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Global stability for a class of HIV infection models with cure of infected cells in eclipse stage and CTL immune response

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Abstract The aim of this work is to investigate the global dynamical behaviors of two human immunodeficiency virus infection models with cure of infected cells in eclipse stage and Cytotoxic T Lymphocytes (CTL) immune response. The first model is formalized by ordinary differential equations and the second is described by partial differential equations. By constructing appropriate Lyapunov functionals, the global stability of both models is established and characterized by two threshold parameters that are the basic reproduction number R_0 and the CTL immune response reproduction number R_1. Furthermore, the models and results presented in many previous studies are extended and improved.

Keywords HIV infection · CTL immune response · Diffusion · Global stability

1 Introduction

During human immunodeficiency virus (HIV) infection, a part of infected cells in eclipse stage returns to the uninfected state. In addition, Cytotoxic T Lymphocytes (CTL) cells play an important role in antiviral defense by killing the productive infected cells. Therefore, many mathematical models has been proposed to model the role of CTL immune response in HIV infection. One of the earliest of these models was proposed by Nowak and Bangham [1] in order to describe the interaction between susceptible cells, infected cells, viruses and CTL cells. Further, the model of [1] was improved by many researchers (see for example, [2–5]). All the above models have not considered the cure of infected cells in eclipse stage. For this reason, Rong et al. [6] constructed an HIV infection model with bilinear incidence rate and cure of infected cells in eclipse stage, but they not considered the CTL immune response and they only established the local stability of equilibria. The global stability was investigated by Buonomo and Vargas-De-L?on [7]. To improve the model [6], Hu et al. [8] replaced the bilinear incidence rate by a saturated incidence rate and they investigated the global stability of the improved model. In 2015, Wang et al. [9] replaced the saturated incidence rate by the Beddington–Deangelis functional response and they established the local and global stability of equilibria. In addition, Maziane et al. [10] replaced the saturated incidence rate by the Hattaf's [11] incidence rate and they extended the ODE model to a system with partial differential equations in order to take into account the mobility of the virus. The global stability of both models is investigated by constructing suitable Lyapunov functionals. In [12], Lv et al. replaced the bilinear incidence rate by the Beddington–DeAngelis functional response and they included the CTL immune response into the model [6]. By constructing suitable Lyapunov functionals, they investigated the global stability of equilibria in the terms of the basic reproduction number and the immune response reproduction number.

To extend the model of Lv et al. [12] and improve the ODE models presented in [6–10] by considering the effect of CTL immune response, we propose the following model

$$\frac{dT}{dt} = \lambda - \mu_T T(t) - f(T(t), V(t))V(t) + \rho E(t),$$

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$$\begin{aligned}
\frac{dE}{dt} &= f(T(t), V(t))V(t) - (\mu_E + \rho + \gamma)E(t),\\
\frac{dI}{dt} &= \gamma E(t) - \mu_I I(t) - pI(t)C(t),\\
\frac{dV}{dt} &= kI(t) - \mu_V V(t),\\
\frac{dC}{dt} &= aI(t)C(t) - \mu_C C(t),
\end{aligned} \tag{1}$$

where $T(t)$, $E(t)$, $I(t)$, $V(t)$ and $C(t)$ denote the densities of uninfected CD4$^+$ T cells, infected cells in the eclipse stage (unproductive infected cells), productive infected cells, free virus particles and CTL cells at time t, respectively. The parameter λ is the production rate of the uninfected cells, μ_T is their death rate and $f(T, V)$ is the rate of uninfected cells to become infected by virus. The parameters μ_E, μ_I and μ_V denote the death rates of unproductive infected cells, productive infected cells and virus, respectively. The constant ρ is the rate at which the unproductive infected cells return to the uninfected cells. The constant γ is the rate at which infected cells in the eclipse stage become productive infected cells and k is the production rate of virions by infected cells. The productive infected cells are killed by CTL cells at rate p while a denotes the proliferation rate of CTL cells. Here, we consider the Hattaf's [11] incidence rate of the form $f(T, V) = \frac{\beta T}{1+\alpha_1 T+\alpha_2 V+\alpha_3 TV}$, where α_1, α_2, $\alpha_3 \geq 0$ are the saturation factors measuring the psychological or inhibitory effect and $\beta > 0$ is the infection coefficient. We recall that this incidence rate includes the common types such as the bilinear incidence (or mass action incidence) when $\alpha_1 = \alpha_2 = \alpha_3 = 0$, the saturated incidence rate when $\alpha_1 = \alpha_3 = 0$ or $\alpha_2 = \alpha_3 = 0$, the Beddington-DeAngelis functional response introduced in [13,14] when $\alpha_3 = 0$, and Crowley-Martin functional response presented in [15] and used in [16,17] when $\alpha_3 = \alpha_1\alpha_2$. It is important to note that the model of Lv et al. [12] is a special case of system (1) when $\alpha_3 = 0$. The first aim of this study is the generalization of the main results presented in [12].

System (1) assumes that cells and viruses are well mixed, and ignores the mobility of cells and viruses. Motivated by the works [18–21] and make the model more realistic by considering the mobility of cells and viruses, we propose the following diffusive HIV infection model

$$\begin{aligned}
\frac{\partial T}{\partial t} &= \lambda - \mu_T T(x,t) - f(T(x,t), V(x,t))V(x,t)\\
&\quad + \rho E(x,t),\\
\frac{\partial E}{\partial t} &= f(T(x,t), V(x,t))V(x,t)\\
&\quad - (\mu_E + \rho + \gamma)E(x,t),\\
\frac{\partial I}{\partial t} &= \gamma E(x,t) - \mu_I I(x,t) - pI(x,t)C(x,t),\\
\frac{\partial V}{\partial t} &= d\triangle V(x,t) + kI(x,t) - \mu_V V(x,t),\\
\frac{\partial C}{\partial t} &= aI(x,t)C(x,t) - \mu_C C(x,t),
\end{aligned} \tag{2}$$

where $T(x,t)$, $I(x,t)$, $E(x,t)$, $V(x,t)$ and $C(x,t)$ are the densities of uninfected CD4$^+$ T cells, infected cells in the eclipse stage, productive infected cells, free virus particles and CTL cells at location x and time t, respectively. The positive constant d is the diffusion coefficient of virus, and the other positive constant parameters have same meanings as in ODE model (1).

In this study, we consider our model (2) with homogenous Neumann boundary condition

$$\frac{\partial V}{\partial \nu} = 0 \text{ on } \partial\Omega \times (0, +\infty), \tag{3}$$

and initial conditions

$$\begin{aligned}
&T(x,0) = \phi_1(x) \geq 0, \quad E(x,0) = \phi_2(x) \geq 0,\\
&I(x,0) = \phi_3(x) \geq 0, \quad V(x,0) = \phi_4(x) \geq 0,\\
&C(x,0) = \phi_5(x) \geq 0, \quad x \in \bar{\Omega},
\end{aligned} \tag{4}$$

where Ω is a bounded domain in $\mathbf{R}^n$ with smooth boundary $\partial\Omega$, $\Delta = \sum_{i=1}^{n} \frac{\partial^2}{\partial x_i^2}$ is the Laplacian operator and $\frac{\partial V}{\partial \nu}$ is the outward normal derivative on $\partial\Omega$. Biologically speaking, the Neumann boundary condition means that the free virus particles do not move across the boundary $\partial\Omega$.

The organization of this paper is as follows. In the next section, we well first determine the equilibria of our ODE model and derive two threshold parameters for viral infection R_0 and for CTL immune response R_1. After, we establish the global stability of these equilibria that are the infection-free equilibrium, the immune-free infection equilibrium and the chronic infection equilibrium. Further, we focus on the global dynamics of our PDE model in Sect. 3. In order to validate our theoretical results, numerical simulations are presented in Sect. 4. Finally, a brief conclusion and discussion are given in Sect. 5.

