ANNALS OF COMMUNICATIONS IN MATHEMATICS
Volume 8, Number 2 (2025), 317-342
DOI: 10.62072/acm.2025.080214
ISSN: 2582-0818
https://www.technoskypub.com/journal/acm/

GLOBAL PROPERTIES OF HIV-1 DYNAMICS WITH CYTOKINES AND ABORTIVE INFECTION

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ABSTRACT. This study presents two mathematical models to improve understanding of cytokine-mediated effects on abortive HIV-1 infection. The models describe interactions among healthy CD4$^+$ T cells, abortively and actively HIV-1-infected CD4$^+$ T cells, inflammatory cytokines, and free HIV-1 particles. In the second model, four types of distributed time delays are incorporated. The biological feasibility of the models is established by demonstrating the non-negativity and boundedness of solutions. Two equilibrium points are identified, and their existence and stability are characterized in terms of the basic reproduction number $\Re_0$. The global stability of the equilibria is analyzed using the Lyapunov method. Numerical simulations support the analytical results. Sensitivity analysis is conducted to identify key parameters influencing $\Re_0$. The impact of time delays on HIV-1 progression is also examined. The findings suggest that longer delays can significantly reduce $\Re_0$, potentially suppressing HIV-1 replication.

1. INTRODUCTION

HIV-1 (Human Immunodeficiency Virus type 1) is a highly aggressive virus that primarily targets CD4$^+$ T cells–key components of the immune defense. Its progression leads to severe impairment of immune function, rendering the body highly susceptible to opportunistic infections that significantly deteriorate overall health. Blood, breast milk, semen, and vaginal secretions are among the bodily fluids through which HIV-1 can be transmitted. According to UNAIDS, in 2023, approximately 630,000 individuals died from HIV-related illnesses, while 1.3 million new infections were recorded. Globally, the number of people living with HIV reached 39.9 million [42]. The adaptive immune system operates through two fundamental mechanisms: the cytotoxic T cell (CTL) response and the antibody-mediated (humoral) response. Cytotoxic T cells, primarily CD8$^+$ T lymphocytes, are responsible for detecting and destroying cells harboring intracellular pathogens like viruses. Meanwhile, the humoral arm, driven by B lymphocytes, generates antibodies

2020 *Mathematics Subject Classification.* 34D20, 34D23, 92B05.
Key words and phrases. CD4$^+$T cells; cytokine-enhanced; abortive HIV-1 infection; distributed delays; Lyapunov method; global stability.
Received: May 28, 2025. Accepted: June 21, 2025. Published: June 30, 2025.

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that bind to pathogens, neutralizing them, preventing their entry into host cells, and facilitating their clearance by other immune components. These complementary pathways work in concert to mount a precise and effective defense against diverse infectious agents.

The use of mathematical models has significantly advanced our understanding of the complex relationship between viral pathogens and the immune system. Through the development and analysis of differential equation-based frameworks, scientists can replicate infection dynamics, explore immune responses, and investigate the effectiveness of therapeutic interventions. Such models provide a theoretical foundation for examining biological processes that are often challenging to capture through experimental methods alone. Mathematical approaches have been applied to analyze the complex behavior and progression of HIV-1 infection (see, e.g., [35]-[41]). Additionally, stability analysis has emerged as one of the most significant and beneficial techniques for comprehending HIV-1 dynamics within hosts (see, e.g., [45]-[4]). The traditional HIV-1 infection model was presented by Nowak [34], and it characterizes the relationship between susceptible CD4$^+$T cells, HIV-1-infected CD4$^+$T cells, and the free HIV-1 particles as follows:

$$\dot{x}(t) = \lambda - d_x x(t) - \beta_1 x(t) v(t), \tag{1.1}$$

$$\dot{y}(t) = \beta_1 x(t) v(t) - d_y y(t), \tag{1.2}$$

$$\dot{v}(t) = \delta_v y(t) - d_v v(t), \tag{1.3}$$

where $x(t)$, $y(t)$ and $v(t)$ are the concentrations of healthy (uninfected) CD4$^+$T cells, infected CD4$^+$T cells, and free HIV-1 particles, at time t, respectively. λ denotes the production rate of healthy CD4$^+$T cells. $\beta_1 xv$ represents the rate of infection. Parameter δ_v refers to production rate of the HIV-1 particles. The compartments x, y and v experience natural mortality at rates $d_x x$, $d_y y$ and $d_v v$, respectively. Several mathematical models have expanded upon this framework by incorporating diverse biological factors, such as time delays [32]-[54]; CTL immune response [34], [18], [28], [9]; antiretroviral therapies [32], [38]; humoral immunity [26], spatial dynamics via reaction-diffusion mechanisms [12], [30], [3]; age structure [25]; and stochastic influences [11], [9].

The mechanism of CD4$^+$T cell death and HIV-1 infection are recognized to be intricate processes that are still being investigated. There are two primary forms of CD4$^+$T cell death: apoptosis and pyroptosis [1], [20]. According to a publication [8], ninety five percentage of CD4$^+$T cell death is attributed to pyroptosis, whereas 5% is attributed to apoptosis. Doitsh et al. [7] demonstrated that caspase-1, a type of cysteine protease, plays a pivotal role in initiating the secretion of pro-inflammatory cytokines such as $1L - 1\beta$. These cytokines contribute to sustained inflammation and attract healthy CD4$^+$ T cells to the site of infection, increasing their susceptibility to cell death. This process establishes a detrimental cycle in which the demise of infected CD4$^+$ T cells triggers further inflammatory responses, promoting the continued depletion of uninfected CD4$^+$ T cells and accelerating the breakdown of the immune system.

The impact of pyroptosis has been integrated into various HIV-1 infection models through the inclusion of distinct biological elements. These include: (i) distinguishing between productively and abortively infected cells [44], (ii) incorporating spatial effects using reaction-diffusion frameworks [48]-[49], and (iii) accounting for age structure within the infected cell population [52]. In the model presented in [44], the persistent inflammation driven by pyroptosis has no influence on the basic reproduction number, indicating that the underlying disease transmission potential remains unaffected by chronic inflammatory responses. Cytokine-enhanced viral infection models were recently created and examined [20]. Zhang et al. [53] developed a model of viral infection that included CTL immune response, discrete-time delays, and inflammatory cytokines. In a recent study, Lv et al. [27] introduced a time delay in the activation of inflammatory cytokines within a cytokine-enhanced viral infection model. However, their model did not differentiate between cells that were productively infected and those that were abortively infected.

This study focuses on formulating two HIV-1 infection models that incorporate the roles of (i) inflammatory cytokines and (ii) abortive infection. The second model further includes four distinct types of distributed time delays to capture biological realism. We begin by analyzing the essential properties of the models, followed by identifying all possible equilibria and examining their existence and global stability. Lyapunov's method is employed to demonstrate the global asymptotic stability of each equilibrium. Numerical simulations are carried out to support and validate the theoretical findings. Finally, the implications of the results are thoroughly discussed.

2. Cytokine-enhanced HIV-1 dynamical system

2.1. **Model development.** We formulate a five-dimensional system of ordinary differential equations (ODEs) as follows:

$$\dot{x}(t) = \lambda - d_x x(t) - [\beta_1 x(t) v(t) + \beta_2 x(t) c(t)], \tag{2.1}$$

$$\dot{y}(t) = (1-q)[\beta_1 x(t) v(t) + \beta_2 x(t) c(t)] - d_y y(t), \tag{2.2}$$

$$\dot{w}(t) = q[\beta_1 x(t) v(t) + \beta_2 x(t) c(t)] - d_w w(t), \tag{2.3}$$

$$\dot{c}(t) = \eta_c d_w w(t) - d_c c(t), \tag{2.4}$$

$$\dot{v}(t) = \delta_v y(t) - d_v v(t), \tag{2.5}$$

where $w(t)$ and $c(t)$ denote the concentrations of abortive HIV-1-infected CD4$^+$T cells and inflammatory cytokines at time t, respectively. $\beta_2 xc$ reflects the infection rate of CD4$^+$ T cells driven by inflammatory cytokines. The quantity of inflammatory cytokines produced by each abortive HIV-1-infected CD4$^+$T cell throughout its life time is denoted by η_c. The compartments w and c experience natural mortality at rates $d_w w$ and $d_c c$, respectively. A portion $q \in (0,1)$ of newly HIV-1-infected cells becomes abortive, whereas the remaining portion, $(1-q)$ will be active.

2.2. **Properties of solutions. Proposition 1.** Solutions of system (2.1)-(2.5) are non-negative and bounded.

Proof. We have

$$\begin{aligned}
&\dot{x}\mid_{x=0} = \lambda > 0,\\
&\dot{y}\mid_{y=0} = (1-q)[\beta_1 xv + \beta_2 xc] \geq 0 \quad \text{for all } x, v, c \geq 0,\\
&\dot{w}\mid_{w=0} = q[\beta_1 xv + \beta_2 xc] \geq 0 \quad \text{for all } x, v, c \geq 0,\\
&\dot{c}\mid_{c=0} = \eta_c d_w w \geq 0 \quad \text{for all } w \geq 0,\\
&\dot{v}\mid_{v=0} = \delta_v y \quad \text{for all } y \geq 0.
\end{aligned}$$

This insures that $(x(t), y(t), w(t), c(t), v(t)) \in \mathbb{R}^5_{\geq 0}$ for all $t \geq 0$, when $(x(0), y(0), w(0), c(0), v(0)) \in \mathbb{R}^5_{\geq 0}$. To show the boundedness of the all state variables, we define the function $\Gamma(t) = x(t) + y(t) + w(t)$. Then, by finding the derivative of that function and using the model's equations, we get

$$\dot{\Gamma}(t) = \lambda - d_x x(t) - d_y y(t) - d_w w(t) \leq \lambda - \sigma(x(t) + y(t) + w(t)) = \lambda - \sigma\Gamma(t),$$

where $\sigma = \min\{d_x, d_y, d_w\}$. Hence, we have $0 \leq \Gamma(t) \leq L_1$ if $\Gamma(0) \leq \frac{\lambda}{\sigma}$ for all $t \geq 0$, where $L_1 = \frac{\lambda}{\sigma}$. It follows that $0 \leq x(t), y(t), w(t) \leq L_1$ if $0 \leq x(0) + y(0) + w(0) \leq L_1$.

Moreover, from Eq. (2.4) we have

$$\dot{c}(t) = \eta_c d_w w(t) - d_c c(t) \leq \eta_c d_w L_1 - d_c c(t).$$

This means that $0 \leq c(t) \leq L_2$ whenever $0 \leq c(0) \leq L_2$ for all $t \geq 0$, where $L_2 = \frac{\eta_c d_w L_1}{d_c}$. Furthermore, Eq. (2.5) yields

$$\dot{v}(t) = \delta_v y(t) - d_v v(t) \leq \delta_v L_1 - d_v v(t).$$

This means that $0 \leq v(t) \leq L_3$ whenever $0 \leq v(0) \leq L_3$ for all $t \geq 0$, where $L_3 = \frac{\delta_v L_1}{d_v}$. □

Proposition 1 states that the set

$$\Theta = \left\{(x, y, w, c, v) \in \mathbb{R}^5_{\geq 0} : x(t) + y(t) + w(t) \leq L_1, 0 \leq c(t) \leq L_2, 0 \leq v(t) \leq L_3\right\},$$

is positively invariant for system (2.1)-(2.5).

2.3. **Steady states and the basic reproduction number.** In this subsection, we will compute the potential steady states of system (2.1)-(2.5) and identify the prerequisites for their existence. Any steady state (x, y, w, c, v) satisfies the below system of algebraic equations:

$$0 = \lambda - d_x x - [\beta_1 x v + \beta_2 x c], \tag{2.6}$$

$$0 = (1-q)[\beta_1 x v + \beta_2 x c] - d_y y, \tag{2.7}$$

$$0 = q[\beta_1 x v + \beta_2 x c] - d_w w, \tag{2.8}$$

$$0 = \eta_c d_w w - d_c c, \tag{2.9}$$

$$0 = \delta_v y - d_v v. \tag{2.10}$$

It is evident that system (2.1)-(2.5) has an infection-free steady state, $\Pi_0 = (x_0, 0, 0, 0, 0)$, where $x_0 = \frac{\lambda}{d_x}$. This signifies a healthy situation in which there is no infection. Additionally, from Eqs. (2.6)-(2.10) there is an infected steady state, $\Pi_1 = (x_1, y_1, w_1, c_1, v_1)$, where

$$x_1 = \frac{d_y d_c d_v}{\beta_1 (1-q)\delta_v d_c + \beta_2 q \eta_c d_y d_v} = \frac{x_0}{\Re_0}, \qquad y_1 = \frac{d_v}{\delta_v} v_1,$$

$$w_1 = \frac{q d_y d_v}{(1-q)\delta_v d_w} v_1, \; c_1 = \frac{q \eta_c d_y d_v}{(1-q)\delta_v d_c} v_1, \quad v_1 = \frac{\lambda (1-q)\delta_v}{d_v d_y \Re_0}(\Re_0 - 1),$$

where $\Re_0$ is the model basic reproduction number (2.1)-(2.5), and it indicates how many further CD4$^+$T cells will become infected from the single infected cell when infections started. Clearly, the existence of Π_1 is guaranteed whenever $\Re_0 > 1$, where $\Re_0$ is defined as:

$$\Re_0 = \Re_{0v} + \Re_{0c},$$

where

$$\Re_{0v} = \frac{\beta_1 x_0 (1-q)\delta_v}{d_y d_v},$$

$$\Re_{0c} = \frac{\beta_2 x_0 q \eta_c}{d_c},$$

Furthermore, it is clear that $\Re_{0v}$ denotes the contribution of viral infection to $\Re_0$, while $\Re_{0c}$ denotes the contribution of inflammatory cytokines.

2.4. **Global stability.** In this part, we will examine the global asymptotic stability of the steady states of system (2.1)-(2.5), and this can be studied by constructing suitable Lyapunov functions and applying LaSalle's invariance principle. Define $\chi(\theta) = \theta - 1 - \ln(\theta)$

and denote $(x, y, w, c, v) = (x(t), y(t), w(t), c(t), v(t))$. Define a Lyapunov function candidate $\Phi_i = \Phi_i(x, y, w, c, v)$ and let Υ_i' be the largest invariant subset of

$$\Upsilon_i = \left\{ (x, y, w, c, v) : \frac{d\Phi_i}{dt} = 0 \right\}, \qquad i = 0, 1, 2, 3.$$

We use the following relation between the arithmetical mean and geometrical mean

$$\frac{\eta_1 + \eta_2 + ... + \eta_n}{n} \geq \sqrt[n]{\eta_1 \eta_2 ... \eta_n}, \text{ for all } \eta_1, \eta_2, ..., \eta_n \geq 0. \tag{2.11}$$

Theorem 1. If $\Re_0 \leq 1$, then the infection-free steady state, $\Pi_0(x_0, 0, 0, 0, 0)$ of system (2.1)-(2.5) is globally asymptotically stable.

