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Global stability of delayed virus infection model including multi-target cells and B-cell impairment

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Abstract

In this paper, we formulate a virus infection model with n classes of target uninfected cells, n classes of latent infected cells, n classes of active infected cells, virus particles, and B cells. Three types of time delays and the impairment of B cells are involved. The Well-posedness of the model is demonstrated. Basic reproduction number of infection $\mathcal{R}_0 > 0$ is established, which determines the existence of equilibria as follows; when $\mathcal{R}_0$ is greater than unity, and then the model has two equilibria. Otherwise, the model has only a single equilibrium. The global stability of equilibria is proven using Lyapunov's direct method and applying LaSalle's invariance principle. To support our theoretical results, we have performed some numerical simulations in case of $n = 2$ where the model can describe the HIV dynamics with two types of target cells, $CD4^+$ T cells and macrophages.

Keywords: Virus dynamics, global stability, multi-target cells, impairment of B cells, time delay.

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1. Introduction

In the last decades, an abundant various mathematical models of human viral infections have been proposed, modified and analyzed [5, 11, 13, 18, 19, 35, 39, 42, 46, 48, 49, 51]. These models can help researchers to (i) discover the interaction between virus particles and different types of human body cells; (ii) predict the future clinical status of patient; (iii) design an efficient drug dose; and (iv) improve a new treatment. The basic virus dynamics model was introduced in [38] which described the interaction between uninfected target cells ($U(t)$), infected cells ($A(t)$) and virus particles ($V(t)$) over time t. Since a part of the infected cells are passing through the latent stage (which is a stage that infected cells cannot produce any virions until they become active later), the basic model have been expanded to consider this stage of infection by taking into account the dynamics of latent infected cells ($L(t)$) in several works (see, e.g., [21, 28, 40]).

Once a virus enters a body, the innate immunity reacts against the attack and the adaptive immunity activates. The adaptive immunity is an important defense line against viruses because it has a specific

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response to any invader and has a memory cells to remember this invader for a quick response in the next time [43]. One of the adaptive immune system army is B cells which generate antibodies to capture the viruses to erase them from the body by other immune cells [39]. However, B cells could confront some factors that impair their functions such as malnutrition, aging, cytotoxic drugs, irradiation, trauma, tumors, some diseases, e.g., diabetes and immunosuppression by microbes, e.g., malaria, measles virus and HIV [1, 6, 9, 36]. The impairment of immune response could lead to fatal complications to patient [43].

During the viral infection process, the time delays are inseparable to several phases of infection such as delays during cell division, delays of virus production and delays in activation of some medications from a prodrug to an active form and so on. Therefore, varied kinds of time lags have been inserted into virus dynamics models to depict the interactions between virus particles and body cells in more realistic way [7, 10, 17, 23–26, 32, 37, 50].

Some viruses target more than one type of cells to take advantage of them to replicate themselves, e.g., HIV-1 invades $CD4^+$ T cells and macrophages [41]. HTLV-1 preferentially infects $CD4^+$ T cells, $CD8^+$ T cells, dendritic cells, and monocytes [30]. Chikungunya virus targets macrophages, fibroblasts and endothelial cells [4]. Thus, the basic virus infection model with multi-target cells has been introduced by Elaiw in [12] and then it has been extended to include the latent stage of infection in the following form:

$$\begin{aligned}
\dot{U}_i(t) &= \rho_i - \gamma_i U_i(t) - \omega_i U_i(t) V(t),\\
\dot{L}_i(t) &= \omega_i U_i(t) V(t) - (\zeta_i + \nu_i) L_i(t),\\
\dot{A}_i(t) &= \nu_i L_i(t) - \beta_i A_i(t),\\
\dot{V}(t) &= \sum_{i=1}^{n} \varkappa_i A_i(t) - \xi V(t),
\end{aligned} \tag{1.1}$$

where $i = 1, 2, \dots, n$. These symbols $U_i(t)$, $L_i(t)$ and $A_i(t)$ denote the populations of uninfected cells, latent infected cells and active infected cells of class i, respectively. ρ_i and γ_i represent the birth and death rate constants of the uninfected cells of class i, respectively. The infection rate is given by $\omega_i U_i V$, where ω_i is rate constant of the virus-target incidence. The latent infected cells of class i are transmitted to active infected cells of class i at rate $\nu_i L_i$ and die at rate $\zeta_i L_i$. The active infected cells of class i and free virus particles die at rates $\beta_i A_i$ and ξV, respectively. An active infected cells of class i produce an average number $\varkappa_i$ of virus particles.

In [14], the authors have improved model (1.1) and involved the dynamics of B cell immunity as:

$$\begin{aligned}
\dot{U}_i(t) &= \rho_i - \gamma_i U_i(t) - \omega_i U_i(t) V(t),\\
\dot{L}_i(t) &= (1-\chi_i)\omega_i U_i(t) V(t) - (\zeta_i + \nu_i) L_i(t),\\
\dot{A}_i(t) &= \chi_i \omega_i U_i(t) V(t) + \nu_i L_i(t) - \beta_i A_i(t),\\
\dot{V}(t) &= \sum_{i=1}^{n} \varkappa_i A_i(t) - \xi V(t) - \rho V(t) B(t),\\
\dot{B}(t) &= \alpha + \delta V(t) B(t) - \mu B(t).
\end{aligned}$$

The virus particles are attacked by antibodies at rate ρVB. The antibodies are produced at constant rate α, proliferated at rate δVB and died at rate μB. A fraction $(1-\chi_i)$ of infected target cells is assumed to be latent infected cells and the remaining χ_i becomes active infected cells, where $0 < \chi_i < 1$. Mathematicians have modified multi-target cells models and discussed them in several works (see, e.g., [44, 45, 47]).

We motivated and inspired by the previous works to introduce our virus dynamics model including: (i) multi-target cells, (ii) latent stage of infection, (iii) multiple time delays, (iv) B-cell impairment.

2. The proposed model

For the sake of understanding the effect of B cell functions impairment on interaction between n classes of uninfected target cells $U_i(t)$, n classes of latent infected cells $L_i(t)$, n classes of active infected

cells $A_i(t)$, virus particles $V(t)$ and B cells $B(t)$, where $i = 1, 2, \ldots, n$, we propose a mathematical model consisting of (3n+2)-differential equations as:

$$\begin{aligned}
\dot{U}_i &= \rho_i - \gamma_i U_i - \omega_i U_i V, \\
\dot{L}_i &= (1-\chi_i) e^{-\tau_i \eta_i} \omega_i U_i(t-\tau_i) V(t-\tau_i) - (\zeta_i + \nu_i) L_i, \\
\dot{A}_i &= \chi_i e^{-\lambda_i \theta_i} \omega_i U_i(t-\lambda_i) V(t-\lambda_i) + \nu_i L_i - \beta_i A_i, \\
\dot{V} &= \sum_{i=1}^{n} \varkappa_i e^{-\pi_i \iota_i} A_i(t-\pi_i) - \xi V - \rho V B, \\
\dot{B} &= \varepsilon V - \mu B - \vartheta V B,
\end{aligned} \tag{2.1}$$

where we use $U_i = U_i(t)$, $L_i = L_i(t)$, $A_i = A_i(t)$, $V = V(t)$ and $B = B(t)$ for simplicity. The B cells decay at the rate ϑVB due to impairment factors. The time from virus enters a target cell of category i to become latent infected is given by τ_i, while λ_i is the time between virus enters a target cell of category i and the production of new virus particles from active infected cell of class i. The probability of latent and active infected cells surviving to the age of τ_i and λ_i are represented by $e^{-\tau_i \eta_i}$ and $e^{-\lambda_i \theta_i}$, respectively, where η_i and θ_i are constants. The parameter π_i represents the time necessary for immature virus to become mature. The factor $e^{-\pi_i \iota_i}$ represents the probability of immature virus surviving to the age of π_i. All the parameters of the model are positive.

3. Preliminaries

The initial conditions for model (2.1) take the form:

$$\begin{cases}
U_i(z) = \varphi_i(z), \; L_i(z) = \varphi_{i+n}(z), \; A_i(z) = \varphi_{i+2n}(z), \; i = 1, 2, \ldots, n, \\
V(z) = \varphi_{3n+1}(z), \quad B(z) = \varphi_{3n+2}(z), \\
\varphi_k(z) \geqslant 0, \quad z \in [-T, 0], \quad k = 1, 2, \ldots, 3n+2,
\end{cases} \tag{3.1}$$

where $T = \max\{\tau_1, \ldots, \tau_n, \lambda_1, \ldots, \lambda_n, \pi_1, \ldots, \pi_n\}$, $\varphi_k(z) \in \mathcal{C}([-T, 0], \mathbb{R}_+)$ and $\mathcal{C}$ is the Banach space of continuous functions mapping the interval $[-T, 0]$ into $\mathbb{R}_+$ with norm $\|\varphi_k\| = \sup_{-T \leqslant z \leqslant 0} |\varphi_k(z)|$ for $\varphi_k \in \mathcal{C}$. Now, by the standard theory of functional differential equations [31], we ensure that model (2.1) has a unique solution satisfying the initial conditions (3.1).

3.1. Non-negativity and boundedness of solution

In the following, we establish the non-negativity and boundedness of solutions of model (2.1).

