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Analysis of delayed HIV-1 dynamics model with inflammatory cytokines and cellular infection

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Abstract

The purpose of this research is to develop a mathematical model to study the dynamics of human immunodeficiency virus type-1 (HIV-1) infection with inflammatory cytokines. The model incorporates two modes of infection (viral and cellular), two immune responses (antibody and cytotoxic T lymphocyte (CTL)) and two types of distributed-time delays. We demonstrate that the model's solutions are non-negative and eventually bounded, demonstrating the suggested model's biological viability. We find the equilibrium points of the model and get the sufficient conditions for their existence and stability. The Lyapunov approach is utilized to investigate the global stability of the equilibria. We determine which parameters most affect the basic reproduction number using sensitivity analysis. We reformulate our model by including the influence of three classes of antiretroviral drug therapies. We determine a critical efficacy for each antiretroviral therapy, after which HIV-1 will be eradicated entirely if treatment effectiveness surpasses this threshold. We also establish that the estimated treatment efficacy will be lower than what is necessary to eliminate the virus entirely if the inflammatory cytokines and/or cellular infection are ignored. Moreover, we show that time delay has an identical effect on virus elimination as antiretroviral therapy. It is also shown that, prolonging time delays can successfully reduce the basic reproduction number and stop HIV-1 replication. According to our findings, time delay, cellular infection, and inflammatory cytokines are crucial components of the HIV-1 model and should not be disregarded. The study's analytical and numerical findings advance our knowledge of HIV-1 dynamics and may help develop more effective HIV-1 management plans.

Keywords: HIV-1, inflammatory cytokines, viral and cellular infections, immune response, time delay, global stability, Lyapunov method.

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1. Introduction

Human immunodeficiency virus type-1 (HIV-1) infection is a fatal virus that raises the risk and severity of other infections and illnesses. The HIV-1 virus interacts with the immune system and primarily

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targets $CD4^+$ T cells, often known as T cells, for infection [35]. As the condition worsens, the population of $CD4^+$ T cells in HIV-positive people gradually decreases. Generally speaking, the infection is said to have progressed to the late stage, or acquired immune deficiency syndrome (AIDS), when the number of $CD4^+$ cells/mm^3 falls below 200. It is challenging for the body to fight off infections and illnesses when the immune system is compromised. The immune system consists of two main arms: antibody immunity, which is composed of B cells that produce antibodies to neutralize HIV-1 particles; and cytotoxic T lymphocyte (CTL) immunity, which is primarily composed of CTLs specific to viral antigens that kill infected cells. Antiretroviral medications have been used to treat HIV-1 patients for the past 20 years, and while there is currently no cure for AIDS, they have been proven to be effective in managing the virus and restoring the body's immune system [38]. HIV-1 may spread through three major channels. First, there is sexual transmission; being sick is more likely when there are several partners or when there is promiscuity. It will spread through intrauterine infection, delivery, nursing, and other methods after mother-to-child transmission. The third kind of transmission involves sharing needles, sharing toiletries, iatrogenic infections, and blood transfusions, among other methods [5].

Viral infection dynamics have been mathematically modeled, which has helped to clarify the intricate relationship between immune response and viral infection. Mathematical models have been used to study the dynamic characteristics of HIV-1 infection [40]. A fundamental model for HIV-1 dynamics inside the host was developed by Nowak and Bangham [39], and it depicts the interactions between uninfected $CD4^+T$ cells (T), infected cells (T^*), and free HIV-1 particles (H). The model has now been expanded in a number of ways, including the inclusion of the effects of the CTL response [6, 10, 39, 48, 56] and the antibody response [11, 36, 45, 57, 58, 67]. Wodarz [59] studied a viral dynamics model that included both CTL and antibody immunity as:

$$\frac{dT}{dt} = \alpha - \xi_T T - \gamma_1 TH, \tag{1.1}$$

$$\frac{dT^*}{dt} = \gamma_1 TH - \xi_{T^*} T^* - \lambda T^* K, \tag{1.2}$$

$$\frac{dH}{dt} = \beta T^* - \xi_H H - \psi AH, \tag{1.3}$$

$$\frac{dK}{dt} = \sigma T^* K - \xi_K K, \tag{1.4}$$

$$\frac{dA}{dt} = \rho AH - \xi_A A, \tag{1.5}$$

where $T = T(t)$, $T^* = T^*(t)$, $C = C(t)$, $H = H(t)$, $K = K(t)$, and $A = A(t)$ are the concentrations of uninfected $CD4^+T$ cells, infected $CD4^+T$ cells, free HIV-1 particles, CTLs, and antibodies at time t, respectively. The production rate of uninfected $CD4^+T$ cells is denoted by α. The $CD4^+T$ cells infection rate by free HIV-1 particles is indicated by $\gamma_1 TH$. This mode of infection is called virus-to-cell transmission (or viral infection). The rate of free HIV-1 production from infected cells is represented by βT^*. The proliferation rates of CTLs and antibodies are denoted, respectively, by $\sigma T^* K$ and ρAH. The term $\lambda T^* K$ accounts for the rate at which CTL immune cells kill the infected cells, while ψAH represents the neutralization rate of the HIV-1 particles due to the antibodies. All compartments have natural death rates that are, respectively, $\xi_T T$, $\xi_{T^*} T^*$, $\xi_H H$, $\xi_K K$, and $\xi_A A$.

The following significant characteristics can be taken into consideration while extending model (1.1)-(1.5).

Time delay: There is an intracellular lag between the time a host cell becomes infected and the time that HIV-1 particles are released. According to estimates, it takes around 0.9 days for HIV-1 to enter a $CD4^+$ T cell and start generating new HIV-1 particles [42]. Model (1.1)-(1.5) was expanded by Yan and Wang [62] by adding a discrete time delay for the generation of infected cells. In [51] and [22], two kinds of distributed time delays were added, delay in generation of infected cells, and maturation delay of new virions.

Cellular infection (or cell-to-cell transmission): Numerous studies have demonstrated that HIV-1 may spread directly through the development of virological synapses from an infected cell to an uninfected cell. (see, e.g., [25, 27, 44]). Cellular infection can reduce the time it takes for HIV-1 particles to produce by 0.9 times and enhance HIV-1 fitness by 3.9 times [19]. In [15, 20, 23, 32, 66], model (1.1)-(1.5) was developed by including the cellular infection.

Pyroptosis: It is extremely inflammatory kind of programmed cell death brought on by an abortive HIV-1 infection. It has been observed that, pyroptosis accounts for 95% of the death of $CD4^+$ T cells [12]. Inflammatory cytokines are released during pyroptosis and can lead to more cell death and attract more $CD4^+$ T cells to be infected [12, 50]. Modeling the impact of pyroptosis on the HIV-1 dynamics was studied in [49]. Then the model was extended by including reaction-diffusion [47, 52, 53, 55] and age-structure [61]. Jiang and Zhang [24] examined how pyroptosis-released inflammatory cytokines affected viral infection-related cell death. The model considered two kinds of discrete-time delays. The model introduced in article [24] was expanded by including the influence of (i) CTL response [65]; (ii) CTL response and reaction-diffusion [5]; (iii) both antibody and CTL responses [7, 9].

One of the most effective methods available to researchers for improving their comprehension of viral dynamics and immune system regulation and elimination is global stability analysis of within-host virus dynamics models. Research has been done on the global stability of HIV-1 infection models with inflammatory cytokines, and antibody and CTL responses in [7, 9]. The intracellular time delay was included in the model that was introduced in [9], but the cellular infection mechanism was not. However, in [7], the intracellular time delay was disregarded while the cellular infection process was incorporated. This section examines a model of HIV-1 dynamics that incorporates distributed time delays. It's important to note that dispersed delays are more widely applicable than discrete delays. The assumption made in [65] was that the duration between the virus's entry into the cell and the generation of new immature virions (υ_1) is constant for every cell. Further, the maturation time (υ_2) of every virus is constant. Furthermore, the immune response delay (υ_3) for every CTL is constant. To avoid such (biologically impossible) assumption, several HIV-1 infection models were built by considering the time delay as a random variable extracted from a probability distribution function (see e.g., [8, 13, 37, 60]). Therefore, distributed delays are more widely applicable than discrete delays.

Our aim in this work is to formulate and analyze an HIV-1 infection model that includes the impact of (i) inflammatory cytokines; (ii) both antibody and CTL responses; (iii) two types of distributed-time delays. Prior to finding all equilibria and discussing their existence and global stability, we first examine the essential properties of the model. The global asymptotic stability of all equilibria is demonstrated using the Lyapunov approach. To illustrate the theoretical results, numerical simulations are performed. The collected results are finally addressed.

2. Model formulation

We formulate an HIV-1 dynamics model with inflammatory cytokines, cellular infection, and distributed-time delays as:

$$\frac{dT}{dt} = \alpha - \xi_T T - T\left(\gamma_1 H + \gamma_2 C + \gamma_3 T^*\right), \tag{2.1}$$

$$\frac{dT^*}{dt} = \int_0^{\delta_1} B_1(\upsilon) e^{-\kappa_1 \upsilon} T_\upsilon \left(\gamma_1 H_\upsilon + \gamma_2 C_\upsilon + \gamma_3 T^*_\upsilon\right) d\upsilon - \left(\mu_1 + \xi_{T^*}\right) T^* - \lambda T^* K, \tag{2.2}$$

$$\frac{dC}{dt} = \mu_2 T^* - \xi_C C, \tag{2.3}$$

$$\frac{dH}{dt} = \beta \int_0^{\delta_2} B_2(\upsilon) e^{-\kappa_2 \upsilon} T^*_\upsilon d\upsilon - \xi_H H - \psi A H, \tag{2.4}$$

$$\frac{dK}{dt} = \sigma T^* K - \xi_K K, \tag{2.5}$$

$$\frac{dA}{dt} = \rho AH - \xi_A A. \tag{2.6}$$

Here, we denote $T_\upsilon = T(t-\upsilon)$, $T^*_\upsilon = T^*(t-\upsilon)$, $C_\upsilon = C(t-\upsilon)$, and $H_\upsilon = H(t-\upsilon)$. The term $\gamma_2 TC$ represents the cytokine-enhanced viral infection rate, while $\gamma_3 TT^*$ is the infection rate due to cellular infection. The proptosis-induced death rate of infected cells is $\mu_1 T^*$. The term $T^*\mu_2$ denotes the proliferation rate of inflammatory cytokines from infected cells. There are two distributed-time delays that explain the interval between the moment the viral particle first interacts with $CD4^+$ T and when the newly generated virions mature. A probability distribution function $B_i(\upsilon)$, $i = 1,2$ across the interval $[0,\delta_i]$ is used to randomly select the delay parameter υ, where δ_i is the limit superior of the delay duration. When uninfected $CD4^+T$ cells come into contact with virus particles at time $t-\upsilon$, the likelihood that they will survive for υ time units and get the infection at time t is represented by the factor $B_1(\upsilon)e^{-\kappa_1\upsilon}$. Factor $B_2(\upsilon)e^{-\kappa_2\upsilon}$ shows the likelihood of newly formed immature virions at time $t-\upsilon$ losing υ time units and maturing at time t. Here κ_i, $i = 1,2$ are positive constants. Functions $B_i(\upsilon) > 0$, $i = 1,2$, satisfy

$$\int_0^{\delta_i} B_i(\upsilon)d\upsilon = 1 \quad \text{and} \quad \int_0^{\delta_i} B_i(\upsilon)e^{-u\upsilon}d\upsilon < \infty, \quad u > 0.$$

We denote

$$\tilde{\mathcal{B}}_i(\upsilon) = B_i(\upsilon)e^{-\kappa_i\upsilon}, \qquad \mathcal{B}_i = \int_0^{\delta_i} \tilde{\mathcal{B}}_i(\upsilon)\,d\upsilon, \quad i = 1,2.$$

This gives $0 < \mathcal{B}_i \leqslant 1$. The initial conditions are

$$\begin{aligned} &T(\varkappa) = \varpi_1(\varkappa), \quad T^*(\varkappa) = \varpi_2(\varkappa), \quad C(\varkappa) = \varpi_3(\varkappa), \quad H(\varkappa) = \varpi_4(\varkappa),\\ &K(\varkappa) = \varpi_5(\varkappa), \quad A(\varkappa) = \varpi_6(\varkappa), \quad \varpi_j(\varkappa) \geqslant 0, \qquad\qquad \varkappa \in [-\delta^*, 0],\ j = 1,2,\dots,6, \end{aligned} \tag{2.7}$$

where $\delta^* = \max\{\delta_1,\delta_2\}$, $\varpi_j(\varkappa) \in \mathcal{C}([-\delta^*,0],\mathbb{R}_{\geqslant 0})$, $j = 1,2,\dots,6$ and $\mathcal{C}$ is the Banach space of continuous functions mapping the interval $[-\delta^*,0]$ into $\mathbb{R}_{\geqslant 0}$ with norm $\|\varpi_j\| = \sup_{-\delta^*\leqslant\varepsilon\leqslant 0}|\varpi_j(\varepsilon)|$ for $\varpi_j \in \mathcal{C}$. Therefore, based on the fundamental theory of functional differential equations, we can say that system (2.1)-(2.6) with initial conditions (2.7) has a unique solution [29].

3. Non-negativity and boundedness of solutions

We shall demonstrate in this section that, assuming the initial conditions (2.7), any solution to the model (2.1)-(2.6) is non-negative and ultimately bounded.

Lemma 3.1. *All solutions of the model (2.1)-(2.6) associated with initial conditions (2.7) are non-negative and ultimately bounded.*

Proof. Clearly, $\frac{dT}{dt}|_{T=0} = \alpha > 0$ and hence, $T(t) > 0$ for any $t \geqslant 0$. Moreover, we have

$$\begin{aligned} T^*(t) &= \varpi_2(0)e^{-\int_0^t[(\mu_1+\xi_{T^*})+\lambda K(\ell)]d\ell}\\ &\quad + \int_0^t e^{-\int_\eta^t[(\mu_1+\xi_{T^*})+\lambda K(\ell)]d\ell}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)T(\eta-\upsilon)(\gamma_1 H(\eta-\upsilon)+\gamma_2 C(\eta-\upsilon)+\gamma_3 T^*(\eta-\upsilon))d\upsilon d\eta \geqslant 0,\\ C(t) &= \varpi_3(0)e^{-\xi_C t} + \mu_2\int_0^t e^{-\xi_C(t-\eta)}T^*(\eta)d\eta \geqslant 0,\\ H(t) &= \varpi_4(0)e^{-\int_0^t(\xi_H+\psi A(\ell))d\ell} + \beta\int_0^t e^{-\int_\eta^t(\xi_H+\psi A(\ell))d\ell}\int_0^{\delta_2}\tilde{\mathcal{B}}_2(\upsilon)T^*(\eta-\upsilon)d\upsilon d\eta \geqslant 0,\\ K(t) &= \varpi_5(0)e^{-\int_0^t(\xi_K-\sigma T^*(\ell))d\ell} \geqslant 0,\\ A(t) &= \varpi_6(0)e^{-\int_0^t(\xi_A-\rho H(\ell))d\ell} \geqslant 0, \end{aligned}$$

for any $t \in [0, \delta^*]$. Thus, $(T(t), T^*(t), C(t), H(t), K(t), A(t)) \in \mathbb{R}^6_{\geqslant 0}$ for any $t \geqslant 0$ is obtained using a recursive argument.

Next, we demonstrate the ultimate boundedness of the solutions to the model. Eq. (2.1) gives $\lim\limits_{t\to\infty} \sup T(t) \leqslant \frac{\alpha}{\xi_T}$. Further, we let

$$\Omega_1 = \int_0^{\delta_1} \tilde{\mathcal{B}}_1(\upsilon) T_\upsilon \, d\upsilon + T^* + \frac{\lambda}{\sigma} K.$$

Then, we get

$$\begin{aligned}
\frac{d\Omega_1}{dt} &= \int_0^{\delta_1} \tilde{\mathcal{B}}_1(\upsilon) \left(\alpha - T_\upsilon \left(\xi_T + \gamma_1 H_\upsilon + \gamma_2 C_\upsilon + \gamma_3 T^*_\upsilon\right)\right) d\upsilon \\
&\quad + \int_0^{\delta_1} \tilde{\mathcal{B}}_1(\upsilon) T_\upsilon \left(\gamma_1 H_\upsilon + \gamma_2 C_\upsilon + \gamma_3 T^*_\upsilon\right) d\upsilon - \left(\mu_1 + \xi_{T^*}\right) T^* - \lambda T^* K + \frac{\lambda}{\sigma} \left(\sigma T^* K - \xi_K K\right) \\
&= \alpha \mathcal{B}_1 - \xi_T \int_0^{\delta_1} \tilde{\mathcal{B}}_1(\upsilon) T_\upsilon \, d\upsilon - \left(\mu_1 + \xi_{T^*}\right) T^* - \frac{\lambda \xi_K}{\sigma} K \leqslant \alpha - \rho_1 \Omega_1,
\end{aligned}$$

where $\rho_1 = \min\{\xi_T, \mu_1 + \xi_{T^*}, \xi_K\}$. Thus, $\lim\limits_{t\to\infty} \sup \Omega_1(t) \leqslant L_1$, where $L_1 = \frac{\alpha}{\rho_1}$, and consequently $\lim\limits_{t\to\infty} \sup T^*(t) \leqslant L_1$ and $\lim\limits_{t\to\infty} \sup K(t) \leqslant \frac{\sigma}{\lambda} L_1 = L_2$. Eq. (2.3) implies that

$$\frac{dC}{dt} = \mu_2 T^* - \xi_C C \leqslant \mu_2 L_1 - \xi_C C,$$

which confirms that $\lim\limits_{t\to\infty} \sup C(t) \leqslant L_3$, where $L_3 = \frac{\mu_2 L_1}{\xi_C}$. Further, we assume that $\Omega_2 = H + \frac{\psi}{\rho} A$. Then, from Eqs. (2.4) and (2.6), we have

$$\begin{aligned}
\frac{d\Omega_2}{dt} &= \beta \int_0^{\delta_2} \tilde{\mathcal{B}}_2(\upsilon) T^*_\upsilon d\upsilon - \xi_H H - \psi A H - \frac{\psi}{\rho} \left(\rho A H - \xi_A A\right) \\
&= \beta \int_0^{\delta_2} \tilde{\mathcal{B}}_2(\upsilon) T^*_\upsilon d\upsilon - \xi_H H - \frac{\psi \xi_A}{\rho} A \leqslant \beta L_1 - \rho_2 \Omega_2,
\end{aligned}$$

where $\rho_2 = \min\{\xi_H, \xi_A\}$. Hence, $\lim\limits_{t\to\infty} \sup \Omega_2(t) \leqslant L_4$, where $L_4 = \frac{\beta L_1}{\rho_2}$. Therefore, we can obtain that $\lim\limits_{t\to\infty} \sup H(t) \leqslant L_4$, and $\lim\limits_{t\to\infty} \sup A(t) \leqslant \frac{\rho}{\psi} L_3 = L_5$. □

Lemma 3.1 allows one to determine the compact set

$$\Xi = \left\{(T, T^*, C, H, K, A) \in \mathcal{C}^6_{\geqslant 0} : \|T\| \leqslant L_1, \|T^*\| \leqslant L_1, \|K\| \leqslant L_2, \|H\| \leqslant L_4, \|C\| \leqslant L_3, \|A\| \leqslant L_5\right\},$$

which can be easily proved that it is positively invariant with respect to system (2.1)-(2.6).

