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Global Properties of HIV-1 Dynamics Models with CTL Immune Impairment and Latent Cell-to-Cell Spread

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Abstract: This paper presents and analyzes two mathematical models for the human immunodeficiency virus type-1 (HIV-1) infection with Cytotoxic T Lymphocyte cell (CTL) immune impairment. These models describe the interactions between healthy $CD4^{+}$T cells, latently and actively infected cells, HIV-1 particles, and CTLs. The healthy $CD4^{+}$T cells might be infected when they make contact with: (i) HIV-1 particles due to virus-to-cell (VTC) contact; (ii) latently infected cells due to latent cell-to-cell (CTC) contact; and (iii) actively infected cells due to active CTC contact. Distributed time delays are considered in the second model. We show the nonnegativity and boundedness of the solutions of the systems. Further, we derive basic reproduction numbers $\Re_0$ and $\tilde{\Re}_0$, that determine the existence and stability of equilibria of our proposed systems. We establish the global asymptotic stability of all equilibria by using the Lyapunov method together with LaSalle's invariance principle. We confirm the theoretical results by numerical simulations. The effect of immune impairment, time delay and CTC transmission on the HIV-1 dynamics are discussed. It is found that weak immunity contributes significantly to the development of the disease. Further, we have established that the presence of time delay can significantly decrease the basic reproduction number and then suppress the HIV-1 replication. On the other hand, the presence of latent CTC spread increases the basic reproduction number and then enhances the viral progression. Thus, neglecting the latent CTC spread in the HIV-1 infection model will lead to an underestimation of the basic reproduction number. Consequently, the designed drug therapies will not be accurate or sufficient to eradicate the viruses from the body. These findings may help to improve the understanding of the dynamics of HIV-1 within a host.

Keywords: HIV-1; cell-to-cell infection; latently infected cells; immune impairment; global stability; distributed delays; Lyapunov function

MSC: 34D20; 34D23; 37N25; 92B05

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1. Introduction

Human immunodeficiency virus type-1 (HIV-1) is one of the chronic viruses that infects humans and causes Acquired Immune Deficiency Syndrome (AIDS). HIV-1 attacks the $CD4^{+}$T cells which are essential in the immune system. Adaptive immune responses play pivotal roles in HIV infection. B cells and cytotoxic T lymphocytes (CTLs) are two potential components of the adaptive immune response. B cells produce antibodies to neutralize the HIV-1 particles, while CTLs kill cells infected by HIV-1. Evaluating interactions between HIV-1 and target cells as well as immune cells can be experimentally expensive. Thus, mathematical modeling of HIV-1 infection has become an important tool for understanding the dynamical behavior of the viruses and their interactions with target cells and immune cells. Nowak and Bangham [1] presented the primary HIV-1 dynamics model which involve three components: healthy CD4$^+$T cells (H), infected CD4$^+$T cells (Y) and free HIV-1 particles (V). In the same paper, the CTL immune response was modeled as:

$$
\begin{aligned}
\text{Healthy CD4}^+\text{T cells:}\quad \dot{H}(t) &= \underbrace{\alpha}_{\text{Production of healthy CD4}^+\text{T cells}} - \underbrace{\eta H(t)}_{\text{Natural death}} - \underbrace{\rho_1 H(t)V(t)}_{\text{Infectious transmission}}, \\
\text{Actively infected CD4}^+\text{T cells:}\quad \dot{Y}(t) &= \underbrace{\rho_1 H(t)V(t)}_{\text{Infectious transmission}} - \underbrace{\tau Y(t)}_{\text{Natural death}} - \underbrace{\gamma I(t)Y(t)}_{\text{Killing of infected cells by CTLs}}, \\
\text{HIV-1 particles:}\quad \dot{V}(t) &= \underbrace{\varepsilon Y(t)}_{\text{Burst size}} - \underbrace{\theta V(t)}_{\text{Natural death}},
\end{aligned} \tag{1}
$$

$$
\text{CTLs:}\quad \dot{I}(t) = \underbrace{\nu Y(t)I(t)}_{\text{CTLs stimulation}} - \underbrace{\pi I(t)}_{\text{Natural death}}, \tag{2}
$$

where $I(t)$ is the concentration of the CTLs at time t. After introducing this model, several virus dynamics models were developed and studied. Let us write the population dynamics of the CTLs as:

$$\dot{I}(t) = \Theta(Y(t), I(t)) - \pi I(t),$$

where $\Theta(Y, I)$ is the stimulation rate of CTLs. It has taken many shapes in the literature:

S1. Self-regulating CTL, $\Theta(Y, I) = \omega$, where $\omega > 0$ [2],
S2. Linear CTL response, $\Theta(Y, I) = \lambda Y$, where $\lambda > 0$ [3–6],
S3. Predator-prey-like CTL, $\Theta(Y, I) = \nu Y I$, where $\nu > 0$ [1,2,7],
S4. Combination of shapes S1–S3, $\Theta(Y, I) = \omega + \lambda Y + \nu Y I$ [2],
S5. Combination of predator-prey-like CTL and self-proliferation CTL: $\Theta(Y, I) = \nu Y I + \varsigma I\left(1 - \frac{I}{I_{\max}}\right)$, where $\varsigma, I_{\max} > 0$ [8].
S6. Saturated CTL response: $\Theta(Y, I) = \frac{\nu Y I}{\vartheta + I}$, $\vartheta > 0$ [9–12].

Some important biological factors were not included in models (1) and (2), such as:

Latently infected cells: these cells are considered one of the main obstacles for eliminating the HIV-1 by current antiviral drug therapies. Such cells contain the HIV-1 virions but do not generate them until they are activated. HIV-1 infection models with CTL immunity and latently infected cells were introduced in other research papers (see, e.g., [7,13]).

Time delay: in [14], it was estimated that the time between the HIV-1 entering a CD4$^+$T cell until generating new HIV-1 particles is about 0.9 days. Viral infection models with both CTL immunity and time delays were introduced in several works (see, e.g., [15–18]).

Cell-to-cell (CTC) transmission: the above model assumes that the infection occurs via virus-to-cell (VTC) contact. However, several research works reported that HIV-1 can be directly transferred from an infected CD4$^+$T cell to a healthy CD4$^+$T cell through the formation of virological synapses (see, e.g., [19–24]). CTC has great influence on HIV-1 infection, which might be 100–1000 times faster than VTC virus spread [25]. In [26,27], viral infection models with latently infected cells and CTC transmission were studied.

Immune impairment: models (1) and (2) assume that the presence of an antigen can only simulate the immune CTL response, and neglect the CTL immune impairment. In fact, HIV-1 is one of the viruses that has the ability to suppress the CTL response and cause CTL immune impairment [28]. In this case, the pollution dynamics of the CTLs can be written as follows (see, e.g., [28–35]):

$$\dot{I}(t) = \lambda Y(t) - \delta I(t)Y(t) - \pi I(t),$$

where, λY is the stimulation of CTL immunity and $\delta I Y$ is the CTL immune impairment. Modeling the latently infected cells and CTL immune impairment was studied in [36,37]. Intracellular time delay was considered in [36], while CTL immune response delay was considered in [37].

A viral infection model with CTL immune impairment, latently infected cells and CTC transmission can be written as [38–40]:

$$\dot{H}(t) = \alpha - \eta H(t) - \rho_1 H(t)V(t) - \rho_3 H(t)Y(t), \tag{3}$$
$$\dot{S}(t) = \rho_1 H(t)V(t) + \rho_3 H(t)Y(t) - (\sigma + \mu)S(t), \tag{4}$$
$$\dot{Y}(t) = \sigma S(t) - \tau Y(t) - \gamma I(t)Y(t), \tag{5}$$
$$\dot{V}(t) = \varepsilon Y(t) - \theta V(t), \tag{6}$$
$$\dot{I}(t) = \lambda Y(t) - \pi I(t) - \delta I(t)Y(t), \tag{7}$$

where, $S(t)$ is the concentration of the latently infected cells at time t. The healthy CD4$^+$T cells become infected by two modes: the VTC infection mode via HIV-1, $\rho_1 HV$ and the CTC infection mode via actively infected cells, $\rho_3 HY$. Latently infected cells are activated at rate σS and die at rate μS. Elaiw et al. [41] studied a virus dynamics model with CTC infection, immune impairment and intracellular time delay. In [40], CTL immune response delay was included. Alofi and Azoz [39] studied a viral infection model with general VTC and CTC infection rates.

We noted that the models presented in [38–40] assume that the CTC transmission is only due to the actively infected cells. However, it was reported in Ref. [42] that latently infected cells can also infect the healthy CD4$^+$T cells through the CTC mechanism. In Refs. [43–49], some virus dynamics models were developed by assuming that both latently and actively infected cells contribute to the CTC mechanism. However, the immune impairment was not considered in these papers.

The aim of the present work is to study two within-host HIV-1 dynamics models by involving latently infected cells, CTL immune impairment and CTC transmission. Both latently and actively infected cells contribute in CTC infection. In the second model, we included three types of distributed time delays. For both models we are investigating the non-negativity and boundedness of solutions, calculating the basic reproduction number, finding the model's equilibria, establishing the global stability of equilibria, confirming the theoretical results by numerical simulation and discussing the obtained results.

2. Model with Latent CTC Transmission and CTL Immune Impairment

2.1. System Description

We propose an HIV-1 dynamics model with immune impairment, latently infected cells and two modes of transmissions, namely VTC and CTC. Both latently and actively infected cells contribute to CTC infection. Under these assumptions, we present the following model:

$$\begin{cases} \dot{H}(t) &= \alpha - \eta H(t) - \rho_1 H(t)V(t) - \rho_2 H(t)S(t) - \rho_3 H(t)Y(t), \\ \dot{S}(t) &= \rho_1 H(t)V(t) + \rho_2 H(t)S(t) + \rho_3 H(t)Y(t) - (\sigma + \mu)S(t), \\ \dot{Y}(t) &= \sigma S(t) - \tau Y(t) - \gamma I(t)Y(t), \\ \dot{V}(t) &= \varepsilon Y(t) - \theta V(t), \\ \dot{I}(t) &= \lambda Y(t) - \pi I(t) - \delta I(t)Y(t). \end{cases} \tag{8}$$

In our proposed model we assume that the healthy CD4$^+$T cells become infected by three rates: the VTC infection rate via HIV-1 particles, $\rho_1 HV$, the CTC infection rate via latently infected cells, $\rho_2 HS$, and the CTC infection rate via actively infected cells, $\rho_3 HY$.

2.2. Basic Properties

2.2.1. Nonnegativity and Boundedness of the Solutions

Lemma 1. *Consider system (8), then there exists a positively invariant compact set*

$$\Omega = \left\{ (H, S, Y, V, I) \in \mathbb{R}^5_{\geq 0} : 0 \leq H(t), S(t), Y(t) \leq \Lambda_1, 0 \leq V(t) \leq \Lambda_2, 0 \leq I(t) \leq \Lambda_3 \right\}.$$

Proof. We have

$$\begin{aligned}
&\dot{H} \mid_{H=0} = \alpha > 0, \\
&\dot{S} \mid_{S=0} = \rho_1 HV + \rho_3 HY \geq 0, \text{ for all } H, V, Y \geq 0, \\
&\dot{Y} \mid_{Y=0} = \sigma S \geq 0, \text{ for all } S \geq 0, \\
&\dot{V} \mid_{V=0} = \varepsilon Y \geq 0, \text{ for all } Y \geq 0, \\
&\dot{I} \mid_{I=0} = \lambda Y \geq 0, \text{ for all } Y \geq 0.
\end{aligned}$$

Therefore, $(H(t), S(t), Y(t), V(t), I(t)) \in \mathbb{R}^5_{\geq 0}$, for all $t \geq 0$ when $(H(0), S(0), Y(0), V(0), I(0)) \in \mathbb{R}^5_{\geq 0}$. Now, we define

$$T(t) = H(t) + S(t) + Y(t) + \frac{\tau}{2\varepsilon} V(t) + \frac{\tau}{4\lambda} I(t).$$

Then, we have

$$\begin{aligned}
\dot{T}(t) &= \dot{H}(t) + \dot{S}(t) + \dot{Y}(t) + \frac{\tau}{2\varepsilon}\dot{V}(t) + \frac{\tau}{4\lambda}\dot{I}(t) \\
&= \alpha - \eta H(t) - \mu S(t) - \frac{\tau}{4} Y(t) - \left(\gamma + \frac{\tau\delta}{4\lambda}\right) I(t) Y(t) - \frac{\tau\theta}{2\varepsilon} V(t) - \frac{\tau\pi}{4\lambda} I(t) \\
&\leq \alpha - \eta H(t) - \mu S(t) - \frac{\tau}{4} Y(t) - \frac{\tau\theta}{2\varepsilon} V(t) - \frac{\tau\pi}{4\lambda} I(t) \\
&\leq \alpha - \phi\Big(H(t) + S(t) + Y(t) + \frac{\tau}{2\varepsilon} V(t) + \frac{\tau}{4\lambda} I(t)\Big) = \alpha - \phi T(t),
\end{aligned}$$

where $\phi = \min\{\eta, \mu, \frac{\tau}{4}, \theta, \pi\}$. Hence,

$$T(t) \leq e^{-\phi t}\left(T(0) - \frac{\alpha}{\phi}\right) + \frac{\alpha}{\phi}.$$

This yields $0 \leq T(t) \leq \Lambda_1$ if $T(0) \leq \Lambda_1$, where $\Lambda_1 = \dfrac{\alpha}{\phi}$. Since all state variables are nonnegative, then $0 \leq H(t), S(t), Y(t) \leq \Lambda_1$, $0 \leq V(t) \leq \Lambda_2$, and $0 \leq I(t) \leq \Lambda_3$, for all $t \geq 0$ if $H(0) + S(0) + Y(0) + \dfrac{\tau}{2\varepsilon} V(0) + \dfrac{\tau}{4\lambda} I(0) \leq \Lambda_1$, where $\Lambda_2 = \dfrac{2\varepsilon\Lambda_1}{\tau}$ and $\Lambda_3 = \dfrac{4\lambda\Lambda_1}{\tau}$. Therefore, $H(t)$,$S(t)$,$Y(t)$,$V(t)$ and $I(t)$ are all bounded, which implies that Ω is a positively invariant compact set with respect to system (8). □

2.2.2. Reproduction Number and Equilibria

Lemma 2. *For system (8), there exists a positive basic reproduction number $\Re_0$ such that*

(i) there exists only one equilibrium point Q_0 when $\Re_0 \leq 1$, and
(ii) there exists two equilibria Q_0 and Q_1 when $\Re_0 > 1$.

Proof. It is clear that system (8) always admits an infection-free equilibrium $Q_0 = (H_0, 0, 0, 0, 0)$, where $H_0 = \dfrac{\alpha}{\eta}$. Now, we apply the method of the next-generation matrix proposed in [50] to determine the basic reproduction number of system (8) based on the infected compartments in model (8), ordered (S, Y, V). The nonlinear terms with new infection $\hat{\Gamma}_1$ and the outflow term $\hat{\Delta}_1$ are given by the following matrices:

$$\hat{\Gamma}_1 = \begin{pmatrix} \rho_1 HV + \rho_2 HS + \rho_3 HY \\ 0 \\ 0 \end{pmatrix}, \quad \hat{\Delta}_1 = \begin{pmatrix} (\sigma + \mu) S \\ -\sigma S + \tau Y + \gamma IY \\ -\varepsilon Y + \theta V \end{pmatrix}.$$

We compute the derivative of $\hat{\Gamma}_1$ and $\hat{\Delta}_1$ at the equilibrium Q_0 to obtain the following matrices:

$$\Gamma_1 = \begin{pmatrix} \rho_2 H_0 & \rho_3 H_0 & \rho_1 H_0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}, \quad \Delta_1 = \begin{pmatrix} \sigma+\mu & 0 & 0 \\ -\sigma & \tau & 0 \\ 0 & -\varepsilon & \theta \end{pmatrix}.$$

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

$$\Gamma_1 \Delta_1^{-1} = \begin{pmatrix} \frac{H_0(\rho_1\varepsilon\sigma+\rho_2\theta\tau+\rho_3\sigma\theta)}{(\sigma+\mu)\theta\tau} & \frac{H_0(\rho_1\varepsilon+\rho_3\theta)}{\theta\tau} & \frac{\rho_1 H_0}{\theta} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}.$$

The basic reproduction number $\Re_0$ is the spectral radius of the matrix $\Gamma_1\Delta_1^{-1}$ and is given as:

$$\Re_0 = \frac{H_0(\rho_1\varepsilon\sigma+\rho_2\theta\tau+\rho_3\sigma\theta)}{(\sigma+\mu)\theta\tau} = \Re_{01}+\Re_{02}+\Re_{03}, \tag{9}$$

where

$$\Re_{01} = \frac{H_0\varepsilon\sigma\rho_1}{\theta\tau(\sigma+\mu)}, \qquad \Re_{02} = \frac{H_0\rho_2}{\sigma+\mu}, \qquad \Re_{03} = \frac{H_0\sigma\rho_3}{\tau(\sigma+\mu)}.$$

Note that the parameter $\Re_{01}$ measures the average number of secondary infected cells caused by the contact between the virus particles and the healthy cells, while $\Re_{02}$ and $\Re_{03}$ measure the average number of secondary infected cells caused by surviving latently and actively infected cells, respectively. To find the other equilibrium in addition to Q_0, we let (H, S, Y, V, I) be any equilibrium satisfying the following equations:

$$0 = \alpha - \eta H - \rho_1 HV - \rho_2 HS - \rho_3 HY, \tag{10}$$
$$0 = \rho_1 HV + \rho_2 HS + \rho_3 HY - (\sigma+\mu)S, \tag{11}$$
$$0 = \sigma S - \tau Y - \gamma IY, \tag{12}$$
$$0 = \varepsilon Y - \theta V, \tag{13}$$
$$0 = \lambda Y - \pi I - \delta IY. \tag{14}$$

From Equations (13) and (14), we obtain

$$V = \frac{\varepsilon Y}{\theta}, \quad I = \frac{\lambda Y}{\pi+\delta Y}. \tag{15}$$

Substituting from Equation (15) into Equation (12), we obtain

$$S = \frac{\pi\tau Y + (\gamma\lambda+\tau\delta)Y^2}{\sigma(\pi+\delta Y)}. \tag{16}$$

