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Stability of a general CTL-mediated immunity HIV infection model with silent infected cell-to-cell spread

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Abstract

This paper proposes and analyzes a CTL-mediated HIV infection model. The model describes the interaction between healthy $CD4^+T$ cells, silent infected cells, active infected cells, free HIV particles, and cytotoxic T lymphocytes (CTLs). The healthy $CD4^+T$ cells can be infected when contacted by one of the following: (i) free HIV particles, (ii) silent infected cells, and (iii) active infected cells. The incidence rates of the healthy $CD4^+T$ cells with free HIV particles, silent infected cells, and active infected cells are given by general functions. Moreover, the production/proliferation and removal/death rates of all compartments are represented by general functions. The model is an improvement of the existing HIV infection models which have neglected the incidence between the silent infected cells and healthy $CD4^+T$ cells. We first show that the model is well posed. The proposed model has three equilibria and their existence is governed by derived two threshold parameters: the basic HIV reproduction number $\Re_0$ and the HIV-specific CTL-mediated immunity reproduction number $\Re_1$. Under a set of conditions on the general functions and the parameters $\Re_0$ and $\Re_1$, we have proven the global asymptotic stability of all equilibria by using Lyapunov method. We have illustrated the theoretical results via numerical simulations. We have studied the effect of cell-to-cell (CTC) transmission on the dynamical behavior of the system. We have shown that inclusion of CTC transmission decreases the concentration of healthy $CD4^+T$ cells and increases the concentrations of infected cells and free HIV particles.

Keywords: HIV infection; Cell-to-cell spread; Global stability; Silent infected cells; CTL-mediated immune response; Lyapunov function

1 Introduction

Acquired immunodeficiency syndrome (AIDS) is one of the fatal human diseases which is caused by human immunodeficiency virus (HIV). HIV infects the healthy (uninfected) $CD4^+T$ cells which play a crucial role in the immune system. HIV-specific cytotoxic T lymphocytes (CTLs) kill the HIV-infected cells. On the other side, B cells generate specific antibodies which in turn neutralize the viruses. Therefore, the HIV infection can be controlled for long period up to 10 years [1]. However, during this period of time the concentration of healthy $CD4^+T$ cells declines. When the concentration of the $CD4^+T$ cells

reaches below 200 cells/mm^3, the patient is said to have progressed to AIDS. During the last decades, mathematical modeling of a within-host HIV infection has witnessed a significant development. Moreover, mathematical analysis of the HIV dynamics models has also become one of the most important and fundamental approaches for understanding the within-host HIV dynamics [2–11]. Nowak and Bangham [2] introduced an HIV infection model which describes the interaction between healthy CD4$^+$T cells (S), active HIV-infected cells (I), free HIV particles (V), and HIV-specific CTLs (C):

$$\begin{cases} \dot{S} = \rho - \alpha S - \eta SV, \\ \dot{I} = \eta SV - aI - \mu CI, \\ \dot{V} = bI - \varepsilon V, \\ \dot{C} = \sigma CI - \pi C. \end{cases} \tag{1}$$

The healthy CD4$^+$T cells are generated at specific constant rate ρ and die at rate αS. The term ηSV refers to the rate at which new infectious appears by virus-cell contact between free HIV particles and healthy CD4$^+$T cells. The active HIV-infected cells die at rate aI. The term μCI is the killing rate of active HIV-infected cells due to their HIV-specific CTL-mediated immunity. The free HIV particles are generated at rate bI and cleared from the plasma at rate εV. The proliferation rate of the effective HIV-specific CTLs is given by σCI. The term πC represents the decay rate of the CTLs. HIV infection models with CTL-mediated immune response have been investigated in many papers (see e.g. [2, 12–16]).

Model (1) has been formulated based on the assumption that HIV can only spread by virus-to-cell (VTC) transmission. However, several works have reported that there is another mode of transmission called cell-to-cell (CTC) where HIV can be transmitted directly from an infected cell to a healthy CD4$^+$T cell through the formation of virological synapses (see e.g. [17–20]). Sourisseau et al. [21] showed that CTC transmission plays an efficient role in the HIV replication. Sigal et al. [22] demonstrated the importance of CTC transmission in the HIV infection process during the antiviral treatment. Iwami et al. [19] showed that more than 50% of HIV infections are due to CTC transmission. The effects of both VTC and CTC transmissions on the virus dynamics have been addressed in several works (see e.g. [23–29]. Moreover, virus dynamics models with CTL-mediated immunity and both VTC and CTC transmissions have been investigated in [30, 31].

It is known that current anti-retroviral drugs can suppress HIV replication to a low level but cannot enucleate HIV from the body. One of the main reasons of this fact is the presence of silent (latent) CD4$^+$T infected cells where the HIV provirus can reside [32, 33]. Silent HIV-infected cells live long, but they can be activated to produce new HIV particles [34]. Silent HIV-infected cells have been included in the virus dynamics models with both VTC and CTC transmissions in [35–39]. In a recent interesting discovery [40], it has been shown that both silent and active infected cells can infect the healthy CD4$^+$T cells through CTC mechanism. In the literature, the viral infection models with CTC transmission and silent infected cells have assumed that the CTC transmission only occurs due to the active infected cells. In a very recent work, Wang et al. [41] formulated a viral infection model by assuming that both silent and active infected cells can participate in CTC infection. However, in [41], the immune response has not been considered.

In the present paper, we first formulate an HIV infection model with CTL-mediated immune response and both VTC and CTC transmissions. The CTC transmission is due to the contact of healthy CD4$^+$T cells with silent or active HIV-infected cells. The incidence rates of the healthy CD4$^+$T cells with free HIV particles, silent HIV-infected cells, and active HIV-infected cells are given by general functions. Moreover, the production/proliferation and removal/death rates of all compartments are represented by general functions. We show that the model is well posed by establishing that the solutions of the model are nonnegative and bounded. We derive two threshold parameters which determine the existence and stability of the three equilibria. Global stability of all equilibria is proven by formulating Lyapunov functions and utilizing LaSalle's invariance principle. We perform some numerical simulations to illustrate the strength of our theoretical results.

2 Model formulation

We formulate an HIV infection model by assuming that the HIV virions can replicate by two mechanisms, VTC and CTC transmissions. The CTC infection has two sources: (i) the contact between healthy CD4$^+$T cells and silent HIV-infected cells and (ii) the contact between healthy CD4$^+$T cells and active HIV-infected cells. Under these assumptions we propose a model that contains five compartments: healthy CD4$^+$T cells (S), silent HIV-infected cells (L), active HIV-infected cells (I), free HIV particles (V), and HIV-specific CTLs (C).

$$\begin{cases} \dot{S} = ¥(S) - \aleph_1(S,V) - \aleph_2(S,L) - \aleph_3(S,I), \\ \dot{L} = \aleph_1(S,V) + \aleph_2(S,L) + \aleph_3(S,I) - (\lambda+\gamma)\mathcal{J}_1(L), \\ \dot{I} = \lambda\mathcal{J}_1(L) - a\mathcal{J}_2(I) - \mu\mathcal{J}_4(C)\mathcal{J}_2(I), \\ \dot{V} = b\mathcal{J}_2(I) - \varepsilon\mathcal{J}_3(V), \\ \dot{C} = \sigma\mathcal{J}_4(C)\mathcal{J}_2(I) - \pi\mathcal{J}_4(C). \end{cases} \tag{2}$$

Here, $(S,L,I,V,C) = (S(t),L(t),I(t),V(t),C(t))$, where t is the time. Function $¥(S)$ refers to the intrinsic growth rate of healthy CD4$^+$T cells accounting for both production and natural mortality. The model assumes nonlinear general forms of virus-cell, silent cell-cell, and active cell-cell incidence rates of infection as $\aleph_1(S,V)$, $\aleph_2(S,L)$, and $\aleph_3(S,I)$, respectively. The terms $\lambda\mathcal{J}_1(L)$ and $\gamma\mathcal{J}_1(L)$ are the rates of silent HIV-infected cells that become active and the natural death of the silent HIV-infected cells, respectively. The term $\mu\mathcal{J}_4(C)\mathcal{J}_2(I)$ is the killing rate of active HIV-infected cells due to their specific CTL-mediated immunity. The proliferation and death rates for effective HIV-specific CTLs are given by $\sigma\mathcal{J}_4(C)\mathcal{J}_2(I)$ and $\pi\mathcal{J}_4(C)$, respectively. The free HIV particles are generated at rate $b\mathcal{J}_2(I)$ and die at rate $\varepsilon\mathcal{J}_3(V)$. All parameters and their definitions are summarized in Table 1. The functions ¥, $\aleph_i$, $i = 1,2,3$, and $\mathcal{J}_k$, $k = 1,2,3,4$, are continuously differentiable and satisfy the following conditions [42–44].

Condition (H1)

(i) There exists S_0 such that $¥(S_0) = 0$ and $¥(S) > 0$ for $S \in [0, S_0)$;

(ii) $¥'(S) < 0$ for all $S > 0$;

(iii) There are $\rho > 0$ and $\alpha_0 > 0$ such that $¥(S) \le \rho - \alpha_0 S$ for $S \ge 0$.

Table 1 Parameters of model (2) and their interpretations

Symbol	Biological meaning
γ	Death rate constant of silent HIV-infected cells
a	Death rate constant of active HIV-infected cells
μ	Killing rate constant of active HIV-infected cells due to their specific CTL-mediated immunity
λ	Transmission rate constant of silent HIV-infected cells that become active HIV-infected cells
b	Generation rate constant of new HIV particles
ε	Death rate constant of free HIV particles
σ	Proliferation rate constant of HIV-specific CTLs
π	Decay rate constant of HIV-specific CTLs

Condition (H2)

(i) $\aleph_i(S,U) > 0$ and $\aleph_i(0,U) = \aleph_i(S,0) = 0$ for all $S > 0$, $U > 0$, $i = 1,2,3$;
(ii) $\frac{\partial \aleph_i(S,U)}{\partial S} > 0$, $\frac{\partial \aleph_i(S,U)}{\partial U} > 0$, and $\frac{\partial \aleph_i(S,U)}{\partial U}|_{U=0} > 0$ for all $S > 0$, $U > 0$, $i = 1,2,3$;
(iii) $\frac{d}{dS}(\frac{\partial \aleph_i(S,U)}{\partial U}|_{U=0}) > 0$ for all $S > 0$, $i = 1,2,3$.

Condition (H3)

(i) $\mathcal{J}_k(x) > 0$ for all $x > 0$, $\mathcal{J}_k(0) = 0$, $k = 1,2,3,4$;
(ii) $\mathcal{J}_k'(x) > 0$ for all $x > 0$, $k = 1,2,3,4$. Further, $\mathcal{J}_k'(0) > 0$, $k = 1,2,3$;
(iii) There are $\alpha_k > 0$ such that $\mathcal{J}_k(x) \geq \alpha_k x$ for all $x \geq 0$, $k = 1,2,3,4$.

Condition (H4) $\frac{\partial}{\partial V}(\frac{\aleph_1(S,V)}{\mathcal{J}_3(V)}) \leq 0$, $\frac{\partial}{\partial L}(\frac{\aleph_2(S,L)}{\mathcal{J}_1(L)}) \leq 0$, and $\frac{\partial}{\partial I}(\frac{\aleph_3(S,I)}{\mathcal{J}_2(I)}) \leq 0$ for all$S$, L, I, $V > 0$.

3 Well-posedness of solutions

Let $\Omega_j > 0$, $j = 1,2,3$, and define

$$\Theta = \left\{(S,L,I,V,C) \in \mathbb{R}^5_{\geq 0} : 0 \leq S(t), L(t), I(t) \leq \Omega_1, 0 \leq V(t) \leq \Omega_2, 0 \leq C(t) \leq \Omega_3\right\}. \quad (3)$$

Proposition 1 *Suppose that Conditions* (H1)–(H3) *are satisfied. Then the compact set* Θ *is positively invariant for system* (2).