4. Existence of equilibrium points

In this section, we calculate the potential equilibrium points of system (2.1)-(2.6) and identify the prerequisites for their existence. Any equilibrium point (T, T^*, C, H, K, A) is recognized in the following system of algebraic equations:

$$0 = \alpha - \xi_T T - \gamma_1 T H - \gamma_2 T C - \gamma_3 T T^*, \tag{4.1}$$
$$0 = \mathcal{B}_1 T \left(\gamma_1 H + \gamma_2 C + \gamma_3 T^*\right) - \left(\mu_1 + \xi_{T^*}\right) T^* - \lambda T^* K, \tag{4.2}$$
$$0 = \mu_2 T^* - \xi_C C, \tag{4.3}$$
$$0 = \beta \mathcal{B}_2 T^* - \xi_H H - \psi A H, \tag{4.4}$$

$$0 = \sigma T^* K - \xi_K K, \tag{4.5}$$
$$0 = \rho A H - \xi_A A. \tag{4.6}$$

Eq. (4.6) admits two solutions $A = 0$ and $H = \frac{\xi_A}{\rho}$. First, we consider the case $A = 0$, then from Eqs. (4.1)-(4.5), we get three equilibria for system (2.1)-(2.6) as follows.

(I) Infection-free equilibrium point, $\mathcal{EP}_0 = (T_0, 0, 0, 0, 0, 0)$, where $T_0 = \frac{\alpha}{\xi_T}$. This instance illustrates a healthy state in which there is no infection.

(II) Chronic infection equilibrium point with inactive immune responses, $\mathcal{EP}_1 = (T_1, T_1^*, C_1, H_1, 0, 0)$, where

$$\begin{aligned}
T_1 &= \frac{\xi_H \xi_C (\mu_1 + \xi_{T^*})}{\mathcal{B}_1 (\beta \xi_C \mathcal{B}_2 \gamma_1 + \xi_H \mu_2 \gamma_2 + \xi_C \xi_H \gamma_3)} = \frac{T_0}{\mathfrak{R}_0}, \\
T_1^* &= \frac{\xi_T \xi_C \xi_H}{\gamma_1 \beta \xi_C \mathcal{B}_2 + \gamma_2 \xi_H \mu_2 + \gamma_3 \xi_C \xi_H} (\mathfrak{R}_0 - 1), \\
C_1 &= \frac{\xi_T \xi_H \mu_2}{\gamma_1 \beta \xi_C \mathcal{B}_2 + \gamma_2 \xi_H \mu_2 + \gamma_3 \xi_C \xi_H} (\mathfrak{R}_0 - 1), \\
H_1 &= \frac{\xi_T \xi_C \beta \mathcal{B}_2}{\gamma_1 \beta \xi_C \mathcal{B}_2 + \gamma_2 \xi_H \mu_2 + \gamma_3 \xi_C \xi_H} (\mathfrak{R}_0 - 1),
\end{aligned}$$

where the parameter $\mathfrak{R}_0$ stands for the basic reproduction number and is defined as the number of newly infected CD4$^+$T cells that can develop from a single infected CD4$^+$T cell in the beginning of the infection. It is stated as follows:

$$\begin{aligned}
\mathfrak{R}_0 &= \frac{T_0 \mathcal{B}_1 (\gamma_1 \beta \xi_C \mathcal{B}_2 + \gamma_2 \xi_H \mu_2 + \gamma_3 \xi_C \xi_H)}{\xi_C \xi_H (\mu_1 + \xi_{T^*})} \\
&= \frac{T_0 \gamma_1 \beta \mathcal{B}_1 \mathcal{B}_2}{\xi_H (\mu_1 + \xi_{T^*})} + \frac{T_0 \gamma_2 \mu_2 \mathcal{B}_1}{\xi_C (\mu_1 + \xi_{T^*})} + \frac{T_0 \gamma_3 \mathcal{B}_1}{\mu_1 + \xi_{T^*}} = \mathfrak{R}_{01} + \mathfrak{R}_{02} + \mathfrak{R}_{03}.
\end{aligned}$$

It is notable that the equilibrium $\mathcal{EP}_1$ exists when $\mathfrak{R}_0 > 1$, which in turn determines whether or not a chronic infection can be established. In fact, $\mathfrak{R}_{01}$, $\mathfrak{R}_{02}$, and $\mathfrak{R}_{03}$ refer to the role of viral infection, inflammatory cytokines, and cellular infection, respectively.

(III) Chronic infection equilibrium point with only CTL response, $\mathcal{EP}_2 = (T_2, T_2^*, C_2, H_2, K_2, 0)$, where

$$\begin{aligned}
T_2 &= \frac{\alpha \xi_H \xi_C \sigma}{\xi_T \xi_H \xi_C \sigma + \gamma_1 \beta \xi_C \xi_K \mathcal{B}_2 + \gamma_2 \xi_H \xi_K \mu_2 + \gamma_3 \xi_H \xi_C \xi_K}, \\
T_2^* &= \frac{\xi_K}{\sigma}, \quad C_2 = \frac{\mu_2 \xi_K}{\sigma \xi_C}, \quad H_2 = \frac{\beta \xi_K \mathcal{B}_2}{\xi_H \sigma}, \quad K_2 = \frac{\mu_1 + \xi_{T^*}}{\lambda} \left(\frac{T_2 \mathfrak{R}_0}{T_0} - 1 \right) = \frac{\mu_1 + \xi_{T^*}}{\lambda} (\mathfrak{R}_1 - 1),
\end{aligned}$$

where

$$\mathfrak{R}_1 = \frac{T_2 \mathfrak{R}_0}{T_0} = \frac{\alpha \sigma \mathcal{B}_1 (\gamma_1 \beta \xi_C \mathcal{B}_2 + \gamma_2 \xi_H \mu_2 + \gamma_3 \xi_H \xi_C)}{(\mu_1 + \xi_{T^*}) (\xi_T \xi_H \xi_C \sigma + \gamma_1 \beta \xi_C \xi_K \mathcal{B}_2 + \gamma_2 \xi_H \xi_K \mu_2 + \gamma_3 \xi_H \xi_C \xi_K)}.$$

Here, $\mathfrak{R}_1$ is the CTL response activation number. Obviously, $\mathcal{EP}_2$ exists if $\mathfrak{R}_1 > 1$. Depending on the value of the parameter $\mathfrak{R}_1$, the CTL response is either activated or not.

Now, we consider the case when $H = \frac{\xi_A}{\rho}$. Then from Eqs. (4.1)-(4.5), we derive two equilibrium points as follows.

(IV) Chronic infection equilibrium point with only antibody response, $\mathcal{EP}_3 = (T_3, T_3^*, C_3, H_3, 0, A_3)$, where

$$T_3 = \frac{\alpha \rho \mu_2}{\xi_T \rho \mu_2 + \gamma_1 \xi_A \mu_2 + \gamma_2 \rho \mu_2 C_3 + \gamma_3 \rho \xi_C C_3}, \quad T_3^* = \frac{\xi_C}{\mu_2} C_3, \quad H_3 = \frac{\xi_A}{\rho}, \quad A_3 = \frac{\xi_H}{\psi} \left(\frac{\beta \xi_C \rho \mathcal{B}_2}{\xi_H \xi_A \mu_2} C_3 - 1 \right),$$

where compartment C_3 satisfies the following quadratic equation:

$$\theta_2 C_3^2 + \theta_1 C_3 + \theta_0 = 0, \tag{4.7}$$

and

$$\begin{aligned}\theta_2 &= \rho\xi_C\left(\mu_1+\xi_{T^*}\right)\left(\gamma_3\xi_C+\gamma_2\mu_2\right),\\ \theta_1 &= -\mu_2\left(\left(\gamma_2\mu_2+\gamma_3\xi_C\right)\mathcal{B}_1\alpha\rho-\left(\mu_1+\xi_{T^*}\right)\left(\xi_T\rho+\gamma_1\xi_A\right)\xi_C\right),\\ \theta_0 &= -\gamma_1\alpha\mu_2^2\xi_A\mathcal{B}_1.\end{aligned}$$

Because, $\theta_2 > 0$ and $\theta_0 < 0$, then $\theta_1^2 - 4\theta_0\theta_2 > 0$ and there are two distinct real roots of Eq. (4.7). The positive root is

$$C_3 = \frac{-\theta_1+\sqrt{\theta_1^2-4\theta_0\theta_2}}{2\theta_2}.$$

Thus, if $\frac{\beta\xi_C\rho\mathcal{B}_2C_3}{\xi_H\xi_A\mu_2} > 1$, then $T_3 > 0$, $T_3^* > 0$, and $A_3 > 0$. The antibody response activation number is now defined as follows:

$$\mathfrak{R}_2 = \frac{\beta\xi_C\rho\mathcal{B}_2}{\xi_H\xi_A\mu_2}C_3.$$

Thus, $A_3 = \frac{\xi_H}{\psi}\left(\mathfrak{R}_2-1\right)$. Depending on the value $\mathfrak{R}_2$, the antibody response is either initiated or not. Therefore, the existence of the equilibrium $\mathcal{EP}_3$ is ensured by the condition $\mathfrak{R}_2$ is greater than 1.

(V) Chronic infection equilibrium point with both CTL and antibody responses, $\mathcal{EP}_4 = (T_4, T_4^*, C_4, H_4, K_4, A_4)$, where

$$\begin{aligned}T_4 &= \frac{\alpha\rho\xi_C\sigma}{\xi_T\xi_C\sigma\rho+\gamma_1\xi_C\xi_A\sigma+\gamma_2\rho\xi_K\mu_2+\gamma_3\rho\xi_C\xi_K},\\ T_4^* &= \frac{\xi_K}{\sigma},\quad C_4 = \frac{\xi_K\mu_2}{\xi_C\sigma},\quad H_4 = \frac{\xi_A}{\rho},\quad K_4 = \frac{\mu_1+\xi_{T^*}}{\lambda}\left(\mathfrak{R}_4-1\right),\quad A_4 = \frac{\xi_H}{\psi}\left(\mathfrak{R}_3-1\right),\end{aligned}$$

where $\mathfrak{R}_3$ and $\mathfrak{R}_4$ represent the antibody and CTL immunity competitive reproductive numbers, respectively, and they are given as

$$\mathfrak{R}_3 = \frac{\xi_K\rho\beta\mathcal{B}_2}{\xi_H\xi_A\sigma},\qquad \mathfrak{R}_4 = \frac{\alpha\sigma\mathcal{B}_1\left(\gamma_1\xi_C\xi_A\sigma+\rho\gamma_2\xi_K\mu_2+\rho\gamma_3\xi_C\xi_K\right)}{\xi_K\left(\mu_1+\xi_{T^*}\right)\left(\xi_T\xi_C\rho\sigma+\gamma_1\xi_C\xi_A\sigma+\gamma_2\rho\xi_K\mu_2+\gamma_3\rho\xi_C\xi_K\right)}.$$

The effectiveness of the CTL and antibody immunological responses is determined by parameters $\mathfrak{R}_3$ and $\mathfrak{R}_4$. Therefore, the existence of the equilibrium $\mathcal{EP}_4$ is ensured by the condition $\mathfrak{R}_3$ and $\mathfrak{R}_4$ are greater than 1.

After putting the talks above into summary, we get at the following lemma.

Lemma 4.1. *There exist five threshold parameters $\mathfrak{R}_0$, $\mathfrak{R}_1$, $\mathfrak{R}_2$, $\mathfrak{R}_3$, and $\mathfrak{R}_4$ such that*

(i) *If $\mathfrak{R}_0 \leqslant 1$, then model (2.1)-(2.6) always has one infection-free equilibrium point, $\mathcal{EP}_0 = (T_0, 0, 0, 0, 0, 0)$.*

(ii) *If $\mathfrak{R}_0 > 1$, then model (2.1)-(2.6) has a chronic infection equilibrium point with inactive immune responses, $\mathcal{EP}_1 = (T_1, T_1^*, C_1, H_1, 0, 0)$.*

(iii) *If $\mathfrak{R}_1 > 1$, then model (2.1)-(2.6) has a chronic infection equilibrium point with only CTL response, $\mathcal{EP}_2 = (T_2, T_2^*, C_2, H_2, K_2, 0)$.*

(iv) *If $\mathfrak{R}_2 > 1$, then model (2.1)-(2.6) has a chronic infection equilibrium point with only antibody response, $\mathcal{EP}_3 = (T_3, T_3^*, C_3, H_3, 0, A_3)$.*

(v) *If $\mathfrak{R}_3 > 1$ and $\mathfrak{R}_4 > 1$, then model (2.1)-(2.6) has a chronic infection equilibrium point with both CTL and antibody responses, $\mathcal{EP}_4 = (T_4, T_4^*, C_4, H_4, K_4, A_4)$.*

5. Global stability

In this part, the global asymptotic stability properties of all equilibrium points will be investigated. For this purpose, we define $\chi(\varkappa) = \varkappa - 1 - \ln(\varkappa)$, $\chi(\varkappa) \geqslant 0$ for all $\varkappa > 0$ and $\chi(1) = 0$. In addition, we define a Lyapunov function candidate $\Phi_i(T, T^*, C, H, K, A)$. Define

$$\Gamma_i = \left\{ (T, T^*, C, H, K, A) : \frac{d\Phi_i}{dt} = 0 \right\}, \qquad i = 0, 1, \ldots, 4,$$

and Γ_i' is the largest invariant subset of Γ_i. Following the investigations in [28, 37, 61], we formulate Lyapunov functions in the ensuing theorems.

Theorem 5.1. *If $\mathfrak{R}_0 \leqslant 1$, then $\mathcal{EP}_0\,(T, 0, 0, 0, 0, 0)$ is globally asymptotically stable (G.A.S).*

Proof. Let $\Phi_0(T, T^*, C, H, K, A)$ be given as:

$$\begin{aligned}\Phi_0 = {} & T_0\chi\left(\frac{T}{T_0}\right) + \frac{1}{\mathcal{B}_1}T^* + \frac{\gamma_2 T_0}{\xi_C}C + \frac{\gamma_1 T_0}{\xi_H}H + \frac{\lambda}{\sigma\mathcal{B}_1}K + \frac{\gamma_1 T_0\psi}{\rho\xi_H}A \\ & + \frac{1}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\int_{t-\upsilon}^{t} T(u)\left(\gamma_1 H(u) + \gamma_2 C(u) + \gamma_3 T^*(u)\right)du\,d\upsilon + \frac{\gamma_1 T_0\beta}{\xi_H}\int_0^{\delta_2}\tilde{\mathcal{B}}_2(\upsilon)\int_{t-\upsilon}^{t} T^*(u)\,du\,d\upsilon.\end{aligned}$$

Clearly, $\Phi_0(T, T^*, C, H, K, A) > 0$ for any $T, T^*, C, H, K, A > 0$ and $\Phi_0 = 0$ at $\mathcal{EP}_0$. Calculating $\frac{d\Phi_0}{dt}$ along the solutions of model (2.1)-(2.6) we get

$$\begin{aligned}\frac{d\Phi_0}{dt} = {} & \left(1 - \frac{T_0}{T}\right)\frac{dT}{dt} + \frac{1}{\mathcal{B}_1}\frac{dT^*}{dt} + \frac{\gamma_2 T_0}{\xi_C}\frac{dC}{dt} + \frac{\gamma_1 T_0}{\xi_H}\frac{dH}{dt} + \frac{\lambda}{\sigma\mathcal{B}_1}\frac{dK}{dt} + \frac{\gamma_1 T_0\psi}{\rho\xi_H}\frac{dA}{dt} \\ & + \frac{1}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\left[T\left(\gamma_1 H + \gamma_2 C + \gamma_3 T^*\right) - T_\upsilon\left(\gamma_1 H_\upsilon + \gamma_2 C_\upsilon + \gamma_3 T^*_\upsilon\right)\right]d\upsilon \\ & + \frac{\gamma_1 T_0\beta}{\xi_H}\int_0^{\delta_2}\tilde{\mathcal{B}}_2(\upsilon)\left(T^* - T^*_\upsilon\right)d\upsilon.\end{aligned}$$

Using model (2.1)-(2.6) we get

$$\begin{aligned}\frac{d\Phi_0}{dt} = {} & \left(1 - \frac{T_0}{T}\right)\left(\alpha - \xi_T T - \gamma_1 T H - \gamma_2 T C - \gamma_3 T T^*\right) \\ & + \frac{1}{\mathcal{B}_1}\left(\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)T_\upsilon\left(\gamma_1 H_\upsilon + \gamma_2 C_\upsilon + \gamma_3 T^*_\upsilon\right)d\upsilon - \left(\mu_1 + \xi_{T^*}\right)T^* - \lambda T^* K\right) \\ & + \frac{\gamma_2 T_0}{\xi_C}\left(\mu_2 T^* - \xi_C C\right) + \frac{\gamma_1 T_0}{\xi_H}\left(\beta\int_0^{\delta_2}\tilde{\mathcal{B}}_2(\upsilon)T^*_\upsilon d\upsilon - \xi_H H - \psi A H\right) + \frac{\lambda}{\sigma\mathcal{B}_1}\left(\sigma T^* K - \xi_K K\right) \\ & + \frac{\gamma_1 T_0\psi}{\rho\xi_H}\left(\rho A H - \xi_A A\right) + \frac{1}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)T\left(\gamma_1 H + \gamma_2 C + \gamma_3 T^*\right)d\upsilon \\ & - \frac{1}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)T_\upsilon\left(\gamma_1 H_\upsilon + \gamma_2 C_\upsilon + \gamma_3 T^*_\upsilon\right)d\upsilon + \frac{\gamma_1 T_0\beta}{\xi_H}\int_0^{\delta_2}\tilde{\mathcal{B}}_2(\upsilon)\left(T^* - T^*_\upsilon\right)d\upsilon.\end{aligned}$$

Collecting terms we obtain

$$\frac{d\Phi_0}{dt} = \left(1 - \frac{T_0}{T}\right)\left(\alpha - \xi_T T\right) + \left(\frac{\gamma_1 T_0\beta\mathcal{B}_2}{\xi_H} + \frac{\gamma_2 T_0\mu_2}{\xi_C} + \gamma_3 T_0 - \frac{\mu_1 + \xi_{T^*}}{\mathcal{B}_1}\right)T^* - \frac{\lambda\xi_K}{\sigma\mathcal{B}_1}K - \frac{\gamma_1 T_0\psi\xi_A}{\rho\xi_H}A. \quad (5.1)$$

Substituting the value $\alpha = \xi_T T_0$ in Eq. (5.1), we obtain

$$\frac{d\Phi_0}{dt} = -\xi_T\frac{(T - T_0)^2}{T} + \frac{\mu_1 + \xi_{T^*}}{\mathcal{B}_1}\left(\frac{T_0\mathcal{B}_1\left(\gamma_1\beta\xi_C\mathcal{B}_2 + \gamma_2\xi_H\mu_2 + \gamma_3\xi_C\xi_H\right)}{\xi_C\xi_H\left(\mu_1 + \xi_{T^*}\right)} - 1\right)T^* - \frac{\lambda\xi_K}{\sigma\mathcal{B}_1}K - \frac{\gamma_1 T_0\psi\xi_A}{\rho\xi_H}A$$

$$= -\xi_T \frac{(T-T_0)^2}{T} + \frac{\mu_1 + \xi_{T^*}}{\mathcal{B}_1}(\mathfrak{R}_0 - 1)T^* - \frac{\lambda \xi_K}{\sigma \mathcal{B}_1} K - \frac{\gamma_1 T_0 \psi \xi_A}{\rho \xi_H} A.$$

