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Global Stability of a Delayed HIV Model Incorporating Cytokine Effects and Impaired Immune Responses

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Abstract. A mathematical model describing HIV infection influenced by inflammatory cytokines and weakened adaptive immune responses is formulated and analyzed. The system is represented by delay differential equations that characterize the interactions among uninfected $CD4^+$T cells, infected $CD4^+$T cells, inflammatory cytokines, HIV particles, cytotoxic T lymphocytes (CTLs), and antibodies. The model incorporates three forms of distributed delays: (i) a delay associated with the infection of healthy $CD4^+$T cells, (ii) a delay representing the activation of cytokine responses, and (iii) a delay corresponding to the maturation period of new HIV virions. The model's biological plausibility is verified by demonstrating essential properties of the solutions, including their non-negativity and ultimate boundedness. The basic reproduction number, $\mathcal{R}_0$, is computed and serves as a threshold parameter governing the existence and stability of the system's equilibrium points. Global stability of both equilibrium states is rigorously analyzed through the construction of Lyapunov functionals. To confirm the analytical results, numerical experiments are carried out, accompanied by a sensitivity study of $\mathcal{R}_0$ to examine how variations in essential parameters affect the system. The impact of increased impairment of the adaptive immune response, as well as the delay time, on the progression of viral activity within the body has been discussed. Our findings indicate that, the greater the impairment in adaptive immune response, the more the virus progresses within the body, worsening the patient's condition. Conversely, an increase in the delay time leads to suppression of viral growth.

1. Introduction

AIDS (acquired immunodeficiency syndrome) is a severe and life-threatening condition that results from infection with the human immunodeficiency virus (HIV) [1]. This virus, which carries its genetic material as single-stranded RNA, primarily targets $CD4^+$T cells, the essential players in the adaptive immune response. By attacking and depleting these cells, HIV progressively impairs

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the immune system's function, leaving the body increasingly vulnerable to various infections and diseases it would normally be able to resist. Upon viral infection, the immune system is triggered to combat the invading pathogen. This immune response is divided into two main components: the innate and adaptive immune systems. The innate immunity serves as the immediate, nonspecific defense and involves cells like macrophages and dendritic cells that detect and respond to foreign invaders quickly. On the other hand, adaptive immunity is highly specific and relies on lymphocytes, particularly cytotoxic T lymphocytes (CTLs) (or known as $CD8^+$T cells) and B-cells. B-cells are responsible for producing antibodies that specifically recognize and neutralize viruses, hindering their ability to spread. Concurrently, CTLs target and eliminate infected host cells, reducing viral replication and aiding in the clearance of the infection. These two branches work in tandem to effectively control viral infections and contribute to lasting immune protection [2].

Previous studies largely attributed the loss of healthy $CD4^+$T cells during HIV infection to apoptosis. However, findings by Doitsh et al. [3] demonstrated that a substantial portion of $CD4^+$T cell death actually occurs through pyroptosis–a highly inflammatory form of programmed cell death. Unlike apoptosis, pyroptosis is driven by abortive HIV-1 infection and is now recognized as a major factor in the progression of HIV-1 disease [4], accounting for approximately 95% of $CD4^+$T cell depletion [3]. Earlier research by the same group [5] identified caspase-1, a cysteine protease, as a critical mediator in this pathway through its role in activating proinflammatory cytokines such as $IL-1\beta$. These cytokines perpetuate chronic immune activation and attract more uninfected $CD4^+$T cells to the site of infection, rendering them susceptible to death. This creates a vicious cycle where ongoing cell death enhances inflammation, leading to further immune cell loss and progressive immune system failure.

Within-host mathematical models of HIV infection are among the most promising tools that significantly contribute to understanding the interactions between the virus and target cells, as well as the immune system's response to the infection. These models can help explain key aspects of HIV dynamics, such as the decline in $CD4^+$T cells and the effects of antiretroviral therapy. They may also be used to predict the progression of the virus within the body, identify critical thresholds for viral control, and evaluate treatment strategies. This, in turn, can support the development of more effective therapies and potential cure strategies. The fundamental HIV infection model typically includes compartments for healthy target cells, infected cells, and circulating free virus particles [6]. More advanced models have been developed to investigate the complex interactions between the immune system and the invading virus. Examples of these HIV infection models include: CTL immunity [7]- [11]; humoral (or) antibody immunity [12]- [16]; and both CTL and humoral immunities [17]- [22]. The influence of inflammatory cytokines has not been incorporated into the models presented in these studies.

1.1. **HIV infection models incorporating the effect of inflammatory cytokines.** Recently, numerous HIV infection models have emerged that take into account the effects of inflammatory

cytokines and their impact on the progression of the virus within the body. In this section, we will present an overview of these models. Jiang and Zhang [23] developed a cytokine-enhanced HIV-1 infection model as:

$$\begin{cases} \frac{dY(t)}{dt} = \omega - \psi_Y Y(t) - \Psi_L(Y(t), L(t))L(t) - \sigma G(t)Y(t), \\ \frac{dX(t)}{dt} = e^{-\varrho_1 m_1}\Psi_L(Y(t-m_1), L(t-m_1))L(t-m_1) + \sigma G(t)Y(t) - (\alpha_1 + \psi_X)\, X(t), \\ \frac{dG(t)}{dt} = \alpha_2 X(t) - \psi_G G(t), \\ \frac{dL(t)}{dt} = \delta e^{-\varrho_2 m_2} X(t-m_2) - \psi_L L(t). \end{cases} \tag{1.1}$$

At time, $Y(t)$, $X(t)$, $G(t)$ and $L(t)$ denote the concentrations of healthy CD4$^+$T cells , HIV-infected CD4$^+$T cells, inflammatory cytokines, and free HIV virions, respectively. The rate at which healthy CD4$^+$T cells are generated is ω. The infection rate $\Psi_L(Y, L)L$ refers to the rate at which free HIV particles infect CD4$^+$T cells; which is termed viral infection. Here, Ψ_L is a general function. The rate σGY describes the viral infection enhanced by cytokines. The terms $\alpha_1 X$ and $\alpha_2 X$ refer to the death rate of infected cells due to proptosis and the rate at which inflammatory cytokines are generated from infected cells. The term δX denotes the rate at which infected cells release free HIV particles. Each compartment λ has its own natural death rate, $\psi_\lambda \lambda$. The model incorporates two distinct discrete delays: m_1 signifies the interval from when a virus infects a cell until it begins producing new viral particles, while m_2 captures the time required for these new virions to mature. The expression $e^{-\varrho_i m_i}$, for $i = 1, 2$, denotes the likelihood that a cell or virion remains viable over the corresponding delay interval $[t - m_i, t]$, where $\varrho_i > 0$. Hong et al. [24] extended model (1.1) by incorporating both modes of HIV transmission: virus-to-cell (viral infection) and cell-to-cell (cellular infection). The model utilizes general functional forms for viral infection, $\Psi_L(Y, L)$, cellular infection, $\Psi_X(Y, X)$, and cytokine-enhanced viral infection, $\Psi_G(Y, G)$. Xu [25] proposed an age-structured viral infection model that includes both virus-to-cell and cell-to-cell transmission mechanisms, along with the effect of cytokine-enhanced viral infection. Wang and Feng [26] developed a partial differential equation (PDE) model that incorporates spatial heterogeneity. The model employs general functions to represent the reproduction of healthy CD4$^+$T cells, $\Psi_Y(Y)$, viral infection, $\Psi_L(Y, L)$, and cellular infection, $\Psi_X(Y, X)$. Models presented in [25] and [26] does not consider time delays.

Recently, several cytokine-enhanced HIV infection models have been developed that incorporate various biological factors, such as:

- **CTL immunity**. Zhang et al. [27] proposed the following cytokine-enhanced HIV infection model with CTL immunity:

$$\begin{cases} \frac{dY(t)}{dt} = \omega - \psi_Y Y(t) - Y(t)\left[\sigma_1 L(t) + \sigma_2 G(t)\right], \\ \frac{dX(t)}{dt} = e^{-\varrho_1 m_1} Y(t-m_1)\left[\sigma_1 L(t-m_1) + \sigma_2 G(t-m_1)\right] - (\alpha_1 + \psi_X)\, X(t) - k_1 X(t)T(t), \\ \frac{dG(t)}{dt} = \alpha_2 X(t) - \psi_G G(t), \\ \frac{dL(t)}{dt} = \delta e^{-\varrho_2 m_2} X(t-m_2) - \psi_L L(t), \\ \frac{dT(t)}{dt} = \beta X(t-m_3)T(t-m_3) - \psi_T T(t). \end{cases}$$

Here, T represents the concentration of CTLs. The term βXT describes the proliferation of CTLs, whereas k_1XT accounts for the rate at which CTLs eliminate infected cells. The delay m_3 represents the time interval between antigenic stimulation and the production of CTL immune cells. In [28], the discrete time delays m_1 and m_2 are generalized to distributed time delays to provide a more realistic representation of biological processes. Furthermore, the model incorporates a saturated CTL response. Chen et al. [29] investigated a delayed HIV infection model with diffusion, incorporating cytokine-enhanced viral dynamics, a general incidence function, and the CTL immune response.

- **CTL and antibody immunity**: Dahy et al. [30] introduced a cytokine-augmented HIV-1 model incorporating antibody-mediated and CTL immune responses, accounting for both viral and cellular infection pathways, together with distributed time delays. The model is expressed as follows:

$$\begin{cases} \frac{dY(t)}{dt} = \omega - \psi_Y Y(t) - Y(t)\left[\sigma_1 L(t) + \sigma_2 G(t) + \sigma_3 X(t)\right], \\ \frac{dX(t)}{dt} = \int_0^{\varkappa_1} n_1(m)\, e^{-\varrho_1 m} Y(t-m)\left[\sigma_1 L(t-m) + \sigma_2 G(t-m)\right. \\ \qquad \left. + \sigma_3 X(t-m)\right] dm - (\alpha_1 + \psi_X) X(t) - k_1 X(t) T(t), \\ \frac{dG(t)}{dt} = \alpha_2 X(t) - \psi_G G(t), \\ \frac{dL(t)}{dt} = \delta \int_0^{\varkappa_2} n_2(m) e^{-\varrho_2 m} X(t-m) dm - \psi_L L(t) - k_2 L(t) S(t), \\ \frac{dT(t)}{dt} = \beta X(t) T(t) - \psi_T T(t), \\ \frac{dS(t)}{dt} = \theta L(t) S(t) - \psi_S S(t). \end{cases} \tag{1.2}$$

Here, S represents the concentration of antibodies. The term $\sigma_3 XY$ is incidence rate due to cellular infection. The term θLS describes the proliferation of antibodies, whereas $k_2 LS$ accounts for the rate at which antibodies neutralize viruses. The delay parameter m is selected from a probability distribution function $n_i(m)$ within the time interval $[0, \varkappa_i]$, $i = 1, 2$ where $\varkappa_i$ is the limit superior of the delay period. The term $n_1(m)\, e^{-\varrho_1 m}$ accounts for the delayed effect in the infection process by representing how interactions between healthy CD4$^+$T cells and factors such as HIV, inflammatory cytokines, and infected cells that occurred m time units ago impact the current infection rate. Moreover, the factor $n_2(m)\, e^{-\varrho_2 m}$ describes the delay in the production and maturation of free HIV particles by infected cells. In [31], the authors proposed a cytokine-augmented HIV-1 model that includes both antibody and CTL responses. The model utilizes generalized functions to capture both viral and cellular infection pathways, as well as cytokine-mediated enhancement of infection. Moreover, it adopts general formulations to describe the rates of production, proliferation, clearance, and death within each compartment. However, the model presented in [31] did not incorporate any time delays in its formulation.

All the aforementioned models generally assumed that HIV and infected cells directly stimulate CTL and antibody responses, without accounting for the possibility of immune suppression mechanisms. As highlighted in [32], HIV has the capacity to impair immune responses, potentially altering the expected dynamics. Numerous investigations have explored immune dysfunction in

the context of viral infections, with some emphasizing CTL impairment (e.g., [33]- [38]) and others focusing on B-cell or antibody-related deficiencies (e.g., [39]- [43]). More integrated approaches, such as those by [44]- [46], have analyzed viral infection dynamics under simultaneous impairment of both CTL and antibody responses. Nonetheless, these works have generally overlooked the contribution of inflammatory cytokines. Although [47] accounted for both CTL impairment and cytokine involvement, the model overlooked the dynamics of the healthy target cell population. In addition, it did not incorporate time delays associated with the activation of inflammatory cytokines.

$IL-1\beta$ activity is controlled through multiple steps, including the production of pro-$IL-1\beta$, its enzymatic processing, and the eventual secretion of the active cytokine [3]. Each phase can involve a measurable delay. Nevertheless, the HIV-1 models presented in the referenced studies do not account for these time delays in cytokine activation. This limitation may affect the precision of the models in predicting immune responses and disease progression. Recent investigations by Lv et al. [48] and Elaiw et al. [49] introduced time delays in the activation of inflammatory cytokines within models of cytokine-enhanced viral infections. While Lv et al. incorporated CTL responses, Elaiw et al. focused on antibody-mediated immunity. Both models attribute the initiation of immune responses exclusively to the presence of HIV and infected cells, without accounting for immune system suppression.

1.2. **Research Aims.**

- Formulate a mathematical framework to capture HIV-1 dynamics, explicitly accounting for the influence of inflammatory cytokines and the functional impairment of both CTLs and B-cells.
- Introduce three types of distributed time delays into the model: (i) delay in the infection process of target cells, (ii) delay in cytokine activation, and (iii) delay in the maturation of newly formed viral particles.
- Establish key model characteristics, including the non-negativity and boundedness of solutions.
- Derive the basic reproduction number and identify the system's equilibrium points.
- Perform a detailed global stability assessment for all equilibria, employing Lyapunov-based methods to derive sufficient conditions for global asymptotic stability.
- Support analytical findings through numerical simulations.
- Carry out sensitivity analysis centered on the basic reproduction number to assess how parameter variations influence infection dynamics.
- Investigate how immune response, and time delays collectively shape HIV-1 disease progression.

Through this approach, the study seeks to provide deeper insights into the progression of HIV-1 infection and its complex interactions with the host immune response.

2. Model Construction

We formulate a distributed time delay model based on delay differential equations to describe the variations in the concentrations of six compartments with respect to time t: healthy CD4$^+$T cells $Y(t)$, HIV-infected CD4$^+$T cells $X(t)$, inflammatory cytokines $G(t)$, free HIV particles $L(t)$, CTLs $T(t)$, and antibodies $S(t)$:

$$\begin{cases} \frac{dY(t)}{dt} = \omega - \psi_Y Y(t) - \sigma_1 Y(t)L(t) - \sigma_2 Y(t)G(t) - \sigma_3 Y(t)X(t), \\ \frac{dX(t)}{dt} = \int_0^{\varkappa_1} n_1(m)\, e^{-\varrho_1 m} Y(t-m)\left(\sigma_1 L(t-m) + \sigma_2 G(t-m)\right. \\ \qquad \left. + \sigma_3 X(t-m)\right) dm - (\alpha_1 + \psi_X) X(t) - k_1 X(t)T(t), \\ \frac{dG(t)}{dt} = \alpha_2 \int_0^{\varkappa_2} n_2(m)\, e^{-\varrho_2 m} X(t-m) dm - \psi_G G(t), \\ \frac{dL(t)}{dt} = \delta \int_0^{\varkappa_3} n_3(m) e^{-\varrho_3 m} X(t-m) dm - \psi_L L(t) - k_2 L(t) S(t), \\ \frac{dT(t)}{dt} = \beta X(t) - \psi_T T(t) - \eta_1 X(t) T(t), \\ \frac{dS(t)}{dt} = \theta L(t) - \psi_S S(t) - \eta_2 L(t) S(t). \end{cases} \tag{2.1}$$

Here, the linear terms βX and θL represent the rates at which CTLs and antibodies proliferate, respectively, from infected cells and free HIV particles. The rates at which CTL and antibody immunities are impaired are labeled as $\eta_1 XT$ and $\eta_2 LS$, respectively. The term $n_1(m)\, e^{-\varrho_1 m}$ accounts for the delayed effect in the infection process by representing how interactions between healthy CD4$^+$T cells and factors such as HIV, inflammatory cytokines, and infected cells that occurred m time units ago impact the current infection rate. In addition, $n_2(m)e^{-\varrho_2 m}$ describes the delay in cytokine production following the activation of infected CD4$^+$T cells. It highlights that cytokines are produced gradually over time, rather than instantly. Moreover, the factor $n_3(m)\, e^{-\varrho_3 m}$ describes the delay in the production and maturation of free HIV particles by infected cells. It emphasizes that viral replication and release occur gradually over time, rather than instantly, where $\varrho_i, i = 1,2,3$ are positive constants. The delay parameter m is selected from a probability distribution function $n_i(m)$ within the time interval $[0, \varkappa_i]$, $i = 1,2,3$ where $\varkappa_i$ is the limit superior of the delay period. The function $n_i(m)$, for $i = 1,2,3$, meets the following conditions:

$$n_i(m) > 0, \quad \int_0^{\varkappa_i} n_i(m)\, dm = 1, \quad \text{and} \quad \int_0^{\varkappa_i} n_i(m)\, e^{-qm} dm < \infty, \quad \text{where} \quad q > 0.$$

Suppose that $\hat{N}_i(m) = n_i(m)e^{-\varrho_i m}$ and $N_i = \int_0^{\varkappa_i} \hat{N}_i(m)dm$, $i = 1,2,3$. Then, $0 < N_i \leq 1$, $i = 1,2,3$.

