AIMS Mathematics, 9(7): 19195–19239.
DOI: 10.3934/math.2024936
Received: 24 April 2024
Revised: 27 May 2024
Accepted: 03 June 2024
Published: 11 June 2024

http://www.aimspress.com/journal/Math

Research article

Stability of HHV-8 and HIV-1 co-infection model with latent reservoirs and multiple distributed delays

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Abstract: Human immunodeficiency virus type 1 (HIV-1) gradually destroys the CD4$^+$ T cells leading to immune system dysfunction. HIV-1 can result in acquired immunodeficiency syndrome (AIDS) if antiretroviral drugs are not used. HIV/AIDS patients are more vulnerable to opportunistic infections or cancers. Human herpesvirus 8 (HHV-8) targets B cells and causes an AIDS-related cancer known as kaposi sarcoma (KS). Numerous investigations have demonstrated co-infection instances between HIV-1 and HHV-8. In this research, we investigated the co-dynamics of HIV-1 and HHV-8 in vivo using a system of delay differential equations (DDEs). The model explained the interactions between uninfected CD4$^+$ T cells, latently/actively HIV-1-infected CD4$^+$ T cells, free HIV-1 particles, uninfected B cells, latently/actively HHV-8-infected B cells, and free HHV-8 particles. Eight distributed-time delays were incorporated into the model to account for the delays that arose during the generation of both actively and latently infected cells, the activation of latent reservoirs, and the maturation of freshly discharged virions. By examining the nonnegativity and boundedness of the solutions, we demonstrated that the model was both mathematically and biologically well-posed. We calculated the model's equilibria and threshold numbers. We studied the global asymptotic stability of the model's equilibria by building appropriate Lyapunov functionals and applying the Lyapunov-LaSalle asymptotic stability theorem. Numerical simulations were used to display the results. For the basic reproduction numbers of HHV-8 single-infection (R_1) and HIV-1 single-infection (R_2), sensitivity analysis was carried out. Comparing HIV-1 or HHV-8 single infections with co-infections of HHV-8 and HIV-1 was shown. It's interesting to note that we detected larger amounts of HHV-8 and HIV-1 when they co-infect than when they are infected alone. This outcome aligned with several findings seen in the literature. The effect of antiviral drugs and time delays on the co-dynamics of HIV-1 and HHV-8 was investigated. We found that the delay parameter and drug effectiveness both contributed to a decrease in the basic reproduction numbers, R_1 and R_2. Less treatment efficacies will be needed to keep the system at the infection-free equilibrium and remove HIV-1 and HHV-8 from the body if a model with time delays is employed.

Keywords: co-infection; HIV-1; HHV-8; time delay; global stability; Lyapunov function
Mathematics Subject Classification: 34D20, 34D23, 37N25, 92B05

1. Introduction

The frightening illness known as acquired immune deficiency syndrome (AIDS) has drawn attention from scientists. About 40.4 million people have died as a result of this terrible issue (estimates from UNAIDS 2023 [1]). Human immunodeficiency virus type 1 (HIV-1) is the cause of AIDS. It targets CD4$^+$ T cells, which manage the adaptive immune response in humans, starting a conflict between the immune system and pathogens. Consequently, the virus progressively erodes the immune system, encouraging the development of cancers and potentially lethal opportunistic infections [2]. Kaposi sarcoma (KS) is a kind of cancer and one of the illnesses associated with AIDS [3]. Human herpesvirus 8 (HHV-8), also referred to as Kaposi's sarcoma-associated herpesvirus (KSHV), is human rhadinovirus and was discovered in 1994 by Chang et al. [4]. HHV-8 is the cause of KS and other diseases such as primary effusion B-cell lymphoma (PEL) [5] and multicentric Castleman disease (MCD) [5]. These diseases frequently occur among individuals living with HIV [6]. HHV-8 primarily targets B cells [7], which, in addition to cytotoxic T-lymphocytes (CTLs), are the main components of adaptive immunity. B cells generate a particular antibody to neutralize the virus directly, while CTLs eliminate the virus-infected cells [8]. Both HIV-1 and HHV-8 share ways of transmission to the human body, such as blood products and sexual contact. Those with HIV-1 are more likely than those without HIV-1 to be HHV-8 seropositive, according to the review of Rohner et al. [9]. The HIV-infected population has an 800-fold higher risk of developing KS compared to the general population, making it the most prevalent cancer among people living with HIV [10]. Several investigations have reported cases of co-infection between HHV-8 and HIV-1 (see, e.g., [11–14]). Therefore, researching the prevalence of HHV-8 in HIV-infected individuals is crucial because it can help predict the risks of complications arising from co-infection in the future.

Mathematical modeling is used to describe real-world problems. Indeed, mathematical models have been used to study the behavior of several biological systems such as dynamics of human viral infections. As a result, understanding and predicting the course of a viral infection has become possible. Recently, many researchers have focused their attention on mathematical modeling of HIV-1 infection, which is interesting and full of research topics. Nowak and Bangham [15] used the derivatives with respect to time t to express the proportion of transfer between three components, uninfected CD4$^+$ T cells, $U(t)$, HIV-1-infected cells, $Y(t)$ and free HIV-1 particles, $V(t)$. As a result, a system of ordinary differential equations (ODEs) was constructed as:

$$\dot{U} = \overbrace{\lambda}^{\text{generation rate of uninfected CD4}^+\text{ T cells}} - \overbrace{dU}^{\text{death rate}} - \overbrace{\beta_1 UV}^{\text{infection rate}}, \tag{1.1}$$

$$\dot{Y} = \overbrace{\beta_1 UV}^{\text{growth rate of infected cells}} - \overbrace{a_1 Y}^{\text{death rate}}, \tag{1.2}$$

$$\dot{V} = \overbrace{k_1 Y}^{\text{generation rate of HIV-1}} - \overbrace{c_1 V}^{\text{viral clearance rate}}. \tag{1.3}$$

Several viral infections can be controlled and eliminated in large part by adaptive immunity. With regard to the impact of B-cell response, model (1.1)–(1.3) can be expressed as [16]:

$$\dot{U} = \lambda - dU - \beta_1 UV, \tag{1.4}$$

$$\dot{Y} = \beta_1 UV - a_1 Y, \tag{1.5}$$

$$\dot{V} = k_1 Y - c_1 V - rVW, \tag{1.6}$$

$$\dot{W} = \Xi(V, W) - \mu W, \tag{1.7}$$

where $W = W(t)$ is the concentration of B cells. The viruses are neutralized via antibodies generated by the B cells, which are rVW. The term μW represents the death rate of B cells. $\Xi(V, W)$ represents the B-cell activation. The literature considered the subsequent special shapes of $\Xi(V, W)$ as follows:

Shape-**1.** Self-regulating B-cell activation, $\Xi(V, W) = \alpha$, where $\alpha > 0$ [16].

Shape-**2.** Linear B-cell activation, $\Xi(V, W) = uV$, where $u > 0$ [17, 18].

Shape-**3.** Predator-prey like B-cell activation, $\Xi(V, W) = qVW$, where $q > 0$ [16, 18–20].

Shape-**4.** Combination of Shape-1, Shape-2, and Shape-3, $\Xi(V, W) = \alpha + uV + qVW$ [16].

Model (1.4)–(1.7) has been extended in several directions by including: (i) time delays [19, 20], (ii) reaction-diffusion [21], (iii) age structure [22], (iv) cell-to-cell transmission [23, 24], and (v) latent reservoirs [25].

Researchers have focused a great deal of work on modeling the dynamics of HIV-1 single-infection inside the host, but they have not given much thought to analyzing the dynamics of HHV-8 single-infection. Chimbola et al. [26] developed an HHV-8 single-infection model. However, only the stability of the infection-free equilibrium was analyzed. The within-host co-dynamics of HIV-1 and other viruses have been the subject of numerous mathematical models developed in recent years. Examples of these models include those between HIV-1 and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [27]; HIV-1 and human T-cell lymphotropic virus (HTLV) [28]; HIV-1 and hepatitis C virus (HCV) [29]; and HIV-1 and hepatitis B virus (HBV) [30]. The evolution of HIV-1 co-infection and KS under the impact of highly active antiretroviral therapy (HAART) is shown in a mathematical model formulated by Nani and Jin [31]. To support this paradigm, adoptive cellular immunotherapy was included by the same authors in [32]. The kinematics of both B cells and free HHV-8 particles, however, were not included in these two papers. Models were developed in [33–35] to show the development of co-infection between HHV-8 and HIV-1. The model from [33] could not account for the population dynamics of uninfected $CD4^+$ T cells and uninfected B cells. Mathematical analysis of the model in [34] was limited to assessing the positivity of the model's solutions. All that was examined in [33, 35] was the stability of the infection-free equilibrium. It is worth noting that the models showcased in [31–35] ignored the function of B cells in the fight against HIV-1. Furthermore, these models disregarded two crucial biological elements: latent reservoirs, which harbor the virus within them but do not secrete it until it activates, and the interval between the virus's collision with the target cell and the generation of new, mature viruses.

In this work, our ultimate goal is to develop and examine a novel mathematical model to explain the co-dynamics between HIV-1 and HHV-8. The model incorporates the function of B cells against HIV-1 and accounts for latent reservoirs. The model also includes eight distributed-time delays to account

the delays that occur during the creation of both actively and latently infected cells, the activation of latently infected cells, and the maturation of freshly emitted virions. We explore the basic properties of the model's solutions in addition to the global stability of the equilibria. We provide numerical simulations to validate the theoretical results. We describe the findings in our conclusion.

2. Model formulation of HHV-8/HIV-1 co-infection with multi-time distributed delays

In this section, we formulate an HHV-8/HIV-1 co-infection model with eight distributed-time delays. Let $Y^L = Y^L(t)$, $Y^A = Y^A(t)$, $Z^L = Z^L(t)$, $Z^A = Z^A(t)$, and $P = P(t)$ be the concentrations of latently HIV-1-infected CD4$^+$ T cells, actively HIV-1-infected CD4$^+$ T cells, latently HHV-8-infected B cells, actively HHV-8-infected B cells, and free HHV-8 particles, respectively. Denote

$$(U, Y^L, Y^A, V, W, Z^L, Z^A, P) = (U, Y^L, Y^A, V, W, Z^L, Z^A, P)(t),$$
$$(U_\tau, Y^L_\tau, Y^A_\tau, V_\tau, W_\tau, Z^L_\tau, Z^A_\tau, P_\tau) = (U, Y^L, Y^A, V, W, Z^L, Z^A, P)(t-\tau).$$

Then, the model is given as:

$$\dot{U} = \lambda - dU - \beta_1 UV, \tag{2.1}$$
$$\dot{Y}^L = (1-\xi_1)\beta_1 \int_0^{\varkappa_1} f_1(\tau) e^{-n_1\tau} U_\tau V_\tau d\tau - (\delta_1 + b_1) Y^L, \tag{2.2}$$
$$\dot{Y}^A = \xi_1\beta_1 \int_0^{\varkappa_2} f_2(\tau) e^{-n_2\tau} U_\tau V_\tau d\tau + \delta_1 \int_0^{\varkappa_3} f_3(\tau) e^{-n_3\tau} Y^L_\tau d\tau - a_1 Y^A, \tag{2.3}$$
$$\dot{V} = k_1 \int_0^{\varkappa_4} f_4(\tau) e^{-n_4\tau} Y^A_\tau d\tau - c_1 V - rVW, \tag{2.4}$$
$$\dot{W} = \alpha + qVW - \mu W - mWP, \tag{2.5}$$
$$\dot{Z}^L = (1-\xi_2)m \int_0^{\varkappa_5} f_5(\tau) e^{-n_5\tau} W_\tau P_\tau d\tau - (\delta_2 + b_2) Z^L \tag{2.6}$$
$$\dot{Z}^A = \xi_2 m \int_0^{\varkappa_6} f_6(\tau) e^{-n_6\tau} W_\tau P_\tau d\tau + \delta_2 \int_0^{\varkappa_7} f_7(\tau) e^{-n_7\tau} Z^L_\tau d\tau - a_2 Z^A, \tag{2.7}$$
$$\dot{P} = k_2 \int_0^{\varkappa_8} f_8(\tau) e^{-n_8\tau} Z^A_\tau d\tau - c_2 P. \tag{2.8}$$

The production rate of uninfected B cells is denoted by α, whereas the rate at which they are infected by HHV-8 is represented as mWP. A fraction $\xi_i \in [0,1]$, $i = 1,2$ of target cells becomes active, while the remaining fraction $1-\xi_i$ remains latent. Actively HIV-1-infected CD4$^+$T cells and actively HHV-8-infected B cells, respectively, produce HIV-1 and HHV-8 particles at rates $k_1 Y^A$ and $k_2 Z^A$. The rates at which latently HIV-1-infected CD4$^+$T cells and latently HHV-8-infected B cells become active are represented by $\delta_1 Y^L$ and $\delta_2 Z^L$, respectively. The B cells undergo proliferation as a result of the presence of HIV-1 at a rate of qVW. The terms $b_1 Y^L$, $a_1 Y^A$, $b_2 Z^L$, $a_2 Z^A$, and $c_2 P$ represent the death rates of compartments Y^L, Y^A, Z^L, Z^A, and P, respectively. Here, n_i, $i = 1, 2, \cdots, 8$ are the positive constants. The delay parameter τ is a random variable picked from probability distribution functions $f_i(\tau)$ over time interval $[0, \varkappa_i]$, $i = 1, 2, \cdots, 8$, where $\varkappa_i$ is the limit superior of the delay period. We have the presumptions.

(I) The likelihood that uninfected CD4$^+$T cells and uninfected B cells contacted by HIV-1 and HHV-8 at time $t-\tau$ survived τ time units and become latently HIV-1-infected CD4$^+$T cells and latently HHV-8-infected B cells at time t, respectively, is represented by the factors $f_i(\tau)e^{-n_i\tau}$, $i = 1, 5$, where $1/n_i$ is the average lifetime of the cell during the period of formation of a latently infected cell [36]. Here, τ denotes the time between viral entry and latent infection (i.e., the integration of viral DNA into cell's DNA has finished) [37–39].

(II) The likelihood that uninfected CD4$^+$T cells and uninfected B cells contacted by HIV-1 and HHV-8 at time $t-\tau$ survived τ time units and became actively HIV-1-infected CD4$^+$T cells and actively HHV-8-infected B cells at time t, respectively, is represented by the factors $f_i(\tau)e^{-n_i\tau}, i = 2, 6$, where $1/n_i$ is the average lifetime of the cell during the period of formation of an actively infected cell. Here, τ represents a time delay between the cell infection and the subsequent generation of new immature virions [37–39].

(III) The likelihood that latently HIV-1-infected CD4$^+$T cells and latently HHV-8-infected B cells would survive for τ time units before becoming active at time t is shown by the factors $f_i(\tau)e^{-n_i\tau}, i = 3, 7$, where $1/n_i$ is the average lifetime of the cell during the period of a latently infected cell's reactivation. Here, τ is a period of time during which latently infected cells are activated to generate actively infected cells [40, 41].

(IV) The likelihood of newly immature HIV-1 and HHV-8 at time $t-\tau$ surviving τ time units and maturing at time t, respectively, is represented by the factors $f_i(\tau)e^{-n_i\tau}, i = 4, 8$, where $1/n_i$ is the average lifetime of an immature virus [36]. Here, τ represents the time it takes from the newly produced virus to be mature and then infectious [39, 42, 43].

Note that the functions $f_i(\tau), i = 1, 2, \cdots, 8$, satisfy $f_i(\tau) > 0$ and

$$\int_0^{\varkappa_i} f_i(\tau)d\tau = 1, \quad \int_0^{\varkappa_i} f_i(\tau)e^{l\tau}d\tau < \infty,$$

where $l > 0$ [44]. Let us denote $\Pi_i(\tau) = f_i(\tau)e^{-n_i\tau}$ and $F_i = \int_0^{\varkappa_i} \Pi_i(\tau)d\tau, i = 1, 2, \cdots, 8$, which implies that $0 < F_i \leq 1$. The initial conditions for model (2.1)–(2.8) are given as follows:

$$\begin{cases} U(\theta) = \phi_1(\theta), Y^L(\theta) = \phi_2(\theta), Y^A(\theta) = \phi_3(\theta), V(\theta) = \phi_4(\theta), \\ W(\theta) = \phi_5(\theta), Z^L(\theta) = \phi_6(\theta), Z^A(\theta) = \phi_7(\theta), P(\theta) = \phi_8(\theta), \\ \quad \phi_i(\theta) \geq 0, i = 1, 2, \ldots, 8, \quad \theta \in [-\tau^*, 0], \end{cases} \tag{2.9}$$

where $\tau^* = \max\{\varkappa_1, \varkappa_2, \ldots, \varkappa_8\}, \phi_i \in C([-\tau^*, 0], \mathbb{R}_{\geq 0})$, and C is the Banach space of continuous functions mapping from $[-\tau^*, 0]$ to $\mathbb{R}_{\geq 0}$ with the norm $\|\phi_i\| = \sup_{-\tau^* \leq \theta \leq 0} |\phi_i(\theta)|$ for $\phi_i \in C$, $i = 1, 2, \ldots, 8$. According to the standard theory of functional differential equations, model (2.1)–(2.8) with initial conditions (2.9) has a single solution [45, 46]. The values of parameters of model (2.1)–(2.8) are given in Table 1.

Table 1. Model parameters.

Symbol	Parameter	Value	Source
λ	Production rate of uninfected CD4$^+$T cells	10 cells mm^{-3} day^{-1}	[47, 48]
d	Death rate of uninfected CD4$^+$T cells	0.01 day^{-1}	[23, 49]
β_1	Infection rate of uninfected CD4$^+$T cells by HIV-1	varied	
a_1	Death rate of actively HIV-1-infected CD4$^+$T cells	0.4 day^{-1}	[47]
k_1	Production rate of HIV-1	38 viruses cells^{-1} day^{-1}	[49, 50]
c_1	Death rate of HIV-1	2.4 day^{-1}	[47–49]
r	Neutralization rate of HIV-1 particles due to B cells	0.1 cells^{-1} mm^3 day^{-1}	
α	Production rate of uninfected B cells	48 cells mm^{-3} day^{-1}	[34]
q	Stimulation rate of B cells	0.01 viruses^{-1} mm^3 day^{-1}	[51]
μ	Death rate of uninfected B cells	0.24 day^{-1}	[34]
m	Infection rate of uninfected B cells by HHV-8	varied	
a_2	Death rate of actively HHV-8-infected B cells	0.33 day^{-1}	[34]
k_2	Production rate of HHV-8	1 viruses cells^{-1} day^{-1}	Assumed
c_2	Death rate of HHV-8	0.57 day^{-1}	[34]
ξ_1	A portion of newly HIV-1-infected CD4$^+$T cells that activate	0.1	[52]
ξ_2	A portion of newly HHV-8-infected B cells that activate	0.001	[26]
δ_1	Activation rate of latently HIV-1-infected CD4$^+$T cells	0.01 day^{-1}	[52]
δ_2	Activation rate of latently HHV-8-infected B cells	1.1 day^{-1}	[26]
b_1	Death rate of latently HIV-1-infected CD4$^+$T cells	4×10^{-3} day^{-1}	[52]
b_2	Death rate of latently HHV-8-infected B-cells	0.30 day^{-1}	[26]
τ	Time delay parameter	varied	
n_i	Average lifetime of the cell or virus during a delay period	1 day^{-1}	Assumed

3. Preliminaries

This section presents the nonnegativity and boundedness of solutions of model (2.1)–(2.8) with initial conditions (2.9), and it also provides the equilibrium points and the threshold parameters.

3.1. Analysis and properties of solutions

This section presents the nonnegativity and boundedness of the solutions to establish that the model (2.1)–(2.8) is biologically acceptable and mathematically well-posed.

Lemma 3.1. *Solutions of model (2.1)–(2.8) with the initial states (2.9) are nonnegative and ultimately bounded.*

Proof. Let us show the nonnegativity of solutions of model (2.1)–(2.8). Clearly, Eq (2.1) and Eq (2.5) of model (2.1)–(2.8) give

$$\dot{U}\big|_{U=0} = \lambda > 0, \ \dot{W}\big|_{W=0} = \alpha > 0.$$

Hence, $U(t) > 0$ and $W(t) > 0$ for any $t \geq 0$. In addition, we have

$$Y^L(t) = e^{-(\delta_1+b_1)t}\phi_2(0) + (1-\xi_1)\beta_1 \int_0^t e^{-(\delta_1+b_1)(t-\theta)} \int_0^{\varkappa_1} \Pi_1(\tau)U(\theta-\tau)V(\theta-\tau)d\tau d\theta \geq 0,$$

$$Y^A(t) = e^{-a_1 t}\phi_3(0) + \int_0^t e^{-a_1(t-\theta)}\left[\xi_1\beta_1\int_0^{\varkappa_2}\Pi_2(\tau)U(\theta-\tau)V(\theta-\tau)d\tau + \delta_1\int_0^{\varkappa_3}\Pi_3(\tau)Y^L(\theta-\tau)d\tau\right]d\theta \geq 0,$$

$$V(t) = e^{-\int_0^t (c_1+rW(x))dx}\phi_4(0) + k_1\int_0^t e^{-\int_\theta^t (c_1+rW(x))dx}\int_0^{\varkappa_4}\Pi_4(\tau)Y^A(\theta-\tau)d\tau d\theta \geq 0,$$

$$Z^L(t) = e^{-(\delta_2+b_2)t}\phi_6(0) + (1-\xi_2)m\int_0^t e^{-(\delta_2+b_2)(t-\theta)}\int_0^{\varkappa_5}\Pi_5(\tau)W(\theta-\tau)P(\theta-\tau)d\tau d\theta \geq 0,$$

$$Z^A(t) = e^{-a_2 t}\phi_7(0) + \int_0^t e^{-a_2(t-\theta)}\left[\xi_2 m\int_0^{\varkappa_6}\Pi_6(\tau)W(\theta-\tau)P(\theta-\tau)d\tau + \delta_2\int_0^{\varkappa_7}\Pi_7(\tau)Z^L(\theta-\tau)d\tau\right]d\theta \geq 0,$$

$$P(t) = e^{-c_2 t}\phi_8(0) + k_2\int_0^t e^{-c_2(t-\theta)}\int_0^{\varkappa_8}\Pi_8(\tau)Z^A(\theta-\tau)d\tau d\theta \geq 0,$$

for any $t \in [0, \tau^*]$. Hence, by recursive argumentation, we obtain that $(Y^L, Y^A, V, Z^L, Z^A, P)(t) \geq 0$ for any $t \geq 0$.