Proof. By formulated a function $\Phi_0(x, y, w, c, v)$ as:

$$\Phi_0 = \Re_0 x_0 \chi \left(\frac{x}{x_0} \right) + \frac{\beta_1 x_0 \delta_v}{d_v d_y} y + \frac{\beta_2 x_0 \eta_c}{d_c} w + \frac{\beta_2 x_0}{d_c} c + \frac{\beta_1 x_0}{d_v} v.$$

Calculating $\frac{d\Phi_0}{dt}$ along the solutions of model (2.1)-(2.5) as:

$$\begin{aligned}
\frac{d\Phi_0}{dt} &= \Re_0 \left(1 - \frac{x_0}{x}\right) (\lambda - d_x x - \beta_1 x v - \beta_2 x c) + \frac{\beta_1 x_0 \delta_v}{d_v d_y} \left((1-q) (\beta_1 x v + \beta_2 x c) - d_y y \right) \\
&+ \frac{\beta_2 x_0 \eta_c}{d_c} \left(q (\beta_1 x v + \beta_2 x c) - d_w w \right) + \frac{\beta_2 x_0}{d_c} (\eta_c d_w w - d_c c) + \frac{\beta_1 x_0}{d_v} (\delta_v y - d_v v) \\
&= \Re_0 \left(1 - \frac{x_0}{x}\right) (\lambda - d_x x) - \beta_2 x_0 c - \beta_1 x_0 v + \beta_1 x_0 \left(\frac{\beta_1 x_0 (1-q) \delta_v}{d_v d_y} + \frac{\beta_2 x_0 \eta_c q}{d_c} \right) v \\
&+ \beta_2 x_0 \left(\frac{\beta_1 x_0 (1-q) \delta_v}{d_v d_y} + \frac{\beta_2 x_0 \eta_c q}{d_c} \right) c.
\end{aligned}$$

Substituting $\lambda = d_x x_0$, we obtain

$$\begin{aligned}
\frac{d\Phi_0}{dt} &= -\frac{\Re_0 d_x (x - x_0)^2}{x} + \beta_1 x_0 (\Re_0 - 1) v + \beta_2 x_0 (\Re_0 - 1) c \\
&= -\frac{\Re_0 d_x (x - x_0)^2}{x} + [\beta_1 x_0 v + \beta_2 x_0 c] (\Re_0 - 1).
\end{aligned}$$

If $\Re_0 \leq 1$ then $\frac{d\Phi_0}{dt} \leq 0$ for all $x, y, w, c, v > 0$. Moreover, $\frac{d\Phi_0}{dt} = 0$ when $x = x_0$ and $[\beta_1 x_0 v + \beta_2 x_0 c] (\Re_0 - 1) = 0$. Solutions of system (2.1)-(2.5) converge to Υ_0' [14], where $x = x_0$ and

$$[\beta_1 x_0 v + \beta_2 x_0 c] (\Re_0 - 1) = 0. \tag{2.12}$$

We have the cases:

Case (I) $\Re_0 = 1$, then from Eq. (2.1) we have

$$0 = \dot{x} = \lambda - d_x x_0 - \beta_1 x_0 v - \beta_2 x_0 c = -(\beta_1 x_0 v + \beta_2 x_0 c) \Longrightarrow v(t) = c(t) = 0, \text{ for all } t.$$

Eqs. (2.4) and (2.5) give

$$0 = \dot{c} = \eta_c d_w w \Longrightarrow w(t) = 0, \text{ for all } t, \tag{2.13}$$

$$0 = \dot{v} = \delta_v y \Longrightarrow y(t) = 0, \text{ for all } t. \tag{2.14}$$

This yields that $\Upsilon_0' = \{\Pi_0\}$

Case (II) $\Re_0 < 1$, and by using Eq. (2.12) we get $v(t) = c(t) = 0$ for all t. Eqs. (2.13) and (2.14) give $w(t) = y(t) = 0$ and then $\Upsilon_0' = \{\Pi_0\}$.

Applying LaSalle's invariance principle [21], we find that Π_0 is globally asymptotically stable. $\square$

Theorem 2. If $\Re_0 > 1$, then the infected steady state, $\Pi_1(x_1, y_1, w_1, c_1, v_1)$ is globally asymptotically stable.

Proof. Construct a function $\Phi_1(x_1, y_1, w_1, c_1, v_1)$ as:

$$\Phi_1 = x_1(\beta_1 v_1 + \beta_2 c_1)\left[\chi\left(\frac{x}{x_1}\right) + \frac{\beta_1}{d_v d_y}\delta_v y_1 \chi\left(\frac{y}{y_1}\right) + \frac{\beta_2}{d_c}\eta_c w_1 \chi\left(\frac{w}{w_1}\right) + \frac{\beta_2}{d_c}c_1 \chi\left(\frac{c}{c_1}\right) + \frac{\beta_1}{d_v}v_1 \chi\left(\frac{v}{v_1}\right)\right].$$

Calculating $\frac{d\Phi_1}{dt}$ along the solutions of (2.1)-(2.5) as:

$$\begin{aligned}
\frac{d\Phi_1}{dt} &= (\beta_1 v_1 + \beta_2 c_1)\left(1 - \frac{x_1}{x}\right)(\lambda - d_x x - \beta_1 x v - \beta_2 x c) \\
&+ \frac{\beta_1 x_1(\beta_1 v_1 + \beta_2 c_1)}{d_v d_y}\delta_v \left(1 - \frac{y_1}{y}\right)((1-q)(\beta_1 x v + \beta_2 x c) - d_y y) \\
&+ \frac{\beta_2 x_1(\beta_1 v_1 + \beta_2 c_1)}{d_c}\eta_c \left(1 - \frac{w_1}{w}\right)(q(\beta_1 x v + \beta_2 x c) - d_w w) \\
&+ \frac{\beta_2 x_1(\beta_1 v_1 + \beta_2 c_1)}{d_c}\left(1 - \frac{c_1}{c}\right)(\eta_c d_w w - d_c c) \\
&+ \frac{\beta_1 x_1(\beta_1 v_1 + \beta_2 c_1)}{d_v}\left(1 - \frac{v_1}{v}\right)(\delta_v y - d_v v). \qquad (2.15)
\end{aligned}$$

Summing terms of Eq. (2.15) and using the following conditions for Π_1:

$$\begin{aligned}
\lambda &= d_x x_1 + \beta_1 x_1 v_1 + \beta_2 x_1 c_1, \\
d_y y_1 &= (1-q)(\beta_1 x_1 v_1 + \beta_2 x_1 c_1), \\
d_w w_1 &= q(\beta_1 x_1 v_1 + \beta_2 x_1 c_1), \\
v_1 &= \frac{\delta_v}{d_v} y_1 = \frac{\delta_v (1-q)(\beta_1 x_1 v_1 + \beta_2 x_1 c_1)}{d_y d_v}, \\
c_1 &= \frac{\eta_c}{d_c} d_w w_1 = \frac{\eta_c q(\beta_1 x_1 v_1 + \beta_2 x_1 c_1)}{d_c},
\end{aligned}$$

we obtain

$$\begin{aligned}
\frac{d\Phi_1}{dt} &= (\beta_1 v_1 + \beta_2 c_1)\left(1 - \frac{x_1}{x}\right)(\lambda - d_x x) + (\beta_1 v_1 + \beta_2 c_1)(\beta_1 x_1 v + \beta_2 x_1 c) \\
&- \frac{\beta_1 x_1(\beta_1 v_1 + \beta_2 c_1)}{d_v d_y}(1-q)\delta_v(\beta_1 x v + \beta_2 x c)\frac{y_1}{y} \\
&+ \frac{\beta_1 x_1(\beta_1 v_1 + \beta_2 c_1)}{d_v}\delta_v y_1 - \frac{\beta_2 x_1(\beta_1 v_1 + \beta_2 c_1)}{d_c} q\eta_c(\beta_1 x v + \beta_2 x c)\frac{w_1}{w} \\
&+ \frac{\beta_2 x_1(\beta_1 v_1 + \beta_2 c_1)}{d_c}\eta_c d_w w_1 - \frac{\beta_2 x_1(\beta_1 v_1 + \beta_2 c_1)}{d_c}\eta_c d_w \frac{w c_1}{c} \\
&- \beta_2 x_1 c(\beta_1 v_1 + \beta_2 c_1) + \beta_2 x_1 c_1(\beta_1 v_1 + \beta_2 c_1) \\
&- \frac{\beta_1 x_1(\beta_1 v_1 + \beta_2 c_1)}{d_v}\delta_v \frac{y v_1}{v} - \beta_1 x_1 v(\beta_1 v_1 + \beta_2 c_1) + \beta_1 x_1 v_1(\beta_1 v_1 + \beta_2 c_1).
\end{aligned}$$

Then, we get

$$\begin{aligned}
\frac{d\Phi_1}{dt} &= (\beta_1 v_1 + \beta_2 c_1)\left(1 - \frac{x_1}{x}\right)(d_x x_1 + \beta_1 x_1 v_1 + \beta_2 x_1 c_1 - d_x x) \\
&- \beta_1^2 x_1 v_1^2 \frac{x v y_1}{x_1 v_1 y} - \beta_1 \beta_2 x_1 v_1 c_1 \frac{x c y_1}{x_1 c_1 y} + \beta_1 x_1 v_1(\beta_1 v_1 + \beta_2 c_1) \\
&- \beta_2 \beta_1 x_1 v_1 c_1 \frac{x v w_1}{x_1 v_1 w} - \beta_2^2 x_1 c_1^2 \frac{x c w_1}{x_1 c_1 w} + \beta_2 x_1 c_1(\beta_1 v_1 + \beta_2 c_1)
\end{aligned}$$

$$- \beta_2 x_1 c_1 (\beta_1 v_1 + \beta_2 c_1) \frac{w c_1}{w_1 c} + \beta_2 x_1 c_1 (\beta_1 v_1 + \beta_2 c_1)$$
$$- \beta_1 x_1 v_1 (\beta_1 v_1 + \beta_2 c_1) \frac{y v_1}{y_1 v} + \beta_1 x_1 v_1 (\beta_1 v_1 + \beta_2 c_1). \tag{2.16}$$

Simplifying Eq. (2.16), we obtain

$$\begin{aligned}
\frac{d\Phi_1}{dt} &= -\frac{d_x \left(\beta_1 v_1 + \beta_2 c_1\right) \left(x - x_1\right)^2}{x} + \beta_1^2 x_1 v_1^2 \left(1 - \frac{x_1}{x}\right) + 2\beta_1 \beta_2 x_1 v_1 c_1 \left(1 - \frac{x_1}{x}\right) \\
&+ \beta_2^2 x_1 c_1^2 \left(1 - \frac{x_1}{x}\right) - \beta_1^2 x_1 v_1^2 \frac{x v y_1}{x_1 v_1 y} - \beta_1 \beta_2 x_1 v_1 c_1 \frac{x c y_1}{x_1 c_1 y} + 2\beta_1^2 x_1 v_1^2 \\
&+ 4\beta_1 \beta_2 x_1 v_1 c_1 - \beta_1 \beta_2 x_1 v_1 c_1 \frac{x v w_1}{x_1 v_1 w} - \beta_2^2 x_1 c_1^2 \frac{x c w_1}{x_1 c_1 w} + 2\beta_2^2 x_1 c_1^2 \\
&- \beta_1 \beta_2 x_1 v_1 c_1 \frac{w c_1}{w_1 c} - \beta_2^2 x_1 c_1^2 \frac{w c_1}{w_1 c} - \beta_1^2 x_1 v_1^2 \frac{y v_1}{y_1 v} - \beta_1 \beta_2 x_1 v_1 c_1 \frac{y v_1}{y_1 v}.
\end{aligned}$$

Then, we obtain

$$\begin{aligned}
\frac{d\Phi_1}{dt} &= -\frac{d_x \left(\beta_1 v_1 + \beta_2 c_1\right) \left(x - x_1\right)^2}{x} + \beta_1^2 x_1 v_1^2 \left(3 - \frac{x_1}{x} - \frac{x v y_1}{x_1 v_1 y} - \frac{y v_1}{y_1 v}\right) \\
&+ \beta_2^2 x_1 c_1^2 \left(3 - \frac{x_1}{x} - \frac{x c w_1}{x_1 c_1 w} - \frac{w c_1}{w_1 c}\right) \\
&+ \beta_1 \beta_2 x_1 v_1 c_1 \left(6 - \frac{x_1}{x} - \frac{x_1}{x} - \frac{x c y_1}{x_1 c_1 y} - \frac{x v w_1}{x_1 v_1 w} - \frac{w c_1}{w_1 c} - \frac{y v_1}{y_1 v}\right).
\end{aligned}$$

Hence, If $\Re_0 > 1$ then inequality (2.11) gives:

$$\frac{\frac{x_1}{x} + \frac{x v y_1}{x_1 v_1 y} + \frac{y v_1}{y_1 v}}{3} \geq \sqrt[3]{\left(\frac{x_1}{x}\right)\left(\frac{x v y_1}{x_1 v_1 y}\right)\left(\frac{y v_1}{y_1 v}\right)} = 1$$

Then, $\dfrac{x_1}{x} + \dfrac{x v y_1}{x_1 v_1 y} + \dfrac{y v_1}{y_1 v} \geq 3.$

Similary we get

$$\frac{x_1}{x} + \frac{x c w_1}{x_1 c_1 w} + \frac{w c_1}{w_1 c} \geq 3$$
$$\frac{x_1}{x} + \frac{x_1}{x} + \frac{x c y_1}{x_1 c_1 y} + \frac{x v w_1}{x_1 v_1 w} + \frac{w c_1}{w_1 c} + \frac{y v_1}{y_1 v} \geq 6$$

Therefore, $\frac{d\Phi_1}{dt} \leq 0$ for all $x, y, w, c, v > 0$. Moreover, $\frac{d\Phi_1}{dt} = 0$ when $x(t) = x_1$, $y(t) = y_1, w(t) = w_1, c(t) = c_1$ and $v(t) = v_1$ for all t. Therefore, all solutions of model (2.1)-(2.5) converge to Υ_1' and this yields that $\Upsilon_1' = \{\Pi_1\}$. Hence, LaSalle's invariance principle implies that Π_1 is globally asymptotically stable. □

3. DISTRIBUTED TIME DELAY MODEL

3.1. **Analysis of the model.** We extend model (2.1)-(2.5) by including four kinds of distributed time delays:

$$\dot{x}(t) = \lambda - d_x x(t) - \beta_1 x(t) v(t) - \beta_2 x(t) c(t), \tag{3.1}$$

$$\dot{y}(t) = (1 - q) \int_0^{k_1} b_1(\varphi) e^{-m_1 \varphi} x(t - \varphi) \left(\beta_1 v(t - \varphi) + \beta_2 c(t - \varphi)\right) d\varphi - d_y y(t), \tag{3.2}$$

$$\dot{w}(t) = q \int_0^{k_2} b_2(\varphi) e^{-m_2 \varphi} x(t - \varphi) \left(\beta_1 v(t - \varphi) + \beta_2 c(t - \varphi)\right) d\varphi - d_w w(t), \tag{3.3}$$

$$\dot{c}\left(t\right)=\eta_c d_w\int_0^{k_3} b_3(\varphi)e^{-m_3\varphi}w\left(t-\varphi\right)d\varphi-d_c c\left(t\right), \tag{3.4}$$

$$\dot{v}\left(t\right)=\delta_v\int_0^{k_4} b_4(\varphi)e^{-m_4\varphi}y\left(t-\varphi\right)d\varphi-d_v v\left(t\right). \tag{3.5}$$

Here, $m_i>0$ are constants. The delay parameter φ is taken randomly from a probability distribution function $b_i(\varphi)$ over the interval of time $[0,k_j]$, $j=1,2,3,4$, where k_j is the limit superior of this delay period. The factor $b_1(\varphi)e^{-m_1\varphi}$ is the probability that a healthy CD4$^+$T cell contacted by viruses at time $t-\varphi$ will survive φ time units and become active HIV-1-infected at time t. $b_2(\varphi)e^{-m_2\varphi}$ is the probability that a healthy CD4$^+$T cell contacted by viruses at time $t-\varphi$ will survive φ time units and become abortive infected cell at time t. The expression $b_3(\varphi)e^{-m_3\varphi}$ represents the likelihood that inactive cytokines persist for a duration of φ time units before transitionary into their active form. The term $b_4(\varphi)e^{-m_4\varphi}$ demonstrates the probability that new immature HIV-1 particles at time $t-\varphi$ will survive for φ time units and become mature at time t.

