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GLOBAL ANALYSIS OF A COCIRCULATING TARGET CELLS HIV MODEL WITH DIFFERENTIAL DRUG EFFICACY AND NONLINEAR INCIDENCE RATE

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This paper is dedicated to the memory of Professor Miklós Farkas.

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Abstract. The main purpose of this work is to investigate the qualitative behavior of an HIV dynamics model with two types of cocirculating target cells. The model takes into account both short-lived and long lived chronically infected cells. In the two types of target cells, the drug efficacy is assumed to be different. The incidence rate is represented by Crowley-Martin functional response. First we have derived the basic reproduction number R_0, then constructed Lyapunov functions to establish the global asymptotic stability of the disease-free and endemic equilibria of the model. We have been proven that, the disease-free equilibrium is globally asymptotically stable (GAS) when $R_0 \leq 1$, and the endemic equilibrium is GAS when $R_0 > 1$. Numerical simulations have been carried out to support our theoretical results.

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1. INTRODUCTION

Although the mathematical modeling of human immunodeficiency virus (HIV) dynamics alone cannot deals with issues associated with HIV infection, it can be a helpful tool for a good understanding the viral dynamics in vivo. Mathematical models can improved strategies of diagnosis and treatment. Today, many anti-HIV drugs are available for patients with HIV, which led to a rapid decrease in viruses and an increase in the major target cells of the virus, $CD4^+$ T cells. There are two main categories of anti-HIV, the reverse-transcriptase inhibitors RTIs drugs which prevent HIV from infecting the target cells, and the protease inhibitors PIs drugs which prevent the infected cells from producing new infectious viruses [1]. In the literature, several mathematical models describing the HIV dynamics in vivo have been proposed (see, e.g. [3], [6–10], [12, 13]). However, these models did not take into account the difference between short-lived infected cells and long lived chronically infected cells. In HIV infection, the short-lived infected cells produce much larger amounts of viruses than long lived chronically infected cells and die at a much faster rate [2]. The basic HIV infection model which takes into account long lived chronically infected cells under the effect of antiviral drug therapy has been proposed in [2] as:

$$\dot{x} = \lambda - dx - (1-\varepsilon)\bar{\beta}xv, \tag{1.1}$$

$$\dot{y} = (1-q)(1-\varepsilon)\bar{\beta}xv - \delta y, \tag{1.2}$$

$$\dot{z} = q(1-\varepsilon)\bar{\beta}xv - az, \tag{1.3}$$

$$\dot{v} = N\delta y + Maz - uv, \tag{1.4}$$

where x, y, z and v represent, respectively, the concentrations of the uninfected CD4$^+$ T cells, short-lived infected cells, long lived chronically infected cells, and free viruses. Parameters λ and d are the birth rate and death rate constants of the uninfected CD4$^+$ T cells. Parameter $\bar{\beta}$ is the infection rate constant. The short-lived infected CD4$^+$ T cells, long lived chronically infected CD4$^+$ T cells and free viruses are die with rate constants δ, a and u, respectively. The fractions $(1-q)$ and q with $0 < q < 1$ are the probabilities during the infection on which an uninfected cell will become either short-lived infected or long lived chronically infected. Parameters N and M are the average number of virus particles generated in the lifetime of the short-lived infected and long lived chronically infected cells, respectively. The model incorporates RTI drug therapy with drug efficacy denoted by ε and $0 \le \varepsilon \le 1$. All the parameters mentioned in the model are positive.

In a very recent work [8], model (1.1)-(1.4) has been modified to consider the antibody immune response. In model (1.1)-(1.4), it was assumed that, the HIV has one class of target cells, CD4$^+$ T cells. Based on the observation of Perelson et al. [9] that, the HIV attack two types of cells CD4$^+$ T cells and macrophages. Recently, many efforts have been devoted to propose and analyze various mathematical models of HIV dynamics with two classes of target cells [2, 5, 6, 8, 10] In [4], the virus dynamics models have been studied by assuming that the virus has multiple classes of uninfected target cells. However, in [5, 6, 8, 10] and [4], only short-lived infected cells has been considered. In [2], the model (1.1)-(1.4) was extended to take into consideration two cocirculating target cells, CD4$^+$ T cells and macrophages as:

$$\dot{x}_1 = \lambda_1 - d_1x_1 - (1-\varepsilon)\bar{\beta}_1x_1v, \tag{1.5}$$

$$\dot{x}_2 = \lambda_2 - d_2x_2 - (1-f\varepsilon)\bar{\beta}_2x_2v, \tag{1.6}$$

$$\dot{y}_1 = (1-q)(1-\varepsilon)\bar{\beta}_1x_1v - \delta y_1, \tag{1.7}$$

$$\dot{y}_2 = (1-q)(1-f\varepsilon)\bar{\beta}_2x_2v - \delta y_2, \tag{1.8}$$

$$\dot{z}_1 = q(1-\varepsilon)\bar{\beta}_1x_1v - az_1, \tag{1.9}$$

$$\dot{z}_2 = q(1-f\varepsilon)\bar{\beta}_2x_2v - az_2, \tag{1.10}$$

$$\dot{v} = N\delta(y_1 + y_2) + Ma(z_1 + z_2) - uv, \tag{1.11}$$

where x_i, y_i, z_i, and v denote the concentrations of uninfected target cells, short-lived infected cells, long lived chronically infected cells, and free viruses, respectively, and $i = 1,2$ correspond to the CD4$^+$ T cells and macrophages, respectively. In the CD4$^+$ T cells, the drug efficacy is ε while in the macrophages the drug efficacy is εf reduced by a factor f where $0 < f < 1$. The definitions of all parameters and variables are identical to those given in Eqs. (1.1)-(1.4).