Proposition 3.1. *For $i = 1, 2, \ldots, n$, let (U_i, L_i, A_i, V, B) be any solution of model (2.1) satisfying the initial conditions (3.1), then U_i, L_i, A_i, V and B are all non-negative and ultimately bounded for $t \geqslant 0$.*

Proof. From the first equation of model (2.1), we get $\dot{U}_i \,|_{U_i=0} = \rho_i > 0$, therefore $U_i > 0$ for all $t \geqslant 0$. Further, for all $t \in [0, T]$, we have

$$\begin{aligned}
L_i(t) =& \varphi_{i+n}(0) e^{-(\zeta_i+\nu_i)t} + (1-\chi_i) e^{-\tau_i \eta_i} \omega_i \int_0^t e^{-(\zeta_i+\nu_i)(t-x)} U_i(x-\tau_i) V(x-\tau_i) dx \geqslant 0, \\
A_i(t) =& \varphi_{i+2n}(0) e^{-\beta_i t} + \int_0^t e^{-\beta_i (t-x)} \left(\chi_i e^{-\lambda_i \theta_i} \omega_i U_i(x-\lambda_i) V(x-\lambda_i) + \nu_i L_i(x) \right) dx \geqslant 0, \\
V(t) =& \varphi_{3n+1}(0) e^{-\int_0^t (\xi + \rho B(y)) dy} + \sum_{i=1}^{n} \varkappa_i e^{-\pi_i \iota_i} \int_0^t e^{-\int_x^t (\xi + \rho B(y)) dy} A_i(x-\pi_i) dx \geqslant 0, \\
B(t) =& \varphi_{3n+2}(0) e^{-\int_0^t (\mu + \vartheta V(y)) dy} + \varepsilon \int_0^t e^{-\int_x^t (\mu + \vartheta V(y)) dy} V(x) dx \geqslant 0.
\end{aligned}$$

By a recursive argument, we have $L_i \geqslant 0$, $A_i \geqslant 0$, $V \geqslant 0$ and $B \geqslant 0$ for all $t \geqslant 0$. Thus, we ensure

the solutions of model (2.1) are non-negative. In order to show the boundedness of solutions, we have $\dot{U}_i \leqslant \rho_i - \gamma_i U_i$ from the first equation of model (2.1) which implies that $\lim_{t\to\infty} \sup U_i(t) \leqslant \rho_i/\gamma_i$ and then U_i is ultimately bounded. Now, let us consider

$$F_i(t) = (1-\chi_i)e^{-\tau_i\eta_i}U_i(t-\tau_i) + \chi_i e^{-\lambda_i\theta_i}U_i(t-\lambda_i) + L_i + A_i,\ i = 1,2,\dots,n,$$

then a time derivative of F_i is given by:

$$\begin{aligned}
\dot{F}_i =&(1-\chi_i)e^{-\tau_i\eta_i}\rho_i - (1-\chi_i)e^{-\tau_i\eta_i}\gamma_i U_i(t-\tau_i) - (1-\chi_i)e^{-\tau_i\eta_i}\omega_i U_i(t-\tau_i)V(t-\tau_i)\\
&+\chi_i e^{-\lambda_i\theta_i}\rho_i - \chi_i e^{-\lambda_i\theta_i}\gamma_i U_i(t-\lambda_i) - \chi_i e^{-\lambda_i\theta_i}\omega_i U_i(t-\lambda_i)V(t-\lambda_i)\\
&+(1-\chi_i)e^{-\tau_i\eta_i}\omega_i U_i(t-\tau_i)V(t-\tau_i) - (\zeta_i+\nu_i)L_i + \chi_i e^{-\lambda_i\theta_i}\omega_i U_i(t-\lambda_i)V(t-\lambda_i) + \nu_i L_i - \beta_i A_i\\
=&(1-\chi_i)e^{-\tau_i\eta_i}\rho_i - (1-\chi_i)e^{-\tau_i\eta_i}\gamma_i U_i(t-\tau_i) + \chi_i e^{-\lambda_i\theta_i}\rho_i - \chi_i e^{-\lambda_i\theta_i}\gamma_i U_i(t-\lambda_i) - \zeta_i L_i - \beta_i A_i\\
\leqslant&\rho_i - \sigma_i\left[(1-\chi_i)e^{-\tau_i\eta_i}U_i(t-\tau_i) + \chi_i e^{-\lambda_i\theta_i}U_i(t-\lambda_i) + L_i + A_i\right]\\
=&\rho_i - \sigma_i F_i(t),
\end{aligned}$$

where $\sigma_i = \min\{\gamma_i, \zeta_i, \beta_i\}$. It follows that

$$\lim_{t\to\infty}\sup F_i(t) \leqslant c_i, \quad \lim_{t\to\infty}\sup L_i(t) \leqslant c_i, \quad \lim_{t\to\infty}\sup A_i(t) \leqslant c_i,$$

where $c_i = \rho_i/\sigma_i$. Now, let $H(t) = V + \frac{\xi}{2\varepsilon}B$, then we obtain

$$\begin{aligned}
\dot{H} &= \sum_{i=1}^{n}\varkappa_i e^{-\pi_i\iota_i}A_i(t-\pi_i) - \xi V - \rho VB + \frac{\xi}{2}V - \frac{\xi\mu}{2\varepsilon}B - \frac{\xi\vartheta}{2\varepsilon}VB\\
&= \sum_{i=1}^{n}\varkappa_i e^{-\pi_i\iota_i}A_i(t-\pi_i) - \frac{\xi}{2}V - \frac{\xi\mu}{2\varepsilon}B - \left(\rho + \frac{\xi\vartheta}{2\varepsilon}\right)VB\\
&\leqslant \sum_{i=1}^{n}\varkappa_i e^{-\pi_i\iota_i}c_i - \frac{\xi}{2}V - \frac{\xi\mu}{2\varepsilon}B\\
&\leqslant \sum_{i=1}^{n}\varkappa_i e^{-\pi_i\iota_i}c_i - \ell\left(V + \frac{\xi}{2\varepsilon}B\right)\\
&= \sum_{i=1}^{n}\varkappa_i e^{-\pi_i\iota_i}c_i - \ell H,
\end{aligned}$$

where $\ell = \min\left\{\frac{\xi}{2}, \mu\right\}$. In a similar way, we have $\lim_{t\to\infty}\sup V(t) \leqslant \overline{c}$ and $\lim_{t\to\infty}\sup B(t) \leqslant \widetilde{c}$, where $\overline{c} = \frac{\sum_{i=1}^{n}\varkappa_i e^{-\pi_i\iota_i}c_i}{\ell}$ and $\widetilde{c} = \frac{2\varepsilon\overline{c}}{\xi}$. Thus, the solutions of model (2.1) are ultimately bounded. □

The previous proof reveals that Ω limit sets of model (2.1) are contained in the following bounded feasible region Γ

$$\Gamma = \{(U_i, L_i, A_i, V, B) \in \mathbb{R}_+^{3n+2} : \|U_i\| \leqslant \frac{\rho_i}{\gamma_i}, \|L_i\| \leqslant c_i, \|A_i\| \leqslant c_i, \|V\| \leqslant \overline{c}, \|B\| \leqslant \widetilde{c}\},$$

which implies that the solutions of model (2.1) point towards the region Ω. For this reason, Ω is positively invariant for model (2.1).

3.2. *Equilibria*

The basic reproduction number of infection for model (2.1) is

$$R_0 = \sum_{i=1}^{n}R_{0i} = \sum_{i=1}^{n}\frac{\rho_i(\psi_i+\phi_i)}{\xi\gamma_i},$$

where $\psi_i = \dfrac{\varkappa_i\omega_i\nu_i(1-\chi_i)e^{-\pi_i\iota_i-\tau_i\eta_i}}{\beta_i(\zeta_i+\nu_i)}$ and $\phi_i = \dfrac{\varkappa_i\omega_i\chi_i e^{-\pi_i\iota_i-\lambda_i\theta_i}}{\beta_i}$.

Lemma 3.2. *Consider model (2.1), then*

(i) *the model has a unique equilibrium* E^0 *if* $R_0 \leqslant 1$;
(ii) *the model has two equilibria* E^0 *and* E^* *if* $R_0 > 1$.