The function $b_j(\varphi)$, $j=1,2,3,4$, satisfies $b_j(\varphi)>0$,

$$\int_0^{k_j} b_j(\varphi)d\varphi=1 \quad\text{and}\quad \int_0^{k_j} b_j(\varphi)e^{-\ell\varphi}d\varphi<\infty,\quad \text{where } \ell>0.$$

Let us denote

$$\tilde{\mathcal{T}}_j\left(\varphi\right)=b_j(\varphi)e^{-m_j\varphi},\qquad \mathcal{T}_j=\int_0^{k_j}\tilde{\mathcal{T}}_j\left(\varphi\right)d\varphi,\quad j=1,2,3,4.$$

Therefore, $0<\mathcal{T}_j\le 1$, $j=1,2,3,4$. The initial conditions of system (3.1)-(3.5) are given by:

$$\begin{aligned}&x(\theta)=\varpi_1(\theta),\quad y(\theta)=\varpi_2(\theta),\quad w(\theta)=\varpi_3(\theta),\quad c(\theta)=\varpi_4(\theta),\quad v(\theta)=\varpi_5(\theta),\\&\varpi_i(\theta)\ge 0,\quad \theta\in\left[-\xi,0\right],\quad i=1,2,...,5.\end{aligned} \tag{3.6}$$

where $\xi=\max\left\{k_1,k_2,k_3,k_4\right\}$, and $\varpi_i(\theta)\in C\left(\left[-\xi,0\right],\mathbb{R}_{\ge 0}\right)$, the Banach space of continuous functions mapping the interval $[-\xi,0]$ into $\mathbb{R}_{\ge 0}$ is denoted by C. With norm $\|\varpi_i\|=\sup\limits_{-\xi\le\theta\le 0}|\varpi_i(\theta)|$ for $\varpi_i\in C$. Thus, when the fundamental theory of functional differential equations is utilized, system (3.1)-(3.5) with initial conditions (3.6) exhibits a unique solution [14], [22].

3.2. **Properties of solutions. Proposition 2.** Solutions of system (3.1)-(3.5) with initial conditions (3.6) are non-negative and ultimately bounded.

Proof. From Eq. (3.1), we have $\dot{x}\mid_{x=0}=\lambda>0$, then $x(t)>0$ for all $t\ge 0$. Moreover, for $t\in[0,\xi]$, we have

$$y(t)=\varpi_2(0)e^{-d_y t}+(1-q)\int_0^t e^{-d_y(t-\varkappa)}\int_0^{k_1}\tilde{\mathcal{T}}_1(\varphi)x(\varkappa-\varphi)\left(\beta_1 v(\varkappa-\varphi)+\beta_2 c(\varkappa-\varphi)\right)d\varphi d\varkappa\ge 0,$$

$$w(t)=\varpi_3(0)e^{-d_w t}+q\int_0^t e^{-d_w(t-\varkappa)}\int_0^{k_2}\tilde{\mathcal{T}}_2(\varphi)x\left(\varkappa-\varphi\right)\left(\beta_1 v\left(\varkappa-\varphi\right)+\beta_2 c\left(\varkappa-\varphi\right)\right)d\varphi d\varkappa\ge 0,$$

$$c(t)=\varpi_4(0)e^{-d_c t}+\eta_c d_w\int_0^t e^{-d_c(t-\varkappa)}\int_0^{k_3}\tilde{\mathcal{T}}_3(\varphi)w\left(\varkappa-\varphi\right)d\varphi d\varkappa\ge 0,$$

$$v(t)=\varpi_5(0)e^{-d_v t}+\delta_v\int_0^t e^{-d_v(t-\varkappa)}\int_0^{k_4}\tilde{\mathcal{T}}_4(\varphi)y\left(\varkappa-\varphi\right)d\varphi d\varkappa\ge 0.$$

Thus, through a recursive argument using, we obtain that $x(t)$, $y(t)$, $w(t)$, $c(t)$, and $v(t)$ remain non-negative for all $t \geq 0$. Next, we show the ultimate boundedness of the model's solutions. The non-negativity of the model's solution implies that $\lim_{t\to\infty} \sup x(t) \leq \frac{\lambda}{d_x}$. Further, we let

$$\Omega_1(t) = \int_0^{k_1} \tilde{\mathcal{T}}_1(\varphi)x(t-\varphi)d\varphi + \frac{1}{1-q}y(t).$$

Then, we get

$$\begin{aligned}\dot{\Omega}_1(t) &= \int_0^{k_1} \tilde{\mathcal{T}}_1(\varphi)\left(\lambda - d_x x(t-\varphi)\right)d\varphi - \frac{d_y}{1-q}y(t)\\ &= \lambda\mathcal{T}_1 - d_x\int_0^{k_1} \tilde{\mathcal{T}}_1(\varphi)x(t-\varphi)d\varphi - \frac{d_y}{1-q}y(t) \leq \lambda - \rho_1\Omega_1,\end{aligned}$$

where $\rho_1 = \min\{d_x, d_y\}$. Hence, $\lim_{t\to\infty} \sup \Omega_1(t) \leq \hat{L}_1$, where $\hat{L}_1 = \frac{\lambda}{\rho_1}$. Therefore, we are able to get that $\lim_{t\to\infty} \sup y(t) \leq \hat{L}_1$. Moreover, we let

$$\Omega_2(t) = \int_0^{k_2} \tilde{\mathcal{T}}_2(\varphi)x(t-\varphi)d\varphi + \frac{1}{q}w(t).$$

Then, we get

$$\begin{aligned}\dot{\Omega}_2(t) &= \int_0^{k_2} \tilde{\mathcal{T}}_2(\varphi)\left(\lambda - d_x x(t-\varphi)\right)d\varphi - \frac{d_w}{q}w(t)\\ &= \lambda\mathcal{T}_2 - d_x\int_0^{k_2} \tilde{\mathcal{T}}_2(\varphi)x(t-\varphi)d\varphi - \frac{d_w}{q}w \leq \lambda - \rho_2\Omega_2,\end{aligned}$$

where $\rho_2 = \min\{d_x, d_w\}$. Hence, $\lim_{t\to\infty} \sup \Omega_2(t) \leq \hat{L}_2$, where $\hat{L}_2 = \frac{\lambda}{\rho_2}$. Therefore, we are able to get that $\lim_{t\to\infty} \sup w(t) \leq \hat{L}_2$. From Eq. (3.4), we have

$$\dot{c}(t) = \eta_c d_w \int_0^{k_3} \tilde{\mathcal{T}}_3(\varphi)w(t-\varphi)d\varphi - d_c c(t) \leq \eta_c d_w \mathcal{T}_3\hat{L}_2 - d_c c(t) \leq \eta_c d_w\hat{L}_2 - d_c c(t),$$

then $\lim_{t\to\infty} \sup c(t) \leq \hat{L}_3$, where $\hat{L}_3 = \dfrac{\eta_c d_w \hat{L}_2}{d_c}$. Furthermore, Eq. (3.5) implies

$$\dot{v}(t) = \delta_v \int_0^{k_4} \tilde{\mathcal{T}}_4(\varphi)y(t-\varphi)d\varphi - d_v v(t) \leq \delta_v\mathcal{T}_4\hat{L}_1 - d_v v(t) \leq \delta_v\hat{L}_1 - d_v v(t),$$

hence, $\lim_{t\to\infty} \sup v(t) \leq \hat{L}_4$, where $\hat{L}_4 = \dfrac{\delta_v \hat{L}_1}{d_v}$. □

Proposition 2 states that the set

$$\hat{\Theta} = \left\{(x,y,w,c,v) \in C^5_{\geq 0} : \|x\|, \|y\| \leq \hat{L}_1, \|w\| \leq \hat{L}_2, \|c\| \leq \hat{L}_3, \|v\| \leq \hat{L}_4\right\},$$

is positively invariant for system (3.1)-(3.5).

3.3. **Steady states and the basic reproduction number.** This subsection finds the steady states of system (3.1)-(3.5) and identifies the prerequisites for their existence. Any steady state satisfies the following:

$$0 = \lambda - d_x x - \beta_1 xv - \beta_2 xc, \tag{3.7}$$

$$0 = (1-q)\mathcal{T}_1\left(\beta_1 xv + \beta_2 xc\right) - d_y y, \tag{3.8}$$

$$0 = q\mathcal{T}_2\left(\beta_1 xv + \beta_2 xc\right) - d_w w, \tag{3.9}$$

$$0 = \eta_c d_w \mathcal{T}_3 w - d_c c, \tag{3.10}$$

$$0 = \delta_v \mathcal{T}_4 y - d_v v. \tag{3.11}$$

It is obvious that system (3.1)-(3.5) has no infection with free steady state, $\hat{\Pi}_0 = (\hat{x}_0, 0, 0, 0, 0)$, where $\hat{x}_0 = \frac{\lambda}{d_x}$. This case is describes the healthy situation state, where the infection is absent. Additionally, from Eqs. (3.7)-(3.11) system (3.1)-(3.5) has an infected steady state, $\hat{\Pi}_1 = (\hat{x}_1, \hat{y}_1, \hat{w}_1, \hat{c}_1, \hat{v}_1)$, where

$$\hat{x}_1 = \frac{d_c d_v d_y}{\beta_1\left(1-q\right)\delta_v d_c \mathcal{T}_1\mathcal{T}_4 + \beta_2 q\eta_c d_y d_v \mathcal{T}_2\mathcal{T}_3} = \frac{\hat{x}_0}{\hat{\Re}_0},\ \ \hat{y}_1 = \frac{d_v}{\delta_v \mathcal{T}_4}\hat{v}_1,$$

$$\hat{w}_1 = \frac{q d_v d_y \mathcal{T}_2}{\left(1-q\right)\delta_v d_w \mathcal{T}_1\mathcal{T}_4}\hat{v}_1,\ \hat{c}_1 = \frac{q\eta_c d_v d_y \mathcal{T}_2\mathcal{T}_3}{\left(1-q\right)\delta_v d_c \mathcal{T}_1\mathcal{T}_4}\hat{v}_1,\ \ \hat{v}_1 = \frac{\left(1-q\right)\lambda\delta_v\mathcal{T}_1\mathcal{T}_4}{d_v d_y \hat{\Re}_0}\left(\hat{\Re}_0 - 1\right).$$

Clearly, the existence of $\hat{\Pi}_1$ is guaranteed whenever $\hat{\Re}_0 > 1$, where $\hat{\Re}_0$ is the basic reproduction number for system (3.1)-(3.5) given as:

$$\hat{\Re}_0 = \hat{\Re}_{0v} + \hat{\Re}_{0c},$$

where

$$\hat{\Re}_{0v} = \frac{\beta_1\left(1-q\right)\delta_v \hat{x}_0 \mathcal{T}_1\mathcal{T}_4}{d_v d_y},$$

$$\hat{\Re}_{0c} = \frac{\beta_2 q\eta_c \hat{x}_0 \mathcal{T}_2\mathcal{T}_3}{d_c}.$$

The parameters $\hat{\Re}_0$ have the same biological meanings of the parameters $\Re_0$ that explained in Section 2.

3.4. **Global stability.** This subsection focuses on analyzing the global asymptotic stability of the steady states of system (3.1)-(3.5). Denote $(x\left(t-\varphi\right), y\left(t-\varphi\right), w\left(t-\varphi\right), c\left(t-\varphi\right), v\left(t-\varphi\right)) = (x_\varphi, y_\varphi, w_\varphi, c_\varphi, v_\varphi)$.

Theorem 3. The infection-free steady state of system (3.1)-(3.5), $\hat{\Pi}_0(\hat{x}_0, 0, 0, 0, 0)$ will be globally asymptotically stable, when $\hat{\Re}_0 \leq 1$.

