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THE EFFECTS OF DELAY AND IMPULSIVE DRUG THERAPY IN AN HIV MODEL WITH CTLS IMMUNE RESPONSE*

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Abstract Considering the effects of immune response and drug therapy on HIV treatment, an HIV mathematical control model with CTLs immune response is therefore proposed, where the delay of virus invasion and impulsive drug therapy are introduced. By utilizing the comparison theorem, differential inequality theories and analytic method, the threshold values for the existence and global stability of the virus-free periodic solution, and the uniform persistence of disease without CTLs immune response are studied. Numerical simulations are performed to illustrate the main theoretical results and the feasibility of drug therapy. Our theoretical results suggest that long-term and standardized medication can prolong the infection process and spread of the virus, or suppress the virus concentration below the detectable level.

Keywords HIV model with CTLs immune response, intercellular delay, impulsive drug therapy, global stability, uniform persistence.

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1. Introduction

HIV, that is, Human Immunodeficiency virus, which attacks the bodys immune system and is spread through certain body fluids, including breast milk. Now and for some time to come, HIV is also major public health problems in many areas all over the world, especially Sub-Saharan Africa, South Asia and Southeast Asia. According to incomplete statistics, HIV causes nearly 12 million deaths worldwide and more than 30 million infections [15, 41].

How to remove and control HIV from various points of view, is a rare problem in the world. Particularly, mathematical modelling has made significant contributions to our understanding the dynamic of HIV infection. For example, Perelson et al. [26] proposed a HIV infection model with uninfected $CD4^+T$ cells, latently infected $CD4^+T$ cells, actively infected $CD4^+T$ cells and free virus, and discussed the existence and stability of the uninfected state and endemically infected state. Phillips [28] introduced a mathematical model of primary HIV infection, and predicted the pattern of changes virus concentration. In addition, during primary HIV infection, the extremely high viral load leads to the activation of $CD8^+T$ cells, which

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are called cytotoxic T cells (CTL) that can inhibit viral replication. Considering the effect of CTLs, many mathematical models with the immune response have been applied to describe the short-term dynamics of HIV infection, and to estimate virus turnover rates in vivo. For example, Burg et al. [3] generalized the model in Ref. [28] to HIV infection model with immune control, and obtained that the immune response may have a significant effect on the control of HIV during the initial infection. For more related results also can be found in Refs. [1,8,20,21,31,39] and the references therein.

Considering the time it takes for the virus to completely invade the cells and the proliferation of the virus, some HIV virus models with delay are structured (see Refs. [9–11,19,32] and the references therein). Particularly, Pereslon et al. [27] introduced the intracellular delay to an HIV dynamical model, and discussed the effects of delays for this model. Zhu et al. [46] constructed an HIV-1 infection model with two delays, and studied the existence and stability of equilibria. Pawelek [23] introduced a delay differential equation model to analysis the effects of intracellular delay and immune delay for HIV infection, and obtained the existence and global stability of infection-free and infected steady states. In recent years, the relevant research work has been ongoing.

At present, there is still a lack of effective drugs to cure HIV infection all over the world. At this stage, the treatment objectives are to reduce viral load to a maximum and lasting extent, to obtain immune function reconstruction and maintain immune function, and to decrease the incidence and mortality of HIV. Based on these concepts, some mathematical models are developed to describe the interaction of CD 4^+T-cells and HIV following drug treatment and then the emergence of drug-resistant virus in [5,6,17,22,25,33] and the references therein. Particularly, Kirschner and Webb [16] proposed an HIV virus model with immune system enhancing drugs, and found that the immunotherapy treatment strategy can be successful in delaying the HIV progression. Notice that drugs are most commonly prescribed to give a fixed dose, fixed time-interval basis. Rong and Perelson [29] proposed a new mathematical model of ordinary differential equations, to discuss the effects of the immune activation of latently infected cells and reverse transcriptase and protease inhibitors. In addition, several papers have recently adopted impulsive differential equations (IDE) to model drug dynamics during HIV therapy in [34,35,43] and the references therein.

Motivated by these facts, we propose an HIV dynamical model, where CTLs immune response, delay and fixed time drug therapy are introduced. The main purpose is to investigate the delay and fixed time drug therapy, which governs whether the disease dies out or not, and further to examine how the delay and fixed time drug therapy affect the HIV infection. This paper is structured as follows. The control model and preliminaries are described in Section 2. In Section 3, the positivity and boundedness of solutions for this control model are investigated. Particularly, we examine the extinction and uniform persistence of HIV infection in Section 4 and Section 5, respectively. Numerical simulations are carried in Section 6 for illustrations and some concluding remarks are outlined in the final section.

2. Model description and preliminaries

In the process of virus from invading uninfected cells, the intracellular delay is ubiquitous, which occurs between initial infection of a cell by virus and the release of new

virions. As Herz et al. [12] pointed that the intracellular delay would substantially shorten the estimate for the half-life of free virus. An HIV infection model with the intracellular delay and CTLs immune response is usually given by the following delay differential equation.

$$\begin{cases} \dfrac{\mathrm{d}T(t)}{\mathrm{d}t} = \lambda - dT(t) - \beta T(t)V(t) \\ \dfrac{\mathrm{d}T^*(t)}{\mathrm{d}t} = \beta e^{-m\theta} T(t-\theta)V(t-\theta) - \delta T^*(t) - qE(t)T^*(t) \\ \dfrac{\mathrm{d}V(t)}{\mathrm{d}t} = \delta N T^*(t) - cV(t) \\ \dfrac{\mathrm{d}E(t)}{\mathrm{d}t} = f(T, T^*, E) - d_E E(t), \end{cases} \tag{2.1}$$

where $T(t)$, $T^*(t)$, $V(t)$ and $E(t)$ represent the concentrations of uninfected $CD4^+$ T-cells, infected $CD4^+$ T-cells, free virus particles and CTLs at time t, respectively. The meaning of other parameters is shown in Table 1. The function $f(T, T^*, E)$ represents the rate of activation of CTLs response, which has several forms based on different mechanism assumptions: (i) $f(T, T^*, E) = pT^*$ (see [2, 4]); (ii) pT^*E (see [21]); (iii) pTT^*E (see [7]). Where, p is CTL responsiveness, that is the average rate at which specific CTLs proliferate after encountering an infected cell. But so far, it is unclear which is more reasonable for the above forms. Considering the notion that precursor CTLs encounter infected cells and subsequently proliferate into mature effectors, the predator-prey form, that is pT^*E is the most popular in the modelling literature and can be found in [21, 47] and the references therein.

Since the proliferation rate of T-cells is density dependent with the rate of proliferation decreasing as the T-cell population increases and approaches a carrying capacity (see Ho et al. [13] and Sachsenberg et al. [30]), some authors included a logistic growth term, $rT(t)[1 - (T(t) + T^*(t))/T_{max}]$, in the first equation of model (2.1). For more details about this term, please see [7, 38] and the references therein.