In the following, the initial conditions adopted for system (2.1), are given as:

$$\begin{cases} Y(v) = \mathcal{B}_1(v), \quad X(v) = \mathcal{B}_2(v), \quad G(v) = \mathcal{B}_3(v), \\ L(v) = \mathcal{B}_4(v), \quad T(v) = \mathcal{B}_5(v), \quad S(v) = \mathcal{B}_6(v), \\ \mathcal{B}_j(v) \geq 0, \qquad j = 1,2,...,6, \qquad v \in [-\varkappa, 0], \qquad \varkappa = \max\{\varkappa_1, \varkappa_2, \varkappa_3\}. \end{cases} \tag{2.2}$$

Here, $\mathcal{B}_j(v) \in C([-\varkappa, 0], \mathbb{R}_{\geq 0})$, $j = 1,2,...,6$ and $C = C([-\varkappa, 0], \mathbb{R}_{\geq 0})$ is the Banach space of continuous functions with norm $\left\|\mathcal{B}_j\right\| = \sup_{-\varkappa \leq \zeta \leq 0} \left|\mathcal{B}_j(\zeta)\right|$ for all $\mathcal{B}_j \in C$. Consequently, system (2.1) with initial conditions (2.2) has a unique solution, as established by the standard theory of functional differential equations [50], [51].

3. Characteristics of Solutions

The following result addresses the non-negativity, and ultimate boundedness of solutions for model (2.1), which describe the densities of healthy CD4$^+$T cells, HIV-infected CD4$^+$T cells, inflammatory cytokines, free HIV particles, CTLs, and antibodies.

Lemma 1. Consider the system (2.1) subjected to the initial conditions (2.2). A positively invariant compact set Φ is guaranteed to exist, defined as:

$$\Phi = \Big\{(Y, X, G, L, T, S) \in C^6_{\geq 0} : \big\|Y(t)\big\| \leq \phi_1, \big\|X(t)\big\| \leq \phi_1, \\ \big\|G(t)\big\| \leq \phi_3, \big\|L(t)\big\| \leq \phi_4, \big\|T(t)\big\| \leq \phi_2, \big\|S(t)\big\| \leq \phi_5\Big\}.$$

Proof. We observe from the first equation of system (2.1) that $\frac{dY(t)}{dt}\,|_{Y=0} = \omega > 0$. Consequently, $Y(t)$ remains positive for all $t \geq 0$. Besides, the other equations in the system (2.1) result in the following:

$$\frac{dX(t)}{dt} + (\alpha_1 + \psi_X + k_1 T(t))\, X(t) \\ = \int_0^{\varkappa_1} \hat{N}_1(m) Y(t-m)\, (\sigma_1 L(t-m) + \sigma_2 G(t-m) + \sigma_3 X(t-m))\, dm$$

$$\Longrightarrow X(t) = \mathcal{B}_2(0) e^{-\int_0^t (\alpha_1 + \psi_X + k_1 T(u))du} + \int_0^t e^{-\int_\ell^t (\alpha_1 + \psi_X + k_1 T(u))du} \\ \times \int_0^{\varkappa_1} \hat{N}_1(m) Y(\ell - m)\, (\sigma_1 L(\ell - m) + \sigma_2 G(\ell - m) + \sigma_3 X(\ell - m))\, dm d\ell \geq 0,$$

$$\frac{dG(t)}{dt} + \psi_G G(t) = \alpha_2 \int_0^{\varkappa_2} \hat{N}_2(m) X(t-m) dm$$

$$\Longrightarrow G(t) = \mathcal{B}_3(0) e^{-\psi_G t} + \alpha_2 \int_0^t e^{-\psi_G (t-\ell)} \int_0^{\varkappa_2} \hat{N}_2(m) X(\ell - m) dm d\ell \geq 0,$$

$$\frac{dL(t)}{dt} + (\psi_L + k_2 S(t))\, L(t) = \delta \int_0^{\varkappa_3} \hat{N}_3(m) X(t-m) dm$$

$$\Longrightarrow L(t) = \mathcal{B}_4(0) e^{-\int_0^t (\psi_L + k_2 S(u))du} + \delta \int_0^t e^{-\int_\ell^t (\psi_L + k_2 S(u))du} \int_0^{\varkappa_3} \hat{N}_3(m) X(\ell - m) dm d\ell \geq 0,$$

$$\frac{dT(t)}{dt} + (\psi_T + \eta_1 X(t))\, T(t) = \beta X(t)$$

$$\Longrightarrow T(t) = \mathcal{B}_5(0) e^{-\int_0^t (\psi_T + \eta_1 X(u))du} + \beta \int_0^t e^{-\int_\ell^t (\psi_T + \eta_1 X(u))du} X(\ell)\, d\ell \geq 0,$$

$$\frac{dS(t)}{dt} + (\psi_S + \eta_2 L(t))\, S(t) = \theta L(t)$$

$$\Longrightarrow S(t) = \mathcal{B}_6(0) e^{-\int_0^t (\psi_S + \eta_2 L(u))du} + \theta \int_0^t e^{-\int_\ell^t (\psi_S + \eta_2 L(u))du} L(\ell)\, d\ell \geq 0,$$

for all $t \in [0, \varkappa]$. We deduce, through a recursive argument, that $(Y(t), X(t), G(t), L(t), T(t), S(t)) \geq 0$ for all $t \geq 0$. As a result, the solutions of system (2.1) satisfy $(Y(t), X(t), G(t), L(t), T(t), S(t)) \in \mathbb{R}^6_{\geq 0}$, for all $t \geq 0$.

Now, we proceed to analyze the solutions' ultimate boundedness to confirm their bounded nature. The first equation in the system (2.1) leads to the conclusion that $\limsup_{t\to\infty} Y(t) \leq \frac{\omega}{\psi_Y}$. Following that, we introduce

$$\mathcal{Z}_1(t) = \int_0^{\varkappa_1} \hat{N}_1(m)Y(t-m)dm + X(t) + \frac{\psi_X}{\beta}T(t).$$

Then,

$$\begin{aligned}\frac{d\mathcal{Z}_1(t)}{dt} &= \int_0^{\varkappa_1} \hat{N}_1(m)\left(\omega - \psi_Y Y(t-m)\right)dm - \alpha_1 X(t) - \frac{\psi_X\psi_T}{\beta}T(t) - \left(k_1 + \frac{\eta_1\psi_X}{\beta}\right)X(t)T(t)\\ &< \omega N_1 - \psi_Y\int_0^{\varkappa_1}\hat{N}_1(m)Y(t-m)dm - \alpha_1 X(t) - \frac{\psi_X\psi_T}{\beta}T(t)\\ &\leq \omega - \mathcal{P}_1\left(\int_0^{\varkappa_1}\hat{N}_1(m)Y(t-m)dm + X(t) + \frac{\psi_X}{\beta}T(t)\right) = \omega - \mathcal{P}_1\mathcal{Z}_1(t),\end{aligned}$$

where $\mathcal{P}_1 = \min\{\psi_Y, \alpha_1, \psi_T\}$. This results in $\limsup_{t\to\infty}\mathcal{Z}_1(t) \leq \frac{\omega}{\mathcal{P}_1} = \phi_1$. Since $\int_0^{\varkappa_1}\hat{N}_1(m)Y(t-m)dm \geq 0$, $X(t) \geq 0$, and $T(t) \geq 0$, then $\limsup_{t\to\infty} X(t) \leq \phi_1$ and $\limsup_{t\to\infty} T(t) \leq \frac{\beta\phi_1}{\psi_X} = \phi_2$. In addition, the third equation in the system (2.1) demonstrates that

$$\frac{dG(t)}{dt} = \alpha_2\int_0^{\varkappa_2}\hat{N}_2(m)X(t-m)dm - \psi_G G(t) \leq \alpha_2\phi_1 - \psi_G G(t).$$

This ensures that $\limsup_{t\to\infty} G(t) \leq \frac{\alpha_2\phi_1}{\psi_G} = \phi_3$. Moreover, we proceed to introduce

$$\mathcal{Z}_2(t) = L(t) + \frac{\psi_L}{2\theta}S(t),$$

which yields

$$\begin{aligned}\frac{d\mathcal{Z}_2(t)}{dt} &= \delta\int_0^{\varkappa_3}\hat{N}_3(m)X(t-m)dm - \frac{\psi_L}{2}L(t) - \frac{\psi_L\psi_S}{2\theta}S(t) - \left(k_2 + \frac{\eta_2\psi_L}{2\theta}\right)L(t)S(t)\\ &< \delta N_3\phi_1 - \frac{\psi_L}{2}L(t) - \frac{\psi_L\psi_S}{2\theta}S(t) \leq \delta\phi_1 - \mathcal{P}_2\left(L(t) + \frac{\psi_L}{2\theta}S(t)\right) = \delta\phi_1 - \mathcal{P}_2\mathcal{Z}_2(t).\end{aligned}$$

where $\mathcal{P}_2 = \min\{\frac{\psi_L}{2}, \psi_S\}$. Consequently, we have $\limsup_{t\to\infty}\mathcal{Z}_2(t) \leq \frac{\delta\phi_1}{\mathcal{P}_2} = \phi_4$. Since $L(t) \geq 0$ and $S(t) \geq 0$, then $\limsup_{t\to\infty} L(t) \leq \phi_4$, and $\limsup_{t\to\infty} S(t) \leq \frac{2\theta\phi_4}{\psi_L} = \phi_5$. Overall, the above results ensure the ultimate boundedness of $Y(t)$, $X(t)$, $G(t)$, $L(t)$, $T(t)$, and $S(t)$. This leads to the conclusion that the compact set Φ, which corresponds to model (2.1), is positively invariant.

4. Study on Equilibria and Reproduction Numbers

In this section, we assess the equilibria and identify the threshold parameter necessary to confirm their existence. The results are outlined in the subsequent lemma:

Lemma 2. Considering system (2.1), a basic reproduction number

$$\mathcal{R}_0 = \frac{Y_0 N_1 \left(\psi_G \delta N_3 \sigma_1 + \psi_L \left(\alpha_2 N_2 \sigma_2 + \psi_G \sigma_3\right)\right)}{\psi_G \psi_L \left(\alpha_1 + \psi_X\right)} > 0$$

can be identified, which fulfills the following statements:

(i) The system ensures that it consistently achieves an HIV-free equilibrium, labeled as $\mathcal{FE} = (Y_0, 0, 0, 0, 0, 0)$, $Y_0 = \omega/\psi_Y$.

(ii) The system also maintains an HIV-persistent equilibrium, labeled as $\mathcal{PE} = (\bar{Y}, \bar{X}, \bar{G}, \bar{L}, \bar{T}, \bar{S})$, in the case of $\mathcal{R}_0 > 1$.

Proof. The basic reproduction number, $\mathcal{R}_0$, is computed through the next-generation matrix technique described in [52]. To accomplish this, we can represent the right-hand side of system (2.1) as $\mathcal{J}_1 - \mathcal{J}_2$ with

$$\mathcal{J}_1 = \begin{pmatrix} N_1 \left(\sigma_1 YL + \sigma_2 YG + \sigma_3 YX\right) \\ 0 \\ 0 \end{pmatrix}, \quad \mathcal{J}_2 = \begin{pmatrix} \left(\alpha_1 + \psi_X\right) X + k_1 XT \\ -\alpha_2 N_2 X + \psi_G G \\ -\delta N_3 X + \psi_L L + k_2 LS \end{pmatrix}.$$

System (2.1) consistently exhibits an HIV-free equilibrium $\mathcal{FE} = (Y_0, 0, 0, 0, 0, 0)$, where $Y_0 = \dfrac{\omega}{\psi_Y}$.

Upon computing the Jacobian matrices, $\mathcal{J}_1$ and $\mathcal{J}_2$, at the equilibrium $\mathcal{FE}$, we find

$$J_1 = \begin{pmatrix} N_1\sigma_3 Y_0 & N_1\sigma_2 Y_0 & N_1\sigma_1 Y_0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}, \quad J_2 = \begin{pmatrix} \alpha_1 + \psi_X & 0 & 0 \\ -\alpha_2 N_2 & \psi_G & 0 \\ -\delta N_3 & 0 & \psi_L \end{pmatrix}.$$

Note that, the next generation matrix is in the following form:

$$J_1 J_2^{-1} = \begin{pmatrix} \frac{Y_0 N_1 (\psi_G \delta N_3 \sigma_1 + \psi_L (\alpha_2 N_2 \sigma_2 + \psi_G \sigma_3))}{\psi_G \psi_L (\alpha_1 + \psi_X)} & \frac{N_1 Y_0 \sigma_2}{\psi_G} & \frac{N_1 Y_0 \sigma_1}{\psi_L} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}.$$

The basic reproduction number $\mathcal{R}_0$ is determined by the spectral radius of the matrix product $J_1 J_2^{-1}$, expressed as:

$$\mathcal{R}_0 = \frac{Y_0 N_1 \left(\psi_G \delta N_3 \sigma_1 + \psi_L \left(\alpha_2 N_2 \sigma_2 + \psi_G \sigma_3\right)\right)}{\psi_G \psi_L \left(\alpha_1 + \psi_X\right)} = \mathcal{R}_{0L} + \mathcal{R}_{0G} + \mathcal{R}_{0X}, \tag{4.1}$$

where

$$\mathcal{R}_{0L} = \frac{Y_0 N_1 \delta N_3 \sigma_1}{\psi_L \left(\alpha_1 + \psi_X\right)}, \quad \mathcal{R}_{0G} = \frac{Y_0 N_1 \alpha_2 N_2 \sigma_2}{\psi_G \left(\alpha_1 + \psi_X\right)}, \quad \mathcal{R}_{0X} = \frac{Y_0 N_1 \sigma_3}{\alpha_1 + \psi_X}.$$

To clarify, the contributions of viral and cellular infections are represented, respectively, by $\mathcal{R}_{0L}$ and $\mathcal{R}_{0X}$, whereas $\mathcal{R}_{0G}$ denotes the influence of inflammatory cytokines.

To identify the additional equilibrium beyond $\mathcal{FE}$, we assume (Y, X, G, L, T, S) represents any equilibrium that fulfills the following equations:

$$0 = \omega - \psi_Y Y - \sigma_1 YL - \sigma_2 YG - \sigma_3 YX, \tag{4.2}$$

$$0 = N_1 \left(\sigma_1 YL + \sigma_2 YG + \sigma_3 YX\right) - \left(\alpha_1 + \psi_X\right) X - k_1 XT, \tag{4.3}$$

$$0 = \alpha_2 N_2 X - \psi_G G, \tag{4.4}$$

$$0 = \delta N_3 X - \psi_L L - k_2 LS, \tag{4.5}$$

$$0 = \beta X - \psi_T T - \eta_1 XT, \tag{4.6}$$

$$0 = \theta L - \psi_S S - \eta_2 LS. \tag{4.7}$$

Referring to Eqs. (4.6) and (4.7), we derive

$$T = \frac{\beta X}{\psi_T + \eta_1 X}, \quad S = \frac{\theta L}{\psi_S + \eta_2 L}. \tag{4.8}$$

Replacing the values from Eq. (4.8) in Eq. (4.5), we obtain

$$X = \frac{\psi_S \psi_L L + (\eta_2 \psi_L + k_2 \theta) L^2}{\delta N_3 (\psi_S + \eta_2 L)}. \tag{4.9}$$

By substituting the expression from Eq. (4.9) into Eq. (4.8), we yield

$$T = \frac{\beta \left(\psi_S \psi_L L + (\eta_2 \psi_L + k_2 \theta) L^2\right)}{\delta N_3 \psi_T (\psi_S + \eta_2 L) + \eta_1 (\psi_S \psi_L L + (\eta_2 \psi_L + k_2 \theta) L^2)}. \tag{4.10}$$

Replacing the values from Eq. (4.9) in Eq. (4.4) gives

$$G = \frac{\alpha_2 N_2 \left(\psi_S \psi_L L + (\eta_2 \psi_L + k_2 \theta) L^2\right)}{\delta N_3 \psi_G (\psi_S + \eta_2 L)}. \tag{4.11}$$

From Eqs. (4.2) and (4.3), we get

$$\omega - \psi_Y Y = \frac{1}{N_1} \left((\alpha_1 + \psi_X) X + k_1 XT \right). \tag{4.12}$$

Substituting from Eqs. (4.9) and (4.10) into Eq. (4.12), we get

$$\begin{aligned} Y = \frac{1}{\psi_Y} \Bigg(\omega - & \frac{(\alpha_1 + \psi_X) (\theta k_2 L + \psi_L (\psi_S + \eta_2 L)) L}{\delta N_1 N_3 (\psi_S + \eta_2 L)} \\ & + \frac{\beta k_1 (\theta k_2 L + \psi_L (\psi_S + \eta_2 L))^2 L^2}{\delta N_1 N_3 (\psi_S + \eta_2 L) (\delta N_3 \psi_T (\psi_S + \eta_2 L) + \eta_1 (\theta k_2 L + \psi_L (\psi_S + \eta_2 L)) L)} \Bigg). \end{aligned} \tag{4.13}$$