From Equations (10) and (11), we obtain

$$\alpha - \eta H = (\sigma+\mu)S. \tag{17}$$

Substituting from Equation (16) into Equation (17), we obtain

$$H = \frac{1}{\eta}\left(\alpha - \frac{(\sigma+\mu)\big(\pi\tau Y + (\gamma\lambda+\tau\delta)Y^2\big)}{\sigma(\pi+\delta Y)}\right). \tag{18}$$

Substituting from Equations (15), (16) and (18) into Equation (11), we obtain

$$\frac{\eta\theta Y}{\sigma(\pi+\delta Y)^2}\Big(AY^3 + BY^2 + CY + D\Big) = 0, \tag{19}$$

where

$$\begin{aligned}
A &= (\sigma+\mu)(\gamma\lambda+\delta\tau)(\theta\rho_2(\delta\tau+\gamma\lambda)+\delta\sigma(\varepsilon\rho_1+\theta\rho_3)),\\
B &= \delta\eta\theta(\sigma+\mu)(\gamma\lambda+\delta\tau)+(\pi\tau(\sigma+\mu)-\alpha\delta)(\delta\sigma(\varepsilon\rho_1+\theta\rho_3)+\theta(\gamma\lambda+\delta\tau)\rho_2)\\
&\quad+\pi(\sigma+\mu)(\gamma\lambda+\delta\tau)(\varepsilon\sigma\rho_1+\theta(\tau\rho_2+\sigma\rho_3)),\\
C &= \eta\theta\pi(\sigma+\mu)(2\delta\tau+\gamma\lambda)-\alpha\pi(\delta\sigma(\varepsilon\rho_1+\theta\rho_3)+\theta(\gamma\lambda+\delta\tau)\rho_2)\\
&\quad+\pi(\pi\tau(\sigma+\mu)-\alpha\delta)(\varepsilon\sigma\rho_1+\theta(\tau\rho_2+\sigma\rho_3)),\\
D &= \eta\theta\tau\pi^2(\sigma+\mu)(1-\Re_0),
\end{aligned}$$

where $\Re_0$ is defined by Equation (9). From Equation (19), we have

1. If $Y=0$, then from Equations (15), (16) and (18) we obtain the infection-free equilibrium Q_0.
2. If $Y\neq 0$, then we have $AY^3+BY^2+CY+D=0$. In this case, let us define a function $\Psi(Y)$ on $[0,\infty)$ as:
$$\Psi(Y)=AY^3+BY^2+CY+D.$$
We have $\Psi(0)=\eta\theta\tau\pi^2(\sigma+\mu)(1-\Re_0)<0$ when $\Re_0>1$ and $\lim_{Y\to\infty}\Psi(Y)=\infty$, which implies that Ψ has a positive real root Y_1. Then, by substituting from Equations (15) and (16) into Equation (10), we obtain
$$H_1=\frac{\alpha}{\eta+\rho_1V_1+\rho_2S_1+\rho_3Y_1},$$
where
$$S_1=\frac{\pi\tau Y_1+(\gamma\lambda+\delta\tau)Y_1^2}{\sigma(\pi+\delta Y_1)},\quad V_1=\frac{\varepsilon Y_1}{\theta},\quad I_1=\frac{\lambda Y_1}{\pi+\delta Y_1}.$$
It is clear that the infected equilibrium $Q_1=(H_1,S_1,Y_1,V_1,I_1)$ exists when $\Re_0>1$. □

2.2.3. Stability of Equilibria Q_0 and Q_1

Theorem 1. *If $\Re_0<1$, then the Q_0 of system (8) is locally asymptotically stable (L.A.S), and unstable when $\Re_0>1$.*

Proof. Following the work by Willems [51], local asymptotic stability of equilibrium Q_0 is determined by the eigenvalues of its corresponding Jacobian matrix which is given by

$$J_1=\begin{pmatrix}
-\eta-\rho_1V-\rho_2S-\rho_3Y & -\rho_2H & -\rho_3H & -\rho_1H & 0\\
\rho_1V+\rho_2S+\rho_3Y & \rho_2H-(\sigma+\mu) & \rho_3H & \rho_1H & 0\\
0 & \sigma & -(\tau+\gamma I) & 0 & -\gamma Y\\
0 & 0 & \varepsilon & -\theta & 0\\
0 & 0 & \lambda-\delta I & 0 & -(\pi+\delta Y)
\end{pmatrix}. \tag{20}$$

For matrix (20), the characteristic equation $|J_1-xI_5|=0$ is solved as $(x+\pi)(x+\eta)K(x)=0$, where

$$K(x)=x^3+m_2x^2+m_1x+m_0, \tag{21}$$

and

$$\begin{aligned}
m_0 &= \theta\tau(\sigma+\mu)(1-\Re_0)>0,\\
m_1 &= \theta\tau+\theta(\sigma+\mu)(1-\Re_{02})+\tau(\sigma+\mu)(1-(\Re_{02}+\Re_{03}))>0,\\
m_2 &= \theta+\tau+(\sigma+\mu)(1-\Re_{02})>0,\\
m_1m_2-m_0 &= \frac{\alpha\varepsilon\sigma\rho_1}{\eta}+(\tau+(\sigma+\mu)(1-\Re_{02}))(\theta(\theta+\tau)+\theta(\sigma+\mu)(1-\Re_{02})\\
&\quad+\tau(\sigma+\mu)(1-(\Re_{02}+\Re_{03})))>0,
\end{aligned}$$

where $\Re_0 < 1$. It is clear that the Jacobian matrix J_1 has two negative eigenvalues, $-\pi$ and $-\eta$. Other eigenvalues are calculated as the roots of the cubic equation presented in (21). All roots of Equation (21) have negative real parts based on Routh-Hurwitz criteria [51]. Therefore, the infection-free equilibrium Q_0 is L.A.S when $\Re_0 < 1$. Let $\Re_0 > 1$, then we have $m_0 < 0$. This means that Equation (21) has at least one positive real root. Hence, Q_0 is unstable when $\Re_0 > 1$. □

In the following theorems, global stability of equilibria will be discussed. Let a function $\digamma$ be defined as $\digamma(z) = z - 1 - \ln(z)$. Denote $(H, S, Y, V, I) = (H(t), S(t), Y(t), V(t), I(t))$.

Theorem 2. *For system (8), if $\Re_0 < 1$, then Q_0 is globally asymptotically stable (G.A.S).*

Proof. We define a Lyapunov function candidate as:

$$\Theta_0 = H_0 \digamma\left(\frac{H}{H_0}\right) + S + \frac{(\sigma+\mu)(1-\Re_{02})}{\sigma} Y + \frac{\rho_1 H_0}{\theta} V + \frac{\tau(\sigma+\mu)(1-\Re_0)}{\lambda\sigma} I.$$

Clearly, $\Theta_0(H, S, Y, V, I) > 0$ for all $H, S, Y, V, I > 0$, and $\Theta_0(H_0, 0, 0, 0, 0) = 0$. We calculate $\frac{d\Theta_0}{dt}$ along the solutions of model (8) as:

$$\begin{aligned}
\frac{d\Theta_0}{dt} &= \left(1 - \frac{H_0}{H}\right)\frac{dH}{dt} + \frac{dS}{dt} + \frac{(\sigma+\mu)(1-\Re_{02})}{\sigma}\frac{dY}{dt} + \frac{\rho_1 H_0}{\theta}\frac{dV}{dt} + \frac{\tau(\sigma+\mu)(1-\Re_0)}{\lambda\sigma}\frac{dI}{dt} \\
&= \left(1 - \frac{H_0}{H}\right)(\alpha - \eta H - \rho_1 HV - \rho_2 HS - \rho_3 HY) + \rho_1 HV + \rho_2 HS + \rho_3 HY - (\sigma+\mu)S \\
&\quad + \frac{(\sigma+\mu)(1-\Re_{02})}{\sigma}(\sigma S - \tau Y - \gamma IY) + \frac{\rho_1 H_0}{\theta}(\varepsilon Y - \theta V) + \frac{\tau(\sigma+\mu)(1-\Re_0)}{\lambda\sigma}(\lambda Y - \pi I - \delta IY) \\
&= \left(1 - \frac{H_0}{H}\right)(\alpha - \eta H) + (\rho_2 H_0 - (\sigma+\mu) + (\sigma+\mu)(1-\Re_{02}))S \\
&\quad + \left(\rho_3 H_0 - \frac{\tau(\sigma+\mu)(1-\Re_{02})}{\sigma} + \frac{\rho_1 H_0 \varepsilon}{\theta} + \frac{\tau(\sigma+\mu)(1-\Re_0)}{\sigma}\right)Y \\
&\quad - \frac{\pi\tau(\sigma+\mu)(1-\Re_0)}{\lambda\sigma} I - \left(\frac{\gamma(\sigma+\mu)(1-\Re_{02})}{\sigma} + \frac{\delta\tau(\sigma+\mu)(1-\Re_0)}{\lambda\sigma}\right) IY.
\end{aligned}$$

After direct calculation and using $H_0 = \alpha/\eta$, we obtain

$$\begin{aligned}
\frac{d\Theta_0}{dt} &= \left(1 - \frac{H_0}{H}\right)(\eta H_0 - \eta H) - \frac{\pi\tau(\sigma+\mu)(1-\Re_0)}{\lambda\sigma} I - \frac{\sigma+\mu}{\lambda\sigma}(\gamma\lambda(1-\Re_{02}) + \tau\delta(1-\Re_0)) IY \\
&= -\frac{\eta(H-H_0)^2}{H} - \frac{\pi\tau(\sigma+\mu)(1-\Re_0)}{\lambda\sigma} I - \frac{\sigma+\mu}{\lambda\sigma}(\gamma\lambda(1-\Re_{02}) + \tau\delta(1-\Re_0)) IY.
\end{aligned}$$

Clearly, $\frac{d\Theta_0}{dt} \le 0$ when $\Re_0 < 1$ with equality holding when $H = H_0$ and $Y = I = 0$. Let $\Phi_0 = \left\{(H, S, Y, V, I) : \frac{d\Theta_0}{dt} = 0\right\}$, and Φ_0' be the largest invariant subset of Φ_0. Therefore, all solutions converge to Φ_0' [52]. All elements in Φ_0' satisfy $H(t) = H_0$ and $Y(t) = I(t) = 0$. Then, the third equation of system (8) gives

$$0 = \dot{Y}(t) = \sigma S(t) \Longrightarrow S(t) = 0, \text{ for all } t.$$

Moreover, the first equation of model (8) yields

$$0 = \dot{H}(t) = \alpha - \eta H_0 - \rho_1 H_0 V(t) \Longrightarrow V(t) = 0, \text{ for all } t.$$

Therefore, $\Phi_0' = \{(H, S, Y, V, I) \in \Phi_0 : H = H_0, S = Y = V = I = 0\} = \{Q_0\}$. Hence, we obtain that when $\Re_0 < 1$, then Q_0 is G.A.S according to the LaSalle's invariance principle (L.I.P) [52]. □

Theorem 3. *For system (8), if $\Re_0 > 1$, then Q_1 is G.A.S.*

Proof. Define

$$\Theta_1 = H_1 F\left(\frac{H}{H_1}\right) + S_1 F\left(\frac{S}{S_1}\right) + \frac{H_1(\rho_1\varepsilon + \rho_3\theta)Y_1}{\theta(\tau + \gamma I_1)} F\left(\frac{Y}{Y_1}\right) + \frac{\rho_1 H_1 V_1}{\theta} F\left(\frac{V}{V_1}\right) + \frac{\gamma H_1(\rho_1\varepsilon + \rho_3\theta)}{2\theta(\tau + \gamma I_1)(\lambda - \delta I_1)}(I - I_1)^2.$$

It is noted from the equilibrium condition Equation (14) that $\lambda - \delta I_1 = \dfrac{\pi I_1}{Y_1} > 0$. Clearly, Θ_1 is positive definite. We calculate $\frac{d\Theta_1}{dt}$ as:

$$\begin{aligned}
\frac{d\Theta_1}{dt} &= \left(1 - \frac{H_1}{H}\right)\frac{dH}{dt} + \left(1 - \frac{S_1}{S}\right)\frac{dS}{dt} + \frac{H_1(\rho_1\varepsilon + \rho_3\theta)}{\theta(\tau + \gamma I_1)}\left(1 - \frac{Y_1}{Y}\right)\frac{dY}{dt} + \frac{\rho_1 H_1}{\theta}\left(1 - \frac{V_1}{V}\right)\frac{dV}{dt} \\
&\quad + \frac{\gamma H_1(\rho_1\varepsilon + \rho_3\theta)}{\theta(\tau + \gamma I_1)(\lambda - \delta I_1)}(I - I_1)\frac{dI}{dt} \\
&= \left(1 - \frac{H_1}{H}\right)(\alpha - \eta H - \rho_1 HV - \rho_2 HS - \rho_3 HY) + \left(1 - \frac{S_1}{S}\right)(\rho_1 HV + \rho_2 HS + \rho_3 HY \\
&\quad -(\sigma + \mu)S) + \frac{H_1(\rho_1\varepsilon + \rho_3\theta)}{\theta(\tau + \gamma I_1)}\left(1 - \frac{Y_1}{Y}\right)(\sigma S - \tau Y - \gamma IY) \\
&\quad + \frac{\rho_1 H_1}{\theta}\left(1 - \frac{V_1}{V}\right)(\varepsilon Y - \theta V) + \frac{\gamma H_1(\rho_1\varepsilon + \rho_3\theta)}{\theta(\tau + \gamma I_1)(\lambda - \delta I_1)}(I - I_1)(\lambda Y - \pi I - \delta IY) \\
&= \left(1 - \frac{H_1}{H}\right)(\alpha - \eta H) + \left(\rho_2 H_1 - (\sigma + \mu) + \frac{\sigma H_1(\rho_1\varepsilon + \rho_3\theta)}{\theta(\tau + \gamma I_1)}\right)S + \rho_3 H_1 Y \\
&\quad - (\rho_1 HV + \rho_2 HS + \rho_3 HY)\left(\frac{S_1}{S}\right) + (\sigma + \mu)S_1 - \frac{\sigma H_1(\rho_1\varepsilon + \rho_3\theta)}{\theta(\tau + \gamma I_1)}\left(\frac{SY_1}{Y}\right) \\
&\quad - \frac{\tau H_1(\rho_1\varepsilon + \rho_3\theta)}{\theta(\tau + \gamma I_1)}(Y - Y_1) - \frac{\gamma H_1(\rho_1\varepsilon + \rho_3\theta)}{\theta(\tau + \gamma I_1)}I(Y - Y_1) + \frac{\rho_1 H_1\varepsilon}{\theta}Y \\
&\quad - \frac{\rho_1 H_1\varepsilon}{\theta}\left(\frac{YV_1}{V}\right) + \rho_1 H_1 V_1 + \frac{\gamma H_1(\rho_1\varepsilon + \rho_3\theta)}{\theta(\tau + \gamma I_1)(\lambda - \delta I_1)}(I - I_1)(\lambda Y - \pi I - \delta IY).
\end{aligned} \tag{22}$$

Using the following equilibrium conditions for Q_1

$$\begin{aligned}
&\alpha = \eta H_1 + \rho_1 H_1 V_1 + \rho_2 H_1 S_1 + \rho_3 H_1 Y_1, \\
&\rho_1 H_1 V_1 + \rho_2 H_1 S_1 + \rho_3 H_1 Y_1 = (\sigma + \mu)S_1, \\
&\sigma S_1 = (\tau + \gamma I_1)Y_1 \Longrightarrow Y_1 = \frac{\sigma S_1}{\tau + \gamma I_1}, \\
&V_1 = \frac{\varepsilon Y_1}{\theta}, \quad \lambda Y_1 - \pi I_1 - \delta I_1 Y_1 = 0,
\end{aligned}$$

We obtain

$$\begin{aligned}
&\rho_1 H_1 V_1 + \rho_3 H_1 Y_1 = \frac{H_1(\rho_1\varepsilon + \rho_3\theta)Y_1}{\theta} = \frac{\sigma H_1(\rho_1\varepsilon + \rho_3\theta)S_1}{\theta(\tau + \gamma I_1)}, \\
&\left(\rho_2 H_1 - (\sigma + \mu) + \frac{\sigma H_1(\rho_1\varepsilon + \rho_3\theta)}{\theta(\tau + \gamma I_1)}\right)S_1 = 0.
\end{aligned}$$