On the other hand, considering that the drug concentration in HIV patients is no longer a constant value, but show a negative correlation with the period of drug-take. In fact, a dose is taken, the concentration of drug increases rapidly and reaches a peak value, and then decreases gradually with time. When another dose is taking, the concentration of a drug is likely to vary in a similar way [34]. In it, they assumed that drugs are taken at fixed time (not necessarily equally spaced) and the effect of the drugs is instantaneous. Particularly, in [17], the intracellular concentration of drug $C(t)$ is modeled by

$$\begin{cases} \dfrac{\mathrm{d}C(t)}{\mathrm{d}t} = -\omega C(t), & t \neq t_i, i = 1, 2, \cdots, \\ \Delta C(t) = C(t^+) - C(t) = C_i, & t = t_i, \end{cases} \tag{2.2}$$

where, ω is the rate at which drug is cleared, and C_i is the dosage which is taken at i-th impulsive time. Further, using the MichaelisCMenten dynamics, the change of drug effectiveness is modeled with the change of drug concentration, $\eta(t) = C(t)/(C(t) + IC_{50})$, where IC_{50} is the concentration necessary to inhibit viral replication by 50%. Therefore, in order to remove the free parameter IC_{50} and simplify the model, let $D(t) = C(t)/IC_{50}$ and $D_i = C_i/IC_{50}$. Thus, model

(2.1) and (2.2) lead to a new HIV infection model wit drug therapy as follows

$$\begin{cases} \dfrac{\mathrm{d}T(t)}{\mathrm{d}t} = \lambda - dT(t) + rT(t)\left(1 - \dfrac{T(t)+T^*(t)}{T_{max}}\right) - \dfrac{\beta T(t)V(t)}{1+D(t)} \\ \dfrac{\mathrm{d}T^*(t)}{\mathrm{d}t} = \dfrac{\beta e^{-m\theta}T(t-\theta)V(t-\theta)}{1+D(t)} - \delta T^*(t) - qT^*(t)E(t) \\ \dfrac{\mathrm{d}V(t)}{\mathrm{d}t} = \delta N T^*(t) - (c + k\beta T(t))V(t) \\ \dfrac{\mathrm{d}E(t)}{\mathrm{d}t} = pT^*(t)E(t) - d_E E(t) \end{cases} \tag{2.3}$$

with

$$\begin{cases} \dfrac{\mathrm{d}D(t)}{\mathrm{d}t} = -\omega D(t), & t \neq t_i, \\ \Delta D(t) = D(t^+) - D(t) = D_i, & t = t_i,\ i = 1, 2, \cdots. \end{cases} \tag{2.4}$$

Here, the term $k\beta T(t)V(t)$ ($k = 0$, or 1), represents ignores or includes the loss of free virus through infection of a cell. The time delay θ represents the time from virus entry to virus production, which also includes the effect of drug action on virus invasion. The meanings and possible values of other parameters of models (2.3) and (2.4) are given in Table 1.

Table 1. The meaning and values of parameters for models (2.3) and (2.4).

Param.	Description	Range	Source
λ	Uninfected cell activation rate($cells/mm^3/day$)	$1e^{-2} \sim 50$	[3]
r	Growth rate of healthy CD4$^+$ T-cells population ($cells/mm^3/day$)	$0.03 \sim 3$	[25,38]
T_{max}	Maximal population level of healthy CD4$^+$ T-cells ($cells/mm^3/day$)	$1.5e^3$	[7,25]
d	Uninfected cell death rate(day^{-1})	$1e^{-4} \sim 0.2$	[3]
β	Infection rate of infected cell($virions\ mm^3/day$)	$1e^{-7} \sim 1e^{-3}$	[3]
δ	Infected cell death rate(day^{-1})	$0.1 \sim 1$	[3]
p	Rate at which infected cells are killed by CTLs(day^{-1})	$1e^{-3} \sim 1$	[2,40]
N	Burst size of the infected cell($virions/cell$)	$1 \sim 2e^3$	[3]
c	Death rate of virus(day^{-1})	$1e^{-1} \sim 1e^1$	[3]
θ	Length of the intercellular delay($days$)	Assumed	–
$e^{-m\theta}$	Probability of infected target cells surviving the period of intracellular delay from$t-\theta$ to t	Assumed	–
p	Immune response activation rate(day^{-1})	$0.001 \sim 1$	[2,40]
d_E	Death rate of CTLs(day^{-1})	$0.05 \sim 0.15$	[2,40]
ω	Rate at which drug is cleared from body(day^{-1})	$1.2 \sim 7.2$	[14]

Remark 2.1. For model (2.3) with $D(t) \equiv 0$, that is the basic and classic model of HIV dynamics which was propose by Nowak et al. [21] and Perelson et al. [26] for $r = k = 0$, is precisely what the delay HIV infection model was proposed by Culshaw et al. [7] for $p = q = d_E = 0$ and $k = 1$, and so on.

Let $\mathbb{R} = (-\infty, \infty)$ and $\mathbb{N} = \{1, 2, 3, \cdots\}$. Supposing that $\tau^l = \min_{i\in\mathbb{N}}\{t_{i+1} - t_i\} > 0$ and $\tau^u = \max_{i\in\mathbb{N}}\{t_{i+1} - t_i\} < \infty$. For any $\theta > 0$, we define $\mathcal{C}([-\theta, 0], \mathbb{R})$ the Banach space of bounded continuous functions $\phi : [-\theta, 0] \to \mathbb{R}$ with the supremum

norm defined by $\|\phi\|_c = \sup_{-\theta\le s\le 0}|\phi(s)|$ for $\phi \in \mathcal{C}$. The nonnegative cone of $\mathcal{C}$ is defined as $\mathcal{C}^+ = \mathcal{C}([-\theta, 0], \mathbb{R}_+)$, where $\mathbb{R}_+ = (0, +\infty)$. Form the biological meanings, the initial conditions for models (2.3) and (2.4) are chosen at $t = 0$ as

$$\varphi = (\phi_1, \phi_2, \phi_3, \phi_4, \phi_5) \in \mathcal{C}^+ \times \mathbb{R}_+ \times \mathcal{C}^+ \times \mathbb{R}_+ \times \mathbb{R}_+ \quad \text{and} \quad \varphi(0) > 0. \tag{2.5}$$

By the fundamental theory of functional differential equations with impulses [18], models (2.3) and (2.4) have a unique solution $(T(t), T^*(t), V(t), E(t), D(t))$ satisfying the initial condition (2.5). For the biological background, we only consider models (2.3) and (2.4) in the biological meaningful region $\mathbb{R}^5_+ = \{(T, T^*, V, E, D) : T \ge 0, T^* \ge 0, V \ge 0, E \ge 0, D \ge 0\}$ and $D_{\min} \le D_i \le D_{\max}$, where $D_{\min}$ and $D_{\max}$ are the minimum and maximum intake for the pharmaceutical therapy.

Next, we consider a linear differential equation with parameter

$$\frac{\mathrm{d}u(t)}{\mathrm{d}t} = \alpha(\gamma) - \beta u(t), \tag{2.6}$$

where β is positive constant, $\alpha(\gamma)$ is a continuous function and positive bounded on $\gamma \in (0, \gamma_0]$, γ_0 is a positive constant.

The following Lemma 2.1 is on the existent and stability of positive equilibrium for equation (2.6). Though its proof is straightforward, but useful.

Lemma 2.1. *For any $\gamma \in (0, \gamma_0]$, equation (2.6) admits a unique positive equilibrium $u^*_\gamma = \alpha(\gamma)/\beta$ and which is globally asymptotically stable. Further, if $\lim_{\gamma\to 0}\alpha(\gamma) = \alpha_0$, then $u^*_\gamma \to \alpha_0/\beta$ as $\gamma \to 0$ and $t \to \infty$.*

Let $A(t)$ be a continuous, cooperative, irreducible, and τ-periodic $k \times k$ matrix function, $\Phi_{A(\cdot)}(t)$ be the fundamental solution matrix of the linear ordinary differential equation

$$\frac{\mathrm{d}x(t)}{\mathrm{d}t} = A(t)x(t) \tag{2.7}$$

and $\rho(\Phi_{A(\cdot)}(\tau))$ is the principal eigenvalue of $\Phi_{A(\cdot)}(\tau)$ in the sense that it is simple and admits an eigenvector $\nu^* \gg 0$.