Substituting from Eqs. (4.9)-(4.11) and (4.13) into Eq. (4.3), we get

$$\frac{L \left(A_5 L^5 + A_4 L^4 + A_3 L^3 + A_2 L^2 + A_1 L + A_0\right)}{\psi_Y \psi_G \delta^2 N_3^2 \left(\delta N_3 \psi_T \psi_S + (\eta_2 \delta \psi_T N_3 + \eta_1 \psi_L \psi_S) L + \eta_1 (\eta_2 \psi_L + \theta k_2) L^2\right) (\psi_S + \eta_2 L)^2} = 0, \tag{4.14}$$

where

$$\begin{aligned} A_5 = & -\Big(\beta k_1 (\eta_2 \psi_L + \theta k_2)^2 - (\eta_2 \eta_1 \psi_L + \eta_1 \theta k_2) (\eta_2 \psi_L (\alpha_1 + \psi_X) + \theta k_2 (\alpha_1 + \psi_X))\Big) \\ & \times (\alpha_2 N_2 \sigma_2 (\eta_2 \psi_L + \theta k_2) + \psi_G (\delta \eta_2 N_3 \sigma_1 + \sigma_3 (\eta_2 \psi_L + \theta k_2))), \end{aligned}$$

$$
\begin{aligned}
A_4 = {} & \beta\delta\eta_2 N_3 k_1 \psi_Y \psi_G \left(\eta_2\psi_L + \theta k_2\right)^2 + \delta\eta_2 N_3 \psi_Y \psi_G \left(\alpha_1 + \psi_X\right)\left(\eta_2\psi_L + \theta k_2\right)\left(\eta_2\eta_1\psi_L + \eta_1\theta k_2\right) \\
& - \Big(\beta k_1 \left(\eta_2\psi_L + \theta k_2\right)^2 - \left(\eta_2\eta_1\psi_L + \eta_1\theta k_2\right)\left(\eta_2\psi_L\left(\alpha_1 + \psi_X\right) + \theta k_2\left(\alpha_1 + \psi_X\right)\right)\Big) \\
& \times \left(\alpha_2 N_2\sigma_2\psi_L\psi_S + \psi_G\left(\delta N_3\sigma_1\psi_S + \sigma_3\psi_L\psi_S\right)\right) \\
& - \left(\alpha_2 N_2\sigma_2\left(\eta_2\psi_L + \theta k_2\right) + \psi_G\left(\delta\eta_2 N_3\sigma_1 + \sigma_3\left(\eta_2\psi_L + \theta k_2\right)\right)\right) \\
& \times \left(2\beta k_1\psi_L\psi_S\left(\eta_2\psi_L + \theta k_2\right) - \left(\eta_2\eta_1\psi_L + \eta_1\theta k_2\right)\left(\psi_L\psi_S\left(\alpha_1 + \psi_X\right) - \delta\eta_2 N_1 N_3\omega\right)\right. \\
& \left. - \left(\eta_1\psi_L\psi_S + \delta\eta_2 N_3\psi_T\right)\left(\eta_2\psi_L\left(\alpha_1 + \psi_X\right) + \theta k_2\left(\alpha_1 + \psi_X\right)\right)\right),
\end{aligned}
$$

$$
\begin{aligned}
A_3 = {} & \beta\delta N_3 k_1 \psi_Y \psi_G \left(3\eta_2^2\psi_L^2\psi_S + 4\eta_2\theta k_2\psi_L\psi_S + \theta^2 k_2^2\psi_S\right) + \delta N_3\psi_Y\psi_G\left(\alpha_1 + \psi_X\right) \\
& \times \left(3\eta_1\eta_2^2\psi_L^2\psi_S + \delta\eta_2^3 N_3\psi_L\psi_T + \delta\eta_2^2\theta N_3 k_2\psi_T + \eta_1\theta^2 k_2^2\psi_S + 4\eta_1\eta_2\theta k_2\psi_L\psi_S\right) \\
& - \left(\alpha_2 N_2\sigma_2\psi_L\psi_S + \psi_G\left(\delta N_3\sigma_1\psi_S + \sigma_3\psi_L\psi_S\right)\right) \\
& \times \left(2\beta k_1\psi_L\psi_S\left(\eta_2\psi_L + \theta k_2\right) - \left(\eta_2\eta_1\psi_L + \eta_1\theta k_2\right)\left(\psi_L\psi_S\left(\alpha_1 + \psi_X\right) - \delta\eta_2 N_1 N_3\omega\right)\right. \\
& \left. - \left(\eta_1\psi_L\psi_S + \delta\eta_2 N_3\psi_T\right)\left(\eta_2\psi_L\left(\alpha_1 + \psi_X\right) + \theta k_2\left(\alpha_1 + \psi_X\right)\right)\right) \\
& - \left(\alpha_2 N_2\sigma_2\left(\eta_2\psi_L + \theta k_2\right) + \psi_G\left(\delta\eta_2 N_3\sigma_1 + \sigma_3\left(\eta_2\psi_L + \theta k_2\right)\right)\right) \\
& \times \left(\delta N_1 N_3\psi_S\omega\left(\eta_2\eta_1\psi_L + \eta_1\theta k_2\right) - \delta N_3\psi_T\psi_S\left(\eta_2\psi_L\left(\alpha_1 + \psi_X\right) + \theta k_2\left(\alpha_1 + \psi_X\right)\right)\right. \\
& \left. + \beta k_1\psi_L^2\psi_S^2 - \left(\eta_1\psi_L\psi_S + \delta\eta_2 N_3\psi_T\right)\left(\psi_L\psi_S\left(\alpha_1 + \psi_X\right) - \delta\eta_2 N_1 N_3\omega\right)\right),
\end{aligned}
$$

$$
\begin{aligned}
A_2 = {} & \beta\delta N_3 k_1 \psi_Y \psi_G \left(3\eta_2\psi_L^2\psi_S^2 + 2\theta k_2\psi_L\psi_S^2\right) + \delta N_3\psi_Y\psi_G\left(\alpha_1 + \psi_X\right) \\
& \times \left(3\eta_1\eta_2\psi_L^2\psi_S^2 + 3\delta\eta_2^2 N_3\psi_L\psi_T\psi_S + 2\delta\eta_2\theta N_3 k_2\psi_T\psi_S + 2\eta_1\theta k_2\psi_L\psi_S^2\right) \\
& - \left(\alpha_2 N_2\sigma_2\left(\eta_2\psi_L + \theta k_2\right) + \psi_G\left(\delta\eta_2 N_3\sigma_1 + \sigma_3\left(\eta_2\psi_L + \theta k_2\right)\right)\right) \\
& \times \left(\delta N_1 N_3\psi_S\omega\left(\eta_1\psi_L\psi_S + \delta\eta_2 N_3\psi_T\right) - \delta N_3\psi_T\psi_S\left(\psi_L\psi_S\left(\alpha_1 + \psi_X\right) - \delta\eta_2 N_1 N_3\omega\right)\right) \\
& - \left(\alpha_2 N_2\sigma_2\psi_L\psi_S + \psi_G\left(\delta N_3\sigma_1\psi_S + \sigma_3\psi_L\psi_S\right)\right) \\
& \times \left(\delta N_1 N_3\psi_S\omega\left(\eta_2\eta_1\psi_L + \eta_1\theta k_2\right) - \delta N_3\psi_T\psi_S\left(\eta_2\psi_L\left(\alpha_1 + \psi_X\right) + \theta k_2\left(\alpha_1 + \psi_X\right)\right)\right. \\
& \left. + \beta k_1\psi_L^2\psi_S^2 - \left(\eta_1\psi_L\psi_S + \delta\eta_2 N_3\psi_T\right)\left(\psi_L\psi_S\left(\alpha_1 + \psi_X\right) - \delta\eta_2 N_1 N_3\omega\right)\right),
\end{aligned}
$$

$$
\begin{aligned}
A_1 = {} & \delta N_3\psi_Y\psi_G\left(\alpha_1 + \psi_X\right)\left(\eta_1\psi_L^2\psi_S^3 + 3\delta\eta_2 N_3\psi_L\psi_T\psi_S^2 + \delta\theta N_3 k_2\psi_T\psi_S^2\right) \\
& - \delta^2 N_1 N_3^2\psi_T\psi_S^2\omega\left(\alpha_2 N_2\sigma_2\left(\eta_2\psi_L + \theta k_2\right) + \psi_G\left(\delta\eta_2 N_3\sigma_1 + \sigma_3\left(\eta_2\psi_L + \theta k_2\right)\right)\right) \\
& + \beta\delta N_3 k_1\psi_Y\psi_G\psi_L^2\psi_S^3 - \left(\alpha_2 N_2\sigma_2\psi_L\psi_S + \psi_G\left(\delta N_3\sigma_1\psi_S + \sigma_3\psi_L\psi_S\right)\right) \\
& \times \left(\delta N_1 N_3\psi_S\omega\left(\eta_1\psi_L\psi_S + \delta\eta_2 N_3\psi_T\right) - \delta N_3\psi_T\psi_S\left(\psi_L\psi_S\left(\alpha_1 + \psi_X\right) - \delta\eta_2 N_1 N_3\omega\right)\right),
\end{aligned}
$$

$$
A_0 = \psi_Y\psi_G\psi_L\psi_T\delta^2\psi_S^3 N_3^2\left(\alpha_1 + \psi_X\right)\left(1 - \mathcal{R}_0\right),
$$

where $\mathcal{R}_0$ is outlined in Eq. (4.1). According to Eq. (4.14), it follows that

(1) If $L = 0$, then based on Eqs. (4.8)-(4.11) and (4.13) we deduce the HIV-free equilibrium, $\mathcal{FE} = (Y_0, 0, 0, 0, 0, 0)$, with $Y_0 = \omega/\psi_Y$.

(2) If $L \neq 0$, the equation $A_5L^5 + A_4L^4 + A_3L^3 + A_2L^2 + A_1L + A_0 = 0$ holds. In this context, we introduce a function $F(L)$ on $[0, \infty)$ as:

$$F(L) = A_5L^5 + A_4L^4 + A_3L^3 + A_2L^2 + A_1L + A_0.$$

We have $F(0) = \psi_Y\psi_G\psi_L\psi_T\delta^2\psi_S^3N_3^2(\alpha_1 + \psi_X)(1 - \mathcal{R}_0) < 0$ when $\mathcal{R}_0 > 1$, and $\lim_{L\to\infty} F(L) = \infty$, which indicates that F possesses a positive real root, $\bar{L}$. By substituting the expressions from Eqs. (4.9) and (4.11) into Eq. (4.2), we get

$$\bar{Y} = \frac{\omega}{\psi_Y + \sigma_1\bar{L} + \sigma_2\bar{G} + \sigma_3\bar{X}},$$

where

$$\bar{X} = \frac{\psi_S\psi_L\bar{L} + (\eta_2\psi_L + k_2\theta)\bar{L}^2}{\delta N_3(\psi_S + \eta_2\bar{L})}, \qquad \bar{G} = \frac{\alpha_2N_2\left(\psi_S\psi_L\bar{L} + (\eta_2\psi_L + k_2\theta)\bar{L}^2\right)}{\delta N_3\psi_G(\psi_S + \eta_2\bar{L})},$$
$$\bar{T} = \frac{\beta\left(\psi_S\psi_L\bar{L} + (\eta_2\psi_L + k_2\theta)\bar{L}^2\right)}{\delta N_3\psi_T(\psi_S + \eta_2\bar{L}) + \eta_1(\psi_S\psi_L\bar{L} + (\eta_2\psi_L + k_2\theta)\bar{L}^2)}, \qquad \bar{S} = \frac{\theta\bar{L}}{\psi_S + \eta_2\bar{L}}.$$

It is evident that the existence of the HIV-persistent equilibrium, $\mathcal{PE} = (\bar{Y}, \bar{X}, \bar{G}, \bar{L}, \bar{T}, \bar{S})$, is confirmed when $\mathcal{R}_0 > 1$.

5. Global Stability Investigation

This section focuses on exploring the global asymptotic stability of all equilibria through the technique of the Lyapunov method. Take the function $\Omega_j(Y, X, G, L, T, S)$ into consideration, and let Θ_j' be the largest invariant subset of Θ_j, where

$$\Theta_j = \left\{(Y, X, G, L, T, S) : \frac{d\Omega_j}{dt} = 0\right\}, \quad j = 0, 1.$$

We introduce a function $\Upsilon(v)$ as follows:

$$\Upsilon(v) = v - 1 - \ln v.$$

The input notation is omitted for the purpose of simplicity, i.e., $(Y, X, G, L, T, S) = (Y(t), X(t), G(t), L(t), T(t), S(t))$.

Theorem 1. The HIV-free equilibrium $\mathcal{FE}$ exhibits global asymptotic stability when $\mathcal{R}_0 \leq 1$.

Proof. Introduce a Lyapunov function $\Omega_0(Y, X, G, L, T, S)$ as follows:

$$\Omega_0 = Y_0\Upsilon\left(\frac{Y}{Y_0}\right) + \frac{1}{N_1}X + \frac{\sigma_2Y_0}{\psi_G}G + \frac{\sigma_1Y_0}{\psi_L}L + \frac{k_1}{2N_1\beta}T^2 + \frac{k_2\sigma_1Y_0}{2\theta\psi_L}S^2$$
$$+ \frac{1}{N_1}\int_0^{\varkappa_1}\hat{N}_1(m)\int_{t-m}^{t}Y(\ell)(\sigma_1L(\ell) + \sigma_2G(\ell) + \sigma_3X(\ell))\,d\ell dm$$
$$+ \frac{\alpha_2\sigma_2Y_0}{\psi_G}\int_0^{\varkappa_2}\hat{N}_2(m)\int_{t-m}^{t}X(\ell)d\ell dm + \frac{\delta\sigma_1Y_0}{\psi_L}\int_0^{\varkappa_3}\hat{N}_3(m)\int_{t-m}^{t}X(\ell)d\ell dm.$$

It is evident that $\Omega_0(Y,X,G,L,T,S) > 0$ for all positive values of Y,X,G,L,T,S, and $\Omega_0(Y_0,0,0,0,0,0) = 0$. The derivative $\frac{d\Omega_0}{dt}$ is computed along the solutions of model (2.1) as:

$$\begin{aligned}
\frac{d\Omega_0}{dt} &= \left(1-\frac{Y_0}{Y}\right)(\omega-\psi_Y Y-\sigma_1 YL-\sigma_2 YG-\sigma_3 YX)\\
&+\frac{1}{N_1}\left(\int_0^{\varkappa_1}\hat{N}_1(m)Y(t-m)\left(\sigma_1 L(t-m)+\sigma_2 G(t-m)+\sigma_3 X(t-m)\right)dm\right.\\
&\left.-\left(\alpha_1+\psi_X\right)X-k_1XT\right)+\frac{\sigma_2 Y_0}{\psi_G}\left(\alpha_2\int_0^{\varkappa_2}\hat{N}_2(m)X(t-m)dm-\psi_G G\right)\\
&+\frac{\sigma_1 Y_0}{\psi_L}\left(\delta\int_0^{\varkappa_3}\hat{N}_3(m)X(t-m)dm-\psi_L L-k_2LS\right)+\frac{k_1T}{N_1\beta}\left(\beta X-\psi_T T-\eta_1 XT\right)\\
&+\frac{k_2\sigma_1 Y_0 S}{\theta\psi_L}\left(\theta L-\psi_S S-\eta_2 LS\right)+\sigma_1 YL+\sigma_2 YG+\sigma_3 YX\\
&-\frac{1}{N_1}\int_0^{\varkappa_1}\hat{N}_1(m)Y(t-m)\left(\sigma_1 L(t-m)+\sigma_2 G(t-m)+\sigma_3 X(t-m)\right)dm\\
&+\frac{\alpha_2\sigma_2 N_2 Y_0}{\psi_G}X-\frac{\alpha_2\sigma_2 Y_0}{\psi_G}\int_0^{\varkappa_2}\hat{N}_2(m)X(t-m)dm+\frac{\delta\sigma_1 N_3 Y_0}{\psi_L}X\\
&-\frac{\delta\sigma_1 Y_0}{\psi_L}\int_0^{\varkappa_3}\hat{N}_3(m)X(t-m)dm\\
&=(\omega-\psi_Y Y)\left(1-\frac{Y_0}{Y}\right)+\sigma_3 Y_0 X-\frac{\alpha_1+\psi_X}{N_1}X-\frac{k_1\psi_T}{N_1\beta}T^2-\frac{k_1\eta_1}{N_1\beta}XT^2\\
&-\frac{k_2\sigma_1\psi_S Y_0}{\theta\psi_L}S^2-\frac{k_2\sigma_1\eta_2 Y_0}{\theta\psi_L}LS^2+\frac{\alpha_2\sigma_2 N_2 Y_0}{\psi_G}X+\frac{\delta\sigma_1 N_3 Y_0}{\psi_L}X.
\end{aligned}$$

By setting $Y_0 = \omega/\psi_Y$, we deduce that

$$\frac{d\Omega_0}{dt} = -\frac{\psi_Y\left(Y-Y_0\right)^2}{Y}+\frac{\alpha_1+\psi_X}{N_1}\left(\mathcal{R}_0-1\right)X-\frac{k_1}{N_1\beta}\left(\psi_T+\eta_1 X\right)T^2-\frac{k_2\sigma_1 Y_0}{\theta\psi_L}\left(\psi_S+\eta_2 L\right)S^2.$$

Therefore, $\frac{d\Omega_0}{dt} \leq 0$ for all $Y,X,T,S,L > 0$ under the condition that $\mathcal{R}_0 \leq 1$. Equality $\frac{d\Omega_0}{dt} = 0$ is achieved in the case when $(Y,X,L,T,S) = (Y_0,0,0,0,0)$. The solutions of system (2.1) converge to $\Theta_0^{'}$. The elements of $\Theta_0^{'}$ satisfy $(Y(t),X(t),L(t),T(t),S(t)) = (Y_0,0,0,0,0)$ for all t. At this point, $\frac{dG(t)}{dt} = \frac{dY(t)}{dt} = 0$. The first equation of system (2.1) simplifies to

$$0 = \frac{dY(t)}{dt} = \omega-\psi_Y Y_0-\sigma_2 Y_0 G(t).$$

From this $G(t) = 0$ for all t, leading to $\Theta_0^{'} = \{\mathcal{FE}\}$. By applying the Lyapunov-LaSalle asymptotic stability theorem [53], it is concluded that the equilibrium $\mathcal{FE}$ is globally asymptotically stable.

