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Effect of cellular reservoirs and delays on the global dynamics of HIV

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Abstract

We investigate general HIV infection models with three types of infected cells: latently infected cells, long-lived productively infected cells, and short-lived productively infected cells. We incorporate three discrete or distributed time delays into the models. Moreover, we consider the effect of humoral immunity on the dynamical behavior of the HIV. The HIV-target incidence rate, production/proliferation, and removal rates of the cells and HIV are represented by general nonlinear functions. We show that the solutions of the proposed model are nonnegative and ultimately bounded. We derive two threshold parameters which fully determine the existence and stability of the three steady states of the model. Using Lyapunov functionals, we establish the global stability of the steady states of the model. The theoretical results are confirmed by numerical simulations.

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Keywords: HIV infection; HAART; Global stability; Humoral immune response; Latency; Viral reservoirs

1 Introduction

Mathematical modeling and analysis of within-host human immunodeficiency virus (HIV) dynamics have become one of the hot topics during the last decades [1–31]. These works can help researchers better understand the HIV dynamical behavior and provide new suggestions for clinical treatment. Most of the mathematical models presented in the literature have focused on modeling the interaction between three main compartments: uninfected $CD4^+$ T cells (s), infected cells (y), and free HIV particles (p). Other models have differentiated between latent and active infected cells by introducing a new variable (w) for the latently infected cells [32–37]. In [38], an HIV mathematical model has been presented by considering three types of infected cells: latently infected cells (w), short-lived productively infected cells (y), and long-lived productively infected cells (u) as follows:

$$\dot{s}(t) = \rho - \beta_1 s(t) + \omega s(t)\left(1 - \frac{s(t)}{s_{\max}}\right) - (1-\varepsilon_1)(\overline{\lambda}_1 + \overline{\lambda}_2 + \overline{\lambda}_3)s(t)p(t), \tag{1}$$

$$\dot{w}(t) = (1-\varepsilon_1)\overline{\lambda}_1 s(t)p(t) - (a_1 + \beta_2)w(t), \tag{2}$$

$$\dot{y}(t) = (1-\varepsilon_1)\overline{\lambda}_2 s(t)p(t) + a_1 w(t) - \beta_3 y(t), \tag{3}$$

$$\dot{u}(t) = (1-\varepsilon_1)\overline{\lambda}_3 s(t)p(t) - \beta_4 u(t), \tag{4}$$

$$\dot{p}(t) = (1-\varepsilon_2)\overline{N}\beta_3 y(t) + (1-\varepsilon_2)\overline{M}\beta_4 u(t) - \beta_5 p(t), \tag{5}$$

where ρ is the creation rate of the uninfected CD4$^+$ T cells, β_i, $i = 1,\dots,5$, are the death rate constants of the five compartments s, w, y, u, and p, respectively. The model incorporates reverse transcriptase inhibitor (RTI) with efficacy ε_1 and protease inhibitor (PI) with efficacy ε_2, where $\varepsilon_1, \varepsilon_2 \in [0,1]$. The parameters ω and $s_{\max}$ are the maximum proliferation rate and the maximum level of concentration of the uninfected CD4$^+$ T cells, respectively. The latently infected cells are activated at rate $a_1 w$. The parameters $\overline{N}$ and $\overline{M}$ are the average numbers of HIV particles generated in the lifetime of the short-lived and long-lived infected cells, respectively. The uninfected CD4$^+$ T cells become infected with infectivity $\overline{\lambda}_1 + \overline{\lambda}_2 + \overline{\lambda}_3$. Elaiw et al. [27] have generalized the above model by incorporating the humoral immune response and considering general nonlinear functions for the generation and removal rates of all compartments:

$$\dot{s}(t) = \pi\big(s(t)\big) - (1-\varepsilon_1)(\overline{\lambda}_1 + \overline{\lambda}_2 + \overline{\lambda}_3)\chi\big(s(t), p(t)\big), \tag{6}$$

$$\dot{w}(t) = (1-\varepsilon_1)\overline{\lambda}_1\chi\big(s(t), p(t)\big) - (a_1 + \beta_2)g_1\big(w(t)\big), \tag{7}$$

$$\dot{y}(t) = (1-\varepsilon_1)\overline{\lambda}_2\chi\big(s(t), p(t)\big) + a_1 g_1\big(w(t)\big) - \beta_3 g_2\big(y(t)\big), \tag{8}$$

$$\dot{u}(t) = (1-\varepsilon_1)\overline{\lambda}_3\chi\big(s(t), p(t)\big) - \beta_4 g_3\big(u(t)\big), \tag{9}$$

$$\begin{aligned}\dot{p}(t) = {}&(1-\varepsilon_2)\overline{N}\beta_3 g_2\big(y(t)\big) + (1-\varepsilon_2)\overline{M}\beta_4 g_3\big(u(t)\big)\\ &- \beta_5 g_4\big(p(t)\big) - q g_4\big(p(t)\big)g_5\big(x(t)\big),\end{aligned} \tag{10}$$

$$\dot{x}(t) = r g_4\big(p(t)\big)g_5\big(x(t)\big) - \beta_6 g_5\big(x(t)\big), \tag{11}$$

where x represents the concentration of the B cells. π, χ, g_i, $i = 1,\dots,5$, are general nonlinear functions. Model (6)–(11) assumes that, once the HIV contacts a CD4$^+$ T cell, it becomes infected in the same time. Neglecting the time delays is an unrealistic assumption (see, e.g., [29, 30]).

The aim of this paper is to propose HIV infection models which improve model (6)–(11) by taking into account three time delays, discrete or distributed. We derive two threshold parameters and present some mild sufficient conditions for the existence and global stability of the steady states of the models.

2 HIV dynamics model with discrete delays

We formulate a nonlinear HIV dynamics model with latent reservoirs, humoral immunity, and discrete time delays:

$$\dot{s} = \pi\big(s(t)\big) - (1-\varepsilon_1)(\overline{\lambda}_1 + \overline{\lambda}_2 + \overline{\lambda}_3)\chi\big(s(t), p(t)\big), \tag{12}$$

$$\dot{w} = (1-\varepsilon_1)\overline{\lambda}_1 e^{-\mu_1\tau_1}\chi\big(s(t-\tau_1), p(t-\tau_1)\big) - (a_1 + \beta_2)g_1\big(w(t)\big), \tag{13}$$

$$\dot{y} = (1-\varepsilon_1)\overline{\lambda}_2 e^{-\mu_2\tau_2}\chi\big(s(t-\tau_2), p(t-\tau_2)\big) + a_1 g_1\big(w(t)\big) - \beta_3 g_2\big(y(t)\big), \tag{14}$$

$$\dot{u} = (1-\varepsilon_1)\overline{\lambda}_3 e^{-\mu_3\tau_3}\chi\big(s(t-\tau_3), p(t-\tau_3)\big) - \beta_4 g_3\big(u(t)\big), \tag{15}$$

$$\dot{p} = (1-\varepsilon_2)\overline{N}\beta_3 g_2\big(y(t)\big) + (1-\varepsilon_2)\overline{M}\beta_4 g_3\big(u(t)\big) - \beta_5 g_4\big(p(t)\big) - q g_4\big(p(t)\big) g_5\big(x(t)\big), \qquad (16)$$

$$\dot{x} = r g_4\big(p(t)\big) g_5\big(x(t)\big) - \beta_6 g_5\big(x(t)\big). \qquad (17)$$

All the parameters are positive. Here, τ_1 is the time between viral entry and latent infection (i.e., the integration of viral DNA into cell's DNA has finished), while τ_2 and τ_3 are the times between viral entry and viral production form short-lived productively infected and long-lived productively infected cells, respectively. The factor $e^{-\mu_i \tau_i}$ accounts for the loss of target cells during the delay period of length τ_i, where μ_i is a constant. Let us define $\lambda_i = (1-\varepsilon_1)\overline{\lambda}_i$, $i = 1,2,3$, $N = (1-\varepsilon_2)\overline{N}$, $M = (1-\varepsilon_2)\overline{M}$, and $\lambda = \lambda_1 + \lambda_2 + \lambda_3$. Functions χ, π, g_i, $i = 1,\dots,5$, are continuously differentiable and satisfy the following hypotheses:

(H1). (i) There exists s_0 such that $\pi(s_0) = 0$, $\pi(s) > 0$ for $s \in [0, s_0)$;
(ii) $\pi'(s) < 0$ for $s \in (0,\infty)$;
(iii) There are $b > 0$ and $\overline{b} > 0$ such that $\pi(s) \leq b - \overline{b}s$ for $s \in [0,\infty)$.

(H2). (i) $\chi(s,p) > 0$ and $\chi(0,p) = \chi(s,0) = 0$ for $s, p \in (0,\infty)$;
(ii) $\frac{\partial\chi(s,p)}{\partial s} > 0$, $\frac{\partial\chi(s,p)}{\partial p} > 0$, and $\frac{\partial\chi(s,0)}{\partial p} > 0$ for all $s, p \in (0,\infty)$;
(iii) $(\frac{\partial\chi(s,0)}{\partial p})' > 0$ for $s \in (0,\infty)$.

(H3). (i) $g_j(\eta) > 0$ for $\eta \in (0,\infty)$, $g_j(0) = 0$, $j = 1,\dots,5$;
(ii) $g_j'(\eta) > 0$ for $\eta \in (0,\infty)$, $j = 1,2,3,5$, $g_4'(\eta) > 0$, for $\eta \in [0,\infty)$;
(iii) there are $\alpha_j > 0$, $j = 1,\dots,5$, such that $g_j(\eta) \geq \alpha_j \eta$ for $\eta \in [0,\infty)$.

(H4). (i) $\frac{\partial}{\partial p}(\frac{\chi(s,p)}{g_4(p)}) \leq 0$ for $p \in (0,\infty)$.

We consider system (12)–(17) with the initial conditions:

$$\begin{aligned}
&s(\theta) = \varphi_1(\theta), \qquad w(\theta) = \varphi_2(\theta), \qquad y(\theta) = \varphi_3(\theta),\\
&u(\theta) = \varphi_4(\theta), \qquad p(\theta) = \varphi_5(\theta), \qquad x(\theta) = \varphi_6(\theta),\\
&\varphi_j(\theta) \geq 0, \quad \theta \in [-\varsigma, 0],\\
&\varphi_j(\theta) \in C\big([-\varsigma,0], \mathbb{R}^6_{\geq 0}\big), \quad j = 1,\dots,6,
\end{aligned} \qquad (18)$$

where $\varsigma = \max\{\tau_1,\tau_2,\tau_3\}$ and C is the Banach space of continuous functions mapping the interval $[-\varsigma, 0]$ into $\mathbb{R}^6_{\geq 0}$. Then the uniqueness of the solution for $t > 0$ is guaranteed [39].

2.1 Preliminaries

Lemma 1 *Let hypotheses* (H1)–(H3) *be valid, then the solutions of system* (12)–(17) *are nonnegative and ultimately bounded.*

Proof Let us write system (12)–(17) in the matrix form $\dot{k}(t) = L(k(t))$, where $k = (s, w, y, u, p, x)^T$, $L = (L_1, L_2, L_3, L_4, L_5, L_6)^T$, and

$$L\big(k(t)\big) = \begin{pmatrix} L_1(k(t)) \\ L_2(k(t)) \\ L_3(k(t)) \\ L_4(k(t)) \\ L_5(k(t)) \\ L_6(k(t)) \end{pmatrix},$$

$$L = \begin{pmatrix} \pi(s(t)) - \lambda\chi(s(t),p(t)) \\ \lambda_1 e^{-\mu_1\tau_1}\chi(s(t-\tau_1),p(t-\tau_1)) - (a_1+\beta_2)g_1(w(t)) \\ \lambda_2 e^{-\mu_2\tau_2}\chi(s(t-\tau_2),p(t-\tau_2)) + a_1 g_1(w(t)) - \beta_3 g_2(y(t)) \\ \lambda_3 e^{-\mu_3\tau_3}\chi(s(t-\tau_3),p(t-\tau_3)) - \beta_4 g_3(u(t)) \\ N\beta_3 g_2(y(t)) + M\beta_4 g_3(u(t)) - \beta_5 g_4(p(t)) - q g_4(p(t))g_5(x(t)) \\ r g_4(p(t))g_5(x(t)) - \beta_6 g_5(x(t)) \end{pmatrix}.$$

We have

$$L_i\big(k(t)\big)\big|_{k_i(t)\in\mathbb{R}^6_{>0}} \geq 0, \quad i = 1,\dots,6.$$

Using Lemma 2 in [40], the solutions of system (12)–(17) with the initial states (18) satisfy $X(t) \in \mathbb{R}^6_{\geq 0}$ for all $t \geq 0$. The nonnegativity of the model's solution implies that $\limsup_{t\to\infty} s(t) \leq M_1$, where $M_1 = \frac{b}{\overline{b}}$. Let

$$\begin{aligned} T(t) &= Ne^{-\mu_1\tau_1}s(t-\tau_1) + Ne^{-\mu_2\tau_2}s(t-\tau_2) + Me^{-\mu_3\tau_3}s(t-\tau_3) \\ &\quad + Nw(t) + Ny(t) + Mu(t) + \frac{1}{2}p(t) + \frac{q}{2r}x(t), \end{aligned}$$

then

$$\begin{aligned} \dot{T}(t) &= Ne^{-\mu_1\tau_1}\big[\pi\big(s(t-\tau_1)\big) - \lambda\chi\big(s(t-\tau_1),p(t-\tau_1)\big)\big] \\ &\quad + Ne^{-\mu_2\tau_2}\big[\pi\big(s(t-\tau_2)\big) - \lambda\chi\big(s(t-\tau_2),p(t-\tau_2)\big)\big] \\ &\quad + Me^{-\mu_3\tau_3}\big[\pi\big(s(t-\tau_3)\big) - \lambda\chi\big(s(t-\tau_3),p(t-\tau_3)\big)\big] \\ &\quad + N\big[\lambda_1 e^{-\mu_1\tau_1}\chi\big(s(t-\tau_1),p(t-\tau_1)\big) - (a_1+\beta_2)g_1\big(w(t)\big)\big] \\ &\quad + N\big[\lambda_2 e^{-\mu_2\tau_2}\chi\big(s(t-\tau_2),p(t-\tau_2)\big) + a_1 g_1\big(w(t)\big) - \beta_3 g_2\big(y(t)\big)\big] \\ &\quad + M\big[\lambda_3 e^{-\mu_3\tau_3}\chi\big(s(t-\tau_3),p(t-\tau_3)\big) - \beta_4 g_3\big(u(t)\big)\big] \\ &\quad + \frac{1}{2}\big(N\beta_3 g_2\big(y(t)\big) + M\beta_4 g_3\big(u(t)\big) - \beta_5 g_4\big(p(t)\big) - q g_4\big(p(t)\big)g_5\big(x(t)\big)\big) \\ &\quad + \frac{q}{2r}\big(r g_4\big(p(t)\big)g_5\big(x(t)\big) - \beta_6 g_5\big(x(t)\big)\big) \\ &\leq Ne^{-\mu_1\tau_1}\big[b - \overline{b}s(t-\tau_1)\big] + Ne^{-\mu_2\tau_2}\big[b - \overline{b}s(t-\tau_2)\big] + Me^{-\mu_3\tau_3}\big[b - \overline{b}s(t-\tau_3)\big] \\ &\quad - N\beta_2\alpha_1 w(t) - \frac{1}{2}N\beta_3\alpha_2 y(t) - \frac{1}{2}M\beta_4\alpha_3 u(t) - \frac{1}{2}\beta_5\alpha_4 p(t) - \frac{q}{2r}\beta_6\alpha_5 p(t) \\ &\leq b\big(Ne^{-\mu_1\tau_1} + Ne^{-\mu_2\tau_2} + Me^{-\mu_3\tau_3}\big) \\ &\quad - \sigma\bigg[Ne^{-\mu_1\tau_1}s(t-\tau_1) + Ne^{-\mu_2\tau_2}s(t-\tau_2) + Me^{-\mu_3\tau_3}s(t-\tau_3) \\ &\quad + Nw(t) + Ny(t) + Mu(t) + \frac{1}{2}p(t) + \frac{q}{2r}x(t)\bigg] \\ &\leq b(2N+M) - \sigma T(t), \end{aligned}$$

where $\sigma = \min\{\overline{b}, \beta_2\alpha_1, \frac{1}{2}\beta_3\alpha_2, \frac{1}{2}\beta_4\alpha_3, \beta_5\alpha_4, \beta_6\alpha_5\}$. Then $\limsup_{t\to\infty} T(t) \leq \frac{b(2N+M)}{\sigma}$. The nonnegativity of the system's variables implies that

$$\limsup_{t\to\infty} w(t) \leq \frac{b(2N+M)}{N\sigma} = M_2,$$

$$\limsup_{t\to\infty} y(t) \le \frac{b(2N+M)}{N\sigma} = M_2,$$
$$\limsup_{t\to\infty} u(t) \le \frac{b(2N+M)}{M\sigma} = M_3,$$
$$\limsup_{t\to\infty} p(t) \le \frac{2b(2N+M)}{\sigma} = M_4,$$
$$\limsup_{t\to\infty} x(t) \le \frac{2rb(2N+M)}{q\sigma} = M_5.$$

Therefore, $s(t)$, $w(t)$, $y(t)$, $u(t)$, $p(t)$, and $x(t)$ are ultimately bounded. □

According to Lemma 1, we can show that the region

$$\begin{aligned}\Omega = \bigl\{&(s,w,y,u,p,x) \in C^6 : \|s\| \le M_1, \|w\| \le M_2, \|y\| \le M_2,\\ &\|u\| \le M_3, \|p\| \le M_4, \|x\| \le M_5\bigr\}\end{aligned} \tag{19}$$

is positively invariant with respect to system (12)–(17), where $\|\phi\| = \sup_{t\to\infty} \phi(t)$.

Lemma 2 *Suppose that hypotheses* (H1)–(H4) *are valid* (12)–(17), *then there exist two bifurcation parameters* R_0 *and* R_1 *with* $R_0 > R_1 > 0$ *such that*

(i) *if* $R_0 \le 1$, *then there exists only one steady state* Π_0;
(ii) *if* $R_1 \le 1 < R_0$, *then there exist two steady states* Π_0 *and* Π_1;
(iii) *if* $R_1 > 1$, *then there exist three steady states* Π_0, Π_1, *and* Π_2.