Proof We have

$$\dot{S}|_{S=0} = ¥(0) > 0,$$

$$\dot{L}|_{L=0} = \aleph_1(S,V) + \aleph_3(S,I) \geq 0 \quad \text{for all } S,V,I \geq 0,$$

$$\dot{I}|_{I=0} = \lambda \mathcal{J}_1(L) \geq 0 \quad \text{for all } L \geq 0,$$

$$\dot{V}|_{V=0} = b\mathcal{J}_2(I) \geq 0 \quad \text{for all } I \geq 0,$$

$$\dot{C}|_{C=0} = 0.$$

This ensures that $(S(t),L(t),I(t),V(t),C(t)) \in \mathbb{R}^5_{\geq 0}$ for all $t \geq 0$ when $(S(0),L(0),I(0),V(0),C(0)) \in \mathbb{R}^5_{\geq 0}$. To show the boundedness of all state variables, we let

$$\Psi = S + L + I + \frac{a}{2b}V + \frac{\mu}{\sigma}C.$$

Then

$$\begin{aligned}\dot{\Psi} &= ¥(S) - \gamma \mathcal{J}_1(L) - \frac{a}{2}\mathcal{J}_2(I) - \frac{a\varepsilon}{2b}\mathcal{J}_3(V) - \frac{\mu\pi}{\sigma}\mathcal{J}_4(C)\\ &\le \rho - \alpha_0 S - \gamma\alpha_1 L - \frac{a\alpha_2}{2}I - \frac{a\varepsilon\alpha_3}{2b}V - \frac{\mu\pi\alpha_4}{\sigma}C\\ &\le \rho - \phi\left(S + L + I + \frac{a}{2b}V + \frac{\mu}{\sigma}C\right) = \rho - \phi\Psi,\end{aligned}$$

where $\phi = \min\{\alpha_0, \gamma\alpha_1, \frac{a\alpha_2}{2}, \varepsilon\alpha_3, \pi\alpha_4\}$. Hence, $0 \le \Psi(t) \le \Omega_1$ if $\Psi(0) \le \Omega_1$ for $t \ge 0$, where $\Omega_1 = \frac{\rho}{\phi}$. Since S, L, I, V, and C are all nonnegative, then $0 \le S(t), L(t), I(t) \le \Omega_1$, $0 \le V(t) \le \Omega_2$, and $0 \le C(t) \le \Omega_3$ if $S(0) + L(0) + I(0) + \frac{a}{2b}V(0) + \frac{\mu}{\sigma}C(0) \le \Omega_1$, where $\Omega_2 = \frac{2b\Omega_1}{a}$ and $\Omega_3 = \frac{\sigma\Omega_1}{\mu}$. □

4 Equilibria

In this section, we study the equilibria of the model and derive the conditions for their existence. Model (2) always admits an infection-free equilibrium $Ð_0 = (S_0, 0, 0, 0, 0)$, where $¥(S_0) = 0$. This case describes the situation of healthy state where the HIV infection is absent. The other equilibria can be computed by letting the right-hand side of system (2) be equal to zero as follows:

$$0 = ¥(S) - \aleph_1(S, V) - \aleph_2(S, L) - \aleph_3(S, I), \tag{4}$$

$$0 = \aleph_1(S, V) + \aleph_2(S, L) + \aleph_3(S, I) - (\lambda + \gamma)\mathcal{J}_1(L), \tag{5}$$

$$0 = \lambda\mathcal{J}_1(L) - a\mathcal{J}_2(I) - \mu\mathcal{J}_4(C)\mathcal{J}_2(I), \tag{6}$$

$$0 = b\mathcal{J}_2(I) - \varepsilon\mathcal{J}_3(V), \tag{7}$$

$$0 = \big(\sigma\mathcal{J}_2(I) - \pi\big)\mathcal{J}_4(C). \tag{8}$$

From Eq. (8) we have two possibilities:

(i) $\mathcal{J}_4(C) = 0$, which leads to $C_1 = 0$. From Eqs. (4)–(7), we get

$$\begin{aligned}¥(S) &= \aleph_1(S, V) + \aleph_2(S, L) + \aleph_3(S, I) = (\lambda + \gamma)\mathcal{J}_1(L)\\ &= \frac{a(\lambda + \gamma)}{\lambda}\mathcal{J}_2(I) = \frac{a\varepsilon(\lambda + \gamma)}{b\lambda}\mathcal{J}_3(V).\end{aligned} \tag{9}$$

Condition (H3) implies that $\mathcal{J}_k^{-1}$ exists, is continuous and strictly increasing. From Eq. (9), we obtain

$$L = f_1(S), \qquad I = f_2(S), \qquad V = f_3(S), \tag{10}$$

where

$$f_1(S) = \mathcal{J}_1^{-1}\left(\frac{¥(S)}{\lambda + \gamma}\right), \qquad f_2(S) = \mathcal{J}_2^{-1}\left(\frac{\lambda¥(S)}{a(\lambda + \gamma)}\right), \qquad f_3(S) = \mathcal{J}_3^{-1}\left(\frac{b\lambda¥(S)}{a\varepsilon(\lambda + \gamma)}\right).$$

Obviously, from Condition (H1), $f_i(S) > 0$ for all $S \in [0, S_0)$ and $f_i(S_0) = 0$, $i = 1, 2, 3$. Let us define

$$\mathcal{F}_1(S) = \aleph_1\big(S, f_3(S)\big) + \aleph_2\big(S, f_1(S)\big) + \aleph_3\big(S, f_2(S)\big) - \frac{a\varepsilon(\lambda + \gamma)}{b\lambda}\mathcal{J}_3\big(f_3(S)\big).$$

Then from Conditions (H1)–(H3), we have

$$\mathcal{F}_1(0) = -\frac{a\varepsilon(\lambda+\gamma)}{b\lambda}\mathcal{J}_3\big(f_3(0)\big) < 0, \qquad \mathcal{F}_1(S_0) = 0.$$

Moreover,

$$\begin{aligned}\mathcal{F}_1'(S) &= \frac{\partial \aleph_1}{\partial S} + f_3'(S)\frac{\partial \aleph_1}{\partial V} + \frac{\partial \aleph_2}{\partial S} + f_1'(S)\frac{\partial \aleph_2}{\partial L} + \frac{\partial \aleph_3}{\partial S} + f_2'(S)\frac{\partial \aleph_3}{\partial I}\\ &\quad - \frac{a\varepsilon(\lambda+\gamma)}{b\lambda}\mathcal{J}_3'\big(f_3(S)\big)f_3'(S),\\ \mathcal{F}_1'(S_0) &= \frac{\partial \aleph_1(S_0,0)}{\partial S} + f_3'(S_0)\frac{\partial \aleph_1(S_0,0)}{\partial V} + \frac{\partial \aleph_2(S_0,0)}{\partial S} + f_1'(S_0)\frac{\partial \aleph_2(S_0,0)}{\partial L}\\ &\quad + \frac{\partial \aleph_3(S_0,0)}{\partial S} + f_2'(S_0)\frac{\partial \aleph_3(S_0,0)}{\partial I} - \frac{a\varepsilon(\lambda+\gamma)}{b\lambda}\mathcal{J}_3'(0)f_3'(S_0).\end{aligned}$$

Condition (H2) implies that $\frac{\partial \aleph_i(S_0,0)}{\partial S} = 0$, $i = 1,2,3$. Also, from Condition (H3), we have $\mathcal{J}_3'(0) > 0$, then

$$\begin{aligned}\mathcal{F}_1'(S_0) &= \frac{a\varepsilon(\lambda+\gamma)}{b\lambda}\mathcal{J}_3'(0)f_3'(S_0)\bigg[\frac{b\lambda\partial \aleph_1(S_0,0)/\partial V}{a\varepsilon(\lambda+\gamma)\mathcal{J}_3'(0)}\\ &\quad + \frac{b\lambda f_1'(S_0)\partial \aleph_2(S_0,0)/\partial L}{a\varepsilon(\lambda+\gamma)\mathcal{J}_3'(0)f_3'(S_0)} + \frac{b\lambda f_2'(S_0)\partial \aleph_3(S_0,0)/\partial I}{a\varepsilon(\lambda+\gamma)\mathcal{J}_3'(0)f_3'(S_0)} - 1\bigg].\end{aligned}$$

From Eqs. (9) and (10), we obtain

$$\mathcal{F}_1'(S_0) = \curlyvee'(S_0)\bigg[\frac{b\lambda\partial \aleph_1(S_0,0)/\partial V}{a\varepsilon(\lambda+\gamma)\mathcal{J}_3'(0)} + \frac{\partial \aleph_2(S_0,0)/\partial L}{(\lambda+\gamma)\mathcal{J}_1'(0)} + \frac{\lambda\partial \aleph_3(S_0,0)/\partial I}{a(\lambda+\gamma)\mathcal{J}_2'(0)} - 1\bigg].$$

From Condition (H1), we have $\curlyvee'(S_0) < 0$. Therefore, if $\frac{b\lambda\partial \aleph_1(S_0,0)/\partial V}{a\varepsilon(\lambda+\gamma)\mathcal{J}_3'(0)} + \frac{\partial \aleph_2(S_0,0)/\partial L}{(\lambda+\gamma)\mathcal{J}_1'(0)} + \frac{\lambda\partial \aleph_3(S_0,0)/\partial I}{a(\lambda+\gamma)\mathcal{J}_2'(0)} > 1$, then $\mathcal{F}_1'(S_0) < 0$ and there exists $S_1 \in (0, S_0)$ such that $\mathcal{F}_1(S_1) = 0$. From Eq. (10) and Condition (H3), we have

$$L_1 = \mathcal{J}_1^{-1}\bigg(\frac{\curlyvee(S_1)}{\lambda+\gamma}\bigg) > 0, \qquad I_1 = \mathcal{J}_2^{-1}\bigg(\frac{\lambda\curlyvee(S_1)}{a(\lambda+\gamma)}\bigg) > 0, \qquad V_1 = \mathcal{J}_3^{-1}\bigg(\frac{b\lambda\curlyvee(S_1)}{a\varepsilon(\lambda+\gamma)}\bigg) > 0.$$

It follows that $Ð_1 = (S_1, L_1, I_1, V_1, 0)$ exists when

$$\frac{b\lambda\partial \aleph_1(S_0,0)/\partial V}{a\varepsilon(\lambda+\gamma)\mathcal{J}_3'(0)} + \frac{\partial \aleph_2(S_0,0)/\partial L}{(\lambda+\gamma)\mathcal{J}_1'(0)} + \frac{\lambda\partial \aleph_3(S_0,0)/\partial I}{a(\lambda+\gamma)\mathcal{J}_2'(0)} > 1.$$

At the equilibrium $Ð_1$ the chronic HIV infection persists, while the CTL-mediated immune response is unstimulated. In order to state the threshold dynamics of infection-free equilibrium, it is necessary to define the basic HIV reproduction number $\Re_0$ of the model. If the antiviral drugs are taken into account in that HIV dynamics model, then $\Re_0$ can be used to determine the minimum drug efficacy which stabilizes the system around the infection-free equilibrium and clears the viruses from the body. The basic HIV reproduction number of model (2) can be calculated by different methods such as (i) the next-generation matrix method of van den Driessche and Watmough [45], (ii) local stability of

the infection-free equilibrium, and (iii) the existence of the chronic HIV infection equilibrium with inactive CTL-mediated immune response. In the present paper we derive $\Re_0$ by method (iii) as follows:

$$\Re_0 = \Re_{01} + \Re_{02} + \Re_{03},$$

where

$$\Re_{01} = \frac{b\lambda}{a\varepsilon(\lambda+\gamma)\mathcal{J}_3'(0)}\frac{\partial \aleph_1(S_0,0)}{\partial V},$$
$$\Re_{02} = \frac{1}{(\lambda+\gamma)\mathcal{J}_1'(0)}\frac{\partial \aleph_2(S_0,0)}{\partial L},$$
$$\Re_{03} = \frac{\lambda}{a(\lambda+\gamma)\mathcal{J}_2'(0)}\frac{\partial \aleph_3(S_0,0)}{\partial I}.$$

The parameter $\Re_0$ determines whether or not the infection will be chronic. In fact, $\Re_{01}$ measures the average number of secondary HIV-infected cells caused by an existing free HIV particle due to VTC transmission, while $\Re_{02}$ and $\Re_{03}$ measure the average numbers of secondary HIV-infected cells caused by living silent and active HIV-infected cell, respectively, due to CTC transmission. Thus, $Ð_1 = (S_1, L_1, I_1, V_1, 0)$ exists when $\Re_0 > 1$. We call $Ð_1$ chronic HIV infection equilibrium with inactive CTL-mediated immune response.

(ii) $\mathcal{J}_2(I) = \frac{\pi}{\sigma}$, which leads to $I_2 = \mathcal{J}_2^{-1}(\frac{\pi}{\sigma})$. From Eqs. (4)–(6) we get

$$¥(S) = \aleph_1(S,V) + \aleph_2(S,L) + \aleph_3(S,I) = (\lambda+\gamma)\mathcal{J}_1(L) = \frac{\lambda+\gamma}{\lambda}\big(a + \mu\mathcal{J}_4(C)\big)\mathcal{J}_2(I). \tag{11}$$

According to Condition (H3) and from Eq. (7), we have

$$V_2 = \mathcal{J}_3^{-1}\left(\frac{b\mathcal{J}_2(I_2)}{\varepsilon}\right) = \mathcal{J}_3^{-1}\left(\frac{b\pi}{\varepsilon\sigma}\right) > 0.$$

From Eq. (11), we get

$$L = \mathcal{J}_1^{-1}\left(\frac{¥(S)}{\lambda+\gamma}\right) = f_4(S). \tag{12}$$

Obviously, from Condition (H1) we have $f_4(S) > 0$ for all $S \in [0, S_0)$ and $f_4(S_0) = 0$. Let $V = V_2$ and $I = I_2$, and using Eq. (12) in Eq. (4), define

$$\mathcal{F}_2(S) = ¥(S) - \aleph_1(S, V_2) - \aleph_2\big(S, f_4(S)\big) - \aleph_3(S, I_2) = 0.$$

Conditions (H1) and (H2) imply that $\mathcal{F}_2(0) = ¥(0) > 0$ and $\mathcal{F}_2(S_0) = -[\aleph_1(S_0, V_2) + \aleph_2(S_0, I_2)] < 0$. Thus, there exists $S_2 \in (0, S_0)$ such that $\mathcal{F}_2(S_2) = 0$. From Eq. (12) and Condition (H3), we obtain

$$L_2 = \mathcal{J}_1^{-1}\left(\frac{¥(S_2)}{\lambda+\gamma}\right) > 0.$$

Further, from Eq. (11), we have

$$C_2 = \mathcal{J}_4^{-1}\left(\frac{a}{\mu}\left[\frac{\sigma\lambda\{\aleph_1(S_2,V_2)+\aleph_2(S_2,L_2)+\aleph_3(S_2,I_2)\}}{a\pi(\lambda+\gamma)}-1\right]\right).$$

Clearly, $C_2 > 0$ when $\frac{\sigma\lambda[\aleph_1(S_2,V_2)+\aleph_2(S_2,L_2)+\aleph_3(S_2,I_2)]}{a\pi(\lambda+\gamma)} > 1$. Now we define the HIV-specific CTL-mediated immunity reproduction number as follows:

$$\begin{aligned}\Re_1 &= \frac{\sigma\lambda[\aleph_1(S_2,V_2)+\aleph_2(S_2,L_2)+\aleph_3(S_2,I_2)]}{a\pi(\lambda+\gamma)}\\ &= \frac{\lambda[\aleph_1(S_2,V_2)+\aleph_2(S_2,L_2)+\aleph_3(S_2,I_2)]}{a(\lambda+\gamma)\mathcal{J}_2(I_2)}\\ &= \frac{b\lambda\aleph_1(S_2,V_2)}{a\varepsilon(\lambda+\gamma)\mathcal{J}_3(V_2)}+\frac{\lambda\aleph_2(S_2,L_2)}{a(\lambda+\gamma)\mathcal{J}_2(I_2)}+\frac{\lambda\aleph_3(S_2,I_2)}{a(\lambda+\gamma)\mathcal{J}_2(I_2)}.\end{aligned}$$

Thus, $C_2 = \mathcal{J}_4^{-1}(\frac{a}{\mu}(\Re_1-1))$. The parameter $\Re_1$ determines whether or not the HIV-specific CTL-mediated immune response is stimulated. Therefore, $\text{Đ}_2 = (S_2, L_2, I_2, V_2, C_2)$ exists when $\Re_1 > 1$. We call Đ_2 chronic HIV infection equilibrium with active CTL-mediated immune response.