Theorem 2. The HIV-persistent equilibrium $\mathcal{PE}$ achieves global asymptotic stability when $\mathcal{R}_0 > 1$.

Proof. Define a function $\Omega_1(Y,X,G,L,T,S)$ as:

$$\Omega_1 = \bar{Y}\mathrm{Y}\left(\frac{Y}{\bar{Y}}\right)+\frac{\bar{X}}{N_1}\mathrm{Y}\left(\frac{X}{\bar{X}}\right)+\frac{\sigma_2\bar{Y}}{\psi_G}\bar{G}\mathrm{Y}\left(\frac{G}{\bar{G}}\right)+\frac{\sigma_1\bar{Y}}{\psi_L+k_2\bar{S}}\bar{L}\mathrm{Y}\left(\frac{L}{\bar{L}}\right)$$

$$+\frac{k_1}{2N_1\left(\beta-\eta_1\bar{T}\right)}\left(T-\bar{T}\right)^2+\frac{k_2\sigma_1\bar{Y}}{2\left(\theta-\eta_2\bar{S}\right)\left(\psi_L+k_2\bar{S}\right)}\left(S-\bar{S}\right)^2$$
$$+\frac{\sigma_1\bar{Y}\bar{L}}{N_1}\int_0^{\varkappa_1}\hat{N}_1(m)\int_{t-m}^{t}\Upsilon\left(\frac{Y(\ell)L(\ell)}{\bar{Y}\bar{L}}\right)d\ell dm+\frac{\sigma_2\bar{Y}\bar{G}}{N_1}\int_0^{\varkappa_1}\hat{N}_1(m)\int_{t-m}^{t}\Upsilon\left(\frac{Y(\ell)G(\ell)}{\bar{Y}\bar{G}}\right)d\ell dm$$
$$+\frac{\sigma_3\bar{Y}\bar{X}}{N_1}\int_0^{\varkappa_1}\hat{N}_1(m)\int_{t-m}^{t}\Upsilon\left(\frac{Y(\ell)X(\ell)}{\bar{Y}\bar{X}}\right)d\ell dm+\frac{\alpha_2\sigma_2\bar{Y}\bar{X}}{\psi_G}\int_0^{\varkappa_2}\hat{N}_2(m)\int_{t-m}^{t}\Upsilon\left(\frac{X(\ell)}{\bar{X}}\right)d\ell dm$$
$$+\frac{\delta\sigma_1\bar{Y}\bar{X}}{\psi_L+k_2\bar{S}}\int_0^{\varkappa_3}\hat{N}_3(m)\int_{t-m}^{t}\Upsilon\left(\frac{X(\ell)}{\bar{X}}\right)d\ell dm.$$

Eqs. (4.6) and (4.7) indicate that $\beta-\eta_1\bar{T}=\dfrac{\psi_T\bar{T}}{\bar{X}}>0$ and $\theta-\eta_2\bar{S}=\dfrac{\psi_S\bar{S}}{\bar{L}}>0$. The computation of $\frac{d\Omega_1}{dt}$ yields

$$\frac{d\Omega_1}{dt}=\left(1-\frac{\bar{Y}}{Y}\right)\left(\omega-\psi_Y Y-\sigma_1 YL-\sigma_2 YG-\sigma_3 YX\right)$$
$$+\frac{1}{N_1}\left(1-\frac{\bar{X}}{X}\right)\left(\int_0^{\varkappa_1}\hat{N}_1(m)Y(t-m)\left(\sigma_1L(t-m)+\sigma_2G(t-m)+\sigma_3X(t-m)\right)dm\right.$$
$$\left.-\left(\alpha_1+\psi_X\right)X-k_1XT\right)+\frac{\sigma_2\bar{Y}}{\psi_G}\left(1-\frac{\bar{G}}{G}\right)\left(\alpha_2\int_0^{\varkappa_2}\hat{N}_2(m)X(t-m)dm-\psi_G G\right)$$
$$+\frac{\sigma_1\bar{Y}}{\psi_L+k_2\bar{S}}\left(1-\frac{\bar{L}}{L}\right)\left(\delta\int_0^{\varkappa_3}\hat{N}_3(m)X(t-m)dm-\psi_L L-k_2LS\right)$$
$$+\frac{k_1\left(T-\bar{T}\right)}{N_1\left(\beta-\eta_1\bar{T}\right)}\left(\beta X-\psi_T T-\eta_1XT\right)+\frac{k_2\sigma_1\bar{Y}\left(S-\bar{S}\right)}{\left(\theta-\eta_2\bar{S}\right)\left(\psi_L+k_2\bar{S}\right)}\left(\theta L-\psi_S S-\eta_2LS\right)$$
$$+\frac{\sigma_1\bar{Y}\bar{L}}{N_1}\int_0^{\varkappa_1}\hat{N}_1(m)\left(\frac{YL}{\bar{Y}\bar{L}}-\frac{Y(t-m)L(t-m)}{\bar{Y}\bar{L}}+\ln\left(\frac{Y(t-m)L(t-m)}{YL}\right)\right)dm$$
$$+\frac{\sigma_2\bar{Y}\bar{G}}{N_1}\int_0^{\varkappa_1}\hat{N}_1(m)\left(\frac{YG}{\bar{Y}\bar{G}}-\frac{Y(t-m)G(t-m)}{\bar{Y}\bar{G}}+\ln\left(\frac{Y(t-m)G(t-m)}{YG}\right)\right)dm$$
$$+\frac{\sigma_3\bar{Y}\bar{X}}{N_1}\int_0^{\varkappa_1}\hat{N}_1(m)\left(\frac{YX}{\bar{Y}\bar{X}}-\frac{Y(t-m)X(t-m)}{\bar{Y}\bar{X}}+\ln\left(\frac{Y(t-m)X(t-m)}{YX}\right)\right)dm$$
$$+\frac{\alpha_2\sigma_2\bar{Y}\bar{X}}{\psi_G}\int_0^{\varkappa_2}\hat{N}_2(m)\left(\frac{X}{\bar{X}}-\frac{X(t-m)}{\bar{X}}+\ln\left(\frac{X(t-m)}{X}\right)\right)dm$$
$$+\frac{\delta\sigma_1\bar{Y}\bar{X}}{\psi_L+k_2\bar{S}}\int_0^{\varkappa_3}\hat{N}_3(m)\left(\frac{X}{\bar{X}}-\frac{X(t-m)}{\bar{X}}+\ln\left(\frac{X(t-m)}{X}\right)\right)dm.$$

After collecting terms, we obtain

$$\frac{d\Omega_1}{dt}=\left(\omega-\psi_Y Y\right)\left(1-\frac{\bar{Y}}{Y}\right)+\sigma_1\bar{Y}L+\sigma_3\bar{Y}X-\frac{\alpha_1+\psi_X}{N_1}\left(X-\bar{X}\right)$$
$$-\frac{k_1}{N_1}T\left(X-\bar{X}\right)-\frac{\sigma_1}{N_1}\int_0^{\varkappa_1}\hat{N}_1(m)\frac{Y(t-m)L(t-m)\bar{X}}{X}dm$$
$$-\frac{\sigma_2}{N_1}\int_0^{\varkappa_1}\hat{N}_1(m)\frac{Y(t-m)G(t-m)\bar{X}}{X}dm-\frac{\sigma_3}{N_1}\int_0^{\varkappa_1}\hat{N}_1(m)\frac{Y(t-m)X(t-m)\bar{X}}{X}dm$$

$$
\begin{aligned}
&- \frac{\alpha_2\sigma_2\bar{Y}}{\psi_G}\int_0^{\varkappa_2}\hat{N}_2(m)\frac{X(t-m)\bar{G}}{G}dm + \sigma_2\bar{Y}\bar{G} - \frac{\sigma_1\psi_L\bar{Y}}{\psi_L+k_2\bar{S}}\left(L-\bar{L}\right)\\
&- \frac{k_2\sigma_1\bar{Y}}{\psi_L+k_2\bar{S}}S\left(L-\bar{L}\right) - \frac{\delta\sigma_1\bar{Y}}{\psi_L+k_2\bar{S}}\int_0^{\varkappa_3}\hat{N}_3(m)\frac{X(t-m)\bar{L}}{L}dm\\
&+ \frac{k_1\left(T-\bar{T}\right)}{N_1\left(\beta-\eta_1\bar{T}\right)}\left(\beta X-\psi_T T-\eta_1 XT\right) + \frac{k_2\sigma_1\bar{Y}\left(S-\bar{S}\right)}{\left(\theta-\eta_2\bar{S}\right)\left(\psi_L+k_2\bar{S}\right)}\left(\theta L-\psi_S S-\eta_2 LS\right)\\
&+ \frac{\sigma_1\bar{Y}\bar{L}}{N_1}\int_0^{\varkappa_1}\hat{N}_1(m)\ln\left(\frac{Y(t-m)L(t-m)}{YL}\right)dm + \frac{\sigma_2\bar{Y}\bar{G}}{N_1}\int_0^{\varkappa_1}\hat{N}_1(m)\\
&\times\ln\left(\frac{Y(t-m)G(t-m)}{YG}\right)dm + \frac{\sigma_3\bar{Y}\bar{X}}{N_1}\int_0^{\varkappa_1}\hat{N}_1(m)\ln\left(\frac{Y(t-m)X(t-m)}{YX}\right)dm\\
&+ \frac{\alpha_2\sigma_2 N_2\bar{Y}}{\psi_G}X + \frac{\delta\sigma_1 N_3\bar{Y}}{\psi_L+k_2\bar{S}}X + \frac{\alpha_2\sigma_2\bar{Y}\bar{X}}{\psi_G}\int_0^{\varkappa_2}\hat{N}_2(m)\ln\left(\frac{X(t-m)}{X}\right)dm\\
&+ \frac{\delta\sigma_1\bar{Y}\bar{X}}{\psi_L+k_2\bar{S}}\int_0^{\varkappa_3}\hat{N}_3(m)\ln\left(\frac{X(t-m)}{X}\right)dm.
\end{aligned}
$$

The equilibrium conditions associated with $\mathcal{PE}$ indicate that

$$
\begin{aligned}
&\omega = \psi_Y\bar{Y} + \sigma_1\bar{Y}\bar{L} + \sigma_2\bar{Y}\bar{G} + \sigma_3\bar{Y}\bar{X},\\
&\sigma_1\bar{Y}\bar{L} + \sigma_2\bar{Y}\bar{G} + \sigma_3\bar{Y}\bar{X} = \frac{1}{N_1}\left(\alpha_1+\psi_X+k_1\bar{T}\right)\bar{X},\\
&\bar{G} = \frac{\alpha_2 N_2\bar{X}}{\psi_G}, \qquad \bar{L} = \frac{\delta N_3\bar{X}}{\psi_L+k_2\bar{S}},\\
&\beta\bar{X} = \psi_T\bar{T} + \eta_1\bar{X}\bar{T}, \qquad \theta\bar{L} = \psi_S\bar{S} + \eta_2\bar{L}\bar{S}.
\end{aligned}
$$

From this, we find

$$
\begin{aligned}
\frac{d\Omega_1}{dt} &= \left(\psi_Y\bar{Y}-\psi_Y Y\right)\left(1-\frac{\bar{Y}}{Y}\right) + \left(\sigma_1\bar{Y}\bar{L}+\sigma_2\bar{Y}\bar{G}+\sigma_3\bar{Y}\bar{X}\right)\left(1-\frac{\bar{Y}}{Y}\right)\\
&+ \sigma_1\bar{Y}L + \sigma_3\bar{Y}X - \frac{\alpha_1+\psi_X}{N_1}\left(X-\bar{X}\right) - \frac{k_1}{N_1}T\left(X-\bar{X}\right) - \frac{\sigma_1\bar{Y}\bar{L}}{N_1}\int_0^{\varkappa_1}\hat{N}_1(m)\\
&\times\frac{Y(t-m)L(t-m)\bar{X}}{\bar{Y}\bar{L}X}dm - \frac{\sigma_2\bar{Y}\bar{G}}{N_1}\int_0^{\varkappa_1}\hat{N}_1(m)\frac{Y(t-m)G(t-m)\bar{X}}{\bar{Y}\bar{G}X}dm\\
&- \frac{\sigma_3\bar{Y}\bar{X}}{N_1}\int_0^{\varkappa_1}\hat{N}_1(m)\frac{Y(t-m)X(t-m)}{\bar{Y}X}dm - \frac{\sigma_2\bar{Y}\bar{G}}{N_2}\int_0^{\varkappa_2}\hat{N}_2(m)\frac{X(t-m)\bar{G}}{\bar{X}G}dm\\
&+ \sigma_2\bar{Y}\bar{G} - \frac{\sigma_1\psi_L\bar{Y}}{\psi_L+k_2\bar{S}}\left(L-\bar{L}\right) - \frac{k_2\sigma_1\bar{Y}}{\psi_L+k_2\bar{S}}S\left(L-\bar{L}\right) - \frac{\sigma_1\bar{Y}\bar{L}}{N_3}\int_0^{\varkappa_3}\hat{N}_3(m)\frac{X(t-m)\bar{L}}{\bar{X}L}dm\\
&+ \frac{k_1\left(T-\bar{T}\right)}{N_1\left(\beta-\eta_1\bar{T}\right)}\left(\beta X-\psi_T T-\eta_1 XT-\beta\bar{X}+\psi_T\bar{T}+\eta_1\bar{X}\bar{T}-\eta_1 X\bar{T}+\eta_1 X\bar{T}\right)\\
&+ \frac{k_2\sigma_1\bar{Y}\left(S-\bar{S}\right)}{\left(\theta-\eta_2\bar{S}\right)\left(\psi_L+k_2\bar{S}\right)}\left(\theta L-\psi_S S-\eta_2 LS-\theta\bar{L}+\psi_S\bar{S}+\eta_2\bar{L}\bar{S}-\eta_2 L\bar{S}+\eta_2 L\bar{S}\right)\\
&+ \frac{\sigma_1\bar{Y}\bar{L}}{N_1}\int_0^{\varkappa_1}\hat{N}_1(m)\ln\left(\frac{Y(t-m)L(t-m)}{YL}\right)dm + \frac{\sigma_2\bar{Y}\bar{G}}{N_1}\int_0^{\varkappa_1}\hat{N}_1(m)
\end{aligned}
$$

$$\times \ln\left(\frac{Y(t-m)G(t-m)}{YG}\right)dm + \frac{\sigma_3\bar{Y}\bar{X}}{N_1}\int_0^{\varkappa_1}\hat{N}_1(m)\ln\left(\frac{Y(t-m)X(t-m)}{YX}\right)dm$$
$$+ \frac{\alpha_2\sigma_2N_2\bar{Y}}{\psi_G}X + \frac{\delta\sigma_1N_3\bar{Y}}{\psi_L+k_2\bar{S}}X + \frac{\sigma_2\bar{Y}\bar{G}}{N_2}\int_0^{\varkappa_2}\hat{N}_2(m)\ln\left(\frac{X(t-m)}{X}\right)dm$$
$$+ \frac{\sigma_1\bar{Y}\bar{L}}{N_3}\int_0^{\varkappa_3}\hat{N}_3(m)\ln\left(\frac{X(t-m)}{X}\right)dm.$$