Let's prove the ultimately boundedness of solution $(U, Y^L, Y^A, V, W, Z^L, Z^A, P)$. From Eq (2.1), we have $\limsup_{t\to\infty} U(t) \leq \Omega_1$ where $\Omega_1 = \frac{\lambda}{d}$. To prove the ultimate boundedness of $Y^L(t)$, we define

$$\Psi_1 = (1-\xi_1)\int_0^{\varkappa_1}\Pi_1(\tau)U_\tau d\tau + Y^L.$$

Then, we get

$$\begin{aligned}
\dot{\Psi}_1 &= (1-\xi_1)\int_0^{\varkappa_1}\Pi_1(\tau)\dot{U}_\tau d\tau + \dot{Y}^L \\
&= (1-\xi_1)\int_0^{\varkappa_1}\Pi_1(\tau)\left[\lambda - dU_\tau - \beta_1 U_\tau V_\tau\right]d\tau + (1-\xi_1)\beta_1\int_0^{\varkappa_1}\Pi_1(\tau)U_\tau V_\tau d\tau - (\delta_1+b_1)Y^L \\
&= (1-\xi_1)\lambda\int_0^{\varkappa_1}\Pi_1(\tau)d\tau - (1-\xi_1)d\int_0^{\varkappa_1}\Pi_1(\tau)U_\tau d\tau - (\delta_1+b_1)Y^L \\
&\leq (1-\xi_1)\lambda F_1 - \zeta_1\left[(1-\xi_1)\int_0^{\varkappa_1}\Pi_1(\tau)U_\tau d\tau + Y^L\right] \\
&\leq (1-\xi_1)\lambda - \zeta_1\left[(1-\xi_1)\int_0^{\varkappa_1}\Pi_1(\tau)U_\tau d\tau + Y^L\right] \\
&= (1-\xi_1)\lambda - \zeta_1\Psi_1,
\end{aligned}$$

where $\zeta_1 = \min\{d, \delta_1 + b_1\}$. It follows that $\limsup_{t\to\infty}\Psi_1(t) \leq \Omega_2$, and then $\limsup_{t\to\infty} Y^L(t) \leq \Omega_2$, where $\Omega_2 = \frac{(1-\xi_1)\lambda}{\zeta_1}$. Define

$$\Psi_2 = \xi_1\int_0^{\varkappa_2}\Pi_2(\tau)U_\tau d\tau + Y^A.$$

Then, we get

$$\begin{aligned}
\dot{\Psi}_2 &= \xi_1\int_0^{\varkappa_2}\Pi_2(\tau)\left[\lambda - dU_\tau - \beta_1 U_\tau V_\tau\right]d\tau + \xi_1\beta_1\int_0^{\varkappa_2}\Pi_2(\tau)U_\tau V_\tau d\tau + \delta_1\int_0^{\varkappa_3}\Pi_3(\tau)Y^L_\tau d\tau - a_1 Y^A \\
&= \xi_1\lambda\int_0^{\varkappa_2}\Pi_2(\tau)d\tau - d\xi_1\int_0^{\varkappa_2}\Pi_2(\tau)U_\tau d\tau + \delta_1\int_0^{\varkappa_3}\Pi_3(\tau)Y^L_\tau d\tau - a_1 Y^A
\end{aligned}$$

$$\leq \xi_1\lambda F_2 + \delta_1 F_3\Omega_2 - \zeta_2\left[\xi_1\int_0^{\varkappa_2}\Pi_2(\tau)U_\tau d\tau + Y^A\right]$$
$$\leq \xi_1\lambda + \delta_1\Omega_2 - \zeta_2\Psi_2,$$

where $\zeta_2 = \min\{d, a_1\}$. It follows that $\limsup_{t\to\infty}\Psi_2(t) \leq \Omega_3$ where $\Omega_3 = \frac{\xi_1\lambda+\delta_1\Omega_2}{\zeta_2}$, then $\limsup_{t\to\infty} Y^A(t) \leq \Omega_3$. Now, let us define

$$\Psi_3 = V + \frac{r}{q}W.$$

Then, we obtain

$$\begin{aligned}\dot{\Psi}_3 &= k_1\int_0^{\varkappa_4}\Pi_4(\tau)Y_\tau^A d\tau - c_1V - rVW + \frac{r}{q}(\alpha + qVW - \mu W - mWP)\\ &= k_1\int_0^{\varkappa_4}\Pi_4(\tau)Y_\tau^A d\tau - c_1V + \frac{\alpha r}{q} - \frac{r\mu}{q}W - \frac{rm}{q}WP\\ &\leq k_1\int_0^{\varkappa_4}\Pi_4(\tau)Y_\tau^A d\tau + \frac{\alpha r}{q} - c_1V - \frac{r\mu}{q}W\\ &\leq k_1F_4\Omega_3 + \frac{\alpha r}{q} - \zeta_3\left[V + \frac{r}{q}W\right]\\ &\leq k_1\Omega_3 + \frac{\alpha r}{q} - \zeta_3\Psi_3,\end{aligned}$$

where $\zeta_3 = \min\{c_1, \mu\}$. It follows that $\limsup_{t\to\infty}\Psi_3(t) \leq \Omega_4$, where $\Omega_4 = \frac{k_1\Omega_3}{\zeta_3} + \frac{\alpha r}{q\zeta_3}$, and, thus, $\limsup_{t\to\infty} V(t) \leq \Omega_4$ and $\limsup_{t\to\infty} W(t) \leq \Omega_5$ where $\Omega_5 = \frac{q}{r}\Omega_4$. We define

$$\Psi_4 = (1-\xi_2)\int_0^{\varkappa_5}\Pi_5(\tau)W_\tau d\tau + Z^L.$$

Then,

$$\begin{aligned}\dot{\Psi}_4 &= (1-\xi_2)\int_0^{\varkappa_5}\Pi_5(\tau)\left[\alpha + qV_\tau W_\tau - \mu W_\tau - mW_\tau P_\tau\right]d\tau + (1-\xi_2)m\int_0^{\varkappa_5}\Pi_5(\tau)W_\tau P_\tau d\tau - (\delta_2+b_2)Z^L\\ &= (1-\xi_2)\alpha\int_0^{\varkappa_5}\Pi_5(\tau)d\tau + (1-\xi_2)q\int_0^{\varkappa_5}\Pi_5(\tau)V_\tau W_\tau d\tau - (1-\xi_2)\mu\int_0^{\varkappa_5}\Pi_5(\tau)W_\tau d\tau - (\delta_2+b_2)Z^L\\ &\leq (1-\xi_2)\alpha F_5 + (1-\xi_2)qF_5\Omega_4\Omega_5 - (1-\xi_2)\mu\int_0^{\varkappa_1}\Pi_5(\tau)W_\tau d\tau - (\delta_2+b_2)Z^L\\ &\leq (1-\xi_2)[\alpha + q\Omega_4\Omega_5] - \zeta_4\Psi_4,\end{aligned}$$

where $\zeta_4 = \min\{\mu, \delta_2 + b_2\}$. It follows that $\limsup_{t\to\infty}\Psi_4(t) \leq \Omega_6$ where $\Omega_6 = \frac{(1-\xi_2)[\alpha+q\Omega_4\Omega_5]}{\zeta_4}$, then $\limsup_{t\to\infty} Z^L(t) \leq \Omega_6$. Consider

$$\Psi_5 = \xi_2\int_0^{\varkappa_6}\Pi_6(\tau)W_\tau d\tau + Z^A.$$

Then, we obtain

$$\dot{\Psi}_5 = \xi_2\int_0^{\varkappa_6}\Pi_6(\tau)\left[\alpha + qV_\tau W_\tau - \mu W_\tau - mW_\tau P_\tau\right]d\tau + \xi_2 m\int_0^{\varkappa_6}\Pi_6(\tau)W_\tau P_\tau d\tau + \delta_2\int_0^{\varkappa_7}\Pi_7(\tau)Z_\tau^L d\tau - a_2Z^A$$

$$= \xi_2\alpha \int_0^{\varkappa_6} \Pi_6(\tau)d\tau + \xi_2 q \int_0^{\varkappa_6} \Pi_6(\tau)V_\tau W_\tau d\tau - \xi_2\mu \int_0^{\varkappa_6} \Pi_6(\tau)W_\tau d\tau + \delta_2 \int_0^{\varkappa_7} \Pi_7(\tau)Z_\tau^L d\tau - a_2 Z^A$$
$$\leq \xi_2\alpha F_6 + \xi_2 q F_6\Omega_4\Omega_5 + \delta_2 F_7\Omega_6 - \zeta_5\left[\xi_2 \int_0^{\varkappa_6} \Pi_6(\tau)W_\tau d\tau + Z^A\right]$$
$$\leq \xi_2\alpha + \xi_2 q\Omega_4\Omega_5 + \delta_2\Omega_6 - \zeta_5\Psi_5,$$

where $\zeta_5 = \min\{\mu, a_2\}$. It follows that $\limsup_{t\to\infty} \Psi_5(t) \leq \Omega_7$ where $\Omega_7 = \frac{\xi_2\alpha+\xi_2 q\Omega_4\Omega_5+\delta_2\Omega_6}{\zeta_5}$, then $\limsup_{t\to\infty} Z^A(t) \leq \Omega_7$. Finally, Eq (2.8) gives

$$\dot{P} = k_2 \int_0^{\varkappa_8} \Pi_8(\tau)Z_\tau^A d\tau - c_2 P \leq k_2\Omega_7 - c_2 P.$$

Thus, $\limsup_{t\to\infty} P(t) \leq \Omega_8$ where $\Omega_8 = \frac{k_2\Omega_7}{c_2}$. Consequently, according to the Lemma 3.1, the region

$$\Gamma = \left\{\left(U, Y^L, Y^A, V, W, Z^L, Z^A, P\right) \in C^8_{\geq 0} : \|U\| \leq \Omega_1, \|Y^L\| \leq \Omega_2, \|Y^A\| \leq \Omega_3, \|V\| \leq \Omega_4, \right.$$
$$\left. \|W\| \leq \Omega_5, \|Z^L\| \leq \Omega_6, \left\|Z^A\right\| \leq \Omega_7, \|P\| \leq \Omega_8\right\}$$

is positively invariant with respect to model (2.1)–(2.8). □

3.2. Equilibrium points and threshold parameters

Lemma 3.2. *For model (2.1)–(2.8), there are four threshold numbers (R_j, $j = 1, 2, 3, 4$) in addition to four equilibria such that*

(I) *There is always infection-free equilibrium, $EP_0 = (U_0, 0, 0, 0, W_0, 0, 0, 0)$.*

(II) *If $R_1 > 1$, then there exists an HHV-8 single-infection equilibrium, $EP_1 = \left(U_1, 0, 0, 0, W_1, Z_1^L, Z_1^A, P_1\right)$ besides EP_0.*

(III) *If $R_2 > 1$, then there exists an HIV-1 single-infection equilibrium, $EP_2 = \left(U_2, Y_2^L, Y_2^A, V_2, W_2, 0, 0, 0\right)$ besides EP_0.*

(IV) *If $R_3 > 1$ and $R_4 > 1$, then then there exists an HHV-8/HIV-1 co-infection equilibrium, $EP_3 = \left(U_3, Y_3^L, Y_3^A, V_3, W_3, Z_3^L, Z_3^A, P_3\right)$ besides EP_0.*

Proof. The equilibrium points $EP = (U, Y^L, Y^A, V, W, Z^L, Z^A, P)$ of model (2.1)–(2.8) can be found by solving the following system of algebraic equations:

$$\begin{cases} 0 = \lambda - dU - \beta_1 UV, \\ 0 = (1-\xi_1)F_1\beta_1 UV - \delta_1 Y^L - b_1 Y^L, \\ 0 = \xi_1 F_2\beta_1 UV + \delta_1 F_3 Y^L - a_1 Y^A, \\ 0 = k_1 F_4 Y^A - c_1 V - rVW, \\ 0 = \alpha + qVW - \mu W - mWP, \\ 0 = (1-\xi_2)F_5 mWP - \delta_2 Z^L - b_2 Z^L, \\ 0 = \xi_2 F_6 mWP + \delta_2 F_7 Z^L - a_2 Z^A, \\ 0 = k_2 F_8 Z^A - c_2 P. \end{cases}$$

We find that the given model (2.1)–(2.8) admits four equilibria as well as four threshold parameters, which are:

(1) Infection-free equilibrium, $EP_0 = (U_0, 0, 0, 0, W_0, 0, 0, 0)$, where $U_0 = \frac{\lambda}{d}$ and $W_0 = \frac{\alpha}{\mu}$.

(2) HHV-8 single-infection equilibrium, $EP_1 = \left(U_1, 0, 0, 0, W_1, Z_1^L, Z_1^A, P_1\right)$, where

$$U_1 = \frac{\lambda}{d},\ W_1 = \frac{a_2c_2\left(\delta_2 + b_2\right)}{k_2mF_8\mathcal{P}_1},\ Z_1^L = \frac{a_2c_2\mu}{F_8k_2m\mathcal{P}_1}\left(1-\xi_2\right)F_5\left(R_1-1\right),$$
$$Z_1^A = \frac{c_2\mu}{k_2mF_8}\left(R_1-1\right),\ P_1 = \frac{\mu}{m}\left(R_1-1\right).$$

Here, R_1 and $\mathcal{P}_1$ are defined as:

$$R_1 = \frac{\alpha k_2mF_8\mathcal{P}_1}{a_2c_2\mu\left(\delta_2+b_2\right)},$$
$$\text{where } \mathcal{P}_1 = (\delta_2+b_2)\xi_2F_6 + \delta_2(1-\xi_2)F_5F_7,$$

where R_1 represents the basic reproduction number for HHV-8 single-infection. Clearly, EP_1 exists when $R_1 > 1$.

(3) HIV-1 single-infection equilibrium, $EP_2 = \left(U_2, Y_2^L, Y_2^A, V_2, W_2, 0, 0, 0\right)$, where

$$U_2 = \frac{\left(\delta_1+b_1\right)Y_2^L}{\left(1-\xi_1\right)F_1\beta_1V_2},\ Y_2^L = \frac{a_1F_1\left(1-\xi_1\right)Y_2^A}{\mathcal{P}_2},$$
$$Y_2^A = \frac{c_1V_2 + rV_2W_2}{k_1F_4},\ W_2 = \frac{\alpha}{\mu - qV_2}, \tag{3.1}$$
$$\text{where } \mathcal{P}_2 = \xi_1F_2(\delta_1+b_1) + F_1F_3\delta_1\left(1-\xi_1\right),$$

and V_2 satisfies the following equation:

$$\frac{A_1V^2 + A_2V + A_3}{\mu - qV} = 0, \quad V \in \left(0, \frac{\mu}{q}\right),$$

where

$$A_1 = a_1c_1\beta_1q\left(\delta_1+b_1\right),$$
$$A_2 = a_1dc_1q\left(\delta_1+b_1\right) - a_1c_1\beta_1\mu\left(\delta_1+b_1\right) - a_1r\alpha\beta_1\left(\delta_1+b_1\right) - \lambda k_1\beta_1qF_4\mathcal{P}_2,$$
$$A_3 = \lambda k_1\beta_1\mu F_4\mathcal{P}_2 - a_1dc_1\mu\left(\delta_1+b_1\right) - a_1dr\alpha\left(\delta_1+b_1\right).$$

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

$$G(V) = \frac{A_1V^2 + A_2V + A_3}{\mu - qV}, \quad V \in \left(0, \frac{\mu}{q}\right).$$

Function $G(V)$ is continuous on $V \in \left(0, \frac{\mu}{q}\right)$. Then, we have

$$G(0) = \frac{a_1d\left(\delta_1+b_1\right)\left(r\alpha + c_1\mu\right)}{\mu}\left(R_2-1\right) > 0, \quad \text{if } R_2 > 1,$$

and

$$\lim_{V\to\left(\frac{\mu}{q}\right)^-} G(V) = -\infty < 0,$$

where

$$R_2 = \frac{\lambda k_1\beta_1\mu F_4\mathcal{P}_2}{a_1 d\,(c_1\mu + r\alpha)\,(\delta_1 + b_1)}.$$

Here, R_2 is the basic reproduction number for HIV-1 single-infection. Thus, there exists V_2 such that $0 < V_2 < \frac{\mu}{q}$ satisfies $G(V_2) = 0$. As a result, we get $U_2 > 0, Y_2^L > 0, Y_2^A > 0,$ and $W_2 > 0$.

(4) HHV-8/HIV-1 co-infection equilibrium, $EP_3 = \left(U_3, Y_3^L, Y_3^A, V_3, W_3, Z_3^L, Z_3^A, P_3\right)$, where

$$\begin{aligned}
U_3 &= \frac{a_1(b_1+\delta_1)\left[a_2c_2r(b_2+\delta_2) + c_1k_2m\mathcal{P}_1F_8\right]}{k_1k_2m\beta_1\mathcal{P}_2F_4\mathcal{P}_1F_8},\\
Y_3^L &= \frac{a_1dF_1(1-\xi_1)(c_1k_2m\mathcal{P}_1F_8 + a_2c_2r(b_2+\delta_2))}{k_1k_2m\beta_1\mathcal{P}_2F_4\mathcal{P}_1F_8}\,(R_3-1),\\
Y_3^A &= \frac{d(c_1k_2m\mathcal{P}_1F_8 + a_2c_2r(b_2+\delta_2))}{k_1k_2m\beta_1\mathcal{P}_1F_8F_4}\,(R_3-1),\\
V_3 &= \frac{d}{\beta_1}\,(R_3-1),\ W_3 = \frac{a_2c_2(b_2+\delta_2)}{k_2m\mathcal{P}_1F_8},\ Z_3^L = \frac{a_2c_2(1-\xi_2)F_5(dq+\beta_1\mu)}{k_2m\beta_1\mathcal{P}_1F_8}\,(R_4-1),\\
Z_3^A &= \frac{c_2(dq+\beta_1\mu)}{k_2m\beta_1F_8}\,(R_4-1),\ \ P_3 = \frac{dq+\beta_1\mu}{m\beta_1}\,(R_4-1),
\end{aligned}$$

where

$$\begin{aligned}
R_3 &= \frac{\lambda k_1k_2m\beta_1\mathcal{P}_1\mathcal{P}_2F_4F_8}{a_1d(\delta_1+b_1)\,(c_1k_2m\mathcal{P}_1F_8 + a_2c_2r(\delta_2+b_2))},\\
R_4 &= \frac{k_2m\beta_1F_8}{(dq+\beta_1\mu)}\left(\frac{\alpha\mathcal{P}_1}{a_2c_2(\delta_2+b_2)} + \frac{k_1q\lambda\mathcal{P}_1F_4\mathcal{P}_2}{a_1(\delta_1+b_1)\,(c_1k_2m\mathcal{P}_1F_8 + a_2c_2r(\delta_2+b_2))}\right).
\end{aligned}$$

We have

$$\begin{aligned}
R_4 &= \frac{k_2m\beta_1F_8}{(dq+\beta_1\mu)}\left(\frac{\alpha\mathcal{P}_1}{a_2c_2(\delta_2+b_2)} + \frac{k_1q\lambda\mathcal{P}_1F_4\mathcal{P}_2}{a_1(\delta_1+b_1)\,(c_1k_2m\mathcal{P}_1F_8 + a_2c_2r(\delta_2+b_2))}\right)\\
&= \frac{\beta_1\mu}{(dq+\beta_1\mu)}\frac{\alpha k_2mF_8\mathcal{P}_1}{a_2c_2\mu(\delta_2+b_2)} + \frac{qd}{(dq+\beta_1\mu)}\frac{\lambda k_1k_2m\beta_1\mathcal{P}_1\mathcal{P}_2F_4F_8}{a_1d(\delta_1+b_1)\,(c_1k_2m\mathcal{P}_1F_8 + a_2c_2r(\delta_2+b_2))}\\
&= \frac{\beta_1\mu}{dq+\beta_1\mu}R_1 + \frac{dq}{dq+\beta_1\mu}R_3\\
&< R_1 + R_3.
\end{aligned}$$

Thus, $R_4 < R_1$ as well as $R_4 < R_3$. Therefore, the co-infection equilibrium, EP_3, exists whenever $R_4 > 1$. The parameter R_4 determines when HIV-1 and HHV-8 will be coexist. □

4. Global stability of equilibria

In this section, the global stability of all equilibria of co-infection model (2.1)–(2.8) is studied. We formulate a suitable Lyapunov function and apply LaSalle's invariant principle given in [36, 53]. Let

us define a function $\mathcal{L}(\theta) = \theta - 1 - \ln\theta$, and let Υ_j' be the largest invariant subset of

$$\Upsilon_j = \left\{\left(U, Y^L, Y^A, V, W, Z^L, Z^A, P\right) : \frac{d\mathcal{H}_j}{dt} = 0\right\}, \quad j = 0, 1, 2, 3.$$

Theorem 4.1. *The co-infection model (2.1)–(2.8) is globally asymptotically stable (GAS) around the infection-free equilibrium EP_0 if $R_1 \leq 1$ and $R_2 \leq 1$. Furthermore, EP_0 is unstable if $R_1 > 1$ or $R_2 > 1$.*

Proof. Define $\mathcal{H}_0(U, Y^L, Y^A, V, W, Z^L, Z^A, P)$ as:

$$\begin{aligned}
\mathcal{H}_0 = {} & \mathcal{P}_2 U_0 \mathcal{L}\left(\frac{U}{U_0}\right) + \delta_1 F_3 Y^L + (\delta_1 + b_1) Y^A + \frac{a_1(\delta_1 + b_1)}{k_1 F_4} V + \frac{a_1 r(\delta_1 + b_1)}{k_1 q F_4} W_0 \mathcal{L}\left(\frac{W}{W_0}\right) + \frac{a_1 r \delta_2 F_7(\delta_1 + b_1)}{k_1 q F_4 \mathcal{P}_1} Z^L \\
& + \frac{a_1 r(\delta_1 + b_1)(\delta_2 + b_2)}{k_1 q F_4 \mathcal{P}_1} Z^A + \frac{a_1 a_2 r(\delta_1 + b_1)(\delta_2 + b_2)}{k_1 k_2 q F_4 F_8 \mathcal{P}_1} P + \delta_1 \beta_1 (1 - \xi_1) F_3 \int_0^{\varkappa_1} \Pi_1(\tau) \int_{t-\tau}^{t} U(\theta) V(\theta) d\theta d\tau \\
& + \xi_1 \beta_1 (\delta_1 + b_1) \int_0^{\varkappa_2} \Pi_2(\tau) \int_{t-\tau}^{t} U(\theta) V(\theta) d\theta d\tau + \delta_1 (\delta_1 + b_1) \int_0^{\varkappa_3} \Pi_3(\tau) \int_{t-\tau}^{t} Y^L(\theta) d\theta d\tau \\
& + \frac{a_1(\delta_1 + b_1)}{F_4} \int_0^{\varkappa_4} \Pi_4(\tau) \int_{t-\tau}^{t} Y^A(\theta) d\theta d\tau + \frac{a_1 r \delta_2 m F_7 (1 - \xi_2)(\delta_1 + b_1)}{k_1 q F_4 \mathcal{P}_1} \int_0^{\varkappa_5} \Pi_5(\tau) \int_{t-\tau}^{t} W(\theta) P(\theta) d\theta d\tau \\
& + \frac{a_1 r \xi_2 m (\delta_1 + b_1)(\delta_2 + b_2)}{k_1 q F_4 \mathcal{P}_1} \int_0^{\varkappa_6} \Pi_6(\tau) \int_{t-\tau}^{t} W(\theta) P(\theta) d\theta d\tau \\
& + \frac{a_1 r \delta_2 (\delta_1 + b_1)(\delta_2 + b_2)}{k_1 q F_4 \mathcal{P}_1} \int_0^{\varkappa_7} \Pi_7(\tau) \int_{t-\tau}^{t} Z^L(\theta) d\theta d\tau \\
& + \frac{a_1 a_2 r(\delta_1 + b_1)(\delta_2 + b_2)}{k_1 q F_4 F_8 \mathcal{P}_1} \int_0^{\varkappa_8} \Pi_8(\tau) \int_{t-\tau}^{t} Z^A(\theta) d\theta d\tau.
\end{aligned}$$