Proof. Define a function $\Phi_2(x, y, w, c, v)$ as:

$$\begin{aligned}\Phi_2 &= \hat{\Re}_0\hat{x}_0\chi\left(\frac{x}{\hat{x}_0}\right) + \frac{\beta_1\hat{x}_0\delta_v\mathcal{T}_4}{d_v d_y}y + \frac{\beta_2\hat{x}_0\eta_c\mathcal{T}_3}{d_c}w + \frac{\beta_2\hat{x}_0}{d_c}c + \frac{\beta_1\hat{x}_0}{d_v}v\\ &+ \frac{\beta_1\left(1-q\right)\delta_v\hat{x}_0\mathcal{T}_4}{d_v d_y}\int_0^{k_1}\tilde{\mathcal{T}}_1(\varphi)\int_{t-\varphi}^{t}\left(\beta_1 x(\theta)v(\theta) + \beta_2 x(\theta)c(\theta)\right)d\theta d\varphi\\ &+ \frac{\beta_2 q\eta_c\hat{x}_0\mathcal{T}_3}{d_c}\int_0^{k_2}\tilde{\mathcal{T}}_2(\varphi)\int_{t-\varphi}^{t}\left(\beta_1 x(\theta)v(\theta) + \beta_2 x(\theta)c(\theta)\right)d\theta d\varphi\\ &+ \frac{\beta_2\hat{x}_0\eta_c d_w}{d_c}\int_0^{k_3}\tilde{\mathcal{T}}_3(\varphi)\int_{t-\varphi}^{t}w(\theta)d\theta d\varphi + \frac{\beta_1\hat{x}_0\delta_v}{d_v}\int_0^{k_4}\tilde{\mathcal{T}}_4(\varphi)\int_{t-\varphi}^{t}y(\theta)d\theta d\varphi.\end{aligned}$$

Clearly, $\Phi_2(x, y, w, c, v) > 0$ for all $x, y, w, c, v > 0$, and $\Phi_2 = 0$ at $\hat{\Pi}_0$. Calculating $\frac{d\Phi_2}{dt}$ as:

$$\frac{d\Phi_2}{dt} = \hat{\Re}_0\left(1 - \frac{\hat{x}_0}{x}\right)\left(\lambda - d_x x - \beta_1 xv - \beta_2 xc\right)$$

$$
\begin{aligned}
&+\frac{\beta_1\hat{x}_0\delta_v\mathcal{T}_4}{d_vd_y}\left((1-q)\int_0^{k_1}\tilde{\mathcal{T}}_1(\varphi)\left(\beta_1x_\varphi v_\varphi+\beta_2x_\varphi c_\varphi\right)d\varphi-d_yy\right)\\
&+\frac{\beta_2\hat{x}_0\eta_c\mathcal{T}_3}{d_c}\left(q\int_0^{k_2}\tilde{\mathcal{T}}_2(\varphi)\left(\beta_1x_\varphi v_\varphi+\beta_2x_\varphi c_\varphi\right)d\varphi-d_ww\right)\\
&+\frac{\beta_2\hat{x}_0}{d_c}\left(\eta_cd_w\int_0^{k_3}\tilde{\mathcal{T}}_3(\varphi)w_\varphi d\varphi-d_cc\right)+\frac{\beta_1\hat{x}_0}{d_v}\left(\delta_v\int_0^{k_4}\tilde{\mathcal{T}}_4(\varphi)y_\varphi d\varphi-d_vv\right)\\
&+\frac{\beta_1\left(1-q\right)\delta_v\hat{x}_0\mathcal{T}_1\mathcal{T}_4}{d_vd_y}\left(\beta_1xv+\beta_2xc\right)-\frac{\beta_1\left(1-q\right)\delta_v\hat{x}_0\mathcal{T}_4}{d_vd_y}\\
&\times\int_0^{k_1}\tilde{\mathcal{T}}_1(\varphi)\left(\beta_1x_\varphi v_\varphi+\beta_2x_\varphi c_\varphi\right)d\varphi+\frac{\beta_2q\eta_c\hat{x}_0\mathcal{T}_2\mathcal{T}_3}{d_c}\left(\beta_1xv+\beta_2xc\right)\\
&-\frac{\beta_2q\eta_c\hat{x}_0\mathcal{T}_3}{d_c}\int_0^{k_2}\tilde{\mathcal{T}}_2(\varphi)\left(\beta_1x_\varphi v_\varphi+\beta_2x_\varphi c_\varphi\right)d\varphi+\frac{\beta_2\hat{x}_0\eta_cd_w\mathcal{T}_3}{d_c}w\\
&-\frac{\beta_2\hat{x}_0\eta_cd_w}{d_c}\int_0^{k_3}\tilde{\mathcal{T}}_3(\varphi)w_\varphi d\varphi+\frac{\beta_1\hat{x}_0\delta_v\mathcal{T}_4}{d_v}y-\frac{\beta_1\hat{x}_0\delta_v}{d_v}\int_0^{k_4}\tilde{\mathcal{T}}_4(\varphi)y_\varphi d\varphi. \quad (3.12)
\end{aligned}
$$

Summing terms of Eq. (3.12), we obtain

$$\frac{d\Phi_2}{dt}=\hat{\Re}_0\left(1-\frac{\hat{x}_0}{x}\right)\left(\lambda-d_xx\right)+\beta_1\hat{x}_0\hat{\Re}_0v-\beta_1\hat{x}_0v+\beta_2\hat{x}_0\hat{\Re}_0c-\beta_2\hat{x}_0c.$$

Substituting $\lambda=d_x\hat{x}_0$, we obtain

$$
\begin{aligned}
\frac{d\Phi_2}{dt}&=-\frac{d_x\hat{\Re}_0\left(x-\hat{x}_0\right)^2}{x}+\beta_2\hat{x}_0\left(\hat{\Re}_0-1\right)c+\beta_1\hat{x}_0\left(\hat{\Re}_0-1\right)v\\
&=-\frac{d_x\hat{\Re}_0\left(x-\hat{x}_0\right)^2}{x}+\left[\beta_2\hat{x}_0c+\beta_1\hat{x}_0v\right]\left(\hat{\Re}_0-1\right).
\end{aligned}
$$

If $\hat{\Re}_0\leq 1$ then $\frac{d\Phi_2}{dt}\leq 0$ for all $x,y,w,c,v>0$. Moreover, $\frac{d\Phi_2}{dt}=0$ when $x=\hat{x}_0$, and $\left[\beta_2\hat{x}_0c+\beta_1\hat{x}_0v\right]\left(\hat{\Re}_0-1\right)=0$. The model solutions (3.1)-(3.5) converge to Υ_2' , where $x\left(t\right)=\hat{x}_0$, and

$$\left[\beta_2\hat{x}_0c+\beta_1\hat{x}_0v\right]\left(\hat{\Re}_0-1\right)=0. \quad (3.13)$$

We have the two cases:

Case (I) $\hat{\Re}_0=1$, then from the Eq. (2.1) we have

$$0=\dot{x}=\lambda-d_xx_0-\beta_1x_0v-\beta_2x_0c=-(\beta_1x_0v+\beta_2x_0c)\Longrightarrow v(t)=c(t)=0,\ \text{for all}\ t.$$

Eqs. (3.4) and (3.5) derive

$$0=\dot{c}\left(t\right)=\eta_cd_w\int_0^{k_3}\tilde{\mathcal{T}}_3(\varphi)w_\varphi d\varphi\Longrightarrow w\left(t\right)=0,\ \text{for all}\ t, \quad (3.14)$$

$$0=\dot{v}\left(t\right)=\delta_v\int_0^{k_4}\tilde{\mathcal{T}}_4(\varphi)y_\varphi d\varphi\Longrightarrow y\left(t\right)=0,\ \text{for all}\ t. \quad (3.15)$$

This yields that $\Upsilon_2'=\left\{\hat{\Pi}_0\right\}$.

Case (II) $\hat{\Re}_0<1$, then from Eq. (3.13) we get $v(t)=c(t)=0$, for all t. Eqs. (3.14) and (3.15) give $w\left(t\right)=y\left(t\right)=0$, for all t, and then $\Upsilon_0'=\{\Pi_0\}$.

Applying LaSalle's invariance principle, we will obtain that $\hat{\Pi}_0$ is globally asymptotically stable. □

Theorem 4. If $\hat{\Re}_0 > 1$, then the infected steady state of system (3.1)-(3.5), $\hat{\Pi}_1(\hat{x}_1, \hat{y}_1, \hat{w}_1, \hat{c}_1, \hat{v}_1)$ is globally asymptotically stable.

Proof. Construct a function $\Phi_3(\hat{x}_1, \hat{y}_1, \hat{w}_1, \hat{c}_1, \hat{v}_1)$ as:

$$\begin{aligned}
\Phi_3 = {} & \hat{x}_1(\beta_1\hat{v}_1 + \beta_2\hat{c}_1)\left[\chi\left(\frac{x}{\hat{x}_1}\right) + \frac{\beta_1\delta_v\mathcal{T}_4}{d_v d_y}\hat{y}_1\chi\left(\frac{y}{\hat{y}_1}\right)\right. \\
& \left. + \frac{\beta_2\eta_c\mathcal{T}_3}{d_c}\hat{w}_1\chi\left(\frac{w}{\hat{w}_1}\right) + \frac{\beta_2}{d_c}\hat{c}_1\chi\left(\frac{c}{\hat{c}_1}\right) + \frac{\beta_1}{d_v}\hat{v}_1\chi\left(\frac{v}{\hat{v}_1}\right)\right] \\
& + \frac{\beta_1^2\hat{x}_1\hat{v}_1^2}{\mathcal{T}_1}\int_0^{\kappa_1}\tilde{\mathcal{T}}_1(\varphi)\int_{t-\varphi}^{t}\chi\left(\frac{x(\theta)v(\theta)}{\hat{x}_1\hat{v}_1}\right)d\theta d\varphi \\
& + \frac{\beta_1\beta_2\hat{x}_1\hat{v}_1\hat{c}_1}{\mathcal{T}_1}\int_0^{\kappa_1}\tilde{\mathcal{T}}_1(\varphi)\int_{t-\varphi}^{t}\chi\left(\frac{x(\theta)c(\theta)}{\hat{x}_1\hat{c}_1}\right)d\theta d\varphi \\
& + \frac{\beta_1\beta_2\hat{x}_1\hat{v}_1\hat{c}_1}{\mathcal{T}_2}\int_0^{\kappa_2}\tilde{\mathcal{T}}_2(\varphi)\int_{t-\varphi}^{t}\chi\left(\frac{x(\theta)v(\theta)}{\hat{x}_1\hat{v}_1}\right)d\theta d\varphi \\
& + \frac{\beta_2^2\hat{x}_1\hat{c}_1^2}{\mathcal{T}_2}\int_0^{\kappa_2}\tilde{\mathcal{T}}_2(\varphi)\int_{t-\varphi}^{t}\chi\left(\frac{x(\theta)c(\theta)}{\hat{x}_1\hat{c}_1}\right)d\theta d\varphi \\
& + \frac{\beta_2\hat{x}_1\hat{w}_1\eta_c d_w(\beta_1\hat{v}_1 + \beta_2\hat{c}_1)}{d_c}\int_0^{\kappa_3}\tilde{\mathcal{T}}_3(\varphi)\int_{t-\varphi}^{t}\chi\left(\frac{w(\theta)}{\hat{w}_1}\right)d\theta d\varphi \\
& + \frac{\beta_1\hat{x}_1\hat{y}_1\delta_v(\beta_1\hat{v}_1 + \beta_2\hat{c}_1)}{d_v}\int_0^{\kappa_4}\tilde{\mathcal{T}}_4(\varphi)\int_{t-\varphi}^{t}\chi\left(\frac{y(\theta)}{\hat{y}_1}\right)d\theta d\varphi.
\end{aligned}$$

Calculating $\frac{d\Phi_3}{dt}$ as:

$$\begin{aligned}
\frac{d\Phi_3}{dt} = {} & (\beta_1\hat{v}_1 + \beta_2\hat{c}_1)\left(1 - \frac{\hat{x}_1}{x}\right)(\lambda - d_x x - \beta_1 xv - \beta_2 xc) + \frac{\beta_1\hat{x}_1(\beta_1\hat{v}_1 + \beta_2\hat{c}_1)\delta_v\mathcal{T}_4}{d_v d_y} \\
& \times\left(1 - \frac{\hat{y}_1}{y}\right)\left((1-q)\int_0^{k_1}\tilde{\mathcal{T}}_1(\varphi)\left(\beta_1 x_\varphi v_\varphi + \beta_2 x_\varphi c_\varphi\right)d\varphi - d_y y\right) \\
& + \frac{\beta_2\hat{x}_1(\beta_1\hat{v}_1 + \beta_2\hat{c}_1)\eta_c\mathcal{T}_3}{d_c}\left(1 - \frac{\hat{w}_1}{w}\right)\left(q\int_0^{k_2}\tilde{\mathcal{T}}_2(\varphi)\left(\beta_1 x_\varphi v_\varphi + \beta_2 x_\varphi c_\varphi\right)d\varphi - d_w w\right) \\
& + \frac{\beta_2\hat{x}_1(\beta_1\hat{v}_1 + \beta_2\hat{c}_1)}{d_c}\left(1 - \frac{\hat{c}_1}{c}\right)\left(\eta_c d_w\int_0^{k_3}\tilde{\mathcal{T}}_3(\varphi)w_\varphi d\varphi - d_c c\right) \\
& + \frac{\beta_1\hat{x}_1(\beta_1\hat{v}_1 + \beta_2\hat{c}_1)}{d_v}\left(1 - \frac{\hat{v}_1}{v}\right)\left(\delta_v\int_0^{k_4}\tilde{\mathcal{T}}_4(\varphi)y_\varphi d\varphi - d_v v\right) \\
& + \frac{\beta_1^2\hat{x}_1\hat{v}_1^2}{\mathcal{T}_1}\int_0^{\kappa_1}\tilde{\mathcal{T}}_1(\varphi)\left(\frac{xv}{\hat{x}_1\hat{v}_1} - \frac{x_\varphi v_\varphi}{\hat{x}_1\hat{v}_1} + \ln\left(\frac{x_\varphi v_\varphi}{xv}\right)\right)d\varphi \\
& + \frac{\beta_1\beta_2\hat{x}_1\hat{v}_1\hat{c}_1}{\mathcal{T}_1}\int_0^{\kappa_1}\tilde{\mathcal{T}}_1(\varphi)\left(\frac{xc}{\hat{x}_1\hat{c}_1} - \frac{x_\varphi c_\varphi}{\hat{x}_1\hat{c}_1} + \ln\left(\frac{x_\varphi c_\varphi}{xc}\right)\right)d\varphi \\
& + \frac{\beta_1\beta_2\hat{x}_1\hat{v}_1\hat{c}_1}{\mathcal{T}_2}\int_0^{\kappa_2}\tilde{\mathcal{T}}_2(\varphi)\left(\frac{xv}{\hat{x}_1\hat{v}_1} - \frac{x_\varphi v_\varphi}{\hat{x}_1\hat{v}_1} + \ln\left(\frac{x_\varphi v_\varphi}{xv}\right)\right)d\varphi \\
& + \frac{\beta_2^2\hat{x}_1\hat{c}_1^2}{\mathcal{T}_2}\int_0^{\kappa_2}\tilde{\mathcal{T}}_2(\varphi)\left(\frac{xc}{\hat{x}_1\hat{c}_1} - \frac{x_\varphi c_\varphi}{\hat{x}_1\hat{c}_1} + \ln\left(\frac{x_\varphi c_\varphi}{xc}\right)\right)d\varphi
\end{aligned}$$

$$+\frac{\beta_2\hat{x}_1\hat{w}_1\eta_c d_w(\beta_1\hat{v}_1+\beta_2\hat{c}_1)}{d_c}\int_0^{\kappa_3}\tilde{\mathcal{T}}_3(\varphi)\left(\frac{w}{\hat{w}_1}-\frac{w_\varphi}{\hat{w}_1}+\ln\left(\frac{w_\varphi}{w}\right)\right)d\varphi$$
$$+\frac{\beta_1\hat{x}_1\hat{y}_1\delta_v(\beta_1\hat{v}_1+\beta_2\hat{c}_1)}{d_v}\int_0^{\kappa_4}\tilde{\mathcal{T}}_4(\varphi)\left(\frac{y}{\hat{y}_1}-\frac{y_\varphi}{\hat{y}_1}+\ln\left(\frac{y_\varphi}{y}\right)\right)d\varphi. \tag{3.16}$$