Simplifying, we arrive at

$$\frac{d\Omega_1}{dt} = -\frac{\psi_Y\left(Y-\bar{Y}\right)^2}{Y} + \left(\sigma_1\bar{Y}\bar{L}+\sigma_2\bar{Y}\bar{G}+\sigma_3\bar{Y}\bar{X}\right)\left(1-\frac{\bar{Y}}{Y}\right) + \sigma_1\bar{Y}L + \sigma_3\bar{Y}X$$
$$- \frac{\alpha_1+\psi_X}{N_1}\left(X-\bar{X}\right) - \frac{k_1}{N_1}T\left(X-\bar{X}\right) + \frac{k_1}{N_1}\bar{T}\left(X-\bar{X}\right) - \frac{k_1}{N_1}\bar{T}\left(X-\bar{X}\right)$$
$$- \frac{\sigma_1\bar{Y}\bar{L}}{N_1}\int_0^{\varkappa_1}\hat{N}_1(m)\frac{Y(t-m)L(t-m)\bar{X}}{\bar{Y}\bar{L}X}dm - \frac{\sigma_2\bar{Y}\bar{G}}{N_1}\int_0^{\varkappa_1}\hat{N}_1(m)\frac{Y(t-m)G(t-m)\bar{X}}{\bar{Y}\bar{G}X}dm$$
$$- \frac{\sigma_3\bar{Y}\bar{X}}{N_1}\int_0^{\varkappa_1}\hat{N}_1(m)\frac{Y(t-m)X(t-m)}{\bar{Y}X}dm - \frac{\sigma_2\bar{Y}\bar{G}}{N_2}\int_0^{\varkappa_2}\hat{N}_2(m)\frac{X(t-m)\bar{G}}{\bar{X}G}dm$$
$$+ \sigma_2\bar{Y}\bar{G} - \frac{\sigma_1\psi_L\bar{Y}}{\psi_L+k_2\bar{S}}\left(L-\bar{L}\right) - \frac{k_2\sigma_1\bar{Y}}{\psi_L+k_2\bar{S}}S\left(L-\bar{L}\right) + \frac{k_2\sigma_1\bar{Y}}{\psi_L+k_2\bar{S}}\bar{S}\left(L-\bar{L}\right)$$
$$- \frac{k_2\sigma_1\bar{Y}}{\psi_L+k_2\bar{S}}\bar{S}\left(L-\bar{L}\right) - \frac{\sigma_1\bar{Y}\bar{L}}{N_3}\int_0^{\varkappa_3}\hat{N}_3(m)\frac{X(t-m)\bar{L}}{\bar{X}L}dm$$
$$+ \frac{k_1}{N_1}\left(T-\bar{T}\right)\left(X-\bar{X}\right) - \frac{k_1\left(\psi_T+\eta_1X\right)}{N_1\left(\beta-\eta_1\bar{T}\right)}\left(T-\bar{T}\right)^2 + \frac{k_2\sigma_1\bar{Y}}{\psi_L+k_2\bar{S}}\left(S-\bar{S}\right)\left(L-\bar{L}\right)$$
$$- \frac{k_2\sigma_1\bar{Y}\left(\psi_S+\eta_2L\right)}{\left(\theta-\eta_2\bar{S}\right)\left(\psi_L+k_2\bar{S}\right)}\left(S-\bar{S}\right)^2 + \frac{\sigma_1\bar{Y}\bar{L}}{N_1}\int_0^{\varkappa_1}\hat{N}_1(m)\ln\left(\frac{Y(t-m)L(t-m)}{YL}\right)dm$$
$$+ \frac{\sigma_2\bar{Y}\bar{G}}{N_1}\int_0^{\varkappa_1}\hat{N}_1(m)\ln\left(\frac{Y(t-m)G(t-m)}{YG}\right)dm + \frac{\sigma_3\bar{Y}\bar{X}}{N_1}\int_0^{\varkappa_1}\hat{N}_1(m)$$
$$\times \ln\left(\frac{Y(t-m)X(t-m)}{YX}\right)dm + \frac{\alpha_2\sigma_2N_2\bar{Y}}{\psi_G}X + \frac{\delta\sigma_1N_3\bar{Y}}{\psi_L+k_2\bar{S}}X$$
$$+ \frac{\sigma_2\bar{Y}\bar{G}}{N_2}\int_0^{\varkappa_2}\hat{N}_2(m)\ln\left(\frac{X(t-m)}{X}\right)dm + \frac{\sigma_1\bar{Y}\bar{L}}{N_3}\int_0^{\varkappa_3}\hat{N}_3(m)\ln\left(\frac{X(t-m)}{X}\right)dm. \tag{5.1}$$

In this way, Eq. (5.1) is rewritten in the form

$$\frac{d\Omega_1}{dt} = -\frac{\psi_Y\left(Y-\bar{Y}\right)^2}{Y} + \left(\sigma_1\bar{Y}\bar{L}+\sigma_2\bar{Y}\bar{G}+\sigma_3\bar{Y}\bar{X}\right)\left(1-\frac{\bar{Y}}{Y}\right) + \sigma_3\bar{Y}X$$
$$- \frac{1}{N_1}\left(\alpha_1+\psi_X+k_1\bar{T}\right)\left(X-\bar{X}\right) - \frac{\sigma_1\bar{Y}\bar{L}}{N_1}\int_0^{\varkappa_1}\hat{N}_1(m)\frac{Y(t-m)L(t-m)\bar{X}}{\bar{Y}\bar{L}X}dm$$
$$- \frac{\sigma_2\bar{Y}\bar{G}}{N_1}\int_0^{\varkappa_1}\hat{N}_1(m)\frac{Y(t-m)G(t-m)\bar{X}}{\bar{Y}\bar{G}X}dm - \frac{\sigma_3\bar{Y}\bar{X}}{N_1}\int_0^{\varkappa_1}\hat{N}_1(m)\frac{Y(t-m)X(t-m)}{\bar{Y}X}dm$$
$$- \frac{\sigma_2\bar{Y}\bar{G}}{N_2}\int_0^{\varkappa_2}\hat{N}_2(m)\frac{X(t-m)\bar{G}}{\bar{X}G}dm + \sigma_2\bar{Y}\bar{G} + \sigma_1\bar{Y}\bar{L} - \frac{\sigma_1\bar{Y}\bar{L}}{N_3}\int_0^{\varkappa_3}\hat{N}_3(m)\frac{X(t-m)\bar{L}}{\bar{X}L}dm$$

$$
\begin{aligned}
&- \frac{k_1\left(\psi_T+\eta_1 X\right)}{N_1\left(\beta-\eta_1 \bar{T}\right)}\left(T-\bar{T}\right)^2 - \frac{k_2\sigma_1\bar{Y}\left(\psi_S+\eta_2 L\right)}{\left(\theta-\eta_2\bar{S}\right)\left(\psi_L+k_2\bar{S}\right)}\left(S-\bar{S}\right)^2 \\
&+ \frac{\sigma_1\bar{Y}\bar{L}}{N_1}\int_0^{\varkappa_1}\hat{N}_1(m)\ln\left(\frac{Y(t-m)L(t-m)}{YL}\right)dm + \frac{\sigma_2\bar{Y}\bar{G}}{N_1}\int_0^{\varkappa_1}\hat{N}_1(m) \\
&\times\ln\left(\frac{Y(t-m)G(t-m)}{YG}\right)dm + \frac{\sigma_3\bar{Y}\bar{X}}{N_1}\int_0^{\varkappa_1}\hat{N}_1(m)\ln\left(\frac{Y(t-m)X(t-m)}{YX}\right)dm \\
&+ \frac{\alpha_2\sigma_2 N_2\bar{Y}}{\psi_G}X + \frac{\delta\sigma_1 N_3\bar{Y}}{\psi_L+k_2\bar{S}}X + \frac{\sigma_2\bar{Y}\bar{G}}{N_2}\int_0^{\varkappa_2}\hat{N}_2(m)\ln\left(\frac{X(t-m)}{X}\right)dm \\
&+ \frac{\sigma_1\bar{Y}\bar{L}}{N_3}\int_0^{\varkappa_3}\hat{N}_3(m)\ln\left(\frac{X(t-m)}{X}\right)dm.
\end{aligned}
$$

Since we have

$$
\left(\frac{\delta\sigma_1 N_3\bar{Y}}{\psi_L+k_2\bar{S}}\bar{X} + \frac{\alpha_2\sigma_2 N_2\bar{Y}}{\psi_G}\bar{X} + \sigma_3\bar{Y}\bar{X} - \frac{\alpha_1+\psi_X+k_1\bar{T}}{N_1}\bar{X}\right)\frac{X}{\bar{X}} = 0.
$$

This results in the following form

$$
\begin{aligned}
\frac{d\Omega_1}{dt} &= -\frac{\psi_Y\left(Y-\bar{Y}\right)^2}{Y} + \left(\sigma_1\bar{Y}\bar{L}+\sigma_2\bar{Y}\bar{G}+\sigma_3\bar{Y}\bar{X}\right)\left(2-\frac{\bar{Y}}{Y}\right) - \frac{\sigma_1\bar{Y}\bar{L}}{N_1}\int_0^{\varkappa_1}\hat{N}_1(m) \\
&\times\frac{Y(t-m)L(t-m)\bar{X}}{\bar{Y}\bar{L}X}dm - \frac{\sigma_2\bar{Y}\bar{G}}{N_1}\int_0^{\varkappa_1}\hat{N}_1(m)\frac{Y(t-m)G(t-m)\bar{X}}{\bar{Y}\bar{G}X}dm \\
&- \frac{\sigma_3\bar{Y}\bar{X}}{N_1}\int_0^{\varkappa_1}\hat{N}_1(m)\frac{Y(t-m)X(t-m)}{\bar{Y}X}dm - \frac{\sigma_2\bar{Y}\bar{G}}{N_2}\int_0^{\varkappa_2}\hat{N}_2(m)\frac{X(t-m)\bar{G}}{\bar{X}G}dm \\
&+ \sigma_2\bar{Y}\bar{G} + \sigma_1\bar{Y}\bar{L} - \frac{\sigma_1\bar{Y}\bar{L}}{N_3}\int_0^{\varkappa_3}\hat{N}_3(m)\frac{X(t-m)\bar{L}}{\bar{X}L}dm - \frac{k_1\left(\psi_T+\eta_1 X\right)}{N_1\left(\beta-\eta_1\bar{T}\right)}\left(T-\bar{T}\right)^2 \\
&- \frac{k_2\sigma_1\bar{Y}\left(\psi_S+\eta_2 L\right)}{\left(\theta-\eta_2\bar{S}\right)\left(\psi_L+k_2\bar{S}\right)}\left(S-\bar{S}\right)^2 + \frac{\sigma_1\bar{Y}\bar{L}}{N_1}\int_0^{\varkappa_1}\hat{N}_1(m)\ln\left(\frac{Y(t-m)L(t-m)}{YL}\right)dm \\
&+ \frac{\sigma_2\bar{Y}\bar{G}}{N_1}\int_0^{\varkappa_1}\hat{N}_1(m)\ln\left(\frac{Y(t-m)G(t-m)}{YG}\right)dm + \frac{\sigma_3\bar{Y}\bar{X}}{N_1}\int_0^{\varkappa_1}\hat{N}_1(m) \\
&\times\ln\left(\frac{Y(t-m)X(t-m)}{YX}\right)dm + \frac{\sigma_2\bar{Y}\bar{G}}{N_2}\int_0^{\varkappa_2}\hat{N}_2(m)\ln\left(\frac{X(t-m)}{X}\right)dm \\
&+ \frac{\sigma_1\bar{Y}\bar{L}}{N_3}\int_0^{\varkappa_3}\hat{N}_3(m)\ln\left(\frac{X(t-m)}{X}\right)dm.
\end{aligned}
$$

Furthermore, we have the following equalities

$$
\begin{aligned}
\ln\left(\frac{Y(t-m)L(t-m)}{YL}\right) &= \ln\left(\frac{Y(t-m)L(t-m)\bar{X}}{\bar{Y}\bar{L}X}\right) + \ln\left(\frac{\bar{Y}}{Y}\right) + \ln\left(\frac{\bar{L}X}{L\bar{X}}\right), \\
\ln\left(\frac{Y(t-m)G(t-m)}{YG}\right) &= \ln\left(\frac{Y(t-m)G(t-m)\bar{X}}{\bar{Y}\bar{G}X}\right) + \ln\left(\frac{\bar{Y}}{Y}\right) + \ln\left(\frac{\bar{G}X}{G\bar{X}}\right), \\
\ln\left(\frac{Y(t-m)X(t-m)}{YX}\right) &= \ln\left(\frac{Y(t-m)X(t-m)}{\bar{Y}X}\right) + \ln\left(\frac{\bar{Y}}{Y}\right), \\
\ln\left(\frac{X(t-m)}{X}\right) &= \ln\left(\frac{X(t-m)\bar{G}}{\bar{X}G}\right) + \ln\left(\frac{G\bar{X}}{\bar{G}X}\right),
\end{aligned}
$$

$$\ln\left(\frac{X(t-m)}{X}\right)=\ln\left(\frac{X(t-m)\bar{L}}{\bar{X}L}\right)+\ln\left(\frac{L\bar{X}}{\bar{L}X}\right). \tag{5.2}$$

Utilizing equality (5.2) gives

$$\begin{aligned}
\frac{d\Omega_1}{dt}=&-\frac{\psi_Y\left(Y-\bar{Y}\right)^2}{Y}-\left(\sigma_1\bar{Y}\bar{L}+\sigma_2\bar{Y}\bar{G}+\sigma_3\bar{Y}\bar{X}\right)\left(\frac{\bar{Y}}{Y}-1-\ln\left(\frac{\bar{Y}}{Y}\right)\right)\\
&-\frac{\sigma_1\bar{Y}\bar{L}}{N_1}\int_0^{\varkappa_1}\hat{N}_1(m)\left(\frac{Y(t-m)L(t-m)\bar{X}}{\bar{Y}\bar{L}X}-1-\ln\left(\frac{Y(t-m)L(t-m)\bar{X}}{\bar{Y}\bar{L}X}\right)\right)dm\\
&-\frac{\sigma_2\bar{Y}\bar{G}}{N_1}\int_0^{\varkappa_1}\hat{N}_1(m)\left(\frac{Y(t-m)G(t-m)\bar{X}}{\bar{Y}\bar{G}X}-1-\ln\left(\frac{Y(t-m)G(t-m)\bar{X}}{\bar{Y}\bar{G}X}\right)\right)dm\\
&-\frac{\sigma_3\bar{Y}\bar{X}}{N_1}\int_0^{\varkappa_1}\hat{N}_1(m)\left(\frac{Y(t-m)X(t-m)}{\bar{Y}X}-1-\ln\left(\frac{Y(t-m)X(t-m)}{\bar{Y}X}\right)\right)dm\\
&-\frac{\sigma_2\bar{Y}\bar{G}}{N_2}\int_0^{\varkappa_2}\hat{N}_2(m)\left(\frac{X(t-m)\bar{G}}{\bar{X}G}-1-\ln\left(\frac{X(t-m)\bar{G}}{\bar{X}G}\right)\right)dm\\
&-\frac{\sigma_1\bar{Y}\bar{L}}{N_3}\int_0^{\varkappa_3}\hat{N}_3(m)\left(\frac{X(t-m)\bar{L}}{\bar{X}L}-1-\ln\left(\frac{X(t-m)\bar{L}}{\bar{X}L}\right)\right)dm\\
&-\frac{k_1\left(\psi_T+\eta_1X\right)}{N_1\left(\beta-\eta_1\bar{T}\right)}\left(T-\bar{T}\right)^2-\frac{k_2\sigma_1\bar{Y}\left(\psi_S+\eta_2L\right)}{\left(\theta-\eta_2\bar{S}\right)\left(\psi_L+k_2\bar{S}\right)}\left(S-\bar{S}\right)^2.
\end{aligned}$$

Upon simplification, we arrive at

$$\begin{aligned}
\frac{d\Omega_1}{dt}=&-\frac{\psi_Y\left(Y-\bar{Y}\right)^2}{Y}-\frac{\sigma_1\bar{Y}\bar{L}}{N_1}\int_0^{\varkappa_1}\hat{N}_1(m)\left(\Upsilon\left(\frac{Y(t-m)L(t-m)\bar{X}}{\bar{Y}\bar{L}X}\right)+\Upsilon\left(\frac{\bar{Y}}{Y}\right)\right)dm\\
&-\frac{\sigma_2\bar{Y}\bar{G}}{N_1}\int_0^{\varkappa_1}\hat{N}_1(m)\left(\Upsilon\left(\frac{Y(t-m)G(t-m)\bar{X}}{\bar{Y}\bar{G}X}\right)+\Upsilon\left(\frac{\bar{Y}}{Y}\right)\right)dm\\
&-\frac{\sigma_3\bar{Y}\bar{X}}{N_1}\int_0^{\varkappa_1}\hat{N}_1(m)\left(\Upsilon\left(\frac{Y(t-m)X(t-m)}{\bar{Y}X}\right)+\Upsilon\left(\frac{\bar{Y}}{Y}\right)\right)dm\\
&-\frac{\sigma_2\bar{Y}\bar{G}}{N_2}\int_0^{\varkappa_2}\hat{N}_2(m)\Upsilon\left(\frac{X(t-m)\bar{G}}{\bar{X}G}\right)dm-\frac{\sigma_1\bar{Y}\bar{L}}{N_3}\int_0^{\varkappa_3}\hat{N}_3(m)\Upsilon\left(\frac{X(t-m)\bar{L}}{\bar{X}L}\right)dm\\
&-\frac{k_1\left(\psi_T+\eta_1X\right)}{N_1\left(\beta-\eta_1\bar{T}\right)}\left(T-\bar{T}\right)^2-\frac{k_2\sigma_1\bar{Y}\left(\psi_S+\eta_2L\right)}{\left(\theta-\eta_2\bar{S}\right)\left(\psi_L+k_2\bar{S}\right)}\left(S-\bar{S}\right)^2.
\end{aligned}$$

At this stage, we guarantee that $\frac{d\Omega_1}{dt}\leq 0$ for all positive values of Y,X,G,L,T,S when $\mathcal{R}_0>1$. Meanwhile, $\frac{d\Omega_1}{dt}=0$ when $Y=\bar{Y}$, $T=\bar{T}$, $S=\bar{S}$ and $\Upsilon=0$. The solutions of model (2.1) approach $\Theta_1^{'}$, where $Y(t)=\bar{Y}$, $T(t)=\bar{T}$, $S(t)=\bar{S}$ and $\Upsilon=0$ for all t, such that

$$\frac{Y(t-m)L(t-m)\bar{X}}{\bar{Y}\bar{L}X}=\frac{Y(t-m)G(t-m)\bar{X}}{\bar{Y}\bar{G}X}=\frac{Y(t-m)X(t-m)}{\bar{Y}X}=\frac{X(t-m)\bar{G}}{\bar{X}G}=\frac{X(t-m)\bar{L}}{\bar{X}L}=1,$$

for all $t\in[0,\varkappa]$. This ensures that $(Y(t),X(t),G(t),L(t),T(t),S(t))=(\bar{Y},\bar{X},\bar{G},\bar{L},\bar{T},\bar{S})$ for all t, and $\Theta_1^{'}=\{\mathcal{PE}\}$. By applying Lyapunov-LaSalle asymptotic stability theorem, we conclude that $\mathcal{PE}$ attains global asymptotic stability.