If $\mathfrak{R}_0 \leqslant 1$, then $\frac{d\Phi_0}{dt} \leqslant 0$ for any $T, T^*, C, H, K, A > 0$. Moreover, $\frac{d\Phi_0}{dt} = 0$ when $T = T_0$, $T^* = 0$, $K = 0$, and $A = 0$. System's solutions approach to Γ_0', which has elements with $T(t) = T_0$, and $T^*(t) = K(t) = A(t) = 0$ ([21]). From Eq. (2.1), we have

$$0 = \frac{dT}{dt} = \alpha - \xi_T T_0 - \gamma_1 T_0 H - \gamma_2 T_0 C, \quad \text{for any } t.$$

Using $T_0 = \frac{\alpha}{\xi_T}$, we get

$$0 = \gamma_1 H + \gamma_2 C \implies H(t) = C(t) = 0 \text{ for any } t.$$

Hence $\Gamma_0' = \{\mathcal{EP}_0\}$ and LaSalle's invariance principle (L.I.P.) shows that $\mathcal{EP}_0$ is G.A.S ([26]). □

The following equalities will be used for the following theorems:

$$\begin{aligned}
\ln\left(\frac{T_\upsilon H_\upsilon}{TH}\right) &= \ln\left(\frac{T_i^* T_\upsilon H_\upsilon}{T^* T_i H_i}\right) + \ln\left(\frac{T_i}{T}\right) + \ln\left(\frac{T^* H_i}{T_i^* H}\right),\\
\ln\left(\frac{T_\upsilon^*}{T^*}\right) &= \ln\left(\frac{T_\upsilon^* H_i}{T_i^* H}\right) + \ln\left(\frac{T_i^* H}{T^* H_i}\right),\\
\ln\left(\frac{T_\upsilon C_\upsilon}{TC}\right) &= \ln\left(\frac{T_i^* T_\upsilon C_\upsilon}{T^* T_i C_i}\right) + \ln\left(\frac{T_i}{T}\right) + \ln\left(\frac{T^* C_i}{T_i^* C}\right),\\
\ln\left(\frac{T_\upsilon T_\upsilon^*}{TT^*}\right) &= \ln\left(\frac{T_i}{T}\right) + \ln\left(\frac{T_i^* T_\upsilon T_\upsilon^*}{T^* T_i T_i^*}\right), \qquad i = 1,2,3,4.
\end{aligned} \tag{5.2}$$

In addition

$$\begin{aligned}
&\frac{\gamma_1 T_i H_i}{\mathcal{B}_1}\int_0^{\delta_1} \tilde{\mathcal{B}}_1(\upsilon)\ln\left(\frac{T_\upsilon H_\upsilon}{TH}\right)d\upsilon + \frac{\gamma_1 T_i H_i}{\mathcal{B}_2}\int_0^{\delta_2} \tilde{\mathcal{B}}_2(\upsilon)\ln\left(\frac{T_\upsilon^*}{T^*}\right)d\upsilon\\
&= \frac{\gamma_1 T_i H_i}{\mathcal{B}_1}\int_0^{\delta_1} \tilde{\mathcal{B}}_1(\upsilon)\left(\ln\left(\frac{T_i^* T_\upsilon H_\upsilon}{T^* T_i H_i}\right) + \ln\left(\frac{T_i}{T}\right) + \ln\left(\frac{T^* H_i}{T_i^* H}\right)\right)d\upsilon\\
&\quad + \frac{\gamma_1 T_i H_i}{\mathcal{B}_2}\int_0^{\delta_2} \tilde{\mathcal{B}}_2(\upsilon)\left(\ln\left(\frac{T_\upsilon^* H_i}{T_i^* H}\right) + \ln\left(\frac{T_i^* H}{T^* H_i}\right)\right)d\upsilon\\
&= \frac{\gamma_1 T_i H_i}{\mathcal{B}_1}\int_0^{\delta_1} \tilde{\mathcal{B}}_1(\upsilon)\left(\ln\left(\frac{T_i^* T_\upsilon H_\upsilon}{T^* T_i H_i}\right) + \ln\left(\frac{T_i}{T}\right)\right)d\upsilon + \frac{\gamma_1 T_i H_i}{\mathcal{B}_2}\int_0^{\delta_2} \tilde{\mathcal{B}}_2(\upsilon)\ln\left(\frac{T_\upsilon^* H_i}{T_i^* H}\right)d\upsilon.
\end{aligned} \tag{5.3}$$

Theorem 5.2. *If $\mathfrak{R}_0 > 1$, $\mathfrak{R}_3 \leqslant 1$, and $\mathfrak{R}_4 \leqslant 1$, then $\mathcal{EP}_1$ is G.A.S.*

Proof. Define $\Phi_1(T, T^*, C, H, K, A)$ as:

$$\begin{aligned}
\Phi_1 &= T_1\chi\left(\frac{T}{T_1}\right) + \frac{1}{\mathcal{B}_1}T_1^*\chi\left(\frac{T^*}{T_1^*}\right) + \frac{\gamma_2 T_1 C_1}{\xi_C}\chi\left(\frac{C}{C_1}\right) + \frac{\gamma_1 T_1 H_1}{\xi_H}\chi\left(\frac{H}{H_1}\right) + \frac{\lambda}{\sigma\mathcal{B}_1}K + \frac{\gamma_1 T_1 \psi}{\xi_H \rho}A\\
&\quad + \frac{\gamma_1 T_1 H_1}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\int_{t-\upsilon}^{t}\chi\left(\frac{T(u)H(u)}{T_1 H_1}\right)du d\upsilon + \frac{\gamma_2 T_1 C_1}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\int_{t-\upsilon}^{t}\chi\left(\frac{T(u)C(u)}{T_1 C_1}\right)du d\upsilon\\
&\quad + \frac{\gamma_3 T_1 T_1^*}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\int_{t-\upsilon}^{t}\chi\left(\frac{T(u)T^*(u)}{T_1 T_1^*}\right)du d\upsilon + \frac{\beta\gamma_1 T_1 T_1^*}{\xi_H}\int_0^{\delta_2}\tilde{\mathcal{B}}_2(\upsilon)\int_{t-\upsilon}^{t}\chi\left(\frac{T^*(u)}{T_1^*}\right)du d\upsilon.
\end{aligned}$$

We calculate $\frac{d\Phi_1}{dt}$ as:

$$\frac{d\Phi_1}{dt} = \left(1 - \frac{T_1}{T}\right)(\alpha - \xi_T T - \gamma_1 TH - \gamma_2 TC - \gamma_3 TT^*) + \frac{1}{\mathcal{B}_1}\left(1 - \frac{T_1^*}{T^*}\right)$$

$$
\begin{aligned}
&\times\left(\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)T_\upsilon\left(\gamma_1H_\upsilon+\gamma_2C_\upsilon+\gamma_3T_\upsilon^*\right)d\upsilon-\left(\mu_1+\xi_{T^*}\right)T^*-\lambda T^*K\right)\\
&+\frac{\gamma_2T_1}{\xi_C}\left(1-\frac{C_1}{C}\right)\left(\mu_2T^*-\xi_CC\right)+\frac{\gamma_1T_1}{\xi_H}\left(1-\frac{H_1}{H}\right)\left(\beta\int_0^{\delta_2}\tilde{\mathcal{B}}_2(\upsilon)T_\upsilon^*d\upsilon-\xi_HH-\psi AH\right)\\
&+\frac{\lambda}{\sigma\mathcal{B}_1}\left(\sigma T^*K-\xi_KK\right)+\frac{\gamma_1T_1\psi}{\xi_H\rho}\left(\rho AH-\xi_AA\right)\\
&+\frac{\gamma_1T_1H_1}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\left(\frac{TH}{T_1H_1}-\frac{T_\upsilon H_\upsilon}{T_1H_1}+\ln\left(\frac{T_\upsilon H_\upsilon}{TH}\right)\right)d\upsilon\\
&+\frac{\gamma_2T_1C_1}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\left(\frac{TC}{T_1C_1}-\frac{T_\upsilon C_\upsilon}{T_1C_1}+\ln\left(\frac{T_\upsilon C_\upsilon}{TC}\right)\right)d\upsilon\\
&+\frac{\gamma_3T_1T_1^*}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\left(\frac{TT^*}{T_1T_1^*}-\frac{T_\upsilon T_\upsilon^*}{T_1T_1^*}+\ln\left(\frac{T_\upsilon T_\upsilon^*}{TT^*}\right)\right)d\upsilon\\
&+\frac{\beta\gamma_1T_1T_1^*}{\xi_H}\int_0^{\delta_2}\tilde{\mathcal{B}}_2(\upsilon)\left(\frac{T^*}{T_1^*}-\frac{T_\upsilon^*}{T_1^*}+\ln\left(\frac{T_\upsilon^*}{T^*}\right)\right)d\upsilon.
\end{aligned}
\tag{5.4}
$$

Summing terms of Eq. (5.4), we derive

$$
\begin{aligned}
\frac{d\Phi_1}{dt}=&\left(1-\frac{T_1}{T}\right)\left(\alpha-\xi_TT\right)+\gamma_3T_1T^*-\frac{\gamma_1}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\frac{T_1^*T_\upsilon H_\upsilon}{T^*}d\upsilon-\frac{\gamma_2}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\frac{T_1^*T_\upsilon C_\upsilon}{T^*}d\upsilon\\
&-\frac{\gamma_3}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\frac{T_1^*T_\upsilon T_\upsilon^*}{T^*}d\upsilon-\frac{1}{\mathcal{B}_1}\left(1-\frac{T_1^*}{T^*}\right)\left(\mu_1+\xi_{T^*}\right)T^*+\frac{1}{\mathcal{B}_1}\lambda T_1^*K+\frac{\gamma_2T_1}{\xi_C}\left(1-\frac{C_1}{C}\right)\mu_2T^*\\
&+\gamma_2T_1C_1-\frac{\gamma_1T_1}{\xi_H}\beta\int_0^{\delta_2}\tilde{\mathcal{B}}_2(\upsilon)\frac{T_\upsilon^*H_1}{H}d\upsilon+\gamma_1T_1H_1+\frac{\psi\gamma_1T_1H_1}{\xi_H}A\\
&-\frac{\lambda\xi_K}{\sigma\mathcal{B}_1}K-\frac{\gamma_1T_1\xi_A\psi}{\xi_H\rho}A+\frac{\gamma_1T_1H_1}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\ln\left(\frac{T_\upsilon H_\upsilon}{TH}\right)d\upsilon\\
&+\frac{\gamma_2T_1C_1}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\ln\left(\frac{T_\upsilon C_\upsilon}{TC}\right)d\upsilon+\frac{\gamma_3T_1T_1^*}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\ln\left(\frac{T_\upsilon T_\upsilon^*}{TT^*}\right)d\upsilon\\
&+\frac{\beta\mathcal{B}_2\gamma_1T_1T^*}{\xi_H}+\frac{\beta\gamma_1T_1T_1^*}{\xi_H}\int_0^{\delta_2}\tilde{\mathcal{B}}_2(\upsilon)\ln\left(\frac{T_\upsilon^*}{T^*}\right)d\upsilon.
\end{aligned}
$$

Using the following conditions for equilibrium $\mathcal{EP}_1$:

$$
\begin{aligned}
&\alpha=\xi_TT_1+\gamma_1T_1H_1+\gamma_2T_1C_1+\gamma_3T_1T_1^*,\\
&\frac{\left(\mu_1+\xi_{T^*}\right)T_1^*}{\mathcal{B}_1}=\gamma_1T_1H_1+\gamma_2T_1C_1+\gamma_3T_1T_1^*,\quad\frac{\mu_2}{\xi_C}=\frac{C_1}{T_1^*},\quad\frac{\beta}{\xi_H}=\frac{H_1}{\mathcal{B}_2T_1^*}.
\end{aligned}
$$

Then, we obtain

$$
\begin{aligned}
\frac{d\Phi_1}{dt}=&\left(1-\frac{T_1}{T}\right)\left(\xi_TT_1-\xi_TT\right)+\gamma_1T_1H_1\left(1-\frac{T_1}{T}\right)+\gamma_2T_1C_1\left(1-\frac{T_1}{T}\right)\\
&+\gamma_3T_1T_1^*\left(1-\frac{T_1}{T}\right)-\frac{\gamma_1T_1H_1}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\frac{T_1^*T_\upsilon H_\upsilon}{T^*T_1H_1}d\upsilon-\frac{\gamma_2T_1C_1}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\frac{T_1^*T_\upsilon C_\upsilon}{T^*T_1C_1}d\upsilon\\
&-\frac{\gamma_3T_1T_1^*}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\frac{T_1^*T_\upsilon T_\upsilon^*}{T^*T_1T_1^*}d\upsilon+\gamma_1T_1H_1+\gamma_2T_1C_1+\gamma_3T_1T_1^*-\gamma_2T_1C_1\frac{T^*C_1}{T_1^*C}+\gamma_2T_1C_1\\
&-\frac{\gamma_1T_1H_1}{\mathcal{B}_2}\int_0^{\delta_2}\tilde{\mathcal{B}}_2(\upsilon)\frac{T_\upsilon^*H_1}{T_1^*H}d\upsilon+\gamma_1T_1H_1+\left(\frac{1}{\mathcal{B}_1}\lambda T_1^*-\frac{\lambda\xi_K}{\sigma\mathcal{B}_1}\right)K+\left(\frac{\psi\gamma_1T_1H_1}{\xi_H}-\frac{\gamma_1T_1\xi_A\psi}{\xi_H\rho}\right)A
\end{aligned}
$$

$$+\frac{\gamma_1 T_1 H_1}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\ln\left(\frac{T_\upsilon H_\upsilon}{TH}\right)d\upsilon+\frac{\gamma_2 T_1 C_1}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\ln\left(\frac{T_\upsilon C_\upsilon}{TC}\right)d\upsilon$$
$$+\frac{\gamma_3 T_1 T_1^*}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\ln\left(\frac{T_\upsilon T_\upsilon^*}{TT^*}\right)d\upsilon+\frac{\gamma_1 T_1 H_1}{\mathcal{B}_2}\int_0^{\delta_2}\tilde{\mathcal{B}}_2(\upsilon)\ln\left(\frac{T_\upsilon^*}{T^*}\right)d\upsilon.$$

Using the equalities represented in Eqs. (5.2) and (5.3) in case of $i=1$, we get

$$\begin{aligned}\frac{d\Phi_1}{dt}=&\left(1-\frac{T_1}{T}\right)(\xi_T T_1-\xi_T T)-\frac{\gamma_1 T_1 H_1}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\left(\frac{T_1}{T}-1-\ln\left(\frac{T_1}{T}\right)\right)d\upsilon\\
&-\frac{\gamma_1 T_1 H_1}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\left(\frac{T_1^* T_\upsilon H_\upsilon}{T^* T_1 H_1}-1-\ln\left(\frac{T_1^* T_\upsilon H_\upsilon}{T^* T_1 H_1}\right)\right)d\upsilon\\
&-\frac{\gamma_1 T_1 H_1}{\mathcal{B}_2}\int_0^{\delta_2}\tilde{\mathcal{B}}_2(\upsilon)\left(\frac{T_\upsilon^* H_1}{T_1^* H}-1-\ln\left(\frac{T_\upsilon^* H_1}{T_1^* H}\right)\right)d\upsilon-\frac{\gamma_2 T_1 C_1}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\left(\frac{T_1}{T}-1-\ln\left(\frac{T_1}{T}\right)\right)d\upsilon\\
&-\frac{\gamma_2 T_1 C_1}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\left(\frac{T_1^* T_\upsilon C_\upsilon}{T^* T_1 C_1}-1-\ln\left(\frac{T_1^* T_\upsilon C_\upsilon}{T^* T_1 C_1}\right)\right)d\upsilon\\
&-\frac{\gamma_2 T_1 C_1}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\left(\frac{T^* C_1}{T_1^* C}-1-\ln\left(\frac{T^* C_1}{T_1^* C}\right)\right)d\upsilon-\frac{\gamma_3 T_1 T_1^*}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\left(\frac{T_1}{T}-1-\ln\left(\frac{T_1}{T}\right)\right)d\upsilon\\
&-\frac{\gamma_3 T_1 T_1^*}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\left(\frac{T_1^* T_\upsilon T_\upsilon^*}{T^* T_1 T_1^*}-1-\ln\left(\frac{T_1^* T_\upsilon T_\upsilon^*}{T^* T_1 T_1^*}\right)\right)d\upsilon\\
&+\left(\frac{\lambda T_1^*}{\mathcal{B}_1}-\frac{\lambda\xi_K}{\sigma\mathcal{B}_1}\right)K+\left(\frac{\psi\gamma_1 T_1 H_1}{\xi_H}-\frac{\gamma_1 T_1\xi_A\psi}{\xi_H\rho}\right)A.\end{aligned}\tag{5.5}$$

In fact, we have

$$\frac{\lambda T_1^*}{\mathcal{B}_1}-\frac{\lambda\xi_K}{\sigma\mathcal{B}_1}=\frac{\lambda}{\mathcal{B}_1}(T_1^*-T_4^*),\qquad \frac{\psi\gamma_1 T_1 H_1}{\xi_H}-\frac{\gamma_1 T_1\xi_A\psi}{\xi_H\rho}=\frac{\gamma_1 T_1\psi}{\xi_H}\left(H_1-\frac{\xi_A}{\rho}\right)=\frac{\gamma_1 T_1\psi}{\xi_H}(H_1-H_4).$$

Therefore, Eq. (5.5) becomes

$$\begin{aligned}\frac{d\Phi_1}{dt}=&-\xi_T\frac{(T-T_1)^2}{T}-\frac{\gamma_1 T_1 H_1}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\left(\chi\left(\frac{T_1}{T}\right)+\chi\left(\frac{T_1^* T_\upsilon H_\upsilon}{T^* T_1 H_1}\right)\right)d\upsilon\\
&-\frac{\gamma_1 T_1 H_1}{\mathcal{B}_2}\int_0^{\delta_2}\tilde{\mathcal{B}}_2(\upsilon)\chi\left(\frac{T_\upsilon^* H_1}{T_1^* H}\right)d\upsilon-\frac{\gamma_2 T_1 C_1}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\left(\chi\left(\frac{T_1}{T}\right)+\chi\left(\frac{T_1^* T_\upsilon C_\upsilon}{T^* T_1 C_1}\right)+\chi\left(\frac{T^* C_1}{T_1^* C}\right)\right)d\upsilon\\
&-\frac{\gamma_3 T_1 T_1^*}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\left(\chi\left(\frac{T_1}{T}\right)+\chi\left(\frac{T_1^* T_\upsilon T_\upsilon^*}{T^* T_1 T_1^*}\right)\right)d\upsilon+\frac{\lambda}{\mathcal{B}_1}(T_1^*-T_4^*)K+\frac{\gamma_1 T_1\psi}{\xi_H}(H_1-H_4)A.\end{aligned}$$

If $\mathfrak{R}_3\leqslant 1$, then $\mathcal{EP}_4$ does not exist because $A_4=\frac{\xi_H}{\psi}(\mathfrak{R}_3-1)\leqslant 0$. This ensures that

$$\frac{dA}{dt}=\rho\left(H-\frac{\xi_A}{\rho}\right)A\leqslant 0\Longrightarrow\frac{dA}{dt}=\rho(H-H_4)A\leqslant 0\text{ for any }H,A>0.$$