2 Global stability of the ODE model

System (1) has always an infection-free equilibrium of the form $Q_0(\frac{\lambda}{\mu_T}, 0, 0, 0, 0)$.
Hence, the basic reproduction number of (1) is given by

$$R_0 = \frac{\lambda\beta k\gamma}{\mu_I\mu_V(\lambda\alpha_1 + \mu_T)(\rho + \mu_E + \gamma)}. \tag{5}$$

We recall that R_0 represents the number of secondary infections produced by one productive infected cell during the period of infection when all cells are uninfected.

The other equilibria of system (1) are solutions of the following system

$$\lambda - \mu_T T - f(T,V)V + \rho E = 0, \tag{6}$$
$$f(T,V)V - (\mu_E + \rho + \gamma)E = 0, \tag{7}$$
$$\gamma E - \mu_I I - pIC = 0, \tag{8}$$
$$kI - \mu_V V = 0, \tag{9}$$
$$aIC - \mu_C C = 0. \tag{10}$$

By (5), we get $C = 0$ or $I = \frac{\mu_C}{a}$.

If $C = 0$, using (6)–(4), we obtain $E = \frac{\lambda - \mu_T T}{\mu_E + \gamma}$, $I = \frac{\gamma(\lambda - \mu_T T)}{\mu_I(\mu_E+\gamma)}$, $V = \frac{k\gamma(\lambda-\mu_T T)}{\mu_I\mu_V(\mu_E+\gamma)}$ and

$$f\left(T, \frac{k\gamma(\lambda-\mu_T T)}{\mu_I\mu_V(\mu_E+\gamma)}\right) = \frac{(\rho+\mu_E+\gamma)\mu_V\mu_I}{k\gamma}.$$

Since $E = \frac{\lambda-\mu_T T}{\mu_E+\gamma} \geq 0$, we have $T \leq \frac{\lambda}{\mu_T}$. So, there is no biological equilibrium when $T > \frac{\lambda}{\mu_T}$. Define the function g_1 on the interval $\left[0, \frac{\lambda}{\mu_T}\right]$ by

$$g_1(T) = f\left(T, \frac{k\gamma(\lambda-\mu_T T)}{\mu_I\mu_V(\mu_E+\gamma)}\right) - \frac{(\rho+\mu_E+\gamma)\mu_V\mu_I}{k\gamma}.$$

We have $g_1(0) = -\frac{(\rho+\mu_E+\gamma)\mu_V\mu_I}{k\gamma} < 0$, $g_1(\frac{\lambda}{\mu_T}) = \frac{(\rho+\mu_E+\gamma)\mu_V\mu_I}{k\gamma}(R_0 - 1)$ and

$$g_1'(T) = \frac{\partial f}{\partial T} - \frac{k\gamma\mu_T}{\mu_I\mu_V(\mu_E+\gamma)}\frac{\partial f}{\partial V} > 0.$$

If $R_0 > 1$, there exist an other biological equilibrium $Q_1(T_1, E_1, I_1, V_1, 0)$ with $T_1 \in (0, \frac{\lambda}{\mu_T})$, $E_1 = \frac{\lambda-\mu_T T_1}{\mu_E+\gamma}$, $I_1 = \frac{\gamma(\lambda-\mu_T T_1)}{\mu_I(\mu_E+\gamma)}$ and $V_1 = \frac{k\gamma(\lambda-\mu_T T_1)}{\mu_I\mu_V(\mu_E+\gamma)}$. This equilibrium correspond to positive levels of healthy cells, unproductive infected cells, productive infected cells and virus, but no CTL immune response.

If $C \neq 0$, then $I = \frac{\mu_C}{a}$. Using (6)–(4), we deduce $E = \frac{\lambda-\mu_T T}{\mu_E+\gamma}$, $V = \frac{k\mu_C}{a\mu_V}$ and

$$f\left(T, \frac{k\mu_C}{a\mu_V}\right) = \frac{a\mu_V(\mu_E+\rho+\gamma)(\lambda-\mu_T T)}{k\mu_C(\mu_E+\gamma)}.$$

Since $C = \frac{a\gamma(\lambda-\mu_T T)-\mu_I\mu_C(\mu_E+\gamma)}{p\mu_C(\mu_E+\gamma)} \geq 0$, we have $T \leq \frac{\lambda}{\mu_T} - \frac{\mu_I\mu_C(\mu_E+\gamma)}{a\gamma\mu_T}$. Then there exists no equilibrium when $T > \frac{\lambda}{\mu_T} - \frac{\mu_I\mu_C(\mu_E+\gamma)}{a\gamma\mu_T}$ or $\frac{\lambda}{\mu_T} - \frac{\mu_I\mu_C(\mu_E+\gamma)}{a\gamma\mu_T} \leq 0$.
Define the function g_2 on the interval $\left[0, \frac{\lambda}{\mu_T} - \frac{\mu_I\mu_C(\mu_E+\gamma)}{a\gamma\mu_T}\right]$ by

$$g_2(T) = f\left(T, \frac{k\mu_C}{a\mu_V}\right) - \frac{a\mu_V(\mu_E+\rho+\gamma)(\lambda-\mu_T T)}{k\mu_C(\mu_E+\gamma)}.$$

We have $g_2(0) = -\frac{\lambda a\mu_V(\mu_E+\rho+\gamma)}{k\mu_C(\mu_E+\gamma)} < 0$ and $g_2'(T) = \frac{\partial f}{\partial T} + \frac{\mu_T a\mu_V(\mu_E+\rho+\gamma)}{k\mu_C(\mu_E+\gamma)} > 0$.

In addition to R_0, we define the CTL immune response reproduction number R_1 of our ODE model by

$$R_1 = \frac{aI_1}{\mu_C}, \tag{11}$$

where $\frac{1}{\mu_C}$ represents the average life expectancy of CTL cells, and I_1 is the number of productive infected cells at Q_1. Hence, R_1 represents the average number of CTL cells activated by the productive infected cells when viral infection is successful.
If $R_1 < 1$, then $I_1 < \frac{\mu_C}{a}$, $T_1 > \frac{\lambda}{\mu_T} - \frac{\mu_I\mu_C(\mu_E+\gamma)}{a\gamma\mu_T}$ and

$$\begin{aligned} g_2\left(\frac{\lambda}{\mu_T} - \frac{\mu_I\mu_C(\mu_E+\gamma)}{a\gamma\mu_T}\right) &= f\left(\frac{\lambda}{\mu_T}\right. \\ &\quad \left. - \frac{\mu_I\mu_C(\mu_E+\gamma)}{a\gamma\mu_T}, \frac{k\mu_C}{a\mu_V}\right) - \frac{(\rho+\mu_E+\gamma)\mu_V\mu_I}{k\gamma} \\ &< f(T_1, V_1) - \frac{(\rho+\mu_E+\gamma)\mu_V\mu_I}{k\gamma}. \end{aligned}$$

Hence, $g_2(\frac{\lambda}{\mu_T} - \frac{\mu_I\mu_C(\mu_E+\gamma)}{a\gamma\mu_T}) < 0$. Then there is no equilibrium when $R_1 < 1$.
If $R_1 > 1$, then $I_1 > \frac{\mu_C}{a}$, $T_1 < \frac{\lambda}{\mu_T} - \frac{\mu_I\mu_C(\mu_E+\gamma)}{a\gamma\mu_T}$ and $g_2(\frac{\lambda}{\mu_T} - \frac{\mu_I\mu_C(\mu_E+\gamma)}{a\gamma\mu_T}) > 0$. Therefore, if $R_1 > 1$, there exists an infection equilibrium $Q_2(T_2, E_2, I_2, V_2, C_2)$ with $T_2 \in (0, \frac{\lambda}{\mu_T} - \frac{\mu_I\mu_C(\mu_E+\gamma)}{a\gamma\mu_T})$, $E_2 = \frac{\lambda-\mu_T T_2}{\mu_E+\gamma}$, $I_2 = \frac{\mu_C}{a}$, $V_2 = \frac{k\mu_C}{a\mu_V}$ and $C_2 = \frac{a\gamma(\lambda-\mu_T T_2)-\mu_I\mu_C(\mu_E+\gamma)}{p\mu_C(\mu_E+\gamma)}$. This equilibrium denotes the state in which both the virus and the CTL immune response are present.

