

Global stability analysis and clinical implications of a modified HIV model with CTL response

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Abstract

A modified mathematical model of the Human Immunodeficiency Virus (HIV) pathogenesis with cytotoxic T lymphocytes (CTL) is introduced in this paper. This model includes a saturated rate function describing the viral infection. It is shown that the disease free steady state is globally asymptotically stable when the virus basic reproduction number is less than one. The existence of two other infection equilibria is established when the virus basic reproduction number is greater than one. The global stability of these endemic equilibria depends on the basic reproduction number and a CTL immune response reproduction indicator. Numerical simulations are performed to illustrate the behavior of solutions and the effectiveness of CTL cells. Moreover, a comparison of the model fitting with some clinical data sets and its implications are also presented.

Keywords: CTL response; global stability; HIV infection; viral dynamics.

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1 Introduction

The human immunodeficiency virus (HIV) is a virus that gradually weakens the immune system. It is considered as the main cause for several deadly diseases

after the resulting acquired immunodeficiency syndrome (AIDS) is reached. After that the immune system fails to play its life-sustaining role [1, 2].

Indeed, it is well known that the cellular immune response, also called the cytotoxic T-lymphocyte (CTL) response, play an indispensable role during the HIV viral infection, the effect of the CTL which attacks and kills the infected cells [3, 4].

The basic viral infection model with CTL cells was first studied in [5] and its global stability was studied in [6, 7]. Noting that CTL cells are responsible for the abrupt decrease HIV virus load after a sharp increase during the primary infection phase [8–11]. In [12], the authors consider the interaction between CTL, viruses and macrophages and study the global stability in a model with mass action infection term. With saturated infection term, the same mathematical question was tackled in [13] with a model consisting of four ordinary differential equations with Beddington-DeAngelis infection term.

More recently the model describing the interaction between the HIV viruses, $CD4^+$ T cells, infected cells with a standard incidence rate function describing saturated viral infection is formulated and studied in [14]. The authors study the local and global stability of the endemic states and illustrate that their model can fit well with some clinical HIV infection data sets. In this paper, we extend their work by incorporating the cytotoxic T lymphocytes (CTL) immune response. The dynamics of HIV infection with CTL response that we consider is given by the following nonlinear system of differential equations:

$$\begin{cases} \dot{x}(t) = \lambda - d_1x(t) - \frac{k_1x(t)v(t)}{x(t) + v(t)}, \\ \dot{y}(t) = \frac{k_1x(t)v(t)}{x(t) + v(t)} - d_2y(t) - py(t)z(t) \\ \dot{v}(t) = ay(t) - d_3v(t), \\ \dot{z}(t) = cy(t)z(t) - bz(t). \end{cases} \quad (1)$$

With the initial conditions $x(0) = x_0$, $y(0) = y_0$, $v(0) = v_0$ and $z(0) = z_0$.

In this model, x , y , v and z denote the concentration of uninfected cells, infected cells, free virus and CTL cells, respectively. λ is the rate of production of the susceptible host cells $CD4^+$ T cells, and d_1 is natural mortality of healthy cells, k_1 is the average of infection, d_2 is the death rate of infected $CD4^+$ T cells, not by CTL killing, p is the clearance rate of infection, a is the rate of production the virus by infected $CD4^+$ T cells, d_3 is the death rate of virus, c is the activation rate CTL cells and b is the death rate of CTL cells.

The paper is organized as follows. The next section is dedicated to presenting the mathematical model. In section 3 we calculate the steady state of our model, followed, in section 4, by the global stability of the model. In section 5, we compare our model with clinical data. We conclude in the last section.

2 Mathematical model

The theoretical analysis to epidemic models and dynamical systems [15–18] shown that time delays play a crucial role to the dynamical properties of the HIV infection models. In order to study the influence of time delay on the spread of HIV, we have illustrated the following model:

$$\begin{cases} \dot{x}(t) = \lambda - d_1x(t) - \frac{k_1x(t)v(t)}{x(t) + v(t)}, \\ \dot{y}(t) = \frac{k_1x(t - \tau_1)v(t - \tau_1)}{x(t - \tau_1) + v(t - \tau_1)} - d_2y(t) - py(t)z(t) \\ \dot{v}(t) = ay(t - \tau_2) - d_3v(t), \\ \dot{z}(t) = cy(t)z(t) - bz(t). \end{cases} \quad (2)$$

where τ_1 represents the delay in the production of productively infected cells and τ_2 represents the delay in the production of virus. Note that this model (2), employs the more realistic standard incidence rate function $\frac{k_1xv}{x + v}$ as in [14, 19, 20] which better describes the rate of viral infection.