We have observed that, the qualitative behavior of model (1.5)-(1.11) are not studied in the literature. Moreover, in model (1.5)-(1.11), the incidence rate between the uninfected target cells and viruses is given by bilinear, i.e., the infection rate per virus and per uninfected cell is constant. However, this bilinear incidence rate may not completely describe the infection process. Therefore, several forms of the incidence rate have been proposed, such as saturated incidence rate, $\frac{\beta x v}{1+\alpha v}$ where $\alpha > 0$ [5], Beddington-DeAngelis functional response, $\frac{\beta x v}{1+\mu x+\alpha v}$, $\alpha, \mu > 0$ [5], [7], [11], Crowley-Martin functional response, $\frac{\beta x v}{(1+\mu x)(1+\alpha v)}$, $\alpha, \mu > 0$ [12], [13].

Our primary goal of the present paper is to propose an HIV dynamics model with two types of cocirculating target cells, CD4$^+$ T cells and macrophages and investigate its qualitative behavior. In the two types of target cells, the drug efficacy is assumed to be different. Both short-lived and long lived chronically infected cells are considered in the mathematical model. The incidence rate is represented by by Crowley-Martin functional response. The global stability of all equilibria of the model is established using direct Lyapunov method. The basic reproduction number R_0 of the model is derived. We have established that, the disease-free equilibrium is globally asymptotically stable (GAS) when $R_0 \le 1$, and the endemic equilibrium is GAS when $R_0 > 1$.

2. The Model

In this section, we introduce a mathematical model of HIV dynamics which describes two cocirculation populations of target cells, CD4$^+$ T cells and macrophages taking into account both of short-lived and long lived chronically infected cells. The model is more general than model (1.5)-(1.11) by assuming that the incidence rate of infection is given by Crowley-Martin functional response and the parameter δ, a, q, N and M for the CD4$^+$ T cells and macrophages are not identically.

$$\dot{x}_i = \lambda_i - d_i x_i - \frac{\beta_i x_i v}{(1+\mu_i x_i)(1+\alpha_i v)}, \qquad i = 1,2, \tag{2.1}$$

$$\dot{y}_i = (1-q_i)\frac{\beta_i x_i v}{(1+\mu_i x_i)(1+\alpha_i v)} - \delta_i y_i, \quad i = 1,2, \tag{2.2}$$

$$\dot{z}_i = q_i \frac{\beta_i x_i v}{(1+\mu_i x_i)(1+\alpha_i v)} - a_i z_i, \qquad i = 1,2, \tag{2.3}$$

$$\dot{v} = \sum_{i=1}^{2} (N_i \delta_i y_i + M_i a_i z_i) - uv, \tag{2.4}$$

where μ_i, α_i, $i = 1,2$ are positive constants and all the parameters and variables of the model have the same meanings as given in (1.5)-(1.11) and $\beta_1 = (1-\varepsilon)\bar{\beta}_1$, $\beta_2 = (1 - f\varepsilon)\bar{\beta}_2$.

3. The analysis of the Model

One can easily show the positive invariance of the non-negative orthant $\mathbb{R}^7_{\geq 0}$ for model (2.1)-(2.4) (see e.g. [6] and [10]).

Proposition 1. *There exist positive numbers L_i, $i = 1,2,3$ such that the compact set $\Omega = \Big\{(x_1, y_1, z_1, x_2, , y_2, , z_2, v) \in \mathbb{R}^7_{\geq 0} : 0 \leq x_1, y_1, z_1 \leq L_1,$ $0 \leq x_2, y_2, z_2 \leq L_2,\ 0 \leq v \leq L_3\}$ is positively invariant.*

Proof. To show the boundedness of the solutions of system (2.1)-(2.4), let $G_i(t) = x_i(t) + y_i(t) + z_i(t)$, $i = 1,2$ then

$$\begin{aligned}
\dot{G}_i(t) &= \lambda_i - d_i x_i(t) - \delta_i y_i(t) - a_i z_i(t)\\
&\leq \lambda_i - \sigma_i (x_i(t) + y_i(t) + z_i(t)) = \lambda_i - \sigma_i G_i(t),
\end{aligned}$$

where $\sigma_i = \min\{d_i, \delta_i, a_i\}$. Hence, $G_i(t) \leq L_i$, if $G_i(0) \leq L_i$ where $L_i = \dfrac{\lambda_i}{\sigma_i}$. Since $x_i(t)$, $y_i(t)$ and $z_i(t)$ are all non-negative, then $0 \leq x_i(t), y_i(t), z_i(t) \leq L_i$, for all $t \geq 0$, if $0 \leq x_i(0) + y_i(0) + z_i(0) \leq L_i$. Moreover,

$$\dot{v} = \sum_{i=1}^{2} (N_i \delta_i y_i + M_i a_i z_i) - uv \leq \sum_{i=1}^{2} (N_i \delta_i + M_i a_i) L_i - uv.$$

Then $v(t) \leq L_3$, if $v(0) \leq L_3$, for all $t \geq 0$, where $L_3 = \sum_{i=1}^{2} \frac{(N_i \delta_i + M_i a_i) L_i}{u}$. □

Lemma 1. *For system (2.1)-(2.4), there exist a threshold parameter $R_0 > 0$ such that*
(i) when $R_0 \leq 1$, there exists only one disease-free equilibrium
$E_0 = (x_1^0, 0, 0, x_2^0, 0, 0, 0)$,
(ii) when $R_0 > 1$, there exist E_0 and an endemic equilibrium
$E_1 = (\tilde{x}_1, \tilde{y}_1, \tilde{z}_1, \tilde{x}_2, \tilde{y}_2, \tilde{z}_2, \tilde{v})$.