Obviously, $\mathcal{H}_0(U, Y^L, Y^A, V, W, Z^L, Z^A, P) > 0$ for any $U, Y^L, Y^A, V, W, Z^L, Z^A, P > 0$, and $\mathcal{H}_0(U_0, 0, 0, 0, W_0, 0, 0, 0) = 0$. Let us calculate $\frac{d\mathcal{H}_0}{dt}$ along the solutions of model (2.1)–(2.8) as:

$$\begin{aligned}
\frac{d\mathcal{H}_0}{dt} = {} & \mathcal{P}_2 \left(1 - \frac{U_0}{U}\right) \dot{U} + \delta_1 F_3 \dot{Y}^L + (\delta_1 + b_1) \dot{Y}^A + \frac{a_1(\delta_1 + b_1)}{k_1 F_4} \dot{V} + \frac{a_1 r(\delta_1 + b_1)}{k_1 q F_4} \left(1 - \frac{W_0}{W}\right) \dot{W} \\
& + \frac{a_1 r \delta_2 F_7 (\delta_1 + b_1)}{k_1 q F_4 \mathcal{P}_1} \dot{Z}^L + \frac{a_1 r(\delta_1 + b_1)(\delta_2 + b_2)}{k_1 q F_4 \mathcal{P}_1} \dot{Z}^A + \frac{a_1 a_2 r(\delta_1 + b_1)(\delta_2 + b_2)}{k_1 k_2 q F_4 F_8 \mathcal{P}_1} \dot{P} \\
& + \delta_1 \beta_1 (1 - \xi_1) F_3 \int_0^{\varkappa_1} \Pi_1(\tau) \left(UV - U_\tau V_\tau\right) d\tau + \xi_1 \beta_1 (\delta_1 + b_1) \int_0^{\varkappa_2} \Pi_2(\tau) \left(UV - U_\tau V_\tau\right) d\tau \\
& + \delta_1 (\delta_1 + b_1) \int_0^{\varkappa_3} \Pi_3(\tau) \left(Y^L - Y^L_\tau\right) d\tau + \frac{a_1(\delta_1 + b_1)}{F_4} \int_0^{\varkappa_4} \Pi_4(\tau) \left(Y^A - Y^A_\tau\right) d\tau \\
& + \frac{a_1 r \delta_2 m F_7 (1 - \xi_2)(\delta_1 + b_1)}{k_1 q F_4 \mathcal{P}_1} \int_0^{\varkappa_5} \Pi_5(\tau) \left(WP - W_\tau P_\tau\right) d\tau \\
& + \frac{a_1 r \xi_2 m (\delta_1 + b_1)(\delta_2 + b_2)}{k_1 q F_4 \mathcal{P}_1} \int_0^{\varkappa_6} \Pi_6(\tau) \left(WP - W_\tau P_\tau\right) d\tau \\
& + \frac{a_1 r \delta_2 (\delta_1 + b_1)(\delta_2 + b_2)}{k_1 q F_4 \mathcal{P}_1} \int_0^{\varkappa_7} \Pi_7(\tau) \left(Z^L - Z^L_\tau\right) d\tau \\
& + \frac{a_1 a_2 r(\delta_1 + b_1)(\delta_2 + b_2)}{k_1 q F_4 F_8 \mathcal{P}_1} \int_0^{\varkappa_8} \Pi_8(\tau) \left(Z^A - Z^A_\tau\right) d\tau.
\end{aligned}$$

Using Eqs (2.1)–(2.8), we obtain

$$\begin{aligned}
\frac{d\mathcal{H}_0}{dt} =& \mathcal{P}_2\left(1-\frac{U_0}{U}\right)(\lambda - dU - \beta_1 UV) + \delta_1 F_3\left((1-\xi_1)\beta_1\int_0^{\varkappa_1}\Pi_1(\tau)U_\tau V_\tau d\tau - (\delta_1+b_1)Y^L\right)\\
&+(\delta_1+b_1)\left(\xi_1\beta_1\int_0^{\varkappa_2}\Pi_2(\tau)U_\tau V_\tau d\tau + \delta_1\int_0^{\varkappa_3}\Pi_3(\tau)Y_\tau^L d\tau - a_1 Y^A\right)\\
&+\frac{a_1(\delta_1+b_1)}{k_1F_4}\left(k_1\int_0^{\varkappa_4}\Pi_4(\tau)Y_\tau^A d\tau - c_1V - rVW\right)\\
&+\frac{a_1r(\delta_1+b_1)}{k_1qF_4}\left(1-\frac{W_0}{W}\right)(\alpha + qVW - \mu W - mWP)\\
&+\frac{a_1r\delta_2F_7(\delta_1+b_1)}{k_1qF_4\mathcal{P}_1}\left((1-\xi_2)m\int_0^{\varkappa_5}\Pi_5(\tau)W_\tau P_\tau d\tau - (\delta_2+b_2)Z^L\right)\\
&+\frac{a_1r(\delta_1+b_1)(\delta_2+b_2)}{k_1qF_4\mathcal{P}_1}\left(\xi_2 m\int_0^{\varkappa_6}\Pi_6(\tau)W_\tau P_\tau d\tau + \delta_2\int_0^{\varkappa_7}\Pi_7(\tau)Z_\tau^L d\tau - a_2 Z^A\right)\\
&+\frac{a_1a_2r(\delta_1+b_1)(\delta_2+b_2)}{k_1k_2qF_4F_8\mathcal{P}_1}\left(k_2\int_0^{\varkappa_8}\Pi_8(\tau)Z_\tau^A d\tau - c_2P\right)\\
&+\delta_1\beta_1(1-\xi_1)F_3\int_0^{\varkappa_1}\Pi_1(\tau)\left(UV - U_\tau V_\tau\right)d\tau + \xi_1\beta_1(\delta_1+b_1)\int_0^{\varkappa_2}\Pi_2(\tau)\left(UV - U_\tau V_\tau\right)d\tau\\
&+\delta_1(\delta_1+b_1)\int_0^{\varkappa_3}\Pi_3(\tau)\left(Y^L - Y_\tau^L\right)d\tau + \frac{a_1(\delta_1+b_1)}{F_4}\int_0^{\varkappa_4}\Pi_4(\tau)\left(Y^A - Y_\tau^A\right)d\tau\\
&+\frac{a_1r\delta_2mF_7(1-\xi_2)(\delta_1+b_1)}{k_1qF_4\mathcal{P}_1}\int_0^{\varkappa_5}\Pi_5(\tau)\left(WP - W_\tau P_\tau\right)d\tau\\
&+\frac{a_1r\xi_2m(\delta_1+b_1)(\delta_2+b_2)}{k_1qF_4\mathcal{P}_1}\int_0^{\varkappa_6}\Pi_6(\tau)\left(WP - W_\tau P_\tau\right)d\tau\\
&+\frac{a_1r\delta_2(\delta_1+b_1)(\delta_2+b_2)}{k_1qF_4\mathcal{P}_1}\int_0^{\varkappa_7}\Pi_7(\tau)\left(Z^L - Z_\tau^L\right)d\tau\\
&+\frac{a_1a_2r(\delta_1+b_1)(\delta_2+b_2)}{k_1qF_4F_8\mathcal{P}_1}\int_0^{\varkappa_8}\Pi_8(\tau)\left(Z^A - Z_\tau^A\right)d\tau.
\end{aligned}$$

Collecting terms and using $\lambda = dU_0$ and $\alpha = \mu W_0$, we obtain

$$\begin{aligned}
\frac{d\mathcal{H}_0}{dt} =& -\mathcal{P}_2\frac{d}{U}(U-U_0)^2 - \frac{a_1r(\delta_1+b_1)}{k_1qF_4}\frac{\mu}{W}(W-W_0)^2\\
&+\frac{a_1(\delta_1+b_1)(c_1\mu+r\alpha)}{k_1\mu F_4}\left(\frac{\lambda k_1\beta_1\mu F_4\mathcal{P}_2}{a_1d(c_1\mu+r\alpha)(\delta_1+b_1)} - 1\right)V\\
&+\frac{a_1a_2rc_2(\delta_1+b_1)(\delta_2+b_2)}{k_1k_2qF_4F_8\mathcal{P}_1}\left(\frac{\alpha k_2mF_8\mathcal{P}_1}{a_2c_2\mu(\delta_2+b_2)} - 1\right)P.
\end{aligned}$$

Finally, we get

$$\begin{aligned}
\frac{d\mathcal{H}_0}{dt} =& -\mathcal{P}_2\frac{d}{U}(U-U_0)^2 - \frac{a_1r(\delta_1+b_1)}{k_1qF_4}\frac{\mu}{W}(W-W_0)^2\\
&+\frac{a_1(\delta_1+b_1)(c_1\mu+r\alpha)}{k_1\mu F_4}(R_2-1)V + \frac{a_1a_2rc_2(\delta_1+b_1)(\delta_2+b_2)}{k_1k_2qF_4F_8\mathcal{P}_1}(R_1-1)P.
\end{aligned}$$

When $R_1 \leq 1$ and $R_2 \leq 1$, then $\frac{d\mathcal{H}_0}{dt} \leq 0$. Furthermore, $\frac{d\mathcal{H}_0}{dt} = 0$ when $U = U_0$, $W = W_0$, $(R_2 - 1)\, V = 0$, and $(R_1 - 1)\, P = 0$. Solutions of the model (2.1)–(2.8) converge to Υ_0' [45]. Any component in Υ_0' fulfills $U = U_0$, $W = W_0$,

$$(R_2 - 1)\, V = 0 \quad \text{and} \quad (R_1 - 1)\, P = 0. \tag{4.1}$$

We have four cases:

Case (I) $R_1 = 1$ and $R_2 = 1$. Then, from Eq (2.1), we get

$$0 = \dot{U} = \lambda - dU_0 - \beta_1 U_0 V \quad \Longrightarrow \quad V(t) = 0 \quad \text{for any } t. \tag{4.2}$$

From Eq (2.4), we have

$$0 = \dot{V} = k_1 \int_0^{\varkappa_4} \Pi_4(\tau) Y_\tau^A d\tau \quad \Longrightarrow \quad Y^A(t) = 0 \quad \text{for any } t, \tag{4.3}$$

and from Eq (2.3), we get

$$0 = \dot{Y}^A = \delta_1 \int_0^{\varkappa_3} \Pi_3(\tau) Y_\tau^L d\tau \quad \Longrightarrow \quad Y^L(t) = 0 \quad \text{for any } t. \tag{4.4}$$

Equation (2.5) implies that

$$0 = \dot{W} = \alpha - \mu W_0 - m W_0 P \quad \Longrightarrow \quad P(t) = 0 \quad \text{for any } t. \tag{4.5}$$

Equation (2.8) gives

$$0 = \dot{P} = k_2 \int_0^{\varkappa_8} \Pi_8(\tau) Z_\tau^A d\tau \quad \Longrightarrow \quad Z^A(t) = 0 \quad \text{for any } t, \tag{4.6}$$

and from Eq (2.7), we get

$$0 = \dot{Z}^A = \delta_2 \int_0^{\varkappa_7} \Pi_7(\tau) Z_\tau^L d\tau \quad \Longrightarrow \quad Z^L(t) = 0 \quad \text{for any } t. \tag{4.7}$$

Thus, $\Upsilon_0' = \{EP_0\}$.

Case (II) $R_1 < 1$ and $R_2 < 1$. Then, from Eq (4.1), we have $V = P = 0$, and Eqs (4.3) and (4.6) give $Y^A = Z^A = 0$. Hence, Eqs (4.4) and (4.7) lead to $Y^L = Z^L = 0$. Therefore, $\Upsilon_0' = \{EP_0\}$.

Case (III) $R_1 = 1$ and $R_2 < 1$. Then, from Eq (4.1), we get $V = 0$. Equations (4.3)–(4.7) imply $Y^A = Y^L = P = Z^A = Z^L = 0$. Thus, $\Upsilon_0' = \{EP_0\}$.

Case (IV) $R_1 < 1$ and $R_2 = 1$. Equation (4.1) implies $P = 0$. Equations (4.2)–(4.4), (4.6), and (4.7) give $V = Y^A = Y^L = Z^A = Z^L = 0$. Thus, $\Upsilon_0' = \{EP_0\}$.

Applying the Lyapunov-LaSalle asymptotic stability theorem [54–56], we get that EP_0 is GAS.

The characteristic equation of model (2.1)–(2.8) at the equilibrium EP_0 is specified by

$$(x + d)(x + \mu)\mathcal{M}(x) = 0, \tag{4.8}$$

where x is the eigenvalue, $\mathcal{M}(x) = \mathcal{M}_1(x)\mathcal{M}_2(x)$ is defined for interval $[0, \infty)$ as:

$$\mathcal{M}_1(x) = \left(\ell_3 x^3 + \ell_2 x^2 + \ell_1 x + \ell_0\right)$$
$$\mathcal{M}_2(x) = \left(\hbar_3 x^3 + \hbar_2 x^2 + \hbar_1 x + \hbar_0\right)$$

and

$$\begin{aligned}
\ell_3 &= \mu,\\
\ell_2 &= a_2\mu + b_2\mu + c_2\mu + \delta_2\mu,\\
\ell_1 &= a_2b_2\mu + a_2c_2\mu + b_2c_2\mu + a_2\delta_2\mu + c_2\delta_2\mu - k_2m\alpha\xi_2\bar{F}_6\bar{F}_8,\\
\ell_0 &= a_2c_2\mu(\delta_2 + b_2) + \alpha k_2m\delta_2\xi_2\bar{F}_5\bar{F}_7\bar{F}_8 - \alpha k_2m\delta_2\bar{F}_5\bar{F}_7\bar{F}_8 - \alpha k_2mb_2\xi_2\bar{F}_6\bar{F}_8 - \alpha k_2m\delta_2\xi_2\bar{F}_6\bar{F}_8,\\
&= a_2c_2\mu(b_2 + \delta_2)\,(1 - R_1)\,.\\
\hbar_3 &= d\mu,\\
\hbar_2 &= dr\alpha + a_1d\mu + b_1d\mu + c_1d\mu + d\delta_1\mu,\\
\hbar_1 &= a_1dr\alpha + b_1dr\alpha + dr\alpha\delta_1 + a_1b_1d\mu + a_1c_1d\mu + b_1c_1d\mu + a_1d\delta_1\mu + c_1d\delta_1\mu - k_1\beta_1\lambda\mu\xi_1\bar{F}_2\bar{F}_4,\\
\hbar_0 &= a_1b_1dr\alpha + a_1dr\alpha\delta_1 + a_1b_1c_1d\mu + a_1c_1d\delta_1\mu - k_1\beta_1\delta_1\lambda\mu\bar{F}_1\bar{F}_3\bar{F}_4 - b_1k_1\beta_1\lambda\mu\xi_1\bar{F}_2\bar{F}_4 - k_1\beta_1\lambda\mu\xi_1\delta_1\bar{F}_2\bar{F}_4\\
&\quad + k_1\beta_1\delta_1\lambda\mu\xi_1\bar{F}_1\bar{F}_3\bar{F}_4,\\
&= a_1d(\delta_1 + b_1)(c_1\mu + r\alpha)\,(1 - R_2)\,,
\end{aligned}$$

where $\bar{F}_i = \int_0^{\varkappa_i} f_i(\tau)e^{-(x+n_i)\tau}d\tau, i = 1, 2, \cdots, 8$. Obviously, $\mathcal{M}(0) < 0$ since $\mathcal{M}_1(0) = a_2c_2\mu(b_2 + \delta_2)\,(1 - R_1) < 0$ if $R_1 > 1$, or $\mathcal{M}_2(0) = a_1d(\delta_1 + b_1)(c_1\mu + r\alpha)\,(1 - R_2) < 0$ if $R_2 > 1$ and $\lim_{x\to\infty} \mathcal{M}(x) = \infty$. This presents that $\mathcal{M}(x)$ has a positive real root. Thus, when $R_1 > 1$ or $R_2 > 1$, we get $\ell_0 < 0$ or $\hbar_0 < 0$, respectively. Consequently, Eq (4.8) has a positive root and then EP_0 is unstable. □

Theorem 4.2. *The co-infection model (2.1)–(2.8) is GAS around the HHV-8 single-infection equilibrium EP_1 when the following conditions are satisfied: $R_1 > 1$ and $R_3 \leq 1$.*

Proof. Consider $\mathcal{H}_1(U, Y^L, Y^A, V, W, Z^L, Z^A, P)$ as:

$$\begin{aligned}
\mathcal{H}_1 &= \mathcal{P}_2U_1\mathcal{L}\left(\frac{U}{U_1}\right) + \delta_1F_3Y^L + (\delta_1 + b_1)Y^A + \frac{a_1(\delta_1 + b_1)}{k_1F_4}V + \frac{a_1r(\delta_1 + b_1)}{k_1qF_4}W_1\mathcal{L}\left(\frac{W}{W_1}\right)\\
&\quad + \frac{a_1r\delta_2F_7(\delta_1 + b_1)}{k_1qF_4\mathcal{P}_1}Z_1^L\mathcal{L}\left(\frac{Z^L}{Z_1^L}\right) + \frac{a_1r(\delta_1 + b_1)(\delta_2 + b_2)}{k_1qF_4\mathcal{P}_1}Z_1^A\mathcal{L}\left(\frac{Z^A}{Z_1^A}\right)\\
&\quad + \frac{a_1a_2r(\delta_1 + b_1)(\delta_2 + b_2)}{k_1k_2qF_4F_8\mathcal{P}_1}P_1\mathcal{L}\left(\frac{P}{P_1}\right) + \delta_1\beta_1(1 - \xi_1)F_3\int_0^{\varkappa_1}\Pi_1(\tau)\int_{t-\tau}^{t}U(\theta)V(\theta)d\theta d\tau\\
&\quad + \xi_1\beta_1(\delta_1 + b_1)\int_0^{\varkappa_2}\Pi_2(\tau)\int_{t-\tau}^{t}U(\theta)V(\theta)d\theta d\tau + \delta_1(\delta_1 + b_1)\int_0^{\varkappa_3}\Pi_3(\tau)\int_{t-\tau}^{t}Y^L(\theta)d\theta d\tau\\
&\quad + \frac{a_1(\delta_1 + b_1)}{F_4}\int_0^{\varkappa_4}\Pi_4(\tau)\int_{t-\tau}^{t}Y^A(\theta)d\theta d\tau\\
&\quad + \frac{a_1r\delta_2mF_7(1 - \xi_2)(\delta_1 + b_1)}{k_1qF_4\mathcal{P}_1}W_1P_1\int_0^{\varkappa_5}\Pi_5(\tau)\int_{t-\tau}^{t}\mathcal{L}\left(\frac{W(\theta)P(\theta)}{W_1P_1}\right)d\theta d\tau\\
&\quad + \frac{a_1r\xi_2m(\delta_1 + b_1)(\delta_2 + b_2)}{k_1qF_4\mathcal{P}_1}W_1P_1\int_0^{\varkappa_6}\Pi_6(\tau)\int_{t-\tau}^{t}\mathcal{L}\left(\frac{W(\theta)P(\theta)}{W_1P_1}\right)d\theta d\tau
\end{aligned}$$

$$+\frac{a_1r\delta_2(\delta_1+b_1)(\delta_2+b_2)}{k_1qF_4\mathcal{P}_1}Z_1^L\int_0^{\varkappa_7}\Pi_7(\tau)\int_{t-\tau}^{t}\mathcal{L}\left(\frac{Z^L(\theta)}{Z_1^L}\right)d\theta d\tau$$
$$+\frac{a_1a_2r(\delta_1+b_1)(\delta_2+b_2)}{k_1qF_4F_8\mathcal{P}_1}Z_1^A\int_0^{\varkappa_8}\Pi_8(\tau)\int_{t-\tau}^{t}\mathcal{L}\left(\frac{Z^A(\theta)}{Z_1^A}\right)d\theta d\tau.$$

