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Stability of a delay-distributed HIV infection model with silent infected cell-to-cell spread and CTL-mediated immunity

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Abstract In this paper, we formulate a mathematical model to investigate a within-host HIV dynamics under the effect of cytotoxic T lymphocytes immune response. The model incorporates two modes of transmission, virus-to-cell (VTC) and cell-to-cell (CTC). The CTC infection is due to the contact of healthy $CD4^+$ T cells with (i) silent HIV-infected cells, and (ii) active HIV-infected cells. The model integrates three types of distributed time delays. We show that the model is well posed and it has three equilibria. The existence and stability of equilibria are governed by two threshold parameters. We prove the global asymptotic stability of all equilibria by utilizing Lyapunov function and LaSalle's invariance principle. We have presented numerical simulations to illustrate the theoretical results. We have studied the effects of CTC transmission and time delays on the dynamical behavior of the system. We have shown that inclusion of time delay can significantly increase the concentration of healthy $CD4^+$ T cells and reduce the concentrations of infected cells and free HIV particles. While the inclusion of CTC transmission decreases the concentration of healthy $CD4^+$ T cells and increases the concentrations of infected cells and free HIV particles.

1 Introduction

Acquired immunodeficiency syndrome (AIDS) is one of the fatal human diseases which is caused by human immunodeficiency virus (HIV). HIV is a retrovirus that mainly infects the healthy (uninfected) $CD4^+$ T cells and other immune cells such as macrophages and dendritic cells. For long period up to 10 years [1], the HIV infection can be controlled by two main components (i) cytotoxic T lymphocytes (CTLs) that kill the HIV-infected cells, and (ii) B cells that generate specific antibodies which in turn neutralize the viruses.

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However, during this period of time the concentration of healthy CD4$^+$ T cells declines. When the concentration of the CD4$^+$ T cells reaches below 200 cells/mm^3, the patient is said to have progressed to AIDS. During the last decades, mathematical modeling of a within-host HIV infection has witnessed a significant development. Moreover, mathematical analysis of the HIV dynamics models has also become one of the most important and fundamental methods for understanding the within-host HIV dynamics [2–8]. Nowak and Bangham [6] have introduced an HIV infection model which describes the interaction between healthy CD4$^+$ T cells (W), active HIV-infected cells (M), free HIV particles (N) and HIV-specific CTLs (P):

$$\begin{cases} \dot{W}(t) = \rho - \alpha W(t) - \eta_1 W(t)N(t), \\ \dot{M}(t) = \eta_1 W(t)N(t) - aM(t) - \mu P(t)M(t), \\ \dot{N}(t) = bM(t) - \varepsilon N(t), \\ \dot{P}(t) = \sigma P(t)M(t) - \pi P(t). \end{cases} \tag{1}$$

The healthy CD4$^+$ T cells are generated at specific constant rate ρ and die at rate αW. The term $\eta_1 WN$ refers to the rate at which new infectious appears by virus-to-cell (VTC) transmission between free HIV particles and healthy CD4$^+$ T cells. The active HIV-infected cells die at rate aM. The term μPM is the killing rate of active HIV-infected cells due to their HIV-specific CTL-mediated immunity. The free HIV particles are generated at rate bM and cleared from the plasma at rate εN. The proliferation rate of the effective HIV-specific CTLs is given by σPM. The term πP represents the decay rate of the CTLs. HIV infection models with CTL-mediated immune response have been investigated in many papers (see, e.g., [2–16]).

Model (1) is formulated on the assumption that HIV can only spread by VTC transmission. However, several works have reported that there is another mode of transmission called cell-to-cell (CTC) where HIV can be transmitted directly from an infected cell to a healthy CD4$^+$ T cell through the formation of virological synapses (see, e.g., [17–20]). Sourisseau et al. [21] have shown that CTC transmission plays an efficient role in the HIV replication. Sigal et al. [22] have demonstrated the importance of CTC transmission in the HIV infection process during the antiviral treatment. Iwami et al. [19] have shown that more than 50% of HIV infections are due to CTC transmission. The effects of both VTC and CTC transmissions on the virus dynamics have been addressed in several works (see, e.g., [23–29]), although the CTL-mediated immunity has not been considered. Virus dynamics models with both VTC and CTC transmissions and CTL-mediated immunity have been investigated in [30–32]. Wang et al. [31] have proposed the following virus dynamics model with CTL-mediated immunity, both VTC and CTC transmissions and a distributed time delay for production of active infected cells:

$$\begin{cases} \dot{W}(t) = \rho - \alpha W(t) - \eta_1 W(t)N(t) - \eta_2 W(t)U(t), \\ \dot{M}(t) = \int_0^\infty \Lambda(\varphi)e^{-\hbar\varphi} W(t-\varphi)\left[\eta_1 N(t-\varphi) + \eta_2 U(t-\varphi)\right] \mathrm{d}\varphi - aM(t) - \mu P(t)M(t), \\ \dot{N}(t) = bM(t) - \varepsilon N(t), \\ \dot{P}(t) = \sigma P(t)M(t) - \pi P(t). \end{cases} \tag{2}$$

The healthy CD4$^+$ T cells are contacted with active CD4$^+$ T infected cells and become infected due to CTC transmission at rate $\eta_2 WU$. The factor $\Lambda(\varphi)e^{-\hbar\varphi}$ represents the probability that healthy CD4$^+$ T cells contacted by HIV particles or active HIV-infected cells at

time $t-\varphi$ survived φ time units and become active infected at time t. The delay parameter φ is random taken from a probability distribution function $\Lambda(\varphi)$ over the time interval $(0,\infty)$.

It is known that current anti-retroviral drugs can suppress HIV replication to a low level but cannot enucleate HIV from the body. One of the main reasons of this fact is the presence of silent (latent) CD4$^+$ T infected cells where the HIV provirus can reside [33,34]. Silent HIV-infected cells live long, but they can be activated to produce new HIV particles. Silent HIV-infected cells have been included in the virus dynamics models with both VTC and CTC transmissions in [35–40]. In a very recent work [41], it has been shown that both silent and active HIV-infected cells can infect the healthy CD4$^+$ T cells through CTC mechanism. In the literature, all viral infection models with CTC transmission and silent infected cells have assumed that the CTC transmission only occurs due to the active infected cells.

In the present paper, we extend model (2) by considering in the dynamics (i) both silent and active HIV-infected cells, (ii) three types of distributed time delays and (iii) three types of infection modes, VTC, silent HIV-infected CTC and active HIV-infected CTC transmissions. The well-posedness of the model is investigated. We deduce two threshold parameters which govern the existence and stability of the three equilibria. Global stability of all equilibria is proven by formulating Lyapunov functions and utilizing LaSalle's invariance principle. We perform some numerical simulations to illustrate the strength of our theoretical results.

2 Model formulation

We formulate a distributed delay HIV infection model with CTL-mediated immunity. We assume that the HIV virions can replicate by two mechanisms VTC and CTC transmissions. The CTC infection has two sources, (i) the contact between healthy CD4$^+$ T cells and silent HIV-infected cells, and (ii) the contact between healthy CD4$^+$ T cells and active HIV-infected cells. Under these assumptions, we propose the following model:

$$\begin{cases} \dot{W}(t) = \rho - \alpha W(t) - \eta_1 W(t)N(t) - \eta_2 W(t)U(t) - \eta_3 W(t)M(t), \\ \dot{U}(t) = \int_0^{\kappa_1} \Lambda_1(\varphi) e^{-\hbar_1\varphi} W(t-\varphi)\left[\eta_1 N(t-\varphi) + \eta_2 U(t-\varphi) + \eta_3 M(t-\varphi)\right] \mathrm{d}\varphi - (\lambda+\gamma)\, U(t), \\ \dot{M}(t) = \lambda \int_0^{\kappa_2} \Lambda_2(\varphi) e^{-\hbar_2\varphi} U(t-\varphi)\mathrm{d}\varphi - aM(t) - \mu P(t)M(t), \\ \dot{N}(t) = b \int_0^{\kappa_3} \Lambda_3(\varphi) e^{-\hbar_3\varphi} M(t-\varphi)\mathrm{d}\varphi - \varepsilon N(t), \\ \dot{P}(t) = \sigma P(t)M(t) - \pi P(t), \end{cases} \tag{3}$$

where $U(t)$ is the concentration of silent HIV-infected cells. The healthy CD4$^+$ T cells are contacted with silent HIV-infected cells and become infected due to CTC transmission at rate $\eta_3 WM$. The term λU is the rate of silent HIV-infected cells that become active HIV-infected cells. γU represents the death rate of the silent HIV-infected cells. The factor $\Lambda_1(\varphi)e^{-\hbar_1\varphi}$ represents the probability that healthy CD4$^+$ T cells contacted by HIV particles or HIV-infected cells at time $t-\varphi$ survived φ time units and become silent infected at time t. The term $\Lambda_2(\varphi)e^{-\hbar_2\varphi}$ is the probability that silent HIV-infected cells survived φ time units before transmitted to be active at time t. Moreover, the factor $\Lambda_3(\varphi)e^{-\hbar_3\varphi}$ demonstrates the probability of new immature HIV particles at time $t-\varphi$ lost φ time units and become mature at time t. Here, $\hbar_i$, $i=1,2,3$ are positive constants. The delay parameter φ is random taken from a probability distribution function $\Lambda_i(\varphi)$ over the time interval $[0,\kappa_i]$, $i=1,2,3$, where κ_i is the limit superior of this delay period. The function $\Lambda_i(\varphi)$, $i=1,2,3$ satisfies

Table 1 Parameters of model (3) and their interpretations

Parameter	Biological meaning
ρ	Recruitment rate for the healthy $CD4^+$ T cells
α	Natural death rate constant for the healthy $CD4^+$ T cells
η_1	Virus-cell incidence rate constant between free HIV particles and healthy $CD4^+$ T cells
η_2	Cell-cell incidence rate constant between silent HIV-infected cells and healthy $CD4^+$ T cells
η_3	Cell-cell incidence rate constant between active HIV-infected cells and healthy $CD4^+$ T cells
γ	Death rate constant of silent HIV-infected cells
a	Death rate constant of active HIV-infected cells
μ	Killing rate constant of active HIV-infected cells due to their specific CTL-mediated immunity
λ	Transmission rate constant of silent HIV-infected cells that become active HIV-infected cells
b	Generation rate constant of new HIV particles
ε	Death rate constant of free HIV particles
σ	Proliferation rate constant of effective HIV-specific CTLs
π	Decay rate constant of HIV-specific CTLs
φ	Delay parameter
$\Lambda_i(\varphi)$	Probability distribution function

$\Lambda_i(\varphi) > 0$ and

$$\int_0^{\kappa_i} \Lambda_i(\varphi)\mathrm{d}\varphi = 1 \text{ and } \int_0^{\kappa_i} \Lambda_i(\varphi)e^{-u\varphi}\mathrm{d}\varphi < \infty,$$

where $u > 0$. Let us denote

$$\bar{\mathcal{H}}_i(\varphi) = \Lambda_i(\varphi)e^{-\hbar_i\varphi} \text{ and } \mathcal{H}_i = \int_0^{\kappa_i} \bar{\mathcal{H}}_i(\varphi)\mathrm{d}\varphi,$$

where $i = 1, 2, 3$. Thus, $0 < \mathcal{H}_i \leq 1$, $i = 1, 2, 3$. The initial conditions of system (3) are given by:

$$\begin{aligned} &W(x) = \epsilon_1(x), U(x) = \epsilon_2(x), M(x) = \epsilon_3(x), N(x) = \epsilon_4(x), P(x) = \epsilon_5(x), \\ &\epsilon_j(x) \geq 0,\ x \in [-\kappa, 0],\ j = 1, 2, \ldots, 5,\ \kappa = \max\{\kappa_1, \kappa_2, \kappa_3\}, \end{aligned} \tag{4}$$

where $\epsilon_j(x) \in \mathcal{C}([-\kappa, 0], \mathbb{R}_{\geq 0})$, $j = 1, 2, \ldots, 5$ and $\mathcal{C} = \mathcal{C}([-\kappa, 0], \mathbb{R}_{\geq 0})$ is the Banach space of continuous functions with norm $\|\epsilon_j\| = \sup_{-\kappa \leq m \leq 0} |\epsilon_j(m)|$ for $\epsilon_j \in \mathcal{C}$. Therefore, system (3) with initial conditions (4) has a unique solution by using the standard theory of functional differential equations [42,43]. All remaining variables and parameters have the same biological meaning as explained in Sect. 1. Table 1 summarizes all parameters and their definitions.

3 Well-posedness of solutions

Proposition 1 *All solutions of system* (3) *with initial conditions* (4) *are nonnegative and ultimately bounded.*

Proof First, we show the nonnegativity of solutions. From the first equation of system (3), we have $\dot{W}\mid_{W=0}= \rho > 0$, then $W(t) > 0$ for all $t \geq 0$. Moreover, the rest equations of system (3) give us the following:

$$\begin{aligned}
U(t) &= \epsilon_2(0)e^{-(\lambda+\gamma)t} \\
&\quad + \int_0^t e^{-(\lambda+\gamma)(t-\varkappa)} \int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi) W(\varkappa-\varphi)\left[\eta_1 N(\varkappa-\varphi) + \eta_2 U(\varkappa-\varphi)\right. \\
&\quad \left. + \eta_3 M(\varkappa-\varphi)\right] \mathrm{d}\varphi \mathrm{d}\varkappa \geq 0, \\
M(t) &= \epsilon_3(0)e^{-\int_0^t (a+\mu P(y))\mathrm{d}y} + \lambda \int_0^t e^{-\int_\varkappa^t (a+\mu P(y))\mathrm{d}y} \int_0^{\kappa_2} \bar{\mathcal{H}}_2(\varphi) U(\varkappa-\varphi)\mathrm{d}\varphi\mathrm{d}\varkappa \geq 0, \\
N(t) &= \epsilon_4(0)e^{-\varepsilon t} + b\int_0^t e^{-\varepsilon(t-\varkappa)} \int_0^{\kappa_3} \bar{\mathcal{H}}_3(\varphi) M(\varkappa-\varphi)\mathrm{d}\varphi\mathrm{d}\varkappa \geq 0, \\
P(t) &= \epsilon_5(0)e^{-\int_0^t (\pi-\sigma M(y))\mathrm{d}y} \geq 0,
\end{aligned}$$

for all $t \in [0, \kappa]$. Thus, by a recursive argument, we get $W(t), U(t), M(t), N(t), P(t) \geq 0$ for all $t \geq 0$. Hence, the solutions of system (3) satisfy $(W(t), U(t), M(t), N(t), P(t)) \in \mathbb{R}^5_{\geq 0}$ for all $t \geq 0$.