Proof Let $\Pi(s,w,y,u,p,x)$ be any steady state of (12)–(17) satisfying the following equations:

$$0 = \pi(s) - \lambda\chi(s,p), \tag{20}$$
$$0 = \lambda_1 e^{-\mu_1\tau_1}\chi(s,p) - (a_1+\beta_2)g_1(w), \tag{21}$$
$$0 = \lambda_2 e^{-\mu_2\tau_2}\chi(s,p) + a_1 g_1(w) - \beta_3 g_2(y), \tag{22}$$
$$0 = \lambda_3 e^{-\mu_3\tau_3}\chi(s,p) - \beta_4 g_3(u), \tag{23}$$
$$0 = N\beta_3 g_2(y) + M\beta_4 g_3(u) - \beta_5 g_4(p) - q g_4(p) g_5(x), \tag{24}$$
$$0 = r g_4(p) g_5(x) - \beta_6 g_5(x). \tag{25}$$

From Eq. (25) we have two possible solutions: $g_5(x) = 0$ and $g_4(p) = \beta_6/r$. The first possibility $g_5(x) = 0$ implies that $x = 0$. Hypothesis (H3) implies that g_i^{-1}, $i = 1,\dots,5$, exist, strictly increasing and $g_i^{-1}(0) = 0$. Let us define

$$\begin{aligned}&\psi_1(s) = g_1^{-1}\left(\frac{\lambda_1 e^{-\mu_1\tau_1}}{\lambda(a_1+\beta_2)}\pi(s)\right),\\ &\psi_2(s) = g_2^{-1}\left(\frac{a_1\lambda_1 e^{-\mu_1\tau_1} + (a_1+\beta_2)\lambda_2 e^{-\mu_2\tau_2}}{\beta_3\lambda(a_1+\beta_2)}\pi(s)\right),\\ &\psi_3(s) = g_3^{-1}\left(\frac{\lambda_3 e^{-\mu_3\tau_3}}{\beta_4\lambda}\pi(s)\right), \qquad \psi_4(s) = g_4^{-1}\left(\frac{\gamma}{\lambda}\pi(s)\right),\end{aligned} \tag{26}$$

where

$$\gamma = \frac{N(a_1\lambda_1 e^{-\mu_1\tau_1} + (a_1+\beta_2)\lambda_2 e^{-\mu_2\tau_2}) + M\lambda_3(a_1+\beta_2)e^{-\mu_3\tau_3}}{\beta_5(a_1+\beta_2)}.$$

It follows from Eqs. (20)–(24) that

$$w = \psi_1(s), \qquad y = \psi_2(s), \qquad u = \psi_3(s), \qquad p = \psi_4(s). \tag{27}$$

Obviously, $\psi_i(s) > 0$ for $s \in [0, s_0)$ and $\psi_i(s_0) = 0$, $i = 1, \ldots, 4$. From Eqs. (20), (26), and (27) we obtain

$$\gamma\chi\big(s, \psi_4(s)\big) - g_4\big(\psi_4(s)\big) = 0. \tag{28}$$

Equation (28) admits a solution $s = s_0$ which gives the infection-free steady state $\Pi_0(s_0, 0, 0, 0, 0, 0)$. Let

$$\Phi_1(s) = \gamma\chi\big(s, \psi_4(s)\big) - g_4\big(\psi_4(s)\big) = 0.$$

It is clear from hypotheses (H1) and (H2) that $\Phi_1(0) = -g_4(\psi_4(0)) < 0$ and $\Phi_1(s_0) = 0$. Moreover,

$$\Phi_1'(s_0) = \gamma\left[\frac{\partial\chi(s_0,0)}{\partial s} + \psi_4'(s_0)\frac{\partial\chi(s_0,0)}{\partial p}\right] - g_4'(0)\psi_4'(s_0).$$

We note from hypothesis (H2) that $\frac{\partial\chi(s_0,0)}{\partial s} = 0$. Then

$$\Phi_1'(s_0) = \psi_4'(s_0)g_4'(0)\left(\frac{\gamma}{g_4'(0)}\frac{\partial\chi(s_0,0)}{\partial p} - 1\right).$$

From Eq. (26), we get

$$\Phi_1'(s_0) = \frac{\gamma}{\lambda}\pi'(s_0)\left(\frac{\gamma}{g_4'(0)}\frac{\partial\chi(s_0,0)}{\partial p} - 1\right).$$

Hence, from hypothesis (H1), we have $\pi'(s_0) < 0$. Therefore, if $\frac{\gamma}{g_4'(0)}\frac{\partial\chi(s_0,0)}{\partial p} > 1$, then $\Phi_1'(s_0) < 0$, and there exists $s_1 \in (0, s_0)$ such that $\Phi_1(s_1) = 0$. Hypotheses (H1)–(H3) imply that

$$w_1 = \psi_1(s_1) > 0, \qquad y_1 = \psi_2(s_1) > 0, \qquad u_1 = \psi_3(s_1) > 0, \qquad p_1 = \psi_4(s_1) > 0. \tag{29}$$

It means that a humoral-inactivated infection steady state $\Pi_1(s_1, w_1, y_1, u_1, p_1, 0)$ exists when $\frac{\gamma}{g_4'(0)}\frac{\partial\chi(s_0,0)}{\partial p} > 1$. Let us define the basic infection reproduction number as follows:

$$R_0 = \frac{\gamma}{g_4'(0)}\frac{\partial\chi(s_0,0)}{\partial p}.$$

The other solution of Eq. (25) is $g_4(p_2) = \frac{\beta_6}{r}$, which yields $p_2 = g_4^{-1}(\frac{\beta_6}{r}) > 0$. Substitute $p = p_2$ in Eq. (20) and let $\Phi_2(s) = \pi(s) - \lambda\chi(s, p_2) = 0$. According to hypotheses (H1) and (H2),

Φ_2 is strictly decreasing, $\Phi_2(0) = \pi(0) > 0$ and $\Phi_2(s_0) = -\lambda\chi(s_0, p_2) < 0$. Thus, there exists unique $s_2 \in (0, s_0)$ such that $\Phi_2(s_2) = 0$. It follows from Eqs. (24) and (27) that

$$w_2 = \psi_1(s_2) > 0, \qquad y_2 = \psi_2(s_2) > 0, \qquad u_2 = \psi_3(s_2) > 0, \qquad p_2 = g_4^{-1}\left(\frac{\beta_6}{r}\right) > 0,$$
$$x_2 = g_5^{-1}\left(\frac{\beta_5}{q}\left(\gamma\frac{\chi(s_2, p_2)}{g_4(p_2)} - 1\right)\right).$$

Thus, $x_2 > 0$ when $\gamma\frac{\chi(s_2,p_2)}{g_4(p_2)} > 1$. Now we define the humoral immune response activation number as follows:

$$R_1 = \gamma\frac{\chi(s_2, p_2)}{g_4(p_2)}.$$

If $R_1 > 1$, then $x_2 = g_5^{-1}(\frac{\beta_5}{q}(R_1 - 1)) > 0$, and there exists a humoral-activated infection steady state $\Pi_2(s_2, w_2, y_2, u_2, p_2, x_2)$.

Clearly, from hypotheses (H2) and (H4), we have

$$R_1 = \gamma\frac{\chi(s_2, p_2)}{g_4(p_2)} \le \gamma \lim_{p\to 0^+}\frac{\chi(s_2, p)}{g_4(p)} = \frac{\gamma}{g_4'(0)}\frac{\partial\chi(s_2, 0)}{\partial p} < \frac{\gamma}{g_4'(0)}\frac{\partial\chi(s_0, 0)}{\partial p} = R_0. \qquad \square$$

We will use the following equalities throughout the paper:

$$\begin{aligned}
&\ln\left(\frac{\chi(s(t-\tau_1), p(t-\tau_1))}{\chi(s,p)}\right) \\
&\quad = \ln\left(\frac{g_1(\hat{w})\chi(s(t-\tau_1), p(t-\tau_1))}{g_1(w)\chi(\hat{s},\hat{p})}\right) + \ln\left(\frac{\chi(\hat{s},\hat{p})}{\chi(s,\hat{p})}\right) \\
&\qquad + \ln\left(\frac{g_4(p)\chi(s,\hat{p})}{g_4(\hat{p})\chi(s,p)}\right) + \ln\left(\frac{g_4(\hat{p})g_2(y)}{g_4(p)g_2(\hat{y})}\right) + \ln\left(\frac{g_2(\hat{y})g_1(w)}{g_2(y)g_1(\hat{w})}\right), \\
&\ln\left(\frac{\chi(s(t-\tau_2), p(t-\tau_2))}{\chi(s,p)}\right) \\
&\quad = \ln\left(\frac{g_2(\hat{y})\chi(s(t-\tau_2), p(t-\tau_2))}{g_2(y)\chi(\hat{s},\hat{p})}\right) + \ln\left(\frac{\chi(\hat{s},\hat{p})}{\chi(s,\hat{p})}\right) \\
&\qquad + \ln\left(\frac{g_4(\hat{p})g_2(y)}{g_4(p)g_2(\hat{y})}\right) + \ln\left(\frac{g_4(p)\chi(s,\hat{p})}{g_4(\hat{p})\chi(s,p)}\right), \\
&\ln\left(\frac{\chi(s(t-\tau_3), p(t-\tau_3))}{\chi(s,p)}\right) \\
&\quad = \ln\left(\frac{g_3(\hat{u})\chi(s(t-\tau_3), p(t-\tau_3))}{g_3(u)\chi(\hat{s},\hat{p})}\right) + \ln\left(\frac{\chi(\hat{s},\hat{p})}{\chi(s,\hat{p})}\right) \\
&\qquad + \ln\left(\frac{g_3(u)g_4(\hat{p})}{g_3(\hat{u})g_4(p)}\right) + \ln\left(\frac{g_4(p)\chi(s,\hat{p})}{g_4(\hat{p})\chi(s,p)}\right).
\end{aligned} \tag{30}$$

2.2 Global properties

The following theorems investigate the global stability of the steady states of system (12)–(17).

Let us define the function $F : (0, \infty) \to [0, \infty)$ as $F(z) = z - 1 - \ln z$. Denote $(s, w, y, u, p, x) = (s(t), w(t), y(t), u(t), p(t), x(t))$.

Theorem 1 *If* $R_0 \leq 1$ *and hypotheses* (H1)–(H4) *are valid, then* Π_0 *is globally asymptotically stable* (*GAS*).

Proof Define a Lyapunov functional V_0 as follows:

$$\begin{aligned} V_0 &= s - s_0 - \int_{s_0}^{s} \lim_{p\to 0^+} \frac{\chi(s_0,p)}{\chi(\eta,p)}\,d\eta + \ell_1 w + \ell_2 y + \ell_3 u \\ &\quad + \ell_1 \int_0^{\tau_1} \lambda_1 e^{-\mu_1\tau_1} \chi\big(s(t-\theta),p(t-\theta)\big)\,d\theta \\ &\quad + \ell_2 \int_0^{\tau_2} \lambda_2 e^{-\mu_2\tau_2} \chi\big(s(t-\theta),p(t-\theta)\big)\,d\theta \\ &\quad + \ell_3 \int_0^{\tau_3} \lambda_3 e^{-\mu_3\tau_3} \chi\big(s(t-\theta),p(t-\theta)\big)\,d\theta + \ell_4 p + \ell_5 x, \end{aligned}$$

where

$$\begin{aligned} &\lambda = \lambda_1\ell_1 e^{-\mu_1\tau_1} + \lambda_2\ell_2 e^{-\mu_2\tau_2} + \lambda_3\ell_3 e^{-\mu_3\tau_3}, \qquad (a_1+\beta_2)\ell_1 = a_1\ell_2, \\ &\ell_2 = N\ell_4, \qquad \ell_3 = M\ell_4, \qquad q\ell_4 = r\ell_5. \end{aligned} \tag{31}$$

The solution of Eqs. (31) is given by

$$\ell_1 = \frac{a_1 N\lambda}{\gamma\beta_5(a_1+\beta_2)}, \qquad \ell_2 = \frac{N\lambda}{\gamma\beta_5}, \qquad \ell_3 = \frac{M\lambda}{\gamma\beta_5}, \qquad \ell_4 = \frac{\lambda}{\gamma\beta_5}, \qquad \ell_5 = \frac{q\lambda}{r\gamma\beta_5}. \tag{32}$$

We calculate $\frac{dV_0}{dt}$ along the trajectories of (12)–(17) as follows:

$$\begin{aligned} \frac{dV_0}{dt} &= \left(1 - \lim_{p\to 0^+}\frac{\chi(s_0,p)}{\chi(s,p)}\right)\big(\pi(s) - \lambda\chi(s,p)\big) \\ &\quad + \ell_1\big(\lambda_1 e^{-\mu_1\tau_1}\chi\big(s(t-\tau_1),p(t-\tau_1)\big) - (a_1+\beta_2)g_1(w)\big) \\ &\quad + \ell_2\big(\lambda_2 e^{-\mu_2\tau_2}\chi\big(s(t-\tau_2),p(t-\tau_2)\big) + a_1 g_1(w) - \beta_3 g_2(y)\big) \\ &\quad + \ell_3\big(\lambda_3 e^{-\mu_3\tau_3}\chi\big(s(t-\tau_3),p(t-\tau_3)\big) - \beta_4 g_3(u)\big) \\ &\quad + \ell_1\lambda_1 e^{-\mu_1\tau_1}\big(\chi(s,p) - \chi\big(s(t-\tau_1),p(t-\tau_1)\big)\big) \\ &\quad + \ell_2\lambda_2 e^{-\mu_2\tau_2}\big(\chi(s,p) - \chi\big(s(t-\tau_2),p(t-\tau_2)\big)\big) \\ &\quad + \ell_3\lambda_3 e^{-\mu_3\tau_3}\big(\chi(s,p) - \chi\big(s(t-\tau_3),p(t-\tau_3)\big)\big) \\ &\quad + \ell_4\big(N\beta_3 g_2(y) + M\beta_4 g_3(u) - \beta_5 g_4(p) - q g_4(p) g_5(x)\big) \\ &\quad + \ell_5\big(r g_4(p) g_5(x) - \beta_6 g_5(x)\big). \end{aligned} \tag{33}$$

Collecting terms of Eq. (33) and using $\pi(s_0) = 0$, we obtain

$$\begin{aligned} \frac{dV_0}{dt} &= \big(\pi(s) - \pi(s_0)\big)\left(1 - \lim_{p\to 0^+}\frac{\chi(s_0,p)}{\chi(s,p)}\right) \\ &\quad + \left(\frac{\lambda\chi(s,p)}{g_4(p)} \lim_{p\to 0^+}\frac{\chi(s_0,p)}{\chi(s,p)} - \ell_4\beta_5\right) g_4(p) - \ell_5\beta_6 g_5(x) \\ &\leq \big(\pi(s) - \pi(s_0)\big)\left(1 - \lim_{p\to 0^+}\frac{\chi(s_0,p)}{\chi(s,p)}\right) \end{aligned}$$

$$
\begin{aligned}
&+\left(\lim_{p\to 0^+}\frac{\lambda\chi(s,p)}{g_4(p)}\lim_{p\to 0^+}\frac{\chi(s_0,p)}{\chi(s,p)}-\ell_4\beta_5\right)g_4(p)-\ell_5\beta_6 g_5(x)\\
&=\left(\pi(s)-\pi(s_0)\right)\left(1-\frac{\partial\chi(s_0,0)/\partial p}{\partial\chi(s,0)/\partial p}\right)\\
&+\ell_4\beta_5\left(\frac{\lambda}{\ell_4\beta_5 g_4'(0)}\frac{\partial\chi(s_0,0)}{\partial p}-1\right)g_4(p)-\ell_5\beta_6 g_5(x)\\
&=\left(\pi(s)-\pi(s_0)\right)\left(1-\frac{\partial\chi(s_0,0)/\partial p}{\partial\chi(s,0)/\partial p}\right)+\ell_4\beta_5(R_0-1)g_4(p)-\ell_5\beta_6 g_5(x).
\end{aligned}
$$

By hypotheses (H1) and (H2), we obtain

$$
\left(\pi(s)-\pi(s_0)\right)\left(1-\frac{\partial\chi(s_0,0)/\partial p}{\partial\chi(s,0)/\partial p}\right)\le 0.
$$

Therefore, if $R_0\le 1$, then $\frac{dV_0}{dt}\le 0$ for $s,p,x>0$. Clearly, $\frac{dV_0}{dt}=0$ at Π_0. Applying LaSalle's invariance principle (LIP), we get that Π_0 is GAS. □

Lemma 3 *If* $R_0>1$ *and hypotheses* (H1)–(H4) *are valid*, *then*

$$
\operatorname{sgn}(R_1-1)=\operatorname{sgn}(p_1-p_2)=\operatorname{sgn}(s_2-s_1).
$$

Proof Using hypotheses (H1) and (H2), for $s_1,s_2,p_1,p_2>0$, we get

$$
(s_1-s_2)\left(\pi(s_2)-\pi(s_1)\right)>0, \tag{34}
$$

$$
(s_2-s_1)\left(\chi(s_2,p_2)-\chi(s_1,p_2)\right)>0, \tag{35}
$$

$$
(p_2-p_1)\left(\chi(s_1,p_2)-\chi(s_1,p_1)\right)>0, \tag{36}
$$

and from hypothesis (H4), we obtain

$$
(p_1-p_2)\left(\frac{\chi(s_1,p_2)}{g_2(p_2)}-\frac{\chi(s_1,p_1)}{g_2(p_1)}\right)>0. \tag{37}
$$

First, we show that $\operatorname{sgn}(p_1-p_2)=\operatorname{sgn}(s_2-s_1)$. Suppose that $\operatorname{sgn}(p_2-p_1)=\operatorname{sgn}(s_2-s_1)$. Using the steady state conditions of Π_1 and Π_2, we obtain

$$
\begin{aligned}
\pi(s_2)-\pi(s_1)&=\lambda\left[\chi(s_2,p_2)-\chi(s_1,p_1)\right]\\
&=\lambda\left[\left(\chi(s_2,p_2)-\chi(s_1,p_2)\right)+\left(\chi(s_1,p_2)-\chi(s_1,p_1)\right)\right].
\end{aligned}
$$