With the initial conditions of model (2) are given by $x(\theta) > 0$, $y(\theta) > 0$, $v(\theta) > 0$ and $z(\theta) > 0$ for $\theta \in [-\rho, 0]$, where $\rho = \max(\tau_1, \tau_2)$. It can be shown that the solution of model (2) with positive initial conditions will remain positive. In order to prove the boundedness of the solutions of the model (2), let us the function:

$$T(t) = x(t) + y(t + \tau_1) + \frac{d_2}{2a}v(t + \tau_1 + \tau_2) + \frac{p}{c}z(t + \tau_1).$$

Then using the equation of (2), we get

$$\begin{aligned} \frac{dT}{dt}(t) &= \lambda - d_1x(t) - \frac{d_2}{2}y(t + \tau_1) - \frac{d_2d_3}{2a}v(t + \tau_1 + \tau_2) - \frac{pb}{c}z(t + \tau_1) \\ &\leq \lambda - \varrho T(t), \end{aligned}$$

where $\varrho = \min(d_1, \frac{d_2}{2}, d_3, b)$. Therefore, we have

$$\limsup_{t \rightarrow +\infty} T(t) \leq \frac{\lambda}{\varrho}.$$

Hence, all solutions of the model (2) are bounded for sufficiently large t .

3 Steady states

The system (2) has an infection-free equilibrium $E_f = (\frac{\lambda}{d_1}, 0, 0, 0)$, corresponding to the maximal level of healthy CD4⁺ T-cells. Based on its biological defi-

dition, the basic reproduction number R_0 is the product of a virus' maximum average lifetime infection production I times the average lifetime virus production V of an infected $CD4^+$ T-cell. It is easy to see that $I = k_1/d_3$, while $V = a/d_2$. Therefore

$$R_0 = IV = \frac{ak_1}{d_2d_3}. \quad (3)$$

Mathematically, system (2) may have three equilibria in addition to the disease free equilibrium. The first endemic steady state is $E_1 = (x_1, y_1, v_1, z_1)$, where

$$x_1 = \frac{\lambda R_0}{k_1(R_0 - 1) + d_1 R_0}, \quad y_1 = \frac{d_3}{a} v_1, \quad v_1 = (R_0 - 1)x_1, \quad z_1 = 0.$$

The second endemic steady state is $E_2 = (x_2, y_2, v_2, z_2)$, where

$$\begin{aligned} x_2 &= \frac{\lambda - (d_1 + k_1)v_2 + \sqrt{(\lambda - k_1v_2)^2 + d_1v_2(d_1v_2 + 2\lambda + 2k_1v_2)}}{2d_1}, \\ y_2 &= \frac{b}{c}, \quad v_2 = \frac{a}{d_3} y_2 \\ z_2 &= \frac{x_2(\frac{v_2}{y_2}k_1 - d_2) - d_2v_2}{p(x_2 + v_2)}. \end{aligned}$$

The third endemic steady state is $E_3 = (x_3, y_3, v_3, z_3)$, where

$$\begin{aligned} x_3 &= \frac{\lambda - (d_1 + k_1)v_3 - \sqrt{(\lambda - k_1v_3)^2 + d_1v_3(d_1v_3 + 2\lambda + 2k_1v_3)}}{2d_1}, \\ y_3 &= \frac{b}{c}, \quad v_3 = \frac{a}{d_3} y_3 \\ z_3 &= \frac{x_3(\frac{v_3}{y_3}k_1 - d_2) - d_2v_3}{p(x_3 + v_3)}. \end{aligned}$$

Since $x_3 < 0$, this last point has no biological meaning and hence it will not be studied below.