Proof. The equilibria of model (2.1)-(2.4) satisfy the following equations:

$$\lambda_i - d_i x_i - \frac{\beta_i x_i v}{(1 + \mu_i x_i)(1 + \alpha_i v)} = 0, \tag{3.1}$$

$$(1-q_i)\frac{\beta_i x_i v}{(1+\mu_i x_i)(1+\alpha_i v)} - \delta_i y_i = 0, \tag{3.2}$$

$$q_i \frac{\beta_i x_i v}{(1+\mu_i x_i)(1+\alpha_i v)} - a_i z_i = 0, \tag{3.3}$$

$$\sum_{i=1}^{2}(N_i \delta_i y_i + M_i a_i z_i) - uv = 0. \tag{3.4}$$

From Eqs. (3.2) and (3.3) we have

$$y_i = \frac{(1-q_i)\beta_i x_i}{\delta_i(1+\mu_i x_i)(1+\alpha_i v)}v, \quad z_i = \frac{q_i \beta_i x_i}{a_i(1+\mu_i x_i)(1+\alpha_i v)}v. \tag{3.5}$$

Inserting y_i and z_i into Eq. (3.4) we obtain

$$\left(\sum_{i=1}^{2}\frac{((1-q_i)N_i + q_i M_i)\beta_i x_i}{u(1+\mu_i x_i)(1+\alpha_i v)} - 1\right)uv = 0. \tag{3.6}$$

Equation (3.6) has two possible solutions

$$v = 0 \text{ or } \sum_{i=1}^{2}\frac{((1-q_i)N_i + q_i M_i)\beta_i x_i}{u(1+\mu_i x_i)(1+\alpha_i v)} - 1 \ = 0.$$

If $v = 0$ then substituting it in Eqs. (3.1) and (3.5), leads to a disease-free equilibrium $E_0 = (x_1^0, 0, 0, x_2^0, 0, 0, 0)$, where $x_i^0 = \frac{\lambda_i}{d_i}, i = 1,2$.
If $v \neq 0$, then solving Eq. (3.1) w.r.t. x_i we get:

$$x_i^{\pm} = \frac{[(\mu_i x_i^0 - 1)(1+\alpha_i v) - \frac{\beta_i v}{d_i}] \pm \sqrt{[(\mu_i x_i^0 - 1)(1+\alpha_i v) - \frac{\beta_i v}{d_i}]^2 + 4\mu_i x_i^0((1+\alpha_i v)^2}}{2\mu_i(1+\alpha_i v)},$$

where $x_i^0 = \frac{\lambda_i}{d_i}$, $i = 1,2$. Clearly if $v > 0$ then $x_i^- < 0$ and $x_i^+ > 0$, then we choose $x_i = x_i^+$

$$x_i = \frac{[(\mu_i x_i^0 - 1)(1+\alpha_i v) - \frac{\beta_i v}{d_i}] + \sqrt{[(\mu_i x_i^0 - 1)(1+\alpha_i v) - \frac{\beta_i v}{d_i}]^2 + 4\mu_i x_i^0(1+\alpha_i v)^2}}{2\mu_i(1+\alpha_i v)}. \tag{3.7}$$

From Eqs. (3.1), (3.4) and (3.5) we get

$$\sum_{i=1}^{2}((1-q_i)N_i + q_i M_i)(\lambda_i - d_i x_i) - uv = 0. \tag{3.8}$$

Since x_i is a function of v, then we can define a function $H(v)$ as:

$$H(v) = \sum_{i=1}^{2}((1-q_i)N_i + q_i M_i)(\lambda_i - d_i x_i(v)) - uv = 0.$$

Now, we want to show that there exist $\tilde{v} > 0$ such that $H(\tilde{v}) = 0$. It is clear that, if $v = 0$ then $x_i = x_i^0$ and $H(0) = 0$, and when

$$v = \bar{v} = \sum_{i=1}^{2}\frac{((1-q_i)N_i + q_i M_i)\lambda_i}{u} > 0,$$

then we have $\bar{x}_i = x_i(\bar{v}) > 0$ and

$$H(\bar{v}) = -\sum_{i=1}^{2}((1-q_i)N_i + q_i M_i)d_i \bar{x}_i < 0.$$

Since $H(v)$ is continuous for all $v \geq 0$, we have that

$$H^{'}(0) =$$

$$\sum_{i=1}^{2}\frac{((1-q_i)N_i + q_i M_i)\beta_i x_i^0}{(1+\mu_i x_i^0)} - u = u\left(\sum_{i=1}^{2}\frac{((1-q_i)N_i + q_i M_i)\beta_i x_i^0}{u(1+\mu_i x_i^0)} - 1\right).$$

Therefore, if $\sum_{i=1}^{2}\frac{((1-q_i)N_i+q_i M_i)\beta_i x_i^0}{u(1+\mu_i x_i^0)} > 1$, then $H^{'}(0) > 0$, and there exists $\tilde{v} \in (0, \bar{v})$ such that $H(\tilde{v}) = 0$. From Eqs. (3.5) and (3), we have $\tilde{x}_i > 0$, $\tilde{y}_i > 0$ and $\tilde{z}_i > 0$, $i = 1, 2$. Therefore, an endemic equilibrium $E_1 = (\tilde{x}_1, \tilde{y}_1, \tilde{z}_1, \tilde{x}_2, \tilde{y}_2, \tilde{z}_2, \tilde{v})$ exists when $\sum_{i=1}^{2}\frac{((1-q_i)N_i+q_i M_i)\beta_i x_i^0}{u(1+\mu_i x_i^0)} > 1$. □

Now, we are ready to define the parameter R_0 as:

$$R_0 = \sum_{i=1}^{2}R_{0i} = \sum_{i=1}^{2}\frac{((1-q_i)N_i + q_i M_i)\beta_i x_i^0}{u(1+\mu_i x_i^0)},$$

where, R_{01} represents the basic infection reproduction number of the HIV dynamics with CD4$^+$ T cells (in the absence of macrophages) and R_{02} represents the basic infection reproduction number of the HIV dynamics with macrophages (in the absence of CD4$^+$ T cells), respectively. The parameter R_0 determines whether the infection can be established.

