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Stability of generalized models for HIV-1 dynamics with impaired CTL immunity and three pathways of infection

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Highly active antiretroviral therapy (HAART) stands out as the most effective treatment for human immunodeficiency virus type-1 (HIV-1). While total eradication is still difficult, HAART can dramatically lower the virus's plasma viral level below the detection threshold. The activation of latently infected cells is considered to be the main obstacle to the total eradication of HIV-1 infection. This study investigates the dynamic characteristics of two generalized HIV-1 infection models taking into account the impairment of cytotoxic T lymphocytes (CTLs). These models include CD4⁺T cells that are latently infected and equipped with the capability to engage in cell-to-cell infection and elude immune responses. We introduce models featuring three infection pathways: virus-to-cell (VTC), latent cell-to-cell (L-CTC), and active cell-to-cell (A-CTC). The three pathways' infection rates are characterized by general functions, which cover the many types of infection rates documented in the literature. The second model integrates three distinct types of distributed-time delays. We demonstrate the validity of the suggested models, through their well-posedness. We determine the basic reproduction ratio (\mathfrak{R}_0) of the systems. Lyapunov functions and LaSalle's invariance principle are employed to verify that the global stability of both the virus-free steady state (O_0) and the virus-persistence steady state (O_1). More precisely, O_0 achieves global asymptotic stability when $\mathfrak{R}_0 \leq 1$, whereas O_1 attains global asymptotic stability when $\mathfrak{R}_0 > 1$. To demonstrate the impact of the parameter values on \mathfrak{R}_0 , we examine the sensitivity analysis. It is illustrated that \mathfrak{R}_0 comprises three components, namely \mathfrak{R}_{0E} , \mathfrak{R}_{0P} , and \mathfrak{R}_{0K} , corresponding to the transmissions of VTC, L-CTC, and A-CTC, respectively. Thus, if the L-CTC pathway is disregarded in the HIV-1 infection model, \mathfrak{R}_0 may be underestimated, which could lead to inadequate or erroneous medication therapy focused on eradicating HIV-1 within the body. To demonstrate the associated mathematical outcomes, we conduct numerical simulations through an illustrative example. Specifically, we delve into how the dynamics of HIV-1 are influenced by both immune impairment and time delay. Our findings suggest a significant role of reduced immunity in the progression of the infection. Furthermore, time delays possess the potential to markedly reduce \mathfrak{R}_0 , thereby impeding the replication of HIV-1.

KEYWORDS

HIV-1, immune impairment, global stability, delays, Lyapunov stability, sensitivity analysis

1 Introduction

In recent years, there has been a significant upsurge in interest regarding the mathematical modeling of human immunodeficiency virus type-1 (HIV-1) dynamics within the host [1]. Researchers have developed mathematical models that have the potential to substantially advance our knowledge of infection and the medication therapy approaches used to combat it. The dynamics of HIV-1 infection within-host have been explored through various mathematical models. The basic model, governing the time evolution (t) of the healthy CD4⁺T cell population (\mathcal{J}), the infected CD4⁺T cell population (\mathcal{K}), and HIV-1 particles (\mathcal{E}), utilizes a set of ordinary differential equations [2]. This model has been extended and modified by using non-integer derivatives [3–5]. The concept described in reference [2] postulated that CD4⁺T cells get infected upon coming into contact with HIV-1 particles is known as the virus-to-cell (VTC) pathway. Numerous studies have demonstrated that HIV-1 may spread directly through the development of virological synapses from an infected cell to an uninfected cell, a process referred to as the cell-to-cell (CTC) pathway (see, e.g., [6–8]). The CTC mechanism can decrease the time required for HIV-1 particle production by 0.9 times and enhance HIV-1 fitness by 3.9 times [9].

A viral infection model with two infection pathways, VTC and CTC, can be formulated as outlined in Graw and Perelson [10]:

$$\begin{cases} \dot{\mathcal{J}} = \theta - \eta_{\mathcal{J}}\mathcal{J} - (\rho_{\mathcal{E}}\mathcal{E} + \rho_{\mathcal{K}}\mathcal{K})\mathcal{J}, \\ \dot{\mathcal{K}} = (\rho_{\mathcal{E}}\mathcal{E} + \rho_{\mathcal{K}}\mathcal{K})\mathcal{J} - \eta_{\mathcal{K}}\mathcal{K}, \\ \dot{\mathcal{E}} = \varpi\mathcal{K} - \eta_{\mathcal{E}}\mathcal{E}, \end{cases} \quad (1)$$

where $\mathcal{J} = \mathcal{J}(t)$, $\mathcal{K} = \mathcal{K}(t)$ and $\mathcal{E} = \mathcal{E}(t)$ represent the concentrations of healthy CD4⁺T cells, actively infected cells and HIV-1 particles at time t , respectively. The production rate of healthy CD4⁺T cells is θ , while their death rate is $\eta_{\mathcal{J}}\mathcal{J}$. At rates of $\rho_{\mathcal{E}}\mathcal{E}\mathcal{J}$ and $\rho_{\mathcal{K}}\mathcal{K}\mathcal{J}$, respectively, the healthy CD4⁺T cells get infected via VTC and CTC routes. HIV-1 particles are generated at a rate of $\varpi\mathcal{K}$ from cells that are actively infected. The HIV-1 and actively infected cell death rates are represented by $\eta_{\mathcal{E}}\mathcal{E}$ and $\eta_{\mathcal{K}}\mathcal{K}$, respectively. Because HIV-1 replication and transmission in lymphoid tissues are so complex, an increasing number of significant biological parameters (such as cell-to-cell transfer, latency, immune response, and time delay). Therefore, many authors have interested in extending model (1) by including different factors.

Cytotoxic T Lymphocyte (CTL) immunity plays an important role against viral infection. Cytotoxic T Lymphocyte (CTLs) kill the cells infected by viruses. Under the effect of CTL immune response, model (1) can be written as [11–15]:

$$\begin{cases} \dot{\mathcal{J}} = \theta - \eta_{\mathcal{J}}\mathcal{J} - (\rho_{\mathcal{E}}\mathcal{E} + \rho_{\mathcal{K}}\mathcal{K})\mathcal{J}, \\ \dot{\mathcal{K}} = (\rho_{\mathcal{E}}\mathcal{E} + \rho_{\mathcal{K}}\mathcal{K})\mathcal{J} - \eta_{\mathcal{K}}\mathcal{K} - \phi\mathcal{L}\mathcal{K}, \\ \dot{\mathcal{E}} = \varpi\mathcal{K} - \eta_{\mathcal{E}}\mathcal{E}, \dot{\mathcal{L}} = \xi\mathcal{L}\mathcal{K} - \eta_{\mathcal{L}}\mathcal{L}, \end{cases} \quad (2)$$

where, $\mathcal{L} = \mathcal{L}(t)$ is the concentration of the CTLs at time t . CTLs are stimulated, die and kill infected cells at rate, $\xi\mathcal{L}\mathcal{K}$, $\eta_{\mathcal{L}}\mathcal{L}$ and $\phi\mathcal{L}\mathcal{K}$, respectively. It has been documented that HIV-1 can impair CTL immunity and inhibit CTL responsiveness [16–22]. By

considering the CTL impairment, the fourth equation of system (2) can be modified as [23–25]:

$$\dot{\mathcal{L}} = \xi\mathcal{K} - \beta\mathcal{L}\mathcal{K} - \eta_{\mathcal{L}}\mathcal{L},$$

where CTL immunological impairment rate is denoted by $\beta\mathcal{L}\mathcal{K}$ and CTL immunity stimulation is represented by $\xi\mathcal{K}$.

Although effective combination therapy often lowers the HIV-1 plasma viral load to below the detection limit, complete virus elimination remains elusive [26]. Despite the advancements in antiviral medication, one of the major challenges in eradicating HIV-1 lies in the persistence of latently infected cells [26, 27]. Latently infected cells harbor HIV-1 virions but remain dormant until activated. In the HIV-1 infection model, which encompasses two infection pathways, CTL immune impairment and latently infected cells, the formulation can be expressed as: [24, 25]:

$$\begin{cases} \dot{\mathcal{J}} = \theta - \eta_{\mathcal{J}}\mathcal{J} - (\rho_{\mathcal{E}}\mathcal{E} + \rho_{\mathcal{K}}\mathcal{K})\mathcal{J}, \\ \dot{\mathcal{P}} = \nu(\rho_{\mathcal{E}}\mathcal{E} + \rho_{\mathcal{K}}\mathcal{K})\mathcal{J} - (\psi + \eta_{\mathcal{P}})\mathcal{P}, \\ \dot{\mathcal{K}} = (1 - \nu)(\rho_{\mathcal{E}}\mathcal{E} + \rho_{\mathcal{K}}\mathcal{K})\mathcal{J} + \psi\mathcal{P} - \eta_{\mathcal{K}}\mathcal{K} - \phi\mathcal{L}\mathcal{K}, \\ \dot{\mathcal{E}} = \varpi\mathcal{K} - \eta_{\mathcal{E}}\mathcal{E}, \\ \dot{\mathcal{L}} = \xi\mathcal{K} - \beta\mathcal{L}\mathcal{K} - \eta_{\mathcal{L}}\mathcal{L}, \end{cases}$$

where $\mathcal{P} = \mathcal{P}(t)$ is the concentration of the latently infected cells at time t . Latently infected cells become active at a rate of $\psi\mathcal{P}$ and undergo cell death at a rate of $\eta_{\mathcal{P}}\mathcal{P}$. Among all infections, a fraction ν becomes latent, while the remaining fraction $1 - \nu$ becomes active.

According to the experimental data by Agosto et al. [28], it has been observed that latently infected cells can spread the infection through the CTC mechanism to uninfected cells. Consequently, in recent works [29–31], viral infection models were developed by including three pathways of infection, (i) VTC, $\rho_{\mathcal{E}}\mathcal{E}\mathcal{J}$, (ii) latent cell-to-cell (L-CTC), $\rho_{\mathcal{P}}\mathcal{P}\mathcal{J}$ and (iii) active cell-to-cell (A-CTC), $\rho_{\mathcal{K}}\mathcal{K}\mathcal{J}$. One crucial factor influencing the spread of viruses is the infection rate [32]. The following types of infection rates were taken into account in the viral dynamics models including CTL immune impairment and/or CTC transmission:

- Bilinear infection rate: $\rho_{\mathcal{E}}\mathcal{E}\mathcal{J}$ [21, 33]; $(\rho_{\mathcal{E}}\mathcal{E} + \rho_{\mathcal{K}}\mathcal{K})\mathcal{J}$ [25]; $(\rho_{\mathcal{E}}\mathcal{E} + \rho_{\mathcal{P}}\mathcal{P} + \rho_{\mathcal{K}}\mathcal{K})\mathcal{J}$, [34, 35]. This situation implies that the rate of infection is precisely proportional to the product of the concentrations, involving viruses or infected cells interacting with uninfected cells, a phenomenon known as the mass-action principle. However, practical applications reveal that this concept is not universally applicable. The law of mass-action, for instance, won't apply if the quantity of viruses or infected cells surpasses the quantity of uninfected cells. In such a scenario, an increase in virus or infected cell concentration won't result in a rise in infection.
- Saturated infection rate: $\frac{\rho_{\mathcal{E}}\mathcal{E}}{1+\epsilon_{\mathcal{E}}\mathcal{E}}\mathcal{J}$ [18]; $\frac{\rho_{\mathcal{E}}\mathcal{E}}{1+\epsilon_{\mathcal{E}}\mathcal{E}}\mathcal{J} + \frac{\rho_{\mathcal{K}}\mathcal{K}}{1+\epsilon_{\mathcal{K}}\mathcal{K}}\mathcal{J}$ [23, 36], where $\epsilon_{\mathcal{E}}, \epsilon_{\mathcal{K}} \geq 0$.
- Beddington-DeAngelis infection rate $\frac{\rho_{\mathcal{E}}\mathcal{E}}{1+\epsilon_{\mathcal{E}}\mathcal{E}+\epsilon_{\mathcal{J}}\mathcal{J}}\mathcal{J}$ [37], where $\epsilon_{\mathcal{E}}, \epsilon_{\mathcal{J}} \geq 0$.
- General infection rate: $\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E})$ [19]; $(\Upsilon_{\mathcal{E}}(\mathcal{E}) + \Upsilon_{\mathcal{P}}(\mathcal{K}))\Upsilon_{\mathcal{K}}(\mathcal{J})$ [24]; $\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E})\mathcal{E} + \Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K})\mathcal{K}$ [38]; $\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E})\mathcal{E} + \Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P})\mathcal{P} + \Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K})\mathcal{K}$ [29], [30]; $\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}) + \Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P}) + \Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K})$ [31], where $\Upsilon_{\mathcal{E}}, \Upsilon_{\mathcal{P}}$ and $\Upsilon_{\mathcal{K}}$ are general functions.

It should be noted that the model in Alofi and Azoz [24] disregarded the L-CTC route, but included consideration for CTL immune impairment. While the models in Wang et al. [29] and Hattaf and Dutta [30] incorporated three infection pathways (VTC, L-CTC, and A-CTC), they did not account for CTL immunity. In another model discussed in Elaiw and AlShamrani [31], the VTC, L-CTC, and A-CTC pathways were considered, yet the model omitted consideration for CTL immunological impairment.

The current study aims to investigate two HIV-1 infection models with CTL immunological impairment, taking into account three different infection pathways: VTC, L-CTC, and A-CTC which are modeled by general nonlinear functions. Additionally, three kinds of distributed-time delays are incorporated into the second model. We examine the fundamental characteristics of the model's solutions in addition to the steady states' global stability. We provide numerical simulations to validate the theoretical results. We wrap up by talking about the outcomes. Our proposed model can be seen as a generalization of several HIV-1 infection models with CTL impairment presented in the literature. Our system's basic reproduction ratio (\mathfrak{R}_0) is more accurate than models that do not account for the L-CTC route. As a result, the acquired (\mathfrak{R}_0) may result in appropriate drug therapy aimed at eliminating HIV-1 from the body.

2 Model with CTL immune impairment, general infection rate and three pathways of infection

2.1 System overview

We introduce a model for HIV-1 that incorporates CTL immune impairment while also accounting for the infection of healthy CD4⁺T cells through VTC, L-CTC, and A-CTC transmission modes. The model is outlined as follows:

$$\begin{cases} \dot{\mathcal{J}} &= \theta - \eta_{\mathcal{J}}\mathcal{J} - \Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}) - \Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P}) - \Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K}), \\ \dot{\mathcal{P}} &= \Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}) + \Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P}) + \Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K}) - (\psi + \eta_{\mathcal{P}})\mathcal{P}, \\ \dot{\mathcal{K}} &= \psi\mathcal{P} - \eta_{\mathcal{K}}\mathcal{K} - \phi\mathcal{L}\mathcal{K}, \\ \dot{\mathcal{E}} &= \varpi\mathcal{K} - \eta_{\mathcal{E}}\mathcal{E}, \\ \dot{\mathcal{L}} &= \xi\mathcal{K} - \eta_{\mathcal{L}}\mathcal{L} - \beta\mathcal{L}\mathcal{K}. \end{cases} \tag{3}$$

The general functions $\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E})$, $\Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P})$ and $\Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K})$ represent, respectively, the VTC, L-CTC and A-CTC routes of infection. The meanings assigned to all remaining parameters and variables remain in line with the explanations provided in Section 1. Model (3) is very general as it considers nonlinear incidences ($\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E})$, $\Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P})$ and $\Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K})$). Additionally, it is crucial to highlight that model (3) encompasses a broad spectrum of pre-existing models, as seen in earlier research [24, 30, 31].

Define $\ell_Z(\mathcal{J})$, $Z \in \{\mathcal{E}, \mathcal{P}, \mathcal{K}\}$ as:

$$\begin{aligned} \ell_{\mathcal{E}}(\mathcal{J}) &= \lim_{\mathcal{E} \rightarrow 0^+} \frac{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E})}{\mathcal{E}} = \frac{\partial \Upsilon_{\mathcal{E}}(\mathcal{J}, 0)}{\partial \mathcal{E}}, \\ \ell_{\mathcal{P}}(\mathcal{J}) &= \lim_{\mathcal{P} \rightarrow 0^+} \frac{\Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P})}{\mathcal{P}} = \frac{\partial \Upsilon_{\mathcal{P}}(\mathcal{J}, 0)}{\partial \mathcal{P}}, \\ \ell_{\mathcal{K}}(\mathcal{J}) &= \lim_{\mathcal{K} \rightarrow 0^+} \frac{\Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K})}{\mathcal{K}} = \frac{\partial \Upsilon_{\mathcal{K}}(\mathcal{J}, 0)}{\partial \mathcal{K}}. \end{aligned}$$

The paper relies on the following conditions regarding the functions $\Upsilon_Z(\mathcal{J}, Z)$, $Z \in \{\mathcal{E}, \mathcal{P}, \mathcal{K}\}$ [39, 40]:

Condition C1. $\Upsilon_Z(\mathcal{J}, Z)$ is continuously differentiable, $\Upsilon_Z(\mathcal{J}, Z) > 0$ and $\Upsilon_Z(0, Z) = \Upsilon_Z(\mathcal{J}, 0) = 0$ for all $\mathcal{J} > 0$ and $Z \in \{\mathcal{E}, \mathcal{P}, \mathcal{K}\} > 0$.

Condition C2. $\frac{\partial \Upsilon_Z(\mathcal{J}, Z)}{\partial \mathcal{J}} > 0$, $\frac{\partial \Upsilon_Z(\mathcal{J}, Z)}{\partial Z} > 0$ for all $\mathcal{J} > 0$ and $Z \in \{\mathcal{E}, \mathcal{P}, \mathcal{K}\} > 0$.

Condition C3. $\ell_Z(\mathcal{J}) > 0$ and $\ell'_Z(\mathcal{J}) > 0$ for all $\mathcal{J} > 0$, $Z \in \{\mathcal{E}, \mathcal{P}, \mathcal{K}\}$.

Condition C4. $\frac{\Upsilon_Z(\mathcal{J}, Z)}{Z}$ is non-increasing with respect to Z for all $Z \in \{\mathcal{E}, \mathcal{P}, \mathcal{K}\} > 0$.

2.2 Fundamental characteristics

2.2.1 Model's well-posedness

To guarantee the biological acceptability of our model, the following assertion establishes a constrained domain for the compartment concentrations. More specifically, the concentrations shouldn't go negative or unbounded.

Proposition 2.1. Assume that Condition C1 is satisfied, then the solutions of system (3) are nonnegative and bounded.

Proof. From system (3) we get the following:

$$\begin{aligned} \dot{\mathcal{J}}|_{\mathcal{J}=0} &= \theta > 0, \\ \dot{\mathcal{P}}|_{\mathcal{P}=0} &= \Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}) + \Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K}) \geq 0, \text{ for all } \mathcal{J}, \mathcal{E}, \mathcal{K} \geq 0, \\ \dot{\mathcal{K}}|_{\mathcal{K}=0} &= \psi\mathcal{P} \geq 0, \text{ for all } \mathcal{P} \geq 0, \\ \dot{\mathcal{E}}|_{\mathcal{E}=0} &= \varpi\mathcal{K} \geq 0, \text{ for all } \mathcal{K} \geq 0, \\ \dot{\mathcal{L}}|_{\mathcal{L}=0} &= \xi\mathcal{K} \geq 0, \text{ for all } \mathcal{K} \geq 0. \end{aligned}$$

Thus, according to Proposition B.7 of Smith and Waltman [41], we conclude that, for all $t \geq 0$, we have $(\mathcal{J}(t), \mathcal{P}(t), \mathcal{K}(t), \mathcal{E}(t), \mathcal{L}(t)) \in \mathbb{S}_{\geq 0}^5$, whenever $(\mathcal{J}(0), \mathcal{P}(0), \mathcal{K}(0), \mathcal{E}(0), \mathcal{L}(0)) \in \mathbb{S}_{\geq 0}^5$. Let

$$\Phi = \mathcal{J} + \mathcal{P} + \mathcal{K} + \frac{\eta_{\mathcal{K}}}{2\varpi}\mathcal{E} + \frac{\eta_{\mathcal{K}}}{4\xi}\mathcal{L}.$$

Then, we have

$$\begin{aligned} \dot{\Phi} &= \dot{\mathcal{J}} + \dot{\mathcal{P}} + \dot{\mathcal{K}} + \frac{\eta_{\mathcal{K}}}{2\varpi}\dot{\mathcal{E}} + \frac{\eta_{\mathcal{K}}}{4\xi}\dot{\mathcal{L}} \\ &= \theta - \eta_{\mathcal{J}}\mathcal{J} - \eta_{\mathcal{P}}\mathcal{P} - \frac{\eta_{\mathcal{K}}}{4}\mathcal{K} - \left(\phi + \frac{\eta_{\mathcal{K}}\beta}{4\xi}\right)\mathcal{L}\mathcal{K} \\ &\quad - \frac{\eta_{\mathcal{K}}\eta_{\mathcal{E}}}{2\varpi}\mathcal{E} - \frac{\eta_{\mathcal{K}}\eta_{\mathcal{L}}}{4\xi}\mathcal{L} \\ &\leq \theta - \eta_{\mathcal{J}}\mathcal{J} - \eta_{\mathcal{P}}\mathcal{P} - \frac{\eta_{\mathcal{K}}}{4}\mathcal{K} - \frac{\eta_{\mathcal{K}}\eta_{\mathcal{E}}}{2\varpi}\mathcal{E} - \frac{\eta_{\mathcal{K}}\eta_{\mathcal{L}}}{4\xi}\mathcal{L} \\ &\leq \theta - \varepsilon \left(\mathcal{J} + \mathcal{P} + \mathcal{K} + \frac{\eta_{\mathcal{K}}}{2\varpi}\mathcal{E} + \frac{\eta_{\mathcal{K}}}{4\xi}\mathcal{L} \right) = \theta - \varepsilon\Phi, \end{aligned}$$

where $\varepsilon = \min \{ \eta_{\mathcal{J}}, \eta_{\mathcal{P}}, \frac{\eta_{\mathcal{K}}}{4}, \eta_{\mathcal{E}}, \eta_{\mathcal{L}} \}$. Hence

$$\Phi(t) \leq e^{-\varepsilon t} \left(\Phi(0) - \frac{\theta}{\varepsilon} \right) + \frac{\theta}{\varepsilon}.$$

This yields $0 \leq \Phi(t) \leq \Gamma_1$ if $\Phi(0) \leq \Gamma_1$, where $\Gamma_1 = \frac{\theta}{\varepsilon}$. Considering that all state variables have non-negative values, $0 \leq \mathcal{J}(t), \mathcal{P}(t), \mathcal{K}(t) \leq \Gamma_1$, $0 \leq \mathcal{E}(t) \leq \Gamma_2$, and $0 \leq \mathcal{L}(t) \leq \Gamma_3$, for all $t \geq 0$ if $\mathcal{J}(0) + \mathcal{P}(0) + \mathcal{K}(0) + \frac{\eta\mathcal{K}}{2\varpi}\mathcal{E}(0) + \frac{\eta\mathcal{K}}{4\xi}\mathcal{L}(0) \leq \Gamma_1$, where $\Gamma_2 = \frac{2\varpi\Gamma_1}{\eta\mathcal{K}}$ and $\Gamma_3 = \frac{4\xi\Gamma_1}{\eta\mathcal{K}}$. To sum up, the boundedness of $\mathcal{J}(t), \mathcal{P}(t), \mathcal{K}(t), \mathcal{E}(t)$ and $\mathcal{L}(t)$ implies that the solutions of system (3) are bounded.

2.2.2 Derivation of reproduction ratios and steady states

Proposition 2.2. Assuming that Conditions C1–C4 are met, there exists a positive basic reproduction ratio $\mathfrak{R}_0 = \frac{\varpi\psi\ell_{\mathcal{E}}(\mathcal{J}_0) + \eta_{\mathcal{E}}\eta_{\mathcal{K}}\ell_{\mathcal{P}}(\mathcal{J}_0) + \psi\eta_{\mathcal{E}}\ell_{\mathcal{K}}(\mathcal{J}_0)}{\eta_{\mathcal{E}}\eta_{\mathcal{K}}(\psi + \eta_{\mathcal{P}})}$ for system (3) in a way that

- (i) ensures the system consistently maintains a virus-free steady state, denoted as O_0 , and
- (ii) if $\mathfrak{R}_0 > 1$, the system additionally possesses a virus-persistence steady state, denoted as O_1 .