Now, we investigate the boundedness. From the first equation of system (3), we obtain $\limsup_{t\to\infty} W(t) \leq \frac{\rho}{\alpha}$. Let $\Psi_1(t) = \int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi) W(t-\varphi)\mathrm{d}\varphi + U(t)$, then

$$\begin{aligned}
\dot{\Psi}_1(t) &= \int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi)\left[\rho - \alpha W(t-\varphi)\right]\mathrm{d}\varphi - (\lambda+\gamma)U(t) \\
&= \rho\mathcal{H}_1 - \alpha\int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi) W(t-\varphi)\mathrm{d}\varphi - (\lambda+\gamma)U(t) \\
&\leq \rho - \phi_1\left[\int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi) W(t-\varphi)\mathrm{d}\varphi + U(t)\right] = \rho - \phi_1\Psi_1(t),
\end{aligned}$$

where $\phi_1 = \min\{\alpha, \lambda+\gamma\}$. It follows that, $\limsup_{t\to\infty} \Psi_1(t) \leq \Omega_1$, where $\Omega_1 = \frac{\rho}{\phi_1}$. Since $\int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi) W(t-\varphi)\mathrm{d}\varphi$ and $U(t)$ are nonnegative, then $\limsup_{t\to\infty} U(t) \leq \Omega_1$. Moreover, we let $\Psi_2(t) = M(t) + \frac{\mu}{\sigma}P(t)$, then

$$\begin{aligned}
\dot{\Psi}_2(t) &= \lambda\int_0^{\kappa_2} \bar{\mathcal{H}}_2(\varphi) U(t-\varphi)\mathrm{d}\varphi - aM(t) - \frac{\mu\pi}{\sigma}P(t) \leq \lambda\mathcal{H}_2\Omega_1 - aM(t) - \frac{\mu\pi}{\sigma}P(t) \\
&\leq \lambda\Omega_1 - aM(t) - \frac{\mu\pi}{\sigma}P(t) \leq \lambda\Omega_1 - \phi_2\left(M(t) + \frac{\mu}{\sigma}P(t)\right) = \lambda\Omega_1 - \phi_2\Psi_2(t),
\end{aligned}$$

where $\phi_2 = \min\{a, \pi\}$. It follows that, $\limsup_{t\to\infty} \Psi_2(t) \le \Omega_2$, where $\Omega_2 = \dfrac{\lambda\Omega_1}{\phi_2}$. Since $M(t) \ge 0$ and $P(t) \ge 0$, then $\limsup_{t\to\infty} M(t) \le \Omega_2$ and $\limsup_{t\to\infty} P(t) \le \Omega_3$, where $\Omega_3 = \frac{\sigma}{\mu}\Omega_2$. Finally, from the fourth equation of system (3), we have

$$\dot{N}(t) = b\int_0^{\kappa_3} \bar{\mathcal{H}}_3(\varphi)M(t-\varphi)\mathrm{d}\varphi - \varepsilon N(t) \le b\mathcal{H}_3\Omega_2 - \varepsilon N(t) \le b\Omega_2 - \varepsilon N(t).$$

Thus, $\limsup_{t\to\infty} N(t) \le \Omega_4$, where $\Omega_4 = \dfrac{b\Omega_2}{\varepsilon}$. □

According to Proposition 1, we can show that the region

$$\Xi = \left\{(W, U, M, N, P) \in \mathcal{C}^5_{\ge 0} : \|W\| \le \Omega_1, \|U\| \le \Omega_1, \|M\| \le \Omega_2, \|P\| \le \Omega_3, \|N\| \le \Omega_4\right\}$$

is positively invariant with respect to system (3). □

4 Equilibria

Let (W, U, M, N, P) be any equilibrium of system (3) satisfying the following equations:

$$0 = \rho - \alpha W - \eta_1 WN - \eta_2 WU - \eta_3 WM, \tag{5}$$
$$0 = \mathcal{H}_1\left(\eta_1 WN + \eta_2 WU + \eta_3 WM\right) - (\lambda + \gamma)\, U, \tag{6}$$
$$0 = \lambda\mathcal{H}_2 U - aM - \mu PM, \tag{7}$$
$$0 = b\mathcal{H}_3 M - \varepsilon N, \tag{8}$$
$$0 = (\sigma M - \pi)\, P. \tag{9}$$

The straightforward calculation finds that system (3) admits five equilibria.

(i) It is obvious that system (3) has an infection-free equilibrium, $Đ_0 = (W_0, 0, 0, 0, 0)$, where $W_0 = \rho/\alpha$. This case describes the situation of healthy state where the HIV infection is absent.

(ii) When $P_1 = 0$, we have a chronic HIV infection equilibrium with inactive CTL-mediated immune response, $Đ_1 = (W_1, U_1, M_1, N_1, 0)$, where

$$W_1 = \frac{a\varepsilon(\gamma+\lambda)}{\mathcal{H}_1\left[a\varepsilon\eta_2 + \lambda\mathcal{H}_2(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3)\right]},$$
$$U_1 = \frac{a\varepsilon\alpha}{a\varepsilon\eta_2 + \lambda\mathcal{H}_2(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3)}\left[\frac{W_0\mathcal{H}_1\{a\varepsilon\eta_2 + \lambda\mathcal{H}_2(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3)\}}{a\varepsilon(\gamma+\lambda)} - 1\right],$$
$$M_1 = \frac{\varepsilon\alpha\lambda\mathcal{H}_2}{a\varepsilon\eta_2 + \lambda\mathcal{H}_2(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3)}\left[\frac{W_0\mathcal{H}_1\{a\varepsilon\eta_2 + \lambda\mathcal{H}_2(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3)\}}{a\varepsilon(\gamma+\lambda)} - 1\right],$$
$$N_1 = \frac{\alpha b\lambda\mathcal{H}_2\mathcal{H}_3}{a\varepsilon\eta_2 + \lambda\mathcal{H}_2(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3)}\left[\frac{W_0\mathcal{H}_1\{a\varepsilon\eta_2 + \lambda\mathcal{H}_2(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3)\}}{a\varepsilon(\gamma+\lambda)} - 1\right].$$

Therefore, $Đ_1$ exists when

$$\frac{W_0\mathcal{H}_1\left[a\varepsilon\eta_2 + \lambda\mathcal{H}_2(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3)\right]}{a\varepsilon(\gamma+\lambda)} > 1.$$

At the equilibrium $Đ_1$, the chronic HIV infection persists while the CTL-mediated immune response is unstimulated. In order to state the threshold dynamics of infection-free equilibrium, it is necessary to define the basic HIV reproduction number $\Re_0$ of the model. If

the antiviral drugs are taken into account in that HIV dynamics model, then $\Re_0$ can be used to determine the minimum drug efficacy which stabilizes the system around the infection-free equilibrium and clears the viruses from the body. The basic HIV reproduction number of model (3) can be calculated by different methods such as (i) the next-generation matrix method of van den Driessche and Watmough [44], (ii) local stability of the infection-free equilibrium, and (iii) the existence of the chronic HIV infection equilibrium with inactive CTL-mediated immune response. In the present paper, we derive $\Re_0$ by method (iii) as:

$$\Re_0 = \frac{W_0\mathcal{H}_1\left[a\varepsilon\eta_2 + \lambda\mathcal{H}_2\left(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3\right)\right]}{a\varepsilon\left(\gamma+\lambda\right)} = \Re_{01} + \Re_{02} + \Re_{03},$$

where

$$\Re_{01} = \frac{W_0\lambda b\eta_1\mathcal{H}_1\mathcal{H}_2\mathcal{H}_3}{a\varepsilon\left(\gamma+\lambda\right)},\ \Re_{02} = \frac{W_0\eta_2\mathcal{H}_1}{\gamma+\lambda},\ \Re_{03} = \frac{W_0\lambda\eta_3\mathcal{H}_1\mathcal{H}_2}{a\left(\gamma+\lambda\right)}.$$

The parameter $\Re_0$ determines whether or not the infection will be chronic in the absence of the immune response. In fact, $\Re_{01}$ determines the average number of secondary HIV-infected cells caused by an existing free HIV particle due to VTC transmission, while $\Re_{02}$ and $\Re_{03}$ determine the average numbers of secondary HIV-infected cells caused by living silent and active HIV-infected cell, respectively, due to CTC transmission. In terms of $\Re_0$, we can write

$$\begin{aligned} W_1 &= \frac{W_0}{\Re_0}, U_1 = \frac{a\varepsilon\alpha}{a\varepsilon\eta_2 + \lambda\mathcal{H}_2\left(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3\right)}\left(\Re_0 - 1\right), \\ M_1 &= \frac{\varepsilon\alpha\lambda\mathcal{H}_2}{a\varepsilon\eta_2 + \lambda\mathcal{H}_2\left(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3\right)}\left(\Re_0 - 1\right), N_1 = \frac{\alpha b\lambda\mathcal{H}_2\mathcal{H}_3}{a\varepsilon\eta_2 + \lambda\mathcal{H}_2\left(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3\right)}\left(\Re_0 - 1\right). \end{aligned} \tag{10}$$

(iii) When $P \neq 0$, we have $M_2 = \dfrac{\pi}{\sigma}$. In this case, we consider a chronic HIV infection equilibrium with active CTL-mediated immune response, $Ð_2 = (W_2, U_2, M_2, N_2, P_2)$, where

$$W_2 = \frac{\rho\varepsilon\sigma}{b\pi\eta_1\mathcal{H}_3 + \varepsilon\left(\pi\eta_3 + \alpha\sigma + \sigma\eta_2U_2\right)}, N_2 = \frac{b\pi\mathcal{H}_3}{\varepsilon\sigma}, P_2 = \frac{a}{\mu}\left(\frac{\lambda\sigma\mathcal{H}_2U_2}{a\pi} - 1\right), \tag{11}$$

and U_2 satisfies the quadratic equation

$$\tilde{A}U_2^2 + \tilde{B}U_2 + \tilde{C} = 0, \tag{12}$$

where

$$\begin{aligned} \tilde{A} &= \varepsilon\eta_2\sigma\left(\gamma+\lambda\right), \\ \tilde{B} &= \pi\left(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3\right)\left(\gamma+\lambda\right) + \varepsilon\sigma\left[\alpha\left(\gamma+\lambda\right) - \eta_2\rho\mathcal{H}_1\right], \\ \tilde{C} &= -\pi\rho\mathcal{H}_1\left(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3\right). \end{aligned} \tag{13}$$

Since $\tilde{A} > 0$ and $\tilde{C} < 0$, then $\tilde{B}^2 - 4\tilde{A}\tilde{C} > 0$ and there are two distinct real roots of Eq. (12). The positive root is given by

$$U_2 = \frac{-\tilde{B} + \sqrt{\tilde{B}^2 - 4\tilde{A}\tilde{C}}}{2\tilde{A}}.$$

It follows that $W_2 > 0$ and $P_2 > 0$ only when $\frac{\lambda\sigma\mathcal{H}_2U_2}{a\pi} > 1$. We define the HIV specific CTL-mediated immunity reproduction number as follows:

$$\Re_1 = \frac{\lambda\sigma\mathcal{H}_2U_2}{a\pi}.$$

Thus, $P_2 = \frac{a}{\mu}(\Re_1 - 1)$. Therefore, $Ð_2$ exists when $\Re_1 > 1$. The parameter $\Re_1$ determines whether or not the HIV-specific CTL-mediated immune response is stimulated.

The threshold parameters are given as follows:

$$\Re_0 = \frac{W_0\mathcal{H}_1\left[a\varepsilon\eta_2 + \lambda\mathcal{H}_2\left(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3\right)\right]}{a\varepsilon\left(\gamma + \lambda\right)},\ \Re_1 = \frac{\lambda\sigma\mathcal{H}_2U_2}{a\pi}.$$

□

5 Global stability analysis

In this section, we prove the global asymptotic stability of all equilibria by constructing Lyapunov functional following the method presented in [45–49]. Define $F(x) = x - 1 - \ln x$. Denote $(W, U, M, N, P) = (W(t), U(t), M(t), N(t), P(t))$ and $(W_\varphi, U_\varphi, M_\varphi, N_\varphi) = (W(t-\varphi), U(t-\varphi), M(t-\varphi), N(t-\varphi))$.

Theorem 1 *If $\Re_0 \le 1$, then $Ð_0$ is globally asymptotically stable (G.A.S).*

Proof Construct a Lyapunov functional candidate $\Theta_0(W, U, M, N, P)$ as follows:

$$\begin{aligned}\Theta_0 = {} & W_0F\left(\frac{W}{W_0}\right) + \frac{1}{\mathcal{H}_1}U + \frac{W_0\left(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3\right)}{a\varepsilon}M + \frac{\eta_1W_0}{\varepsilon}N + \frac{\mu W_0\left(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3\right)}{\sigma a\varepsilon}P \\ & + \frac{1}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\int_{t-\varphi}^{t}W(\varkappa)\left[\eta_1N(\varkappa) + \eta_2U(\varkappa) + \eta_3M(\varkappa)\right]\mathrm{d}\varkappa\mathrm{d}\varphi \\ & + \frac{\lambda W_0\left(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3\right)}{a\varepsilon}\int_0^{\kappa_2}\bar{\mathcal{H}}_2(\varphi)\int_{t-\varphi}^{t}U(\varkappa)\mathrm{d}\varkappa\mathrm{d}\varphi + \frac{b\eta_1W_0}{\varepsilon}\int_0^{\kappa_3}\bar{\mathcal{H}}_3(\varphi)\int_{t-\varphi}^{t}M(\varkappa)\mathrm{d}\varkappa\mathrm{d}\varphi.\end{aligned}$$

It is seen that, $\Theta_0(W, U, M, N, P) > 0$ for all $W, U, M, N, P > 0$, and Θ_0 has a global minimum at $Ð_0$. We calculate $\frac{\mathrm{d}\Theta_0}{\mathrm{d}t}$ along the solutions of model (3) as:

$$\begin{aligned}\frac{\mathrm{d}\Theta_0}{\mathrm{d}t} = {} & \left(1 - \frac{W_0}{W}\right)\left(\rho - \alpha W - \eta_1WN - \eta_2WU - \eta_3WM\right) \\ & + \frac{1}{\mathcal{H}_1}\left[\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)W_\varphi\left(\eta_1N_\varphi + \eta_2U_\varphi + \eta_3M_\varphi\right)\mathrm{d}\varphi - \left(\lambda + \gamma\right)U\right] \\ & + \frac{W_0\left(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3\right)}{a\varepsilon}\left[\lambda\int_0^{\kappa_2}\bar{\mathcal{H}}_2(\varphi)U_\varphi\mathrm{d}\varphi - aM - \mu PM\right] \\ & + \frac{\eta_1W_0}{\varepsilon}\left[b\int_0^{\kappa_3}\bar{\mathcal{H}}_3(\varphi)M_\varphi\mathrm{d}\varphi - \varepsilon N\right] + \frac{\mu W_0\left(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3\right)}{\sigma a\varepsilon}\left(\sigma PM - \pi P\right)\end{aligned}$$

$$+\frac{1}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\left[W\left(\eta_1 N+\eta_2 U+\eta_3 M\right)-W_\varphi\left(\eta_1 N_\varphi+\eta_2 U_\varphi+\eta_3 M_\varphi\right)\right]\mathrm{d}\varphi$$

$$+\frac{\lambda W_0\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{a\varepsilon}\int_0^{\kappa_2}\bar{\mathcal{H}}_2(\varphi)\left(U-U_\varphi\right)\mathrm{d}\varphi+\frac{b\eta_1 W_0}{\varepsilon}\int_0^{\kappa_3}\bar{\mathcal{H}}_3(\varphi)\left(M-M_\varphi\right)\mathrm{d}\varphi \tag{14}$$

Collecting terms of Eq. (14), we get

$$\frac{\mathrm{d}\Theta_0}{\mathrm{d}t}=\left(1-\frac{W_0}{W}\right)(\rho-\alpha W)+\eta_2 W_0 U-\frac{\lambda+\gamma}{\mathcal{H}_1}U$$
$$+\frac{\lambda W_0\mathcal{H}_2\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{a\varepsilon}U-\frac{\mu\pi W_0\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{\sigma a\varepsilon}P.$$