Lemma 2.2 (Lemma 2.1, [44])**.** *Let $\mu = (\ln \Phi_{A(\cdot)}(\tau))/\tau$, then there exists a positive, τ-periodic function $\nu(t)$ such that $e^{\mu}\nu(t)$ is a solution of equation (2.7).*

3. The basic properties

Firstly, on drug dynamical model (2.4), we have the following result.

Lemma 3.1. *If $t_{i+1} - t_i \equiv \tau$ and $D_i \equiv D_0$, where τ and D_0 are positive constants, then model (2.4) has the following periodic solution*

$$D^*(t) = \frac{D_0 e^{-\omega(t-i\tau)}}{1 - e^{-\omega\tau}}, \qquad i\tau < t \le (i+1)\tau. \tag{3.1}$$

The proof of Lemma 3.1 is easy to obtain by the theory of impulsive differential equation, we hence omit it here.

The following Theorem 3.1 indicates that the solutions of models (2.3) and (2.4) are positivity and bounded.

Theorem 3.1. *Each component of solution of models* (2.3) *and* (2.4) *with the initial value* (2.5) *is positive and ultimately bounded for all* $t \in [0, +\infty)$.

Proof. The proof of the non-negativity and positiveness of solution is obvious. Now, we turn to the ultimate boundedness. From Lemma 3.1, it follows that $\limsup_{t\to\infty} D(t) \leq D_{\max}/(1 - e^{-\omega\tau^l}) := \widetilde{D}$. By the first equation of (2.3), we have

$$\frac{\mathrm{d}T(t)}{\mathrm{d}t} \leq \lambda - dT(t) + rT(t)\left(1 - \frac{T(t)}{T_{max}}\right).$$

It is obvious that $\limsup_{t\to+\infty} T(t) \leq \widetilde{T}$, where

$$\widetilde{T} = \frac{T_{max}}{2r}\left(r - d + \sqrt{(r-d)^2 + \frac{4\lambda r}{T_{max}}}\right). \tag{3.2}$$

Let $H_1(t) = T(t) + [(1 + \widetilde{D})\beta e^{-m\theta}]^{-1}T^*(t + \theta)$, it follows from the derivative of function $H_1(t)$ along the solutions of model (2.3) that

$$\begin{aligned}\frac{\mathrm{d}H_1(t)}{\mathrm{d}t} &\leq -dT(t) - \frac{\delta}{(1+\widetilde{D})\beta e^{-m\theta}}T^*(t+\theta) + \lambda + rT(t)\left(1 - \frac{T(t)}{T_{max}}\right)\\ &\leq -\gamma H_1(t) + c_0\end{aligned}$$

for sufficiently large time t, where $c_0 = \lambda + rT_{max}/4$ and $\gamma_1 = \min\{d, \delta\}$. Thus, this shows that $T^*(t)$ has an ultimate bound $\widetilde{T}^*$. From the fact and the third equation of model (2.3), it implies that $\mathrm{d}V(t)/\mathrm{d}t \leq \delta N\widetilde{T}^* - cV(t)$, and $\limsup_{t\to\infty} V(t) \leq \delta N\widetilde{T}^*/c := \widetilde{V}$.

Finally, let function $H_2(t) = pT^*(t) + qE(t)$ and calculate the derivative of function $H_2(t)$ along the solutions of model (2.3), one have

$$\frac{\mathrm{d}H_2(t)}{\mathrm{d}t} \leq -p\delta T^*(t) - qd_E E(t) + \beta e^{-m\theta}\widetilde{T}\widetilde{V} \leq -\gamma_2 H_2(t) + \beta e^{-m\theta}\widetilde{T}\widetilde{V}$$

for sufficiently large time t, where $\gamma_2 = \min\{\delta, d_E\}$. Similarly, $E(t)$ admits an ultimate bound $\widetilde{E}$. Let $M = \max\{\widetilde{T}^*, \widetilde{V}, \widetilde{E}\}$. From the above discussion, we finally obtain that $T(t) \leq \widetilde{T}$, $T^*(t) \leq M$, $V(t) \leq M$, $E(t) \leq M$ and $D(t) \leq \widetilde{D}$ for sufficiently large time t. The proof is complete. □

Remark 3.1. For any small enough constant $\epsilon > 0$, let $\Omega_\epsilon = \{(T, T^*, V, E, D) \in \mathbb{R}^5_+ : T \leq \widetilde{T} + \epsilon, 0 < T^*(t), V(t), E(t) \leq M + \epsilon, D \leq \widetilde{D} + \epsilon\}$. Obviously, Ω_ϵ is a positively invariant set with respect to models (2.3) and (2.4), and is also a global attractor of all positive solutions of models (2.3) and (2.4) from Theorem 3.1.

4. The extinction of disease

Since the drug is present, there is no equilibrium for models (2.3) and (2.4). Supposing that the medication is administered at regular time intervals with a fixed dosage, that is, $t_{i+1} - t_i \equiv \tau$ and $D_i \equiv D_0$ for $i = 1, 2, \cdots$, where τ and D_0 are positive constants. From Lemma 3.1, models (2.3) and (2.4) have a virus-free periodic

solution $(\widetilde{T},0,0,0,D^*(t))$. Further, (2.3) and (2.4) are equivalent to the following delay system in a periodic environment

$$\begin{cases} \dfrac{\mathrm{d}E(t)}{\mathrm{d}t} = pT^*(t)E(t) - d_E E(t) \\ \dfrac{\mathrm{d}T(t)}{\mathrm{d}t} = \lambda - dT(t) + rT(t)\left(1 - \dfrac{T(t)+T^*(t)}{T_{max}}\right) - \dfrac{1}{1+D^*(t)}\beta T(t)V(t) \\ \dfrac{\mathrm{d}T^*(t)}{\mathrm{d}t} = \dfrac{1}{1+D^*(t)}\beta e^{-m\theta}T(t-\theta)V(t-\theta) - \delta T^*(t) - qT^*(t)E(t) \\ \dfrac{\mathrm{d}V(t)}{\mathrm{d}t} = \delta N T^*(t) - (c + k\beta T(t))V(t). \end{cases} \tag{4.1}$$

Obviously, (4.1) has a virus-free equilibrium $(0,\widetilde{T},0,0)$. To discuss the stability of $(0,\widetilde{T},0,0)$, we define three matrices at the virus-free periodic solution $(0,\widetilde{T},0,0)$ by

$$\mathbf{A} = \begin{bmatrix} -d_E & 0 \\ 0 & -\sqrt{(\gamma-d)^2 + \frac{4\lambda r}{T_{max}}} \end{bmatrix},\ \mathbf{F}(t) = \begin{bmatrix} 0 & \frac{\beta\widetilde{T}e^{-m\theta}}{1+D^*(t)} \\ \delta N & 0 \end{bmatrix},\ \mathbf{W} = \begin{bmatrix} \delta & 0 \\ 0 & c + k\beta\widetilde{T} \end{bmatrix}. \tag{4.2}$$

Firstly, on the locally asymptotical stability of virus-free equilibrium $(0,\widetilde{T},0,0)$ of model (4.1), we have the following Theorem 4.1.

