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Dynamics of an HIV pathogenesis model with CTL immune response and two saturated rates *

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Abstract. In this paper, we propose an HIV infection model with CTL immune response which includes the cure of infected cells and the effect of immune impairment caused by HIV infection. Both the infection transmission process and the proliferation of CTL immune response are modeled by two saturated functions. Moreover, the qualitative analysis of the model is investigated and numerical simulations are given to illustrate our theoretical results.

Keywords: HIV infection, CTL immune response, saturated rate, stability

1 Introduction

Human immunodeficiency virus (HIV) is a virus that causes acquired immunodeficiency syndrome (AIDS). According to the World Health Organization (WHO) more than 35.3 million people living with HIV, 2.5 million new infections, and 1.6 million AIDS-related deaths in 2012[1]. Therefore, mathematical models have been used in order to understand the dynamics of HIV infection[2–11].

In this paper, we consider the basic model presented by Nowak and Bangham in [2], this model contains four variables, that are, uninfected cells (T), infected cells (I), free virus (V), and Cytotoxic T Lymphocytes (CTL) cells (Z). The model is given by the following nonlinear system of differential equations:

$$\begin{cases} \frac{dT}{dt} = s - dT - \beta VT \\ \frac{dI}{dt} = \beta VT - \delta I - pIZ \\ \frac{dV}{dt} = N\delta I - \mu V \\ \frac{dZ}{dt} = cIZ - bZ, \end{cases} \tag{1}$$

where $T(0) = T_0$, $I(0) = I_0$, $V(0) = V_0$ and $Z(0) = Z_0$ are given. Susceptible host cells $CD4^+$ T-cells (T) are produced at a rate s, die at a rate dT and become infected by virus at a rate βVT. Infected cells die at a rate δI and are killed by the CTL response at a rate pIZ. Free virus is produced by infected cells at a rate $N\delta I$ and decays at a rate μV. CTLs expand in response to viral antigen derived from infected cells at a rate cIZ and decay in the absence of antigenic stimulation at a rate bZ.

Note that the rate of infection in Eq. (1) is assumed to be bilinear in the virus V and the uninfected target cells T, which is not reasonable to describe the HIV infection. Hence, we replace this bilinear form

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by a saturated mass action presented by Song and Neumann in [12]. Furthermore, the proliferation of CTL response in Eq. (1) is bilinear in I and Z. However, in the presence of immune impairment effects caused by HIV infection, CTL proliferation is reduced [13]. On the other hand, the cure of infected cells by non-cytolytic elimination of the cccDNA in their nucleus, was omitted in Eq. (1). Recently, this cure of infected cells is considered by several works[3–5, 10, 14–16]. For these three reasons, we extend the basic model (1) to following model given by

$$\begin{cases} \frac{dT}{dt} = s - dT - \frac{\beta VT}{1+aV} + \rho I \\ \frac{dI}{dt} = \frac{\beta VT}{1+aV} - (\delta + \rho)I - pIZ \\ \frac{dV}{dt} = N\delta I - \mu V \\ \frac{dZ}{dt} = \frac{cIZ}{1+\alpha I} - bZ, \end{cases} \tag{2}$$

where ρ is the cure rate of infected cells and α represents the immune impairment rate. When $a = \rho = \alpha = 0$, we obtain the basic model (1).

The aim of this work is to study the dynamical behavior of our Eq. (2) which includes the effect of immune impairment caused by HIV infection and the cure of infected cells.

The rest of the paper is organized as follows. Section 2 illustrates some properties of the model's solutions. The model analysis and simulation are given in section 3. Discussion and conclusion of this research are presented in section 4.

2 Positivity and boundedness of solutions

In this section, we establish the positivity and boundedness of solutions of Eq. (2) because this model describes the evolution of a cell population. Hence the cell densities should remain non-negative and bounded. These properties imply global existence of the solutions. In addition, for biological reasons, we assume that the initial data for system (2) satisfy :

$$T_0 \geq 0,\ I_0 \geq 0,\ V_0 \geq 0,\ Z_0 \geq 0.$$

Proposition 2.1 *All solutions starting from non-negative initial conditions exist for all $t > 0$ and remain bounded and nonnegative. Moreover we have*

i) $T_1(t) \leq T_1(0) + \frac{s}{\delta_1}$,
ii) $V(t) \leq V(0) + \frac{N\delta}{\mu} \|I\|_\infty$,
iii) $Z(t) \leq Z(0) + \frac{c}{p}[\max(1; 2 - \frac{d}{b})T(0) + I(0) + \max(\frac{s}{b}, \frac{s}{d}) + \max(0; 1 - \frac{\delta}{b}) \|I\|_\infty]$

where $T_1(t) = T(t) + I(t)$ represents the T-cells and $\delta_1 = \min(d, \delta)$.