Using $W_0=\rho/\alpha$, we obtain

$$\frac{\mathrm{d}\Theta_0}{\mathrm{d}t}=-\alpha\frac{(W-W_0)^2}{W}+\frac{\lambda+\gamma}{\mathcal{H}_1}\left[\frac{W_0\mathcal{H}_1\left\{a\varepsilon\eta_2+\lambda\mathcal{H}_2\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)\right\}}{a\varepsilon\left(\lambda+\gamma\right)}-1\right]U$$
$$-\frac{\mu\pi W_0\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{\sigma a\varepsilon}P$$
$$=-\alpha\frac{(W-W_0)^2}{W}+\frac{\lambda+\gamma}{\mathcal{H}_1}\left(\Re_0-1\right)U-\frac{\mu\pi W_0\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{\sigma a\varepsilon}P.$$

Therefore, $\frac{\mathrm{d}\Theta_0}{\mathrm{d}t}\leq 0$ for all $W,U,M,N,P>0$ with equality holding when $W=W_0$ and $U=P=0$. Let $\Upsilon_0=\left\{(W,U,M,N,P):\frac{\mathrm{d}\Theta_0}{\mathrm{d}t}=0\right\}$ and $\Upsilon_0^{'}$ be the largest invariant subset of Υ_0. The solutions of system (3) converge to $\Upsilon_0^{'}$ [42]. The set $\Upsilon_0^{'}$ is invariant and contains elements which satisfy $W(t)=W_0$ and $U(t)=P(t)=0$. According to the LaSalle's invariance principle, $\lim_{t\to\infty}W(t)=W_0$ and $\lim_{t\to\infty}U(t)=\lim_{t\to\infty}P(t)=0$. Then, $\dot{W}(t)=0$ and $\dot{U}(t)=\dot{P}(t)=0$. From the third and fourth equations of system (3), we have

$$\dot{M}(t)=-aM(t), \tag{15}$$

$$\dot{N}(t)=b\int_0^{\kappa_3}\bar{\mathcal{H}}_3(\varphi)M_\varphi\mathrm{d}\varphi-\varepsilon N(t). \tag{16}$$

We define a Lyapunov function:

$$\tilde{\Theta}_0=M(t)+\frac{a}{2b\mathcal{H}_3}N(t)+\frac{a}{2\mathcal{H}_3}\int_0^{\kappa_3}\bar{\mathcal{H}}_3(\varphi)\int_{t-\varphi}^{t}M(\varkappa)\mathrm{d}\varkappa\mathrm{d}\varphi.$$

Therefore, the time derivative of $\tilde{\Theta}_0$ along the solutions of system (15)–(16) can be calculated as follows:

$$\frac{\mathrm{d}\tilde{\Theta}_0}{\mathrm{d}t}=-\frac{a}{2}\left(M(t)+\frac{\varepsilon}{b\mathcal{H}_3}N(t)\right)\leq 0.$$

Clearly, $\frac{\mathrm{d}\tilde{\Theta}_0}{\mathrm{d}t}=0$ if and only if $M(t)=N(t)=0$ for all t. Let $\Upsilon_0^{''}=\left\{(W,U,M,N,P)\in\Upsilon_0^{'}:\frac{\mathrm{d}\tilde{\Theta}_0}{\mathrm{d}t}=0\right\}$. It follows that $\Upsilon_0^{''}=\left\{(W,U,M,N,P)\in\Upsilon_0^{'}:\right.$

$W = W_0, U = M = N = P = 0\} = \{\mathcal{D}_0\}$. Hence, all solution trajectories approach Đ_0 and this means that Đ_0 is G.A.S [42,43]. □

Lemma 1 *If* $\Re_1 \leq 1$, *then* $M_1 \leq M_2$.

Proof Let $\Re_1 \leq 1$, then $\frac{\lambda\sigma\mathcal{H}_2U_2}{a\pi} \leq 1$ and hence

$$\begin{aligned} U_2 \leq \frac{a\pi}{\lambda\sigma\mathcal{H}_2} &\Longrightarrow \frac{-\tilde{B} + \sqrt{\tilde{B}^2 - 4\tilde{A}\tilde{C}}}{2\tilde{A}} \leq \frac{a\pi}{\lambda\sigma\mathcal{H}_2} \\ &\Longrightarrow \sqrt{\tilde{B}^2 - 4\tilde{A}\tilde{C}} \leq \frac{2\tilde{A}a\pi + \lambda\sigma\mathcal{H}_2\tilde{B}}{\lambda\sigma\mathcal{H}_2} \\ &\Longrightarrow \left(\frac{2\tilde{A}a\pi + \lambda\sigma\mathcal{H}_2\tilde{B}}{\lambda\sigma\mathcal{H}_2}\right)^2 + 4\tilde{A}\tilde{C} - \tilde{B}^2 \geq 0. \end{aligned}$$

Using Eqs. (10) and (13), we obtain

$$\frac{4a\pi\varepsilon\eta_2\sigma(\gamma+\lambda)^2\left[a\varepsilon\eta_2 + \lambda\mathcal{H}_2\left(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3\right)\right]}{\lambda^2\mathcal{H}_2^2}(M_2 - M_1) \geq 0.$$

Hence, $M_1 \leq M_2$. □

We consider the following equalities to be used in the proceeding theorems:

$$\begin{aligned} &\ln\left(\frac{W_\varphi N_\varphi}{WN}\right) = \ln\left(\frac{W_\varphi N_\varphi U_n}{W_n N_n U}\right) + \ln\left(\frac{W_n}{W}\right) + \ln\left(\frac{N_n U}{NU_n}\right), \\ &\ln\left(\frac{W_\varphi U_\varphi}{WU}\right) = \ln\left(\frac{W_\varphi U_\varphi}{W_n U}\right) + \ln\left(\frac{W_n}{W}\right), \\ &\ln\left(\frac{W_\varphi M_\varphi}{WM}\right) = \ln\left(\frac{W_\varphi M_\varphi U_n}{W_n M_n U}\right) + \ln\left(\frac{W_n}{W}\right) + \ln\left(\frac{M_n U}{MU_n}\right), \\ &\ln\left(\frac{U_\varphi}{U}\right) = \ln\left(\frac{U_\varphi M_n}{U_n M}\right) + \ln\left(\frac{U_n M}{U M_n}\right), \\ &\ln\left(\frac{M_\varphi}{M}\right) = \ln\left(\frac{M_\varphi N_n}{M_n N}\right) + \ln\left(\frac{M_n N}{M N_n}\right), \quad n = 1, 2. \end{aligned} \tag{17}$$

□

Theorem 2 *Suppose that* $\Re_1 \leq 1 < \Re_0$, *then* Đ_1 *is G.A.S.*

Proof We define a functional $\Theta_1(W, U, M, N, P)$ as:

$$\begin{aligned} \Theta_1 = {} & W_1 F\left(\frac{W}{W_1}\right) + \frac{1}{\mathcal{H}_1}U_1 F\left(\frac{U}{U_1}\right) \\ & + \frac{W_1\left(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3\right)}{a\varepsilon}M_1 F\left(\frac{M}{M_1}\right) + \frac{\eta_1 W_1}{\varepsilon}N_1 F\left(\frac{N}{N_1}\right) \\ & + \frac{\mu W_1\left(b\eta_1\mathcal{H}_3 + \varepsilon\eta_3\right)}{\sigma a\varepsilon}P + \frac{\eta_1 W_1 N_1}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\int_{t-\varphi}^{t} F\left(\frac{W(\varkappa)N(\varkappa)}{W_1 N_1}\right)\mathrm{d}\varkappa\mathrm{d}\varphi \\ & + \frac{\eta_2 W_1 U_1}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\int_{t-\varphi}^{t} F\left(\frac{W(\varkappa)U(\varkappa)}{W_1 U_1}\right)\mathrm{d}\varkappa\mathrm{d}\varphi \end{aligned}$$

$$+\frac{\eta_3 W_1 M_1}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\int_{t-\varphi}^{t}F\left(\frac{W(\varkappa)M(\varkappa)}{W_1M_1}\right)\mathrm{d}\varkappa\mathrm{d}\varphi$$

$$+\frac{\lambda W_1\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)U_1}{a\varepsilon}\int_0^{\kappa_2}\bar{\mathcal{H}}_2(\varphi)\int_{t-\varphi}^{t}F\left(\frac{U(\varkappa)}{U_1}\right)\mathrm{d}\varkappa\mathrm{d}\varphi$$

$$+\frac{b\eta_1 W_1 M_1}{\varepsilon}\int_0^{\kappa_3}\bar{\mathcal{H}}_3(\varphi)\int_{t-\varphi}^{t}F\left(\frac{M(\varkappa)}{M_1}\right)\mathrm{d}\varkappa\mathrm{d}\varphi.$$

Calculating $\frac{\mathrm{d}\Theta_1}{\mathrm{d}t}$ as:

$$\begin{aligned}\frac{\mathrm{d}\Theta_1}{\mathrm{d}t}=&\left(1-\frac{W_1}{W}\right)(\rho-\alpha W-\eta_1 WN-\eta_2 WU-\eta_3 WM)\\&+\frac{1}{\mathcal{H}_1}\left(1-\frac{U_1}{U}\right)\left[\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)W_\varphi\left(\eta_1N_\varphi+\eta_2U_\varphi+\eta_3M_\varphi\right)\mathrm{d}\varphi-(\lambda+\gamma)U\right]\\&+\frac{W_1\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{a\varepsilon}\left(1-\frac{M_1}{M}\right)\left[\lambda\int_0^{\kappa_2}\bar{\mathcal{H}}_2(\varphi)U_\varphi\mathrm{d}\varphi-aM-\mu PM\right]\\&+\frac{\eta_1W_1}{\varepsilon}\left(1-\frac{N_1}{N}\right)\left[b\int_0^{\kappa_3}\bar{\mathcal{H}}_3(\varphi)M_\varphi\mathrm{d}\varphi-\varepsilon N\right]+\frac{\mu W_1\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{\sigma a\varepsilon}\\&\times(\sigma PM-\pi P)+\frac{\eta_1W_1N_1}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\left[\frac{WN}{W_1N_1}-\frac{W_\varphi N_\varphi}{W_1N_1}+\ln\left(\frac{W_\varphi N_\varphi}{WN}\right)\right]\mathrm{d}\varphi\\&+\frac{\eta_2W_1U_1}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\left[\frac{WU}{W_1U_1}-\frac{W_\varphi U_\varphi}{W_1U_1}+\ln\left(\frac{W_\varphi U_\varphi}{WU}\right)\right]\mathrm{d}\varphi\\&+\frac{\eta_3W_1M_1}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\left[\frac{WM}{W_1M_1}-\frac{W_\varphi M_\varphi}{W_1M_1}+\ln\left(\frac{W_\varphi M_\varphi}{WM}\right)\right]\mathrm{d}\varphi\\&+\frac{\lambda W_1\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)U_1}{a\varepsilon}\int_0^{\kappa_2}\bar{\mathcal{H}}_2(\varphi)\left[\frac{U}{U_1}-\frac{U_\varphi}{U_1}+\ln\left(\frac{U_\varphi}{U}\right)\right]\mathrm{d}\varphi\\&+\frac{b\eta_1W_1M_1}{\varepsilon}\int_0^{\kappa_3}\bar{\mathcal{H}}_3(\varphi)\left[\frac{M}{M_1}-\frac{M_\varphi}{M_1}+\ln\left(\frac{M_\varphi}{M}\right)\right]\mathrm{d}\varphi.\end{aligned}\tag{18}$$

Collecting terms of Eq. (18), we derive

$$\frac{\mathrm{d}\Theta_1}{\mathrm{d}t}=\left(1-\frac{W_1}{W}\right)(\rho-\alpha W)+\eta_2W_1U-\frac{\lambda+\gamma}{\mathcal{H}_1}U-\frac{\eta_1}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\frac{W_\varphi N_\varphi U_1}{U}\mathrm{d}\varphi$$

$$
\begin{aligned}
&- \frac{\eta_2}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\frac{W_\varphi U_\varphi U_1}{U}\mathrm{d}\varphi - \frac{\eta_3}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\frac{W_\varphi M_\varphi U_1}{U}\mathrm{d}\varphi + \frac{\lambda+\gamma}{\mathcal{H}_1}U_1\\
&- \frac{\lambda W_1\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{a\varepsilon}\int_0^{\kappa_2}\bar{\mathcal{H}}_2(\varphi)\frac{U_\varphi M_1}{M}\mathrm{d}\varphi + \frac{W_1\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{\varepsilon}M_1\\
&+ \frac{\mu W_1\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{a\varepsilon}PM_1 - \frac{b\eta_1 W_1}{\varepsilon}\int_0^{\kappa_3}\bar{\mathcal{H}}_3(\varphi)\frac{M_\varphi N_1}{N}\mathrm{d}\varphi + \eta_1 W_1 N_1\\
&- \frac{\mu\pi W_1\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{\sigma a\varepsilon}P + \frac{\eta_1 W_1 N_1}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\ln\left(\frac{W_\varphi N_\varphi}{WN}\right)\mathrm{d}\varphi\\
&+ \frac{\eta_2 W_1 U_1}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\ln\left(\frac{W_\varphi U_\varphi}{WU}\right)\mathrm{d}\varphi + \frac{\eta_3 W_1 M_1}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\ln\left(\frac{W_\varphi M_\varphi}{WM}\right)\mathrm{d}\varphi\\
&+ \frac{\lambda W_1\mathcal{H}_2\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{a\varepsilon}U + \frac{\lambda W_1\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)U_1}{a\varepsilon}\int_0^{\kappa_2}\bar{\mathcal{H}}_2(\varphi)\ln\left(\frac{U_\varphi}{U}\right)\mathrm{d}\varphi\\
&+ \frac{b\eta_1 W_1 M_1}{\varepsilon}\int_0^{\kappa_3}\bar{\mathcal{H}}_3(\varphi)\ln\left(\frac{M_\varphi}{M}\right)\mathrm{d}\varphi. \qquad (19)
\end{aligned}
$$

Using the equilibrium conditions for $Đ_1$, we get

$$
\begin{aligned}
&\rho = \alpha W_1 + \eta_1 W_1 N_1 + \eta_2 W_1 U_1 + \eta_3 W_1 M_1,\\
&\eta_1 W_1 N_1 + \eta_2 W_1 U_1 + \eta_3 W_1 M_1 = \frac{\lambda+\gamma}{\mathcal{H}_1}U_1,\\
&\frac{\lambda\mathcal{H}_2 U_1}{a} = M_1,\ \ N_1 = \frac{b\mathcal{H}_3 M_1}{\varepsilon}.
\end{aligned}
$$

In addition,

$$
\eta_1 W_1 N_1 + \eta_3 W_1 M_1 = \frac{W_1\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{\varepsilon}M_1 = \frac{\lambda W_1\mathcal{H}_2\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{a\varepsilon}U_1.
$$