Therefore, from inequalities (34)–(36) we obtain $\operatorname{sgn}(s_2-s_1)=\operatorname{sgn}(s_1-s_2)$, which is a contradiction; hence, $\operatorname{sgn}(p_1-p_2)=\operatorname{sgn}(s_2-s_1)$. Using Eq. (29) and the definition of R_1, we get

$$
\begin{aligned}
R_1-1&=\gamma\left(\frac{\chi(s_2,p_2)}{g_4(p_2)}-\frac{\chi(s_1,p_1)}{g_4(p_1)}\right)\\
&=\gamma\left[\frac{1}{g_4(p_2)}\left(\chi(s_2,p_2)-\chi(s_1,p_2)\right)+\frac{\chi(s_1,p_2)}{g_4(p_2)}-\frac{\chi(s_1,p_1)}{g_4(p_1)}\right].
\end{aligned}
$$

Thus, from Eqs. (35) and (37) we obtain $\operatorname{sgn}(R_1-1)=\operatorname{sgn}(p_1-p_2)$. □

Theorem 2 *If $R_1 \le 1 < R_0$ and hypotheses* (H1)–(H4) *are valid, then Π_1 is GAS.*

Proof Let

$$\begin{aligned} V_1 &= s - s_1 - \int_{s_1}^{s} \frac{\chi(s_1,p_1)}{\chi(\eta,p_1)}\,d\eta + \ell_1\left(w - w_1 - \int_{w_1}^{w} \frac{g_1(w_1)}{g_1(\eta)}\,d\eta\right) \\ &\quad + \ell_2\left(y - y_1 - \int_{y_1}^{y} \frac{g_2(y_1)}{g_2(\eta)}\,d\eta\right) + \ell_3\left(u - u_1 - \int_{u_1}^{u} \frac{g_3(u_1)}{g_3(\eta)}\,d\eta\right) \\ &\quad + \ell_1\lambda_1\chi(s_1,p_1)e^{-\mu_1\tau_1}\int_0^{\tau_1} F\left(\frac{\chi(s(t-\theta),p(t-\theta))}{\chi(s_1,p_1)}\right)d\theta \\ &\quad + \ell_2\lambda_2\chi(s_1,p_1)e^{-\mu_2\tau_2}\int_0^{\tau_2} F\left(\frac{\chi(s(t-\theta),p(t-\theta))}{\chi(s_1,p_1)}\right)d\theta \\ &\quad + \ell_3\lambda_3\chi(s_1,p_1)e^{-\mu_3\tau_3}\int_0^{\tau_3} F\left(\frac{\chi(s(t-\theta),p(t-\theta))}{\chi(s_1,p_1)}\right)d\theta \\ &\quad + \ell_4\left(p - p_1 - \int_{p_1}^{p} \frac{g_4(p_1)}{g_4(\eta)}\,d\eta\right) + \ell_5 x. \end{aligned}$$

Calculating $\frac{dV_1}{dt}$ along the solutions of (12)–(17), we obtain

$$\begin{aligned} \frac{dV_1}{dt} &= \left(1 - \frac{\chi(s_1,p_1)}{\chi(s,p_1)}\right)\bigl(\pi(s) - \lambda\chi(s,p)\bigr) \\ &\quad + \ell_1\left(1 - \frac{g_1(w_1)}{g_1(w)}\right)\bigl(\lambda_1 e^{-\mu_1\tau_1}\chi\bigl(s(t-\tau_1),p(t-\tau_1)\bigr) - (a_1+\beta_2)g_1(w)\bigr) \\ &\quad + \ell_2\left(1 - \frac{g_2(y_1)}{g_2(y)}\right)\bigl(\lambda_2 e^{-\mu_2\tau_2}\chi\bigl(s(t-\tau_2),p(t-\tau_2)\bigr) + a_1 g_1(w) - \beta_3 g_2(y)\bigr) \\ &\quad + \ell_3\left(1 - \frac{g_3(u_1)}{g_3(u)}\right)\bigl(\lambda_3 e^{-\mu_3\tau_3}\chi\bigl(s(t-\tau_3),p(t-\tau_3)\bigr) - \beta_4 g_3(u)\bigr) \\ &\quad + \ell_1\lambda_1 e^{-\mu_1\tau_1}\bigl(\chi(s,p) - \chi\bigl(s(t-\tau_1),p(t-\tau_1)\bigr)\bigr) \\ &\quad + \ell_1\lambda_1\chi(s_1,p_1)e^{-\mu_1\tau_1}\ln\left(\frac{\chi(s(t-\tau_1),p(t-\tau_1))}{\chi(s,p)}\right) \\ &\quad + \ell_2\lambda_2 e^{-\mu_2\tau_2}\bigl(\chi(s,p) - \chi\bigl(s(t-\tau_2),p(t-\tau_2)\bigr)\bigr) \\ &\quad + \ell_2\lambda_2\chi(s_1,p_1)e^{-\mu_2\tau_2}\ln\left(\frac{\chi(s(t-\tau_2),p(t-\tau_2))}{\chi(s,p)}\right) \\ &\quad + \ell_3\lambda_3 e^{-\mu_3\tau_3}\bigl(\chi(s,p) - \chi\bigl(s(t-\tau_3),p(t-\tau_3)\bigr)\bigr) \\ &\quad + \ell_3\lambda_3\chi(s_1,p_1)e^{-\mu_3\tau_3}\ln\left(\frac{\chi(s(t-\tau_3),p(t-\tau_3))}{\chi(s,p)}\right) \\ &\quad + \ell_4\left(1 - \frac{g_4(p_1)}{g_4(p)}\right)\bigl(N\beta_3 g_2(y) + M\beta_4 g_3(u) - \beta_5 g_4(p) - q g_4(p)g_5(x)\bigr) \\ &\quad + \ell_5\bigl(r g_4(p)g_5(x) - \beta_6 g_5(x)\bigr). \end{aligned} \tag{38}$$

Collecting terms of Eq. (38) and applying the conditions of the steady state Π_1

$$\pi(s_1) = \lambda\chi(s_1,p_1),$$

$$
\begin{aligned}
&(a_1+\beta_2)g_1(w_1)=\lambda_1 e^{-\mu_1\tau_1}\chi(s_1,p_1),\\
&\ell_2\beta_3 g_2(y_1)=\left(\ell_1\lambda_1 e^{-\mu_1\tau_1}+\ell_2\lambda_2 e^{-\mu_2\tau_2}\right)\chi(s_1,p_1),\\
&\beta_4 g_3(u_1)=\lambda_3 e^{-\mu_3\tau_3}\chi(s_1,p_1),\qquad \ell_4\beta_5 g_4(p_1)=\lambda\chi(s_1,p_1),
\end{aligned}
$$

we get

$$
\begin{aligned}
\frac{dV_1}{dt}={}&\left(\pi(s)-\pi(s_1)\right)\left(1-\frac{\chi(s_1,p_1)}{\chi(s,p_1)}\right)+\lambda\chi(s_1,p_1)\left(1-\frac{\chi(s_1,p_1)}{\chi(s,p_1)}\right)\\
&+\lambda\chi(s_1,p_1)\left(\frac{\chi(s,p)}{\chi(s,p_1)}-\frac{g_4(p)}{g_4(p_1)}\right)\\
&-\ell_1\lambda_1 e^{-\mu_1\tau_1}\chi(s_1,p_1)\frac{g_1(w_1)\chi(s(t-\tau_1),p(t-\tau_1))}{g_1(w)\chi(s_1,p_1)}+\ell_1\lambda_1 e^{-\mu_1\tau_1}\chi(s_1,p_1)\\
&-\ell_2\lambda_2 e^{-\mu_2\tau_2}\chi(s_1,p_1)\frac{g_2(y_1)\chi(s(t-\tau_2),p(t-\tau_2))}{g_2(y)\chi(s_1,p_1)}\\
&-\ell_1\lambda_1 e^{-\mu_1\tau_1}\chi(s_1,p_1)\frac{g_2(y_1)g_1(w)}{g_2(y)g_1(w_1)}\\
&+\left(\ell_1\lambda_1 e^{-\mu_1\tau_1}+\ell_2\lambda_2 e^{-\mu_2\tau_2}\right)\chi(s_1,p_1)\\
&-\ell_3\lambda_3 e^{-\mu_3\tau_3}\chi(s_1,p_1)\frac{g_3(u_1)\chi(s(t-\tau_3),p(t-\tau_3))}{\chi(s_1,p_1)g_3(u)}\\
&+\ell_3\lambda_3 e^{-\mu_3\tau_3}\chi(s_1,p_1)+\ell_1\lambda_1 e^{-\mu_1\tau_1}\chi(s_1,p_1)\ln\left(\frac{\chi(s(t-\tau_1),p(t-\tau_1))}{\chi(s,p)}\right)\\
&+\ell_2\lambda_2 e^{-\mu_2\tau_2}\chi(s_1,p_1)\ln\left(\frac{\chi(s(t-\tau_2),p(t-\tau_2))}{\chi(s,p)}\right)\\
&+\ell_3\lambda_3 e^{-\mu_3\tau_3}\chi(s_1,p_1)\ln\left(\frac{\chi(s(t-\tau_3),p(t-\tau_3))}{\chi(s,p)}\right)\\
&-\left(\ell_1\lambda_1 e^{-\mu_1\tau_1}+\ell_2\lambda_2 e^{-\mu_2\tau_2}\right)\chi(s_1,p_1)\frac{g_2(y)g_4(p_1)}{g_2(y_1)g_4(p)}\\
&-\ell_3\lambda_3 e^{-\mu_3\tau_3}\chi(s_1,p_1)\frac{g_3(u)g_4(p_1)}{g_3(u_1)g_4(p)}\\
&+\lambda\chi(s_1,p_1)+r\ell_5\left(g_4(p_1)-\frac{\beta_6}{r}\right)g_5(x).
\end{aligned}\tag{39}
$$

Using inequalities (30) with $\hat{s}=s_1$, $\hat{w}=w_1$, $\hat{y}=y_1$, and $\hat{p}=p_1$, we can obtain

$$
\begin{aligned}
\frac{dV_1}{dt}={}&\left(\pi(s)-\pi(s_1)\right)\left(1-\frac{\chi(s_1,p_1)}{\chi(s,p_1)}\right)+\lambda\chi(s_1,p_1)\left(\frac{\chi(s,p)}{\chi(s,p_1)}-\frac{g_4(p)}{g_4(p_1)}\right)\left(1-\frac{\chi(s,p_1)}{\chi(s,p)}\right)\\
&-\lambda\chi(s_1,p_1)\left[F\left(\frac{\chi(s_1,p_1)}{\chi(s,p_1)}\right)+F\left(\frac{g_4(p)\chi(s,p_1)}{g_4(p_1)\chi(s,p)}\right)\right]\\
&-\ell_1\lambda_1 e^{-\mu_1\tau_1}\chi(s_1,p_1)\left[F\left(\frac{g_1(w_1)\chi(s(t-\tau_1),p(t-\tau_1))}{g_1(w)\chi(s_1,p_1)}\right)+F\left(\frac{g_2(y_1)g_1(w)}{g_2(y)g_1(w_1)}\right)\right]\\
&-\ell_2\lambda_2 e^{-\mu_2\tau_2}\chi(s_1,p_1)F\left(\frac{g_2(y_1)\chi(s(t-\tau_2),p(t-\tau_2))}{g_2(y)\chi(s_1,p_1)}\right)\\
&-\ell_3\lambda_3 e^{-\mu_3\tau_3}\chi(s_1,p_1)\left[F\left(\frac{g_3(u_1)\chi(s(t-\tau_3),p(t-\tau_3))}{g_3(u)\chi(s_1,p_1)}\right)+F\left(\frac{g_3(u)g_4(p_1)}{g_3(u_1)g_4(p)}\right)\right]
\end{aligned}
$$

$$- \left(\ell_1\lambda_1 e^{-\mu_1\tau_1} + \ell_2\lambda_2 e^{-\mu_2\tau_2}\right)\chi(s_1,p_1)F\left(\frac{g_2(y)g_4(p_1)}{g_2(y_1)g_4(p)}\right)$$
$$+ r\ell_5\left(g_4(p_1) - g_4(p_2)\right)g_5(x).$$

Hypotheses (H1), (H2), (H4), Lemma 3, and the condition $R_1 \le 1$ imply that

$$\left(\pi(s) - \pi(s_1)\right)\left(1 - \frac{\chi(s_1,p_1)}{\chi(s,p_1)}\right) \le 0,$$
$$\left(\frac{\chi(s,p)}{\chi(s,p_1)} - \frac{g_4(p)}{g_4(p_1)}\right)\left(1 - \frac{\chi(s,p_1)}{\chi(s,p)}\right) \le 0,$$
$$g_4(p_1) - g_4(p_2) \le 0.$$

It follows that, for all $s, y, p, x > 0$, we have $\frac{dV_1}{dt} \le 0$ and $\frac{dV_1}{dt} = 0$ at Π_1. By LIP Π_1 is GAS. □

Theorem 3 *If* $R_1 > 1$ *and hypotheses* (H1)–(H4) *are valid, then* Π_2 *is GAS.*

Proof Define

$$\begin{aligned}
V_2 = {} & s - s_2 - \int_{s_2}^{s} \frac{\chi(s_2,p_2)}{\chi(\eta,p_2)}\,d\eta + \ell_1\left(w - w_2 - \int_{w_2}^{w}\frac{g_1(w_2)}{g_1(\eta)}\,d\eta\right) \\
& + \ell_2\left(y - y_2 - \int_{y_2}^{y}\frac{g_2(y_2)}{g_2(\eta)}\,d\eta\right) + \ell_3\left(u - u_2 - \int_{u_2}^{u}\frac{g_3(u_2)}{g_3(\eta)}\,d\eta\right) \\
& + \ell_1\lambda_1\chi(s_2,p_2)e^{-\mu_1\tau_1}\int_0^{\tau_1} F\left(\frac{\chi(s(t-\theta),p(t-\theta))}{\chi(s_2,p_2)}\right)d\theta \\
& + \ell_2\lambda_2\chi(s_2,p_2)e^{-\mu_2\tau_2}\int_0^{\tau_2} F\left(\frac{\chi(s(t-\theta),p(t-\theta))}{\chi(s_2,p_2)}\right)d\theta \\
& + \ell_3\lambda_3\chi(s_2,p_2)e^{-\mu_3\tau_3}\int_0^{\tau_3} F\left(\frac{\chi(s(t-\theta),p(t-\theta))}{\chi(s_2,p_2)}\right)d\theta \\
& + \ell_4\left(p - p_2 - \int_{p_2}^{p}\frac{g_4(p_2)}{g_4(\eta)}\,d\eta\right) + \ell_5\left(x - x_2 - \int_{x_2}^{x}\frac{g_5(x_2)}{g_5(\eta)}\,d\eta\right).
\end{aligned}$$

Calculating $\frac{dV_2}{dt}$ along the solutions of model (12)-(17), we get

$$\begin{aligned}
\frac{dV_2}{dt} = {} & \left(1 - \frac{\chi(s_2,p_2)}{\chi(s,p_2)}\right)\left(\pi(s) - \lambda\chi(s,p)\right) \\
& + \ell_1\left(1 - \frac{g_1(w_2)}{g_1(w)}\right)\left(\lambda_1 e^{-\mu_1\tau_1}\chi\left(s(t-\tau_1),p(t-\tau_1)\right) - (a_1+\beta_2)g_1(w)\right) \\
& + \ell_2\left(1 - \frac{g_2(y_2)}{g_2(y)}\right)\left(\lambda_2 e^{-\mu_2\tau_2}\chi\left(s(t-\tau_2),p(t-\tau_2)\right) + a_1g_1(w) - \beta_3g_2(y)\right) \\
& + \ell_3\left(1 - \frac{g_3(u_2)}{g_3(u)}\right)\left(\lambda_3 e^{-\mu_3\tau_3}\chi\left(s(t-\tau_3),p(t-\tau_3)\right) - \beta_4g_3(u)\right) \\
& + \ell_1\lambda_1 e^{-\mu_1\tau_1}\left(\chi(s,p) - \chi\left(s(t-\tau_1),p(t-\tau_1)\right)\right) \\
& + \ell_1\lambda_1 e^{-\mu_1\tau_1}\chi(s_2,p_2)\ln\left(\frac{\chi(s(t-\tau_1),p(t-\tau_1))}{\chi(s,p)}\right) \\
& + \ell_2\lambda_2 e^{-\mu_2\tau_2}\left(\chi(s,p) - \chi\left(s(t-\tau_2),p(t-\tau_2)\right)\right)
\end{aligned}$$

$$
\begin{aligned}
&+ \ell_2\lambda_2 e^{-\mu_2\tau_2}\chi(s_2,p_2)\ln\left(\frac{\chi(s(t-\tau_2),p(t-\tau_2))}{\chi(s,p)}\right)\\
&+ \ell_3\lambda_3 e^{-\mu_3\tau_3}\big(\chi(s,p)-\chi\big(s(t-\tau_3),p(t-\tau_3)\big)\big)\\
&+ \ell_3\lambda_3 e^{-\mu_3\tau_3}\chi(s_2,p_2)\ln\left(\frac{\chi(s(t-\tau_3),p(t-\tau_3))}{\chi(s,p)}\right)\\
&+ \ell_4\left(1-\frac{g_4(p_2)}{g_4(p)}\right)\big(N\beta_3 g_2(y)+M\beta_4 g_3(u)-\beta_5 g_4(p)-q g_4(p) g_5(x)\big)\\
&+ \ell_5\left(1-\frac{g_5(x_2)}{g_5(x)}\right)\big(r g_4(p) g_5(x)-\beta_6 g_5(x)\big).
\end{aligned} \tag{40}
$$