In what follows, we will make use of the following CTL immune response reproduction number R_{CTL} to classify the model system dynamics.

$$R_{CTL} = \frac{cy_1}{b} = \frac{\lambda cd_3 R_0 (1 - \frac{1}{R_0})}{ab(d_1 + k_1(1 - \frac{1}{R_0}))}.$$

Observe that the second endemic state E_2 exists when $R_{CTL} > 1$. This endemic state is also called an interior equilibrium.

We explain the existence of this endemic equilibrium as follow. We recall first, that in this state both the free viruses and CTL cells are present. Assume that $R_0 > 1$, in the absence of CTL immune response, the infected cell load per unit time is $\frac{\lambda d_3 R_0 (R_0 - 1)}{a k_1 (R_0 - 1) + a d_1 R_0}$. Via the fourth equation of model (2), CTL cells reproduced due to infected cells stimulating per unit time is $\frac{c \lambda d_3 R_0 (R_0 - 1)}{a k_1 (R_0 - 1) + a d_1 R_0} = c y_1$. The CTL load during the lifespan of a CTL cell is $\frac{c \lambda d_3 R_0 (R_0 - 1)}{a b k_1 (R_0 - 1) + a b d_1 R_0} = R_{CTL}$. If $R_{CTL} > 1$, then we have the existence of the endemic equilibrium E_2 .

4 Global stability results

In this section, we study the global asymptotic stability of the steady states using the method of Lyapunov function construction. For this reason we consider the function

$$F(x) = x - 1 - \ln(x), \forall x > 0.$$

Note that $F(x) > 0, \forall x > 0$ and that $F(x) = 0$ if and only if $x = 1$. We consider the positive real numbers $x_1, x_2, \dots, x_n$, then

$$1 - x_i + \ln x_i = -F(x_i) \leq 0, \quad \forall i = 1, \dots, n$$

By summing for $i = 1, \dots, n$, we get:

$$n - \sum_{i=1}^n x_i + \ln \prod_{i=1}^n x_i \leq 0,$$

if we take $x_i = \frac{p_i}{q_i}$, we will have

$$n - \sum_{i=1}^n \frac{p_i}{q_i} + \ln \prod_{i=1}^n \frac{p_i}{q_i} \leq 0, \quad (4)$$

when $\prod_{i=1}^n p_i = \prod_{i=1}^n q_i$, ($\prod_{i=1}^n \frac{p_i}{q_i} = 1$), we will have

$$n - \sum_{i=1}^n \frac{p_i}{q_i} \leq 0.$$

First, we will study the global stability of the disease-free equilibrium.

Theorem 4.1 *If $R_0 \leq 1$, then the disease-free equilibrium E_f is globally asymptotically stable, for any delay $\tau_1 > 0$, $\tau_2 > 0$.*

proof We would like to show $\lim_{t \rightarrow \infty} (y, v, z) = (0, 0, 0)$. To this end, we consider the following Let the following Lyapunov functional:

$$\mathcal{L}_f(x, y, v, z) = y + \frac{d_2}{a}v + k_1 \int_{t-\tau_1}^t \frac{x(\xi)v(\xi)}{x(\xi) + v(\xi)} d\xi + d_2 \int_{t-\tau_2}^t y(\xi) d\xi + \frac{p}{c}z.$$

The time derivative is given by:

$$\begin{aligned} \dot{\mathcal{L}}_f(x, y, v, z) &= \dot{y} + \frac{d_2}{a}\dot{v} + k_1 \left(\frac{x(t)v(t)}{x(t) + v(t)} - \frac{x(t-\tau_1)v(t-\tau_1)}{x(t-\tau_1) + v(t-\tau_1)} \right) \\ &\quad + d_2 (y(t) - y(t-\tau_2)) + \frac{p}{c}\dot{z}, \\ &= \frac{k_1 x(t)v(t)}{x(t) + v(t)} - \frac{d_2 d_3}{a}v(t) \\ &\leq k_1 v(t) - \frac{d_2 d_3}{a}v(t) \\ &\leq \frac{d_2 d_3}{a} (R_0 - 1) v(t) \end{aligned}$$