Proof. For positivity, we show that any solution starting in non negative orthant $\mathbb{R}^4_+ = \{(T, I, V, Z) \in \mathbb{R}^4 : T \geq 0, I \geq 0, V \geq 0, E \geq 0\}$ remains there forever. In fact, $(T(t), I(t), V(t), Z(t)) \in \mathbb{R}^4_+$ we have
$\dot{T}\,|_{T=0} = s + \rho I \geq 0$, $\dot{I}\,|_{I=0} = \frac{\beta VT}{1+aV} \geq 0$, $\dot{V}\,|_{V=0} = N\delta I \geq 0$, $\dot{Z}\,|_{Z=0} = 0 \geq 0$
Hence, positivity of all solutions initiating in $\mathbb{R}^4_+$ is guaranteed.

Now, we prove that the solutions are bounded. As $\dot{T}_1 = s - dT - \delta I - pZ$, we deduce that

$$T_1(t) \leq T_1(0)e^{-\delta_1 t} + \frac{s}{\delta_1}(1 - e^{-\delta_1 t}), \tag{3}$$

since $0 \leq e^{-\delta_1 t} \leq 1$ and $1 - e^{-\delta_1 t} \leq 1$, thus $i)$.

Now we show $ii)$. The equation $\dot{V} = N\delta I - \mu V$, implies that

$$V(t) = V(0)e^{-\mu t} + N\delta \int_0^t I(\xi)e^{(\xi - t)\mu} d\xi, \tag{4}$$

then,

$$V(t) \leq V(0) + \frac{N\delta}{\mu} \|I\|_\infty (1 - e^{-\mu t}).$$

Sine $1 - e^{-\mu t} \leq 1$, we deduce $ii)$. Finally, we show $iii)$. The equation $\dot{Z} = \frac{cIZ}{1+\alpha I} - bZ$ implies that

$$\dot{Z} - bZ \leq cIZ.$$

Since

$$cIZ = \frac{c}{p}[s - (\dot{T} + dT) + (\dot{I} + \delta I)],$$

we get

$$\begin{aligned} Z(t) \leq & \big[\frac{c}{p}(T(0) + I(0) - \frac{s}{b}) + Z(0)\big]e^{-bt} \\ & + \frac{c}{p}\Big\{\frac{s}{b} + \int_0^t \big[(b-d)T(\xi) + (b-\delta)I(\xi)\big]e^{b(\xi - t)}d\xi - T(t) - I(t)\Big\}. \end{aligned} \tag{5}$$

If $b - d \leq 0$ and $b - \delta \leq 0$, we have

$$Z(t) \leq Z(0) + \frac{c}{p}\Big[\frac{s}{b} + T(0) + I(0)\Big]. \tag{6}$$

If $b - d \leq 0$ and $b - \delta \geq 0$, we have

$$Z(t) \leq Z(0) + \frac{c}{p}\Big[\frac{s}{b} + T(0) + I(0) + \left(1 - \frac{\delta}{b}\right)\|I\|_\infty\Big]. \tag{7}$$

If $b - d \geq 0$ and $b - \delta \leq 0$, we have

$$Z(t) \leq Z(0) + \frac{c}{p}\Big[\frac{s}{d} + \left(2 - \frac{d}{b}\right)T(0) + I(0)\Big]. \tag{8}$$

If $b - d \geq 0$ and $b - \delta \geq 0$, we have

$$Z(t) \leq Z(0) + \frac{c}{p}\left[\frac{s}{d} + \left(2 - \frac{d}{b}\right)T(0) + I(0) + \left(1 - \frac{\delta}{b}\right)\|I\|_\infty\right]. \tag{9}$$

From Eq. (5)-(9), we deduce $iii)$.