Then, we obtain

$$
\begin{aligned}
\frac{\mathrm{d}\Theta_1}{\mathrm{d}t} &= \left(1-\frac{W_1}{W}\right)\left(\alpha W_1 - \alpha W\right) + \left(\eta_1 W_1 N_1 + \eta_2 W_1 U_1 + \eta_3 W_1 M_1\right)\left(1-\frac{W_1}{W}\right)\\
&- \frac{\eta_1 W_1 N_1}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\frac{W_\varphi N_\varphi U_1}{W_1 N_1 U}\mathrm{d}\varphi - \frac{\eta_2 W_1 U_1}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\frac{W_\varphi U_\varphi}{W_1 U}\mathrm{d}\varphi\\
&- \frac{\eta_3 W_1 M_1}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\frac{W_\varphi M_\varphi U_1}{W_1 M_1 U}\mathrm{d}\varphi + \eta_1 W_1 N_1 + \eta_2 W_1 U_1 + \eta_3 W_1 M_1\\
&- \frac{\eta_1 W_1 N_1 + \eta_3 W_1 M_1}{\mathcal{H}_2}\int_0^{\kappa_2}\bar{\mathcal{H}}_2(\varphi)\frac{U_\varphi M_1}{U_1 M}\mathrm{d}\varphi + \eta_1 W_1 N_1 + \eta_3 W_1 M_1
\end{aligned}
$$

$$+\frac{\mu W_1\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{a\varepsilon}PM_1-\frac{\eta_1W_1N_1}{\mathcal{H}_3}\int_0^{\kappa_3}\bar{\mathcal{H}}_3(\varphi)\frac{M_\varphi N_1}{M_1N}\mathrm{d}\varphi+\eta_1W_1N_1$$
$$-\frac{\mu\pi W_1\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{\sigma a\varepsilon}P+\frac{\eta_1W_1N_1}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\ln\left(\frac{W_\varphi N_\varphi}{WN}\right)\mathrm{d}\varphi$$
$$+\frac{\eta_2W_1U_1}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\ln\left(\frac{W_\varphi U_\varphi}{WU}\right)\mathrm{d}\varphi+\frac{\eta_3W_1M_1}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\ln\left(\frac{W_\varphi M_\varphi}{WM}\right)\mathrm{d}\varphi$$
$$+\frac{\eta_1W_1N_1+\eta_3W_1M_1}{\mathcal{H}_2}\int_0^{\kappa_2}\bar{\mathcal{H}}_2(\varphi)\ln\left(\frac{U_\varphi}{U}\right)\mathrm{d}\varphi+\frac{\eta_1W_1N_1}{\mathcal{H}_3}\int_0^{\kappa_3}\bar{\mathcal{H}}_3(\varphi)\ln\left(\frac{M_\varphi}{M}\right)\mathrm{d}\varphi.$$

Using the equalities given by (17) in case of $n=1$, we get

$$\frac{\mathrm{d}\Theta_1}{\mathrm{d}t}=-\alpha\frac{(W-W_1)^2}{W}-\left(\eta_1W_1N_1+\eta_2W_1U_1+\eta_3W_1M_1\right)\left[\frac{W_1}{W}-1-\ln\left(\frac{W_1}{W}\right)\right]$$
$$-\frac{\eta_1W_1N_1}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\left[\frac{W_\varphi N_\varphi U_1}{W_1N_1U}-1-\ln\left(\frac{W_\varphi N_\varphi U_1}{W_1N_1U}\right)\right]\mathrm{d}\varphi$$
$$-\frac{\eta_2W_1U_1}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\left[\frac{W_\varphi U_\varphi}{W_1U}-1-\ln\left(\frac{W_\varphi U_\varphi}{W_1U}\right)\right]\mathrm{d}\varphi$$
$$-\frac{\eta_3W_1M_1}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\left[\frac{W_\varphi M_\varphi U_1}{W_1M_1U}-1-\ln\left(\frac{W_\varphi M_\varphi U_1}{W_1M_1U}\right)\right]\mathrm{d}\varphi$$
$$-\frac{\eta_1W_1N_1+\eta_3W_1M_1}{\mathcal{H}_2}\int_0^{\kappa_2}\bar{\mathcal{H}}_2(\varphi)\left[\frac{U_\varphi M_1}{U_1M}-1-\ln\left(\frac{U_\varphi M_1}{U_1M}\right)\right]\mathrm{d}\varphi$$
$$-\frac{\eta_1W_1N_1}{\mathcal{H}_3}\int_0^{\kappa_3}\bar{\mathcal{H}}_3(\varphi)\left[\frac{M_\varphi N_1}{M_1N}-1-\ln\left(\frac{M_\varphi N_1}{M_1N}\right)\right]\mathrm{d}\varphi$$
$$+\frac{\mu W_1\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{a\varepsilon}\left(M_1-\frac{\pi}{\sigma}\right)P. \tag{20}$$

Therefore, Eq. (20) becomes

$$\frac{\mathrm{d}\Theta_1}{\mathrm{d}t}=-\alpha\frac{(W-W_1)^2}{W}-\frac{\eta_1W_1N_1}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\left[F\left(\frac{W_\varphi N_\varphi U_1}{W_1N_1U}\right)+F\left(\frac{W_1}{W}\right)\right]\mathrm{d}\varphi$$
$$-\frac{\eta_2W_1U_1}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\left[F\left(\frac{W_\varphi U_\varphi}{W_1U}\right)+F\left(\frac{W_1}{W}\right)\right]\mathrm{d}\varphi$$
$$-\frac{\eta_3W_1M_1}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\left[F\left(\frac{W_\varphi M_\varphi U_1}{W_1M_1U}\right)+F\left(\frac{W_1}{W}\right)\right]\mathrm{d}\varphi$$

$$
\begin{aligned}
&- \frac{\eta_1 W_1 N_1 + \eta_3 W_1 M_1}{\mathcal{H}_2} \int_0^{\kappa_2} \bar{\mathcal{H}}_2(\varphi) F\left(\frac{U_\varphi M_1}{U_1 M}\right) \mathrm{d}\varphi \\
&- \frac{\eta_1 W_1 N_1}{\mathcal{H}_3} \int_0^{\kappa_3} \bar{\mathcal{H}}_3(\varphi) F\left(\frac{M_\varphi N_1}{M_1 N}\right) \mathrm{d}\varphi \\
&+ \frac{\mu W_1 \left(b\eta_1 \mathcal{H}_3 + \varepsilon\eta_3\right)}{a\varepsilon} \left(M_1 - M_2\right) P.
\end{aligned}
$$

Using Lemma 1 and since $\Re_1 \leq 1$ then $M_1 \leq M_2$ and $\frac{\mathrm{d}\Theta_1}{\mathrm{d}t} \leq 0$ for all $W, U, M, N, P > 0$ with equality holding when $W = W_1$, $P = 0$ and $F = 0$. Let Υ_1' be the largest invariant subset of $\Upsilon_1 = \left\{(W, U, M, N, P) : \frac{\mathrm{d}\Theta_1}{\mathrm{d}t} = 0\right\}$. The trajectories of system (3) converge to $\Upsilon_1^{'}$. The set $\Upsilon_1^{'}$ is invariant and contains elements with $W(t) = W_1$ and $F = 0$, i.e.,

$$
\frac{W_\varphi N_\varphi U_1}{W_1 N_1 U} = \frac{W_\varphi U_\varphi}{W_1 U} = \frac{W_\varphi M_\varphi U_1}{W_1 M_1 U} = \frac{U_\varphi M_1}{U_1 M} = \frac{M_\varphi N_1}{M_1 N} = 1, \tag{21}
$$

for all $t \in [0, \kappa]$. If $W(t) = W_1$, then from Eq. (21), we get $U(t) = U_1$, $M(t) = M_1$ and $N(t) = N_1$. Then, $\Upsilon_1' = \{\mathcal{D}_1\}$ and $\mathcal{D}_1$ is G.A.S using LaSalle's invariance principle. □

Theorem 3 *Suppose that* $\Re_1 > 1$*, then* $\mathcal{D}_2$ *is G.A.S.*

Proof Define a function $\Theta_2(W, U, M, N, P)$ as:

$$
\begin{aligned}
\Theta_2 = {} & W_2 F\left(\frac{W}{W_2}\right) + \frac{1}{\mathcal{H}_1} U_2 F\left(\frac{U}{U_2}\right) + \frac{W_2 \left(b\eta_1 \mathcal{H}_3 + \varepsilon\eta_3\right)}{\varepsilon \left(a + \mu P_2\right)} M_2 F\left(\frac{M}{M_2}\right) \\
& + \frac{\eta_1 W_2}{\varepsilon} N_2 F\left(\frac{N}{N_2}\right) + \frac{\mu W_2 \left(b\eta_1 \mathcal{H}_3 + \varepsilon\eta_3\right)}{\sigma\varepsilon \left(a + \mu P_2\right)} P_2 F\left(\frac{P}{P_2}\right) \\
& + \frac{\eta_1 W_2 N_2}{\mathcal{H}_1} \int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi) \int_{t-\varphi}^{t} F\left(\frac{W(\varkappa) N(\varkappa)}{W_2 N_2}\right) \mathrm{d}\varkappa \mathrm{d}\varphi \\
& + \frac{\eta_2 W_2 U_2}{\mathcal{H}_1} \int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi) \int_{t-\varphi}^{t} F\left(\frac{W(\varkappa) U(\varkappa)}{W_2 U_2}\right) \mathrm{d}\varkappa \mathrm{d}\varphi \\
& + \frac{\eta_3 W_2 M_2}{\mathcal{H}_1} \int_0^{\kappa_1} \bar{\mathcal{H}}_1(\varphi) \int_{t-\varphi}^{t} F\left(\frac{W(\varkappa) M(\varkappa)}{W_2 M_2}\right) \mathrm{d}\varkappa \mathrm{d}\varphi \\
& + \frac{\lambda W_2 \left(b\eta_1 \mathcal{H}_3 + \varepsilon\eta_3\right) U_2}{\varepsilon \left(a + \mu P_2\right)} \int_0^{\kappa_2} \bar{\mathcal{H}}_2(\varphi) \int_{t-\varphi}^{t} F\left(\frac{U(\varkappa)}{U_2}\right) \mathrm{d}\varkappa \mathrm{d}\varphi \\
& + \frac{b\eta_1 W_2 M_2}{\varepsilon} \int_0^{\kappa_3} \bar{\mathcal{H}}_3(\varphi) \int_{t-\varphi}^{t} F\left(\frac{M(\varkappa)}{M_2}\right) \mathrm{d}\varkappa \mathrm{d}\varphi.
\end{aligned}
$$

We calculate $\frac{\mathrm{d}\Theta_2}{\mathrm{d}t}$ as:

$$
\frac{\mathrm{d}\Theta_2}{\mathrm{d}t} = \left(1 - \frac{W_2}{W}\right) \left(\rho - \alpha W - \eta_1 W N - \eta_2 W U - \eta_3 W M\right)
$$

$$
\begin{aligned}
&+\frac{1}{\mathcal{H}_1}\left(1-\frac{U_2}{U}\right)\left[\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)W_\varphi\left(\eta_1 N_\varphi+\eta_2 U_\varphi+\eta_3 M_\varphi\right)\mathrm{d}\varphi-(\lambda+\gamma)\,U\right]\\
&+\frac{W_2\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{\varepsilon\left(a+\mu P_2\right)}\left(1-\frac{M_2}{M}\right)\left[\lambda\int_0^{\kappa_2}\bar{\mathcal{H}}_2(\varphi)U_\varphi\mathrm{d}\varphi-aM-\mu PM\right]\\
&+\frac{\eta_1 W_2}{\varepsilon}\left(1-\frac{N_2}{N}\right)\left[b\int_0^{\kappa_3}\bar{\mathcal{H}}_3(\varphi)M_\varphi\mathrm{d}\varphi-\varepsilon N\right]+\frac{\mu W_2\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{\sigma\varepsilon\left(a+\mu P_2\right)}\left(1-\frac{P_2}{P}\right)\\
&\times(\sigma PM-\pi P)+\frac{\eta_1 W_2 N_2}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\left[\frac{WN}{W_2N_2}-\frac{W_\varphi N_\varphi}{W_2N_2}+\ln\left(\frac{W_\varphi N_\varphi}{WN}\right)\right]\mathrm{d}\varphi\\
&+\frac{\eta_2 W_2 U_2}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\left[\frac{WU}{W_2U_2}-\frac{W_\varphi U_\varphi}{W_2U_2}+\ln\left(\frac{W_\varphi U_\varphi}{WU}\right)\right]\mathrm{d}\varphi\\
&+\frac{\eta_3 W_2 M_2}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\left[\frac{WM}{W_2M_2}-\frac{W_\varphi M_\varphi}{W_2M_2}+\ln\left(\frac{W_\varphi M_\varphi}{WM}\right)\right]\mathrm{d}\varphi\\
&+\frac{\lambda W_2\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)U_2}{\varepsilon\left(a+\mu P_2\right)}\int_0^{\kappa_2}\bar{\mathcal{H}}_2(\varphi)\left[\frac{U}{U_2}-\frac{U_\varphi}{U_2}+\ln\left(\frac{U_\varphi}{U}\right)\right]\mathrm{d}\varphi\\
&+\frac{b\eta_1 W_2 M_2}{\varepsilon}\int_0^{\kappa_3}\bar{\mathcal{H}}_3(\varphi)\left[\frac{M}{M_2}-\frac{M_\varphi}{M_2}+\ln\left(\frac{M_\varphi}{M}\right)\right]\mathrm{d}\varphi. \qquad (22)
\end{aligned}
$$

Collecting terms of Eq. (22), we derive

$$
\begin{aligned}
\frac{\mathrm{d}\Theta_2}{\mathrm{d}t}=&\left(1-\frac{W_2}{W}\right)(\rho-\alpha W)+\eta_2 W_2 U+\eta_3 W_2 M-\frac{\lambda+\gamma}{\mathcal{H}_1}U-\frac{\eta_1}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\frac{W_\varphi N_\varphi U_2}{U}\mathrm{d}\varphi\\
&-\frac{\eta_2}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\frac{W_\varphi U_\varphi U_2}{U}\mathrm{d}\varphi-\frac{\eta_3}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\frac{W_\varphi M_\varphi U_2}{U}\mathrm{d}\varphi\\
&+\frac{\lambda+\gamma}{\mathcal{H}_1}U_2-\frac{aW_2\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{\varepsilon\left(a+\mu P_2\right)}M-\frac{\lambda W_2\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{\varepsilon\left(a+\mu P_2\right)}\int_0^{\kappa_2}\bar{\mathcal{H}}_2(\varphi)\frac{U_\varphi M_2}{M}\mathrm{d}\varphi\\
&+\frac{aW_2\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{\varepsilon\left(a+\mu P_2\right)}M_2+\frac{\mu W_2\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{\varepsilon\left(a+\mu P_2\right)}PM_2-\frac{b\eta_1 W_2}{\varepsilon}\int_0^{\kappa_3}\bar{\mathcal{H}}_3(\varphi)\frac{M_\varphi N_2}{N}\mathrm{d}\varphi\\
&+\eta_1 W_2 N_2-\frac{\mu\pi W_2\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{\sigma\varepsilon\left(a+\mu P_2\right)}P-\frac{\mu W_2\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{\varepsilon\left(a+\mu P_2\right)}P_2M\\
&+\frac{\mu\pi W_2\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{\sigma\varepsilon\left(a+\mu P_2\right)}P_2+\frac{\eta_1 W_2 N_2}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\ln\left(\frac{W_\varphi N_\varphi}{WN}\right)\mathrm{d}\varphi
\end{aligned}
$$

$$+\frac{\eta_2 W_2 U_2}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\ln\left(\frac{W_\varphi U_\varphi}{WU}\right)\mathrm{d}\varphi+\frac{\eta_3 W_2 M_2}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\ln\left(\frac{W_\varphi M_\varphi}{WM}\right)\mathrm{d}\varphi$$
$$+\frac{\lambda W_2\mathcal{H}_2\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{\varepsilon\left(a+\mu P_2\right)}U+\frac{\lambda W_2\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)U_2}{\varepsilon\left(a+\mu P_2\right)}\int_0^{\kappa_2}\bar{\mathcal{H}}_2(\varphi)\ln\left(\frac{U_\varphi}{U}\right)\mathrm{d}\varphi$$
$$+\frac{b\mathcal{H}_3\eta_1 W_2}{\varepsilon}M+\frac{b\eta_1 W_2 M_2}{\varepsilon}\int_0^{\kappa_3}\bar{\mathcal{H}}_3(\varphi)\ln\left(\frac{M_\varphi}{M}\right)\mathrm{d}\varphi. \tag{23}$$