Further, if $\mathfrak{R}_4\leqslant 1$, then $\mathcal{EP}_4$ does not exist because $K_4=\frac{\mu_1+\xi_{T^*}}{\lambda}(\mathfrak{R}_4-1)\leqslant 0$. This ensures that

$$\frac{dK}{dt}=\sigma\left(T^*-\frac{\xi_K}{\sigma}\right)K\leqslant 0\Longrightarrow\frac{dK}{dt}=\sigma(T^*-T_4^*)K\leqslant 0\text{ for any }T^*,K>0,$$

which implies that $H_1\leqslant H_4$, and $T_1^*\leqslant T_4^*$. So $\frac{d\Phi_1}{dt}\leqslant 0$ for any $T,T^*,C,H,K,A>0$. Moreover, $\frac{d\Phi_1}{dt}=0$ when $T=T_1$, and $K=A=0$. The solutions of system (2.1)-(2.6) approach to Γ_1', which contains elements with $T(t)=T_1$, $K(t)=A(t)=0$, and $\chi=0$ such that

$$\frac{T_1^* T_\upsilon H_\upsilon}{T^* T_1 H_1}=\frac{T_\upsilon^* H_1}{T_1^* H}=\frac{T_1^* T_\upsilon C_\upsilon}{T^* T_1 C_1}=\frac{T^* C_1}{T_1^* C}=\frac{T_1^* T_\upsilon T_\upsilon^*}{T^* T_1 T_1^*}=1,\quad\text{for almost}\quad\upsilon\in[0,\delta^*].\tag{5.6}$$

Because $T(t) = T_1$, then from Eq. (5.6) we get $T^*(t) = T_1^*$, $H(t) = H_1$, and $C(t) = C_1$ for any t. Therefore, $\Gamma_1' = \{\mathcal{EP}_1\}$ and L.I.P shows that $\mathcal{EP}_1$ is G.A.S. □

Theorem 5.3. *If $\Re_1 > 1$ and $\Re_3 \leqslant 1$, then $\mathcal{EP}_2$ is G.A.S.*

Proof. Construct a function $\Phi_2(T, T^*, C, H, K, A)$ as:

$$\begin{aligned}\Phi_2 = {} & T_2\chi\left(\frac{T}{T_2}\right) + \frac{1}{\mathcal{B}_1}T_2^*\chi\left(\frac{T^*}{T_2^*}\right) + \frac{\gamma_2 T_2 C_2}{\xi_C}\chi\left(\frac{C}{C_2}\right) + \frac{\gamma_1 T_2 H_2}{\xi_H}\chi\left(\frac{H}{H_2}\right) + \frac{\lambda K_2}{\sigma\mathcal{B}_1}\chi\left(\frac{K}{K_2}\right) + \frac{\gamma_1 T_2\psi}{\xi_H\rho}A \\ & + \frac{\gamma_1 T_2 H_2}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\int_{t-\upsilon}^{t}\chi\left(\frac{T(u)H(u)}{T_2H_2}\right)du d\upsilon + \frac{\gamma_2 T_2 C_2}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\int_{t-\upsilon}^{t}\chi\left(\frac{T(u)C(u)}{T_2C_2}\right)du d\upsilon \\ & + \frac{\gamma_3 T_2 T_2^*}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\int_{t-\upsilon}^{t}\chi\left(\frac{T(u)T^*(u)}{T_2T_2^*}\right)du d\upsilon + \frac{\beta\gamma_1 T_2 T_2^*}{\xi_H}\int_0^{\delta_2}\tilde{\mathcal{B}}_2(\upsilon)\int_{t-\upsilon}^{t}\chi\left(\frac{T^*(u)}{T_2^*}\right)du d\upsilon.\end{aligned}$$

We calculate $\frac{d\Phi_2}{dt}$ as:

$$\begin{aligned}\frac{d\Phi_2}{dt} = {} & \left(1-\frac{T_2}{T}\right)(\alpha - \xi_T T - \gamma_1 TH - \gamma_2 TC - \gamma_3 TT^*) + \frac{1}{\mathcal{B}_1}\left(1-\frac{T_2^*}{T^*}\right) \\ & \times\left(\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)T_\upsilon(\gamma_1 H_\upsilon + \gamma_2 C_\upsilon + \gamma_3 T_\upsilon^*)\,d\upsilon - (\mu_1 + \xi_{T^*})T^* - \lambda T^* K\right) \\ & + \frac{\gamma_2 T_2}{\xi_C}\left(1-\frac{C_2}{C}\right)(\mu_2 T^* - \xi_C C) + \frac{\gamma_1 T_2}{\xi_H}\left(1-\frac{H_2}{H}\right)\left(\beta\int_0^{\delta_2}\tilde{\mathcal{B}}_2(\upsilon)T_\upsilon^* d\upsilon - \xi_H H - \psi A H\right) \\ & + \frac{\lambda}{\sigma\mathcal{B}_1}\left(1-\frac{K_2}{K}\right)(\sigma T^* K - \xi_K K) + \frac{\gamma_1 T_2\psi}{\xi_H\rho}(\rho A H - \xi_A A) \\ & + \frac{\gamma_1 T_2 H_2}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\left(\frac{TH}{T_2H_2} - \frac{T_\upsilon H_\upsilon}{T_2H_2} + \ln\left(\frac{T_\upsilon H_\upsilon}{TH}\right)\right)d\upsilon \\ & + \frac{\gamma_2 T_2 C_2}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\left(\frac{TC}{T_2C_2} - \frac{T_\upsilon C_\upsilon}{T_2C_2} + \ln\left(\frac{T_\upsilon C_\upsilon}{TC}\right)\right)d\upsilon \\ & + \frac{\gamma_3 T_2 T_2^*}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\left(\frac{TT^*}{T_2T_2^*} - \frac{T_\upsilon T_\upsilon^*}{T_2T_2^*} + \ln\left(\frac{T_\upsilon T_\upsilon^*}{TT^*}\right)\right)d\upsilon \\ & + \frac{\beta\gamma_1 T_2 T_2^*}{\xi_H}\int_0^{\delta_2}\tilde{\mathcal{B}}_2(\upsilon)\left(\frac{T^*}{T_2^*} - \frac{T_\upsilon^*}{T_2^*} + \ln\left(\frac{T_\upsilon^*}{T^*}\right)\right)d\upsilon.\end{aligned} \tag{5.7}$$

Collecting terms of Eq. (5.7), we get

$$\begin{aligned}\frac{d\Phi_2}{dt} = {} & \left(1-\frac{T_2}{T}\right)(\alpha - \xi_T T) + \gamma_3 T_2 T^* - \frac{\gamma_1}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\frac{T_2^* T_\upsilon H_\upsilon}{T^*}d\upsilon - \frac{\gamma_2}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\frac{T_2^* T_\upsilon C_\upsilon}{T^*}d\upsilon \\ & - \frac{\gamma_3}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\frac{T_2^* T_\upsilon T_\upsilon^*}{T^*}d\upsilon - \frac{1}{\mathcal{B}_1}\left(1-\frac{T_2^*}{T^*}\right)(\mu_1 + \xi_{T^*})T^* + \frac{1}{\mathcal{B}_1}\lambda T_2^* K + \frac{\gamma_2 T_2}{\xi_C}\left(1-\frac{C_2}{C}\right)\mu_2 T^* \\ & + \gamma_2 T_2 C_2 - \frac{\gamma_1 T_2}{\xi_H}\beta\int_0^{\delta_2}\tilde{\mathcal{B}}_2(\upsilon)\frac{T_\upsilon^* H_2}{H}d\upsilon + \gamma_1 T_2 H_2 + \frac{\gamma_1 T_2}{\xi_H}\psi A H_2 - \frac{\lambda}{\mathcal{B}_1}T^* K_2 - \frac{\lambda}{\sigma\mathcal{B}_1}\xi_K K \\ & + \frac{\lambda}{\sigma\mathcal{B}_1}\xi_K K_2 - \frac{\gamma_1 T_2\psi}{\xi_H\rho}\xi_A A + \frac{\gamma_1 T_2 H_2}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\ln\left(\frac{T_\upsilon H_\upsilon}{TH}\right)d\upsilon + \frac{\gamma_2 T_2 C_2}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\ln\left(\frac{T_\upsilon C_\upsilon}{TC}\right)d\upsilon \\ & + \frac{\gamma_3 T_2 T_2^*}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\ln\left(\frac{T_\upsilon T_\upsilon^*}{TT^*}\right)d\upsilon + \frac{\beta\mathcal{B}_2\gamma_1 T_2 T^*}{\xi_H} + \frac{\beta\gamma_1 T_2 T_2^*}{\xi_H}\int_0^{\delta_2}\tilde{\mathcal{B}}_2(\upsilon)\ln\left(\frac{T_\upsilon^*}{T^*}\right)d\upsilon.\end{aligned}$$

Using the following conditions for equilibrium $\mathcal{EP}_2$:

$$\alpha = \xi_T T_2 + \gamma_1 T_2 H_2 + \gamma_2 T_2 C_2 + \gamma_3 T_2 T_2^*,$$

$$\frac{(\mu_1+\xi_{T^*})\,T_2^*}{\mathcal{B}_1}+\frac{\lambda T_2^* K_2}{\mathcal{B}_1}=\gamma_1 T_2 H_2+\gamma_2 T_2 C_2+\gamma_3 T_2 T_2^*,\quad \frac{\mu_2}{\xi_C}=\frac{C_2}{T_2^*},\quad \frac{\beta}{\xi_H}=\frac{H_2}{\mathcal{B}_2 T_2^*},\quad T_2^*=\frac{\xi_K}{\sigma}.$$

Then, we obtain

$$\begin{aligned}\frac{d\Phi_2}{dt}&=\left(1-\frac{T_2}{T}\right)(\xi_T T_2-\xi_T T)+\gamma_1 T_2 H_2\left(1-\frac{T_2}{T}\right)+\gamma_2 T_2 C_2\left(1-\frac{T_2}{T}\right)\\&+\gamma_3 T_2 T_2^*\left(1-\frac{T_2}{T}\right)-\frac{\gamma_1 T_2 H_2}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\frac{T_2^* T_\upsilon H_\upsilon}{T^* T_2 H_2}d\upsilon-\frac{\gamma_2 T_2 C_2}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\frac{T_2^* T_\upsilon C_\upsilon}{T^* T_2 C_2}d\upsilon\\&-\frac{\gamma_3 T_2 T_2^*}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\frac{T_2^* T_\upsilon T_\upsilon^*}{T^* T_2 T_2^*}d\upsilon+\gamma_1 T_2 H_2+\gamma_2 T_2 C_2+\gamma_3 T_2 T_2^*-\gamma_2 T_2 C_2\frac{T^* C_2}{T_2^* C}+\gamma_2 T_2 C_2\\&-\frac{\gamma_1 T_2 H_2}{\mathcal{B}_2}\int_0^{\delta_2}\tilde{\mathcal{B}}_2(\upsilon)\frac{T_\upsilon^* H_2}{T_2^* H}d\upsilon+\gamma_1 T_2 H_2+\left(\frac{\gamma_1 T_2\psi H_2}{\xi_H}-\frac{\gamma_1 T_2\psi\xi_A}{\xi_H\rho}\right)A\\&+\frac{\gamma_1 T_2 H_2}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\ln\left(\frac{T_\upsilon H_\upsilon}{TH}\right)d\upsilon+\frac{\gamma_2 T_2 C_2}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\ln\left(\frac{T_\upsilon C_\upsilon}{TC}\right)d\upsilon\\&+\frac{\gamma_3 T_2 T_2^*}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\ln\left(\frac{T_\upsilon T_\upsilon^*}{TT^*}\right)d\upsilon+\frac{\gamma_1 T_2 H_2}{\mathcal{B}_2}\int_0^{\delta_2}\tilde{\mathcal{B}}_2(\upsilon)\ln\left(\frac{T_\upsilon^*}{T^*}\right)d\upsilon.\end{aligned}$$

Using the equalities given by Eqs. (5.2) and (5.3) in case of $i=2$, we get

$$\begin{aligned}\frac{d\Phi_2}{dt}&=-\xi_T\frac{(T-T_2)^2}{T}-\frac{\gamma_1 T_2 H_2}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\left(\frac{T_2}{T}-1-\ln\left(\frac{T_2}{T}\right)\right)d\upsilon\\&-\frac{\gamma_1 T_2 H_2}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\left(\frac{T_2^* T_\upsilon H_\upsilon}{T^* T_2 H_2}-1-\ln\left(\frac{T_2^* T_\upsilon H_\upsilon}{T^* T_2 H_2}\right)\right)d\upsilon\\&-\frac{\gamma_1 T_2 H_2}{\mathcal{B}_2}\int_0^{\delta_2}\tilde{\mathcal{B}}_2(\upsilon)\left(\frac{T_\upsilon^* H_2}{T_2^* H}-1-\ln\left(\frac{T_\upsilon^* H_2}{T_2^* H}\right)\right)d\upsilon-\frac{\gamma_2 T_2 C_2}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\left(\frac{T_2}{T}-1-\ln\left(\frac{T_2}{T}\right)\right)d\upsilon\\&-\frac{\gamma_2 T_2 C_2}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\left(\frac{T^* C_2}{T_2^* C}-1-\ln\left(\frac{T^* C_2}{T_2^* C}\right)\right)d\upsilon\\&-\frac{\gamma_2 T_2 C_2}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\left(\frac{T_2^* T_\upsilon C_\upsilon}{T^* T_2 C_2}d\upsilon-1-\ln\left(\frac{T_2^* T_\upsilon C_\upsilon}{T^* T_2 C_2}\right)\right)d\upsilon\\&-\frac{\gamma_3 T_2 T_2^*}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\left(\frac{T_2}{T}-1-\ln\left(\frac{T_2}{T}\right)\right)\\&-\frac{\gamma_3 T_2 T_2^*}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\left(\frac{T_2^* T_\upsilon T_\upsilon^*}{T^* T_2 T_2^*}-1-\ln\left(\frac{T_2^* T_\upsilon T_\upsilon^*}{T^* T_2 T_2^*}\right)\right)d\upsilon+\frac{\gamma_1 T_2\psi\xi_A}{\xi_H\rho}\left(\frac{\rho\xi_K\beta\mathcal{B}_2}{\sigma\xi_H\xi_A}-1\right)A.\end{aligned}\tag{5.8}$$

Eq. (5.8) can be rewritten as

$$\begin{aligned}\frac{d\Phi_2}{dt}&=-\xi_T\frac{(T-T_2)^2}{T}-\frac{\gamma_1 T_2 H_2}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\left(\chi\left(\frac{T_2}{T}\right)+\chi\left(\frac{T_2^* T_\upsilon H_\upsilon}{T^* T_2 H_2}\right)\right)d\upsilon\\&-\frac{\gamma_1 T_2 H_2}{\mathcal{B}_2}\int_0^{\delta_2}\tilde{\mathcal{B}}_2(\upsilon)\chi\left(\frac{T_\upsilon^* H_2}{T_2^* H}\right)d\upsilon-\frac{\gamma_2 T_2 C_2}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\left(\chi\left(\frac{T_2}{T}\right)+\chi\left(\frac{T^* C_2}{T_2^* C}\right)+\chi\left(\frac{T_2^* T_\upsilon C_\upsilon}{T^* T_2 C_2}d\upsilon\right)\right)d\upsilon\\&-\frac{\gamma_3 T_2 T_2^*}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\left(\chi\left(\frac{T_2}{T}\right)+\chi\left(\frac{T_2^* T_\upsilon T_\upsilon^*}{T^* T_2 T_2^*}\right)\right)+\frac{\gamma_1 T_2\psi\xi_A}{\xi_H\rho}(\mathfrak{R}_3-1)A.\end{aligned}$$

If $\mathfrak{R}_1>1$ and $\mathfrak{R}_3\leqslant 1$, then $\frac{d\Phi_2}{dt}\leqslant 0$ for any $T,T^*,C,H,K,A>0$. Moreover, $\frac{d\Phi_2}{dt}=0$ when $T=T_2$, and $A=0$. System's solutions (2.1)-(2.6) approach to Γ_2' which has elements with $T(t)=T_2$, and $\chi=0$, such that

$$\frac{T_\upsilon^* H_2}{T_2^* H}=\frac{T_2^* T_\upsilon H_\upsilon}{T^* T_2 H_2}=\frac{T^* C_2}{T_2^* C}=\frac{T_2^* T_\upsilon C_\upsilon}{T^* T_2 C_2}=\frac{T_2^* T_\upsilon T_\upsilon^*}{T^* T_2 T_2^*}=1,\quad \text{for almost}\quad \upsilon\in[0,\delta^*].\tag{5.9}$$

Because of $T(t) = T_2$, then from Eq. (5.9) we obtain $H(t) = H_2$, $T^*(t) = T_2^*$, and $C(t) = C_2$ for any t. In addition, from Eq. (2.2), we obtain

$$0 = \frac{dT^*}{dt} = \mathcal{B}_1 T_2 \left(\gamma_1 H_2 + \gamma_2 C_2 + \gamma_3 T_2^*\right) - \left(\mu_1 + \xi_{T^*}\right) T_2^* - \lambda T_2^* K, \quad \text{for any t.}$$

This guarantees that $K(t) = K_2$ for any t. Thus, $\Gamma_2' = \{\mathcal{EP}_2\}$ and consequently from L.I.P we can say that $\mathcal{EP}_2$ is G.A.S. □

Theorem 5.4. *If $\mathfrak{R}_2 > 1$ and $\mathfrak{R}_4 \leqslant 1$, then $\mathcal{EP}_3$ is G.A.S.*

Proof. We define a functional $\Phi_3(T, T^*, C, H, K, A)$ as:

$$\begin{aligned}
\Phi_3 = {} & T_3 \chi\left(\frac{T}{T_3}\right) + \frac{1}{\mathcal{B}_1} T_3^* \chi\left(\frac{T^*}{T_3^*}\right) + \frac{\gamma_2 T_3 C_3}{\xi_C} \chi\left(\frac{C}{C_3}\right) + \frac{\gamma_1 T_3 H_3}{\xi_H + \psi A_3} \chi\left(\frac{H}{H_3}\right) + \frac{\lambda}{\sigma \mathcal{B}_1} K \\
& + \frac{\gamma_1 T_3 \psi}{\rho\left(\xi_H + \psi A_3\right)} A_3 \chi\left(\frac{A}{A_3}\right) + \frac{\gamma_1 T_3 H_3}{\mathcal{B}_1} \int_0^{\delta_1} \tilde{\mathcal{B}}_1(\upsilon) \int_{t-\upsilon}^{t} \chi\left(\frac{T(u) H(u)}{T_3 H_3}\right) du d\upsilon \\
& + \frac{\gamma_2 T_3 C_3}{\mathcal{B}_1} \int_0^{\delta_1} \tilde{\mathcal{B}}_1(\upsilon) \int_{t-\upsilon}^{t} \chi\left(\frac{T(u) C(u)}{T_3 C_3}\right) du d\upsilon \\
& + \frac{\gamma_3 T_3 T_3^*}{\mathcal{B}_1} \int_0^{\delta_1} \tilde{\mathcal{B}}_1(\upsilon) \int_{t-\upsilon}^{t} \chi\left(\frac{T(u) T^*(u)}{T_3 T_3^*}\right) du d\upsilon + \frac{\beta \gamma_1 T_3 T_3^*}{\xi_H + \psi A_3} \int_0^{\delta_2} \tilde{\mathcal{B}}_2(\upsilon) \int_{t-\upsilon}^{t} \chi\left(\frac{T^*(u)}{T_3^*}\right) du d\upsilon.
\end{aligned}$$