3 Analysis of the model

In this section, we show that there exists a disease free equilibrium point and two infection equilibrium points, we study the stability of these equilibrium points.

3.1 Stability of free equilibria

By a simple calculation, system (2) has always one disease-free equilibrium $E_f = (\frac{s}{d}, 0, 0, 0)$, corresponding to the maximal level of healthy CD4$^+$ T-cells. Therefore, the basic reproduction number of (2) is given by

$$R_0 = \frac{\beta N \delta s}{d\mu(\delta + \rho)}. \tag{10}$$

The Jacobian matrix of the system (2) at an arbitrary point is given by

$$J = \begin{pmatrix} -d - \frac{\beta V}{1+aV} & \rho & -\frac{\beta T}{(1+aV)^2} & 0 \\ \frac{\beta V}{1+aV} & -(\delta + \rho) - pZ & \frac{\beta T}{(1+aV)^2} & -pI \\ 0 & N\delta & -\mu & 0 \\ 0 & \frac{cZ}{(1+\alpha I)^2} & 0 & \frac{cI}{1+\alpha I} - b \end{pmatrix}. \tag{11}$$

Proposition 3.1

1. If $R_0 < 1$, then the disease free equilibrium, E_f, is locally asymptotically stable.
2. If $R_0 > 1$, then E_f is unstable.

Proof. The Jacobian matrix evaluated at E_f is

$$J_{E_f} = \begin{pmatrix} -d & \rho & -\frac{\beta s}{d} & 0 \\ 0 & -(\delta+\rho) & \frac{\beta s}{d} & 0 \\ 0 & N\delta & -\mu & 0 \\ 0 & 0 & 0 & -b \end{pmatrix}. \tag{12}$$

The characteristic polynomial of J_{E_f} is

$$P_{E_f}(\xi) = (\xi+d)(\xi+b)[\xi^2 + (\delta+\rho+\mu)\xi + (\delta+\rho)\mu(1-R_0)],$$

then the eigenvalues of the matrix J_{E_f} are

$$\begin{aligned} \xi_1 &= -d, \\ \xi_2 &= -b, \\ \xi_3 &= \frac{-(\delta+\rho+\mu) - \sqrt{(\delta+\rho+\mu)^2 - 4(\delta+\rho)\mu(1-R_0)}}{2}, \\ \xi_4 &= \frac{-(\delta+\rho+\mu) + \sqrt{(\delta+\rho+\mu)^2 - 4(\delta+\rho)\mu(1-R_0)}}{2}, \end{aligned}$$

it is clear that ξ_1, ξ_2 and ξ_3 are negative. Moreover, ξ_4 is negative when $R_0 < 1$, thus E_f is locally asymptotically stable.