From the above discussion we have the following result.

Lemma 1 *Suppose that Conditions (H1)–(H3) hold true, then there exist two positive threshold parameters* $\Re_0$ *and* $\Re_1$ *such that*

(i) *if* $\Re_0 \le 1$, *then there exists only one equilibrium* Đ_0;

(ii) *if* $\Re_1 \le 1 < \Re_0$, *then there exist only two equilibria* Đ_0 *and* Đ_1; *and*

(iii) *if* $\Re_1 > 1$, *then there exist three equilibria* Đ_0, Đ_1, *and* Đ_2.

5 Global stability analysis

In this section, we prove the global asymptotic stability of all equilibria by constructing Lyapunov functional following the method presented in [46–49]. Define

$$F_1(S) = \lim_{V\to 0^+}\frac{\aleph_1(S,V)}{\mathcal{J}_3(V)}, \qquad F_2(S) = \lim_{L\to 0^+}\frac{\aleph_2(S,L)}{\mathcal{J}_1(L)}, \qquad F_3(S) = \lim_{I\to 0^+}\frac{\aleph_3(S,I)}{\mathcal{J}_2(I)}. \tag{13}$$

From Conditions (H2) and (H3), we obtain

$$\begin{aligned}F_1(S) &= \frac{1}{\mathcal{J}_3'(0)}\frac{\partial\aleph_1(S,0)}{\partial V} > 0,\\ F_2(S) &= \frac{1}{\mathcal{J}_1'(0)}\frac{\partial\aleph_2(S,0)}{\partial L} > 0,\\ F_3(S) &= \frac{1}{\mathcal{J}_2'(0)}\frac{\partial\aleph_3(S,0)}{\partial I} > 0 \quad \text{for any } S > 0.\end{aligned}$$

Moreover,

$$F_i'(S) > 0, \quad i = 1,2,3. \tag{14}$$

Therefore, the parameter $\Re_0$ can be rewritten as

$$\Re_0 = \frac{b\lambda F_1(S_0)}{a\varepsilon(\lambda+\gamma)} + \frac{F_2(S_0)}{\lambda+\gamma} + \frac{\lambda F_3(S_0)}{a(\lambda+\gamma)}.$$

To investigate the next theorem, we need the following condition [50].

Condition (H5)

(i) The supremum of $\frac{F_2(S)}{F_1(S)}$ is achieved at $S = S_0$ for all $S \in (0, S_0]$;

(ii) The supremum of $\frac{F_3(S)}{F_1(S)}$ is achieved at $S = S_0$ for all $S \in (0, S_0]$.

Theorem 1 *Let $\Re_0 \le 1$ and Conditions (H1)–(H5) be satisfied, then $\mathrm{Đ}_0$ is globally asymptotically stable* (*G.A.S.*).

Proof Construct a Lyapunov functional candidate:

$$\Phi_0(S,L,I,V,C) = S - S_0 - \int_{S_0}^{S} \frac{F_1(S_0)}{F_1(\theta)}d\theta + L + \frac{bF_1(S_0)+\varepsilon F_3(S_0)}{a\varepsilon}I + \frac{F_1(S_0)}{\varepsilon}V + \frac{\mu(bF_1(S_0)+\varepsilon F_3(S_0))}{\sigma a\varepsilon}C.$$

We note that $\Phi_0(S,L,I,V,C) > 0$ for all $S,L,I,V,C > 0$, and $\Phi_0(S_0,0,0,0,0) = 0$. We calculate $\frac{d\Phi_0}{dt}$ along the solutions of model (2) as follows:

$$\begin{aligned}
\frac{d\Phi_0}{dt} &= \left(1 - \frac{F_1(S_0)}{F_1(S)}\right)\big(¥(S) - \aleph_1(S,V) - \aleph_2(S,L) - \aleph_3(S,I)\big) + \aleph_1(S,V) + \aleph_2(S,L) \\
&\quad + \aleph_3(S,I) - (\lambda+\gamma)\mathcal{J}_1(L) \\
&\quad + \frac{bF_1(S_0)+\varepsilon F_3(S_0)}{a\varepsilon}\big(\lambda\mathcal{J}_1(L) - a\mathcal{J}_2(I) - \mu\mathcal{J}_4(C)\mathcal{J}_2(I)\big) \\
&\quad + \frac{F_1(S_0)}{\varepsilon}\big(b\mathcal{J}_2(I) - \varepsilon\mathcal{J}_3(V)\big) + \frac{\mu(bF_1(S_0)+\varepsilon F_3(S_0))}{\sigma a\varepsilon}\big(\sigma\mathcal{J}_4(C)\mathcal{J}_2(I) - \pi\mathcal{J}_4(C)\big) \\
&= ¥(S)\left(1 - \frac{F_1(S_0)}{F_1(S)}\right) + \aleph_1(S,V)\frac{F_1(S_0)}{F_1(S)} + \aleph_2(S,L)\frac{F_1(S_0)}{F_1(S)} + \aleph_3(S,I)\frac{F_1(S_0)}{F_1(S)} \\
&\quad - (\lambda+\gamma)\mathcal{J}_1(L) + \frac{\lambda(bF_1(S_0)+\varepsilon F_3(S_0))}{a\varepsilon}\mathcal{J}_1(L) - F_3(S_0)\mathcal{J}_2(I) - F_1(S_0)\mathcal{J}_3(V) \\
&\quad - \frac{\mu\pi(bF_1(S_0)+\varepsilon F_3(S_0))}{\sigma a\varepsilon}\mathcal{J}_4(C). \qquad (15)
\end{aligned}$$

From Condition (H4) and Eq. (13), we get

$$\begin{aligned}
&\frac{\aleph_1(S,V)}{\mathcal{J}_3(V)} \le \lim_{V\to 0^+}\frac{\aleph_1(S,V)}{\mathcal{J}_3(V)} = F_1(S), \\
&\frac{\aleph_2(S,L)}{\mathcal{J}_1(L)} \le \lim_{L\to 0^+}\frac{\aleph_2(S,L)}{\mathcal{J}_1(L)} = F_2(S), \\
&\frac{\aleph_3(S,I)}{\mathcal{J}_2(I)} \le \lim_{I\to 0^+}\frac{\aleph_3(S,I)}{\mathcal{J}_2(I)} = F_3(S).
\end{aligned}$$

Then we obtain

$$\aleph_1(S,V) \le F_1(S)\mathcal{J}_3(V), \qquad \aleph_2(S,L) \le F_2(S)\mathcal{J}_1(L), \qquad \aleph_3(S,I) \le F_3(S)\mathcal{J}_2(I).$$

Therefore, Eq. (15) will become

$$\begin{aligned}
\frac{d\Phi_0}{dt} &\le \Upsilon(S)\left(1-\frac{F_1(S_0)}{F_1(S)}\right)+\frac{F_1(S_0)F_2(S)}{F_1(S)}\mathcal{J}_1(L)+\frac{F_1(S_0)F_3(S)}{F_1(S)}\mathcal{J}_2(I)\\
&\quad-(\lambda+\gamma)\mathcal{J}_1(L)+\frac{\lambda(bF_1(S_0)+\varepsilon F_3(S_0))}{a\varepsilon}\mathcal{J}_1(L)-F_3(S_0)\mathcal{J}_2(I)\\
&\quad-\frac{\mu\pi(bF_1(S_0)+\varepsilon F_3(S_0))}{\sigma a\varepsilon}\mathcal{J}_4(C)\\
&=\Upsilon(S)\left(1-\frac{F_1(S_0)}{F_1(S)}\right)+\left[\frac{F_1(S_0)F_3(S)}{F_1(S)}-F_3(S_0)\right]\mathcal{J}_2(I)\\
&\quad+(\lambda+\gamma)\left[\frac{F_1(S_0)F_2(S)}{(\lambda+\gamma)F_1(S)}+\frac{\lambda(bF_1(S_0)+\varepsilon F_3(S_0))}{a\varepsilon(\lambda+\gamma)}-1\right]\mathcal{J}_1(L)\\
&\quad-\frac{\mu\pi(bF_1(S_0)+\varepsilon F_3(S_0))}{\sigma a\varepsilon}\mathcal{J}_4(C).
\end{aligned} \tag{16}$$

Condition (H5) implies that

$$\begin{aligned}
&\frac{F_1(S_0)F_2(S)}{F_1(S)} \le F_1(S_0)\frac{F_2(S_0)}{F_1(S_0)} = F_2(S_0),\\
&\frac{F_1(S_0)F_3(S)}{F_1(S)} \le F_1(S_0)\frac{F_3(S_0)}{F_1(S_0)} = F_3(S_0) \quad \text{for } 0 < S \le S_0.
\end{aligned} \tag{17}$$

Substituting inequality (17) into Eq. (16) and using $\Upsilon(S_0) = 0$, we get

$$\begin{aligned}
\frac{d\Phi_0}{dt} &\le \big(\Upsilon(S)-\Upsilon(S_0)\big)\left(1-\frac{F_1(S_0)}{F_1(S)}\right)\\
&\quad+(\lambda+\gamma)\left[\frac{\lambda bF_1(S_0)}{a\varepsilon(\lambda+\gamma)}+\frac{F_2(S_0)}{\lambda+\gamma}+\frac{\lambda F_3(S_0)}{a(\lambda+\gamma)}-1\right]\mathcal{J}_1(L)\\
&\quad-\frac{\mu\pi(bF_1(S_0)+\varepsilon F_3(S_0))}{\sigma a\varepsilon}\mathcal{J}_4(C)\\
&=\big(\Upsilon(S)-\Upsilon(S_0)\big)\left(1-\frac{F_1(S_0)}{F_1(S)}\right)+(\lambda+\gamma)(\Re_0-1)\mathcal{J}_1(L)\\
&\quad-\frac{\mu\pi(bF_1(S_0)+\varepsilon F_3(S_0))}{\sigma a\varepsilon}\mathcal{J}_4(C).
\end{aligned}$$

Conditions (H1), (H2) and Eq. (14) provide that $\Upsilon(S)$ is a strictly decreasing function of S, while $F_1(S)$ is a strictly increasing function of S. Then

$$\big(\Upsilon(S)-\Upsilon(S_0)\big)\left(1-\frac{F_1(S_0)}{F_1(S)}\right) \le 0.$$

Therefore, $\frac{d\Phi_0}{dt} \le 0$ for all $S,L,I,V,C > 0$ with equality holding when $S = S_0$ and $L = C = 0$. Let $\Upsilon_0 = \{(S,L,I,V,C) : \frac{d\Phi_0}{dt} = 0\}$ and Υ_0' be the largest invariant subset of Υ_0. Therefore, the solutions of system (2) converge to Υ_0' [51]. The set Υ_0' is invariant and contains elements

which satisfy $S(t) = S_0$ and $L(t) = C(t) = 0$. Then $\dot{S}(t) = 0$ and $\dot{L}(t) = \dot{C}(t) = 0$. From the third and fourth equations of system (2), we have

$$\dot{I} = -a\mathcal{J}_2(I), \tag{18}$$

$$\dot{V} = b\mathcal{J}_2(I) - \varepsilon\mathcal{J}_3(V). \tag{19}$$

Let us define a Lyapunov function as follows:

$$\tilde{\Phi}_0 = I + \frac{a}{2b}V.$$

Therefore, the time derivative of $\tilde{\Phi}_0$ along the solutions of system (18)–(19) can be calculated as follows:

$$\frac{d\tilde{\Phi}_0}{dt} = -\frac{a}{2}\left(\mathcal{J}_2(I) + \frac{\varepsilon}{b}\mathcal{J}_3(V)\right) \leq 0.$$

Utilizing Condition (H3) it is clear that $\frac{d\tilde{\Phi}_0}{dt} = 0$ if and only if $I(t) = V(t) = 0$ for all t. Let $\Upsilon_0'' = \{(S, L, I, V, C) \in \Upsilon_0' : \frac{d\tilde{\Phi}_0}{dt} = 0\}$. Then $\Upsilon_0'' = \{(S, L, I, V, C) \in \Upsilon_0' : S = S_0, L = I = V = C = 0\} = \{\text{Đ}_0\}$. Hence, all solution trajectories approach Đ_0, and this means that Đ_0 is G.A.S. [51]. □

Remark 1 From Conditions (H2) and (H4), we get

$$\left(\aleph_1(S, V) - \aleph_1(S, V_i)\right)\left(\frac{\aleph_1(S, V)}{\mathcal{J}_3(V)} - \frac{\aleph_1(S, V_i)}{\mathcal{J}_3(V_i)}\right) \leq 0, \quad S, V, V_i > 0, i = 1, 2,$$

which leads to

$$\left(1 - \frac{\aleph_1(S, V_i)}{\aleph_1(S, V)}\right)\left(\frac{\aleph_1(S, V)}{\aleph_1(S, V_i)} - \frac{\mathcal{J}_3(V)}{\mathcal{J}_3(V_i)}\right) \leq 0, \quad S, V, V_i > 0, i = 1, 2. \tag{20}$$

Define the following functions [50]:

$$\mathcal{G}_i^L(S, L) = \frac{\aleph_2(S, L)}{\aleph_1(S, V_i)}, \qquad \mathcal{G}_i^I(S, I) = \frac{\aleph_3(S, I)}{\aleph_1(S, V_i)}, \quad i = 1, 2. \tag{21}$$

We state the following condition:

Condition (H6)

(i) $\left(\mathcal{G}_i^L(S, L) - \mathcal{G}_i^L(S_i, L_i)\right)\left(\frac{\mathcal{G}_i^L(S, L)}{\mathcal{J}_1(L)} - \frac{\mathcal{G}_i^L(S_i, L_i)}{\mathcal{J}_1(L_i)}\right) \leq 0,$

(ii) $\left(\mathcal{G}_i^I(S, I) - \mathcal{G}_i^I(S_i, I_i)\right)\left(\frac{\mathcal{G}_i^I(S, I)}{\mathcal{J}_2(I)} - \frac{\mathcal{G}_i^I(S_i, I_i)}{\mathcal{J}_2(I_i)}\right) \leq 0,$

for all $L, L_i, I, I_i > 0$, $i = 1, 2, S \in (0, S_0)$.