Calculate $\frac{d\mathcal{H}_1}{dt}$ as:

$$\begin{aligned}\frac{d\mathcal{H}_1}{dt}=&\mathcal{P}_2\left(1-\frac{U_1}{U}\right)(\lambda-dU-\beta_1UV)+\delta_1F_3\left((1-\xi_1)\beta_1\int_0^{\varkappa_1}\Pi_1(\tau)U_\tau V_\tau d\tau-(\delta_1+b_1)Y^L\right)\\
&+(\delta_1+b_1)\left(\xi_1\beta_1\int_0^{\varkappa_2}\Pi_2(\tau)U_\tau V_\tau d\tau+\delta_1\int_0^{\varkappa_3}\Pi_3(\tau)e^{-n_2\tau}Y_\tau^L d\tau-a_1Y^A\right)\\
&+\frac{a_1(\delta_1+b_1)}{k_1F_4}\left(k_1\int_0^{\varkappa_4}\Pi_4(\tau)Y_\tau^A d\tau-c_1V-rVW\right)\\
&+\frac{a_1r(\delta_1+b_1)}{k_1qF_4}\left(1-\frac{W_1}{W}\right)(\alpha+qVW-\mu W-mWP)\\
&+\frac{a_1r\delta_2F_7(\delta_1+b_1)}{k_1qF_4\mathcal{P}_1}\left(1-\frac{Z_1^L}{Z^L}\right)\left((1-\xi_2)m\int_0^{\varkappa_5}\Pi_5(\tau)W_\tau P_\tau d\tau-(\delta_2+b_2)Z^L\right)\\
&+\frac{a_1r(\delta_1+b_1)(\delta_2+b_2)}{k_1qF_4\mathcal{P}_1}\left(1-\frac{Z_1^A}{Z^A}\right)\left(\xi_2m\int_0^{\varkappa_6}\Pi_6(\tau)W_\tau P_\tau d\tau+\delta_2\int_0^{\varkappa_7}\Pi_7(\tau)Z_\tau^L d\tau-a_2Z^A\right)\\
&+\frac{a_1a_2r(\delta_1+b_1)(\delta_2+b_2)}{k_1k_2qF_4F_8\mathcal{P}_1}\left(1-\frac{P_1}{P}\right)\left(k_2\int_0^{\varkappa_8}\Pi_8(\tau)Z_\tau^A d\tau-c_2P\right)\\
&+\delta_1\beta_1(1-\xi_1)F_3\int_0^{\varkappa_1}\Pi_1(\tau)\left(UV-U_\tau V_\tau\right)d\tau+\xi_1\beta_1(\delta_1+b_1)\int_0^{\varkappa_2}\Pi_2(\tau)\left(UV-U_\tau V_\tau\right)d\tau\\
&+\delta_1(\delta_1+b_1)\int_0^{\varkappa_3}\Pi_3(\tau)\left(Y^L-Y_\tau^L\right)d\tau+\frac{a_1(\delta_1+b_1)}{F_4}\int_0^{\varkappa_4}\Pi_4(\tau)\left(Y^A-Y_\tau^A\right)d\tau\\
&+\frac{a_1r\delta_2mF_7(1-\xi_2)(\delta_1+b_1)}{k_1qF_4\mathcal{P}_1}W_1P_1\int_0^{\varkappa_5}\Pi_5(\tau)\left[\frac{WP}{W_1P_1}-\frac{W_\tau P_\tau}{W_1P_1}+\ln\left(\frac{W_\tau P_\tau}{WP}\right)\right]d\tau\\
&+\frac{a_1r\xi_2m(\delta_1+b_1)(\delta_2+b_2)}{k_1qF_4\mathcal{P}_1}W_1P_1\int_0^{\varkappa_6}\Pi_6(\tau)\left[\frac{WP}{W_1P_1}-\frac{W_\tau P_\tau}{W_1P_1}+\ln\left(\frac{W_\tau P_\tau}{WP}\right)\right]d\tau\\
&+\frac{a_1r\delta_2(\delta_1+b_1)(\delta_2+b_2)}{k_1qF_4\mathcal{P}_1}Z_1^L\int_0^{\varkappa_7}\Pi_7(\tau)\left[\frac{Z^L}{Z_1^L}-\frac{Z_\tau^L}{Z_1^L}+\ln\left(\frac{Z_\tau^L}{Z^L}\right)\right]d\tau\\
&+\frac{a_1a_2r(\delta_1+b_1)(\delta_2+b_2)}{k_1qF_4F_8\mathcal{P}_1}Z_1^A\int_0^{\varkappa_8}\Pi_8(\tau)\left[\frac{Z^A}{Z_1^A}-\frac{Z_\tau^A}{Z_1^A}+\ln\left(\frac{Z_\tau^A}{Z^A}\right)\right]d\tau.\end{aligned}$$

Summing the terms and using the equilibrium conditions of EP_1:

$$\begin{cases}\lambda=dU_1,\\ \alpha=\mu W_1+mW_1P_1,\\ (1-\xi_2)mF_5W_1P_1=(\delta_2+b_2)Z_1^L,\\ \xi_2mF_6W_1P_1+\delta_2F_7Z_1^L=a_2Z_1^A,\\ k_2F_8Z_1^A=c_2P_1.\end{cases}$$

We get

$$\begin{aligned}\frac{d\mathcal{H}_1}{dt} &= -\mathcal{P}_2\frac{d}{U}(U-U_1)^2 - \frac{a_1 r(\delta_1+b_1)}{k_1 qF_4}\frac{\mu}{W}(W-W_1)^2 - \frac{a_1 r(\delta_1+b_1)}{k_1 qF_4}\mathcal{L}\left(\frac{W_1}{W}\right)mW_1P_1\\ &+ \frac{a_1(\delta_1+b_1)\left(c_1k_2m\mathcal{P}_1F_8 + a_2c_2r(\delta_2+b_2)\right)}{k_1k_2m\mathcal{P}_1F_4F_8}(R_3-1)V\\ &- \frac{a_1r\delta_2(1-\xi_2)mF_7(\delta_1+b_1)}{k_1qF_4\mathcal{P}_1}W_1P_1\int_0^{\varkappa_5}\Pi_5(\tau)\mathcal{L}\left(\frac{W_\tau P_\tau Z_1^L}{W_1P_1Z^L}\right)d\tau\\ &- \frac{a_1r\xi_2m(\delta_1+b_1)(\delta_2+b_2)}{k_1qF_4\mathcal{P}_1}W_1P_1\int_0^{\varkappa_6}\Pi_6(\tau)\mathcal{L}\left(\frac{W_\tau P_\tau Z_1^A}{W_1P_1Z^A}\right)d\tau\\ &- \frac{a_1r\delta_2(\delta_1+b_1)(\delta_2+b_2)}{k_1qF_4\mathcal{P}_1}Z_1^L\int_0^{\varkappa_7}\Pi_7(\tau)\mathcal{L}\left(\frac{Z_\tau^LZ_1^A}{Z_1^LZ^A}\right)d\tau\\ &- \frac{a_1a_2r(\delta_1+b_1)(\delta_2+b_2)}{k_1qF_4F_8\mathcal{P}_1}Z_1^A\int_0^{\varkappa_8}\Pi_8(\tau)\mathcal{L}\left(\frac{Z_\tau^AP_1}{Z_1^AP}\right)d\tau.\end{aligned}$$

If $R_1 > 1$, $R_3 \leq 1$, we conclude that $\frac{d\mathcal{H}_1}{dt} \leq 0$ for any $U, Y^L, Y^A, V, W, Z^L, Z^A, P > 0$. Further, we have $\frac{d\mathcal{H}_1}{dt} = 0$ if $U = U_1, W = W_1, Z^L = Z_1^L, Z^A = Z_1^A, P = P_1$, and $(R_3-1)V = 0$. Solutions of system (2.1)–(2.8) converge to Υ_1' where $U = U_1, W = W_1, Z^L = Z_1^L, Z^A = Z_1^A, P = P_1$, and

$$(R_3-1)V = 0. \tag{4.9}$$

We have two cases:

Case (I) $R_3 = 1$, then from Eq (2.1),

$$0 = \dot{U} = \lambda - dU_1 - \beta_1U_1V \quad \Longrightarrow \quad V(t) = 0 \quad \text{for any } t. \tag{4.10}$$

From Eq (2.4), we have

$$0 = \dot{V} = k_1\int_0^{\varkappa_4}\Pi_4(\tau)Y_\tau^Ad\tau \quad \Longrightarrow \quad Y^A(t) = 0 \quad \text{for any } t, \tag{4.11}$$

and from Eq (2.3) we get

$$0 = \dot{Y}^A = \delta_1\int_0^{\varkappa_3}\Pi_3(\tau)Y_\tau^Ld\tau \quad \Longrightarrow \quad Y^L(t) = 0 \quad \text{for any } t. \tag{4.12}$$

Then, $\Upsilon_1' = \{EP_1\}$.

Case (II) $R_3 < 1$, then Eq (4.9) implies that $V = 0$ and Eqs (4.11), (4.12) give $Y^A = Y^L = 0$. Thus, $\Upsilon_1' = \{EP_1\}$.

Hence, by applying the Lyapunov-LaSalle asymptotic stability theorem, we obtain that EP_1 is GAS. □

Theorem 4.3. *The co-infection model (2.1)–(2.8) is GAS around the HIV-1 single-infection equilibrium EP_2 when $R_2 > 1$ and $R_4 \leq 1$.*

Proof. Construct $\mathcal{H}_2(U, Y^L, Y^A, V, W, Z^L, Z^A, P)$ as:

$$\begin{aligned}
\mathcal{H}_2 = &\mathcal{P}_2 U_2 \mathcal{L}\left(\frac{U}{U_2}\right) + \delta_1 F_3 Y_2^L \mathcal{L}\left(\frac{Y^L}{Y_2^L}\right) + (\delta_1 + b_1) Y_2^A \mathcal{L}\left(\frac{Y^A}{Y_2^A}\right) + \frac{a_1(\delta_1 + b_1)}{k_1 F_4} V_2 \mathcal{L}\left(\frac{V}{V_2}\right) \\
&+ \frac{a_1 r(\delta_1 + b_1)}{k_1 q F_4} W_2 \mathcal{L}\left(\frac{W}{W_2}\right) + \frac{a_1 r \delta_2 F_7(\delta_1 + b_1)}{k_1 q F_4 \mathcal{P}_1} Z^L + \frac{a_1 r(\delta_1 + b_1)(\delta_2 + b_2)}{k_1 q F_4 \mathcal{P}_1} Z^A \\
&+ \frac{a_1 a_2 r(\delta_1 + b_1)(\delta_2 + b_2)}{k_1 k_2 q F_4 F_8 \mathcal{P}_1} P + \delta_1 \beta_1 (1 - \xi_1) F_3 U_2 V_2 \int_0^{\varkappa_1} \Pi_1(\tau) \int_{t-\tau}^{t} \mathcal{L}\left(\frac{U(\theta)V(\theta)}{U_2 V_2}\right) d\theta d\tau \\
&+ \xi_1 \beta_1 (\delta_1 + b_1) U_2 V_2 \int_0^{\varkappa_2} \Pi_2(\tau) \int_{t-\tau}^{t} \mathcal{L}\left(\frac{U(\theta)V(\theta)}{U_2 V_2}\right) d\theta d\tau \\
&+ \delta_1(\delta_1 + b_1) Y_2^L \int_0^{\varkappa_3} \Pi_3(\tau) \int_{t-\tau}^{t} \mathcal{L}\left(\frac{Y^L(\theta)}{Y_2^L}\right) d\theta d\tau \\
&+ \frac{a_1(\delta_1 + b_1)}{F_4} Y_2^A \int_0^{\varkappa_4} \Pi_4(\tau) \int_{t-\tau}^{t} \mathcal{L}\left(\frac{Y^A(\theta)}{Y_2^A}\right) d\theta d\tau \\
&+ \frac{a_1 r \delta_2 m F_7(1 - \xi_2)(\delta_1 + b_1)}{k_1 q F_4 \mathcal{P}_1} \int_0^{\varkappa_5} \Pi_5(\tau) \int_{t-\tau}^{t} W(\theta) P(\theta) d\theta d\tau \\
&+ \frac{a_1 r \xi_2 m(\delta_1 + b_1)(\delta_2 + b_2)}{k_1 q F_4 \mathcal{P}_1} \int_0^{\varkappa_6} \Pi_6(\tau) \int_{t-\tau}^{t} W(\theta) P(\theta) d\theta d\tau \\
&+ \frac{a_1 r \delta_2 (\delta_1 + b_1)(\delta_2 + b_2)}{k_1 q F_4 \mathcal{P}_1} \int_0^{\varkappa_7} \Pi_7(\tau) \int_{t-\tau}^{t} Z^L(\theta) d\theta d\tau \\
&+ \frac{a_1 a_2 r(\delta_1 + b_1)(\delta_2 + b_2)}{k_1 q F_4 F_8 \mathcal{P}_1} \int_0^{\varkappa_8} \Pi_8(\tau) \int_{t-\tau}^{t} Z^A(\theta) d\theta d\tau.
\end{aligned}$$

Take the derivative of $\mathcal{H}_2$ along the solution of model (2.1)–(2.8) as:

$$\begin{aligned}
\frac{d\mathcal{H}_2}{dt} = &\mathcal{P}_2 \left(1 - \frac{U_2}{U}\right)(\lambda - dU - \beta_1 UV) + \delta_1 F_3 \left(1 - \frac{Y_2^L}{Y^L}\right)\left((1 - \xi_1)\beta_1 \int_0^{\varkappa_1} \Pi_1(\tau) U_\tau V_\tau d\tau - (\delta_1 + b_1) Y^L\right) \\
&+ (\delta_1 + b_1)\left(1 - \frac{Y_2^A}{Y^A}\right)\left(\xi_1 \beta_1 \int_0^{\varkappa_2} \Pi_2(\tau) U_\tau V_\tau d\tau + \delta_1 \int_0^{\varkappa_3} \Pi_3(\tau) Y_\tau^L d\tau - a_1 Y^A\right) \\
&+ \frac{a_1(\delta_1 + b_1)}{k_1 F_4}\left(1 - \frac{V_2}{V}\right)\left(k_1 \int_0^{\varkappa_4} \Pi_4(\tau) Y_\tau^A d\tau - c_1 V - rVW\right) \\
&+ \frac{a_1 r(\delta_1 + b_1)}{k_1 q F_4}\left(1 - \frac{W_2}{W}\right)(\alpha + qVW - \mu W - mWP) \\
&+ \frac{a_1 r \delta_2 F_7(\delta_1 + b_1)}{k_1 q F_4 \mathcal{P}_1}\left((1 - \xi_2) m \int_0^{\varkappa_5} \Pi_5(\tau) W_\tau P_\tau d\tau - (\delta_2 + b_2) Z^L\right) \\
&+ \frac{a_1 r(\delta_1 + b_1)(\delta_2 + b_2)}{k_1 q F_4 \mathcal{P}_1}\left(\xi_2 m \int_0^{\varkappa_6} \Pi_6(\tau) W_\tau P_\tau d\tau + \delta_2 \int_0^{\varkappa_7} \Pi_7(\tau) Z_\tau^L d\tau - a_2 Z^A\right) \\
&+ \frac{a_1 a_2 r(\delta_1 + b_1)(\delta_2 + b_2)}{k_1 k_2 q F_4 F_8 \mathcal{P}_1}\left(k_2 \int_0^{\varkappa_8} \Pi_8(\tau) Z_\tau^A d\tau - c_2 P\right) \\
&+ \delta_1 \beta_1 (1 - \xi_1) F_3 U_2 V_2 \int_0^{\varkappa_1} \Pi_1(\tau)\left[\frac{UV}{U_2 V_2} - \frac{U_\tau V_\tau}{U_2 V_2} + \ln\left(\frac{U_\tau V_\tau}{UV}\right)\right] d\tau
\end{aligned}$$

$$
\begin{aligned}
&+\xi_1\beta_1(\delta_1+b_1)U_2V_2\int_0^{\varkappa_2}\Pi_2(\tau)\left[\frac{UV}{U_2V_2}-\frac{U_\tau V_\tau}{U_2V_2}+\ln\left(\frac{U_\tau V_\tau}{UV}\right)\right]d\tau\\
&+\delta_1(\delta_1+b_1)Y_2^L\int_0^{\varkappa_3}\Pi_3(\tau)\left[\frac{Y^L}{Y_2^L}-\frac{Y_\tau^L}{Y_2^L}+\ln\left(\frac{Y_\tau^L}{Y^L}\right)\right]d\tau\\
&+\frac{a_1(\delta_1+b_1)}{F_4}Y_2^A\int_0^{\varkappa_4}\Pi_4(\tau)\left[\frac{Y^A}{Y_2^A}-\frac{Y_\tau^A}{Y_2^A}+\ln\left(\frac{Y_\tau^A}{Y^A}\right)\right]d\tau\\
&+\frac{a_1r\delta_2mF_7(1-\xi_2)(\delta_1+b_1)}{k_1qF_4\mathcal{P}_1}\int_0^{\varkappa_5}\Pi_5(\tau)\left(WP-W_\tau P_\tau\right)d\tau\\
&+\frac{a_1r\xi_2m(\delta_1+b_1)(\delta_2+b_2)}{k_1qF_4\mathcal{P}_1}\int_0^{\varkappa_6}\Pi_6(\tau)\left(WP-W_\tau P_\tau\right)d\tau\\
&+\frac{a_1r\delta_2(\delta_1+b_1)(\delta_2+b_2)}{k_1qF_4\mathcal{P}_1}\int_0^{\varkappa_7}\Pi_7(\tau)\left(Z^L-Z_\tau^L\right)d\tau\\
&+\frac{a_1a_2r(\delta_1+b_1)(\delta_2+b_2)}{k_1qF_4F_8\mathcal{P}_1}\int_0^{\varkappa_8}\Pi_8(\tau)\left(Z^A-Z_\tau^A\right)d\tau.
\end{aligned}
$$

Summing the terms and using the following equilibrium conditions,

$$
\begin{cases}
\lambda=dU_2+\beta_1U_2V_2,\\
(1-\xi_1)F_1\beta_1U_2V_2=(\delta_1+b_1)Y_2^L,\\
\xi_1F_2\beta_1U_2V_2+\delta_1F_3Y_2^L=a_1Y_2^A,\\
k_1F_4Y_2^A=c_1V_2+rV_2W_2,\\
\alpha=\mu W_2-qV_2W_2.
\end{cases}
$$

We obtain

$$
\begin{aligned}
\frac{d\mathcal{H}_2}{dt}=&-\mathcal{P}_2\frac{d}{U}(U-U_2)^2-\frac{a_1r(\delta_1+b_1)}{k_1qF_4}\frac{\alpha}{WW_2}(W-W_2)^2-\mathcal{P}_2\mathcal{L}\left(\frac{U_2}{U}\right)\beta_1U_2V_2\\
&+\frac{a_1rm(\delta_1+b_1)}{k_1qF_4}(W_2-W_3)P-\delta_1\beta_1(1-\xi_1)F_3U_2V_2\int_0^{\varkappa_1}\Pi_1(\tau)\mathcal{L}\ln\left(\frac{U_\tau V_\tau Y_2^L}{U_2V_2Y^L}\right)d\tau\\
&-\xi_1\beta_1(\delta_1+b_1)U_2V_2\int_0^{\varkappa_2}\Pi_2(\tau)\mathcal{L}\left(\frac{U_\tau V_\tau Y_2^A}{U_2V_2Y^A}\right)d\tau-\delta_1(\delta_1+b_1)Y_2^L\int_0^{\varkappa_3}\Pi_3(\tau)\mathcal{L}\left(\frac{Y_\tau^LY_2^A}{Y_2^LY^A}\right)d\tau\\
&-\frac{a_1(\delta_1+b_1)}{F_4}Y_2^A\int_0^{\varkappa_4}\Pi_4(\tau)\mathcal{L}\left(\frac{Y_\tau^AV_2}{Y_2^AV}\right)d\tau.
\end{aligned}
$$

Now, we show that if $R_4\le 1$, then $W_2\le W_3$. If $R_4\le 1$, then the HHV-8/HIV-1 co-infection equilibrium, EP_3, does not exist since $Z_3^L\le 0$, $Z_3^A\le 0$, and $P_3\le 0$. In this case,

$$
\begin{aligned}
\dot{Z}^L&=(1-\xi_2)m\int_0^{\varkappa_5}\Pi_5(\tau)W_\tau P_\tau d\tau-(\delta_2+b_2)Z^L\le 0,\\
\dot{Z}^A&=\xi_2m\int_0^{\varkappa_6}\Pi_6(\tau)W_\tau P_\tau d\tau+\delta_2\int_0^{\varkappa_7}\Pi_7(\tau)Z_\tau^Ld\tau-a_2Z^A\le 0,\\
\dot{P}&=k_2\int_0^{\varkappa_8}\Pi_8(\tau)Z_\tau^Ad\tau-c_2P\le 0.
\end{aligned}
$$

We want to determine the value $\bar{W}$ where $0 < W(t) \leq \bar{W}$ such that $\dot{Z}^L(t) \leq 0$, $\dot{Z}^A(t) \leq 0$, and $\dot{P} \leq 0$. Let's consider

$$\begin{aligned}\Lambda = &\frac{\delta_2 F_7}{\mathcal{P}_1} Z^L + \frac{(\delta_2 + b_2)}{\mathcal{P}_1} Z^A + \frac{a_2(\delta_2 + b_2)}{k_2 F_8 \mathcal{P}_1} P + \frac{\delta_2 m F_7 (1 - \xi_2)}{\mathcal{P}_1} \int_0^{\varkappa_5} \Pi_5(\tau) \int_{t-\tau}^{t} W(\theta) P(\theta) d\theta d\tau \\ &+ \frac{\xi_2 m(\delta_2 + b_2)}{\mathcal{P}_1} \int_0^{\varkappa_6} \Pi_6(\tau) \int_{t-\tau}^{t} W(\theta) P(\theta) d\tau + \frac{\delta_2(\delta_2 + b_2)}{\mathcal{P}_1} \int_0^{\varkappa_7} \Pi_7(\tau) \int_{t-\tau}^{t} Z^L(\theta) d\tau \\ &+ \frac{a_2(\delta_2 + b_2)}{F_8 \mathcal{P}_1} \int_0^{\varkappa_8} \Pi_8(\tau) \int_{t-\tau}^{t} Z^A(\theta) d\theta d\tau.\end{aligned}$$

Then,

$$\begin{aligned}\frac{d\Lambda}{dt} = &\frac{\delta_2 F_7}{\mathcal{P}_1} \left((1 - \xi_2) m \int_0^{\varkappa_5} \Pi_5(\tau) W_\tau P_\tau d\tau - (\delta_2 + b_2) Z^L \right) \\ &+ \frac{(\delta_2 + b_2)}{\mathcal{P}_1} \left(\xi_2 m \int_0^{\varkappa_6} \Pi_6(\tau) W_\tau P_\tau d\tau + \delta_2 \int_0^{\varkappa_7} \Pi_7(\tau) Z^L_\tau d\tau - a_2 Z^A \right) \\ &+ \frac{a_2(\delta_2 + b_2)}{k_2 F_8 \mathcal{P}_1} \left(k_2 \int_0^{\varkappa_8} \Pi_8(\tau) Z^A_\tau d\tau - c_2 P \right) + \frac{\delta_2 m F_7 (1 - \xi_2)}{\mathcal{P}_1} \int_0^{\varkappa_5} \Pi_5(\tau) \left(WP - W_\tau P_\tau \right) d\tau \\ &+ \frac{\xi_2 m(\delta_2 + b_2)}{\mathcal{P}_1} \int_0^{\varkappa_6} \Pi_6(\tau) \left(WP - W_\tau P_\tau \right) d\tau + \frac{\delta_2(\delta_2 + b_2)}{\mathcal{P}_1} \int_0^{\varkappa_7} \Pi_7(\tau) \left(Z^L - Z^L_\tau \right) d\tau \\ &+ \frac{a_2(\delta_2 + b_2)}{F_8 \mathcal{P}_1} \int_0^{\varkappa_8} \Pi_8(\tau) \left(Z^A - Z^A_\tau \right) d\tau \\ = &\frac{\delta_2 m F_5 F_7 (1 - \xi_2)}{\mathcal{P}_1} WP + \frac{\xi_2 m F_6 (\delta_2 + b_2)}{\mathcal{P}_1} WP - \frac{a_2 c_2 (\delta_2 + b_2)}{k_2 F_8 \mathcal{P}_1} P \\ = &\, m \left(\frac{\delta_2 (1 - \xi_2) F_5 F_7 + (\delta_2 + b_2) \xi_2 F_6}{\mathcal{P}_1} \right) WP - \frac{a_2 c_2 (\delta_2 + b_2)}{k_2 F_8 \mathcal{P}_1} P \\ = &\, mWP - \frac{a_2 c_2 (\delta_2 + b_2)}{k_2 F_8 \mathcal{P}_1} P \\ = &\, m \left(W - \frac{a_2 c_2 (\delta_2 + b_2)}{k_2 m F_8 \mathcal{P}_1} \right) P \leq 0 \qquad \text{for any } P > 0.\end{aligned}$$

This occurs when $W_2 \leq \bar{W} = \frac{a_2 c_2 (\delta_2 + b_2)}{k_2 m F_8 \mathcal{P}_1} = W_3$. Obviously, $\frac{d\mathcal{H}_2}{dt} \leq 0$ for any $U, Y^L, Y^A, V, W, Z^L, Z^A, P > 0$. Moreover, $\frac{d\mathcal{H}_2}{dt} = 0$ if $U = U_2$, $Y^L = Y^L_2$, $Y^A = Y^A_2$, $V = V_2$, $W = W_2$, and $(W_2 - W_3) P = 0$. Solutions of the model converge to Υ'_2 where $U = U_2$, $Y^L = Y^L_2$, $Y^A = Y^A_2$, $V = V_2$, $W = W_2$, and

$$(W_2 - W_3) P = 0. \tag{4.13}$$

We have two cases:

Case (I) $W_2 = W_3$. From Eq (2.5), we have

$$0 = \dot{W} = \alpha + q V_2 W_2 - \mu W_2 - m W_2 P \qquad \Longrightarrow \qquad P(t) = 0 \quad \text{for any } t.$$

Equation (2.8) leads to

$$0 = \dot{P} = k_2 \int_0^{\varkappa_8} \Pi_8(\tau) Z^A_\tau \qquad \Longrightarrow \qquad Z^A(t) = 0 \quad \text{for any } t, \tag{4.14}$$

and from Eq (2.7) we get

$$0 = \dot{Z}^A = \delta_2 \int_0^{\varkappa_7} \Pi_7(\tau) Z_\tau^L \quad \Longrightarrow \quad Z^L(t) = 0 \quad \text{for any } t. \tag{4.15}$$

Consequently, $\Upsilon_2' = \{EP_2\}$.