Theorem 4.1. *If $\mathcal{R}_0 = \rho(\Phi_{\mathbf{F}(\cdot)-\mathbf{W}}(\tau)) < 1$, then virus-free equilibrium $(0,\widetilde{T},0,0)$ of model (4.1) is locally asymptotically stable. Further, the virus-free periodic solution $(\widetilde{T},0,0,0,D^*(t))$ of models (2.3) and (2.4) is locally asymptotically stable.*

Proof. The Jacobian matrix of model (4.1) at $(0,\widetilde{T},0,0)$ as follow

$$\mathcal{J} = \begin{bmatrix} -d_E & 0 & 0 & 0 \\ 0 & -\sqrt{(\gamma-d)^2 + \frac{4\lambda r}{T_{max}}} - \frac{r\widetilde{T}}{T_{max}} & -\frac{\beta\widetilde{T}}{1+D^*(t)} \\ 0 & 0 & -\delta & \frac{\beta e^{-m\theta}\widetilde{T}}{1+D^*(t)} \\ 0 & 0 & \delta N & -c - k\beta\widetilde{T} \end{bmatrix} := \begin{bmatrix} \mathbf{A} & \mathbf{B} \\ \mathbf{0} & \mathbf{F}(t) - \mathbf{W} \end{bmatrix},$$

where $\mathbf{A}$ and $\mathbf{B}$ stand for 2×2 matrixes.

Since $\rho(\mathbf{A}) < 1$ and $\rho(\Phi_{\mathbf{F}(t)-\mathbf{W}}(\tau)) < 1$, then it follows that $(0,\widetilde{T},0,0)$ is locally asymptotically stable. Therefore, $(\widetilde{T},0,0,0,D^*(t))$ of models (2.3) and (2.4) is locally asymptotically stable. The proof is complete. □

The following Theorem 4.2 is on the globally asymptotically stability of the virus-free periodic solution $(\widetilde{T},0,0,0,D^*(t))$ of models (2.3) and (2.4).

Theorem 4.2. *If $\mathcal{R}_0 < 1$ and $\mathcal{R}_* = \rho(\Phi_{\mathbf{F}_*(\cdot)-\mathbf{W}_*}(\tau)) < 1$, where $\mathbf{F}_*(\cdot)$ and $\mathbf{W}_*$ are given by (4.3), respectively, then $(\widetilde{T},0,0,0,D^*(t))$ of models (2.3) and (2.4) is globally asymptotically stable.*

Proof. We have proved that the virus-free periodic solution $(\widetilde{T},0,0,0,D^*(t))$ is locally asymptotically stable for $\mathcal{R}_0 < 1$, now it is sufficient to show that the global attractivity of $(\widetilde{T},0,0,0,D^*(t))$ for $\mathcal{R}_* < 1$.

Firstly, according to $\mathcal{R}_* = \rho(\Phi_{\mathbf{F}_*(\cdot)-\mathbf{W}_*}(\tau)) < 1$, we can choose small enough positive constants ε_1 and ε_2 such that $\rho(\Phi_{\mathbf{F}_*(\cdot)-\mathbf{W}_*+\mathbf{G}(\cdot,\varepsilon_1,\varepsilon_2)}(\tau)) < 1$, where

$$\mathbf{F}_*(t) = \begin{bmatrix} 0 & \frac{\beta\widetilde{T}e^{-(m-c-k\beta\widetilde{T})\theta}}{1+D^*(t)} \\ \delta N & 0 \end{bmatrix}, \quad \mathbf{W}_* = \begin{bmatrix} \delta & 0 \\ 0 & c \end{bmatrix} \tag{4.3}$$

and

$$\mathbf{G}(t,\varepsilon_1,\varepsilon_2) = \begin{bmatrix} 0 & \left(\varepsilon_2\widetilde{T} + \frac{\varepsilon_1}{1+D^*(t)} + \varepsilon_1\varepsilon_2\right)\beta e^{-(m-c-k\beta\widetilde{T})\theta} \\ 0 & 0 \end{bmatrix}.$$

By the first equation of model (2.3) and the nonnegativity of solutions, it is easy to obtain that

$$\frac{\mathrm{d}T(t)}{\mathrm{d}t} \le \lambda - dT(t) + rT(t)\left(1 - \frac{T(t)}{T_{max}}\right).$$

From the comparison theorem, for the above ε_1, there is a time $t_1 > 0$ such that $T(t) \le \widetilde{T} + \varepsilon_1$ for all $t \ge t_1$. Further, from the third equation of model (2.3), it follows that

$$\frac{\mathrm{d}V(t)}{\mathrm{d}t} \ge -(c + k\beta\widetilde{T})V(t).$$

Integrating this inequality from $t-\theta$ to t, it shows that $V(t-\theta) \le V(t)e^{(c+k\beta\widetilde{T})\theta}$ for all $t \ge t_1$. From the first equation of model (2.4) and Lemma 3.1, for the above ε_2, there is a time $t_2 \ge t_1$ and a positive constant σ such that $D(t) \ge D^*(t) - \sigma > 0$ for all $t \ge t_2$, where σ satisfies equation $\sigma/(1-\sigma) \le \varepsilon_2$. From this, it implies that

$$\frac{1}{1+D(t)} \le \frac{1}{1+D^*(t)-\sigma} \le \frac{1}{1+D^*(t)} + \varepsilon_2$$

for all $t \ge t_2$. Moreover, from the second and third equations of model (2.3), it holds that for $t \ge t_2$

$$\begin{cases} \dfrac{\mathrm{d}T^*(t)}{\mathrm{d}t} \le \left(\dfrac{1}{1+D^*(t)} + \varepsilon_2\right)\beta e^{(c+k\beta\widetilde{T}-m)\theta}\left(\widetilde{T}+\varepsilon_1\right)V(t) - \delta T^*(t) \\ \dfrac{\mathrm{d}V(t)}{\mathrm{d}t} \le \delta N T^*(t) - cV(t). \end{cases} \tag{4.4}$$

Nextly, we consider the following auxiliary system

$$\frac{\mathrm{d}X(t)}{\mathrm{d}t} = (\mathbf{F}_*(t) - \mathbf{W}_* + \mathbf{G}(t,\varepsilon_1,\varepsilon_2))X(t), \tag{4.5}$$

where $X(t) = (x_1(t), x_2(t))^{\mathcal{T}}$. Using Lemma 2.2, there exists a positive τ-periodic solution $\nu(t) = (\nu_1(t), \nu_2(t))$ such that $e^{\mu t}\nu(t)$ is a solution of (4.5), where $\mu = (\ln\rho(\Phi_{\mathbf{F}_*(t)-\mathbf{W}_*+\mathbf{G}(t,\varepsilon_1,\varepsilon_2)}(\tau)))/\tau$. This follows from $\rho(\Phi_{\mathbf{F}_*(t)-\mathbf{W}_*+\mathbf{G}(t,\varepsilon_1,\varepsilon_2)}(\tau)) < 1$, it implies that $\mu < 0$. This can be easily shown that $X(t) \to (0,0)^{\mathcal{T}}$ as $t \to \infty$. For any nonnegative initial value $(T^*(t_2), V(t_2))^{\mathcal{T}}$, we can choose a sufficiently large positive constant C^* such that $(T^*(t_2), V(t_2))^{\mathcal{T}} \le C^*\nu(0)$. Moreover, by the comparison theorem, we get $(T^*(t), V(t))^{\mathcal{T}} \le X(t-t_2) = C^*e^{\mu(t-t_2)}\nu(t)$ for all $t \ge t_2$. Thus, we can obtain that $T^*(t) \to 0$ and $V(t) \to 0$ as $t \to \infty$. From the first, fourth and fifth equations of model (2.3), it can be easily obtained that $T(t) \to \widetilde{T}$ and $E(t) \to 0$ as $t \to \infty$. The proof is complete. □