Remark 2 From Condition (H6), we get

$$\begin{aligned}&\left(1-\frac{\mathcal{G}_i^L(S_i,L_i)}{\mathcal{G}_i^L(S,L)}\right)\left(\frac{\mathcal{G}_i^L(S,L)}{\mathcal{G}_i^L(S_i,L_i)}-\frac{\mathcal{J}_1(L)}{\mathcal{J}_1(L_i)}\right)\leq 0,\quad S\in(0,S_0),L,L_i,>0,\\&\left(1-\frac{\mathcal{G}_i^I(S_i,I_i)}{\mathcal{G}_i^I(S,I)}\right)\left(\frac{\mathcal{G}_i^I(S,I)}{\mathcal{G}_i^I(S_i,I_i)}-\frac{\mathcal{J}_2(I)}{\mathcal{J}_2(I_i)}\right)\leq 0,\quad S\in(0,S_0),I,I_i>0.\end{aligned}\tag{22}$$

Theorem 2 *Suppose that* $\Re_1\leq 1<\Re_0$ *and Conditions* (H1)–(H4) *and* (H6) *hold true, then* $Ð_1$ *is G.A.S.*

Proof Define $\Phi_1(S,L,I,V,C)$ as follows:

$$\begin{aligned}\Phi_1&=S-S_1-\int_{S_1}^{S}\frac{\aleph_1(S_1,V_1)}{\aleph_1(\varkappa,V_1)}\,d\varkappa+L-L_1-\int_{L_1}^{L}\frac{\mathcal{J}_1(L_1)}{\mathcal{J}_1(\varkappa)}\,d\varkappa\\&\quad+\frac{b\mathcal{J}_2(I_1)\aleph_1(S_1,V_1)+\varepsilon\mathcal{J}_3(V_1)\aleph_3(S_1,I_1)}{a\varepsilon\mathcal{J}_2(I_1)\mathcal{J}_3(V_1)}\left(I-I_1-\int_{I_1}^{I}\frac{\mathcal{J}_2(I)}{\mathcal{J}_2(\varkappa)}\,d\varkappa\right)\\&\quad+\frac{\aleph_1(S_1,V_1)}{\varepsilon\mathcal{J}_3(V_1)}\left(V-V_1-\int_{V_1}^{V}\frac{\mathcal{J}_3(V_1)}{\mathcal{J}_3(\varkappa)}\,d\varkappa\right)\\&\quad+\frac{\mu[b\mathcal{J}_2(I_1)\aleph_1(S_1,V_1)+\varepsilon\mathcal{J}_3(V_1)\aleph_3(S_1,I_1)]}{\sigma a\varepsilon\mathcal{J}_2(I_1)\mathcal{J}_3(V_1)}C.\end{aligned}$$

Calculate $\frac{d\Phi_1}{dt}$ as follows:

$$\begin{aligned}\frac{d\Phi_1}{dt}&=\left(1-\frac{\aleph_1(S_1,V_1)}{\aleph_1(S,V_1)}\right)\big(¥(S)-\aleph_1(S,V)-\aleph_2(S,L)-\aleph_3(S,I)\big)\\&\quad+\left(1-\frac{\mathcal{J}_1(L_1)}{\mathcal{J}_1(L)}\right)\big(\aleph_1(S,V)+\aleph_2(S,L)+\aleph_3(S,I)-(\lambda+\gamma)\mathcal{J}_1(L)\big)\\&\quad+\frac{b\mathcal{J}_2(I_1)\aleph_1(S_1,V_1)+\varepsilon\mathcal{J}_3(V_1)\aleph_3(S_1,I_1)}{a\varepsilon\mathcal{J}_2(I_1)\mathcal{J}_3(V_1)}\left(1-\frac{\mathcal{J}_2(I_1)}{\mathcal{J}_2(I)}\right)\big(\lambda\mathcal{J}_1(L)-a\mathcal{J}_2(I)\\&\quad-\mu\mathcal{J}_4(C)\mathcal{J}_2(I)\big)+\frac{\aleph_1(S_1,V_1)}{\varepsilon\mathcal{J}_3(V_1)}\left(1-\frac{\mathcal{J}_3(V_1)}{\mathcal{J}_3(V)}\right)\big(b\mathcal{J}_2(I)-\varepsilon\mathcal{J}_3(V)\big)\\&\quad+\frac{\mu[b\mathcal{J}_2(I_1)\aleph_1(S_1,V_1)+\varepsilon\mathcal{J}_3(V_1)\aleph_3(S_1,I_1)]}{\sigma a\varepsilon\mathcal{J}_2(I_1)\mathcal{J}_3(V_1)}\big(\sigma\mathcal{J}_4(C)\mathcal{J}_2(I)-\pi\mathcal{J}_4(C)\big).\end{aligned}\tag{23}$$

Collecting terms of Eq. (23) and using the following equilibrium conditions for $Ð_1$

$$\begin{aligned}&¥(S_1)=\aleph_1(S_1,V_1)+\aleph_2(S_1,L_1)+\aleph_3(S_1,I_1)=(\lambda+\gamma)\mathcal{J}_1(L_1),\\&\frac{\lambda\mathcal{J}_1(L_1)}{a}=\mathcal{J}_2(I_1),\qquad\mathcal{J}_3(V_1)=\frac{b\mathcal{J}_2(I_1)}{\varepsilon},\end{aligned}$$

we get

$$\begin{aligned}\aleph_1(S_1,V_1)+\aleph_3(S_1,I_1)&=\frac{b\mathcal{J}_2(I_1)\aleph_1(S_1,V_1)+\varepsilon\mathcal{J}_3(V_1)\aleph_3(S_1,I_1)}{\varepsilon\mathcal{J}_2(I_1)\mathcal{J}_3(V_1)}\mathcal{J}_2(I_1)\\&=\frac{\lambda[b\mathcal{J}_2(I_1)\aleph_1(S_1,V_1)+\varepsilon\mathcal{J}_3(V_1)\aleph_3(S_1,I_1)]}{a\varepsilon\mathcal{J}_2(I_1)\mathcal{J}_3(V_1)}\mathcal{J}_1(L_1).\end{aligned}$$

Further, we obtain

$$\begin{aligned}\frac{d\Phi_1}{dt} &= \big(\curlyvee(S)-\curlyvee(S_1)\big)\left(1-\frac{\aleph_1(S_1,V_1)}{\aleph_1(S,V_1)}\right)+\big(\aleph_1(S_1,V_1)+\aleph_2(S_1,L_1)+\aleph_3(S_1,I_1)\big)\\&\quad\times\left(1-\frac{\aleph_1(S_1,V_1)}{\aleph_1(S,V_1)}\right)+\aleph_1(S_1,V_1)\frac{\aleph_1(S,V)}{\aleph_1(S,V_1)}+\aleph_2(S_1,L_1)\frac{\aleph_2(S,L)\aleph_1(S_1,V_1)}{\aleph_2(S_1,L_1)\aleph_1(S,V_1)}\\&\quad+\aleph_3(S_1,I_1)\frac{\aleph_3(S,I)\aleph_1(S_1,V_1)}{\aleph_3(S_1,I_1)\aleph_1(S,V_1)}-\aleph_2(S_1,L_1)\frac{\mathcal{J}_1(L)}{\mathcal{J}_1(L_1)}-\aleph_1(S_1,V_1)\frac{\aleph_1(S,V)\mathcal{J}_1(L_1)}{\aleph_1(S_1,V_1)\mathcal{J}_1(L)}\\&\quad-\aleph_2(S_1,L_1)\frac{\aleph_2(S,L)\mathcal{J}_1(L_1)}{\aleph_2(S_1,L_1)\mathcal{J}_1(L)}-\aleph_3(S_1,I_1)\frac{\aleph_3(S,I)\mathcal{J}_1(L_1)}{\aleph_3(S_1,I_1)\mathcal{J}_1(L)}\\&\quad+\aleph_1(S_1,V_1)+\aleph_2(S_1,L_1)+\aleph_3(S_1,I_1)-\aleph_3(S_1,I_1)\frac{\mathcal{J}_2(I)}{\mathcal{J}_2(I_1)}\\&\quad-\aleph_1(S_1,V_1)\frac{\mathcal{J}_1(L)\mathcal{J}_2(I_1)}{\mathcal{J}_1(L_1)\mathcal{J}_2(I)}-\aleph_3(S_1,I_1)\frac{\mathcal{J}_1(L)\mathcal{J}_2(I_1)}{\mathcal{J}_1(L_1)\mathcal{J}_2(I)}+\aleph_1(S_1,V_1)\\&\quad+\aleph_3(S_1,I_1)-\aleph_1(S_1,V_1)\frac{\mathcal{J}_3(V)}{\mathcal{J}_3(V_1)}-\aleph_1(S_1,V_1)\frac{\mathcal{J}_2(I)\mathcal{J}_3(V_1)}{\mathcal{J}_2(I_1)\mathcal{J}_3(V)}+\aleph_1(S_1,V_1)\\&\quad+\frac{\mu[b\mathcal{J}_2(I_1)\aleph_1(S_1,V_1)+\varepsilon\mathcal{J}_3(V_1)\aleph_3(S_1,I_1)]}{a\varepsilon\mathcal{J}_2(I_1)\mathcal{J}_3(V_1)}\left(\mathcal{J}_2(I_1)-\frac{\pi}{\sigma}\right)\mathcal{J}_4(C).\end{aligned}\tag{24}$$

Rearranging Eq. (24), we have

$$\begin{aligned}\frac{d\Phi_1}{dt} &= \big(\curlyvee(S)-\curlyvee(S_1)\big)\left(1-\frac{\aleph_1(S_1,V_1)}{\aleph_1(S,V_1)}\right)\\&\quad+\aleph_1(S_1,V_1)\left[5-\frac{\aleph_1(S_1,V_1)}{\aleph_1(S,V_1)}-\frac{\aleph_1(S,V)\mathcal{J}_1(L_1)}{\aleph_1(S_1,V_1)\mathcal{J}_1(L)}\right.\\&\quad\left.-\frac{\mathcal{J}_1(L)\mathcal{J}_2(I_1)}{\mathcal{J}_1(L_1)\mathcal{J}_2(I)}-\frac{\mathcal{J}_2(I)\mathcal{J}_3(V_1)}{\mathcal{J}_2(I_1)\mathcal{J}_3(V)}-\frac{\aleph_1(S,V_1)\mathcal{J}_3(V)}{\aleph_1(S,V)\mathcal{J}_3(V_1)}\right]+\aleph_2(S_1,L_1)\left[3-\frac{\aleph_1(S_1,V_1)}{\aleph_1(S,V_1)}\right.\\&\quad\left.-\frac{\aleph_2(S,L)\mathcal{J}_1(L_1)}{\aleph_2(S_1,L_1)\mathcal{J}_1(L)}-\frac{\aleph_1(S,V_1)\aleph_2(S_1,L_1)\mathcal{J}_1(L)}{\aleph_1(S_1,V_1)\aleph_2(S,L)\mathcal{J}_1(L_1)}\right]+\aleph_3(S_1,I_1)\left[4-\frac{\aleph_1(S_1,V_1)}{\aleph_1(S,V_1)}\right.\\&\quad\left.-\frac{\aleph_3(S,I)\mathcal{J}_1(L_1)}{\aleph_3(S_1,I_1)\mathcal{J}_1(L)}-\frac{\mathcal{J}_1(L)\mathcal{J}_2(I_1)}{\mathcal{J}_1(L_1)\mathcal{J}_2(I)}-\frac{\aleph_1(S,V_1)\aleph_3(S_1,I_1)\mathcal{J}_2(I)}{\aleph_1(S_1,V_1)\aleph_3(S,I)\mathcal{J}_2(I_1)}\right]\\&\quad+\aleph_1(S_1,V_1)\left[\frac{\aleph_1(S,V)}{\aleph_1(S,V_1)}-\frac{\mathcal{J}_3(V)}{\mathcal{J}_3(V_1)}-1+\frac{\aleph_1(S,V_1)\mathcal{J}_3(V)}{\aleph_1(S,V)\mathcal{J}_3(V_1)}\right]\\&\quad+\aleph_2(S_1,L_1)\left[\frac{\aleph_2(S,L)\aleph_1(S_1,V_1)}{\aleph_2(S_1,L_1)\aleph_1(S,V_1)}-\frac{\mathcal{J}_1(L)}{\mathcal{J}_1(L_1)}-1+\frac{\aleph_1(S,V_1)\aleph_2(S_1,L_1)\mathcal{J}_1(L)}{\aleph_1(S_1,V_1)\aleph_2(S,L)\mathcal{J}_1(L_1)}\right]\\&\quad+\aleph_3(S_1,I_1)\left[\frac{\aleph_3(S,I)\aleph_1(S_1,V_1)}{\aleph_3(S_1,I_1)\aleph_1(S,V_1)}-\frac{\mathcal{J}_2(I)}{\mathcal{J}_2(I_1)}-1+\frac{\aleph_1(S,V_1)\aleph_3(S_1,I_1)\mathcal{J}_2(I)}{\aleph_1(S_1,V_1)\aleph_3(S,I)\mathcal{J}_2(I_1)}\right]\\&\quad+\frac{\mu[b\mathcal{J}_2(I_1)\aleph_1(S_1,V_1)+\varepsilon\mathcal{J}_3(V_1)\aleph_3(S_1,I_1)]}{a\varepsilon\mathcal{J}_2(I_1)\mathcal{J}_3(V_1)}\big(\mathcal{J}_2(I_1)-\mathcal{J}_2(I_2)\big)\mathcal{J}_4(C).\end{aligned}$$