Collecting terms of Eq. (40) and using the steady state conditions for Π_2:

$$
\begin{aligned}
&\pi(s_2)=\lambda\chi(s_2,p_2),\\
&(a_1+\beta_2)g_1(w_2)=\lambda_1 e^{-\mu_1\tau_1}\chi(s_2,p_2),\\
&\ell_2\beta_3 g_2(y_2)=\big(\ell_1\lambda_1 e^{-\mu_1\tau_1}+\ell_2\lambda_2 e^{-\mu_2\tau_2}\big)\chi(s_2,p_2),\\
&\beta_4 g_3(u_2)=\lambda_3 e^{-\mu_3\tau_3}\chi(s_2,p_2),\qquad \ell_4\beta_5 g_4(p_2)=\lambda\chi(s_2,p_2)-q\ell_4 g_4(p_2) g_5(x_2),\\
&\ell_4\beta_5 g_4(p)=\lambda\chi(s_2,p_2)\frac{g_4(p)}{g_4(p_2)}-q\ell_4 g_4(p) g_5(x_2),
\end{aligned}
$$

we obtain

$$
\begin{aligned}
\frac{dV_2}{dt} ={}& \big(\pi(s)-\pi(s_2)\big)\left(1-\frac{\chi(s_2,p_2)}{\chi(s,p_2)}\right)+\lambda\chi(s_2,p_2)\left(1-\frac{\chi(s_2,p_2)}{\chi(s,p_2)}\right)\\
&+\lambda\chi(s_2,p_2)\left(\frac{\chi(s,p)}{\chi(s,p_2)}-\frac{g_4(p)}{g_4(p_2)}\right)\\
&-\ell_1\lambda_1 e^{-\mu_1\tau_1}\chi(s_2,p_2)\frac{g_1(w_2)\chi(s(t-\tau_1),p(t-\tau_1))}{g_1(w)\chi(s_2,p_2)}+\ell_1\lambda_1 e^{-\mu_1\tau_1}\chi(s_2,p_2)\\
&-\ell_2\lambda_2 e^{-\mu_2\tau_2}\chi(s_2,p_2)\frac{g_2(y_2)\chi(s(t-\tau_2),p(t-\tau_2))}{g_2(y)\chi(s_2,p_2)}\\
&-\ell_1\lambda_1 e^{-\mu_1\tau_1}\chi(s_2,p_2)\frac{g_2(y_2)g_1(w)}{g_2(y)g_1(w_2)}\\
&+\big(\ell_1\lambda_1 e^{-\mu_1\tau_1}+\ell_2\lambda_2 e^{-\mu_2\tau_2}\big)\chi(s_2,p_2)\\
&-\ell_3\lambda_3 e^{-\mu_3\tau_3}\chi(s_2,p_2)\frac{g_3(u_2)\chi(s(t-\tau_3),p(t-\tau_3))}{g_3(u)\chi(s_2,p_2)}\\
&+\ell_3\lambda_3 e^{-\mu_3\tau_3}\chi(s_2,p_2)+\ell_1\lambda_1 e^{-\mu_1\tau_1}\chi(s_2,p_2)\ln\left(\frac{\chi(s(t-\tau_1),p(t-\tau_1))}{\chi(s,p)}\right)\\
&+\ell_2\lambda_2 e^{-\mu_2\tau_2}\chi(s_2,p_2)\ln\left(\frac{\chi(s(t-\tau_2),p(t-\tau_2))}{\chi(s,p)}\right)\\
&+\ell_3\lambda_3 e^{-\mu_3\tau_3}\chi(s_2,p_2)\ln\left(\frac{\chi(s(t-\tau_3),p(t-\tau_3))}{\chi(s,p)}\right)\\
&-\big(\ell_1\lambda_1 e^{-\mu_1\tau_1}+\ell_2\lambda_2 e^{-\mu_2\tau_2}\big)\chi(s_2,p_2)\frac{g_2(y)g_4(p_2)}{g_2(y_2)g_4(p)}\\
&-\ell_3\lambda_3 e^{-\mu_3\tau_3}\chi(s_2,p_2)\frac{g_3(u)g_4(p_2)}{g_3(u_2)g_4(p)}+\lambda\chi(s_2,p_2).
\end{aligned} \tag{41}
$$

By inequalities (30) with $\hat{s} = s_2$, $\hat{w} = w_2$, $\hat{y} = y_2$, and $\hat{p} = p_2$, we can get

$$\begin{aligned}
\frac{dV_2}{dt} &= \big(\pi(s) - \pi(s_2)\big)\left(1 - \frac{\chi(s_2,p_2)}{\chi(s,p_2)}\right) + \lambda\chi(s_2,p_2)\left(\frac{\chi(s,p)}{\chi(s,p_2)} - \frac{g_4(p)}{g_4(p_2)}\right)\left(1 - \frac{\chi(s,p_2)}{\chi(s,p)}\right) \\
&\quad - \lambda\chi(s_2,p_2)\left[F\left(\frac{\chi(s_2,p_2)}{\chi(s,p_2)}\right) + F\left(\frac{g_4(p)\chi(s,p_2)}{g_4(p_2)\chi(s,p)}\right)\right] \\
&\quad - \ell_1\lambda_1 e^{-\mu_1\tau_1}\chi(s_2,p_2)\left[F\left(\frac{g_1(w_2)\chi(s(t-\tau_1),p(t-\tau_1))}{g_1(w)\chi(s_2,p_2)}\right) + F\left(\frac{g_2(y_2)g_1(w)}{g_2(y)g_1(w_2)}\right)\right] \\
&\quad - \ell_2\lambda_2 e^{-\mu_2\tau_2}\chi(s_2,p_2)F\left(\frac{g_2(y_2)\chi(s(t-\tau_2),p(t-\tau_2))}{g_2(y)\chi(s_2,p_2)}\right) \\
&\quad - \ell_3\lambda_3 e^{-\mu_3\tau_3}\chi(s_2,p_2)\left[F\left(\frac{g_3(u_2)\chi(s(t-\tau_3),p(t-\tau_3))}{g_3(u)\chi(s_2,p_2)}\right) + F\left(\frac{g_3(u)g_4(p_2)}{g_3(u_2)g_4(p)}\right)\right] \\
&\quad - \big(\ell_1\lambda_1 e^{-\mu_1\tau_1} + \ell_2\lambda_2 e^{-\mu_2\tau_2}\big)\chi(s_2,p_2)F\left(\frac{g_2(y)g_4(p_2)}{g_2(y_2)g_4(p)}\right).
\end{aligned}$$

According to hypotheses (H1), (H2), and (H4), we get $\frac{dV_2}{dt} \le 0$ and $\frac{dV_2}{dt} = 0$ at Π_2. LIP implies that Π_2 is GAS. □

3 Model with delay-distributed

In the next model, we consider a general delay-distributed HIV infection model with humoral immunity as follows:

$$\dot{s} = \pi\big(s(t)\big) - \lambda\chi\big(s(t),p(t)\big), \tag{42}$$

$$\dot{w} = \lambda_1\int_0^{h_1} f_1(\tau)e^{-\mu_1\tau}\chi\big(s(t-\tau),p(t-\tau)\big)\,d\tau - (a_1+\beta_2)g_1\big(w(t)\big), \tag{43}$$

$$\dot{y} = \lambda_2\int_0^{h_2} f_2(\tau)e^{-\mu_2\tau}\chi\big(s(t-\tau),p(t-\tau)\big)\,d\tau + a_1g_1\big(w(t)\big) - \beta_3g_2\big(y(t)\big), \tag{44}$$

$$\dot{u} = \lambda_3\int_0^{h_3} f_3(\tau)e^{-\mu_3\tau}\chi\big(s(t-\tau),p(t-\tau)\big)\,d\tau - \beta_4g_3\big(u(t)\big), \tag{45}$$

$$\dot{p} = N\beta_3g_2\big(y(t)\big) + M\beta_4g_3\big(u(t)\big) - \beta_5g_4\big(p(t)\big) - qg_4\big(p(t)\big)g_5\big(x(t)\big), \tag{46}$$

$$\dot{x} = rg_4\big(p(t)\big)g_5\big(x(t)\big) - \beta_6g_5\big(x(t)\big), \tag{47}$$

where $f_i(\tau)e^{-\mu_i\tau}$ over the time interval $[0,h_i]$, $i = 1,2,3$, represent the probabilities that uninfected cells contacted by HIV at time $t-\tau$ survived τ time units and became infected at time t.

The probability distribution function $f_i(\tau)$ is assumed to satisfy $f_i(\tau) > 0$ and

$$\int_0^{h_i} f_i(\tau)\,d\tau = 1, \qquad \int_0^{h_i} f_i(\eta)e^{\upsilon\eta}\,d\eta < \infty, \quad i = 1,2,3,$$

where υ is a positive constant. Let us denote $\Theta_i(\tau) = f_i(\tau)e^{-\mu_i\tau}$ and $F_i = \int_0^{h_i}\Theta_i(\tau)\,d\tau$; thus $0 < F_i \le 1$, $i = 1,2,3$.

Lemma 4 *Let hypotheses* (H1)–(H3) *be valid, then the solutions of system* (42)–(47) *are nonnegative and ultimately bounded.*

Proof The nonnegativity of solutions of system (42)–(47) can easily be shown as given in Lemma 1.

From Eq. (42) we have that $\limsup_{t\to\infty} s(t) \le \frac{b}{\bar{b}} = M_1$. Let

$$\begin{aligned} G(t) &= N\int_0^{h_1} \Theta_1(\tau)s(t-\tau)\,d\tau + N\int_0^{h_2} \Theta_2(\tau)s(t-\tau)\,d\tau + M\int_0^{h_3} \Theta_3(\tau)s(t-\tau)\,d\tau \\ &\quad + Nw(t) + Ny(t) + Mu(t) + \frac{1}{2}p(t) + \frac{q}{2r}x(t), \end{aligned}$$

then

$$\begin{aligned} \dot{G}(t) &= N\int_0^{h_1} \Theta_1(\tau)\big[\pi\big(s(t-\tau)\big) - \lambda\chi\big(s(t-\tau),p(t-\tau)\big)\big]\,d\tau \\ &\quad + N\int_0^{h_2} \Theta_2(\tau)\big[\pi\big(s(t-\tau)\big) - \lambda\chi\big(s(t-\tau),p(t-\tau)\big)\big]\,d\tau \\ &\quad + M\int_0^{h_3} \Theta_3(\tau)\big[\pi\big(s(t-\tau)\big) - \lambda\chi\big(s(t-\tau),p(t-\tau)\big)\big]\,d\tau \\ &\quad + N\bigg[\lambda_1\int_0^{h_1} \Theta_1(\tau)\chi\big(s(t-\tau),p(t-\tau)\big)\,d\tau - (a_1+\beta_2)g_1\big(w(t)\big)\bigg] \\ &\quad + N\bigg[\lambda_2\int_0^{h_2} \Theta_2(\tau)\chi\big(s(t-\tau),p(t-\tau)\big)\,d\tau + a_1g_1\big(w(t)\big) - \beta_3g_2\big(y(t)\big)\bigg] \\ &\quad + M\bigg[\lambda_3\int_0^{h_3} \Theta_3(\tau)\chi\big(s(t-\tau),p(t-\tau)\big)\,d\tau - \beta_4g_3\big(u(t)\big)\bigg] \\ &\quad + \frac{1}{2}\big[N\beta_3g_2\big(y(t)\big) + M\beta_4g_3\big(u(t)\big) - \beta_5g_4\big(p(t)\big) - qg_4\big(p(t)\big)g_5\big(x(t)\big)\big] \\ &\quad + \frac{q}{2r}\big[rg_4\big(p(t)\big)g_5\big(x(t)\big) - \beta_6g_5\big(x(t)\big)\big] \\ &\le N\int_0^{h_1} \Theta_1(\tau)\big[b - \bar{b}s(t-\tau)\big]\,d\tau + N\int_0^{h_2} \Theta_2(\tau)\big[b - \bar{b}s(t-\tau)\big]\,d\tau \\ &\quad + M\int_0^{h_3} \Theta_3(\tau)\big[b - \bar{b}s(t-\tau)\big]\,d\tau \\ &\quad - N\beta_2\alpha_1w(t) - \frac{1}{2}N\beta_3\alpha_2y(t) - \frac{1}{2}M\beta_4\alpha_3u(t) - \frac{1}{2}\beta_5\alpha_4p(t) - \frac{q}{2r}\beta_6\alpha_5x(t) \\ &\le b(NF_1 + NF_2 + MF_3) - \sigma\bigg[N\int_0^{h_1} \Theta_1(\tau)s(t-\tau)\,d\tau + N\int_0^{h_2} \Theta_2(\tau)s(t-\tau)\,d\tau \\ &\quad + M\int_0^{h_3} \Theta_3(\tau)s(t-\tau)\,d\tau + Nw(t) + Ny(t) + Mu(t) + \frac{1}{2}p(t) + \frac{q}{2r}x(t)\bigg] \\ &\le b(2N+M) - \sigma G(t). \end{aligned}$$

Hence, $\limsup_{t\to\infty} G(t) \le \frac{b(2N+M)}{\sigma}$ and

$$\begin{aligned} &\limsup_{t\to\infty} w(t) \le M_2, \qquad \limsup_{t\to\infty} y(t) \le M_2, \qquad \limsup_{t\to\infty} u(t) \le M_3, \\ &\limsup_{t\to\infty} p(t) \le M_4, \qquad \limsup_{t\to\infty} x(t) \le M_5, \end{aligned}$$

where $\sigma, M_1, \dots, M_5$ are given in the previous section. Therefore, $s(t)$, $w(t)$, $y(t)$, $u(t)$, $p(t)$, and $x(t)$ are ultimately bounded. Moreover, the set Ω defined by (19) is also positively invariant with respect to system (42)–(47). □

3.1 Steady states

Lemma 5 *Suppose that hypotheses* (H1)–(H4) *are valid* (42)–(47), *then there exist two bifurcation parameters* R_0 *and* R_1 *with* $R_0 > R_1 > 0$ *such that*

(i) *if* $R_0 \le 1$, *then there exists only one steady state* Π_0;

(ii) *if* $R_1 \le 1 < R_0$, *then there exist two steady states* Π_0 *and* Π_1;

(iii) *if* $R_1 > 1$, *then there exist three steady states* Π_0, Π_1, *and* Π_2.

Proof Let $\Pi(s,w,y,u,p,x)$ be any steady state of (42)–(47) satisfying the following equations:

$$0 = \pi(s) - \lambda\chi(s,p), \tag{48}$$

$$0 = \lambda_1 F_1 \chi(s,p) - (a_1 + \beta_2) g_1(w), \tag{49}$$

$$0 = \lambda_2 F_2 \chi(s,p) + a_1 g_1(w) - \beta_3 g_2(y), \tag{50}$$

$$0 = \lambda_3 F_3 \chi(s,p) - \beta_4 g_3(u), \tag{51}$$

$$0 = N\beta_3 g_2(y) + M\beta_4 g_3(u) - \beta_5 g_4(p) - q g_4(p) g_5(x), \tag{52}$$

$$0 = r g_4(p) g_5(x) - \beta_6 g_5(x). \tag{53}$$

From Eq. (53) we obtain two possible solutions: $g_5(x) = 0$ and $g_4(p) = \beta_6/r$. First, we consider the case $g_5(x) = 0$, then from hypothesis (H3) we have $x = 0$. Hypothesis (H3) implies that g_i^{-1}, $i = 1, \dots, 5$, exist, strictly increasing and $g_i^{-1}(0) = 0$. Let us define

$$\begin{aligned} &\alpha_1(s) = g_1^{-1}\left(\frac{\lambda_1 F_1}{\lambda(a_1 + \beta_2)}\pi(s)\right), \qquad \alpha_2(s) = g_2^{-1}\left(\frac{a_1\lambda_1 F_1 + (a_1 + \beta_2)\lambda_2 F_2}{\beta_3\lambda(a_1 + \beta_2)}\pi(s)\right), \\ &\alpha_3(s) = g_3^{-1}\left(\frac{\lambda_3 F_3}{\beta_4\lambda}\pi(s)\right), \qquad \alpha_4(s) = g_4^{-1}\left(\frac{\zeta}{\lambda}\pi(s)\right), \end{aligned} \tag{54}$$

where

$$\zeta = \frac{N(a_1\lambda_1 F_1 + (a_1 + \beta_2)\lambda_2 F_2) + M\lambda_3(a_1 + \beta_2)F_3}{\beta_5(a_1 + \beta_2)}.$$

From Eqs. (48)–(53) we can get

$$w = \alpha_1(s), \qquad y = \alpha_2(s), \qquad u = \alpha_3(s), \qquad p = \alpha_4(s). \tag{55}$$

Obviously, $\alpha_i(s) > 0$ for $s \in [0, s_0)$ and $\alpha_i(s_0) = 0$, $i = 1, \dots, 4$. From Eqs. (48), (54), and (55) we obtain

$$\zeta\chi\big(s, \alpha_4(s)\big) - g_4\big(\alpha_4(s)\big) = 0. \tag{56}$$

Equation (56) admits a solution $s = s_0$ which gives the infection-free steady state $\Pi_0(s_0, 0, 0, 0, 0, 0)$. Let

$$\Psi_1(s) = \zeta\chi\big(s, \alpha_4(s)\big) - g_4\big(\alpha_4(s)\big) = 0.$$

By hypotheses (H1) and (H2) we have $\Psi_1(0) = -g_4(\alpha_4(0)) < 0$ and $\Psi_1(s_0) = 0$. Moreover,

$$\Psi_1'(s_0) = \zeta\left[\frac{\partial\chi(s_0, 0)}{\partial s} + \alpha_4'(s_0)\frac{\partial\chi(s_0, 0)}{\partial p}\right] - g_4'(0)\alpha_4'(s_0).$$

From hypothesis (H2) we note that $\frac{\partial\chi(s_0,0)}{\partial s} = 0$. Then

$$\Psi_1'(s_0) = \alpha_4'(s_0)g_4'(0)\left(\frac{\zeta}{g_4'(0)}\frac{\partial\chi(s_0, 0)}{\partial p} - 1\right).$$

From Eq. (54), we get

$$\Psi_1'(s_0) = \frac{\zeta}{\lambda}\pi'(s_0)\left(\frac{\zeta}{g_4'(0)}\frac{\partial\chi(s_0, 0)}{\partial p} - 1\right).$$

Therefore, using hypothesis (H1), we get $\pi'(s_0) < 0$. So that, if $\frac{\zeta}{g_4'(0)}\frac{\partial\chi(s_0,0)}{\partial p} > 1$, then $\Psi_1'(s_0) < 0$ and there exists $s_1 \in (0, s_0)$ such that $\Psi_1(s_1) = 0$. Hypotheses (H1)–(H3) imply that

$$w_1 = \alpha_1(s_1) > 0, \qquad y_1 = \alpha_2(s_1) > 0, \qquad u_1 = \alpha_3(s_1) > 0, \qquad p_1 = \alpha_4(s_1) > 0. \tag{57}$$

It means that a humoral-inactivated infection steady state $\Pi_1(s_1, w_1, y_1, u_1, p_1, 0)$ exists when $\frac{\zeta}{g_4'(0)}\frac{\partial\chi(s_0,0)}{\partial p} > 1$. Now we can define

$$R_0 = \frac{\zeta}{g_4'(0)}\frac{\partial\chi(s_0, 0)}{\partial p}.$$

The other solution of Eq. (53) is $g_4(p_2) = \frac{\beta_6}{r}$, which yields $p_2 = g_4^{-1}(\frac{\beta_6}{r}) > 0$. Substitute $p = p_2$ in Eq. (48) and let $\Psi_2(s) = \pi(s) - \lambda\zeta(s, p_2) = 0$. According to hypotheses (H1) and (H2), Ψ_2 is strictly decreasing, $\Psi_2(0) = \pi(0) > 0$, and $\Psi_2(s_0) = -\lambda\zeta(s_0, p_2) < 0$. Thus, there exists a unique $s_2 \in (0, s_0)$ such that $\Psi_2(s_2) = 0$. It follows from Eqs. (52) and (55) that

$$w_2 = \alpha_1(s_2) > 0, \qquad y_2 = \alpha_2(s_2) > 0, \qquad u_2 = \alpha_3(s_2) > 0, \qquad p_2 = g_4^{-1}\left(\frac{\beta_6}{r}\right) > 0,$$

$$x_2 = g_5^{-1}\left(\frac{\beta_5}{q}\left(\zeta\frac{\chi(s_2, p_2)}{g_4(p_2)} - 1\right)\right).$$

Thus, $x_2 > 0$ when $\zeta\frac{\chi(s_2,p_2)}{g_4(p_2)} > 1$. Let us define the parameter R_1 as follows:

$$R_1 = \zeta\frac{\chi(s_2, p_2)}{g_4(p_2)}.$$

If $R_1 > 1$, then $x_2 = g_5^{-1}(\frac{\beta_5}{q}(R_1 - 1)) > 0$, and there exists a humoral-activated infection steady state $\Pi_2(s_2, w_2, y_2, u_2, p_2, x_2)$.