Using the equilibrium conditions for Ð $_2$:

$$\rho=\alpha W_2+\eta_1 W_2 N_2+\eta_2 W_2 U_2+\eta_3 W_2 M_2,$$
$$\eta_1 W_2 N_2+\eta_2 W_2 U_2+\eta_3 W_2 M_2=\frac{\lambda+\gamma}{\mathcal{H}_1}U_2,$$
$$\lambda\mathcal{H}_2 U_2=\left(a+\mu P_2\right)M_2,\ \ M_2=\frac{\pi}{\sigma},\ \ N_2=\frac{b\mathcal{H}_3}{\varepsilon}M_2.$$

Further,

$$\eta_1 W_2 N_2+\eta_3 W_2 M_2=\frac{W_2\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{\varepsilon}M_2=\frac{\lambda W_2\mathcal{H}_2\left(b\eta_1\mathcal{H}_3+\varepsilon\eta_3\right)}{\varepsilon\left(a+\mu P_2\right)}U_2.$$

Therefore, we obtain

$$\frac{\mathrm{d}\Theta_2}{\mathrm{d}t}=\left(1-\frac{W_2}{W}\right)\left(\alpha W_2-\alpha W\right)+\left(\eta_1 W_2 N_2+\eta_2 W_2 U_2+\eta_3 W_2 M_2\right)\left(1-\frac{W_2}{W}\right)$$
$$-\frac{\eta_1 W_2 N_2}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\frac{W_\varphi N_\varphi U_2}{W_2 N_2 U}\mathrm{d}\varphi-\frac{\eta_2 W_2 U_2}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\frac{W_\varphi U_\varphi}{W_2 U}\mathrm{d}\varphi$$
$$-\frac{\eta_3 W_2 M_2}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\frac{W_\varphi M_\varphi U_2}{W_2 M_2 U}\mathrm{d}\varphi+\eta_1 W_2 N_2+\eta_2 W_2 U_2+\eta_3 W_2 M_2$$
$$-\frac{\eta_1 W_2 N_2+\eta_3 W_2 M_2}{\mathcal{H}_2}\int_0^{\kappa_2}\bar{\mathcal{H}}_2(\varphi)\frac{U_\varphi M_2}{U_2 M}\mathrm{d}\varphi+\eta_1 W_2 N_2+\eta_3 W_2 M_2$$
$$-\frac{\eta_1 W_2 N_2}{\mathcal{H}_3}\int_0^{\kappa_3}\bar{\mathcal{H}}_3(\varphi)\frac{M_\varphi N_2}{M_2 N}\mathrm{d}\varphi+\eta_1 W_2 N_2+\frac{\eta_1 W_2 N_2}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\ln\left(\frac{W_\varphi N_\varphi}{WN}\right)\mathrm{d}\varphi$$
$$+\frac{\eta_2 W_2 U_2}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\ln\left(\frac{W_\varphi U_\varphi}{WU}\right)\mathrm{d}\varphi+\frac{\eta_3 W_2 M_2}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\ln\left(\frac{W_\varphi M_\varphi}{WM}\right)\mathrm{d}\varphi$$
$$+\frac{\eta_1 W_2 N_2+\eta_3 W_2 M_2}{\mathcal{H}_2}\int_0^{\kappa_2}\bar{\mathcal{H}}_2(\varphi)\ln\left(\frac{U_\varphi}{U}\right)\mathrm{d}\varphi+\frac{\eta_1 W_2 N_2}{\mathcal{H}_3}\int_0^{\kappa_3}\bar{\mathcal{H}}_3(\varphi)\ln\left(\frac{M_\varphi}{M}\right)\mathrm{d}\varphi. \tag{24}$$

Using the equalities given by (17) in case of $n = 2$, we get

$$\begin{aligned}\frac{\mathrm{d}\Theta_2}{\mathrm{d}t} &= -\alpha\frac{(W-W_2)^2}{W} - (\eta_1 W_2N_2 + \eta_2 W_2U_2 + \eta_3 W_2M_2)\left[\frac{W_2}{W} - 1 - \ln\left(\frac{W_2}{W}\right)\right]\\ &- \frac{\eta_1 W_2N_2}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\left[\frac{W_\varphi N_\varphi U_2}{W_2N_2U} - 1 - \ln\left(\frac{W_\varphi N_\varphi U_2}{W_2N_2U}\right)\right]\mathrm{d}\varphi\\ &- \frac{\eta_2 W_2U_2}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\left[\frac{W_\varphi U_\varphi}{W_2U} - 1 - \ln\left(\frac{W_\varphi U_\varphi}{W_2U}\right)\right]\mathrm{d}\varphi\\ &- \frac{\eta_3 W_2M_2}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\left[\frac{W_\varphi M_\varphi U_2}{W_2M_2U} - 1 - \ln\left(\frac{W_\varphi M_\varphi U_2}{W_2M_2U}\right)\right]\mathrm{d}\varphi\\ &- \frac{\eta_1 W_2N_2 + \eta_3 W_2M_2}{\mathcal{H}_2}\int_0^{\kappa_2}\bar{\mathcal{H}}_2(\varphi)\left[\frac{U_\varphi M_2}{U_2M} - 1 - \ln\left(\frac{U_\varphi M_2}{U_2M}\right)\right]\mathrm{d}\varphi\\ &- \frac{\eta_1 W_2N_2}{\mathcal{H}_3}\int_0^{\kappa_3}\bar{\mathcal{H}}_3(\varphi)\left[\frac{M_\varphi N_2}{M_2N} - 1 - \ln\left(\frac{M_\varphi N_2}{M_2N}\right)\right]\mathrm{d}\varphi. \end{aligned} \tag{25}$$

Eq. (25) can be rewritten as follows:

$$\begin{aligned}\frac{\mathrm{d}\Theta_2}{\mathrm{d}t} &= -\alpha\frac{(W-W_2)^2}{W} - \frac{\eta_1 W_2N_2}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi))\left[F\left(\frac{W_\varphi N_\varphi U_2}{W_2N_2U}\right) + F\left(\frac{W_2}{W}\right)\right]\mathrm{d}\varphi\\ &- \frac{\eta_2 W_2U_2}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\left[F\left(\frac{W_\varphi U_\varphi}{W_2U}\right) + F\left(\frac{W_2}{W}\right)\right]\mathrm{d}\varphi\\ &- \frac{\eta_3 W_2M_2}{\mathcal{H}_1}\int_0^{\kappa_1}\bar{\mathcal{H}}_1(\varphi)\left[F\left(\frac{W_\varphi M_\varphi U_2}{W_2M_2U}\right) + F\left(\frac{W_2}{W}\right)\right]\mathrm{d}\varphi\\ &- \frac{\eta_1 W_2N_2 + \eta_3 W_2M_2}{\mathcal{H}_2}\int_0^{\kappa_2}\bar{\mathcal{H}}_2(\varphi)F\left(\frac{U_\varphi M_2}{U_2M}\right)\mathrm{d}\varphi\\ &- \frac{\eta_1 W_2N_2}{\mathcal{H}_3}\int_0^{\kappa_3}\bar{\mathcal{H}}_3(\varphi)F\left(\frac{M_\varphi N_2}{M_2N}\right)\mathrm{d}\varphi. \end{aligned}$$

Hence, if $\Re_1 > 1$, then $\frac{\mathrm{d}\Theta_2}{\mathrm{d}t} \leq 0$ for all $W, U, M, N, P > 0$ with equality holding when $W = W_2$ and $F = 0$. The solutions of system (3) tend to $\Upsilon_2^{'}$ the largest invariant subset of $\Upsilon_2 = \left\{(W, U, M, N, P) : \frac{\mathrm{d}\Theta_2}{\mathrm{d}t} = 0\right\}$. The set $\Upsilon_2^{'}$ contains elements with $W(t) = W_2$ and $F = 0$, i.e.,

$$\frac{W_\varphi N_\varphi U_2}{W_2N_2U} = \frac{W_\varphi U_\varphi}{W_2U} = \frac{W_\varphi M_\varphi U_2}{W_2M_2U} = \frac{U_\varphi M_2}{U_2M} = \frac{M_\varphi N_2}{M_2N} = 1, \tag{26}$$

Table 2 Some values of the parameters of model (27)

Parameter	Value	Parameter	Value	Parameter	Value	Parameter	Value
ρ	10	a	0.5	μ	0.2	$\hbar_3$	0.3
α	0.01	γ	0.2	ε	2	φ_1	Varied
η_1	Varied	λ	0.2	σ	Varied	φ_2	Varied
η_2	Varied	b	5	$\hbar_1$	0.1	φ_3	Varied
η_3	Varied	π	0.1	$\hbar_2$	0.2		

for all $t \in [0, \kappa]$. If $W(t) = W_2$, then from Eq. (26), we get $U(t) = U_2$, $M(t) = M_2$ and $N(t) = N_2$. Substituting in the third equation of system (3), we obtain

$$0 = \dot{M}(t) = \lambda U_2 - aM_2 - \mu P(t) M_2,$$

which yields $P(t) = P_2$ for all t. Therefore, $\Upsilon_2^{'} = \{\text{Đ}_2\}$. LaSalle's invariance principle implies that Đ_2 is G.A.S.

□

6 Numerical results

In this section, we illustrate the results of Theorems 1-3 by performing numerical simulations. We address the influence of antiviral drugs efficacy, CTC transmission and time delays on the dynamical behavior of the system. For numerical purposes, we transform the distributed-time delay model (3) to a discrete-time delay one by choosing a Dirac delta function $D(.)$ as a special form of the kernel $\Lambda_i(.)$ as [9]:

$$\Lambda_i(x) = D(x - \varphi_i), \ \varphi_i \in [0, \kappa_i], \ i = 1, 2, 3.$$

Let κ_i tends to ∞, then the properties of $D(.)$ imply that:

$$\int_0^\infty \Lambda_j(\varsigma) \mathrm{d}\varsigma = 1, \ \mathcal{H}_j = \int_0^\infty D\left(\varsigma - \varphi_j\right) e^{-\hbar_j \varsigma} \mathrm{d}\varsigma = e^{-\hbar_j \varphi_j}, \ j = 1, 2, 3.$$

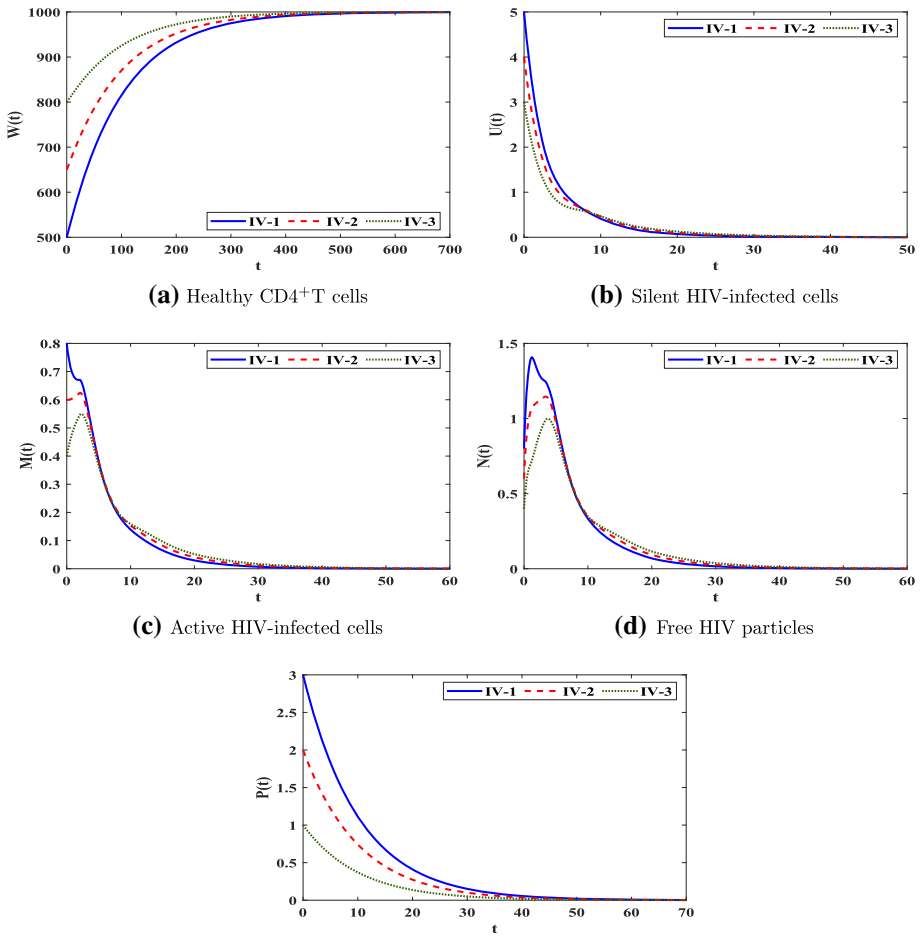
Thus, model (3) becomes:

$$\begin{cases} \dot{W} = \rho - \alpha W - \eta_1 WN - \eta_2 WU - \eta_3 WM, \\ \dot{U} = e^{-\hbar_1 \varphi_1} W_{\varphi_1} \left(\eta_1 N_{\varphi_1} + \eta_2 U_{\varphi_1} + \eta_3 M_{\varphi_1}\right) - (\lambda + \gamma) U, \\ \dot{M} = \lambda e^{-\hbar_2 \varphi_2} U_{\varphi_2} - aM - \mu PM, \\ \dot{N} = be^{-\hbar_3 \varphi_3} M_{\varphi_3} - \varepsilon N, \\ \dot{P} = \sigma PM - \pi P. \end{cases} \tag{27}$$

For model (27), the threshold parameters are given by:

$$\Re_0 = \frac{W_0 e^{-\hbar_1 \varphi_1} \left[a\varepsilon\eta_2 + \lambda e^{-\hbar_2 \varphi_2} \left(b\eta_1 e^{-\hbar_3 \varphi_3} + \varepsilon\eta_3\right)\right]}{a\varepsilon(\gamma + \lambda)}, \ \Re_1 = \frac{\lambda\sigma e^{-\hbar_2 \varphi_2} U_2}{a\pi}. \tag{28}$$

To solve system (27) numerically, we fix the values of some parameters (see Table 2) and the others will be varied. We have chosen the values of parameters of the model just to perform the numerical simulations. This is indeed because the difficulty of getting real