Proof. It is observed that a virus-free steady state labeled as $O_0 = (\mathcal{J}_0, 0, 0, 0, 0)$ consistently exists in system (3), where $\mathcal{J}_0 = \frac{\theta}{\eta_{\mathcal{J}}}$. In the upcoming analysis, we plan to calculate the basic reproduction ratio for system (3) using the next-generation matrix (NGM) approach, as introduced by Driessche and Watmough [42]. The model (3) features infected compartments, denoted as $(\mathcal{P}, \mathcal{K}, \mathcal{E})$, and is defined by matrices that describe the nonlinear components related to the new infection $\hat{\Omega}_1$ and the outflow term $\hat{\Lambda}_1$ within these compartments as given below.

$$\hat{\Omega}_1 = \begin{pmatrix} \Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}) + \Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P}) + \Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K}) & & \\ & 0 & \\ & & 0 \end{pmatrix},$$

$$\hat{\Lambda}_1 = \begin{pmatrix} (\psi + \eta_{\mathcal{P}})\mathcal{P} & & \\ -\psi\mathcal{P} + \eta_{\mathcal{K}}\mathcal{K} + \phi\mathcal{L}\mathcal{K} & & \\ -\varpi\mathcal{K} + \eta_{\mathcal{E}}\mathcal{E} & & \end{pmatrix}.$$

The derivatives of $\hat{\Omega}_1$ and $\hat{\Lambda}_1$ at the steady state O_0 are calculated, yielding the following matrices:

$$\Omega_1 = \begin{pmatrix} \frac{\partial \Upsilon_{\mathcal{P}}(\mathcal{J}_0, 0)}{\partial \mathcal{P}} & \frac{\partial \Upsilon_{\mathcal{K}}(\mathcal{J}_0, 0)}{\partial \mathcal{K}} & \frac{\partial \Upsilon_{\mathcal{E}}(\mathcal{J}_0, 0)}{\partial \mathcal{E}} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix},$$

$$\Lambda_1 = \begin{pmatrix} \psi + \eta_{\mathcal{P}} & 0 & 0 \\ -\psi & \eta_{\mathcal{K}} & 0 \\ 0 & -\varpi & \eta_{\mathcal{E}} \end{pmatrix}.$$

The form of the NGM is as follows:

$$= \begin{pmatrix} \frac{\varpi\psi\ell_{\mathcal{E}}(\mathcal{J}_0)}{\eta_{\mathcal{E}}\eta_{\mathcal{K}}(\psi + \eta_{\mathcal{P}})} + \frac{\ell_{\mathcal{P}}(\mathcal{J}_0)}{\psi + \eta_{\mathcal{P}}} + \frac{\psi\ell_{\mathcal{K}}(\mathcal{J}_0)}{\eta_{\mathcal{K}}(\psi + \eta_{\mathcal{P}})} & \frac{\varpi\ell_{\mathcal{E}}(\mathcal{J}_0)}{\eta_{\mathcal{E}}\eta_{\mathcal{K}}} + \frac{\ell_{\mathcal{K}}(\mathcal{J}_0)}{\eta_{\mathcal{K}}} & \frac{\ell_{\mathcal{E}}(\mathcal{J}_0)}{\eta_{\mathcal{E}}} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}.$$

The spectral radius of matrix $\Omega_1\Lambda_1^{-1}$, symbolized as \mathfrak{R}_0 , defines the basic reproduction ratio. Its calculation is determined by the following expression:

$$\mathfrak{R}_0 = \frac{\varpi\psi\ell_{\mathcal{E}}(\mathcal{J}_0) + \eta_{\mathcal{E}}\eta_{\mathcal{K}}\ell_{\mathcal{P}}(\mathcal{J}_0) + \psi\eta_{\mathcal{E}}\ell_{\mathcal{K}}(\mathcal{J}_0)}{\eta_{\mathcal{E}}\eta_{\mathcal{K}}(\psi + \eta_{\mathcal{P}})} = \mathfrak{R}_{0\mathcal{E}} + \mathfrak{R}_{0\mathcal{P}} + \mathfrak{R}_{0\mathcal{K}}, \tag{4}$$

where

$$\mathfrak{R}_{0\mathcal{E}} = \frac{\varpi\psi\ell_{\mathcal{E}}(\mathcal{J}_0)}{\eta_{\mathcal{E}}\eta_{\mathcal{K}}(\psi + \eta_{\mathcal{P}})}, \quad \mathfrak{R}_{0\mathcal{P}} = \frac{\ell_{\mathcal{P}}(\mathcal{J}_0)}{\psi + \eta_{\mathcal{P}}},$$

$$\mathfrak{R}_{0\mathcal{K}} = \frac{\psi\ell_{\mathcal{K}}(\mathcal{J}_0)}{\eta_{\mathcal{K}}(\psi + \eta_{\mathcal{P}})}.$$

The clinical relevance of the parameter \mathfrak{R}_0 holds significance as it plays a crucial role in determining whether the HIV-1 infection will progress into a chronic state. Within this framework, \mathfrak{R}_{0Z} symbolizes the average quantities of secondary infected cells generated from engagements with viruses and infected cells, where $Z \in \{\mathcal{E}, \mathcal{P}, \mathcal{K}\}$. To extend our exploration beyond O_0 , we scrutinize $(\mathcal{J}, \mathcal{P}, \mathcal{K}, \mathcal{E}, \mathcal{L})$ as a potential steady state governed by the following set of algebraic equations:

$$0 = \theta - \eta_{\mathcal{J}}\mathcal{J} - \Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}) - \Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P}) - \Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K}), \tag{5}$$

$$0 = \Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}) + \Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P}) + \Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K}) - (\psi + \eta_{\mathcal{P}})\mathcal{P}, \tag{6}$$

$$0 = \psi\mathcal{P} - \eta_{\mathcal{K}}\mathcal{K} - \phi\mathcal{L}\mathcal{K}, \tag{7}$$

$$0 = \varpi\mathcal{K} - \eta_{\mathcal{E}}\mathcal{E}, \tag{8}$$

$$0 = \xi\mathcal{K} - \eta_{\mathcal{L}}\mathcal{L} - \beta\mathcal{L}\mathcal{K}. \tag{9}$$

From Equations (8, 9), we get

$$\mathcal{E} = \Theta_1(\mathcal{K}) = \frac{\varpi\mathcal{K}}{\eta_{\mathcal{E}}}, \quad \mathcal{L} = \frac{\xi\mathcal{K}}{\eta_{\mathcal{L}} + \beta\mathcal{K}}. \tag{10}$$

Clearly, $\Theta_1(0) = 0$. The following outcome is obtained after inserting Equation (10) into Equation (7):

$$\mathcal{P} = \Theta_2(\mathcal{K}) = \frac{\eta_{\mathcal{L}}\eta_{\mathcal{K}}\mathcal{K} + (\phi\xi + \eta_{\mathcal{K}}\beta)\mathcal{K}^2}{\psi(\eta_{\mathcal{L}} + \beta\mathcal{K})}. \tag{11}$$

It is clear that $\Theta_2(0) = 0$. From Equations (5, 6), we get

$$\theta - \eta_{\mathcal{J}}\mathcal{J} = (\psi + \eta_{\mathcal{P}})\mathcal{P}. \tag{12}$$

The following outcome is obtained after inserting Equation (11) into Equation (12):

$$\mathcal{J} = \Theta_3(\mathcal{K}) = \frac{1}{\eta_{\mathcal{J}}} \left(\theta - \frac{(\psi + \eta_{\mathcal{P}})(\eta_{\mathcal{L}}\eta_{\mathcal{K}}\mathcal{K} + (\phi\xi + \eta_{\mathcal{K}}\beta)\mathcal{K}^2)}{\psi(\eta_{\mathcal{L}} + \beta\mathcal{K})} \right). \tag{13}$$

Note that $\Theta_3(0) = \mathcal{J}_0$. Upon substitution of Equations (10, 11, 13) into Equation (6), the result is as follows:

$$\Upsilon_{\mathcal{E}}(\Theta_3(\mathcal{K}), \Theta_1(\mathcal{K})) + \Upsilon_{\mathcal{P}}(\Theta_3(\mathcal{K}), \Theta_2(\mathcal{K})) + \Upsilon_{\mathcal{K}}(\Theta_3(\mathcal{K}), \mathcal{K}) - \frac{(\psi + \eta_{\mathcal{P}})(\eta_{\mathcal{L}}\eta_{\mathcal{K}}\mathcal{K} + (\phi\xi + \eta_{\mathcal{K}}\beta)\mathcal{K}^2)}{\psi(\eta_{\mathcal{L}} + \beta\mathcal{K})} = 0. \tag{14}$$

From Equation (14), we have

- When $\mathcal{K} = 0$, the virus-free steady state O_0 is derived from Equations (10, 11, 12, 13).
- When $\mathcal{K} \neq 0$, let us define a function $\Psi(\mathcal{K})$ on $[0, \infty)$ as:

$$\Psi(\mathcal{K}) = \Upsilon_{\mathcal{E}}(\Theta_3(\mathcal{K}), \Theta_1(\mathcal{K})) + \Upsilon_{\mathcal{P}}(\Theta_3(\mathcal{K}), \Theta_2(\mathcal{K})) + \Upsilon_{\mathcal{K}}(\Theta_3(\mathcal{K}), \mathcal{K}) - \frac{(\psi + \eta_{\mathcal{P}})(\eta_{\mathcal{L}}\eta_{\mathcal{K}}\mathcal{K} + (\phi\xi + \eta_{\mathcal{K}}\beta)\mathcal{K}^2)}{\psi(\eta_{\mathcal{L}} + \beta\mathcal{K})}.$$

We have $\Psi(0) = 0$. Let $\hat{\mathcal{K}}$ be such that $\Theta_3(\hat{\mathcal{K}}) = 0$, i.e.,

$$\mathcal{J}_0 - \frac{(\psi + \eta_{\mathcal{P}})(\eta_{\mathcal{L}}\eta_{\mathcal{K}}\hat{\mathcal{K}} + (\phi\xi + \eta_{\mathcal{K}}\beta)\hat{\mathcal{K}}^2)}{\eta_{\mathcal{J}}\psi(\eta_{\mathcal{L}} + \beta\hat{\mathcal{K}})} = 0,$$

which implies that

$$(\phi\xi + \eta_{\mathcal{K}}\beta)(\psi + \eta_{\mathcal{P}})\hat{\mathcal{K}}^2 + (\eta_{\mathcal{L}}\eta_{\mathcal{K}}(\psi + \eta_{\mathcal{P}}) - \eta_{\mathcal{J}}\psi\beta\mathcal{J}_0)\hat{\mathcal{K}} - \eta_{\mathcal{J}}\psi\eta_{\mathcal{L}}\mathcal{J}_0 = 0. \tag{15}$$

Therefore, Equation (15) has a positive solution

$$\hat{\mathcal{K}} = \frac{-B + \sqrt{B^2 - 4AC}}{2A},$$

where

$$\begin{aligned} A &= (\phi\xi + \eta_{\mathcal{K}}\beta)(\psi + \eta_{\mathcal{P}}), \\ B &= \eta_{\mathcal{L}}\eta_{\mathcal{K}}(\psi + \eta_{\mathcal{P}}) - \eta_{\mathcal{J}}\psi\beta\mathcal{J}_0, \\ C &= -\eta_{\mathcal{J}}\psi\eta_{\mathcal{L}}\mathcal{J}_0. \end{aligned}$$

We can see that

$$\begin{aligned} \Psi(\hat{\mathcal{K}}) &= \Upsilon_{\mathcal{E}}(0, \Theta_1(\hat{\mathcal{K}})) + \Upsilon_{\mathcal{P}}(0, \Theta_2(\hat{\mathcal{K}})) + \Upsilon_{\mathcal{K}}(0, \hat{\mathcal{K}}) \\ &\quad - \frac{(\psi + \eta_{\mathcal{P}})(\eta_{\mathcal{L}}\eta_{\mathcal{K}}\hat{\mathcal{K}} + (\phi\xi + \eta_{\mathcal{K}}\beta)\hat{\mathcal{K}}^2)}{\psi(\eta_{\mathcal{L}} + \beta\hat{\mathcal{K}})} \\ &= - \frac{(\psi + \eta_{\mathcal{P}})(\eta_{\mathcal{L}}\eta_{\mathcal{K}}\hat{\mathcal{K}} + (\phi\xi + \eta_{\mathcal{K}}\beta)\hat{\mathcal{K}}^2)}{\psi(\eta_{\mathcal{L}} + \beta\hat{\mathcal{K}})} < 0. \end{aligned}$$

In addition

$$\begin{aligned} \Psi'(\mathcal{K}) &= \Theta'_3(\mathcal{K}) \frac{\partial \Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E})}{\partial \mathcal{J}} + \Theta'_1(\mathcal{K}) \frac{\partial \Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E})}{\partial \mathcal{E}} \\ &\quad + \Theta'_3(\mathcal{K}) \frac{\partial \Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P})}{\partial \mathcal{J}} + \Theta'_2(\mathcal{K}) \frac{\partial \Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P})}{\partial \mathcal{P}} \\ &\quad + \Theta'_3(\mathcal{K}) \frac{\partial \Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K})}{\partial \mathcal{J}} + \frac{\partial \Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K})}{\partial \mathcal{K}} \\ &\quad - \frac{\psi + \eta_{\mathcal{P}}}{\psi} \left(\eta_{\mathcal{K}} + \frac{\phi\xi(2\eta_{\mathcal{L}} + \beta\mathcal{K})\mathcal{K}}{(\eta_{\mathcal{L}} + \beta\mathcal{K})^2} \right). \end{aligned}$$

Condition C1 implies that $\frac{\partial \Upsilon_{\mathcal{Z}}(\mathcal{J}_0, 0)}{\partial \mathcal{J}} = 0$, $Z \in \{\mathcal{E}, \mathcal{P}, \mathcal{K}\}$. Then

$$\begin{aligned} \Psi'(0) &= \Theta'_1(0) \frac{\partial \Upsilon_{\mathcal{E}}(\mathcal{J}_0, 0)}{\partial \mathcal{E}} + \Theta'_2(0) \frac{\partial \Upsilon_{\mathcal{P}}(\mathcal{J}_0, 0)}{\partial \mathcal{P}} \\ &\quad + \frac{\partial \Upsilon_{\mathcal{K}}(\mathcal{J}_0, 0)}{\partial \mathcal{K}} - \frac{\eta_{\mathcal{K}}(\psi + \eta_{\mathcal{P}})}{\psi} \end{aligned}$$

$$\begin{aligned} &= \frac{\varpi}{\eta_{\mathcal{E}}} \frac{\partial \Upsilon_{\mathcal{E}}(\mathcal{J}_0, 0)}{\partial \mathcal{E}} + \frac{\eta_{\mathcal{K}}}{\psi} \frac{\partial \Upsilon_{\mathcal{P}}(\mathcal{J}_0, 0)}{\partial \mathcal{P}} + \frac{\partial \Upsilon_{\mathcal{K}}(\mathcal{J}_0, 0)}{\partial \mathcal{K}} \\ &\quad - \frac{\eta_{\mathcal{K}}(\psi + \eta_{\mathcal{P}})}{\psi} \\ &= \frac{\varpi \ell_{\mathcal{E}}(\mathcal{J}_0)}{\eta_{\mathcal{E}}} + \frac{\eta_{\mathcal{K}} \ell_{\mathcal{P}}(\mathcal{J}_0)}{\psi} + \ell_{\mathcal{K}}(\mathcal{J}_0) - \frac{\eta_{\mathcal{K}}(\psi + \eta_{\mathcal{P}})}{\psi} \\ &= \frac{\eta_{\mathcal{K}}(\psi + \eta_{\mathcal{P}})}{\psi} (\mathfrak{R}_0 - 1), \end{aligned}$$

where \mathfrak{R}_0 is defined in Equation (4). Therefore, if $\mathfrak{R}_0 > 1$ then $\Psi'(0) > 0$ and there exists $\mathcal{K}_1 \in (0, \hat{\mathcal{K}})$ such that $\Psi(\mathcal{K}_1) = 0$. Let $\mathcal{K} = \mathcal{K}_1$ in Equation (5) and define

$$\mathfrak{N}(\mathcal{J}) = \theta - \eta_{\mathcal{J}}\mathcal{J} - \Upsilon_{\mathcal{E}}(\mathcal{J}, \Theta_1(\mathcal{K}_1)) - \Upsilon_{\mathcal{P}}(\mathcal{J}, \Theta_2(\mathcal{K}_1)) - \Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K}_1).$$

Subsequently, based on Condition C1, we obtain $\mathfrak{N}(0) = \theta > 0$ and

$$\begin{aligned} \mathfrak{N}(\mathcal{J}_0) &= -(\Upsilon_{\mathcal{E}}(\mathcal{J}_0, \Theta_1(\mathcal{K}_1)) + \Upsilon_{\mathcal{P}}(\mathcal{J}_0, \Theta_2(\mathcal{K}_1)) \\ &\quad + \Upsilon_{\mathcal{K}}(\mathcal{J}_0, \mathcal{K}_1)) < 0. \end{aligned}$$

Under Condition C2, it follows that $\mathfrak{N}(\mathcal{J})$ decreases strictly as a function of \mathcal{J} . Consequently, there is a unique value \mathcal{J}_1 within the interval $(0, \mathcal{J}_0)$ for which $\mathfrak{N}(\mathcal{J}_1)$ equals zero. Moreover, considering Equations (10, 11), we find

$$\begin{aligned} \mathcal{P}_1 &= \frac{\eta_{\mathcal{L}}\eta_{\mathcal{K}}\mathcal{K}_1 + (\phi\xi + \beta\eta_{\mathcal{K}})\mathcal{K}_1^2}{\psi(\eta_{\mathcal{L}} + \beta\mathcal{K}_1)}, \quad \mathcal{E}_1 = \frac{\varpi\mathcal{K}_1}{\eta_{\mathcal{E}}}, \\ \mathcal{L}_1 &= \frac{\xi\mathcal{K}_1}{\eta_{\mathcal{L}} + \beta\mathcal{K}_1}. \end{aligned}$$

The presence of the virus-persistence steady state $O_1 = (\mathcal{J}_1, \mathcal{P}_1, \mathcal{K}_1, \mathcal{E}_1, \mathcal{L}_1)$ becomes evident when $\mathfrak{R}_0 > 1$.

2.2.3 Global stability of steady states

The forthcoming theorems explore the global asymptotic stability of both virus-free and virus-persistence steady states. The development of the Lyapunov function will adhere to the approach outlined in Korobeinikov [43].

In the remaining work, we focus on a function $\Xi_i(\mathcal{J}, \mathcal{P}, \mathcal{K}, \mathcal{E}, \mathcal{L})$, and we characterize M'_i as the largest invariant subset of

$$M_i = \left\{ (\mathcal{J}, \mathcal{P}, \mathcal{K}, \mathcal{E}, \mathcal{L}) : \frac{d\Xi_i}{dt} = 0 \right\}, \quad i = 1, \dots, 4.$$

In order to examine whether the steady state O_0 is globally asymptotically stable (G.A.S), we necessitate adherence to Condition C5 as outlined below [40]:

Condition C5. The supremum of $\frac{\ell_Z(\mathcal{J})}{\ell_{\mathcal{E}}(\mathcal{J})}$ on $(0, \theta/\eta_{\mathcal{J}}]$ is attained at $\mathcal{J} = \frac{\theta}{\eta_{\mathcal{J}}}$, where $Z \in \{\mathcal{P}, \mathcal{K}\}$.

Theorem 2.1. For system (3), let $\mathfrak{R}_0 \leq 1$ and Conditions C1–C5 are satisfied, then O_0 is G.A.S.

Proof. Let's contemplate a potential Lyapunov function as:

$$\Xi_1 = \mathcal{J} - \mathcal{J}_0 - \int_{\mathcal{J}_0}^{\mathcal{J}} \frac{\ell_{\mathcal{E}}(\mathcal{J}_0)}{\ell_{\mathcal{E}}(\lambda)} d\lambda + \mathcal{P} + \frac{\varpi \ell_{\mathcal{E}}(\mathcal{J}_0) + \eta_{\mathcal{E}} \ell_{\mathcal{K}}(\mathcal{J}_0)}{\eta_{\mathcal{K}} \eta_{\mathcal{E}}} \mathcal{K} + \frac{\ell_{\mathcal{E}}(\mathcal{J}_0)}{\eta_{\mathcal{E}}} \mathcal{E} + \frac{\phi(\varpi \ell_{\mathcal{E}}(\mathcal{J}_0) + \eta_{\mathcal{E}} \ell_{\mathcal{K}}(\mathcal{J}_0))}{2\xi \eta_{\mathcal{K}} \eta_{\mathcal{E}}} \mathcal{L}^2.$$

Evidently, $\Xi_1(\mathcal{J}, \mathcal{P}, \mathcal{K}, \mathcal{E}, \mathcal{L}) > 0$ for every $\mathcal{J}, \mathcal{P}, \mathcal{K}, \mathcal{E}, \mathcal{L} > 0$, as well as $\Xi_1(\mathcal{J}_0, 0, 0, 0, 0) = 0$. Computing $\frac{d\Xi_1}{dt}$, we derive

$$\begin{aligned} \frac{d\Xi_1}{dt} &= \left(1 - \frac{\ell_{\mathcal{E}}(\mathcal{J}_0)}{\ell_{\mathcal{E}}(\mathcal{J})}\right) \dot{\mathcal{J}} + \dot{\mathcal{P}} + \frac{\varpi \ell_{\mathcal{E}}(\mathcal{J}_0) + \eta_{\mathcal{E}} \ell_{\mathcal{K}}(\mathcal{J}_0)}{\eta_{\mathcal{K}} \eta_{\mathcal{E}}} \dot{\mathcal{K}} \\ &+ \frac{\ell_{\mathcal{E}}(\mathcal{J}_0)}{\eta_{\mathcal{E}}} \dot{\mathcal{E}} + \frac{\phi(\varpi \ell_{\mathcal{E}}(\mathcal{J}_0) + \eta_{\mathcal{E}} \ell_{\mathcal{K}}(\mathcal{J}_0))}{\xi \eta_{\mathcal{K}} \eta_{\mathcal{E}}} \dot{\mathcal{L}} \\ &= \left(1 - \frac{\ell_{\mathcal{E}}(\mathcal{J}_0)}{\ell_{\mathcal{E}}(\mathcal{J})}\right) (\theta - \eta_{\mathcal{J}} \mathcal{J} - \Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}) - \Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P}) \\ &- \Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K})) + \Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}) + \Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P}) + \Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K}) \\ &- (\psi + \eta_{\mathcal{P}}) \mathcal{P} \\ &+ \frac{\varpi \ell_{\mathcal{E}}(\mathcal{J}_0) + \eta_{\mathcal{E}} \ell_{\mathcal{K}}(\mathcal{J}_0)}{\eta_{\mathcal{K}} \eta_{\mathcal{E}}} (\psi \mathcal{P} - \eta_{\mathcal{K}} \mathcal{K} - \phi \mathcal{L} \mathcal{K}) \\ &+ \frac{\ell_{\mathcal{E}}(\mathcal{J}_0)}{\eta_{\mathcal{E}}} (\varpi \mathcal{K} - \eta_{\mathcal{E}} \mathcal{E}) \\ &+ \frac{\phi(\varpi \ell_{\mathcal{E}}(\mathcal{J}_0) + \eta_{\mathcal{E}} \ell_{\mathcal{K}}(\mathcal{J}_0))}{\xi \eta_{\mathcal{K}} \eta_{\mathcal{E}}} \mathcal{L} (\xi \mathcal{K} - \eta_{\mathcal{L}} \mathcal{L} - \beta \mathcal{L} \mathcal{K}) \\ &= \left(1 - \frac{\ell_{\mathcal{E}}(\mathcal{J}_0)}{\ell_{\mathcal{E}}(\mathcal{J})}\right) (\theta - \eta_{\mathcal{J}} \mathcal{J}) \\ &+ \left(\frac{\ell_{\mathcal{E}}(\mathcal{J}_0)}{\ell_{\mathcal{E}}(\mathcal{J})} \frac{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E})}{\mathcal{E}} - \ell_{\mathcal{E}}(\mathcal{J}_0)\right) \mathcal{E} \\ &+ \left(\frac{\ell_{\mathcal{E}}(\mathcal{J}_0)}{\ell_{\mathcal{E}}(\mathcal{J})} \frac{\Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P})}{\mathcal{P}} - (\psi + \eta_{\mathcal{P}})\right) \mathcal{P} \\ &+ \left(\frac{\ell_{\mathcal{E}}(\mathcal{J}_0)}{\ell_{\mathcal{E}}(\mathcal{J})} \frac{\Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K})}{\mathcal{K}} - \ell_{\mathcal{K}}(\mathcal{J}_0)\right) \mathcal{K} \\ &- \frac{\phi(\varpi \ell_{\mathcal{E}}(\mathcal{J}_0) + \eta_{\mathcal{E}} \ell_{\mathcal{K}}(\mathcal{J}_0))}{\xi \eta_{\mathcal{K}} \eta_{\mathcal{E}}} (\eta_{\mathcal{L}} + \beta \mathcal{K}) \mathcal{L}^2. \end{aligned} \tag{16}$$

From Condition C4, we have

$$\begin{aligned} \frac{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E})}{\mathcal{E}} &\leq \lim_{\mathcal{E} \rightarrow 0^+} \frac{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E})}{\mathcal{E}} = \ell_{\mathcal{E}}(\mathcal{J}), \quad \text{for all } \mathcal{J}, \mathcal{E} > 0, \\ \frac{\Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P})}{\mathcal{P}} &\leq \lim_{\mathcal{P} \rightarrow 0^+} \frac{\Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P})}{\mathcal{P}} = \ell_{\mathcal{P}}(\mathcal{J}), \quad \text{for all } \mathcal{J}, \mathcal{P} > 0, \\ \frac{\Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K})}{\mathcal{K}} &\leq \lim_{\mathcal{K} \rightarrow 0^+} \frac{\Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K})}{\mathcal{K}} = \ell_{\mathcal{K}}(\mathcal{J}), \quad \text{for all } \mathcal{J}, \mathcal{K} > 0. \end{aligned} \tag{17}$$

Then

$$\frac{\ell_{\mathcal{E}}(\mathcal{J}_0)}{\ell_{\mathcal{E}}(\mathcal{J})} \frac{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E})}{\mathcal{E}} - \ell_{\mathcal{E}}(\mathcal{J}_0) \leq \frac{\ell_{\mathcal{E}}(\mathcal{J}_0)}{\ell_{\mathcal{E}}(\mathcal{J})} \ell_{\mathcal{E}}(\mathcal{J}) - \ell_{\mathcal{E}}(\mathcal{J}_0) = 0.$$

Further, Conditions C4 and C5 in case of $\mathcal{J}_0 = \frac{\theta}{\eta_{\mathcal{J}}}$ imply that

$$\begin{aligned} &\frac{\ell_{\mathcal{E}}(\mathcal{J}_0)}{\ell_{\mathcal{E}}(\mathcal{J})} \frac{\Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P})}{\mathcal{P}} - (\psi + \eta_{\mathcal{P}}) + \frac{\psi(\varpi \ell_{\mathcal{E}}(\mathcal{J}_0) + \eta_{\mathcal{E}} \ell_{\mathcal{K}}(\mathcal{J}_0))}{\eta_{\mathcal{K}} \eta_{\mathcal{E}}} \\ &\leq \frac{\ell_{\mathcal{E}}(\mathcal{J}_0) \ell_{\mathcal{P}}(\mathcal{J})}{\ell_{\mathcal{E}}(\mathcal{J})} - (\psi + \eta_{\mathcal{P}}) + \frac{\psi(\varpi \ell_{\mathcal{E}}(\mathcal{J}_0) + \eta_{\mathcal{E}} \ell_{\mathcal{K}}(\mathcal{J}_0))}{\eta_{\mathcal{K}} \eta_{\mathcal{E}}} \end{aligned}$$

$$\begin{aligned} &\leq \frac{\ell_{\mathcal{E}}(\mathcal{J}_0) \ell_{\mathcal{P}}(\mathcal{J}_0)}{\ell_{\mathcal{E}}(\mathcal{J}_0)} - (\psi + \eta_{\mathcal{P}}) + \frac{\psi(\varpi \ell_{\mathcal{E}}(\mathcal{J}_0) + \eta_{\mathcal{E}} \ell_{\mathcal{K}}(\mathcal{J}_0))}{\eta_{\mathcal{K}} \eta_{\mathcal{E}}} \\ &= \ell_{\mathcal{P}}(\mathcal{J}_0) - (\psi + \eta_{\mathcal{P}}) + \frac{\psi(\varpi \ell_{\mathcal{E}}(\mathcal{J}_0) + \eta_{\mathcal{E}} \ell_{\mathcal{K}}(\mathcal{J}_0))}{\eta_{\mathcal{K}} \eta_{\mathcal{E}}} \\ &= \frac{\psi(\varpi \ell_{\mathcal{E}}(\mathcal{J}_0) + \eta_{\mathcal{E}} \ell_{\mathcal{K}}(\mathcal{J}_0)) + \eta_{\mathcal{K}} \eta_{\mathcal{E}} \ell_{\mathcal{P}}(\mathcal{J}_0)}{\eta_{\mathcal{K}} \eta_{\mathcal{E}}} - (\psi + \eta_{\mathcal{P}}) \\ &= (\psi + \eta_{\mathcal{P}}) (\mathfrak{R}_0 - 1). \end{aligned}$$

Furthermore

$$\begin{aligned} &\frac{\ell_{\mathcal{E}}(\mathcal{J}_0)}{\ell_{\mathcal{E}}(\mathcal{J})} \frac{\Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K})}{\mathcal{K}} - \ell_{\mathcal{K}}(\mathcal{J}_0) \leq \frac{\ell_{\mathcal{E}}(\mathcal{J}_0) \ell_{\mathcal{K}}(\mathcal{J})}{\ell_{\mathcal{E}}(\mathcal{J})} \\ &- \ell_{\mathcal{K}}(\mathcal{J}_0) \leq \frac{\ell_{\mathcal{E}}(\mathcal{J}_0) \ell_{\mathcal{K}}(\mathcal{J}_0)}{\ell_{\mathcal{E}}(\mathcal{J}_0)} - \ell_{\mathcal{K}}(\mathcal{J}_0) = 0. \end{aligned}$$

Upon conducting a computation and substituting the value $\mathcal{J}_0 = \theta/\eta_{\mathcal{J}}$, Equation (16) transforms into the following expression:

$$\begin{aligned} \frac{d\Xi_1}{dt} &\leq \theta \left(1 - \frac{\ell_{\mathcal{E}}(\mathcal{J}_0)}{\ell_{\mathcal{E}}(\mathcal{J})}\right) \left(1 - \frac{\mathcal{J}}{\mathcal{J}_0}\right) + (\psi + \eta_{\mathcal{P}}) (\mathfrak{R}_0 - 1) \mathcal{P} \\ &- \frac{\phi(\varpi \ell_{\mathcal{E}}(\mathcal{J}_0) + \eta_{\mathcal{E}} \ell_{\mathcal{K}}(\mathcal{J}_0))}{\xi \eta_{\mathcal{K}} \eta_{\mathcal{E}}} (\eta_{\mathcal{L}} + \beta \mathcal{K}) \mathcal{L}^2. \end{aligned}$$

From Condition C3, we have

$$\left(1 - \frac{\ell_{\mathcal{E}}(\mathcal{J}_0)}{\ell_{\mathcal{E}}(\mathcal{J})}\right) \left(1 - \frac{\mathcal{J}}{\mathcal{J}_0}\right) \leq 0.$$

Clearly, $\frac{d\Xi_1}{dt} \leq 0$ when $\mathfrak{R}_0 \leq 1$ and $\frac{d\Xi_1}{dt} = 0$ when $\mathcal{J} = \mathcal{J}_0$ and $\mathcal{P} = \mathcal{K} = \mathcal{L} = 0$. All solutions convey to M'_1 , wherein every element fulfills $\mathcal{J}(t) = \mathcal{J}_0$ and $\mathcal{P}(t) = \mathcal{K}(t) = \mathcal{L}(t) = 0$ for all t [44]. Following that, the first equation of system (3) in conjunction with Condition C1 results in

$$\begin{aligned} 0 = \dot{\mathcal{J}} = \theta - \eta_{\mathcal{J}} \mathcal{J}_0 - \Upsilon_{\mathcal{E}}(\mathcal{J}_0, \mathcal{E}(t)) &\implies \Upsilon_{\mathcal{E}}(\mathcal{J}_0, \mathcal{E}(t)) = 0 \\ &\implies \mathcal{E}(t) = 0, \text{ for all } t. \end{aligned}$$

Therefore, with $M'_1 = \{O_0\}$, our conclusion asserts that O_0 is G.A.S under the condition $\mathfrak{R}_0 \leq 1$, in accordance with LaSalle's invariance principle (L.I.P) [45].