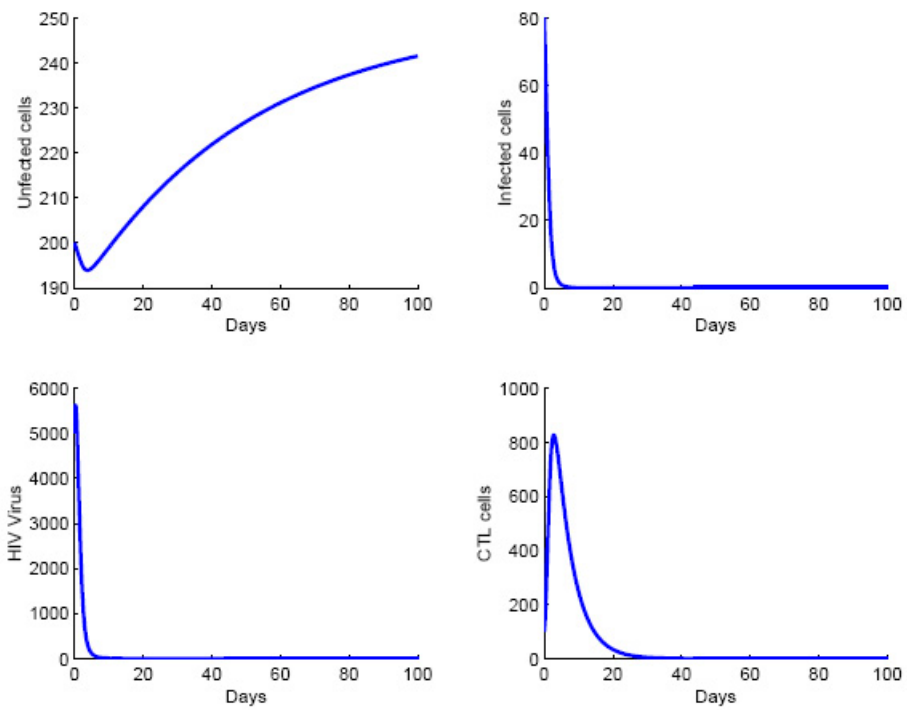

Fig. 1. The infection dies out when $R_0 < 1$ as shown in the case of the equilibrium E_f. For this simulation, we choose $s = 5$, $\beta = 0.000024$, $d = 0.02$, $\delta = 0.5$, $p = 0.001$, $N = 500$, $\mu = 3$, $\rho = 0.01$, $a = 0.001$, $\alpha = 0.001$, c=0.03 and $b = 0.2$

3.2 Infection steady states

In this section, we focus on the existence and stability of the no-disease-free disease steady states that we are going to name : infection steady states. In fact, it is easily verified that the system (2) has two of them: $E_1 = (T_1, I_1, V_1, 0)$, where $T_1 = \frac{s}{d}\frac{aNs+\mu}{aNs+\mu R_0}$, $I_1 = \frac{s}{\delta}\frac{\mu(R_0-1)}{aNs+\mu R_0}$, $V_1 = \frac{Ns(R_0-1)}{aNs+\mu R_0}$; $E_2 = (T_2, I_2, V_2, Z_2)$, where

$$
\begin{aligned}
T_2 &= \frac{(aN\delta\rho)I_2^2 + (aNs\delta + \mu\rho)I_2 + \mu s}{N\delta(ad+\beta)I_2 + \mu d},\\
I_2 &= \frac{b}{c-\alpha b},\\
V_2 &= \frac{N\delta I_2}{\mu},\\
Z_2 &= \frac{-N\delta[ad\rho + \delta(ad+\beta)]I_2 + (\beta Ns\delta - d\mu(\rho+\delta))}{p(N\delta(ad+\beta)I_2 + \mu d)}).
\end{aligned}
$$

From the biological point of view, the point E_1 represents absent of CTL immune response and E_2 represents HIV chronic of disease with CTL response. In order to study the local stability of the points E_1 and E_2, we define the following numbers :

$$D_0 = \frac{cs}{b\delta}, \tag{13}$$

$$\widetilde{D_0} = D_0\frac{\mu\delta R_0}{\delta(aNs+\mu R_0) + \alpha\mu s(R_0-1)}, \tag{14}$$

$$H_0 = \frac{1}{\frac{1}{R_0} + \frac{1}{\widetilde{D_0}}}. \tag{15}$$

The number D_0 represents the basic defence rate and H_0 is the half harmonic mean of R_0 and $\widetilde{D_0}$. The importance of these parameters is related the following results.

Theorem 3.2

1. If $R_0 < 1$, then the point E_1 does not exists and $E_1 = E_f$ when $R_0 = 1$.
2. If $R_0 > 1$ and $H_0 < 1$, then E_1 is locally asymptotically stable.
3. If $R_0 > 1$ and $H_0 > 1$, then E_1 is unstable.

Proof. It easy to verified that if $R_0 < 1$, then the point E_1 does not exists and $E_1 = E_f$ when $R_0 = 1$. We assume that $R_0 > 1$, the Jacobian matrix at E_1 is

$$J = \begin{pmatrix}
-d - \frac{\beta V_1}{1+aV_1} & \rho & -\frac{\beta T_1}{(1+aV_1)^2} & 0\\
\frac{\beta V_1}{1+aV_1} & -(\delta+\rho) & \frac{\beta T_1}{(1+aV_1)^2} & -pI_1\\
0 & N\delta & -\mu & 0\\
0 & 0 & 0 & \frac{cI_1}{1+\alpha I_1} - b
\end{pmatrix}.$$