Summarizing the above discussions in the following result.

Theorem 2.1 *(i) When $R_0 \leq 1$, the system (1) has always an infection-free equilibrium of the form $Q_0(\frac{\lambda}{\mu_T}, 0, 0, 0, 0)$.*
(ii) When $R_0 > 1$, the system (1) has an immune-free infection equilibrium of the form $Q_1(T_1, E_1, I_1, V_1, 0)$ with $T_1 \in (0, \frac{\lambda}{\mu_T})$, $E_1 = \frac{\lambda-\mu_T T_1}{\mu_E+\gamma}$, $I_1 = \frac{\gamma(\lambda-\mu_T T_1)}{\mu_I(\mu_E+\gamma)}$ and $V_1 = \frac{k\gamma(\lambda-\mu_T T_1)}{\mu_I\mu_V(\mu_E+\gamma)}$.
(iii) When $R_1 > 1$, the system (1) has an infection equilibrium of the form $Q_2(T_2, E_2, I_2, V_2, C_2)$ with $T_2 \in (0, \frac{\lambda}{\mu_T} - \frac{\mu_I\mu_C(\mu_E+\gamma)}{a\gamma\mu_T})$, $E_2 = \frac{\lambda-\mu_T T_2}{\mu_E+\gamma}$, $I_2 = \frac{\mu_C}{a}$, $V_2 = \frac{k\mu_C}{a\mu_V}$ and $C_2 = \frac{a\gamma(\lambda-\mu_T T_2)-\mu_I\mu_C(\mu_E+\gamma)}{p\mu_C(\mu_E+\gamma)}$.

Now, we focus on the global stability of the three equilibria of system (1). At first, we have

Theorem 2.2 *If $R_0 \leq 1$, then the infection-free equilibrium Q_0 is globally asymptotically stable.*

Proof Consider the following Lyapunov functional

$$W_0(T,E,I,V,C) = T - T_0 - \int_{T_0}^{T} \frac{f(T_0,0)}{f(S,0)}dS + \frac{\rho(T-T_0+E)^2}{2(1+\alpha_1 T_0)(\mu_T+\mu_E+\gamma)T_0} + \frac{\rho+\mu_E+\gamma}{\gamma}I + E + \frac{\mu_I(\rho+\mu_E+\gamma)}{k\gamma}V + \frac{p(\rho+\mu_E+\gamma)}{a\gamma}C,$$

where $T_0 = \frac{\lambda}{\mu_T}$.
Calculating the time derivative of W_0 along the positive solutions of system (1), we obtain

$$\frac{dW_0}{dt} = \left(1 - \frac{f(T_0,0)}{f(T,0)}\right)\dot{T} + \frac{\rho}{(1+\alpha_1 T_0)(\mu_T+\mu_E+\gamma)T_0}(T-T_0+E)(\dot{T}+\dot{E}) + \frac{\rho+\mu_E+\gamma}{\gamma}\dot{I} + \dot{E} + \frac{\mu_I(\rho+\mu_E+\gamma)}{k\gamma}\dot{V} + \frac{p(\rho+\mu_E+\gamma)}{a\gamma}\dot{C}.$$

Noting that $\lambda = \mu_T T_0$, we get

$$\begin{aligned}\frac{dW_0}{dt} &= \left(1 - \frac{f(T_0,0)}{f(T,0)}\right)\mu_T(T_0-T) + \frac{f(T_0,0)f(T,V)}{f(T,0)}V \\ &\quad + \rho\left(1 - \frac{f(T_0,0)}{f(T,0)}\right)E - \frac{\rho\mu_T(T-T_0)^2}{(1+\alpha_1 T_0)(\mu_T+\mu_E+\gamma)T_0} \\ &\quad - \frac{\rho(\mu_E+\gamma)E^2}{(1+\alpha_1 T_0)(\mu_T+\mu_E+\gamma)T_0} \\ &\quad + \frac{\rho E}{(1+\alpha_1 T_0)T_0}(T_0-T) - \frac{\mu_I\mu_V(\rho+\mu_E+\gamma)}{k\gamma}V \\ &\quad - \frac{\mu_C p(\rho+\mu_E+\gamma)}{a\gamma}C \\ &= -\left(\frac{1}{T} + \frac{\rho}{(\mu_T+\mu_E+\gamma)T_0}\right)\frac{\mu_T(T-T_0)^2}{1+\alpha_1 T_0} \\ &\quad - \frac{\rho(\mu_E+\gamma)E^2}{(1+\alpha_1 T_0)(\mu_T+\mu_E+\gamma)T_0} \\ &\quad - \frac{\rho(T-T_0)^2 E}{(1+\alpha_1 T_0)TT_0} + \frac{\mu_I\mu_V(\rho+\mu_E+\gamma)}{k\gamma}(R_0-1)V \\ &\quad - \frac{(\alpha_2+\alpha_3 T)V^2}{1+\alpha_1 T+\alpha_2 V+\alpha_3 TV}f(T_0,0) \\ &\quad - \frac{\mu_C p(\rho+\mu_E+\gamma)}{a\gamma}C.\end{aligned}$$

Therefore, $\frac{dW_0}{dt} \le 0$ if $R_0 \le 1$. Further, $\frac{dW_0}{dt} = 0$ if and only if $T = \frac{\lambda}{\mu_T}$, $E = 0$, $I = 0$, $V = 0$ and $C = 0$. Hence, the largest compact invariant set in $\{(T,E,I,V,C) | \frac{dW_0}{dt} = 0\}$ is just the singleton $\{Q_0\}$. Thus, the global stability of the infection-free equilibrium Q_0 follows from LaSalle's invariance principle [22]. □

Theorem 2.3 *The immune-free infection equilibrium Q_1 of system (1) is globally asymptotically stable if $R_1 \le 1 < R_0$ and*

$$R_0 \le 1 + \frac{[\mu_T\mu_I\mu_V(\mu_E+\gamma)+\alpha_2\mu_T\lambda k\gamma](\mu_E+\rho+\gamma)+\rho\alpha_3 k\gamma\lambda^2}{\rho\mu_I\mu_V(\mu_E+\rho+\gamma)(\mu_T+\alpha_1\lambda)}. \tag{12}$$

Proof Construct a Lyapunov functional W_1 as follows

$$W_1(T,E,I,V,C) = T - T_1 - \int_{T_1}^{T}\frac{f(T_1,V_1)}{f(S,V_1)}dS + \frac{\rho(1+\alpha_2 V_1)(T-T_1+E-E_1)^2}{2(1+\alpha_1 T_1+\alpha_2 V_1+\alpha_3 T_1 V_1)(\mu_T+\mu_E+\gamma)T_1} + \frac{f(T_1,V_1)V_1}{\gamma E_1}I_1\Phi\left(\frac{I}{I_1}\right) + E_1\Phi\left(\frac{E}{E_1}\right) + \frac{\mu_I f(T_1,V_1)V_1}{k\gamma E_1}V_1\Phi\left(\frac{V}{V_1}\right) + \frac{pf(T_1,V_1)V_1}{a\gamma E_1}C,$$

where $\Phi(x) = x - 1 - \ln(x)$.
The time derivative of W_0 along the positive solutions of system (1) satisfies

$$\begin{aligned}\frac{dW_1}{dt} &= \left(1 - \frac{f(T_1,V_1)}{f(T,V_1)}\right)\dot{T} \\ &\quad + \frac{\rho(1+\alpha_2 V_1)(T-T_1+E-E_1)(\dot{T}+\dot{E})}{(1+\alpha_1 T_1+\alpha_2 V_1+\alpha_3 T_1 V_1)(\mu_T+\mu_E+\gamma)T_1} \\ &\quad + \frac{f(T_1,V_1)V_1}{\gamma E_1}\left(1 - \frac{I_1}{I}\right)\dot{I} + \left(1 - \frac{E_1}{E}\right)\dot{E} \\ &\quad + \frac{\mu_I f(T_1,V_1)V_1}{k\gamma E_1}\left(1 - \frac{V_1}{V}\right)\dot{V} \\ &\quad \times \frac{pf(T_1,V_1)V_1}{a\gamma E_1}\dot{C}.\end{aligned}$$