In investigating the global stability of O_1 , we define $F(\alpha) = \alpha - 1 - \ln(\alpha)$. Besides, the following remarks and Condition will be essential.

Remark 2.1. Considering Conditions C2 and C4, it is established that, for every positive $\mathcal{J}, \mathcal{E}, \mathcal{E}^*$, we have

$$\left(\frac{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E})}{\mathcal{E}} - \frac{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}^*)}{\mathcal{E}^*}\right) (\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}) - \Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}^*)) \leq 0,$$

which implies that

$$\left(\frac{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E})}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}^*)} - \frac{\mathcal{E}}{\mathcal{E}^*}\right) \left(1 - \frac{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}^*)}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E})}\right) \leq 0, \tag{18}$$

where $\mathcal{E}^* \in \{\mathcal{E}_1, \tilde{\mathcal{E}}_1\}$.

Condition C6. For any \mathcal{J} within the interval $(0, \theta/\eta_{\mathcal{J}})$, and positive values of \mathcal{P} and \mathcal{K} , the following condition is satisfied

$$1. \left(\frac{\Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P})}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}^*)\mathcal{P}} - \frac{\Upsilon_{\mathcal{P}}(\mathcal{J}^*, \mathcal{P}^*)}{\Upsilon_{\mathcal{E}}(\mathcal{J}^*, \mathcal{E}^*)\mathcal{P}^*} \right) \times \left(\frac{\Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P})}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}^*)} - \frac{\Upsilon_{\mathcal{P}}(\mathcal{J}^*, \mathcal{P}^*)}{\Upsilon_{\mathcal{E}}(\mathcal{J}^*, \mathcal{E}^*)} \right) \leq 0,$$

$$2. \left(\frac{\Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K})}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}^*)\mathcal{K}} - \frac{\Upsilon_{\mathcal{K}}(\mathcal{J}^*, \mathcal{K}^*)}{\Upsilon_{\mathcal{E}}(\mathcal{J}^*, \mathcal{E}^*)\mathcal{K}^*} \right) \times \left(\frac{\Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K})}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}^*)} - \frac{\Upsilon_{\mathcal{K}}(\mathcal{J}^*, \mathcal{K}^*)}{\Upsilon_{\mathcal{E}}(\mathcal{J}^*, \mathcal{E}^*)} \right) \leq 0,$$

where $\mathcal{J}^* \in \{\mathcal{J}_1, \tilde{\mathcal{J}}_1\} > 0, \mathcal{P}^* \in \{\mathcal{P}_1, \tilde{\mathcal{P}}_1\} > 0, \mathcal{K}^* \in \{\mathcal{K}_1, \tilde{\mathcal{K}}_1\} > 0$, and $\mathcal{E}^* \in \{\mathcal{E}_1, \tilde{\mathcal{E}}_1\} > 0$.

Remark 2.2. From Condition C6, For any \mathcal{J} within the interval $(0, \theta/\eta_{\mathcal{J}})$, and positive values of \mathcal{P} and \mathcal{K} , we get

$$\left(\frac{\Upsilon_{\mathcal{E}}(\mathcal{J}^*, \mathcal{E}^*)\Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P})}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}^*)\Upsilon_{\mathcal{P}}(\mathcal{J}^*, \mathcal{P}^*)} - \frac{\mathcal{P}}{\mathcal{P}^*} \right) \times \left(1 - \frac{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}^*)\Upsilon_{\mathcal{P}}(\mathcal{J}^*, \mathcal{P}^*)}{\Upsilon_{\mathcal{E}}(\mathcal{J}^*, \mathcal{E}^*)\Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P})} \right) \leq 0, \tag{19}$$

$$\left(\frac{\Upsilon_{\mathcal{E}}(\mathcal{J}^*, \mathcal{E}^*)\Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K})}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}^*)\Upsilon_{\mathcal{K}}(\mathcal{J}^*, \mathcal{K}^*)} - \frac{\mathcal{K}}{\mathcal{K}^*} \right) \times \left(1 - \frac{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}^*)\Upsilon_{\mathcal{K}}(\mathcal{J}^*, \mathcal{K}^*)}{\Upsilon_{\mathcal{E}}(\mathcal{J}^*, \mathcal{E}^*)\Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K})} \right) \leq 0, \tag{20}$$

where $\mathcal{J}^* \in \{\mathcal{J}_1, \tilde{\mathcal{J}}_1\} > 0, \mathcal{P}^* \in \{\mathcal{P}_1, \tilde{\mathcal{P}}_1\} > 0, \mathcal{K}^* \in \{\mathcal{K}_1, \tilde{\mathcal{K}}_1\} > 0$, and $\mathcal{E}^* \in \{\mathcal{E}_1, \tilde{\mathcal{E}}_1\} > 0$.

Theorem 2.2. Given $\mathfrak{N}_0 > 1$ and the fulfillment of Conditions C1-C4 and C6, it can be concluded that the steady state O_1 for system (3) is guaranteed to be G.A.S.

Proof. We formulate $\Xi_2(\mathcal{J}, \mathcal{P}, \mathcal{K}, \mathcal{E}, \mathcal{L})$ given by Equation (21) as:

$$\begin{aligned} \Xi_2 = & \mathcal{J} - \mathcal{J}_1 - \int_{\mathcal{J}_1}^{\mathcal{J}} \frac{\Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1)}{\Upsilon_{\mathcal{E}}(\lambda, \mathcal{E}_1)} d\lambda + \mathcal{P}_1 F \left(\frac{\mathcal{P}}{\mathcal{P}_1} \right) \\ & + \frac{\varpi \mathcal{K}_1 \Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1) + \eta_{\mathcal{E}} \mathcal{E}_1 \Upsilon_{\mathcal{K}}(\mathcal{J}_1, \mathcal{K}_1)}{\eta_{\mathcal{E}} \mathcal{K}_1 \mathcal{E}_1 (\eta_{\mathcal{K}} + \phi \mathcal{L}_1)} F \left(\frac{\mathcal{K}}{\mathcal{K}_1} \right) \\ & + \frac{\Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1)}{\eta_{\mathcal{E}}} F \left(\frac{\mathcal{E}}{\mathcal{E}_1} \right) \\ & + \frac{\phi (\varpi \mathcal{K}_1 \Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1) + \eta_{\mathcal{E}} \mathcal{E}_1 \Upsilon_{\mathcal{K}}(\mathcal{J}_1, \mathcal{K}_1))}{2\eta_{\mathcal{E}} \mathcal{K}_1 \mathcal{E}_1 (\eta_{\mathcal{K}} + \phi \mathcal{L}_1) (\xi - \beta \mathcal{L}_1)} (\mathcal{L} - \mathcal{L}_1)^2. \end{aligned} \tag{21}$$

Steady state condition Equation (9) guarantees that $\xi - \beta \mathcal{L}_1 = \frac{\eta_{\mathcal{L}} \mathcal{L}_1}{\mathcal{K}_1} > 0$. Clearly, Ξ_2 is positive definite. Calculating $\frac{d\Xi_2}{dt}$:

$$\begin{aligned} \frac{d\Xi_2}{dt} = & \left(1 - \frac{\Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1)}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}_1)} \right) \dot{\mathcal{J}} + \left(1 - \frac{\mathcal{P}_1}{\mathcal{P}} \right) \dot{\mathcal{P}} \\ & + \frac{\varpi \mathcal{K}_1 \Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1) + \eta_{\mathcal{E}} \mathcal{E}_1 \Upsilon_{\mathcal{K}}(\mathcal{J}_1, \mathcal{K}_1)}{\eta_{\mathcal{E}} \mathcal{K}_1 \mathcal{E}_1 (\eta_{\mathcal{K}} + \phi \mathcal{L}_1)} \left(1 - \frac{\mathcal{K}_1}{\mathcal{K}} \right) \dot{\mathcal{K}} \\ & + \frac{\Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1)}{\eta_{\mathcal{E}} \mathcal{E}_1} \left(1 - \frac{\mathcal{E}_1}{\mathcal{E}} \right) \dot{\mathcal{E}} \end{aligned}$$

$$\begin{aligned} & + \frac{\phi (\varpi \mathcal{K}_1 \Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1) + \eta_{\mathcal{E}} \mathcal{E}_1 \Upsilon_{\mathcal{K}}(\mathcal{J}_1, \mathcal{K}_1))}{\eta_{\mathcal{E}} \mathcal{K}_1 \mathcal{E}_1 (\eta_{\mathcal{K}} + \phi \mathcal{L}_1) (\xi - \beta \mathcal{L}_1)} (\mathcal{L} - \mathcal{L}_1) \dot{\mathcal{L}} \\ = & \left(1 - \frac{\Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1)}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}_1)} \right) (\theta - \eta_{\mathcal{J}} \mathcal{J} - \Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}) - \Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P}) \\ & - \Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K})) \\ & + \left(1 - \frac{\mathcal{P}_1}{\mathcal{P}} \right) (\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}) + \Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P}) + \Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K}) \\ & - (\psi + \eta_{\mathcal{P}}) \mathcal{P}) \\ & + \frac{\varpi \mathcal{K}_1 \Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1) + \eta_{\mathcal{E}} \mathcal{E}_1 \Upsilon_{\mathcal{K}}(\mathcal{J}_1, \mathcal{K}_1)}{\eta_{\mathcal{E}} \mathcal{K}_1 \mathcal{E}_1 (\eta_{\mathcal{K}} + \phi \mathcal{L}_1)} \left(1 - \frac{\mathcal{K}_1}{\mathcal{K}} \right) \\ & \times (\psi \mathcal{P} - \eta_{\mathcal{K}} \mathcal{K} - \phi \mathcal{L} \mathcal{K}) \\ & + \frac{\Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1)}{\eta_{\mathcal{E}} \mathcal{E}_1} \left(1 - \frac{\mathcal{E}_1}{\mathcal{E}} \right) (\varpi \mathcal{K} - \eta_{\mathcal{E}} \mathcal{E}) \\ & + \frac{\phi (\varpi \mathcal{K}_1 \Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1) + \eta_{\mathcal{E}} \mathcal{E}_1 \Upsilon_{\mathcal{K}}(\mathcal{J}_1, \mathcal{K}_1))}{\eta_{\mathcal{E}} \mathcal{K}_1 \mathcal{E}_1 (\eta_{\mathcal{K}} + \phi \mathcal{L}_1) (\xi - \beta \mathcal{L}_1)} (\mathcal{L} - \mathcal{L}_1) \\ & \times (\xi \mathcal{K} - \eta_{\mathcal{L}} \mathcal{L} - \beta \mathcal{L} \mathcal{K}) \\ = & \left(1 - \frac{\Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1)}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}_1)} \right) (\theta - \eta_{\mathcal{J}} \mathcal{J}) + \frac{\Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1)}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}_1)} \\ & \times (\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}) + \Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P}) + \Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K})) \\ & - (\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}) + \Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P}) + \Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K})) \frac{\mathcal{P}_1}{\mathcal{P}} \\ & - (\psi + \eta_{\mathcal{P}}) \mathcal{P} + (\psi + \eta_{\mathcal{P}}) \mathcal{P}_1 \\ & + \frac{\psi (\varpi \mathcal{K}_1 \Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1) + \eta_{\mathcal{E}} \mathcal{E}_1 \Upsilon_{\mathcal{K}}(\mathcal{J}_1, \mathcal{K}_1))}{\eta_{\mathcal{E}} \mathcal{K}_1 \mathcal{E}_1 (\eta_{\mathcal{K}} + \phi \mathcal{L}_1)} \mathcal{P} \\ & - \frac{\psi (\varpi \mathcal{K}_1 \Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1) + \eta_{\mathcal{E}} \mathcal{E}_1 \Upsilon_{\mathcal{K}}(\mathcal{J}_1, \mathcal{K}_1))}{\eta_{\mathcal{E}} \mathcal{K}_1 \mathcal{E}_1 (\eta_{\mathcal{K}} + \phi \mathcal{L}_1)} \frac{\mathcal{P} \mathcal{K}_1}{\mathcal{K}} \\ & - \frac{\eta_{\mathcal{K}} (\varpi \mathcal{K}_1 \Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1) + \eta_{\mathcal{E}} \mathcal{E}_1 \Upsilon_{\mathcal{K}}(\mathcal{J}_1, \mathcal{K}_1))}{\eta_{\mathcal{E}} \mathcal{K}_1 \mathcal{E}_1 (\eta_{\mathcal{K}} + \phi \mathcal{L}_1)} (\mathcal{K} - \mathcal{K}_1) \\ & - \frac{\phi (\varpi \mathcal{K}_1 \Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1) + \eta_{\mathcal{E}} \mathcal{E}_1 \Upsilon_{\mathcal{K}}(\mathcal{J}_1, \mathcal{K}_1))}{\eta_{\mathcal{E}} \mathcal{K}_1 \mathcal{E}_1 (\eta_{\mathcal{K}} + \phi \mathcal{L}_1)} \mathcal{L} (\mathcal{K} - \mathcal{K}_1) \\ & + \Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1) \frac{\varpi \mathcal{K}}{\eta_{\mathcal{E}} \mathcal{E}_1} - \Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1) \frac{\varpi \mathcal{K}}{\eta_{\mathcal{E}} \mathcal{E}} - \Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1) \frac{\mathcal{E}}{\mathcal{E}_1} \\ & + \Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1) \\ & + \frac{\phi (\varpi \mathcal{K}_1 \Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1) + \eta_{\mathcal{E}} \mathcal{E}_1 \Upsilon_{\mathcal{K}}(\mathcal{J}_1, \mathcal{K}_1))}{\eta_{\mathcal{E}} \mathcal{K}_1 \mathcal{E}_1 (\eta_{\mathcal{K}} + \phi \mathcal{L}_1) (\xi - \beta \mathcal{L}_1)} (\mathcal{L} - \mathcal{L}_1) \\ & \times (\xi \mathcal{K} - \eta_{\mathcal{L}} \mathcal{L} - \beta \mathcal{L} \mathcal{K}). \end{aligned} \tag{22}$$

Using the following steady state conditions for O_1

$$\begin{aligned} \theta = & \eta_{\mathcal{J}} \mathcal{J}_1 + \Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1) + \Upsilon_{\mathcal{P}}(\mathcal{J}_1, \mathcal{P}_1) + \Upsilon_{\mathcal{K}}(\mathcal{J}_1, \mathcal{K}_1), \\ \Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1) + \Upsilon_{\mathcal{P}}(\mathcal{J}_1, \mathcal{P}_1) + \Upsilon_{\mathcal{K}}(\mathcal{J}_1, \mathcal{K}_1) = & (\psi + \eta_{\mathcal{P}}) \mathcal{P}_1, \\ \mathcal{K}_1 = \frac{\psi \mathcal{P}_1}{\eta_{\mathcal{K}} + \phi \mathcal{L}_1}, \quad \mathcal{E}_1 = \frac{\varpi \mathcal{K}_1}{\eta_{\mathcal{E}}}, \quad \xi \mathcal{K}_1 = & \eta_{\mathcal{L}} \mathcal{L}_1 + \beta \mathcal{L}_1 \mathcal{K}_1, \end{aligned}$$

we get

$$\begin{aligned} & \Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1) + \Upsilon_{\mathcal{K}}(\mathcal{J}_1, \mathcal{K}_1) \\ = & \frac{\varpi \mathcal{K}_1 \Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1) + \eta_{\mathcal{E}} \mathcal{E}_1 \Upsilon_{\mathcal{K}}(\mathcal{J}_1, \mathcal{K}_1)}{\eta_{\mathcal{E}} \mathcal{E}_1} \\ = & \frac{\psi \mathcal{P}_1 (\varpi \mathcal{K}_1 \Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1) + \eta_{\mathcal{E}} \mathcal{E}_1 \Upsilon_{\mathcal{K}}(\mathcal{J}_1, \mathcal{K}_1))}{\eta_{\mathcal{E}} \mathcal{K}_1 \mathcal{E}_1 (\eta_{\mathcal{K}} + \phi \mathcal{L}_1)}. \end{aligned}$$

Consequently, the representation of Equation (22) will be as follows:

$$\frac{d\Xi_2}{dt} = \left(1 - \frac{\Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1)}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}_1)} \right) (\eta_{\mathcal{J}} \mathcal{J}_1 - \eta_{\mathcal{J}} \mathcal{J})$$

Under the AM-GM inequality, we discern that

$$\begin{aligned}
 5 &\leq \frac{\Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1)}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}_1)} + \frac{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}) \mathcal{P}_1}{\Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1) \mathcal{P}} + \frac{\mathcal{P} \mathcal{K}_1}{\mathcal{P}_1 \mathcal{K}} + \frac{\mathcal{K} \mathcal{E}_1}{\mathcal{K}_1 \mathcal{E}} \\
 &\quad + \frac{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}_1) \mathcal{E}}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}) \mathcal{E}_1}, \\
 4 &\leq \frac{\Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1)}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}_1)} + \frac{\Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K}) \mathcal{P}_1}{\Upsilon_{\mathcal{K}}(\mathcal{J}_1, \mathcal{K}_1) \mathcal{P}} + \frac{\mathcal{P} \mathcal{K}_1}{\mathcal{P}_1 \mathcal{K}} \\
 &\quad + \frac{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}_1) \Upsilon_{\mathcal{K}}(\mathcal{J}_1, \mathcal{K}_1) \mathcal{K}}{\Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1) \Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K}) \mathcal{K}_1}, \\
 3 &\leq \frac{\Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1)}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}_1)} + \frac{\Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P}) \mathcal{P}_1}{\Upsilon_{\mathcal{P}}(\mathcal{J}_1, \mathcal{P}_1) \mathcal{P}} + \frac{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}_1) \Upsilon_{\mathcal{P}}(\mathcal{J}_1, \mathcal{P}_1) \mathcal{P}}{\Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1) \Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P}) \mathcal{P}_1}.
 \end{aligned}$$

Moreover, from Equations (18–20), we conclude

$$\begin{aligned}
 &\left(\frac{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E})}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}_1)} - \frac{\mathcal{E}}{\mathcal{E}_1} \right) \left(1 - \frac{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}_1)}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E})} \right) \leq 0, \\
 &\left(\frac{\Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1) \Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P})}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}_1) \Upsilon_{\mathcal{P}}(\mathcal{J}_1, \mathcal{P}_1)} - \frac{\mathcal{P}}{\mathcal{P}_1} \right) \\
 &\times \left(1 - \frac{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}_1) \Upsilon_{\mathcal{P}}(\mathcal{J}_1, \mathcal{P}_1)}{\Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1) \Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P})} \right) \leq 0, \\
 &\left(\frac{\Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1) \Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K})}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}_1) \Upsilon_{\mathcal{K}}(\mathcal{J}_1, \mathcal{K}_1)} - \frac{\mathcal{K}}{\mathcal{K}_1} \right) \\
 &\times \left(1 - \frac{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}_1) \Upsilon_{\mathcal{K}}(\mathcal{J}_1, \mathcal{K}_1)}{\Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1) \Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K})} \right) \leq 0.
 \end{aligned}$$

Therefore, when $\mathfrak{R}_0 > 1$, it implies that $\frac{d\mathfrak{E}_2}{dt} \leq 0$ for all $\mathcal{J}, \mathcal{P}, \mathcal{K}, \mathcal{E}, \mathcal{L} > 0$. Moreover, $\frac{d\mathfrak{E}_2}{dt} = 0$ when $\mathcal{J} = \mathcal{J}_1, \mathcal{P} = \mathcal{P}_1, \mathcal{K} = \mathcal{K}_1, \mathcal{E} = \mathcal{E}_1$, and $\mathcal{L} = \mathcal{L}_1$. Consequently, $M'_2 = \{O_1\}$. Applying the L.I.P allows us to infer that if $\mathfrak{R}_0 > 1$, the steady state O_1 is being G.A.S [44, 45].

3 HIV-1 model with distributed delays

According to estimates, it takes HIV-1 0.9 days to penetrate a target cell and start creating new HIV-1 particles. Perelson et al. [46]. Numerous studies have delved into models of HIV-1 infection, considering time delays and dual infection routes (see e.g., [47–51]). This section enhances the previously introduced model by integrating three varieties of distributed time delays.

3.1 System overview

The system of delay differential equations (DDEs) presented below will be studied.

$$\begin{cases}
 \dot{\mathcal{J}} = \theta - \eta_{\mathcal{J}} \mathcal{J} - \Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}) - \Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P}) - \Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K}), \\
 \dot{\mathcal{P}} = \int_0^{f_1} \pi_1(r) e^{-b_1 r} (\Upsilon_{\mathcal{E}}(\mathcal{J}(t-r), \mathcal{E}(t-r)) \\
 \quad + \Upsilon_{\mathcal{P}}(\mathcal{J}(t-r), \mathcal{P}(t-r)) + \Upsilon_{\mathcal{K}}(\mathcal{J}(t-r), \\
 \quad \mathcal{K}(t-r))) dr - (\psi + \eta_{\mathcal{P}}) \mathcal{P}, \\
 \dot{\mathcal{K}} = \psi \int_0^{f_2} \pi_2(r) e^{-b_2 r} \mathcal{P}(t-r) dr - \eta_{\mathcal{K}} \mathcal{K} - \phi \mathcal{L} \mathcal{K}, \\
 \dot{\mathcal{E}} = \varpi \int_0^{f_3} \pi_3(r) e^{-b_3 r} \mathcal{K}(t-r) dr - \eta_{\mathcal{E}} \mathcal{E}, \\
 \dot{\mathcal{L}} = \xi \mathcal{K} - \eta_{\mathcal{L}} \mathcal{L} - \beta \mathcal{L} \mathcal{K}.
 \end{cases}$$

Here, system (23) includes the following assumptions:

- At the moment t , healthy cells are encountering either HIV-1 particles or infected cells transition to a latent infection state r units of time later. The emergence of latently infected cells at time t depends on the count of cells recently contacted at time $t - r$, which persists until time t .
- After a latency period of r units of time after infection, cells that were initially latent and became actively infected. The emergence of actively infected cells at the time t depends on the count of cells recently transitioned into latent infection at time $t - r$, which persist until time t .
- Newly formed mature HIV-1 particles emerge from actively infected cells r units of time after infection. The occurrence of HIV-1 particle production at time t relies on the count of cells that recently transitioned into actively infected status at time $t - r$ that remain viable until time t .

As such, the likelihood of surviving the time frame from $t - r$ to t is represented by $\pi_i(r) e^{-b_i r}$, where b_i are positive constants and $i = 1, 2, 3$. Besides, we choose the delay parameter, r , at random. It is drawn from a probability distribution function $\pi_i(r)$, which spans the interval $[0, f_i]$, in which f_i refers to the maximum delay duration. The functions $\pi_i(r)$, for $i = 1, 2, 3$ adhere to and fulfill the following specified conditions:

$$\pi_i(r) > 0, \quad \int_0^{f_i} \pi_i(r) dr = 1, \quad \text{and} \quad \int_0^{f_i} \pi_i(r) e^{-\mu r} dr < \infty,$$

where $\mu > 0$.

Assuming that

$$\bar{\Pi}_i(r) = \pi_i(r) e^{-b_i r}, \quad \Pi_i = \int_0^{f_i} \bar{\Pi}_i(r) dr, \quad i = 1, 2, 3,$$

implies the fact that $0 < \Pi_i \leq 1, i = 1, 2, 3$.

System (23) has the outlined initial conditions below:

$$\begin{cases}
 (\mathcal{J}(v), \mathcal{P}(v), \mathcal{K}(v), \mathcal{E}(v), \mathcal{L}(v)) \\
 = (k_1(v), k_2(v), k_3(v), k_4(v), k_5(v)), \\
 k_i(v) \geq 0, \quad i = 1, 2, \dots, 5, \quad v \in [-f, 0], \quad f = \max\{f_1, f_2, f_3\},
 \end{cases}$$

where $k_i(v) \in C([-f, 0], \mathbb{R}_{\geq 0}), i = 1, 2, \dots, 5$ and $C = C([-f, 0], \mathbb{R}_{\geq 0})$ is the Banach space comprising continuous functions, and it is equipped with the norm $\|k_i\| = \sup_{-f \leq \zeta \leq 0} |k_i(\zeta)|$

for all $k_i \in C$. Thus, a unique solution for system (23) under the specified initial conditions (24) is guaranteed, as affirmed by references [44] and [52]. The meanings assigned to all remaining parameters and variables remain in line with the explanations provided earlier. We presume that functions $\Upsilon_Z(\mathcal{J}, Z), Z \in \{\mathcal{E}, \mathcal{P}, \mathcal{K}\}$, satisfy Conditions C1– C6 as presented previously.

3.2 Fundamental characteristics

3.2.1 Model’s well-posedness

Proposition 3.1. Assuming that Condition C1 is fulfilled, then the solutions of system (23) under initial conditions (24) are nonnegative and ultimately bounded.

Proof. Since $\dot{\mathcal{J}}|_{\mathcal{J}=0} = \theta > 0$, then it can be inferred that $\mathcal{J}(t)$ is always positive for every $t \geq 0$. Furthermore, other equations within system (23) can be expressed as:

$$\begin{aligned} \dot{\mathcal{P}} + (\psi + \eta\mathcal{P})\mathcal{P} &= \int_0^{f_1} \bar{\Pi}_1(r) (\Upsilon_{\mathcal{E}}(\mathcal{J}(t-r), \mathcal{E}(t-r)) \\ &\quad + \Upsilon_{\mathcal{P}}(\mathcal{J}(t-r), \mathcal{P}(t-r)) \\ &\quad + \Upsilon_{\mathcal{K}}(\mathcal{J}(t-r), \mathcal{K}(t-r))) dr \\ \implies \mathcal{P}(t) &= k_2(0)e^{-(\psi+\eta\mathcal{P})t} + \int_0^t e^{-(\psi+\eta\mathcal{P})(t-\lambda)} \\ &\quad \times \int_0^{f_1} \bar{\Pi}_1(r) (\Upsilon_{\mathcal{E}}(\mathcal{J}(\lambda-r), \mathcal{E}(\lambda-r)) \\ &\quad + \Upsilon_{\mathcal{P}}(\mathcal{J}(\lambda-r), \mathcal{P}(\lambda-r)) + \Upsilon_{\mathcal{K}}(\mathcal{J}(\lambda-r), \mathcal{K}(\lambda-r))) dr d\lambda \\ &\geq 0. \\ \dot{\mathcal{K}} + (\eta\mathcal{K} + \phi\mathcal{L}(t))\mathcal{K} &= \psi \int_0^{f_2} \bar{\Pi}_2(r) \mathcal{P}(t-r) dr \\ \implies \mathcal{K}(t) &= k_3(0)e^{-\int_0^t (\eta\mathcal{K} + \phi\mathcal{L}(u)) du} + \psi \int_0^t e^{-\int_{\lambda}^t (\eta\mathcal{K} + \phi\mathcal{L}(u)) du} \\ &\quad \times \int_0^{f_2} \bar{\Pi}_2(r) \mathcal{P}(\lambda-r) dr d\lambda \geq 0. \\ \dot{\mathcal{E}} + \eta\mathcal{E} &= \varpi \int_0^{f_3} \bar{\Pi}_3(r) \mathcal{K}(t-r) dr \\ \implies \mathcal{E}(t) &= k_4(0)e^{-\eta\mathcal{E}t} + \varpi \int_0^t e^{-\eta\mathcal{E}(t-\lambda)} \\ &\quad \times \int_0^{f_3} \bar{\Pi}_3(r) \mathcal{K}(\lambda-r) dr d\lambda \geq 0. \\ \dot{\mathcal{L}} + (\eta\mathcal{L} + \beta\mathcal{K})\mathcal{L} &= \xi\mathcal{K} \\ \implies \mathcal{L}(t) &= k_5(0)e^{-\int_0^t (\eta\mathcal{L} + \beta\mathcal{K}(u)) du} \\ &\quad + \xi \int_0^t e^{-\int_{\lambda}^t (\eta\mathcal{L} + \beta\mathcal{K}(u)) du} \mathcal{K}(r) dr \geq 0, \end{aligned}$$

for every $t \in [0, f]$. By employing a recursive argumentation approach, it can be shown that $\mathcal{J}(t)$, $\mathcal{P}(t)$, $\mathcal{K}(t)$, $\mathcal{E}(t)$, and $\mathcal{L}(t)$ remain nonnegative for every $t \geq 0$. As a result, system (23) only admits solutions where $(\mathcal{J}(t), \mathcal{P}(t), \mathcal{K}(t), \mathcal{E}(t), \mathcal{L}(t)) \in \mathbb{R}_{\geq 0}^5$ for every $t \geq 0$.