Proof. At any equilibrium, we have

$$\begin{aligned}
\rho_i - \gamma_i U_i - \omega_i U_i V &= 0,\\
(1-\chi_i)e^{-\tau_i\eta_i}\omega_i U_i V - (\zeta_i+\nu_i)L_i &= 0,\\
\chi_i e^{-\lambda_i\theta_i}\omega_i U_i V + \nu_i L_i - \beta_i A_i &= 0,\\
\sum_{i=1}^{n} \varkappa_i e^{-\pi_i\iota_i} A_i - \xi V - \rho V B &= 0, \qquad (3.2)\\
\varepsilon V - \mu B - \vartheta V B &= 0. \qquad (3.3)
\end{aligned}$$

We obtain U_i, L_i, A_i and B as functions of V as follow:

$$\begin{aligned}
U_i &= \frac{\rho_i}{\gamma_i+\omega_i V},\\
L_i &= \frac{e^{-\tau_i\eta_i}\omega_i\rho_i(1-\chi_i)V}{(\zeta_i+\nu_i)(\gamma_i+\omega_i V)},\\
A_i &= \frac{\omega_i\rho_i\left(\nu_i(1-\chi_i)e^{-\tau_i\eta_i}+\chi_i e^{-\lambda_i\theta_i}(\zeta_i+\nu_i)\right)V}{\beta_i(\zeta_i+\nu_i)(\gamma_i+\omega_i V)}, \qquad (3.4)\\
B &= \frac{\varepsilon V}{\mu+\vartheta V}. \qquad (3.5)
\end{aligned}$$

Substituting Eqs. (3.4) and (3.5) into Eq. (3.2), then we get

$$\sum_{i=1}^{n} \frac{\varkappa_i\omega_i\rho_i e^{-\pi_i\iota_i}\left(\nu_i(1-\chi_i)e^{-\tau_i\eta_i}+\chi_i e^{-\lambda_i\theta_i}(\zeta_i+\nu_i)\right)V}{\beta_i(\zeta_i+\nu_i)(\gamma_i+\omega_i V)} - \xi V - \frac{\rho\varepsilon V^2}{\mu+\vartheta V} = 0. \qquad (3.6)$$

Clearly, $V=0$ is a solution of Eq. (3.6), therefore we have the infection-free equilibrium $E^0 = \left(U_i^0, 0, 0, 0, 0\right)$, where $U_i^0 = \frac{\rho_i}{\gamma_i}$. The other possibility of Eq. (3.6) is

$$\sum_{i=1}^{n} \frac{\varkappa_i\omega_i\rho_i e^{-\pi_i\iota_i}\left(\nu_i(1-\chi_i)e^{-\tau_i\eta_i}+\chi_i e^{-\lambda_i\theta_i}(\zeta_i+\nu_i)\right)}{\beta_i(\zeta_i+\nu_i)(\gamma_i+\omega_i V)} - \xi - \frac{\rho\varepsilon V}{\mu+\vartheta V} = 0.$$

Let us define a function $Y(V)$ as:

$$Y(V) = \sum_{i=1}^{n} \frac{\varkappa_i\omega_i\rho_i e^{-\pi_i\iota_i}\left(\nu_i(1-\chi_i)e^{-\tau_i\eta_i}+\chi_i e^{-\lambda_i\theta_i}(\zeta_i+\nu_i)\right)}{\beta_i(\zeta_i+\nu_i)(\gamma_i+\omega_i V)} - \xi - \frac{\rho\varepsilon V}{\mu+\vartheta V}.$$

It is seen that $Y(V)$ is monotonic decreasing since

$$Y'(V) = -\left(\sum_{i=1}^{n} \frac{\varkappa_i\omega_i^2\rho_i e^{-\pi_i\iota_i}\left(\nu_i(1-\chi_i)e^{-\tau_i\eta_i}+\chi_i e^{-\lambda_i\theta_i}(\zeta_i+\nu_i)\right)}{\beta_i(\zeta_i+\nu_i)(\gamma_i+\omega_i V)^2} + \frac{\varepsilon\rho\mu}{(\mu+\vartheta V)^2}\right).$$

On the other hand, $\lim_{V\to\infty} Y(V) = -\frac{\xi\vartheta+\rho\varepsilon}{\vartheta}$. Further,

$$Y(0) = \sum_{i=1}^{n} \frac{\varkappa_i\omega_i\rho_i e^{-\pi_i\iota_i}\left(\nu_i(1-\chi_i)e^{-\tau_i\eta_i}+\chi_i e^{-\lambda_i\theta_i}(\zeta_i+\nu_i)\right)}{\beta_i\gamma_i(\zeta_i+\nu_i)} - \xi = \xi\left(R_0-1\right).$$

It implies that $Y(V)$ has a unique positive solution V^* if $R_0 > 1$. Thus, we have the endemic-infection equilibrium $E^* = (U_i^*, L_i^*, A_i^*, V^*, B^*)$, where

$$U_i^* = \frac{\rho_i}{\gamma_i + \omega_i V^*}, \qquad L_i^* = \frac{e^{-\tau_i \eta_i}\omega_i \rho_i (1-\chi_i) V^*}{(\zeta_i + \nu_i)(\gamma_i + \omega_i V^*)},$$
$$A_i^* = \frac{\omega_i \rho_i \left(\nu_i (1-\chi_i) e^{-\tau_i \eta_i} + \chi_i e^{-\lambda_i \theta_i}(\zeta_i + \nu_i)\right) V^*}{\beta_i (\zeta_i + \nu_i)(\gamma_i + \omega_i V^*)}, \qquad B^* = \frac{\varepsilon V^*}{\mu + \vartheta V^*}.$$

Therefore, we have proved the existence of endemic-infection equilibrium E^* under the condition $R_0 > 1$. □

4. Global stability of equilibria

In the following, we demonstrate the global stability of equilibria according to the value of R_0. To state the global stability results, we need to define a function $G(q) = q - 1 - \ln(q)$, where $q > 0$.

Theorem 4.1. *If $R_0 < 1$, then the equilibrium E^0 is globally asymptotically stable (G.A.S).*

Proof. Construct a candidate Lyapunov functional as:

$$M_0 = \sum_{i=1}^{n} \frac{\psi_i + \phi_i}{\omega_i} U_i^0 G\left(\frac{U_i}{U_i^0}\right) + \sum_{i=1}^{n} \frac{\nu_i \varkappa_i e^{-\pi_i \iota_i}}{\beta_i (\zeta_i + \nu_i)} L_i + \sum_{i=1}^{n} \frac{\varkappa_i e^{-\pi_i \iota_i}}{\beta_i} A_i + V$$
$$+ \frac{\xi(1-R_0)}{\varepsilon} B + \sum_{i=1}^{n} \psi_i \int_{t-\tau_i}^{t} U_i(x) V(x) dx + \sum_{i=1}^{n} \phi_i \int_{t-\lambda_i}^{t} U_i(x) V(x) dx + \sum_{i=1}^{n} \varkappa_i e^{-\pi_i \iota_i} \int_{t-\pi_i}^{t} A_i(x) dx.$$

It's obvious that $M_0 > 0$ for all $(U_i, L_i, A_i, V, B) > 0$ and $M_0 = 0$ at E^0. Now, the time derivative of M_0 along the solutions of model (2.1) is given by:

$$\begin{aligned}
\frac{dM_0}{dt} &= \sum_{i=1}^{n} \frac{\psi_i + \phi_i}{\omega_i} \left(1 - \frac{U_i^0}{U_i}\right)(\rho_i - \gamma_i U_i - \omega_i U_i V) \\
&+ \sum_{i=1}^{n} \frac{\nu_i \varkappa_i e^{-\pi_i \iota_i}}{\beta_i (\zeta_i + \nu_i)} \left((1-\chi_i) e^{-\tau_i \eta_i} \omega_i U_i(t-\tau_i) V(t-\tau_i) - (\zeta_i + \nu_i) L_i\right) \\
&+ \sum_{i=1}^{n} \frac{\varkappa_i e^{-\pi_i \iota_i}}{\beta_i} \left(\chi_i e^{-\lambda_i \theta_i} \omega_i U_i(t-\lambda_i) V(t-\lambda_i) + \nu_i L_i - \beta_i A_i\right) \\
&+ \sum_{i=1}^{n} \varkappa_i e^{-\pi_i \iota_i} A_i(t-\pi_i) - \xi V - \rho V B + \frac{\xi(1-R_0)}{\varepsilon}(\varepsilon V - \mu B - \vartheta V B) \\
&+ \sum_{i=1}^{n} \psi_i \left(U_i V - U_i(t-\tau_i) V(t-\tau_i)\right) + \sum_{i=1}^{n} \phi_i \left(U_i V - U_i(t-\lambda_i) V(t-\lambda_i)\right) \\
&+ \sum_{i=1}^{n} \varkappa_i e^{-\pi_i \iota_i} \left(A_i - A_i(t-\pi_i)\right) \\
&= -\sum_{i=1}^{n} \frac{\gamma_i (\psi_i + \phi_i)(U_i - U_i^0)^2}{\omega_i U_i} - \frac{\xi \mu (1-R_0)}{\varepsilon} B - \left(\rho + \frac{\vartheta \xi (1-R_0)}{\varepsilon}\right) V B.
\end{aligned}$$

Thus $\frac{dM_0}{dt} \leqslant 0$ as long as $R_0 < 1$. Moreover, $\frac{dM_0}{dt} = 0$ when $U_i(t) = U_i^0$ and $B(t) = 0$. Let $\Delta = \{(U_i, L_i, A_i, V, B) : \frac{dM_0}{dt} = 0\}$ and $\bar{\Delta}$ be the largest invariant subset of Δ. Thus, the trajectories of model

(2.1) tend to $\bar{\Delta}$ where every components of $\bar{\Delta}$ satisfy $U_i(t) = U_i^0$ and $B(t) = 0$. Then, the last equation of model (2.1) yields

$$\dot{B}(t) = 0 = \varepsilon V(t) \quad \Longrightarrow \quad V(t) = 0.$$

From the 4th equation of model (2.1), we obtain

$$\dot{V}(t) = 0 = \sum_{i=1}^{n} \varkappa_i e^{-\pi_i \iota_i} A_i(t-\pi_i) \quad \Longrightarrow \quad A_i(t) = 0.$$