We obtain $\frac{d\Phi_3}{dt}$ as

$$\begin{aligned}
\frac{d\Phi_3}{dt} = {} & \left(1 - \frac{T_3}{T}\right)\left(\alpha - \xi_T T - \gamma_1 T H - \gamma_2 T C - \gamma_3 T T^*\right) + \frac{1}{\mathcal{B}_1}\left(1 - \frac{T_3^*}{T^*}\right) \\
& \times \left(\int_0^{\delta_1} \tilde{\mathcal{B}}_1(\upsilon) T_\upsilon \left(\gamma_1 H_\upsilon + \gamma_2 C_\upsilon + \gamma_3 T_\upsilon^*\right) d\upsilon - \left(\mu_1 + \xi_{T^*}\right) T^* - \lambda T^* K\right) \\
& + \frac{\gamma_2 T_3}{\xi_C}\left(1 - \frac{C_3}{C}\right)\left(\mu_2 T^* - \xi_C C\right) + \frac{\gamma_1 T_3}{\xi_H + \psi A_3}\left(1 - \frac{H_3}{H}\right)\left(\beta \int_0^{\delta_2} \tilde{\mathcal{B}}_2(\upsilon) T_\upsilon^* d\upsilon - \xi_H H - \psi A H\right) \\
& + \frac{\lambda}{\sigma \mathcal{B}_1}\left(\sigma T^* K - \xi_K K\right) + \frac{\gamma_1 T_3 \psi}{\rho\left(\xi_H + \psi A_3\right)}\left(1 - \frac{A_3}{A}\right)\left(\rho A H - \xi_A A\right) \\
& + \frac{\gamma_1 T_3 H_3}{\mathcal{B}_1} \int_0^{\delta_1} \tilde{\mathcal{B}}_1(\upsilon)\left(\frac{T H}{T_3 H_3} - \frac{T_\upsilon H_\upsilon}{T_3 H_3} + \ln\left(\frac{T_\upsilon H_\upsilon}{T H}\right)\right) d\upsilon \\
& + \frac{\gamma_2 T_3 C_3}{\mathcal{B}_1} \int_0^{\delta_1} \tilde{\mathcal{B}}_1(\upsilon)\left(\frac{T C}{T_3 C_3} - \frac{T_\upsilon C_\upsilon}{T_3 C_3} + \ln\left(\frac{T_\upsilon C_\upsilon}{T C}\right)\right) d\upsilon \\
& + \frac{\gamma_3 T_3 T_3^*}{\mathcal{B}_1} \int_0^{\delta_1} \tilde{\mathcal{B}}_1(\upsilon)\left(\frac{T T^*}{T_3 T_3^*} - \frac{T_\upsilon T_\upsilon^*}{T_3 T_3^*} + \ln\left(\frac{T_\upsilon T_\upsilon^*}{T T^*}\right)\right) d\upsilon \\
& + \frac{\beta \gamma_1 T_3 T_3^*}{\xi_H + \psi A_3} \int_0^{\delta_2} \tilde{\mathcal{B}}_2(\upsilon)\left(\frac{T^*}{T_3^*} - \frac{T_\upsilon^*}{T_3^*} + \ln\left(\frac{T_\upsilon^*}{T^*}\right)\right) d\upsilon. \qquad (5.10)
\end{aligned}$$

Collecting terms of Eq. (5.10), yields

$$\begin{aligned}
\frac{d\Phi_3}{dt} = {} & \left(1 - \frac{T_3}{T}\right)\left(\alpha - \xi_T T\right) + \gamma_1 T_3 H + \gamma_3 T_3 T^* - \frac{\gamma_1}{\mathcal{B}_1} \int_0^{\delta_1} \tilde{\mathcal{B}}_1(\upsilon) \frac{T_3^* T_\upsilon H_\upsilon}{T^*} d\upsilon \\
& - \frac{\gamma_2}{\mathcal{B}_1} \int_0^{\delta_1} \tilde{\mathcal{B}}_1(\upsilon) \frac{T_3^* T_\upsilon C_\upsilon}{T^*} d\upsilon - \frac{\gamma_3}{\mathcal{B}_1} \int_0^{\delta_1} \tilde{\mathcal{B}}_1(\upsilon) \frac{T_3^* T_\upsilon T_\upsilon^*}{T^*} d\upsilon - \frac{1}{\mathcal{B}_1}\left(1 - \frac{T_3^*}{T^*}\right) \\
& \times \left(\mu_1 + \xi_{T^*}\right) T^* + \frac{1}{\mathcal{B}_1} \lambda T_3^* K + \frac{\gamma_2 T_3 \mu_2}{\xi_C} T^* - \frac{\gamma_2 T_3 \mu_2}{\xi_C} \frac{T^* C_3}{C} + \gamma_2 T_3 C_3
\end{aligned}$$

$$
\begin{aligned}
&- \frac{\gamma_1 T_3}{\xi_H + \psi A_3}\beta \int_0^{\delta_2} \tilde{\mathcal{B}}_2(\upsilon)\frac{T_\upsilon^* H_3}{H}\,d\upsilon - \frac{\gamma_1 T_3}{\xi_H + \psi A_3}\xi_H H + \frac{\gamma_1 T_3}{\xi_H + \psi A_3}\xi_H H_3 \\
&+ \frac{\gamma_1 T_3}{\xi_H + \psi A_3}\psi A H_3 - \frac{\lambda}{\sigma \mathcal{B}_1}\xi_K K - \frac{\gamma_1 T_3 \psi}{\xi_H + \psi A_3}A_3 H - \frac{\gamma_1 T_3 \psi}{\rho\,(\xi_H + \psi A_3)}\xi_A A \\
&+ \frac{\gamma_1 T_3 \psi}{\rho\,(\xi_H + \psi A_3)}\xi_A A_3 + \frac{\gamma_1 T_3 H_3}{\mathcal{B}_1}\int_0^{\delta_1} \tilde{\mathcal{B}}_1(\upsilon)\ln\left(\frac{T_\upsilon H_\upsilon}{TH}\right)d\upsilon \\
&+ \frac{\gamma_2 T_3 C_3}{\mathcal{B}_1}\int_0^{\delta_1} \tilde{\mathcal{B}}_1(\upsilon)\ln\left(\frac{T_\upsilon C_\upsilon}{TC}\right)d\upsilon + \frac{\gamma_3 T_3 T_3^*}{\mathcal{B}_1}\int_0^{\delta_1} \tilde{\mathcal{B}}_1(\upsilon)\ln\left(\frac{T_\upsilon T_\upsilon^*}{TT^*}\right)d\upsilon \\
&+ \frac{\beta \mathcal{B}_2 \gamma_1 T_3 T^*}{\xi_H + \psi A_3} + \frac{\beta \gamma_1 T_3 T_3^*}{\xi_H + \psi A_3}\int_0^{\delta_2} \tilde{\mathcal{B}}_2(\upsilon)\ln\left(\frac{T_\upsilon^*}{T^*}\right)d\upsilon.
\end{aligned}
$$

Using the following conditions for equilibrium $\mathcal{EP}_3$:

$$
\begin{aligned}
\alpha &= \xi_T T_3 + \gamma_1 T_3 H_3 + \gamma_2 T_3 C_3 + \gamma_3 T_3 T_3^*, \\
\frac{(\mu_1 + \xi_{T^*})\,T_3^*}{\mathcal{B}_1} &= \gamma_1 T_3 H_3 + \gamma_2 T_3 C_3 + \gamma_3 T_3 T_3^*, \quad \frac{C_3}{T_3^*} = \frac{\mu_2}{\xi_C}, \quad H_3 = \frac{\xi_A}{\rho}, \quad \xi_H + \psi A_3 = \frac{\beta \mathcal{B}_2 T_3^*}{H_3}.
\end{aligned}
$$

Then, we obtain

$$
\begin{aligned}
\frac{d\Phi_3}{dt} &= \left(1 - \frac{T_3}{T}\right)(\xi_T T_3 - \xi_T T) + \gamma_1 T_3 H_3\left(1 - \frac{T_3}{T}\right) + \gamma_2 T_3 C_3\left(1 - \frac{T_3}{T}\right) \\
&+ \gamma_3 T_3 T_3^*\left(1 - \frac{T_3}{T}\right) - \frac{\gamma_1 T_3 H_3}{\mathcal{B}_1}\int_0^{\delta_1} \tilde{\mathcal{B}}_1(\upsilon)\frac{T_3^* T_\upsilon H_\upsilon}{T^* T_3 H_3}\,d\upsilon \\
&- \frac{\gamma_2 T_3 C_3}{\mathcal{B}_1}\int_0^{\delta_1} \tilde{\mathcal{B}}_1(\upsilon)\frac{T_3^* T_\upsilon C_\upsilon}{T^* T_3 C_3}\,d\upsilon - \frac{\gamma_3 T_3 T_3^*}{\mathcal{B}_1}\int_0^{\delta_1} \tilde{\mathcal{B}}_1(\upsilon)\frac{T_3^* T_\upsilon T_\upsilon^*}{T^* T_3 T_3^*}\,d\upsilon \\
&+ \gamma_1 T_3 H_3 + \gamma_2 T_3 C_3 + \gamma_3 T_3 T_3^* - \gamma_2 T_3 C_3\frac{T^* C_3}{T_3^* C} + \gamma_2 T_3 C_3 \\
&- \frac{\gamma_1 T_3 H_3}{\mathcal{B}_2}\int_0^{\delta_2} \tilde{\mathcal{B}}_2(\upsilon)\frac{T_\upsilon^* H_3}{T_3^* H}\,d\upsilon + \gamma_1 T_3 H_3 + \frac{\gamma_1 T_3 H_3}{\mathcal{B}_1}\int_0^{\delta_1} \tilde{\mathcal{B}}_1(\upsilon)\ln\left(\frac{T_\upsilon H_\upsilon}{TH}\right)d\upsilon \\
&+ \frac{\gamma_2 T_3 C_3}{\mathcal{B}_1}\int_0^{\delta_1} \tilde{\mathcal{B}}_1(\upsilon)\ln\left(\frac{T_\upsilon C_\upsilon}{TC}\right)d\upsilon + \frac{\gamma_3 T_3 T_3^*}{\mathcal{B}_1}\int_0^{\delta_1} \tilde{\mathcal{B}}_1(\upsilon)\ln\left(\frac{T_\upsilon T_\upsilon^*}{TT^*}\right)d\upsilon \\
&+ \frac{\gamma_1 T_3 H_3}{\mathcal{B}_2}\int_0^{\delta_2} \tilde{\mathcal{B}}_2(\upsilon)\ln\left(\frac{T_\upsilon^*}{T^*}\right)d\upsilon + \left(\frac{1}{\mathcal{B}_1}\lambda T_3^* - \frac{\lambda \xi_K}{\sigma \mathcal{B}_1}\right)K.
\end{aligned}
$$

Using the equalities given by Eqs. (5.2) and (5.3) in case of $i = 3$, we get

$$
\begin{aligned}
\frac{d\Phi_3}{dt} &= -\xi_T\frac{(T - T_3)^2}{T} - \frac{\gamma_1 T_3 H_3}{\mathcal{B}_1}\int_0^{\delta_1} \tilde{\mathcal{B}}_1(\upsilon)\left(\frac{T_3}{T} - 1 - \ln\left(\frac{T_3}{T}\right)\right)d\upsilon \\
&- \frac{\gamma_1 T_3 H_3}{\mathcal{B}_1}\int_0^{\delta_1} \tilde{\mathcal{B}}_1(\upsilon)\left(\frac{T_3^* T_\upsilon H_\upsilon}{T^* T_3 H_3} - 1 - \ln\left(\frac{T_3^* T_\upsilon H_\upsilon}{T^* T_3 H_3}\right)\right)d\upsilon \\
&- \frac{\gamma_1 T_3 H_3}{\mathcal{B}_2}\int_0^{\delta_2} \tilde{\mathcal{B}}_2(\upsilon)\left(\frac{T_\upsilon^* H_3}{T_3^* H} - 1 - \ln\left(\frac{T_\upsilon^* H_3}{T_3^* H}\right)\right)d\upsilon - \frac{\gamma_2 T_3 C_3}{\mathcal{B}_1}\int_0^{\delta_1} \tilde{\mathcal{B}}_1(\upsilon)\left(\frac{T_3}{T} - 1 - \ln\left(\frac{T_3}{T}\right)\right)d\upsilon \\
&- \frac{\gamma_2 T_3 C_3}{\mathcal{B}_1}\int_0^{\delta_1} \tilde{\mathcal{B}}_1(\upsilon)\left(\frac{T_3^* T_\upsilon C_\upsilon}{T^* T_3 C_3} - 1 - \ln\left(\frac{T_3^* T_\upsilon C_\upsilon}{T^* T_3 C_3}\right)\right)d\upsilon \\
&- \frac{\gamma_2 T_3 C_3}{\mathcal{B}_1}\int_0^{\delta_1} \tilde{\mathcal{B}}_1(\upsilon)\left(\frac{T^* C_3}{T_3^* C} - 1 - \ln\left(\frac{T^* C_3}{T_3^* C}\right)\right)d\upsilon - \frac{\gamma_3 T_3 T_3^*}{\mathcal{B}_1}\int_0^{\delta_1} \tilde{\mathcal{B}}_1(\upsilon)\left(\frac{T_3}{T} - 1 - \ln\left(\frac{T_3}{T}\right)\right)d\upsilon \\
&- \frac{\gamma_3 T_3 T_3^*}{\mathcal{B}_1}\int_0^{\delta_1} \tilde{\mathcal{B}}_1(\upsilon)\left(\frac{T_3^* T_\upsilon T_\upsilon^*}{T^* T_3 T_3^*} - 1 - \ln\left(\frac{T_3^* T_\upsilon T_\upsilon^*}{T^* T_3 T_3^*}\right)\right)d\upsilon + \frac{\lambda}{\mathcal{B}_1}\left(T_3^* - \frac{\xi_K}{\sigma}\right)K.
\end{aligned} \tag{5.11}
$$

Eq. (5.11) can be rewritten as

$$\begin{aligned}\frac{d\Phi_3}{dt} &= -\xi_T\frac{(T-T_3)^2}{T} - \frac{\gamma_1 T_3 H_3}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\left(\chi\left(\frac{T_3}{T}\right)+\chi\left(\frac{T_3^* T_\upsilon H_\upsilon}{T^* T_3 H_3}\right)\right)d\upsilon - \frac{\gamma_1 T_3 H_3}{\mathcal{B}_2}\int_0^{\delta_2}\tilde{\mathcal{B}}_2(\upsilon)\chi\left(\frac{T_\upsilon^* H_3}{T_3^* H}\right)d\upsilon\\ &- \frac{\gamma_2 T_3 C_3}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\left(\chi\left(\frac{T_3}{T}\right)+\chi\left(\frac{T_3^* T_\upsilon C_\upsilon}{T^* T_3 C_3}\right)+\chi\left(\frac{T^* C_3}{T_3^* C}\right)\right)d\upsilon\\ &- \frac{\gamma_3 T_3 T_3^*}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\left(\chi\left(\frac{T_3}{T}\right)+\chi\left(\frac{T_3^* T_\upsilon T_\upsilon^*}{T^* T_3 T_3^*}\right)\right)d\upsilon + \frac{\lambda}{\mathcal{B}_1}\left(T_3^* - T_4^*\right)K.\end{aligned}$$

Hence, if $\mathfrak{R}_4 \leqslant 1$, then $\mathcal{EP}_4$ does not exist since $K_4 = \frac{\mu_1+\xi_{T^*}}{\lambda}(\mathfrak{R}_4 - 1) \leqslant 0$. This ensures that

$$\frac{dK}{dt} = \sigma\left(T^* - \frac{\xi_K}{\sigma}\right)K \leqslant 0 \Longrightarrow \frac{dK}{dt} = \sigma\left(T^* - T_4^*\right)K \leqslant 0 \ \text{ for any } \ T^*, K > 0,$$

which implies that $T_3^* \leqslant T_4^*$. We have $\frac{d\Phi_3}{dt} \leqslant 0$ for any $T, T^*, C, H, K, A > 0$. Moreover, $\frac{d\Phi_3}{dt} = 0$, when $T = T_3$, and $K = 0$. System's solutions approach to Γ_3', where $T(t) = T_3$ and $\chi = 0$, such that

$$\frac{T_3^* T_\upsilon H_\upsilon}{T^* T_3 H_3} = \frac{T_\upsilon^* H_3}{T_3^* H} = \frac{T_3^* T_\upsilon C_\upsilon}{T^* T_3 C_3} = \frac{T^* C_3}{T_3^* C} = \frac{T_3^* T_\upsilon T_\upsilon^*}{T^* T_3 T_3^*} = 1, \quad \text{for almost } \upsilon \in [0, \delta^*]. \tag{5.12}$$

Because of $T(t) = T_3$, then from Eq. (5.12) we get $T^*(t) = T_3^*$, $C(t) = C_3$, and $H(t) = H_3$, for any t. In addition, Eq. (2.4) gives

$$0 = \frac{dH}{dt} = \beta\mathcal{B}_2 T_3^* - \xi_H H_3 - \psi A(t) H_3.$$

This yields $A(t) = A_3$, for any t. Hence, $\Gamma_3' = \{\mathcal{EP}_3\}$ and from L.I.P we show that $\mathcal{EP}_3$ is G.A.S. □

Theorem 5.5. *If $\mathfrak{R}_3 > 1$ and $\mathfrak{R}_4 > 1$, then $\mathcal{EP}_4$ is G.A.S.*

Proof. Define $\Phi_4(T, T^*, C, H, K, A)$ as:

$$\begin{aligned}\Phi_4 &= T_4\chi\left(\frac{T}{T_4}\right) + \frac{1}{\mathcal{B}_1}T_4^*\chi\left(\frac{T^*}{T_4^*}\right) + \frac{\gamma_2 T_4 C_4}{\xi_C}\chi\left(\frac{C}{C_4}\right) + \frac{\gamma_1 T_4 H_4}{\xi_H + \psi A_4}\chi\left(\frac{H}{H_4}\right) + \frac{\lambda}{\sigma\mathcal{B}_1}K_4\chi\left(\frac{K}{K_4}\right)\\ &+ \frac{\gamma_1 T_4\psi}{\rho(\xi_H + \psi A_4)}A_4\chi\left(\frac{A}{A_4}\right) + \frac{\gamma_1 T_4 H_4}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\int_{t-\upsilon}^{t}\chi\left(\frac{T(u)H(u)}{T_4 H_4}\right)du d\upsilon\\ &+ \frac{\gamma_2 T_4 C_4}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\int_{t-\upsilon}^{t}\chi\left(\frac{T(u)C(u)}{T_4 C_4}\right)du d\upsilon + \frac{\gamma_3 T_4 T_4^*}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\int_{t-\upsilon}^{t}\chi\left(\frac{T(u)T^*(u)}{T_4 T_4^*}\right)du d\upsilon\\ &+ \frac{\beta\gamma_1 T_4 T_4^*}{\xi_H + \psi A_4}\int_0^{\delta_2}\tilde{\mathcal{B}}_2(\upsilon)\int_{t-\upsilon}^{t}\chi\left(\frac{T^*(u)}{T_4^*}\right)du d\upsilon.\end{aligned}$$