The characteristic equation associated with J_{E_1} is given by

$$\left(\xi + b - \frac{cI_1}{1+\alpha I_1}\right)(\xi^3 + a_1\xi^2 + a_2\xi + a_3) = 0,$$

where

$$
\begin{aligned}
a_1 &= d + \delta + \mu + \rho + \frac{\beta V_1}{1+aV_1},\\
a_2 &= (\delta+\mu+\rho)d + (\mu+\delta)\frac{\beta V_1}{1+aV_1} + \mu(\delta+\rho)\frac{aV_1}{1+aV_1},\\
a_3 &= \mu d(\delta+\rho)\frac{aV_1}{1+aV_1} + \mu\delta\frac{\beta V_1}{1+aV_1}.
\end{aligned}
$$

Then $\frac{cI_1}{1+\alpha I_1}-b=\frac{b\widetilde{D_0}(H_0-1)}{H_0}$ is an eigenvalue of J_{E_1}. The sign of the eigenvalue $\frac{b\widetilde{D_0}(H_0-1)}{H_0}$ is negative if $H_0<1$.Then the stability of E_1 is determined by the distribution of the roots of the equation $\xi^3+a_1\xi^2+a_2\xi+a_3=0$ Using the same technique as that defined in [4] by K. Hattaf and N. Yousfi, and from the Routh-Hurwitz Theorem given in [17], the equation $\xi^3+a_1\xi^2+a_2\xi+a_3=0$ has all its roots negative real parts if $R_0>1$. Then E_1 is locally asymptotically stable when $R_0>1$ and $H_0<1$.
If $H_0>1$, the eigenvalue $\frac{b\widetilde{D_0}(H_0-1)}{H_0}$ is not negative, then E_1 is unstable.

As shown in Fig. 2, the situation where $R_0>1$ and $H_0<1$ is characterized by the fast decline of the CTLs cells, and the persistence of the infection when time goes by. By a simple calculation, we can show that if $R_0>1$ then the condition of local asymptotic stability of E_1 is equivalent to

$$D_0<(\frac{R_0}{R_0-1})(\frac{\delta(aNs+\mu R_0)+\alpha\mu s(R_0-1)}{\mu\delta R_0}),$$

which means that if the basic defense number by CTLs response is below the threshold $(\frac{R_0}{R_0-1})(\frac{\delta(aNs+\mu R_0)+\alpha\mu s(R_0-1)}{\mu\delta R_0})$, then immune response cannot keep up with the infection, and it eventually vanishes.

Theorem 3.3

1. If $\alpha>\frac{c}{b}$ or $H_0<1$, then the point E_2 does not exists and $E_2=E_1$ when $H_0=1$.
2. If $\alpha<\frac{c}{b}$ and $H_0>1$, then E_2 is locally asymptotically stable.

Proof. We notice that the condition $\alpha<\frac{c}{b}$ and $H_0>1$ is equivalent to $I_2<I_1$.
Then it easy to verified that the point E_2 does not exists if $H_0<1$ or $\alpha>\frac{c}{b}$ and $E_2=E_1$ when $H_0=1$.
We assume that $\alpha<\frac{c}{b}$ and $H_0>1$,the Jacobian matrix at E_2 is

$$J_{E_2}=\begin{pmatrix} -d-C_1 & \rho & -C_2 & 0 \\ C_1 & -\rho-\delta-pZ_2 & C_2 & -pI^* \\ 0 & N\delta & -\mu-\xi & 0 \\ 0 & \frac{cZ_2}{(1+\alpha I_2)^2} & 0 & 0 \end{pmatrix},$$

where $C_1=\frac{\beta V_2}{1+aV_2}$ and $C_2=\frac{\beta T_2}{(1+aV_2)^2}$. The characteristic equation associated with J_{E_2} is given by

$$(\xi^4+b_1\xi^3+b_2\xi^2+b_3\xi+b_4)=0, \tag{16}$$

where

$$\begin{aligned} b_1&=d+C_1+\mu+\rho+\delta+pZ_2,\\ b_2&=\mu(d+C_1+\rho)+(d+C_1)(\delta+pZ_2)+p\frac{b}{(1+\alpha I_2)}Z_2+d\rho,\\ b_3&=\mu d\rho+\mu C_1(\delta+pZ_2)+p\frac{b}{(1+\alpha I_2)}Z_2(\mu+d+C_1),\\ b_4&=p\frac{b}{(1+\alpha I_2)}Z_2\mu(d+C_1). \end{aligned}$$

From the Routh-Hurwitz Theorem given in [17], the eigenvalues of the above matrix have negative real parts when $H_0>1$. Consequently, E_2 is locally asymptotically stable when $H_0>1$.