If $R_0 < 1$; then $\dot{\mathcal{L}}_f \leq 0$ Moreover, $\dot{\mathcal{L}}_f \leq 0$ when $v = 0$. The largest compact invariant.

$$E = \{(x, y, v, z) \in \mathbb{R}_*^+ | v = 0\}$$

According to LaSalle's invariance principle, $\lim_{t \rightarrow +\infty} v(t) = 0$, the limit system of equations is:

$$\begin{cases} \dot{x} = \lambda - d_1 x \\ \dot{y} = -d_2 y - p y z \\ \dot{z} = c y z - b z \end{cases}$$

We define :

$$\mathcal{L}_f(x, y, z) = \frac{1}{x_0} \left(x - x_0 - x_0 \ln \frac{x}{x_0} \right) + y + \frac{p}{c}z.$$

Since $x_0 = \frac{\lambda}{d_1}$, then

$$\dot{\mathcal{L}}_f(x, y, z) = d_1 \left(2 - \frac{x}{x_0} - \frac{x_0}{x} \right) - d_2 y - \frac{pb}{c}z,$$

Since the arithmetic mean is greater than or equal to the geometric mean, it follows

$$2 - \frac{x}{x_0} - \frac{x_0}{x} \leq 0$$

Therefore $\dot{\mathcal{L}}_f \leq 0$ and the equality holds if $x = x_0$, $y = 0$ and $z = 0$, which complete the proof.

Theorem 4.2 *If $R_0 \geq 1$ and $R_{CTL} \leq 1$; then the endemic point E_1 is globally asymptotically stable.*

proof Let the following Lyapunov functional:

$$\begin{aligned}\mathcal{L}_1(x, y, v, z) = & x - x_1 - \int_{x_1}^x \frac{d_2 y_1}{k_1 u v_1} du + y - y_1 - y_1 \ln \frac{y}{y_1} \\ & + \frac{d_2}{a} (v - v_1 - v_1 \ln \frac{v}{v_1}) + \frac{p}{c} z \\ & + k_1 \frac{x_1 v_1}{x_1 + v_1} \int_{t-\tau_1}^t F\left(\frac{x(\xi)v(\xi)}{x_1 v_1} \frac{x_1 + v_1}{x(\xi) + v(\xi)}\right) d\xi \\ & + d_2 y_1 \int_{t-\tau_2}^t F\left(\frac{y(\xi)}{y_1}\right) d\xi.\end{aligned}$$

The time derivative of this functional is given by

$$\begin{aligned}\dot{\mathcal{L}}_1(x, y, v, z) = & -\frac{d_1 v_1}{x(x_1 + v_1)} (x - x_1)^2 \\ & + d_2 y_1 \left(-1 - \frac{v}{v_1} + \frac{v}{v_1} \frac{x + v_1}{x + v} + \frac{x + v}{x + v_1} \right) \\ & + d_2 y_1 \left(4 - \frac{x_1}{x} \frac{x + v_1}{x_1 + v_1} - \frac{y_1}{y} \frac{x(t - \tau_1)v(t - \tau_1)}{x_1 v_1} \frac{x_1 + v_1}{x(t - \tau_1) + v(t - \tau_1)} \right. \\ & \left. - \frac{y(t - \tau_2)v_1}{y_1 v} - \frac{x + v}{x + v_1} + \ln\left(\frac{x(t - \tau_1) + v(t - \tau_1)}{xv} \frac{x + v}{x(t - \tau_1) + v(t - \tau_1)} \frac{y(t - \tau_2)}{y}\right) \right) \\ & + pz\left(y_1 - \frac{b}{c}\right),\end{aligned}$$

this fact, implies that

$$\begin{aligned}\dot{\mathcal{L}}_1(x, y, v, z) = & -\frac{d_1 v_1}{x(x_1 + v_1)} (x - x_1)^2 \\ & - (d_2 + k_2) s_1 \left(\frac{x(v - v_1)^2}{v_1(x + v_1)(x + v)} \right) \\ & + d_2 y_1 \left(4 - \frac{x_1}{x} \frac{x + v_1}{x_1 + v_1} - \frac{y_1}{y} \frac{x(t - \tau_1)v(t - \tau_1)}{x_1 v_1} \frac{x_1 + v_1}{x(t - \tau_1) + v(t - \tau_1)} \right. \\ & \left. - \frac{y(t - \tau_2)v_1}{y_1 v} - \frac{x + v}{x + v_1} + \ln\left(\frac{x(t - \tau_1)v(t - \tau_1)}{xv} \frac{x + v}{x(t - \tau_1) + v(t - \tau_1)} \frac{y(t - \tau_2)}{y}\right) \right) \\ & + pz\left(y_1 - \frac{b}{c}\right)\end{aligned}$$