Calculating $\frac{d\Phi_4}{dt}$ as:

$$\begin{aligned}\frac{d\Phi_4}{dt} &= \left(1 - \frac{T_4}{T}\right)(\alpha - \xi_T T - \gamma_1 T H - \gamma_2 T C - \gamma_3 T T^*) + \frac{1}{\mathcal{B}_1}\left(1 - \frac{T_4^*}{T^*}\right)\\ &\times\left(\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)T_\upsilon\left(\gamma_1 H_\upsilon + \gamma_2 C_\upsilon + \gamma_3 T_\upsilon^*\right)d\upsilon - \left(\mu_1 + \xi_{T^*}\right)T^* - \lambda T^* K\right)\\ &+ \frac{\gamma_2 T_4}{\xi_C}\left(1 - \frac{C_4}{C}\right)(\mu_2 T^* - \xi_C C) + \frac{\gamma_1 T_4}{\xi_H + \psi A_4}\left(1 - \frac{H_4}{H}\right)\left(\beta\int_0^{\delta_2}\tilde{\mathcal{B}}_2(\upsilon)T_\upsilon^* d\upsilon - \xi_H H - \psi A H\right)\\ &+ \frac{\lambda}{\sigma\mathcal{B}_1}\left(1 - \frac{K_4}{K}\right)(\sigma T^* K - \xi_K K) + \frac{\gamma_1 T_4\psi}{\rho(\xi_H + \psi A_4)}\left(1 - \frac{A_4}{A}\right)(\rho A H - \xi_A A)\end{aligned} \tag{5.13}$$

$$+\frac{\gamma_1 T_4 H_4}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\left(\frac{TH}{T_4H_4}-\frac{T_\upsilon H_\upsilon}{T_4H_4}+\ln\left(\frac{T_\upsilon H_\upsilon}{TH}\right)\right)d\upsilon$$
$$+\frac{\gamma_2 T_4 C_4}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\left(\frac{TC}{T_4C_4}-\frac{T_\upsilon C_\upsilon}{T_4C_4}+\ln\left(\frac{T_\upsilon C_\upsilon}{TC}\right)\right)d\upsilon$$
$$+\frac{\gamma_3 T_4 T_4^*}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\left(\frac{TT^*}{T_4T_4^*}-\frac{T_\upsilon T_\upsilon^*}{T_4T_4^*}+\ln\left(\frac{T_\upsilon T_\upsilon^*}{TT^*}\right)\right)d\upsilon$$
$$+\frac{\beta\gamma_1 T_4 T_4^*}{\xi_H+\psi A_4}\int_0^{\delta_2}\tilde{\mathcal{B}}_2(\upsilon)\left(\frac{T^*}{T_4^*}-\frac{T_\upsilon^*}{T_4^*}+\ln\left(\frac{T_\upsilon^*}{T^*}\right)\right)d\upsilon,$$

and collecting terms of Eq. (5.13), we get

$$\frac{d\Phi_4}{dt}=\left(1-\frac{T_4}{T}\right)(\alpha-\xi_T T)+\gamma_1 T_4 H+\gamma_3 T_4 T^*-\frac{\gamma_1}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\frac{T_4^* T_\upsilon H_\upsilon}{T^*}d\upsilon-\frac{\gamma_2}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\frac{T_4^* T_\upsilon C_\upsilon}{T^*}d\upsilon$$
$$-\frac{\gamma_3}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\frac{T_4^* T_\upsilon T_\upsilon^*}{T^*}d\upsilon-\frac{1}{\mathcal{B}_1}\left(1-\frac{T_4^*}{T^*}\right)(\mu_1+\xi_{T^*})T^*+\frac{\lambda}{\mathcal{B}_1}T_4^* K+\frac{\gamma_2 T_4}{\xi_C}\mu_2 T^*$$
$$-\frac{\gamma_2 T_4\mu_2}{\xi_C}\frac{T^* C_4}{C}+\gamma_2 T_4 C_4-\frac{\gamma_1 T_4}{\xi_H+\psi A_4}\beta\int_0^{\delta_2}\tilde{\mathcal{B}}_2(\upsilon)\frac{T_\upsilon^* H_4}{H}d\upsilon$$
$$-\frac{\gamma_1 T_4}{\xi_H+\psi A_4}\xi_H H+\frac{\gamma_1 T_4}{\xi_H+\psi A_4}\xi_H H_4+\frac{\gamma_1 T_4}{\xi_H+\psi A_4}\psi A H_4-\frac{\lambda}{\mathcal{B}_1}T^* K_4$$
$$-\frac{\lambda}{\sigma\mathcal{B}_1}\xi_K K+\frac{\lambda}{\sigma\mathcal{B}_1}\xi_K K_4-\frac{\gamma_1 T_4\psi}{\xi_H+\psi A_4}A_4 H-\frac{\gamma_1 T_4\psi}{\rho(\xi_H+\psi A_4)}\xi_A A$$
$$+\frac{\gamma_1 T_4\psi}{\rho(\xi_H+\psi A_4)}\xi_A A_4+\frac{\gamma_1 T_4 H_4}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\ln\left(\frac{T_\upsilon H_\upsilon}{TH}\right)d\upsilon+\frac{\gamma_2 T_4 C_4}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\ln\left(\frac{T_\upsilon C_\upsilon}{TC}\right)d\upsilon$$
$$+\frac{\gamma_3 T_4 T_4^*}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\ln\left(\frac{T_\upsilon T_\upsilon^*}{TT^*}\right)d\upsilon+\frac{\beta\mathcal{B}_2\gamma_1 T_4 T^*}{\xi_H+\psi A_4}+\frac{\beta\gamma_1 T_4 T_4^*}{\xi_H+\psi A_4}\int_0^{\delta_2}\tilde{\mathcal{B}}_2(\upsilon)\ln\left(\frac{T_\upsilon^*}{T^*}\right)d\upsilon.$$

Using the following conditions for equilibrium $\mathcal{EP}_4$:

$$\alpha=\xi_T T_4+\gamma_1 T_4 H_4+\gamma_2 T_4 C_4+\gamma_3 T_4 T_4^*,$$
$$\frac{(\mu_1+\xi_{T^*})T_4^*}{\mathcal{B}_1}+\frac{\lambda T_4^* K_4}{\mathcal{B}_1}=\gamma_1 T_4 H_4+\gamma_2 T_4 C_4+\gamma_3 T_4 T_4^*,$$
$$\frac{\mu_2}{\xi_C}=\frac{C_4}{T_4^*},\quad H_4=\frac{\xi_A}{\rho},\quad \xi_H+\psi A_4=\frac{\beta\mathcal{B}_2 T_4^*}{H_4},\quad T_4^*=\frac{\xi_K}{\sigma},$$

then, we obtain

$$\frac{d\Phi_4}{dt}=\left(1-\frac{T_4}{T}\right)(\xi_T T_4-\xi_T T)+\gamma_1 T_4 H_4\left(1-\frac{T_4}{T}\right)+\gamma_2 T_4 C_4\left(1-\frac{T_4}{T}\right)$$
$$+\gamma_3 T_4 T_4^*\left(1-\frac{T_4}{T}\right)-\frac{\gamma_1 T_4 H_4}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\frac{T_4^* T_\upsilon H_\upsilon}{T^* T_4 H_4}d\upsilon$$
$$-\frac{\gamma_2 T_4 C_4}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\frac{T_4^* T_\upsilon C_\upsilon}{T^* T_4 C_4}d\upsilon-\frac{\gamma_3 T_4 T_4^*}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\frac{T_4^* T_\upsilon T_\upsilon^*}{T^* T_4 T_4^*}d\upsilon$$
$$+\gamma_1 T_4 H_4+\gamma_2 T_4 C_4+\gamma_3 T_4 T_4^*-\gamma_2 T_4 C_4\frac{T^* C_4}{T_4^* C}+\gamma_2 T_4 C_4-\frac{\gamma_1 T_4 H_4}{\mathcal{B}_2}\int_0^{\delta_2}\tilde{\mathcal{B}}_2(\upsilon)\frac{T_\upsilon^* H_4}{T_4^* H}d\upsilon+\gamma_1 T_4 H_4$$
$$+\frac{\gamma_1 T_4 H_4}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\ln\left(\frac{T_\upsilon H_\upsilon}{TH}\right)d\upsilon+\frac{\gamma_2 T_4 C_4}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\ln\left(\frac{T_\upsilon C_\upsilon}{TC}\right)d\upsilon$$
$$+\frac{\gamma_3 T_4 T_4^*}{\mathcal{B}_1}\int_0^{\delta_1}\tilde{\mathcal{B}}_1(\upsilon)\ln\left(\frac{T_\upsilon T_\upsilon^*}{TT^*}\right)d\upsilon+\frac{\gamma_1 T_4 H_4}{\mathcal{B}_2}\int_0^{\delta_2}\tilde{\mathcal{B}}_2(\upsilon)\ln\left(\frac{T_\upsilon^*}{T^*}\right)d\upsilon.$$

Using the equalities given by Eqs. (5.2) and (5.3) in case of $i = 4$, we get

$$\begin{aligned}
\frac{d\Phi_4}{dt} = &-\xi_T \frac{(T-T_4)^2}{T} - \frac{\gamma_1 T_4 H_4}{\mathcal{B}_1}\int_0^{\delta_1} \tilde{\mathcal{B}}_1(\upsilon)\left(\frac{T_4}{T} - 1 - \ln\left(\frac{T_4}{T}\right)\right) d\upsilon \\
&- \frac{\gamma_1 T_4 H_4}{\mathcal{B}_1}\int_0^{\delta_1} \tilde{\mathcal{B}}_1(\upsilon)\left(\frac{T_4^* T_\upsilon H_\upsilon}{T^* T_4 H_4} - 1 - \ln\left(\frac{T_4^* T_\upsilon H_\upsilon}{T^* T_4 H_4}\right)\right) d\upsilon \\
&- \frac{\gamma_1 T_4 H_4}{\mathcal{B}_2}\int_0^{\delta_2} \tilde{\mathcal{B}}_2(\upsilon)\left(\frac{T_\upsilon^* H_4}{T_4^* H} - 1 - \ln\left(\frac{T_\upsilon^* H_4}{T_4^* H}\right)\right) d\upsilon - \frac{\gamma_2 T_4 C_4}{\mathcal{B}_1}\int_0^{\delta_1} \tilde{\mathcal{B}}_1(\upsilon)\left(\frac{T_4}{T} - 1 - \ln\left(\frac{T_4}{T}\right)\right) d\upsilon \\
&- \frac{\gamma_2 T_4 C_4}{\mathcal{B}_1}\int_0^{\delta_1} \tilde{\mathcal{B}}_1(\upsilon)\left(\frac{T_4^* T_\upsilon C_\upsilon}{T^* T_4 C_4} - 1 - \ln\left(\frac{T_4^* T_\upsilon C_\upsilon}{T^* T_4 C_4}\right)\right) d\upsilon \qquad (5.14) \\
&- \frac{\gamma_2 T_4 C_4}{\mathcal{B}_1}\int_0^{\delta_1} \tilde{\mathcal{B}}_1(\upsilon)\left(\frac{T^* C_4}{T_4^* C} - 1 - \ln\left(\frac{T^* C_4}{T_4^* C}\right)\right) d\upsilon - \frac{\gamma_3 T_4 T_4^*}{\mathcal{B}_1}\int_0^{\delta_1} \tilde{\mathcal{B}}_1(\upsilon)\left(\frac{T_4}{T} - 1 - \ln\left(\frac{T_4}{T}\right)\right) d\upsilon \\
&- \frac{\gamma_3 T_4 T_4^*}{\mathcal{B}_1}\int_0^{\delta_1} \tilde{\mathcal{B}}_1(\upsilon)\left(\frac{T_4^* T_\upsilon T_\upsilon^*}{T^* T_4 T_4^*} - 1 - \ln\left(\frac{T_4^* T_\upsilon T_\upsilon^*}{T^* T_4 T_4^*}\right)\right) d\upsilon.
\end{aligned}$$

Eq. (5.14) can be rewritten as

$$\begin{aligned}
\frac{d\Phi_4}{dt} = &-\xi_T \frac{(T-T_4)^2}{T} - \frac{\gamma_1 T_4 H_4}{\mathcal{B}_1}\int_0^{\delta_1} \tilde{\mathcal{B}}_1(\upsilon)\left(\chi\left(\frac{T_4}{T}\right) + \chi\left(\frac{T_4^* T_\upsilon H_\upsilon}{T^* T_4 H_4}\right)\right) d\upsilon - \frac{\gamma_1 T_4 H_4}{\mathcal{B}_2}\int_0^{\delta_2} \tilde{\mathcal{B}}_2(\upsilon)\chi\left(\frac{T_\upsilon^* H_4}{T_4^* H}\right) d\upsilon \\
&- \frac{\gamma_2 T_4 C_4}{\mathcal{B}_1}\int_0^{\delta_1} \tilde{\mathcal{B}}_1(\upsilon)\left(\chi\left(\frac{T_4}{T}\right) + \chi\left(\frac{T_4^* T_\upsilon C_\upsilon}{T^* T_4 C_4}\right) + \chi\left(\frac{T^* C_4}{T_4^* C}\right)\right) d\upsilon \\
&- \frac{\gamma_3 T_4 T_4^*}{\mathcal{B}_1}\int_0^{\delta_1} \tilde{\mathcal{B}}_1(\upsilon)\left(\chi\left(\frac{T_4}{T}\right) + \chi\left(\frac{T_4^* T_\upsilon T_\upsilon^*}{T^* T_4 T_4^*}\right)\right) d\upsilon.
\end{aligned}$$

If $\mathfrak{R}_3 > 1$ and $\mathfrak{R}_4 > 1$, then $\frac{d\Phi_4}{dt} \leqslant 0$ for any $T, T^*, C, H, K, A > 0$. Similarly, one can show that $\frac{d\Phi_4}{dt} = 0$, when $T = T_4$, $T^* = T_4^*$, $C = C_4$, and $H = H_4$. System's solutions approach to Γ_4', where $T(t) = T_4$, $T^*(t) = T_4^*$, $C(t) = C_4$, and $H(t) = H_4$ ([21]). From Eqs. (2.2) and (2.3), we have

$$0 = \frac{dT^*}{dt} = \mathcal{B}_1 T_4(\gamma_1 H_4 + \gamma_2 C_4 + \gamma_3 T_4^*) - (\mu_1 + \xi_{T^*}) T_4^* - \lambda T_4^* K, \quad 0 = \frac{dH}{dt} = \beta \mathcal{B}_2 T_4^* - \xi_H H_4 - \psi A(t) H_4.$$

This yields that $K(t) = K_4$ and $A(t) = A_4$, for any t. Hence, $\Gamma_4' = \{\mathcal{EP}_4\}$ and L.I.P shows that $\mathcal{EP}_4$ is G.A.S ([21]). □

Table 1 provides an overview of the five equilibrium points' global stability criteria and existence.

Table 1: Sufficient conditions of existence and global stability of equilibria.

Equilibrium point	Existence conditions	Global stability conditions
$\mathcal{EP}_0 = (T_0, 0, 0, 0, 0, 0)$	None	$\mathfrak{R}_0 \leqslant 1$
$\mathcal{EP}_1 = (T_1, T_1^*, C_1, H_1, 0, 0)$	$\mathfrak{R}_0 > 1$	$\mathfrak{R}_0 > 1$, $\mathfrak{R}_3 \leqslant 1$, and $\mathfrak{R}_4 \leqslant 1$
$\mathcal{EP}_2 = (T_2, T_2^*, C_2, H_2, K_2, 0)$	$\mathfrak{R}_1 > 1$	$\mathfrak{R}_1 > 1$ and $\mathfrak{R}_3 \leqslant 1$
$\mathcal{EP}_3 = (T_3, T_3^*, C_3, H_3, 0, A_3)$	$\mathfrak{R}_2 > 1$	$\mathfrak{R}_2 > 1$ and $\mathfrak{R}_4 \leqslant 1$
$\mathcal{EP}_4 = (T_4, T_4^*, C_4, H_4, K_4, A_4)$	$\mathfrak{R}_3 > 1$ and $\mathfrak{R}_4 > 1$	$\mathfrak{R}_3 > 1$ and $\mathfrak{R}_4 > 1$

6. Effect of cellular infection and inflammatory cytokines on the dynamics of HIV-1

This section examines the impact of cellular infection and inflammatory cytokines on the dynamic characteristics of HIV-1. We examine the application of three different forms of medication therapy for: (i) preventing infection through a viral infection pathway [40]; (ii) preventing pyroptotic cell death [43, 52]; and (iii) preventing infection through a cellular infection pathway [54]. Let $\omega_i \in [0,1]$, $i = 1,2,3$ be the efficacies of the above drug therapies, respectively. Model (2.1)-(2.6) under the effect of these treatments becomes:

$$\frac{dT}{dt} = \alpha - \xi_T T - (1-\omega_1)\gamma_1 TH - (1-\omega_2)\gamma_2 TC - (1-\omega_3)\gamma_3 TT^*, \tag{6.1}$$

$$\frac{dT^*}{dt} = \int_0^{\delta_1} B_1(\upsilon)e^{-\kappa_1\upsilon}T_\upsilon\left((1-\omega_1)\gamma_1 H_\upsilon + (1-\omega_2)\gamma_2 C_\upsilon + (1-\omega_3)\gamma_3 T^*_\upsilon\right)d\upsilon - (\mu_1+\xi_{T^*})T^* - \lambda T^* K, \tag{6.2}$$

$$\frac{dC}{dt} = \mu_2 T^* - \xi_C C, \tag{6.3}$$

$$\frac{dH}{dt} = \beta\int_0^{\delta_2} B_2(\upsilon)e^{-\kappa_2\upsilon}T^*_\upsilon d\upsilon - \xi_H H - \psi A H, \tag{6.4}$$

$$\frac{dK}{dt} = \sigma T^* K - \xi_K K, \tag{6.5}$$

$$\frac{dA}{dt} = \rho A H - \xi_A A. \tag{6.6}$$

We calculate the basic reproduction number for model (6.1)-(6.6) as:

$$\mathfrak{R}_0 = \frac{(1-\omega_1)T_0\gamma_1\beta\mathcal{B}_1\mathcal{B}_2}{\xi_H(\mu_1+\xi_{T^*})} + \frac{(1-\omega_2)T_0\gamma_2\mu_2\mathcal{B}_1}{\xi_C(\mu_1+\xi_{T^*})} + \frac{(1-\omega_3)T_0\gamma_3\mathcal{B}_1}{\mu_1+\xi_{T^*}}.$$

Let us assume that $\omega = \omega_1 = \omega_2 = \omega_3$, then $\mathfrak{R}_0$ becomes

$$\mathfrak{R}_0^\omega = (1-\omega)\left[\frac{T_0\gamma_1\beta\mathcal{B}_1\mathcal{B}_2}{\xi_H(\mu_1+\xi_{T^*})} + \frac{T_0\gamma_2\mu_2\mathcal{B}_1}{\xi_C(\mu_1+\xi_{T^*})} + \frac{T_0\gamma_3\mathcal{B}_1}{\mu_1+\xi_{T^*}}\right] = (1-\omega)\mathfrak{R}_0.$$

The drug efficacy ω that makes $\mathfrak{R}_0^\omega \leqslant 1$ and stabilizes system (6.1)-(6.6) around $\mathcal{EP}_0$ is calculated as:

$$1 \geqslant \omega \geqslant \tilde{\omega}_{\text{critical}} = \max\left\{0, 1-\frac{1}{\mathfrak{R}_0}\right\}. \tag{6.7}$$

Let us first disregard the cellular infection in model (6.1)-(6.6), then we get

$$\frac{dT}{dt} = \alpha - \xi_T T - (1-\omega)\gamma_1 TH - (1-\omega)\gamma_2 TC, \tag{6.8}$$

$$\frac{dT^*}{dt} = \int_0^{\delta_1} B_1(\upsilon)e^{-\kappa_1\upsilon}T_\upsilon\left((1-\omega)\gamma_1 H_\upsilon + (1-\omega)\gamma_2 C_\upsilon\right)d\upsilon - (\mu_1+\xi_{T^*})T^* - \lambda T^* K, \tag{6.9}$$

$$\frac{dC}{dt} = \mu_2 T^* - \xi_C C, \tag{6.10}$$

$$\frac{dH}{dt} = \beta\int_0^{\delta_2} B_2(\upsilon)e^{-\kappa_2\upsilon}T^*_\upsilon d\upsilon - \xi_H H - \psi A H, \tag{6.11}$$

$$\frac{dK}{dt} = \sigma T^* K - \xi_K K, \tag{6.12}$$

$$\frac{dA}{dt} = \rho A H - \xi_A A. \tag{6.13}$$

The basic reproduction number of model (6.8)-(6.13) is calculated as:

$$\hat{\mathfrak{R}}_0^\omega = (1-\omega)\left[\frac{T_0\gamma_1\beta\mathcal{B}_1\mathcal{B}_2}{\xi_H(\mu_1+\xi_{T^*})} + \frac{T_0\gamma_2\mu_2\mathcal{B}_1}{\xi_C(\mu_1+\xi_{T^*})}\right] = (1-\omega)\hat{\mathfrak{R}}_0.$$

The drug efficacy ω that makes $\hat{\mathfrak{R}}_0^{\omega} \leqslant 1$ and stabilizes system (6.8)-(6.13) around $\mathcal{EP}_0$ is determined as:

$$1 \geqslant \omega \geqslant \hat{\omega}_{\text{critical}} = \max\left\{0, 1 - \frac{1}{\hat{\mathfrak{R}}_0}\right\}. \tag{6.14}$$

Evidently, $\hat{\mathfrak{R}}_0 < \mathfrak{R}_0$, therefore an HIV-1 model that downplays the significance of cellular infection will underestimate its basic reproduction number. We obtain that $\hat{\omega}_{\text{critical}} \leqslant \tilde{\omega}_{\text{critical}}$ by comparing (6.7) and (6.14). Consequently, using medications with an efficacy of ω such that $\hat{\omega}_{\text{critical}} \leqslant \omega < \tilde{\omega}_{\text{critical}}$ ensures $\hat{\mathfrak{R}}_0^{\omega} \leqslant 1$ and the global stability of $\mathcal{EP}_0$ of system (6.8)-(6.13). On the other hand this makes $\mathfrak{R}_0^{\omega} > 1$ and then $\mathcal{EP}_0$ of system (6.1)-(6.6) will be unstable. Because of this, the basic reproduction number $\hat{\mathfrak{R}}_0^{\omega}$ determines a treatment quantity that is less than what is required to completely eliminate the virus.