5. The persistence of disease without CTLs immune response

If the CTL immune response is ignored, then models (2.3) and (2.4) degenerate to

$$\begin{cases} \dfrac{\mathrm{d}T(t)}{\mathrm{d}t} = \lambda - dT(t) + rT(t)\left(1 - \dfrac{T(t)+T^*(t)}{T_{max}}\right) - \dfrac{1}{1+D^*(t)}\beta T(t)V(t) \\ \dfrac{\mathrm{d}T^*(t)}{\mathrm{d}t} = \dfrac{1}{1+D^*(t)}\beta e^{-m\theta}T(t-\theta)V(t-\theta) - \delta T^*(t) \\ \dfrac{\mathrm{d}V(t)}{\mathrm{d}t} = \delta N T^*(t) - (c + k\beta T(t))V(t). \end{cases} \tag{5.1}$$

In order to discuss the uniformly persistence of the disease of model (5.1), we introduce a auxiliary function as follows

$$L(t) = T^*(t) + \frac{1}{N}V(t) + \int_{t-\theta}^{t} \frac{\beta e^{-m\theta}}{1+D^*(t+\theta)}T(s)V(s)\,\mathrm{d}s. \tag{5.2}$$

Theorem 5.1. *If*

$$\mathcal{R}^* = \frac{\beta e^{-m\theta}(1-e^{-\omega\tau})\widetilde{T}}{D_{in}+1-e^{-\omega\tau}}\frac{N}{c+k\beta\widetilde{T}} > 1, \tag{5.3}$$

then model (5.1) *is uniformly persistent. That is, there is a positive constant* κ *such that the solution of model* (5.1) *satisfies that* $\liminf_{t\to\infty}(T(t), T^*(t), V(t)) > (\kappa, \kappa, \kappa)$.

Proof. We will use the following four steps to complete the proof of this theorem.

(i) There exists a constant $\kappa_1 > 0$ such that

$$\limsup_{t\to\infty} T^*(t) \geq \kappa_1 \tag{5.4}$$

for any solution of model (5.1), where κ_1 is small enough and satisfies the following inequality

$$\frac{\beta m^{-m\theta}(1-e^{-\omega\tau})}{D_{in}+1-e^{-\omega\tau}}\widehat{T}(\kappa_1) - \frac{c+k\beta\widetilde{T}}{N} > 0. \tag{5.5}$$

Here we used the fact (5.3) and

$$\begin{aligned} \widehat{T}(\kappa_1) =& \frac{T_{max}}{2r}\Bigg\{ r - d - \frac{r\kappa_1}{T_{max}} - \frac{(e^{\omega\tau}-1)\beta N\kappa_1\eta}{(D_{in}+e^{\omega\tau}-1)} \\ &+ \sqrt{\left[r - d - \frac{r\kappa_1}{T_{max}} - \frac{(e^{\omega\tau}-1)\beta N\kappa_1\eta}{(D_{in}+e^{\omega\tau}-1)}\right]^2 + \frac{4\lambda r}{T_{max}}}\Bigg\} \end{aligned} \tag{5.6}$$

is the positive root of the algebraic equation $G(T, \kappa_1) = 0$ and $G(T, \kappa_1)$ is given by (5.7).

Supposing that (5.4) is invalid, that is $\limsup_{t\to\infty} T^*(t) < \kappa_1$. From the third equation of model (5.1), it follows that $\mathrm{d}V(t)/\mathrm{d}t \leq \delta N\kappa_1 - cV(t)$. From this and

Lemma 2.1, we have $\limsup_{t\to\infty} V(t) < \delta N\kappa_1/c$. Further, from the second equation of model (5.1), one have

$$\begin{aligned}\frac{\mathrm{d}T(t)}{\mathrm{d}t} &\geq \lambda - dT(t) + rT(t)\left(1 - \frac{T(t)+\kappa_1}{T_{\max}}\right) - \frac{e^{\omega\tau}-1}{D_{in}+e^{\omega\tau}-1}\beta T(t)N\kappa_1\eta \\ &:= G(T,\kappa_1), \end{aligned} \tag{5.7}$$

where $\eta = \max\{1, \delta/c\}$. By using the comparison theorem of ordinary differential equation, it follows that $\liminf_{t\to\infty} T(t) \geq \widehat{T}(\kappa_1)$. According to the definition of function $L(t)$ in (5.2) and the fact (5.5), it implies that

$$\begin{aligned}\frac{\mathrm{d}L(t)}{\mathrm{d}t} &= \left[\frac{\beta m^{-m\theta}}{1+D^*(t+\theta)}T(t) - \frac{c+k\beta T(t)}{N}\right]V(t) \\ &\geq \left[\frac{\beta m^{-m\theta}(1-e^{-\omega\tau})}{D_{in}+1-e^{-\omega\tau}}\widehat{T}(\kappa_1) - \frac{c+k\beta\widetilde{T}}{N}\right]V(t) > 0. \end{aligned} \tag{5.8}$$

This means that $L(t)$ is increasing. By Theorem 3.1, we have $L(t)$ is positive bounded. Then, there is a positive constant $\widetilde{L}$ such that $L(t) \to \widetilde{L}$ as $t \to \infty$. This leads to $\lim_{t\to\infty} \mathrm{d}L(t)/\mathrm{d}t = 0$. That is, $V(t) \to 0$ as $t \to \infty$. And then $\lim_{t\to\infty} T^*(t) = 0$ by Lemma 2.1. Hence, this follows that from the definition of $L(t)$ that $\lim_{t\to\infty} L(t) = 0$. This generates a contradiction with $L(t) > L(0) > 0$. Thus, $\limsup_{t\to\infty} T^*(t) \geq \kappa_1$ is valid.

(ii) There exists a positive constant ρ_1 such that $L(t) \geq \rho_1$ for all $t \geq 0$.

From (5.2) and (5.4), it can be easily shown that, for any $t_0 > 0$, $L(t) < \kappa_1$ is impossible for all $t \geq t_0$. Therefore, we only consider the two remaining possibilities:

(a) $L(t) > \kappa_1$ for all t large enough.

(b) $L(t)$ is oscillate about κ_1 for all t large enough.

If the case (a) is hold, this is exactly what our aim. Therefore, we only need to consider the case (b). Let t_1 and t_2 be large sufficiently times satisfying $L(t_1) = L(t_2) = \kappa_1$, $L(t) < \kappa_1$, $t \in (t_1, t_2)$. From (5.2), one have $L(t) \geq T^*(t)$ and $L(t) \geq V(t)/N$. Thus, $V(t) \leq \kappa_1 N$ and $T^*(t) \leq \kappa_1$ for all $t \in (t_1, t_2)$. For any $t_0 \geq 0$, we consider the following auxiliary

$$\frac{\mathrm{d}T(t)}{\mathrm{d}t} \geq \lambda - dT(t) + rT(t)\left(1 - \frac{T(t)+\kappa_1}{T_{max}}\right) - \frac{\beta\kappa_1\eta}{1+D^*(t)}T(t)N.$$

From the comparison theorem, there is a constant $p^* > 0$ and which is independent of t_0, such that $T(t) \geq \widehat{T}(\kappa_1)$ for all $t \geq t_0 + p^*$.