Obviously, $\limsup_{t \rightarrow \infty} \mathcal{J}(t) \leq \frac{\theta}{\eta_{\mathcal{J}}}$, as deduced from the first equation in system (23). Following that, we proceed with defining Φ_1 as follows:

$$\Phi_1 = \int_0^{f_1} \bar{\Pi}_1(r) \mathcal{J}(t-r) dr + \mathcal{P}.$$

Therefore

$$\begin{aligned} \dot{\Phi}_1 &= \int_0^{f_1} \bar{\Pi}_1(r) \frac{d\mathcal{J}(t-r)}{dt} dr + \dot{\mathcal{P}} \\ &= \int_0^{f_1} \bar{\Pi}_1(r) (\theta - \eta_{\mathcal{J}}\mathcal{J}(t-r)) dr - (\psi + \eta\mathcal{P})\mathcal{P} \\ &= \theta\Pi_1 - \eta_{\mathcal{J}} \int_0^{f_1} \bar{\Pi}_1(r)\mathcal{J}(t-r) dr - (\psi + \eta\mathcal{P})\mathcal{P} \\ &\leq \theta - \varepsilon_1 \left(\int_0^{f_1} \bar{\Pi}_1(r)\mathcal{J}(t-r) dr + \mathcal{P} \right) = \theta - \varepsilon_1 \Phi_1, \end{aligned}$$

where $\varepsilon_1 = \min\{\eta_{\mathcal{J}}, \psi + \eta\mathcal{P}\}$. This indicates that $\limsup_{t \rightarrow \infty} \Phi_1(t) \leq \frac{\theta}{\varepsilon_1} = \hat{\Gamma}_1$. Based on the nonnegativity of $\int_0^{f_1} \bar{\Pi}_1(r) \mathcal{J}(t-r) dr$ and \mathcal{P} , then $\limsup_{t \rightarrow \infty} \mathcal{P}(t) \leq \hat{\Gamma}_1$ is confirmed. Furthermore, we let

$$\Phi_2 = \mathcal{K} + \frac{\eta\mathcal{K}}{2\xi}\mathcal{L}.$$

This produces

$$\begin{aligned} \dot{\Phi}_2 &= \dot{\mathcal{K}} + \frac{\eta\mathcal{K}}{2\xi}\dot{\mathcal{L}} \\ &= \psi \int_0^{f_2} \bar{\Pi}_2(r) \mathcal{P}(t-r) dr - \eta\mathcal{K}\mathcal{K} - \phi\mathcal{L}\mathcal{K} \\ &\quad + \frac{\eta\mathcal{K}}{2\xi} (\xi\mathcal{K} - \eta\mathcal{L}\mathcal{L} - \beta\mathcal{L}\mathcal{K}) \\ &= \psi \int_0^{f_2} \bar{\Pi}_2(r) \mathcal{P}(t-r) dr - \frac{\eta\mathcal{K}}{2}\mathcal{K} \\ &\quad - \frac{\eta\mathcal{K}\eta\mathcal{L}}{2\xi}\mathcal{L} - \left(\phi + \frac{\eta\mathcal{K}\beta}{2\xi}\right)\mathcal{L}\mathcal{K} \\ &\leq \psi \int_0^{f_2} \bar{\Pi}_2(r) \mathcal{P}(t-r) dr - \frac{\eta\mathcal{K}}{2}\mathcal{K} - \frac{\eta\mathcal{K}\eta\mathcal{L}}{2\xi}\mathcal{L} \\ &\leq \psi\hat{\Gamma}_1 - \varepsilon_2 \left(\mathcal{K} + \frac{\eta\mathcal{K}}{2\xi}\mathcal{L} \right) = \psi\hat{\Gamma}_1 - \varepsilon_2\Phi_2, \end{aligned}$$

where $\varepsilon_2 = \min\{\frac{\eta\mathcal{K}}{2}, \eta\mathcal{L}\}$. Thus, $\limsup_{t \rightarrow \infty} \Phi_2(t) \leq \frac{\psi\hat{\Gamma}_1}{\varepsilon_2} = \hat{\Gamma}_2$. Based on the nonnegativity of \mathcal{K} and \mathcal{L} , one can guarantee that $\limsup_{t \rightarrow \infty} \mathcal{K}(t) \leq \hat{\Gamma}_2$, and $\limsup_{t \rightarrow \infty} \mathcal{L}(t) \leq \frac{2\xi\hat{\Gamma}_2}{\eta\mathcal{K}} = \hat{\Gamma}_3$. As a result of the fourth equation in system (23), one can acquire

$$\begin{aligned} \dot{\mathcal{E}} &= \varpi \int_0^{f_3} \bar{\Pi}_3(r) \mathcal{K}(t-r) dr - \eta\mathcal{E}\mathcal{E} \leq \varpi\Pi_3\hat{\Gamma}_2 - \eta\mathcal{E}\mathcal{E} \\ &\leq \varpi\hat{\Gamma}_2 - \eta\mathcal{E}\mathcal{E}. \end{aligned}$$

Then, $\limsup_{t \rightarrow \infty} \mathcal{E}(t) \leq \frac{\varpi\hat{\Gamma}_2}{\eta\mathcal{E}} = \hat{\Gamma}_4$. Consequently, it can be inferred that $\mathcal{J}(t)$, $\mathcal{P}(t)$, $\mathcal{K}(t)$, $\mathcal{E}(t)$, and $\mathcal{L}(t)$ are being ultimately bounded.

3.2.2 Derivation of reproduction ratios and steady states

Proposition 3.2. Assuming that Conditions C1–C4 are met, there exists a positive basic reproduction ratio $\tilde{\mathfrak{R}}_0 = \frac{\Pi_1(\varpi\psi\Pi_2\Pi_3\ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0) + \eta_{\mathcal{E}}\eta_{\mathcal{K}}\ell_{\mathcal{P}}(\tilde{\mathcal{J}}_0) + \psi\eta_{\mathcal{E}}\Pi_2\ell_{\mathcal{K}}(\tilde{\mathcal{J}}_0))}{\eta_{\mathcal{E}}\eta_{\mathcal{K}}(\psi + \eta\mathcal{P})}$ for system (23) in a way that

1. ensures the system consistently maintains a virus-free steady state, denoted as $\tilde{\mathcal{O}}_0$, and
2. if $\tilde{\mathfrak{R}}_0 > 1$, the system additionally possesses a virus-persistence steady state, denoted as $\tilde{\mathcal{O}}_1$.

Proof. It is observed that a virus-free steady state labeled as $\tilde{\mathcal{O}}_0 = (\tilde{\mathcal{J}}_0, 0, 0, 0, 0)$ consistently exists in system (23), where $\tilde{\mathcal{J}}_0 = \frac{\theta}{\eta_{\mathcal{J}}}$. Using NGM, the matrices below characterize the nonlinear terms,

denoted as $\hat{\Omega}_2$ and responsible for new infections, as well as $\hat{\Lambda}_2$, representing the outflow.

$$\hat{\Omega}_2 = \begin{pmatrix} \Pi_1 (\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}) + \Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P}) + \Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K})) \\ 0 \\ 0 \end{pmatrix},$$

$$\hat{\Lambda}_2 = \begin{pmatrix} (\psi + \eta_{\mathcal{P}})\mathcal{P} \\ -\psi\Pi_2\mathcal{P} + \eta_{\mathcal{K}}\mathcal{K} + \phi\mathcal{L}\mathcal{K} \\ -\varpi\Pi_3\mathcal{K} + \eta_{\mathcal{E}}\mathcal{E} \end{pmatrix}.$$

We compute the derivatives of $\hat{\Omega}_2$ and $\hat{\Lambda}_2$ at the steady state \tilde{O}_0 , leading to the generation of the subsequent matrices:

$$\Omega_2 = \begin{pmatrix} \Pi_1 \frac{\partial \Upsilon_{\mathcal{P}}(\tilde{\mathcal{J}}_0, 0)}{\partial \mathcal{P}} & \Pi_1 \frac{\partial \Upsilon_{\mathcal{K}}(\tilde{\mathcal{J}}_0, 0)}{\partial \mathcal{K}} & \Pi_1 \frac{\partial \Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_0, 0)}{\partial \mathcal{E}} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix},$$

$$\Lambda_2 = \begin{pmatrix} \psi + \eta_{\mathcal{P}} & 0 & 0 \\ -\psi\Pi_2 & \eta_{\mathcal{K}} & 0 \\ 0 & -\varpi\Pi_3 & \eta_{\mathcal{E}} \end{pmatrix}.$$

The form of the NGM is as follows:

$$= \begin{pmatrix} \frac{\varpi\psi\Pi_1\Pi_2\Pi_3\ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0)}{\eta_{\mathcal{E}}\eta_{\mathcal{K}}(\psi + \eta_{\mathcal{P}})} + \frac{\Pi_1\ell_{\mathcal{P}}(\tilde{\mathcal{J}}_0)}{\psi + \eta_{\mathcal{P}}} + \frac{\psi\Pi_1\Pi_2\ell_{\mathcal{K}}(\tilde{\mathcal{J}}_0)}{\eta_{\mathcal{K}}(\psi + \eta_{\mathcal{P}})} & \frac{\varpi\Pi_1\Pi_2\ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0)}{\eta_{\mathcal{E}}\eta_{\mathcal{K}}} + \frac{\Pi_1\ell_{\mathcal{K}}(\tilde{\mathcal{J}}_0)}{\eta_{\mathcal{K}}} & \frac{\Pi_1\ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0)}{\eta_{\mathcal{E}}} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}.$$

The expression representing the basic reproduction ratio $\tilde{\mathfrak{R}}_0$ is outlined as follows:

$$\tilde{\mathfrak{R}}_0 = \frac{\Pi_1(\varpi\psi\Pi_2\Pi_3\ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0) + \eta_{\mathcal{E}}\eta_{\mathcal{K}}\ell_{\mathcal{P}}(\tilde{\mathcal{J}}_0) + \psi\eta_{\mathcal{E}}\Pi_2\ell_{\mathcal{K}}(\tilde{\mathcal{J}}_0))}{\eta_{\mathcal{E}}\eta_{\mathcal{K}}(\psi + \eta_{\mathcal{P}})}$$

$$= \tilde{\mathfrak{R}}_{0\mathcal{E}} + \tilde{\mathfrak{R}}_{0\mathcal{P}} + \tilde{\mathfrak{R}}_{0\mathcal{K}}, \tag{25}$$

where

$$\tilde{\mathfrak{R}}_{0\mathcal{E}} = \frac{\varpi\psi\Pi_1\Pi_2\Pi_3\ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0)}{\eta_{\mathcal{E}}\eta_{\mathcal{K}}(\psi + \eta_{\mathcal{P}})}, \quad \tilde{\mathfrak{R}}_{0\mathcal{P}} = \frac{\Pi_1\ell_{\mathcal{P}}(\tilde{\mathcal{J}}_0)}{\psi + \eta_{\mathcal{P}}},$$

$$\tilde{\mathfrak{R}}_{0\mathcal{K}} = \frac{\psi\Pi_1\Pi_2\ell_{\mathcal{K}}(\tilde{\mathcal{J}}_0)}{\eta_{\mathcal{K}}(\psi + \eta_{\mathcal{P}})}.$$

The parameters $\tilde{\mathfrak{R}}_{0Z}$, $Z \in \{\mathcal{E}, \mathcal{P}, \mathcal{K}\}$ share the identical biological meaning as those elucidated in Section 2. To extend our exploration beyond \tilde{O}_0 , we scrutinize $(\mathcal{J}, \mathcal{P}, \mathcal{K}, \mathcal{E}, \mathcal{L})$ as a potential steady state governed by the following set of algebraic equations:

$$0 = \theta - \eta_{\mathcal{J}}\mathcal{J} - \Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}) - \Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P}) - \Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K}), \tag{26}$$

$$0 = \Pi_1 (\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}) + \Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P}) + \Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K})) - (\psi + \eta_{\mathcal{P}})\mathcal{P}, \tag{27}$$

$$0 = \psi\Pi_2\mathcal{P} - \eta_{\mathcal{K}}\mathcal{K} - \phi\mathcal{L}\mathcal{K}, \tag{28}$$

$$0 = \varpi\Pi_3\mathcal{K} - \eta_{\mathcal{E}}\mathcal{E}, \tag{29}$$

$$0 = \xi\mathcal{K} - \eta_{\mathcal{L}}\mathcal{L} - \beta\mathcal{L}\mathcal{K}. \tag{30}$$

From Equations (29, 30), we get

$$\mathcal{E} = \tilde{\Theta}_1(\mathcal{K}) = \frac{\varpi\Pi_3\mathcal{K}}{\eta_{\mathcal{E}}}, \quad \mathcal{L} = \frac{\xi\mathcal{K}}{\eta_{\mathcal{L}} + \beta\mathcal{K}}. \tag{31}$$

Clearly, $\tilde{\Theta}_1(0) = 0$. The following outcome is obtained after inserting Equation (31) into Equation (28):

$$\mathcal{P} = \tilde{\Theta}_2(\mathcal{K}) = \frac{\eta_{\mathcal{L}}\eta_{\mathcal{K}}\mathcal{K} + (\phi\xi + \eta_{\mathcal{K}}\beta)\mathcal{K}^2}{\psi\Pi_2(\eta_{\mathcal{L}} + \beta\mathcal{K})}. \tag{32}$$

It is clear that $\tilde{\Theta}_2(0) = 0$. From Equations (26, 27), we get

$$\theta - \eta_{\mathcal{J}}\mathcal{J} = \frac{\psi + \eta_{\mathcal{P}}}{\Pi_1}\mathcal{P}. \tag{33}$$

The following outcome is obtained after inserting Equation (32) into Equation (33):

$$\mathcal{J} = \tilde{\Theta}_3(\mathcal{K})$$

$$= \frac{1}{\eta_{\mathcal{J}}} \left(\theta - \frac{(\psi + \eta_{\mathcal{P}})(\eta_{\mathcal{L}}\eta_{\mathcal{K}}\mathcal{K} + (\phi\xi + \eta_{\mathcal{K}}\beta)\mathcal{K}^2)}{\psi\Pi_1\Pi_2(\eta_{\mathcal{L}} + \beta\mathcal{K})} \right). \tag{34}$$

Note that $\tilde{\Theta}_3(0) = \tilde{\mathcal{J}}_0$. Upon substitution of Equations (31, 32, 34) into Equation (27), the result is as follows:

$$\Upsilon_{\mathcal{E}}(\tilde{\Theta}_3(\mathcal{K}), \tilde{\Theta}_1(\mathcal{K})) + \Upsilon_{\mathcal{P}}(\tilde{\Theta}_3(\mathcal{K}), \tilde{\Theta}_2(\mathcal{K}))$$

$$+ \Upsilon_{\mathcal{K}}(\tilde{\Theta}_3(\mathcal{K}), \mathcal{K}) - \frac{(\psi + \eta_{\mathcal{P}})(\eta_{\mathcal{L}}\eta_{\mathcal{K}}\mathcal{K} + (\phi\xi + \eta_{\mathcal{K}}\beta)\mathcal{K}^2)}{\psi\Pi_1\Pi_2(\eta_{\mathcal{L}} + \beta\mathcal{K})}$$

$$= 0. \tag{35}$$

From Equation (35), we have

1. When $\mathcal{K} = 0$, the virus-free steady state \tilde{O}_0 is derived from Equations (31, 32, 33, 34).
2. When $\mathcal{K} \neq 0$, let us define a function $\tilde{\Psi}(\mathcal{K})$ on $[0, \infty)$ as:

$$\tilde{\Psi}(\mathcal{K}) = \Upsilon_{\mathcal{E}}(\tilde{\Theta}_3(\mathcal{K}), \tilde{\Theta}_1(\mathcal{K})) + \Upsilon_{\mathcal{P}}(\tilde{\Theta}_3(\mathcal{K}), \tilde{\Theta}_2(\mathcal{K}))$$

$$+ \Upsilon_{\mathcal{K}}(\tilde{\Theta}_3(\mathcal{K}), \mathcal{K})$$

$$- \frac{(\psi + \eta_{\mathcal{P}})(\eta_{\mathcal{L}}\eta_{\mathcal{K}}\mathcal{K} + (\phi\xi + \eta_{\mathcal{K}}\beta)\mathcal{K}^2)}{\psi\Pi_1\Pi_2(\eta_{\mathcal{L}} + \beta\mathcal{K})}.$$

We have $\tilde{\Psi}(0) = 0$. Let $\check{\mathcal{K}}$ be such that $\tilde{\Theta}_3(\check{\mathcal{K}}) = 0$, i.e.,

$$\tilde{\mathcal{J}}_0 - \frac{(\psi + \eta_{\mathcal{P}})(\eta_{\mathcal{L}}\eta_{\mathcal{K}}\check{\mathcal{K}} + (\phi\xi + \eta_{\mathcal{K}}\beta)\check{\mathcal{K}}^2)}{\eta_{\mathcal{J}}\psi\Pi_1\Pi_2(\eta_{\mathcal{L}} + \beta\check{\mathcal{K}})} = 0,$$

which implies that

$$(\phi\xi + \eta_{\mathcal{K}}\beta)(\psi + \eta_{\mathcal{P}})\check{\mathcal{K}}^2$$

$$+ (\eta_{\mathcal{L}}\eta_{\mathcal{K}}(\psi + \eta_{\mathcal{P}}) - \eta_{\mathcal{J}}\psi\beta\Pi_1\Pi_2\tilde{\mathcal{J}}_0)\check{\mathcal{K}}$$

$$- \eta_{\mathcal{J}}\psi\eta_{\mathcal{L}}\Pi_1\Pi_2\tilde{\mathcal{J}}_0 = 0. \tag{36}$$

Therefore, Equation (36) has a positive solution

$$\check{\mathcal{K}} = \frac{-\tilde{B} + \sqrt{\tilde{B}^2 - 4\tilde{A}\tilde{C}}}{2\tilde{A}},$$

where

$$\tilde{A} = (\phi\xi + \eta_{\mathcal{K}}\beta)(\psi + \eta_{\mathcal{P}}),$$

$$\begin{aligned} \tilde{B} &= (\eta_{\mathcal{L}}\eta_{\mathcal{K}}(\psi + \eta_{\mathcal{P}}) - \eta_{\mathcal{J}}\psi\beta\Pi_1\Pi_2\tilde{\mathcal{J}}_0), \\ \tilde{C} &= -\eta_{\mathcal{J}}\psi\eta_{\mathcal{L}}\Pi_1\Pi_2\tilde{\mathcal{J}}_0. \end{aligned}$$

We can see that

$$\begin{aligned} \tilde{\Psi}(\tilde{\mathcal{K}}) &= \Upsilon_{\mathcal{E}}(0, \tilde{\Theta}_1(\tilde{\mathcal{K}})) + \Upsilon_{\mathcal{P}}(0, \tilde{\Theta}_2(\tilde{\mathcal{K}})) + \Upsilon_{\mathcal{K}}(0, \tilde{\mathcal{K}}) \\ &\quad - \frac{(\psi + \eta_{\mathcal{P}})(\eta_{\mathcal{L}}\eta_{\mathcal{K}}\tilde{\mathcal{K}} + (\phi\xi + \eta_{\mathcal{K}}\beta)\tilde{\mathcal{K}}^2)}{\psi\Pi_1\Pi_2(\eta_{\mathcal{L}} + \beta\tilde{\mathcal{K}})} \\ &= -\frac{(\psi + \eta_{\mathcal{P}})(\eta_{\mathcal{L}}\eta_{\mathcal{K}}\tilde{\mathcal{K}} + (\phi\xi + \eta_{\mathcal{K}}\beta)\tilde{\mathcal{K}}^2)}{\psi\Pi_1\Pi_2(\eta_{\mathcal{L}} + \beta\tilde{\mathcal{K}})} < 0. \end{aligned}$$

In addition

$$\begin{aligned} \tilde{\Psi}'(\mathcal{K}) &= \tilde{\Theta}'_3(\mathcal{K}) \frac{\partial \Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E})}{\partial \mathcal{J}} + \tilde{\Theta}'_1(\mathcal{K}) \frac{\partial \Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E})}{\partial \mathcal{E}} \\ &\quad + \tilde{\Theta}'_3(\mathcal{K}) \frac{\partial \Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P})}{\partial \mathcal{J}} + \tilde{\Theta}'_2(\mathcal{K}) \frac{\partial \Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P})}{\partial \mathcal{P}} \\ &\quad + \tilde{\Theta}'_3(\mathcal{K}) \frac{\partial \Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K})}{\partial \mathcal{J}} + \frac{\partial \Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K})}{\partial \mathcal{K}} \\ &\quad - \frac{\psi + \eta_{\mathcal{P}}}{\psi\Pi_1\Pi_2} \left(\eta_{\mathcal{K}} + \frac{\phi\xi(2\eta_{\mathcal{L}} + \beta\mathcal{K})\mathcal{K}}{(\eta_{\mathcal{L}} + \beta\mathcal{K})^2} \right). \end{aligned}$$

Condition C1 implies that $\frac{\partial \Upsilon_Z(\tilde{\mathcal{J}}_0, 0)}{\partial \mathcal{J}} = 0, Z \in \{\mathcal{E}, \mathcal{P}, \mathcal{K}\}$. Then

$$\begin{aligned} \tilde{\Psi}'(0) &= \tilde{\Theta}'_1(0) \frac{\partial \Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_0, 0)}{\partial \mathcal{E}} + \tilde{\Theta}'_2(0) \frac{\partial \Upsilon_{\mathcal{P}}(\tilde{\mathcal{J}}_0, 0)}{\partial \mathcal{P}} \\ &\quad + \frac{\partial \Upsilon_{\mathcal{K}}(\tilde{\mathcal{J}}_0, 0)}{\partial \mathcal{K}} - \frac{\eta_{\mathcal{K}}(\psi + \eta_{\mathcal{P}})}{\psi\Pi_1\Pi_2} \\ &= \frac{\varpi\Pi_3}{\eta_{\mathcal{E}}} \frac{\partial \Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_0, 0)}{\partial \mathcal{E}} + \frac{\eta_{\mathcal{K}}}{\psi\Pi_2} \frac{\partial \Upsilon_{\mathcal{P}}(\tilde{\mathcal{J}}_0, 0)}{\partial \mathcal{P}} \\ &\quad + \frac{\partial \Upsilon_{\mathcal{K}}(\tilde{\mathcal{J}}_0, 0)}{\partial \mathcal{K}} - \frac{\eta_{\mathcal{K}}(\psi + \eta_{\mathcal{P}})}{\psi\Pi_1\Pi_2} \\ &= \frac{\varpi\Pi_3\ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0)}{\eta_{\mathcal{E}}} + \frac{\eta_{\mathcal{K}}\ell_{\mathcal{P}}(\tilde{\mathcal{J}}_0)}{\psi\Pi_2} + \ell_{\mathcal{K}}(\tilde{\mathcal{J}}_0) \\ &\quad - \frac{\eta_{\mathcal{K}}(\psi + \eta_{\mathcal{P}})}{\psi\Pi_1\Pi_2} \\ &= \frac{\eta_{\mathcal{K}}(\psi + \eta_{\mathcal{P}})}{\psi\Pi_1\Pi_2} (\tilde{\mathfrak{H}}_0 - 1), \end{aligned}$$

where $\tilde{\mathfrak{H}}_0$ is defined in Equation (25). Therefore, if $\tilde{\mathfrak{H}}_0 > 1$ then $\tilde{\Psi}'(0) > 0$ and there exists $\tilde{\mathcal{K}}_1 \in (0, \tilde{\mathcal{K}})$ such that $\tilde{\Psi}(\tilde{\mathcal{K}}_1) = 0$. Let $\mathcal{K} = \tilde{\mathcal{K}}_1$ in Equation (26) and define

$$\begin{aligned} \tilde{\mathfrak{S}}(\mathcal{J}) &= \theta - \eta_{\mathcal{J}}\mathcal{J} - \Upsilon_{\mathcal{E}}(\mathcal{J}, \tilde{\Theta}_1(\tilde{\mathcal{K}}_1)) - \Upsilon_{\mathcal{P}}(\mathcal{J}, \tilde{\Theta}_2(\tilde{\mathcal{K}}_1)) \\ &\quad - \Upsilon_{\mathcal{K}}(\mathcal{J}, \tilde{\mathcal{K}}_1). \end{aligned}$$

Subsequently, based on Condition C1, we obtain $\tilde{\mathfrak{S}}(0) = \theta > 0$ and

$$\begin{aligned} \tilde{\mathfrak{S}}(\tilde{\mathcal{J}}_0) &= -(\Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_0, \tilde{\Theta}_1(\tilde{\mathcal{K}}_1)) + \Upsilon_{\mathcal{P}}(\tilde{\mathcal{J}}_0, \tilde{\Theta}_2(\tilde{\mathcal{K}}_1))) \\ &\quad + \Upsilon_{\mathcal{K}}(\tilde{\mathcal{J}}_0, \tilde{\mathcal{K}}_1) < 0. \end{aligned}$$

Under Condition C2, it follows that $\tilde{\mathfrak{S}}(\mathcal{J})$ decreases strictly as a function of \mathcal{J} . Consequently, there is a unique value $\tilde{\mathcal{J}}_1$ within the interval $(0, \tilde{\mathcal{J}}_0)$ for which $\tilde{\mathfrak{S}}(\tilde{\mathcal{J}}_1)$ equals zero. Moreover, considering Equations (31, 32), we find

$$\begin{aligned} \tilde{\mathcal{P}}_1 &= \frac{\eta_{\mathcal{L}}\eta_{\mathcal{K}}\tilde{\mathcal{K}}_1 + (\phi\xi + \eta_{\mathcal{K}}\beta)\tilde{\mathcal{K}}_1^2}{\psi\Pi_2(\eta_{\mathcal{L}} + \beta\tilde{\mathcal{K}}_1)}, & \tilde{\mathcal{E}}_1 &= \frac{\varpi\Pi_3\tilde{\mathcal{K}}_1}{\eta_{\mathcal{E}}}, \\ \tilde{\mathcal{L}}_1 &= \frac{\xi\tilde{\mathcal{K}}_1}{\eta_{\mathcal{L}} + \beta\tilde{\mathcal{K}}_1}. \end{aligned}$$

The presence of the virus-persistence steady state $\tilde{O}_1 = (\tilde{\mathcal{J}}_1, \tilde{\mathcal{P}}_1, \tilde{\mathcal{K}}_1, \tilde{\mathcal{E}}_1, \tilde{\mathcal{L}}_1)$ becomes evident when $\tilde{\mathfrak{H}}_0 > 1$.

3.2.3 Global stability of steady states

The forthcoming theorems explore the global asymptotic stability of both virus-free and virus-persistence steady states. For clarity's sake, let's demonstrate $(\mathcal{J}(t-r), \mathcal{P}(t-r), \mathcal{K}(t-r), \mathcal{E}(t-r))$ by $(\mathcal{J}_r, \mathcal{P}_r, \mathcal{K}_r, \mathcal{E}_r)$.