Therefore, Equation (22) will take the following form:

$$\begin{aligned}
\frac{d\Theta_1}{dt} &= \left(1 - \frac{H_1}{H}\right)(\eta H_1 - \eta H) + (\rho_1 H_1 V_1 + \rho_2 H_1 S_1 + \rho_3 H_1 Y_1)\left(1 - \frac{H_1}{H}\right) + \rho_3 H_1 Y \\
&\quad - \rho_1 H_1 V_1\left(\frac{HVS_1}{H_1 V_1 S}\right) - \rho_2 H_1 S_1\left(\frac{H}{H_1}\right) - \rho_3 H_1 Y_1\left(\frac{HYS_1}{H_1 Y_1 S}\right) + \rho_1 H_1 V_1 + \rho_2 H_1 S_1
\end{aligned}$$

$$
\begin{aligned}
&+\rho_3 H_1 Y_1 - \frac{\sigma H_1(\rho_1\varepsilon+\rho_3\theta)S_1}{\theta(\tau+\gamma I_1)}\left(\frac{SY_1}{S_1Y}\right) - \frac{\tau H_1(\rho_1\varepsilon+\rho_3\theta)}{\theta(\tau+\gamma I_1)}(Y-Y_1) \\
&- \frac{\gamma H_1(\rho_1\varepsilon+\rho_3\theta)}{\theta(\tau+\gamma I_1)}I(Y-Y_1) + \frac{\gamma H_1(\rho_1\varepsilon+\rho_3\theta)}{\theta(\tau+\gamma I_1)}I_1(Y-Y_1) - \frac{\gamma H_1(\rho_1\varepsilon+\rho_3\theta)}{\theta(\tau+\gamma I_1)}I_1(Y-Y_1) \\
&+ \frac{\rho_1 H_1 \varepsilon Y_1}{\theta}\left(\frac{Y}{Y_1}\right) - \frac{\rho_1 H_1 \varepsilon Y_1}{\theta}\left(\frac{YV_1}{Y_1V}\right) + \rho_1 H_1 V_1 + \frac{\gamma H_1(\rho_1\varepsilon+\rho_3\theta)}{\theta(\tau+\gamma I_1)(\lambda-\delta I_1)}(I-I_1)(\lambda Y - \pi I - \delta IY \\
&-\lambda Y_1 + \pi I_1 + \delta I_1 Y_1 + \delta I_1 Y - \delta I_1 Y) \\
={}& -\frac{\eta(H-H_1)^2}{H} + (\rho_1 H_1 V_1 + \rho_2 H_1 S_1 + \rho_3 H_1 Y_1)\left(2-\frac{H_1}{H}\right) + \rho_3 H_1 Y \\
&- \rho_1 H_1 V_1\left(\frac{HVS_1}{H_1V_1S}\right) - \rho_2 H_1 S_1\left(\frac{H}{H_1}\right) - \rho_3 H_1 Y_1\left(\frac{HYS_1}{H_1Y_1S}\right) - (\rho_1 H_1 V_1 + \rho_3 H_1 Y_1)\left(\frac{SY_1}{S_1Y}\right) \\
&- \frac{H_1(\rho_1\varepsilon+\rho_3\theta)}{\theta(\tau+\gamma I_1)}(\tau+\gamma I_1)(Y-Y_1) - \frac{\gamma H_1(\rho_1\varepsilon+\rho_3\theta)}{\theta(\tau+\gamma I_1)}(I-I_1)(Y-Y_1) + \rho_1 H_1 V_1\left(\frac{Y}{Y_1}\right) \\
&- \rho_1 H_1 V_1\left(\frac{YV_1}{Y_1V}\right) + \rho_1 H_1 V_1 + \frac{\gamma\lambda H_1(\rho_1\varepsilon+\rho_3\theta)}{\theta(\tau+\gamma I_1)(\lambda-\delta I_1)}(I-I_1)(Y-Y_1) \\
&- \frac{\gamma H_1(\rho_1\varepsilon+\rho_3\theta)(\pi+\delta Y)}{\theta(\tau+\gamma I_1)(\lambda-\delta I_1)}(I-I_1)^2 - \frac{\delta\gamma H_1(\rho_1\varepsilon+\rho_3\theta)I_1}{\theta(\tau+\gamma I_1)(\lambda-\delta I_1)}(I-I_1)(Y-Y_1).
\end{aligned}
$$

This implies that

$$
\begin{aligned}
\frac{d\Theta_1}{dt} ={}& -\frac{\eta(H-H_1)^2}{H} + (\rho_1 H_1 V_1 + \rho_2 H_1 S_1 + \rho_3 H_1 Y_1)\left(2-\frac{H_1}{H}\right) + \rho_3 H_1 Y \\
&- \rho_1 H_1 V_1\left(\frac{HVS_1}{H_1V_1S}\right) - \rho_2 H_1 S_1\left(\frac{H}{H_1}\right) - \rho_3 H_1 Y_1\left(\frac{HYS_1}{H_1Y_1S}\right) \\
&- (\rho_1 H_1 V_1 + \rho_3 H_1 Y_1)\left(\frac{SY_1}{S_1Y}\right) - \frac{H_1(\rho_1\varepsilon+\rho_3\theta)}{\theta}(Y-Y_1) \\
&- \frac{\gamma H_1(\rho_1\varepsilon+\rho_3\theta)}{\theta(\tau+\gamma I_1)}(I-I_1)(Y-Y_1) + \rho_1 H_1 V_1\left(\frac{Y}{Y_1}\right) - \rho_1 H_1 V_1\left(\frac{YV_1}{Y_1V}\right) + \rho_1 H_1 V_1 \\
&+ \frac{\gamma H_1(\rho_1\varepsilon+\rho_3\theta)}{\theta(\tau+\gamma I_1)(\lambda-\delta I_1)}(\lambda-\delta I_1)(I-I_1)(Y-Y_1) - \frac{\gamma H_1(\rho_1\varepsilon+\rho_3\theta)(\pi+\delta Y)}{\theta(\tau+\gamma I_1)(\lambda-\delta I_1)}(I-I_1)^2 \\
={}& -\frac{\eta(H-H_1)^2}{H} + (\rho_1 H_1 V_1 + \rho_2 H_1 S_1 + \rho_3 H_1 Y_1)\left(2-\frac{H_1}{H}\right) + \rho_3 H_1 Y \\
&- \rho_1 H_1 V_1\left(\frac{HVS_1}{H_1V_1S}\right) - \rho_2 H_1 S_1\left(\frac{H}{H_1}\right) - \rho_3 H_1 Y_1\left(\frac{HYS_1}{H_1Y_1S}\right) \\
&- (\rho_1 H_1 V_1 + \rho_3 H_1 Y_1)\left(\frac{SY_1}{S_1Y}\right) - \frac{H_1(\rho_1\varepsilon+\rho_3\theta)Y_1}{\theta}\left(\frac{Y}{Y_1}-1\right) + \rho_1 H_1 V_1\left(\frac{Y}{Y_1}\right) \\
&- \rho_1 H_1 V_1\left(\frac{YV_1}{Y_1V}\right) + \rho_1 H_1 V_1 - \frac{\gamma H_1(\rho_1\varepsilon+\rho_3\theta)(\pi+\delta Y)}{\theta(\tau+\gamma I_1)(\lambda-\delta I_1)}(I-I_1)^2 \\
={}& -\frac{\eta(H-H_1)^2}{H} + (\rho_1 H_1 V_1 + \rho_2 H_1 S_1 + \rho_3 H_1 Y_1)\left(2-\frac{H_1}{H}\right) + \rho_3 H_1 Y \\
&- \rho_1 H_1 V_1\left(\frac{HVS_1}{H_1V_1S}\right) - \rho_2 H_1 S_1\left(\frac{H}{H_1}\right) - \rho_3 H_1 Y_1\left(\frac{HYS_1}{H_1Y_1S}\right) \\
&- (\rho_1 H_1 V_1 + \rho_3 H_1 Y_1)\left(\frac{SY_1}{S_1Y}\right) - (\rho_1 H_1 V_1 + \rho_3 H_1 Y_1)\left(\frac{Y}{Y_1}-1\right) \\
&+ \rho_1 H_1 V_1\left(\frac{Y}{Y_1}\right) - \rho_1 H_1 V_1\left(\frac{YV_1}{Y_1V}\right) + \rho_1 H_1 V_1 - \frac{\gamma H_1(\rho_1\varepsilon+\rho_3\theta)(\pi+\delta Y)}{\theta(\tau+\gamma I_1)(\lambda-\delta I_1)}(I-I_1)^2.
\end{aligned}
$$

Finally, we obtain

$$
\begin{aligned}
\frac{d\Theta_1}{dt} ={}& -\frac{(\eta+\rho_2 S_1)(H-H_1)^2}{H} + \rho_1 H_1 V_1\left(4-\frac{H_1}{H}-\frac{HVS_1}{H_1V_1S}-\frac{SY_1}{S_1Y}-\frac{YV_1}{Y_1V}\right) \\
&+ \rho_3 H_1 Y_1\left(3-\frac{H_1}{H}-\frac{HYS_1}{H_1Y_1S}-\frac{SY_1}{S_1Y}\right) - \frac{\gamma H_1(\rho_1\varepsilon+\rho_3\theta)(\pi+\delta Y)}{\theta(\tau+\gamma I_1)(\lambda-\delta I_1)}(I-I_1)^2.
\end{aligned}
$$

The geometrical and arithmetical means relationship implies

$$4 \le \frac{H_1}{H} + \frac{HVS_1}{H_1V_1S} + \frac{SY_1}{S_1Y} + \frac{YV_1}{Y_1V},$$
$$3 \le \frac{H_1}{H} + \frac{HYS_1}{H_1Y_1S} + \frac{SY_1}{S_1Y}.$$

Hence, if $\Re_0 > 1$, then $\frac{d\Theta_1}{dt} \le 0$ for all $H, S, Y, V, I > 0$. Additionally, $\frac{d\Theta_1}{dt} = 0$ when $H = H_1, S = S_1, Y = Y_1, V = V_1$ and $I = I_1$. Let Φ_1' be the largest invariant subset of $\Phi_1 = \left\{(H,S,Y,V,I) : \frac{d\Theta_1}{dt} = 0\right\}$. Therefore, $\Phi_1' = \{Q_1\}$. Applying L.I.P, we obtain that if $\Re_0 > 1$, then Q_1 is G.A.S [52]. □

3. Model with Distributed Time Delays

3.1. System Description

In the following model, we consider the distributed time delays in system (8) to become represented by delay differential equations (DDEs):

$$\begin{cases} \dot{H}(t) &= \alpha - \eta H(t) - \rho_1 H(t)V(t) - \rho_2 H(t)S(t) - \rho_3 H(t)Y(t), \\ \dot{S}(t) &= \int_0^{k_1} f_1(\varrho)e^{-h_1\varrho} H(t-\varrho)(\rho_1 V(t-\varrho) + \rho_2 S(t-\varrho) \\ & \quad +\rho_3 Y(t-\varrho))d\varrho - (\sigma+\mu)S(t), \\ \dot{Y}(t) &= \sigma \int_0^{k_2} f_2(\varrho)e^{-h_2\varrho} S(t-\varrho)d\varrho - \tau Y(t) - \gamma I(t)Y(t), \\ \dot{V}(t) &= \varepsilon \int_0^{k_3} f_3(\varrho)e^{-h_3\varrho} Y(t-\varrho)d\varrho - \theta V(t), \\ \dot{I}(t) &= \lambda Y(t) - \pi I(t) - \delta I(t)Y(t). \end{cases} \tag{23}$$

Here, $f_1(\varrho)e^{-h_1\varrho}$ demonstrates the probability that healthy CD4$^+$T cells contacted by HIV-1 particles or infected cells at time $t-\varrho$ and after surviving ϱ time units become latently infected cells at time t. The factor $f_2(\varrho)e^{-h_2\varrho}$ is the probability that latently infected cells after surviving ϱ time units turned to actively infected cells at time t. Further, the factor $f_3(\varrho)e^{-h_3\varrho}$ represents the probability of new HIV-1 particles after surviving ϱ time units and maturing at time t. Here, $h_i > 0$, $i = 1,2,3$ are constants. ϱ is the delay parameter taken from a probability distribution function $f_i(\varrho)$ over the interval $[0, k_i]$, $i = 1,2,3$, where k_i is the limit superior of the delay period. Function $f_i(\varrho)$, $i = 1,2,3$ satisfies the following conditions:

$$f_i(\varrho) > 0, \quad \int_0^{k_i} f_i(\varrho)d\varrho = 1, \quad \text{and} \quad \int_0^{k_i} f_i(\varrho)e^{-\beta\varrho}d\varrho < \infty, \quad \text{where} \quad \beta > 0.$$

Let $\bar{F}_i(\varrho) = f_i(\varrho)e^{-h_i\varrho}$ and $F_i = \int_0^{k_i} \bar{F}_i(\varrho)d\varrho$, $i = 1,2,3$. Therefore, $0 < F_i \le 1$, $i = 1,2,3$. The initial conditions of system (23) are:

$$\begin{cases} H(r) = a_1(r), & S(r) = a_2(r), \quad Y(r) = a_3(r), \quad V(r) = a_4(r), \quad I(r) = a_5(r), \\ a_j(r) \ge 0, & j = 1,2,\ldots,5, \quad r \in [-k, 0], \quad k = \max\{k_1, k_2, k_3\}, \end{cases} \tag{24}$$

where $a_j(r) \in C([-k,0], \mathbb{R}_{\ge 0})$, $j = 1,2,\ldots,5$ and $C = C([-k,0], \mathbb{R}_{\ge 0})$ is the Banach space of continuous functions with norm $\|a_j\| = \sup_{-k \le \zeta \le 0} |a_j(\zeta)|$ for all $a_j \in C$. Therefore, system (23) with initial conditions (24) has a unique solution [52,53]. The biological meaning of all remaining variables and parameters follow the same identifications as given in Section 2.

3.2. Basic Properties

3.2.1. Nonnegativity and Ultimate Boundedness of the Solutions

Lemma 3. *For system (23) together with initial conditions (24), there exists a compact set $\hat{\Omega}$ that is positively invariant, where*

$$\hat{\Omega} = \{(H,S,Y,V,I) \in C^5_{\ge 0} : \|H(t)\| \le \hat{\Lambda}_1, \|S(t)\| \le \hat{\Lambda}_1, \|Y(t)\| \le \hat{\Lambda}_2, \|I(t)\| \le \hat{\Lambda}_3, \|V(t)\| \le \hat{\Lambda}_4\}.$$

Proof. In the beginning we show the nonnegativity of solutions. From the first equation of system (23), we have $\dot{H}\mid_{H=0}=\alpha>0$, then $H(t)>0$, for all $t\geq 0$. In addition, from the remaining equations of system (23) we have

$$\begin{aligned}
&\dot{S}(t)+(\sigma+\mu)S(t)=\int_0^{k_1}\bar{F}_1(\varrho)H(t-\varrho)(\rho_1 V(t-\varrho)+\rho_2 S(t-\varrho)+\rho_3 Y(t-\varrho))d\varrho\\
&\Longrightarrow S(t)=a_2(0)e^{-(\sigma+\mu)t}+\int_0^t e^{-(\sigma+\mu)(t-\varkappa)}\int_0^{k_1}\bar{F}_1(\varrho)H(\varkappa-\varrho)(\rho_1 V(\varkappa-\varrho)\\
&\qquad\qquad+\rho_2 S(\varkappa-\varrho)+\rho_3 Y(\varkappa-\varrho))d\varrho d\varkappa\geq 0.\\
&\dot{Y}(t)+(\tau+\gamma I(t))Y(t)=\sigma\int_0^{k_2}\bar{F}_2(\varrho)S(t-\varrho)d\varrho\\
&\Longrightarrow Y(t)=a_3(0)e^{-\int_0^t(\tau+\gamma I(u))du}+\sigma\int_0^t e^{-\int_\varkappa^t(\tau+\gamma I(u))du}\int_0^{k_2}\bar{F}_2(\varrho)S(\varkappa-\varrho)d\varrho d\varkappa\geq 0.\\
&\dot{V}(t)+\theta V(t)=\varepsilon\int_0^{k_3}\bar{F}_3(\varrho)Y(t-\varrho)d\varrho\\
&\Longrightarrow V(t)=a_4(0)e^{-\theta t}+\varepsilon\int_0^t e^{-\theta(t-\varkappa)}\int_0^{k_3}\bar{F}_3(\varrho)Y(\varkappa-\varrho)d\varrho d\varkappa\geq 0.\\
&\dot{I}(t)+(\pi+\delta Y(t))I(t)=\lambda Y(t)\\
&\Longrightarrow I(t)=a_5(0)e^{-\int_0^t(\pi+\delta Y(u))du}+\lambda\int_0^t e^{-\int_\varkappa^t(\pi+\delta Y(u))du}Y(\varrho)d\varrho\geq 0,
\end{aligned}$$

for all $t\in[0,k]$. Then, by a recursive argument we have $H(t), S(t), Y(t), V(t)$ and $I(t)$ are nonnegative for all $t\geq 0$. Therefore, the solutions of system (23) satisfy $(H(t),S(t),Y(t),V(t),I(t))\in\mathbb{R}^5_{\geq 0}$, for all $t\geq 0$. Next, we prove the ultimate boundedness of all solutions. From the first equation of system (23), we have $\lim\limits_{t\to\infty}\sup H(t)\leq\dfrac{\alpha}{\eta}$. Next, we define

$$T_1(t)=\int_0^{k_1}\bar{F}_1(\varrho)H(t-\varrho)d\varrho+S(t).$$

Then

$$\begin{aligned}
\dot{T}_1(t)&=\int_0^{k_1}\bar{F}_1(\varrho)\dot{H}(t-\varrho)d\varrho+\dot{S}(t)\\
&=\int_0^{k_1}\bar{F}_1(\varrho)(\alpha-\eta H(t-\varrho))d\varrho-(\sigma+\mu)S(t)\\
&=\alpha F_1-\eta\int_0^{k_1}\bar{F}_1(\varrho)H(t-\varrho)d\varrho-(\sigma+\mu)S(t)\\
&\leq\alpha-\phi_1\left(\int_0^{k_1}\bar{F}_1(\varrho)H(t-\varrho)d\varrho+S(t)\right)=\alpha-\phi_1 T_1(t),
\end{aligned}$$

where $\phi_1=\min\{\eta,\sigma+\mu\}$. This implies that $\lim\limits_{t\to\infty}\sup T_1(t)\leq\dfrac{\alpha}{\phi_1}=\hat{\Lambda}_1$. Since $\int_0^{k_1}\bar{F}_1(\varrho)H(t-\varrho)d\varrho$ and $S(t)$ are nonnegative, then $\lim\limits_{t\to\infty}\sup S(t)\leq\hat{\Lambda}_1$. In addition, we let

$$T_2(t)=Y(t)+\frac{\tau}{2\lambda}I(t).$$

This yields

$$\begin{aligned}
\dot{T}_2(t) &= \dot{Y}(t) + \frac{\tau}{2\lambda}\dot{I}(t) \\
&= \sigma \int_0^{k_2} \bar{F}_2(\varrho)S(t-\varrho)d\varrho - \tau Y(t) - \gamma I(t)Y(t) \\
&\quad + \frac{\tau}{2\lambda}(\lambda Y(t) - \pi I(t) - \delta I(t)Y(t)) \\
&= \sigma \int_0^{k_2} \bar{F}_2(\varrho)S(t-\varrho)d\varrho - \frac{\tau}{2}Y(t) - \frac{\tau\pi}{2\lambda}I(t) - (\gamma + \frac{\tau\delta}{2\lambda})I(t)Y(t) \\
&\leq \sigma \int_0^{k_2} \bar{F}_2(\varrho)S(t-\varrho)d\varrho - \frac{\tau}{2}Y(t) - \frac{\tau\pi}{2\lambda}I(t) \\
&\leq \sigma\hat{\Lambda}_1 - \phi_2\Big(Y(t) + \frac{\tau}{2\lambda}I(t)\Big) = \sigma\hat{\Lambda}_1 - \phi_2 T_2(t),
\end{aligned}$$

where $\phi_2 = \min\{\frac{\tau}{2}, \pi\}$. Hence, $\limsup_{t\to\infty} T_2(t) \leq \frac{\sigma\hat{\Lambda}_1}{\phi_2} = \hat{\Lambda}_2$. Since $Y(t)$ and $I(t)$ are nonnegative, then $\limsup_{t\to\infty} Y(t) \leq \hat{\Lambda}_2$, and $\limsup_{t\to\infty} I(t) \leq \frac{2\lambda\hat{\Lambda}_2}{\tau} = \hat{\Lambda}_3$. Finally, from the fourth equation of system (23), we obtain

$$\dot{V}(t) = \varepsilon \int_0^{k_3} \bar{F}_3(\varrho)Y(t-\varrho)d\varrho - \theta V(t) \leq \varepsilon F_3\hat{\Lambda}_2 - \theta V(t) \leq \varepsilon\hat{\Lambda}_2 - \theta V(t).$$

Therefore, $\limsup_{t\to\infty} V(t) \leq \frac{\varepsilon\hat{\Lambda}_2}{\theta} = \hat{\Lambda}_4$. We conclude that $H(t), S(t), Y(t), V(t)$ and $I(t)$ are ultimately bounded. Thus, the compact set $\hat{\Omega}$ is positively invariant with respect to system (23). □

3.2.2. Reproduction Number and Equilibria

Lemma 4. *For system* (23)*, there exists a positive basic reproduction number* $\tilde{\Re}_0$ *such that*

(i) there exists only one equilibrium point $\tilde{Q}_0$ *when* $\tilde{\Re}_0 \leq 1$*, and*
(ii) there exists two equilibria $\tilde{Q}_0$ *and* $\tilde{Q}_1$ *when* $\tilde{\Re}_0 > 1$.

