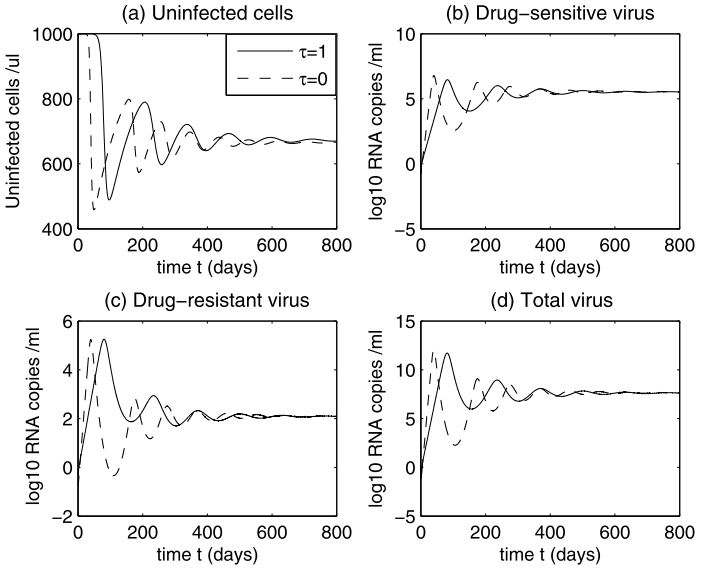


Fig. 3. Model dynamics when $f = \lambda - dT$ for different values of the delay τ. The intracellular delay prolongs the time to peak for every population, and decreases the amplitude of oscillations, but it does not have any effect on the stability results. Parameters are given by Data1 values in Table 1.

4. Conclusion

We have studied an HIV model including a general form of target cell density, an intracellular delay and drug resistance under ART. Analytically, we obtained two basic reproductive ratios for the drug-sensitive and drug-resistant strains, and established sufficient conditions (corresponding to the two basic reproductive ratios) for global asymptotic stability of the disease-free (E_0) and drug-resistant (E_r) steady states. Moreover, we proved the local asymptotic stability of the positive steady state (E_e) under two different properties of target cell density. Numerically, we demonstrated the average viral load and infected cell count can be underestimated if the T-cell proliferation rate r is ignored. We also demonstrated that sustained oscillations can be induced under certain conditions when the proliferation rate $r > 0$. Our simulations