Taking $p_1 = x_1(x + v_1)$, $p_2 = y_1(x(t - \tau_1)v(t - \tau_1))$, $p_3 = y(t - \tau_2)v_1$, $p_4 = x + v$, $q_1 = x(x_1 + v_1)$, $q_2 = y(x_1v_1)$, $q_3 = y_1v$, $q_4 = x + v_1$ and using the inequality (4) for $n = 4$, we obtain

$$4 - \frac{x_1}{x} \frac{x + v_1}{x_1 + v_1} - \frac{y_1}{y} \frac{x(t - \tau_1)v(t - \tau_1)}{x_1v_1} \frac{x_1 + v_1}{x(t - \tau_1) + v(t - \tau_1)} - \frac{y(t - \tau_2)v_1}{y_1v} - \frac{x + v}{x + v_1} + \ln\left(\frac{x(t - \tau_1) + v(t - \tau_1)}{xv} \frac{x + v}{x(t - \tau_1) + v(t - \tau_1)} \frac{y(t - \tau_2)}{y}\right) \leq 0$$

Also when $R_{CTL} \leq 1$, we will have $y_1 - \frac{b}{c} \leq 0$; which means that $\dot{\mathcal{L}}_1 \leq 0$, and the equality holds when $x = x_1$, $y = y_1$, $sv = v_1$ and $z = z_1$. By the LaSalle invariance principle, the endemic point E_1 is asymptotically stable when $R_0 \geq 1$ and $R_{CTL} \leq 1$.

Theorem 4.3 *If $R_0 \geq 1$ and $R_{CTL} \geq 1$, then the endemic point E_2 is globally asymptotically stable for any delay $\tau_1 > 0$, $\tau_2 > 0$.*

proof Let the following Lyapunov functional:

$$\begin{aligned} \mathcal{L}_2(x, y, v, z) = & x - x_2 - \int_{x_2}^x \frac{d_2y_2 + py_2z_2}{\frac{k_1uv_2}{u + v_2}} du + y - y_2 - y_2 \ln \frac{y}{y_2} \\ & + \frac{d_2 + pz_2}{a} (v - v_2 - v_2 \ln \frac{v}{v_2}) \\ & + \frac{p}{c} (z - z_2 - z_2 \ln \frac{z}{z_2}) \\ & + k_1 \frac{x_1v_2}{x_2 + v_2} \int_{t-\tau_1}^t F\left(\frac{x(\xi)v(\xi)}{x_2v_2} \frac{x_2 + v_2}{x(\xi) + v(\xi)}\right) d\xi \\ & + (d_2y_2 + py_2z_2) \int_{t-\tau_2}^t F\left(\frac{y(\xi)}{y_2}\right) d\xi. \end{aligned}$$

The time derivative of this Lyapunov functional is given by

$$\begin{aligned}
\dot{\mathcal{L}}_2(x, y, v, z) = & \dot{x} - (d_2 y_2 + p y_2 z_2) \frac{x + v_2}{k_1 x v_2} \dot{x} + \dot{y} - \frac{y_2}{y} \dot{y} \\
& + \frac{d_2 + p z_2}{a} \left(\dot{v} - \frac{v_2}{v} \dot{v} \right) \\
& + \frac{p}{c} \left(\dot{z} - \frac{z_2}{z} \dot{z} \right) \\
& - k_1 \frac{x_2 v_2}{x_2 + v_2} \left(F \left(\frac{x(t - \tau_1) v(t - \tau_1)}{x_2 v_2} \frac{x_2 + v_2}{x(t - \tau_1) + v(t - \tau_1)} \right) \right. \\
& \left. - F \left(\frac{x v}{x_2 v_2} \frac{x_2 + v_2}{x + v} \right) \right) + (d_2 y_2 + p y_2 z_2) \left(F \left(\frac{y}{y_2} \right) \right. \\
& \left. - F \left(\frac{y(t - \tau_2)}{y_2} \right) \right).
\end{aligned}$$