Proof. It is clear that system (23) always has an infection-free equilibrium $\tilde{Q}_0 = (\tilde{H}_0, 0, 0, 0, 0)$, where $\tilde{H}_0 = \dfrac{\alpha}{\eta}$. In the following, we will apply the method of next generation matrix to determine the basic reproduction number of system (23). Based on the infected compartments in model (23), ordered (S, Y, V). The nonlinear terms with new infection $\hat{\Gamma}_2$ and the outflow term $\hat{\Delta}_2$ are given by the following matrices:

$$\hat{\Gamma}_2 = \begin{pmatrix} F_1(\rho_1 HV + \rho_2 HS + \rho_3 HY) \\ 0 \\ 0 \end{pmatrix}, \quad \hat{\Delta}_2 = \begin{pmatrix} (\sigma+\mu)S \\ -\sigma F_2 S + \tau Y + \gamma IY \\ -\varepsilon F_3 Y + \theta V \end{pmatrix}.$$

We compute the derivative of $\hat{\Gamma}_2$ and $\hat{\Delta}_2$ at the equilibrium $\tilde{Q}_0$ to obtain the following matrices:

$$\Gamma_2 = \begin{pmatrix} F_1\rho_2\tilde{H}_0 & F_1\rho_3\tilde{H}_0 & F_1\rho_1\tilde{H}_0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}, \quad \Delta_2 = \begin{pmatrix} \sigma+\mu & 0 & 0 \\ -\sigma F_2 & \tau & 0 \\ 0 & -\varepsilon F_3 & \theta \end{pmatrix}.$$

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

$$\Gamma_2\Delta_2^{-1} = \begin{pmatrix} \frac{F_1\tilde{H}_0(F_2\sigma(F_3\rho_1\varepsilon+\rho_3\theta)+\rho_2\theta\tau)}{(\sigma+\mu)\theta\tau} & \frac{F_1\tilde{H}_0(F_3\rho_1\varepsilon+\rho_3\theta)}{\theta\tau} & \frac{F_1\tilde{H}_0\rho_1}{\theta} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}.$$

The basic reproduction number $\tilde{\Re}_0$ is the spectral radius of the matrix $\Gamma_2\Delta_2^{-1}$ and is given as:

$$\tilde{\Re}_0 = \frac{F_1\tilde{H}_0(F_2\sigma(F_3\rho_1\varepsilon + \rho_3\theta) + \rho_2\theta\tau)}{(\sigma+\mu)\theta\tau} = \tilde{\Re}_{01} + \tilde{\Re}_{02} + \tilde{\Re}_{03}, \tag{25}$$

where

$$\tilde{\Re}_{01} = \frac{F_1F_2F_3\tilde{H}_0\varepsilon\sigma\rho_1}{\theta\tau(\sigma+\mu)}, \qquad \tilde{\Re}_{02} = \frac{F_1\tilde{H}_0\rho_2}{\sigma+\mu}, \qquad \tilde{\Re}_{03} = \frac{F_1F_2\tilde{H}_0\sigma\rho_3}{\tau(\sigma+\mu)}.$$

Note that all parameters $\tilde{\Re}_{0i}$, $i = 1,2,3$ have the same biological meaning as the parameters $\Re_{0i}$, $i = 1,2,3$ that are explained in Section 2. To find the other equilibrium in addition to $\tilde{Q}_0$, we let (H, S, Y, V, I) be any equilibrium satisfying the following equations:

$$0 = \alpha - \eta H - \rho_1 HV - \rho_2 HS - \rho_3 HY, \tag{26}$$
$$0 = F_1(\rho_1 HV + \rho_2 HS + \rho_3 HY) - (\sigma+\mu)S, \tag{27}$$
$$0 = \sigma F_2 S - \tau Y - \gamma IY, \tag{28}$$
$$0 = \varepsilon F_3 Y - \theta V, \tag{29}$$
$$0 = \lambda Y - \pi I - \delta IY. \tag{30}$$

From Equations (29) and (30), we obtain

$$V = \frac{\varepsilon F_3 Y}{\theta}, \qquad I = \frac{\lambda Y}{\pi + \delta Y}. \tag{31}$$

Substituting from Equation (31) into Equation (28), we obtain

$$S = \frac{\pi\tau Y + (\gamma\lambda + \tau\delta)Y^2}{\sigma F_2(\pi + \delta Y)}. \tag{32}$$

From Equations (26) and (27), we obtain

$$\alpha - \eta H = \frac{(\sigma+\mu)S}{F_1}. \tag{33}$$

Substituting from Equation (32) into Equation (33), we obtain

$$H = \frac{1}{\eta}\left(\alpha - \frac{(\sigma+\mu)\left(\pi\tau Y + (\gamma\lambda+\tau\delta)Y^2\right)}{\sigma F_1 F_2(\pi+\delta Y)}\right). \tag{34}$$

Substituting from Equations (31), (32) and (34) into Equation (27), we obtain

$$\frac{Y}{\eta\theta\sigma^2 F_2^2(\pi+\delta Y)^2}\left(\tilde{A}Y^3 + \tilde{B}Y^2 + \tilde{C}Y + \tilde{D}\right) = 0, \tag{35}$$

where

$$\begin{aligned}
\tilde{A} &= (\sigma+\mu)(\gamma\lambda+\tau\delta)(\theta\rho_2(\gamma\lambda+\tau\delta) + \delta\sigma F_2(\varepsilon F_3\rho_1 + \theta\rho_3)),\\
\tilde{B} &= (\sigma+\mu)(\gamma\lambda+\tau\delta)(\delta\sigma\eta\theta F_2 + \pi\theta\tau\rho_2 + \pi\sigma F_2(\varepsilon F_3\rho_1 + \theta\rho_3))\\
&\quad + (\pi\tau(\sigma+\mu) - \alpha\delta\sigma F_1F_2)(\theta\rho_2(\gamma\lambda+\tau\delta) + \delta\sigma F_2(\varepsilon F_3\rho_1 + \theta\rho_3)),\\
\tilde{C} &= \pi\Big(\pi\theta\rho_2\tau^2(\sigma+\mu) - 2\alpha\delta\sigma^2F_1F_2^2(\varepsilon F_3\rho_1 + \theta\rho_3) + \sigma F_2(\pi\varepsilon\tau F_3\rho_1(\sigma+\mu)\\
&\quad + \theta(\gamma\lambda + 2\tau\delta)(\eta(\sigma+\mu) - \alpha F_1\rho_2) + \pi\theta\tau\rho_3(\sigma+\mu)),\\
\tilde{D} &= \sigma\eta\theta\tau F_2\pi^2(\sigma+\mu)(1 - \tilde{\Re}_0),
\end{aligned}$$

where $\tilde{\Re}_0$ is defined by Equation (25). From Equation (35), we have

1. If $Y = 0$, then from Equations (31), (32) and (34) we obtain the infection-free equilibrium $\tilde{Q}_0$.
2. If $Y \neq 0$, then we have $\tilde{A}Y^3 + \tilde{B}Y^2 + \tilde{C}Y + \tilde{D} = 0$. In this case, let us define a function $\bar{\Psi}(Y)$ on $[0, \infty)$ as:
$$\bar{\Psi}(Y) = \tilde{A}Y^3 + \tilde{B}Y^2 + \tilde{C}Y + \tilde{D}.$$
We have
$$\bar{\Psi}(0) = \sigma\eta\theta\tau F_2\pi^2(\sigma+\mu)(1-\tilde{\Re}_0) < 0 \text{ if } \tilde{\Re}_0 > 1,$$
$$\lim_{Y\to\infty} \bar{\Psi}(Y) = \infty,$$
which show that $\bar{\Psi}$ has a positive real root $\tilde{Y}_1$. Then, by substituting from Equations (31) and (32) into Equation (26), we obtain
$$\tilde{H}_1 = \frac{\alpha}{\eta + \rho_1\tilde{V}_1 + \rho_2\tilde{S}_1 + \rho_3\tilde{Y}_1},$$
where
$$\tilde{S}_1 = \frac{\pi\tau\tilde{Y}_1 + (\gamma\lambda + \tau\delta)\tilde{Y}_1^2}{\sigma F_2(\pi + \delta\tilde{Y}_1)}, \quad \tilde{V}_1 = \frac{\varepsilon F_3\tilde{Y}_1}{\theta}, \quad \tilde{I}_1 = \frac{\lambda\tilde{Y}_1}{\pi + \delta\tilde{Y}_1}.$$

It is clear that the infected equilibrium $\tilde{Q}_1 = (\tilde{H}_1, \tilde{S}_1, \tilde{Y}_1, \tilde{V}_1, \tilde{I}_1)$ exists when $\tilde{\Re}_0 > 1$. □

3.2.3. Stability of Equilibria $\tilde{Q}_0$ and $\tilde{Q}_1$

In the following theorems, global asymptotic stability of equilibria will be discussed.

Theorem 4. *For system (23), if $\tilde{\Re}_0 < 1$, then $\tilde{Q}_0$ is G.A.S and it is unstable when $\tilde{\Re}_0 > 1$.*

Proof. Consider
$$\begin{aligned}
\tilde{\Theta}_0 &= \tilde{H}_0 F\left(\frac{H}{\tilde{H}_0}\right) + \frac{1}{F_1}S + \frac{(\sigma+\mu)(1-\tilde{\Re}_{02})}{\sigma F_1 F_2}Y + \frac{\rho_1\tilde{H}_0}{\theta}V + \frac{\tau(\sigma+\mu)(1-\tilde{\Re}_0)}{\lambda\sigma F_1F_2}I \\
&+ \frac{1}{F_1}\int_0^{k_1}\bar{F}_1(\varrho)\int_{t-\varrho}^{t} H(\varkappa)(\rho_1V(\varkappa) + \rho_2S(\varkappa) + \rho_3Y(\varkappa))d\varkappa d\varrho \\
&+ \frac{(\sigma+\mu)(1-\tilde{\Re}_{02})}{F_1F_2}\int_0^{k_2}\bar{F}_2(\varrho)\int_{t-\varrho}^{t} S(\varkappa)d\varkappa d\varrho \\
&+ \frac{\rho_1\tilde{H}_0\varepsilon}{\theta}\int_0^{k_3}\bar{F}_3(\varrho)\int_{t-\varrho}^{t} Y(\varkappa)d\varkappa d\varrho.
\end{aligned}$$

Clearly, $\tilde{\Theta}_0(H, S, Y, V, I) > 0$ for all $H, S, Y, V, I > 0$, and $\tilde{\Theta}_0(H_0, 0, 0, 0, 0) = 0$. We calculate $\frac{d\tilde{\Theta}_0}{dt}$ as:
$$\begin{aligned}
\frac{d\tilde{\Theta}_0}{dt} &= \left(1 - \frac{\tilde{H}_0}{H}\right)\frac{dH}{dt} + \frac{1}{F_1}\frac{dS}{dt} + \frac{(\sigma+\mu)(1-\tilde{\Re}_{02})}{\sigma F_1F_2}\frac{dY}{dt} + \frac{\rho_1\tilde{H}_0}{\theta}\frac{dV}{dt} + \frac{\tau(\sigma+\mu)(1-\tilde{\Re}_0)}{\lambda\sigma F_1F_2}\frac{dI}{dt} \\
&+ H(\rho_1V + \rho_2S + \rho_3Y) - \frac{1}{F_1}\int_0^{k_1}\bar{F}_1(\varrho)H(t-\varrho)(\rho_1V(t-\varrho) + \rho_2S(t-\varrho) + \rho_3Y(t-\varrho))d\varrho \\
&+ \frac{(\sigma+\mu)(1-\tilde{\Re}_{02})}{F_1}S - \frac{(\sigma+\mu)(1-\tilde{\Re}_{02})}{F_1F_2}\int_0^{k_2}\bar{F}_2(\varrho)S(t-\varrho)d\varrho \\
&+ \frac{\rho_1\tilde{H}_0\varepsilon F_3}{\theta}Y - \frac{\rho_1\tilde{H}_0\varepsilon}{\theta}\int_0^{k_3}\bar{F}_3(\varrho)Y(t-\varrho)d\varrho \\
&= \left(1 - \frac{\tilde{H}_0}{H}\right)(\alpha - \eta H - \rho_1HV - \rho_2HS - \rho_3HY) + \frac{1}{F_1}\int_0^{k_1}\bar{F}_1(\varrho)H(t-\varrho)(\rho_1V(t-\varrho)
\end{aligned}$$

$$
\begin{aligned}
&+\rho_2 S(t-\varrho)+\rho_3 Y(t-\varrho))d\varrho-\frac{(\sigma+\mu)S}{F_1}+\frac{(\sigma+\mu)(1-\tilde{\Re}_{02})}{F_1F_2}\int_0^{k_2}\bar{F}_2(\varrho)S(t-\varrho)d\varrho\\
&-\frac{\tau(\sigma+\mu)(1-\tilde{\Re}_{02})}{\sigma F_1F_2}Y-\frac{\gamma(\sigma+\mu)(1-\tilde{\Re}_{02})}{\sigma F_1F_2}IY+\frac{\rho_1\tilde{H}_0\varepsilon}{\theta}\int_0^{k_3}\bar{F}_3(\varrho)Y(t-\varrho)d\varrho\\
&-\rho_1\tilde{H}_0V+\frac{\tau(\sigma+\mu)(1-\tilde{\Re}_0)}{\lambda\sigma F_1F_2}(\lambda Y-\pi I-\delta IY)+\rho_1 HV+\rho_2 HS+\rho_3 HY\\
&-\frac{1}{F_1}\int_0^{k_1}\bar{F}_1(\varrho)H(t-\varrho)(\rho_1 V(t-\varrho)+\rho_2 S(t-\varrho)+\rho_3 Y(t-\varrho))d\varrho\\
&+\frac{(\sigma+\mu)(1-\tilde{\Re}_{02})}{F_1}S-\frac{(\sigma+\mu)(1-\tilde{\Re}_{02})}{F_1F_2}\int_0^{k_2}\bar{F}_2(\varrho)S(t-\varrho)d\varrho+\frac{\rho_1\tilde{H}_0\varepsilon F_3}{\theta}Y\\
&-\frac{\rho_1\tilde{H}_0\varepsilon}{\theta}\int_0^{k_3}\bar{F}_3(\varrho)Y(t-\varrho)d\varrho.
\end{aligned}
$$

After direct calculation and using $\tilde{H}_0=\alpha/\eta$, we obtain

$$
\begin{aligned}
\frac{d\tilde{\Theta}_0}{dt}&=\left(1-\frac{\tilde{H}_0}{H}\right)(\eta\tilde{H}_0-\eta H)-\frac{\pi\tau(\sigma+\mu)(1-\tilde{\Re}_0)}{\lambda\sigma F_1F_2}I-\frac{\sigma+\mu}{\lambda\sigma F_1F_2}(\gamma\lambda(1-\tilde{\Re}_{02})+\tau\delta(1-\tilde{\Re}_0))IY\\
&=-\frac{\eta(H-\tilde{H}_0)^2}{H}-\frac{\pi\tau(\sigma+\mu)(1-\tilde{\Re}_0)}{\lambda\sigma F_1F_2}I-\frac{\sigma+\mu}{\lambda\sigma F_1F_2}(\gamma\lambda(1-\tilde{\Re}_{02})+\tau\delta(1-\tilde{\Re}_0))IY.
\end{aligned}
$$

Clearly, $\frac{d\tilde{\Theta}_0}{dt}\leq 0$ when $\tilde{\Re}_0<1$ with equality holding when $H=\tilde{H}_0$ and $Y=I=0$. Let $\bar{\Phi}_0=\left\{(H,S,Y,V,I):\frac{d\tilde{\Theta}_0}{dt}=0\right\}$, and $\bar{\Phi}_0'$ be the largest invariant subset of $\bar{\Phi}_0$. Therefore, all solutions converge to $\bar{\Phi}_0'$ [52]. All elements in $\bar{\Phi}_0'$ satisfy $H(t)=\tilde{H}_0$ and $Y(t)=I(t)=0$. Then, the third equation of system (23) gives

$$0=\dot{Y}(t)=\sigma\int_0^{k_2}\bar{F}_2(\varrho)S(t-\varrho)d\varrho.$$

The nonnegativity of S implies that $S(t)=0$ for all t. Moreover, the first equation of model (23) yields

$$0=\dot{H}(t)=\alpha-\eta\tilde{H}_0-\rho_1\tilde{H}_0V(t)\Longrightarrow V(t)=0,\ \text{for all } t.$$

Therefore, $\bar{\Phi}_0'=\{(H,S,Y,V,I)\in\bar{\Phi}_0:H=\tilde{H}_0,S=Y=V=I=0\}=\{\tilde{Q}_0\}$. Hence, according to L.I.P, we obtain that when $\tilde{\Re}_0<1$, then $\tilde{Q}_0$ is G.A.S [52].