Here, we establish the global stability of the two equilibria of system (2.1)-(2.4) employing the direct Lyapunov method and LaSalle's invariance principle. The following function will be used throughout the paper $F:(0,\infty)\to[0,\infty)$ as:

$$F(s) = s - 1 - \ln s. \tag{3.9}$$

Theorem 1. *The disease-free equilibrium E_0 of system (2.1)-(2.4) is GAS when $R_0 \le 1$.*

Proof. Define Lyapunov functional W_0 as:

$$W_0 = \sum_{i=1}^{2}\gamma_i\left[x_i - x_i^0 - \int_{x_i^0}^{x_i}\frac{x_i^0(1+\mu_i s)}{s(1+\mu_i x_i^0)}ds + \frac{N_i}{(1-q_i)N_i+q_iM_i}y_i + \frac{M_i}{(1-q_i)N_i+q_iM_i}z_i\right] + v,$$

where $\gamma_i = (1-q_i)N_i + q_iM_i$, $i = 1,2$.

We calculate $\frac{dW_0}{dt}$ along the trajectories of system of (2.1)-(2.4) as:

$$\begin{aligned}
\frac{dW_0}{dt} = \sum_{i=1}^{2}\gamma_i\Bigg[&\left(1-\frac{x_i^0(1+\mu_i x_i)}{x_i(1+\mu_i x_i^0)}\right)\left(\lambda_i - d_i x_i - \frac{\beta_i x_i v}{(1+\mu_i x_i)(1+\alpha_i v)}\right)\\
&+\frac{N_i}{(1-q_i)N_i+q_iM_i}\left(\frac{(1-q_i)\beta_i x_i v}{(1+\mu_i x_i)(1+\alpha_i v)} - \delta_i y_i\right)\\
&+\frac{M_i}{(1-q_i)N_i+q_iM_i}\left(\frac{q_i\beta_i x_i v}{(1+\mu_i x_i)(1+\alpha_i v)} - a_i z_i\right)\Bigg] \qquad (3.10)\\
&+\sum_{i=1}^{2}(N_i\delta_i y_i + M_i a_i z_i) - uv. \qquad (3.11)
\end{aligned}$$

Collecting terms of Eq. (3.11) we get

$$\begin{aligned}
\frac{dW_0}{dt} &= \sum_{i=1}^{2}\gamma_i\left[d_i\left(1-\frac{x_i^0(1+\mu_i x_i)}{x_i(1+\mu_i x_i^0)}\right)(x_i^0 - x_i) + \frac{\beta_i x_i^0 v}{(1+\mu_i x_i^0)(1+\alpha_i v)}\right] - uv\\
&= -\sum_{i=1}^{2}\gamma_i\frac{d_i(x_i-x_i^0)^2}{x_i(1+\mu_i x_i^0)} - uv + uv\sum_{i=1}^{2}\frac{R_{0i}}{(1+\alpha_i v)}\\
&= -\sum_{i=1}^{2}\gamma_i\frac{d_i(x_i-x_i^0)^2}{x_i(1+\mu_i x_i^0)} - \sum_{i=1}^{2}\frac{R_{0i}\alpha_i u v^2}{(1+\alpha_i v)} + (R_0-1)uv. \qquad (3.12)
\end{aligned}$$

Then $\frac{dW_0}{dt} \le 0$ for all $x_1, x_2, v > 0$ when $R_0 \le 1$. We note that, the solutions of system (2.1)-(2.4) converge to Γ, the largest invariant subset of $\left\{\frac{dW_0}{dt} = 0\right\}$. From Eq. (3.12), we have $\frac{dW_0}{dt} = 0$ if and only if $x_i = x_i^0$, $i = 1,2$ and $v = 0$. The set Γ

is invariant and for any element belongs to Γ satisfies $v=0$ and then $\dot{v}=0$. We can see from Eq. (2.4) that

$$\sum_{i=1}^{2}(N_i\delta_i y_i + M_i a_i z_i) = 0.$$

Since y_i and z_i are non-negative for $i=1,2$, then $y_i = z_i = 0$, $i=1,2$. It follows that, $\frac{dW_0}{dt} = 0$ iff $x_i = x_i^0$, $y_i = 0$, $z_i = 0$, $i = 1{,}2$ and $v = 0$. From LaSalle's invariance principle, E_0 is GAS. □

Theorem 2. *The endemic equilibrium E_1 of system (2.1)-(2.4) is GAS when $R_0 >$ 1.*

Proof. We consider the Lyapunov functional W_1 as:

$$W_1 = \sum_{i=1}^{2}\gamma_i\left[x_i - \tilde{x}_i - \int_{\tilde{x}_i}^{x_i}\frac{\tilde{x}_i(1+\mu_i s)}{s(1+\mu_i\tilde{x}_i)}ds + \frac{N_i}{(1-q_i)N_i+q_iM_i}\tilde{y}_i F\left(\frac{y_i}{\tilde{y}_i}\right)\right.$$
$$\left.+\frac{M_i}{(1-q_i)N_i+q_iM_i}\tilde{z}_i F\left(\frac{z_i}{\tilde{z}_i}\right)\right] + \tilde{v}F\left(\frac{v}{\tilde{v}}\right).$$