By $\lambda = \mu_T T_1 + f(T_1,V_1)V_1 - \rho E_1$, we get

$$\begin{aligned}\frac{dW_1}{dt} &= -\frac{(1+\alpha_2 V_1)(T-T_1)^2}{TT_1(1+\alpha_1 T_1+\alpha_2 V_1+\alpha_3 T_1 V_1)}\left((\mu_T T_1 - \rho E_1) + \frac{\rho\mu_T T}{\mu_T+\mu_E+\gamma} + \rho E\right) \\ &\quad - \frac{\rho(E-E_1)^2(1+\alpha_2 V_1)(\mu_E+\gamma)}{T_1(1+\alpha_1 T_1+\alpha_2 V_1+\alpha_3 T_1 V_1)(\mu_T+\mu_E+\gamma)} \\ &\quad + f(T_1,V_1)V_1\left(5 - \frac{f(T_1,V_1)}{f(T,V_1)} - \frac{I_1 E}{E_1 I} - \frac{f(T,V)}{f(T_1,V_1)}\frac{VE_1}{V_1 E} - \frac{V_1 I}{VI_1} - \frac{f(T,V_1)}{f(T,V)}\right)\end{aligned}$$

$$-\frac{f(T_1,V_1)(1+\alpha_1T)(\alpha_2+\alpha_3T)(V-V_1)^2}{(1+\alpha_1T+\alpha_2V_1+\alpha_3TV_1)(1+\alpha_1T+\alpha_2V+\alpha_3TV)}+\frac{p\mu_C f(T_1,V_1)V_1}{a\gamma E_1}(R_1-1)C.$$

Using the arithmetic-geometric inequality, we get

$$5-\frac{f(T_i,V_i)}{f(T,V_i)}-\frac{I_iE}{E_iI}-\frac{f(T,V)}{f(T_i,V_i)}\frac{VE_i}{V_iE}-\frac{V_iI}{VI_i}-\frac{f(T,V_i)}{f(T,V)}\le 0,\quad \text{for all } i=1,2. \tag{13}$$

Therefore, $\frac{dW_1}{dt}\le 0$ if $R_1\le 1$ and $\rho E_1\leqslant \mu_T T_1$. Obviously, the condition $\rho E_1\leqslant \mu_T T_1$ is equivalent to

$$R_0\le 1+\frac{[\mu_T\mu_I\mu_V(\mu_E+\gamma)+\alpha_2\mu_T\lambda k\gamma](\mu_E+\rho+\gamma)+\rho\alpha_3k\gamma\lambda^2}{\rho\mu_I\mu_V(\mu_E+\rho+\gamma)(\mu_T+\alpha_1\lambda)}.$$

In addition, $\frac{dW_1}{dt}=0$ if and only if $T=T_1$, $E=E_1$, $I=I_1$, $V=V_1$ and $C=0$. Hence, the largest compact invariant set in $\{(T,E,I,V,C)|\frac{dW_1}{dt}=0\}$ is the singleton $\{Q_1\}$. This proves the global stability of Q_1 by using LaSalle invariance principle. □

Remark 2.4 If $\alpha_3=0$, then the condition (12) becomes

$$R_0\le 1+\frac{[\mu_T\mu_I\mu_V(\mu_E+\gamma)+\alpha_2\mu_T\lambda k\gamma](\mu_E+\rho+\gamma)}{\rho\mu_I\mu_V(\mu_E+\rho+\gamma)(\mu_T+\alpha_1\lambda)},$$

which is the condition given by Lv et al. [12] that ensures the global asymptotic stability of the immune-free infection equilibrium.

It is important to see that

$$\lim_{\rho\to 0}\frac{[\mu_T\mu_I\mu_V(\mu_E+\gamma)+\alpha_2\mu_T\lambda k\gamma](\mu_E+\rho+\gamma)+\rho\alpha_3k\gamma\lambda^2}{\rho\mu_I\mu_V(\mu_E+\rho+\gamma)(\mu_T+\alpha_1\lambda)}=\infty,$$

$$\lim_{\gamma\to\infty}\frac{[\mu_T\mu_I\mu_V(\mu_E+\gamma)+\alpha_2\mu_T\lambda k\gamma](\mu_E+\rho+\gamma)+\rho\alpha_3k\gamma\lambda^2}{\rho\mu_I\mu_V(\mu_E+\rho+\gamma)(\mu_T+\alpha_1\lambda)}=\infty.$$

According to theorem 2.3, we get the following result

Corollary 2.5 *(i) The immune-free infection equilibrium Q_1 is globally asymptotically stable if $R_1\le 1<R_0$ and ρ sufficiently small.*

(ii) The immune-free infection equilibrium Q_1 is globally asymptotically stable if $R_1\le 1<R_0$ and γ sufficiently large.

Finally, we investigate the global stability of the third equilibrium Q_2.

Theorem 2.6 *The chronic infection equilibrium with immune response Q_2 is globally asymptotically stable if $R_1>1$ and*

$$k\beta\mu_C\rho\le\alpha_1\lambda\rho a\mu_V+\mu_T(\rho+\mu_E+\gamma)(\alpha_2k\mu_C+a\mu_V)+\alpha_3\rho\lambda k\mu_C. \tag{14}$$

Proof Define a Lyapunov functional W_2 as follows

$$W_2(T,E,I,V,C)=T-T_2-\int_{T_2}^{T}\frac{f(T_2,V_2)}{f(S,V_2)}dS+\frac{\rho(1+\alpha_2V_2)(T-T_2+E-E_1)^2}{2(1+\alpha_1T_2+\alpha_2V_2+\alpha_3T_2V_2)(\mu_T+\mu_E+\gamma)T_2}+\frac{f(T_2,V_2)V_2}{\gamma E_2}I_2\Phi\left(\frac{I}{I_2}\right)+E_2\Phi\left(\frac{E}{E_2}\right)+\frac{(\mu_I+pC_2)f(T_2,V_2)V_2}{k\gamma E_2}V_2\Phi\left(\frac{V}{V_2}\right)+\frac{pf(T_2,V_2)V_2}{a\gamma E_2}C_2\Phi\left(\frac{C}{C_2}\right).$$

Calculating the derivative of W_2 along the positive solutions of the system (1), we have

$$\frac{dW_2}{dt}=\left(1-\frac{f(T_2,V_2)}{f(T,V_2)}\right)\dot T+\frac{\rho(1+\alpha_2V_2)(T-T_2+E-E_2)}{(1+\alpha_1T_2+\alpha_2V_2+\alpha_3T_2V_2)(\mu_T+\mu_E+\gamma)T_2}(\dot T+\dot E)+\frac{f(T_2,V_2)V_2}{\gamma E_2}\left(1-\frac{I_2}{I}\right)\dot I+\left(1-\frac{E_2}{E}\right)\dot E+\frac{f(T_2,V_2)V_2}{k\gamma E_2}(\mu_I+pC_2)\times\left(1-\frac{V_2}{V}\right)\dot V\frac{pf(T_2,V_2)V_2}{a\gamma E_2}\left(1-\frac{C_2}{C}\right)\dot C.$$