(a) Healthy CD4$^+$T cells **(b)** Silent HIV-infected cells

(c) Active HIV-infected cells **(d)** Free HIV particles

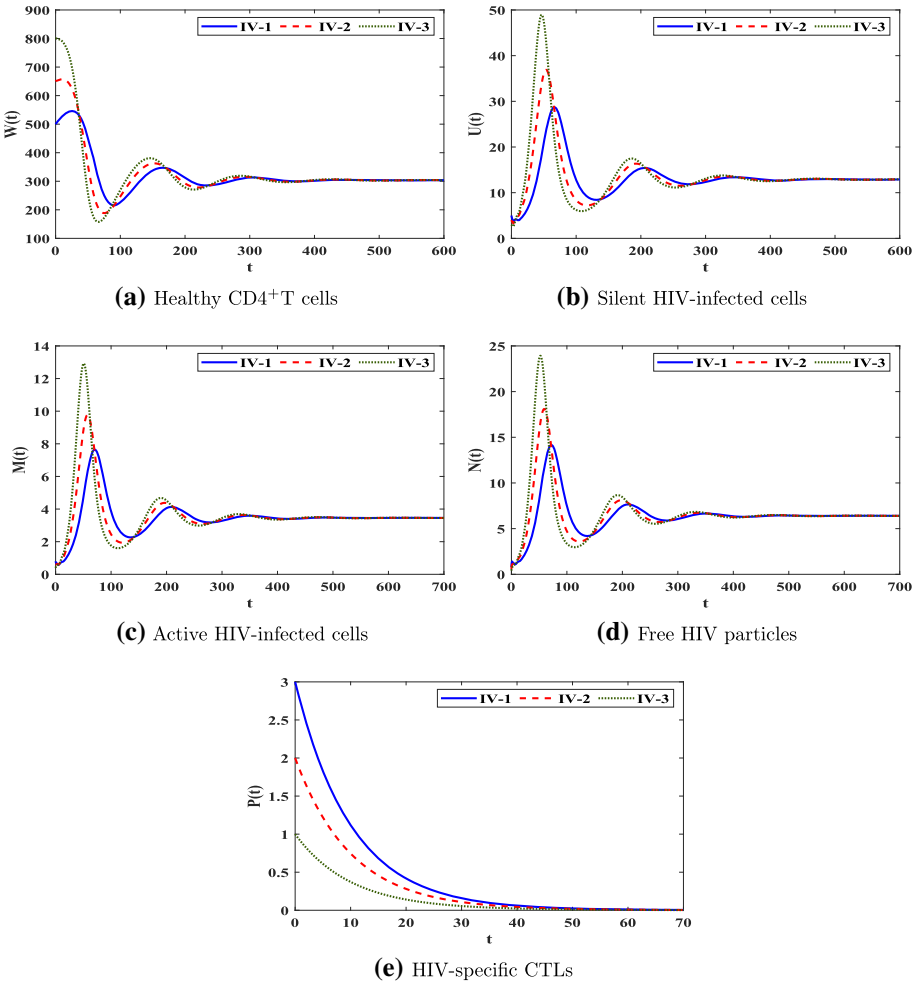
(e) HIV-specific CTLs

Fig. 1 The behavior of solution trajectories of system (27) in case of $\Re_0 \leq 1$

data from HIV infected patients; however, if one has real data, then the parameters of the model can be estimated and the validity of the model can be established. We note that the stability of the three equilibria is controlled by two threshold parameters $\Re_0$ and $\Re_1$. We can see that $\Re_0$ depends on the incidence rate constants η_1, η_2 and η_3. These parameters can significantly affected by the antiviral drug therapy as will be shown below. On the other hand, the proliferation rate constant for effective HIV-specific CTLs σ can significantly change the parameter $\Re_1$. Therefore, to verify the results of Theorems 1-3 we vary the parameters η_1, η_2, η_3 and σ. In addition, to address the effect of the time delays on the HIV dynamics we vary the delays parameters φ_1, φ_2 and φ_3.

6.1 Stability of the equilibria

We consider the values $\varphi_1 = 3$, $\varphi_2 = 2$, $\varphi_3 = 1$ and choose the following three different initial conditions for model (27):



(a) Healthy CD4$^+$T cells

(b) Silent HIV-infected cells

(c) Active HIV-infected cells

(d) Free HIV particles

(e) HIV-specific CTLs

Fig. 2 The behavior of solution trajectories of system (27) in case of $\Re_1 \leq 1 < \Re_0$

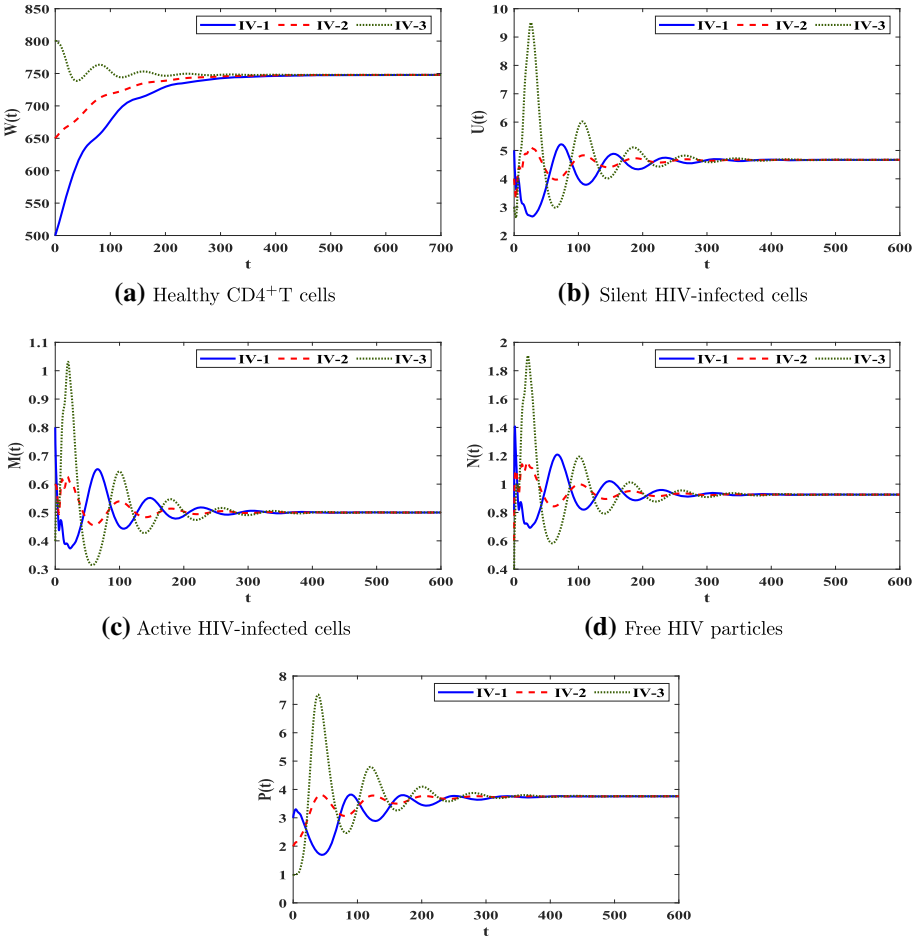
IV-1 : $(W(\varphi), U(\varphi), M(\varphi), N(\varphi), P(\varphi)) = (500, 5, 0.8, 0.8, 3)$, (Solid lines in the figures),

IV-2: $(W(\varphi), U(\varphi), M(\varphi), N(\varphi), P(\varphi)) = (650, 4, 0.6, 0.6, 2)$, (Dashed lines in the figures),

IV-3: $(W(\varphi), U(\varphi), M(\varphi), N(\varphi), P(\varphi)) = (800, 3, 0.4, 0.4, 1)$, (Dotted lines in the figures), where $\varphi \in [-3, 0]$. Choosing selected values of η_1 , η_2, η_3 and σ under the mentioned initial conditions leads to the following cases:

Stability of $Đ_0$. $\eta_1 = 0.0003$, $\eta_2 = 0.00001$, $\eta_3 = 0.0001$ and $\sigma = 0.002$. With these parameters, we have $\Re_0 = 0.34 < 1$. Figure 1 displays that the trajectories initiating with IV-1, IV2 and IV-3 reach the equilibrium $Đ_0 = (1000, 0, 0, 0, 0)$. This shows that $Đ_0$ is G.A.S according to Theorem 1. In this case, the HIV particles will be cleared from the body.

Stability of $Đ_1$. $\eta_1 = 0.003$, $\eta_2 = 0.00002$, $\eta_3 = 0.001$ and $\sigma = 0.002$. With such a choice, we get $\Re_1 = 0.10 < 1 < 3.29 = \Re_0$. It is clear that the equilibrium point $Đ_1$ exists



(a) Healthy CD4$^+$T cells **(b)** Silent HIV-infected cells

(c) Active HIV-infected cells **(d)** Free HIV particles

(e) HIV-specific CTLs

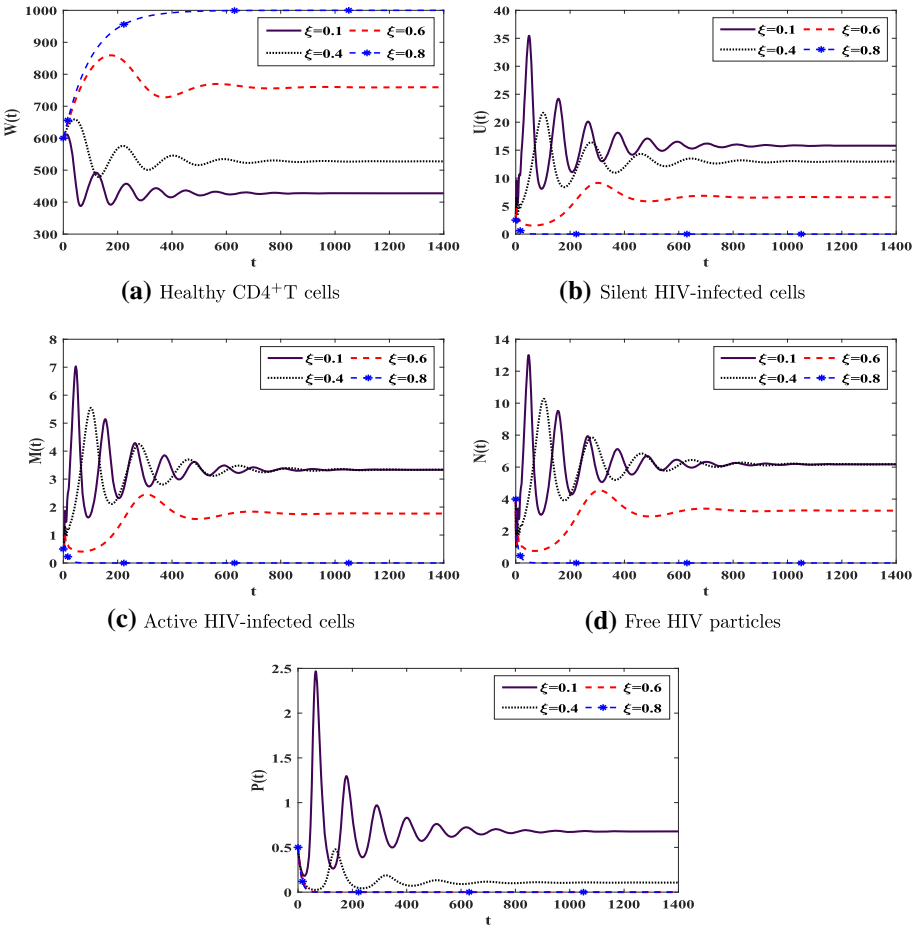
Fig. 3 The behavior of solution trajectories of system (27) in case of $\Re_1 > 1$

with $Đ_1 = (303.7, 12.90, 3.46, 6.40, 0)$. Figure 2 displays that the trajectories initiating with IV-1, IV2 and IV-3 tend to $Đ_1$. Therefore, the numerical results support Theorem 2. Hence, a chronic HIV infection with inactivated CTL-mediated immune response is attained.

Stability of $Đ_2$. $\eta_1 = 0.003$, $\eta_2 = 0.00002$, $\eta_3 = 0.001$ and $\sigma = 0.2$. Then, we calculate $\Re_1 = 2.50 > 1$. In Fig. 3, we show that $Đ_2 = (747.86, 4.67, 0.5, 0.93, 3.76)$ exists and it is G.A.S and this agrees with Theorem 3. Hence, a chronic HIV infection with CTL-mediated immune response is attained.

6.2 Effect of antiviral drugs

To study the effect of antiviral drugs on the HIV dynamics, we incorporate three types of antiviral drugs into model (27) as:



(a) Healthy CD4$^+$T cells **(b)** Silent HIV-infected cells

(c) Active HIV-infected cells **(d)** Free HIV particles

(e) HIV-specific CTLs

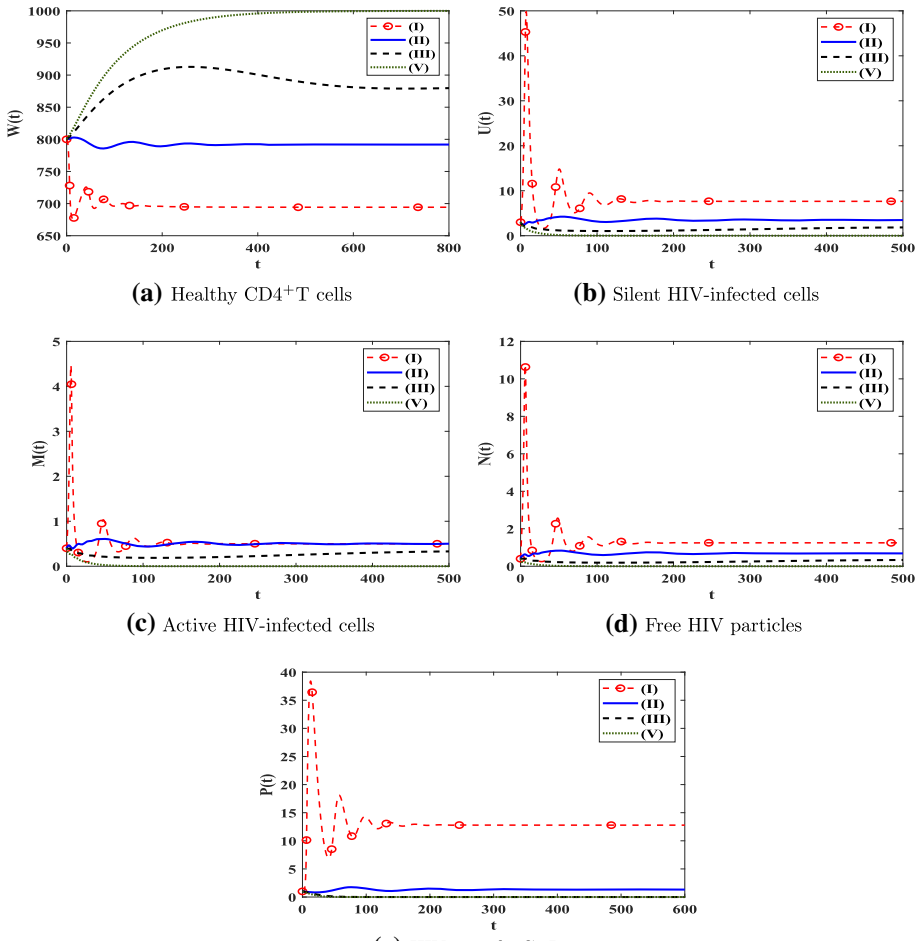
Fig. 4 The influence of antiviral drug efficacy on the behavior of solution trajectories of system (29)

$$\begin{cases} \dot{W} = \rho - \alpha W - (1-\xi_1)\eta_1 WN - (1-\xi_2)\eta_2 WU - (1-\xi_3)\eta_3 WM, \\ \dot{U} = e^{-\hbar_1\varphi_1} W_{\varphi_1}\left[(1-\xi_1)\eta_1 N_{\varphi_1} + (1-\xi_2)\eta_2 U_{\varphi_1} + (1-\xi_3)\eta_3 M_{\varphi_1}\right] - (\lambda+\gamma)\,U, \\ \dot{M} = \lambda e^{-\hbar_2\varphi_2} U_{\varphi_2} - aM - \mu PM, \\ \dot{N} = be^{-\hbar_3\varphi_3} M_{\varphi_3} - \varepsilon N, \\ \dot{P} = \sigma\, PM - \pi\, P, \end{cases} \tag{29}$$

where $\xi_1 \in [0, 1]$ is the efficacy of antiviral therapy in blocking infection by VTC mechanism. Moreover, $\xi_2 \in [0, 1]$ and $\xi_3 \in [0, 1]$ are efficacies of therapy in blocking infection by silent HIV-infected CTC and active HIV-infected CTC mechanisms, respectively [50].