Calculating $\frac{dW_1}{dt}$ along the solutions of system (2.1)-(2.4) we obtain

$$\frac{dW_1}{dt} = \sum_{i=1}^{2}\gamma_i\left[\left(1-\frac{\tilde{x}_i(1+\mu_i x_i)}{x_i(1+\mu_i\tilde{x}_i)}\right)\left(\lambda_i - d_i x_i - \frac{\beta_i x_i v}{(1+\mu_i x_i)(1+\alpha_i v)}\right)\right.$$
$$+\frac{N_i}{(1-q_i)N_i+q_iM_i}\left(1-\frac{\tilde{y}_i}{y_i}\right)\left(\frac{(1-q_i)\beta_i x_i v}{(1+\mu_i x_i)(1+\alpha_i v)} - \delta_i y_i\right)$$
$$\left.+\frac{M_i}{(1-q_i)N_i+q_iM_i}\left(1-\frac{\tilde{z}_i}{z_i}\right)\left(\frac{q_i\beta_i x_i v}{(1+\mu_i x_i)(1+\alpha_i v)} - a_i z_i\right)\right]$$
$$+\left(1-\frac{\tilde{v}}{v}\right)\left(\sum_{i=1}^{2}(N_i\delta_i y_i + M_i a_i z_i) - uv\right). \tag{3.13}$$

Collecting terms of Eq. (3.13) we get

$$\frac{dW_1}{dt} = \sum_{i=1}^{2}\gamma_i\left[\left(1-\frac{\tilde{x}_i(1+\mu_i x_i)}{x_i(1+\mu_i\tilde{x}_i)}\right)(\lambda_i - d_i x_i) + \frac{\beta_i\tilde{x}_i v}{(1+\mu_i\tilde{x}_i)(1+\alpha_i v)}\right.$$
$$-\frac{(1-q_i)N_i}{(1-q_i)N_i+q_iM_i}\frac{\tilde{y}_i}{y_i}\frac{\beta_i x_i v}{(1+\mu_i x_i)(1+\alpha_i v)} + \frac{N_i\delta_i}{(1-q_i)N_i+q_iM_i}\tilde{y}_i$$
$$\left.-\frac{q_iM_i}{(1-q_i)N_i+q_iM_i}\frac{\tilde{z}_i}{z_i}\frac{\beta_i x_i v}{(1+\mu_i x_i)(1+\alpha_i v)} + \frac{M_i a_i}{(1-q_i)N_i+q_iM_i}\tilde{z}_i\right]$$

$$-uv - \frac{\tilde{v}}{v}\sum_{i=1}^{2} N_i\delta_i y_i - \frac{\tilde{v}}{v}\sum_{i=1}^{2} M_i a_i z_i + u\tilde{v}.$$

Using the equilibrium conditions for E_1:

$$\lambda_i = d_i\tilde{x}_i + \frac{\beta_i\tilde{x}_i\tilde{v}}{(1+\mu_i\tilde{x}_i)(1+\alpha_i\tilde{v})}, \quad \frac{(1-q_i)\beta_i\tilde{x}_i\tilde{v}}{(1+\mu_i\tilde{x}_i)(1+\alpha_i\tilde{v})} = \delta_i\tilde{y}_i,$$

$$\frac{q_i\beta_i\tilde{x}_i\tilde{v}}{(1+\mu_i\tilde{x}_i)(1+\alpha_i\tilde{v})} = a_i\tilde{z}_i, \quad u\tilde{v} = \sum_{i=1}^{2}(N_i\delta_i\tilde{y}_i + M_i a_i\tilde{z}_i),$$

and the following equality

$$uv = u\tilde{v}\frac{v}{\tilde{v}} = \frac{v}{\tilde{v}}\left(\sum_{i=1}^{2}(N_i\delta_i\tilde{y}_i + M_i a_i\tilde{z}_i)\right) = \frac{v}{\tilde{v}}\sum_{i=1}^{2}\gamma_i\frac{\beta_i\tilde{x}_i\tilde{v}}{(1+\mu_i\tilde{x}_i)(1+\alpha_i\tilde{v})},$$

we obtain

$$\begin{aligned}
\frac{dW_1}{dt} = \sum_{i=1}^{2}\gamma_i\Bigg[& -\frac{d_i(x_i-\tilde{x}_i)^2}{x_i(1+\mu_i\tilde{x}_i)} + \frac{\beta_i\tilde{x}_i\tilde{v}}{(1+\mu_i\tilde{x}_i)(1+\alpha_i\tilde{v})}\left(1 - \frac{\tilde{x}_i(1+\mu_i x_i)}{x_i(1+\mu_i\tilde{x}_i)}\right) \\
& + \frac{\beta_i\tilde{x}_i\tilde{v}}{(1+\mu_i\tilde{x}_i)(1+\alpha_i\tilde{v})}\left(\frac{v(1+\alpha_i\tilde{v})}{\tilde{v}(1+\alpha_i v)} - \frac{v}{\tilde{v}}\right) \\
& + \frac{2N_i\delta_i}{(1-q_i)N_i+q_iM_i}\tilde{y}_i + \frac{2M_i a_i}{(1-q_i)N_i+q_iM_i}\tilde{z}_i \\
& - \frac{N_i\delta_i\tilde{y}_i}{(1-q_i)N_i+q_iM_i}\frac{x_i v\tilde{y}_i(1+\mu_i\tilde{x}_i)(1+\alpha_i\tilde{v})}{\tilde{x}_i\tilde{v}y_i(1+\mu_i x_i)(1+\alpha_i v)} \\
& - \frac{M_i a_i\tilde{z}_i}{(1-q_i)N_i+q_iM_i}\frac{x_i v\tilde{z}_i(1+\mu_i\tilde{x}_i)(1+\alpha_i\tilde{v})}{\tilde{x}_i\tilde{v}z_i(1+\mu_i x_i)(1+\alpha_i v)} \\
& - \frac{N_i\delta_i\tilde{y}_i}{(1-q_i)N_i+q_iM_i}\frac{y_i\tilde{v}}{\tilde{y}_i v} - \frac{M_i a_i\tilde{z}_i}{(1-q_i)N_i+q_iM_i}\frac{z_i\tilde{v}}{\tilde{z}_i v}\Bigg].
\end{aligned} \tag{3.14}$$