Applying the equality $\lambda=\mu_TT_2+f(T_2,V_2)V_2-\rho E_2$, we get

$$\begin{aligned}\frac{dW_2}{dt}=&\left(1-\frac{f(T_2,V_2)}{f(T,V_2)}\right)\mu_T(T_2-T)+\frac{f(T_2,V_2)f(T,V)}{f(T,V_2)}V\\&-\frac{\mu_T\rho(1+\alpha_2V_2)}{(1+\alpha_1T_2+\alpha_2V_2+\alpha_3T_2V_2)(\mu_T+\mu_E+\gamma)T_2}(T-T_2)^2\\&-\frac{\rho(1+\alpha_2V_2)(\mu_E+\gamma)}{(1+\alpha_1T_2+\alpha_2V_2+\alpha_3T_2V_2)(\mu_T+\mu_E+\gamma)T_2}(E-E_2)^2\\&-\frac{\rho(1+\alpha_2V_2)(E-E_2)(T-T_2)}{(1+\alpha_1T_2+\alpha_2V_2+\alpha_3T_2V_2)T_2}\\&+\left(1-\frac{f(T_2,V_2)}{f(T,V_2)}\right)((\mu_E+\gamma)E_2+\rho E)\\&+f(T_2,V_2)V_2\Big[-\frac{I_2E}{IE_2}+\frac{\mu_II_2}{\gamma E_2}\\&-\frac{\mu_VV(\mu_I+pC_2)}{k\gamma E_2}-\frac{V_2I(\mu_I+pC_2)}{V\gamma E_2}\\&+\frac{\mu_VV_2(\mu_I+pC_2)}{k\gamma E_2}+\frac{p\mu_CC_2}{a\gamma E_2}\Big]\end{aligned}$$

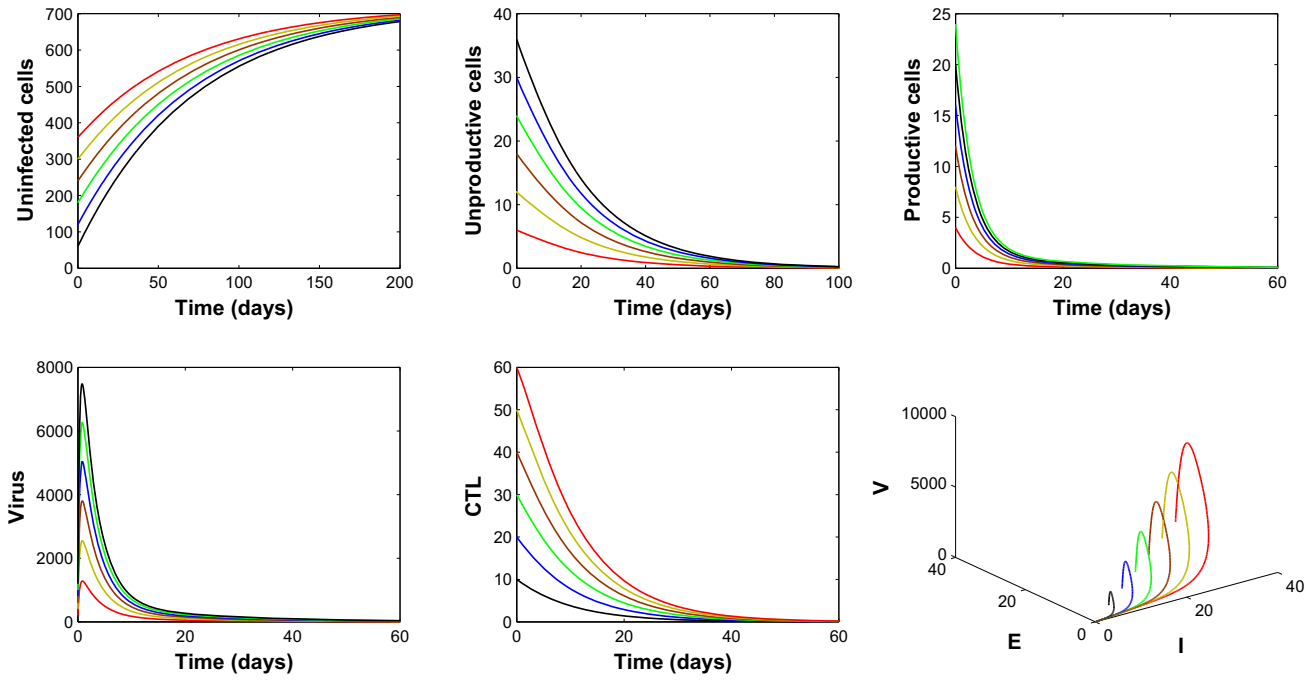

Fig. 1 Stability of the infection-free equilibrium Q_0 for system (1)

$$
\begin{aligned}
&- \frac{f(T,V)E_2}{E} + f(T_2,V_2)V_2,\\
&= -\frac{(1+\alpha_2 V_2)(T-T_2)^2}{TT_2(1+\alpha_1 T_2+\alpha_2 V_2+\alpha_3 T_2 V_2)}\Big((\mu_T T_2-\rho E_2)\\
&\quad + \frac{\rho\mu_T T}{\mu_T+\mu_E+\gamma} + \rho E\Big)\\
&\quad - \frac{\rho(E-E_2)^2(1+\alpha_2 V_2)(\mu_E+\gamma)}{T_2(1+\alpha_1 T_2+\alpha_2 V_2+\alpha_3 T_2 V_2)(\mu_T+\mu_E+\gamma)}\\
&\quad + f(T_2,V_2)V_2\Big(5 - \frac{f(T_2,V_2)}{f(T,V_2)} - \frac{I_2 E}{E_2 I}\\
&\quad - \frac{f(T,V)}{f(T_2,V_2)}\frac{VE_2}{V_2E} - \frac{V_2 I}{VI_2} - \frac{f(T,V_2)}{f(T,V)}\Big)\\
&\quad - \frac{f(T_2,V_2)V_2(1+\alpha_1 T)(\alpha_2+\alpha_3 T)(V-V_2)^2}{V_2(1+\alpha_1 T+\alpha_2 V_2+\alpha_3 TV_1)(1+\alpha_1 T+\alpha_2 V+\alpha_3 TV)}.
\end{aligned}
$$

From (13), we deduce that $\frac{dW_2}{dt} \leq 0$ if $R_1 > 1$ and $\rho E_2 \leqslant \mu_T T_2$.
However, this last condition is equivalent to

$$
\begin{aligned}
k\beta\mu_C\rho \leq{}& \alpha_1\lambda\rho a\mu_V + \mu_T(\rho+\mu_E+\gamma)(\alpha_2 k\mu_C + a\mu_V)\\
&+\alpha_3\rho\lambda k\mu_C.
\end{aligned}
$$

Note that $\frac{dW_1}{dt} = 0$ if and only if $T = T_2$, $E = E_2$, $I = I_2$, $V = V_2$ and $C = C_2$. Hence, the largest compact invariant set in $\{(T, E, I, V, C) | \frac{dW_2}{dt} = 0\}$ is the singleton $\{Q_2\}$. Based on the LaSalle invariance principle, we deduce that Q_2 is globally asymptotically stable. This completes the proof. □

We remark that the condition (14) holds for ρ sufficiently small, or γ sufficiently large. Hence, we have the following corollary.

Corollary 2.7 *(i) The chronic infection equilibrium Q_2 is globally asymptotically stable if $R_1 > 1$ and ρ sufficiently small.*
(ii) The chronic infection equilibrium Q_2 is globally asymptotically stable if $R_1 > 1$ and γ sufficiently large.

In addition, we have the following remark.

Remark 2.8 If $\alpha_3 = 0$, then the condition (14) becomes

$$k\beta\mu_C\rho \leq \alpha_1\lambda\rho a\mu_V + \mu_T(\rho+\mu_E+\gamma)(\alpha_2 k\mu_C + a\mu_V),$$

which is the condition given by Lv et al. [12] that ensures the global asymptotic stability of the chronic infection equilibrium.

3 Global stability of the PDE model

It is not hard to see that the PDE model (2) has the same three equilibria as the ODE model (1), namely, the infection-free equilibrium Q_0, the immune-free infection equilibrium Q_1 which exists whenever $R_0 > 1$and the chronic infection equilibrium Q_2 which exists if $R_1 > 1$.