On the other hand, model (23) can be rewritten as:

$$\dot{U}(t)=\mathcal{F}(U(t),U(t-\varrho)),$$

where $U(t)=(H(t),S(t),Y(t),V(t),I(t))^T$. This system is a coupled system of ordinary differential equations with a delay parameter, using total differentiation at $\tilde{Q}_0$ we have

$$
\begin{cases}
\dot{H}=\frac{\partial\mathcal{F}}{\partial H}|_{\tilde{Q}_0}H+\frac{\partial\mathcal{F}}{\partial S}|_{\tilde{Q}_0}S+\frac{\partial\mathcal{F}}{\partial Y}|_{\tilde{Q}_0}Y+\frac{\partial\mathcal{F}}{\partial V}|_{\tilde{Q}_0}V+\frac{\partial\mathcal{F}}{\partial I}|_{\tilde{Q}_0}I,\\
\dot{S}=\frac{\partial\mathcal{F}}{\partial H}|_{\tilde{Q}_0}H+\frac{\partial\mathcal{F}}{\partial S}|_{\tilde{Q}_0}S+\frac{\partial\mathcal{F}}{\partial Y}|_{\tilde{Q}_0}Y+\frac{\partial\mathcal{F}}{\partial V}|_{\tilde{Q}_0}V+\frac{\partial\mathcal{F}}{\partial I}|_{\tilde{Q}_0}I,\\
\dot{Y}=\frac{\partial\mathcal{F}}{\partial H}|_{\tilde{Q}_0}H+\frac{\partial\mathcal{F}}{\partial S}|_{\tilde{Q}_0}S+\frac{\partial\mathcal{F}}{\partial Y}|_{\tilde{Q}_0}Y+\frac{\partial\mathcal{F}}{\partial V}|_{\tilde{Q}_0}V+\frac{\partial\mathcal{F}}{\partial I}|_{\tilde{Q}_0}I,\\
\dot{V}=\frac{\partial\mathcal{F}}{\partial H}|_{\tilde{Q}_0}H+\frac{\partial\mathcal{F}}{\partial S}|_{\tilde{Q}_0}S+\frac{\partial\mathcal{F}}{\partial Y}|_{\tilde{Q}_0}Y+\frac{\partial\mathcal{F}}{\partial V}|_{\tilde{Q}_0}V+\frac{\partial\mathcal{F}}{\partial I}|_{\tilde{Q}_0}I,\\
\dot{I}=\frac{\partial\mathcal{F}}{\partial H}|_{\tilde{Q}_0}H+\frac{\partial\mathcal{F}}{\partial S}|_{\tilde{Q}_0}S+\frac{\partial\mathcal{F}}{\partial Y}|_{\tilde{Q}_0}Y+\frac{\partial\mathcal{F}}{\partial V}|_{\tilde{Q}_0}V+\frac{\partial\mathcal{F}}{\partial I}|_{\tilde{Q}_0}I.
\end{cases}
\tag{36}
$$

Suppose that the linear DDEs system (36) has exponential solutions.

$$H=e^{xt}W_H,\quad S=e^{xt}W_S,\quad Y=e^{xt}W_Y,\quad V=e^{xt}W_V,\quad I=e^{xt}W_I.$$

Substituting this ansatz into system (36) and rearranging it, we obtain $AW = 0$, where

$$A = \begin{bmatrix} x+\eta & \rho_2\tilde{H}_0 & \rho_3\tilde{H}_0 & \rho_1\tilde{H}_0 & 0 \\ 0 & x+\sigma+\mu-\rho_2\tilde{H}_0\hat{F}_1 & -\rho_3\tilde{H}_0\hat{F}_1 & -\rho_1\tilde{H}_0\hat{F}_1 & 0 \\ 0 & -\sigma\hat{F}_2 & x+\tau & 0 & 0 \\ 0 & 0 & -\varepsilon\hat{F}_3 & x+\theta & 0 \\ 0 & 0 & -\lambda & 0 & x+\pi \end{bmatrix}, \quad W = \begin{bmatrix} W_H \\ W_S \\ W_Y \\ W_V \\ W_I \end{bmatrix}.$$

Note that the characteristic equation is the set of x such that matrix A is not invertible, which means $\det(A) = 0$, then the characteristic equation of system (23) at $\tilde{Q}_0$ is given by $(x+\pi)(x+\eta)\tilde{K}(x) = 0$, where $\tilde{K}(x)$ is a continuous function defined on $[0,\infty)$ as:

$$\begin{aligned} \tilde{K}(x) = {} & x^3 + \left(\theta+\sigma+\mu+\tau-\tilde{H}_0\hat{F}_1\rho_2\right)x^2 \\ & + \left(\tau\left(\sigma+\mu-\tilde{H}_0\hat{F}_1\rho_2\right) + \theta\left(\sigma+\mu+\tau-\tilde{H}_0\hat{F}_1\rho_2\right) - \sigma\tilde{H}_0\hat{F}_1\hat{F}_2\rho_3\right)x \\ & - \sigma\varepsilon\tilde{H}_0\hat{F}_1\hat{F}_2\hat{F}_3\rho_1 + \theta\left(\tau\left(\sigma+\mu-\tilde{H}_0\hat{F}_1\rho_2\right) - \sigma\tilde{H}_0\hat{F}_1\hat{F}_2\rho_3\right), \end{aligned}$$

where $\hat{F}_i = \int_0^{k_i} f_i(\varrho)e^{-(x+h_i)\varrho}d\varrho$, $i = 1,2,3$. Let $\tilde{\Re}_0 > 1$, then we have $\tilde{K}(0) = \theta\tau(\sigma+\mu)\left(1-\tilde{\Re}_0\right) < 0$ and $\lim\limits_{x\to\infty}\tilde{K}(x) = \infty$, which implies that $\tilde{K}(x)$ has a positive real root. Hence, $\tilde{Q}_0$ is unstable when $\tilde{\Re}_0 > 1$. □

Theorem 5. *For system (23), if $\tilde{\Re}_0 > 1$, then $\tilde{Q}_1$ is G.A.S.*

Proof. Define

$$\begin{aligned} \tilde{\Theta}_1 = {} & \tilde{H}_1 F\left(\frac{H}{\tilde{H}_1}\right) + \frac{\tilde{S}_1}{F_1}F\left(\frac{S}{\tilde{S}_1}\right) + \frac{\tilde{H}_1(F_3\rho_1\varepsilon+\rho_3\theta)\tilde{Y}_1}{\theta(\tau+\gamma\tilde{I}_1)}F\left(\frac{Y}{\tilde{Y}_1}\right) + \frac{\rho_1\tilde{H}_1\tilde{V}_1}{\theta}F\left(\frac{V}{\tilde{V}_1}\right) \\ & + \frac{\gamma\tilde{H}_1(F_3\rho_1\varepsilon+\rho_3\theta)}{2\theta(\tau+\gamma\tilde{I}_1)(\lambda-\delta\tilde{I}_1)}\left(I-\tilde{I}_1\right)^2 + \frac{\rho_1\tilde{H}_1\tilde{V}_1}{F_1}\int_0^{k_1}\bar{F}_1(\varrho)\int_{t-\varrho}^{t}F\left(\frac{H(\varkappa)V(\varkappa)}{\tilde{H}_1\tilde{V}_1}\right)d\varkappa d\varrho \\ & + \frac{\rho_2\tilde{H}_1\tilde{S}_1}{F_1}\int_0^{k_1}\bar{F}_1(\varrho)\int_{t-\varrho}^{t}F\left(\frac{H(\varkappa)S(\varkappa)}{\tilde{H}_1\tilde{S}_1}\right)d\varkappa d\varrho + \frac{\rho_3\tilde{H}_1\tilde{Y}_1}{F_1}\int_0^{k_1}\bar{F}_1(\varrho)\int_{t-\varrho}^{t}F\left(\frac{H(\varkappa)Y(\varkappa)}{\tilde{H}_1\tilde{Y}_1}\right)d\varkappa d\varrho \\ & + \frac{\sigma\tilde{H}_1\tilde{S}_1(F_3\rho_1\varepsilon+\rho_3\theta)}{\theta(\tau+\gamma\tilde{I}_1)}\int_0^{k_2}\bar{F}_2(\varrho)\int_{t-\varrho}^{t}F\left(\frac{S(\varkappa)}{\tilde{S}_1}\right)d\varkappa d\varrho \\ & + \frac{\rho_1\tilde{H}_1\varepsilon\tilde{Y}_1}{\theta}\int_0^{k_3}\bar{F}_3(\varrho)\int_{t-\varrho}^{t}F\left(\frac{Y(\varkappa)}{\tilde{Y}_1}\right)d\varkappa d\varrho. \end{aligned}$$

It is noted from the equilibrium condition Equation (30) that $\lambda - \delta\tilde{I}_1 = \dfrac{\pi\tilde{I}_1}{\tilde{Y}_1} > 0$. It is clear that $\tilde{\Theta}_1$ is positive definite. We calculate $\frac{d\tilde{\Theta}_1}{dt}$ along the solutions of model (23) as:

$$\begin{aligned} \frac{d\tilde{\Theta}_1}{dt} = {} & \left(1-\frac{\tilde{H}_1}{H}\right)\frac{dH}{dt} + \frac{1}{F_1}\left(1-\frac{\tilde{S}_1}{S}\right)\frac{dS}{dt} + \frac{\tilde{H}_1(F_3\rho_1\varepsilon+\rho_3\theta)}{\theta(\tau+\gamma\tilde{I}_1)}\left(1-\frac{\tilde{Y}_1}{Y}\right)\frac{dY}{dt} + \frac{\rho_1\tilde{H}_1}{\theta}\left(1-\frac{\tilde{V}_1}{V}\right)\frac{dV}{dt} \\ & + \frac{\gamma\tilde{H}_1(F_3\rho_1\varepsilon+\rho_3\theta)}{\theta(\tau+\gamma\tilde{I}_1)(\lambda-\delta\tilde{I}_1)}\left(I-\tilde{I}_1\right)\frac{dI}{dt} + \frac{\rho_1\tilde{H}_1\tilde{V}_1}{F_1}\int_0^{k_1}\bar{F}_1(\varrho)\left(\frac{HV}{\tilde{H}_1\tilde{V}_1} - 1 - \ln\left(\frac{HV}{\tilde{H}_1\tilde{V}_1}\right)\right. \\ & \left. - \frac{H(t-\varrho)V(t-\varrho)}{\tilde{H}_1\tilde{V}_1} + 1 + \ln\left(\frac{H(t-\varrho)V(t-\varrho)}{\tilde{H}_1\tilde{V}_1}\right)\right)d\varrho + \frac{\rho_2\tilde{H}_1\tilde{S}_1}{F_1}\int_0^{k_1}\bar{F}_1(\varrho)\left(\frac{HS}{\tilde{H}_1\tilde{S}_1} - 1\right. \\ & \left. - \ln\left(\frac{HS}{\tilde{H}_1\tilde{S}_1}\right) - \frac{H(t-\varrho)S(t-\varrho)}{\tilde{H}_1\tilde{S}_1} + 1 + \ln\left(\frac{H(t-\varrho)S(t-\varrho)}{\tilde{H}_1\tilde{S}_1}\right)\right)d\varrho \\ & + \frac{\rho_3\tilde{H}_1\tilde{Y}_1}{F_1}\int_0^{k_1}\bar{F}_1(\varrho)\left(\frac{HY}{\tilde{H}_1\tilde{Y}_1} - 1 - \ln\left(\frac{HY}{\tilde{H}_1\tilde{Y}_1}\right) - \frac{H(t-\varrho)Y(t-\varrho)}{\tilde{H}_1\tilde{Y}_1}\right. \\ & \left. + 1 + \ln\left(\frac{H(t-\varrho)Y(t-\varrho)}{\tilde{H}_1\tilde{Y}_1}\right)\right)d\varrho + \frac{\sigma\tilde{H}_1\tilde{S}_1(F_3\rho_1\varepsilon+\rho_3\theta)}{\theta(\tau+\gamma\tilde{I}_1)}\int_0^{k_2}\bar{F}_2(\varrho)\left(\frac{S}{\tilde{S}_1} - 1 - \ln\left(\frac{S}{\tilde{S}_1}\right)\right. \end{aligned}$$

$$
\begin{aligned}
&-\frac{S(t-\varrho)}{\tilde{S}_1}+1+\ln\left(\frac{S(t-\varrho)}{\tilde{S}_1}\right)\bigg)d\varrho+\frac{\rho_1\tilde{H}_1\varepsilon\tilde{Y}_1}{\theta}\int_0^{k_3}\bar{F}_3(\varrho)\bigg(\frac{Y}{\tilde{Y}_1}-1-\ln\left(\frac{Y}{\tilde{Y}_1}\right)\\
&-\frac{Y(t-\varrho)}{\tilde{Y}_1}+1+\ln\left(\frac{Y(t-\varrho)}{\tilde{Y}_1}\right)\bigg)d\varrho\\
=&\left(1-\frac{\tilde{H}_1}{H}\right)(\alpha-\eta H-\rho_1 HV-\rho_2 HS-\rho_3 HY)\\
&+\frac{1}{F_1}\left(1-\frac{\tilde{S}_1}{S}\right)\left(\int_0^{k_1}\bar{F}_1(\varrho)H(t-\varrho)(\rho_1 V(t-\varrho)+\rho_2 S(t-\varrho)+\rho_3 Y(t-\varrho))d\varrho-(\sigma+\mu)S\right)\\
&+\frac{\tilde{H}_1(F_3\rho_1\varepsilon+\rho_3\theta)}{\theta(\tau+\gamma\tilde{I}_1)}\left(1-\frac{\tilde{Y}_1}{Y}\right)\left(\sigma\int_0^{k_2}\bar{F}_2(\varrho)S(t-\varrho)d\varrho-\tau Y-\gamma IY\right)\\
&+\frac{\rho_1\tilde{H}_1}{\theta}\left(1-\frac{\tilde{V}_1}{V}\right)\left(\varepsilon\int_0^{k_3}\bar{F}_3(\varrho)Y(t-\varrho)d\varrho-\theta V\right)\\
&+\frac{\gamma\tilde{H}_1(F_3\rho_1\varepsilon+\rho_3\theta)}{\theta(\tau+\gamma\tilde{I}_1)(\lambda-\delta\tilde{I}_1)}(I-\tilde{I}_1)(\lambda Y-\pi I-\delta IY)\\
&+\frac{\rho_1\tilde{H}_1\tilde{V}_1}{F_1}\left(\frac{F_1 HV}{\tilde{H}_1\tilde{V}_1}-\int_0^{k_1}\bar{F}_1(\varrho)\left(\frac{H(t-\varrho)V(t-\varrho)}{\tilde{H}_1\tilde{V}_1}-\ln\left(\frac{H(t-\varrho)V(t-\varrho)}{HV}\right)\right)d\varrho\right)\\
&+\frac{\rho_2\tilde{H}_1\tilde{S}_1}{F_1}\left(\frac{F_1 HS}{\tilde{H}_1\tilde{S}_1}-\int_0^{k_1}\bar{F}_1(\varrho)\left(\frac{H(t-\varrho)S(t-\varrho)}{\tilde{H}_1\tilde{S}_1}-\ln\left(\frac{H(t-\varrho)S(t-\varrho)}{HS}\right)\right)d\varrho\right)\\
&+\frac{\rho_3\tilde{H}_1\tilde{Y}_1}{F_1}\left(\frac{F_1 HY}{\tilde{H}_1\tilde{Y}_1}-\int_0^{k_1}\bar{F}_1(\varrho)\left(\frac{H(t-\varrho)Y(t-\varrho)}{\tilde{H}_1\tilde{Y}_1}-\ln\left(\frac{H(t-\varrho)Y(t-\varrho)}{HY}\right)\right)d\varrho\right)\\
&+\frac{\sigma\tilde{H}_1\tilde{S}_1(F_3\rho_1\varepsilon+\rho_3\theta)}{\theta(\tau+\gamma\tilde{I}_1)}\left(\frac{F_2 S}{\tilde{S}_1}-\int_0^{k_2}\bar{F}_2(\varrho)\left(\frac{S(t-\varrho)}{\tilde{S}_1}-\ln\left(\frac{S(t-\varrho)}{S}\right)\right)d\varrho\right)\\
&+\frac{\rho_1\tilde{H}_1\varepsilon\tilde{Y}_1}{\theta}\left(\frac{F_3 Y}{\tilde{Y}_1}-\int_0^{k_3}\bar{F}_3(\varrho)\left(\frac{Y(t-\varrho)}{\tilde{Y}_1}-\ln\left(\frac{Y(t-\varrho)}{Y}\right)\right)d\varrho\right).
\end{aligned}
$$