Theorem 3.1. For system (23), let $\tilde{\mathfrak{H}}_0 \leq 1$ and Conditions C1-C5 satisfied, then \tilde{O}_0 is G.A.S.

Proof. Let's contemplate a potential Lyapunov function, $\Xi_3(\mathcal{J}, \mathcal{P}, \mathcal{K}, \mathcal{E}, \mathcal{L})$, in the following manner:

$$\begin{aligned} \Xi_3 &= \mathcal{J} - \tilde{\mathcal{J}}_0 - \int_{\tilde{\mathcal{J}}_0}^{\mathcal{J}} \frac{\ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0)}{\ell_{\mathcal{E}}(\lambda)} d\lambda + \frac{1}{\Pi_1} \mathcal{P} \\ &\quad + \frac{\varpi\Pi_3\ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0) + \eta_{\mathcal{E}}\ell_{\mathcal{K}}(\tilde{\mathcal{J}}_0)}{\eta_{\mathcal{K}}\eta_{\mathcal{E}}} \mathcal{K} + \frac{\ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0)}{\eta_{\mathcal{E}}} \mathcal{E} \\ &\quad + \frac{\phi(\varpi\Pi_3\ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0) + \eta_{\mathcal{E}}\ell_{\mathcal{K}}(\tilde{\mathcal{J}}_0))}{2\xi\eta_{\mathcal{K}}\eta_{\mathcal{E}}} \mathcal{L}^2 \\ &\quad + \frac{1}{\Pi_1} \int_0^{\mathcal{J}} \bar{\Pi}_1(r) \int_{t-r}^t (\Upsilon_{\mathcal{E}}(\mathcal{J}(\lambda), \mathcal{E}(\lambda)) \\ &\quad + \Upsilon_{\mathcal{P}}(\mathcal{J}(\lambda), \mathcal{P}(\lambda)) + \Upsilon_{\mathcal{K}}(\mathcal{J}(\lambda), \mathcal{K}(\lambda))) d\lambda dr \\ &\quad + \frac{\psi(\varpi\Pi_3\ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0) + \eta_{\mathcal{E}}\ell_{\mathcal{K}}(\tilde{\mathcal{J}}_0))}{\eta_{\mathcal{K}}\eta_{\mathcal{E}}} \int_0^{\mathcal{J}} \bar{\Pi}_2(r) \\ &\quad \times \int_{t-r}^t \mathcal{P}(\lambda) d\lambda dr + \frac{\varpi\ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0)}{\eta_{\mathcal{E}}} \int_0^{\mathcal{J}} \bar{\Pi}_3(r) \int_{t-r}^t \mathcal{K}(\lambda) d\lambda dr. \end{aligned}$$

Evidently, $\Xi_3(\mathcal{J}, \mathcal{P}, \mathcal{K}, \mathcal{E}, \mathcal{L}) > 0$ for every $\mathcal{J}, \mathcal{P}, \mathcal{K}, \mathcal{E}, \mathcal{L} > 0$, as well as $\Xi_3(\tilde{\mathcal{J}}_0, 0, 0, 0, 0) = 0$. Further, $\frac{d\Xi_3}{dt}$ is given by:

$$\begin{aligned} \frac{d\Xi_3}{dt} &= \left(1 - \frac{\ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0)}{\ell_{\mathcal{E}}(\mathcal{J})} \right) \dot{\mathcal{J}} + \frac{1}{\Pi_1} \dot{\mathcal{P}} \\ &\quad + \frac{\varpi\Pi_3\ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0) + \eta_{\mathcal{E}}\ell_{\mathcal{K}}(\tilde{\mathcal{J}}_0)}{\eta_{\mathcal{K}}\eta_{\mathcal{E}}} \dot{\mathcal{K}} + \frac{\ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0)}{\eta_{\mathcal{E}}} \dot{\mathcal{E}} \\ &\quad + \frac{\phi(\varpi\Pi_3\ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0) + \eta_{\mathcal{E}}\ell_{\mathcal{K}}(\tilde{\mathcal{J}}_0))}{\xi\eta_{\mathcal{K}}\eta_{\mathcal{E}}} \dot{\mathcal{L}} \\ &\quad + \Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}) + \Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P}) + \Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K}) \end{aligned}$$

$$\begin{aligned}
 & - \frac{1}{\Pi_1} \int_0^{j_1} \bar{\Pi}_1(r) (\Upsilon_{\mathcal{E}}(\mathcal{J}_r, \mathcal{E}_r) + \Upsilon_{\mathcal{P}}(\mathcal{J}_r, \mathcal{P}_r) \\
 & + \Upsilon_{\mathcal{K}}(\mathcal{J}_r, \mathcal{K}_r)) dr \\
 & + \frac{\psi \Pi_2 (\varpi \Pi_3 \ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0) + \eta_{\mathcal{E}} \ell_{\mathcal{K}}(\tilde{\mathcal{J}}_0))}{\eta_{\mathcal{K}} \eta_{\mathcal{E}}} \mathcal{P} \\
 & - \frac{\psi (\varpi \Pi_3 \ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0) + \eta_{\mathcal{E}} \ell_{\mathcal{K}}(\tilde{\mathcal{J}}_0))}{\eta_{\mathcal{K}} \eta_{\mathcal{E}}} \int_0^{j_2} \bar{\Pi}_2(r) \mathcal{P}_r dr \\
 & + \frac{\varpi \Pi_3 \ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0)}{\eta_{\mathcal{E}}} \mathcal{K} \\
 & - \frac{\varpi \ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0)}{\eta_{\mathcal{E}}} \int_0^{j_3} \bar{\Pi}_3(r) \mathcal{K}_r dr \\
 & = \left(1 - \frac{\ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0)}{\ell_{\mathcal{E}}(\mathcal{J})} \right) (\theta - \eta_{\mathcal{J}} \mathcal{J} - \Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}) \\
 & - \Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P}) - \Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K})) \\
 & + \frac{1}{\Pi_1} \int_0^{j_1} \bar{\Pi}_1(r) (\Upsilon_{\mathcal{E}}(\mathcal{J}_r, \mathcal{E}_r) + \Upsilon_{\mathcal{P}}(\mathcal{J}_r, \mathcal{P}_r) \\
 & + \Upsilon_{\mathcal{K}}(\mathcal{J}_r, \mathcal{K}_r)) dr \\
 & - \frac{\psi + \eta_{\mathcal{P}}}{\Pi_1} \mathcal{P} + \frac{\varpi \Pi_3 \ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0) + \eta_{\mathcal{E}} \ell_{\mathcal{K}}(\tilde{\mathcal{J}}_0)}{\eta_{\mathcal{K}} \eta_{\mathcal{E}}} \\
 & \times \left(\psi \int_0^{j_2} \bar{\Pi}_2(r) \mathcal{P}_r dr - \eta_{\mathcal{K}} \mathcal{K} - \phi \mathcal{L} \mathcal{K} \right) \\
 & + \frac{\ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0)}{\eta_{\mathcal{E}}} \left(\varpi \int_0^{j_3} \bar{\Pi}_3(r) \mathcal{K}_r dr - \eta_{\mathcal{E}} \mathcal{E} \right) \\
 & + \frac{\phi (\varpi \Pi_3 \ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0) + \eta_{\mathcal{E}} \ell_{\mathcal{K}}(\tilde{\mathcal{J}}_0)) \mathcal{L}}{\xi \eta_{\mathcal{K}} \eta_{\mathcal{E}}} (\xi \mathcal{K} \\
 & - \eta_{\mathcal{L}} \mathcal{L} - \beta \mathcal{L} \mathcal{K}) + \Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}) + \Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P}) + \Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K}) \\
 & - \frac{1}{\Pi_1} \int_0^{j_1} \bar{\Pi}_1(r) (\Upsilon_{\mathcal{E}}(\mathcal{J}_r, \mathcal{E}_r) + \Upsilon_{\mathcal{P}}(\mathcal{J}_r, \mathcal{P}_r) \\
 & + \Upsilon_{\mathcal{K}}(\mathcal{J}_r, \mathcal{K}_r)) dr \\
 & + \frac{\psi \Pi_2 (\varpi \Pi_3 \ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0) + \eta_{\mathcal{E}} \ell_{\mathcal{K}}(\tilde{\mathcal{J}}_0))}{\eta_{\mathcal{K}} \eta_{\mathcal{E}}} \mathcal{P} \\
 & - \frac{\psi (\varpi \Pi_3 \ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0) + \eta_{\mathcal{E}} \ell_{\mathcal{K}}(\tilde{\mathcal{J}}_0))}{\eta_{\mathcal{K}} \eta_{\mathcal{E}}} \int_0^{j_2} \bar{\Pi}_2(r) \mathcal{P}_r dr \\
 & + \frac{\varpi \Pi_3 \ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0)}{\eta_{\mathcal{E}}} \mathcal{K} - \frac{\varpi \ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0)}{\eta_{\mathcal{E}}} \int_0^{j_3} \bar{\Pi}_3(r) \mathcal{K}_r dr \\
 & = \left(1 - \frac{\ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0)}{\ell_{\mathcal{E}}(\mathcal{J})} \right) (\theta - \eta_{\mathcal{J}} \mathcal{J}) \\
 & + \left(\frac{\ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0)}{\ell_{\mathcal{E}}(\mathcal{J})} \frac{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E})}{\mathcal{E}} - \ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0) \right) \mathcal{E} \\
 & + \left(\frac{\ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0)}{\ell_{\mathcal{E}}(\mathcal{J})} \frac{\Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P})}{\mathcal{P}} - \frac{\psi + \eta_{\mathcal{P}}}{\Pi_1} \right. \\
 & \left. + \frac{\psi \Pi_2 (\varpi \Pi_3 \ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0) + \eta_{\mathcal{E}} \ell_{\mathcal{K}}(\tilde{\mathcal{J}}_0))}{\eta_{\mathcal{K}} \eta_{\mathcal{E}}} \right) \mathcal{P} \\
 & + \left(\frac{\ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0)}{\ell_{\mathcal{E}}(\mathcal{J})} \frac{\Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K})}{\mathcal{K}} - \ell_{\mathcal{K}}(\tilde{\mathcal{J}}_0) \right) \mathcal{K} \\
 & - \frac{\phi (\varpi \Pi_3 \ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0) + \eta_{\mathcal{E}} \ell_{\mathcal{K}}(\tilde{\mathcal{J}}_0))}{\xi \eta_{\mathcal{K}} \eta_{\mathcal{E}}} (\eta_{\mathcal{L}} + \beta \mathcal{K}) \mathcal{L}^2. \tag{37}
 \end{aligned}$$

Using inequality (17), we obtain

$$\frac{\ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0)}{\ell_{\mathcal{E}}(\mathcal{J})} \frac{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E})}{\mathcal{E}} - \ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0) \leq \frac{\ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0)}{\ell_{\mathcal{E}}(\mathcal{J})} \ell_{\mathcal{E}}(\mathcal{J}) - \ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0) = 0.$$

Further, Condition C4 and C5 in case of $\tilde{\mathcal{J}}_0 = \frac{\theta}{\eta_{\mathcal{J}}}$ imply that

$$\begin{aligned}
 & \frac{\ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0)}{\ell_{\mathcal{E}}(\mathcal{J})} \frac{\Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P})}{\mathcal{P}} - \frac{\psi + \eta_{\mathcal{P}}}{\Pi_1} \\
 & + \frac{\psi \Pi_2 (\varpi \Pi_3 \ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0) + \eta_{\mathcal{E}} \ell_{\mathcal{K}}(\tilde{\mathcal{J}}_0))}{\eta_{\mathcal{K}} \eta_{\mathcal{E}}} \\
 & \leq \frac{\ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0) \ell_{\mathcal{P}}(\mathcal{J})}{\ell_{\mathcal{E}}(\mathcal{J})} - \frac{\psi + \eta_{\mathcal{P}}}{\Pi_1} \\
 & + \frac{\psi \Pi_2 (\varpi \Pi_3 \ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0) + \eta_{\mathcal{E}} \ell_{\mathcal{K}}(\tilde{\mathcal{J}}_0))}{\eta_{\mathcal{K}} \eta_{\mathcal{E}}} \\
 & \leq \frac{\ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0) \ell_{\mathcal{P}}(\tilde{\mathcal{J}}_0)}{\ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0)} - \frac{\psi + \eta_{\mathcal{P}}}{\Pi_1} \\
 & + \frac{\psi \Pi_2 (\varpi \Pi_3 \ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0) + \eta_{\mathcal{E}} \ell_{\mathcal{K}}(\tilde{\mathcal{J}}_0))}{\eta_{\mathcal{K}} \eta_{\mathcal{E}}} \\
 & = \ell_{\mathcal{P}}(\tilde{\mathcal{J}}_0) - \frac{\psi + \eta_{\mathcal{P}}}{\Pi_1} + \frac{\psi \Pi_2 (\varpi \Pi_3 \ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0) + \eta_{\mathcal{E}} \ell_{\mathcal{K}}(\tilde{\mathcal{J}}_0))}{\eta_{\mathcal{K}} \eta_{\mathcal{E}}} \\
 & = \frac{\psi \Pi_2 (\varpi \Pi_3 \ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0) + \eta_{\mathcal{E}} \ell_{\mathcal{K}}(\tilde{\mathcal{J}}_0)) + \eta_{\mathcal{K}} \eta_{\mathcal{E}} \ell_{\mathcal{P}}(\tilde{\mathcal{J}}_0)}{\eta_{\mathcal{K}} \eta_{\mathcal{E}}} \\
 & - \frac{\psi + \eta_{\mathcal{P}}}{\Pi_1} \\
 & = \frac{\psi + \eta_{\mathcal{P}}}{\Pi_1} (\tilde{\mathfrak{H}}_0 - 1).
 \end{aligned}$$

Furthermore

$$\begin{aligned}
 & \frac{\ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0)}{\ell_{\mathcal{E}}(\mathcal{J})} \frac{\Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K})}{\mathcal{K}} - \ell_{\mathcal{K}}(\tilde{\mathcal{J}}_0) \leq \frac{\ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0) \ell_{\mathcal{K}}(\mathcal{J})}{\ell_{\mathcal{E}}(\mathcal{J})} - \ell_{\mathcal{K}}(\tilde{\mathcal{J}}_0) \\
 & \leq \frac{\ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0) \ell_{\mathcal{K}}(\tilde{\mathcal{J}}_0)}{\ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0)} - \ell_{\mathcal{K}}(\tilde{\mathcal{J}}_0) = 0.
 \end{aligned}$$

Upon conducting a straightforward computation and incorporating the value $\tilde{\mathcal{J}}_0 = \theta/\eta_{\mathcal{J}}$, Equation (37) will manifest in the subsequent manner:

$$\frac{d\Xi_3}{dt} \leq \theta \left(1 - \frac{\ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0)}{\ell_{\mathcal{E}}(\mathcal{J})} \right) \left(1 - \frac{\mathcal{J}}{\tilde{\mathcal{J}}_0} \right) + \frac{\psi + \eta_{\mathcal{P}}}{\Pi_1} (\tilde{\mathfrak{N}}_0 - 1) \mathcal{P} - \frac{\phi \left(\varpi \Pi_3 \ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0) + \eta_{\mathcal{E}} \ell_{\mathcal{K}}(\tilde{\mathcal{J}}_0) \right)}{\xi \eta_{\mathcal{K}} \eta_{\mathcal{E}}} (\eta_{\mathcal{L}} + \beta \mathcal{K}) \mathcal{L}^2.$$

From Condition C3, we have

$$\left(1 - \frac{\ell_{\mathcal{E}}(\tilde{\mathcal{J}}_0)}{\ell_{\mathcal{E}}(\mathcal{J})} \right) \left(1 - \frac{\mathcal{J}}{\tilde{\mathcal{J}}_0} \right) \leq 0.$$

Evidently, for $\tilde{\mathfrak{N}}_0 \leq 1$, the rate $\frac{d\Xi_3}{dt}$ remains non-positive. Furthermore, $\frac{d\Xi_3}{dt}$ equals zero at $\mathcal{J} = \tilde{\mathcal{J}}_0$, with $\mathcal{P} = \mathcal{K} = \mathcal{L} = 0$. It follows that all solutions convey to M'_3 . Within M'_3 , every element satisfy $\mathcal{J}(t) = \tilde{\mathcal{J}}_0$ and $\mathcal{P}(t) = \mathcal{K}(t) = \mathcal{L}(t) = 0$ for all t . Following this, the first equation of model (23) along with Condition C1 results in:

$$0 = \dot{\mathcal{J}} = \theta - \eta_{\mathcal{J}} \tilde{\mathcal{J}}_0 - \Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_0, \mathcal{E}(t)) \implies \Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_0, \mathcal{E}(t)) = 0 \implies \mathcal{E}(t) = 0, \text{ for all } t.$$

Then, $M'_3 = \{\tilde{O}_0\}$. Consequently, according to the L.I.P, the inference can be drawn that \tilde{O}_0 exhibits global asymptotic stability whenever $\tilde{\mathfrak{N}}_0 \leq 1$ [44, 45].

Theorem 3.2. Given $\tilde{\mathfrak{N}}_0 > 1$ and the fulfillment of Conditions C1-C4 and C6, it can be concluded that the steady state \tilde{O}_1 for system (23) is guaranteed to be G.A.S.

Proof. Building up $\Xi_4(\mathcal{J}, \mathcal{P}, \mathcal{K}, \mathcal{E}, \mathcal{L})$ according to Equation (38) as follows:

$$\begin{aligned} \Xi_4 = & \mathcal{J} - \tilde{\mathcal{J}}_1 - \int_{\tilde{\mathcal{J}}_1}^{\mathcal{J}} \frac{\Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{E}}_1)}{\Upsilon_{\mathcal{E}}(\lambda, \tilde{\mathcal{E}}_1)} d\lambda + \frac{\tilde{\mathcal{P}}_1}{\Pi_1} F\left(\frac{\mathcal{P}}{\tilde{\mathcal{P}}_1}\right) \\ & + \frac{\varpi \Pi_3 \tilde{\mathcal{K}}_1 \Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{E}}_1) + \eta_{\mathcal{E}} \tilde{\mathcal{E}}_1 \Upsilon_{\mathcal{K}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{K}}_1)}{\eta_{\mathcal{E}} \tilde{\mathcal{E}}_1 (\eta_{\mathcal{K}} + \phi \tilde{\mathcal{L}}_1)} F\left(\frac{\mathcal{K}}{\tilde{\mathcal{K}}_1}\right) \\ & + \frac{\Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{E}}_1)}{\eta_{\mathcal{E}}} F\left(\frac{\mathcal{E}}{\tilde{\mathcal{E}}_1}\right) \\ & + \frac{\phi \left(\varpi \Pi_3 \tilde{\mathcal{K}}_1 \Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{E}}_1) + \eta_{\mathcal{E}} \tilde{\mathcal{E}}_1 \Upsilon_{\mathcal{K}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{K}}_1) \right)}{2\eta_{\mathcal{E}} \tilde{\mathcal{K}}_1 \tilde{\mathcal{E}}_1 (\eta_{\mathcal{K}} + \phi \tilde{\mathcal{L}}_1) (\xi - \beta \tilde{\mathcal{L}}_1)} (\mathcal{L} - \tilde{\mathcal{L}}_1)^2 \\ & + \frac{\Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{E}}_1)}{\Pi_1} \int_0^{\mathcal{J}} \tilde{\Pi}_1(r) \int_{t-r}^t F\left(\frac{\Upsilon_{\mathcal{E}}(\mathcal{J}(\lambda), \mathcal{E}(\lambda))}{\Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{E}}_1)}\right) d\lambda dr \\ & + \frac{\Upsilon_{\mathcal{P}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{P}}_1)}{\Pi_1} \int_0^{\mathcal{P}} \tilde{\Pi}_1(r) \int_{t-r}^t F\left(\frac{\Upsilon_{\mathcal{P}}(\mathcal{J}(\lambda), \mathcal{P}(\lambda))}{\Upsilon_{\mathcal{P}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{P}}_1)}\right) d\lambda dr \\ & + \frac{\Upsilon_{\mathcal{K}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{K}}_1)}{\Pi_1} \int_0^{\mathcal{K}} \tilde{\Pi}_1(r) \int_{t-r}^t F\left(\frac{\Upsilon_{\mathcal{K}}(\mathcal{J}(\lambda), \mathcal{K}(\lambda))}{\Upsilon_{\mathcal{K}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{K}}_1)}\right) d\lambda dr \\ & + \frac{\psi \tilde{\mathcal{P}}_1 \left(\varpi \Pi_3 \tilde{\mathcal{K}}_1 \Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{E}}_1) + \eta_{\mathcal{E}} \tilde{\mathcal{E}}_1 \Upsilon_{\mathcal{K}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{K}}_1) \right)}{\eta_{\mathcal{E}} \tilde{\mathcal{K}}_1 \tilde{\mathcal{E}}_1 (\eta_{\mathcal{K}} + \phi \tilde{\mathcal{L}}_1)} \end{aligned}$$

$$\begin{aligned} & \int_0^{\mathcal{J}} \tilde{\Pi}_2(r) \int_{t-r}^t F\left(\frac{\mathcal{P}(\lambda)}{\tilde{\mathcal{P}}_1}\right) d\lambda dr \\ & + \frac{\varpi \tilde{\mathcal{K}}_1 \Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{E}}_1)}{\eta_{\mathcal{E}} \tilde{\mathcal{E}}_1} \int_0^{\mathcal{K}} \tilde{\Pi}_3(r) \int_{t-r}^t F\left(\frac{\mathcal{K}(\lambda)}{\tilde{\mathcal{K}}_1}\right) d\lambda dr. \end{aligned} \tag{38}$$

We can deduce from the steady state condition Equation (30) that $\xi - \beta \tilde{\mathcal{L}}_1 = \frac{\eta_{\mathcal{L}} \tilde{\mathcal{L}}_1}{\tilde{\mathcal{K}}_1} > 0$. The positivity definiteness of Ξ_4 becomes evident. When calculating $\frac{d\Xi_4}{dt}$ along the trajectories of the model described in Equation (23), we obtain

$$\begin{aligned} \frac{d\Xi_4}{dt} = & \left(1 - \frac{\Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{E}}_1)}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \tilde{\mathcal{E}}_1)} \right) \dot{\mathcal{J}} + \frac{1}{\Pi_1} \left(1 - \frac{\tilde{\mathcal{P}}_1}{\mathcal{P}} \right) \dot{\mathcal{P}} \\ & + \frac{\varpi \Pi_3 \tilde{\mathcal{K}}_1 \Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{E}}_1) + \eta_{\mathcal{E}} \tilde{\mathcal{E}}_1 \Upsilon_{\mathcal{K}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{K}}_1)}{\eta_{\mathcal{E}} \tilde{\mathcal{K}}_1 \tilde{\mathcal{E}}_1 (\eta_{\mathcal{K}} + \phi \tilde{\mathcal{L}}_1)} \left(1 - \frac{\tilde{\mathcal{K}}_1}{\mathcal{K}} \right) \dot{\mathcal{K}} \\ & + \frac{\Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{E}}_1)}{\eta_{\mathcal{E}} \tilde{\mathcal{E}}_1} \left(1 - \frac{\tilde{\mathcal{E}}_1}{\mathcal{E}} \right) \dot{\mathcal{E}} \\ & + \frac{\phi \left(\varpi \Pi_3 \tilde{\mathcal{K}}_1 \Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{E}}_1) + \eta_{\mathcal{E}} \tilde{\mathcal{E}}_1 \Upsilon_{\mathcal{K}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{K}}_1) \right)}{\eta_{\mathcal{E}} \tilde{\mathcal{K}}_1 \tilde{\mathcal{E}}_1 (\eta_{\mathcal{K}} + \phi \tilde{\mathcal{L}}_1) (\xi - \beta \tilde{\mathcal{L}}_1)} \\ & \times (\mathcal{L} - \tilde{\mathcal{L}}_1) \dot{\mathcal{L}} \\ & + \frac{\Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{E}}_1)}{\Pi_1} \int_0^{\mathcal{J}} \tilde{\Pi}_1(r) \left(\frac{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E})}{\Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{E}}_1)} - \frac{\Upsilon_{\mathcal{E}}(\mathcal{J}_r, \mathcal{E}_r)}{\Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{E}}_1)} \right) \\ & + \ln\left(\frac{\Upsilon_{\mathcal{E}}(\mathcal{J}_r, \mathcal{E}_r)}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E})}\right) dr \\ & + \frac{\Upsilon_{\mathcal{P}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{P}}_1)}{\Pi_1} \int_0^{\mathcal{P}} \tilde{\Pi}_1(r) \left(\frac{\Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P})}{\Upsilon_{\mathcal{P}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{P}}_1)} - \frac{\Upsilon_{\mathcal{P}}(\mathcal{J}_r, \mathcal{P}_r)}{\Upsilon_{\mathcal{P}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{P}}_1)} \right) \\ & + \ln\left(\frac{\Upsilon_{\mathcal{P}}(\mathcal{J}_r, \mathcal{P}_r)}{\Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P})}\right) dr \\ & + \frac{\Upsilon_{\mathcal{K}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{K}}_1)}{\Pi_1} \int_0^{\mathcal{K}} \tilde{\Pi}_1(r) \left(\frac{\Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K})}{\Upsilon_{\mathcal{K}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{K}}_1)} - \frac{\Upsilon_{\mathcal{K}}(\mathcal{J}_r, \mathcal{K}_r)}{\Upsilon_{\mathcal{K}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{K}}_1)} \right) \\ & + \ln\left(\frac{\Upsilon_{\mathcal{K}}(\mathcal{J}_r, \mathcal{K}_r)}{\Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K})}\right) dr \\ & + \frac{\psi \tilde{\mathcal{P}}_1 \left(\varpi \Pi_3 \tilde{\mathcal{K}}_1 \Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{E}}_1) + \eta_{\mathcal{E}} \tilde{\mathcal{E}}_1 \Upsilon_{\mathcal{K}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{K}}_1) \right)}{\eta_{\mathcal{E}} \tilde{\mathcal{K}}_1 \tilde{\mathcal{E}}_1 (\eta_{\mathcal{K}} + \phi \tilde{\mathcal{L}}_1)} \\ & \times \int_0^{\mathcal{J}} \tilde{\Pi}_2(r) \left(\frac{\mathcal{P}}{\tilde{\mathcal{P}}_1} - \frac{\mathcal{P}_r}{\tilde{\mathcal{P}}_1} + \ln\left(\frac{\mathcal{P}_r}{\mathcal{P}}\right) \right) dr \\ & + \frac{\varpi \tilde{\mathcal{K}}_1 \Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{E}}_1)}{\eta_{\mathcal{E}} \tilde{\mathcal{E}}_1} \int_0^{\mathcal{K}} \tilde{\Pi}_3(r) \left(\frac{\mathcal{K}}{\tilde{\mathcal{K}}_1} - \frac{\mathcal{K}_r}{\tilde{\mathcal{K}}_1} + \ln\left(\frac{\mathcal{K}_r}{\mathcal{K}}\right) \right) dr \\ = & \left(1 - \frac{\Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{E}}_1)}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \tilde{\mathcal{E}}_1)} \right) (\theta - \eta_{\mathcal{J}} \mathcal{J} - \Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E})) \\ & - \Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P}) - \Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K}) \\ & + \frac{1}{\Pi_1} \left(1 - \frac{\tilde{\mathcal{P}}_1}{\mathcal{P}} \right) \left(\int_0^{\mathcal{J}} \tilde{\Pi}_1(r) (\Upsilon_{\mathcal{E}}(\mathcal{J}_r, \mathcal{E}_r) + \Upsilon_{\mathcal{P}}(\mathcal{J}_r, \mathcal{P}_r)) \right) \end{aligned}$$

$$\begin{aligned}
 & + \Upsilon_{\mathcal{P}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{P}}_1) \left(\frac{\Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{E}}_1) \Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P})}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \tilde{\mathcal{E}}_1) \Upsilon_{\mathcal{P}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{P}}_1)} - \frac{\mathcal{P}}{\tilde{\mathcal{P}}_1} \right) \\
 & \times \left(1 - \frac{\Upsilon_{\mathcal{E}}(\mathcal{J}, \tilde{\mathcal{E}}_1) \Upsilon_{\mathcal{P}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{P}}_1)}{\Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{E}}_1) \Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P})} \right) \\
 & + \Upsilon_{\mathcal{K}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{K}}_1) \left(\frac{\Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{E}}_1) \Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K})}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \tilde{\mathcal{E}}_1) \Upsilon_{\mathcal{K}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{K}}_1)} - \frac{\mathcal{K}}{\tilde{\mathcal{K}}_1} \right) \\
 & \times \left(1 - \frac{\Upsilon_{\mathcal{E}}(\mathcal{J}, \tilde{\mathcal{E}}_1) \Upsilon_{\mathcal{K}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{K}}_1)}{\Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{E}}_1) \Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K})} \right) \\
 & - \frac{\Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{E}}_1)}{\Pi_1} \int_0^{f_1} \tilde{\Pi}_1(r) \left[F \left(\frac{\Upsilon_{\mathcal{E}}(\mathcal{J}_r, \mathcal{E}(t-r)) \tilde{\mathcal{P}}_1}{\Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{E}}_1) \mathcal{P}} \right) \right. \\
 & + F \left(\frac{\Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{E}}_1)}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \tilde{\mathcal{E}}_1)} \right) \\
 & + F \left. \left(\frac{\Upsilon_{\mathcal{E}}(\mathcal{J}, \tilde{\mathcal{E}}_1) \mathcal{E}}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}) \tilde{\mathcal{E}}_1} \right) \right] dr - \frac{\Upsilon_{\mathcal{P}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{P}}_1)}{\Pi_1} \int_0^{f_1} \tilde{\Pi}_1(r) \\
 & \times \left[F \left(\frac{\Upsilon_{\mathcal{P}}(\mathcal{J}_r, \mathcal{P}_r) \tilde{\mathcal{P}}_1}{\Upsilon_{\mathcal{P}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{P}}_1) \mathcal{P}} \right) + F \left(\frac{\Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{E}}_1)}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \tilde{\mathcal{E}}_1)} \right) \right. \\
 & + F \left. \left(\frac{\Upsilon_{\mathcal{E}}(\mathcal{J}, \tilde{\mathcal{E}}_1) \Upsilon_{\mathcal{P}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{P}}_1) \mathcal{P}}{\Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{E}}_1) \Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P}) \tilde{\mathcal{P}}_1} \right) \right] dr \\
 & - \frac{\Upsilon_{\mathcal{K}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{K}}_1)}{\Pi_1} \int_0^{f_1} \tilde{\Pi}_1(r) \left[F \left(\frac{\Upsilon_{\mathcal{K}}(\mathcal{J}_r, \mathcal{K}_r) \tilde{\mathcal{P}}_1}{\Upsilon_{\mathcal{K}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{K}}_1) \mathcal{P}} \right) \right. \\
 & + F \left(\frac{\Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{E}}_1)}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \tilde{\mathcal{E}}_1)} \right) \\
 & + F \left. \left(\frac{\Upsilon_{\mathcal{E}}(\mathcal{J}, \tilde{\mathcal{E}}_1) \Upsilon_{\mathcal{K}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{K}}_1) \mathcal{K}}{\Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{E}}_1) \Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K}) \tilde{\mathcal{K}}_1} \right) \right] dr \\
 & - \frac{\Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{E}}_1) + \Upsilon_{\mathcal{K}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{K}}_1)}{\Pi_2} \int_0^{f_2} \tilde{\Pi}_2(r) \\
 & \times F \left(\frac{\mathcal{P}_r \tilde{\mathcal{K}}_1}{\tilde{\mathcal{P}}_1 \mathcal{K}} \right) dr - \frac{\Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{E}}_1)}{\Pi_3} \int_0^{f_3} \tilde{\Pi}_3(r) F \left(\frac{\mathcal{K}_r \tilde{\mathcal{E}}_1}{\tilde{\mathcal{K}}_1 \mathcal{E}} \right) dr \\
 & - \frac{\phi(\Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{E}}_1) + \Upsilon_{\mathcal{K}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{K}}_1))}{\tilde{\mathcal{K}}_1(\eta_{\mathcal{K}} + \phi \tilde{\mathcal{L}}_1)} (\xi - \beta \tilde{\mathcal{L}}_1) \\
 & \times (\eta_{\mathcal{L}} + \beta \mathcal{K}) (\mathcal{L} - \tilde{\mathcal{L}}_1)^2.
 \end{aligned}$$