Clearly, from hypotheses (H2) and (H4), we have

$$R_1 = \zeta \frac{\chi(s_2,p_2)}{g_4(p_2)} \leq \zeta \lim_{p\to 0^+} \frac{\chi(s_2,p)}{g_4(p)} = \frac{\zeta}{g_4'(0)} \frac{\partial \chi(s_2,0)}{\partial p} < \frac{\zeta}{g_4'(0)} \frac{\partial \chi(s_0,0)}{\partial p} = R_0. \qquad \square$$

3.2 Global properties

Theorem 4 *If* $R_0 \leq 1$ *and hypotheses* (H1)–(H4) *hold true for system* (42)–(47), *then* Π_0 *is GAS.*

Proof Define

$$\begin{aligned} W_0 &= s - s_0 - \int_{s_0}^{s} \lim_{p\to 0^+} \frac{\chi(s_0,p)}{\chi(\eta,p)} \, d\eta + \kappa_1 w + \kappa_2 y + \kappa_3 u \\ &\quad + \kappa_1\lambda_1 \int_0^{h_1} \Theta_1(\tau) \int_0^{\tau} \chi\big(s(t-\theta),p(t-\theta)\big)\, d\theta \, d\tau \\ &\quad + \kappa_2\lambda_2 \int_0^{h_2} \Theta_2(\tau) \int_0^{\tau} \chi\big(s(t-\theta),p(t-\theta)\big)\, d\theta \, d\tau \\ &\quad + \kappa_3\lambda_3 \int_0^{h_3} \Theta_3(\tau) \int_0^{\tau} \chi\big(s(t-\theta),p(t-\theta)\big)\, d\theta \, d\tau \\ &\quad + \kappa_4 p + \kappa_5 x, \end{aligned} \tag{58}$$

where

$$\begin{aligned} &\lambda = \lambda_1\kappa_1 F_1 + \lambda_2\kappa_2 F_2 + \lambda_3\kappa_3 F_3, \qquad (a_1+\beta_2)\kappa_1 = a_1\kappa_2, \\ &\kappa_2 = N\kappa_4, \qquad \kappa_3 = M\kappa_4, \qquad q\kappa_4 = r\kappa_5. \end{aligned} \tag{59}$$

The solution of Eqs. (59) is given by

$$\kappa_1 = \frac{a_1 N\lambda}{\zeta\beta_5(a_1+\beta_2)}, \qquad \kappa_2 = \frac{N\lambda}{\zeta\beta_5}, \qquad \kappa_3 = \frac{M\lambda}{\zeta\beta_5}, \qquad \kappa_4 = \frac{\lambda}{\zeta\beta_5}, \qquad \kappa_5 = \frac{q\lambda}{r\zeta\beta_5}. \tag{60}$$

We evaluate $\frac{dW_0}{dt}$ along the solutions of (42)-(47) as follows:

$$\begin{aligned} \frac{dW_0}{dt} &= \left(1 - \lim_{p\to 0^+} \frac{\chi(s_0,p)}{\chi(s,p)}\right)\big(\pi(s) - \lambda\chi(s,p)\big) + \kappa_1\lambda_1 \int_0^{h_1} \Theta_1(\tau)\chi\big(s(t-\tau),p(t-\tau)\big)\, d\tau \\ &\quad - \kappa_1(a_1+\beta_2)g_1(w) + \kappa_2\lambda_2 \int_0^{h_2} \Theta_2(\tau)\chi\big(s(t-\tau),p(t-\tau)\big)\, d\tau + a_1\kappa_2 g_1(w) \\ &\quad - \kappa_2\beta_3 g_2(y) + \kappa_3\lambda_3 \int_0^{h_3} \Theta_3(\tau)\chi\big(s(t-\tau),p(t-\tau)\big)\, d\tau - \kappa_3\beta_4 g_3(u) \\ &\quad + \kappa_1\lambda_1 \int_0^{h_1} \Theta_1(\tau)\big(\chi(s,p) - \chi\big(s(t-\tau),p(t-\tau)\big)\big)\, d\tau \\ &\quad + \kappa_2\lambda_2 \int_0^{h_2} \Theta_2(\tau)\big(\chi(s,p) - \chi\big(s(t-\tau),p(t-\tau)\big)\big)\, d\tau \\ &\quad + \kappa_3\lambda_3 \int_0^{h_3} \Theta_3(\tau)\big(\chi(s,p) - \chi\big(s(t-\tau),p(t-\tau)\big)\big)\, d\tau \end{aligned}$$

$$
\begin{aligned}
&+\kappa_4\big(N\beta_3 g_2(y)+M\beta_4 g_3(u)-\beta_5 g_4(p)-q g_4(p)g_5(x)\big)\\
&+\kappa_5\big(r g_4(p)g_5(x)-\beta_6 g_5(x)\big).
\end{aligned}
\tag{61}
$$

Collecting terms of Eq. (61) and using $\pi(s_0)=0$, we obtain

$$
\begin{aligned}
\frac{dW_0}{dt} &= \big(\pi(s)-\pi(s_0)\big)\left(1-\lim_{p\to 0^+}\frac{\chi(s_0,p)}{\chi(s,p)}\right)\\
&\quad+\left(\frac{\lambda\chi(s,p)}{g_4(p)}\lim_{p\to 0^+}\frac{\chi(s_0,p)}{\chi(s,p)}-\kappa_4\beta_5\right)g_4(p)-\kappa_5\beta_6 g_5(x)\\
&\le \big(\pi(s)-\pi(s_0)\big)\left(1-\lim_{p\to 0^+}\frac{\chi(s_0,p)}{\chi(s,p)}\right)\\
&\quad+\left(\lim_{p\to 0^+}\frac{\lambda\chi(s,p)}{g_4(p)}\lim_{p\to 0^+}\frac{\chi(s_0,p)}{\chi(s,p)}-\kappa_4\beta_5\right)g_4(p)-\kappa_5\beta_6 g_5(x)\\
&= \big(\pi(s)-\pi(s_0)\big)\left(1-\frac{\partial\chi(s_0,0)/\partial p}{\partial\chi(s,0)/\partial p}\right)\\
&\quad+\kappa_4\beta_5\left(\frac{\lambda}{\kappa_4\beta_5 g_4'(0)}\frac{\partial\chi(s_0,0)}{\partial p}-1\right)g_4(p)-\kappa_5\beta_6 g_5(x)\\
&= \big(\pi(s)-\pi(s_0)\big)\left(1-\frac{\partial\chi(s_0,0)/\partial p}{\partial\chi(s,0)/\partial p}\right)+\kappa_4\beta_5(R_0-1)g_4(p)-\kappa_5\beta_6 g_5(x).
\end{aligned}
\tag{62}
$$

From hypotheses (H1) and (H2), we have

$$
\big(\pi(s)-\pi(s_0)\big)\left(1-\frac{\partial\chi(s_0,0)/\partial p}{\partial\chi(s,0)/\partial p}\right)\le 0.
$$

Therefore, if $R_0\le 1$, then $\frac{dW_0}{dt}\le 0$. Thus, Π_0 is GAS. □

Theorem 5 *If* $R_1\le 1<R_0$ *and hypotheses* (H1)–(H4) *are valid for* (42)–(47), *then* Π_1 *is GAS.*

Proof We introduce

$$
\begin{aligned}
W_1 &= s-s_1-\int_{s_1}^{s}\frac{\chi(s_1,p_1)}{\chi(\eta,p_1)}\,d\eta+\kappa_1\left(w-w_1-\int_{w_1}^{w}\frac{g_1(w_1)}{g_1(\eta)}\,d\eta\right)\\
&\quad+\kappa_2\left(y-y_1-\int_{y_1}^{y}\frac{g_2(y_1)}{g_2(\eta)}\,d\eta\right)+\kappa_3\left(u-u_1-\int_{u_1}^{u}\frac{g_3(u_1)}{g_3(\eta)}\,d\eta\right)\\
&\quad+\kappa_1\lambda_1\chi(s_1,p_1)\int_0^{h_1}\Theta_1(\tau)\int_0^{\tau}F\left(\frac{\chi(s(t-\theta),p(t-\theta))}{\chi(s_1,p_1)}\right)d\theta\,d\tau\\
&\quad+\kappa_2\lambda_2\chi(s_1,p_1)\int_0^{h_2}\Theta_2(\tau)\int_0^{\tau}F\left(\frac{\chi(s(t-\theta),p(t-\theta))}{\chi(s_1,p_1)}\right)d\theta\,d\tau\\
&\quad+\kappa_3\lambda_3\chi(s_1,p_1)\int_0^{h_3}\Theta_3(\tau)\int_0^{\tau}F\left(\frac{\chi(s(t-\theta),p(t-\theta))}{\chi(s_1,p_1)}\right)d\theta\,d\tau\\
&\quad+\kappa_4\left(p-p_1-\int_{p_1}^{p}\frac{g_4(p_1)}{g_4(\eta)}\,d\eta\right)+\kappa_5 x.
\end{aligned}
$$

Evaluating $\frac{dW_1}{dt}$ along the trajectories of (42)–(47), we have

$$\begin{aligned}
\frac{dW_1}{dt} &= \left(1-\frac{\chi(s_1,p_1)}{\chi(s,p_1)}\right)\big(\pi(s)-\lambda\chi(s,p)\big)\\
&\quad+\kappa_1\left(1-\frac{g_1(w_1)}{g_1(w)}\right)\left(\lambda_1\int_0^{h_1}\Theta_1(\tau)\chi\big(s(t-\tau),p(t-\tau)\big)\,d\tau-(a_1+\beta_2)g_1(w)\right)\\
&\quad+\kappa_2\left(1-\frac{g_2(y_1)}{g_2(y)}\right)\left(\lambda_2\int_0^{h_2}\Theta_2(\tau)\chi\big(s(t-\tau),p(t-\tau)\big)\,d\tau+a_1g_1(w)-\beta_3g_2(y)\right)\\
&\quad+\kappa_3\left(1-\frac{g_3(u_1)}{g_3(u)}\right)\left(\lambda_3\int_0^{h_3}\Theta_3(\tau)\chi\big(s(t-\tau),p(t-\tau)\big)\,d\tau-\beta_4g_3(u)\right)\\
&\quad+\kappa_1\lambda_1\int_0^{h_1}\Theta_1(\tau)\Bigg(\chi(s,p)-\chi\big(s(t-\tau),p(t-\tau)\big)+\chi(s_1,p_1)\\
&\quad\times\ln\left(\frac{\chi(s(t-\tau),p(t-\tau))}{\chi(s,p)}\right)\Bigg)\,d\tau\\
&\quad+\kappa_2\lambda_2\int_0^{h_2}\Theta_2(\tau)\Bigg(\chi(s,p)-\chi\big(s(t-\tau),p(t-\tau)\big)+\chi(s_1,p_1)\\
&\quad\times\ln\left(\frac{\chi(s(t-\tau),p(t-\tau))}{\chi(s,p)}\right)\Bigg)\,d\tau\\
&\quad+\kappa_3\lambda_3\int_0^{h_3}\Theta_3(\tau)\Bigg(\chi(s,p)-\chi\big(s(t-\tau),p(t-\tau)\big)+\chi(s_1,p_1)\\
&\quad\times\ln\left(\frac{\chi(s(t-\tau),p(t-\tau))}{\chi(s,p)}\right)\Bigg)\,d\tau\\
&\quad+\kappa_4\left(1-\frac{g_4(p_1)}{g_4(p)}\right)\big(N\beta_3g_2(y)+M\beta_4g_3(u)-\beta_5g_4(p)-qg_4(p)g_5(x)\big)\\
&\quad+\kappa_5\big(rg_4(p)g_5(x)-\beta_6g_5(x)\big). \qquad (63)
\end{aligned}$$

Collecting terms of Eq. (63) and applying the conditions of the steady state Π_1:

$$\begin{aligned}
&\pi(s_1)=\lambda\chi(s_1,p_1),\\
&(a_1+\beta_2)g_1(w_1)=\lambda_1F_1\chi(s_1,p_1),\qquad \kappa_2\beta_3g_2(y_1)=(\kappa_1\lambda_1F_1+\kappa_2\lambda_2F_2)\chi(s_1,p_1),\\
&\beta_4g_3(u_1)=\lambda_3F_3\chi(s_1,p_1),\qquad \kappa_4\beta_5g_4(p_1)=\lambda\chi(s_1,p_1),
\end{aligned}$$

we get

$$\begin{aligned}
\frac{dW_1}{dt} &= \big(\pi(s)-\pi(s_1)\big)\left(1-\frac{\chi(s_1,p_1)}{\chi(s,p_1)}\right)\\
&\quad+\lambda\chi(s_1,p_1)\left(1-\frac{\chi(s_1,p_1)}{\chi(s,p_1)}\right)+\lambda\chi(s_1,p_1)\left(\frac{\chi(s,p)}{\chi(s,p_1)}-\frac{g_4(p)}{g_4(p_1)}\right)\\
&\quad-\kappa_1\lambda_1\chi(s_1,p_1)\int_0^{h_1}\Theta_1(\tau)\frac{\chi(s(t-\tau),p(t-\tau))g_1(w_1)}{\chi(s_1,p_1)g_1(w)}\,d\tau+\kappa_1\lambda_1F_1\chi(s_1,p_1)\\
&\quad-\kappa_2\lambda_2\chi(s_1,p_1)\int_0^{h_2}\Theta_2(\tau)\frac{\chi(s(t-\tau),p(t-\tau))g_2(y_1)}{\chi(s_1,p_1)g_2(y)}\,d\tau
\end{aligned}$$

$$\begin{aligned}
&- \kappa_1\lambda_1 F_1 \chi(s_1,p_1)\frac{g_2(y_1)g_1(w)}{g_2(y)g_1(w_1)} + (\kappa_1\lambda_1 F_1 + \kappa_2\lambda_2 F_2)\chi(s_1,p_1) \\
&- \kappa_3\lambda_3\chi(s_1,p_1)\int_0^{h_3}\Theta_3(\tau)\frac{\chi(s(t-\tau),p(t-\tau)g_3(u_1))}{\chi(s_1,p_1)g_3(u)}\,d\tau + \kappa_3\lambda_3 F_3\chi(s_1,p_1) \\
&+ \kappa_1\lambda_1\chi(s_1,p_1)\int_0^{h_1}\Theta_1(\tau)\ln\left(\frac{\chi(s(t-\tau),p(t-\tau))}{\chi(s,p)}\right)d\tau \\
&+ \kappa_2\lambda_2\chi(s_1,p_1)\int_0^{h_2}\Theta_2(\tau)\ln\left(\frac{\chi(s(t-\tau),p(t-\tau))}{\chi(s,p)}\right)d\tau \\
&+ \kappa_3\lambda_3\chi(s_1,p_1)\int_0^{h_3}\Theta_3(\tau)\ln\left(\frac{\chi(s(t-\tau),p(t-\tau))}{\chi(s,p)}\right)d\tau \\
&- (\kappa_1\lambda_1 F_1 + \kappa_2\lambda_2 F_2)\chi(s_1,p_1)\frac{g_2(y)g_4(p_1)}{g_2(y_1)g_4(p)} - \kappa_3\lambda_3 F_3\chi(s_1,p_1)\frac{g_3(u)g_4(p_1)}{g_3(u_1)g_4(p)} \\
&+ \lambda\chi(s_1,p_1) + r\kappa_5\left(g_4(p_1) - \frac{\beta_6}{r}\right)g_5(x).
\end{aligned}$$