Case (II) $W_2 < W_3$, and from Eq (4.13) we get $P = 0$. Equations (4.14) and (4.15) give $Z^L = Z^A = 0$. Hence, $\Upsilon_2' = \{EP_2\}$.

Thus, by the Lyapunov-LaSalle asymptotic stability theorem, EP_2 is GAS. □

Theorem 4.4. *The co-infection model (2.1)–(2.8) is GAS around the HHV-8/HIV-1 co-infection equilibrium EP_3 when $R_4 > 1$ and $R_3 \leq 1 + \frac{\mu\beta_1}{dq}$.*

Proof. We construct $\mathcal{H}_3(U, Y^L, Y^A, V, W, Z^L, Z^A, P)$ as:

$$\begin{aligned}
\mathcal{H}_3 = {} & \mathcal{P}_2 U_3 \mathcal{L}\left(\frac{U}{U_3}\right) + \delta_1 F_3 Y_3^L \mathcal{L}\left(\frac{Y^L}{Y_3^L}\right) + (\delta_1 + b_1) Y_3^A \mathcal{L}\left(\frac{Y^A}{Y_3^A}\right) + \frac{a_1(\delta_1 + b_1)}{k_1 F_4} V_3 \mathcal{L}\left(\frac{V}{V_3}\right) \\
& + \frac{a_1 r(\delta_1 + b_1)}{k_1 q F_4} W_3 \mathcal{L}\left(\frac{W}{W_3}\right) + \frac{a_1 r \delta_2 F_7(\delta_1 + b_1)}{k_1 q F_4 \mathcal{P}_1} Z_3^L \mathcal{L}\left(\frac{Z^L}{Z_3^L}\right) + \frac{a_1 r(\delta_1 + b_1)(\delta_2 + b_2)}{k_1 q F_4 \mathcal{P}_1} Z_3^A \mathcal{L}\left(\frac{Z^A}{Z_3^A}\right) \\
& + \frac{a_1 a_2 r(\delta_1 + b_1)(\delta_2 + b_2)}{k_1 k_2 q F_4 F_8 \mathcal{P}_1} P_3 \mathcal{L}\left(\frac{P}{P_3}\right) + \delta_1 \beta_1 (1 - \xi_1) F_3 U_3 V_3 \int_0^{\varkappa_1} \Pi_1(\tau) \int_{t-\tau}^t \mathcal{L}\left(\frac{U(\theta)V(\theta)}{U_3 V_3}\right) d\theta d\tau \\
& + \xi_1 \beta_1 (\delta_1 + b_1) U_3 V_3 \int_0^{\varkappa_2} \Pi_2(\tau) \int_{t-\tau}^t \mathcal{L}\left(\frac{U(\theta)V(\theta)}{U_3 V_3}\right) d\theta d\tau \\
& + \delta_1(\delta_1 + b_1) Y_3^L \int_0^{\varkappa_3} \Pi_3(\tau) \int_{t-\tau}^t \mathcal{L}\left(\frac{Y^L(\theta)}{Y_3^L}\right) d\theta d\tau + \frac{a_1(\delta_1 + b_1)}{F_4} Y_3^A \int_0^{\varkappa_4} \Pi_4(\tau) \int_{t-\tau}^t \mathcal{L}\left(\frac{Y^A(\theta)}{Y_3^A}\right) d\theta d\tau \\
& + \frac{a_1 r \delta_2 m F_7(1 - \xi_2)(\delta_1 + b_1)}{k_1 q F_4 \mathcal{P}_1} W_3 P_3 \int_0^{\varkappa_5} \Pi_5(\tau) \int_{t-\tau}^t \mathcal{L}\left(\frac{W(\theta)P(\theta)}{W_3 P_3}\right) d\theta d\tau \\
& + \frac{a_1 r \xi_2 m(\delta_1 + b_1)(\delta_2 + b_2)}{k_1 q F_4 \mathcal{P}_1} W_3 P_3 \int_0^{\varkappa_6} \Pi_6(\tau) \int_{t-\tau}^t \mathcal{L}\left(\frac{W(\theta)P(\theta)}{W_3 P_3}\right) d\theta d\tau \\
& + \frac{a_1 r \delta_2(\delta_1 + b_1)(\delta_2 + b_2)}{k_1 q F_4 \mathcal{P}_1} Z_3^L \int_0^{\varkappa_7} \Pi_7(\tau) \int_{t-\tau}^t \mathcal{L}\left(\frac{Z^L(\theta)}{Z_3^L}\right) d\theta d\tau \\
& + \frac{a_1 a_2 r(\delta_1 + b_1)(\delta_2 + b_2)}{k_1 q F_4 F_8 \mathcal{P}_1} Z_3^A \int_0^{\varkappa_8} \Pi_8(\tau) \int_{t-\tau}^t \mathcal{L}\left(\frac{Z^A(\theta)}{Z_3^A}\right) d\theta d\tau.
\end{aligned}$$

Calculate $\frac{d\mathcal{H}_3}{dt}$ as:

$$\begin{aligned}
\frac{d\mathcal{H}_3}{dt} = {} & \mathcal{P}_2 \left(1 - \frac{U_3}{U}\right)(\lambda - dU - \beta_1 UV) \\
& + \delta_1 F_3 \left(1 - \frac{Y_3^L}{Y^L}\right)\left((1 - \xi_1)\beta_1 \int_0^{\varkappa_1} \Pi_1(\tau) U_\tau V_\tau d\tau - (\delta_1 + b_1) Y^L\right) \\
& + (\delta_1 + b_1)\left(1 - \frac{Y_3^A}{Y^A}\right)\left(\xi_1 \beta_1 \int_0^{\varkappa_2} \Pi_2(\tau) U_\tau V_\tau d\tau + \delta_1 \int_0^{\varkappa_3} \Pi_3(\tau) Y_\tau^L d\tau - a_1 Y^A\right)
\end{aligned}$$

$$
\begin{aligned}
&+\frac{a_1(\delta_1+b_1)}{k_1F_4}\left(1-\frac{V_3}{V}\right)\left(k_1\int_0^{\varkappa_4}\Pi_4(\tau)Y_\tau^A d\tau-c_1V-rVW\right)\\
&+\frac{a_1r(\delta_1+b_1)}{k_1qF_4}\left(1-\frac{W_3}{W}\right)(\alpha+qVW-\mu W-mWP)\\
&+\frac{a_1r\delta_2F_7(\delta_1+b_1)}{k_1qF_4\mathcal{P}_1}\left(1-\frac{Z_3^L}{Z^L}\right)\left((1-\xi_2)m\int_0^{\varkappa_5}\Pi_5(\tau)W_\tau P_\tau d\tau-(\delta_2+b_2)Z^L\right)\\
&+\frac{a_1r(\delta_1+b_1)(\delta_2+b_2)}{k_1qF_4\mathcal{P}_1}\left(1-\frac{Z_3^A}{Z^A}\right)\left(\xi_2m\int_0^{\varkappa_6}\Pi_6(\tau)W_\tau P_\tau d\tau+\delta_2\int_0^{\varkappa_7}\Pi_7(\tau)Z_\tau^L d\tau-a_2Z^A\right)\\
&+\frac{a_1a_2r(\delta_1+b_1)(\delta_2+b_2)}{k_1k_2qF_4F_8\mathcal{P}_1}\left(1-\frac{P_3}{P}\right)\left(k_2\int_0^{\varkappa_8}\Pi_8(\tau)Z_\tau^A d\tau-c_2P\right)\\
&+\delta_1\beta_1(1-\xi_1)F_3U_3V_3\int_0^{\varkappa_1}\Pi_1(\tau)\left[\frac{UV}{U_3V_3}-\frac{U_\tau V_\tau}{U_3V_3}+\ln\left(\frac{U_\tau V_\tau}{UV}\right)\right]d\tau\\
&+\xi_1\beta_1(\delta_1+b_1)U_3V_3\int_0^{\varkappa_2}\Pi_2(\tau)\left[\frac{UV}{U_3V_3}-\frac{U_\tau V_\tau}{U_3V_3}+\ln\left(\frac{U_\tau V_\tau}{UV}\right)\right]d\tau\\
&+\delta_1(\delta_1+b_1)Y_3^L\int_0^{\varkappa_3}\Pi_3(\tau)\left[\frac{Y^L}{Y_3^L}-\frac{Y_\tau^L}{Y_3^L}+\ln\left(\frac{Y_\tau^L}{Y^L}\right)\right]d\tau\\
&+\frac{a_1(\delta_1+b_1)}{F_4}Y_3^A\int_0^{\varkappa_4}\Pi_4(\tau)\left[\frac{Y^A}{Y_3^A}-\frac{Y_\tau^A}{Y_3^A}+\ln\left(\frac{Y_\tau^A}{Y^A}\right)\right]d\tau\\
&+\frac{a_1r\delta_2mF_7(1-\xi_2)(\delta_1+b_1)}{k_1qF_4\mathcal{P}_1}W_3P_3\int_0^{\varkappa_5}\Pi_5(\tau)\left[\frac{WP}{W_3P_3}-\frac{W_\tau P_\tau}{W_3P_3}+\ln\left(\frac{W_\tau P_\tau}{WP}\right)\right]d\tau\\
&+\frac{a_1r\xi_2m(\delta_1+b_1)(\delta_2+b_2)}{k_1qF_4\mathcal{P}_1}W_3P_3\int_0^{\varkappa_6}\Pi_6(\tau)\left[\frac{WP}{W_3P_3}-\frac{W_\tau P_\tau}{W_3P_3}+\ln\left(\frac{W_\tau P_\tau}{WP}\right)\right]d\tau\\
&+\frac{a_1r\delta_2(\delta_1+b_1)(\delta_2+b_2)}{k_1qF_4\mathcal{P}_1}Z_3^L\int_0^{\varkappa_7}\Pi_7(\tau)\left[\frac{Z^L}{Z_3^L}-\frac{Z_\tau^L}{Z_3^L}+\ln\left(\frac{Z_\tau^L}{Z^L}\right)\right]d\tau\\
&+\frac{a_1a_2r(\delta_1+b_1)(\delta_2+b_2)}{k_1qF_4F_8\mathcal{P}_1}Z_3^A\int_0^{\varkappa_8}\Pi_8(\tau)\left[\frac{Z^A}{Z_3^A}-\frac{Z_\tau^A}{Z_3^A}+\ln\left(\frac{Z_\tau^A}{Z^A}\right)\right]d\tau.
\end{aligned}
$$

Collecting terms and using the following equilibrium conditions:

$$
\begin{cases}
\lambda = dU_3+\beta_1U_3V_3,\\
(1-\xi_1)F_1\beta_1U_3V_3 = (\delta_1+b_1)Y_3^L,\\
\xi_1F_2\beta_1U_3V_3+\delta_1F_3Y_3^L = a_1Y_3^A,\\
k_1F_4Y_3^A = c_1V_3+rV_3W_3,\\
\alpha = \mu W_3-qV_3W_3+mW_3P_3,\\
(1-\xi_2)mF_5W_3P_3 = (\delta_2+b_2)Z_3^L,\\
\xi_2mF_6W_3P_3+\delta_2F_7Z_3^L = a_2Z_3^A,\\
k_2F_8Z_3^A = c_2P_3,
\end{cases}
$$

we finally obtain

$$\begin{aligned}\frac{d\mathcal{H}_3}{dt} =& -\mathcal{P}_2\frac{d}{U}(U-U_3)^2 + \frac{a_1 rd(\delta_1+b_1)}{k_1\beta_1 F_4}\frac{1}{W}(W-W_3)^2\left(R_3 - 1 - \frac{\mu\beta_1}{dq}\right) - \mathcal{P}_2\mathcal{L}\left(\frac{U_3}{U}\right)\beta_1 U_3 V_3\\ &- \frac{a_1 rm(\delta_1+b_1)}{k_1 qF_4}\mathcal{L}\left(\frac{W_3}{W}\right)W_3P_3 - \delta_1\beta_1(1-\xi_1)F_3U_3V_3\int_0^{\varkappa_1}\Pi_1(\tau)\mathcal{L}\left(\frac{U_\tau V_\tau Y_3^L}{U_3V_3Y^L}\right)d\tau\\ &- \xi_1\beta_1(\delta_1+b_1)U_3V_3\int_0^{\varkappa_2}\Pi_2(\tau)\mathcal{L}\left(\frac{U_\tau V_\tau Y_3^A}{U_3V_3Y^A}\right)d\tau - \delta_1(\delta_1+b_1)Y_3^L\int_0^{\varkappa_3}\Pi_3(\tau)\mathcal{L}\left(\frac{Y_\tau^L Y_3^A}{Y_3^L Y^A}\right)d\tau\\ &- \frac{a_1(\delta_1+b_1)}{F_4}Y_3^A\int_0^{\varkappa_4}\Pi_4(\tau)\mathcal{L}\left(\frac{Y_\tau^A V_3}{Y_3^A V}\right)d\tau\\ &- \frac{a_1 r\delta_2(1-\xi_2)mF_7(\delta_1+b_1)}{k_1qF_4\mathcal{P}_1}W_3P_3\int_0^{\varkappa_5}\Pi_5(\tau)\mathcal{L}\left(\frac{W_\tau P_\tau Z_3^L}{W_3P_3Z^L}\right)d\tau\\ &- \frac{a_1 r\xi_2 m(\delta_1+b_1)(\delta_2+b_2)}{k_1qF_4\mathcal{P}_1}W_3P_3\int_0^{\varkappa_6}\Pi_6(\tau)\mathcal{L}\left(\frac{W_\tau P_\tau Z_3^A}{W_3P_3Z^A}\right)d\tau\\ &- \frac{a_1 r\delta_2(\delta_1+b_1)(\delta_2+b_2)}{k_1qF_4\mathcal{P}_1}Z_3^L\int_0^{\varkappa_7}\Pi_7(\tau)\mathcal{L}\left(\frac{Z_\tau^L Z_3^A}{Z_3^L Z^A}\right)d\tau\\ &- \frac{a_1a_2 r(\delta_1+b_1)(\delta_2+b_2)}{k_1qF_4F_8\mathcal{P}_1}Z_3^A\int_0^{\varkappa_8}\Pi_8(\tau)\mathcal{L}\left(\frac{Z_\tau^A P_3}{Z_3^A P}\right)d\tau.\end{aligned}$$

Thus, when $R_3 \leq 1 + \frac{\mu\beta_1}{dq}$, we obtain that $\frac{d\mathcal{H}_3}{dt} \leq 0$ for any $U, Y^L, Y^A, V, W, Z^L, Z^A, P > 0$. Furthermore, $\frac{d\mathcal{H}_3}{dt} = 0$ if $U = U_3$, $Y^L = Y_3^L$, $Y^A = Y_3^A$, $V = V_3$, $W = W_3$, $Z^L = Z_3^L$, $Z^A = Z_3^A$, and $P = P_3$. Solutions of system (2.1)–(2.8) converge to Υ_3' where $U = U_3$, $Y^L = Y_3^L$, $Y^A = Y_3^A$, $V = V_3$, $W = W_3$, $Z^L = Z_3^L$, $Z^A = Z_3^A$, and $P = P_3$. Hence, $\Upsilon_3' = \{EP_3\}$, and by applying the Lyapunov-LaSalle asymptotic stability theorem, EP_3 is GAS. □

A summary of global stability conditions for any equilibria of model (2.1)–(2.8) are given in Table 2.

Table 2. Conditions of existence and global stability of equilibria.

Equilibrium	Existence condition	Stability condition
$EP_0 = (U_0, 0, 0, 0, W_0, 0, 0, 0)$	-	$R_1 \leq 1$ and $R_2 \leq 1$
$EP_1 = \left(U_1, 0, 0, 0, W_1, Z_1^L, Z_1^A, P_1\right)$	$R_1 > 1$	$R_1 > 1$ and $R_3 \leq 1$
$EP_2\left(U_2, Y_2^L, Y_2^A, V_2, W_2, 0, 0, 0\right)$	$R_2 > 1$	$R_2 > 1$ and $R_4 \leq 1$
$EP_3 = \left(U_3, Y_3^L, Y_3^A, V_3, W_3, Z_3^L, Z_3^A, P_3\right)$	$R_4 > 1$	$R_4 > 1$ and $R_3 \leq 1 + \frac{\mu\beta_1}{dq}$

HHV-8/HIV-1 co-dynamics under the effect of antiviral therapy

An analysis is given of the co-dynamics of HIV-1 and HHV-8 in the context of antiviral therapy and time delays. Examining two different antiviral therapies: (i) reverse transcriptase inhibitors whose medication efficacy is $\eta_V \in [0, 1]$ to stop the HIV-1 from infecting the CD4$^+$T cells [16], and (ii) endocytic pathway inhibitors whose medication efficacy is $\eta_P \in [0, 1]$ that block the mechanism, which the HHV-8 uses to infect the B cells [26, 57]. The model of co-infection between HHV-8 and HIV-1

under antiviral therapy and time delays is provided as follows:

$$\begin{cases} \dot{U} = \lambda - dU - (1-\eta_V)\beta_1 UV, \\ \dot{Y}^L = (1-\eta_V)(1-\xi_1)\beta_1 \int_0^{\varkappa_1} \Pi_1(\tau) U_\tau V_\tau d\tau - (\delta_1 + b_1) Y^L, \\ \dot{Y}^A = (1-\eta_V)\xi_1\beta_1 \int_0^{\varkappa_2} \Pi_2(\tau) U_\tau V_\tau d\tau + \delta_1 \int_0^{\varkappa_3} \Pi_3(\tau) Y_\tau^L d\tau - a_1 Y^A, \\ \dot{V} = k_1 \int_0^{\varkappa_4} \Pi_4(\tau) Y_\tau^A d\tau - c_1 V - rVW, \\ \dot{W} = \alpha + qVW - \mu W - (1-\eta_P) mWP, \\ \dot{Z}^L = (1-\eta_P)(1-\xi_2) m \int_0^{\varkappa_5} \Pi_5(\tau) W_\tau P_\tau d\tau - (\delta_2 + b_2) Z^L, \\ \dot{Z}^A = (1-\eta_P)\xi_2 m \int_0^{\varkappa_6} \Pi_6(\tau) W_\tau P_\tau d\tau + \delta_2 \int_0^{\varkappa_7} \Pi_7(\tau) Z_\tau^L d\tau - a_2 Z^A, \\ \dot{P} = k_2 \int_0^{\varkappa_8} \Pi_8(\tau) Z_\tau^A d\tau - c_2 P. \end{cases} \tag{4.16}$$

The basic reproduction numbers for model (4.16) are given as:

$$R_1^{\text{With delay}}(\eta_P) = (1-\eta_P)\frac{\alpha k_2 m F_8 \left[(\delta_2 + b_2)\xi_2 F_6 + \delta_2(1-\xi_2)F_5 F_7\right]}{a_2 c_2 \mu (\delta_2 + b_2)} = (1-\eta_P) R_1^{\text{With delay}}(0),$$

$$R_2^{\text{With delay}}(\eta_V) = (1-\eta_V)\frac{\lambda k_1 \beta_1 \mu F_4 \left[\xi_1 F_2(\delta_1 + b_1) + F_1 F_3 \delta_1 (1-\xi_1)\right]}{a_1 d (c_1\mu + r\alpha)(\delta_1 + b_1)} = (1-\eta_V) R_2^{\text{With delay}}(0).$$

Following the fixation of all other parameters, we compute the drug efficacies η_P and η_V resulting in $R_1^{\text{With delay}}(\eta_P) \leq 1$ and $R_2^{\text{With delay}}(\eta_V) \leq 1$:

$$R_1^{\text{With delay}}(\eta_P) \leq 1 \Longleftrightarrow 1 \geq \eta_P \geq \eta_{P,\min}^{\text{With delay}} = \max\left\{0, \frac{R_1^{\text{With delay}}(0) - 1}{R_1^{\text{With delay}}(0)}\right\}, \tag{4.17}$$

$$R_2^{\text{With delay}}(\eta_V) \leq 1 \Longleftrightarrow 1 \geq \eta_V \geq \eta_{V,\min}^{\text{With delay}} = \max\left\{0, \frac{R_2^{\text{With delay}}(0) - 1}{R_2^{\text{With delay}}(0)}\right\}. \tag{4.18}$$

Hence, if $\eta_{P,\min}^{\text{With delay}} \leq \eta_P \leq 1$ and $\eta_{V,\min}^{\text{With delay}} \leq \eta_V \leq 1$, then infection-free equilibrium EP_0 of system (4.16) is GAS.