Using the definition of $\mathcal{G}_1^U(S,U)$ given in (21), we obtain

$$\begin{aligned}&\frac{\aleph_2(S,L)\aleph_1(S_1,V_1)}{\aleph_2(S_1,L_1)\aleph_1(S,V_1)}-\frac{\mathcal{J}_1(L)}{\mathcal{J}_1(L_1)}-1+\frac{\aleph_1(S,V_1)\aleph_2(S_1,L_1)\mathcal{J}_1(L)}{\aleph_1(S_1,V_1)\aleph_2(S,L)\mathcal{J}_1(L_1)}\\&\quad=\frac{\mathcal{G}_1^L(S,L)}{\mathcal{G}_1^L(S_1,L_1)}-\frac{\mathcal{J}_1(L)}{\mathcal{J}_1(L_1)}-1+\frac{\mathcal{J}_1(L)\mathcal{G}_1^L(S_1,L_1)}{\mathcal{J}_1(L_1)\mathcal{G}_1^L(S,L)}\end{aligned}$$

and

$$\frac{\aleph_3(S,I)\aleph_1(S_1,V_1)}{\aleph_3(S_1,I_1)\aleph_1(S,V_1)}-\frac{\mathcal{J}_2(I)}{\mathcal{J}_2(I_1)}-1+\frac{\aleph_1(S,V_1)\aleph_3(S_1,I_1)\mathcal{J}_2(I)}{\aleph_1(S_1,V_1)\aleph_3(S,I)\mathcal{J}_2(I_1)}$$
$$=\frac{\mathcal{G}_1^I(S,I)}{\mathcal{G}_1^I(S_1,I_1)}-\frac{\mathcal{J}_2(I)}{\mathcal{J}_2(I_1)}-1+\frac{\mathcal{J}_2(I)\mathcal{G}_1^I(S_1,I_1)}{\mathcal{J}_2(I_1)\mathcal{G}_1^I(S,I)}.$$

Then

$$\begin{aligned}\frac{d\Phi_1}{dt}&=\big(¥(S)-¥(S_1)\big)\left(1-\frac{\aleph_1(S_1,V_1)}{\aleph_1(S,V_1)}\right)+\aleph_1(S_1,V_1)\left[5-\frac{\aleph_1(S_1,V_1)}{\aleph_1(S,V_1)}\right.\\&\quad\left.-\frac{\aleph_1(S,V)\mathcal{J}_1(L_1)}{\aleph_1(S_1,V_1)\mathcal{J}_1(L)}-\frac{\mathcal{J}_1(L)\mathcal{J}_2(I_1)}{\mathcal{J}_1(L_1)\mathcal{J}_2(I)}-\frac{\mathcal{J}_2(I)\mathcal{J}_3(V_1)}{\mathcal{J}_2(I_1)\mathcal{J}_3(V)}-\frac{\aleph_1(S,V_1)\mathcal{J}_3(V)}{\aleph_1(S,V)\mathcal{J}_3(V_1)}\right]\\&\quad+\aleph_2(S_1,L_1)\left[3-\frac{\aleph_1(S_1,V_1)}{\aleph_1(S,V_1)}-\frac{\aleph_2(S,L)\mathcal{J}_1(L_1)}{\aleph_2(S_1,L_1)\mathcal{J}_1(L)}-\frac{\aleph_1(S,V_1)\aleph_2(S_1,L_1)\mathcal{J}_1(L)}{\aleph_1(S_1,V_1)\aleph_2(S,L)\mathcal{J}_1(L_1)}\right]\\&\quad+\aleph_3(S_1,I_1)\left[4-\frac{\aleph_1(S_1,V_1)}{\aleph_1(S,V_1)}-\frac{\aleph_3(S,I)\mathcal{J}_1(L_1)}{\aleph_3(S_1,I_1)\mathcal{J}_1(L)}-\frac{\mathcal{J}_1(L)\mathcal{J}_2(I_1)}{\mathcal{J}_1(L_1)\mathcal{J}_2(I)}\right.\\&\quad\left.-\frac{\aleph_1(S,V_1)\aleph_3(S_1,I_1)\mathcal{J}_2(I)}{\aleph_1(S_1,V_1)\aleph_3(S,I)\mathcal{J}_2(I_1)}\right]\\&\quad+\aleph_1(S_1,V_1)\left(1-\frac{\aleph_1(S,V_1)}{\aleph_1(S,V)}\right)\left(\frac{\aleph_1(S,V)}{\aleph_1(S,V_1)}-\frac{\mathcal{J}_3(V)}{\mathcal{J}_3(V_1)}\right)\\&\quad+\aleph_2(S_1,L_1)\left(1-\frac{\mathcal{G}_1^L(S_1,L_1)}{\mathcal{G}_1^L(S,L)}\right)\left(\frac{\mathcal{G}_1^L(S,L)}{\mathcal{G}_1^L(S_1,L_1)}-\frac{\mathcal{J}_1(L)}{\mathcal{J}_1(L_1)}\right)\\&\quad+\aleph_3(S_1,I_1)\left(1-\frac{\mathcal{G}_1^I(S_1,I_1)}{\mathcal{G}_1^I(S,I)}\right)\left(\frac{\mathcal{G}_1^I(S,I)}{\mathcal{G}_1^I(S_1,I_1)}-\frac{\mathcal{J}_2(I)}{\mathcal{J}_2(I_1)}\right)\\&\quad+\frac{\mu[b\mathcal{J}_2(I_1)\aleph_1(S_1,V_1)+\varepsilon\mathcal{J}_3(V_1)\aleph_3(S_1,I_1)]}{a\varepsilon\mathcal{J}_2(I_1)\mathcal{J}_3(V_1)}\big(\mathcal{J}_2(I_1)-\mathcal{J}_2(I_2)\big)\mathcal{J}_4(C).\end{aligned}\tag{25}$$

The arithmetic–geometric mean inequality ($\frac{1}{n}\sum_{i=1}^n \chi_i \geq \sqrt[n]{\prod_{i=1}^n \chi_i}$) implies that

$$\begin{aligned}&\frac{\aleph_1(S_1,V_1)}{\aleph_1(S,V_1)}+\frac{\aleph_1(S,V)\mathcal{J}_1(L_1)}{\aleph_1(S_1,V_1)\mathcal{J}_1(L)}+\frac{\mathcal{J}_1(L)\mathcal{J}_2(I_1)}{\mathcal{J}_1(L_1)\mathcal{J}_2(I)}+\frac{\mathcal{J}_2(I)\mathcal{J}_3(V_1)}{\mathcal{J}_2(I_1)\mathcal{J}_3(V)}+\frac{\aleph_1(S,V_1)\mathcal{J}_3(V)}{\aleph_1(S,V)\mathcal{J}_3(V_1)}\geq 5,\\&\frac{\aleph_1(S_1,V_1)}{\aleph_1(S,V_1)}+\frac{\aleph_3(S,I)\mathcal{J}_1(L_1)}{\aleph_3(S_1,I_1)\mathcal{J}_1(L)}+\frac{\mathcal{J}_1(L)\mathcal{J}_2(I_1)}{\mathcal{J}_1(L_1)\mathcal{J}_2(I)}+\frac{\aleph_1(S,V_1)\aleph_3(S_1,I_1)\mathcal{J}_2(I)}{\aleph_1(S_1,V_1)\aleph_3(S,I)\mathcal{J}_2(I_1)}\geq 4,\\&\frac{\aleph_1(S_1,V_1)}{\aleph_1(S,V_1)}+\frac{\aleph_2(S,L)\mathcal{J}_1(L_1)}{\aleph_2(S_1,L_1)\mathcal{J}_1(L)}+\frac{\aleph_1(S,V_1)\aleph_2(S_1,L_1)\mathcal{J}_1(L)}{\aleph_1(S_1,V_1)\aleph_2(S,L)\mathcal{J}_1(L_1)}\geq 3.\end{aligned}$$

We have $C_2=\mathcal{J}_4^{-1}(\frac{a}{\mu}(\Re_1-1))\leq 0$ when $\Re_1\leq 1$. It follows that $\dot{C}(t)=\sigma(\mathcal{J}_2(I)-\frac{\pi}{\sigma})\mathcal{J}_4(C)=\sigma(\mathcal{J}_2(I(t))-\mathcal{J}_2(I_2))\mathcal{J}_4(C(t))\leq 0$ for all $C>0$, which implies that $\mathcal{J}_2(I_1)\leq\mathcal{J}_2(I_2)$. Moreover, since Φ_1 is always positive and approaches its global minimum at $Ð_1$, then from Eq. (25) we have $\frac{d\Phi_1}{dt}\leq 0$ for all $S,L,I,V,C>0$ with equality holding when $S=S_1$, $L=L_1$, $I=I_1$, $V=V_1$, and $C=0$. Let Υ_1' be the largest invariant subset of $\Upsilon_1=\{(S,L,I,V,C):\frac{d\Phi_1}{dt}=0\}$. It can be seen that $\Upsilon_1'=\{Ð_1\}$ and $Ð_1$ is G.A.S. using LaSalle's invariance principle. □

Theorem 3 *Let* $\Re_1>1$ *and Conditions* (H1)–(H4) *and* (H6) *be satisfied, then* $Ð_2$ *is G.A.S.*

Proof Define a function $\Phi_2(S,L,I,V,C)$ as follows:

$$\begin{aligned}\Phi_2 &= S - S_2 - \int_{S_2}^{S} \frac{\aleph_1(S_2,V_2)}{\aleph_1(\varkappa,V_2)}\,d\varkappa + L - L_2 - \int_{L_2}^{L} \frac{\mathcal{J}_1(L_2)}{\mathcal{J}_1(\varkappa)}\,d\varkappa \\ &\quad + \frac{b\mathcal{J}_2(I_2)\aleph_1(S_2,V_2) + \varepsilon\mathcal{J}_3(V_2)\aleph_3(S_2,I_2)}{\varepsilon(a+\mu\mathcal{J}_4(C_2))\mathcal{J}_2(I_2)\mathcal{J}_3(V_2)}\left(I - I_2 - \int_{I_2}^{I} \frac{\mathcal{J}_2(I)}{\mathcal{J}_2(\varkappa)}\,d\varkappa\right) \\ &\quad + \frac{\aleph_1(S_2,V_2)}{\varepsilon\mathcal{J}_3(V_2)}\left(V - V_2 - \int_{V_2}^{V} \frac{\mathcal{J}_3(V_2)}{\mathcal{J}_3(\varkappa)}\,d\varkappa\right) \\ &\quad + \frac{\mu[b\mathcal{J}_2(I_2)\aleph_1(S_2,V_2) + \varepsilon\mathcal{J}_3(V_2)\aleph_3(S_2,I_2)]}{\sigma\varepsilon(a+\mu\mathcal{J}_4(C_2))\mathcal{J}_2(I_2)\mathcal{J}_3(V_2)}\left(C - C_2 - \int_{C_2}^{C} \frac{\mathcal{J}_4(C_2)}{\mathcal{J}_4(\varkappa)}\,d\varkappa\right).\end{aligned}$$

We calculate $\frac{d\Phi_2}{dt}$ as follows:

$$\begin{aligned}\frac{d\Phi_2}{dt} &= \left(1 - \frac{\aleph_1(S_2,V_2)}{\aleph_1(S,V_2)}\right)\big(¥(S) - \aleph_1(S,V) - \aleph_2(S,L) - \aleph_3(S,I)\big) \\ &\quad + \left(1 - \frac{\mathcal{J}_1(L_2)}{\mathcal{J}_1(L)}\right)\big(\aleph_1(S,V) + \aleph_2(S,L) + \aleph_3(S,I) - (\lambda+\gamma)\mathcal{J}_1(L)\big) \\ &\quad + \frac{b\mathcal{J}_2(I_2)\aleph_1(S_2,V_2) + \varepsilon\mathcal{J}_3(V_2)\aleph_3(S_2,I_2)}{\varepsilon(a+\mu\mathcal{J}_4(C_2))\mathcal{J}_2(I_2)\mathcal{J}_3(V_2)}\left(1 - \frac{\mathcal{J}_2(I_2)}{\mathcal{J}_2(I)}\right) \\ &\quad \times \big(\lambda\mathcal{J}_1(L) - a\mathcal{J}_2(I) - \mu\mathcal{J}_4(C)\mathcal{J}_2(I)\big) + \frac{\aleph_1(S_2,V_2)}{\varepsilon\mathcal{J}_3(V_2)}\left(1 - \frac{\mathcal{J}_3(V_2)}{\mathcal{J}_3(V)}\right) \\ &\quad \times \big(b\mathcal{J}_2(I) - \varepsilon\mathcal{J}_3(V)\big) + \frac{\mu[b\mathcal{J}_2(I_2)\aleph_1(S_2,V_2) + \varepsilon\mathcal{J}_3(V_2)\aleph_3(S_2,I_2)]}{\sigma\varepsilon(a+\mu\mathcal{J}_4(C_2))\mathcal{J}_2(I_2)\mathcal{J}_3(V_2)} \\ &\quad \times \left(1 - \frac{\mathcal{J}_4(C_2)}{\mathcal{J}_4(C)}\right)\big(\sigma\mathcal{J}_4(C)\mathcal{J}_2(I) - \pi\mathcal{J}_4(C)\big). \qquad (26)\end{aligned}$$