Similarly, from the 3th equation of model (2.1), we get $L_i(t) = 0$. Immediately, we can see that $\bar{\Delta}$ contains a single point E^0. Thus, according to LaSalle's invariance principle (L.I.P) [34], E^0 is G.A.S if $R_0 < 1$. □

Theorem 4.2. *If $R_0 > 1$, then the equilibrium E^* is G.A.S.*

Proof. Construct a candidate Lyapunov functional as:

$$\begin{aligned}
M_1 =& \sum_{i=1}^{n} \frac{\psi_i + \phi_i}{\omega_i} U_i^* G\left(\frac{U_i}{U_i^*}\right) + \sum_{i=1}^{n} \frac{\nu_i \varkappa_i e^{-\pi_i \iota_i}}{\beta_i(\zeta_i + \nu_i)} L_i^* G\left(\frac{L_i}{L_i^*}\right) \\
&+ \sum_{i=1}^{n} \frac{\varkappa_i e^{-\pi_i \iota_i}}{\beta_i} A_i^* G\left(\frac{A_i}{A_i^*}\right) + V^* G\left(\frac{V}{V^*}\right) + \frac{\rho}{2(\varepsilon - \vartheta B^*)} (B - B^*)^2 \\
&+ \sum_{i=1}^{n} \psi_i U_i^* V^* \int_{t-\tau_i}^{t} G\left(\frac{U_i(x)V(x)}{U_i^* V^*}\right) dx + \sum_{i=1}^{n} \phi_i U_i^* V^* \int_{t-\lambda_i}^{t} G\left(\frac{U_i(x)V(x)}{U_i^* V^*}\right) dx \\
&+ \sum_{i=1}^{n} \varkappa_i e^{-\pi_i \iota_i} A_i^* \int_{t-\pi_i}^{t} G\left(\frac{A_i(x)}{A_i^*}\right) dx.
\end{aligned}$$

It is obvious from Eq. (3.3) that $\varepsilon - \vartheta B^* = \frac{\mu B^*}{V^*} > 0$. Thus $M_1 > 0$ for all $(U_i, L_i, A_i, V, B) > 0$ and $M_1 = 0$ at E^*. Now, the time derivative of M_1 is:

$$\begin{aligned}
\frac{dM_1}{dt} =& \frac{\psi_i + \phi_i}{\omega_i} \left(1 - \frac{U_i^*}{U_i}\right) (\rho_i - \gamma_i U_i - \omega_i U_i V) \\
&+ \sum_{i=1}^{n} \frac{\nu_i \varkappa_i e^{-\pi_i \iota_i}}{\beta_i(\zeta_i + \nu_i)} \left(1 - \frac{L_i^*}{L_i}\right) \left((1-\chi_i) e^{-\tau_i \eta_i} \omega_i U_i(t-\tau_i) V(t-\tau_i) - (\zeta_i + \nu_i) L_i\right) \\
&+ \sum_{i=1}^{n} \frac{\varkappa_i e^{-\pi_i \iota_i}}{\beta_i} \left(1 - \frac{A_i^*}{A_i}\right) \left(\chi_i e^{-\lambda_i \theta_i} \omega_i U_i(t-\lambda_i) V(t-\lambda_i) + \nu_i L_i - \beta_i A_i\right) \\
&+ \left(1 - \frac{V^*}{V}\right) \left(\sum_{i=1}^{n} \varkappa_i e^{-\pi_i \iota_i} A_i(t-\pi_i) - \xi V - \rho V B\right) + \frac{\rho}{\varepsilon - \vartheta B^*} (B - B^*) (\varepsilon V - \mu B - \vartheta V B) \\
&+ \sum_{i=1}^{n} \psi_i U_i^* V^* \left[\frac{U_i V}{U_i^* V^*} - \frac{U_i(t-\tau_i) V(t-\tau_i)}{U_i^* V^*} + \ln\left(\frac{U_i(t-\tau_i) V(t-\tau_i)}{U_i V}\right)\right] \\
&+ \sum_{i=1}^{n} \phi_i U_i^* V^* \left[\frac{U_i V}{U_i^* V^*} - \frac{U_i(t-\lambda_i) V(t-\lambda_i)}{U_i^* V^*} + \ln\left(\frac{U_i(t-\lambda_i) V(t-\lambda_i)}{U_i V}\right)\right] \\
&+ \sum_{i=1}^{n} \varkappa_i e^{-\pi_i \iota_i} A_i^* \left[\frac{A_i}{A_i^*} - \frac{A_i(t-\pi_i)}{A_i^*} + \ln\left(\frac{A_i(t-\pi_i)}{A_i}\right)\right] \\
=& \sum_{i=1}^{n} \frac{\psi_i + \phi_i}{\omega_i} \left(1 - \frac{U_i^*}{U_i}\right) (\rho_i - \gamma_i U_i) + \sum_{i=1}^{n} \frac{\psi_i + \phi_i}{\omega_i} \omega_i U_i^* V
\end{aligned}$$

$$
\begin{aligned}
&- \sum_{i=1}^{n} \psi_i U_i(t-\tau_i) V(t-\tau_i) \frac{L_i^*}{L_i} + \sum_{i=1}^{n} \frac{\nu_i \varkappa_i e^{-\pi_i \iota_i}}{\beta_i} L_i^* \\
&- \sum_{i=1}^{n} \phi_i U_i(t-\lambda_i) V(t-\lambda_i) \frac{A_i^*}{A_i} - \sum_{i=1}^{n} \frac{\varkappa_i e^{-\pi_i \iota_i}}{\beta_i} \nu_i L_i \frac{A_i^*}{A_i} \\
&+ \sum_{i=1}^{n} \varkappa_i e^{-\pi_i \iota_i} A_i^* - \frac{V^*}{V} \sum_{i=1}^{n} \varkappa_i e^{-\pi_i \iota_i} A_i(t-\pi_i) - \xi(V-V^*) - \rho(V-V^*)B \\
&+ \frac{\rho}{\varepsilon - \vartheta B^*} (B-B^*) (\varepsilon V - \mu B - \vartheta V B) + \sum_{i=1}^{n} \psi_i U_i^* V^* \ln \left(\frac{U_i(t-\tau_i) V(t-\tau_i)}{U_i V} \right) \\
&+ \sum_{i=1}^{n} \phi_i U_i^* V^* \ln \left(\frac{U_i(t-\lambda_i) V(t-\lambda_i)}{U_i V} \right) + \sum_{i=1}^{n} \varkappa_i e^{-\pi_i \iota_i} A_i^* \ln \left(\frac{A_i(t-\pi_i)}{A_i} \right).
\end{aligned}
$$

Utilizing the endemic-infection equilibrium conditions

$$
\rho_i = \gamma_i U_i^* + \omega_i U_i^* V^*, \qquad L_i^* = \frac{(1-\chi_i) e^{-\tau_i \eta_i} \omega_i U_i^* V^*}{(\zeta_i + \nu_i)},
$$

$$
A_i^* = \frac{\chi_i e^{-\lambda_i \theta_i} \omega_i U_i^* V^*}{\beta_i} + \frac{\nu_i (1-\chi_i) e^{-\tau_i \eta_i} \omega_i U_i^* V^*}{\beta_i (\zeta_i + \nu_i)}, \qquad \varepsilon V^* = \mu B^* + \vartheta V^* B^*,
$$

into the last equation of $\frac{dM_1}{dt}$, we get

$$
\begin{aligned}
\frac{dM_1}{dt} =& \sum_{i=1}^{n} \frac{\psi_i + \phi_i}{\omega_i} \left(1 - \frac{U_i^*}{U_i}\right) (\gamma_i U_i^* - \gamma_i U_i) \\
&+ \sum_{i=1}^{n} \psi_i U_i^* V^* \left[3 - \frac{U_i^*}{U_i} + \frac{V}{V^*} - \frac{U_i(t-\tau_i) V(t-\tau_i) L_i^*}{U_i^* V^* L_i} \right. \\
&\left. - \frac{A_i^* L_i}{A_i L_i^*} - \frac{V^* A_i(t-\pi_i)}{V A_i^*} + \ln \left(\frac{U_i(t-\tau_i) V(t-\tau_i)}{U_i V} \right) + \ln \left(\frac{A_i(t-\pi_i)}{A_i} \right) \right] \\
&+ \sum_{i=1}^{n} \phi_i U_i^* V^* \left[2 - \frac{U_i^*}{U_i} + \frac{V}{V^*} - \frac{U_i(t-\lambda_i) V(t-\lambda_i) A_i^*}{U_i^* V^* A_i} \right. \\
&\left. - \frac{V^* A_i(t-\pi_i)}{V A_i^*} + \ln \left(\frac{U_i(t-\lambda_i) V(t-\lambda_i)}{U_i V} \right) + \ln \left(\frac{A_i(t-\pi_i)}{A_i} \right) \right] \\
&- \xi(V-V^*) - \rho(V-V^*)B + \rho(V-V^*)B^* - \rho(V-V^*)B^* \\
&+ \frac{\rho(B-B^*)}{\varepsilon - \vartheta B^*} (\varepsilon V - \mu B - \vartheta V B - \varepsilon V^* + \mu B^* + \vartheta V^* B^* + \vartheta V B^* - \vartheta V B^*) \\
=& - \sum_{i=1}^{n} \frac{\gamma_i (\psi_i + \phi_i)(U_i - U_i^*)^2}{\omega_i U_i} + \sum_{i=1}^{n} \psi_i U_i^* V^* \left[3 - \frac{U_i^*}{U_i} + \frac{V}{V^*} - \frac{U_i(t-\tau_i) V(t-\tau_i) L_i^*}{U_i^* V^* L_i} \right. \\
&\left. - \frac{A_i^* L_i}{A_i L_i^*} - \frac{V^* A_i(t-\pi_i)}{V A_i^*} + \ln \left(\frac{U_i(t-\tau_i) V(t-\tau_i)}{U_i V} \right) + \ln \left(\frac{A_i(t-\pi_i)}{A_i} \right) \right] \\
&+ \sum_{i=1}^{n} \phi_i U_i^* V^* \left[2 - \frac{U_i^*}{U_i} + \frac{V}{V^*} - \frac{U_i(t-\lambda_i) V(t-\lambda_i) A_i^*}{U_i^* V^* A_i} \right. \\
&\left. - \frac{V^* A_i(t-\pi_i)}{V A_i^*} + \ln \left(\frac{U_i(t-\lambda_i) V(t-\lambda_i)}{U_i V} \right) + \ln \left(\frac{A_i(t-\pi_i)}{A_i} \right) \right] \\
&- (\xi + \rho B^*)(V-V^*) - \rho(V-V^*)(B-B^*) + \frac{\rho(\varepsilon - \vartheta B^*)}{(\varepsilon - \vartheta B^*)} (B-B^*)(V-V^*) - \frac{\rho(\mu + \vartheta V)}{(\varepsilon - \vartheta B^*)} (B-B^*)^2.
\end{aligned}
$$