We rewrite system (4.16) without accounting for time delays in order to examine how time delays affect the minimum drug efficacies required for the stabilization of infection-free equilibrium:

$$\begin{cases} \dot{U} = \lambda - dU - (1-\eta_V)\beta_1 UV, \\ \dot{Y}^L = (1-\eta_V)(1-\xi_1)\beta_1 UV - (\delta_1 + b_1) Y^L, \\ \dot{Y}^A = (1-\eta_V)\xi_1\beta_1 UV + \delta_1 Y^L - a_1 Y^A, \\ \dot{V} = k_1 Y^A - c_1 V - rVW, \\ \dot{W} = \alpha + qVW - \mu W - (1-\eta_P) mWP, \\ \dot{Z}^L = (1-\eta_P)(1-\xi_2) mWP - (\delta_2 + b_2) Z^L, \\ \dot{Z}^A = (1-\eta_P)\xi_2 mWP + \delta_2 Z^L - a_2 Z^A, \\ \dot{P} = k_2 Z^A - c_2 P. \end{cases} \tag{4.19}$$

Model (4.19) has two reproduction numbers, which are given by:

$$R_1^{\text{Without delay}}(\eta_P) = (1-\eta_P)\frac{\alpha k_2 m (\delta_2 + b_2\xi_2)}{a_2 c_2 \mu (\delta_2 + b_2)} = (1-\eta_P) R_1^{\text{Without delay}}(0),$$

$$R_2^{\text{Without delay}}(\eta_V) = (1-\eta_V)\frac{\lambda k_1\beta_1\mu(\delta_1+b_1\xi_1)}{a_1 d(c_1\mu+r\alpha)(\delta_1+b_1)} = (1-\eta_V)R_2^{\text{Without delay}}(0).$$

We determine the drug efficacies η_P and η_V, which make $R_1^{\text{Without delay}}(\eta_P) \leq 1$ and $R_2^{\text{Without delay}}(\eta_V) \leq 1$ and stabilizes the infection-free equilibrium of system (4.19) as:

$$R_1^{\text{Without delay}}(\eta_P) \leq 1 \Longleftrightarrow 1 \geq \eta_P \geq \eta_{P,\min}^{\text{Without delay}} = \max\left\{0, \frac{R_1^{\text{Without delay}}(0)-1}{R_1^{\text{Without delay}}(0)}\right\}, \tag{4.20}$$

$$R_2^{\text{Without delay}}(\eta_V) \leq 1 \Longleftrightarrow 1 \geq \eta_V \geq \eta_{V,\min}^{\text{Without delay}} = \max\left\{0, \frac{R_2^{\text{Without delay}}(0)-1}{R_2^{\text{Without delay}}(0)}\right\}. \tag{4.21}$$

Since $F_i > 0,\ i = 1, 2, ...8$, then

$$\begin{aligned} R_1^{\text{With delay}}(0) &= \frac{\alpha k_2 m F_8\left[(\delta_2+b_2)\xi_2 F_6 + \delta_2(1-\xi_2)F_5F_7\right]}{a_2c_2\mu(\delta_2+b_2)} \\ &< \frac{\alpha k_2 m(\delta_2+b_2\xi_2)}{a_2c_2\mu(\delta_2+b_2)} = R_1^{\text{Without delay}}(0), \end{aligned}$$

$$\begin{aligned} R_2^{\text{With delay}}(0) &= \frac{\lambda k_1\beta_1\mu F_4\left[\xi_1F_2(\delta_1+b_1)+F_1F_3\delta_1(1-\xi_1)\right]}{a_1 d(c_1\mu+r\alpha)(\delta_1+b_1)} \\ &< \frac{\lambda k_1\beta_1\mu(\delta_1+b_1\xi_1)}{a_1 d(c_1\mu+r\alpha)(\delta_1+b_1)} = R_2^{\text{Without delay}}(0). \end{aligned}$$

Hence, $R_1^{\text{With delay}}(\eta_P) < R_1^{\text{Without delay}}(\eta_P)$ and $R_2^{\text{With delay}}(\eta_V) < R_2^{\text{Without delay}}(\eta_V)$, and, thus, eliminating the time delays from the co-dynamics model would lead to an overestimation of the basic reproduction numbers. By comparing Eqs (4.17), (4.18) and (4.20), (4.21), we get that $\eta_{P,\min}^{\text{With delay}} < \eta_{P,\min}^{\text{Without delay}}$ and $\eta_{V,\min}^{\text{With delay}} < \eta_{V,\min}^{\text{Without delay}}$. Thus, using a model with delays will require fewer treatment efficacies to maintain the system at the infection-free equilibrium and eliminate HIV-1 and HHV-8 from the body. This illustrates how crucial it is to take time delays into account in order to reduce the quantity of antiviral medication required, which stabilizes the model close to the equilibrium EP_0. In light of this, the model (2.1)–(2.8) that describes the HIV-1 co-dynamics with HHV-8 is more accurate.

5. Numerical simulations

This section provides numerical simulations of model (2.1)–(2.8) to enhance the theoretical findings given in Theorems 4.1–4.4. To achieve that, we transform the model with distributed-time delay (2.1)–(2.8) to a discrete one by using a particular form of the probability distributed function called Dirac delta function $D(.)$. Define

$$f_i(\tau) = D(\tau-\tau_i), i = 1, 2, \cdots, 8.$$

In case $\varkappa_i \to \infty, i = 1, 2, \cdots, 8$, we have

$$\int_0^\infty f_i(\tau)d\tau = 1 \text{ and } F_i = \int_0^\infty D(\tau-\tau_i)e^{-n_i\tau}d\tau = e^{-n_i\tau_i}, i = 1, 2, \cdots, 8.$$

Then,

$$\int_0^\infty D(\tau-\tau_1)e^{-n_1\tau}U_\tau V_\tau d\tau = e^{-n_1\tau_1}U_{\tau_1}V_{\tau_1}, \qquad \int_0^\infty D(\tau-\tau_2)e^{-n_2\tau}U_\tau V_\tau d\tau = e^{-n_2\tau_2}U_{\tau_2}V_{\tau_2},$$
$$\int_0^\infty D(\tau-\tau_3)e^{-n_3\tau}Y^L_\tau d\tau = e^{-n_3\tau_3}Y^L_{\tau_3}, \qquad \int_0^\infty D(\tau-\tau_4)e^{-n_4\tau}Y^A_\tau d\tau = e^{-n_4\tau_4}Y^A_{\tau_4},$$
$$\int_0^\infty D(\tau-\tau_5)e^{-n_5\tau}W_\tau P_\tau d\tau = e^{-n_5\tau_5}W_{\tau_5}P_{\tau_5}, \qquad \int_0^\infty D(\tau-\tau_6)e^{-n_6\tau}W_\tau P_\tau d\tau = e^{-n_6\tau_6}W_{\tau_6}P_{\tau_6},$$
$$\int_0^\infty D(\tau-\tau_7)e^{-n_7\tau}Z^L_\tau d\tau = e^{-n_7\tau_7}Z^L_{\tau_7}, \qquad \int_0^\infty D(\tau-\tau_8)e^{-n_8\tau}Z^A_\tau d\tau = e^{-n_8\tau_8}Z^A_{\tau_8}.$$

Hence, model (2.1)–(2.8) can be written as:

$$\begin{cases} \dot{U} = \lambda - dU - \beta_1 UV, \\ \dot{Y}^L = (1-\xi_1)\beta_1 e^{-n_1\tau_1}U_{\tau_1}V_{\tau_1} - (\delta_1+b_1)Y^L, \\ \dot{Y}^A = \xi_1\beta_1 e^{-n_2\tau_2}U_{\tau_2}V_{\tau_2} + \delta_1 e^{-n_3\tau_3}Y^L_{\tau_3} - a_1 Y^A, \\ \dot{V} = k_1 e^{-n_4\tau_4}Y^A_{\tau_4} - c_1 V - rVW, \\ \dot{W} = \alpha + qVW - \mu W - mWP, \\ \dot{Z}^L = (1-\xi_2)me^{-n_5\tau_5}W_{\tau_5}P_{\tau_5} - (\delta_2+b_2)Z^L, \\ \dot{Z}^A = \xi_2 me^{-n_6\tau_6}W_{\tau_6}P_{\tau_6} + \delta_2 e^{-n_7\tau_7}Z^L_{\tau_7} - a_2 Z^A, \\ \dot{P} = k_2 e^{-n_8\tau_8}Z^A_{\tau_8} - c_2 P. \end{cases} \tag{5.1}$$

The threshold parameters of model (5.1) are provided as:

$$\begin{cases} R_1 = \dfrac{\alpha k_2 m\tilde{\mathcal{P}}_1 e^{-n_8\tau_8}}{a_2c_2\mu(\delta_2+b_2)}, \\ R_2 = \dfrac{\lambda k_1\beta_1\mu\tilde{\mathcal{P}}_2 e^{-n_4\tau_4}}{a_1 d(c_1\mu+r\alpha)(\delta_1+b_1)}, \\ R_3 = \dfrac{\lambda k_1 k_2 m\beta_1\tilde{\mathcal{P}}_2\tilde{\mathcal{P}}_1 e^{-(n_4\tau_4+n_8\tau_8)}}{a_1 d(\delta_1+b_1)\left(c_1k_2m\tilde{\mathcal{P}}_1e^{-n_8\tau_8}+a_2c_2r(\delta_2+b_2)\right)}, \\ R_4 = \dfrac{k_2 m\beta_1 e^{-n_8\tau_8}}{(dq+\beta_1\mu)}\left(\dfrac{\alpha\tilde{\mathcal{P}}_1}{a_2c_2(\delta_2+b_2)} + \dfrac{k_1 q\lambda\tilde{\mathcal{P}}_1\tilde{\mathcal{P}}_2 e^{-n_4\tau_4}}{a_1(\delta_1+b_1)\left(c_1k_2m\tilde{\mathcal{P}}_1e^{-n_8\tau_8}+a_2c_2r(\delta_2+b_2)\right)}\right), \end{cases} \tag{5.2}$$

where

$$\tilde{\mathcal{P}}_1 = \xi_2 e^{-n_6\tau_6}(\delta_2+b_2) + \delta_2 e^{-(n_5\tau_5+n_7\tau_7)}(1-\xi_2),$$
$$\tilde{\mathcal{P}}_2 = \xi_1 e^{-n_2\tau_2}(\delta_1+b_1) + e^{-(n_1\tau_1+n_3\tau_3)}\delta_1(1-\xi_1).$$

5.1. Numerical simulations for model (5.1)

By using the dde23 solver in MATLAB, we solve numerically the system of DDEs (5.1). In this subsection, for simplicity, let us choose the delay parameters as: $\tau_i = 0.1, i = 1, 2, \cdots, 8$. Moreover, the three distinct initial conditions (IC) are picked as:

IC-1 : $U(\theta) = 200, Y^L(\theta) = 300, Y^A(\theta) = 6, V(\theta) = 8, W(\theta) = 150, Z^L(\theta) = 8, Z^A(\theta) = 25, P(\theta) = 40,$
IC-2 : $U(\theta) = 400, Y^L(\theta) = 200, Y^A(\theta) = 3, V(\theta) = 5, W(\theta) = 170, Z^L(\theta) = 5, Z^A(\theta) = 15, P(\theta) = 30,$
IC-3 : $U(\theta) = 600, Y^L(\theta) = 100, Y^A(\theta) = 1, V(\theta) = 2, W(\theta) = 190, Z^L(\theta) = 2, Z^A(\theta) = 10, P(\theta) = 20,$

where $\theta \in [-0.1, 0]$.

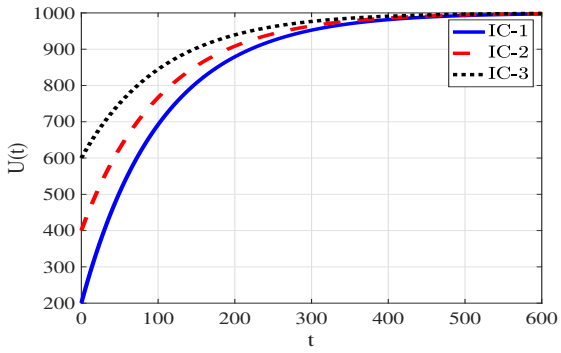
By varying the values of the parameters β_1 and m, and fixing other parameters, the four following scenarios are risen as:

Scenario 1 (Stability of EP_0): $\beta_1 = 0.0001$ and $m = 0.0005$. With this choice, we find the basic reproduction numbers R_1 and R_2 take the following values: $R_1 = 0.23 < 1$ and $R_2 = 0.18 < 1$, then the stability conditions in Theorem 4.1 are satisfied. Figure 1 presents that the trajectories starting with IC-1, IC-2, and IC-3 arrive at the equilibrium $EP_0 = (1000, 0, 0, 0, 200, 0, 0, 0)$. This provides EP_0 is GAS which is consistent with the result in Theorem 4.1. In this situation, both HIV-1 and HHV-8 will be cleared out from patients.

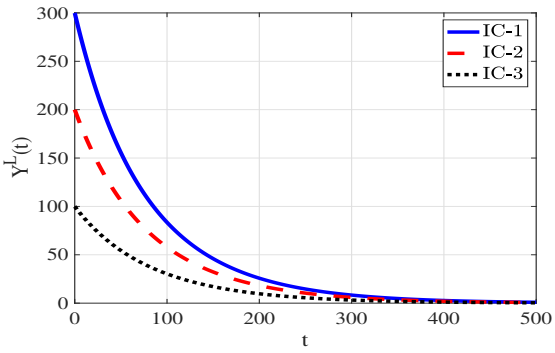
Scenario 2 (Stability of EP_1): $\beta_1 = 0.0001$ and $m = 0.002$. This gives us $R_1 = 1.24 > 1$ and $R_3 = 0.29 < 1$, then the stability conditions in Theorem 4.2 are held true. Thus, the equilibrium EP_1 exists and the numerical results show that $EP_1 = (1000, 0, 0, 0, 161.51, 5.96, 18.01, 28.60)$. Figure 2 illustrates that the trajectories starting with IC-1, IC-2, and IC-3 reach to the equilibrium EP_1, and then is EP_1 GAS as we have proven in Theorem 4.2. This situation leads to the case of HHV-8 single-infection. Evidently, in this case, the concentration of $CD4^+$T cells is not affected by this infection, while the concentration of B cells are reduced.

Scenario 3 (Stability of EP_2): $\beta_1 = 0.001$ and $m = 0.0001$. For this set of parameters, we calculate $R_2 = 2.37 > 1$ and $R_4 = 0.09 < 1$, hence, the presented conditions in Table 2 are satisfied and the equilibrium EP_2 exists. Figure 3 shows that the solutions initiating with IC-1, IC-2, and IC-3 tend to the equilibrium $EP_2 = (582.81, 242.67, 6.43, 7.16, 285.01, 0, 0, 0)$, which agrees with the results in Theorem 4.3. This case represents the appearance of a single HIV-1 single-infection. Without doubt, HIV-1 infection leads to a decrease in $CD4^+$ T cells concentration besides increasing the B cells concentration.

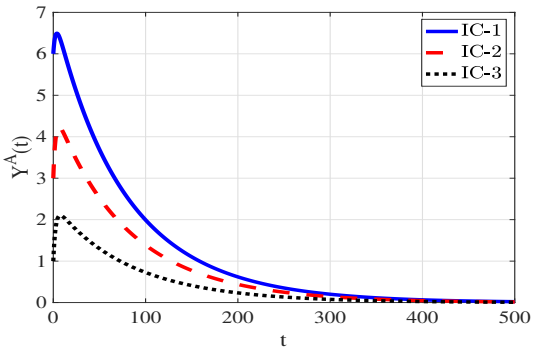
Scenario 4 (Stability of EP_3): $\beta_1 = 0.001$ and $m = 0.0013$. This leads to $R_4 = 1.14 > 1$, $R_3 = 1.95$, and $R_3 < 1 + \frac{\beta_1 \mu}{dq} = 3.4$, then the stability conditions in Theorem 4.4 are held true. Figure 4 shows that the equilibrium $EP_3 = (513.91, 282.75, 7.50, 9.46, 248.48, 7.66, 23.14, 36.74)$ is GAS, which supports the result in Theorem 4.4. In this case, an HIV-1 patient becomes infected by HHV-8, which leads to a decrease in the concentration of both $CD4^+$ T cells and B cells.



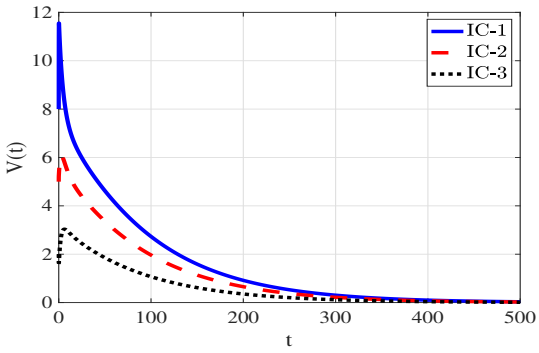
(a) Uninfected CD4$^+$T cells



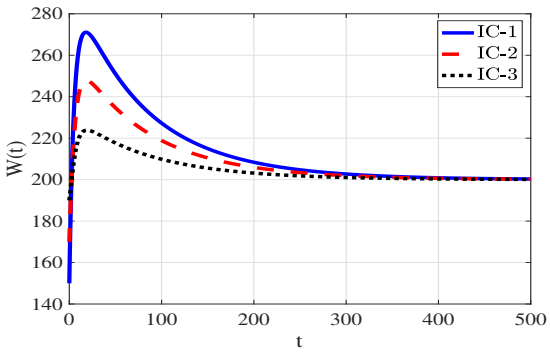
(b) Latently HIV-1-infected CD4$^+$T cells



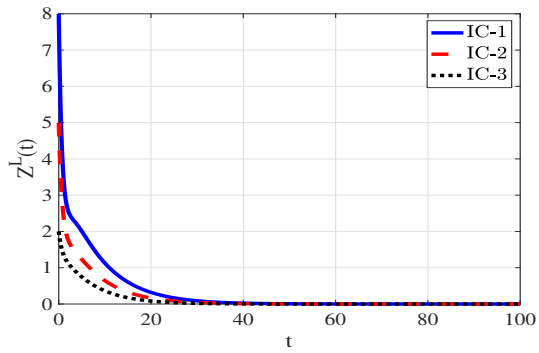
(c) Actively HIV-1-infected CD4$^+$T cells



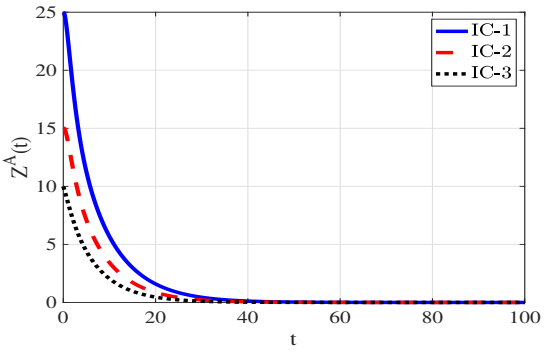
(d) Free HIV-1 virus



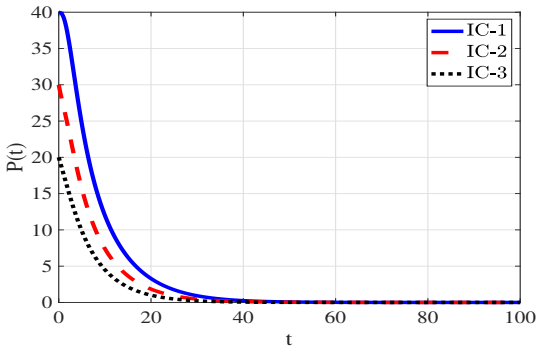
(e) Uninfected B cells



(f) Latently HHV-8-infected B cells

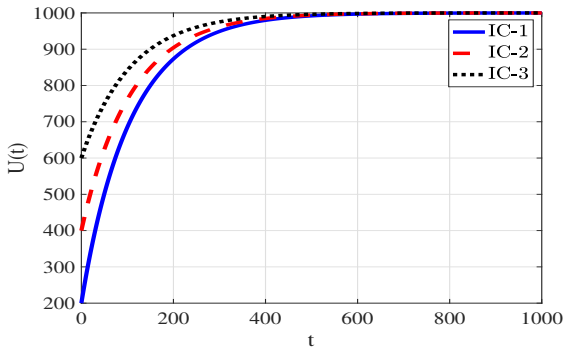


(g) Actively HHV-8-infected B cells

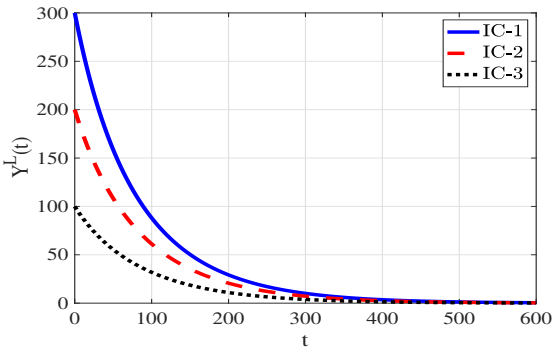


(h) Free HHV-8 virus

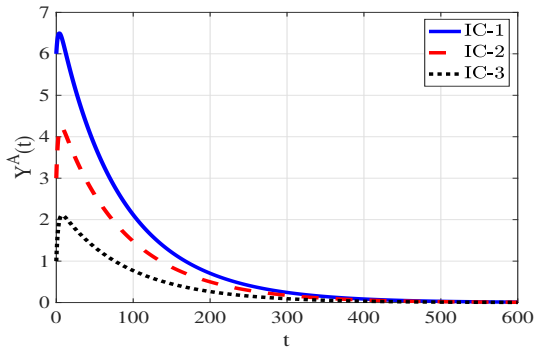
Figure 1. Solutions of system (5.1) with three different initials conditions reach the equilibrium $EP_0 = (1000, 0, 0, 0, 200, 0, 0, 0)$ (Scenario 1).