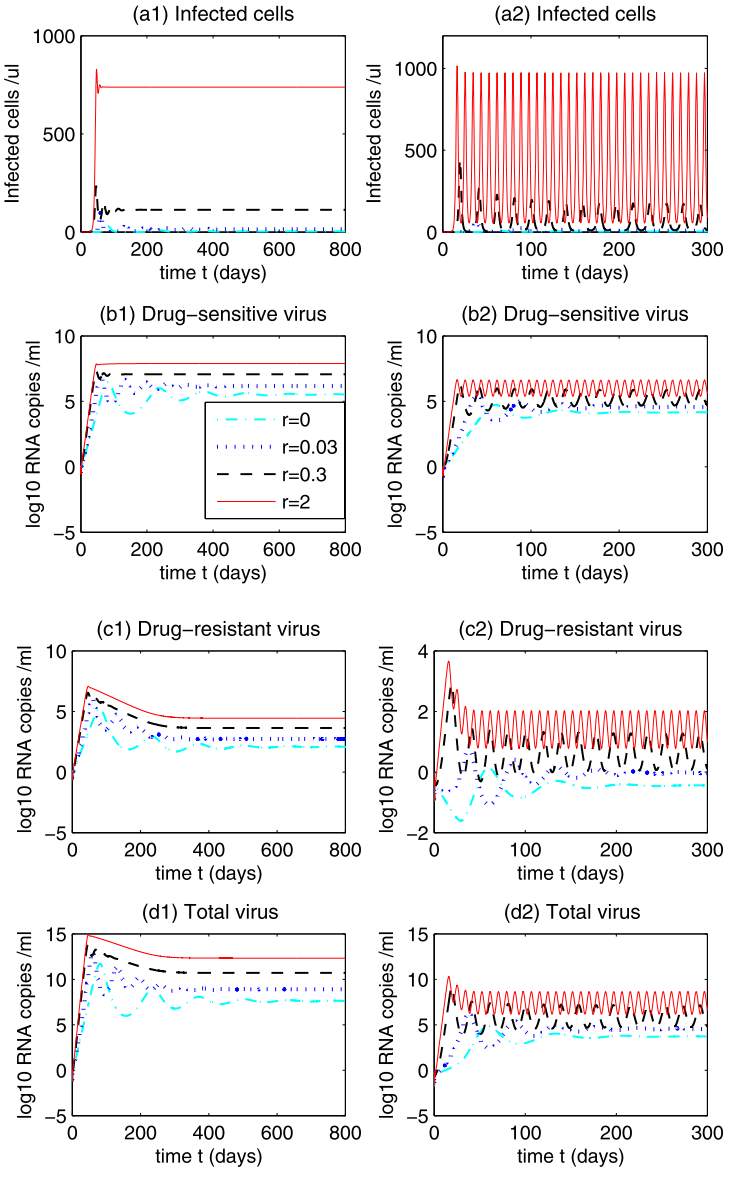


Fig. 4. Model dynamics when proliferation is included. Here, $f = \lambda - dT + rT(1 - T/T_{max})$ and the proliferation rate r is varied. The proliferation rate affects the stability dynamics for certain data sets. Data1 (left) and Data2 (right) result in different dynamics for increasing r. The initial values are chosen as the disease-free steady state with $r = 0$.

indicate that the occurrence of these oscillations mainly depends on the target cell density, rather than the intracellular delay which the previous authors have done [6,19,43,48].

Sustained oscillations are indicative of the existence of a Hopf bifurcation. Our model exhibits these oscillations in biologically meaningful parameter space. This will affect the evolution of resistance and the success of any ART regimen since these oscillations demonstrate a rapid turnover of viral strains. Previous studies [3,43,45] have also found that sustained oscillations may exist in realistic parameter space for HIV. Ciupe et al. [3] explained that the delay model with an immune response leading to sustained oscillations arguably fits the clinical data better than the basic HIV model by Monte Carlo simulations. Wodarz et al. [45] also admitted sustained oscillations biologically for certain parameter values in a dynamical HIV model with an immune response.

System (1) does not consider the cytotoxic T lymphocyte (CTL) population. CTL play a critical part in antiviral defense by attacking virus-infected cells. It is believed that CTL are the main host immune factor

that limits the extent of virus replication *in vivo* and thus determines the viral load [31]. An extension to our model involving the effects of CTL will be an avenue for future work. Future work will also involve a study of the effect of different treatment regimens on the emergence of resistance.

Acknowledgments

This research was supported by National Natural Science Foundation of China (No. 11226260, No. 11326246 and No. 11301543) and the Fundamental Research Funds for the Central Universities (No. 13CX02014A) (Y. Wang); by Natural Sciences and Engineering Research Council of Canada and Mathematics for Information Technology and Complex Systems (F. Brauer, J. Wu and J.M. Heffernan); by the Ontario Government Early Research Award program (J.M. Heffernan). We are grateful to the anonymous referees for their careful reading, constructive criticisms and helpful comments, which helped us to improve our study.

Appendix A

If $u = 0$ in system (1), then the positive steady state E_e reduces to only the drug-sensitive strain steady state E_s if $\mathcal{R}_s > 1$ (see Section 3.2). We can easily obtain the local asymptotic stability of E_s through Theorem 3.6 if $\mathcal{R}_s > 1$ and $\sigma > 1$ are satisfied.

Theorem A.1. *If $\mathcal{R}_s > 1$ and $\sigma > 1$, then the drug-sensitive steady state E_s is globally asymptotically stable for all $\tau \geqslant 0$ under assumption* (A3).