Collecting the terms of Eq. (26) and using the equilibrium conditions for $Ð_2$

$$¥(S_2) = \aleph_1(S_2,V_2) + \aleph_2(S_2,L_2) + \aleph_3(S_2,I_2) = (\lambda+\gamma)\mathcal{J}_1(L_2),$$

$$\lambda\mathcal{J}_1(L_2) = \big(a + \mu\mathcal{J}_4(C_2)\big)\mathcal{J}_2(I_2), \qquad \mathcal{J}_2(I_2) = \frac{\pi}{\sigma}, \qquad \mathcal{J}_3(V_2) = \frac{b\mathcal{J}_2(I_2)}{\varepsilon},$$

we obtain

$$\begin{aligned}\aleph_1(S_2,V_2) + \aleph_3(S_2,I_2) &= \frac{b\mathcal{J}_2(I_2)\aleph_1(S_2,V_2) + \varepsilon\mathcal{J}_3(V_2)\aleph_3(S_2,I_2)}{\varepsilon\mathcal{J}_2(I_2)\mathcal{J}_3(V_2)}\mathcal{J}_2(I_2) \\ &= \frac{\lambda[b\mathcal{J}_2(I_2)\aleph_1(S_2,V_2) + \varepsilon\mathcal{J}_3(V_2)\aleph_3(S_2,I_2)]}{\varepsilon(a+\mu\mathcal{J}_4(C_2))\mathcal{J}_2(I_2)\mathcal{J}_3(V_2)}\mathcal{J}_1(L_2).\end{aligned}$$

In addition, we get

$$\begin{aligned}\frac{d\Phi_2}{dt} &= \big(¥(S) - ¥(S_2)\big)\left(1 - \frac{\aleph_1(S_2,V_2)}{\aleph_1(S,V_2)}\right) + \big(\aleph_1(S_2,V_2) + \aleph_2(S_2,L_2) + \aleph_3(S_2,I_2)\big) \\ &\quad \times \left(1 - \frac{\aleph_1(S_2,V_2)}{\aleph_1(S,V_2)}\right) + \aleph_1(S_2,V_2)\frac{\aleph_1(S,V)}{\aleph_1(S,V_2)} + \aleph_2(S_2,L_2)\frac{\aleph_2(S,L)\aleph_1(S_2,V_2)}{\aleph_2(S_2,L_2)\aleph_1(S,V_2)} \\ &\quad + \aleph_3(S_2,I_2)\frac{\aleph_3(S,I)\aleph_1(S_2,V_2)}{\aleph_3(S_2,I_2)\aleph_1(S,V_2)} - \aleph_2(S_2,L_2)\frac{\mathcal{J}_1(L)}{\mathcal{J}_1(L_2)} - \aleph_1(S_2,V_2)\frac{\aleph_1(S,V)\mathcal{J}_1(L_2)}{\aleph_1(S_2,V_2)\mathcal{J}_1(L)}\end{aligned}$$

$$
\begin{aligned}
&- \aleph_2(S_2,L_2)\frac{\aleph_2(S,L)\mathcal{J}_1(L_2)}{\aleph_2(S_2,L_2)\mathcal{J}_1(L)} - \aleph_3(S_2,I_2)\frac{\aleph_3(S,I)\mathcal{J}_1(L_2)}{\aleph_3(S_2,I_2)\mathcal{J}_1(L)}\\
&+ \aleph_1(S_2,V_2) + \aleph_2(S_2,L_2) + \aleph_3(S_2,I_2) - \aleph_3(S_2,I_2)\frac{\mathcal{J}_2(I)}{\mathcal{J}_2(I_2)}\\
&- \aleph_1(S_2,V_2)\frac{\mathcal{J}_1(L)\mathcal{J}_2(I_2)}{\mathcal{J}_1(L_2)\mathcal{J}_2(I)} - \aleph_3(S_2,I_2)\frac{\mathcal{J}_1(L)\mathcal{J}_2(I_2)}{\mathcal{J}_1(L_2)\mathcal{J}_2(I)} + \aleph_1(S_2,V_2) + \aleph_3(S_2,I_2)\\
&- \aleph_1(S_2,V_2)\frac{\mathcal{J}_3(V)}{\mathcal{J}_3(V_2)} - \aleph_1(S_2,V_2)\frac{\mathcal{J}_2(I)\mathcal{J}_3(V_2)}{\mathcal{J}_2(I_2)\mathcal{J}_3(V)} + \aleph_1(S_2,V_2). \qquad (27)
\end{aligned}
$$

Rearranging Eq. (27), we obtain

$$
\begin{aligned}
\frac{d\Phi_2}{dt} &= \big(\curlyvee(S) - \curlyvee(S_2)\big)\left(1 - \frac{\aleph_1(S_2,V_2)}{\aleph_1(S,V_2)}\right)\\
&\quad + \aleph_1(S_2,V_2)\left[5 - \frac{\aleph_1(S_2,V_2)}{\aleph_1(S,V_2)} - \frac{\aleph_1(S,V)\mathcal{J}_1(L_2)}{\aleph_1(S_2,V_2)\mathcal{J}_1(L)}\right.\\
&\quad \left. - \frac{\mathcal{J}_1(L)\mathcal{J}_2(I_2)}{\mathcal{J}_1(L_2)\mathcal{J}_2(I)} - \frac{\mathcal{J}_2(I)\mathcal{J}_3(V_2)}{\mathcal{J}_2(I_2)\mathcal{J}_3(V)} - \frac{\aleph_1(S,V_2)\mathcal{J}_3(V)}{\aleph_1(S,V)\mathcal{J}_3(V_2)}\right] + \aleph_2(S_2,L_2)\left[3 - \frac{\aleph_1(S_2,V_2)}{\aleph_1(S,V_2)}\right.\\
&\quad \left. - \frac{\aleph_2(S,L)\mathcal{J}_1(L_2)}{\aleph_2(S_2,L_2)\mathcal{J}_1(L)} - \frac{\aleph_1(S,V_2)\aleph_2(S_2,L_2)\mathcal{J}_1(L)}{\aleph_1(S_2,V_2)\aleph_2(S,L)\mathcal{J}_1(L_2)}\right] + \aleph_3(S_2,I_2)\left[4 - \frac{\aleph_1(S_2,V_2)}{\aleph_1(S,V_2)}\right.\\
&\quad \left. - \frac{\aleph_3(S,I)\mathcal{J}_1(L_2)}{\aleph_3(S_2,I_2)\mathcal{J}_1(L)} - \frac{\mathcal{J}_1(L)\mathcal{J}_2(I_2)}{\mathcal{J}_1(L_2)\mathcal{J}_2(I)} - \frac{\aleph_1(S,V_2)\aleph_3(S_2,I_2)\mathcal{J}_2(I)}{\aleph_1(S_2,V_2)\aleph_3(S,I)\mathcal{J}_2(I_2)}\right]\\
&\quad + \aleph_1(S_2,V_2)\left[\frac{\aleph_1(S,V)}{\aleph_1(S,V_2)} - \frac{\mathcal{J}_3(V)}{\mathcal{J}_3(V_2)} - 1 + \frac{\aleph_1(S,V_2)\mathcal{J}_3(V)}{\aleph_1(S,V)\mathcal{J}_3(V_2)}\right]\\
&\quad + \aleph_2(S_2,L_2)\left[\frac{\aleph_2(S,L)\aleph_1(S_2,V_2)}{\aleph_2(S_2,L_2)\aleph_1(S,V_2)} - \frac{\mathcal{J}_1(L)}{\mathcal{J}_1(L_2)} - 1 + \frac{\aleph_1(S,V_2)\aleph_2(S_2,L_2)\mathcal{J}_1(L)}{\aleph_1(S_2,V_2)\aleph_2(S,L)\mathcal{J}_1(L_2)}\right]\\
&\quad + \aleph_3(S_2,I_2)\left[\frac{\aleph_3(S,I)\aleph_1(S_2,V_2)}{\aleph_3(S_2,I_2)\aleph_1(S,V_2)} - \frac{\mathcal{J}_2(I)}{\mathcal{J}_2(I_2)} - 1 + \frac{\aleph_1(S,V_2)\aleph_3(S_2,I_2)\mathcal{J}_2(I)}{\aleph_1(S_2,V_2)\aleph_3(S,I)\mathcal{J}_2(I_2)}\right].
\end{aligned}
$$

Using the definition of $\mathcal{G}_2^U(S,U)$ given in (21), we obtain

$$
\begin{aligned}
&\frac{\aleph_2(S,L)\aleph_1(S_2,V_2)}{\aleph_2(S_2,L_2)\aleph_1(S,V_2)} - \frac{\mathcal{J}_1(L)}{\mathcal{J}_1(L_2)} - 1 + \frac{\aleph_1(S,V_2)\aleph_2(S_2,L_2)\mathcal{J}_1(L)}{\aleph_1(S_2,V_2)\aleph_2(S,L)\mathcal{J}_1(L_2)}\\
&\quad = \frac{\mathcal{G}_2^L(S,L)}{\mathcal{G}_2^L(S_2,L_2)} - \frac{\mathcal{J}_1(L)}{\mathcal{J}_1(L_2)} - 1 + \frac{\mathcal{J}_1(L)\mathcal{G}_2^L(S_2,L_2)}{\mathcal{J}_1(L_2)\mathcal{G}_2^L(S,L)}
\end{aligned}
$$

and

$$
\begin{aligned}
&\frac{\aleph_3(S,I)\aleph_1(S_2,V_2)}{\aleph_3(S_2,I_2)\aleph_1(S,V_2)} - \frac{\mathcal{J}_2(I)}{\mathcal{J}_2(I_2)} - 1 + \frac{\aleph_1(S,V_2)\aleph_3(S_2,I_2)\mathcal{J}_2(I)}{\aleph_1(S_2,V_2)\aleph_3(S,I)\mathcal{J}_2(I_2)}\\
&\quad = \frac{\mathcal{G}_2^I(S,I)}{\mathcal{G}_2^I(S_2,I_2)} - \frac{\mathcal{J}_2(I)}{\mathcal{J}_2(I_2)} - 1 + \frac{\mathcal{J}_2(I)\mathcal{G}_2^I(S_2,I_2)}{\mathcal{J}_2(I_2)\mathcal{G}_2^I(S,I)}.
\end{aligned}
$$

Then

$$
\begin{aligned}
\frac{d\Phi_2}{dt} &= \big(\curlyvee(S) - \curlyvee(S_2)\big)\left(1 - \frac{\aleph_1(S_2,V_2)}{\aleph_1(S,V_2)}\right) + \aleph_1(S_2,V_2)\left[5 - \frac{\aleph_1(S_2,V_2)}{\aleph_1(S,V_2)}\right.\\
&\quad \left. - \frac{\aleph_1(S,V)\mathcal{J}_1(L_2)}{\aleph_1(S_2,V_2)\mathcal{J}_1(L)} - \frac{\mathcal{J}_1(L)\mathcal{J}_2(I_2)}{\mathcal{J}_1(L_2)\mathcal{J}_2(I)} - \frac{\mathcal{J}_2(I)\mathcal{J}_3(V_2)}{\mathcal{J}_2(I_2)\mathcal{J}_3(V)} - \frac{\aleph_1(S,V_2)\mathcal{J}_3(V)}{\aleph_1(S,V)\mathcal{J}_3(V_2)}\right]
\end{aligned}
$$

$$
\begin{aligned}
&+\aleph_2(S_2,L_2)\left[3-\frac{\aleph_1(S_2,V_2)}{\aleph_1(S,V_2)}-\frac{\aleph_2(S,L)\mathcal{J}_1(L_2)}{\aleph_2(S_2,L_2)\mathcal{J}_1(L)}-\frac{\aleph_1(S,V_2)\aleph_2(S_2,L_2)\mathcal{J}_1(L)}{\aleph_1(S_2,V_2)\aleph_2(S,L)\mathcal{J}_1(L_2)}\right]\\
&+\aleph_3(S_2,I_2)\left[4-\frac{\aleph_1(S_2,V_2)}{\aleph_1(S,V_2)}-\frac{\aleph_3(S,I)\mathcal{J}_1(L_2)}{\aleph_3(S_2,I_2)\mathcal{J}_1(L)}-\frac{\mathcal{J}_1(L)\mathcal{J}_2(I_2)}{\mathcal{J}_1(L_2)\mathcal{J}_2(I)}\right.\\
&\left.-\frac{\aleph_1(S,V_2)\aleph_3(S_2,I_2)\mathcal{J}_2(I)}{\aleph_1(S_2,V_2)\aleph_3(S,I)\mathcal{J}_2(I_2)}\right]\\
&+\aleph_1(S_2,V_2)\left(1-\frac{\aleph_1(S,V_2)}{\aleph_1(S,V)}\right)\left(\frac{\aleph_1(S,V)}{\aleph_1(S,V_2)}-\frac{\mathcal{J}_3(V)}{\mathcal{J}_3(V_2)}\right)\\
&+\aleph_2(S_2,L_2)\left(1-\frac{\mathcal{G}_2^L(S_2,L_2)}{\mathcal{G}_2^L(S,L)}\right)\left(\frac{\mathcal{G}_2^L(S,L)}{\mathcal{G}_2^L(S_2,L_2)}-\frac{\mathcal{J}_1(L)}{\mathcal{J}_1(L_2)}\right)\\
&+\aleph_3(S_2,I_2)\left(1-\frac{\mathcal{G}_2^I(S_2,I_2)}{\mathcal{G}_2^I(S,I)}\right)\left(\frac{\mathcal{G}_2^I(S,I)}{\mathcal{G}_2^I(S_2,I_2)}-\frac{\mathcal{J}_2(I)}{\mathcal{J}_2(I_2)}\right).
\end{aligned}
$$