Note that

$$-(\xi+\rho B^*)(V-V^*)=\sum_{i=1}^{n}(\psi_i+\phi_i)U_i^*V^*\left(1-\frac{V}{V^*}\right).$$

In addition, we have

$$\ln\left(\frac{U_i(t-\tau_i)V(t-\tau_i)}{U_iV}\right)=\ln\left(\frac{U_i^*}{U_i}\right)+\ln\left(\frac{U_i(t-\tau_i)V(t-\tau_i)L_i^*}{U_i^*V^*L_i}\right)+\ln\left(\frac{A_i^*L_i}{A_iL_i^*}\right)+\ln\left(\frac{A_iV^*}{A_i^*V}\right),$$
$$\ln\left(\frac{U_i(t-\lambda_i)V(t-\lambda_i)}{U_iV}\right)=\ln\left(\frac{U_i^*}{U_i}\right)+\ln\left(\frac{U_i(t-\lambda_i)V(t-\lambda_i)A_i^*}{U_i^*V^*A_i}\right)+\ln\left(\frac{A_iV^*}{A_i^*V}\right),$$
$$\ln\left(\frac{A_i(t-\pi_i)}{A_i}\right)=\ln\left(\frac{V^*A_i(t-\pi_i)}{VA_i^*}\right)+\ln\left(\frac{A_i^*V}{A_iV^*}\right).$$

Simplifying the $\frac{dM_1}{dt}$ equation, we obtain

$$\begin{aligned}\frac{dM_1}{dt}=&-\sum_{i=1}^{n}\frac{\gamma_i(\psi_i+\phi_i)(U_i-U_i^*)^2}{\omega_iU_i}-\frac{\rho(\mu+\vartheta V)}{\varepsilon-\vartheta B^*}(B-B^*)^2\\&-\sum_{i=1}^{n}\psi_iU_i^*V^*\left[G\left(\frac{U_i^*}{U_i}\right)+G\left(\frac{U_i(t-\tau_i)V(t-\tau_i)L_i^*}{U_i^*V^*L_i}\right)+G\left(\frac{A_i^*L_i}{A_iL_i^*}\right)+G\left(\frac{V^*A_i(t-\pi_i)}{VA_i^*}\right)\right]\\&-\sum_{i=1}^{n}\phi_iU_i^*V^*\left[G\left(\frac{U_i^*}{U_i}\right)+G\left(\frac{U_i(t-\lambda_i)V(t-\lambda_i)A_i^*}{U_i^*V^*A_i}\right)+G\left(\frac{V^*A_i(t-\pi_i)}{VA_i^*}\right)\right].\end{aligned}$$

Therefore, $\frac{dM_1}{dt}\leqslant 0$ for all $U_i,L_i,A_i,V,B>0$. In addition, $\frac{dM_1}{dt}=0$ if $U_i=U_i^*$, $L_i=L_i^*$, $A_i=A_i^*$, $V=V^*$ and $B=B^*$. In the same way as the proof of Theorem 4.1 we get that the largest invariance subset contains a single point E^*. Applying L.I.P, we obtain that E^* is G.A.S if $R_0>0$. □

5. Example and numerical simulations

In the following, we carry out a special case of model (2.1) and perform some numerical simulations to illustrate the theoretical results and to investigate the effect of some parameters. It was reported in [41] that HIV infects two types of immune system cells: $CD4^+$ T cells and macrophages, i.e., $n=2$. Let us introduce an HIV infection model under the effect of highly active anti-retroviral therapy (HAART) consisting of a combination of reverse transcriptase inhibitor (RTI) and protease inhibitor (PI):

$$\begin{aligned}\dot{U}_1&=\rho_1-\gamma_1U_1-(1-\epsilon_{r_1})\omega_1U_1V,\\\dot{U}_2&=\rho_2-\gamma_2U_2-(1-\epsilon_{r_2})\omega_2U_2V,\\\dot{L}_1&=(1-\epsilon_{r_1})(1-\chi_1)e^{-\tau_1\eta_1}\omega_1U_1(t-\tau_1)V(t-\tau_1)-(\zeta_1+\nu_1)L_1,\\\dot{L}_2&=(1-\epsilon_{r_2})(1-\chi_2)e^{-\tau_2\eta_2}\omega_2U_2(t-\tau_2)V(t-\tau_2)-(\zeta_2+\nu_2)L_2,\\\dot{A}_1&=(1-\epsilon_{r_1})\chi_1e^{-\lambda_1\theta_1}\omega_1U_1(t-\lambda_1)V(t-\lambda_1)+\nu_1L_1-\beta_1A_1,\\\dot{A}_2&=(1-\epsilon_{r_2})\chi_2e^{-\lambda_2\theta_2}\omega_2U_2(t-\lambda_2)V(t-\lambda_2)+\nu_2L_2-\beta_2A_2,\\\dot{V}&=(1-\epsilon_{p_1})\varkappa_1e^{-\pi_1\iota_1}A_1(t-\pi_1)+(1-\epsilon_{p_2})\varkappa_2e^{-\pi_2\iota_2}A_2(t-\pi_2)-\xi V-\rho VB,\\\dot{B}&=\varepsilon V-\mu B-\vartheta VB,\end{aligned}\tag{5.1}$$

where $\epsilon_{r_i}\in[0,1]$ is the efficacy of the RTI drugs, while $\epsilon_{p_i}\in[0,1]$ is the efficacy of the PI drugs. Consequently, the parameter R_0 of model (5.1) is given by:

$$R_0=\sum_{i=1}^{2}\frac{\varkappa_i\omega_i\rho_i\left(1-\epsilon_{p_i}\right)\left(1-\epsilon_{r_i}\right)\left(\chi_i\left(\zeta_i+\nu_i\right)e^{-\lambda_i\theta_i}+\nu_i\left(1-\chi_i\right)e^{-\tau_i\eta_i}\right)e^{-\pi_i\iota_i}}{\xi\beta_i\gamma_i\left(\zeta_i+\nu_i\right)}.\tag{5.2}$$

We perform some numerical simulation for model (5.1) using the values of parameters given in Table 1. All the computations will be carried out by MATLAB. We have chosen the values of parameters of the model to perform the numerical simulations.

5.1. *Stability of equilibria*

In this case, we want to show that the theoretical results of Theorems 1-2 are consistent with the numerical simulations. Thus, we consider three different initial conditions as follows:

IC1: $U_i(s) = 300$, $L_i(s) = 10$, $A_i(s) = 30$, $V(s) = 8$, $B(s) = 25$;
IC2: $U_i(s) = 400$, $L_i(s) = 7$, $A_i(s) = 20$, $V(s) = 5$, $B(s) = 20$;
IC3: $U_i(s) = 600$, $L_i(s) = 3$, $A_i(s) = 10$, $V(s) = 3$, $B(s) = 15$,

where $s \in [-\tilde{T}, 0]$ and $\tilde{T} = \max\{\tau_1, \tau_2, \lambda_1, \lambda_2, \pi_1, \pi_2\}$.

We figure out the following:

(i) when $\omega_i = 5 \times 10^{-5}$, then $R_0 = 0.609164 < 1$ which means that by Theorem 4.1 the trajectories of solution tend to the infection-free equilibrium E^0 (see Figure 1). From the biological viewpoint, the HIV is cleared from patient's body;

(ii) when $\omega_i = 5 \times 10^{-4}$, then $R_0 = 6.09164 > 1$. According to Theorem 4.2, the trajectories of solution head for the chronic-infection equilibrium $E^* = (486.7, 469.5, 4.885, 3.679, 16.07, 9.638, 30.16, 19.36)$ (see Figure 1). In this case the HIV is deep-seated in patient's plasma.