For model (29), the basic HIV reproduction number is given by:

$$\Re_{0(29)}(\xi_1, \xi_2, \xi_3) = \frac{W_0 e^{-\hbar_1\varphi_1}\left[a\varepsilon(1-\xi_2)\eta_2 + \lambda e^{-\hbar_2\varphi_2}\left\{b\eta_1(1-\xi_1)e^{-\hbar_3\varphi_3} + \varepsilon\eta_3(1-\xi_3)\right\}\right]}{a\varepsilon\,(\gamma+\lambda)}.$$



(a) Healthy CD4$^+$T cells **(b)** Silent HIV-infected cells

(c) Active HIV-infected cells **(d)** Free HIV particles

(e) HIV-specific CTLs

Fig. 5 The influence of time delay parameters on the behavior of solution trajectories of system (29)

We let $\xi = \xi_1 = \xi_2 = \xi_3$, then

$$\Re_{0(29)}(\xi) = (1-\xi)\frac{W_0 e^{-\hbar_1\varphi_1}\left[a\varepsilon\eta_2 + \lambda e^{-\hbar_2\varphi_2}\left(b\eta_1 e^{-\hbar_3\varphi_3} + \varepsilon\eta_3\right)\right]}{a\varepsilon\left(\gamma+\lambda\right)}. \tag{30}$$

Now, we want to determine the minimum drug efficacy that stabilizes the system around the infection-free equilibrium and consequently the viruses will be cleared from the body. Let $\Re_{0(29)}(\xi) \leq 1$, then we obtain

$$\begin{aligned} 1-\xi &\leq \frac{a\varepsilon\left(\gamma+\lambda\right)}{W_0 e^{-\hbar_1\varphi_1}\left[a\varepsilon\eta_2 + \lambda e^{-\hbar_2\varphi_2}\left(b\eta_1 e^{-\hbar_3\varphi_3} + \varepsilon\eta_3\right)\right]} \\ \Longrightarrow \xi &\geq 1 - \frac{a\varepsilon\left(\gamma+\lambda\right)}{W_0 e^{-\hbar_1\varphi_1}\left[a\varepsilon\eta_2 + \lambda e^{-\hbar_2\varphi_2}\left(b\eta_1 e^{-\hbar_3\varphi_3} + \varepsilon\eta_3\right)\right]}. \end{aligned}$$

Since $0 \leq \xi \leq 1$, then for $\xi^{\min}_{(29)} < \xi \leq 1$, the infection-free equilibrium $Đ_0$ of model (29) is G.A.S, where

$$\xi^{\min}_{(29)} = \max\left\{0, 1 - \frac{a\varepsilon\,(\gamma+\lambda)}{W_0 e^{-\hbar_1\varphi_1}\left[a\varepsilon\eta_2 + \lambda e^{-\hbar_2\varphi_2}\left(b\eta_1 e^{-\hbar_3\varphi_3} + \varepsilon\eta_3\right)\right]}\right\}. \tag{31}$$

Using the values of the parameters given in Table 2 and choosing the parameters $\varphi_1 = 3$, $\varphi_2 = 2$, $\varphi_3 = 1$, $\eta_1 = 0.003$, $\eta_2 = 0.00002$, $\eta_3 = 0.001$ and $\sigma = 0.2$. We compute $\xi^{\min}_{(29)}$ as $\xi^{\min}_{(29)} = 0.6963$ and then we have the following scenarios:

(i) If $0.6963 \leq \xi \leq 1$, then $\Re_{0(29)}(\xi) \leq 1$ and hence $Đ_0$ is G.A.S. In this scenario, the virus particles will be removed from the body due to the strength of antiviral treatment.

(ii) If $0 \leq \xi < 0.6963$, then $\Re_{0(29)}(\xi) > 1$ and thus one of the other equilibria is G.A.S. This means that the HIV particles cannot be eradicated from the body due to less efficient treatment.

To study the influence of drug efficacies on the HIV dynamics model (29), we consider different values of ξ and solve system (29) under the following initial condition:

$$(W(\varphi), U(\varphi), M(\varphi), N(\varphi), P(\varphi)) = (600, 2.5, 0.5, 4, 0.5), \text{ where } \varphi \in [-3, 0].$$

The plots given in Fig. 4 show the solution trajectories of the system with different drug efficacies. We observe that as the drug efficacy is increased, the concentration of healthy $CD4^+$ T cells is increased, while the concentrations of silent/active HIV-infected cells, free HIV particles, and HIV-specific CTLs are decreased due to the strength of the usage drugs.

6.3 Effect of time delays on the HIV dynamics

In this part, we vary the delay parameters φ_1, φ_2, φ_3 and fix the parameters $\eta_1 = 0.003$, $\eta_2 = 0.00002$, $\eta_3 = 0.001$, $\sigma = 0.2$ and $\xi = 0$. Since $\Re_0$ given by Eq. (30) depends on φ_1, φ_2 and φ_3, then changing the parameters φ_1, φ_2 and φ_3 will change the stability of equilibria. Let us take the following values:

(I) $\varphi_1 = \varphi_2 = \varphi_3 = 0$,
(II) $\varphi_1 = 4, \varphi_2 = 3$ and $\varphi_3 = 2$,
(III) $\varphi_1 = 5, \varphi_2 = 4$ and $\varphi_3 = 3$,
(V) $\varphi_1 = 7, \varphi_2 = 6$ and $\varphi_3 = 5$.

With these values, we solve system (29) under initial condition IV-3. The numerical solutions are displayed in Fig. 5. We observe that inclusion of time delays can significantly increase the concentration of healthy $CD4^+$ T cells and reduce the concentrations of other compartments.

In Table 3, we present the values $\Re_{0(29)}$ for selected values of φ_1, φ_2 and φ_3. It is clear that, $\Re_{0(29)}$ is decreased when φ_1, φ_2 and φ_3 are increased and the stability of $Đ_0$ will be changed. Now, we want to calculate the critical value of the time delay that changes the stability of $Đ_0$. To do so, we fix the parameters φ_2 and φ_3 and write $\Re_{0(29)}$ as a function of φ_1 as:

Table 3 The variation of $\Re_{0(29)}$ with respect to the delay parameters

Delay parameters	$\Re_{0(29)}$
$\varphi_1 = \varphi_2 = \varphi_3 = 0$	8.55
$\varphi_1 = 3, \varphi_2 = 2, \varphi_3 = 1$	3.29
$\varphi_1 = 5, \varphi_2 = 4, \varphi_3 = 3$	1.13
$\varphi_1 = 6, \varphi_2 = 5, \varphi_3 = 4$	0.69
$\varphi_1 = 7, \varphi_2 = 6, \varphi_3 = 5$	0.42

$$\Re_{0(29)}(\varphi_1) = \frac{W_0 e^{-\hbar_1\varphi_1}\left[a\varepsilon\eta_2 + \lambda e^{-\hbar_2\varphi_2}\left(b\eta_1 e^{-\hbar_3\varphi_3} + \varepsilon\eta_3\right)\right]}{a\varepsilon\left(\gamma + \lambda\right)}.$$

When $\Re_{0(29)}(\varphi_1) \leq 1$, we obtain

$$\varphi_1 \geq \varphi_1^{\min}, \text{ where } \varphi_1^{\min} = \max\left\{0, \frac{1}{\hbar_1}\ln\frac{W_0\left\{a\varepsilon\eta_2 + \lambda e^{-\hbar_2\varphi_2}\left(b\eta_1 e^{-\hbar_3\varphi_3} + \varepsilon\eta_3\right)\right\}}{a\varepsilon\left(\gamma + \lambda\right)}\right\}.$$

Therefore, if $\varphi_1 \geq \varphi_1^{\min}$, then $Ð_0$ is G.A.S. Let $\varphi_2 = 5$ and $\varphi_3 = 4$ and compute $\varphi_1^{\min}$ as $\varphi_1^{\min} = 2.22266$. It follows that:

(i) If $\varphi_1 \geq 2.22266$, then $\Re_{0(29)}(\varphi_1) \leq 1$ and $Ð_0$ is G.A.S.
(ii) If $\varphi_1 < 2.22266$, then $\Re_{0(29)}(\varphi_1) > 1$ and $Ð_0$ will lose its stability and one of the other equilibria will be G.A.S.

We observe that the time delay has a similar effect as the drug efficacy. This gives some impression to develop a new class of treatment which causes an increase in the delay period and then suppress the HIV replication.

6.4 Effects of CTC transmission

Here, we investigate the influence of different modes of transmission on the HIV dynamics (29). We use the parameters given in Table 2 and choose the values $\sigma = 0.05$, $\varphi_1 = 3$, $\varphi_2 = 2$, $\varphi_3 = 1$ and $\xi = 0$ with the following initial condition:

IV-4. $(W(\varphi), U(\varphi), M(\varphi), N(\varphi), P(\varphi)) = (600, 10, 2, 0.5, 1)$, where $\varphi \in [-3, 0]$.

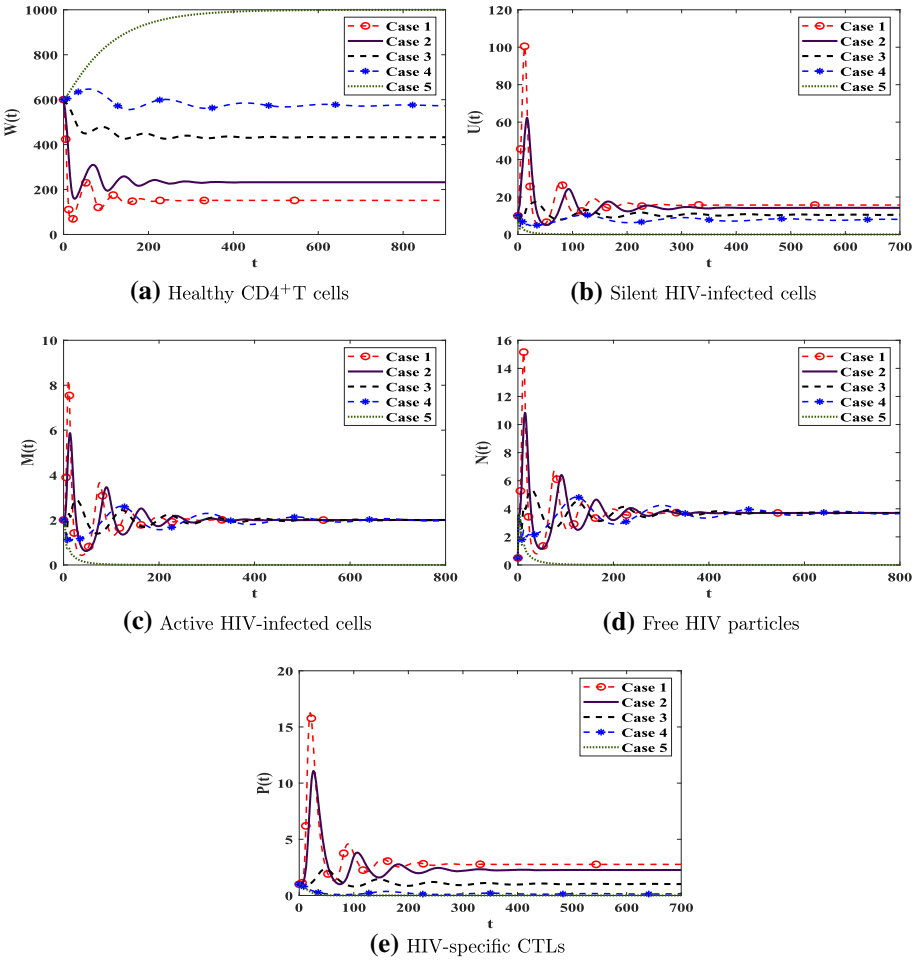
We choose three sets of parameters η_1, η_2, η_3 and investigate the following illustrative cases:

Case 1: HIV dynamics with VTC, silent HIV-infected CTC and active HIV-infected CTC transmissions: Here, we consider the parameters $\eta_1 = 0.005$, $\eta_2 = 0.002$ and $\eta_3 = 0.003$. Figure 6 shows that the solutions of the system approach the equilibrium $Ð_4 = (151.64, 15.71, 2, 3.70, 2.77)$.

Case 2: HIV dynamics with VTC, silent HIV-infected CTC and active HIV-infected CTC transmissions: In this case, we choose the parameters $\eta_1 = 0.004$, $\eta_2 = 0.001$ and $\eta_3 = 0.002$. We can see from Fig. 6 that the trajectories of the system tend to the equilibrium $Ð_4 = (232.38, 14.22, 2, 3.70, 2.26)$.

Case 3: HIV dynamics with both VTC and active HIV-infected CTC transmissions: In this case, we select the values $\eta_1 = 0.003$, $\eta_2 = 0$ and $\eta_3 = 0.001$. From Fig. 6, we observe that the solution trajectories converge to the equilibrium $Ð_3 = (432.67, 10.51, 2, 3.70, 1.02)$.

Case 4: HIV dynamics with only VTC transmission: Here, we consider the values $\eta_1 = 0.002$ and $\eta_2 = \eta_3 = 0$. Figure 6 displays that the solution trajectories approach the equilibrium $Ð_3 = (574.44, 7.88, 2, 3.70, 0.14)$.



(a) Healthy CD4$^+$T cells **(b)** Silent HIV-infected cells

(c) Active HIV-infected cells **(d)** Free HIV particles

(e) HIV-specific CTLs

Fig. 6 The evolution of HIV dynamics (29) under different modes of transmission

Case 5: HIV dynamics with only VTC transmission: In this situation, we pick the parameters $\eta_1 = 0.001$ and $\eta_2 = \eta_3 = 0$. It is clear from Fig. 6 that the solution trajectories reach the equilibrium $Ð_0 = (1000, 0, 0, 0, 0)$.

From the above discussion, we note that the presence of silent HIV-infected CTC and/or active HIV-infected CTC transmissions increases the infection rate. As a result, the concentration of healthy CD4$^+$ T cells is decreased, while the concentrations of silent/active HIV-infected cells, free HIV particles and HIV-specific CTLs are increased as shown in Fig. 6.

7 Conclusion and discussion

In this paper, we formulated and analyzed an HIV dynamics model with CTL-mediated immunity. We incorporated both VTC and CTC transmissions. We assumed that the CTC infection has two sources, (i) the contact between healthy CD4$^+$ T cells and silent HIV-infected cells, and (ii) the contact between healthy CD4$^+$ T cells and active HIV-infected cells.

We incorporated three types of distributed-time delays into the model. We established that the model is well posed by proving that the solutions of the model are nonnegative and bounded. We calculated the three possible equilibria of the model, the infection-free equilibrium, $Đ_0$, the chronic HIV infection equilibrium with inactive CTL-mediated immune response, $Đ_1$, and the chronic HIV infection equilibrium with active CTL-mediated immune response, $Đ_2$. The existence and global stability of the three equilibria are governed by two threshold parameters, $\Re_0$ (the basic HIV reproduction number) and $\Re_1$ (the HIV specific CTL-mediated immunity reproduction number). The global asymptotic stability of the three equilibria $Đ_0$, $Đ_1$ and $Đ_2$ was investigated by constructing Lyapunov functionals and utilizing LaSalle's invariance principle. To illustrate the theoretical results, we performed some numerical simulations. We developed the model to take into account three types of antiviral drugs. We showed that the inclusion of CTC transmission decreases the concentration of healthy $CD4^+$ T cells and increases the concentrations of infected cells and free HIV particles. On the other side, the inclusion of time delay can significantly suppress the HIV replication and increase the concentration of healthy $CD4^+$ T cells.