Thus,

$$
\begin{aligned}
\frac{d\tilde{\Theta}_1}{dt}=&\left(1-\frac{\tilde{H}_1}{H}\right)(\alpha-\eta H)+\left(\rho_2\tilde{H}_1-\frac{\sigma+\mu}{F_1}+\frac{\sigma F_2\tilde{H}_1(F_3\rho_1\varepsilon+\rho_3\theta)}{\theta(\tau+\gamma\tilde{I}_1)}\right)S+\rho_3\tilde{H}_1 Y\\
&-\frac{1}{F_1}\int_0^{k_1}\bar{F}_1(\varrho)\frac{H(t-\varrho)\tilde{S}_1}{S}(\rho_1 V(t-\varrho)+\rho_2 S(t-\varrho)+\rho_3 Y(t-\varrho))d\varrho+\frac{(\sigma+\mu)\tilde{S}_1}{F_1}\\
&-\frac{\sigma\tilde{H}_1(F_3\rho_1\varepsilon+\rho_3\theta)}{\theta(\tau+\gamma\tilde{I}_1)}\int_0^{k_2}\bar{F}_2(\varrho)\frac{S(t-\varrho)\tilde{Y}_1}{Y}d\varrho-\frac{\tau\tilde{H}_1(F_3\rho_1\varepsilon+\rho_3\theta)}{\theta(\tau+\gamma\tilde{I}_1)}(Y-\tilde{Y}_1)\\
&-\frac{\gamma\tilde{H}_1(F_3\rho_1\varepsilon+\rho_3\theta)}{\theta(\tau+\gamma\tilde{I}_1)}I(Y-\tilde{Y}_1)-\frac{\rho_1\tilde{H}_1\varepsilon}{\theta}\int_0^{k_3}\bar{F}_3(\varrho)\frac{Y(t-\varrho)\tilde{V}_1}{V}d\varrho+\rho_1\tilde{H}_1\tilde{V}_1\\
&+\frac{\gamma\tilde{H}_1(F_3\rho_1\varepsilon+\rho_3\theta)}{\theta(\tau+\gamma\tilde{I}_1)(\lambda-\delta\tilde{I}_1)}(I-\tilde{I}_1)(\lambda Y-\pi I-\delta IY)\\
&+\frac{\rho_1\tilde{H}_1\tilde{V}_1}{F_1}\int_0^{k_1}\bar{F}_1(\varrho)\ln\left(\frac{H(t-\varrho)V(t-\varrho)}{HV}\right)d\varrho\\
&+\frac{\rho_2\tilde{H}_1\tilde{S}_1}{F_1}\int_0^{k_1}\bar{F}_1(\varrho)\ln\left(\frac{H(t-\varrho)S(t-\varrho)}{HS}\right)d\varrho\\
&+\frac{\rho_3\tilde{H}_1\tilde{Y}_1}{F_1}\int_0^{k_1}\bar{F}_1(\varrho)\ln\left(\frac{H(t-\varrho)Y(t-\varrho)}{HY}\right)d\varrho\\
&+\frac{\sigma\tilde{H}_1\tilde{S}_1(F_3\rho_1\varepsilon+\rho_3\theta)}{\theta(\tau+\gamma\tilde{I}_1)}\int_0^{k_2}\bar{F}_2(\varrho)\ln\left(\frac{S(t-\varrho)}{S}\right)d\varrho\\
&+\frac{\rho_1\tilde{H}_1\varepsilon F_3\tilde{Y}_1}{\theta}\left(\frac{Y}{\tilde{Y}_1}\right)+\frac{\rho_1\tilde{H}_1\varepsilon\tilde{Y}_1}{\theta}\int_0^{k_3}\bar{F}_3(\varrho)\ln\left(\frac{Y(t-\varrho)}{Y}\right)d\varrho. \qquad (37)
\end{aligned}
$$

Using the following equilibrium conditions for $\tilde{Q}_1$

$$\alpha = \eta\tilde{H}_1 + \rho_1\tilde{H}_1\tilde{V}_1 + \rho_2\tilde{H}_1\tilde{S}_1 + \rho_3\tilde{H}_1\tilde{Y}_1,$$
$$\rho_1\tilde{H}_1\tilde{V}_1 + \rho_2\tilde{H}_1\tilde{S}_1 + \rho_3\tilde{H}_1\tilde{Y}_1 = \frac{(\sigma+\mu)\tilde{S}_1}{F_1},$$
$$\sigma\tilde{S}_1 = \left(\frac{\tau+\gamma\tilde{I}_1}{F_2}\right)\tilde{Y}_1 \Longrightarrow \tilde{Y}_1 = \frac{\sigma F_2\tilde{S}_1}{\tau+\gamma\tilde{I}_1},$$
$$\tilde{V}_1 = \frac{\varepsilon F_3\tilde{Y}_1}{\theta}, \quad \lambda\tilde{Y}_1 - \pi\tilde{I}_1 - \delta\tilde{I}_1\tilde{Y}_1 = 0,$$

We obtain

$$\rho_1\tilde{H}_1\tilde{V}_1 + \rho_3\tilde{H}_1\tilde{Y}_1 = \frac{\tilde{H}_1(F_3\rho_1\varepsilon+\rho_3\theta)\tilde{Y}_1}{\theta} = \frac{\sigma F_2\tilde{H}_1(F_3\rho_1\varepsilon+\rho_3\theta)\tilde{S}_1}{\theta(\tau+\gamma\tilde{I}_1)},$$
$$\left(\rho_2\tilde{H}_1 - \frac{\sigma+\mu}{F_1} + \frac{\sigma F_2\tilde{H}_1(F_3\rho_1\varepsilon+\rho_3\theta)}{\theta(\tau+\gamma\tilde{I}_1)}\right)\tilde{S}_1 = 0.$$

Therefore, Equation (37) will take the following form:

$$\begin{aligned}
\frac{d\tilde{\Theta}_1}{dt} &= \left(1-\frac{\tilde{H}_1}{H}\right)(\eta\tilde{H}_1 - \eta H) + \left(\rho_1\tilde{H}_1\tilde{V}_1 + \rho_2\tilde{H}_1\tilde{S}_1 + \rho_3\tilde{H}_1\tilde{Y}_1\right)\left(1-\frac{\tilde{H}_1}{H}\right) + \rho_3\tilde{H}_1 Y \\
&- \frac{1}{F_1}\int_0^{k_1}\bar{F}_1(\varrho)\frac{H(t-\varrho)\tilde{S}_1}{S}(\rho_1 V(t-\varrho) + \rho_2 S(t-\varrho) + \rho_3 Y(t-\varrho))d\varrho \\
&+ \rho_1\tilde{H}_1\tilde{V}_1 + \rho_2\tilde{H}_1\tilde{S}_1 + \rho_3\tilde{H}_1\tilde{Y}_1 - \frac{\sigma\tilde{H}_1(F_3\rho_1\varepsilon+\rho_3\theta)\tilde{S}_1}{\theta(\tau+\gamma\tilde{I}_1)}\int_0^{k_2}\bar{F}_2(\varrho)\frac{S(t-\varrho)\tilde{Y}_1}{\tilde{S}_1 Y}d\varrho \\
&- \frac{\tau\tilde{H}_1(F_3\rho_1\varepsilon+\rho_3\theta)}{\theta(\tau+\gamma\tilde{I}_1)}(Y-\tilde{Y}_1) - \frac{\gamma\tilde{H}_1(F_3\rho_1\varepsilon+\rho_3\theta)}{\theta(\tau+\gamma\tilde{I}_1)}I(Y-\tilde{Y}_1) + \frac{\gamma\tilde{H}_1(F_3\rho_1\varepsilon+\rho_3\theta)}{\theta(\tau+\gamma\tilde{I}_1)}\tilde{I}_1(Y-\tilde{Y}_1) \\
&- \frac{\gamma\tilde{H}_1(F_3\rho_1\varepsilon+\rho_3\theta)}{\theta(\tau+\gamma\tilde{I}_1)}\tilde{I}_1(Y-\tilde{Y}_1) - \frac{\rho_1\tilde{H}_1\varepsilon\tilde{Y}_1}{\theta}\int_0^{k_3}\bar{F}_3(\varrho)\frac{Y(t-\varrho)\tilde{V}_1}{\tilde{Y}_1 V}d\varrho + \rho_1\tilde{H}_1\tilde{V}_1 \\
&+ \frac{\gamma\tilde{H}_1(F_3\rho_1\varepsilon+\rho_3\theta)}{\theta(\tau+\gamma\tilde{I}_1)(\lambda-\delta\tilde{I}_1)}(I-\tilde{I}_1)\left(\lambda Y - \pi I - \delta IY - \lambda\tilde{Y}_1 + \pi\tilde{I}_1 + \delta\tilde{I}_1\tilde{Y}_1 - \delta\tilde{I}_1 Y + \delta\tilde{I}_1 Y\right) \\
&+ \frac{\rho_1\tilde{H}_1\tilde{V}_1}{F_1}\int_0^{k_1}\bar{F}_1(\varrho)\ln\left(\frac{H(t-\varrho)V(t-\varrho)}{HV}\right)d\varrho + \frac{\rho_2\tilde{H}_1\tilde{S}_1}{F_1}\int_0^{k_1}\bar{F}_1(\varrho)\ln\left(\frac{H(t-\varrho)S(t-\varrho)}{HS}\right)d\varrho \\
&+ \frac{\rho_3\tilde{H}_1\tilde{Y}_1}{F_1}\int_0^{k_1}\bar{F}_1(\varrho)\ln\left(\frac{H(t-\varrho)Y(t-\varrho)}{HY}\right)d\varrho + \rho_1\tilde{H}_1\tilde{V}_1\left(\frac{Y}{\tilde{Y}_1}\right) \\
&+ \frac{\sigma\tilde{H}_1\tilde{S}_1(F_3\rho_1\varepsilon+\rho_3\theta)}{\theta(\tau+\gamma\tilde{I}_1)}\int_0^{k_2}\bar{F}_2(\varrho)\ln\left(\frac{S(t-\varrho)}{S}\right)d\varrho + \frac{\rho_1\tilde{H}_1\varepsilon\tilde{Y}_1}{\theta}\int_0^{k_3}\bar{F}_3(\varrho)\ln\left(\frac{Y(t-\varrho)}{Y}\right)d\varrho.
\end{aligned}$$

This implies that

$$\begin{aligned}
\frac{d\tilde{\Theta}_1}{dt} &= -\frac{\eta(H-\tilde{H}_1)^2}{H} + \left(\rho_1\tilde{H}_1\tilde{V}_1 + \rho_2\tilde{H}_1\tilde{S}_1 + \rho_3\tilde{H}_1\tilde{Y}_1\right)\left(2-\frac{\tilde{H}_1}{H}\right) + \rho_3\tilde{H}_1 Y \\
&- \frac{\rho_1\tilde{H}_1\tilde{V}_1}{F_1}\int_0^{k_1}\bar{F}_1(\varrho)\frac{H(t-\varrho)V(t-\varrho)\tilde{S}_1}{\tilde{H}_1\tilde{V}_1 S}d\varrho - \frac{\rho_2\tilde{H}_1\tilde{S}_1}{F_1}\int_0^{k_1}\bar{F}_1(\varrho)\frac{H(t-\varrho)S(t-\varrho)}{\tilde{H}_1 S}d\varrho \\
&- \frac{\rho_3\tilde{H}_1\tilde{Y}_1}{F_1}\int_0^{k_1}\bar{F}_1(\varrho)\frac{H(t-\varrho)Y(t-\varrho)\tilde{S}_1}{\tilde{H}_1\tilde{Y}_1 S}d\varrho - \frac{\rho_1\tilde{H}_1\tilde{V}_1 + \rho_3\tilde{H}_1\tilde{Y}_1}{F_2}\int_0^{k_2}\bar{F}_2(\varrho)\frac{S(t-\varrho)\tilde{Y}_1}{\tilde{S}_1 Y}d\varrho \\
&- \frac{\tilde{H}_1\tilde{Y}_1(F_3\rho_1\varepsilon+\rho_3\theta)}{\theta}\left(\frac{Y}{\tilde{Y}_1}-1\right) - \frac{\rho_1\tilde{H}_1\tilde{V}_1}{F_3}\int_0^{k_3}\bar{F}_3(\varrho)\frac{Y(t-\varrho)\tilde{V}_1}{\tilde{Y}_1 V}d\varrho + \rho_1\tilde{H}_1\tilde{V}_1 \\
&- \frac{\gamma\tilde{H}_1(F_3\rho_1\varepsilon+\rho_3\theta)(\pi+\delta Y)}{\theta(\tau+\gamma\tilde{I}_1)(\lambda-\delta\tilde{I}_1)}(I-\tilde{I}_1)^2 + \frac{\rho_1\tilde{H}_1\tilde{V}_1}{F_1}\int_0^{k_1}\bar{F}_1(\varrho)\ln\left(\frac{H(t-\varrho)V(t-\varrho)}{HV}\right)d\varrho
\end{aligned}$$

$$
\begin{aligned}
&+\frac{\rho_2\tilde{H}_1\tilde{S}_1}{F_1}\int_0^{k_1}\bar{F}_1(\varrho)\ln\left(\frac{H(t-\varrho)S(t-\varrho)}{HS}\right)d\varrho+\frac{\rho_3\tilde{H}_1\tilde{Y}_1}{F_1}\int_0^{k_1}\bar{F}_1(\varrho)\ln\left(\frac{H(t-\varrho)Y(t-\varrho)}{HY}\right)d\varrho\\
&+\frac{\rho_1\tilde{H}_1\tilde{V}_1+\rho_3\tilde{H}_1\tilde{Y}_1}{F_2}\int_0^{k_2}\bar{F}_2(\varrho)\ln\left(\frac{S(t-\varrho)}{S}\right)d\varrho+\rho_1\tilde{H}_1\tilde{V}_1\left(\frac{Y}{\tilde{Y}_1}\right)\\
&+\frac{\rho_1\tilde{H}_1\tilde{V}_1}{F_3}\int_0^{k_3}\bar{F}_3(\varrho)\ln\left(\frac{Y(t-\varrho)}{Y}\right)d\varrho\\
=&-\frac{\eta\left(H-\tilde{H}_1\right)^2}{H}+\left(\rho_1\tilde{H}_1\tilde{V}_1+\rho_2\tilde{H}_1\tilde{S}_1+\rho_3\tilde{H}_1\tilde{Y}_1\right)\left(2-\frac{\tilde{H}_1}{H}\right)-\frac{\gamma\tilde{H}_1(F_3\rho_1\varepsilon+\rho_3\theta)(\pi+\delta Y)}{\theta\left(\tau+\gamma\tilde{I}_1\right)\left(\lambda-\delta\tilde{I}_1\right)}\left(I-\tilde{I}_1\right)^2\\
&-\frac{\rho_1\tilde{H}_1\tilde{V}_1}{F_1}\int_0^{k_1}\bar{F}_1(\varrho)\frac{H(t-\varrho)V(t-\varrho)\tilde{S}_1}{\tilde{H}_1\tilde{V}_1S}d\varrho-\frac{\rho_2\tilde{H}_1\tilde{S}_1}{F_1}\int_0^{k_1}\bar{F}_1(\varrho)\frac{H(t-\varrho)S(t-\varrho)}{\tilde{H}_1S}d\varrho\\
&-\frac{\rho_3\tilde{H}_1\tilde{Y}_1}{F_1}\int_0^{k_1}\bar{F}_1(\varrho)\frac{H(t-\varrho)Y(t-\varrho)\tilde{S}_1}{\tilde{H}_1\tilde{Y}_1S}d\varrho-\frac{\rho_1\tilde{H}_1\tilde{V}_1+\rho_3\tilde{H}_1\tilde{Y}_1}{F_2}\int_0^{k_2}\bar{F}_2(\varrho)\frac{S(t-\varrho)\tilde{Y}_1}{\tilde{S}_1Y}d\varrho\\
&+2\rho_1\tilde{H}_1\tilde{V}_1+\rho_3\tilde{H}_1\tilde{Y}_1-\frac{\rho_1\tilde{H}_1\tilde{V}_1}{F_3}\int_0^{k_3}\bar{F}_3(\varrho)\frac{Y(t-\varrho)\tilde{V}_1}{\tilde{Y}_1V}d\varrho\\
&+\frac{\rho_1\tilde{H}_1\tilde{V}_1}{F_1}\int_0^{k_1}\bar{F}_1(\varrho)\ln\left(\frac{H(t-\varrho)V(t-\varrho)}{HV}\right)d\varrho+\frac{\rho_2\tilde{H}_1\tilde{S}_1}{F_1}\int_0^{k_1}\bar{F}_1(\varrho)\ln\left(\frac{H(t-\varrho)S(t-\varrho)}{HS}\right)d\varrho\\
&+\frac{\rho_3\tilde{H}_1\tilde{Y}_1}{F_1}\int_0^{k_1}\bar{F}_1(\varrho)\ln\left(\frac{H(t-\varrho)Y(t-\varrho)}{HY}\right)d\varrho+\frac{\rho_1\tilde{H}_1\tilde{V}_1+\rho_3\tilde{H}_1\tilde{Y}_1}{F_2}\int_0^{k_2}\bar{F}_2(\varrho)\ln\left(\frac{S(t-\varrho)}{S}\right)d\varrho\\
&+\frac{\rho_1\tilde{H}_1\tilde{V}_1}{F_3}\int_0^{k_3}\bar{F}_3(\varrho)\ln\left(\frac{Y(t-\varrho)}{Y}\right)d\varrho.
\end{aligned}
$$

Moreover, we have

$$
\begin{aligned}
\ln\left(\frac{H(t-\varrho)V(t-\varrho)}{HV}\right)&=\ln\left(\frac{H(t-\varrho)V(t-\varrho)\tilde{S}_1}{\tilde{H}_1\tilde{V}_1S}\right)+\ln\left(\frac{\tilde{H}_1}{H}\right)+\ln\left(\frac{\tilde{V}_1S}{V\tilde{S}_1}\right),\\
\ln\left(\frac{H(t-\varrho)Y(t-\varrho)}{HY}\right)&=\ln\left(\frac{H(t-\varrho)Y(t-\varrho)\tilde{S}_1}{\tilde{H}_1\tilde{Y}_1S}\right)+\ln\left(\frac{\tilde{H}_1}{H}\right)+\ln\left(\frac{\tilde{Y}_1S}{Y\tilde{S}_1}\right),\\
\ln\left(\frac{H(t-\varrho)S(t-\varrho)}{HS}\right)&=\ln\left(\frac{H(t-\varrho)S(t-\varrho)}{\tilde{H}_1S}\right)+\ln\left(\frac{\tilde{H}_1}{H}\right),\\
\ln\left(\frac{S(t-\varrho)}{S}\right)&=\ln\left(\frac{S(t-\varrho)\tilde{Y}_1}{\tilde{S}_1Y}\right)+\ln\left(\frac{\tilde{S}_1Y}{S\tilde{Y}_1}\right),\\
\ln\left(\frac{Y(t-\varrho)}{Y}\right)&=\ln\left(\frac{Y(t-\varrho)\tilde{V}_1}{\tilde{Y}_1V}\right)+\ln\left(\frac{\tilde{Y}_1V}{Y\tilde{V}_1}\right).
\end{aligned}
$$