As we can see from Figure 1, the outcomes are agreed with the theoretical results. The values of parameters we take in this case are listed in Table 1 with the following values of the rest of parameters: $\tau_1 = 0.05$, $\tau_2 = 0.01$, $\lambda_1 = 0.2$, $\lambda_2 = 0.08$, $\pi_1 = 0.05$, $\pi_2 = 0.02$, $\epsilon_{r_1} = 0.3$, $\epsilon_{r_2} = 0.25$, $\epsilon_{p_1} = 0.15$, $\epsilon_{p_2} = 0.17$, and $\vartheta = 0.01$.

5.2. *The effect of B cells impairment parameter*

Since the main contribution of our model is to incorporate the impaired B cells, so we want to study its impact on the virus dynamics. We consider different values of ϑ to see what will happen to other components. Figure 2 indicates that there is a positive correlation between the value of impairment parameter and the amount of HIV particles. In other words, the HIV particles are increased as ϑ is increased which leads to more infection of uninfected cells and then increasing of concentrations of all types of infected cells. When the uninfected cells' concentrations are too low, then the patient is said to have acquired immunodeficiency syndrome (AIDS). Therefore, the impaired B cells will help HIV particles to reach AIDS stage more rapidly. The data we take in this case are listed in Table 1 with the following values of the rest of parameters: $\tau_1 = 0.05$, $\tau_2 = 0.01$, $\lambda_1 = 0.2$, $\lambda_2 = 0.08$, $\pi_1 = 0.05$, $\pi_2 = 0.02$, $\epsilon_{r_1} = 0.3$, $\epsilon_{r_2} = 0.25$, $\epsilon_{p_1} = 0.15$, $\epsilon_{p_2} = 0.17$ and $\omega_i = 0.001$; $i = 1, 2$.

5.3. *The effect of HAART*

Let $\epsilon = \epsilon_{r_i} = \epsilon_{p_i}$, $i = 1, 2$ to examine what is the value of ϵ that makes $R_0 = 1$ for model (5.1). In this case, we use the values of parameters listed in Table 1 with the following values of the rest of parameters $\tau_1 = 0.05$, $\tau_2 = 0.01$, $\lambda_1 = 0.2$, $\lambda_2 = 0.08$, $\pi_1 = 0.05$, $\pi_2 = 0.02$, $\vartheta = 0.01$, and $\omega_i = 0.001$; $i = 1, 2$ into Eq. (5.2) then we get $\epsilon^{\text{critical}} = 0.777664$, i.e., we have two situations:

(i) if $0 < \epsilon < 0.777664$, then $R_0 > 1$ and HIV particles are persistent;
(ii) if $0.777664 < \epsilon \leqslant 1$, then $R_0 < 1$ and the patient is healed.

Moreover, the behaviours of the variables with different values of efficiencies of drugs are presented in Figure 3. We employ the following data:

group (1): $\epsilon_{r_1} = 0.04$, $\epsilon_{r_1} = 0.03$, $\epsilon_{p_1} = 0.05$, and $\epsilon_{p_2} = 0.07$.

group (2): $\epsilon_{r_1} = 0.3$, $\epsilon_{r_1} = 0.1$, $\epsilon_{p_1} = 0.5$, and $\epsilon_{p_2} = 0.6$.

group (3): $\epsilon_{r_1} = 0.4$, $\epsilon_{r_1} = 0.5$, $\epsilon_{p_1} = 0.7$, and $\epsilon_{p_2} = 0.6$.

group (4): $\epsilon_{r_1} = 0.8$, $\epsilon_{r_1} = 0.8$, $\epsilon_{p_1} = 0.8$, and $\epsilon_{p_2} = 0.8$.

From the figure, we can see that the increasing of the efficacy of drugs will increase the concentration of the uninfected cells and decrease the concentrations of latent infected cells, active infected cells, HIV particles and B cells.

5.4. The effect of time delays parameters

Figure 4 depicts the effect of time delays on the virus dynamics. We consider these values of time delays:

set (1): $\tau_1 = 0.5$, $\tau_2 = 0.2$, $\lambda_1 = 0.9$, $\lambda_2 = 0.7$, $\pi_1 = 0.5$, and $\pi_2 = 0.4$.

set (2): $\tau_1 = 0.7$, $\tau_2 = 0.4$, $\lambda_1 = 1$, $\lambda_2 = 0.9$, $\pi_1 = 0.8$, and $\pi_2 = 0.6$.

set (3): $\tau_1 = 0.9$, $\tau_2 = 0.6$, $\lambda_1 = 1.2$, $\lambda_2 = 1.1$, $\pi_1 = 1.1$, and $\pi_2 = 0.8$.

set (4): $\tau_1 = 1.4$, $\tau_2 = 1.4$, $\lambda_1 = 1.4$, $\lambda_2 = 1.4$, $\pi_1 = 1.4$, and $\pi_2 = 1.4$.

It is observed that the effect of time delays on the dynamical behavior of the HIV is similar as the effect of HAART. So it may help to develop a new class of treatment to enlarge the delay period and then suppress the HIV replication. In addition, we let $S = \tau_i = \lambda_i = \pi_i$; $i = 1, 2$ and solve Eq. (5.2) using the values of parameter given in Table 1 with the following values of the rest of parameters $\epsilon_{r_1} = 0.3$, $\epsilon_{r_2} = 0.25$, $\epsilon_{p_1} = 0.15$, $\epsilon_{p_2} = 0.17$, $\vartheta = 0.01$ and $\omega_i = 0.001$; $i = 1, 2$ to find the critical value of time delays that make $R_0 = 1$. We obtain $S^{\text{critical}} = 1.32035$. When $0 < S < 1.32035$, the trajectories tend to E^* while, if $S > 1.32035$, the trajectories tend towards E^0 and the body is cleared from HIV particles.

6. Conclusion and discussion

The intention of this paper was to incorporate the effect of impairment of B cell functions into the virus infection model with multi-target cells. We have introduced a virus dynamics model taking into account multi-target cells, latent stage of infection, three different types of time delays and impairment of B cell response. We have found out that the model is biologically acceptable in the sense that all solutions are nonnegative and bounded. We have demonstrated the basic reproduction number R_0 which determined the existence and global stability of equilibria. We have proved that the infection-free equilibrium E^0 always exists, while an endemic-infection equilibrium E^* exists only if $R_0 > 1$. We have constructed proper Lyapunov functionals and then applied LaSalle's invariance principle to show that if $R_0 < 1$, then E^0 is G.A.S, on the other hand, if $R_0 > 1$, the other equilibrium E^* is G.A.S. The basic reproduction number R_0 of model (2.1) is given as $R_0 = \sum_{i=1}^{n} R_{0i} > R_{01}$, where R_{01} is the basic reproduction number of HIV model with one class of target cells. Therefore, neglecting multi-target cells will lead to under-estimated basic reproduction number.

We have set $n = 2$ in model (2.1) to generate an HIV model with two types of target cells, $CD4^+$ T cells and macrophages. We have combined HAART into the proposed model and showed that the theoretical results are convenient with the visual results. The effects of impairment of B cells functions, time delays and HAART treatment on the virus dynamics were addressed. We conclude that

- the time delays play the same influence of HAART treatment in stabilizing the system around the infection-free equilibrium;
- when the B cells lose their functions during the viral infection, the amount of antibodies produced by the B cells decreases and then the amount of HIV particles increases. Therefore, HAART treatment is needed to improve the health of the infected patient.

For comparison purposes, we consider the model (5.1) by neglecting the immune impairment, i.e., $\vartheta = 0$ as:

$$\begin{aligned}
\dot{U_1} &= \rho_1 - \gamma_1 U_1 - (1-\epsilon_{r_1})\omega_1 U_1 V,\\
\dot{U_2} &= \rho_2 - \gamma_2 U_2 - (1-\epsilon_{r_2})\omega_2 U_2 V,\\
\dot{L_1} &= (1-\epsilon_{r_1})(1-\chi_1)e^{-\tau_1\eta_1}\omega_1 U_1(t-\tau_1)V(t-\tau_1) - (\zeta_1+\nu_1)L_1,\\
\dot{L_2} &= (1-\epsilon_{r_2})(1-\chi_2)e^{-\tau_2\eta_2}\omega_2 U_2(t-\tau_2)V(t-\tau_2) - (\zeta_2+\nu_2)L_2,\\
\dot{A_1} &= (1-\epsilon_{r_1})\chi_1 e^{-\lambda_1\theta_1}\omega_1 U_1(t-\lambda_1)V(t-\lambda_1) + \nu_1 L_1 - \beta_1 A_1,\\
\dot{A_2} &= (1-\epsilon_{r_2})\chi_2 e^{-\lambda_2\theta_2}\omega_2 U_2(t-\lambda_2)V(t-\lambda_2) + \nu_2 L_2 - \beta_2 A_2,\\
\dot{V} &= (1-\epsilon_{p_1})\varkappa_1 e^{-\pi_1\iota_1}A_1(t-\pi_1) + (1-\epsilon_{p_2})\varkappa_2 e^{-\pi_2\iota_2}A_2(t-\pi_2) - \xi V - \rho V B,\\
\dot{B} &= \varepsilon V - \mu B.
\end{aligned} \tag{6.1}$$

Let the endemic-infection equilibrium thought as a function of $\epsilon = \epsilon_{r_i} = \epsilon_{p_i}$, $i = 1,2$ be given as: $E^*(\epsilon) = (U_1^*(\epsilon), U_2^*(\epsilon), L_1^*(\epsilon), L_2^*(\epsilon), A_1^*(\epsilon), A_2^*(\epsilon), V^*(\epsilon), B^*(\epsilon))$. Then the objective is to design treatment with efficacy ϵ to keep the concentration of the HIV particles below a given level, i.e.,

$$0 \leqslant V^*(\epsilon) \leqslant \bar{V}, \quad \text{for all} \quad \epsilon^* \leqslant \epsilon \leqslant \epsilon^{**}. \tag{6.2}$$

Let us use the value of parameters in Table 1 and the values of parameters given in Case 5.3, $\bar{V} = 0.2$ and ϑ is varied. We calculate ϵ^* and ϵ^{**} for two models.