Now, we investigate the global stability of problem (2)–(4) by constructing appropriate Lyapunov functionals. The construction of these Lyapunov functionals is based on the method proposed by Hattaf and Yousfi [23].

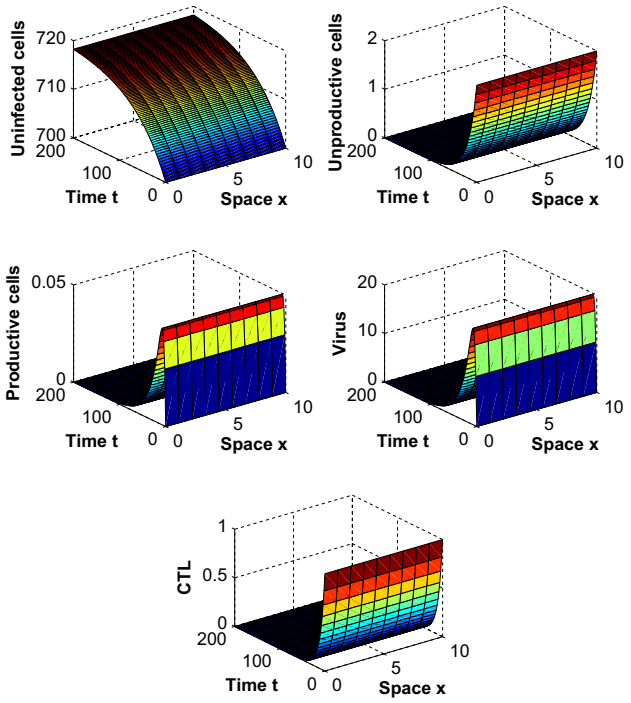

Fig. 2 Stability of the infection-free equilibrium Q_0 for system (2)

Theorem 3.1 *For all diffusion coefficients, we have*

(i) The infection-free equilibrium Q_0 of problem (2)–(4) is globally asymptotically stable if $R_0 \leq 1$.

(ii) The immune-free infection equilibrium Q_1 of problem (2)–(4) is globally asymptotically stable if $R_1 \leq 1 < R_0$ and the condition (12) holds .

(iii) The chronic infection equilibrium Q_2 of problem (2)–(4) is globally asymptotically stable if $R_1 > 1$ and the condition (14) holds.

Proof Let $u(t,x) = \big(T(t,x), I(t,x), V(t,x), E(t,x), C(t,x)\big)$ be a solution of (2)–(4), and we put

$$L_i = \int_\Omega W_i\big(u(x,t)\big)dx,$$

where W_i is the Lyapunov functional for the ODE model (1) at Q_i, $i = 0, 1, 2$.
It is easy to check that W_i satisfies the condition (15) given in [23], for all $i = 0, 1, 2$. From Proposition 2.1 given in Ref. [23], we deduce that L_i is a Lyapunov functional for problem (2)–(4) at Q_i. This completes the proof. □

4 Numerical simulations

In this section, we present some numerical simulations to validate our theoretical results. Firstly, we consider parameter values $\Lambda = 10$ cells μl^{-1} day^{-1}, $\mu_T = 0.0139$ day^{-1}, $\beta = 2.4 \times 10^{-5}$ μl virion^{-1} day^{-1}, $\alpha_1 = 0.1$, $\alpha_2 = 0.01$, $\alpha_3 = 0.00001$, $\rho = 0.01$ day^{-1}, $\gamma = 0.01$ day^{-1}, $\mu_I = 0.27$ day^{-1}, $\mu_E = 0.0347$ day^{-1}, $p = 0.001$ cell^{-1} μl day^{-1}, $k = 1200$ virion cell^{-1} day^{-1}, $\mu_V = 3$ day^{-1}, $a = 0.002$ cell^{-1} μl day^{-1}, $\mu_C = 0.1$ day^{-1} and $d = 0.1$. Here, the values p, a and μ_C are taken from [1,5], while the other parameter values are chosen from [10]. For these set of parameter values, we have $R_0 = 0.1141 < 1$. Hence, systems (1) and (2) have an

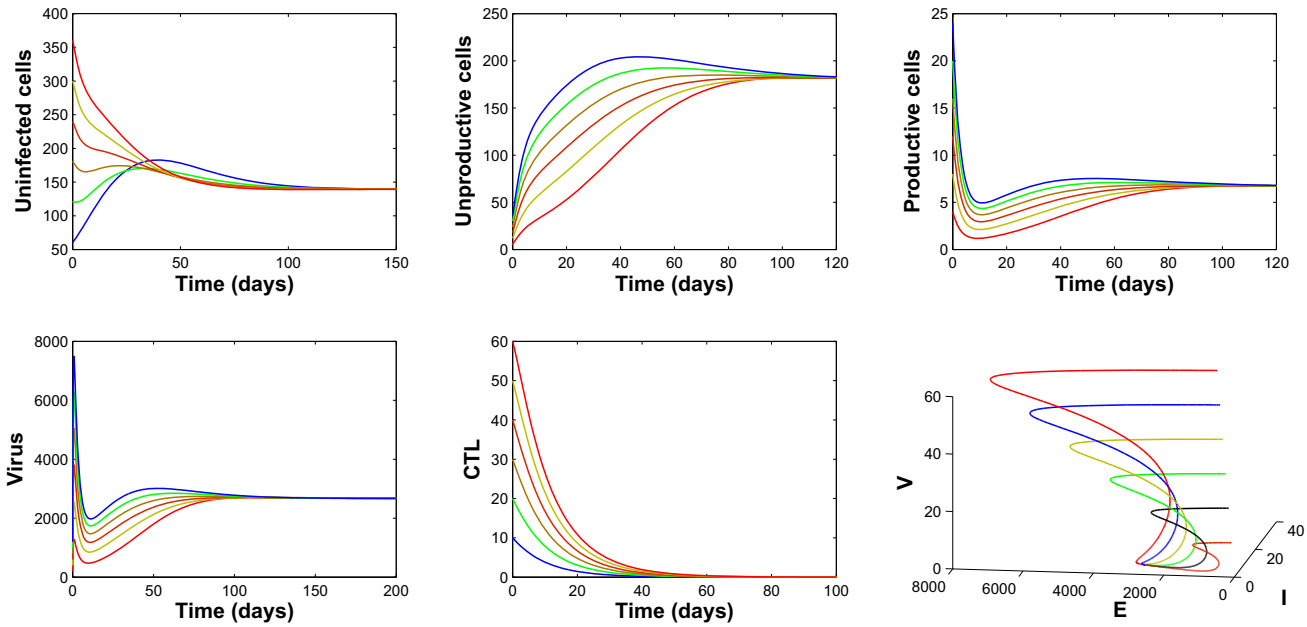

Fig. 3 Stability of the immune-free infection equilibrium Q_1 for system (1)

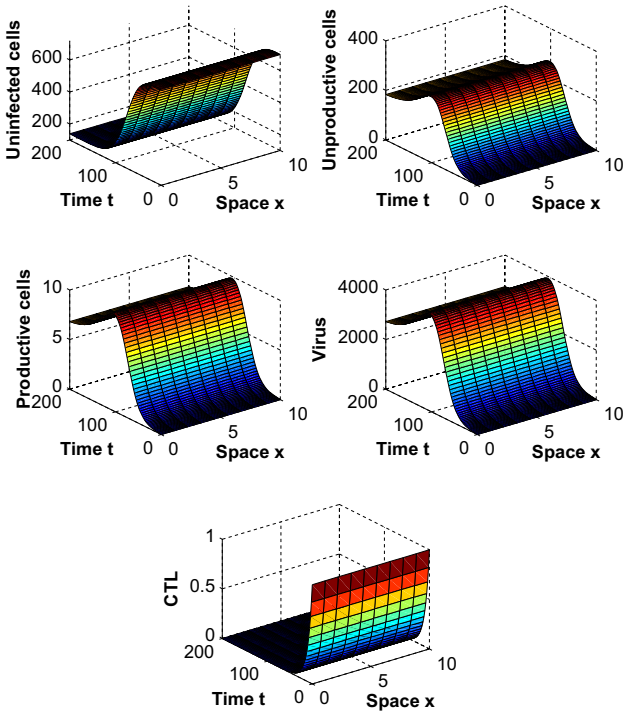

Fig. 4 Stability of the immune-free infection equilibrium Q_1 for system (2)

infection-free equilibrium $Q_0(719, 4245, 0, 0, 0, 0)$ which is globally asymptotically stable according to Theorems 2.2 and 3.1 (i). Figures 1 and 2 illustrate this result.