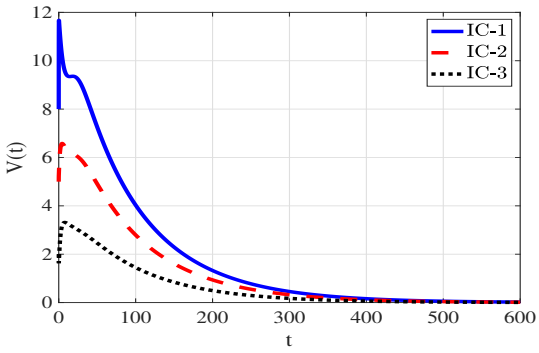
(a) Uninfected CD4$^+$T cells



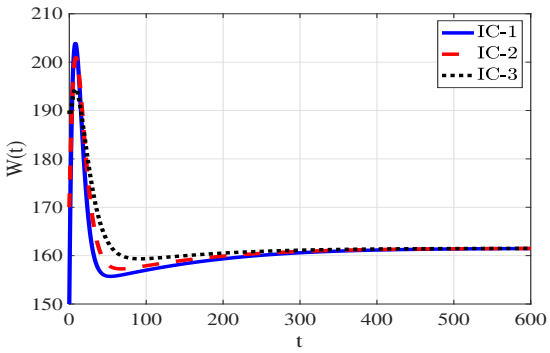
(b) Latently HIV-1-infected CD4$^+$T cells



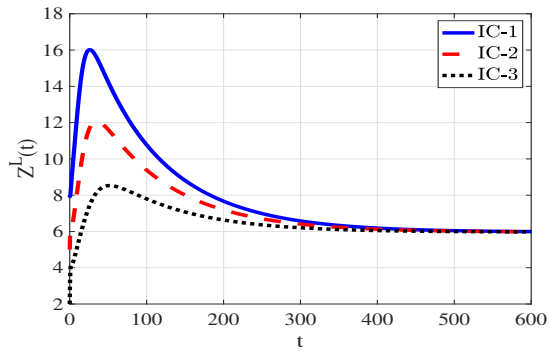
(c) Actively HIV-1-infected CD4$^+$T cells



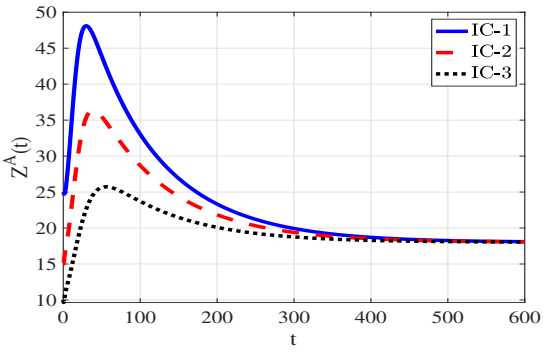
(d) Free HIV-1 virus



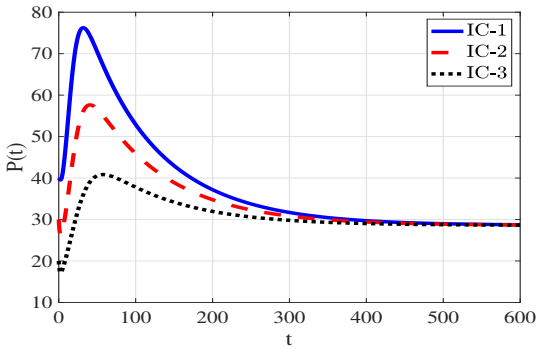
(e) Uninfected *B* cells



(f) Latently HHV-8-infected B cells

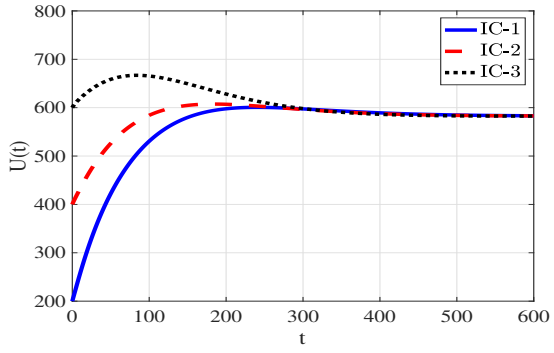


(g) Actively HHV-8-infected B cells

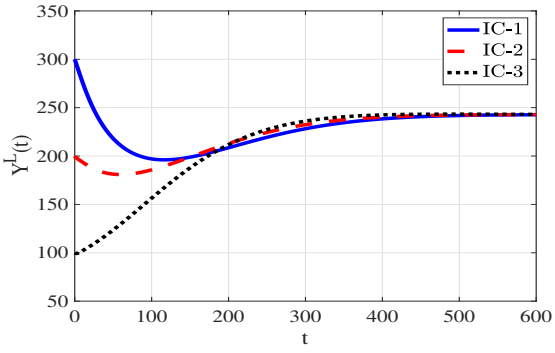


(h) Free HHV-8 virus

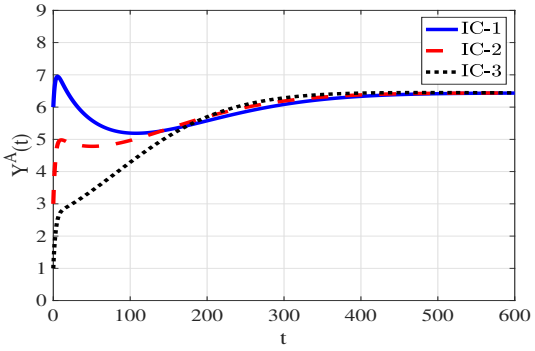
Figure 2. Solutions of system (5.1) with three different initials conditions reach the equilibrium $EP_1 = (1000, 0, 0, 0, 161.51, 5.96, 18.01, 28.60)$ (Scenario 2).



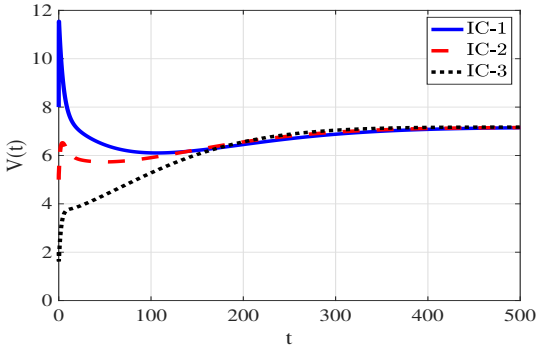
(a) Uninfected CD4$^+$T cells



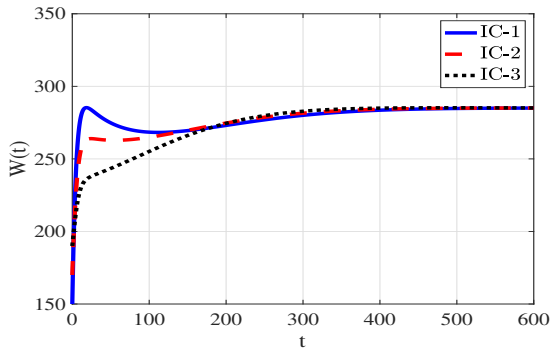
(b) Latently HIV-1-infected CD4$^+$T cells



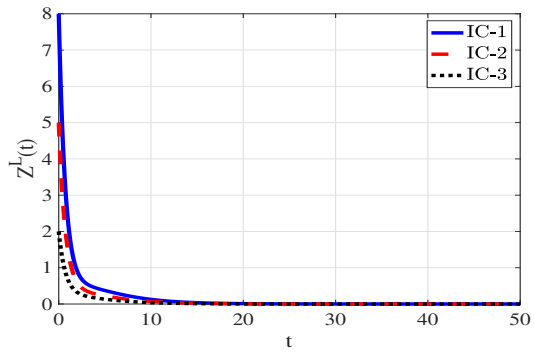
(c) Actively HIV-1-infected CD4$^+$T cells



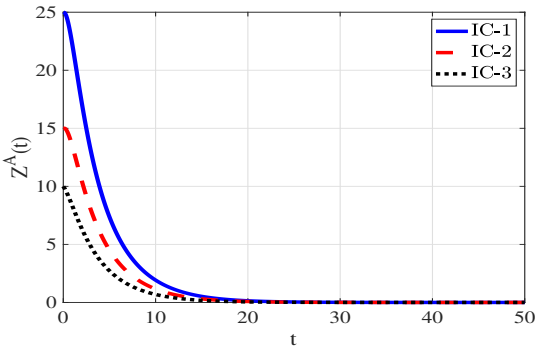
(d) Free HIV-1 virus



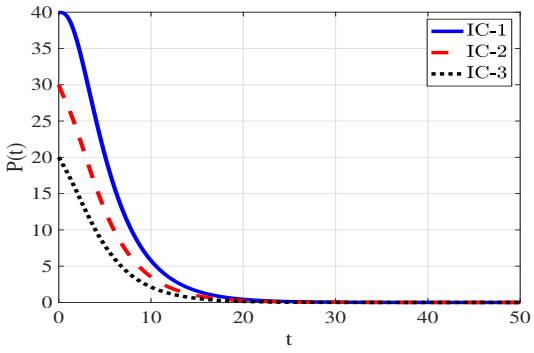
(e) Uninfected *B* cells



(f) Latently HHV-8-infected B cells

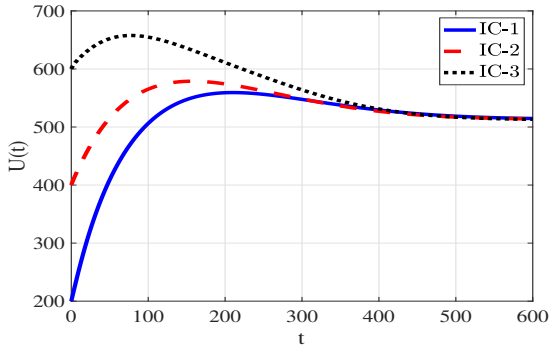


(g) Actively HHV-8-infected B cells

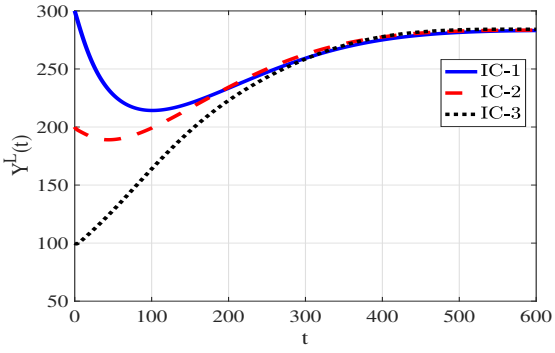


(h) Free HHV-8 virus

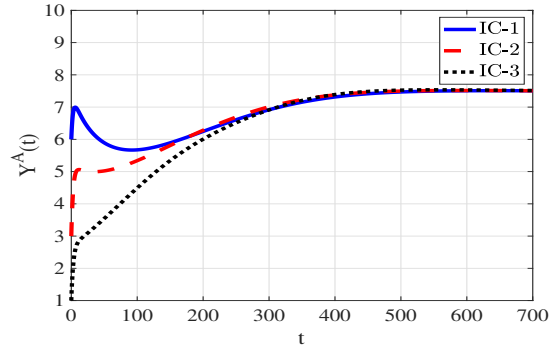
Figure 3. Solutions of system (5.1) with three different initials conditions reach the equilibrium $EP_2 = (582.81, 242.67, 6.43, 7.16, 285.01, 0, 0, 0)$ (Scenario 3).



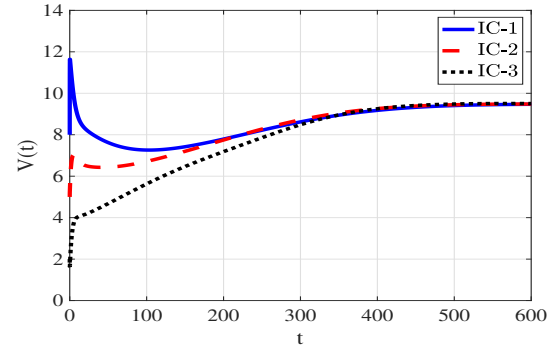
(a) Uninfected CD4$^+$T cells



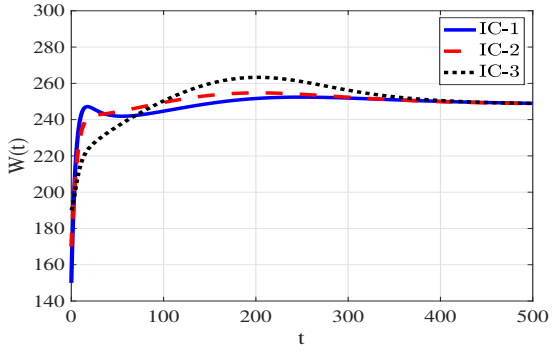
(b) Latently HIV-1-infected CD4$^+$T cells



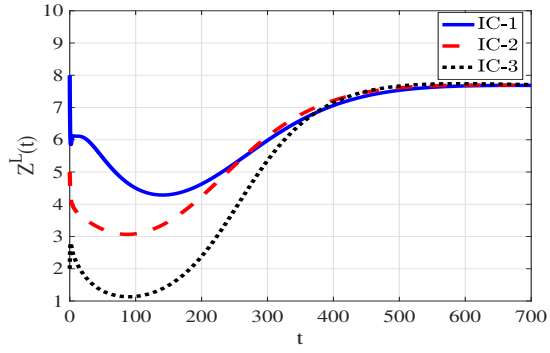
(c) Actively HIV-1-infected CD4$^+$T cells



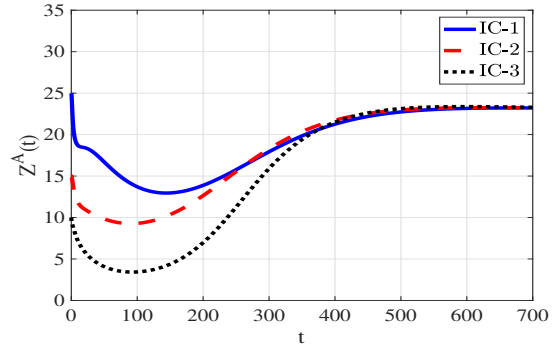
(d) Free HIV-1 virus



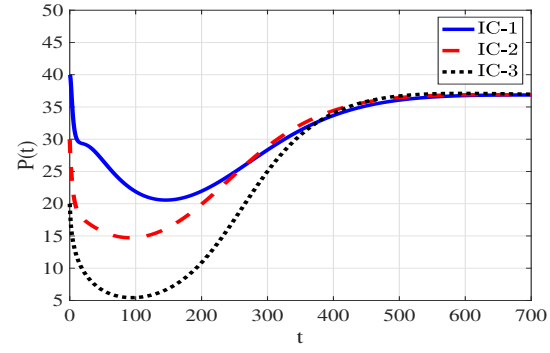
(e) Uninfected B cells



(f) Latently HHV-8-infected B cells



(g) Actively HHV-8-infected B cells



(h) Free HHV-8 virus

Figure 4. Solutions of system (5.1) with three different initials conditions converge to the equilibrium, $EP_3 = (513.91, 282.75, 7.50, 9.46, 248.48, 7.66, 23.14, 36.74)$ (Scenario 4).

5.2. Impact of time delays on HHV-8/HIV-1 co-dynamics

By fixing the following parameters: $\beta_1 = 0.001$, $m = 0.0013$ and $\tau_i = 0.01, i = 1, 2, 3, 5, 6, 7$, and varying $\tau_i, i = 4, 8$, we study the impact of the inclusion of time delays on the stability of EP_0. Since R_1 and R_2 that are provided in (5.2) are based on $\tau_i, i = 4, 8$, any changing the parameters $\tau_i, i = 4, 8$ will change the stability of EP_0. Obviously, any small increase in the value of $\tau_i, i = 4, 8$ will lead to a decrease in the values of R_1 and R_2, which is our aim (see Table 3). Let us consider the following cases:

T.D-1 $\tau_4 = \tau_8 = 0$,

T.D-2 $\tau_4 = 0.5, \tau_8 = 0.01$,

T.D-3 $\tau_4 = 0.7, \tau_8 = 0.05$,

T.D-4 $\tau_4 = 1.3, \tau_8 = 0.08$,

T.D-5 $\tau_4 = 1.5, \tau_8 = 0.1$.

Table 3. The variation of R_1 and R_2 with respect to the delay parameters.

Delay parameter τ_8	R_1	Delay parameter τ_4	R_2
0	1.06485	0	3.0923
0.01	1.05425	0.5	1.87558
0.05	1.01291	0.7	1.53559
0.06283	1	1.12892	1
0.08	0.98298	1.3	0.84275
0.1	0.96351	1.5	0.68999

Let us solve system (5.1) under the following initial condition:

$$\mathbf{IC-4}: U(\theta) = 500, Y^L(\theta) = 200, Y^A(\theta) = 5, V(\theta) = 6, W(\theta) = 190, Z^L(\theta) = 10, Z^A(\theta) = 30, P(\theta) = 50,$$

where $\theta \in [-1.5, 0]$.

Let us compute the critical value of the time delay that alters the stability of EP_0. By fixing the other parameters, R_1 and R_2 can be written as functions of τ_8, τ_4, respectively, as follows:

$$\begin{cases} R_1(\tau_8) = \dfrac{\alpha k_2 m \tilde{\mathcal{P}}_1 e^{-n_8\tau_8}}{a_2 c_2 \mu\,(\delta_2 + b_2)}, \\ R_2(\tau_4) = \dfrac{\lambda k_1 \beta_1 \mu \tilde{\mathcal{P}}_2 e^{-n_4\tau_4}}{a_1 d\,(c_1\mu + r\alpha)\,(\delta_1 + b_1)}. \end{cases}$$

To fulfill that $R_1(\tau_8) \leq 1$ and $R_2(\tau_4) \leq 1$, we take τ_4 and τ_8 as:

$$\tau_8 \geq \tau_8^{cr} \text{ where } \tau_8^{cr} = \max\left\{0, \frac{1}{n_8}\ln\left(\frac{\alpha k_2 m \tilde{\mathcal{P}}_1}{a_2 c_2 \mu\,(\delta_2 + b_2)}\right)\right\},$$

and

$$\tau_4 \geq \tau_4^{cr} \text{ where } \tau_4^{cr} = \max\left\{0, \frac{1}{n_4}\ln\left(\frac{\lambda k_1 \beta_1 \mu \tilde{\mathcal{P}}_2}{a_1 d\,(c_1\mu + r\alpha)\,(\delta_1 + b_1)}\right)\right\}.$$

Thus, when $\tau_8 \geq \tau_8^{cr}$ and $\tau_4 \geq \tau_4^{cr}$, then EP_0 is GAS. Using the values of parameters given in Table 1, we obtain $\tau_8^{cr} = 0.06283$ and $\tau_4^{cr} = 1.12892$, respectively. Consequently,

(i) if $\tau_8 \geq 0.06283$ and $\tau_4 \geq 1.12892$, then $R_1(\tau_8) \leq 1$, $R_2(\tau_4) \leq 1$, and EP_0 is GAS;

(ii) if $\tau_8 < 0.06283$ and/or $\tau_4 < 1.12892$, then $R_1(\tau_8) > 1$ and/or $R_2(\tau_4) > 1$, and EP_0 will lose its stability and, in this case, another equilibrium will be GAS.

Figure 5 displays the numerical solutions of system (5.1). We can see that inclusion of time delays leads to significant increase in the concentration of uninfected $CD4^+T$ cells and B cells; on the contrary, it contributes in reducing the concentrations of other compartments. Since the increasing of the delay period can control the HHV-8 and HIV developing in the patients, we can notice that the time delay has a comparable effect as the drug efficacy. Thus, inserting time delays contributes in developing new effective treatment methods.

5.3. Sensitivity analysis

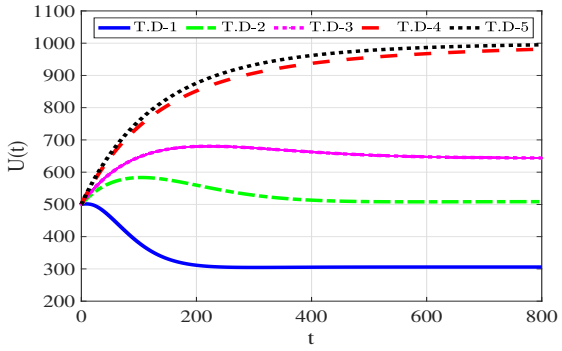
In biological systems, sensitivity analysis is utilized to illustrate the relation between parameters and model outcomes and, hence, increasing the understanding of studying models [58]. This leads to place the key operators that affect the model's output [59]. To measure the biological responses to any change in model's parameters, there is diverse approaches such as direct differentiation, use of a Latin hypercube sampling technique, or linearizing the system and resolving the resultant equations [60]. For our model (5.1), we use derivative-based sensitivity which can be calculated analytically by partial derivatives with respect to model parameters. We study the sensitivity analysis for R_1 and R_2 due to their contribution to determining the stability of the uninfected equilibrium EP_0. The normalized forward sensitivity index is generally given by

$$S_{\gamma}^{R_\iota} = \frac{\partial R_\iota}{\partial \gamma} \cdot \frac{\gamma}{R_\iota}, \quad \iota = 1, 2, \tag{5.3}$$

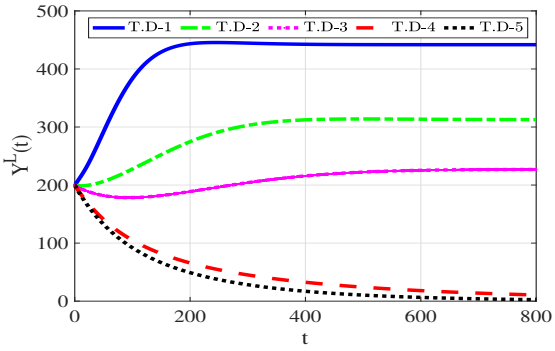
where γ is a parameter. Study sensitivity analysis for both R_1 and R_2 is proceeded as the following:

5.3.1. Sensitivity analysis of R_1

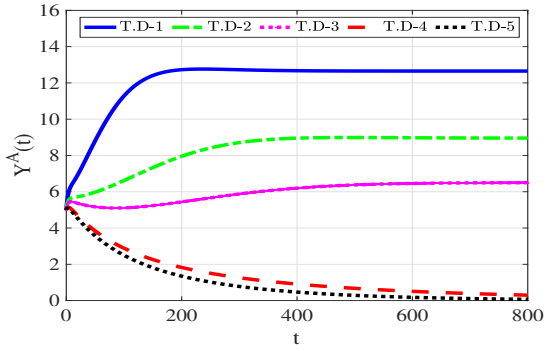
The normalized forward sensitivity index of R_1 that is responsible in the developing of the HHV-8 in the body can be computed by using Eq (5.3). By fixing $m = 0.002$, the sensitivity index for each parameter is presented in Table 4 and Figure 6.