(I) Model (6.1) (i.e., ignoring the impairment of B cells): we find that the inequality (6.2) is satisfied when $0.782704 \leqslant \epsilon \leqslant 0.816749$.

(II) Model (5.1) (i.e., incorporating the impairment of B cells): we take $\vartheta = 0.4$ and find that the inequality (6.2) is satisfied when $0.81237 \leqslant \epsilon \leqslant 0.816749$.

Therefore, if we apply drug with efficacy ϵ such that $0.782704 \leqslant \epsilon \leqslant 0.81237$, this guarantees that $V^*(\epsilon) \leqslant 0.2$ for model (6.1), but $V^*(\epsilon) > 0.2$ for model (5.1). Therefore, a more accurate drug efficacy required to reduce the concentration of the virus particle to a lower value is calculated by using our model. This shows the importance of considering the effect of immune impairment in the virus dynamics models.

Table 1: Values of fixed parameters.

Parameter	Value	Parameter	Value
ρ_i	10	η_i	1
γ_i	0.01	θ_i	1
χ_1	0.3	ι_i	1
χ_2	0.44	ν_1	0.4
ζ_1	0.3	ν_2	0.2
ζ_2	0.6	β_1	0.2
$\varkappa_1$	5	β_2	0.3
$\varkappa_2$	3	ξ	1
ρ	0.1	ε	0.2
μ	0.01		

We noticed that our proposed virus dynamics model is developed with one mode of infection namely virus-to-cell infection. Therefore our model can be extended to incorporate cell-to-cell transmission mode where the infected cells could directly infect the adjacent uninfected target cells [8, 22, 27]. We mentioned that our virus infection model assumed that the incidence rate is given by bilinear form. However, when the concentration of virus in plasma is high, the bilinear form cannot characterize the virus dynamics accurately [20, 33]. Our proposed model can be generalized to combine another types of incidence rates such as saturated, Holling type-II, Beddington-DeAngelis, Crowley-Martin and general incidence rate. In addition, the effect of diffusion [2, 3, 15, 16] as well as stochastic interactions [29] were neglected in our proposed model. However, it is more practical to improve our model to include these natural phenomena.

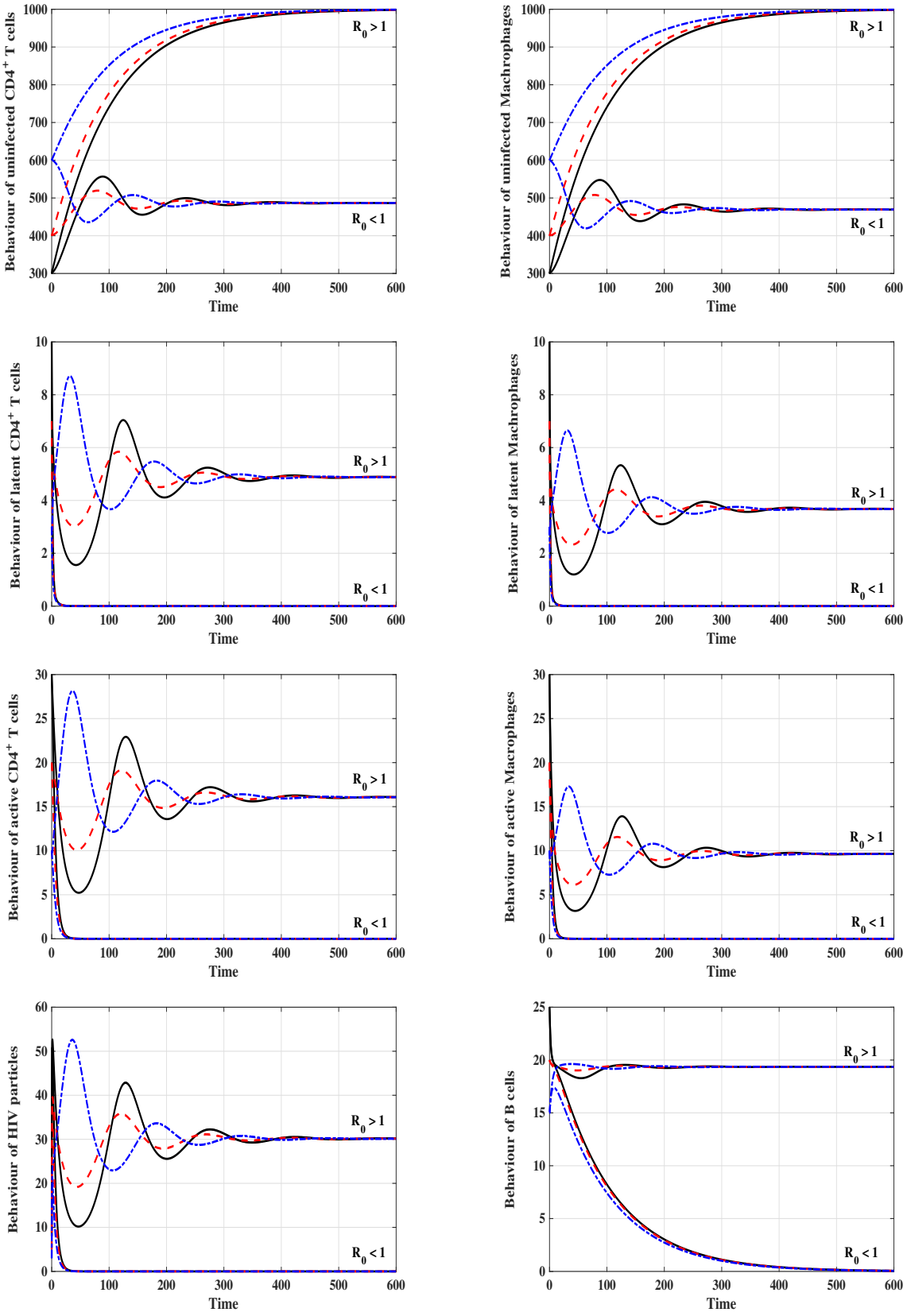

Figure 1: Solution trajectories when $\mathcal{R}_0 < 1$ and $\mathcal{R}_0 > 1$ with different initial conditions.