Hence, if $\Re_1>1$, then $\frac{d\Phi_2}{dt}\le 0$ for all $S,L,I,V,C>0$ and $\frac{d\Phi_2}{dt}=0$ when $S=S_2$, $L=L_2$, $I=I_2$, and $V=V_2$. Define $\Upsilon_2=\{(S,L,I,V,C):\frac{d\Phi_2}{dt}=0\}$ and Υ_2' is the largest invariant subset of Υ_2. The solutions of system (2) converge to Υ_2' which contains elements with $S(t)=S_2$, $L(t)=L_2$, $I(t)=I_2$, $V(t)=V_2$. Then $\dot I(t)=0$ and from the third equation of system (2), we have $0=\dot I(t)=\lambda\mathcal{J}_1(L_2)-a\mathcal{J}_2(I_2)-\mu\mathcal{J}_4(C(t))\mathcal{J}_2(I_2)$, which gives $C(t)=C_2$ for all t. Therefore, $\Upsilon_2'=\{Đ_2\}$. Applying LaSalle's invariance principle, we get that $Đ_2$ is G.A.S. □

6 Example and numerical simulations

In this section, we consider the following illustrative example:

$$
\begin{cases}
\dot S(t)=\rho-\alpha S+\zeta S(1-\frac{S}{S_{\max}})-\frac{S^n}{1+\delta S^n}(\frac{\eta_1 V}{1+\beta_1 V}+\frac{\eta_2 L}{1+\beta_2 L}+\frac{\eta_3 I}{1+\beta_3 I}),\\
\dot L(t)=\frac{S^n}{1+\delta S^n}(\frac{\eta_1 V}{1+\beta_1 V}+\frac{\eta_2 L}{1+\beta_2 L}+\frac{\eta_3 I}{1+\beta_3 I})-(\lambda+\gamma)L,\\
\dot I(t)=\lambda L-aI-\mu CI,\\
\dot V(t)=bI-\varepsilon V,\\
\dot C(t)=\sigma CI-\pi C.
\end{cases}
\tag{28}
$$

This example is a special case of system (2) which considers the following forms:

- The intrinsic growth rate of healthy CD4$^+$T cells

$$
¥(S)=\rho-\alpha S+\zeta S\left(1-\frac{S}{S_{\max}}\right).
$$

Here, we consider another source for producing healthy CD4$^+$T cells that is the proliferation of existing healthy cells in the body [4]. The maximum proliferation rate of healthy CD4$^+$T cells is given by $\zeta>0$. It is well known that there is a maximum level of healthy CD4$^+$T cell concentration in the body which is described by the parameter $S_{\max}>0$. If the concentration reaches $S_{\max}$, it should decrease. We assume that $\zeta<\alpha$ [52]. It is clear that $¥(0)=\rho>0$ and $¥(S_0)=0$, where

$$
S_0=\frac{S_{\max}}{2\zeta}\left(\zeta-\alpha+\sqrt{(\zeta-\alpha)^2+\frac{4\rho\zeta}{S_{\max}}}\right).
$$

In addition, we have

$$\curlyvee'(S) = \zeta - \alpha - \frac{2\zeta S}{S_{\max}} < 0. \tag{29}$$

Clearly, $\curlyvee(S) > 0$ whereas $\curlyvee'(S) < 0$ for all $S \in [0, S_0)$. Hence, Condition (H1) holds true.

- The virus-cell, silent cell-cell, and active cell-cell incidence rates of infection are, respectively, given by

$$\aleph_1(S,V) = \frac{\eta_1 S^n V}{(1+\delta S^n)(1+\beta_1 V)},$$
$$\aleph_2(S,L) = \frac{\eta_2 S^n L}{(1+\delta S^n)(1+\beta_2 L)},$$
$$\aleph_3(S,I) = \frac{\eta_3 S^n I}{(1+\delta S^n)(1+\beta_3 I)}.$$

The parameters $\eta_i > 0$, $i = 1,2,3$, account for the infection rate constants. Parameters n, δ, β_i, $i = 1,2,3$, are positive constants. It is clear that

$$\aleph_1(S,V) > 0, \quad \aleph_2(S,L) > 0, \quad \aleph_3(S,I) > 0 \quad \text{for all } S,L,I,V > 0,$$
$$\aleph_1(0,V) = \aleph_2(0,L) = \aleph_3(0,I) = 0 \quad \text{for all } L,I,V > 0,$$
$$\aleph_1(S,0) = \aleph_2(S,0) = \aleph_3(S,0) = 0 \quad \text{for all } S > 0.$$

Further, we have

$$\frac{\partial \aleph_1(S,V)}{\partial S} = \frac{n\eta_1 S^{n-1} V}{(1+\delta S^n)^2(1+\beta_1 V)} > 0, \quad \frac{\partial \aleph_2(S,L)}{\partial S} = \frac{n\eta_2 S^{n-1} L}{(1+\delta S^n)^2(1+\beta_2 L)} > 0,$$
$$\frac{\partial \aleph_3(S,I)}{\partial S} = \frac{n\eta_3 S^{n-1} I}{(1+\delta S^n)^2(1+\beta_3 I)} > 0, \quad \frac{\partial \aleph_1(S,V)}{\partial V} = \frac{\eta_1 S^n}{(1+\delta S^n)(1+\beta_1 V)^2} > 0,$$
$$\frac{\partial \aleph_2(S,L)}{\partial L} = \frac{\eta_2 S^n}{(1+\delta S^n)(1+\beta_2 L)^2} > 0, \quad \frac{\partial \aleph_3(S,I)}{\partial I} = \frac{\eta_3 S^n}{(1+\delta S^n)(1+\beta_3 I)^2} > 0,$$
$$\frac{\partial \aleph_1(S,0)}{\partial V} = \frac{\eta_1 S^n}{1+\delta S^n} > 0, \quad \frac{\partial \aleph_2(S,0)}{\partial L} = \frac{\eta_2 S^n}{1+\delta S^n} > 0, \quad \frac{\partial \aleph_3(S,0)}{\partial I} = \frac{\eta_3 S^n}{1+\delta S^n} > 0,$$

for all $S,L,I,V > 0$. Furthermore, we have

$$\frac{d}{dS}\left(\frac{\partial \aleph_1(S,0)}{\partial V}\right) = \frac{n\eta_1 S^{n-1}}{(1+\delta S^n)^2} > 0,$$
$$\frac{d}{dS}\left(\frac{\partial \aleph_2(S,0)}{\partial L}\right) = \frac{n\eta_2 S^{n-1}}{(1+\delta S^n)^2} > 0,$$
$$\frac{d}{dS}\left(\frac{\partial \aleph_3(S,0)}{\partial I}\right) = \frac{n\eta_3 S^{n-1}}{(1+\delta S^n)^2} > 0 \text{ for all } S > 0.$$

All the above discussion ensures that Condition (H2) is confirmed.

- The natural death rate of the silent/active HIV-infected cells, HIV particles, and HIV-specific CTLs

$$\mathcal{J}_k(x) = x, \quad k = 1, 2, 3, 4.$$

Obviously, Condition (H3) is valid.

In addition, we have

$$\begin{aligned}
&\frac{\partial}{\partial V}\left(\frac{\aleph_1(S,V)}{\mathcal{J}_3(V)}\right) = \frac{\partial}{\partial V}\left(\frac{\eta_1 S^n}{(1+\delta S^n)(1+\beta_1 V)}\right) = -\frac{\eta_1\beta_1 S^n}{(1+\beta_1 V)^2(1+\delta S^n)} < 0,\\
&\frac{\partial}{\partial L}\left(\frac{\aleph_2(S,L)}{\mathcal{J}_1(L)}\right) = \frac{\partial}{\partial L}\left(\frac{\eta_2 S^n}{(1+\delta S^n)(1+\beta_2 L)}\right) = -\frac{\eta_2\beta_2 S^n}{(1+\beta_2 L)^2(1+\delta S^n)} < 0,\\
&\frac{\partial}{\partial I}\left(\frac{\aleph_3(S,I)}{\mathcal{J}_2(I)}\right) = \frac{\partial}{\partial I}\left(\frac{\eta_3 S^n}{(1+\delta S^n)(1+\beta_3 I)}\right) = -\frac{\eta_3\beta_3 S^n}{(1+\beta_3 I)^2(1+\delta S^n)} < 0,
\end{aligned}$$

for all $S, L, I, V > 0$. Therefore, Condition (H4) is also verified. On the other hand, we have $\mathcal{J}_k'(x) = 1$, and then

$$\begin{aligned}
&\digamma_1(S) = \frac{\partial \aleph_1(S,0)}{\partial V} = \frac{\eta_1 S^n}{1+\delta S^n},\\
&\digamma_2(S) = \frac{\partial \aleph_2(S,0)}{\partial L} = \frac{\eta_2 S^n}{1+\delta S^n},\\
&\digamma_3(S) = \frac{\partial \aleph_3(S,0)}{\partial L} = \frac{\eta_3 S^n}{1+\delta S^n}.
\end{aligned}$$

Clearly, $\frac{\digamma_2(S)}{\digamma_1(S)} = \frac{\eta_2}{\eta_1}$ and $\frac{\digamma_3(S)}{\digamma_1(S)} = \frac{\eta_3}{\eta_1}$, hence Condition (H5) is satisfied. In addition,

$$\begin{aligned}
&\mathcal{G}_i^L(S,L) = \frac{\aleph_2(S,L)}{\aleph_1(S,V_i)} = \frac{\eta_2(1+\beta_1 V_i)L}{\eta_1(1+\beta_2 L)V_i}, \qquad \mathcal{G}_i^L(S_i,L_i) = \frac{\aleph_2(S_i,L_i)}{\aleph_1(S_i,V_i)} = \frac{\eta_2(1+\beta_1 V_i)L_i}{\eta_1(1+\beta_2 L_i)V_i},\\
&\mathcal{G}_i^I(S,I) = \frac{\aleph_3(S,I)}{\aleph_1(S,V_i)} = \frac{\eta_3(1+\beta_1 V_i)I}{\eta_1(1+\beta_3 I)V_i}, \qquad \mathcal{G}_i^I(S_i,I_i) = \frac{\aleph_3(S_i,I_i)}{\aleph_1(S_i,V_i)} = \frac{\eta_3(1+\beta_1 V_i)I_i}{\eta_1(1+\beta_3 I_i)V_i},
\end{aligned}$$

and

$$\begin{aligned}
&\left(\mathcal{G}_i^L(S,L) - \mathcal{G}_i^L(S_i,L_i)\right)\left(\frac{\mathcal{G}_i^L(S,L)}{L} - \frac{\mathcal{G}_i^L(S_i,L_i)}{L_i}\right) = -\frac{\beta_2\eta_2^2(1+\beta_1 V_i)^2(L-L_i)^2}{\eta_1^2 V_1^2(1+\beta_2 L_i)^2(1+\beta_2 L)^2} \le 0,\\
&\left(\mathcal{G}_i^I(S,I) - \mathcal{G}_i^I(S_i,I_i)\right)\left(\frac{\mathcal{G}_i^I(S,I)}{I} - \frac{\mathcal{G}_i^I(S_i,I_i)}{I_i}\right) = -\frac{\beta_3\eta_3^2(1+\beta_1 V_i)^2(I-I_i)^2}{\eta_1^2 V_1^2(1+\beta_3 I_i)^2(1+\beta_3 I)^2} \le 0,
\end{aligned}$$

for all $L, I > 0$, $S \in (0, S_0)$, where $i = 1, 2$. Hence, Condition (H6) is ensured. Consequently, the validity of Conditions (H1)–(H6) guarantees that the global stability results demonstrated in Theorems 1–3 are valid for this example. Thus, the threshold parameters for system (28) are given by

$$\begin{aligned}
&\Re_0 = \frac{S_0^n[b\lambda\eta_1 + \varepsilon(a\eta_2 + \lambda\eta_3)]}{a\varepsilon(\lambda+\gamma)(1+\delta S_0^n)},\\
&\Re_1 = \frac{\sigma\lambda S_2^n}{a\pi(\lambda+\gamma)(1+\delta S_2^n)}\left(\frac{b\pi\eta_1}{\varepsilon\sigma + b\pi\beta_1} + \frac{\eta_2 L_2}{1+\beta_2 L_2} + \frac{\pi\eta_3}{\sigma + \pi\beta_3}\right).
\end{aligned} \tag{30}$$

Table 2 Some values of the parameters of model (28)

Parameter	Value	Parameter	Value	Parameter	Value
ρ	10	η_2	Varied	μ	0.2
α	0.01	η_3	Varied	ε	2
ζ	0.005	a	0.5	β_1	0.1
S_{max}	1200	γ	0.2	β_2	0.2
δ	0.7	λ	0.2	β_3	0.3
n	2	b	5	σ	Varied
η_1	Varied	π	0.1	ϖ	0.3

To solve system (28) numerically, we fix the values of some parameters (see Table 2) and the others will be varied.