Using inequalities (30) with $\hat{s} = s_1$, $\hat{w} = w_1$, $\hat{y} = y_1$, $\hat{p} = p_1$, and $\tau_1 = \tau_2 = \tau_3 = \tau$, we can obtain

$$\begin{aligned}
\frac{dW_1}{dt} &= \big(\pi(s) - \pi(s_1)\big)\left(1 - \frac{\chi(s_1,p_1)}{\chi(s,p_1)}\right) \\
&+ \lambda\chi(s_1,p_1)\left(\frac{\chi(s,p)}{\chi(s,p_1)} - \frac{g_4(p)}{g_4(p_1)}\right)\left(1 - \frac{\chi(s,p_1)}{\chi(s,p)}\right) \\
&- \lambda\chi(s_1,p_1)\left[F\left(\frac{\chi(s_1,p_1)}{\chi(s,p_1)}\right) + F\left(\frac{g_4(p)\chi(s,p_1)}{g_4(p_1)\chi(s,p)}\right)\right] \\
&- \kappa_1\lambda_1\chi(s_1,p_1)\int_0^{h_1}\Theta_1(\tau)F\left(\frac{g_1(w_1)\chi(s(t-\tau),p(t-\tau))}{g_1(w)\chi(s_1,p_1)}\right)d\tau \\
&- \kappa_2\lambda_2\chi(s_1,p_1)\int_0^{h_2}\Theta_2(\tau)F\left(\frac{g_2(y_1)\chi(s(t-\tau),p(t-\tau))}{g_2(y)\chi(s_1,p_1)}\right)d\tau \\
&- \kappa_3\lambda_3\chi(s_1,p_1)\int_0^{h_3}\Theta_3(\tau)F\left(\frac{g_3(u_1)\chi(s(t-\tau),p(t-\tau))}{g_3(u)\chi(s_1,p_1)}\right) \\
&- \kappa_1\lambda_1 F_1\chi(s_1,p_1)F\left(\frac{g_2(y_1)g_1(w)}{g_2(y)g_1(w_1)}\right) \\
&- (\kappa_1\lambda_1 F_1 + \kappa_2\lambda_2 F_2)\chi(s_1,p_1)F\left(\frac{g_2(y)g_4(p_1)}{g_2(y_1)g_4(p)}\right) \\
&- \kappa_3\lambda_3 F_3\chi(s_1,p_1)F\left(\frac{g_3(u)g_4(p_1)}{g_3(u_1)g_4(p)}\right) + r\kappa_5\big(g_4(p_1) - g_4(p_2)\big)g_5(x).
\end{aligned}$$

Using hypotheses (H1), (H2), (H4), and Lemma 3, we get $\frac{dW_1}{dt} \le 0$, where the equality occurs at Π_1. By LIP, Π_1 is GAS. □

Theorem 6 *If* $R_1 > 1$ *and hypotheses* (H1)–(H4) *are valid for* (42)–(47), *then* Π_2 *is GAS.*

Proof Define

$$W_2 = s - s_2 - \int_{s_2}^{s}\frac{\chi(s_2,p_2)}{\chi(\eta,p_2)}\,d\eta + \kappa_1\left(w - w_2 - \int_{w_2}^{w}\frac{g_1(w_2)}{g_1(\eta)}\,d\eta\right)$$

$$
\begin{aligned}
&+\kappa_2\left(y-y_2-\int_{y_2}^{y}\frac{g_2(y_2)}{g_2(\eta)}\,d\eta\right)+\kappa_3\left(u-u_2-\int_{u_2}^{u}\frac{g_3(u_2)}{g_3(\eta)}\,d\eta\right)\\
&+\kappa_1\lambda_1\chi(s_2,p_2)\int_0^{h_1}\Theta_1(\tau)\int_0^{\tau}F\left(\frac{\chi(s(t-\theta),p(t-\theta))}{\chi(s_2,p_2)}\right)d\theta\,d\tau\\
&+\kappa_2\lambda_2\chi(s_2,p_2)\int_0^{h_2}\Theta_2(\tau)\int_0^{\tau}F\left(\frac{\chi(s(t-\theta),p(t-\theta))}{\chi(s_2,p_2)}\right)d\theta\,d\tau\\
&+\kappa_3\lambda_3\chi(s_2,p_2)\int_0^{h_3}\Theta_3(\tau)\int_0^{\tau}F\left(\frac{\chi(s(t-\theta),p(t-\theta))}{\chi(s_2,p_2)}\right)d\theta\,d\tau\\
&+\kappa_4\left(p-p_2-\int_{p_2}^{p}\frac{g_4(p_2)}{g_4(\eta)}\,d\eta\right)+\kappa_5\left(x-x_2-\int_{x_2}^{x}\frac{g_5(x_2)}{g_5(\eta)}\,d\eta\right).
\end{aligned}
$$

Calculating $\frac{dW_2}{dt}$ along the solutions of model (42)–(47), we get

$$
\begin{aligned}
\frac{dW_2}{dt}={}&\left(1-\frac{\chi(s_2,p_2)}{\chi(s,p_2)}\right)\bigl(\pi(s)-\lambda\chi(s,p)\bigr)\\
&+\kappa_1\left(1-\frac{g_1(w_2)}{g_1(w)}\right)\left(\lambda_1\int_0^{h_1}\Theta_1(\tau)\chi\bigl(s(t-\tau),p(t-\tau)\bigr)\,d\tau-(a_1+\beta_2)g_1(w)\right)\\
&+\kappa_2\left(1-\frac{g_2(y_2)}{g_2(y)}\right)\left(\lambda_2\int_0^{h_2}\Theta_2(\tau)\chi\bigl(s(t-\tau),p(t-\tau)\bigr)\,d\tau+a_1g_1(w)-\beta_3g_2(y)\right)\\
&+\kappa_3\left(1-\frac{g_3(u_2)}{g_3(u)}\right)\left(\lambda_3\int_0^{h_3}\Theta_3(\tau)\chi\bigl(s(t-\tau),p(t-\tau)\bigr)\,d\tau-\beta_4g_3(u)\right)\\
&+\kappa_1\lambda_1\int_0^{h_1}\Theta_1(\tau)\biggl(\chi(s,p)-\chi\bigl(s(t-\tau),p(t-\tau)\bigr)+\chi(s_2,p_2)\\
&\times\ln\left(\frac{\chi(s(t-\tau),p(t-\tau))}{\chi(s,p)}\right)\biggr)\,d\tau\\
&+\kappa_2\lambda_2\int_0^{h_2}\Theta_2(\tau)\biggl(\chi(s,p)-\chi\bigl(s(t-\tau),p(t-\tau)\bigr)+\chi(s_2,p_2)\\
&\times\ln\left(\frac{\chi(s(t-\tau),p(t-\tau))}{\chi(s,p)}\right)\biggr)\,d\tau\\
&+\kappa_3\lambda_3\int_0^{h_3}\Theta_3(\tau)\biggl(\chi(s,p)-\chi\bigl(s(t-\tau),p(t-\tau)\bigr)+\chi(s_2,p_2)\\
&\times\ln\left(\frac{\chi(s(t-\tau),p(t-\tau))}{\chi(s,p)}\right)\biggr)\,d\tau\\
&+\kappa_4\left(1-\frac{g_4(p_2)}{g_4(p)}\right)\bigl(N\beta_3g_2(y)+M\beta_4g_3(u)-\beta_5g_4(p)-qg_4(p)g_5(x)\bigr)\\
&+\kappa_5\left(1-\frac{g_5(x_2)}{g_5(x)}\right)\bigl(rg_4(p)g_5(x)-\beta_6g_5(x)\bigr).
\end{aligned}
\tag{64}
$$

Collecting terms of Eq. (64) and applying the steady state conditions for Π_2:

$$
\begin{aligned}
&\pi(s_2)=\lambda\chi(s_2,p_2),\\
&(a_1+\beta_2)g_1(w_2)=\lambda_1F_1\chi(s_2,p_2),\qquad \kappa_2\beta_3g_2(y_2)=(\kappa_1\lambda_1F_1+\kappa_2\lambda_2F_2)\chi(s_2,p_2),\\
&\beta_4g_3(u_2)=\lambda_3F_3\chi(s_2,p_2),\qquad \kappa_4\beta_5g_4(p_2)=\lambda\chi(s_2,p_2)-q\kappa_4g_4(p_2)g_5(x_2),
\end{aligned}
$$

$$\kappa_4\beta_5 g_4(p) = \lambda\chi(s_2,p_2)\frac{g_4(p)}{g_4(p_2)} - q\kappa_4 g_4(p)g_5(x_2)$$

we obtain

$$\begin{aligned}
\frac{dW_2}{dt} &= \bigl(\pi(s)-\pi(s_2)\bigr)\left(1-\frac{\chi(s_2,p_2)}{\chi(s,p_2)}\right) + \lambda\chi(s_2,p_2)\left(1-\frac{\chi(s_2,p_2)}{\chi(s,p_2)}\right)\\
&\quad + \lambda\chi(s_2,p_2)\left(\frac{\chi(s,p)}{\chi(s,p_2)} - \frac{g_4(p)}{g_4(p_2)}\right)\\
&\quad - \kappa_1\lambda_1\chi(s_2,p_2)\int_0^{h_1}\Theta_1(\tau)\frac{g_1(w_2)\chi(s(t-\tau),p(t-\tau))}{g_1(w)\chi(s_2,p_2)}\,d\tau\\
&\quad + \kappa_1\lambda_1F_1\chi(s_2,p_2) - \kappa_2\lambda_2\chi(s_2,p_2)\int_0^{h_2}\Theta_2(\tau)\frac{g_2(y_2)\chi(s(t-\tau),p(t-\tau))}{g_2(y)\chi(s_2,p_2)}\,d\tau\\
&\quad - \kappa_1\lambda_1F_1\chi(s_2,p_2)\frac{g_2(y_2)g_1(w)}{g_2(y)g_1(w_2)} + (\kappa_1\lambda_1F_1+\kappa_2\lambda_2F_2)\chi(s_2,p_2)\\
&\quad - \kappa_3\lambda_3\chi(s_2,p_2)\int_0^{h_3}\Theta_3(\tau)\frac{g_3(u_2)\chi(s(t-\tau),p(t-\tau))}{g_3(u)\chi(s_2,p_2)}\,d\tau + \kappa_3\lambda_3F_3\chi(s_2,p_2)\\
&\quad + \kappa_1\lambda_1\chi(s_2,p_2)\int_0^{h_1}\Theta_1(\tau)\ln\left(\frac{\chi(s(t-\tau),p(t-\tau))}{\chi(s,p)}\right)d\tau\\
&\quad + \kappa_2\lambda_2\chi(s_2,p_2)\int_0^{h_2}\Theta_2(\tau)\ln\left(\frac{\chi(s(t-\tau),p(t-\tau))}{\chi(s,p)}\right)d\tau\\
&\quad + \kappa_3\lambda_3\chi(s_2,p_2)\int_0^{h_3}\Theta_3(\tau)\ln\left(\frac{\chi(s(t-\tau),p(t-\tau))}{\chi(s,p)}\right)d\tau\\
&\quad - (\kappa_1\lambda_1F_1+\kappa_2\lambda_2F_2)\chi(s_2,p_2)\frac{g_2(y)g_4(p_2)}{g_2(y_2)g_4(p)}\\
&\quad - \kappa_3\lambda_3F_3\chi(s_2,p_2)\frac{g_3(u)g_4(p_2)}{g_3(u_2)g_4(p)} + \lambda\chi(s_2,p_2).
\end{aligned} \tag{65}$$

Using inequalities (30) with $\hat{s} = s_2$, $\hat{w} = w_2$, $\hat{y} = y_2$, $\hat{p} = p_2$, and $\tau_1 = \tau_2 = \tau_3 = \tau$, we can obtain

$$\begin{aligned}
\frac{dW_2}{dt} &= \bigl(\pi(s)-\pi(s_2)\bigr)\left(1-\frac{\chi(s_2,p_2)}{\chi(s,p_2)}\right)\\
&\quad + \lambda\chi(s_2,p_2)\left(\frac{\chi(s,p)}{\chi(s,p_2)} - \frac{g_4(p)}{g_4(p_2)}\right)\left(1-\frac{\chi(s,p_2)}{\chi(s,p)}\right)\\
&\quad - \lambda\chi(s_2,p_2)\left[F\left(\frac{\chi(s_2,p_2)}{\chi(s,p_2)}\right) + F\left(\frac{g_4(p)\chi(s,p_2)}{g_4(p_2)\chi(s,p)}\right)\right]\\
&\quad - \kappa_1\lambda_1\chi(s_2,p_2)\int_0^{h_1}\Theta_1(\tau)F\left(\frac{g_1(w_2)\chi(s(t-\tau),p(t-\tau))}{g_1(w)\chi(s_2,p_2)}\right)d\tau\\
&\quad - \kappa_2\lambda_2\chi(s_2,p_2)\int_0^{h_2}\Theta_2(\tau)F\left(\frac{g_2(y_2)\chi(s(t-\tau),p(t-\tau))}{g_2(y)\chi(s_2,p_2)}\right)d\tau\\
&\quad - \kappa_3\lambda_3\chi(s_2,p_2)\int_0^{h_3}\Theta_3(\tau)F\left(\frac{g_3(u_2)\chi(s(t-\tau),p(t-\tau))}{g_3(u)\chi(s_2,p_2)}\right)d\tau\\
&\quad - \kappa_1\lambda_1F_1\chi(s_2,p_2)F\left(\frac{g_2(y_2)g_1(w)}{g_2(y)g_1(w_2)}\right)
\end{aligned}$$

$$
\begin{aligned}
&- (\kappa_1\lambda_1 F_1 + \kappa_2\lambda_2 F_2)\chi(s_2,p_2)F\left(\frac{g_2(y)g_4(p_2)}{g_2(y_2)g_4(p)}\right) \\
&- \kappa_3\lambda_3 F_3\chi(s_2,p_2)F\left(\frac{g_3(u)g_4(p_2)}{g_3(u_2)g_4(p)}\right).
\end{aligned}
$$

According to hypotheses (H1), (H2), and (H4), we get $\frac{dW_2}{dt} \leq 0$. Applying LIP, one can show that Π_2 is GAS. □

4 Numerical simulations

We now perform some computer simulations on the following application:

$$\dot{s}(t) = \rho - \beta_1 s(t) + \omega s(t)\left(1 - \frac{s(t)}{s_{\max}}\right) - \frac{(1-\varepsilon_1)\overline{\lambda} s(t)p(t)}{1+\eta p(t)}, \tag{66}$$

$$\dot{w}(t) = \frac{(1-\varepsilon_1)\overline{\lambda}_1 e^{-\mu_1\tau_1} s(t-\tau_1)p(t-\tau_1)}{1+\eta p(t-\tau_1)} - (a_1+\beta_2)w(t), \tag{67}$$

$$\dot{y}(t) = \frac{(1-\varepsilon_1)\overline{\lambda}_2 e^{-\mu_2\tau_2} s(t-\tau_2)p(t-\tau_2)}{1+\eta p(t-\tau_2)} + a_1 w(t) - \beta_3 y(t), \tag{68}$$

$$\dot{u}(t) = \frac{(1-\varepsilon_1)\overline{\lambda}_3 e^{-\mu_3\tau_3} s(t-\tau_3)p(t-\tau_3)}{1+\eta p(t-\tau_3)} - \beta_4 u(t), \tag{69}$$

$$\dot{p}(t) = (1-\varepsilon_2)\overline{N}\beta_3 y(t) + (1-\varepsilon_2)\overline{M}\beta_4 u(t) - \beta_5 p(t) - q p(t)x(t), \tag{70}$$

$$\dot{x}(t) = r p(t)x(t) - \beta_6 x(t). \tag{71}$$

We assume that $\omega < \beta_1$. In this application, we consider the following specific forms of the general functions:

$$
\begin{aligned}
&\pi\bigl(s(t)\bigr) = \rho - \beta_1 s(t) + \omega s(t)\left(1 - \frac{s(t)}{s_{\max}}\right), \qquad \chi\bigl(s(t),p(t)\bigr) = \frac{s(t)p(t)}{1+\eta p(t)}, \\
&g_i(\theta) = \theta, \quad i = 1,\ldots,5.
\end{aligned}
$$

First we verify hypotheses (H1)–(H4) for the chosen forms, then we solve the system using MATLAB. Clearly, $\pi(0) = \rho > 0$ and $\pi(s_0) = 0$, where

$$s_0 = \frac{s_{\max}}{2\omega}\left(\omega - \beta_1 + \sqrt{(\omega-\beta_1)^2 + \frac{4\rho\omega}{s_{\max}}}\right).$$

We have

$$\pi'(s) = -\beta_1 + \omega - \frac{2\omega s}{s_{\max}} < 0. \tag{72}$$

Clearly, $\pi(s) > 0$ for $s \in [0, s_0)$ and

$$\pi(s) = \rho - (\beta_1 - \omega)s - \omega\frac{s^2}{s_{\max}} \leq \rho - (\beta_1 - \omega)s.$$

Then hypothesis (H1) is satisfied. We also have $\chi(s,p) > 0$, $\chi(0,p) = \chi(s,0) = 0$ for $s,p \in (0,\infty)$, and

$$\frac{\partial \chi(s,p)}{\partial s} = \frac{p}{1+\eta p}, \qquad \frac{\partial \chi(s,p)}{\partial p} = \frac{s}{(1+\eta p)^2}, \qquad \frac{\partial \chi(s,0)}{\partial p} = s.$$

Then $\frac{\partial \chi(s,p)}{\partial s} > 0$, $\frac{\partial \chi(s,p)}{\partial p} > 0$, and $\frac{\partial \chi(s,0)}{\partial p} > 0$ for $s,p \in (0,\infty)$. Therefore, hypothesis (H1) is satisfied. In addition,

$$\chi(s,p) = \frac{sp}{1+\eta p} \le sp = p\frac{\partial \chi(s,0)}{\partial p},$$
$$\left(\frac{\partial \chi(s,0)}{\partial p}\right)' = 1 > 0 \quad \text{for all } s > 0.$$

It follows that (H2) is satisfied. Clearly, hypothesis (H3) holds true. Moreover,

$$\frac{\partial}{\partial p}\left(\frac{\chi(s,p)}{g_4(p)}\right) = \frac{-\eta s}{(1+\eta p)^2} < 0.$$

Therefore, hypothesis (H4) holds true and Theorems 1–3 are applicable. The parameters R_0 and R_1 for this application are given by

$$R_0 = \frac{(1-\varepsilon_1)(1-\varepsilon_2)\{\overline{N}(a_1\overline{\lambda}_1 e^{-\mu_1\tau_1} + (a_1+\beta_2)\overline{\lambda}_2 e^{-\mu_2\tau_2}) + \overline{M\lambda}_3 e^{-\mu_3\tau_3}(a_1+\beta_2)\}}{\beta_5(a_1+\beta_2)} s_0,$$
$$R_1 = \frac{(1-\varepsilon_1)(1-\varepsilon_2)\{\overline{N}(a_1\overline{\lambda}_1 e^{-\mu_1\tau_1} + (a_1+\beta_2)\overline{\lambda}_2 e^{-\mu_2\tau_2}) + \overline{M\lambda}_3 e^{-\mu_3\tau_3}(a_1+\beta_2)\}}{\beta_5(a_1+\beta_2)} \frac{s_2}{1+\eta p_2}.$$

Remark There are several forms of the general function $\chi(s,p)$ where (H1)–(H4) can be satisfied such as:

(i) Holling-type incidence $\chi(s,p) = \frac{sp}{1+\eta_1 s}$,
(ii) Beddington–DeAngelis incidence $\chi(s,p) = \frac{sp}{1+\eta_1 s+\eta_2 p}$,
(iii) Crowley–Martin incidence $\chi(s,p) = \frac{sp}{(1+\eta_1 s)(1+\eta_2 p)}$,
(iv) Hill-type incidence $\chi(s,p) = \frac{s^m p}{\eta^m + s^m}$.