Proof. Construct a Lyapunov function $W_3 : C \times \mathbb{R}_+ \times C \times \mathbb{R}_+ \times C \to \mathbb{R}$

$$W_3 = T_s g\left(\frac{T(t)}{T_s}\right) + e^{m\tau} T^*_{ss} g\left(\frac{T^*_s(t)}{T^*_{ss}}\right) + \frac{e^{m\tau}}{\bar{N}_s} V_{ss} g\left(\frac{V_s(t)}{V_{ss}}\right) + e^{m\tau} T^*_r(t)$$
$$+ \frac{e^{m\tau}}{\bar{N}_r} V_r(t) + \bar{k}_s T_s V_{ss} \int_{-\tau}^{0} g\left(\frac{\psi_1(t+s)\psi_3(t+s)}{T_s V_{ss}}\right) ds + \bar{k}_r \int_{-\tau}^{0} \psi_1(t+s)\psi_5(t+s)\, ds.$$

Calculating the derivative of W_3 along with the solution of system (1), we obtain

$$\dot{W}_3 = f\big(T(t)\big)\left(1 - \frac{T_s}{T(t)}\right) + \bar{k}_s T_s V_s(t) + \bar{k}_r T_s V_r(t) - \bar{k}_s T(t-\tau) V_s(t-\tau) \frac{T^*_{ss}}{T^*_s}$$
$$+ e^{m\tau} \delta T^*_{ss} - \frac{c e^{m\tau}}{\bar{N}_s} V_s(t) - e^{m\tau} \delta T^*_s(t) \frac{V_{ss}}{V_s(t)} + \frac{c e^{m\tau}}{\bar{N}_s} V_{ss} - \frac{c e^{m\tau}}{\bar{N}_r} V_r(t)$$
$$- \bar{k}_s T_s V_{ss} \ln\left(\frac{\psi_1(t)\psi_3(t)}{\psi_1(t-\tau)\psi_3(t-\tau)}\right).$$

Using the equalities $f(T_s) = \bar{k}_s T_s V_{ss} = e^{m\tau} \delta T^*_{ss}$, $\bar{N}_s \delta T^*_{ss} = c V_{ss}$ and $T_s = \frac{T_0}{\mathcal{R}_s}$ at E_s into the above equation, then

$$\dot{W}_3 = \big(f\big(T(t)\big) - f(T_s)\big)\left(1 - \frac{T_s}{T(t)}\right) + e^{m\tau} \delta T^*_{ss} \left(1 - \frac{T_s}{T(t)}\right)$$
$$+ \left(\bar{k}_r T_s - \frac{c e^{m\tau}}{\bar{N}_r}\right) V_r(t) - e^{m\tau} \delta T^*_{ss} \frac{T(t-\tau) V_s(t-\tau) T^*_{ss}}{T_s V_{ss} T^*_s(t)} + e^{m\tau} \delta T^*_{ss}$$
$$- e^{m\tau} \delta T^*_{ss} \frac{V_{ss} T^*_s(t)}{T^*_{ss} V_s(t)} + e^{m\tau} \delta T^*_{ss} - e^{m\tau} \delta T^*_{ss} \ln\left(\frac{\psi_1(t)\psi_3(t)}{\psi_1(t-\tau)\psi_3(t-\tau)}\right)$$

$$= \big(f(T(t)) - f(T_s)\big)\left(1 - \frac{T_s}{T(t)}\right) - \left(1 - \frac{1}{\sigma}\right)\frac{ce^{m\tau}}{\bar{N}_r}V_r(t)$$
$$- e^{m\tau}\delta T^*_{ss}\left[g\left(\frac{T_s}{T(t)}\right) + g\left(\frac{T(t-\tau)V_s(t-\tau)T^*_{ss}}{T_sV_{ss}T^*_s(t)}\right) + g\left(\frac{V_{ss}T^*_s(t)}{T^*_{ss}V_s(t)}\right)\right].$$