6. Numerical Simulations

This section presents numerical simulations to validate the theoretical findings of our study. Moreover, we investigate how CTL and antibody immune impairments, along with time delay, affect HIV replication. Furthermore, a detailed sensitivity analysis will be conducted for each parameter.

To facilitate the numerical calculations, we adopt a particular structure for the probability distribution functions $n_i(m)$, where $i = 1, 2, 3$, as described below:

$$n_i(m) = \delta_*(m - m_i), \quad m_i \in [0, \varkappa_i], \quad i = 1, 2, 3.$$

Here, $\delta_*(.)$ refers to the Dirac delta function. As $\varkappa_i \to \infty$, we have the following result:

$$\int_0^\infty n_i(m)\, dm = 1, \quad i = 1, 2, 3.$$

Further, we obtain

$$N_i = \int_0^\infty \delta_*(m - m_i)\, e^{-\varrho_i m} dm = e^{-\varrho_i m_i}, \qquad i = 1, 2, 3.$$

Therefore, system (2.1) is reformulated into the discrete time delay system shown below:

$$\begin{cases} \frac{dY(t)}{dt} = \omega - \psi_Y Y(t) - \sigma_1 Y(t)L(t) - \sigma_2 Y(t)G(t) - \sigma_3 Y(t)X(t), \\ \frac{dX(t)}{dt} = e^{-\varrho_1 m_1} Y(t - m_1)\left(\sigma_1 L(t - m_1) + \sigma_2 G(t - m_1)\right. \\ \qquad \left. + \sigma_3 X(t - m_1)\right) - (\alpha_1 + \psi_X) X(t) - k_1 X(t)T(t), \\ \frac{dG(t)}{dt} = \alpha_2 e^{-\varrho_2 m_2} X(t - m_2) - \psi_G G(t), \\ \frac{dL(t)}{dt} = \delta e^{-\varrho_3 m_3} X(t - m_3) - \psi_L L(t) - k_2 L(t)S(t), \\ \frac{dT(t)}{dt} = \beta X(t) - \psi_T T(t) - \eta_1 X(t)T(t), \\ \frac{dS(t)}{dt} = \theta L(t) - \psi_S S(t) - \eta_2 L(t)S(t). \end{cases} \tag{6.1}$$

In the case of system (6.1), the basic reproduction number can be written as:

$$\tilde{\mathcal{R}}_0 = \frac{Y_0 e^{-\varrho_1 m_1}\left(\psi_G \delta e^{-\varrho_3 m_3}\sigma_1 + \psi_L\left(\alpha_2 e^{-\varrho_2 m_2}\sigma_2 + \psi_G \sigma_3\right)\right)}{\psi_G \psi_L\left(\alpha_1 + \psi_X\right)}. \tag{6.2}$$

For numerical calculations, the parameters associated with infection rates, immune impairment, and delays (i.e. σ_1, σ_2, σ_3, η_1, η_2, m_1, m_2, m_3) are varied, while the other parameters are kept constant as specified in Table 1. These parameters are sourced from existing literature, except for ϱ_1, ϱ_2, ϱ_3, and k_2, which are predetermined.

TABLE 1. The values of the model's parameters.

Parameter	Value	Source	Parameter	Value	Source
ω	10	[54]	ψ_Y	0.01	[54]
$\sigma_1, \sigma_2, \sigma_3$	Varied		ψ_X	0.75	[55]
α_1	0.1	[55]	ψ_G	0.1	[55]
α_2	0.1	[30]	ψ_L	1	[56]
k_1	0.001	[55]	ψ_T	0.2	[57], [58]
k_2	0.01	Assumed	ψ_S	0.01	[56]
δ	3	[56]	m_1, m_2, m_3		Varied
β	0.5	[57]	ϱ_1	0.1	Assumed
θ	0.2	[56]	ϱ_2	0.1	Assumed
η_1, η_2	Varied		ϱ_3	0.1	Assumed

6.1. **Stability of equilibrium points.** Here, we undertake a numerical investigation into the global stability of all equilibria. Based on Theorems 1 and 2 which ensure the global stability of both equilibria, convergence is guaranteed irrespective of the initial values. Therefore, the initial conditions for system (6.1) are chosen randomly as follows:

$$\begin{cases} Y(v) = 700 + 2\sin(v) - 30j, & X(v) = 0.9 + 0.1\sin(v) + 0.5j, \\ G(v) = 3 + 0.1\sin(v) + 0.4j, & L(v) = 2 + 0.05\sin(v) + 0.5j, \\ T(v) = 2 + 0.01\sin(v) + 1.5j, & S(v) = 60 + 0.03\sin(v) + 4j, \\ j = 1, 2, ..., 12, & v \in [-m, 0], \qquad m = \max\{m_1, m_2, m_3\}. \end{cases} \tag{IC1}$$

To carry out our numerical calculations in this subsection, the values of infection rates parameters ω_1, ω_2, and ω_3 are varied, whereas the immune impairment and delays parameters are set to $\eta_1 = \eta_2 = 0.001$, $m_1 = 0.7$, $m_2 = 0.6$, and $m_3 = 0.5$. Meanwhile, the other parameters are kept constant as specified in Table 1. Therefore, the following cases arise:

Case 1. Assigning $\sigma_1 = 0.0001$, $\sigma_2 = 0.0003$, and $\sigma_3 = 0.0002$, the basic reproduction number $\tilde{\mathcal{R}}_0$ is calculated to be 0.84, which is less than unity. In accordance with Theorem 1, the equilibrium point $\mathcal{FE} = (1000, 0, 0, 0, 0, 0)$ demonstrates global asymptotic stability, as depicted in Figure 1. This finding indicates the successful clearance of HIV infection from the human body, highlighting the conditions under which the virus cannot persist.

Case 2. The values $\sigma_1 = 0.0003$, $\sigma_2 = 0.0007$, and $\sigma_3 = 0.0006$ are assigned. With these parameters, the basic reproduction number, $\tilde{\mathcal{R}}_0$, is determined to be 2.32, exceeding unity. Theorem 2 confirms that the equilibrium point $\mathcal{PE} = (538.23, 4.99, 4.70, 7.64, 12.18, 86.60)$ exhibits global asymptotic stability, as depicted in Figure 2. This analysis reflects the ability of the virus to maintain a stable presence in the human body under this condition and cause chronic infection, highlighting the persistence of HIV infection.

6.2. **Role of time delays in the stability of equilibrium points.** Here, we investigate how different delay values affect the system's dynamics (6.1). To conduct this analysis, we set $\sigma_1 = 0.0003$, $\sigma_2 = 0.0007$, $\sigma_3 = 0.0006$, and $\eta_1 = \eta_2 = 0.001$, while the remaining parameters are drawn from

Table 1. Furthermore, the delay parameters m_i, for $i = 1, 2, 3$ will be adjusted throughout the analysis as needed. The stability of equilibrium points is highly sensitive to changes in m_i, causing notable variations in $\tilde{\mathcal{R}}_0$ (as defined in Eq. (6.2)), which is dependent on m_i. As a result, the dynamical system undergoes substantial shifts in stability whenever m_i changes. We begin by considering the delay parameters provided in Table 2, and subsequently solve system (6.1) using the prescribed initial condition below.

$$\begin{cases} (Y(v), X(v), G(v), L(v), T(v), S(v)) = (700, 3, 2, 3.5, 7, 40)\,, \\ v \in [-m, 0], \qquad m = \max\{m_1, m_2, m_3\}. \end{cases} \tag{IC2}$$

The computed values of $\tilde{\mathcal{R}}_0$ corresponding to specific choices of m_i $(i = 1, 2, 3)$ are displayed in Table 2. The findings indicate that a significant decline in $\tilde{\mathcal{R}}_0$ occurs as m_i increases. The numerical simulations, depicted in Figure 3, demonstrate that longer time delays lead to a higher concentration of healthy CD4$^+$T cells while simultaneously reducing the levels of other compartments.

Table 2. Different values of $\tilde{\mathcal{R}}_0$ corresponding to m_i.

Case	Delay parameters (m_1, m_2, m_3)	Equilibrium points	$\tilde{R}_0$
DP1	0.1 , 0.2, 0.3	$\mathcal{PE}_{(6.1)} = (501.62, 5.71, 5.60, 8.63, 13.88, 92.65)$	2.52
DP2	0.5, 1.5, 2.5	$\mathcal{PE}_{(6.1)} = (566.93, 4.78, 4.11, 6.30, 11.67, 77.30)$	2.13
DP3	2, 3, 4	$\mathcal{PE}_{(6.1)} = (694.33, 2.92, 2.16, 3.79, 7.19, 54.96)$	1.66
DP4	3, 4, 5	$\mathcal{PE}_{(6.1)} = (788.64, 1.83, 1.23, 2.40, 4.54, 38.75)$	1.41
DP5	6, 7, 8	$\mathcal{FE}_{(6.1)} = (1000, 0, 0, 0, 0, 0)$	0.87
DP6	9, 10, 11	$\mathcal{FE}_{(6.1)} = (1000, 0, 0, 0, 0, 0)$	0.55

6.3. **Role of CTL and antibody immune impairments.** To explore the influence of CTL and antibody immune impairments, we set $\sigma_1 = 0.0003$, $\sigma_2 = 0.0007$, $\sigma_3 = 0.0006$, $m_1 = 0.7$, $m_2 = 0.6$, and $m_3 = 0.5$, while the remaining parameters are drawn from Table 1. In addition, the immune impairment parameters η_i, for $i = 1, 2$, will be modified throughout the analysis as needed. Although the stability of equilibrium points is not affected by changes in η_i, since $\tilde{\mathcal{R}}_0$ (as defined in Eq. (6.2)) does not depend on η_i, we still aim to investigate the role of immune impairments in the behavior of solution trajectories. To do so, we begin by utilizing the immune impairment parameter values listed in Table 3 and subsequently solve system (6.1) using the prescribed initial condition below.

$$\begin{cases} (Y(v), X(v), G(v), L(v), T(v), S(v)) = (510, 5, 5, 9, 7, 60)\,, \\ v \in [-m, 0], \qquad m = \max\{m_1, m_2, m_3\}. \end{cases} \tag{IC3}$$

Table 3. Equilibrium points corresponding to different values of η_i.

Set	Immune impairment parameters (η_1, η_2)	Equilibrium points
1	0, 0	$\mathcal{PE}_{(6.1)} = (561.90, 4.74, 4.46, 6.10, 11.85, 121.90)$
2	0.007, 0.001	$\mathcal{PE}_{(6.1)} = (537.39, 5.01, 4.72, 7.66, 10.66, 86.74)$
3	0.02, 0.005	$\mathcal{PE}_{(6.1)} = (485.63, 5.58, 5.26, 11.87, 8.96, 34.23)$
4	0.07, 0.01	$\mathcal{PE}_{(6.1)} = (462.87, 5.86, 5.52, 14.09, 4.80, 18.67)$

As observed in Table 3 and Figure 4, it is evident that a higher η_i results in a decline in the population of CTLs and antibodies. This, in turn, corresponds with an increase in HIV-infected $CD4^+$T cells, inflammatory cytokines, as well as free HIV particles. As a result, the count of healthy $CD4^+$T cells declines.

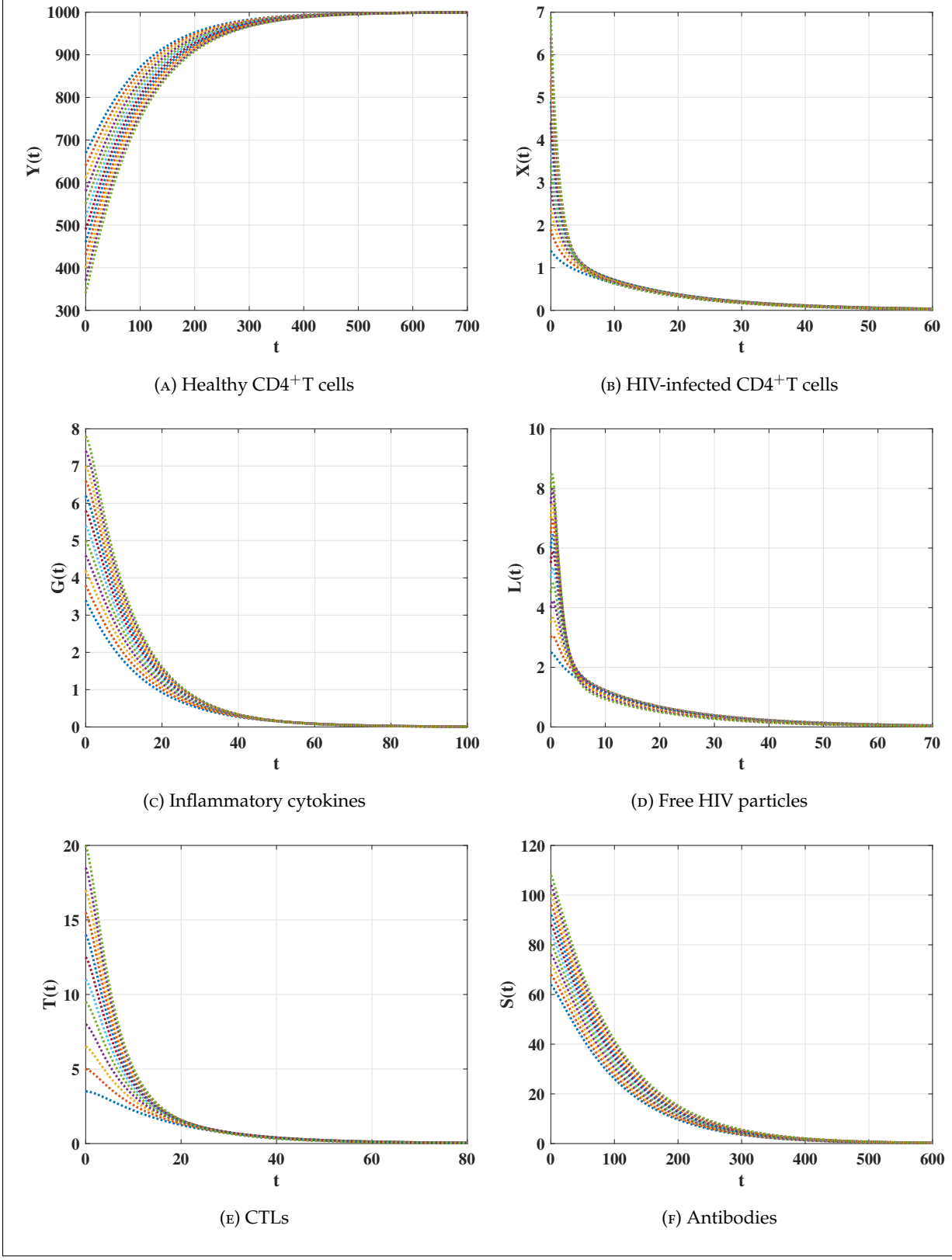
6.4. **Sensitivity analysis.** The main objective of this subsection is to discuss the sensitivity analysis of model (6.1). Specifically, the analysis aims to assess the impact of various parameters on the advancement of HIV infection in a host, offering insights that can be useful for the development of novel antiviral therapies. The sensitivity index will be determined by employing partial derivatives to examine how variables fluctuate in accordance to parameter changes. The following formula represents the normalized forward sensitivity index of $\tilde{\mathcal{R}}_0$ in relation to the parameter:

$$Q_\tau = \frac{\tau}{\tilde{\mathcal{R}}_0} \times \frac{\partial \tilde{\mathcal{R}}_0}{\partial \tau}. \tag{6.3}$$

Here, τ accounts for a specified parameter. The values of Q_τ range from -1 to 1, with a positive Q_τ indicating a positive correlation and a negative value reflecting a negative correlation. The absolute value of Q_τ signifies the level of sensitivity: values close to zero imply a minimal effect, whereas values near one point to a strong impact [59]. The sensitivity indices for $\tilde{\mathcal{R}}_0$ were computed using Eq. (6.3) by applying the parameter values provided in Table 1, including $\sigma_1 = 0.0003$, $\sigma_2 = 0.0007$, $\sigma_3 = 0.0006$, $\eta_1 = \eta_2 = 0.001$, $m_1 = 0.7$, $m_2 = 0.6$, and $m_3 = 0$. The calculated sensitivity indices, derived from these values, are summarized in Table 4. The sensitivity indices of $\tilde{\mathcal{R}}_0$, as demonstrated in Table 4 and Figure 5, shed light on the varying influences of each parameter. From these, it is apparent that parameters ω, σ_1, σ_2, σ_3, δ, and α_2 exhibit positive index values. This indicates that an increase in the values of these parameters is linked to a higher $\tilde{\mathcal{R}}_0$ value, leading to a greater level of HIV endemicity. In contrast, the parameters ψ_Y, α_1, ψ_X, ψ_G, ψ_L, ϱ_1, ϱ_2, ϱ_3, m_1, m_2, and m_3 show negative sensitivity indices, meaning that as their values rise, $\tilde{\mathcal{R}}_0$ decreases. Among all the parameters, the most influential are ω, σ_1, and δ, while σ_2, σ_3, and α_2 have relatively minor impacts. Moreover, the parameters related to CTL and antibody responsiveness, η_1 and η_2, seem to have no impact on $\tilde{\mathcal{R}}_0$.