Now we are ready to perform some numerical simulations for system (66)–(71). The data of system (66)–(71) are provided in Table 1. We let $\tau_1 = \tau_2 = \tau_3 = \tau$.

•*Effect of the parameters λ_i and r on the stability of the steady states*

To discuss our global results, we choose three different initial conditions:

IC1: $(s(0), w(0), y(0), u(0), p(0), x(0)) = (900, 5, 5, 15, 3, 3)$.

Table 1 The data of example (66)–(71)

Parameter	Value	Parameter	Value	Parameter	Value	Parameter	Value
ρ	10	β_2	0.02	μ_1	1	$\overline{N}$	6
β_1	0.01	β_3	0.36	μ_2	1	$\overline{M}$	3
ω	0.0001	β_4	0.031	μ_3	1	$\varepsilon_1, \varepsilon_2, \tau$	Varied
s_{max}	1200	β_5	3.0	η	0.01	$\lambda_i, i = 1,2,3$	Varied
q	0.5	β_6	0.1	a_1	0.2	r	Varied

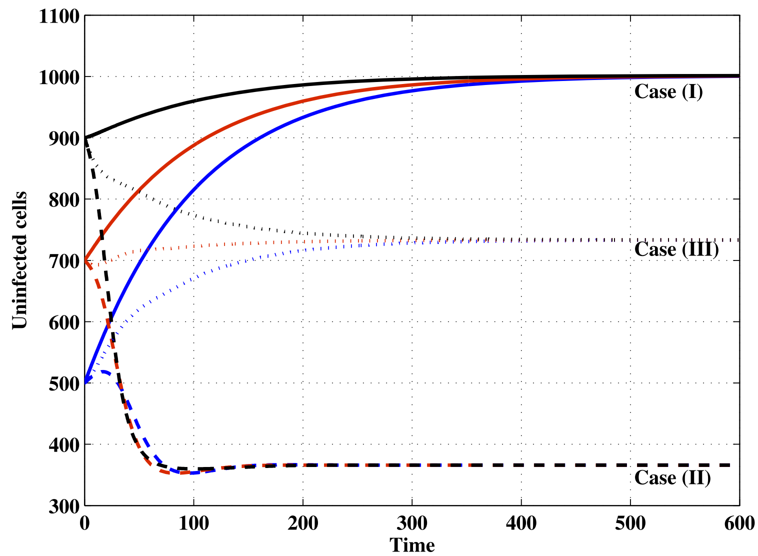

Figure 1 The concentration of uninfected CD4$^+$ T cells for system (66)–(71)

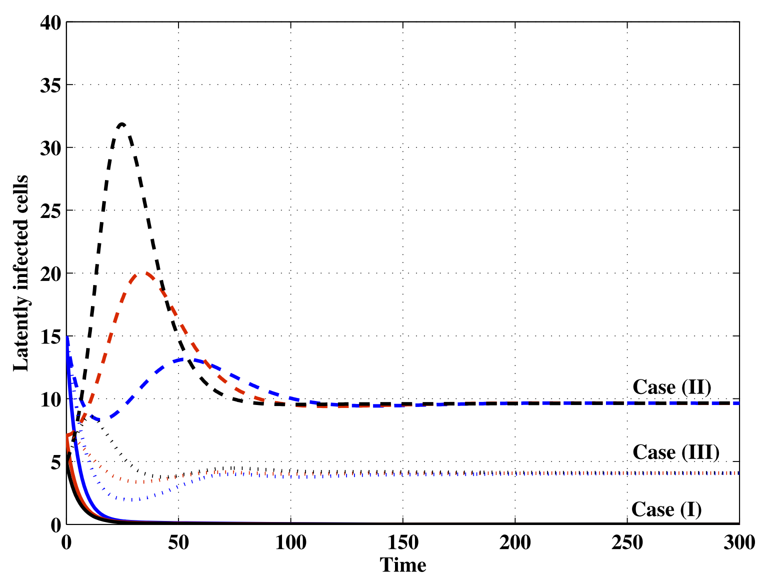

Figure 2 The concentration of latently infected cells for system (66)–(71)

IC2: $(s(0), w(0), y(0), u(0), p(0), x(0)) = (700, 7, 8, 30, 5, 5)$.

IC3: $(s(0), w(0), y(0), u(0), p(0), x(0)) = (500, 15, 18, 60, 12, 7)$.

Let us address three cases for the parameters λ_i, $i = 1, 2, 3$, and r. We assume that $\varepsilon_1 = \varepsilon_2 = 0$ (there is no treatment) and $\tau_i = 0$ (there is no time delay).

Case (I): Choose $\lambda_i = 0.0000625$ and $r = 0.005$, which gives $R_0 = 0.3016 < 1$ and $R_1 = 0.1917 < 1$. Therefore, based on Lemma 2 and Theorem 1, the system has unique steady state, that is, Π_0, and it is GAS. As we can see from Figs. 1–6, the concentration of the uninfected CD4$^+$ T cells is increased and approaches its normal value before infection,

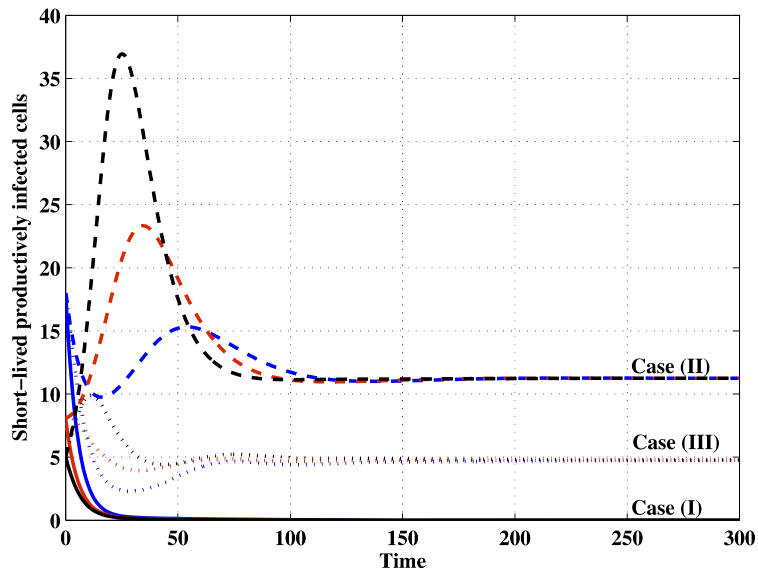

Figure 3 The concentration of short-lived productively infected cells for system (66)–(71)

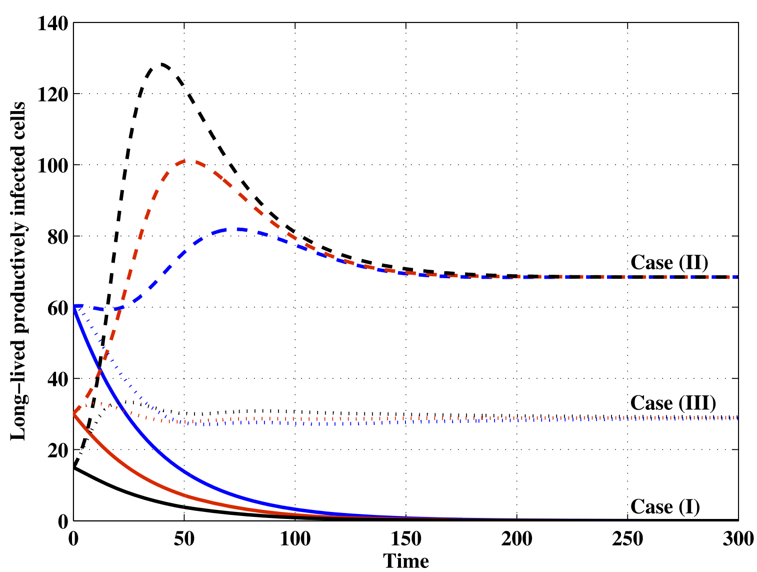

Figure 4 The concentration of long-lived productively infected cells for system (66)–(71)

that is, $s_0 = 1001.98$; while concentrations of the other compartments converge to zero for all the three initial conditions. As a result, the HIV-1 is removed from the plasma.

Case (II): By taking $\lambda_i = 0.000625$ and $r = 0.005$. For these values, $R_1 = 0.6095 < 1 < R_0 = 3.0163$. Consequently, based on Lemma 2 and Theorem 2, the humoral-inactivated infection steady state Π_1 is positive and is GAS. Figures 1–6 confirm that the numerical results support the theoretical results presented in Theorem 2. It can be observed that the variables of the model eventually converge to $\Pi_1 = (366.317, 9.72758, 11.3488, 69.0344,$

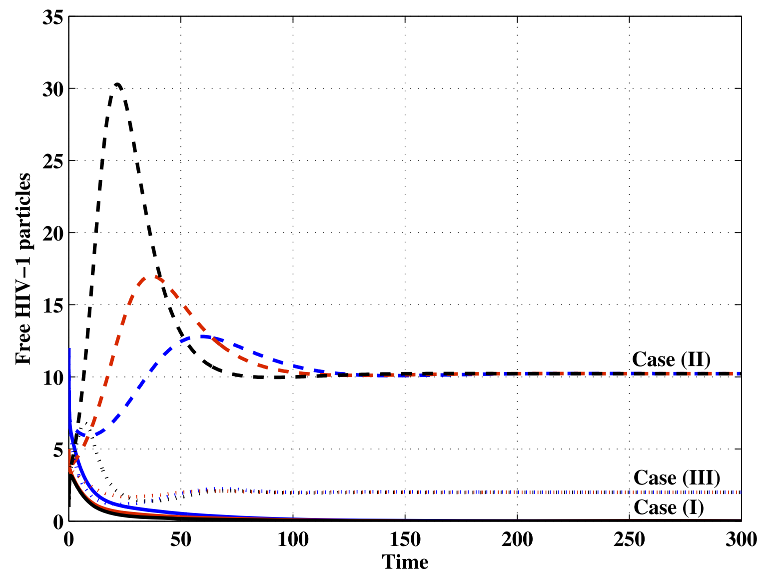

Figure 5 The concentration of free virus particles for system (66)–(71)

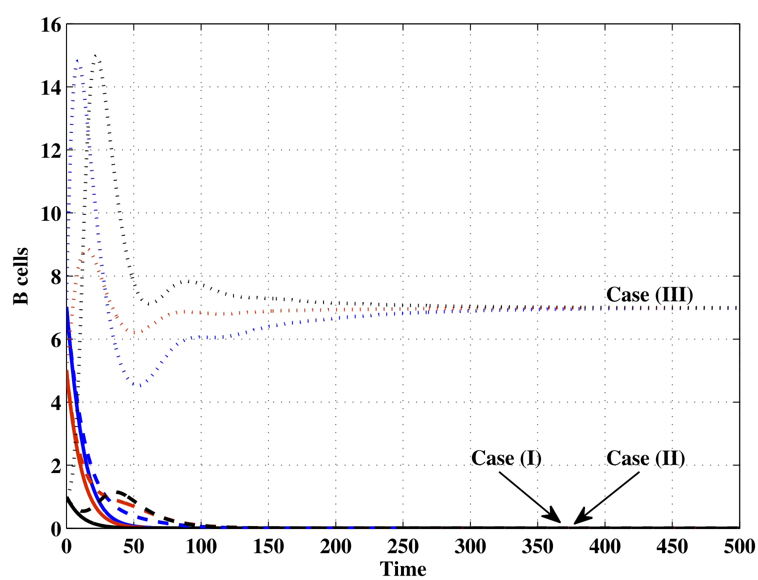

Figure 6 The concentration of B cells for system (66)–(71)

10.3112, 0.0) for all the three initial conditions. This case corresponds to a chronic HIV-1 infection in the absence of immune response.

Case (III): $\lambda_i = 0.000625$ and $r = 0.05$. Then we calculate $R_0 = 3.0163 > 1$ and $R_1 = 2.1648 > 1$. According to Lemma 2 and Theorem 3, the humoral-activated infection steady state Π_2 is positive and is GAS. We can see from Figs. 1–6 that there is a consistency between the numerical results and theoretical results of Theorem 3. The states of the system converge to $\Pi_2 = (734.586, 4.09194, 4.77393, 29.0396, 2.0, 7.01238)$ for all the three initial

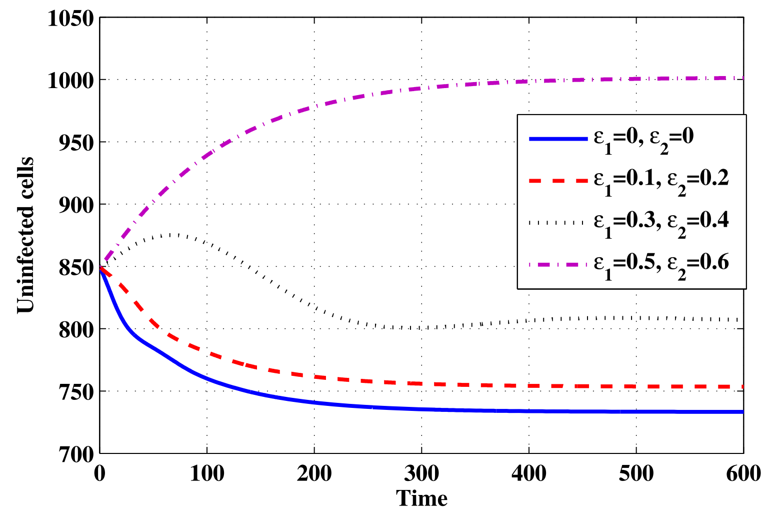

Figure 7 The concentration of uninfected CD4^{+} T cells for system (66)–(71)

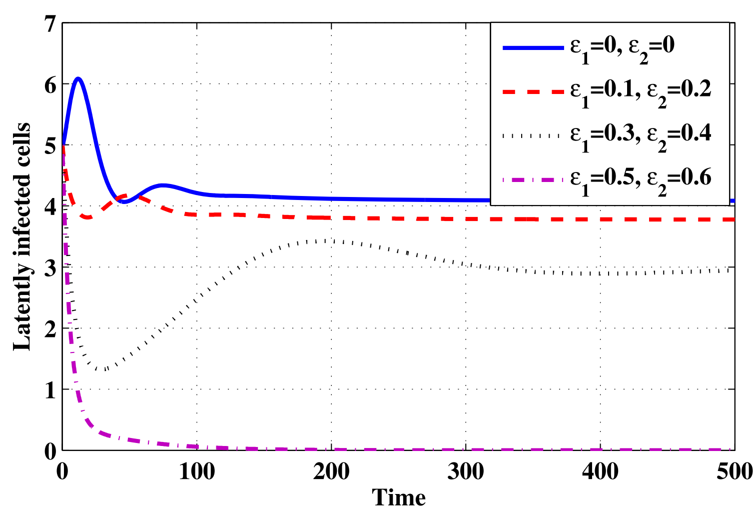

Figure 8 The concentration of latently infected cells for system (66)–(71)

conditions. In this case the humoral immune response is activated and can control the disease.

•*Effect of the HAART on the HIV dynamics*

We take $\tau_i = 0$, $\lambda_i = 0.000625$, and $r = 0.05$. We choose the initial conditions $(s(0), w(0), y(0), u(0), p(0), x(0)) = (850, 5, 6, 17, 1.5, 5)$. In Figs. 7–12 we show the effect of the drug efficacy parameters ε_1 and ε_2 on the HIV dynamics. Also, we can observe that, as the drug efficacy parameters ε_1 and ε_2 are increased, the concentration of uninfected cells is increased, while the concentrations of free virus particles and the three types of infected cells are decreased. Table 2 shows that the values of R_0 and R_1 are decreased as ε_1 and ε_2 are increased.