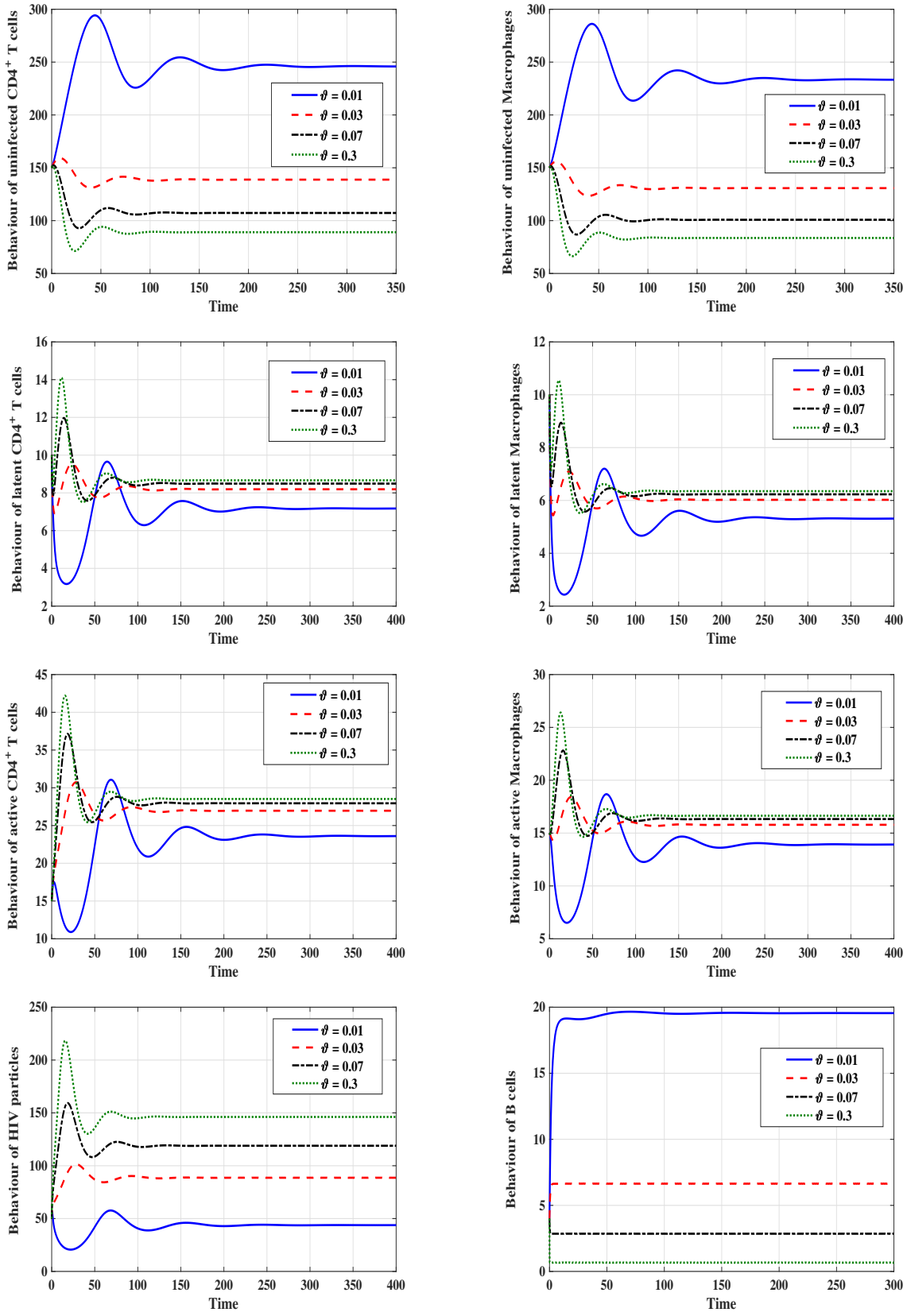

Figure 2: Solution trajectories for different values of ϑ.

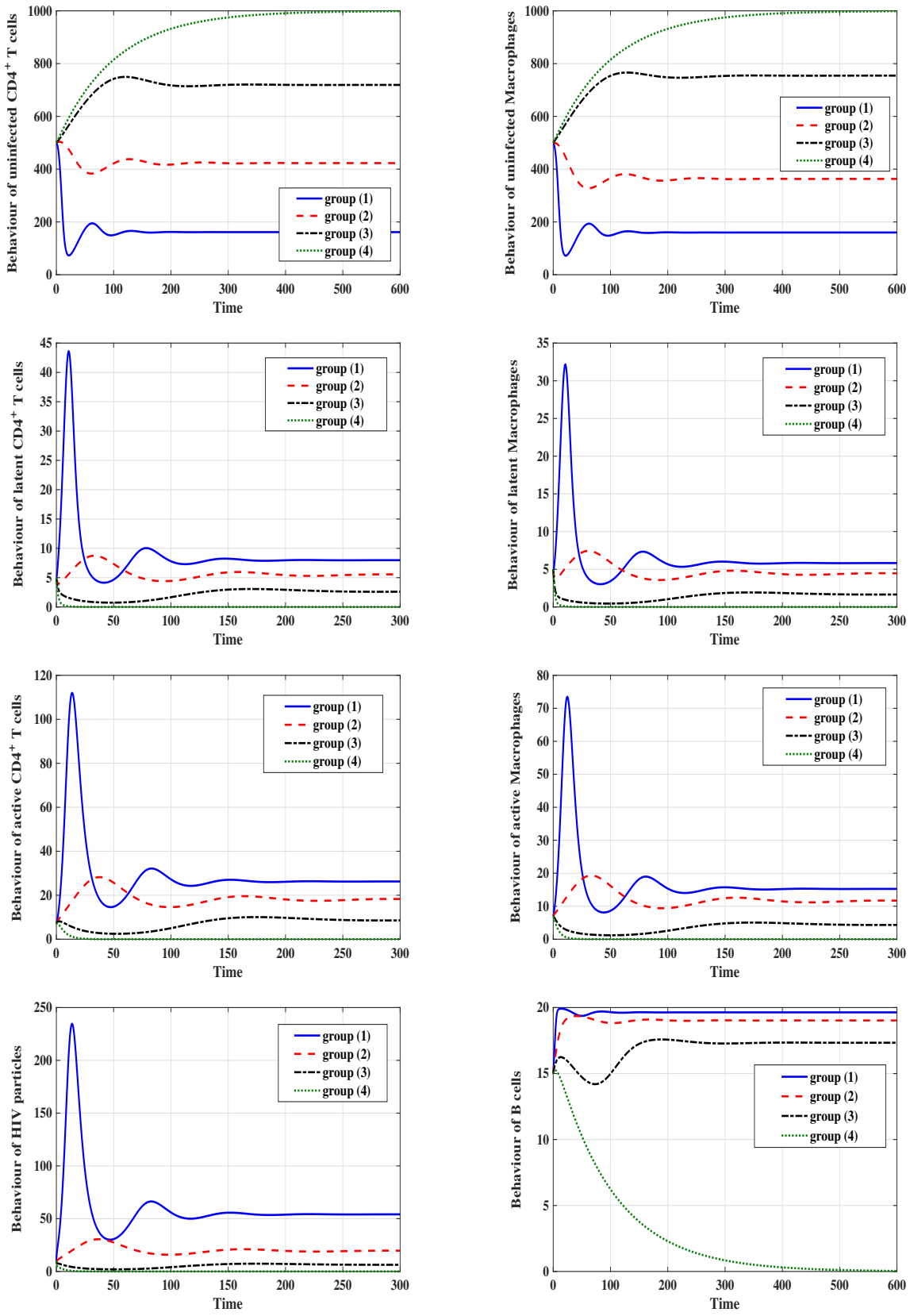

Figure 3: Solution trajectories for different values of the efficacy of PI and RTI drugs.

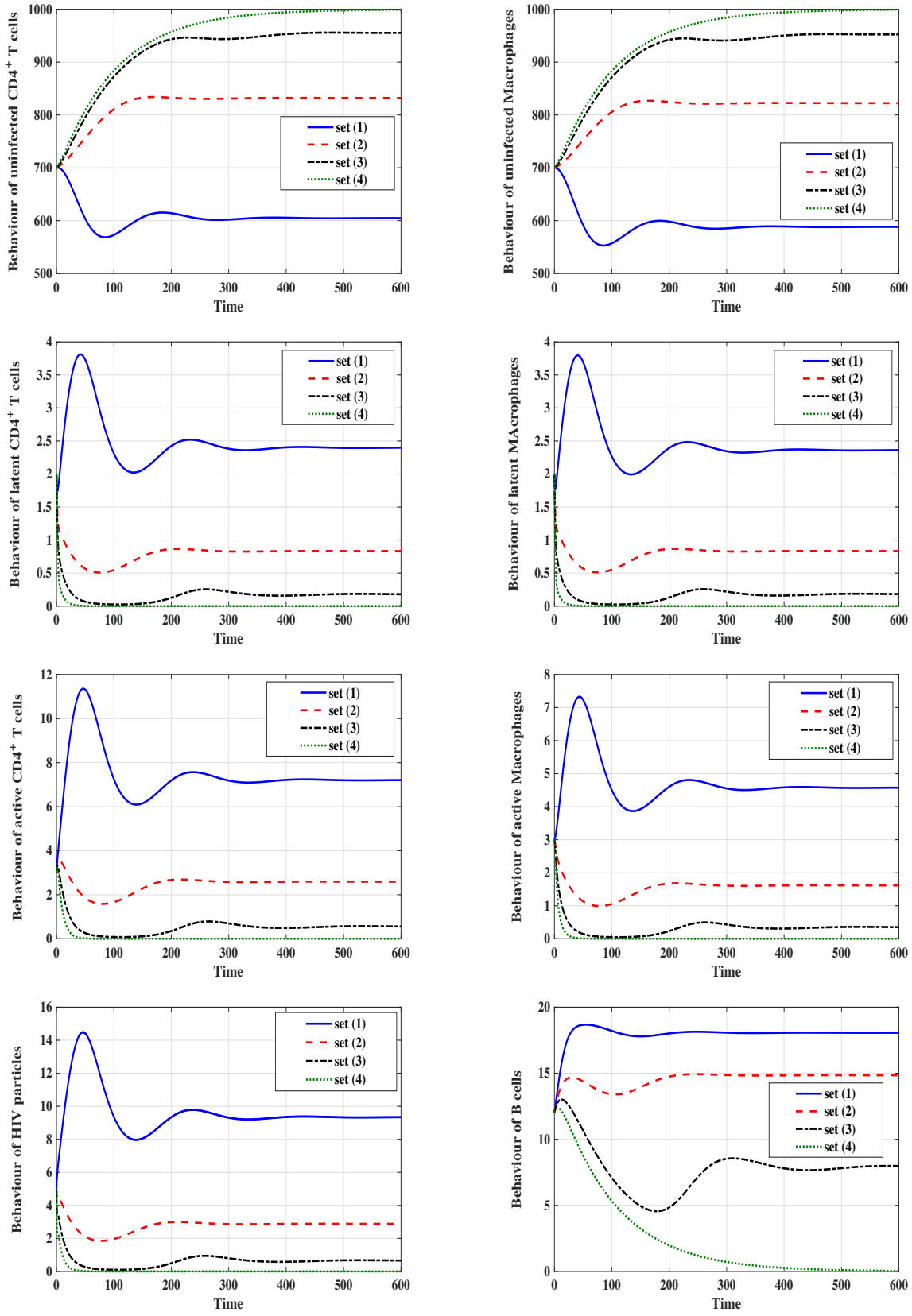

Figure 4: Solution trajectories for different values of time delays.

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