TABLE 4. Quantifying parameters' influence on $\tilde{\mathcal{R}}_0$ in model (6.1): sensitivity index

Parameter τ	Value of Q_τ	Parameter τ	Value of Q_τ	Parameter τ	Value of Q_τ
ω	1	α_1	-0.118	ϱ_2	-0.019
ψ_Y	-1	α_2	0.312	ϱ_3	-0.020
σ_1	0.405	ψ_X	-0.882	m_1	-0.07
σ_2	0.312	ψ_G	-0.312	m_2	-0.019
σ_3	0.284	ψ_L	-0.405	m_3	-0.020
δ	0.405	ϱ_1	-0.07		



(A) Healthy CD4$^+$T cells

(B) HIV-infected CD4$^+$T cells

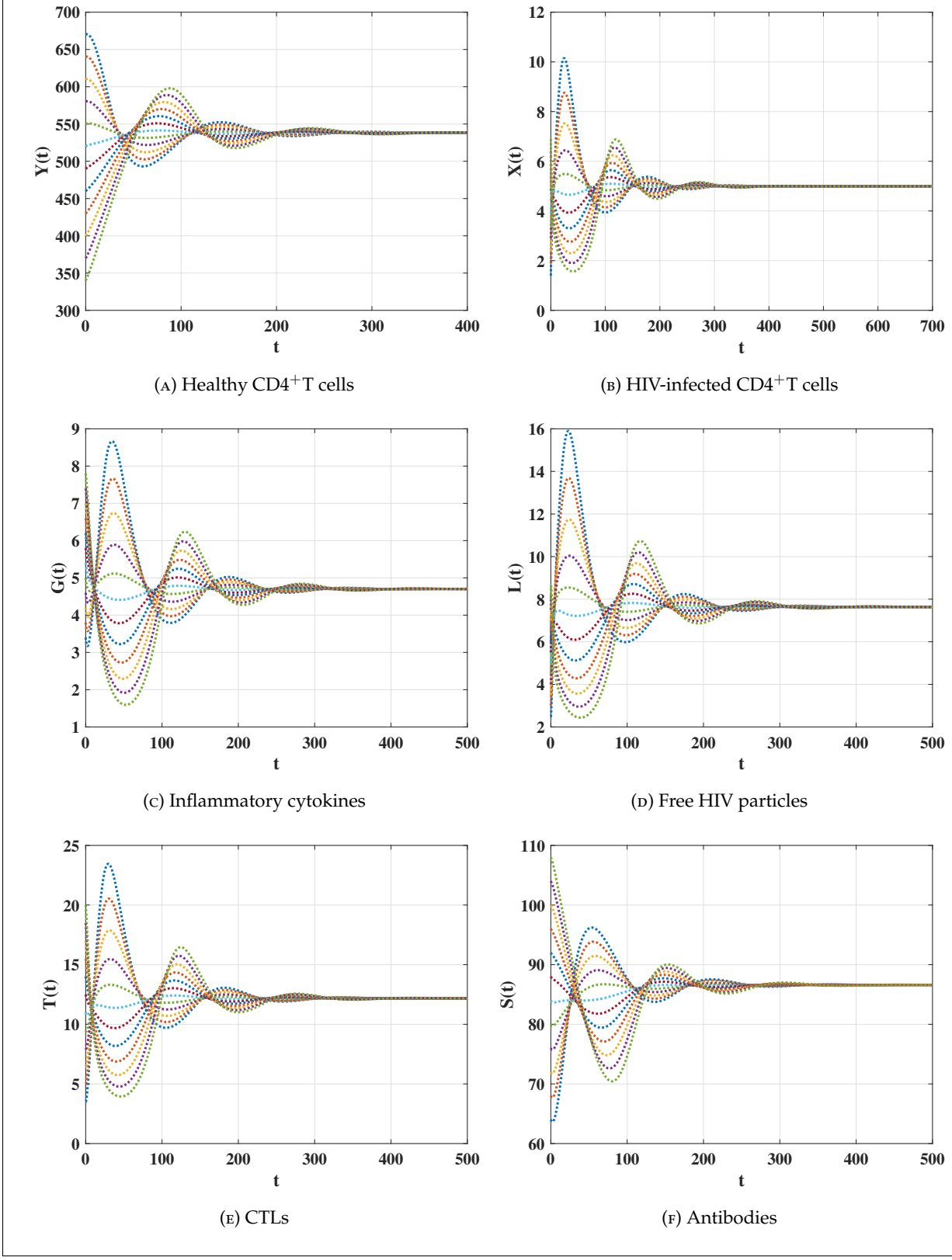
(C) Inflammatory cytokines

(D) Free HIV particles

(E) CTLs

(F) Antibodies

FIGURE 1. Numerical simulations reveal that the solution of system (6.1) stabilizes at the HIV-free equilibrium $\mathcal{FE} = (1000, 0, 0, 0, 0, 0)$ when $\tilde{\mathcal{R}}_0 \leq 1$ (Case 1).



(A) Healthy CD4$^+$T cells

(B) HIV-infected CD4$^+$T cells

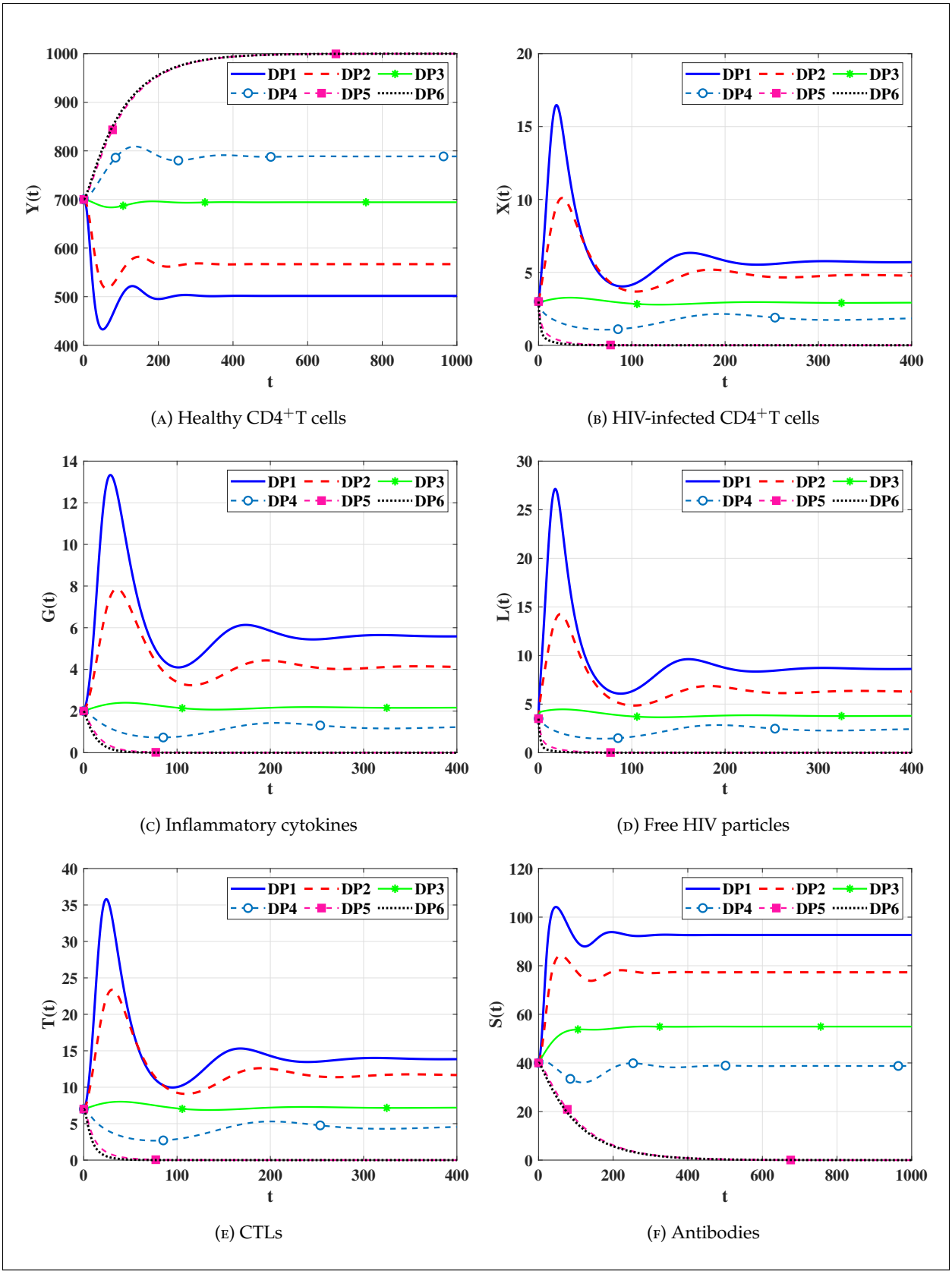
(C) Inflammatory cytokines

(D) Free HIV particles

(E) CTLs

(F) Antibodies

FIGURE 2. Numerical simulations reveal that the solution of system (6.1) stabilizes at the HIV-persistent equilibrium $\mathcal{PE} = (538.23, 4.99, 4.70, 7.64, 12.18, 86.60)$ when $\tilde{\mathcal{R}}_0 > 1$ (Case 2).



(A) Healthy CD4$^+$T cells

(B) HIV-infected CD4$^+$T cells

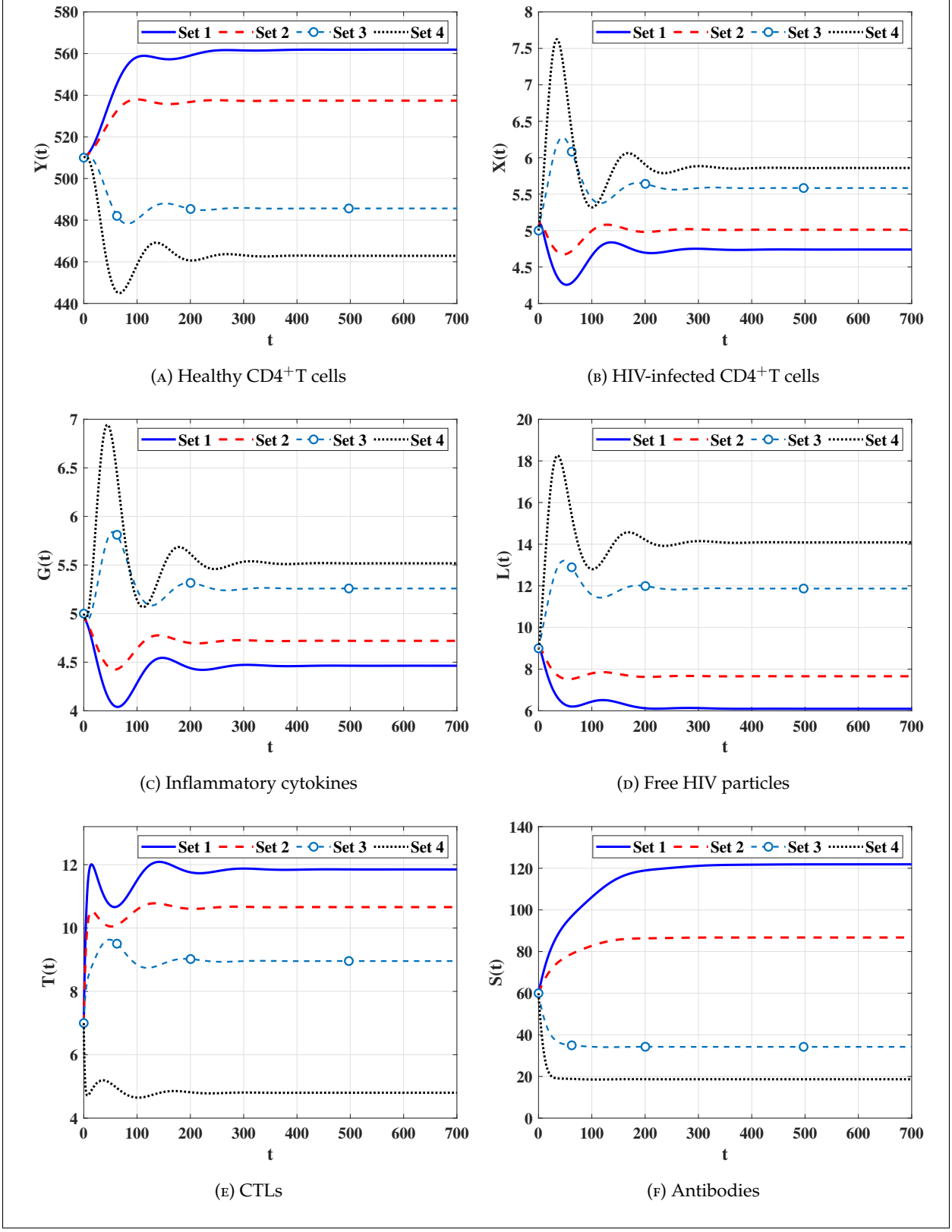
(C) Inflammatory cytokines

(D) Free HIV particles

(E) CTLs

(F) Antibodies

FIGURE 3. Role of time delay parameters in shaping the dynamic patterns of solution trajectories in system (6.1).



(A) Healthy CD4$^+$T cells

(B) HIV-infected CD4$^+$T cells

(C) Inflammatory cytokines

(D) Free HIV particles

(E) CTLs

(F) Antibodies

FIGURE 4. Role of immune impairment parameters in shaping the evolution of solution trajectories in system (6.1).

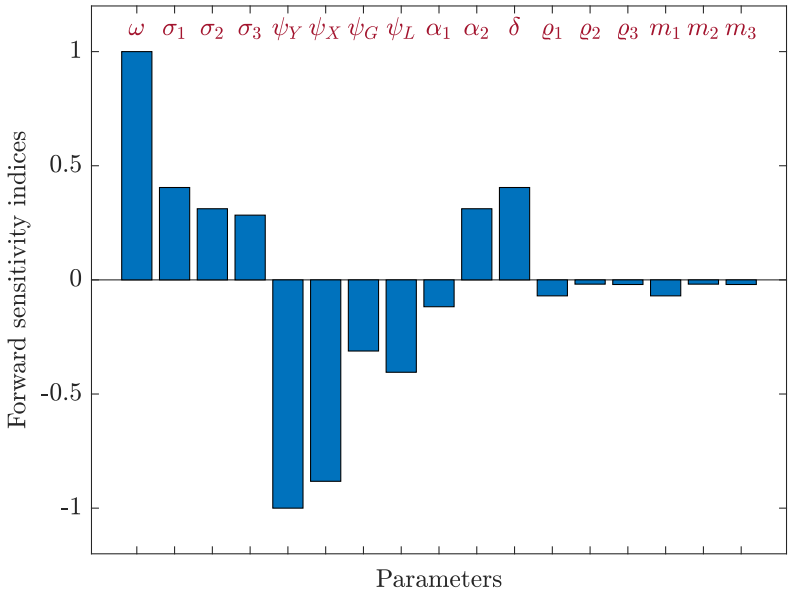


FIGURE 5. Assessment of parameter influence on $\tilde{\mathcal{R}}_0$ in system (6.1) using forward sensitivity analysis

7. CONCLUSION

This study investigated a cytokine-enhanced HIV infection model that incorporates impairments in both CTL and antibody-mediated immune responses. The model captures three modes of $CD4^+$T cell infection: (i) virus-to-cell transmission via free HIV particles, (ii) cell-to-cell spread through direct contact with infected cells, and (iii) cytokine-enhanced infection, in which inflammatory cytokines attract uninfected $CD4^+$T cells to inflamed tissues, increasing their vulnerability to infection. The model also accounts for three biologically relevant distributed time delays: in infection, cytokine activation, and virion maturation.