From Condition C2, we have

$$\left(1 - \frac{\Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{E}}_1)}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \tilde{\mathcal{E}}_1)} \right) \left(1 - \frac{\mathcal{J}}{\tilde{\mathcal{J}}_1} \right) \leq 0.$$

In addition, from Equations (18–20), we conclude

$$\begin{aligned}
 & \left(\frac{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E})}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \tilde{\mathcal{E}}_1)} - \frac{\mathcal{E}}{\tilde{\mathcal{E}}_1} \right) \left(1 - \frac{\Upsilon_{\mathcal{E}}(\mathcal{J}, \tilde{\mathcal{E}}_1)}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E})} \right) \leq 0, \\
 & \left(\frac{\Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{E}}_1) \Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P})}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \tilde{\mathcal{E}}_1) \Upsilon_{\mathcal{P}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{P}}_1)} - \frac{\mathcal{P}}{\tilde{\mathcal{P}}_1} \right) \\
 & \times \left(1 - \frac{\Upsilon_{\mathcal{E}}(\mathcal{J}, \tilde{\mathcal{E}}_1) \Upsilon_{\mathcal{P}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{P}}_1)}{\Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{E}}_1) \Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P})} \right) \leq 0, \\
 & \left(\frac{\Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{E}}_1) \Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K})}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \tilde{\mathcal{E}}_1) \Upsilon_{\mathcal{K}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{K}}_1)} - \frac{\mathcal{K}}{\tilde{\mathcal{K}}_1} \right) \\
 & \times \left(1 - \frac{\Upsilon_{\mathcal{E}}(\mathcal{J}, \tilde{\mathcal{E}}_1) \Upsilon_{\mathcal{K}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{K}}_1)}{\Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{E}}_1) \Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K})} \right) \leq 0.
 \end{aligned}$$

Consequently, when $\tilde{\mathfrak{R}}_0 > 1$, it is established that $\frac{d\tilde{\mathcal{E}}_1}{dt} \leq 0$ holds true for all positive values of $\mathcal{J}, \mathcal{P}, \mathcal{K}, \mathcal{E}$ and \mathcal{L} . Additionally, $\frac{d\tilde{\mathcal{E}}_1}{dt} = 0$ is realized when $\mathcal{J} = \tilde{\mathcal{J}}_1, \mathcal{P} = \tilde{\mathcal{P}}_1, \mathcal{K} = \tilde{\mathcal{K}}_1, \mathcal{E} = \tilde{\mathcal{E}}_1$, and $\mathcal{L} = \tilde{\mathcal{L}}_1$. As a result, with $M'_4 = \{\tilde{\mathcal{O}}_1\}$, we can affirm that the steady state $\tilde{\mathcal{O}}_1$ is G.A.S under the condition $\tilde{\mathfrak{R}}_0 > 1$ in accordance of L.I.P [44, 45].

4 Illustrative examples and numerical simulations

Dive into the real world! This section brings our theoretical predictions to life through numerical simulations. We use the MATLAB solvers' ode45 and dde23 to explore the dynamics of systems (3) and (23), respectively. We utilize saturated incidence functions for the incidence rates in the system (3), while choosing Holling type-II incidence for system (23). Additionally, within the framework of model (3), we investigate the dynamic impact of CTL immune impairment and saturation effects. Furthermore, our analysis extends to exploring the influences of time delays and the Holling effect on the dynamics of the system (23). We utilize sensitivity analysis to reveal how basic reproduction ratios respond to variations in parameter values.

4.1 Numerical simulation for model (3)

The subsequent saturation incidence rates will be selected for system (3):

$$\begin{aligned}
 \Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}) &= \frac{\rho_{\mathcal{E}} \mathcal{J} \mathcal{E}}{1 + \epsilon_{\mathcal{E}} \mathcal{E}}, & \Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P}) &= \frac{\rho_{\mathcal{P}} \mathcal{J} \mathcal{P}}{1 + \epsilon_{\mathcal{P}} \mathcal{P}}, \\
 \Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K}) &= \frac{\rho_{\mathcal{K}} \mathcal{J} \mathcal{K}}{1 + \epsilon_{\mathcal{K}} \mathcal{K}},
 \end{aligned}$$

where $\rho_Z > 0, Z \in \{\mathcal{E}, \mathcal{P}, \mathcal{K}\}$, account for the infection rate constants. Parameters $\epsilon_Z > 0, Z \in \{\mathcal{E}, \mathcal{P}, \mathcal{K}\}$, represent the

saturation infection rate constants. Hence, the structure of system (3) will be as follows:

$$\begin{cases} \dot{J} = \theta - \eta_{\mathcal{J}}\mathcal{J} - \frac{\rho_{\mathcal{E}}\mathcal{J}\mathcal{E}}{1 + \epsilon_{\mathcal{E}}\mathcal{E}} - \frac{\rho_{\mathcal{P}}\mathcal{J}\mathcal{P}}{1 + \epsilon_{\mathcal{P}}\mathcal{P}} - \frac{\rho_{\mathcal{K}}\mathcal{J}\mathcal{K}}{1 + \epsilon_{\mathcal{K}}\mathcal{K}}, \\ \dot{P} = \frac{\rho_{\mathcal{E}}\mathcal{J}\mathcal{E}}{1 + \epsilon_{\mathcal{E}}\mathcal{E}} + \frac{\rho_{\mathcal{P}}\mathcal{J}\mathcal{P}}{1 + \epsilon_{\mathcal{P}}\mathcal{P}} + \frac{\rho_{\mathcal{K}}\mathcal{J}\mathcal{K}}{1 + \epsilon_{\mathcal{K}}\mathcal{K}} - (\psi + \eta_{\mathcal{P}})\mathcal{P}, \\ \dot{K} = \psi\mathcal{P} - \eta_{\mathcal{K}}\mathcal{K} - \phi\mathcal{L}\mathcal{K}, \\ \dot{E} = \varpi\mathcal{K} - \eta_{\mathcal{E}}\mathcal{E}, \\ \dot{L} = \xi\mathcal{K} - \eta_{\mathcal{L}}\mathcal{L} - \beta\mathcal{L}\mathcal{K}. \end{cases} \tag{40}$$

Clearly, $\Upsilon_Z(\mathcal{J}, Z)$, $Z \in \{\mathcal{E}, \mathcal{P}, \mathcal{K}\}$ are continuously differentiable functions. In addition, $\Upsilon_Z(\mathcal{J}, Z)$, $Z \in \{\mathcal{E}, \mathcal{P}, \mathcal{K}\}$ satisfying the following: $\Upsilon_Z(\mathcal{J}, Z) > 0$ and $\Upsilon_Z(0, Z) = \Upsilon_Z(\mathcal{J}, 0) = 0$ for all $\mathcal{J} > 0$ and $Z > 0$. Hence, Condition C1 is fulfilled. Moreover, we have

$$\begin{aligned} \frac{\partial \Upsilon_Z(\mathcal{J}, Z)}{\partial \mathcal{J}} &= \frac{\rho_Z Z}{1 + \epsilon_Z Z} > 0, \quad \text{for all } Z > 0, \\ \frac{\partial \Upsilon_Z(\mathcal{J}, Z)}{\partial Z} &= \frac{\rho_Z \mathcal{J}}{(1 + \epsilon_Z Z)^2} > 0, \quad \text{for all } \mathcal{J}, Z > 0, \end{aligned}$$

where $Z \in \{\mathcal{E}, \mathcal{P}, \mathcal{K}\}$. This means that Condition C2 is valid. It is obvious that

$$\ell_Z(\mathcal{J}) = \frac{\partial \Upsilon_Z(\mathcal{J}, 0)}{\partial Z} = \rho_Z \mathcal{J} > 0, \quad \text{for all } \mathcal{J} > 0, Z \in \{\mathcal{E}, \mathcal{P}, \mathcal{K}\}.$$

Furthermore

$$\ell'_Z(\mathcal{J}) = \frac{d}{d\mathcal{J}} \left(\frac{\partial \Upsilon_Z(\mathcal{J}, 0)}{\partial Z} \right) = \rho_Z > 0, \quad Z \in \{\mathcal{E}, \mathcal{P}, \mathcal{K}\},$$

which confirms that Condition C3 is also met. Moreover, we have

$$\frac{\partial}{\partial Z} \left(\frac{\Upsilon_Z(\mathcal{J}, Z)}{Z} \right) = -\frac{\rho_Z \epsilon_Z \mathcal{J}}{(1 + \epsilon_Z Z)^2} < 0, \quad \text{for all } \mathcal{J}, Z > 0, \\ Z \in \{\mathcal{E}, \mathcal{P}, \mathcal{K}\}.$$

Then Condition C4 is verified. It is observable that $\frac{\ell_Z(\mathcal{J})}{\ell_{\mathcal{E}}(\mathcal{J})} = \frac{\rho_Z}{\rho_{\mathcal{E}}}$, $Z \in \{\mathcal{P}, \mathcal{K}\}$. Hence, Condition C5 is satisfied. Furthermore, we have

$$\frac{\Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P})}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}_1)} = \frac{\rho_{\mathcal{P}}\mathcal{P}(1 + \epsilon_{\mathcal{E}}\mathcal{E}_1)}{\rho_{\mathcal{E}}\mathcal{E}_1(1 + \epsilon_{\mathcal{P}}\mathcal{P})},$$

$$\begin{aligned} \frac{\Upsilon_{\mathcal{P}}(\mathcal{J}_1, \mathcal{P}_1)}{\Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1)} &= \frac{\rho_{\mathcal{P}}\mathcal{P}_1(1 + \epsilon_{\mathcal{E}}\mathcal{E}_1)}{\rho_{\mathcal{E}}\mathcal{E}_1(1 + \epsilon_{\mathcal{P}}\mathcal{P}_1)}, \\ \frac{\Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K})}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}_1)} &= \frac{\rho_{\mathcal{K}}\mathcal{K}(1 + \epsilon_{\mathcal{E}}\mathcal{E}_1)}{\rho_{\mathcal{E}}\mathcal{E}_1(1 + \epsilon_{\mathcal{K}}\mathcal{K})}, \\ \frac{\Upsilon_{\mathcal{K}}(\mathcal{J}_1, \mathcal{K}_1)}{\Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1)} &= \frac{\rho_{\mathcal{K}}\mathcal{K}_1(1 + \epsilon_{\mathcal{E}}\mathcal{E}_1)}{\rho_{\mathcal{E}}\mathcal{E}_1(1 + \epsilon_{\mathcal{K}}\mathcal{K}_1)}, \end{aligned}$$

and

$$\begin{aligned} &\left(\frac{\Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P})}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}_1)\mathcal{P}} - \frac{\Upsilon_{\mathcal{P}}(\mathcal{J}_1, \mathcal{P}_1)}{\Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1)\mathcal{P}_1} \right) \\ &\times \left(\frac{\Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P})}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}_1)} - \frac{\Upsilon_{\mathcal{P}}(\mathcal{J}_1, \mathcal{P}_1)}{\Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1)} \right) \\ &= -\frac{\epsilon_{\mathcal{P}}\rho_{\mathcal{P}}^2(1 + \epsilon_{\mathcal{E}}\mathcal{E}_1)^2(\mathcal{P} - \mathcal{P}_1)^2}{\rho_{\mathcal{E}}^2\mathcal{E}_1^2(1 + \epsilon_{\mathcal{P}}\mathcal{P})^2(1 + \epsilon_{\mathcal{P}}\mathcal{P}_1)^2} \leq 0, \\ &\left(\frac{\Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K})}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}_1)\mathcal{K}} - \frac{\Upsilon_{\mathcal{K}}(\mathcal{J}_1, \mathcal{K}_1)}{\Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1)\mathcal{K}_1} \right) \\ &\times \left(\frac{\Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K})}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}_1)} - \frac{\Upsilon_{\mathcal{K}}(\mathcal{J}_1, \mathcal{K}_1)}{\Upsilon_{\mathcal{E}}(\mathcal{J}_1, \mathcal{E}_1)} \right) \\ &= -\frac{\epsilon_{\mathcal{K}}\rho_{\mathcal{K}}^2(1 + \epsilon_{\mathcal{E}}\mathcal{E}_1)^2(\mathcal{K} - \mathcal{K}_1)^2}{\rho_{\mathcal{E}}^2\mathcal{E}_1^2(1 + \epsilon_{\mathcal{K}}\mathcal{K})^2(1 + \epsilon_{\mathcal{K}}\mathcal{K}_1)^2} \leq 0, \end{aligned}$$

for all $\mathcal{P}, \mathcal{K} > 0, \mathcal{J} \in (0, \mathcal{J}_0)$. Consequently, Condition C6 is also satisfied. Given that Conditions C1-C6 are fulfilled, the conclusions regarding global stability, as outlined in Theorems 2.1 and 2.2, persist. System (40) is associated with the basic reproduction ratio, provided as

$$\begin{aligned} \mathfrak{R}_{0(40)} &= \frac{\mathcal{J}_0(\varpi\psi\rho_{\mathcal{E}} + \eta_{\mathcal{E}}\eta_{\mathcal{K}}\rho_{\mathcal{P}} + \psi\eta_{\mathcal{E}}\rho_{\mathcal{K}})}{\eta_{\mathcal{E}}\eta_{\mathcal{K}}(\psi + \eta_{\mathcal{P}})} \\ &= \mathfrak{R}_{0\mathcal{E}(40)} + \mathfrak{R}_{0\mathcal{P}(40)} + \mathfrak{R}_{0\mathcal{K}(40)}, \end{aligned} \tag{41}$$

where

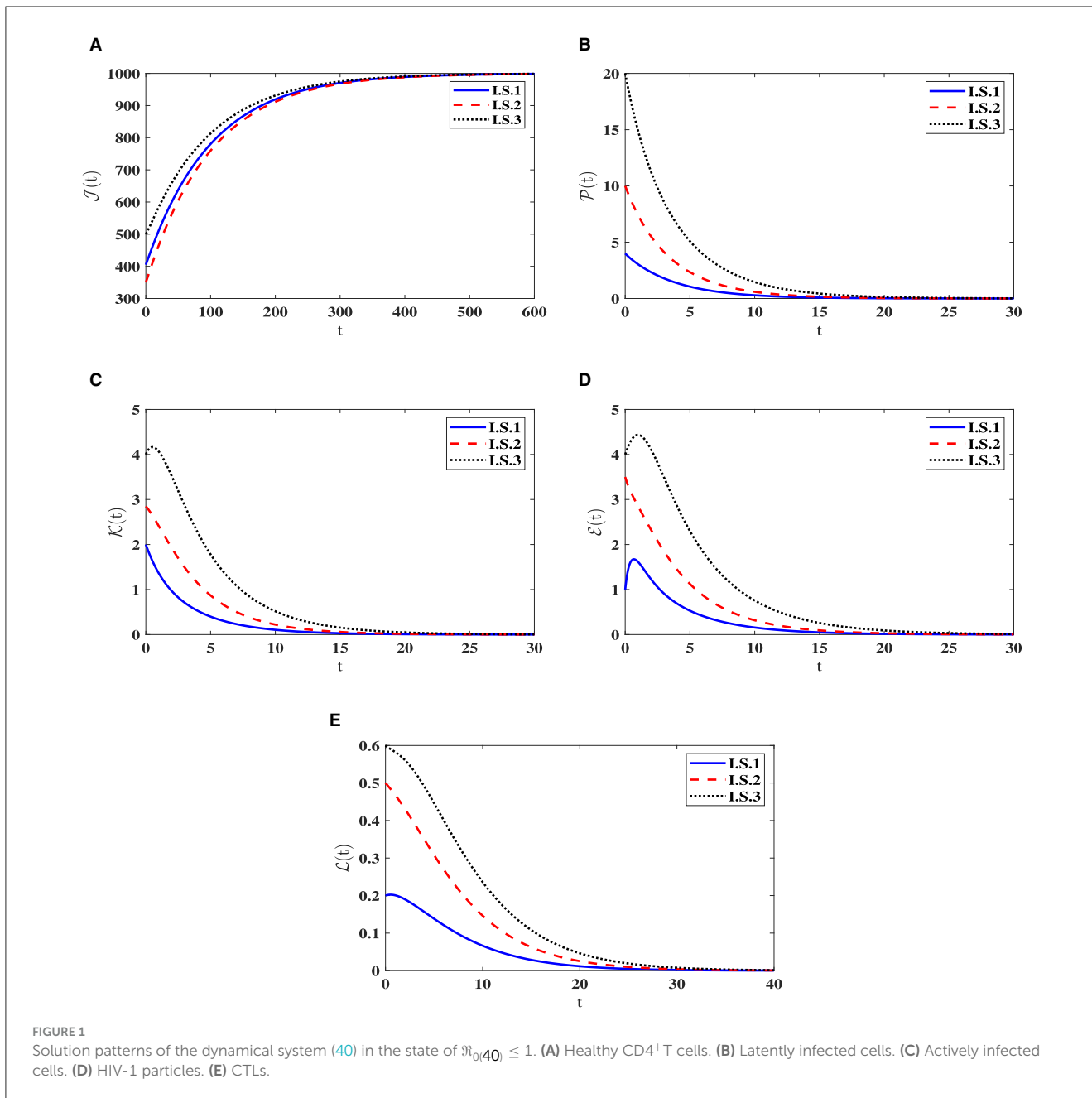
$$\begin{aligned} \mathfrak{R}_{0\mathcal{E}(40)} &= \frac{\varpi\psi\mathcal{J}_0\rho_{\mathcal{E}}}{\eta_{\mathcal{E}}\eta_{\mathcal{K}}(\psi + \eta_{\mathcal{P}})}, \quad \mathfrak{R}_{0\mathcal{P}(40)} = \frac{\mathcal{J}_0\rho_{\mathcal{P}}}{\psi + \eta_{\mathcal{P}}}, \\ \mathfrak{R}_{0\mathcal{K}(40)} &= \frac{\psi\mathcal{J}_0\rho_{\mathcal{K}}}{\eta_{\mathcal{K}}(\psi + \eta_{\mathcal{P}})}. \end{aligned}$$

4.1.1 Stability of steady states

We conduct numerical simulations for the system described in Equation (40), employing the parameter with values outlined

TABLE 1 Summary of model parameters and references.

Parameter	Value	References	Parameter	Value	References
θ	10	[53-55]	ϖ	2.6	[60, 61]
$\eta_{\mathcal{J}}$	0.01	[53, 56, 57]	$\eta_{\mathcal{E}}$	2.4	[60, 61]
$\rho_{\mathcal{E}}$	Varied	-	ξ	0.025	[18, 20]
$\rho_{\mathcal{P}}$	Varied	-	$\eta_{\mathcal{L}}$	0.2	[18, 20]
$\rho_{\mathcal{K}}$	Varied	-	β	Varied	-
ψ	0.2	[53, 58]	$\epsilon_{\mathcal{E}}$	Varied	-
$\eta_{\mathcal{P}}$	0.17	[53, 58]	$\epsilon_{\mathcal{P}}$	varied	-
$\eta_{\mathcal{K}}$	0.8	[20, 59]	$\epsilon_{\mathcal{K}}$	varied	-
ϕ	0.04	[18, 20]			



in Table 1. Several parameters have been drawn from previous research, complemented by specific choices (ρ_Z , β , and $\epsilon = \epsilon_Z$ for $Z \in \{\mathcal{E}, \mathcal{P}, \mathcal{K}\}$) made for this study. For the assessment of steady state stability in system the (40), we commence simulations using three varied sets of initial states:

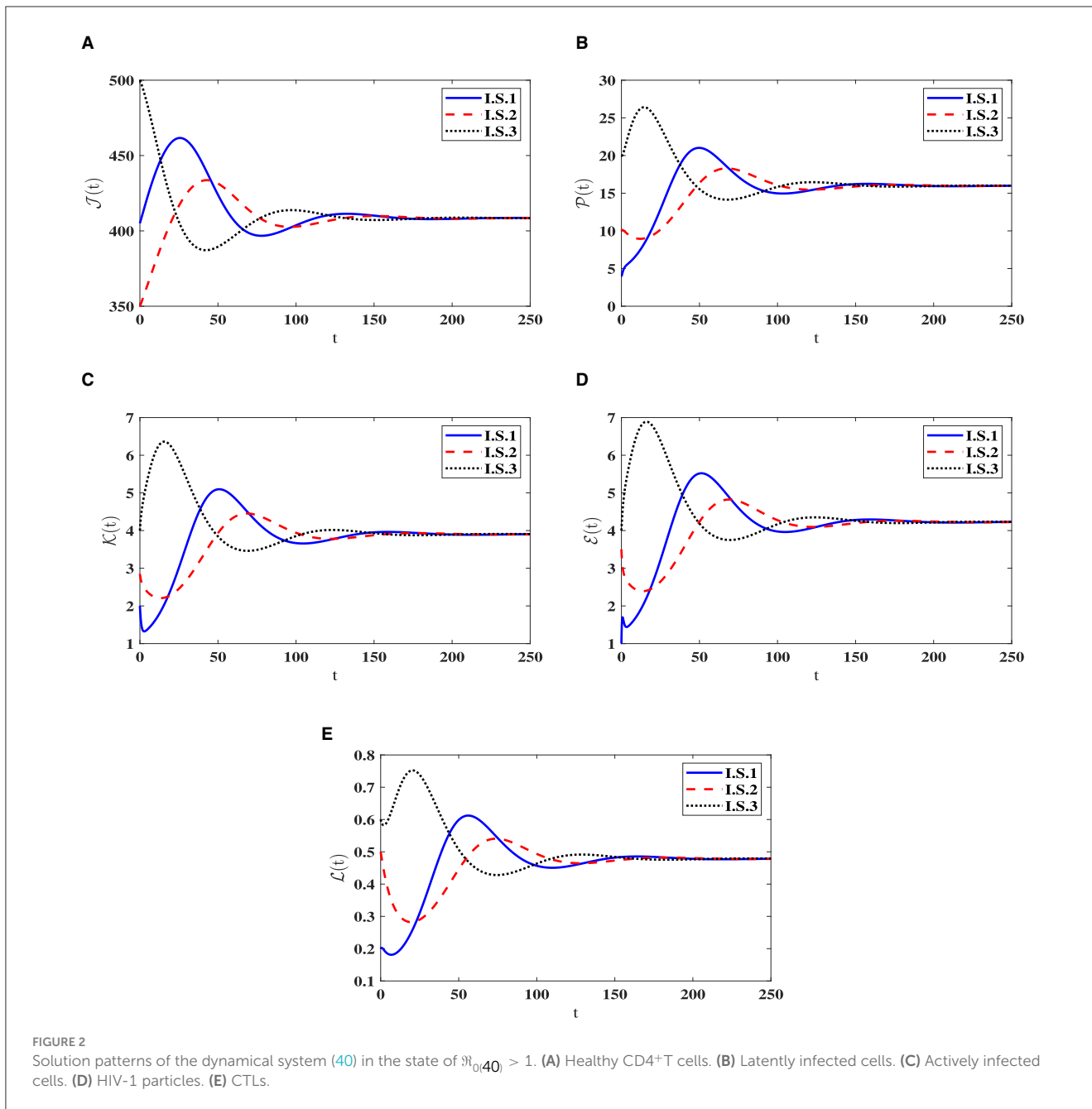
- I.S.1:** $(\mathcal{J}(0), \mathcal{P}(0), \mathcal{K}(0), \mathcal{E}(0), \mathcal{L}(0)) = (405, 4, 2, 1, 0.2)$,
- I.S.2:** $(\mathcal{J}(0), \mathcal{P}(0), \mathcal{K}(0), \mathcal{E}(0), \mathcal{L}(0)) = (350, 10, 2.85, 3.5, 0.5)$,
- I.S.3:** $(\mathcal{J}(0), \mathcal{P}(0), \mathcal{K}(0), \mathcal{E}(0), \mathcal{L}(0)) = (500, 20, 4, 4, 0.6)$.