If $t_2 - t_1 \leq \theta + 2p^*$, from (5.2), we get

$$\frac{\mathrm{d}L(t)}{\mathrm{d}t} \geq -\frac{c+k\beta\widetilde{T}}{N}V(t) \geq -\frac{c+k\beta\widetilde{T}}{N}L(t).$$

Integrating the above inequality from t_1 to t_2, it can be easily shown that

$$L(t) \geq L(t_1)\exp\left\{\int_{t_1}^{t_2} -\frac{c+k\beta\widetilde{T}}{N}\,\mathrm{d}t\right\} \geq \kappa_1\exp\left\{-\frac{c+k\beta\widetilde{T}}{N}(\theta+2p^*)\right\} := \rho_1.$$

If $t_2 - t_2 > \theta + 2p^*$, from (5.2), From these, it follows that

$$\frac{\mathrm{d}L(t)}{\mathrm{d}t} \geq \left[\frac{\beta m^{-m\theta}(1-e^{-\omega\tau})}{D_{in}+1-e^{-\omega\tau}}\widehat{T}(\kappa_1) - \frac{c+k\beta\widetilde{T}}{N}\right]V(t) > 0$$

due to the face (5.5). By the monotonicity of $L(t)$ in $[t_1+\theta+2p^*, t_2]$, we have

$$L(t) \geq L(t_1+\theta+2p^*) \geq \rho_1 \qquad \text{for all } t \in [t_1+\theta+2p^*, t_2].$$

Therefore, there exists a positive constant ρ_1 such that $L(t) \geq \rho_1$ for all t large enough.

(iii) There is a constant $\kappa_2 > 0$ such that $\liminf_{t\to\infty} V(t) \geq \kappa_2$, where

$$\kappa_2 = \frac{\delta N \rho_1}{2(\delta N \mu_1 + c + k\beta\widetilde{T})},\ \mu_1 = e^{(c+k\beta\widetilde{T})\theta},\ \mu_2 = \frac{1}{N} + \frac{(e^{\omega\tau}-1)\beta e^{-m\theta}}{D_{in}+e^{\omega\tau}-1}\mu_1\widetilde{T}.$$

If the claim is invalid, that is, $\liminf_{t\to\infty} V(t) < \kappa_2$. By the definition of inferior limit of $V(t)$, there is a time-sequence $\{t_n\}$ such that $V(t_n) \leq \kappa_2$, $t_n \to \infty$ as $n \to \infty$.

From the third equation of model (5.1), it can be easily shown that

$$V(t_n - s) \leq V(t_n)e^{(c+k\beta\widetilde{T})\theta} = \mu_1 V(t_n) \qquad \text{for all } 0 \leq s \leq \theta.$$

Therefore, from the definition of (5.2) and claim (**ii**), we have

$$\rho_1 \leq L(t_n) \leq T^*(t_n) + \left(\frac{1}{N} + \frac{(e^{\omega\tau}-1)\beta e^{-m\theta}}{D_{in}+e^{\omega\tau}-1}\mu_1\widetilde{T}\right) V(t_n) = T^*(t_n) + \mu_2 V(t_n).$$

That is, $T^*(t_n) \geq \rho_1 - \mu_2 V(t_n) \geq \rho_1 - \mu_2 V(t_n)$. From the third equation of model (5.1), we can obtain that

$$\begin{aligned}\frac{\mathrm{d}V(t_n)}{\mathrm{d}t} &\geq \delta N(\rho_1 - \mu_2 V(t_n)) - (c + k\beta\widetilde{T})V(t_n) \\ &= \delta N\rho_1 - (\delta N\mu_2 + c + k\beta\widetilde{T})V(t_n) \\ &\geq \delta N\rho_1 - (\delta N\mu_2 + c + k\beta\widetilde{T})\kappa_2 > 0. \end{aligned} \tag{5.9}$$

We only consider, now, the following three cases.

(C_1) $V(t_n)$ is oscillate about κ_2.

Obviously, there exists a subsequence $\{t_{n_j}\}$ such that t_{n_j} as $j \to \infty$, and $\mathrm{d}V(t_{n_j})/\mathrm{d}t = 0$. This is a contradiction with $\mathrm{d}V(t_n)/\mathrm{d}t > 0$.

(C_2) $V(t_n) < \kappa_2$ and $V(t_n)$ is uniformly increasing.

For this case, there exists $\varpi_n > 0$ such that $V(\varpi_n) < V^* \leq \kappa_2$ as $n \to \infty$, where V^* is a constant. Then, $\mathrm{d}V(\varpi_n)\mathrm{d}t \to 0$ as $n \to \infty$. We have, however, $\lim_{n\to\infty} \mathrm{d}V(t_n)/\mathrm{d}t > \delta N\rho_1/2$ by the fact (5.9). This leads to a contradiction.

(C_3) $V(t_n) < \kappa_2$ and $V(t_n)$ is not uniformly increasing.

For any $t_* > 0$ there is a $t^* > t_*$ such that $\mathrm{d}V(t^*)/\mathrm{d}t < 0$ and $V(t^*) < \kappa_2$. This leads to a contradiction again.

From the above discussion, we finally obtain that $\liminf_{t\to\infty} V(t) \geq \kappa_2$.

(iv) $\liminf_{t\to\infty} T^*(t) \geq \kappa_3$, where κ_3 is given by (5.10).

From the second equation of model (5.1), we have

$$\frac{\mathrm{d}T^*(t)}{\mathrm{d}t} = \frac{\beta e^{-m\theta}}{1+D^*(t)}T(t-\theta)V(t-\theta) - \delta T^*(t) \geq \frac{(1-e^{-m\theta})\beta e^{-m\theta}}{D_{in}+1-e^{-\omega\tau}}\kappa_2 - \delta T^*(t)$$

for all t large enough. Therefore, this is obvious that

$$\liminf_{t\to\infty} T^*(t) \geq \frac{(1-e^{-m\theta})\beta e^{-m\theta}}{D_{in}+1-e^{-\omega\tau}}\frac{\kappa_2}{\delta} := \kappa_3 \tag{5.10}$$

by using Lemma 2.1.

According to the above results, one have $\liminf_{t\to\infty}(T(t), T^*(t), V(t)) > (\kappa, \kappa, \kappa)$, where $\kappa = \min\{\kappa_1, \kappa_2, \kappa_3\}$. The proof is complete. □

As a consequence of Theorem 5.1, from the Theorem 1 in Ref. [36], on the existence of positive solutions for the general population dynamical systems, we have the following result.

Corollary 5.1. *If $\mathcal{R}^* > 1$, then models* (2.3) *and* (2.4) *without CTLs immune response admits at least a positive τ-periodic solution.*

6. Numerical simulation and discussion

In this section, to illustrate the theoretical results and feasibility of impulsive pharmaceutical therapy, we perform some numerical simulations for different control parameters using the Runge-Kutta method in the software MATLAB. The values of parameters for models (2.3) and (2.4) are listed in Table 1.

Firstly, we discuss how the delay and pharmaceutical therapy affect the prevention and treatment of HIV infection. According to Table 1, we choose model parameters $\lambda = 10$, $d = 0.02$, $r = 0.1$, $T_{max} = 180$, $\delta = 0.25$, $N = 1000$, $\beta = 2.5 \times 10^{-5}$, $c = 0.24$, $k = 1$, $\omega = 3.6$, $m = 0.36$, $q = 0.02$, $p = 0.12$, $d_E = 0.2$, $\theta = 10$, $\tau = 1$ and the drug dosage $D(0) = D_{in} = 10(mg)$. The plots in Figures 1(a)-1(d) show that the concentrations of the infected CD4$^+$ T-cells and free infectious virus could be maintained at a lower stage level under the action of delay and pharmaceutical therapy. This implies that the delay and pharmaceutical therapy plays crucial roles in treatment and control of HIV infection.