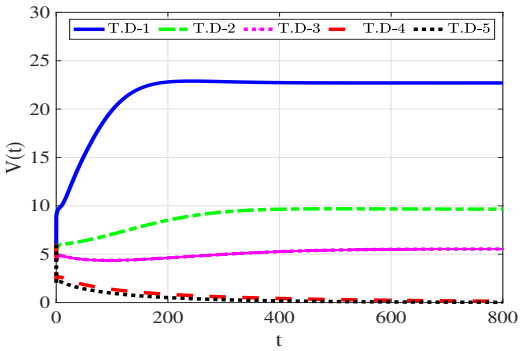
(a) Uninfected CD4$^+$T cells



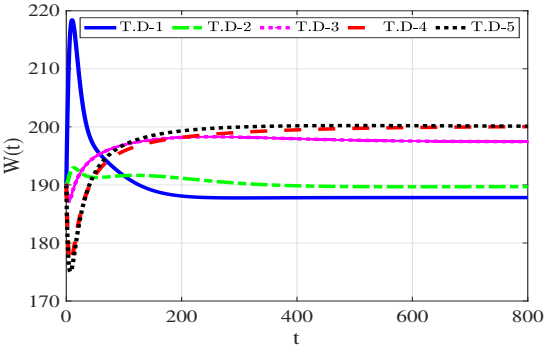
(b) Latently HIV-1-infected CD4$^+$T cells



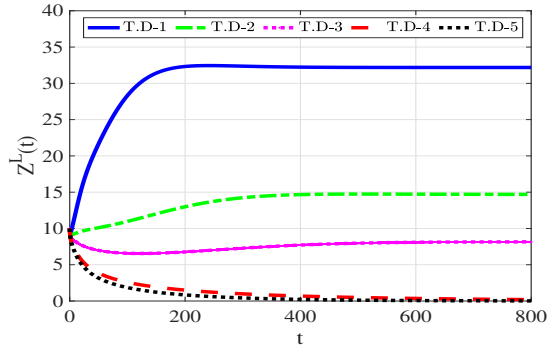
(c) Actively HIV-1-infected CD4$^+$T cells



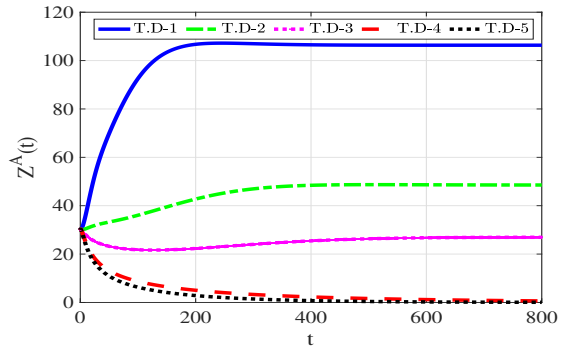
(d) Free HIV-1 virus



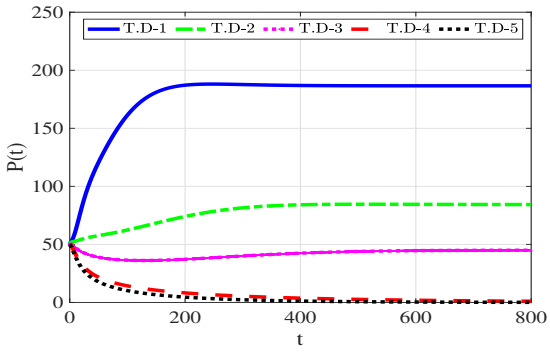
(e) Uninfected *B* cells



(f) Latently HHV-8-infected B cells



(g) Actively HHV-8-infected B cells



(h) Free HHV-8 virus

Figure 5. Solutions of system (5.1) for different maturation delays τ_8 and τ_4.

Table 4. Sensitivity index of R_1.

Parameter	$S_\gamma^{R_1}$	Parameter	$S_\gamma^{R_1}$	Parameter	$S_\gamma^{R_1}$
α	1	c_2	-1	n_8	-0.1
k_2	1	μ	-1	τ_5	-0.0999
m	1	b_2	-0.2140	τ_6	-0.0001
δ_2	0.2140	n_5	-0.0999	τ_7	-0.0999
ξ_2	0.0004	n_6	-0.0001	τ_8	-0.1000
a_2	-1	n_7	-0.0999		

According to the sign of the indices, we obtain that:

- α, k_2, m, δ_2, and ξ_2 have positive indices and have a positive effect on R_1. Because of that, these parameters contribute to the development of HHV-8 in the body. Obviously, α, k_2, and m have the most positive sensitivity index, while δ_2 and ξ_2 have the least positive sensitivity index. For example, increasing (or decreasing) δ_2 by 10% will increase (or decrease) the R_1 value by 2.14%.

- a_2, c_2, μ, b_2, n_4, n_5, n_6, τ_5, τ_6, τ_7, and τ_8 have negative indices and, hence, have a negative effect in R_1. That means when the values of these parameters increase (or decrease), the value of R_1 decreases (or increases). As an example, the sensitivity index of b_2 is -0.2140. This indicates that increasing (or decreasing) b_2 by 10% will decrease (or increase) the R_1 value by 2.14%. We note that a_2, c_2, and μ have the most negative sensitivity index.

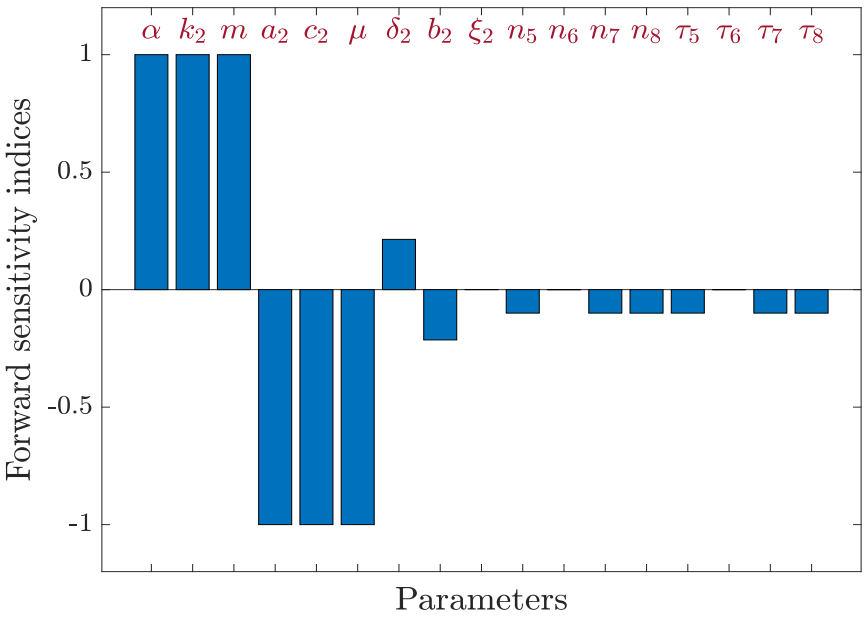


Figure 6. Forward sensitivity analysis of the parameters on R_1.

5.3.2. Sensitivity analysis of R_2

By applying Eq (5.3) and taking $\beta_1 = 0.001$, we calculate the sensitivity analysis of R_2 which explains the effect of the parameters on the HIV-1 progression in the body. The results are provided in Table 5 and Figure 7.

Table 5. Sensitivity index of R_2.

Parameter	$S_\gamma^{R_2}$	Parameter	$S_\gamma^{R_2}$	Parameter	$S_\gamma^{R_2}$
λ	1	d	-1	n_3	-0.0853
k_1	1	r	-0.8929	n_4	-0.1000
β_1	1	α	-0.8929	τ_1	-0.0853
μ	0.8929	c_1	-0.1071	τ_2	-0.0147
δ_1	0.2438	b_1	-0.2438	τ_3	-0.0853
ξ_1	0.0519	n_1	-0.0853	τ_4	-0.1000
a_1	-1	n_2	-0.0147		

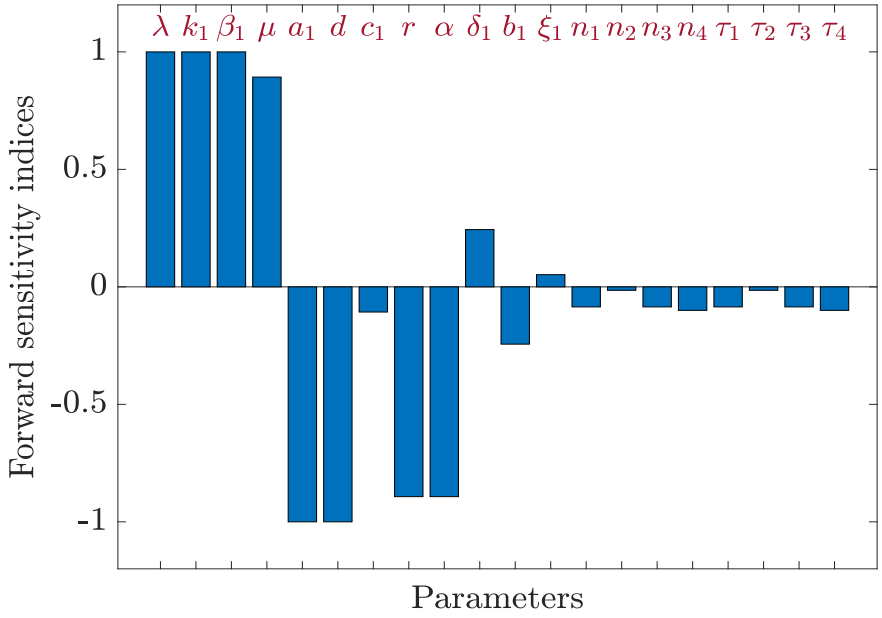


Figure 7. Forward sensitivity analysis of the parameters on R_2.

5.4. Comparison study

In this section, let us fix the delay parameters as $\tau_i = 0.1$, $i = 1, 2, \cdots, 8$. The influence of HHV-8 infection on the dynamic of the HIV-1 single-infection and vice versa will be studied.

5.4.1. Comparison between HIV-1 single-infection and HHV-8/HIV-1 co-infection

The solutions of HHV-8/HIV-1 co-infection model (5.1) in comparison with solutions of the following HIV-1 single-infection system are presented:

$$\begin{cases} \dot{U} = \lambda - dU - \beta_1 UV, \\ \dot{Y}^L = (1-\xi_1)\beta_1 e^{-n_1\tau_1} U_{\tau_1} V_{\tau_1} - (\delta_1 + b_1)Y^L, \\ \dot{Y}^A = \xi_1\beta_1 e^{-n_2\tau_2} U_{\tau_2} V_{\tau_2} + \delta_1 e^{-n_3\tau_3} Y^L_{\tau_3} - a_1 Y^A, \\ \dot{V} = k_1 e^{-n_4\tau_4} Y^A_{\tau_4} - c_1 V - rVW, \\ \dot{W} = \alpha + qVW - \mu W. \end{cases} \tag{5.4}$$

Let us select the parameter's values $\beta_1 = 0.001$ and $m = 0.0013$ and the following initial condition:

$$\textbf{IC-5}: U(\theta) = 550, Y^L(\theta) = 260, Y^A(\theta) = 7, V(\theta) = 8, W(\theta) = 275, Z^L(\theta) = 20, Z^A(\theta) = 40, P(\theta) = 50,$$

where $\theta \in [-0.1, 0]$. Figure 8 represents the solutions of two systems (5.1) and (5.4). It can be seen that in the case of HIV-1 patients becoming infected by HHV-8 infections, then concentration of uninfected $CD4^+T$ cells decreases and the concentration of HIV-1 particles increases. This observation is compatible with studies that have been published in [61, 62], which suggest that HHV-8 may raise the HIV-1 load and spread, hastening the onset of AIDS. The appearance of HHV-8 infection in HIV-positive patients leads to the risk of developing opportunistic diseases, including KS and other proliferative diseases, such as PEL and MCD [63].

5.4.2. Comparison between HHV-8 single-infection and HHV-8/HIV-1 co-infection

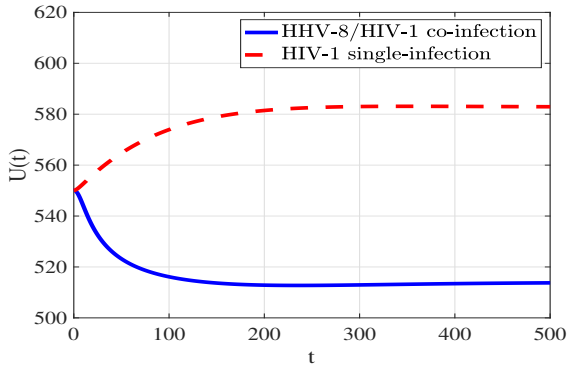
We compare the solutions of HHV-8/HIV-1 co-infection model (5.1) and the following HHV-8 single-infection system:

$$\begin{cases} \dot{W} = \alpha - \mu W - mWP, \\ \dot{Z}^L = (1-\xi_2)me^{-n_5\tau_5} W_{\tau_5} P_{\tau_5} - (\delta_2 + b_2)Z^L, \\ \dot{Z}^A = \xi_2 me^{-n_6\tau_6} W_{\tau_6} P_{\tau_6} + \delta_2 e^{-n_7\tau_7} Z^L_{\tau_7} - a_2 Z^A, \\ \dot{P} = k_2 e^{-n_8\tau_8} Z^A_{\tau_8} - c_2 P. \end{cases} \tag{5.5}$$

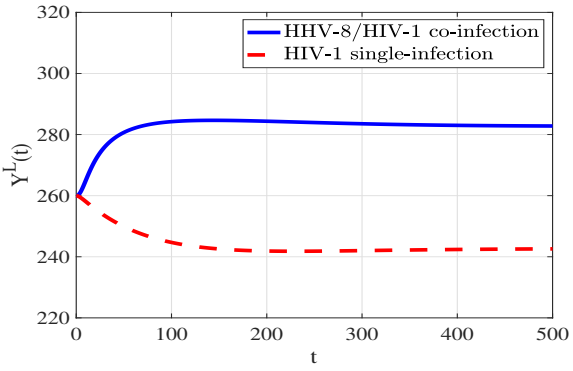
We select the values $\beta_1 = 0.001$ and $m = 0.003$. We take the initial condition as:

$$\textbf{IC-6}: U(\theta) = 200, Y^L(\theta) = 300, Y^A(\theta) = 3, V(\theta) = 50, W(\theta) = 100, Z^L(\theta) = 10, Z^A(\theta) = 40, P(\theta) = 70,$$

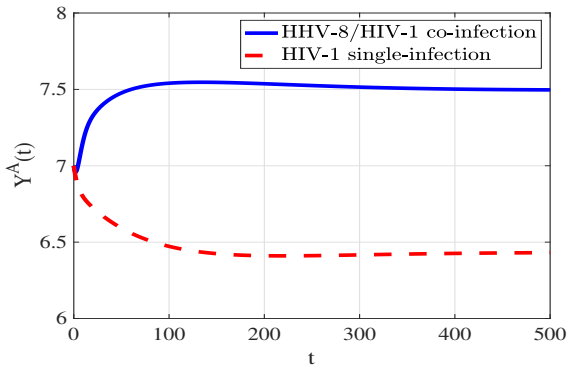
where $\theta \in [-0.1, 0]$. Figure 9 displays the solutions of two models (5.1) and (5.5). Evidently, the concentrations of the B cell in both models gradually approach the same value, $W_3 = W_1$. Although, latently HHV-8-infected B cells, actively HHV-8-infected B cells, and free HHV-8 particles are more diffused in patients with co-infection with HIV-1 than in those without it. This is harmonic with the results stated in [64], which proposed that there is a possibility that high HIV-1 DNA levels might stimulate HHV-8 reactivation by either directly activating HHV-8 or by increasing immunosuppression. According to the paper of Mercader, et al. [65], HIV-1 may contribute to the enhancement of HHV-8 lytic replication and, hence, increase the likelihood of tumor formation.



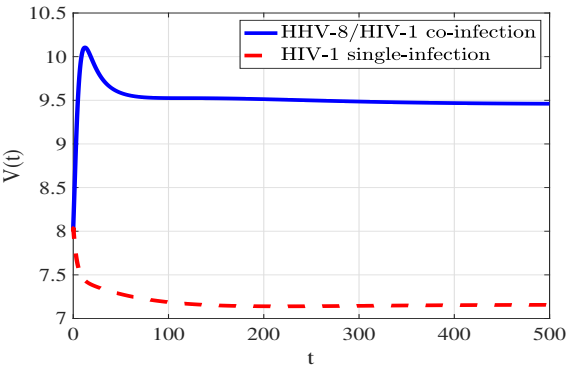
(a) Uninfected CD4$^+$T cells



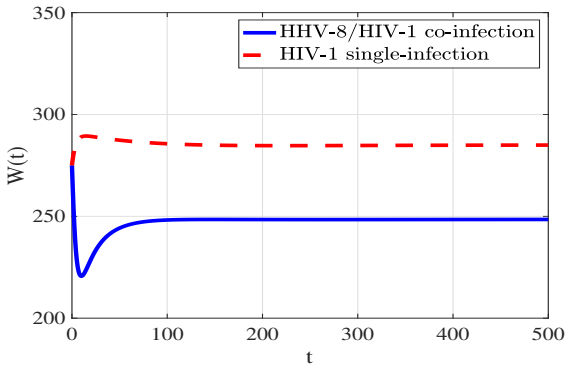
(b) Latently HIV-1-infected CD4$^+$T cells



(c) Actively HIV-1-infected CD4$^+$T cells

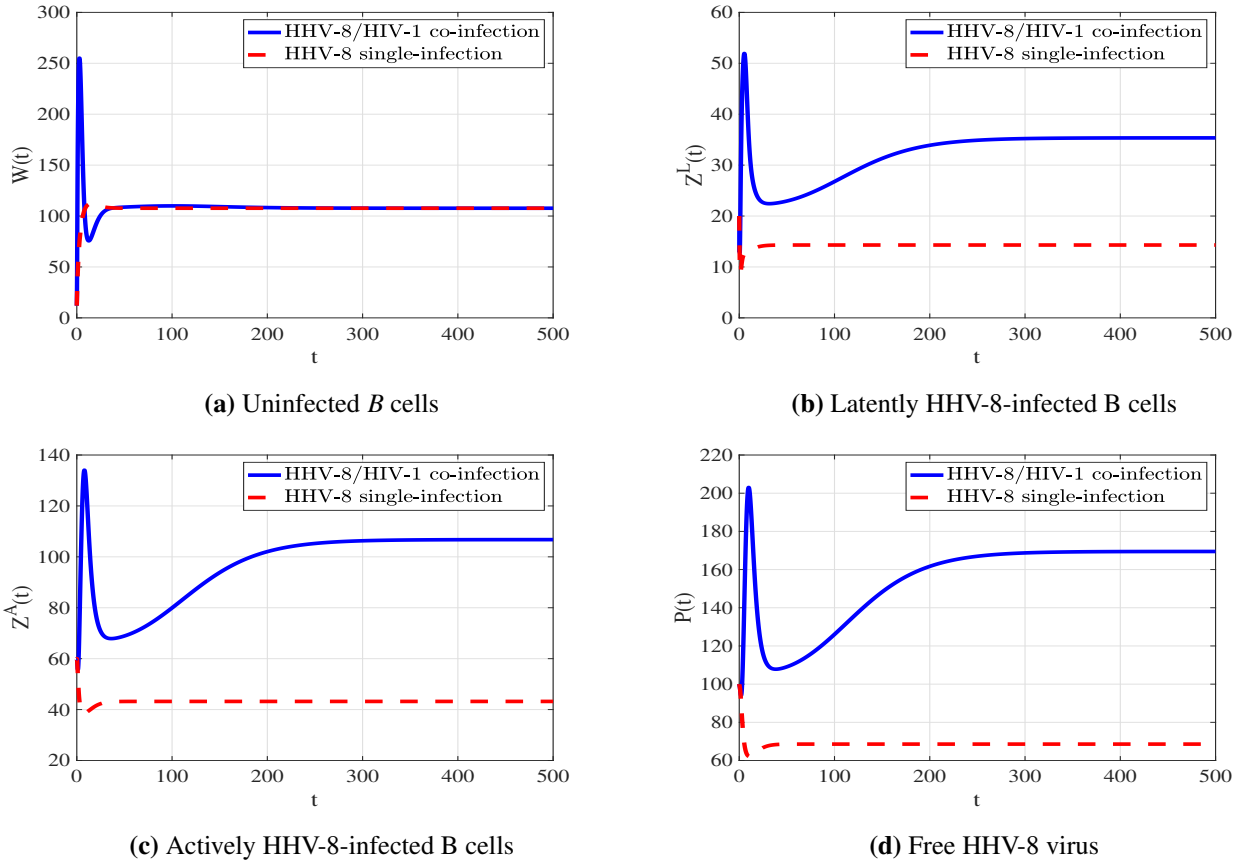


(d) Free HIV-1 virus



(e) Uninfected *B* cells

Figure 8. Comparison between the solutions of models for HIV-1 single-infection and HHV-8/HIV-1 co-infection.



(a) Uninfected B cells

(b) Latently HHV-8-infected B cells

(c) Actively HHV-8-infected B cells

(d) Free HHV-8 virus

Figure 9. Comparison between the solutions of models for HHV-8 single-infection and HHV-8/HIV-1 co-infection.

6. Conclusions and discussion

Since mathematical modeling is an essential tool in helping experimental studies to understand new diseases, co-infection between HHV-8/HIV-1 with distributed time-delays have been studied in this paper. Our presented model describes the contacts between uninfected $CD4^+$ T cells, latently and actively HIV-1-infected $CD4^+$ T cells, free HIV-1 particles, uninfected B cells, latently and actively HHV-8-infected B cells, and free HHV-8 particles. We first demonstrated the two primary characteristics of the solutions: boundedness and nonnegativity. After that, we showed that the model has four equilibria as well as four threshold parameters R_i, $i = 1, 2, 3, 4$. The global asymptotic stability of the model's equilibria are determined by four threshold parameters. The Lyapunov-LaSalle asymptotic stability theorem and the Lyapunov technique allowed us to demonstrate the global asymptotic stability for every equilibrium point. These are the outcomes that we have:

- Infection-free equilibrium EP_0 always exists and is GAS if $R_1 \leq 1$ and $R_2 \leq 1$. This state represents the situation of a person without HIV-1 and HHV-8.
- HHV-8 single-infection equilibrium EP_1 exists if $R_1 > 1$ and is GAS if $R_3 \leq 1$. This state represents the person has only an HHV-8 infection.

- HIV-1 single-infection equilibrium EP_2 exists if $R_2 > 1$ and is GAS if $R_4 \leq 1$. This state represents the person has only an HIV-1 infection.
- HHV-8/HIV-1 co-infection equilibrium EP_3 exists if $R_4 > 1$ and is GAS if $R_3 \leq 1 + \frac{\mu\beta_1}{dq}$. This state represents a person who suffers from both HIV-1 and HHV-8 co-infection.

We presented numerical simulations that coincided with the theoretical results. We studied sensitivity analysis for both R_1 and R_2 and established which parameters have most effect on the spread of HIV-1 and HHV-8 in the body. We discussed the effect of time delays on HHV-8/HIV-1 co-dynamics. We found that the delay parameter and drug effectiveness both contribute to a decrease in the basic reproduction numbers. This provides us with some insight into creating treatments that lengthen the time of delay. Furthermore, we demonstrated that using a time-delay model will require fewer treatment efficacies to keep the system at infection-free equilibrium and remove HIV-1 and HHV-8 from the body. These results imply that time delays have a significant and unavoidable influence on the HHV-8/HIV-1 co-dynamics.

We are confident that the approach proposed in our paper can be further developed. An interesting perspective would be the modeling of the in-host dynamics focused on the competition between the immune system and invasive particles. Active-particle methods have recently been used to model epidemics through a detailed description of the immune competition at the cellular scale (see [66, 67]).

Author contributions

Conceptualization, A.M.E. and E.A.A; Formal analysis, A.M.E, E.A.A. and A.D.H.; Investigation, A.M.E. and E.A.A; Methodology, A.M.E and A.D.H.;Writing—original draft, E.A.A.; Writing—review & editing, A.M.E. and E.A.A. All authors have read and agreed to the published version of the manuscript.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Conflict of interest

The authors declare no conflicts of interest.

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