Mathematically, we demonstrated that all solutions remain nonnegative and ultimately bounded. Two equilibria were identified: the HIV-free equilibrium ($\mathcal{FE}$) and the HIV-persistent equilibrium ($\mathcal{PE}$). Their existence and stability depend on the basic reproduction number $\mathcal{R}_0$, derived using the next-generation matrix method. Lyapunov functionals were constructed to show that $\mathcal{FE}$ is globally asymptotically stable when $\mathcal{R}_0 \leq 1$, while $\mathcal{PE}$ is globally asymptotically stable when $\mathcal{R}_0 > 1$.

Numerical simulations supported the analytical results and revealed how variations in model parameters influence infection dynamics. Sensitivity analysis of $\mathcal{R}_0$ identified key factors driving viral persistence and immune control. In particular, increased impairment of the adaptive immune response led to more severe infection progression, whereas longer delay times were associated with suppressed viral growth.

These findings underscore the complex interplay between immune dysfunction, cytokine activity, and time delays in HIV infection, offering valuable insights for future immunological and therapeutic research.

Conflicts of Interest: The author declares that there are no conflicts of interest regarding the publication of this paper.

References

[1] D. Wodarz, D.N. Levy, Human Immunodeficiency Virus Evolution Towards Reduced Replicative Fitness in Vivo and the Development of AIDS, Proc. R. Soc. B: Biol. Sci. 274 (2007), 2481–2491. https://doi.org/10.1098/rspb.2007.0413.

[2] M.A. Nowak, R.M. May, Virus Dynamics, Oxford University Press, (2000).

[3] G. Doitsh, N.L.K. Galloway, X. Geng, Z. Yang, K.M. Monroe, et al., Cell Death by Pyroptosis Drives CD4 T-Cell Depletion in Hiv-1 Infection, Nature 505 (2013), 509–514. https://doi.org/10.1038/nature12940.

[4] W. Wang, W. Ma, Z. Feng, Complex Dynamics of a Time Periodic Nonlocal and Time-Delayed Model of Reaction–Diffusion Equations for Modeling $CD4^+$ T Cells Decline, J. Comput. Appl. Math. 367 (2020), 112430. https://doi.org/10.1016/j.cam.2019.112430.

[5] G. Doitsh, M. Cavrois, K.G. Lassen, O. Zepeda, Z. Yang, et al., Abortive HIV Infection Mediates CD4 T Cell Depletion and Inflammation in Human Lymphoid Tissue, Cell 143 (2010), 789–801. https://doi.org/10.1016/j.cell.2010.11.001.

[6] M.A. Nowak, C.R.M. Bangham, Population Dynamics of Immune Responses to Persistent Viruses, Science 272 (1996), 74–79. https://doi.org/10.1126/science.272.5258.74.

[7] J. Deng, H. Shu, L. Wang, X. Wang, Viral Dynamics with Immune Responses: Effects of Distributed Delays and Filippov Antiretroviral Therapy, J. Math. Biol. 86 (2023), 37. https://doi.org/10.1007/s00285-023-01869-w.

[8] C. Chen, Y. Zhou, Dynamic Analysis of HIV Model with a General Incidence, CTLs Immune Response and Intracellular Delays, Math. Comput. Simul. 212 (2023), 159–181. https://doi.org/10.1016/j.matcom.2023.04.029.

[9] M. Tan, G. Lan, C. Wei, Dynamic Analysis of HIV Infection Model with CTL Immune Response and Cell-to-Cell Transmission, Appl. Math. Lett. 156 (2024), 109140. https://doi.org/10.1016/j.aml.2024.109140.

[10] L. Lv, J. Yang, Z. Hu, D. Fan, Dynamics Analysis of a Delayed HIV Model with Latent Reservoir and Both Viral and Cellular Infections, Math. Methods Appl. Sci. 48 (2024), 6063–6080. https://doi.org/10.1002/mma.10655.

[11] H. Hmarrass, R. Qesmi, Global Stability and Hopf Bifurcation of a Delayed HIV Model with Macrophages, CD4+T Cells with Latent Reservoirs and Immune Response, Eur. Phys. J. Plus 140 (2025), 335. https://doi.org/10.1140/epjp/s13360-025-06001-z.

[12] M. Dhar, S. Samaddar, P. Bhattacharya, Modeling the Cell-To-Cell Transmission Dynamics of Viral Infection Under the Exposure of Non-Cytolytic Cure, J. Appl. Math. Comput. 65 (2020), 885–911. https://doi.org/10.1007/s12190-020-01420-w.

[13] J. Lin, R. Xu, X. Tian, Threshold Dynamics of an HIV-1 Virus Model with Both Virus-To-Cell and Cell-To-Cell Transmissions, Intracellular Delay, and Humoral Immunity, Appl. Math. Comput. 315 (2017), 516–530. https://doi.org/10.1016/j.amc.2017.08.004.

[14] Y. Luo, L. Zhang, T. Zheng, Z. Teng, Analysis of a Diffusive Virus Infection Model with Humoral Immunity, Cell-To-Cell Transmission and Nonlinear Incidence, Physica A: Stat. Mech. Appl. 535 (2019), 122415. https://doi.org/10.1016/j.physa.2019.122415.

[15] A.D. AlAgha, A.M. Elaiw, Stability of a General Reaction-Diffusion HIV-1 Dynamics Model with Humoral Immunity, Eur. Phys. J. Plus 134 (2019), 390. https://doi.org/10.1140/epjp/i2019-12740-9.

[16] Z. Xie, X. Liu, Global Dynamics in an Age-Structured HIV Model with Humoral Immunity, Int. J. Biomath. 14 (2021), 2150047. https://doi.org/10.1142/s1793524521500479.

[17] J. Wang, M. Guo, X. Liu, Z. Zhao, Threshold Dynamics of HIV-1 Virus Model with Cell-To-Cell Transmission, Cell-Mediated Immune Responses and Distributed Delay, Appl. Math. Comput. 291 (2016), 149–161. https://doi.org/10.1016/j.amc.2016.06.032.

[18] Á.G. Cervantes-Pérez, E. Ávila-Vales, Dynamical Analysis of Multipathways and Multidelays of General Virus Dynamics Model, Int. J. Bifurc. Chaos 29 (2019), 1950031. https://doi.org/10.1142/s0218127419500317.

[19] J. Lin, R. Xu, X. Tian, Threshold Dynamics of an HIV-1 Model with Both Viral and Cellular Infections, Cell-Mediated and Humoral Immune Responses, Math. Biosci. Eng. 16 (2019), 292–319. https://doi.org/10.3934/mbe.2019015.

[20] N. AlShamrani, Stability of a General Adaptive Immunity HIV Infection Model with Silent Infected Cell-To-Cell Spread, Chaos, Solitons Fractals 150 (2021), 110422. https://doi.org/10.1016/j.chaos.2020.110422.

[21] Z. Zhang, Y. Chen, X. Wang, L. Rong, Dynamic Analysis of a Latent HIV Infection Model with CTL Immune and Antibody Responses, Int. J. Biomath. 17 (2023), 2350079. https://doi.org/10.1142/s1793524523500791.

[22] T. Guo, Q. Deng, S. Gao, Z. Qiu, L. Rong, HIV Infection Dynamics with Broadly Neutralizing Antibodies and CTL Immune Response, Discret. Contin. Dyn. Syst. - S 18 (2025), 3631–3660. https://doi.org/10.3934/dcdss.2024151.

[23] Y. Jiang, T. Zhang, Global Stability of a Cytokine-Enhanced Viral Infection Model with Nonlinear Incidence Rate and Time Delays, Appl. Math. Lett. 132 (2022), 108110. https://doi.org/10.1016/j.aml.2022.108110.

[24] L. Hong, J. Li, L. Rong, X. Wang, Global Dynamics of a Delayed Model with Cytokine-Enhanced Viral Infection and Cell-To-Cell Transmission, AIMS Math. 9 (2024), 16280–16296. https://doi.org/10.3934/math.2024788.

[25] J. Xu, Dynamic Analysis of a Cytokine-Enhanced Viral Infection Model with Infection Age, Math. Biosci. Eng. 20 (2023), 8666–8684. https://doi.org/10.3934/mbe.2023380.

[26] W. Wang, Z. Feng, Global Dynamics of a Diffusive Viral Infection Model with Spatial Heterogeneity, Nonlinear Anal.: Real World Appl. 72 (2023), 103763. https://doi.org/10.1016/j.nonrwa.2022.103763.

[27] T. Zhang, X. Xu, X. Wang, Dynamic Analysis of a Cytokine-Enhanced Viral Infection Model with Time Delays and CTL Immune Response, Chaos Solitons Fractals 170 (2023), 113357. https://doi.org/10.1016/j.chaos.2023.113357.

[28] X. Cao, S. Hou, X. Kong, A Cytokine-Enhanced Viral Infection Model with CTL Immune Response, Distributed Delay and Saturation Incidence, arXiv:2409.10223 (2024). http://arxiv.org/abs/2409.10223v1.

[29] C. Chen, Z. Ye, Y. Zhou, Z. Zheng, Dynamics of a Delayed Cytokine-Enhanced Diffusive HIV Model with a General Incidence and CTL Immune Response, Eur. Phys. J. Plus 138 (2023), 1083. https://doi.org/10.1140/epjp/s13360-023-04734-3.

[30] E. Dahy, A.M. Elaiw, A.A. Raezah, H.Z. Zidan, A.E.A. Abdellatif, Global Properties of Cytokine-Enhanced HIV-1 Dynamics Model with Adaptive Immunity and Distributed Delays, Computation 11 (2023), 217. https://doi.org/10.3390/computation11110217.

[31] C. Chen, Y. Zhou, Z. Ye, Stability and Optimal Control of a Cytokine-Enhanced General HIV Infection Model with Antibody Immune Response and CTLs Immune Response, Comput. Methods Biomech. Biomed. Eng. 27 (2023), 2199–2230. https://doi.org/10.1080/10255842.2023.2275248.

[32] P. Lydyard, A. Whelan, M. Fanger, BIOS Instant Notes in Immunology, Taylor & Francis, 2005. https://doi.org/10.4324/9780203488287.

[33] N. Bai, R. Xu, Mathematical Analysis of an HIV Model with Latent Reservoir, Delayed CTL Immune Response and Immune Impairment, Math. Biosci. Eng. 18 (2021), 1689-1707. https://doi.org/10.3934/mbe.2021087.

[34] Y. Yang, R. Xu, Mathematical Analysis of a Delayed HIV Infection Model with Saturated CTL Immune Response and Immune Impairment, J. Appl. Math. Comput. 68 (2021), 2365–2380. https://doi.org/10.1007/s12190-021-01621-x.

[35] L. Zhang, R. Xu, Dynamics Analysis of an HIV Infection Model with Latent Reservoir, Delayed CTL Immune Response and Immune Impairment, Nonlinear Anal.: Model. Control. 28 (2023), 1–19. https://doi.org/10.15388/namc.2023.28.29615.

[36] K. Guo, S. Guo, Lyapunov Functionals for a General Time-Delayed Virus Dynamic Model with Different CTL Responses, Chaos: Interdiscip. J. Nonlinear Sci. 34 (2024), 053138. https://doi.org/10.1063/5.0204169.

[37] N.H. AlShamrani, R.H. Halawani, A.M. Elaiw, Stability of Generalized Models for HIV-1 Dynamics with Impaired CTL Immunity and Three Pathways of Infection, Front. Appl. Math. Stat. 10 (2024), 1412357. https://doi.org/10.3389/fams.2024.1412357.

[38] S. Hou, X. Tian, Stability and Hopf Bifurcation Analysis of an HIV Infection Model with Latent Reservoir, Immune Impairment and Delayed CTL Immune Response, Int. J. Biomath. (2025), 2550084. https://doi.org/10.1142/s1793524525500846.

[39] H. Miao, X. Abdurahman, Z. Teng, L. Zhang, Dynamical Analysis of a Delayed Reaction-Diffusion Virus Infection Model with Logistic Growth and Humoral Immune Impairment, Chaos Solitons Fractals 110 (2018), 280–291. https://doi.org/10.1016/j.chaos.2018.03.006.

[40] A.M. Elaiw, S.F. Alshehaiween, A.D. Hobiny, Global Properties of HIV Dynamics Models Including Impairment of B-Cell Functions, J. Biol. Syst. 28 (2020), 1–25. https://doi.org/10.1142/s0218339020500011.

[41] N.H. AlShamrani, R.H. Halawani, W. Shammakh, A.M. Elaiw, Stability of Impaired Humoral Immunity HIV-1 Models with Active and Latent Cellular Infections, Computation 11 (2023), 207. https://doi.org/10.3390/computation11100207.

[42] A.M. Elaiw, S.F. Alshehaiween, Global Stability of Delay-distributed Viral Infection Model with Two Modes of Viral Transmission and B-Cell Impairment, Math. Methods Appl. Sci. 43 (2020), 6677–6701. https://doi.org/10.1002/mma.6408.

[43] A.M. Elaiw, S.F. Alshehaiween, A.D. Hobiny, Impact of B-Cell Impairment on Virus Dynamics with Time Delay and Two Modes of Transmission, Chaos Solitons Fractals 130 (2020), 109455. https://doi.org/10.1016/j.chaos.2019.109455.

[44] N.H. AlShamrani, R.H. Halawani, A.M. Elaiw, Effect of Impaired B-Cell and CTL Functions on HIV-1 Dynamics, Mathematics 11 (2023), 4385. https://doi.org/10.3390/math11204385.

[45] N.H. AlShamrani, R.H. Halawani, A.M. Elaiw, Analysis of General HIV-1 Infection Models with Weakened Adaptive Immunity and Three Transmission Modalities, Alex. Eng. J. 106 (2024), 101–146. https://doi.org/10.1016/j.aej.2024.06.033.

[46] K. Guo, D. Zhao, Z. Feng, Lyapunov Functionals for a Virus Dynamic Model with General Monotonic Incidence, Two Time Delays, CTL and Antibody Immune Responses, Appl. Math. Lett. 158 (2024), 109212. https://doi.org/10.1016/j.aml.2024.109212.

[47] Q. Song, S. Wang, F. Xu, Robustness and Bistability in a Cytokine-Enhanced Viral Infection Model, Appl. Math. Lett. 158 (2024), 109215. https://doi.org/10.1016/j.aml.2024.109215.

[48] C. Lv, X. Chen, C. Du, Global Dynamics of a Cytokine-Enhanced Viral Infection Model with Distributed Delays and Optimal Control Analysis, AIMS Math. 10 (2025), 9493–9515. https://doi.org/10.3934/math.2025438.

[49] A.M. Elaiw, E. Dahy, H.Z. Zidan, A.A. Abdellatif, Stability of an HIV-1 Abortive Infection Model with Antibody Immunity and Delayed Inflammatory Cytokine Production, Eur. Phys. J. Plus 140 (2025), 563. https://doi.org/10.1140/epjp/s13360-025-06475-x.

[50] J.K. Hale, S.M.V. Lunel, Introduction to Functional Differential Equations, Springer-Verlag, New York, (1993).

[51] Y. Kuang, Delay Differential Equations With Applications in Population Dynamics, Academic Press, San Diego, (1993).

[52] P. van den Driessche, J. Watmough, Reproduction Numbers and Sub-Threshold Endemic Equilibria for Compartmental Models of Disease Transmission, Math. Biosci. 180 (2002), 29–48. https://doi.org/10.1016/s0025-5564(02)00108-6.

[53] H.K. Khalil, Nonlinear Systems, Prentice Hall, Upper Saddle River, (2002).

[54] S.K. Sahani, Yashi, Effects of Eclipse Phase and Delay on the Dynamics of HIV Infection, J. Biol. Syst. 26 (2018), 421–454. https://doi.org/10.1142/s0218339018500195.

[55] T. Zhang, X. Xu, X. Wang, Dynamic Analysis of a Cytokine-Enhanced Viral Infection Model with Time Delays and CTL Immune Response, Chaos Solitons Fractals 170 (2023), 113357. https://doi.org/10.1016/j.chaos.2023.113357.

[56] A.M. Elaiw, S.F. Alshehaiween, A.D. Hobiny, Impact of B-Cell Impairment on Virus Dynamics with Time Delay and Two Modes of Transmission, Chaos Solitons Fractals 130 (2020), 109455. https://doi.org/10.1016/j.chaos.2019.109455.

[57] A.M. Elaiw, A.A. Raezah, B.S. Alofi, Dynamics of Delayed Pathogen Infection Models with Pathogenic and Cellular Infections and Immune Impairment, AIP Adv. 8 (2018), 025323. https://doi.org/10.1063/1.5023752.

[58] S. Wang, X. Song, Z. Ge, Dynamics Analysis of a Delayed Viral Infection Model with Immune Impairment, Appl. Math. Model. 35 (2011), 4877–4885. https://doi.org/10.1016/j.apm.2011.03.043.

[59] A. Elaiw, E. Almohaimeed, A. Hobiny, Stability Analysis of a Diffusive HTLV-2 and HIV-1 Co-Infection Model, Alex. Eng. J. 116 (2025), 232–270. https://doi.org/10.1016/j.aej.2024.11.074.