Secondly, we choose $\beta = 0.0012\ \mu l$ virion^{-1} day^{-1} and do not change the other parameter values. By calculation, we have $R_0 = 3.2055 > 1$, $R_1 = 0.1427 < 1$ and $\frac{[\mu_T\mu_I\mu_V(\mu_E+\gamma)+\alpha_2\mu_T\lambda k\gamma](\mu_E+\rho+\gamma)+\rho\alpha_3 k\gamma\lambda^2}{\rho\mu_I\mu_V(\mu_E+\rho+\gamma)(\mu_T+\alpha_1\lambda)} = 2.2725$. In this case, both systems have an immune-free equilibrium $Q_1(138.53, 183.16, 6.80, 2724.2, 0)$. By Theorems 2.3 and 3.1 (ii), Q_1 is globally asymptotically stable (see Figs. 3 and 4). We see that in the absence of CTL cells, the number of CD4$^+$ T cells decreases to the value 138.53, which means that the patient enters in the phase AIDS (< 200 cell mm^{-3}).

Thirdly, we change one parameter which is $a = 0.065$ cell^{-1} μl day^{-1}. By calculation, we have $R_1 = 4.6379 > 1$. Then systems (1) and (2) have a chronic infection equilibrium $Q_2(370.56, 106.97, 1.57, 629.65, 409.12)$. Therefore, by Theorems 2.6 and 3.1 (iii), Q_2 is globally asymptotically stable (see Figs. 5 and 6). In this case, we see that in the presence of CTL cells, the number of CD4$^+$ T cells increases to the value $252.0792 > 200$ cell mm^{-3}, which means that the patient is no longer in the phase AIDS.

Finally, in Fig. 7, we see that the dynamics of HIV infection converges to steady state Q_1 for all initial conditions. However, the condition (12) is not satisfied with $R_0 = 4.1501 > 1$, $R_1 = 0.0999 < 1$ and

$$1 + \frac{[\mu_T\mu_I\mu_V(\mu_E+\gamma)+\alpha_2\mu_T\lambda k\gamma](\mu_E+\rho+\gamma)+\rho\alpha_3 k\gamma\lambda^2}{\rho\mu_I\mu_V(\mu_E+\rho+\gamma)(\mu_T+\alpha_1\lambda)} = 2.3910.$$

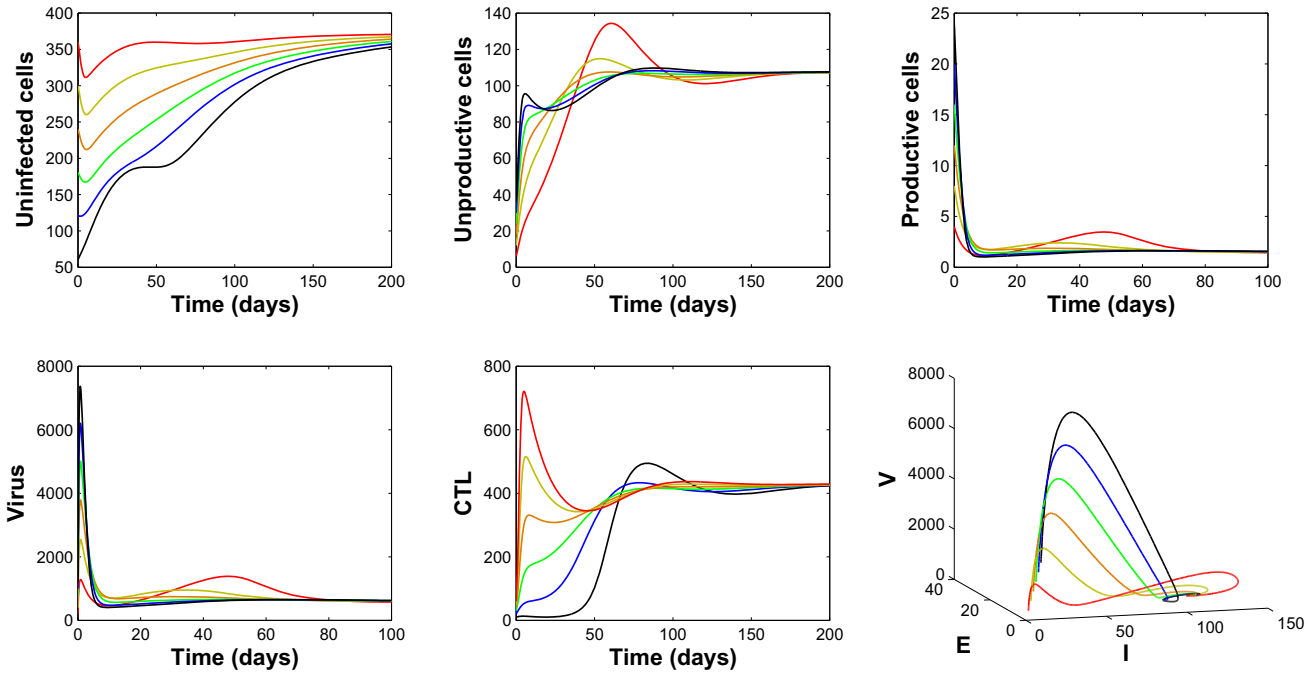

Fig. 5 Stability of the chronic infection equilibrium Q_2 for system (1)

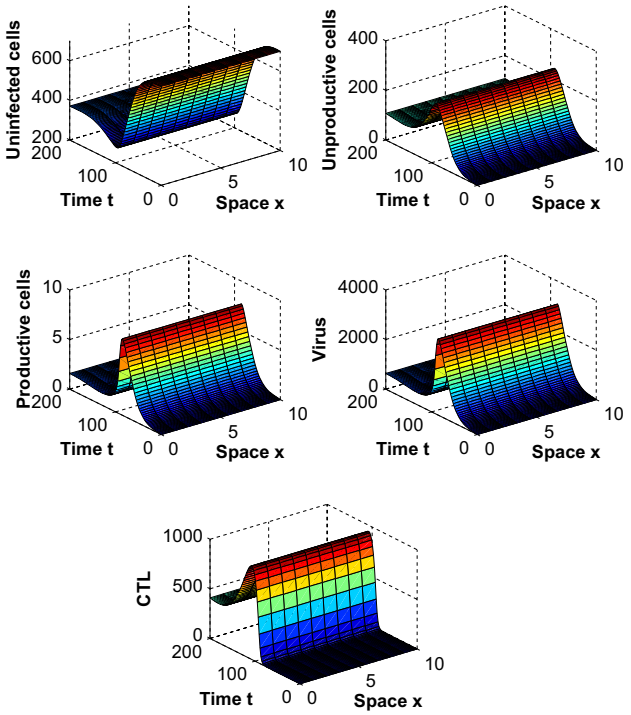

Fig. 6 Stability of the chronic infection equilibrium Q_2 for system (2)

Similarly, in Fig. 8, we see that the dynamics of HIV infection converges to steady state Q_2 for all initial conditions. However, the condition (14) is not satisfied with $R_1 = 3.4338$ and $\alpha_1\lambda\rho a\mu_V + \mu_T(\rho + \mu_E + \gamma)(\alpha_2 k\mu_C + a\mu_V) + \alpha_3\rho\lambda k\mu_C - k\beta\mu_C\rho = -0.0041 < 0$. Therefore, the conditions (12) and (14) are not necessary for the global stability of Q_1 and Q_2.