We observe that the inclusion of silent HIV-infected CTC and active HIV-infected CTC transmissions into the HIV infection model increases the basic HIV reproduction number $\Re_{0(29)}$, since $\Re_{0(29)} = \Re_{01(29)} + \Re_{02(29)} + \Re_{03(29)} > \Re_{01(29)}$. Therefore, neglecting the CTC transmission will lead to under-evaluated basic reproduction number. When the CTC is neglected then model (29) leads to the following form:

$$\begin{cases} \dot{W} = \rho - \alpha W - (1-\xi)\eta_1 W N, \\ \dot{U} = (1-\xi)e^{-\hbar_1\varphi_1}\eta_1 W_{\varphi_1} N_{\varphi_1} - (\lambda+\gamma)\, U, \\ \dot{M} = \lambda e^{-\hbar_2\varphi_2} U_{\varphi_2} - aM - \mu P M, \\ \dot{N} = be^{-\hbar_3\varphi_3} M_{\varphi_3} - \varepsilon N, \\ \dot{P} = \sigma P M - \pi P, \end{cases} \tag{32}$$

and the basic HIV reproduction number is given by

$$\Re_{0(32)}(\xi) = (1-\xi)\frac{W_0 \lambda b \eta_1 e^{-(\hbar_1\varphi_1+\hbar_2\varphi_2+\hbar_3\varphi_3)}}{a\varepsilon\,(\gamma+\lambda)}.$$

Then, the infection-free equilibrium $Đ_0$ can be stabilized for $\xi^{\min}_{(32)} < \xi \leq 1$, where

$$\xi^{\min}_{(32)} = \max\left\{0, 1 - \frac{a\varepsilon\,(\gamma+\lambda)}{W_0 \lambda b \eta_1 e^{-(\hbar_1\varphi_1+\hbar_2\varphi_2+\hbar_3\varphi_3)}}\right\}. \tag{33}$$

Comparing Eqs. (31) and (33), we get that $\xi^{\min}_{(32)} \leq \xi^{\min}_{(29)}$. Therefore, if we apply drugs with ξ such that $\xi^{\min}_{(32)} \leq \xi < \xi^{\min}_{(29)}$, this guarantees that $\Re_{0(32)}(\xi) \leq 1$ and then $Đ_0$ of system (32) is G.A.S, however, $\Re_{0(29)} > 1$ and then $Đ_0$ of system (29) is unstable. Therefore, more accurate drug efficacy which is required to clear the HIV from the body is calculated by using our proposed model. This shows the importance of considering the effect of CTC transmission in the HIV dynamics. Consequently, this observation sheds a light on the great importance of considering the influence of CTC transmission in the HIV dynamics. Our proposed model (3) can be extended by incorporating age structure of the infected cells or diffusion [51–54]. Looking ahead to further developments an interesting perspective would be introducing a stochastic internal variable, as in [55], to account for virus mutations which generally develops by a stochastic dynamics. Moreover, since the exact analytical solution of our proposed HIV dynamics model is not known, therefore, we can only obtain an approximate solution of the model. Therefore, the discrete-time version

of the model needs to be investigated (see, e.g., [56–58]). These extensions, indeed, require more investigations; therefore, we leave it for future works.

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References

1. H. Burger, A.L. Belman, R. Grimson, A. Kaell, K. Flaherty, J. Gulla, R.A. Gibbs, P.N. Nguyun, B. Weiser, Long HIV-1 incubation periods and dynamics of transmission within a family. The Lancet **336**(8708), 134–136 (1990)
2. M.A. Nowak, R.M. May, *Virus Dynamics: Mathematical Principles of Immunology and Virology* (Oxford University Press, Oxford, 2000)
3. A.M. Elaiw, I.A. Hassanien, S.A. Azoz, Global stability of HIV infection models with intracellular delays. J. Korean Math. Soc. **49**(4), 779–794 (2012)
4. A.M. Elaiw, S.A. Azoz, Global properties of a class of HIV infection models with Beddington–DeAngelis functional response. Math. Methods Appl. Sci. **36**, 383–394 (2013)
5. A.M. Elaiw, N.A. Almuallem, Global dynamics of delay-distributed HIV infection models with differential drug efficacy in cocirculating target cells. Math. Methods Appl. Sci. **39**(1), 4–31 (2016)
6. M.A. Nowak, C.R.M. Bangham, Population dynamics of immune responses to persistent viruses. Science **272**(5258), 74–79 (1996)
7. A.M. Elaiw, E.Kh. Elnahary, A.A. Raezah, Effect of cellular reservoirs and delays on the global dynamics of HIV. Adv. Differ. Equ. Article Number: 85 (2018)
8. A.M. Elaiw, A.A. Raezah, S.A. Azoz, Stability of delayed HIV dynamics models with two latent reservoirs and immune impairment. Adv. Differ. Equ. Article Number: 414 (2018)
9. H. Shu, L. Wang, J. Watmough, Global stability of a nonlinear viral infection model with infinitely distributed intracellular delays and CTL imune responses. SIAM J. Appl. Math. **73**(3), 1280–1302 (2013)
10. X. Li, S. Fu, Global stability of a virus dynamics model with intracellular delay and CTL immune response. Math. Methods Appl. Sci. **38**(3), 420–430 (2015)
11. D. Huang, X. Zhang, Y. Guo, H. Wang, Analysis of an HIV infection model with treatments and delayed immune response. Appl. Math. Model. **40**(4), 3081–3089 (2016)
12. C. Lv, L. Huang, Z. Yuan, Global stability for an HIV-1 infection model with Beddington–DeAngelis incidence rate and CTL immune response. Commun. Nonlinear Sci. Numer. Simul. **19**(1), 121–127 (2014)
13. X. Shi, X. Zhou, X. Song, Dynamical behavior of a delay virus dynamics model with CTL immune response. Nonlinear Anal. Real World Appl. **11**(3), 1795–1809 (2010)
14. X. Tian, R. Xu, Global stability and Hopf bifurcation of an HIV-1 infection model with saturation incidence and delayed CTL immune response. Appl. Math. Comput. **237**, 146–154 (2014)
15. H. Zhu, Y. Luo, M. Chen, Stability and Hopf bifurcation of a HIV infection model with CTL-response delay. Comput. Math. Appl. **62**(8), 3091–3102 (2011)
16. J. Wang, C. Qin, Y. Chen, X. Wang, Hopf bifurcation in a CTL-inclusive HIV-1 infection model with two time delays. Math. Biosci. Eng. **16**(4), 2587–2612 (2019)
17. C. Jolly, Q. Sattentau, Retroviral spread by induction of virological synapses. Traffic **5**, 643–650 (2004)
18. H. Sato, J. Orenstein, D. Dimitrov, M. Martin, Cell-to-cell spread of HIV-1 occurs within minutes and may not involve the participation of virus particles. Virology **186**(2), 712–724 (1992)
19. S. Iwami, J.S. Takeuchi, S. Nakaoka, F. Mammano, F. Clavel, H. Inaba, T. Kobayashi, N. Misawa, K. Aihara, Y. Koyanagi, K. Sato, Cell-to-cell infection by HIV contributes over half of virus infection. Elife **4**, e08150 (2015)
20. N.L. Komarova, D. Wodarz, Virus dynamics in the presence of synaptic transmission. Math. Biosci. **242**(2), 161–171 (2013)
21. M. Sourisseau, N. Sol-Foulon, F. Porrot, F. Blanchet, O. Schwartz, Inefficient human immunodeficiency virus replication in mobile lymphocytes. J. Virol. **81**(2), 1000–1012 (2007)
22. A. Sigal, J.T. Kim, A.B. Balazs, E. Dekel, A. Mayo, R. Milo, D. Baltimore, Cell-to-cell spread of HIV permits ongoing replication despite antiretroviral therapy. Nature **477**(7362), 95–98 (2011)
23. R.V. Culshaw, S. Ruan, G. Webb, A mathematical model of cell-to-cell spread of HIV-1 that includes a time delay. J. Math. Biol. **46**(5), 425–444 (2003)
24. A.M. Elaiw, S.F. Alshehaiween, Global stability of delay-distributed viral infection model with two modes of viral transmission and B-cell impairment. Math. Methods Appl. Sci. **43**(11), 6677–6701 (2020)

25. X. Lai, X. Zou, Modelling HIV-1 virus dynamics with both virus-to-cell infection and cell-to-cell transmission. SIAM J. Appl. Math. **74**(3), 898–917 (2014)
26. A.M. Elaiw, A.A. Raezah, Stability of general virus dynamics models with both cellular and viral infections and delays. Math. Methods Appl. Sci. **40**(16), 5863–5880 (2017)
27. D. Adak, N. Bairagi, Analysis and computation of multi-pathways and multi-delays HIV-1 infection model. Appl. Math. Model. **54**, 517–536 (2018)
28. X. Lai, X. Zou, Modeling cell-to-cell spread of HIV-1 with logistic target cell growth. J. Math. Anal. Appl. **426**(1), 563–584 (2015)
29. Y. Yang, L. Zou, S. Ruan, Global dynamics of a delayed within-host viral infection model with both virus-to-cell and cell-to-cell transmissions. Math. Biosci. **270**, 183–191 (2015)
30. Y. Yang, T. Zhang, Y. Xu, J. Zhou, A delayed virus infection model with cell-to-cell transmission and CTL immune response. Int. J. Bifurc. Chaos **27**(10), 175015011–175015015 (2017)
31. J. Wang, M. Guo, X. Liu, Z. Zhao, Threshold dynamics of HIV-1 virus model with cell-to-cell transmission, cell-mediated immune responses and distributed delay. Appl. Math. Comput. **291**, 149–161 (2016)
32. A.G. Cervantes-Perez, E. Avila-Vales, Dynamical analysis of multipathways and multidelays of general virus dynamics model. Int. J. Bifurc. Chaos **29**(3), 195003-301 (2019)
33. T.-W. Chun, L. Stuyver, S.B. Mizell, L.A. Ehler, J.A.M. Mican, M. Baseler, A.L. Lloyd, M.A. Nowak, A.S. Fauci, Presence of an inducible HIV-1 latent reservoir during highly active antiretroviral therapy. Proc. Natl. Acad. Sci. USA **94**(24), 13193–13197 (1997)
34. J.K. Wong, M. Hezareh, H.F. Gunthard, D.V. Havlir, C.C. Ignacio, C.A. Spina, D.D. Richman, Recovery of replication-competent HIV despite prolonged suppression of plasma viremia. Science **278**(5341), 1291–1295 (1997)
35. A.M. Elaiw, N.H. AlShamrani, Stability of a general adaptive immunity virus dynamics model with multi-stages of infected cells and two routes of infection. Math. Methods Appl. Sci. **43**(3), 1145–1175 (2020)
36. A. Mojaver, H. Kheiri, Mathematical analysis of a class of HIV infection models of CD4+T-cells with combined antiretroviral therapy. Appl. Math. Computat. **259**, 258–270 (2015)
37. A.M. Elaiw, A. Almatrafi, A.D. Hobiny, K. Hattaf, Global properties of a general latent pathogen dynamics model with delayed pathogenic and cellular infections. Discrete Dyn. Nat. Soc. **2019**, Article ID 9585497 (2019)
38. A.D. Hobiny, A.M. Elaiw, A. Almatrafi, Stability of delayed pathogen dynamics models with latency and two routes of infection. Adv. Differ. Equ. **2018**(1), Article Number: 276 (2018)
39. T. Guo, Z. Qiu, The effects of CTL immune response on HIV infection model with potent therapy, latently infected cells and cell-to-cell viral transmission. Math. Biosci. Eng. **16**(6), 6822–6841 (2019)
40. A.M. Elaiw, N.H. AlShamrani, Global stability of a delayed adaptive immunity viral infection with two routes of infection and multi-stages of infected cells. Commun. Nonlinear Sci. Numer. Simul. **86**, Article ID 105259 (2020)
41. L. Agosto, M. Herring, W. Mothes, A. Henderson, HIV-1-infected CD4+ T cells facilitate latent infection of resting CD4+ T cells through cell-cell contact. Cell **24**(8), 2088–2100 (2018)
42. J.K. Hale, S.V. Lunel, *Introduction to Functional Differential Equations* (Springer, New York, 1993)
43. Y. Kuang, *Delay Differential Equations with Applications in Population Dynamics* (Academic Press, San Diego, 1993)
44. P. van den Driessche, J. Watmough, Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. Math. Biosci. **180**(1), 29–48 (2002)
45. A. Korobeinikov, Global properties of basic virus dynamics models. Bull. Math. Biol. **66**(4), 879–883 (2004)
46. A.M. Elaiw, Global properties of a class of HIV models. Nonlinear Anal. Real World Appl. **11**(4), 2253–2263 (2010)
47. A.M. Elaiw, S.F. Alshehaiween, A.D. Hobiny, Global properties of a delay-distributed HIV dynamics model including impairment of B-cell functions. Mathematics **7**(9), Article Number: 837 (2019)
48. A.M. Elaiw, E.K. Elnahary, Analysis of general humoral immunity HIV dynamics model with HAART and distributed delays. Mathematics **7**(2), Article Number: 157 (2019)
49. A.M. Elaiw, N.H. AlShamrani, Global stability of humoral immunity virus dynamics models with nonlinear infection rate and removal. Nonlinear Anal. Real World Appl. **26**, 161–190 (2015)
50. X. Wang, L. Rong, HIV low viral load persistence under treatment: Insights from a model of cell-to-cell viral transmission. Appl. Math. Lett. **94**, 44–51 (2019)
51. C.C. McCluskey, Delay versus age-of-infection-Global stability. Appl. Math. Comput. **217**(7), 3046–3049 (2010)
52. N. Bellomo, K.J. Painter, Y. Tao, M. Winkler, Occurrence vs absence of taxis-driven instabilities in a May-Nowak model for virus infection. SIAM J. Appl. Math. **79**(5), 1990–2010 (2019)

53. A.M. Elaiw, A.D. AlAgha, Analysis of a delayed and diffusive oncolytic M1 virotherapy model with immune response. Nonlinear Anal. Real World Appl. **55**, Article 103116 (2020)
54. A.M. Elaiw, A.D. AlAgha, Global dynamics of reaction-diffusion oncolytic M1 virotherapy with immune response. Appl. Math. Comput. **367**, Article 124758 (2020)
55. L. Gibelli, A. Elaiw, M.A. Alghamdi, A.M. Althiabi, Heterogeneous population dynamics of active particles: progression, mutations, and selection dynamics. Math. Models Methods Appl. Sci. **27**(4), 617–640 (2017)
56. H. Sun, J. Wang, Dynamics of a diffusive virus model with general incidence function, cell-to-cell transmission and time delay. Comput. Math. Appl. **77**(1), 284–301 (2019)
57. A.M. Elaiw, M.A. Alshaikh, Stability analysis of a general discrete-time pathogen infection model with humoral immunity. J. Differ. Equ. Appl. **25**(8), 1149–1172 (2019)
58. A.M. Elaiw, M.A. Alshaikh, Stability of discrete-time HIV dynamics models with three categories of infected $CD4^+$ T-cells. Adv. Diff. Eqn. **2019**, 407 (2019)