From assumption (A3), we know that $(f(T(t)) - f(T_s))(1 - \frac{T_s}{T(t)}) < 0$. If $\sigma > 1$, through the property of $g(x)$, we obtain that $\dot{W}_3 \leqslant 0$. $\dot{W}_3 = 0$ if and only if

$$\frac{T_s}{T(t)} = \frac{T(t-\tau)V_s(t-\tau)T^*_{ss}}{T_sV_{ss}T^*_s(t)} = \frac{V_{ss}T^*_s(t)}{T^*_{ss}V_s(t)} = 1 \quad \text{and} \quad V_r(t) = 0$$

are satisfied. It means the maximum invariant set in $\{\psi \in \Gamma | \dot{W}_3 = 0\}$ is the singleton E_s. Therefore, all solutions in Γ with non-negative initial values converge to E_s by the LaSalle's invariance principle [20]. This and the local stability of E_s imply the global asymptotic stability of E_s for all given $\tau \geqslant 0$. This completes the proof. □

References

[1] H.K. Altes, V.A.A. Jansen, Intra-host competition between nef-defective escape mutants and wild-type human immunodeficiency virus type 1, Proc. R. Soc. Lond. B Bio. 267 (2000) 183–189.
[2] S. Bonhoeffer, M.A. Nowak, Pre-existence and emergence of drug resistance in HIV-1 infection, Proc. R. Soc. Lond. B Bio. 264 (1997) 631–637.
[3] M.S. Ciupe, B.L. Bivort, D.M. Bortz, et al., Estimating kinetic parameters from HIV primary infection data through the eyes of three different mathematical models, Math. Biosci. 200 (2006) 1–27.
[4] F. Clavel, A.J. Hance, Medical progress: HIV drug resistance, N. Engl. J. Med. 350 (2004) 1023–1035.
[5] K.L. Cooke, P. van den Driessche, On zeroes of some transcendental equations, Funkcial. Ekvac. 29 (1986) 77–90.
[6] R.V. Culshaw, S.G. Ruan, A delay-differential equation model of HIV infection of CD4$^+$ T-cells, Math. Biosci. 165 (2000) 27–39.
[7] R.V. Culshaw, S.G. Ruan, R.J. Spiteri, Optimal HIV treatment by maximising immune response, J. Math. Biol. 48 (2004) 545–562.
[8] P. de Leenheer, S.S. Pilyugin, Multistrain virus dynamics with mutations: a global analysis, Math. Med. Biol. 25 (2008) 285–322.
[9] P. de Leenheer, H.L. Smith, Virus dynamics: a global analysis, SIAM J. Appl. Math. 63 (2003) 1313–1327.
[10] N.M. Dixit, A.S. Perelson, Complex patterns of viral load decay under antiretroviral therapy: influence of pharmacokinetics and intracellular delay, J. Theoret. Biol. 226 (2004) 95–109.
[11] H.I. Freedman, Y. Kuang, Stability switches in linear scalar neutral delay equations, Funkcial. Ekvac. 34 (1991) 187–209.