As shown in Fig. 3, the situation where $\alpha<\frac{c}{b}$ and $H_0>1$ is characterized by an increase CD4$^+$ cells number and a light decrease of the virus load. by a simple calculation, we show that under the condition $\alpha<\frac{c}{b}$, E_2 is locally asymptotically stable is equivalent to

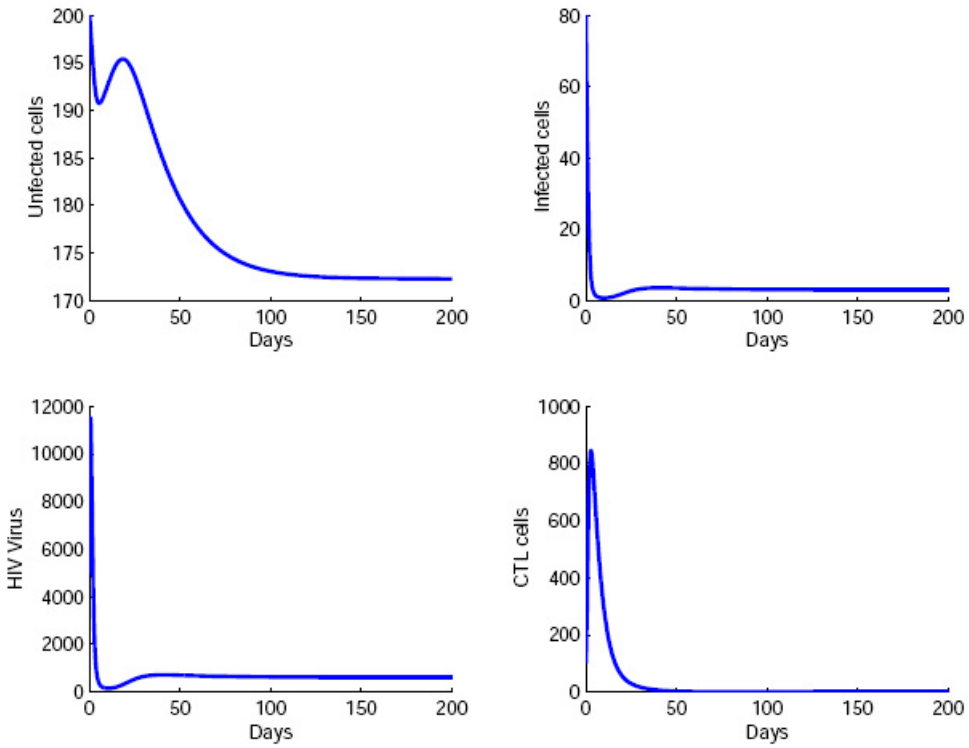

Fig. 2. The virus persists in the absence of the CTLS response as shown in the case of the equilibrium E_1. For this simulation, we choose $s = 5$, $\beta = 0.000024$, $d = 0.02$, $\delta = 0.5$, $p = 0.001$, $N = 1200$, $\mu = 3$, $\rho = 0.01$, $a = 0.001$, $\alpha = 0.001$, $c = 0.03$ and $b = 0.2$, which correspond to $R_0 > 1$ and $H_0 < 1$.

$$D_0 > (\frac{R_0}{R_0 - 1})(\frac{\delta(aNs + \mu R_0) + \alpha\mu s(R_0 - 1)}{\mu\delta R_0}),$$

which means that if the basic defense number by CTL response is above the threshold $(\frac{R_0}{R_0-1})(\frac{\delta(aNs+\mu R_0)+\alpha\mu s(R_0-1)}{\mu\delta R_0})$, then immune response CTL can reduce the concentration of virus.