Let us define the overall HAART effect as $\varepsilon_e = \varepsilon_1 + \varepsilon_2 - \varepsilon_1\varepsilon_2$ [13]. If $\varepsilon_e = 0$, then the HAART has no effect, if $\varepsilon_e = 1$, the HIV growth is completely halted. Consequently, the

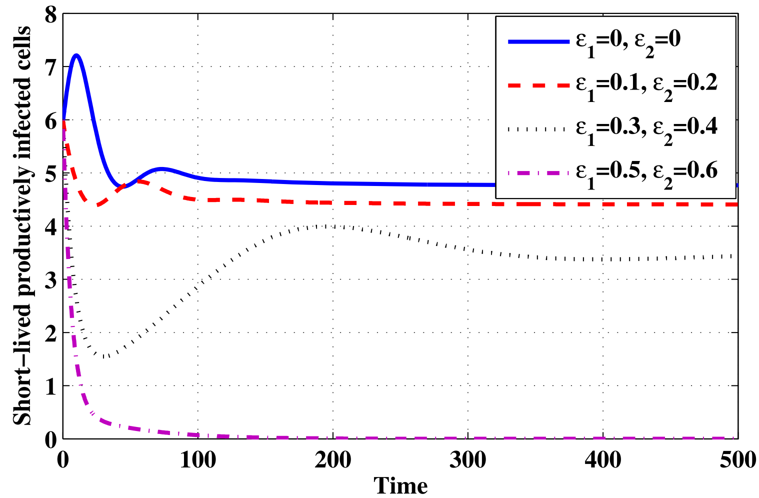

Figure 9 The concentration of short-lived productively infected cells for system (66)–(71)

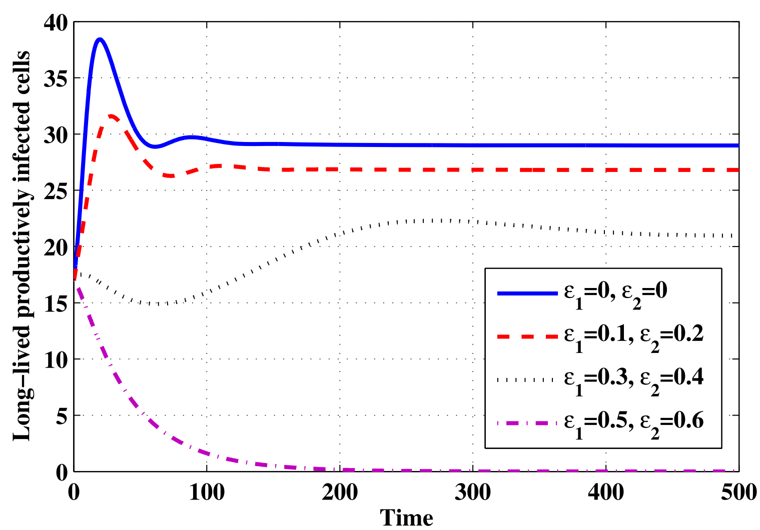

Figure 10 The concentration of long-lived productively infected cells for system (66)–(71)

parameter R_0 is given by

$$R_0(\varepsilon_e) = \frac{(1-\varepsilon_e)\{\overline{N}(a_1\overline{\lambda}_1 e^{-\mu_1\tau_1} + (a_1+\beta_2)\overline{\lambda}_2 e^{-\mu_2\tau_2}) + \overline{M\lambda}_3 e^{-\mu_3\tau_3}(a_1+\beta_2)\}}{\beta_5(a_1+\beta_2)} s_0.$$

Since the goal is to clear the viruses from the body, we have to determine the drug efficacy that makes $R_0(\varepsilon_e) \le 1$ for system (66)–(71). In this case, we get the critical drug efficacy (i.e., the efficacy needed in order to stabilize the system around the uninfected steady state). For the model (66)–(71), Π_0 is GAS when $R_0(\varepsilon_e) \le 1$, i.e.,

$$\varepsilon_e^{\text{crit}} \le \varepsilon_e < 1, \qquad \varepsilon_e^{\text{crit}} = \max\left\{0, \frac{R_0(0)-1}{R_0(0)}\right\}.$$

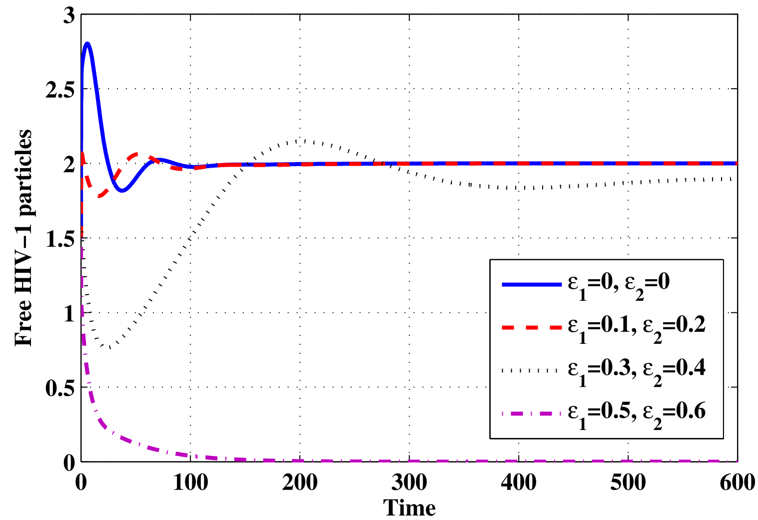

Figure 11 The concentration of free virus particles for system (66)–(71)

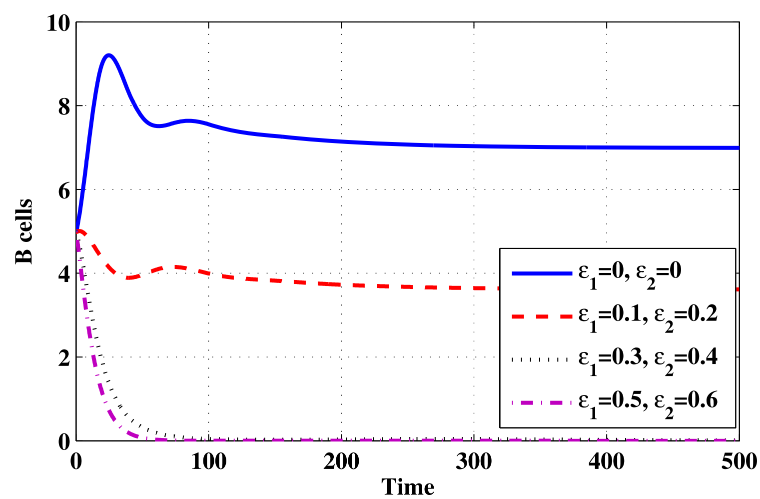

Figure 12 The concentration of B cells for system (66)–(71)

Table 2 The values of steady states R_0 and R_1 for model (66)–(71) with different values of ε_1 and ε_2

Drug	Steady states	R_0	R_1
$\varepsilon_1 = 0, \varepsilon_2 = 0$	$\Pi_2 = (734.586, 4.09194, 4.77393, 29.0396, 2.0, 7.01238)$	3.01635	2.16484
$\varepsilon_1 = 0.1, \varepsilon_2 = 0.2$	$\Pi_2 = (734.586, 3.68275, 4.29654, 26.1356, 2.0, 3.36892)$	2.17177	1.55868
$\varepsilon_1 = 0.3, \varepsilon_2 = 0.4$	$\Pi_1 = (801.457, 2.14802, 2.50603, 15.244, 1.36614, 0)$	1.26687	0.909233
$\varepsilon_1 = 0.5, \varepsilon_2 = 0.6$	$\Pi_0 = (1001.98, 0, 0, 0, 0, 0)$	0.60327	0.432968

Using the data in Table 1, we have $\varepsilon_e^{\text{crit}} = 0.668473$.

•*Effect of the time delay on the stability of the system*

Choosing $\varepsilon_1 = \varepsilon_2 = 0$, $\lambda_i = 0.000625$, and $r = 0.05$. The initial conditions are considered to be $(s(0), w(0), y(0), u(0), p(0), x(0)) = (850, 2, 3, 17, 1, 5)$. Figures 13–18 and Table 3 show

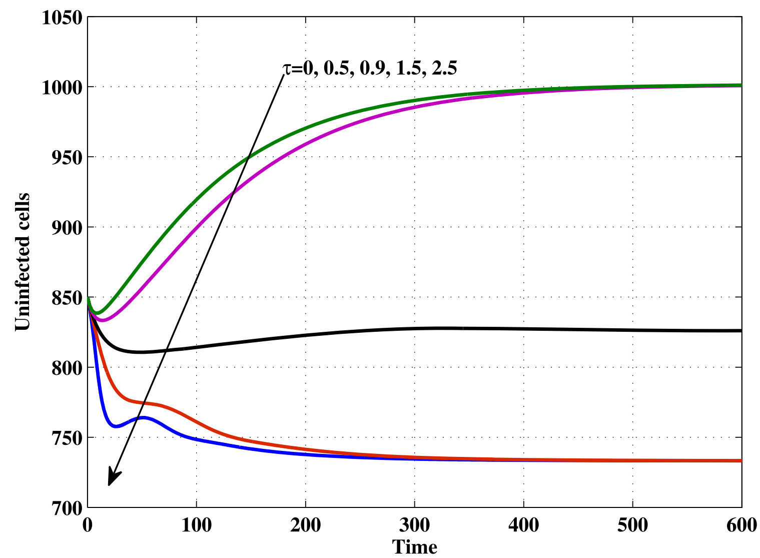

Figure 13 The concentration of uninfected CD4$^+$ T cells for system (66)–(71)

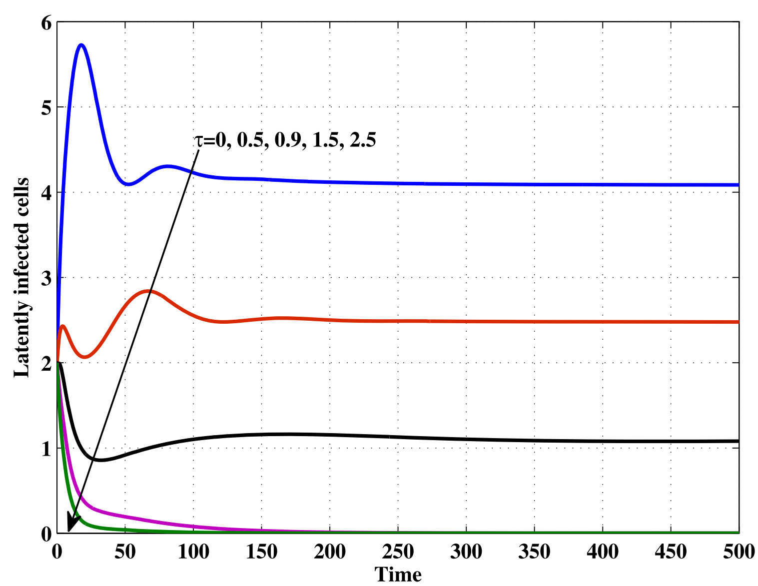

Figure 14 The concentration of latently infected cells for system (66)–(71)

the effect of the time delay parameter τ on the stability of Π_0, Π_1, and Π_2. Clearly, the parameter τ has similar effect as the drug efficacy parameters ε_1 and ε_2.

5 Conclusion

In this paper, we have proposed and analyzed two general nonlinear HIV infection models with humoral immune response. We have considered three types of infected cells: latently infected cells, long-lived productively infected cells, and short-lived productively infected cells. We have incorporated three discrete or distributed time delays into the models. We have considered more general nonlinear functions for the HIV-target incidence rate, pro-

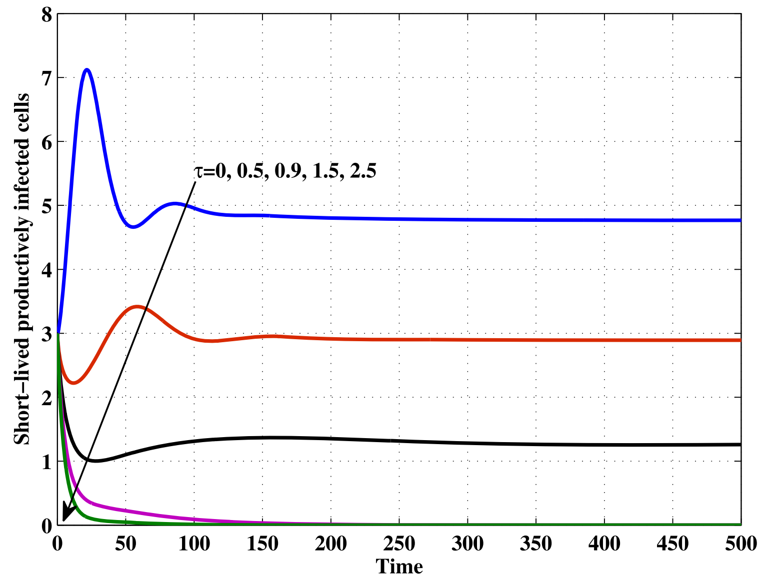

Figure 15 The concentration of short-lived productively infected cells for system (66)–(71)

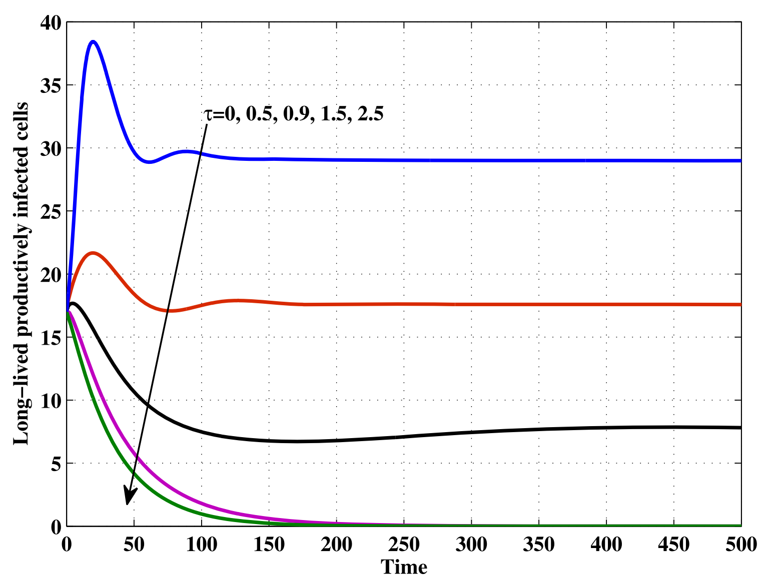

Figure 16 The concentration of long-lived productively infected cells for system (66)–(71)

duction/proliferation, and removal rates of the cells and HIV. We have derived a set of conditions on these general functions and have determined two threshold parameters: the basic reproduction number R_0 and the humoral immune response activation number R_1. We have proved the nonnegativity and ultimate boundedness of the model's solutions and the existence and stability of the model's steady states. Using Lyapunov functionals, we have established the global stability of the three steady states of the models. We have presented an example and performed some numerical simulations to support our theoretical results.

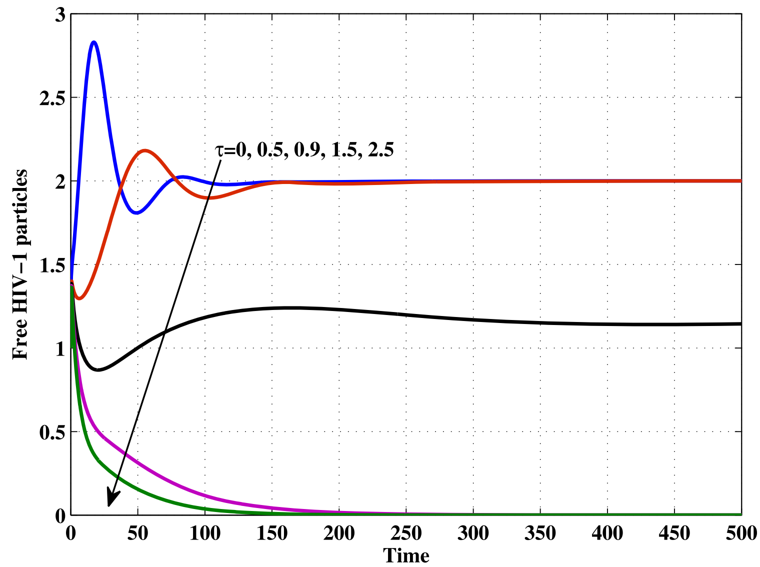

Figure 17 The concentration of free virus particles for system (66)–(71)

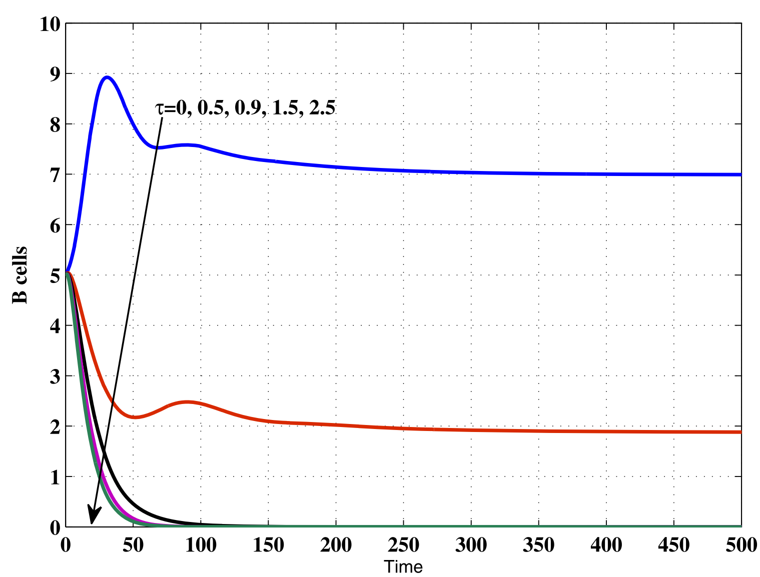

Figure 18 The concentration of B cells for system (66)–(71)

Table 3 The values of steady states R_0 and R_1 for model (66)–(71) with different values of τ

Drug	Steady states	R_0	R_1
$\tau = 0$	$\Pi_2 = (734.586, 4.09194, 4.77393, 29.0396, 2.0, 7.01238)$	3.01635	2.16484
$\tau = 0.5$	$\Pi_2 = (734.586, 2.48189, 2.89554, 17.6134, 2.0, 1.89241)$	1.82951	1.31304
$\tau = 0.9$	$\Pi_1 = (826.24, 1.09341, 1.27564, 7.75968, 1.15901, 0)$	1.22636	0.880158
$\tau = 1.5$	$\Pi_0 = (1001.98, 0, 0, 0, 0, 0)$	0.673038	0.483041
$\tau = 2.5$	$\Pi_0 = (1001.98, 0, 0, 0, 0, 0)$	0.247597	0.177701

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Competing interests
The authors declare that they have no competing interests.

Authors' contributions
All authors contributed equally to the writing of this paper. All authors read and approved the final manuscript.

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