[12] J. Hale, S.M. Verduyn Lunel, Introduction to Functional Differential Equations, Springer-Verlag, New York, 1993.
[13] J.M. Heffernan, R.J. Smith, L.M. Wahl, Perspectives on the basic reproductive ratio, J. R. Soc. Interface 2 (2005) 281–293.
[14] A.V.M. Herz, S. Bonhoeffer, R.M. Anderson, R.M. May, M.A. Nowak, Viral dynamics in vivo: limitations on estimates of intracellular delay and virus decay, Proc. Natl. Acad. Sci. USA 93 (1996) 7247–7251.
[15] D.D. Ho, A.U. Neumann, A.S. Perelson, W.L. Chen, J.M. Leonard, M. Markowitz, Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection, Nature 373 (1995) 123–126.
[16] G. Huang, Y. Takeuchi, W.B. Ma, Lyapunov functionals for delay differential equations model of viral infections, SIAM J. Appl. Math. 70 (2010) 2693–2708.
[17] Y.X. Huang, S.L. Rosenkranz, H.L. Wu, Modeling HIV dynamics and antiviral response with consideration of time-varying drug exposures, adherence and phenotypic sensitivity, Math. Biosci. 184 (2003) 165–186.
[18] A. Iggidr, J. Mbang, G. Sallet, Stability analysis of within-host parasite models with delays, Math. Biosci. 209 (2007) 51–75.
[19] X.W. Jiang, X.Y. Zhou, X.Y. Shi, X.Y. Song, Analysis of stability and Hopf bifurcation for a delay-differential equation model of HIV infection of CD4$^+$ T-cells, Chaos Solitons Fractals 38 (2008) 447–460.
[20] J.P. LaSalle, The Stability of Dynamical Systems, Regional Conf. Ser. in Appl. Math., SIAM, Philadelphia, 1976.
[21] M.Y. Li, H.Y. Shu, Global dynamics of an in-host viral model with intracellular delay, Bull. Math. Biol. 72 (2010) 1492–1505.
[22] M.Y. Li, H.Y. Shu, Impact of intracellular delays and target-cell dynamics on in vivo viral infections, SIAM J. Appl. Math. 70 (2010) 2434–2448.
[23] J. Lou, Y.J. Lou, J.H. Wu, Threshold virus dynamics with impulsive antiretroviral drug effects, J. Math. Biol. 65 (2012) 623–652.
[24] L.M. Mansky, H.M. TeminLower, Lower in vivo mutation rate of human immunodeficiency virus type 1 than that predicted from the fidelity of purified reverse transcriptase, J. Virol. 69 (1995) 5087–5094.
[25] M. Markowitz, M. Louie, A. Hurley, E. Sun, M. Di Mascio, A.S. Perelson, D.D. Ho, A novel antiviral intervention results in more accurate assessment of human immunodeficiency virus type 1 replication dynamics and T-cell decay in vivo, J. Virol. 77 (2003) 5037–5038.