5 Conclusion and discussion

In this paper, we have proposed two HIV infection models. The first is an ODE model with cure of infected cells in eclipse stage, CTL immune response and Hattaf's incidence rate which includes the traditional bilinear incidence rate, the saturated incidence rate, the Beddington–DeAngelis functional response and the Crowley-Martin functional response. The second is a PDE model that extends the first one by taking into account the diffusion of virus. The two models admits three equilibria, namely, the infection-free equilibrium Q_0, the immune-free infection equilibrium Q_1 which exists whenever $R_0 > 1$ and the chronic infection equilibrium Q_2 which exists if $R_1 > 1$. The global stability of these three equilibria have obtained in terms of the basic reproduction number R_0 and the CTL immune response reproduction number R_1. It is shown that Q_f is globally asymptotically stable when $R_0 \leq 1$, Q_1 is globally asymptotically stable when $R_1 \leq 1 < R_0$ and the condition (12) holds, and Q_2 is globally asymptotically stable when $R_1 > 1$ and the condition (14) holds.

In addition, we remark that if the cure rate ρ is sufficiently small or the value of γ is sufficiently large, the conditions (12) and (14) are satisfied. From the numerical simulations

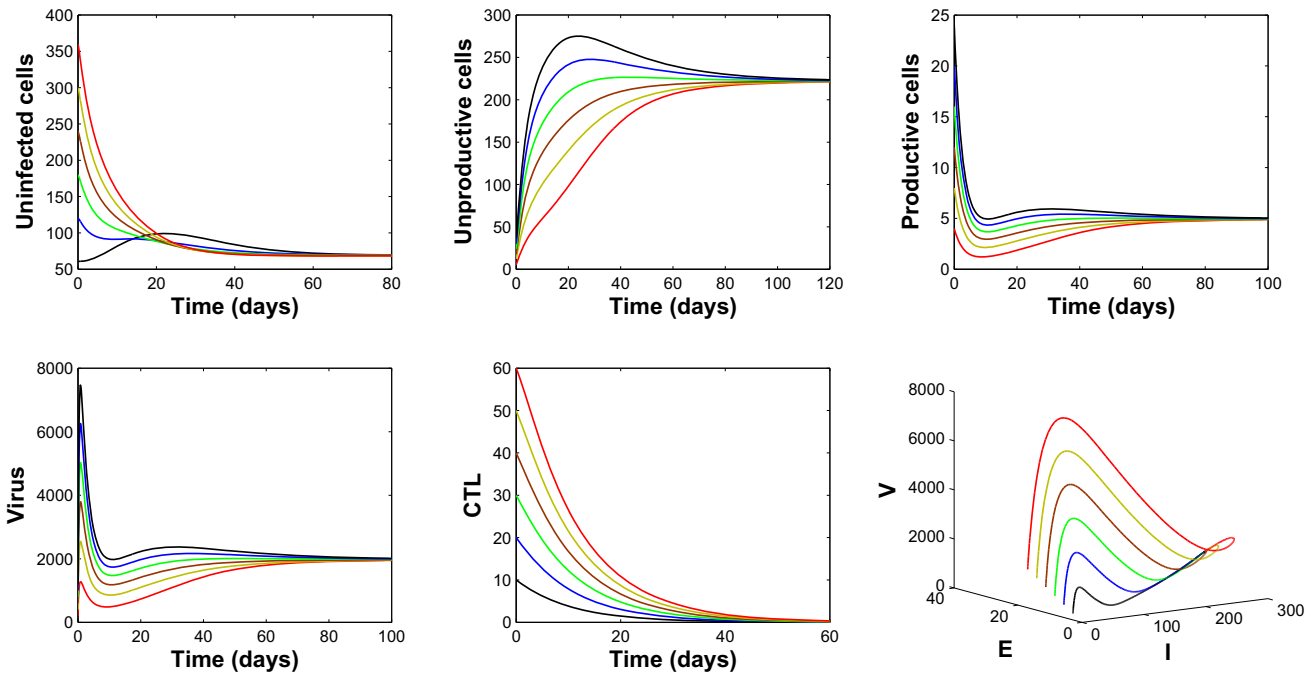

Fig. 7 Stability of the immune-free infection equilibrium Q_1 with condition (12) not satisfied

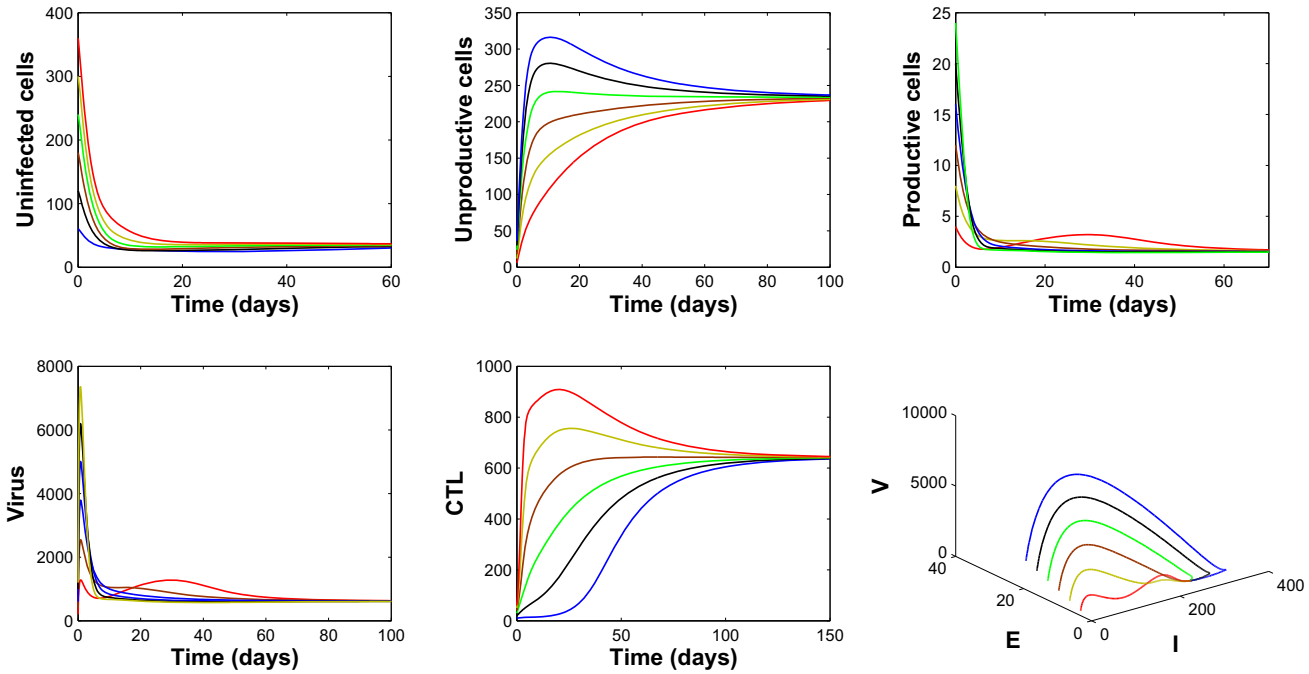

Fig. 8 Stability of the chronic infection equilibrium Q_2 with condition (14) not satisfied

(Figs. 7 and 8), we see that both equilibria Q_1 and Q_2 remain globally asymptotically stable without the conditions (12) and (14) are satisfied.

Observing that the basic reproduction number R_0 is independent of the CTL immune parameters. Further, by comparing the components of healthy cells, infected cells in the eclipse stage, productive infected cells and viral load before and after the activation of CTL response, we have $T_2 > T_1$, $E_2 < E_1$, $I_2 < I_1$ and $V_2 < V_1$ when $R_1 > 1$. Therefore, we deduce that the activation of CTL immune response is unable to eliminate the virus in the host population, but plays an important role in HIV infection by reducing the viral load, increasing the healthy cells and decreasing the two classes of infected cells.

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