Therefore, $\frac{d\tilde{\Theta}_1}{dt}$ will be

$$
\begin{aligned}
\frac{d\tilde{\Theta}_1}{dt}=&-\frac{\eta\left(H-\tilde{H}_1\right)^2}{H}+\left(\rho_1\tilde{H}_1\tilde{V}_1+\rho_2\tilde{H}_1\tilde{S}_1+\rho_3\tilde{H}_1\tilde{Y}_1\right)\left(2-\frac{\tilde{H}_1}{H}\right)\\
&-\frac{\gamma\tilde{H}_1(F_3\rho_1\varepsilon+\rho_3\theta)(\pi+\delta Y)}{\theta\left(\tau+\gamma\tilde{I}_1\right)\left(\lambda-\delta\tilde{I}_1\right)}\left(I-\tilde{I}_1\right)^2-\frac{\rho_1\tilde{H}_1\tilde{V}_1}{F_1}\int_0^{k_1}\bar{F}_1(\varrho)\frac{H(t-\varrho)V(t-\varrho)\tilde{S}_1}{\tilde{H}_1\tilde{V}_1S}d\varrho\\
&-\frac{\rho_2\tilde{H}_1\tilde{S}_1}{F_1}\int_0^{k_1}\bar{F}_1(\varrho)\frac{H(t-\varrho)S(t-\varrho)}{\tilde{H}_1S}d\varrho-\frac{\rho_3\tilde{H}_1\tilde{Y}_1}{F_1}\int_0^{k_1}\bar{F}_1(\varrho)\frac{H(t-\varrho)Y(t-\varrho)\tilde{S}_1}{\tilde{H}_1\tilde{Y}_1S}d\varrho\\
&-\frac{\rho_1\tilde{H}_1\tilde{V}_1+\rho_3\tilde{H}_1\tilde{Y}_1}{F_2}\int_0^{k_2}\bar{F}_2(\varrho)\frac{S(t-\varrho)\tilde{Y}_1}{\tilde{S}_1Y}d\varrho+2\rho_1\tilde{H}_1\tilde{V}_1+\rho_3\tilde{H}_1\tilde{Y}_1\\
&-\frac{\rho_1\tilde{H}_1\tilde{V}_1}{F_3}\int_0^{k_3}\bar{F}_3(\varrho)\frac{Y(t-\varrho)\tilde{V}_1}{\tilde{Y}_1V}d\varrho\\
&+\frac{\rho_1\tilde{H}_1\tilde{V}_1}{F_1}\int_0^{k_1}\bar{F}_1(\varrho)\left[\ln\left(\frac{H(t-\varrho)V(t-\varrho)\tilde{S}_1}{\tilde{H}_1\tilde{V}_1S}\right)+\ln\left(\frac{\tilde{H}_1}{H}\right)+\ln\left(\frac{\tilde{V}_1S}{V\tilde{S}_1}\right)\right]d\varrho
\end{aligned}
$$

$$+\frac{\rho_2\tilde{H}_1\tilde{S}_1}{F_1}\int_0^{k_1}\bar{F}_1(\varrho)\left[\ln\left(\frac{H(t-\varrho)S(t-\varrho)}{\tilde{H}_1 S}\right)+\ln\left(\frac{\tilde{H}_1}{H}\right)\right]d\varrho$$
$$+\frac{\rho_3\tilde{H}_1\tilde{Y}_1}{F_1}\int_0^{k_1}\bar{F}_1(\varrho)\left[\ln\left(\frac{H(t-\varrho)Y(t-\varrho)\tilde{S}_1}{\tilde{H}_1\tilde{Y}_1 S}\right)+\ln\left(\frac{\tilde{H}_1}{H}\right)+\ln\left(\frac{\tilde{Y}_1 S}{Y\tilde{S}_1}\right)\right]d\varrho$$
$$+\frac{\rho_1\tilde{H}_1\tilde{V}_1+\rho_3\tilde{H}_1\tilde{Y}_1}{F_2}\int_0^{k_2}\bar{F}_2(\varrho)\left[\ln\left(\frac{S(t-\varrho)\tilde{Y}_1}{\tilde{S}_1 Y}\right)+\ln\left(\frac{\tilde{S}_1 Y}{S\tilde{Y}_1}\right)\right]d\varrho$$
$$+\frac{\rho_1\tilde{H}_1\tilde{V}_1}{F_3}\int_0^{k_3}\bar{F}_3(\varrho)\left[\ln\left(\frac{Y(t-\varrho)\tilde{V}_1}{\tilde{Y}_1 V}\right)+\ln\left(\frac{\tilde{Y}_1 V}{Y\tilde{V}_1}\right)\right]d\varrho.$$

Finally, we obtain

$$\frac{d\tilde{\Theta}_1}{dt}=-\frac{\eta\left(H-\tilde{H}_1\right)^2}{H}-\frac{\rho_1\tilde{H}_1\tilde{V}_1}{F_1}\int_0^{k_1}\bar{F}_1(\varrho)\left[F\left(\frac{H(t-\varrho)V(t-\varrho)\tilde{S}_1}{\tilde{H}_1\tilde{V}_1 S}\right)+F\left(\frac{\tilde{H}_1}{H}\right)\right]d\varrho$$
$$-\frac{\rho_2\tilde{H}_1\tilde{S}_1}{F_1}\int_0^{k_1}\bar{F}_1(\varrho)\left[F\left(\frac{H(t-\varrho)S(t-\varrho)}{\tilde{H}_1 S}\right)+F\left(\frac{\tilde{H}_1}{H}\right)\right]d\varrho$$
$$-\frac{\rho_3\tilde{H}_1\tilde{Y}_1}{F_1}\int_0^{k_1}\bar{F}_1(\varrho)\left[F\left(\frac{H(t-\varrho)Y(t-\varrho)\tilde{S}_1}{\tilde{H}_1\tilde{Y}_1 S}\right)+F\left(\frac{\tilde{H}_1}{H}\right)\right]d\varrho$$
$$-\frac{\rho_1\tilde{H}_1\tilde{V}_1+\rho_3\tilde{H}_1\tilde{Y}_1}{F_2}\int_0^{k_2}\bar{F}_2(\varrho)F\left(\frac{S(t-\varrho)\tilde{Y}_1}{\tilde{S}_1 Y}\right)d\varrho$$
$$-\frac{\rho_1\tilde{H}_1\tilde{V}_1}{F_3}\int_0^{k_3}\bar{F}_3(\varrho)F\left(\frac{Y(t-\varrho)\tilde{V}_1}{\tilde{Y}_1 V}\right)d\varrho-\frac{\gamma\tilde{H}_1(F_3\rho_1\varepsilon+\rho_3\theta)(\pi+\delta Y)}{\theta\left(\tau+\gamma\tilde{I}_1\right)\left(\lambda-\delta\tilde{I}_1\right)}\left(I-\tilde{I}_1\right)^2.$$

Hence, if $\tilde{\Re}_0>1$ then $\frac{d\tilde{\Theta}_1}{dt}\leq 0$ for all $H,S,Y,V,I>0$. In addition, $\frac{d\tilde{\Theta}_1}{dt}=0$ when $H=\tilde{H}_1, S=\tilde{S}_1, Y=\tilde{Y}_1, V=\tilde{V}_1$ and $I=\tilde{I}_1$. Let $\bar{\Phi}_1'$ be the largest invariant subset of $\tilde{\Phi}_1=\left\{(H,S,Y,V,I):\frac{d\tilde{\Theta}_1}{dt}=0\right\}$. Therefore, $\bar{\Phi}_1'=\{\tilde{Q}_1\}$. Applying L.I.P, we obtain $\tilde{Q}_1$ is G.A.S when $\tilde{\Re}_0>1$ [52]. □

4. Numerical Simulations

In this section, we perform some numerical simulations for systems (8) and (23) to confirm our theoretical findings. Further, we will investigate the effects of the CTL immune impairment on model (8), in addition to the effect of time delays on the dynamics of model (23).

4.1. Numerical Simulation for Model (8)

4.1.1. Effect of ρ_i, $i=1,2,3$ and δ on Stability of Equilibria

Here, we solve system (8) numerically with values of the parameters listed in Table 1. To investigate the stability of equilibria for system (8), we choose three different initial conditions as follows:

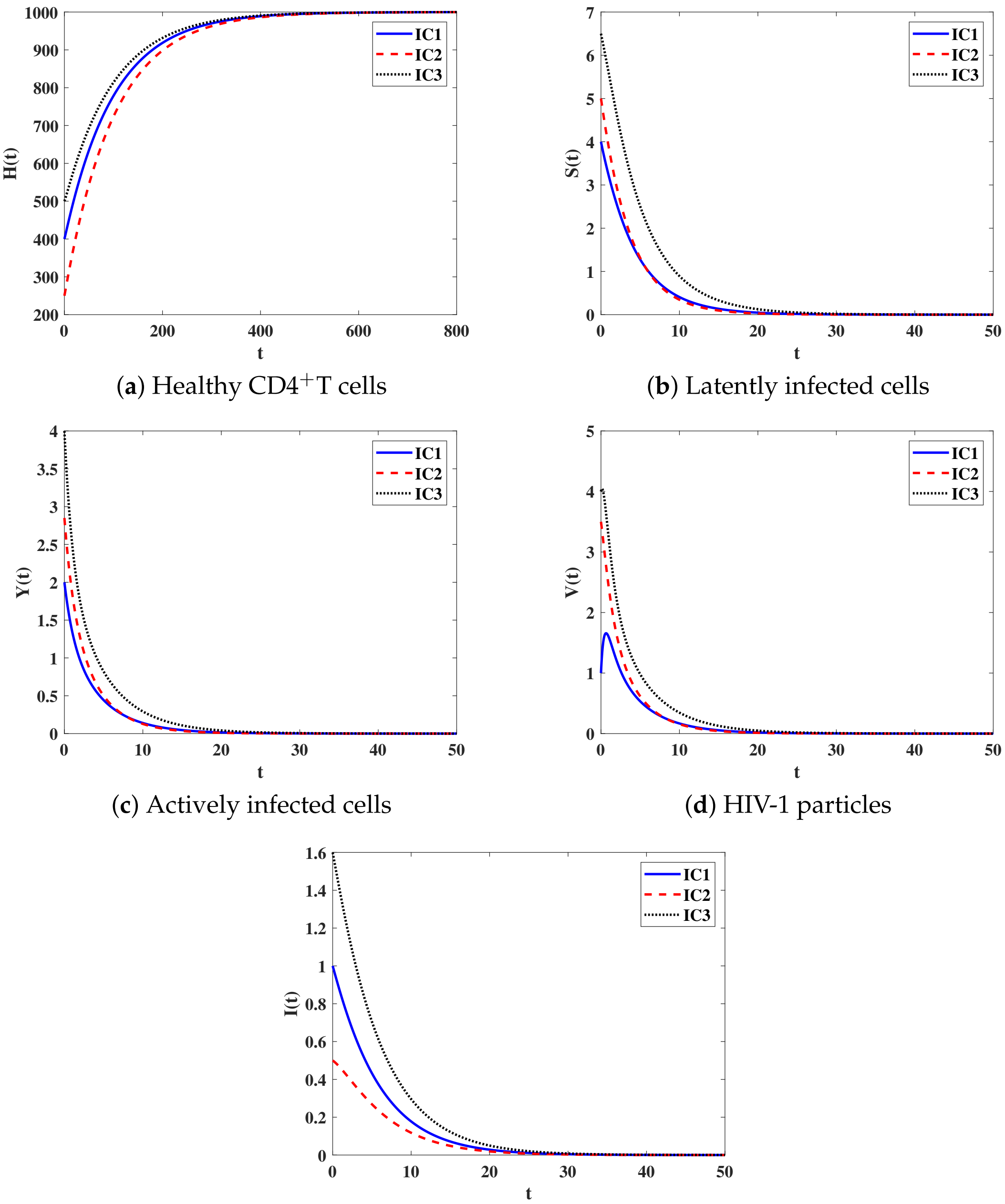
IC1 : $(H(0),S(0),Y(0),V(0),I(0))=(400,4,2,1,1)$,
IC2: $(H(0),S(0),Y(0),V(0),I(0))=(250,5,2.85,3.5,0.5)$,
IC3: $(H(0),S(0),Y(0),V(0),I(0))=(500,6.5,4,4,1.6)$.

Since the basic reproduction number $\Re_0$ is used to control the stability of equilibria, and it depends on the infection rates ρ_i, $i=1,2,3$, we vary the parameters ρ_i, $i=1,2,3$ and present the following two situations:

Stability of Q_0. We let $\rho_1=0.0002$, $\rho_2=0.0001$, $\rho_3=0.0004$ and $\delta=0.001$. For this set of parameters, we have $\Re_0=0.6869<1$. Figure 1 illustrates that the solution trajectories initiating with IC1-IC3 reach the equilibrium $Q_0=(1000,0,0,0,0)$. This ensures that Q_0 is G.A.S according to the result of Theorem 2. From a biological point of view, we know this case means that the disease will die out and the human body will be cleared of the infection.

Table 1. Model parameters.

Parameter	Value	Reference	Parameter	Value	Reference
α	10	[54]	τ	0.8	[32]
η	0.01	[54]	γ	0.04	[32]
ρ_1	varied	-	ε	2.6	[55]
ρ_2	varied	-	θ	2.4	[55]
ρ_3	varied	-	λ	0.025	[32]
σ	0.2	[54]	π	0.2	[32]
μ	0.17	[54]	δ	varied	-



(**a**) Healthy CD4$^+$T cells (**b**) Latently infected cells

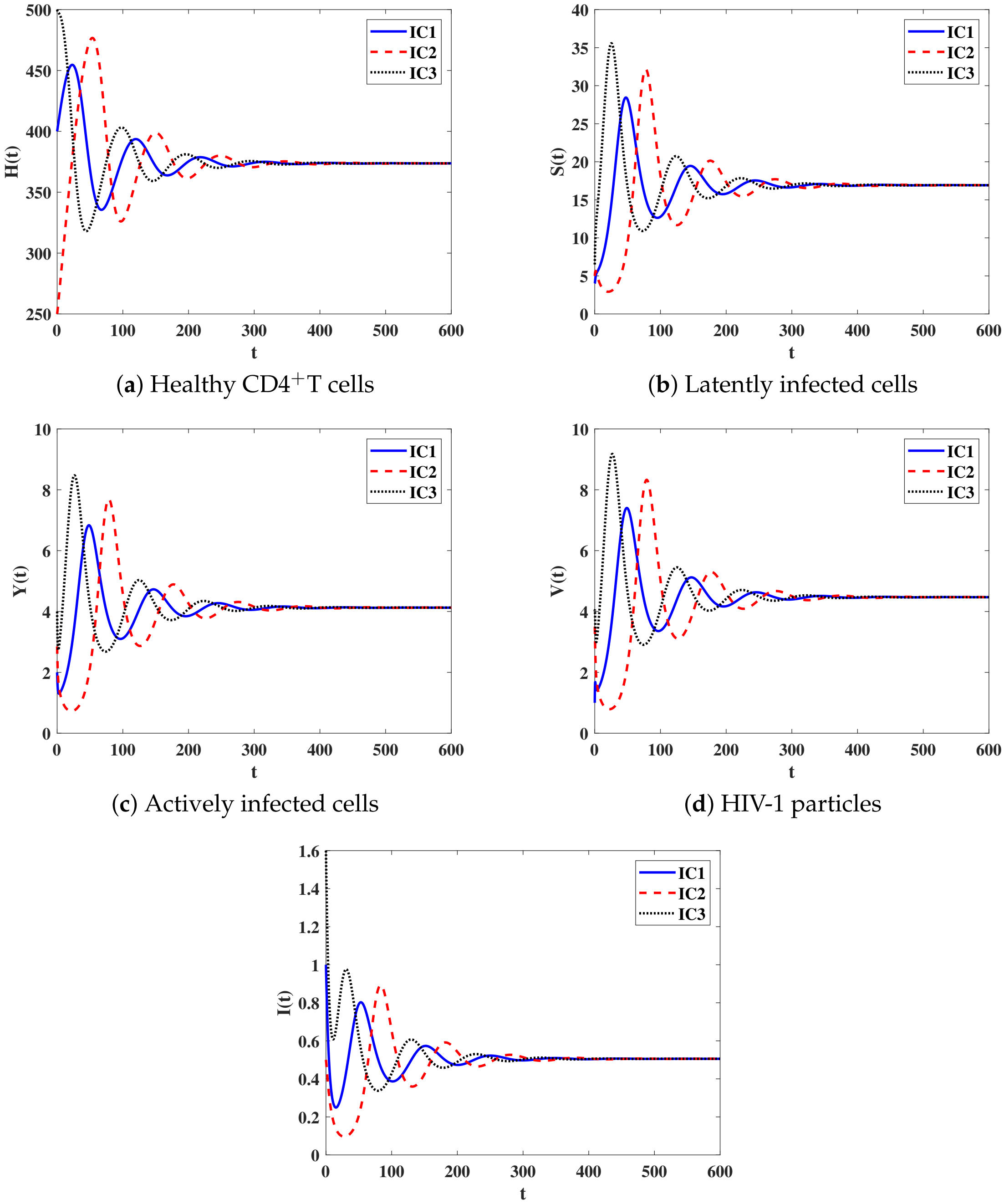
(**c**) Actively infected cells (**d**) HIV-1 particles

(**e**) CTLs

Figure 1. Solutions of system (8) when $\Re_0 < 1$.

Stability of Q_1. We let $\rho_1 = 0.003$, $\rho_2 = 0.0001$, $\rho_3 = 0.0004$ and $\delta = 0.001$. With such choice we obtain $\Re_0 = 2.7365 > 1$. It is clear that the equilibrium point Q_1 exists when

$\Re_0 > 1$ with $Q_1 = (373.74, 16.93, 4.13, 4.47, 0.51)$. Figure 2 shows that the numerical results confirm the theoretical results of Theorem 3 as the solutions of system (8) converge to Q_1 when $\Re_0 > 1$ for all IC1–IC3. Biologically, this case sheds light on the fact that the HIV-1 particles and CTL cells will persist in the host.