6.1 Stability of the equilibria

In this subsection, we consider the following initial condition for model (28):

IV-1: $(S(0), L(0), I(0), V(0), C(0)) = (930, 2, 0.6, 1.6, 0.4)$.

Choose the values of parameters η_1, η_2, η_3, and σ as follows.

Stability of $Ð_0$: $\eta_1 = 0.03$, $\eta_2 = 0.01$, $\eta_3 = 0.02$, and $\sigma = 0.03$. For this set of parameters, we have $\Re_0 = 0.17 < 1$. Figure 1 displays that the trajectories initiating with IV-1 reach the equilibrium $Ð_0 = (1061.32, 0, 0, 0, 0)$. This shows that $Ð_0$ is G.A.S. according to Theorem 1. In this case, the HIV particles will be cleared from the body.

Stability of $Ð_1$: $\eta_1 = 0.3$, $\eta_2 = 0.1$, $\eta_3 = 0.2$, and $\sigma = 0.03$. With such a choice, we get $\Re_1 = 0.85 < 1 < 1.71 = \Re_0$. It is clear that the equilibrium point $Ð_1$ exists with $Ð_1 = (878.74, 5.97, 2.39, 5.97, 0)$. Figure 1 displays that the trajectories initiating with IV-1 tend to $Ð_1$. Therefore, the numerical results support Theorem 2. This case represents the persistence of the HIV infection but with unstimulated CTL-mediated immune response.

Stability of $Ð_2$: $\eta_1 = 0.3$, $\eta_2 = 0.1$, $\eta_3 = 0.2$, and $\sigma = 0.1$. Then we calculate $\Re_1 = 1.37 > 1$. In Fig. 1, we show that $Ð_2 = (959.47, 3.42, 1, 2.5, 0.92)$ exists and it is G.A.S., and this agrees with Theorem 3. Hence, a chronic HIV infection with CTL-mediated immune response is attained.

6.2 Effect of CTC transmission

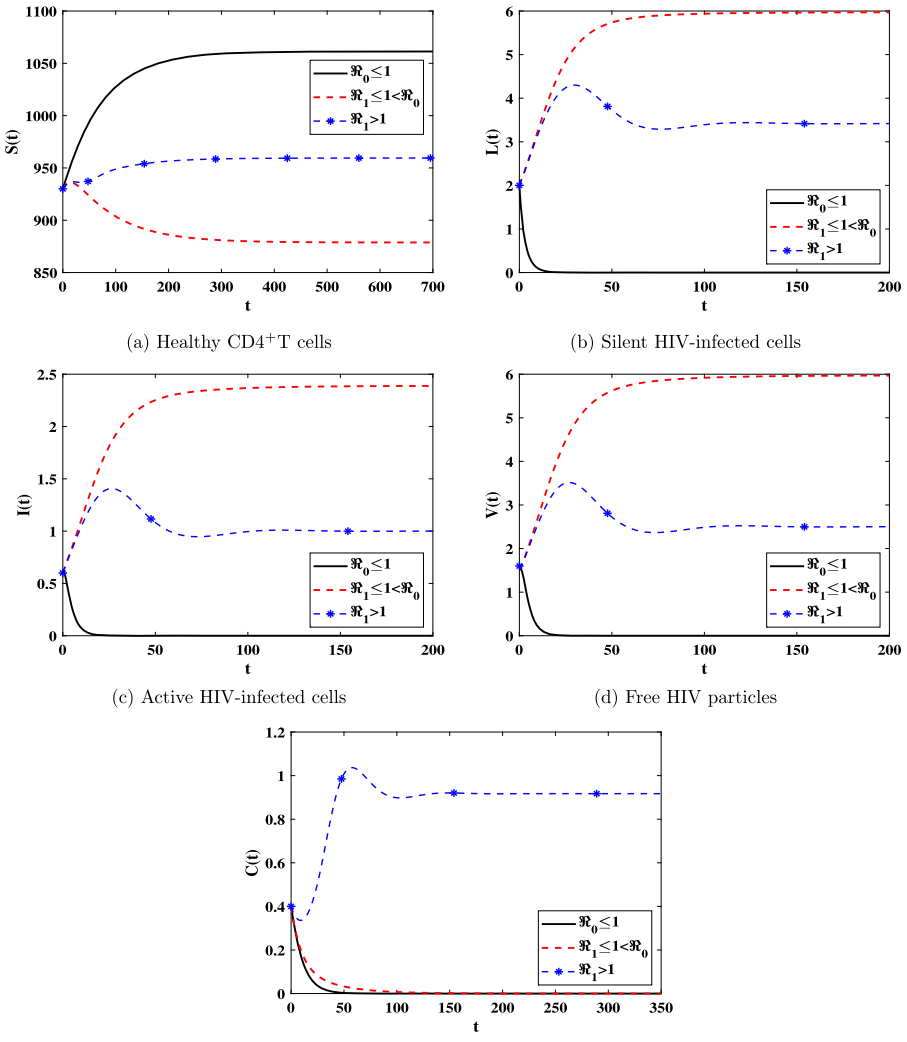
In this subsection, we investigate the influence of different modes of transmission on the HIV dynamics (28). We use the parameters given in Table 2 and choose the value $\sigma = 0.1$ with the following initial condition:

IV-2: $(S(0), L(0), I(0), V(0), C(0)) = (1000, 1.5, 0.5, 1.2, 0.2)$.

We choose four sets of parameters η_1, η_2, and η_3 and investigate the following illustrative cases:

Case (1): HIV dynamics with VTC, silent HIV-infected CTC, and active HIV-infected CTC transmissions: Here, we consider the parameters $\eta_1 = 0.3$, $\eta_2 = 0.1$, and $\eta_3 = 0.2$. Figure 2 and Table 3 show that the solutions of the system approach the equilibrium $Ð_2 = (959.47, 3.42, 1, 2.5, 0.92)$.

Case (2): HIV dynamics with both VTC and active HIV-infected CTC transmissions: In this case, we select the values $\eta_1 = 0.3$, $\eta_2 = 0$, and $\eta_3 = 0.2$. From Fig. 2 and



(a) Healthy CD4$^+$T cells (b) Silent HIV-infected cells

(c) Active HIV-infected cells (d) Free HIV particles

(e) HIV-specific CTLs

Figure 1 The behavior of solution trajectories of system (28)

Table 3, we observe that the solution trajectories converge to the equilibrium $Đ_2 = (981.63, 2.69, 1, 2.5, 0.19)$.

Case (3): HIV dynamics with only VTC transmission: Here, we consider the values $\eta_1 = 0.3$, $\eta_2 = \eta_3 = 0$. Figure 2 and Table 3 display that the solution trajectories approach the equilibrium $Đ_1 = (1040.56, 0.71, 0.29, 0.71, 0)$.

Case (4): HIV dynamics with only VTC transmission: In this situation, we pick the parameters $\eta_1 = 0.1$, $\eta_2 = \eta_3 = 0$. It is clear from Fig. 2 and Table 3 that the solution trajectories reach the equilibrium $Đ_0 = (1061.32, 0, 0, 0, 0)$.

From the above discussion, we note that the presence of silent HIV-infected CTC and/or active HIV-infected CTC transmissions increases the infection rate. As a result, the concentration of healthy CD4$^+$T cells is decreased, while the concentrations of silent/active HIV-infected cells, free HIV particles, and HIV-specific CTLs are increased as shown in Fig. 2 and Table 3.

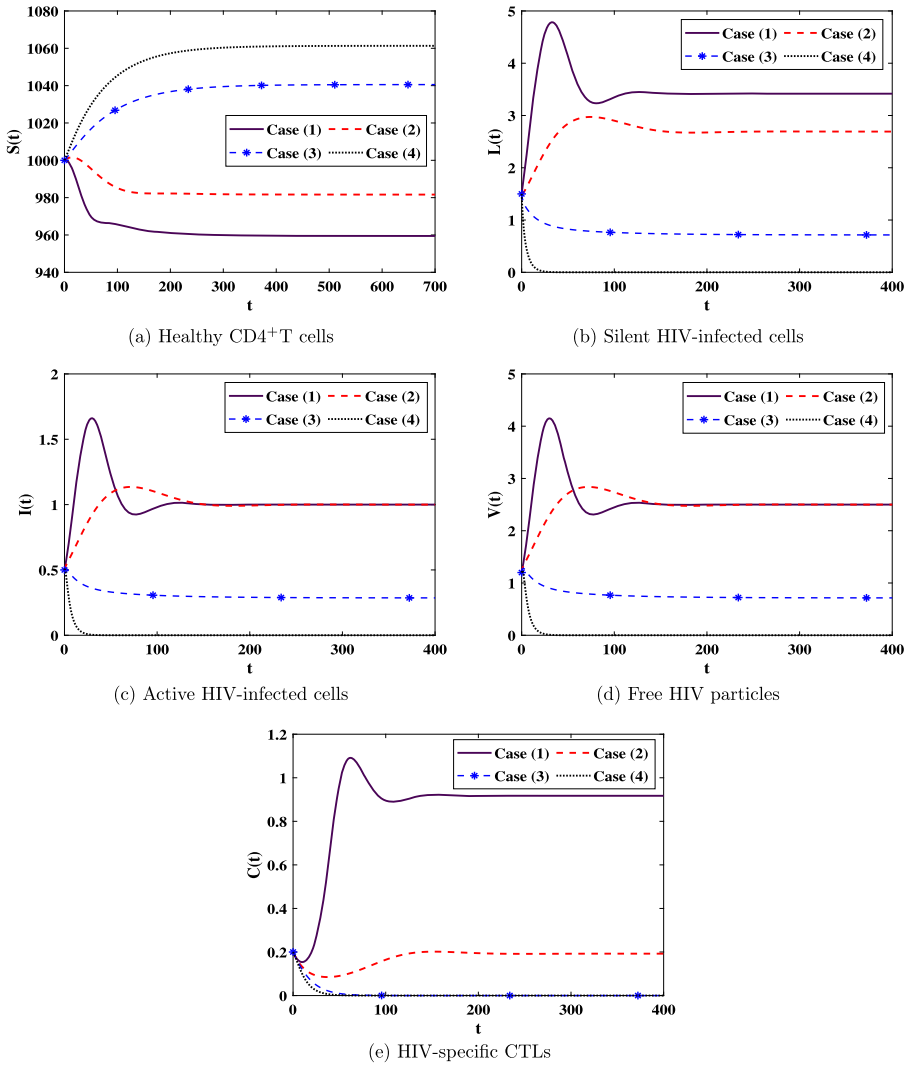


Figure 2 The evolution of HIV dynamics (28) under different modes of transmission

Table 3 Effect of the infection parameters η_i, $i = 1, 2, 3$, on HIV dynamics (28)

η_1	η_2	η_3	The equilibrium point
0.1	0	0	$Ð_0 = (1061.32, 0, 0, 0, 0)$
0.2	0	0	$Ð_0 = (1061.32, 0, 0, 0, 0)$
0.3	0	0	$Ð_1 = (1040.56, 0.71, 0.29, 0.71, 0)$
0.3	0	0.1	$Ð_1 = (999.65, 2.10, 0.84, 2.10, 0)$
0.3	0	0.2	$Ð_2 = (981.63, 2.69, 1, 2.5, 0.19)$
0.3	0.01	0.2	$Ð_2 = (979.70, 2.76, 1, 2.5, 0.26)$
0.3	0.1	0.2	$Ð_2 = (959.47, 3.42, 1, 2.5, 0.92)$
0.7	0.3	0.5	$Ð_2 = (743.87, 9.94, 1, 2.5, 7.44)$

7 Conclusion

In this paper, we developed and analyzed a general HIV dynamics model with CTL immune response. We incorporated two modes of transmission, VTC and CTC. The CTC infection is due to (i) the contact between healthy CD4$^+$T cells and silent HIV-infected cells, and (ii) the contact between healthy CD4$^+$T cells and active HIV-infected cells.

The incidence rates between the healthy CD4$^+$T cells and free HIV particles, silent infected cells, and active infected cells were given by general functions. Further, the production/proliferation as well as removal/death rates of all compartments were given by general nonlinear functions. We proved that the solutions of the model are nonnegative and bounded. We showed that the model has three possible equilibria: the infection-free equilibrium $Đ_0$, the chronic HIV infection equilibrium with inactive CTL-mediated immune response $Đ_1$, and the chronic HIV infection equilibrium with active CTL-mediated immune response $Đ_2$. The existence and global stability of the three equilibria were governed by two threshold parameters, $\Re_0$ (the basic HIV reproduction number) and $\Re_1$ (the HIV specific CTL-mediated immunity reproduction number). The global asymptotic stability of $Đ_0$, $Đ_1$, and $Đ_2$ was investigated by constructing Lyapunov functionals and utilizing LaSalle's invariance principle. We performed numerical simulations to illustrate the theoretical results. We showed that the inclusion of CTC transmission decreases the concentration of healthy CD4$^+$T cells and increases the concentrations of infected cells and free HIV particles. We observed that the inclusion of silent HIV-infected CTC and active HIV-infected CTC transmissions into the HIV infection model increases the basic reproduction number $\Re_0$, since $\Re_0 = \Re_{01} + \Re_{02} + \Re_{03} > \Re_{01}$. Therefore, neglecting the CTC transmission will lead to under-evaluated basic HIV reproduction number. We mention that our model can be extended to take into account time delay [53–56], reaction–diffusion [57, 58], and stochastic interactions [59].

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