Summing the terms of Eq. (3.16), we get

$$\begin{aligned}
\frac{d\Phi_3}{dt} &= (\beta_1\hat{v}_1+\beta_2\hat{c}_1)\left(1-\frac{\hat{x}_1}{x}\right)(\lambda-d_x x)\\
&+\frac{\beta_1\hat{x}_1\delta_v(1-q)(\beta_1\hat{v}_1+\beta_2\hat{c}_1)\mathcal{T}_4}{d_v d_y}\int_0^{k_1}\tilde{\mathcal{T}}_1(\varphi)(\beta_1 x_\varphi v_\varphi+\beta_2 x_\varphi c_\varphi)\,d\varphi\\
&-\frac{\beta_1\hat{x}_1\delta_v(1-q)(\beta_1\hat{v}_1+\beta_2\hat{c}_1)\mathcal{T}_4}{d_v d_y}\int_0^{k_1}\tilde{\mathcal{T}}_1(\varphi)(\beta_1 x_\varphi v_\varphi+\beta_2 x_\varphi c_\varphi)\frac{\hat{y}_1}{y}d\varphi\\
&+\frac{\beta_1\hat{x}_1\delta_v(\beta_1\hat{v}_1+\beta_2\hat{c}_1)\mathcal{T}_4}{d_v}\hat{y}_1+\frac{\beta_2\hat{x}_1\eta_c q(\beta_1\hat{v}_1+\beta_2\hat{c}_1)\mathcal{T}_3}{d_c}\\
&\times\int_0^{k_2}\tilde{\mathcal{T}}_2(\varphi)(\beta_1 x_\varphi v_\varphi+\beta_2 x_\varphi c_\varphi)\,d\varphi-\frac{\beta_2\hat{x}_1\eta_c q(\beta_1\hat{v}_1+\beta_2\hat{c}_1)\mathcal{T}_3}{d_c}\\
&\times\int_0^{k_2}\tilde{\mathcal{T}}_2(\varphi)(\beta_1 x_\varphi v_\varphi+\beta_2 x_\varphi c_\varphi)\frac{\hat{w}_1}{w}d\varphi+\frac{\beta_2\hat{x}_1\eta_c d_w(\beta_1\hat{v}_1+\beta_2\hat{c}_1)\mathcal{T}_3\hat{w}_1}{d_c}\\
&-\frac{\beta_2\hat{x}_1\eta_c d_w(\beta_1\hat{v}_1+\beta_2\hat{c}_1)}{d_c}\int_0^{k_3}\tilde{\mathcal{T}}_3(\varphi)\frac{w_\varphi\hat{c}_1}{c}d\varphi+\beta_2\hat{x}_1\hat{c}_1(\beta_1\hat{v}_1+\beta_2\hat{c}_1)\\
&-\frac{\beta_1\hat{x}_1\delta_v(\beta_1\hat{v}_1+\beta_2\hat{c}_1)}{d_v}\int_0^{k_4}\tilde{\mathcal{T}}_4(\varphi)\frac{y_\varphi\hat{v}_1}{v}d\varphi+\beta_1\hat{x}_1\hat{v}_1(\beta_1\hat{v}_1+\beta_2\hat{c}_1)\\
&-\frac{\beta_1^2\hat{x}_1\hat{v}_1^2}{\mathcal{T}_1}\int_0^{\kappa_1}\tilde{\mathcal{T}}_1(\varphi)\frac{x_\varphi v_\varphi}{\hat{x}_1\hat{v}_1}d\varphi+\frac{\beta_1^2\hat{x}_1\hat{v}_1^2}{\mathcal{T}_1}\int_0^{\kappa_1}\tilde{\mathcal{T}}_1(\varphi)\ln\left(\frac{x_\varphi v_\varphi}{xv}\right)d\varphi\\
&-\frac{\beta_1\beta_2\hat{x}_1\hat{v}_1\hat{c}_1}{\mathcal{T}_1}\int_0^{\kappa_1}\tilde{\mathcal{T}}_1(\varphi)\frac{x_\varphi c_\varphi}{\hat{x}_1\hat{c}_1}d\varphi+\frac{\beta_1\beta_2\hat{x}_1\hat{v}_1\hat{c}_1}{\mathcal{T}_1}\int_0^{\kappa_1}\tilde{\mathcal{T}}_1(\varphi)\ln\left(\frac{x_\varphi c_\varphi}{xc}\right)d\varphi\\
&-\frac{\beta_1\beta_2\hat{x}_1\hat{v}_1\hat{c}_1}{\mathcal{T}_2}\int_0^{\kappa_2}\tilde{\mathcal{T}}_2(\varphi)\frac{x_\varphi v_\varphi}{\hat{x}_1\hat{v}_1}d\varphi+\frac{\beta_1\beta_2\hat{x}_1\hat{v}_1\hat{c}_1}{\mathcal{T}_2}\int_0^{\kappa_2}\tilde{\mathcal{T}}_2(\varphi)\ln\left(\frac{x_\varphi v_\varphi}{xv}\right)d\varphi\\
&-\frac{\beta_2^2\hat{x}_1\hat{c}_1^2}{\mathcal{T}_2}\int_0^{\kappa_2}\tilde{\mathcal{T}}_2(\varphi)\frac{x_\varphi c_\varphi}{\hat{x}_1\hat{c}_1}d\varphi+\frac{\beta_2^2\hat{x}_1\hat{c}_1^2}{\mathcal{T}_2}\int_0^{\kappa_2}\tilde{\mathcal{T}}_2(\varphi)\ln\left(\frac{x_\varphi c_\varphi}{xc}\right)d\varphi\\
&+\frac{\beta_2\hat{x}_1\hat{w}_1\eta_c d_w(\beta_1\hat{v}_1+\beta_2\hat{c}_1)}{d_c}\int_0^{\kappa_3}\tilde{\mathcal{T}}_3(\varphi)\ln\left(\frac{w_\varphi}{w}\right)d\varphi\\
&+\frac{\beta_1\hat{x}_1\hat{y}_1\delta_v(\beta_1\hat{v}_1+\beta_2\hat{c}_1)}{d_v}\int_0^{\kappa_4}\tilde{\mathcal{T}}_4(\varphi)\ln\left(\frac{y_\varphi}{y}\right)d\varphi.
\end{aligned}$$

Using the following conditions for $\hat{\Pi}_1$:

$$\begin{aligned}
\lambda &= d_x\hat{x}_1+\beta_1\hat{x}_1\hat{v}_1+\beta_2\hat{x}_1\hat{c}_1,\\
d_y\hat{y}_1 &= (1-q)\mathcal{T}_1(\beta_1\hat{x}_1\hat{v}_1+\beta_2\hat{x}_1\hat{c}_1),\\
d_w\hat{w}_1 &= q\mathcal{T}_2(\beta_1\hat{x}_1\hat{v}_1+\beta_2\hat{x}_1\hat{c}_1),\\
\hat{c}_1 &= \frac{\eta_c\mathcal{T}_3}{d_c}d_w\hat{w}_1=\frac{\eta_c q\mathcal{T}_2\mathcal{T}_3(\beta_1\hat{x}_1\hat{v}_1+\beta_2\hat{x}_1\hat{c}_1)}{d_c},\\
\hat{v}_1 &= \frac{\delta_v\mathcal{T}_4}{d_v}\hat{y}_1=\frac{\delta_v(1-q)\mathcal{T}_1\mathcal{T}_4(\beta_1\hat{x}_1\hat{v}_1+\beta_2\hat{x}_1\hat{c}_1)}{d_v d_y},
\end{aligned}$$

we obtain

$$
\begin{aligned}
\frac{d\Phi_3}{dt} &= (\beta_1\hat{v}_1+\beta_2\hat{c}_1)\left(1-\frac{\hat{x}_1}{x}\right)(d_x\hat{x}_1+\beta_1\hat{x}_1\hat{v}_1+\beta_2\hat{x}_1\hat{c}_1-d_x x)\\
&\quad+\frac{\beta_1\hat{v}_1}{\mathcal{T}_1}\int_0^{k_1}\tilde{\mathcal{T}}_1(\varphi)\left(\beta_1x_\varphi v_\varphi+\beta_2x_\varphi c_\varphi\right)d\varphi-\frac{\hat{v}_1}{\mathcal{T}_1}\beta_1^2\hat{x}_1\hat{v}_1\int_0^{k_1}\tilde{\mathcal{T}}_1(\varphi)\frac{\hat{y}_1x_\varphi v_\varphi}{y\hat{x}_1\hat{v}_1}d\varphi\\
&\quad-\frac{\hat{v}_1}{\mathcal{T}_1}\beta_1\beta_2\hat{x}_1\hat{c}_1\int_0^{k_1}\tilde{\mathcal{T}}_1(\varphi)\frac{\hat{y}_1x_\varphi c_\varphi}{y\hat{x}_1\hat{c}_1}d\varphi+\beta_1\hat{x}_1\hat{v}_1(\beta_1\hat{v}_1+\beta_2\hat{c}_1)\\
&\quad+\frac{\hat{c}_1}{\mathcal{T}_2}\beta_2\int_0^{k_2}\tilde{\mathcal{T}}_2(\varphi)\left(\beta_1x_\varphi v_\varphi+\beta_2x_\varphi c_\varphi\right)d\varphi-\frac{\hat{c}_1}{\mathcal{T}_2}\beta_1\beta_2\hat{x}_1\hat{v}_1\int_0^{k_2}\tilde{\mathcal{T}}_2(\varphi)\frac{\hat{w}_1x_\varphi v_\varphi}{w\hat{x}_1\hat{v}_1}d\varphi\\
&\quad-\frac{\hat{c}_1}{\mathcal{T}_2}\beta_2^2\hat{x}_1\hat{c}_1\int_0^{k_2}\tilde{\mathcal{T}}_2(\varphi)\frac{\hat{w}_1x_\varphi c_\varphi}{w\hat{x}_1\hat{c}_1}d\varphi+\beta_2\hat{x}_1\hat{c}_1(\beta_1\hat{v}_1+\beta_2\hat{c}_1)\\
&\quad-\frac{(\beta_1\hat{v}_1+\beta_2\hat{c}_1)\beta_2\hat{x}_1\hat{c}_1}{\mathcal{T}_3}\int_0^{k_3}\tilde{\mathcal{T}}_3(\varphi)\frac{w_\varphi\hat{c}_1}{\hat{w}_1c}d\varphi+\beta_2\hat{x}_1\hat{c}_1(\beta_1\hat{v}_1+\beta_2\hat{c}_1)\\
&\quad-\frac{(\beta_1\hat{v}_1+\beta_2\hat{c}_1)\beta_1\hat{x}_1\hat{v}_1}{\mathcal{T}_4}\int_0^{k_4}\tilde{\mathcal{T}}_4(\varphi)\frac{y_\varphi\hat{v}_1}{\hat{y}_1v}d\varphi+\beta_1\hat{x}_1\hat{v}_1(\beta_1\hat{v}_1+\beta_2\hat{c}_1)\\
&\quad-\frac{\beta_1^2\hat{x}_1\hat{v}_1^2}{\mathcal{T}_1}\int_0^{\kappa_1}\tilde{\mathcal{T}}_1(\varphi)\frac{x_\varphi v_\varphi}{\hat{x}_1\hat{v}_1}d\varphi+\frac{\beta_1^2\hat{x}_1\hat{v}_1^2}{\mathcal{T}_1}\int_0^{\kappa_1}\tilde{\mathcal{T}}_1(\varphi)\ln\left(\frac{x_\varphi v_\varphi}{xv}\right)d\varphi\\
&\quad-\frac{\beta_1\beta_2\hat{x}_1\hat{v}_1\hat{c}_1}{\mathcal{T}_1}\int_0^{\kappa_1}\tilde{\mathcal{T}}_1(\varphi)\frac{x_\varphi c_\varphi}{\hat{x}_1\hat{c}_1}d\varphi+\frac{\beta_1\beta_2\hat{x}_1\hat{v}_1\hat{c}_1}{\mathcal{T}_1}\int_0^{\kappa_1}\tilde{\mathcal{T}}_1(\varphi)\ln\left(\frac{x_\varphi c_\varphi}{xc}\right)d\varphi\\
&\quad-\frac{\beta_1\beta_2\hat{x}_1\hat{v}_1\hat{c}_1}{\mathcal{T}_2}\int_0^{\kappa_2}\tilde{\mathcal{T}}_2(\varphi)\frac{x_\varphi v_\varphi}{\hat{x}_1\hat{v}_1}d\varphi+\frac{\beta_1\beta_2\hat{x}_1\hat{v}_1\hat{c}_1}{\mathcal{T}_2}\int_0^{\kappa_2}\tilde{\mathcal{T}}_2(\varphi)\ln\left(\frac{x_\varphi v_\varphi}{xv}\right)d\varphi\\
&\quad-\frac{\beta_2^2\hat{x}_1\hat{c}_1^2}{\mathcal{T}_2}\int_0^{\kappa_2}\tilde{\mathcal{T}}_2(\varphi)\frac{x_\varphi c_\varphi}{\hat{x}_1\hat{c}_1}d\varphi+\frac{\beta_2^2\hat{x}_1\hat{c}_1^2}{\mathcal{T}_2}\int_0^{\kappa_2}\tilde{\mathcal{T}}_2(\varphi)\ln\left(\frac{x_\varphi c_\varphi}{xc}\right)d\varphi\\
&\quad+\frac{\beta_2\hat{x}_1\hat{c}_1(\beta_1\hat{v}_1+\beta_2\hat{c}_1)}{\mathcal{T}_3}\int_0^{\kappa_3}\tilde{\mathcal{T}}_3(\varphi)\ln\left(\frac{w_\varphi}{w}\right)d\varphi+\frac{\beta_1\hat{x}_1\hat{v}_1(\beta_1\hat{v}_1+\beta_2\hat{c}_1)}{\mathcal{T}_4}\int_0^{\kappa_4}\tilde{\mathcal{T}}_4(\varphi)\ln\left(\frac{y_\varphi}{y}\right)d\varphi.
\end{aligned}
$$