Secondly, if we neglect the inflammatory cytokines, then model (6.1)-(6.6) becomes:

$$\frac{dT}{dt} = \alpha - \xi_T T - (1-\omega)\gamma_1 T H - (1-\omega)\gamma_3 T T^*, \tag{6.15}$$

$$\frac{dT^*}{dt} = \int_0^{\delta_1} B_1(\upsilon) e^{-\kappa_1 \upsilon} T_\upsilon \left((1-\omega)\gamma_1 H_\upsilon + (1-\omega)\gamma_3 T_\upsilon^*\right) d\upsilon - \xi_{T^*} T^* - \lambda T^* K, \tag{6.16}$$

$$\frac{dH}{dt} = \beta \int_0^{\delta_2} B_2(\upsilon) e^{-\kappa_2 \upsilon} T_\upsilon^* d\upsilon - \xi_H H - \psi A H, \tag{6.17}$$

$$\frac{dK}{dt} = \sigma T^* K - \xi_K K, \tag{6.18}$$

$$\frac{dA}{dt} = \rho A H - \xi_A A. \tag{6.19}$$

The basic reproduction number for model (6.15)-(6.19) is given by:

$$\tilde{\mathfrak{R}}_0^{\omega} = (1-\omega)\left[\frac{T_0 \gamma_1 \beta \mathcal{B}_1 \mathcal{B}_2}{\xi_H \xi_{T^*}} + \frac{T_0 \gamma_3 \mathcal{B}_1}{\xi_{T^*}}\right] = (1-\omega)\tilde{\mathfrak{R}}_0.$$

Similar to the above discussion, we find that the basic reproduction number $\tilde{\mathfrak{R}}_0^{\omega}$ determines a treatment quantity that is less than what is required to completely eliminate the virus. Therefore, compared to the models given in [9, 22, 51], our suggested model is more pertinent in explaining the dynamics of HIV-1.

7. Numerical simulations

In this section, we use a particular version of the probability distribution to do some numerical simulations for the model (2.1)-(2.6). Let $\upsilon_i \in [0, \delta_i]$, $i = 1, 2$ be constants and consider

$$B_i(\upsilon) = \varphi(\upsilon - \upsilon_i),$$

where $\varphi(.)$ is the Dirac delta function. In addition, we let δ_i tends to ∞ to obtain the following properties:

$$\int_0^{\infty} B_i(\upsilon) d\upsilon = 1, \quad \mathcal{B}_i = \int_0^{\infty} \varphi(\upsilon - \upsilon_i)\, e^{-\kappa_i \upsilon} d\upsilon = e^{-\kappa_i \upsilon_i}, \quad i = 1, 2.$$

Then, model (2.1)-(2.6) becomes:

$$\frac{dT}{dt} = \alpha - \xi_T T - \gamma_1 T H - \gamma_2 T C - \gamma_3 T T^*, \tag{7.1}$$

$$\frac{dT^*}{dt} = e^{-\kappa_1 \upsilon_1}\left(\gamma_1 T_{\upsilon_1} H_{\upsilon_1} + \gamma_2 T_{\upsilon_1} C_{\upsilon_1} + \gamma_3 T_{\upsilon_1} T_{\upsilon_1}^*\right) - \left(\mu_1 + \xi_{T^*}\right) T^* - \lambda T^* K, \tag{7.2}$$

$$\frac{dC}{dt} = \mu_2 T^* - \xi_C C, \tag{7.3}$$

$$\frac{dH}{dt} = \beta e^{-\kappa_2 \upsilon_2} T^*_{\upsilon_2} - \xi_H H - \psi A H, \tag{7.4}$$
$$\frac{dK}{dt} = \sigma T^* K - \xi_K K, \tag{7.5}$$
$$\frac{dA}{dt} = \rho A H - \xi_A A, \tag{7.6}$$

where $U_{\upsilon_i} = U(t-\upsilon_i)$, for $U \in \{T, T^*, C, H\}$, $i = 1, 2$. The threshold parameters for this model become as below:

$$\begin{aligned}
\mathfrak{R}_0 &= \frac{T_0 e^{-\kappa_1 \upsilon_1} (\gamma_1 \beta \xi_C e^{-\kappa_2 \upsilon_2} + \gamma_2 \xi_H \mu_2 + \gamma_3 \xi_C \xi_H)}{\xi_C \xi_H (\mu_1 + \xi_{T^*})}, \\
\mathfrak{R}_1 &= \frac{\alpha \sigma e^{-\kappa_1 \upsilon_1} (\gamma_1 \beta \xi_C e^{-\kappa_2 \upsilon_2} + \gamma_2 \xi_H \mu_2 + \gamma_3 \xi_H \xi_C)}{(\mu_1 + \xi_{T^*})(\xi_T \xi_H \xi_C \sigma + \gamma_1 \beta \xi_C \xi_K e^{-\kappa_2 \upsilon_2} + \gamma_2 \xi_H \xi_K \mu_2 + \gamma_3 \xi_H \xi_C \xi_K)}, \\
\mathfrak{R}_2 &= \frac{\beta \xi_C \rho e^{-\kappa_2 \upsilon_2} C_3}{\xi_H \xi_A \mu_2}, \\
\mathfrak{R}_3 &= \frac{\xi_K \rho \beta e^{-\kappa_2 \upsilon_2}}{\xi_H \xi_A \sigma}, \\
\mathfrak{R}_4 &= \frac{\alpha \sigma e^{-\kappa_1 \upsilon_1} (\gamma_1 \xi_C \xi_A \sigma + \rho \gamma_2 \xi_K \mu_2 + \rho \gamma_3 \xi_C \xi_K)}{\xi_K (\mu_1 + \xi_{T^*})(\xi_T \xi_C \rho \sigma + \gamma_1 \xi_C \xi_A \sigma + \gamma_2 \rho \xi_K \mu_2 + \gamma_3 \rho \xi_C \xi_K)}.
\end{aligned}$$

We fix the values of some parameters (see Table 2) and vary the others, then solving the system of delay differential equations system (DDEs) (7.1)-(7.6) numerically to get the results in the next subsections. The dde23 solver in MATLAB is used to solve the system of DDEs.

Table 2: Model parameters.

Parameter	Value	Source	Parameter	Value	Source	Parameter	Value	Source
α	10	[30, 38, 41]	λ	0.001	[65]	ψ	0.8	[1]
ξ_T	0.01	[3, 34]	ξ_C	0.1	[65]	ξ_K	0.32	[65]
μ_1	0.1	[65]	β	5	[16, 18]	ξ_A	0.1	[1]
ξ_{T^*}	0.75	[65]	ξ_H	0.3	[64]	κ_1	0.2	[17]
κ_2	0.1	[18]	μ_2	0.1	[9]			

7.1. *Analyzing the sensitivity of* $\mathfrak{R}_0$

Identifying the crucial parameters influencing infection mitigation is a foundational task achieved through sensitivity analysis. Particularly, forward sensitivity analysis plays a vital role in disease modeling, providing valuable insights into the factors shaping disease dynamics. A key strategy in curtailing HIV-1 infection is reducing the basic reproduction number $\mathfrak{R}_0$ below unity. Therefore, it is essential to investigate the relationship between the model parameters and the basic reproduction number.

In this section, we employ the local sensitivity analysis method to delineate the sensitivity of $\mathfrak{R}_0$ to the associated parameters in the proposed model (7.1)-(7.6). This analytical technique has gained considerable attention from researchers for its relevance in understanding disease infection [33].

In our examination, we present the normalized forward sensitivity index (Λ_ϵ) concerning $\Re_0$, a crucial virological measure. This sensitivity index gauges the influence of a parameter ϵ on $\Re_0$ and is expressed as follows:

$$\Lambda_\epsilon = \frac{\epsilon}{\Re_0}\frac{\partial \Re_0}{\partial \epsilon}. \tag{7.7}$$

Using relation (7.7) to all parameters of $\Re_0$, we get:

$$\begin{cases} \Lambda_\alpha = 1, \quad \Lambda_{\xi_T} = -1, \quad \Lambda_{\gamma_1} = \Lambda_\beta = -\Lambda_{\xi_H} = \dfrac{\gamma_1 \xi_C e^{-\kappa_2 \upsilon_2}\beta}{\gamma_1 \beta \xi_C e^{-\kappa_2\upsilon_2} + \gamma_2 \xi_H \mu_2 + \gamma_3 \xi_C \xi_H}, \\ \Lambda_{\gamma_2} = \Lambda_{\mu_2} = -\Lambda_{\xi_C} = \dfrac{\gamma_2 \xi_H \mu_2}{\gamma_1 \beta \xi_C e^{-\kappa_2\upsilon_2} + \gamma_2 \xi_H \mu_2 + \gamma_3 \xi_C \xi_H}, \\ \Lambda_{\gamma_3} = \dfrac{\gamma_3 \xi_C \xi_H}{\gamma_1 \beta \xi_C e^{-\kappa_2\upsilon_2} + \gamma_2 \xi_H \mu_2 + \gamma_3 \xi_C \xi_H}, \quad \Lambda_{\kappa_1} = \Lambda_{\upsilon_1} = -\kappa_1\upsilon_1, \quad \Lambda_{\mu_1} = -\dfrac{\mu_1}{\mu_1 + \xi_{T^*}}, \\ \Lambda_{\xi_{T^*}} = -\dfrac{\xi_{T^*}}{\mu_1 + \xi_{T^*}}, \quad \Lambda_{\kappa_2} = \Lambda_{\upsilon_2} = -\kappa_2\upsilon_2\Lambda_{\gamma_1}, \quad \Lambda_\lambda = \Lambda_\psi = \Lambda_\sigma = \Lambda_{\xi_K} = \Lambda_\rho = \Lambda_{\xi_A} = 0. \end{cases} \tag{7.8}$$

As shown by the equations (7.8), the parameters, $\alpha, \gamma_1, \gamma_2, \gamma_3, \mu_2$, and β, exhibit a positive influence on the basic reproduction number $\Re_0$. This suggests that changes in these variables cause commensurate adjustments in $\Re_0$, either fostering its increase or decrease. Conversely, the parameters $\xi_T, \kappa_1, \upsilon_1, \mu_1, \xi_{T^*}, \xi_C, \kappa_2$, υ_2, and ξ_H exert a negative influence on $\Re_0$, suggesting that a rise in their values causes $\Re_0$ to fall. The parameters $\lambda, \psi, \sigma, \xi_K, \rho$, and ξ_A do not affect the value of $\Re_0$. It is noteworthy that, time delay and $\Re_0$ have an inverse association, meaning that while time delay grows, $\Re_0$ usually lowers, indicating a lower probability of infection. It should be noted that the value of $\Re_0$ is heavily influenced by the time delay. Extended periods of time are linked to lower $\Re_0$ values and a decrease in the production of both mature viruses and infected cells. Understanding this relationship is crucial for devising effective treatment strategies. These findings provide valuable guidance for understanding the factors that drive a decreased risk of disease during HIV-1 infection and for formulating effective strategies to control the disease within the host.

In order to offer a numerical simulation, we assign the value $\upsilon_1 = 1, \upsilon_2 = 2, \gamma_1 = 0.0001$, $\gamma_2 = 0.001$, and $\gamma_3 = 0.001$. Figure 1 shows the sensitivity indices for the different model parameters graphically. Moreover, a summary is presented in Table 3. It is evident that a 10% increase or decrease in the values of $\alpha, \gamma_1, \gamma_2, \gamma_3, \mu_2$, and β results in a corresponding $10\%, 4.056\%, 2.976\%, 2.976\%, 2.976$ and 4.056% and 4.056% increase or decrease in $\Re_0$, respectively. In contrast, a 10% increase in the values of $\xi_T, \kappa_1, \upsilon_1, \mu_1, \xi_{T^*}, \xi_C, \kappa_2, \upsilon_2$, and ξ_H leads to a reduction in $\Re_0$ by 10%, $2\%, 2\%, 1.18\%, 8.82\%, 2.97\%, 0.81\%$, and 0.81%, respectively.

Table 3: Indexes of sensitivity for $\Re_0$.

Parameter	Sensitivity index	Parameter	Sensitivity index
α	1	μ_1	-0.118
ξ_T	-1	ξ_{T^*}	-0.882
γ_1	0.406	μ_2	0.297
γ_2	0.297	ξ_C	-0.297
γ_3	0.297	β	0.406
κ_1	-0.2	κ_2	-0.081
υ_1	-0.2	ξ_H	-0.406
υ_2	-0.081		

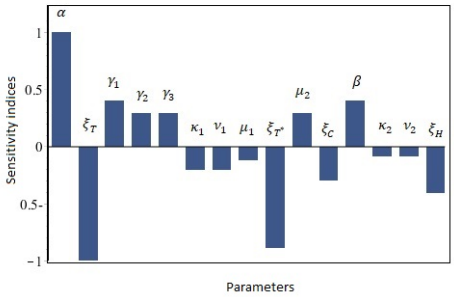


Figure 1: Forward sensitivity analysis for $\mathfrak{R}_0$.

7.2. Stability of the equilibria

We set the delay parameters to $\upsilon_1 = 1$ and $\upsilon_2 = 2$ in this subsection. We use numerical simulation to show our results on global stability from Theorems 5.1 through 5.5. To achieve this, we demonstrate that only one of the system's five equilibria will be reached by the system's solution initiating from any feasible state (any stage of infection). As a result, we select three distinct starting conditions:

I.1: $(T(\varkappa), T^*(\varkappa), C(\varkappa), H(\varkappa), K(\varkappa), A(\varkappa)) = (500, 10, 12, 25, 400, 4)$;
I.2: $(T(\varkappa), T^*(\varkappa), C(\varkappa), H(\varkappa), K(\varkappa), A(\varkappa)) = (300, 8, 9, 15, 300, 3)$;
I.3: $(T(\varkappa), T^*(\varkappa), C(\varkappa), H(\varkappa), K(\varkappa), A(\varkappa)) = (100, 5, 3, 5, 100, 1)$, $\varkappa \in [-2, 0]$.

Choosing values for γ_1, γ_2, γ_3, σ, and ρ under the previously mentioned initials yields the following situations.

Situation 1 (Stability of $\mathcal{EP}_0$): $\gamma_1 = 0.00001$, $\gamma_2 = 0.0001$, $\gamma_3 = 0.0001$, $\sigma = 0.001$, and $\rho = 0.001$. These values give $\mathfrak{R}_0 = 0.32 \leqslant 1$ with the fact that $\mathcal{EP}_0 = (1000, 0, 0, 0, 0, 0)$ is G.A.S as shown in Figure 2. The study's findings in Theorem 5.1 are consistent with the numerical results displayed in Figure 2. This suggests that HIV-1 particles will eventually be eliminated.

Situation 2 (Stability of $\mathcal{EP}_1$): $\gamma_1 = 0.0001$, $\gamma_2 = 0.001$, $\gamma_3 = 0.001$, $\sigma = 0.001$, and $\rho = 0.00001$. These choice give $\mathfrak{R}_0 = 3.24 > 1$, $\mathfrak{R}_3 = 0.44 \leqslant 1$, and $\mathfrak{R}_4 = 0.03 \leqslant 1$. Further, they ensure the existence of the equilibrium point $\mathcal{EP}_1 = (308.57, 6.66, 6.66, 90.88, 0, 0)$. Figure 3 illustrates the global stability of $\mathcal{EP}_1$ which was proved in Theorem 5.2. This situation indicates that the infection will become endemic, however, the immune cells are not stimulated to destroy infected cells and viruses.

Situation 3 (Stability of $\mathcal{EP}_2$): $\gamma_1 = 0.0001$, $\gamma_2 = 0.001$, $\gamma_3 = 0.001$, $\sigma = 0.057$, and $\rho = 0.0002$. This gives $\mathfrak{R}_1 = 1.12 > 1$ and $\mathfrak{R}_3 = 0.15 \leqslant 1$. Then, the equilibrium point $\mathcal{EP}_2 = (346.16, 5.61, 5.61, 76.61, 103.54, 0)$ is G.A.S. Figure 4 shows that the solutions of model (7.1)-(7.6) with the different initials **I.1-I.3** lead to the equilibrium $\mathcal{EP}_2$. This finding aligns with Theorem 5.3's conclusions, which indicates that the infection will become endemic in the availability of CTL immunity, however, the antibodies are not stimulated to destroy viruses.

Situation 4 (Stability of $\mathcal{EP}_3$): $\gamma_1 = 0.0001$, $\gamma_2 = 0.001$, $\gamma_3 = 0.001$, $\sigma = 0.001$, and $\rho = 0.01$. Then we get $\mathfrak{R}_2 = 6.89 > 1$ and $\mathfrak{R}_4 = 0.03 \leqslant 1$. Therefore, the equilibrium point $\mathcal{EP}_3 = (472.58, 5.08, 5.08, 10, 0, 2.22)$ is G.A.S (see Figure 5). Figure 5 illustrates how the concentrations of all compartments gradually converge to $\mathcal{EP}_3$ with time, beginning from any initial. This finding aligns with Theorem 5.4's conclusions, which indicates that the infection will become endemic in the availability of antibody immunity, however, the CTLs are not stimulated to destroy infected cells.