[26] C.C. McCluskey, Complete global stability for an SIR epidemic model with delay-Distributed or discrete, Nonlinear Anal. Real World Appl. 11 (2010) 55–59.
[27] A.R. McLean, C.A. Michie, In vivo estimates of division and death rates of human lymphocytes, Proc. Natl. Acad. Sci. USA 92 (1995) 3707–3711.
[28] H. Mohri, S. Bonhoeffer, S. Monard, A.S. Perelson, D.D. Ho, Rapid turnover of T lymphocytes in SIV-infected rhesus macaques, Science 279 (1998) 1223–1227.
[29] P.W. Nelson, J.E. Mittler, A.S. Perelson, Effect of drug efficacy and the eclipse phase of the viral life cycle on estimates of HIV viral dynamic parameters, J. Acquir. Immune Defic. Syndr. 26 (2001) 405–412.
[30] M.A. Nowak, S. Bonhoeffer, G.M. Shaw, R.M. May, Anti-viral drug treatment: Dynamics of resistance in free virus and infected cell populations, J. Theoret. Biol. 184 (1997) 205–219.
[31] M.A. Nowak, R.M. May, Virus Dynamics: Mathematical Principles of Immunology and Virology, Oxford University, Oxford, 2000.
[32] A.S. Perelson, D.E. Kirschner, R. de boer, Dynamics of HIV-infection of $CD4^+$ T-cells, Math. Biosci. 114 (1993) 81–125.
[33] A.S. Perelson, P.W. Nelson, Mathematical analysis of HIV-1 dynamics in vivo, SIAM Rev. 41 (1999) 3–44.
[34] A.S. Perelson, A.U. Neumann, M. Markowitz, J.M. Leonard, D.D. Ho, HIV-1 dynamics in vivo: virion clearance rate, infected cell life-span, and viral generation time, Science 271 (1996) 1582–1586.
[35] B. Ramratnam, S. Bonhoeffer, J. Binley, A. Hurley, L. Zhang, J.E. Mittler, M. Minarkowitz, J.P. Moore, A.S. Perelson, D.D. Ho, Rapid production and clearance of HIV-1 and hepatitis C virus assessed by large volume plasma apheresis, Lancet 354 (1999) 1782–1785.
[36] L.B. Rong, Z.L. Feng, A.S. Perelson, Emergence of HIV-1 drug resistance during antiretroviral treatment, Bull. Math. Biol. 69 (2007) 2027–2060.
[37] L.B. Rong, M.A. Gilchrist, Z.L. Feng, A.S. Perelson, Modeling within-host HIV-1 dynamics and the evolution of drug resistance: trade-offs between viral enzyme function and drug susceptibility, J. Theoret. Biol. 247 (2007) 804–818.
[38] N. Sachsenberg, A.S. Perelson, S. Yerly, G.A. Schockmel, D. Leduc, B. Hirschel, L. Perrin, Turnover of $CD4^+$ and $CD8^+$ T lymphocytes in HIV-1 infection as measured by ki-67 antigen, J. Exp. Med. 187 (1998) 1295–1303.
[39] H.L. Smith, Monotone Dynamical Systems: An Introduction to the Theory of Competitive and Cooperative Systems, Amer. Math. Soc., Providence, 1995.
[40] R.J. Smith, L.M. Wahl, Drug resistance in an immunological model of HIV-1 infection with impulsive drug effects, Bull. Math. Biol. 67 (2005) 783–813.
[41] L.M. Wahl, M.A. Nowak, Adherence and drug resistance: predictions for therapy outcome, Proc. Biol. Sci. 267 (2000) 835–843.
[42] L. Wang, M.Y. Li, Mathematical analysis of the global dynamics of a model for HIV infection of $CD4^+$ T cells, Math. Biosci. 200 (2006) 44–57.
[43] Y. Wang, Y.C. Zhou, J.H. Wu, J. Heffernan, Oscillatory viral dynamics in a delayed HIV pathogenesis model, Math. Biosci. 219 (2009) 104–112.
[44] D. Wodarz, A.L. Lloyd, Immune responses and the emergence of drug-resistant virus strains in vivo, Proc. R. Soc. Lond. B Bio. 271 (2004) 1101–1109.
[45] D. Wodarz, K.M. Page, R.A. Arnaout, A.R. Thomsen, J.D. Lifsen, M.A. Nowak, A new theory of cytotoxic T-lymphocyte memory: implications for HIV treatment, Philos. Trans. R. Soc. B Biol. Sci. 355 (2000) 329–343.
[46] J.H. Wu, P. Yan, C. Archibald, Modelling the evolution of drug resistance in the presence of antiviral drugs, BMC Public Health 7 (2007) 300.
[47] R. Xu, Global stability of an HIV-1 infection model with saturation infection and intracellular delay, J. Math. Anal. Appl. 375 (2011) 75–81.
[48] J.Y. Yang, X.Y. Wang, X.Z. Li, Hopf bifurcation for a model of HIV infection of $CD4^+$ T cells with virus released delay, Discrete Dyn. Nat. Soc. 2011 (2011) 1–24.
[49] P.G. Yeni, S.M. Hammer, C.C. Carpenter, D.A. Cooper, M.A. Fischl, J.M. Gatell, B.G. Gazzard, M.S. Hirsch, D.M. Jacobsen, D.A. Katzenstein, J.S.G. Montaner, D.D. Richman, M.S. Saag, M. Schechter, R.T. Schooley, M.A. Thompson, S. Vella, P.A. Volberding, Antiretroviral treatment for adult HIV infection in 2002: updated recommendations of the international AIDS society-USA panel, J. Am. Med. Assoc. 288 (2002) 222–235.
[50] H.Y. Zhu, X.F. Zou, Impact of delays in cell infection and virus production on HIV-1 dynamics, Math. Med. Biol. 25 (2008) 99–112.