Eq. (3.14) can be rewritten as:

$$\begin{aligned}
\frac{dW_1}{dt} = \sum_{i=1}^{2}\gamma_i\Bigg[& -\frac{d_i(x_i-\tilde{x}_i)^2}{x_i(1+\mu_i\tilde{x}_i)} + \frac{\beta_i\tilde{x}_i\tilde{v}}{(1+\mu_i\tilde{x}_i)(1+\alpha_i\tilde{v})}\left(\frac{v(1+\alpha_i\tilde{v})}{\tilde{v}(1+\alpha_i v)} - \frac{v}{\tilde{v}}\right) \\
& + \frac{N_i\delta_i}{(1-q_i)N_i+q_iM_i}\tilde{y}_i\left(3 - \frac{\tilde{x}_i(1+\mu_i x_i)}{x_i(1+\mu_i\tilde{x}_i)} - \frac{x_i\tilde{y}_i v(1+\mu_i\tilde{x}_i)(1+\alpha_i\tilde{v})}{\tilde{x}_i y_i\tilde{v}(1+\mu_i x_i)(1+\alpha_i v)} - \frac{y_i\tilde{v}}{\tilde{y}_i v}\right) \\
& + \frac{M_i a_i}{(1-q_i)N_i+q_iM_i}\tilde{z}_i\left(3 - \frac{\tilde{x}_i(1+\mu_i x_i)}{x_i(1+\mu_i\tilde{x}_i)} - \frac{x_i\tilde{z}_i v(1+\mu_i\tilde{x}_i)(1+\alpha_i\tilde{v})}{\tilde{x}_i z_i\tilde{v}(1+\mu_i x_i)(1+\alpha_i v)} - \frac{z_i\tilde{v}}{\tilde{z}_i v}\right)\Bigg] \\
= \sum_{i=1}^{2}\gamma_i\Bigg[& -\frac{d_i(x_i-\tilde{x}_i)^2}{x_i(1+\mu_i\tilde{x}_i)}
\end{aligned}$$

$$
\begin{aligned}
&+\frac{\beta_i\tilde{x}_i\tilde{v}}{(1+\mu_i\tilde{x}_i)(1+\alpha_i\tilde{v})}\left(\frac{v(1+\alpha_i\tilde{v})}{\tilde{v}(1+\alpha_i v)}-\frac{v}{\tilde{v}}-1+\frac{1+\alpha_i v}{1+\alpha_i\tilde{v}}\right)\\
&+\frac{N_i\delta_i}{(1-q_i)N_i+q_iM_i}\tilde{y}_i\left(4-\frac{\tilde{x}_i(1+\mu_i x_i)}{x_i(1+\mu_i\tilde{x}_i)}-\frac{x_i\tilde{y}_i v(1+\mu_i\tilde{x}_i)(1+\alpha_i\tilde{v})}{\tilde{x}_i y_i\tilde{v}(1+\mu_i x_i)(1+\alpha_i v)}\right.\\
&\left.-\frac{y_i\tilde{v}}{\tilde{y}_i v}-\frac{1+\alpha_i v}{1+\alpha_i\tilde{v}}\right)+\frac{M_ia_i}{(1-q_i)N_i+q_iM_i}\tilde{z}_i\left(4-\frac{\tilde{x}_i(1+\mu_i x_i)}{x_i(1+\mu_i\tilde{x}_i)}\right.\\
&\left.\left.-\frac{x_i\tilde{z}_i v(1+\mu_i\tilde{x}_i)(1+\alpha_i\tilde{v})}{\tilde{x}_i z_i\tilde{v}(1+\mu_i x_i)(1+\alpha_i v)}-\frac{z_i\tilde{v}}{\tilde{z}_i v}-\frac{1+\alpha_i v}{1+\alpha_i\tilde{v}}\right)\right]\\
&=\sum_{i=1}^{2}\gamma_i\left[-\frac{d_i(x_i-\tilde{x}_i)^2}{x_i(1+\mu_i\tilde{x}_i)}-\frac{\beta_i\tilde{x}_i\alpha_i(v-\tilde{v})^2}{(1+\mu_i\tilde{x}_i)(1+\alpha_i\tilde{v})^2(1+\alpha_i v)}\right.\\
&+\frac{N_i\delta_i}{(1-q_i)N_i+q_iM_i}\tilde{y}_i\left(4-\frac{\tilde{x}_i(1+\mu_i x_i)}{x_i(1+\mu_i\tilde{x}_i)}-\frac{x_i\tilde{y}_i v(1+\mu_i\tilde{x}_i)(1+\alpha_i\tilde{v})}{\tilde{x}_i y_i\tilde{v}(1+\mu_i x_i)(1+\alpha_i v)}\right.\\
&\left.-\frac{y_i\tilde{v}}{\tilde{y}_i v}-\frac{1+\alpha_i v}{1+\alpha_i\tilde{v}}\right)+\frac{M_ia_i}{(1-q_i)N_i+q_iM_i}\tilde{z}_i\left(4-\frac{\tilde{x}_i(1+\mu_i x_i)}{x_i(1+\mu_i\tilde{x}_i)}\right.\\
&\left.\left.-\frac{x_i\tilde{z}_i v(1+\mu_i\tilde{x}_i)(1+\alpha_i\tilde{v})}{\tilde{x}_i z_i\tilde{v}(1+\mu_i x_i)(1+\alpha_i v)}-\frac{z_i\tilde{v}}{\tilde{z}_i v}-\frac{1+\alpha_i v}{1+\alpha_i\tilde{v}}\right)\right]. \qquad (3.15)
\end{aligned}
$$