Utilizing the infection rates ρ_Z for $Z \in \{\mathcal{E}, \mathcal{P}, \mathcal{K}\}$, the stability of steady states is governed by $\mathfrak{R}_0(40)$, as defined in Equation (41). To scrutinize the impact of variations in these parameters, we explore two distinct scenarios:

Stability of $O_0(40)$. For the parameters $\rho_{\mathcal{E}} = 0.0003$, $\rho_{\mathcal{P}} = 0.0001$, $\rho_{\mathcal{K}} = 0.00002$, $\epsilon = 0.02$, and $\beta = 0.001$, the computed

value of $\mathfrak{R}_0(40) = 0.503$ is below 1. As illustrated in Figure 1, the trajectories originating I.S.1-I.S.3 approach the steady state $O_0(40) = (1000, 0, 0, 0, 0)$. This observation reinforces the assertion that $O_0(40)$ is being G.A.S, aligning with the outcome established in Theorem 2.1. Biologically speaking, this situation implies the complete eradication of the infection, signifying the successful elimination of the pathogen by the human body.

Stability of $O_1(40)$. Choosing $\rho_{\mathcal{E}} = 0.003$, $\rho_{\mathcal{P}} = 0.0002$, $\rho_{\mathcal{K}} = 0.0001$, $\epsilon = 0.02$, and $\beta = 0.001$, yields $\mathfrak{R}_0(40) = 2.804 > 1$. Consequently, the steady state $O_1(40)$ exists when $\mathfrak{R}_0(40) > 1$, with specific values given by $O_1(40) = (408.467, 15.987, 3.903, 4.229, 0.479)$. In Figure 2, the numerical results align with the findings of Theorem 2.2, indicating the convergence of solutions for system (40) to $O_1(40)$ when $\mathfrak{R}_0(40) > 1$



across all I.S.1-I.S.3. From a biological standpoint, this situation implies the coexistence of both HIV-1 particles and CTLs within the host organism.

4.1.2 Impact of impaired CTL immunity

In this given context, we introduce fluctuations in the β value while maintaining specific values for $\rho_{\mathcal{E}} = 0.003$, $\rho_{\mathcal{P}} = 0.0002$, $\rho_{\mathcal{K}} = 0.0001$, and $\epsilon = \epsilon_Z = 0.02$, where $Z \in \{\mathcal{E}, \mathcal{P}, \mathcal{K}\}$. We aim to explore how CTL immune impairment impacts the dynamics of the system (40), by obtaining numerical solutions with different β values as provided in Table 2. Under these circumstances, we employ the subsequent initial state:

I.S.4: $(\mathcal{J}(0), \mathcal{P}(0), \mathcal{K}(0), \mathcal{E}(0), \mathcal{L}(0)) = (405, 16.06, 4, 4.3, 0.3)$.

TABLE 2 Effect of the immune impairment parameter of CTLs on system (40).

β	Steady states $O_1(40)$
0	(408.596, 15.984, 3.901, 4.226, 0.488)
0.03	(406.058, 16.053, 3.952, 4.281, 0.31)
0.1	(404, 16.108, 3.994, 4.327, 0.167)
0.9	(401.983, 16.163, 4.035, 4.372, 0.026)

As β increases, we notice a decline in the quantity of CTLs, as shown in Table 2. This decrease is accompanied by a greater quantity of infected cells, whether latent or active, along with a

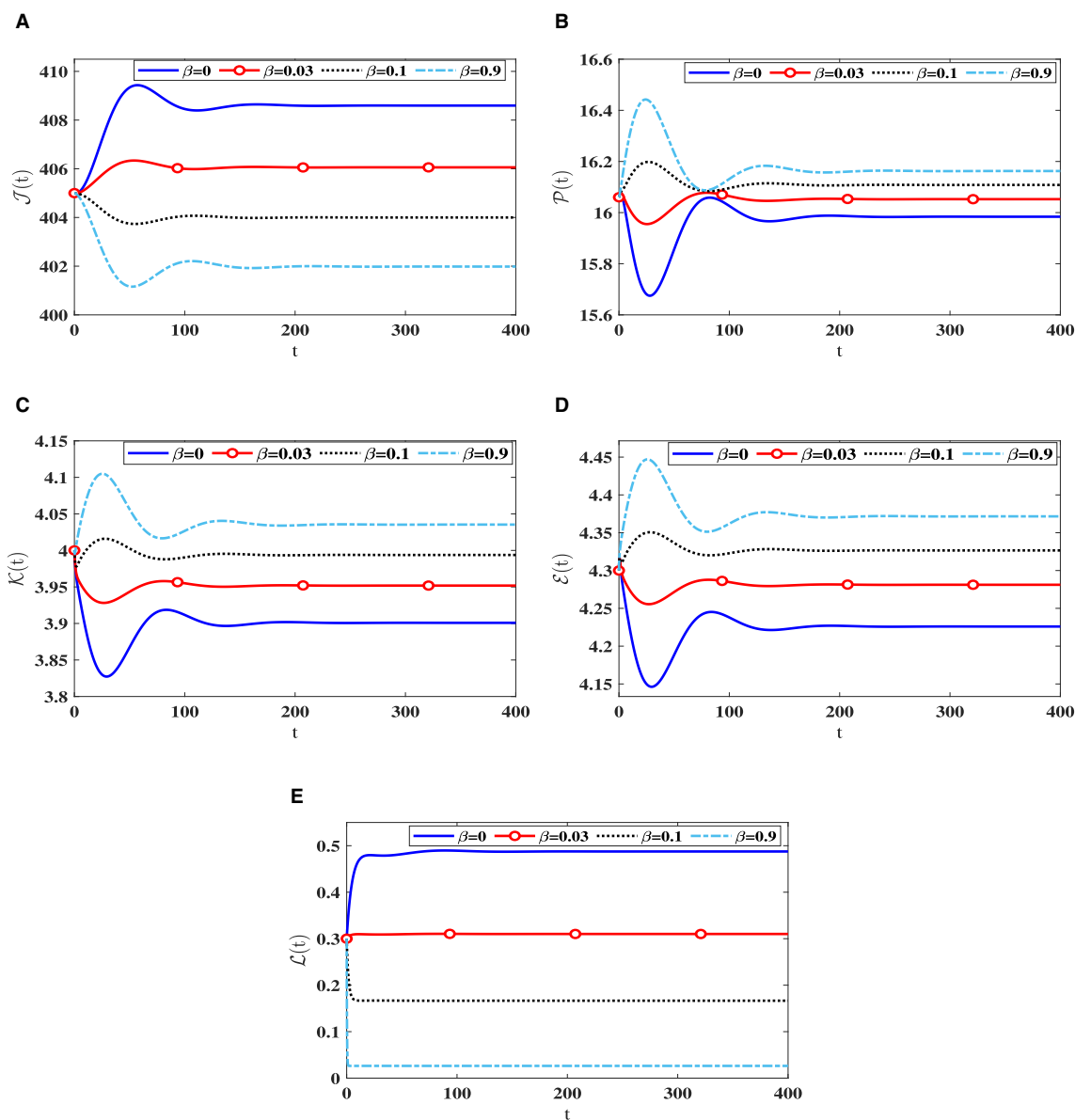


FIGURE 3 Solution patterns of the dynamical system (40) along different β values. (A) Healthy CD4⁺T cells. (B) Latently infected cells. (C) Actively infected cells. (D) HIV-1 particles. (E) CTLs.

higher quantity of HIV-1 particles. Due to this, there is a reduction in the count of healthy cells. Notably, Figure 3 reveals that the stability criteria of the steady states remain unaffected by CTL immune impairment. This is a consequence of the fact that the parameter $\mathfrak{N}_0(40)$ stays constant regardless of varying β values.

4.1.3 The saturation infection rates effect on the system dynamics

In this instance, we fix specific values for $\rho_E = 0.003$, $\rho_P = 0.0002$, $\rho_K = 0.0001$, and $\beta = 0.001$. We numerically solve system (40) with various values of $\epsilon = \epsilon_Z$ for $Z \in \{E, P, K\}$, accompanied by the following initial state:

$$I.S.5: (J(0), P(0), K(0), E(0), L(0)) = (500, 12, 4, 4.3, 0.3).$$

TABLE 3 Exploring system (40) dynamics under the influence of saturation infection rates.

ϵ	Steady states $O_1(40)$
0	(363.974, 17.19, 4.19, 4.539, 0.513)
0.1	(527.349, 12.774, 3.133, 3.394, 0.386)
0.5	(757.406, 6.557, 1.623, 1.758, 0.201)
2	(913.612, 2.335, 0.582, 0.63, 0.072)

Upon examining the results in Table 3, a positive correlation is apparent between ϵ and healthy cells, meaning that when ϵ becomes higher, the concentration of healthy cells becomes

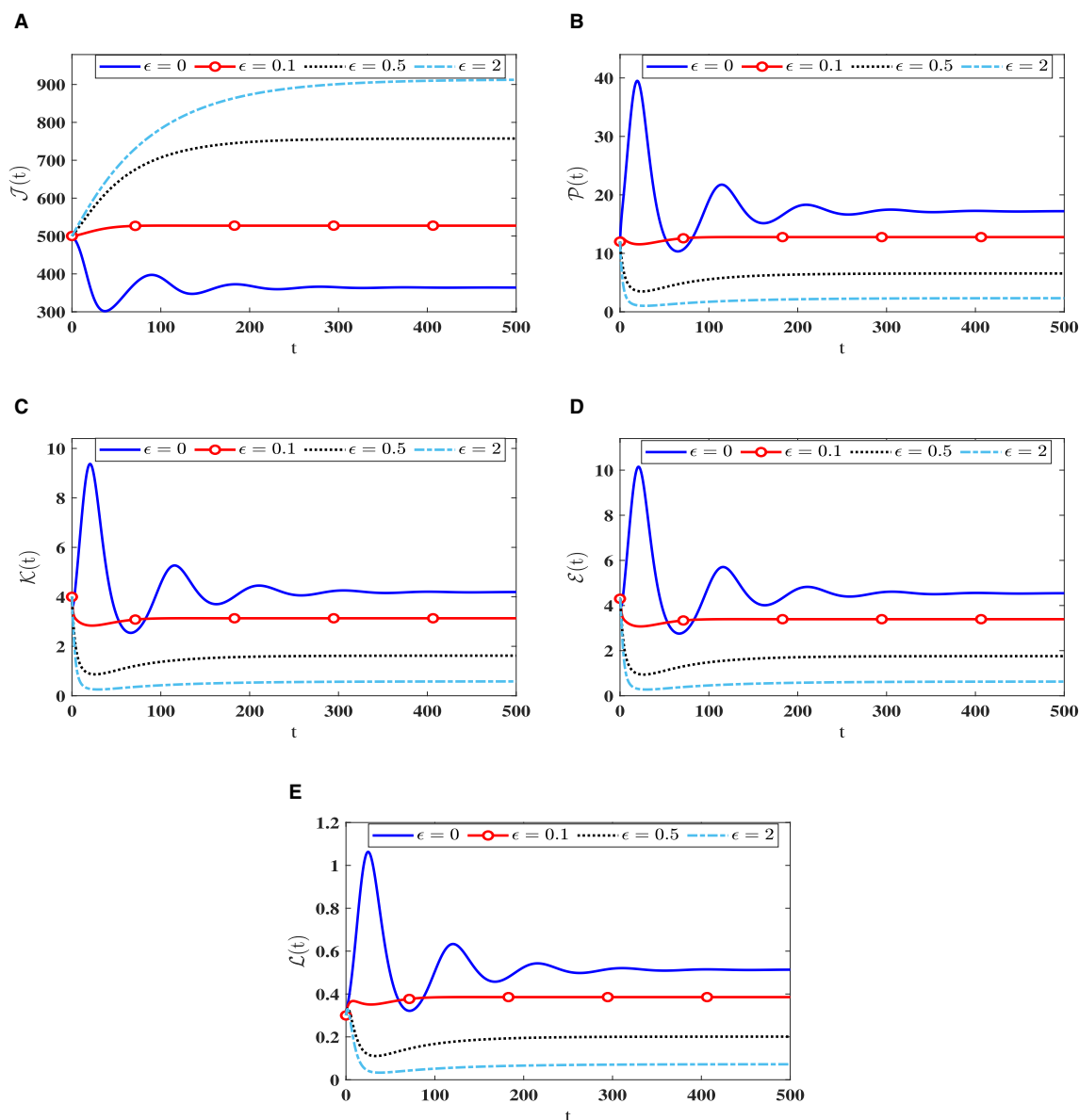


FIGURE 4 The influence of saturation infection rates on the solution patterns in system (40). (A) Healthy CD4⁺T cells. (B) Latently infected cells. (C) Actively infected cells. (D) HIV-1 particles. (E) CTLs.

higher too. In contrast, the counts of other compartments become lower. Notably, the parameter $\mathfrak{M}_{0(40)}$ remains independent of ϵ . Consequently, Figure 4 illustrates that altering ϵ does not have an impact on the steady states' stability.

4.2 Numerical simulation for model (23)

In the context of numerical analysis, we adopt the following specific form regarding the probability distribution functions $\pi_i(r)$, for $i = 1, 2, 3$:

$$\pi_i(r) = \beta_*(r - r_i), \quad r_i \in [0, f_i], \quad i = 1, 2, 3,$$

where $\beta_*(\cdot)$ is the Dirac delta function. When $f_i \rightarrow \infty$, we observe

$$\int_0^\infty \pi_i(r) dr = 1, \quad i = 1, 2, 3.$$

Furthermore, we obtain

$$\Pi_i = \int_0^\infty \beta_*(r - r_i) e^{-b_i r} dr = e^{-b_i r_i}, \quad i = 1, 2, 3.$$

Additionally, we will select the Holling type-II incidence rates of infection as follows:

$$\Upsilon_{\mathcal{E}}(\mathcal{J}, \mathcal{E}) = \frac{\rho_{\mathcal{E}} \mathcal{J} \mathcal{E}}{1 + \vartheta \mathcal{J}}, \quad \Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P}) = \frac{\rho_{\mathcal{P}} \mathcal{J} \mathcal{P}}{1 + \vartheta \mathcal{J}},$$

$$\Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K}) = \frac{\rho_{\mathcal{K}} \mathcal{J} \mathcal{K}}{1 + \vartheta \mathcal{J}},$$

Here, the positive constants ρ_Z for $Z \in \{\mathcal{E}, \mathcal{P}, \mathcal{K}\}$ denote the infection rate constants, while $\vartheta > 0$ represents the Holling infection rate constant. Consequently, Based on the aforementioned reasoning, system (23) was modified into a system with a discrete time delay, as illustrated below:

$$\begin{cases} \dot{\mathcal{J}} &= \theta - \eta_{\mathcal{J}}\mathcal{J} - \frac{\rho_{\mathcal{E}}\mathcal{J}\mathcal{E}}{1 + \vartheta\mathcal{J}} - \frac{\rho_{\mathcal{P}}\mathcal{J}\mathcal{P}}{1 + \vartheta\mathcal{J}} - \frac{\rho_{\mathcal{K}}\mathcal{J}\mathcal{K}}{1 + \vartheta\mathcal{J}}, \\ \dot{\mathcal{P}} &= e^{-b_1r_1} \left(\frac{\rho_{\mathcal{E}}\mathcal{J}(t-r_1)\mathcal{E}(t-r_1)}{1 + \vartheta\mathcal{J}(t-r_1)} \right. \\ &\quad \left. + \frac{\rho_{\mathcal{P}}\mathcal{J}(t-r_1)\mathcal{P}(t-r_1)}{1 + \vartheta\mathcal{J}(t-r_1)} \right. \\ &\quad \left. + \frac{\rho_{\mathcal{K}}\mathcal{J}(t-r_1)\mathcal{K}(t-r_1)}{1 + \vartheta\mathcal{J}(t-r_1)} \right) - (\psi + \eta_{\mathcal{P}})\mathcal{P}, \\ \dot{\mathcal{K}} &= \psi e^{-b_2r_2}\mathcal{P}(t-r_2) - \eta_{\mathcal{K}}\mathcal{K} - \phi\mathcal{L}\mathcal{K}, \\ \dot{\mathcal{E}} &= \varpi e^{-b_3r_3}\mathcal{K}(t-r_3) - \eta_{\mathcal{E}}\mathcal{E}, \\ \dot{\mathcal{L}} &= \xi\mathcal{K} - \eta_{\mathcal{L}}\mathcal{L} - \beta\mathcal{L}\mathcal{K}. \end{cases} \quad (42)$$

The functions $\Upsilon_Z(\mathcal{J}, Z)$ for $Z \in \{\mathcal{E}, \mathcal{P}, \mathcal{K}\}$ are evidently continuously differentiable. Additionally, for each $Z \in \{\mathcal{E}, \mathcal{P}, \mathcal{K}\}$, these functions satisfy the conditions: $\Upsilon_Z(\mathcal{J}, Z) > 0$ and $\Upsilon_Z(0, Z) = \Upsilon_Z(\mathcal{J}, 0) = 0$ for all $\mathcal{J} > 0$ and $Z > 0$. Thus, the fulfillment of Condition C1 is evident. Furthermore, we observe

$$\begin{aligned} \frac{\partial \Upsilon_Z(\mathcal{J}, Z)}{\partial \mathcal{J}} &= \frac{\rho_Z Z}{(1 + \vartheta \mathcal{J})^2} > 0, \quad \text{for all } \mathcal{J}, Z > 0, \\ \frac{\partial \Upsilon_Z(\mathcal{J}, Z)}{\partial Z} &= \frac{\rho_Z \mathcal{J}}{1 + \vartheta \mathcal{J}} > 0, \quad \text{for all } \mathcal{J} > 0, \end{aligned}$$

where $Z \in \{\mathcal{E}, \mathcal{P}, \mathcal{K}\}$. This can be expressed by stating that Condition C2 is valid. It is obvious that

$$\ell_Z(\mathcal{J}) = \frac{\partial \Upsilon_Z(\mathcal{J}, 0)}{\partial Z} = \frac{\rho_Z \mathcal{J}}{1 + \vartheta \mathcal{J}} > 0, \quad \text{for all } \mathcal{J} > 0, Z \in \{\mathcal{E}, \mathcal{P}, \mathcal{K}\}.$$

Furthermore

$$\ell'_Z(\mathcal{J}) = \frac{d}{d\mathcal{J}} \left(\frac{\partial \Upsilon_Z(\mathcal{J}, 0)}{\partial Z} \right) = \frac{\rho_Z}{(1 + \vartheta \mathcal{J})^2} > 0, \quad Z \in \{\mathcal{E}, \mathcal{P}, \mathcal{K}\},$$

which confirms that Condition C3 is also met. Moreover, we have

$$\frac{\partial}{\partial Z} \left(\frac{\Upsilon_Z(\mathcal{J}, Z)}{Z} \right) = 0, \quad Z \in \{\mathcal{E}, \mathcal{P}, \mathcal{K}\}.$$

Hence, the verification of Condition C4 is straightforward. Additionally, it is evident that $\frac{\ell'_Z(\mathcal{J})}{\ell_Z(\mathcal{J})} = \frac{\rho_Z}{\rho_{\mathcal{E}}}$ for $Z \in \{\mathcal{P}, \mathcal{K}\}$. Consequently, Condition C5 is satisfied. Moreover, we have:

$$\begin{aligned} \frac{\Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P})}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \tilde{\mathcal{E}}_1)} &= \frac{\rho_{\mathcal{P}}\mathcal{P}}{\rho_{\mathcal{E}}\tilde{\mathcal{E}}_1}, & \frac{\Upsilon_{\mathcal{P}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{P}}_1)}{\Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{E}}_1)} &= \frac{\rho_{\mathcal{P}}\tilde{\mathcal{P}}_1}{\rho_{\mathcal{E}}\tilde{\mathcal{E}}_1}, \\ \frac{\Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K})}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \tilde{\mathcal{E}}_1)} &= \frac{\rho_{\mathcal{K}}\mathcal{K}}{\rho_{\mathcal{E}}\tilde{\mathcal{E}}_1}, & \frac{\Upsilon_{\mathcal{K}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{K}}_1)}{\Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{E}}_1)} &= \frac{\rho_{\mathcal{K}}\tilde{\mathcal{K}}_1}{\rho_{\mathcal{E}}\tilde{\mathcal{E}}_1}, \end{aligned}$$

and

$$\left(\frac{\Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P})}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \tilde{\mathcal{E}}_1)\mathcal{P}} - \frac{\Upsilon_{\mathcal{P}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{P}}_1)}{\Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{E}}_1)\tilde{\mathcal{P}}_1} \right)$$

TABLE 4 Analyzing the influence of delay parameters, r_i , on System (42).

Delay parameters r_1, r_2, r_3	Steady states	$\tilde{\mathfrak{R}}_0(42)$
0.003, 0.001, 0.002	$\tilde{O}_1(42) = (388.427, 16.524, 4.031, 4.364, 0.494)$	2.485
0.01, 0.02, 0.03	$\tilde{O}_1(42) = (392.726, 16.396, 3.985, 4.279, 0.488)$	2.459
0.8, 0.6, 0.7	$\tilde{O}_1(42) = (554.534, 11.114, 2.428, 2.132, 0.3)$	1.753
1.189, 1.5, 2.5	$\tilde{O}_0(42) = (1000, 0, 0, 0, 0)$	1
3, 4, 5	$\tilde{O}_0(42) = (1000, 0, 0, 0, 0)$	0.412
5, 6, 7	$\tilde{O}_0(42) = (1000, 0, 0, 0, 0)$	0.239

$$\begin{aligned} &\times \left(\frac{\Upsilon_{\mathcal{P}}(\mathcal{J}, \mathcal{P})}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \tilde{\mathcal{E}}_1)} - \frac{\Upsilon_{\mathcal{P}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{P}}_1)}{\Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{E}}_1)} \right) = 0, \\ &\left(\frac{\Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K})}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \tilde{\mathcal{E}}_1)\mathcal{K}} - \frac{\Upsilon_{\mathcal{K}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{K}}_1)}{\Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{E}}_1)\tilde{\mathcal{K}}_1} \right) \\ &\times \left(\frac{\Upsilon_{\mathcal{K}}(\mathcal{J}, \mathcal{K})}{\Upsilon_{\mathcal{E}}(\mathcal{J}, \tilde{\mathcal{E}}_1)} - \frac{\Upsilon_{\mathcal{K}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{K}}_1)}{\Upsilon_{\mathcal{E}}(\tilde{\mathcal{J}}_1, \tilde{\mathcal{E}}_1)} \right) = 0, \end{aligned}$$

for all $\mathcal{P}, \mathcal{K} > 0, \mathcal{J} \in (0, \tilde{\mathcal{J}}_0)$. Hence, Condition C6 is fulfilled as well. With the fulfillment of Conditions C1–C6, the global stability results stated in Theorems 3.1 and 3.2 persist. Accordingly, the determination of the basic reproduction ratio for system (42) is outlined below:

$$\begin{aligned} \tilde{\mathfrak{R}}_0(42) &= \frac{\tilde{\mathcal{J}}_0 e^{-b_1r_1} \left(\psi e^{-b_2r_2} \left(\rho_{\mathcal{E}} \varpi e^{-b_3r_3} + \rho_{\mathcal{K}} \eta_{\mathcal{E}} \right) + \rho_{\mathcal{P}} \eta_{\mathcal{E}} \eta_{\mathcal{K}} \right)}{\eta_{\mathcal{E}} \eta_{\mathcal{K}} (\psi + \eta_{\mathcal{P}}) (1 + \vartheta \tilde{\mathcal{J}}_0)} \\ &= \tilde{\mathfrak{R}}_{0\mathcal{E}}(42) + \tilde{\mathfrak{R}}_{0\mathcal{P}}(42) + \tilde{\mathfrak{R}}_{0\mathcal{K}}(42), \end{aligned} \quad (43)$$

where

$$\begin{aligned} \tilde{\mathfrak{R}}_{0\mathcal{E}}(42) &= \frac{\varpi \psi \tilde{\mathcal{J}}_0 \rho_{\mathcal{E}} e^{-b_1r_1 - b_2r_2 - b_3r_3}}{\eta_{\mathcal{E}} \eta_{\mathcal{K}} (\psi + \eta_{\mathcal{P}}) (1 + \vartheta \tilde{\mathcal{J}}_0)}, \\ \tilde{\mathfrak{R}}_{0\mathcal{P}}(42) &= \frac{\tilde{\mathcal{J}}_0 \rho_{\mathcal{P}} e^{-b_1r_1}}{(\psi + \eta_{\mathcal{P}}) (1 + \vartheta \tilde{\mathcal{J}}_0)}, \\ \tilde{\mathfrak{R}}_{0\mathcal{K}}(42) &= \frac{\psi \tilde{\mathcal{J}}_0 \rho_{\mathcal{K}} e^{-b_1r_1 - b_2r_2}}{\eta_{\mathcal{K}} (\psi + \eta_{\mathcal{P}}) (1 + \vartheta \tilde{\mathcal{J}}_0)}. \end{aligned}$$

4.2.1 The stability implications of time delays on steady states

To assess how time delay parameters affect the solutions of system (42), we maintain constant values for parameters $\rho_{\mathcal{E}} = 0.003, \rho_{\mathcal{P}} = 0.0001, \rho_{\mathcal{K}} = 0.0004, \beta = 0.001, b_1 = 0.1, b_2 = 0.2, b_3 = 0.3$, and set $\vartheta = 0.0001$. Furthermore, you can refer to Table 1 for the values of the other parameters. Next, we examine how the dynamics are affected by experimenting with different

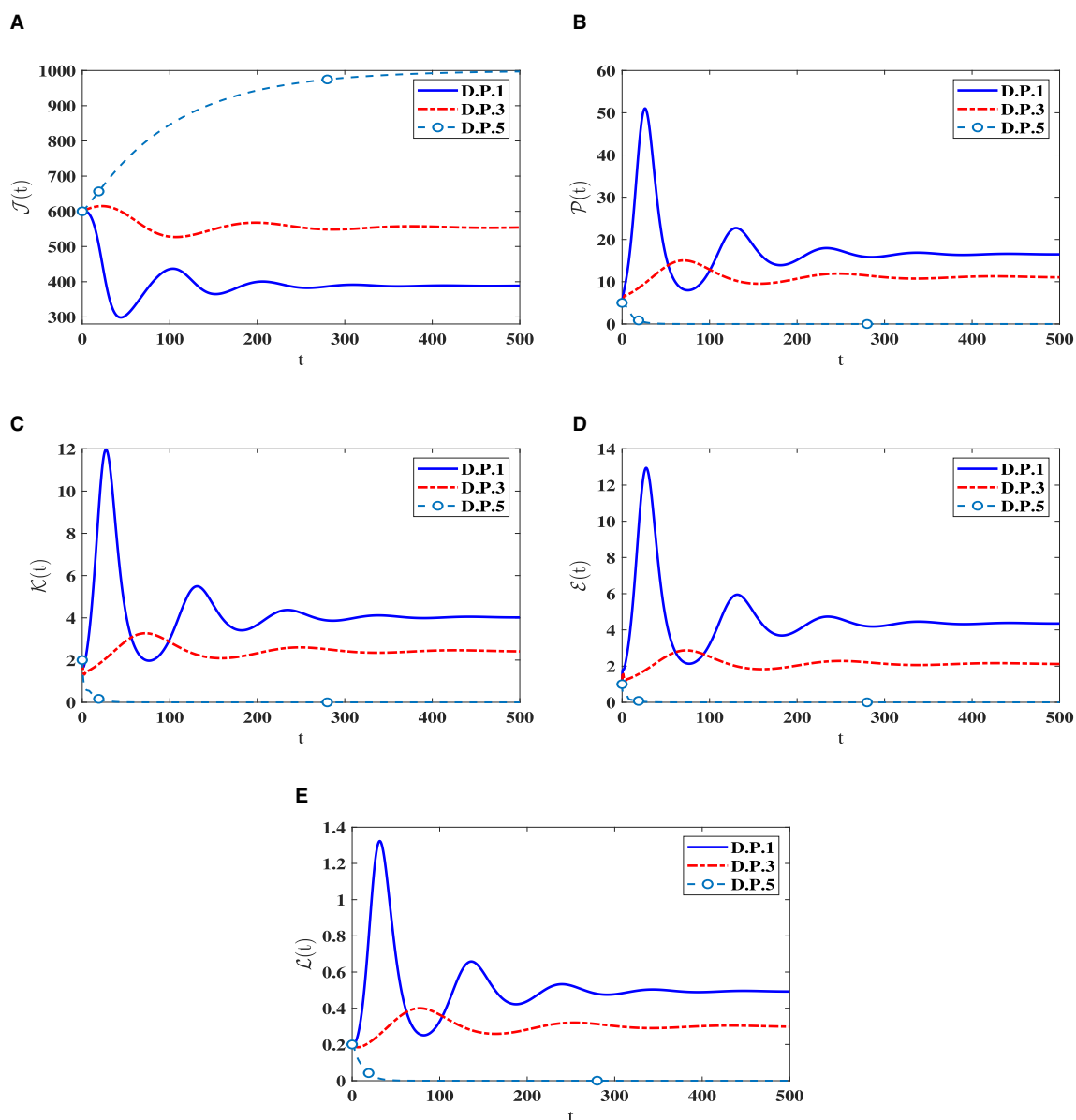


FIGURE 5 The influence of r_i on the solution patterns in system (42). (A) Healthy CD4⁺T cells. (B) Latently infected cells. (C) Actively infected cells. (D) HIV-1 particles. (E) CTLs.

variations of the delay parameters r_i , where i takes values from 1 to 3. The stability of steady states is highly sensitive to changes in the parameters r_i due to the dependence of $\tilde{\mathfrak{H}}_0(42)$ on them [as indicated in Equation (43)]. Let's delve into the following choices for the delay parameters:

- D.P.1: $r_1 = 0.003, r_2 = 0.001, r_3 = 0.002$.
- D.P.2: $r_1 = 0.01, r_2 = 0.02, r_3 = 0.03$.
- D.P.3: $r_1 = 0.8, r_2 = 0.6, r_3 = 0.7$.
- D.P.4: $r_1 = 1.189, r_2 = 1.5, r_3 = 2.5$.
- D.P.5: $r_1 = 3, r_2 = 4, r_3 = 5$.
- D.P.6: $r_1 = 5, r_2 = 6, r_3 = 7$.