(**a**) Healthy CD4$^+$T cells (**b**) Latently infected cells (**c**) Actively infected cells (**d**) HIV-1 particles (**e**) CTLs

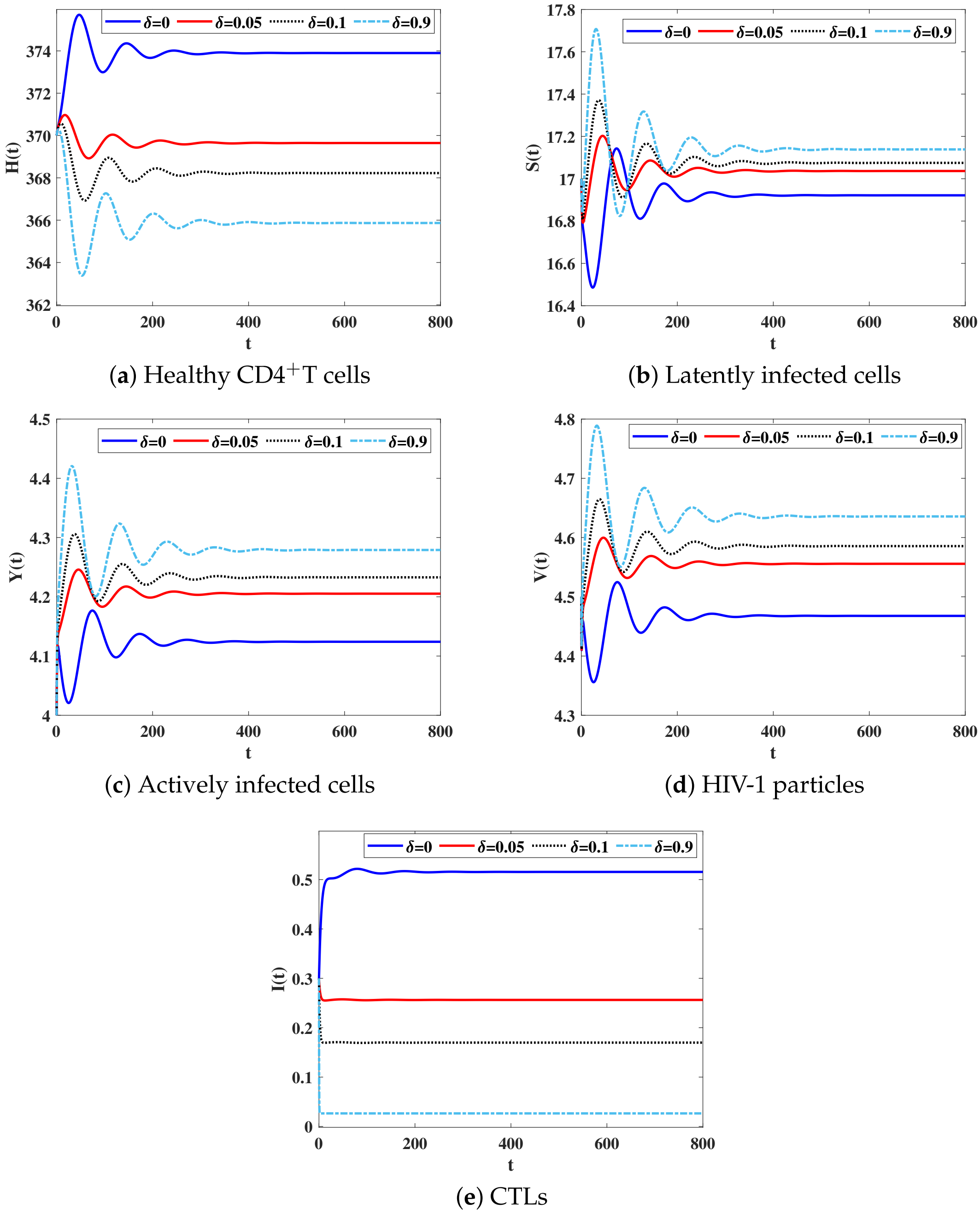
Figure 2. Solutions of system (8) when $\Re_0 > 1$.

4.1.2. Effect of the CTL Immune Impairment

In this case, we vary the parameter δ and choose $\rho_1 = 0.003$, $\rho_2 = 0.0001$ and $\rho_3 = 0.0004$. To investigate the immune impairment effects on the dynamics of system (8) we solve the system numerically taking under consideration different values of δ as shown in Table 2. In this case, we select the following initial condition:

IC4: $(H(0), S(0), Y(0), V(0), I(0)) = (370, 17, 4, 4.5, 0.3)$.

Table 2 shows that as δ is increased, the concentration of CTLs is decreased. Consequently, the concentration of latently and actively infected cells and free HIV-1 particles are increased. In the mean time, the concentration of healthy CD4$^+$T cells is decreased. We observe from Figure 3, that the CTL immune impairment does not change the stability properties of the equilibria, since the parameter $\Re_0$ does not depend on δ.



(**a**) Healthy CD4$^+$T cells (**b**) Latently infected cells (**c**) Actively infected cells (**d**) HIV-1 particles (**e**) CTLs

Figure 3. Solutions of system (8) with different values of the impairment parameter δ.

Table 2. Effect of the CTL immune impairment parameter.

δ	Equilibria
$\delta = 0$	$Q_1 = (373.8995, 16.9216, 4.1241, 4.4678, 0.5155)$
$\delta = 0.05$	$Q_1 = (369.6465, 17.0366, 4.2053, 4.5557, 0.2563)$
$\delta = 0.1$	$Q_1 = (368.2255, 17.0750, 4.2328, 4.5855, 0.1698)$
$\delta = 0.9$	$Q_1 = (365.8669, 17.1387, 4.2790, 4.6356, 0.0264)$

4.2. Numerical Simulation for Model (23)

In this subsection, for numerical purposes, we take a specific form of the probability distributed functions $f_i(\varrho)$, $i = 1, 2, 3$, as follows:

$$f_i(\varrho) = \delta_*(\varrho - \varrho_i), \quad \varrho_i \in [0, k_i], \quad i = 1, 2, 3,$$

where $\delta_*(.)$ is the Dirac delta function. When $k_i \to \infty$, we have

$$\int_0^\infty f_i(\varrho) d\varrho = 1, \quad i = 1, 2, 3.$$

Further, we have

$$F_i = \int_0^\infty \delta_*(\varrho - \varrho_i) e^{-h_i \varrho} d\varrho = e^{-h_i \varrho_i}, \qquad i = 1, 2, 3.$$

Hence, the distributed time delay system (23) will be transformed to a discrete time delay system as:

$$\begin{cases} \dot{H}(t) &= \alpha - \eta H(t) - \rho_1 H(t) V(t) - \rho_2 H(t) S(t) - \rho_3 H(t) Y(t), \\ \dot{S}(t) &= e^{-h_1 \varrho_1} H(t - \varrho_1)(\rho_1 V(t - \varrho_1) + \rho_2 S(t - \varrho_1) \\ & \quad + \rho_3 Y(t - \varrho_1)) - (\sigma + \mu) S(t), \\ \dot{Y}(t) &= \sigma e^{-h_2 \varrho_2} S(t - \varrho_2) - \tau Y(t) - \gamma I(t) Y(t), \\ \dot{V}(t) &= \varepsilon e^{-h_3 \varrho_3} Y(t - \varrho_3) - \theta V(t), \\ \dot{I}(t) &= \lambda Y(t) - \pi I(t) - \delta I(t) Y(t). \end{cases} \tag{38}$$

For system (38), the basic reproduction number is given as:

$$\tilde{\Re}_{0(38)} = \frac{\tilde{H}_0 e^{-h_1 \varrho_1} \left(\sigma e^{-h_2 \varrho_2} \left(\rho_1 \varepsilon e^{-h_3 \varrho_3} + \rho_3 \theta \right) + \rho_2 \theta \tau \right)}{(\sigma + \mu) \theta \tau}. \tag{39}$$

The effect of time delays on stability of equilibria

To investigate the impact of delay parameters on the solutions of system (38), we fix the parameters $\rho_1 = 0.003$, $\rho_2 = 0.0001$, $\rho_3 = 0.0004$, $\delta = 0.001$, $h_1 = 0.1$, $h_2 = 0.2$ and $h_3 = 0.3$. On the other hand, the other parameters will be taken from Table 1. Moreover, we vary the delay parameters ϱ_i, $i = 1, 2, 3$. Since $\tilde{\Re}_{0(38)}$ given in Equation (39) depends on ϱ_i, then changing the parameters ϱ_i will change the stability of equilibria. Let us take the following cases of the delay values:

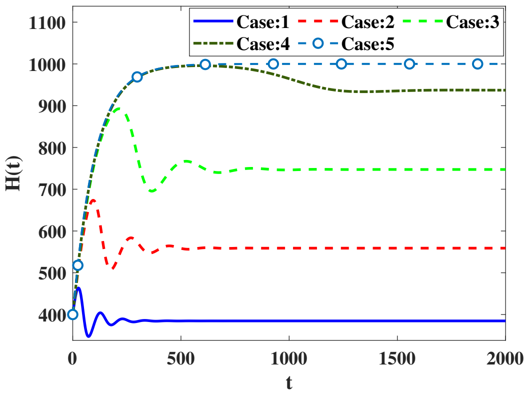
Case: 1 $\varrho_1 = 0.07$, $\varrho_2 = 0.06$, $\varrho_3 = 0.05$.
Case: 2 $\varrho_1 = 0.8$, $\varrho_2 = 0.7$, $\varrho_3 = 0.9$.
Case: 3 $\varrho_1 = 1.3$, $\varrho_2 = 1.4$, $\varrho_3 = 1.5$.
Case: 4 $\varrho_1 = 1.8$, $\varrho_2 = 1.9$, $\varrho_3 = 2$.
Case: 5 $\varrho_1 = 4$, $\varrho_2 = 3$, $\varrho_3 = 5$.

We solve system (38) under initial condition IC5

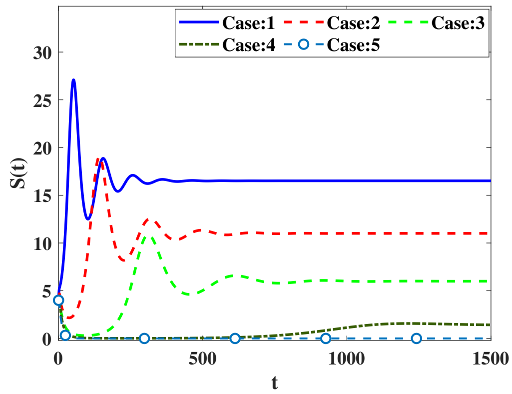
IC5 : $(H(r), S(r), Y(r), V(r), L(r)) = (400, 4, 2, 1, 1)$, $r \in [-\varrho, 0]$, $\varrho = \max\{\varrho_1, \varrho_2, \varrho_3\}$.
In Table 3, we demonstrate the values of $\tilde{\Re}_{0(38)}$ for different values of ϱ_i, $i = 1, 2, 3$. We observe that as the parameters ϱ_i are increased, the values of $\tilde{\Re}_{0(38)}$ are decreased. The numerical solutions are displayed in Figure 4. We conclude that a significant effect is caused by the inclusion of time delays which causes increasing in the concentration of healthy $CD4^+T$ cells and decreasing in the concentrations of latently and actively infected cells, HIV-1 particles and CTL cells.

Table 3. The disparity of $\tilde{\mathfrak{R}}_{0(38)}$ with respect to the delay parameters.

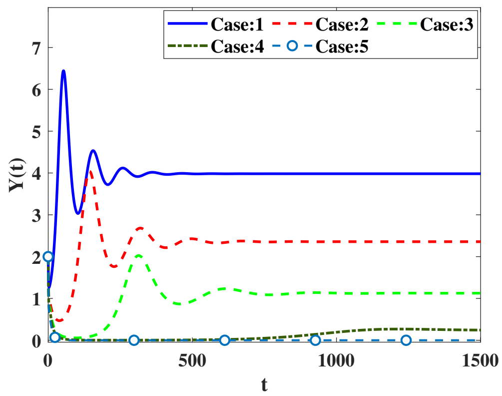
Delay Parameters $(\varrho_1, \varrho_2, \varrho_3)$	Equilibria	$\tilde{\mathfrak{R}}_{0(38)}$
$(0.07, 0.06, 0.05)$	$\tilde{Q}_{1(38)} = (384.729, 16.513, 3.982, 4.249, 0.488)$	2.656
$(0.8, 0.7, 0.9)$	$\tilde{Q}_{1(38)} = (558.891, 11.005, 2.358, 1.95, 0.291)$	1.812
$(1.3, 1.4, 1.5)$	$\tilde{Q}_{1(38)} = (747.257, 5.998, 1.125, 0.777, 0.14)$	1.346
$(1.8, 1.9, 2)$	$\tilde{Q}_{1(38)} = (936.985, 1.423, 0.243, 0.144, 0.03)$	1.069
$(4, 3, 5)$	$\tilde{Q}_{0(38)} = (1000, 0, 0, 0, 0)$	0.461



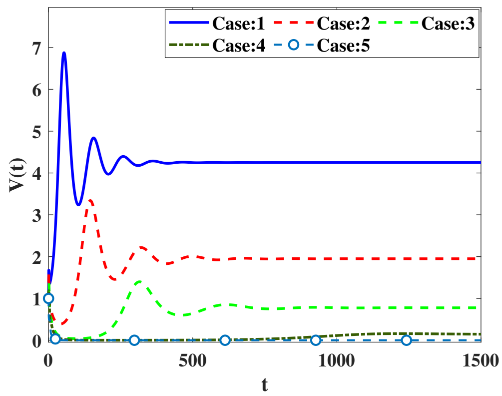
(**a**) Healthy CD4$^+$T cells



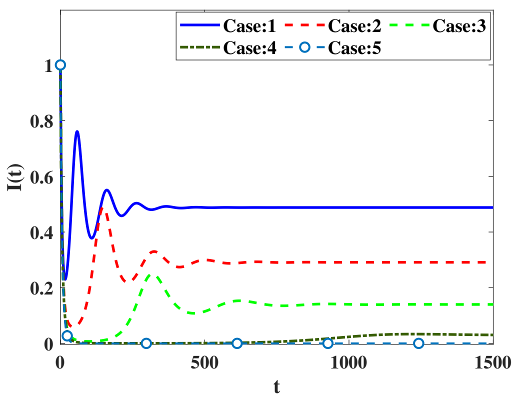
(**b**) Latently infected cells



(**c**) Actively infected cells



(**d**) HIV-1 particles



(**e**) CTLs

Figure 4. Effect of the delay parameters on the solutions of system (38).

5. Conclusions and Discussion

In this paper, we introduced two HIV-1 dynamic models with CTL immune impairment. The models consist of five compartments: healthy CD4$^+$T cells, latently and actively infected cells, free HIV-1 particles and CTLs. We considered that the healthy CD4$^+$T cells become infected by coming into contact with free HIV-1 particles, latently infected cells and actively infected cells. In the second model, we took into account three distributed time delays to be more realistic. We showed that the solutions of the models are nonnegative and bounded. We concluded that each model has two equilibria, the infection-free equilibrium, and the infected equilibrium. We found the basic reproduction number $\Re_0$ (or $\tilde{\Re}_0$) that controls the existence and global stability of the two equilibria. Number $\Re_0$ (or $\tilde{\Re}_0$) consists of three parts: the first is the contribution from the VTC infection, the second part is the contribution from the latent CTC spread, and the third part is the contribution from the active CTC spread. For both models, we formulated Lyapunov functions and applied L.I.P to establish the global asymptotic stability of the two equilibria. We proved that if the basic reproduction number $\Re_0 < 1$ (or $\tilde{\Re}_0 < 1$), then the infection-free equilibrium Q_0 (or $\tilde{Q}_0$) is G.A.S, and thus the infection dies out. Moreover, if $\Re_0 > 1$ (or $\tilde{\Re}_0 > 1$), then Q_0 (or $\tilde{Q}_0$) is unstable and the infected equilibrium Q_1 (or $\tilde{Q}_1$) is G.A.S, and thus the infection becomes chronic. Finally, we performed some numerical simulations to illustrate our theoretical results. We showed that the numerical results are consistent with theoretical results

We discussed the effect of immune impairment and time delay on the HIV-1 dynamics. We found that weak immunity contributes significantly to the development of the disease. Moreover, the presence of time delay can significantly decrease the basic reproduction number $\tilde{\Re}_0$ and then suppress the HIV-1 replication. Therefore, to eliminate HIV-1 from the body, one should focus on designing control strategies which make $\tilde{\Re}_0 < 1$. Increasing delay parameters ϱ_i, $i = 1, 2, 3$ may be observed when infected patients are treated with drug therapies against HIV-1.

We note that, when we ignore the latent CTC spread then model (8) leads to model (3)–(7). The basic reproduction number of system (3)–(7) is given by:

$$\hat{\Re}_0 = \frac{H_0 \varepsilon \sigma \rho_1}{\theta \tau (\sigma + \mu)} + \frac{H_0 \sigma \rho_3}{\tau (\sigma + \mu)}.$$

Clearly, $\hat{\Re}_0 < \Re_0$, and thus the presence of latent CTC transmission increases the basic reproduction number and then enhances the viral progression. Neglecting the latent CTC spread in the HIV-1 infection model will lead to underestimation of the basic reproduction number. Consequently, the designed drug therapies will not be accurate or sufficient to eradicate the viruses from the body.

Model (8) can be extended by including the diffusion of the cells and viruses as per Refs. [56,57]:

$$\begin{aligned}
\frac{\partial H(t,p)}{\partial t} - \xi_H \Delta H(t,p) &= \alpha - \eta H(t,p) - \rho_1 H(t,p)V(t,p) - \rho_2 H(t,p)S(t,p) - \rho_3 H(t,p)Y(t,p), \\
\frac{\partial S(t,p)}{\partial t} - \xi_S \Delta S(t,p) &= \int_0^{k_1} f_1(\varrho) e^{-h_1 \varrho} H(t-\varrho,p)(\rho_1 V(t-\varrho,p) + \rho_2 S(t-\varrho,p) \\
&\quad + \rho_3 Y(t-\varrho,p))d\varrho - (\sigma+\mu)S(t,p), \\
\frac{\partial Y(t,p)}{\partial t} - \xi_Y \Delta Y(t,p) &= \sigma \int_0^{k_2} f_2(\varrho) e^{-h_2 \varrho} S(t-\varrho,p)d\varrho - \tau Y(t,p) - \gamma I(t,p)Y(t,p), \\
\frac{\partial V(t,p)}{\partial t} - \xi_V \Delta V(t,p) &= \varepsilon \int_0^{k_3} f_3(\varrho) e^{-h_3 \varrho} Y(t-\varrho,p)d\varrho - \theta V(t,p), \\
\frac{\partial I(t,p)}{\partial t} - \xi_I \Delta I(t,p) &= \lambda Y(t,p) - \pi I(t,p) - \delta I(t,p)Y(t,p),
\end{aligned}$$

where p is the position, ξ_w is the diffusion coefficient of compartment w and $\Delta = \frac{\partial^2}{\partial p^2}$. Some other types of diffusion can also be included in our models (see e.g., [58–60]). We leave these points for future work.

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