4 Discussion and conclusion

In this work, we gave a rigorous local stability analysis of a new mathematical model describing the interactions between human imunodeficiency virus (HIV) infection of CD4+ T-cells and cytotoxic T lymphocytes (CTL) immune response. The disease free equilibrium is locally asymptotically stable if the basic infection reproduction number satisfies $R_0 < 1$. For $R_0 > 1$, the stability of the two endemic equilibrium points is dependent on the basic defence number by CTLs response D_0. Indeed, If

$$D_0 < (\frac{R_0}{R_0 - 1})(\frac{\delta(aNs + \mu R_0) + \alpha\mu s(R_0 - 1)}{\mu\delta R_0}),$$

then E_1 is locally asymptotically stable while E_2 is is locally asymptotically stable, when

$$D_0 > (\frac{R_0}{R_0 - 1})(\frac{\delta(aNs + \mu R_0) + \alpha\mu s(R_0 - 1)}{\mu\delta R_0}).$$

From the R_0 formula, we notice that R_0 is independent of the parameters of the activation of CTL that are b,c, α and p. which means that CTL do not permit to eliminate the virus. However, they can reduce the concentration of viral load and increase the concentration of CD4+ healthy cells, this can be seen when comparing the components of the viral load and those of the concentration of CD4+ before and after the

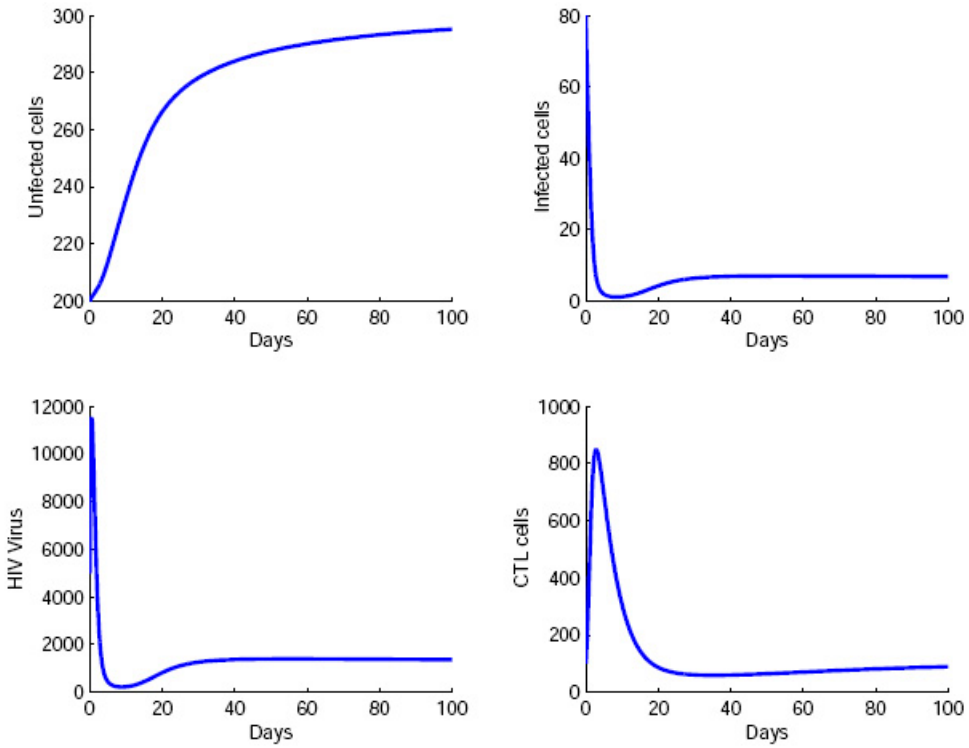

Fig. 3. an increase of the CD4$^+$ cells and light decrease of the virus load as shown in the case of the equilibrium E_2. For this simulation, we choose $s = 10$, $\beta = 0.000024$, $d = 0.02$, $\delta = 0.5$, $p = 0.001$, $N = 1200$,$\mu = 3$, $\rho = 0.01$, $a = 0.001$, $\alpha = 0.001$, c=0.03 and $b = 0.2$, which correspond to $H_0 > 1$ and $\alpha < \frac{c}{b}$.

activation of CTL, that is to say under the condition $H_0 > 1$. In fact, By simple calculations show that: $T_1 < T_2$ and $V_2 < V_1$ where T_1, T_2, V_1 and V_2 are given above. So the cellular immune can control the load of virus.

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