We address the initial state for solving system (42) as follows:

I.S.6: $(\mathcal{J}(v), \mathcal{P}(v), \mathcal{K}(v), \mathcal{E}(v), \mathcal{L}(v)) = (600, 5, 2, 1, 0.2), v \in [-r, 0], r = \max\{r_1, r_2, r_3\}$.

Table 4 displays the values of $\tilde{\mathfrak{H}}_0(42)$ corresponding to different r_i values, where $i = 1, 2, 3$. Significantly reducing $\tilde{\mathfrak{H}}_0(42)$ is noteworthy when the r_i parameters increase. Figure 5 visually depicts the numerical solutions derived from the system, emphasizing the significant impact of the included time-delays. Specifically, a positive correlation exists between r_i and the count of healthy cells, indicating that their values increase simultaneously, while a decrease is observed in the counts of other compartments. This suggests the potential creation of a new category of medication aimed at extending delay times and ultimately mitigating HIV-1 multiplication.

TABLE 5 The dynamics of system (42) affected by Holling infection rates.

ϑ	Steady states	$\tilde{\mathfrak{R}}_0(42)$
0.00001	$\tilde{O}_1(42) = (375.501, 16.875, 4.113, 4.454, 0.504)$	2.707
0.00084	$\tilde{O}_1(42) = (541.024, 12.402, 3.042, 3.294, 0.375)$	1.486
0.0014	$\tilde{O}_1(42) = (763.525, 6.39, 1.581, 1.712, 0.196)$	1.139
0.0017336	$\tilde{O}_0(42) = (1000, 0, 0, 0, 0)$	1
0.02	$\tilde{O}_0(42) = (1000, 0, 0, 0, 0)$	0.13

4.2.2 The Holling type-II infection rates effect on the system dynamics

In this scenario, we set $\rho_E = 0.003, \rho_P = 0.0001, \rho_K = 0.0004, b_1 = 0.1, b_2 = 0.2, b_3 = 0.3, \beta = 0.001$, and $r_i = 0.002$ for $i = 1, 2, 3$. We consider different values of ϑ and numerically solve system (42) with the initial state I.S.6 to analyze the impact of Holling infection rates on the dynamics of the system (42). Analyzing Table 5 reveals a correlation wherein an augmentation in ϑ leads to an increase in the count of healthy cells, while there is a reduction in the counts of other compartments. Clearly, the parameter $\tilde{\mathfrak{R}}_0(42)$ depends on ϑ . Therefore, Figure 6 confirms that the Holling infection alters the stability properties of steady states. Furthermore, we derive the subsequent observations:

- $\tilde{O}_1(42)$ is being G.A.S under the condition $0 < \vartheta < 0.0017336$.
- $\tilde{O}_0(42)$ is being G.A.S under the condition $\vartheta \geq 0.0017336$.

4.3 Analysis of parameter sensitivity

4.3.1 Investigating the sensitivity of parameters for model (40)

The principal goal of analyzing parameter sensitivity is to determine the variable that has the most substantial impact on \mathfrak{R}_0 , which should be the focus of control strategies. To achieve this, we will employ direct differentiation, a method that calculates sensitivity indices by considering changes in variables based on parameters. We can define the normalized forward sensitivity index of \mathfrak{R}_0 , which depends on the differentiability with respect to a parameter ϱ , as follows:

$$S_\varrho = \frac{\varrho}{\mathfrak{R}_0} \frac{\partial \mathfrak{R}_0}{\partial \varrho}. \tag{44}$$

For each parameter belonging to $\mathfrak{R}_0(40)$, we utilized Equation (44) to compute the sensitivity index values. For this purpose, we considered the parameters specified in Table 1, while also incorporating supplementary values for $\rho_E = 0.003, \rho_P = 0.0002$, and $\rho_K = 0.0001$. Sensitivity index values for $\mathfrak{R}_0(40)$ are showcased in Table 6 and Figure 7, revealing positive index values for $\theta, \rho_E, \rho_P, \rho_K, \varpi$, and ψ . In this context, higher values of these parameters correspond to a higher prevalence of HIV-1 infection within this population. In contrast, the remaining indices show negativity, implying that an increase in η_J, η_P, η_K , and η_E corresponds to a reduction in the $\mathfrak{R}_0(40)$ value. Notably, the parameters θ, ρ_E , and ϖ emerge as the pivotal factors in terms

of sensitivity, whereas ρ_P, ρ_K , and ψ are considered less critical. Interestingly, the parameter ξ , representing CTLs responsiveness, demonstrates no impact on $\mathfrak{R}_0(40)$.

4.3.2 Investigating the sensitivity of parameters for model (42)

Here, Equation (44) will be applied to calculate sensitivity indices concerning $\tilde{\mathfrak{R}}_0(42)$, considering each parameter contributing to the basic reproduction ratio. The calculations were performed with the parameters specified in Table 1, supplemented by the inclusion of the additional parameters: $\rho_E = 0.003, \rho_P = 0.0001, \rho_K = 0.0004, b_1 = 0.1, b_2 = 0.2, b_3 = 0.3, r_1 = 0.8, r_2 = 0.6, r_3 = 0.7$, and $\vartheta = 0.0001$. The sensitivity index values for $\tilde{\mathfrak{R}}_0(42)$ are presented in Table 7, and Figure 8 provides a graphical representation. Positive indices for $\theta, \rho_E, \rho_P, \rho_K, \varpi$, and ψ suggest that an increase in these values will elevate the prevalence of HIV-1 disease. Conversely, negative indices, including $\eta_J, \eta_P, \eta_K, \eta_E, b_1, b_2, b_3, r_1, r_2, r_3$, and ϑ , indicate that an increase in these values will lower the parameter $\tilde{\mathfrak{R}}_0(42)$. Notably, θ, ρ_E , and ϖ emerge as the most influential parameters, while ρ_P, ρ_K , and ψ are considered less critical. Furthermore, the parameter representing CTLs responsiveness, ξ , demonstrates no discernible effect on $\tilde{\mathfrak{R}}_0(42)$.

5 Discussion

To emphasize the importance of integrating L-CTC spread into our investigated models, we analyze model (3) in the context of various antiviral interventions, outlined as follows:

$$\begin{cases} \dot{J} = \theta - \eta_J J - (1 - \varsigma_1) \Upsilon_E(J, E) - (1 - \varsigma_2) \Upsilon_P(J, P) \\ \quad - (1 - \varsigma_3) \Upsilon_K(J, K), \\ \dot{P} = (1 - \varsigma_1) \Upsilon_E(J, E) + (1 - \varsigma_2) \Upsilon_P(J, P) \\ \quad + (1 - \varsigma_3) \Upsilon_K(J, K) - (\psi + \eta_P) P, \\ \dot{K} = \psi P - \eta_K K - \phi L K, \\ \dot{E} = \varpi K - \eta_E E, \\ \dot{L} = \xi K - \eta_L L - \beta L K. \end{cases} \tag{45}$$

The parameter $0 \leq \varsigma_1 \leq 1$ represents the effectiveness of antiviral therapy in inhibiting VTC transmission, while $0 \leq \varsigma_2, \varsigma_3 \leq 1$ denote the therapeutic efficacies in blocking L-CTC and A-CTC transmissions, respectively [62].

For system (45), the following establishes the basic reproduction ratio:

$$\mathfrak{R}_0 = \frac{(1 - \varsigma_1) \varpi \psi}{\eta_E \eta_K (\psi + \eta_P)} \frac{\partial \Upsilon_E(J_0, 0)}{\partial E} + \frac{(1 - \varsigma_2) \partial \Upsilon_P(J_0, 0)}{\psi + \eta_P} \frac{\partial \Upsilon_P}{\partial P} + \frac{(1 - \varsigma_3) \psi}{\eta_K (\psi + \eta_P)} \frac{\partial \Upsilon_K(J_0, 0)}{\partial K}.$$

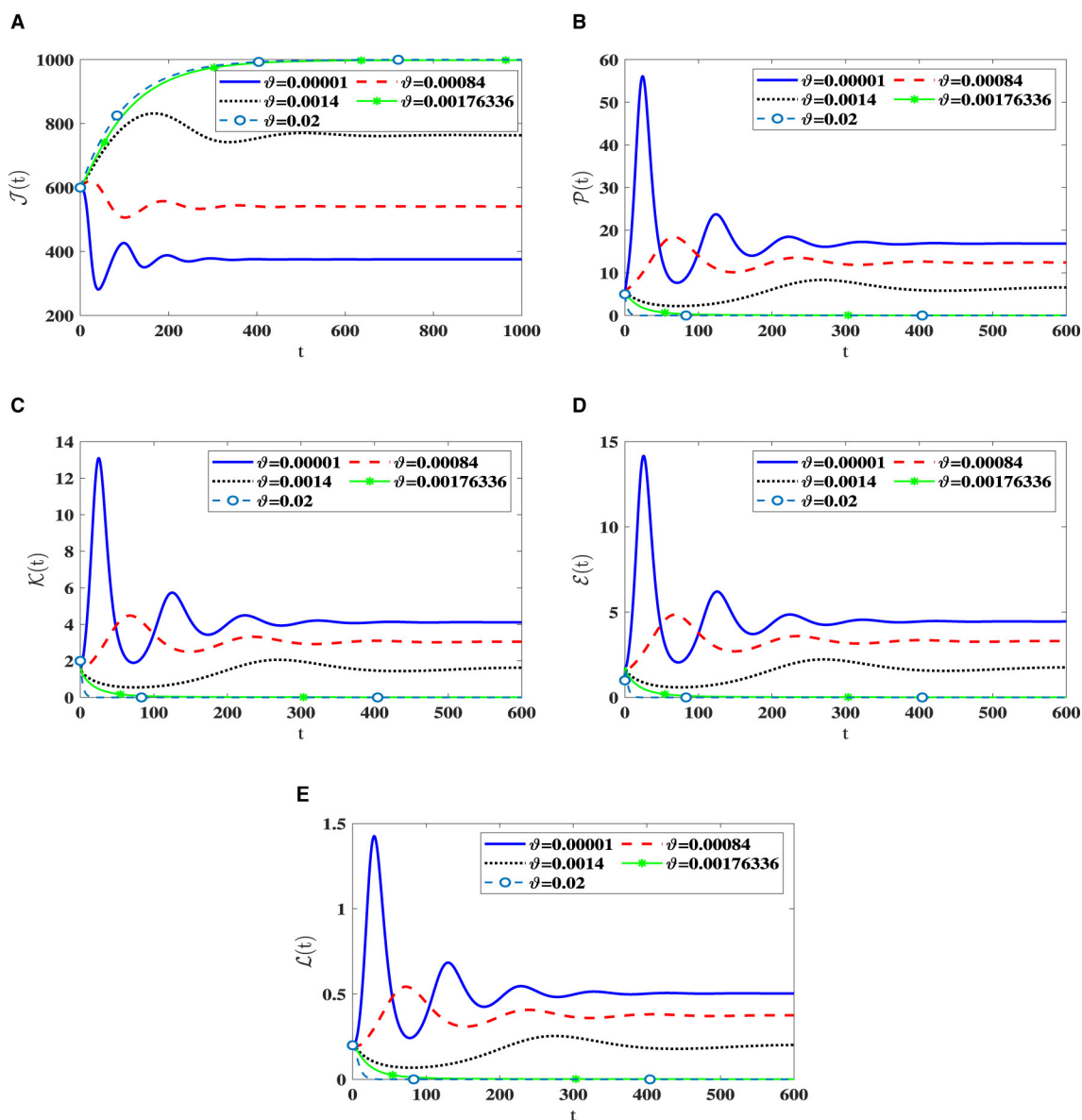


FIGURE 6 The influence of Holling infection rates on the solution patterns in system (42). (A) Healthy CD4⁺T cells. (B) Latently infected cells. (C) Actively infected cells. (D) HIV-1 particles. (E) CTLs.

Assuming ζ to be equal to ζ_1 , ζ_2 , and ζ_3 , we obtain:

$$\mathfrak{R}_0^\zeta = (1 - \zeta) \left[\frac{\varpi \psi}{\eta_\varepsilon \eta_\kappa (\psi + \eta_P)} \frac{\partial \Upsilon_\varepsilon(\mathcal{J}_0, 0)}{\partial \varepsilon} + \frac{1}{\psi + \eta_P} \frac{\partial \Upsilon_P(\mathcal{J}_0, 0)}{\partial P} + \frac{\psi}{\eta_\kappa (\psi + \eta_P)} \frac{\partial \Upsilon_\kappa(\mathcal{J}_0, 0)}{\partial \kappa} \right] = (1 - \zeta) \mathfrak{R}_0.$$

Currently, we compute the drug efficacy, ζ , which results in $\mathfrak{R}_0^\zeta < 1$ and stabilizes O_0 in system (45) as follows:

$$1 \geq \zeta > \tilde{\zeta}_{\min} = \max \left\{ 0, 1 - \frac{1}{\mathfrak{R}_0} \right\}. \tag{46}$$

Neglecting the spread of L-CTC in model (45) yields

$$\begin{cases} \dot{\mathcal{J}} = \theta - \eta_{\mathcal{J}} \mathcal{J} - (1 - \zeta) \Upsilon_\varepsilon(\mathcal{J}, \varepsilon) - (1 - \zeta) \Upsilon_\kappa(\mathcal{J}, \kappa), \\ \dot{\mathcal{P}} = (1 - \zeta) \Upsilon_\varepsilon(\mathcal{J}, \varepsilon) + (1 - \zeta) \Upsilon_\kappa(\mathcal{J}, \kappa) - (\psi + \eta_P) \mathcal{P}, \\ \dot{\mathcal{K}} = \psi \mathcal{P} - \eta_\kappa \mathcal{K} - \phi \mathcal{L} \mathcal{K}, \\ \dot{\mathcal{E}} = \varpi \mathcal{K} - \eta_\varepsilon \mathcal{E}, \\ \dot{\mathcal{L}} = \xi \mathcal{K} - \eta_{\mathcal{L}} \mathcal{L} - \beta \mathcal{L} \mathcal{K}, \end{cases} \tag{47}$$

and the definition of the basic reproduction ratio of model (47) will be

$$\hat{\mathfrak{R}}_0^\zeta = (1 - \zeta) \left[\frac{\varpi \psi}{\eta_\varepsilon \eta_\kappa (\psi + \eta_P)} \frac{\partial \Upsilon_\varepsilon(\mathcal{J}_0, 0)}{\partial \varepsilon} + \frac{\psi}{\eta_\kappa (\psi + \eta_P)} \frac{\partial \Upsilon_\kappa(\mathcal{J}_0, 0)}{\partial \kappa} \right] = (1 - \zeta) \hat{\mathfrak{R}}_0.$$

TABLE 6 Examining sensitivity in parameters regarding $\mathfrak{R}_0(40)$.

Parameter ϱ	S_{ϱ}	Value	Parameter ϱ	S_{ϱ}	Value
θ	S_{θ}	1	ϖ	S_{ϖ}	0.783
$\eta_{\mathcal{J}}$	$S_{\eta_{\mathcal{J}}}$	-1	ψ	S_{ψ}	0.267
$\rho_{\mathcal{E}}$	$S_{\rho_{\mathcal{E}}}$	0.783	$\eta_{\mathcal{E}}$	$S_{\eta_{\mathcal{E}}}$	-0.783
$\rho_{\mathcal{P}}$	$S_{\rho_{\mathcal{P}}}$	0.193	$\eta_{\mathcal{P}}$	$S_{\eta_{\mathcal{P}}}$	-0.459
$\rho_{\mathcal{K}}$	$S_{\rho_{\mathcal{K}}}$	0.024	$\eta_{\mathcal{K}}$	$S_{\eta_{\mathcal{K}}}$	-0.807

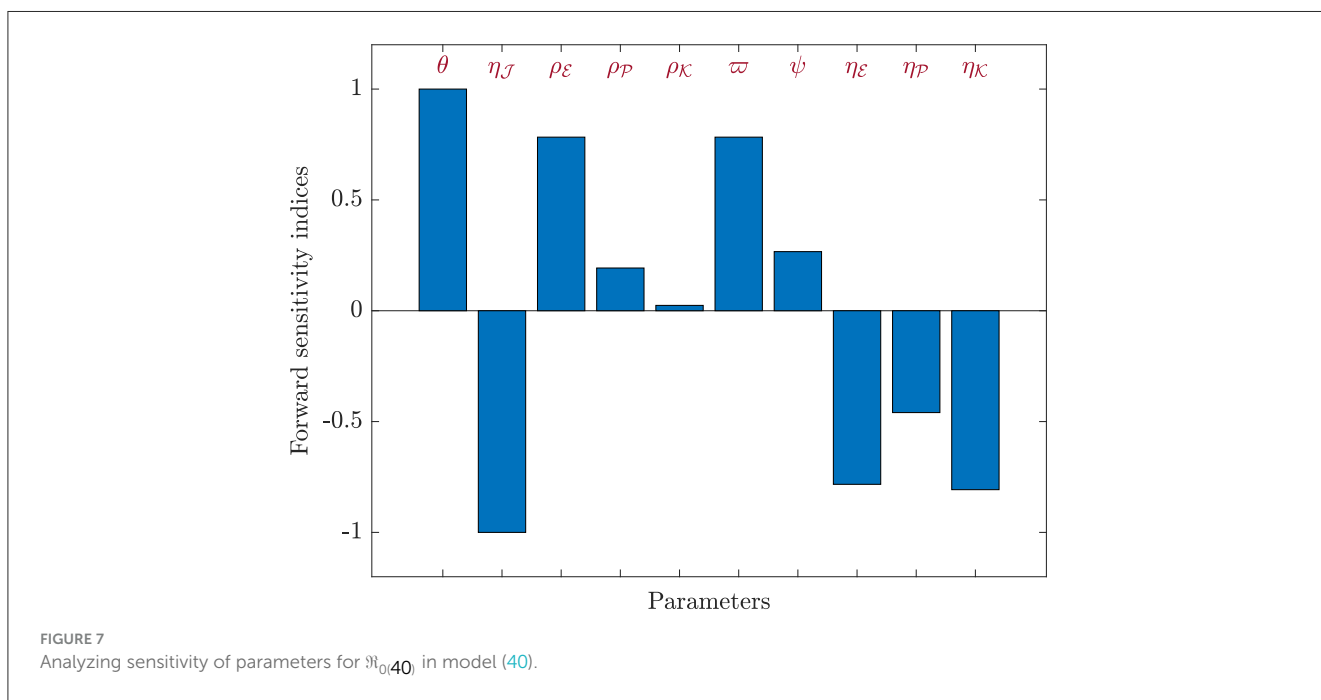


TABLE 7 Examining sensitivity in parameters regarding $\tilde{\mathfrak{R}}_0(42)$.

Parameter ϱ	S_{ϱ}	Value	Parameter ϱ	S_{ϱ}	Value
θ	S_{θ}	0.909	$\eta_{\mathcal{K}}$	$S_{\eta_{\mathcal{K}}}$	-0.871
$\eta_{\mathcal{J}}$	$S_{\eta_{\mathcal{J}}}$	-0.909	b_1	S_{b_1}	-0.08
$\rho_{\mathcal{E}}$	$S_{\rho_{\mathcal{E}}}$	0.756	b_2	S_{b_2}	-0.104
$\rho_{\mathcal{P}}$	$S_{\rho_{\mathcal{P}}}$	0.129	b_3	S_{b_3}	-0.159
$\rho_{\mathcal{K}}$	$S_{\rho_{\mathcal{K}}}$	0.115	r_1	S_{r_1}	-0.08
ϖ	S_{ϖ}	0.756	r_2	S_{r_2}	-0.104
ψ	S_{ψ}	0.33	r_3	S_{r_3}	-0.159
$\eta_{\mathcal{E}}$	$S_{\eta_{\mathcal{E}}}$	-0.756	ϑ	S_{ϑ}	-0.091
$\eta_{\mathcal{P}}$	$S_{\eta_{\mathcal{P}}}$	-0.459			

We identify the drug efficacy, denoted as ς , that ensures $\hat{\mathfrak{R}}_0^{\varsigma} < 1$, thereby stabilizing the steady state O_0 of system (47). The condition is expressed as:

$$1 \geq \varsigma > \hat{\varsigma}_{\min} = \max \left\{ 0, 1 - \frac{1}{\hat{\mathfrak{R}}_0} \right\}. \tag{48}$$

It is evident that $\hat{\mathfrak{R}}_0 < \mathfrak{R}_0$. Interestingly, comparing Equations (46, 48) reveal that $\hat{\varsigma}_{\min}$ is always smaller than $\tilde{\varsigma}_{\min}$. Therefore, applying drugs with efficacy ς in case of $\hat{\varsigma}_{\min} \leq \varsigma < \tilde{\varsigma}_{\min}$ will guarantee that $\hat{\mathfrak{R}}_0^{\varsigma} < 1$, ensuring the global asymptotic stability of O_0 in the system (47). However, $\mathfrak{R}_0^{\varsigma} > 1$, indicating the instability of O_0 in system (45). As a result, drug therapies are designed without considering the spread of L-CTC may be inaccurate or insufficient for achieving

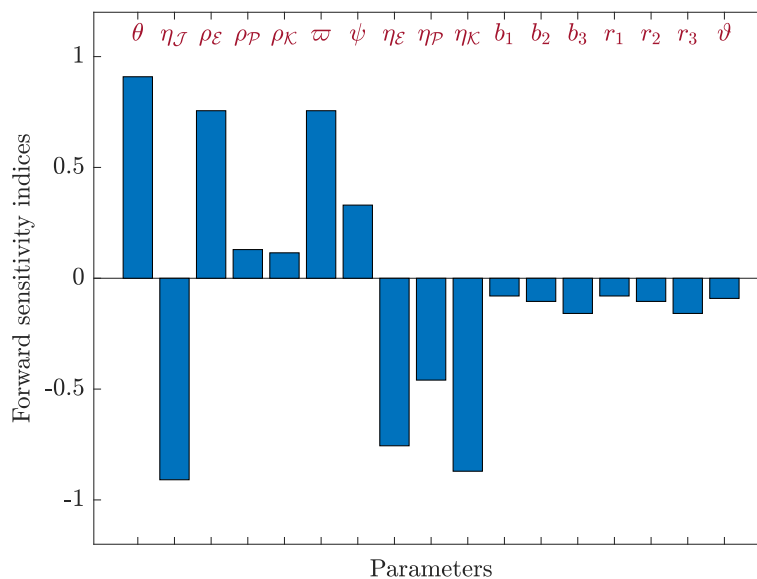


FIGURE 8 Analyzing sensitivity of parameters for $\tilde{\mathfrak{R}}_0(42)$ in model (42).

viral eradication from the body. Therefore, compared to the model given in Alofi and Azoz [24] and Zhang and Xu [25], our suggested models are more pertinent in explaining HIV-1 infections.

6 Conclusion

This work formulates two HIV-1 dynamics models with CTL immune impairment. These models comprise five compartments: healthy CD4⁺T cells, latently infected cells, actively infected cells, free HIV-1 and CTLs. To enhance realism, we introduced a scenario in which healthy cells acquire susceptibility to infection upon exposure to infectious compartments (HIV-1 particles, latently infected cells and actively infected cells). The second model takes the first model a step further by incorporating multiple distributed-time delays. Both models incorporate general functions to represent the incidence rates. Notably, the solutions produced by these models display properties of nonnegativity and boundedness. Within this framework, we identified two crucial steady states: the virus-free steady state, O_0 (\tilde{O}_0), and the virus-persistence steady state, O_1 (\tilde{O}_1). We calculated the basic reproduction ratios, referred to as \mathfrak{R}_0 ($\tilde{\mathfrak{R}}_0$), which are essential for determining whether the steady states mentioned earlier exist and remain stable over time. It is noteworthy that \mathfrak{R}_0 ($\tilde{\mathfrak{R}}_0$) consists of three separate components, representing the contributions from VTC, L-CTC, and A-CTC. The Lyapunov function technique and L.I.P. are employed to comprehend the system's behavior over time by studying the global asymptotic stability of the steady states. Two key findings emerged from our investigation: firstly, the virus-free steady state O_0 (\tilde{O}_0) is being G.A.S whenever $\mathfrak{R}_0 < 1$ ($\tilde{\mathfrak{R}}_0 < 1$), ultimately leading to the disappearance of the infection. In contrast, the steady state O_0 (\tilde{O}_0) loses its stability and the virus-persistence steady state O_1 (\tilde{O}_1) is being G.A.S whenever $\mathfrak{R}_0 > 1$ ($\tilde{\mathfrak{R}}_0 > 1$), indicating a long-term infection. For experimental verification of

our theoretical derivations, we employed numerical simulations, which yielded results consistent with our analytical solutions. Our exploration encompassed the influence of CTL immune impairment, time delays, and L-CTC on HIV-1 dynamics, revealing reduced immune function as a key factor contributing significantly to disease progression. Moreover, time delays significantly reduced the basic reproduction ratio ($\tilde{\mathfrak{R}}_0$), leading to suppressed HIV-1 reproduction. Therefore, eliminating HIV-1 requires prioritizing strategies that keep $\tilde{\mathfrak{R}}_0$ below 1. Our study also highlights the critical role of L-CTC spread in HIV-1 dynamics. Additionally, a sensitivity analysis revealed key factors influencing the system's behavior, deepening our understanding of HIV-1 dynamics.

We are optimistic that the strategy outlined in our article may be improved upon. The modeling of the in-host dynamics with an emphasis on the immune system vs invading particles would be an intriguing viewpoint. Recently, active-particle approaches have been utilized to describe the immunological rivalry in detail at the cellular level, allowing for the modeling of epidemics (see [63]).

It seems like an interesting avenue to investigate the memory impact on the dynamics of our model with fractional differential equations (FDEs) [64–66]. Non-local and memory-dependent effects, which are frequently essential in virological systems, can be captured by FDEs. In our proposed modeled we assumed that the production rate of healthy CD4⁺T cells is constant. Nonetheless, HIV-1 infection possesses the capability to infect and disrupt the thymus's supply of these cells. As a result, rather than being constant, the thymus's supply of new cells has been seen to be changeable [55, 67]. These topics are left for later research.

Data availability statement

The original contributions presented in the study are included in the article/supplementary

material, further inquiries can be directed to the corresponding author.

Author contributions

AE: Conceptualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. NA: Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. RH: Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing.

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