Because the geometrical mean is less than or equal to the arithmetical mean, then the last two terms of Eq. (3.15) are less than or equal zero. Therefore, if $R_0 > 1$, then $\tilde{x}_1, \tilde{x}_2, \tilde{y}_1, \tilde{y}_2, \tilde{z}_1, \tilde{z}_2, \tilde{v} > 0$, and $\frac{dW_1}{dt} \leq 0$ for all $x_1, x_2, y_1, y_2, z_1, z_2,\ v > 0$. It is clear that, the set $\{\frac{dW_1}{dt} = 0\}$ contains only the invariant singleton set $\{E_1\}$. The global stability of E_1 is induced from LaSalle's invariance principle. □

4. Numerical results and discussions

In this section, we use numerical simulations to illustrate theoretical results given in Theorems 1 and 2 for model (2.1)-(2.4). We shall fix the following parameters: $\lambda_1 = 10$, $\lambda_2 = 6$, $d_1 = 0.01$, $d_2 = 0.01$, $\delta_1 = 0.5$, $\delta_2 = 0.3$, $a_1 = 0.3$, $a_2 = 0.1$, $\alpha_1 = 0.05$, $\alpha_2 = 0.05$, $\mu_1 = 0.0005$, $\mu_2 = 0.0005$, $N_1 = 20$, $N_2 = 10$, $M_1 = 10$, $M_2 = 5$, $\bar{\beta}_1 = 0.0005$, $\bar{\beta}_2 = 0.0008$, $q_1 = q_2 = 0.5$, $f = 0.5$ and $u = 2$. The parameter ε will be chosen below:

(i) $R_0 \leq 1$. Let $\varepsilon = 0.98$, then we get $R_0 = 0.88$. According to Theorem 1, E_0 is GAS. Figures 1-7 show that the numerical results are compatible with the results of Theorem 1. We can see that, the concentrations of uninfected CD4$^+$T cells and macrophages are increasing and converge to their normal values $\frac{\lambda_1}{d_1} = 1000$, $\frac{\lambda_2}{d_2} = 600$, respectively, while the concentrations of infected cells and free viruses are decaying and tend to zero. In this case, the treatment succeeded to eliminate the viruses from the blood.

(ii) $R_0 > 1$. We choose $\varepsilon = 0$, then we compute $R_0 = 4.73$. From Figures 1-7 we can see that, our simulation results are consistent with the theoretical results of Theorem 2, where is E_1 GAS. We can observe that, the trajectory of system (2.1)-(2.4) converges to $E_1 = (630.16, 3.69, 6.16, 300.38, 4.99, 14.98,\ 38.97)$. We note that, when $\varepsilon = 0$, i.e. there is no treatment the infection becomes chronic.

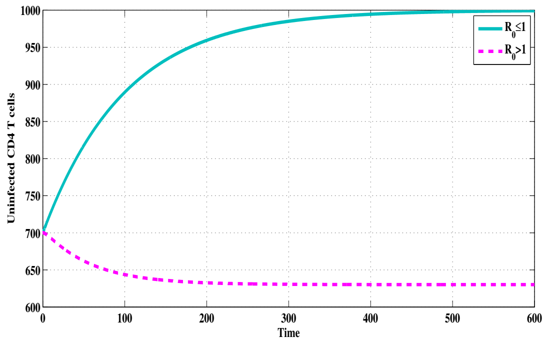

FIGURE 1. The evolution of uninfected CD4$^+$T cells for model (2.1)-(2.4).

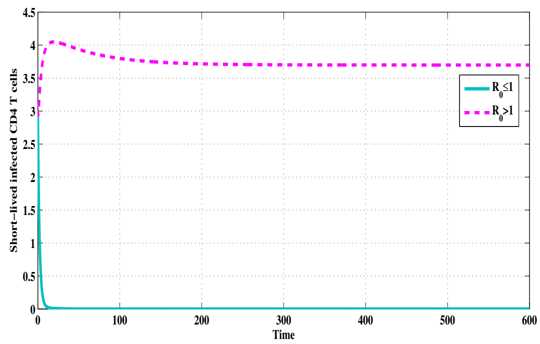

FIGURE 2. The evolution of short-lived infected CD4$^+$T cells for model (2.1)-(2.4).

5. CONCLUSION

In this paper, we have investigated the qualitative behavior of an HIV infection model which describes the interaction of the HIV with two classes of target cells, CD4$^+$T cells and macrophages with different drug efficacy. Both short-lived and

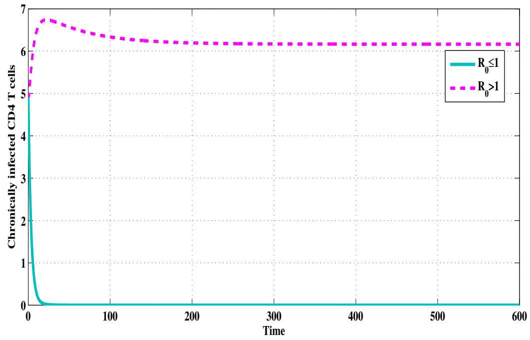

FIGURE 3. The evolution of chronically infected CD4^{+}T cells for model (2.1)-(2.4).

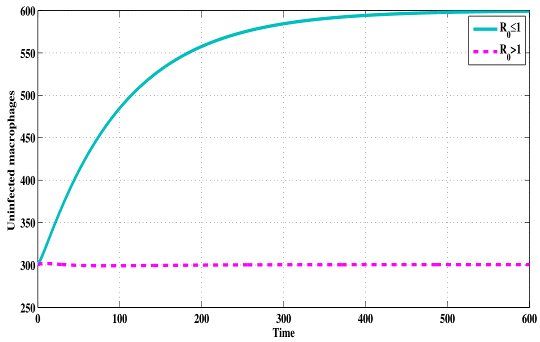

FIGURE 4. The evolution of uninfected macrophages cells for model (2.1)-(2.4).