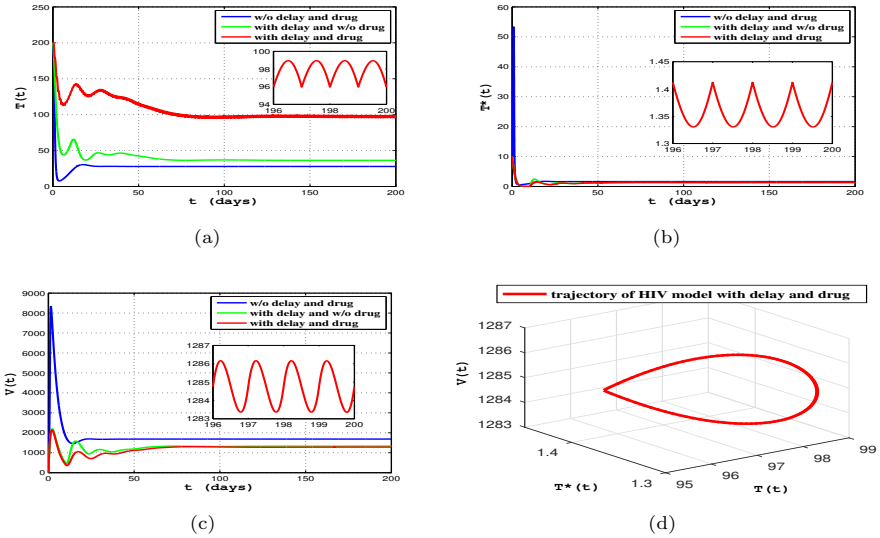


Figure 1. The effect of delay and drug for HIV models (2.3) and (2.4) with $\lambda = 10$, $d = 0.02$, $r = 0.1$, T_{max}, $\delta = 0.25$, $N = 1000$, $\beta = 2.5 \times 10^{-5}$, $c = 0.24$, $k = 1$, $\omega = 3.6$, $m = 0.36$, $p = 0.02$, $p = 0.12$, $d_E = 0.2$, $\theta = 10$, $\tau = 1$ and the drug dosage $D(0) = D_{in} = 10(mg)$, where blue curves, green curves and red curves represent (2.3) and (2.4) without delay and drug therapy, with delay and without drug therapy, and with delay and drug therapy, respectively.

Nextly, we choose $\lambda = 1$, $T_{max} = 80$, $\beta = 2.4 \times 10^{-5}$, $\theta = 2$, $D_0 = 16$, $\tau = 0.5$ and other parameters are fixed as above. Numerical calculation yields $\mathcal{R}_0 \approx 0.9305 < 1$ and $\mathcal{R}_* \approx 0.7307 < 1$, that is models (2.3) and (2.4) have a globally asymptotically stable virus-free periodic solution $(74.7083, 0, 0, D^*(t))$ by Theorems 4.1 and 4.2, where $D^*(t) = 16e^{-3.6(t-0.5)}/(1 - e^{-1.8})$, $0.5i < t \leq 0.5(i + 1)(i = 1, 2, \cdots)$. The concentrations of uninfected CD4$^+$ T-cells $T(t)$, infected CD4$^+$ T-cells $T^*(t)$ and virus $V(t)$ are plotted against time in Figures 2(a)-2(c) with the red lines. Additionally, numerical simulations also show that (2.3) and (2.4) without drug therapy or without delay and drug therapy have stable endemic equilibria. This is illustrated in Figure 2(a)-2(c) with green line and blue line, respectively. This is similar to the theoretical results in Refs. [3, 7, 9, 11, 25, 32]. It is confirmed that the drug therapy is effective for eradicating the virus, of course drugs are taken with sufficient frequency.

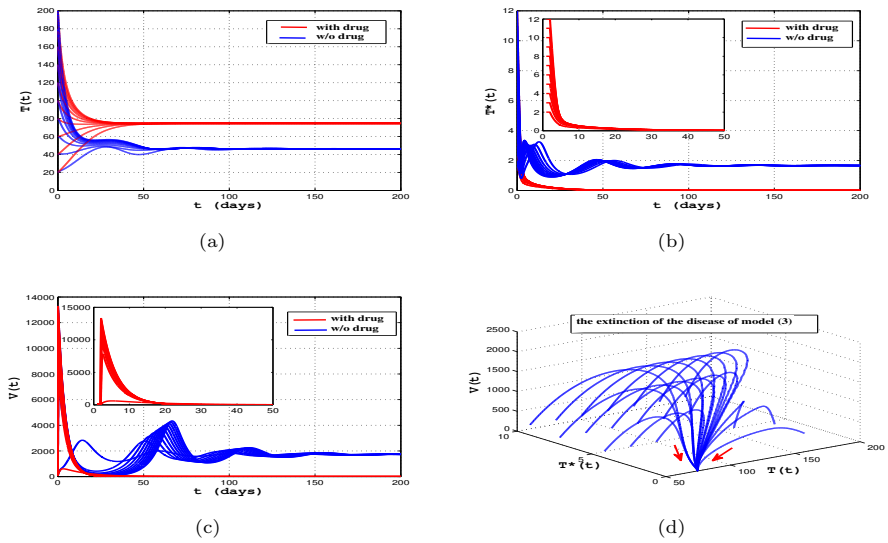
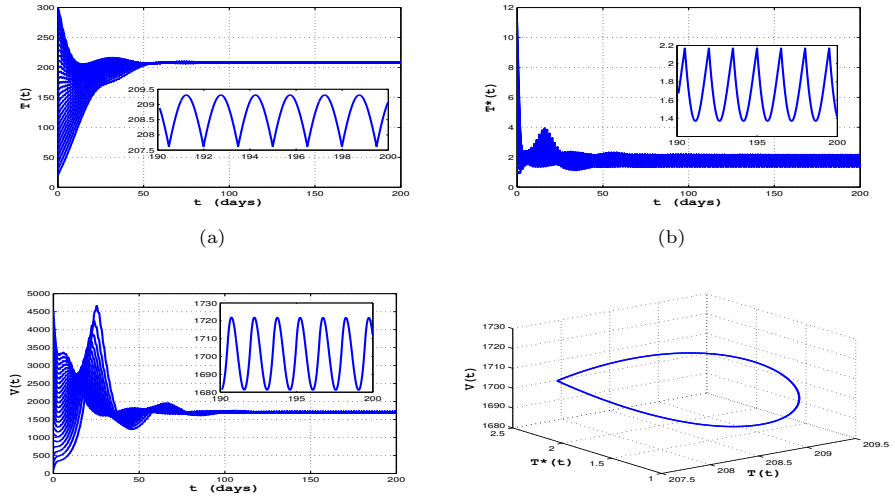


Figure 2. The existence and stability of the virus-free periodic solution of HIV models (2.3) and (2.4) with $\lambda = 1$, $d = 0.02$, T_{max}, $\delta = 0.24$, $N = 1000$, $\beta = 2.4 \times 10^{-5}$, $c = 0.24$, $\omega = 3.6$, $k = 1$, $m = 0.36$ and $\theta = 2$, $D(0) = D_{in} = 16(mg)$ and $\tau = 0.5$, where the blue curves and red curves represent models (2.3) and (2.4) with drug therapy and without drug therapy, respectively.