Therefore, by collecting terms we get

$$
\begin{aligned}
\frac{d\Phi_3}{dt} &= -\frac{d_x(\beta_1\hat{v}_1+\beta_2\hat{c}_1)\,(x-\hat{x}_1)^2}{x}+\beta_1^2\hat{x}_1\hat{v}_1^2+2\beta_1\beta_2\hat{x}_1\hat{v}_1\hat{c}_1+\beta_2^2\hat{x}_1\hat{c}_1^2-\beta_1^2\hat{x}_1\hat{v}_1^2\frac{\hat{x}_1}{x}\\
&\quad-2\beta_1\beta_2\hat{x}_1\hat{v}_1\hat{c}_1\frac{\hat{x}_1}{x}-\beta_2^2\hat{x}_1\hat{c}_1^2\frac{\hat{x}_1}{x}-\frac{1}{\mathcal{T}_1}\beta_1^2\hat{x}_1\hat{v}_1^2\int_0^{k_1}\tilde{\mathcal{T}}_1(\varphi)\frac{\hat{y}_1x_\varphi v_\varphi}{y\hat{x}_1\hat{v}_1}d\varphi\\
&\quad-\frac{1}{\mathcal{T}_1}\beta_1\beta_2\hat{x}_1\hat{v}_1\hat{c}_1\int_0^{k_1}\tilde{\mathcal{T}}_1(\varphi)\frac{\hat{y}_1x_\varphi c_\varphi}{y\hat{x}_1\hat{c}_1}d\varphi+\beta_1^2\hat{x}_1\hat{v}_1^2+\beta_1\beta_2\hat{x}_1\hat{v}_1\hat{c}_1\\
&\quad-\frac{1}{\mathcal{T}_2}\beta_1\beta_2\hat{x}_1\hat{v}_1\hat{c}_1\int_0^{k_2}\tilde{\mathcal{T}}_2(\varphi)\frac{\hat{w}_1x_\varphi v_\varphi}{w\hat{x}_1\hat{v}_1}d\varphi-\frac{1}{\mathcal{T}_2}\beta_2^2\hat{x}_1\hat{c}_1^2\int_0^{k_2}\tilde{\mathcal{T}}_2(\varphi)\frac{\hat{w}_1x_\varphi c_\varphi}{w\hat{x}_1\hat{c}_1}d\varphi+\beta_2^2\hat{x}_1\hat{c}_1^2\\
&\quad+\beta_1\beta_2\hat{x}_1\hat{v}_1\hat{c}_1-\frac{\beta_2^2\hat{x}_1\hat{c}_1^2}{\mathcal{T}_3}\int_0^{k_3}\tilde{\mathcal{T}}_3(\varphi)\frac{w_\varphi\hat{c}_1}{\hat{w}_1c}d\varphi-\frac{\beta_1\beta_2\hat{x}_1\hat{v}_1\hat{c}_1}{\mathcal{T}_3}\int_0^{k_3}\tilde{\mathcal{T}}_3(\varphi)\frac{w_\varphi\hat{c}_1}{\hat{w}_1c}d\varphi+\beta_2^2\hat{x}_1\hat{c}_1^2\\
&\quad+\beta_1\beta_2\hat{x}_1\hat{v}_1\hat{c}_1-\frac{\beta_1^2\hat{x}_1\hat{v}_1^2}{\mathcal{T}_4}\int_0^{k_4}\tilde{\mathcal{T}}_4(\varphi)\frac{y_\varphi\hat{v}_1}{\hat{y}_1v}d\varphi-\frac{\beta_1\beta_2\hat{x}_1\hat{v}_1\hat{c}_1}{\mathcal{T}_4}\int_0^{k_4}\tilde{\mathcal{T}}_4(\varphi)\frac{y_\varphi\hat{v}_1}{\hat{y}_1v}d\varphi+\beta_1^2\hat{x}_1\hat{v}_1^2\\
&\quad+\beta_1\beta_2\hat{x}_1\hat{v}_1\hat{c}_1+\frac{\beta_1^2\hat{x}_1\hat{v}_1^2}{\mathcal{T}_1}\int_0^{\kappa_1}\tilde{\mathcal{T}}_1(\varphi)\ln\left(\frac{x_\varphi v_\varphi}{xv}\right)d\varphi+\frac{\beta_1\beta_2\hat{x}_1\hat{v}_1\hat{c}_1}{\mathcal{T}_1}\int_0^{\kappa_1}\tilde{\mathcal{T}}_1(\varphi)\ln\left(\frac{x_\varphi c_\varphi}{xc}\right)d\varphi
\end{aligned}
$$

$$+\frac{\beta_1\beta_2\hat{x}_1\hat{v}_1\hat{c}_1}{\mathcal{T}_2}\int_0^{\kappa_2}\tilde{\mathcal{T}}_2(\varphi)\ln\left(\frac{x_\varphi v_\varphi}{xv}\right)d\varphi+\frac{\beta_2^2\hat{x}_1\hat{c}_1^2}{\mathcal{T}_2}\int_0^{\kappa_2}\tilde{\mathcal{T}}_2(\varphi)\ln\left(\frac{x_\varphi c_\varphi}{xc}\right)d\varphi$$
$$+\frac{\beta_2^2\hat{x}_1\hat{c}_1^2}{\mathcal{T}_3}\int_0^{\kappa_3}\tilde{\mathcal{T}}_3(\varphi)\ln\left(\frac{w_\varphi}{w}\right)d\varphi+\frac{\beta_1\beta_2\hat{x}_1\hat{v}_1\hat{c}_1}{\mathcal{T}_3}\int_0^{\kappa_3}\tilde{\mathcal{T}}_3(\varphi)\ln\left(\frac{w_\varphi}{w}\right)d\varphi$$
$$+\frac{\beta_1^2\hat{x}_1\hat{v}_1^2}{\mathcal{T}_4}\int_0^{\kappa_4}\tilde{\mathcal{T}}_4(\varphi)\ln\left(\frac{y_\varphi}{y}\right)d\varphi+\frac{\beta_1\beta_2\hat{x}_1\hat{v}_1\hat{c}_1}{\mathcal{T}_4}\int_0^{\kappa_4}\tilde{\mathcal{T}}_4(\varphi)\ln\left(\frac{y_\varphi}{y}\right)d\varphi.$$

Then, rearranging the terms we obtain

$$\begin{aligned}\frac{d\Phi_3}{dt}=&-\frac{d_x(\beta_1\hat{v}_1+\beta_2\hat{c}_1)\left(x-\hat{x}_1\right)^2}{x}+\beta_1\beta_2\hat{x}_1\hat{v}_1\hat{c}_1\Bigg[6-2\frac{\hat{x}_1}{x}-\frac{1}{\mathcal{T}_1}\int_0^{k_1}\tilde{\mathcal{T}}_1(\varphi)\frac{\hat{y}_1x_\varphi c_\varphi}{y\hat{x}_1\hat{c}_1}d\varphi\\
&-\frac{1}{\mathcal{T}_2}\int_0^{k_2}\tilde{\mathcal{T}}_2(\varphi)\frac{\hat{w}_1x_\varphi v_\varphi}{w\hat{x}_1\hat{v}_1}d\varphi-\frac{1}{\mathcal{T}_3}\int_0^{k_3}\tilde{\mathcal{T}}_3(\varphi)\frac{w_\varphi\hat{c}_1}{\hat{w}_1c}d\varphi-\frac{1}{\mathcal{T}_4}\int_0^{k_4}\tilde{\mathcal{T}}_4(\varphi)\frac{y_\varphi\hat{v}_1}{\hat{y}_1v}d\varphi\\
&+\frac{1}{\mathcal{T}_1}\int_0^{\kappa_1}\tilde{\mathcal{T}}_1(\varphi)\ln\left(\frac{x_\varphi c_\varphi}{xc}\right)d\varphi+\frac{1}{\mathcal{T}_2}\int_0^{\kappa_2}\tilde{\mathcal{T}}_2(\varphi)\ln\left(\frac{x_\varphi v_\varphi}{xv}\right)d\varphi\\
&+\frac{1}{\mathcal{T}_3}\int_0^{\kappa_3}\tilde{\mathcal{T}}_3(\varphi)\ln\left(\frac{w_\varphi}{w}\right)d\varphi+\frac{1}{\mathcal{T}_4}\int_0^{\kappa_4}\tilde{\mathcal{T}}_4(\varphi)\ln\left(\frac{y_\varphi}{y}\right)d\varphi\Bigg]\\
&+\beta_1^2\hat{x}_1\hat{v}_1^2\Bigg[3-\frac{\hat{x}_1}{x}-\frac{1}{\mathcal{T}_1}\int_0^{k_1}\tilde{\mathcal{T}}_1(\varphi)\frac{\hat{y}_1x_\varphi v_\varphi}{y\hat{x}_1\hat{v}_1}d\varphi-\frac{1}{\mathcal{T}_4}\int_0^{k_4}\tilde{\mathcal{T}}_4(\varphi)\frac{y_\varphi\hat{v}_1}{\hat{y}_1v}d\varphi\\
&+\frac{1}{\mathcal{T}_1}\int_0^{\kappa_1}\tilde{\mathcal{T}}_1(\varphi)\ln\left(\frac{x_\varphi v_\varphi}{xv}\right)d\varphi+\frac{1}{\mathcal{T}_4}\int_0^{\kappa_4}\tilde{\mathcal{T}}_4(\varphi)\ln\left(\frac{y_\varphi}{y}\right)d\varphi\Bigg]\\
&+\beta_2^2\hat{x}_1\hat{c}_1^2\Bigg[3-\frac{\hat{x}_1}{x}-\frac{1}{\mathcal{T}_2}\int_0^{k_2}\tilde{\mathcal{T}}_2(\varphi)\frac{\hat{w}_1x_\varphi c_\varphi}{w\hat{x}_1\hat{c}_1}d\varphi-\frac{1}{\mathcal{T}_3}\int_0^{k_3}\tilde{\mathcal{T}}_3(\varphi)\frac{w_\varphi\hat{c}_1}{\hat{w}_1c}d\varphi\\
&+\frac{1}{\mathcal{T}_2}\int_0^{\kappa_2}\tilde{\mathcal{T}}_2(\varphi)\ln\left(\frac{x_\varphi c_\varphi}{xc}\right)d\varphi+\frac{1}{\mathcal{T}_3}\int_0^{\kappa_3}\tilde{\mathcal{T}}_3(\varphi)\ln\left(\frac{w_\varphi}{w}\right)d\varphi\Bigg].\end{aligned}$$

Moreover, using the following equalities:

$$\begin{aligned}\ln\left(\frac{x_\varphi c_\varphi}{xc}\right)&=\ln\left(\frac{\hat{y}_1x_\varphi c_\varphi}{y\hat{x}_1\hat{c}_1}\right)+2\ln\left(\frac{\hat{x}_1}{x}\right)+\ln\left(\frac{\hat{c}_1yx}{c\hat{y}_1\hat{x}_1}\right),\\
\ln\left(\frac{x_\varphi v_\varphi}{xv}\right)&=\ln\left(\frac{\hat{w}_1x_\varphi v_\varphi}{w\hat{x}_1\hat{v}_1}\right)+\ln\left(\frac{\hat{x}_1\hat{v}_1w}{xv\hat{w}_1}\right),\\
\ln\left(\frac{w_\varphi}{w}\right)&=\ln\left(\frac{w_\varphi\hat{c}_1}{\hat{w}_1c}\right)+\ln\left(\frac{\hat{w}_1c}{w\hat{c}_1}\right),\\
\ln\left(\frac{y_\varphi}{y}\right)&=\ln\left(\frac{y_\varphi\hat{v}_1}{\hat{y}_1v}\right)+\ln\left(\frac{\hat{y}_1v}{y\hat{v}_1}\right),\end{aligned}$$

$$\begin{aligned}\ln\left(\frac{x_\varphi v_\varphi}{xv}\right)&=\ln\left(\frac{\hat{x}_1}{x}\right)+\ln\left(\frac{\hat{y}_1x_\varphi v_\varphi}{y\hat{x}_1\hat{v}_1}\right)+\ln\left(\frac{y\hat{v}_1}{\hat{y}_1v}\right),\\
\ln\left(\frac{y_\varphi}{y}\right)&=\ln\left(\frac{y_\varphi\hat{v}_1}{\hat{y}_1v}\right)+\ln\left(\frac{\hat{y}_1v}{y\hat{v}_1}\right),\\
\ln\left(\frac{x_\varphi c_\varphi}{xc}\right)&=\ln\left(\frac{\hat{x}_1}{x}\right)+\ln\left(\frac{\hat{w}_1x_\varphi c_\varphi}{w\hat{x}_1\hat{c}_1}\right)+\ln\left(\frac{w\hat{c}_1}{\hat{w}_1c}\right),\end{aligned}$$

we get

$$
\begin{aligned}
\frac{d\Phi_3}{dt} &= -\frac{d_x(\beta_1\hat{v}_1+\beta_2\hat{c}_1)\,(x-\hat{x}_1)^2}{x} - \frac{2\beta_1\beta_2\hat{x}_1\hat{v}_1\hat{c}_1}{\mathcal{T}_1}\int_0^{\kappa_1}\tilde{\mathcal{T}}_1(\varphi)\left(\frac{\hat{x}_1}{x}-1-\ln\left(\frac{\hat{x}_1}{x}\right)\right)d\varphi \\
&- \frac{\beta_1\beta_2\hat{x}_1\hat{v}_1\hat{c}_1}{\mathcal{T}_1}\int_0^{k_1}\tilde{\mathcal{T}}_1(\varphi)\left(\frac{\hat{y}_1x_\varphi c_\varphi}{y\hat{x}_1\hat{c}_1}-1-\ln\left(\frac{\hat{y}_1x_\varphi c_\varphi}{y\hat{x}_1\hat{c}_1}\right)\right)d\varphi \\
&- \frac{\beta_1\beta_2\hat{x}_1\hat{v}_1\hat{c}_1}{\mathcal{T}_2}\int_0^{k_2}\tilde{\mathcal{T}}_2(\varphi)\left(\frac{\hat{w}_1x_\varphi v_\varphi}{w\hat{x}_1\hat{v}_1}-1-\ln\left(\frac{\hat{w}_1x_\varphi v_\varphi}{w\hat{x}_1\hat{v}_1}\right)\right)d\varphi \\
&- \frac{\beta_1\beta_2\hat{x}_1\hat{v}_1\hat{c}_1}{\mathcal{T}_3}\int_0^{k_3}\tilde{\mathcal{T}}_3(\varphi)\left(\frac{w_\varphi\hat{c}_1}{\hat{w}_1c}-1-\ln\left(\frac{w_\varphi\hat{c}_1}{\hat{w}_1c}\right)\right)d\varphi \\
&- \frac{\beta_1\beta_2\hat{x}_1\hat{v}_1\hat{c}_1}{\mathcal{T}_4}\int_0^{k_4}\tilde{\mathcal{T}}_4(\varphi)\left(\frac{y_\varphi\hat{v}_1}{\hat{y}_1v}-1-\ln\left(\frac{y_\varphi\hat{v}_1}{\hat{y}_1v}\right)\right)d\varphi \\
&- \frac{\beta_1^2\hat{x}_1\hat{v}_1^2}{\mathcal{T}_1}\int_0^{\kappa_1}\tilde{\mathcal{T}}_1(\varphi)\left(\frac{\hat{x}_1}{x}-1-\ln\left(\frac{\hat{x}_1}{x}\right)\right)d\varphi \\
&- \frac{1}{\mathcal{T}_1}\beta_1^2\hat{x}_1\hat{v}_1^2\int_0^{k_1}\tilde{\mathcal{T}}_1(\varphi)\left(\frac{\hat{y}_1x_\varphi v_\varphi}{y\hat{x}_1\hat{v}_1}-1-\ln\left(\frac{\hat{y}_1x_\varphi v_\varphi}{y\hat{x}_1\hat{v}_1}\right)\right)d\varphi \\
&- \frac{\beta_1^2\hat{x}_1\hat{v}_1^2}{\mathcal{T}_4}\int_0^{k_4}\tilde{\mathcal{T}}_4(\varphi)\left(\frac{y_\varphi\hat{v}_1}{\hat{y}_1v}-1-\ln\left(\frac{y_\varphi\hat{v}_1}{\hat{y}_1v}\right)\right)d\varphi \\
&- \frac{\beta_2^2\hat{x}_1\hat{c}_1^2}{\mathcal{T}_3}\int_0^{\kappa_3}\tilde{\mathcal{T}}_3(\varphi)\left(\frac{\hat{x}_1}{x}-1-\ln\left(\frac{\hat{x}_1}{x}\right)\right)d\varphi \\
&- \frac{\beta_2^2\hat{x}_1\hat{c}_1^2}{\mathcal{T}_2}\int_0^{k_2}\tilde{\mathcal{T}}_2(\varphi)\left(\frac{\hat{w}_1x_\varphi c_\varphi}{w\hat{x}_1\hat{c}_1}-1-\ln\left(\frac{\hat{w}_1x_\varphi c_\varphi}{w\hat{x}_1\hat{c}_1}\right)\right)d\varphi \\
&- \frac{\beta_2^2\hat{x}_1\hat{c}_1^2}{\mathcal{T}_3}\int_0^{k_3}\tilde{\mathcal{T}}_3(\varphi)\left(\frac{w_\varphi\hat{c}_1}{\hat{w}_1c}-1-\ln\left(\frac{w_\varphi\hat{c}_1}{\hat{w}_1c}\right)\right)d\varphi. \qquad (3.17)
\end{aligned}
$$