Situation 5 (Stability of $\mathcal{EP}_4$): $\gamma_1 = 0.0013$, $\gamma_2 = 0.002$, $\gamma_3 = 0.002$, $\sigma = 0.057$, and $\rho = 0.013$. This gives $\mathfrak{R}_3 = 9.96 > 1$ and $\mathfrak{R}_4 = 1.31 > 1$. Then, the equilibrium point $\mathcal{EP}_4 = (235.54, 5.61, 5.61, 7.69, 264.87, 3.36)$ is G.A.S (see Figure 6). Figure 6 illustrates how, over time, the concentrations of all compartments eventually trend to $\mathcal{EP}_4$ from any initial values. Consequently, we sum up a consistency between this observation and the outcomes of Theorem 5.5, which indicates that the infection will become endemic in the availability of both CTL and antibody immunities.

7.3. Impact of time delays on HIV-1 dynamics

This section demonstrates the impact of time delays on the system's solutions. We fix the values $\gamma_1 = 0.0013$, $\gamma_2 = 0.002$, $\gamma_3 = 0.002$, $\sigma = 0.057$, and $\rho = 0.013$. Let us take $\upsilon = \upsilon_1 = \upsilon_2$, as a result $\mathfrak{R}_0$ becomes

$$\mathfrak{R}_0 = \frac{T_0 e^{-\kappa_1 \upsilon}\left(\gamma_1 \beta \xi_C e^{-\kappa_2 \upsilon} + \gamma_2 \xi_H \mu_2 + \gamma_3 \xi_C \xi_H\right)}{\xi_C \xi_H \left(\mu_1 + \xi_{T^*}\right)}.$$

It is observed that $\mathfrak{R}_0$ decreases as υ increases. As a result, the system's equilibrium points' stability will be changed as the delay parameter υ is changed. The stability of the uninfected equilibrium point $\mathcal{EP}_0$ is of importance to us, thus, we calculate the critical value of the delay parameter $\upsilon^{\text{critical}}$ so that

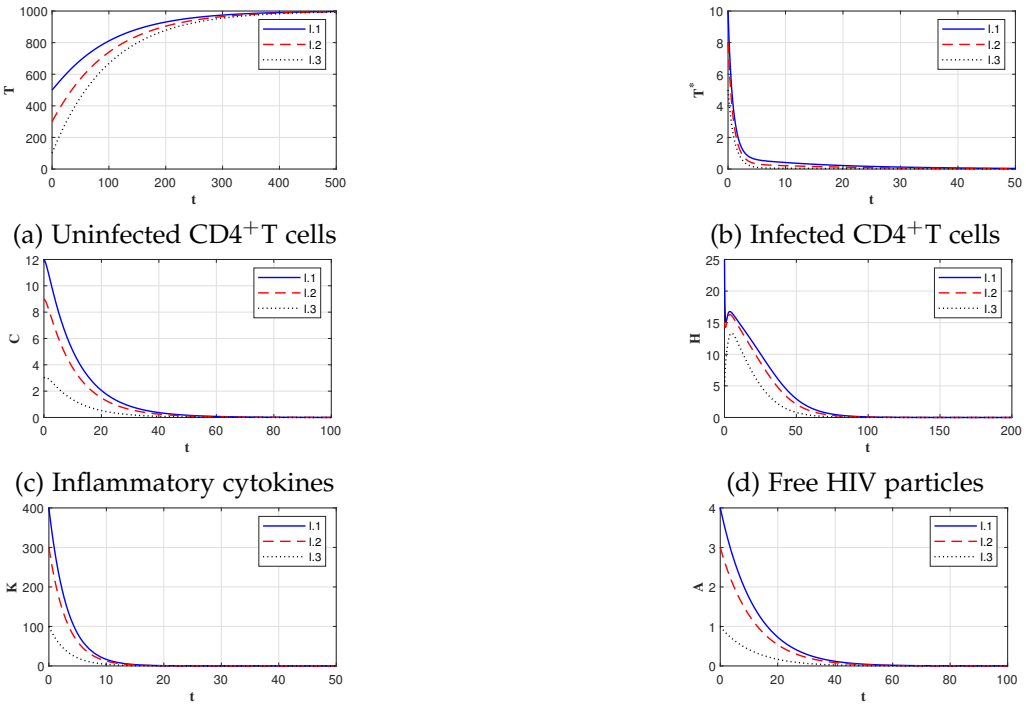
$$\mathfrak{R}_0 = \frac{T_0 e^{-\kappa_1 \upsilon^{\text{critical}}}\left(\gamma_1 \beta \xi_C e^{-\kappa_2 \upsilon^{\text{critical}}} + \gamma_2 \xi_H \mu_2 + \gamma_3 \xi_C \xi_H\right)}{\xi_C \xi_H \left(\mu_1 + \xi_{T^*}\right)} = 1. \tag{7.9}$$

By solving Eq. (7.9) numerically we get $\upsilon^{\text{critical}} = 12.445$. Then we have if $\upsilon \geqslant 12.445$, then $\mathfrak{R}_0 \leqslant 1$ and $\mathcal{EP}_0$ is G.A.S, resulting the eradication of the virus. We now demonstrate how the delay parameter υ affects the system's solutions. We consider the initial condition:

I.4: $(T(\varkappa), T^*(\varkappa), C(\varkappa), H(\varkappa), K(\varkappa), A(\varkappa)) = (700, 15, 4, 20, 500, 3)$, where $\varkappa \in [-\upsilon, 0]$.

The impact of υ on the system's solutions is seen in Figure 7. We find that when υ is raised, the proportion of uninfected CD4$^+$T cells rises and the proportion of other compartments falls.

Time delays are beneficial to the HIV-1 infection process from a biological perspective, helping to eradicate the virus. In summary, long enough lags cause HIV-1 to evolve more slowly, stabilize, and maybe even stop altogether. This might indicate that new HIV-1 medications will be developed based on the delay time extension.

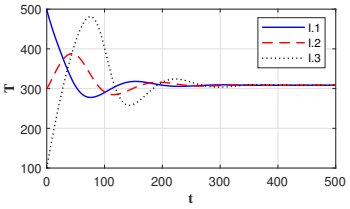


(a) Uninfected CD4$^+$T cells (b) Infected CD4$^+$T cells

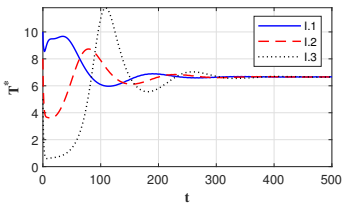
(c) Inflammatory cytokines (d) Free HIV particles

(e) CTLs (f) Antibodies

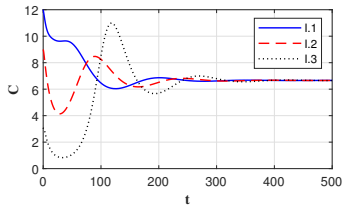
Figure 2: The equilibrium point $\mathcal{EP}_0 = (1000, 0, 0, 0, 0, 0)$ is G.A.S whenever $\mathfrak{R}_0 \leqslant 1$ (Situation 1).



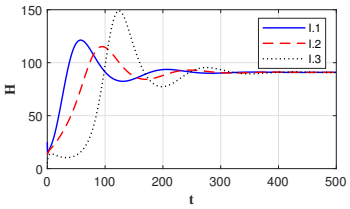
(a) Uninfected CD4$^+$T cells



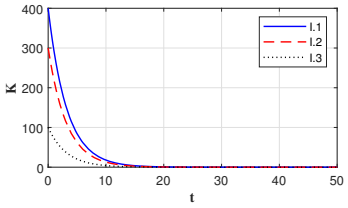
(b) Infected CD4$^+$T cells



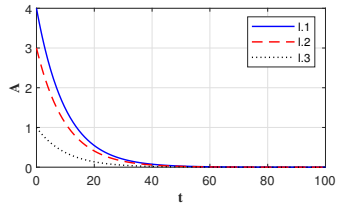
(c) Inflammatory cytokines



(d) Free HIV particles

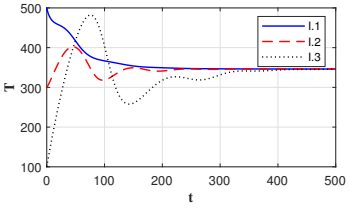


(e) CTLs

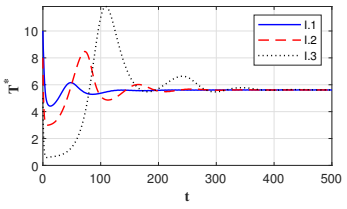


(f) Antibodies

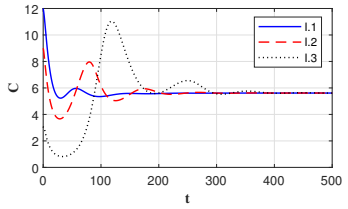
Figure 3: The equilibrium point $\mathcal{EP}_1 = (308.57, 6.66, 6.66, 90.88, 0, 0)$ is G.A.S whenever $\mathfrak{R}_0 > 1$, $\mathfrak{R}_3 \leqslant 1$, and $\mathfrak{R}_4 \leqslant 1$ (Situation 2).



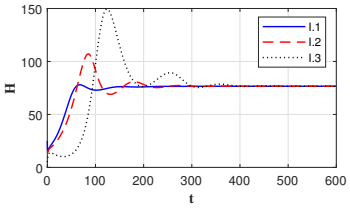
(a) Uninfected CD4$^+$T cells



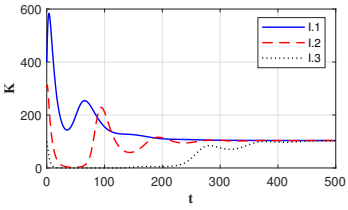
(b) Infected CD4$^+$T cells



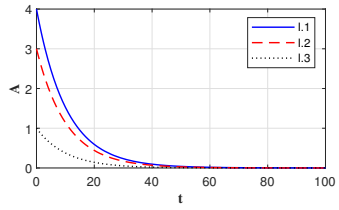
(c) Inflammatory cytokines



(d) Free HIV particles

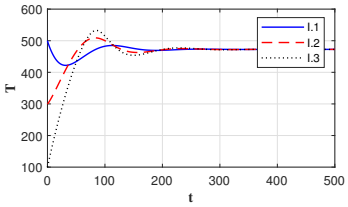


(e) CTLs

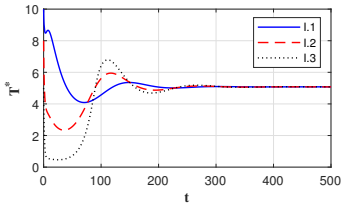


(f) Antibodies

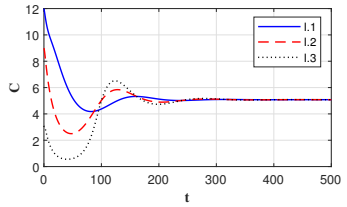
Figure 4: The equilibrium point $\mathcal{EP}_2 = (346.16, 5.61, 5.61, 76.61, 103.54, 0)$ is G.A.S whenever $\mathfrak{R}_1 > 1$ and $\mathfrak{R}_3 \leqslant 1$ (Situation 3) .



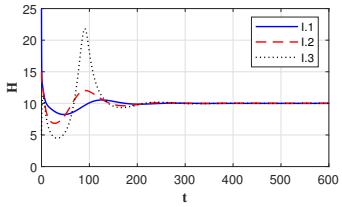
(a) Uninfected CD4$^+$T cells



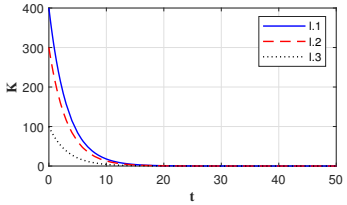
(b) Infected CD4$^+$T cells



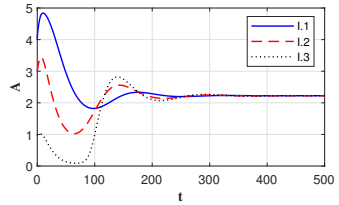
(c) Inflammatory cytokines



(d) Free HIV particles

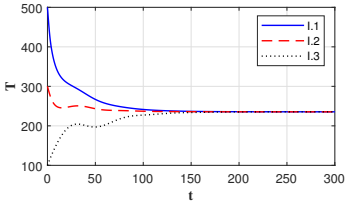


(e) CTLs

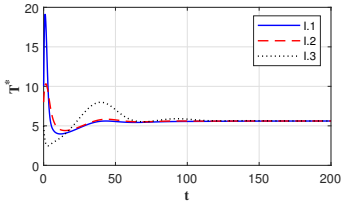


(f) Antibodies

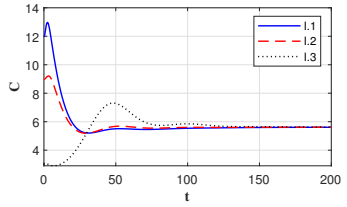
Figure 5: The equilibrium point $\mathcal{EP}_3 = (472.58, 5.08, 5.08, 10, 0, 2.22)$ is G.A.S whenever $\mathfrak{R}_2 > 1$ and $\mathfrak{R}_4 \leqslant 1$ (Situation 4).



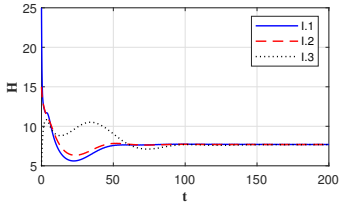
(a) Uninfected CD4$^+$T cells



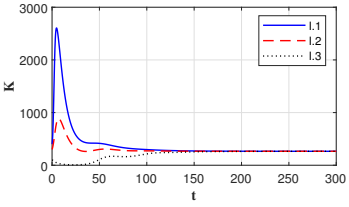
(b) Infected CD4$^+$T cells



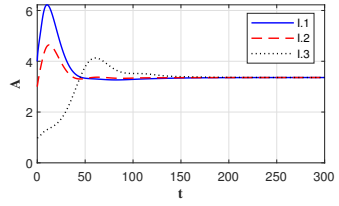
(c) Inflammatory cytokines



(d) Free HIV particles

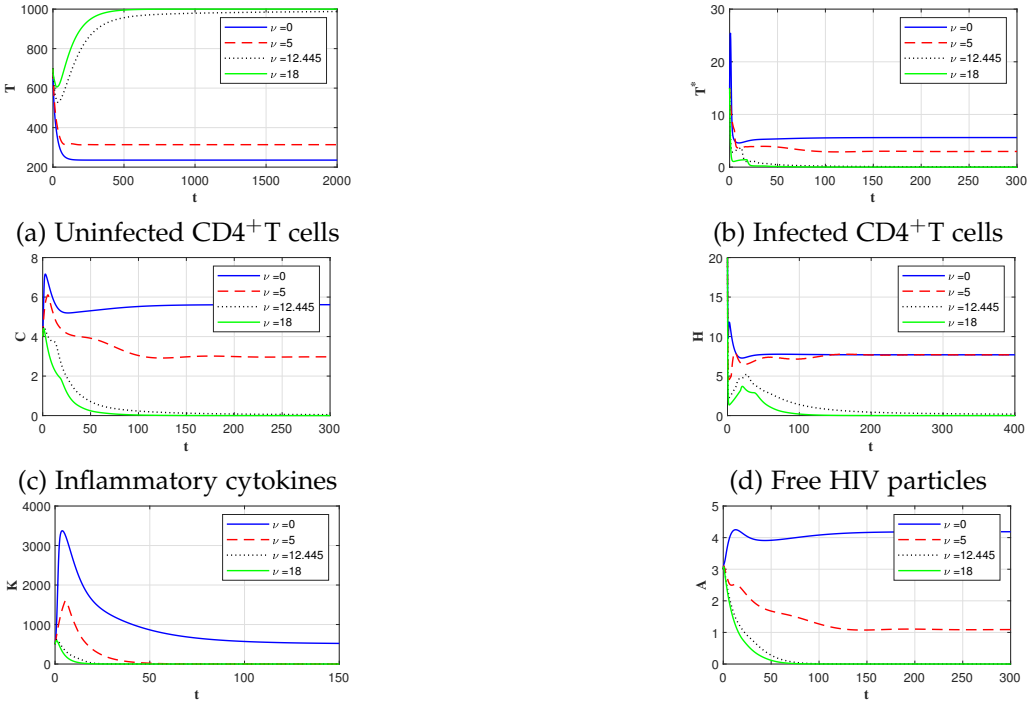


(e) CTLs



(f) Antibodies

Figure 6: The equilibrium point $\mathcal{EP}_4 = (235.53, 5.61, 5.61, 7.69, 264.86, 3.35)$ is G.A.S. whenever $\mathfrak{R}_3 > 1$ and $\mathfrak{R}_4 > 1$ (Situation 5).



(a) Uninfected CD4$^+$T cells

(b) Infected CD4$^+$T cells

(c) Inflammatory cytokines

(d) Free HIV particles

(e) CTLs

(f) Antibodies

Figure 7: Impact of the delay parameter υ on the model's solutions.

8. Conclusion

In this study, we proposed a novel mathematical model to explain the roles of inflammatory cytokines and adaptive immunity (antibody and CTL) in HIV-1 infection. The model has taken into account both viral and cellular infection modes. In addition, the model included two kinds of distributed-time delays during infection processes and viral production. First, we demonstrated nonnegativity and boundedness, which are the key characteristics of the solutions. Next, we proved that the model admits five equilibria, denoted as $\mathcal{EP}_i$, for $i = 0, 1, \ldots, 4$. Five threshold parameters, $\mathfrak{R}_i$, $i = 0, 1, \ldots, 4$, have been determined. These threshold parameters decide whether the model's equilibria exist and are globally stable. We demonstrated the global asymptotic stability for every equilibrium point using the Lyapunov approach. We used a numerical method to solve the model, and then we displayed the findings graphically. We found a correlation between the theoretical and numerical results. To determine how the basic reproduction number $\mathfrak{R}_0$ is impacted by the model's parameter values, sensitivity analysis was carried out. The impact of inflammatory cytokines, time delays, and cellular infection on the dynamics of HIV-1 were deliberated. Cellular infection and inflammatory cytokines both contribute to the number $\mathfrak{R}_0$; therefore, if any of them are neglected, $\mathfrak{R}_0$ will be underestimated. We revised our model to incorporate the impact of three categories of antiretroviral medication treatments. Each antiretroviral medication has a crucial efficacy that we have identified; if treatment effectiveness exceeds this threshold, HIV-1 will be completely eliminated. Additionally, we showed that if cellular infection and/or inflammatory cytokines are disregarded, the projected treatment effectiveness would be less than what is required to completely eradicate the virus. Furthermore, we demonstrated that the elimination of viruses is impacted by the length of the time delay in the same way as antiretroviral treatment. Additionally, it has been demonstrated that extending time delays can effectively lower $\mathfrak{R}_0$ and halt HIV-1 replication. This might mean that novel therapies are being developed, which would cause the delay to increase. Our results indicate that inflammatory cytokines, time delay, and cellular infection are essential elements of the HIV-1 model that cannot be ignored.

Our study's main flaw is that, we were unable to use actual data to determine the values of the model's

parameters. This is because real-world data on HIV-1 infection are still few. Our model can be extended by including (i) viral mutations [2]; (ii) mobility of cells and viruses [14]; (iii) immunologic memory by formulation the model by fractional differential equations [4]; (iv) age-structured [31]; and (v) stochastic interactions [46, 63] .

Acknowledgment

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