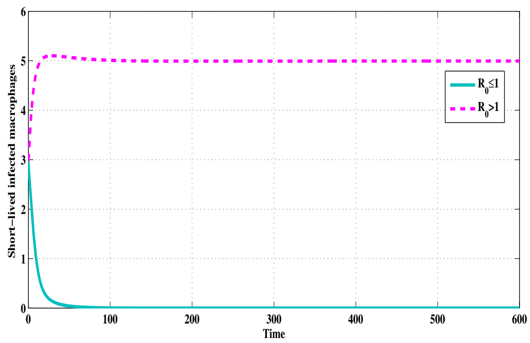

FIGURE 5. The evolution of short-lived infected macrophages cells for model (2.1)-(2.4).

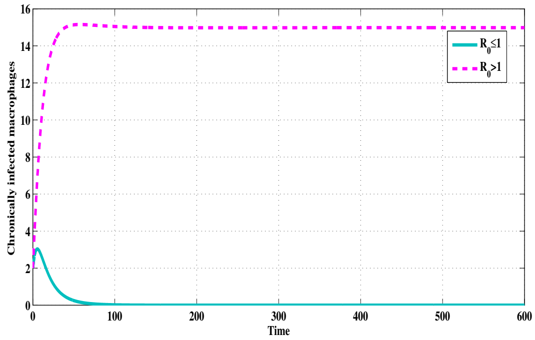

FIGURE 6. The evolution of chronically infected macrophages cells for model (2.1)-(2.4).

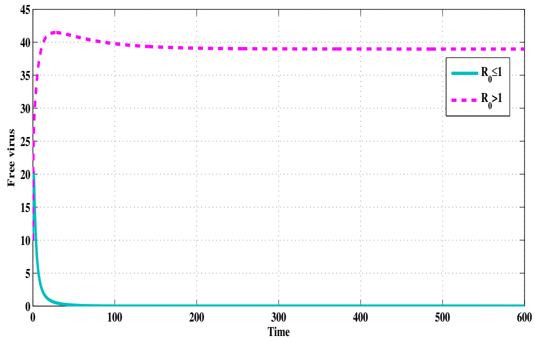

FIGURE 7. The evolution of free virus for model (2.1)-(2.4).

long lived chronically infected cells have been taken into account. The infection rate is given by Crowley-Martin functional response. The global stability of the disease-free equilibrium and endemic equilibrium of the model has been established by constructing suitable Lyapunov functionals and using LaSalle's invariant principle. We have derived the basic infection reproduction number R_0 for the model. We have proven that, the disease-free equilibrium E_0 is GAS when $R_0 \leq 1$, and the endemic equilibrium E_1 is GAS when $R_0 > 1$.

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REFERENCES

[1] S. Bonhoeffer, R. M. May, G. Shaw, and M. A. Nowak, "Virus dynamics and drug therapy," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 94, pp. 6971–6976, 1997.

[2] D. S. Callaway and A. S. Perelson, "HIV-1 infection and low steady state viral loads," *Bulletin of Mathematical Biology*, vol. 64, pp. 29–64, 2002, doi: 10.1006/bulm.2001.0266.

[3] A. M. Elaiw, "Global dynamics of an HIV infection model with two classes of target cells and distributed delays," *Discrete Dynamics in Nature and Society*, pp. 2425–2432, 2012.

[4] A. M. Elaiw, "Global properties of a class of virus infection models with multitarget cells," *Nonlinear Dynamics*, vol. 69, pp. 423–435, 2012, doi: 10.1007/s11071-011-0275-0.

[5] A. M. Elaiw, I. Hassanien, and S. A. Azoz, "Global stability of HIV infection models with intracellular delays," *Journal of the Korean Mathematical Society*, vol. 49, no. 4, pp. 779–794, 2012, doi: 10.4134/JKMS.2012.49.4.779.

[6] A. M. Elaiw and X. Xia, "HIV dynamics: Analysis and robust multirate MPC-based treatment schedules," *Journal of Mathematical Analysis and Applications*, vol. 356, pp. 285–301, 2009, doi: 10.1016/j.jmaa.2009.05.038.

[7] G. Huang, W. Ma, and Y. Takeuchi, "Global properties for virus dynamics model with Beddington-DeAngelis functional response," *Applied Mathematics Letters*, vol. 22, pp. 1690–1693, 2009, doi: 10.1016/j.aml.2009.06.004.

[8] M. A. Obaid and A. M. Elaiw, "Stability of virus infection models with antibodies and chronically infected cells," *Abstract and Applied Analysis*, vol. 217, pp. 2425–2432, 2014, Article ID 650371, doi: 10.1155/2014/650371.

[9] A. S. Perelson, P. Essunger, and Y. C. et al., "Decay characteristics of HIV-1-infected compartments during combination therapy," *Nature*, vol. 397, no. 6629, pp. 188–191, 1997, doi: 10.1038/387188a0.

[10] A. S. Perelson, D. Kirschner, and R. D. Boer, "Dynamics of HIV infection of CD4^{+} T cells," *Mathematical Biosciences*, vol. 114, no. 1, pp. 81–125, 1993, doi: 10.1016/0025-5564(93)90043-A.

[11] X. Wang, Y. Tao, and X. Song, "Delayed HIV-1 infection model Beddington-DeAngelis functional response," *Nonlinear Dynamics*, vol. 62, no. 1-2, pp. 67–72, 2009, doi: 10.1007/s11071-010-9699-1.

[12] S. Xu, "Global stability of the virus dynamics model with Crowley-Martin functional response," *Electronic Journal of Qualitative Theory of Differential Equations*, vol. 9, pp. 1–10, 2012.

[13] X. Zhou and J. Cui, "Global stability of the viral dynamics with Crowley-Martin functional response," *Bulletin of Kerala Mathematics Association*, vol. 48, pp. 555–574, 2011.

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