Finally Eq. (3.17) can be rewritten as:

$$
\begin{aligned}
\frac{d\Phi_3}{dt} &= -\frac{d_x(\beta_1\hat{v}_1+\beta_2\hat{c}_1)\,(x-\hat{x}_1)^2}{x} - \hat{x}_1\,(\beta_1\hat{v}_1+\beta_2\hat{c}_1)^2\,\chi\left(\frac{\hat{x}_1}{x}\right) \\
&- \frac{\beta_1\beta_2\hat{x}_1\hat{v}_1\hat{c}_1}{\mathcal{T}_1}\int_0^{k_1}\tilde{\mathcal{T}}_1(\varphi)\chi\left(\frac{\hat{y}_1x_\varphi c_\varphi}{y\hat{x}_1\hat{c}_1}\right)d\varphi - \frac{\beta_1\beta_2\hat{x}_1\hat{v}_1\hat{c}_1}{\mathcal{T}_2}\int_0^{k_2}\tilde{\mathcal{T}}_2(\varphi)\chi\left(\frac{\hat{w}_1x_\varphi v_\varphi}{w\hat{x}_1\hat{v}_1}\right)d\varphi \\
&- \frac{\beta_1\beta_2\hat{x}_1\hat{v}_1\hat{c}_1}{\mathcal{T}_3}\int_0^{k_3}\tilde{\mathcal{T}}_3(\varphi)\chi\left(\frac{w_\varphi\hat{c}_1}{\hat{w}_1c}\right)d\varphi - \frac{\beta_1\beta_2\hat{x}_1\hat{v}_1\hat{c}_1}{\mathcal{T}_4}\int_0^{k_4}\tilde{\mathcal{T}}_4(\varphi)\chi\left(\frac{y_\varphi\hat{v}_1}{\hat{y}_1v}\right)d\varphi \\
&- \frac{\beta_1^2\hat{x}_1\hat{v}_1^2}{\mathcal{T}_1}\int_0^{k_1}\tilde{\mathcal{T}}_1(\varphi)\chi\left(\frac{\hat{y}_1x_\varphi v_\varphi}{y\hat{x}_1\hat{v}_1}\right)d\varphi - \frac{\beta_1^2\hat{x}_1\hat{v}_1^2}{\mathcal{T}_4}\int_0^{k_4}\tilde{\mathcal{T}}_4(\varphi)\chi\left(\frac{y_\varphi\hat{v}_1}{\hat{y}_1v}\right)d\varphi \\
&- \frac{\beta_2^2\hat{x}_1\hat{c}_1^2}{\mathcal{T}_2}\int_0^{k_2}\tilde{\mathcal{T}}_2(\varphi)\chi\left(\frac{\hat{w}_1x_\varphi c_\varphi}{w\hat{x}_1\hat{c}_1}\right)d\varphi - \frac{\beta_2^2\hat{x}_1\hat{c}_1^2}{\mathcal{T}_3}\int_0^{k_3}\tilde{\mathcal{T}}_3(\varphi)\chi\left(\frac{w_\varphi\hat{c}_1}{\hat{w}_1c}\right)d\varphi.
\end{aligned}
$$

Hence, if $\hat{\Re}_0 > 1$ then $\frac{d\Phi_3}{dt} \leq 0$ for all $x, y, w, c, v > 0$. Moreover, $\frac{d\Phi_3}{dt} = 0$ when $x = \hat{x}_1$ and $\chi\,(.) = 0$. The model solutions (3.1)-(3.5) converge to Υ_3' , where $x\,(t) = \hat{x}_1$ and

$$
\frac{\hat{y}_1x_\varphi c_\varphi}{yx_1\hat{c}_1} = \frac{\hat{w}_1x_\varphi v_\varphi}{w\hat{x}_1\hat{v}_1} = \frac{w_\varphi\hat{c}_1}{\hat{w}_1c} = \frac{y_\varphi\hat{v}_1}{\hat{y}_1v} = \frac{\hat{y}_1x_\varphi v_\varphi}{yx_1\hat{v}_1} = \frac{\hat{w}_1x_\varphi c_\varphi}{w\hat{x}_1\hat{c}_1} = 1, \text{ for all } t \in [0, \xi]. \qquad (3.18)
$$

If $x(t) = \hat{x}_1$, then from Eq. (3.18), we obtain $y(t) = \hat{y}_1$, $w(t) = \hat{w}_1$, $c(t) = \hat{c}_1$, and $v(t) = \hat{v}_1$, for all t. This produces that $\Upsilon_3' = \left\{\hat{\Pi}_1\right\}$, and by using LaSalle's invariance principle we get that $\hat{\Pi}_1$ is globally asymptotically stable. □

4. Numerical simulations

In this section, we perform the numerical simulations for systems (2.1)-(2.5) and (3.1)-(3.5) to confirm the theoretical findings. Besides, the effect of time delays on the model dynamics (3.1)-(3.5) will be studied. To numerically solve systems (2.1)-(2.5) and (3.1)-(3.5), we use parameter values listed in Table-1. The analytical conclusions obtained in Sections 2 and 3 will also be illustrated by changing a few parameter values that significantly affect the threshold parameters, and consequently, the stability behavior of their associated steady states

Parameter	Value	Source
λ	10	[24], [37]
d_x	0.01	[2], [31]
q	0.95	[8], [44]
d_y	0.5	[32], [38], [51]
d_v	2.4	[37], [51], [5]
d_w	0.75	[53], [6]
d_c	6.6	[44], [48], [15]
δ_v	38	[13], [16]
η_c	15	[44]
m_1	0.1	[46], [53]
m_2, m_3	0.1	Assumed
m_4	0.1	[53]

TABLE 1. The values of parameters of model (2.1)-(2.5) and (3.1)-(3.5).

4.1. **Numerical simulations for model (2.1)-(2.5).**

Here, numerical simulation are performed to demonstrate the outcomes of Theorems 1 and 2.

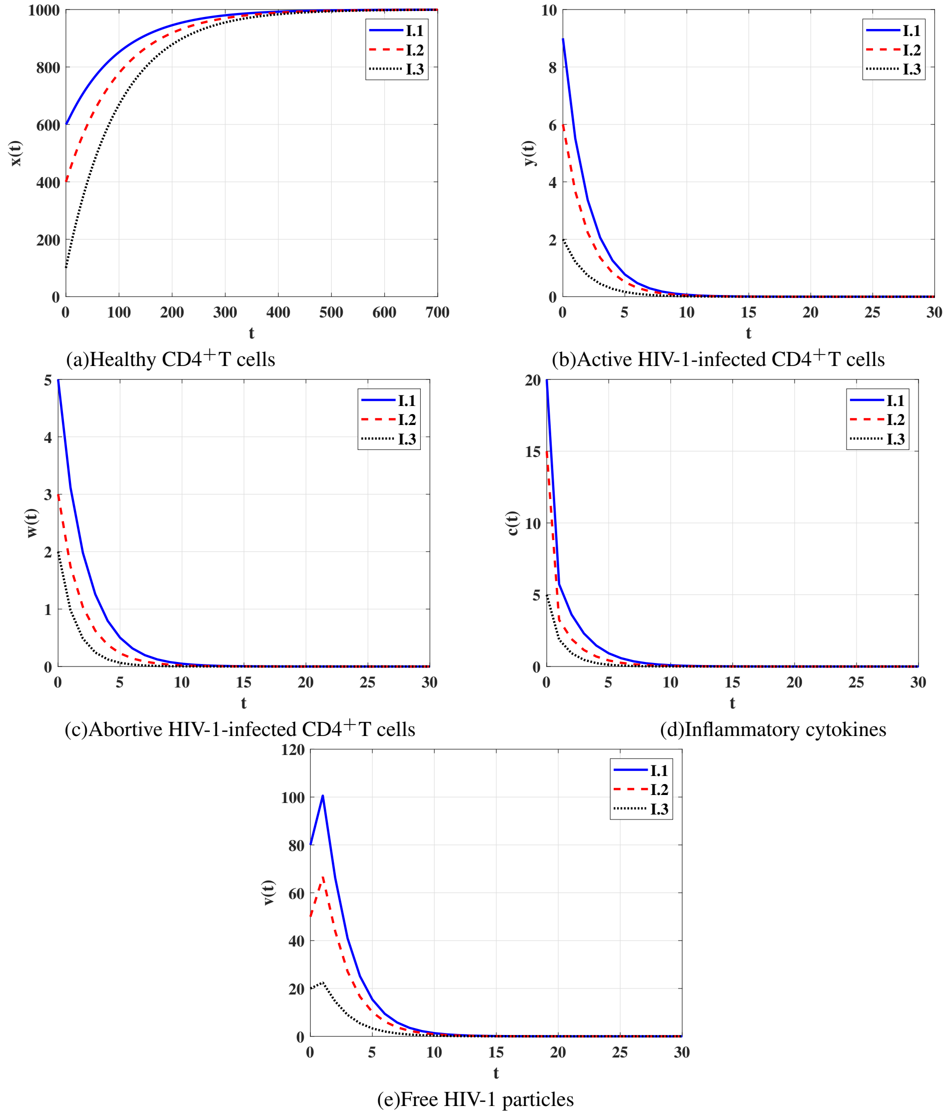
4.1.1. *Stability of the steady states.* We will illustrate the analytic results given in Section 2. The following distinct initial values will be used:

I.1: $(x(0), y(0), w(0), c(0), v(0)) = (600, 9, 5, 20, 80)$,
I.2: $(x(0), y(0), w(0), c(0), v(0)) = (400, 6, 3, 15, 50)$,
I.3: $(x(0), y(0), w(0), c(0), v(0)) = (100, 2, 2, 5, 20)$.

Under initials I.1-I.3, we choose different parameter values of β_1 and β_2, which give the following scenarios:

Stability of $\mathbf{\Pi_0}$: $\beta_1 = 0.00001$ and $\beta_2 = 0.0001$. These values give $\Re_0 = 0.23174 < 1$ with the fact that the steady state $\Pi_0 = (1000, 0, 0, 0, 0)$ is globally asymptotically stable as presented in Figure 1. The results of the numerical solutions that illustrated in Figure 1 are consistent with the study's findings in Theorem 1. This implies the eventual eradication of HIV-1 particles.

Stability of $\mathbf{\Pi_1}$: $\beta_1 = 0.0001$ and $\beta_2 = 0.001$. These choices give $\Re_0 = 2.31742 > 1$. Further, they ensure the existence of the infected steady state Π_1 =(431.514, 0.5684,



(a)Healthy CD4$^+$T cells

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

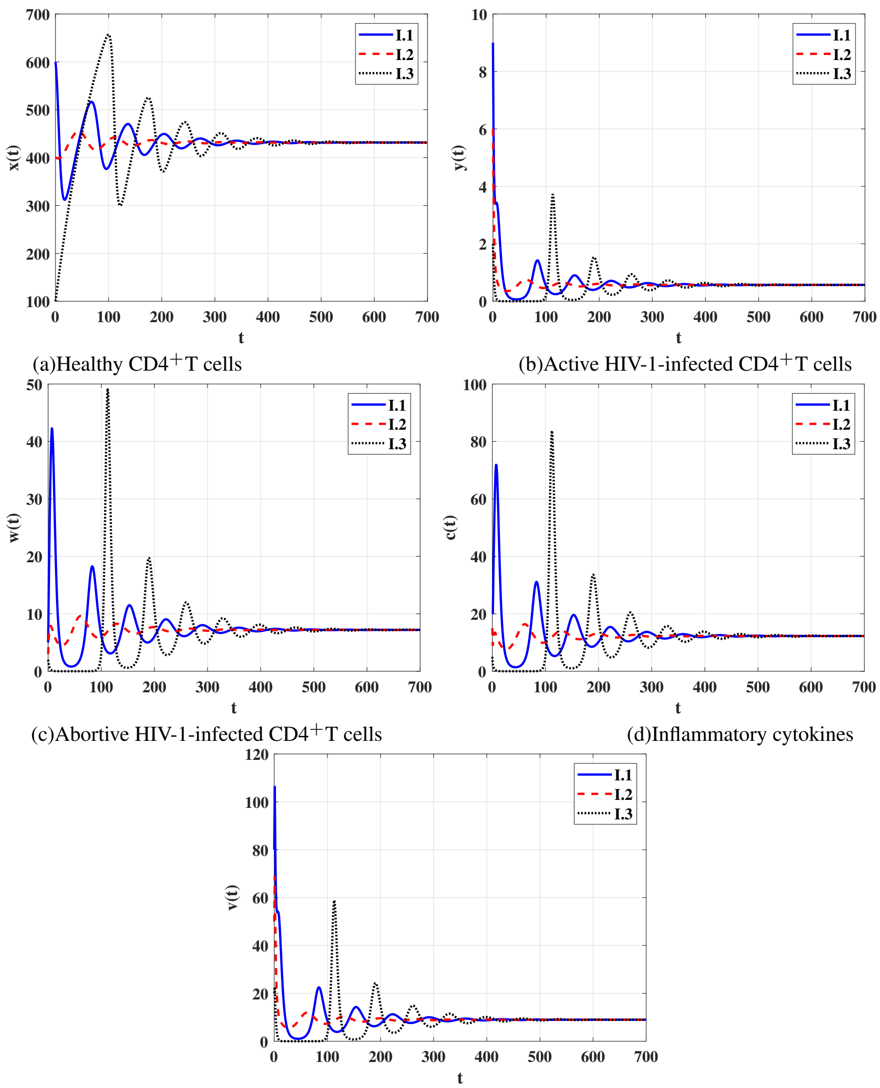
(c)Abortive HIV-1-infected CD4$^+$T cells

(d)Inflammatory cytokines

(e)Free HIV-1 particles

FIGURE 1. Illustration of the solution trajectories of system (2.1)-(2.5) corresponding to initial conditions I.1, I.2, and I.3. In each case, the system evolves toward the infection-free steady state $\Pi_0 = (1000, 0, 0, 0, 0)$, confirming global stability when $\Re_0 \leq 1$.

$7.283, 12.2741, 9.00104)$. It can be seen that solutions starting from different states eventually tend to Π_1, as shown in Figure 2. As a result, we summarize a correspondence between this finding and the conclusions of Theorem 2, indicating that the infection will spread and become endemic.