However, we choose parameters $\lambda = 5$, $\tau = 1.5$, $T_{max} = 250$, $\beta = 3.6 \times 10^{-5}$ and other parameters are fixed as above. Numerical calculation follows that $\mathcal{R}_* \approx 3.1573 > 1$ and $\mathcal{R}^* \approx 1.0305 > 1$, Theorem 5.1 and Corollary 5.1 indicate that model 5.1, that is, models (2.3) and (2.4) without CTLs immune response, is uniformly persistent and has a positive periodic solution. In fact, numerical simulations in Figures 3(a)-3(d) show that the disease of models (2.3) and (2.4) is uniformly persistent for $\mathcal{R}^* > 1$, and models (2.3) and (2.4) admit a positive periodic solution which is globally asymptotically stable. Therefore, we propose the following interesting open question: *if* $\mathcal{R}^* > 1$*, then the disease of models* (2.3) *and* (2.4) *is uniformly persistent.*

Finally, we consider the dynamical behaviors of models (2.3) and (2.4) when $\mathcal{R}_* > 1$ and $\mathcal{R}^* < 1$. We choose, firstly, $\lambda = 4$, T_{max}, and other parameters are fixed as Figure 3. This can be easily compute that $\mathcal{R}_* \approx 2.8394 > 1$ and



(a) (b) (c) (d)

Figure 3. The existence and stability of the endemic periodic solution of HIV models (2.3) and (2.4) with $\lambda = 5$, $d = 0.02$, $T_{max} = 250$, $\delta = 0.24$, $N = 1000$, $\beta = 3.6 \times 10^{-5}$, $c = 0.24$, $k = 1$, $\omega = 3.6$, $m = 0.36$ and $\theta = 2$, $\tau = 1.5$ and $D(0) = D_{in} = 16(mg)$.

$\mathcal{R}^* \approx 0.8304 < 1$. Use these parameter values, the movement paths of $T(t)$, $T^*(t)$ and $V(t)$ are presented in Figures 4(a)-4(c) with blue lines, which show that the virus is permanence, and models (2.3) and (2.4) have a stable positive periodic solution with these parameters. We change, however, $\tau = 0.4$, it follows that $\mathcal{R}_* \approx 1.2037 > 1$ and $\mathcal{R}^* \approx 0.6454 < 1$. The plots in Figures 4(a)-4(c) with red lines show that the virus is die out. These show that the dynamical behaviors of (2.3) and (2.4) are complex since the effects of drug therapy and delay. At the same time, the plots in Figure 4(d) show that the relation of dynamical behaviors of (2.3), (2.4) and the period of drug therapy. Numerical simulations that the disease dies out if the period of drug therapy is frequently, however, the disease is permanence if the period is long. This implies that the period of drug therapy is crucial to the treatment of HIV. Additionally, numerical simulations show that the length of intercellular delay θ is also play an important role in treatment and control of HIV infection. That is, longer the intercellular delay will be more helpful more conducive to eliminate the disease.

7. Conclusion

We propose a mathematical model to describe the process of HIV virus proliferation and replication in vivo. Here, we not only introduce the time delay of virus invasion and CTL immune response, but also consider the drug intake at a fixed time. The main purpose is to examine how the delay and fixed time drug therapy affect the prevention and control of HIV infection. This is the highlight of our article.

By utilizing the comparison theorem, differential inequality theories and analytic method, analytic method, we investigate threshold dynamics of the control model. Particularly, we show that $\mathcal{R}_0 < 1$ implies that the disease-free periodic solution

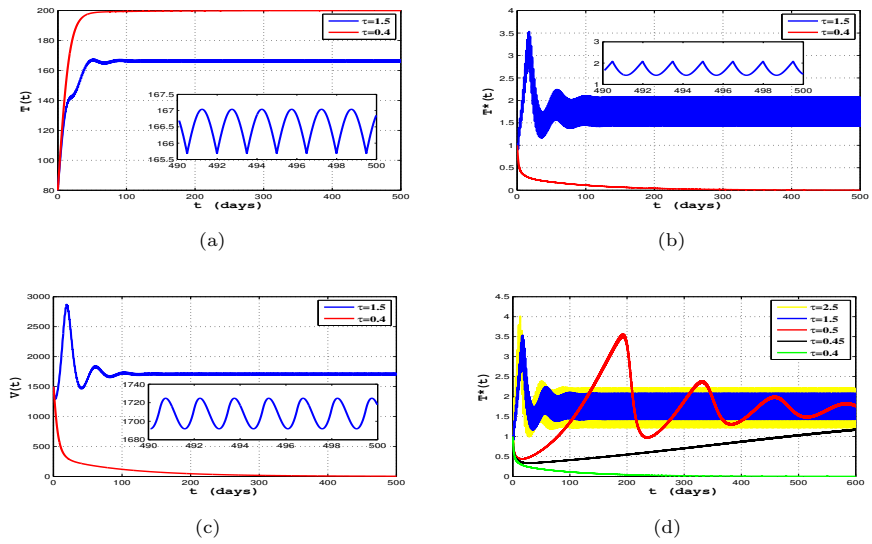


Figure 4. The permanence and extinction of HIV models (2.3) and (2.4) with different drug therapy periodic, $\lambda = 4$, $d = 0.02$, $T_{max} = 200$, $\delta = 0.24$, $N = 1000$, $\beta = 2.4 \times 10^{-5}$, $c = 0.24$, $\omega = 2.3$, $m = 0.36$ and $\theta = 2$ and $D(0) = D_{in} = 16(mg)$, where, (a)-(c): the blue lines are $\tau = 1.5$ and the red lines are $\tau = 0.4$; (d) $\tau = 2.5$, 1.5, 0.5, 0.45 and 0.4, respectively.

is locally asymptotically stable, $\mathcal{R}_* < 1$ implies that the disease-free periodic solution is globally asymptotically stable, and HIV infection without CTLs immune response is uniform persistence for $\mathcal{R}^* > 1$. Further, we also obtain the existence of positive periodic solution by uniform persistence. These theoretical results demonstrate that the delay and drug therapy HIV model exhibit much more complicated dynamical behaviors than non-delay and non-drug HIV model since a time delay and drug therapy could cause a stable equilibrium to become unstable and cause the population to fluctuate. At the same time, theoretical results and numerical simulations also show that eradication could be achieved, if drugs are taken with sufficient frequency. Or the density of virus can be largely controlled at a low level by adjusting the periodic and dosed of drug therapy. These results are completely new and are not discussed in detail in the existing literatures.

However, we have only discussed, in this article, three cases: (i) $\mathcal{R}_* < 1$; (ii) $\mathcal{R}_0 < 1$ and (iii) $\mathcal{R}^* > 1$. But for closed intervals $[\mathcal{R}_*, \mathcal{R}_0]$ and $[\mathcal{R}_0, \mathcal{R}^*]$, the dynamical behaviors of models (2.3) and (2.4) have not been studied, and the threshold values for the reproducing number between the extinction of disease and the uniform persistence of the disease for whole model has not been obtained. In addition, this article only discusses the effect of reverse transcriptase inhibitors, while ignoring the effect of protease inhibitors. In fact, the HIV model with the combination antiretroviral therapy is more reasonable. Due to the intervention of drugs, the proliferation and replication of HIV virus in the organism are inevitably inhibited. These inhibitory effects may affect the time delay of virus invasion, and may also affect the immune activation time. These issues would be left as our future consideration.

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