(a)Healthy CD4^{+}T cells (b)Active HIV-1-infected CD4^{+}T cells

(c)Abortive HIV-1-infected CD4^{+}T cells (d)Inflammatory cytokines

(e)Free HIV-1 particles

FIGURE 2. Illustration of the solution trajectories of system (2.1)-(2.5) corresponding to initial conditions I.1, I.2, and I.3. In each case, the system evolves toward the infected steady state $\Pi_1 = (431.514, 0.5684, 7.283, 12.2741, 9.00104)$, confirming global stability when $\Re_0 > 1$.

4.2. **Numerical simulations for model (3.1)-(3.5).** In this section, we will run a few numerical simulations for model (3.1)-(3.5) using the following specific form for the probability distribution functions:

$$b_i(\varphi) = \varsigma\left(\varphi - \varphi_j\right),$$

where $\varsigma(\cdot)$ is the Dirac delta function and $\varphi_j \in [0, k_j]$, $j = 1, 2, 3, 4$ are constants. Let k_j tend to ∞, we obtain

$$\int_0^\infty b_j(\varphi)d\varphi = 1, \quad \mathcal{T}_i = \int_0^\infty \varsigma(\varphi - \varphi_j)\, e^{-m_j\varphi}d\varphi = e^{-m_j\varphi_j}, \quad j = 1, 2, ..., 4.$$

Therefore, model (3.1)-(3.5) becomes :

$$\begin{aligned}
\dot{x} &= \lambda - d_x x - x\left[\beta_1 v + \beta_2 c\right], \\
\dot{y} &= (1-q)\, e^{-m_1\varphi_1} x_{\varphi_1}\left[\beta_1 v_{\varphi_1} + \beta_2 c_{\varphi_1}\right] - d_y y, \\
\dot{w} &= q e^{-m_2\varphi_2} x_{\varphi_2}\left[\beta_1 v_{\varphi_1} + \beta_2 c_{\varphi_1}\right] - d_w w, \\
\dot{c} &= \eta_c d_w e^{-m_3\varphi_3} w_{\varphi_3} - d_c c, \\
\dot{v} &= \delta_v e^{-m_4\varphi_4} y_{\varphi_4} - d_v v.
\end{aligned} \tag{4.1}$$

For the new model 4.1, the threshold parameter is

$$\hat{\Re}_{0_{(4.1)}} = \frac{\lambda\left[\beta_1(1-q)\,\delta_v d_c e^{-(m_1\varphi_1 + m_4\varphi_4)} + \beta_2 q\eta_c d_y d_v e^{-(m_2\varphi_2 + m_3\varphi_3)}\right]}{d_x d_v d_c d_y}.$$

Delay parameter φ	Steady state	$\hat{\Re}_{0_{(4.1)}}$
0	$\hat{\Pi}_{1_{(4.1)}} = (431.514, 0.5684, 7.283, 12.2741, 9.00104)$	2.31742
1	$\hat{\Pi}_{1_{(4.1)}} = (527.052, 0.42794, 5.42059, 8.36037, 6.13094)$	1.89735
4.20228	$\hat{\Pi}_{0_{(4.1)}} = (1000, 0, 0, 0, 0)$	1
20	$\hat{\Pi}_{0_{(4.1)}} = (1000, 0, 0, 0, 0)$	0.076

TABLE 2. Impact of the delay parameter φ on the basic reproduction number $\hat{\Re}_{0_{(4.1)}}$.

4.2.1. *Time delays' effect on HIV-1 dynamics.* In this section, the delay parameters φ_j, $j = 1, 2, 3, 4$ will be varied, and fix the $\beta_1 = 0.0001$ and $\beta_2 = 0.001$ parameters. Alternatively, the value of other parameters is listed in the Table-1. For simplicity, let us take $\varphi_1 = \varphi_2 = \varphi_3 = \varphi_4 = \varphi$. The basic reproduction number $\hat{\Re}_{0_{(4.1)}}$ becomes

$$\hat{\Re}_{0_{(4.1)}} = \frac{\lambda\left(\beta_1(1-q)\,\delta_v d_c e^{-(m_1+m_4)\varphi} + \beta_2 q\eta_c d_v d_y e^{-(m_2+m_3)\varphi}\right)}{d_x d_v d_c d_y}.$$

We notice that $\hat{\Re}_{0_{(4.1)}}$ depending on φ, and it will be a decreasing function of φ. Therefore, the stability of the steady states will renew if φ changed. The stability of the infection-free steady state $\hat{\Pi}_{0_{(4.1)}}$ is important for this studying. Let φ_{cr} is the solution of $\hat{\Re}_{0_{(4.1)}} = 1$ as:

$$\hat{\Re}_{0_{(4.1)}} = \frac{\lambda\left(\beta_1(1-q)\,\delta_v d_c e^{-(m_1+m_4)\varphi_{cr}} + \beta_2 q\eta_c d_v d_y e^{-(m_2+m_3)\varphi_{cr}}\right)}{d_x d_v d_c d_y} = 1. \tag{4.2}$$

By finding the solution of Equation (4.2), we obtain φ_{cr} =4.20228. Then, it is easily to notice that $\hat{\Re}_{0_{(4.1)}} \leq 1$ if $\varphi \geq 4.20228$. This ensures that $\hat{\Pi}_{0_{(4.1)}}$ is globally asymptotically stable and the virus will be eradicated from the body. Now, we study the impact of delay parameter φ on the system solutions (4.1) with the following initial state:

I.4:$(x(\theta), y(\theta), w(\theta), c(\theta), v(\theta)) = (600, 4, 30, 50, 80)$, where $\theta \in [-\varphi, 0]$.

The effect of φ on the system's solutions is illustrated in Figure 3 and Table-2. We found that while the levels of other compartments decrease, the number of healthy CD4$^+$T cells increases as φ increases. Time delays play a crucial role in the progression of HIV-1 and provide valuable insights for managing the viral infection. Adequate time lags can slow down the development of HIV-1, help keep it under control, and potentially lead to its extinction. This suggests a promising strategy for developing new HIV-1 treatments aimed at extending these delay periods.

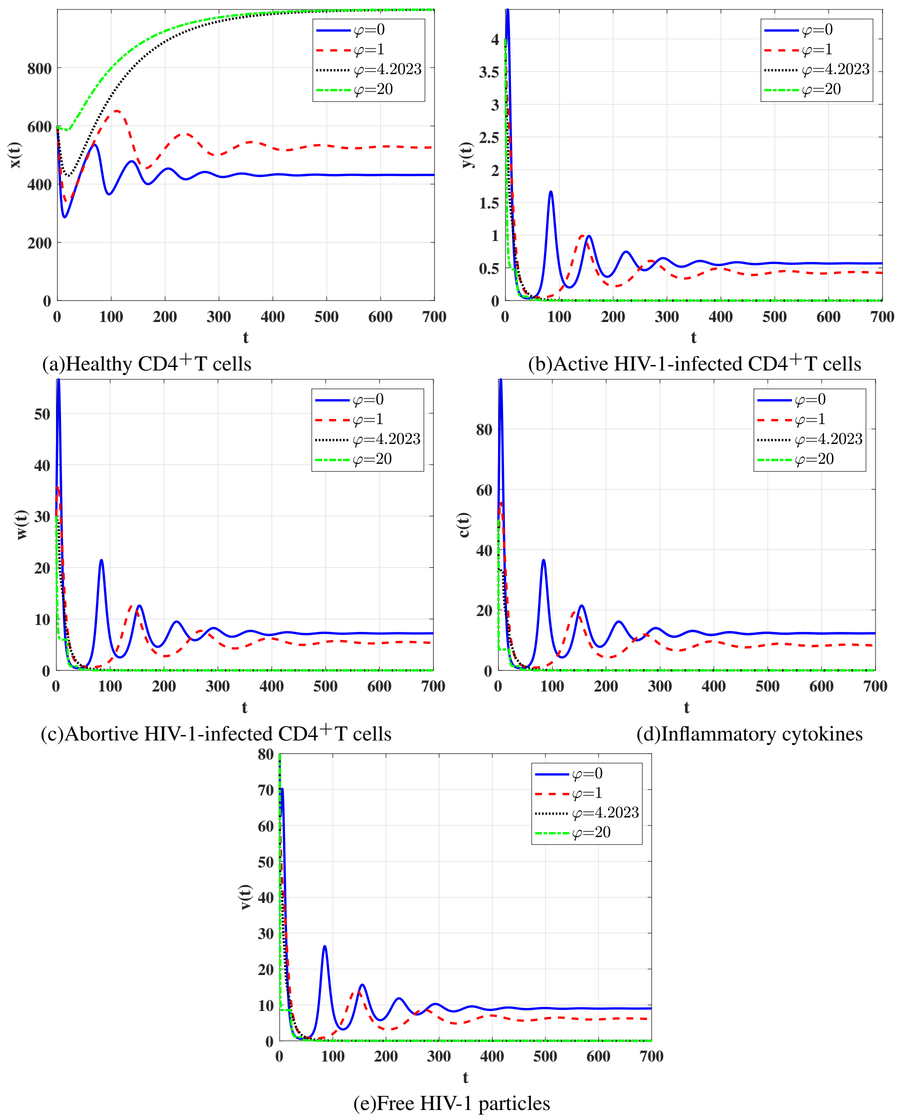


FIGURE 3. Impact of the delay parameter φ on the HIV-1 dynamics model (4.1).

4.3. **Sensitivity analysis.** In this subsection, we aim to determine the parameter that has the most impact on $\Re_0$ by using direct differentiation. The normalized forward sensitivity index for $\Re_0$ with respect to a parameter α is given by:

$$\Xi_\alpha = \frac{\alpha}{\Re_0}\frac{\partial \Re_0}{\partial \alpha}. \tag{4.3}$$

We determine the sensitivity indices based on the value of parameters listed in Table-1.

4.3.1. *Sensitivity analysis for model (2.1)-(2.5).* Here, we consider the values $\beta_1 = 0.0001$ and $\beta_2 = 0.001$ and utilize Eq. (4.3) with respect to $\Re_0$. The results are presented in Table-3.

As shown in Table-3 and Figure 4, increasing the parameters with positive indices, λ, β_1, β_2, η_c and δ_v, results in higher $\Re_0$, thereby intensifying the HIV-1 disease endemic. On the other hand, increasing the remaining parameters decreases $\Re_0$. Notably, λ, β_2 and η_c are the most significant parameters, while d_x, d_c and q have the least impact on the threshold parameter.

Parameters α	Value of Ξ_α	Parameters α	Value of Ξ_α
λ	1	d_c	-0.931677
d_x	-1	δ_v	0.06832298
β_1	0.068322981	η_c	0.93167701
β_2	0.931677518	d_v	-0.06832298
q	-0.366459	d_y	-0.0683229

TABLE 3. Sensitivity index of $\Re_0$ of model (2.1)-(2.5).

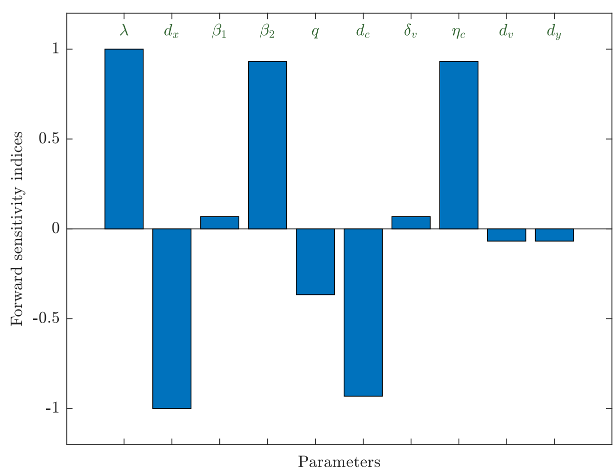


FIGURE 4. Sensitivity analysis of $\Re_0$ of model (2.1)-(2.5).

4.3.2. *Sensitivity analysis for model (4.1).* We applied Eq. (4.3) with respect to $\hat{\Re}_{0_{(4.1)}}$ with the following parameter: $\beta_1 = 0.0001$, $\beta_2 = 0.001$, $m_1 = 0.1$, $m_2 = 0.1$, $m_3 = 0.1$, $m_4 = 0.1$ and $\varphi = 1$. Figure 5 and Table4 are present the sensitivity index values for $\hat{\Re}_{0_{(4.1)}}$. From Table-4 and Figure 5 we notice that increasing the parameters with positive indices will increase $\hat{\Re}_{0_{(4.1)}}$. The most significant parameters are λ, β_1 and δ_v.

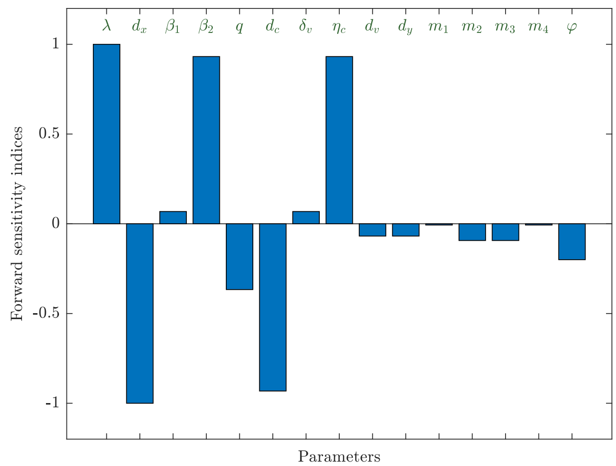


FIGURE 5. Sensitivity analysis of $\hat{\Re}_{0_{(4.1)}}$ system (4.1).

5. CONCLUSIONS

This study developed two mathematical models of HIV-1 infection to explore the influence of inflammatory cytokines and abortively infected CD4$^+$ T cells. The second model extends the first by incorporating four types of distributed time delays to better reflect biological processes. We first established key properties of the models, including nonnegativity, boundedness, and well-posedness of solutions. Two equilibrium states were identified: the infection-free state and the infected (endemic) state. The basic reproduction number ($\Re_0$) was derived and shown to govern the existence and global stability of these equilibria. Global asymptotic stability of both steady states was proven using Lyapunov functionals and LaSalle's invariance principle. Numerical simulations were performed to validate the analytical findings, showing strong agreement with the theoretical predictions. Additionally, sensitivity analysis highlighted the impact of various parameters on $\Re_0$. Notably, the results suggest that increasing the time delays can lower $\Re_0$ and potentially suppress HIV-1 replication.

Parameters α	Value of Ξ_α	Parameters α	Value of Ξ_α
λ	1	η_c	0.931677
d_x	-1	d_v	-0.068322
β_1	0.068322981	dy	-0.068322
β_2	0.931677518	m_1	-0.0068322
q	-0.36645	m_2	-0.0931677
d_c	-0.931677	m_3	-0.0931677
δ_v	0.068322	m_4	-0.0006832298
φ	-0.200		

TABLE 4. Sensitivity index of $\hat{\Re}_{0_{(4.1)}}$ for system (4.1).

6. ACKNOWLEDGEMENTS

The authors are grateful to the anonymous referees for careful checking of the details and for helpful comments that improved this paper.

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