Then,

$$\begin{aligned}
\dot{\mathcal{L}}_2 = & - \frac{d_1 v_2}{x(x_2 + v_2)} (x - x_2)^2 + ((d_2 + k_2) y_2 + p y_2 z_2) \left(-1 - \frac{v}{v_2} + \frac{v}{v_2} \frac{x_2 + v_2}{x + v} + \frac{x + v}{x + v_2} \right) \\
& + ((d_2 + k_2) y_2 + p y_2 z_2) \left(4 - \frac{x_2}{x} \frac{x + v_2}{x_2 + v_2} - \frac{y_2}{y} \frac{x(t - \tau_1) v(t - \tau_1)}{x_2 v_2} \frac{x_2 + v_2}{x(t - \tau_1) + v(t - \tau_1)} \right. \\
& \left. - \frac{y(t - \tau_2) v_2}{y_2 v} - \frac{x + v}{x + v_2} + \ln \left(\frac{x(t - \tau_1) + v(t - \tau_1)}{x v} \frac{x + v}{x(t - \tau_1) + v(t - \tau_1)} \frac{y(t - \tau_2)}{y} \right) \right).
\end{aligned}$$

Hence

$$\begin{aligned}
\dot{\mathcal{L}}_2 = & - \frac{d_1 v_2}{x(x_2 + v_2)} (x - x_2)^2 + (d_2 y_2 + p y_2 z_2) \left(- \frac{x(v - v_2)^2}{v_2(x + v_2)(x + v)} \right) \\
& + (d_2 y_2 + p y_2 z_2) \left(4 - \frac{x_2}{x} \frac{x + v_2}{x_2 + v_2} - \frac{y_2}{y} \frac{x(t - \tau_1) v(t - \tau_1)}{x_2 v_2} \frac{x_2 + v_2}{x(t - \tau_1) + v(t - \tau_1)} \right. \\
& \left. - \frac{y(t - \tau_2) v_2}{y_2 v} - \frac{x + v}{x + v_2} + \ln \left(\frac{x(t - \tau_1) + v(t - \tau_1)}{x v} \frac{x + v}{x(t - \tau_1) + v(t - \tau_1)} \frac{y(t - \tau_2)}{y} \right) \right).
\end{aligned}$$

Taking $p_1 = x_1(x + v_1)$, $p_2 = y_1(x(t - \tau_1)v(t - \tau_1))$, $p_3 = y(t - \tau_2)v_1$, $p_4 = x + v$, $q_1 = x(x_1 + v_1)$, $q_2 = y(x_1 v_1)$, $q_3 = y_1 v$, $q_4 = x + v_1$ and using the inequality (4) for $n = 4$, we obtain

$$\begin{aligned}
& 4 - \frac{x_2}{x} \frac{x + v_2}{x_2 + v_2} - \frac{y_2}{y} \frac{x(t - \tau_1) v(t - \tau_1)}{x_2 v_2} \frac{x_2 + v_2}{x(t - \tau_1) + v(t - \tau_1)} - \frac{y(t - \tau_2) v_2}{y_2 v} \\
& - \frac{x + v}{x + v_2} + \ln \left(\frac{x(t - \tau_1) + v(t - \tau_1)}{x v} \frac{x + v}{x(t - \tau_1) + v(t - \tau_1)} \frac{y(t - \tau_2)}{y} \right) \leq 0
\end{aligned}$$

which means that $\dot{\mathcal{L}}_2 \leq 0$, and the equality holds when $x = x_2$, $y = y_2$, $v = v_2$ and $z = z_2$. By the LaSalle invariance principle, the endemic point E_2 is asymptotically stable when $R_{CTL} \geq 1$ and $R_0 \geq 1$.

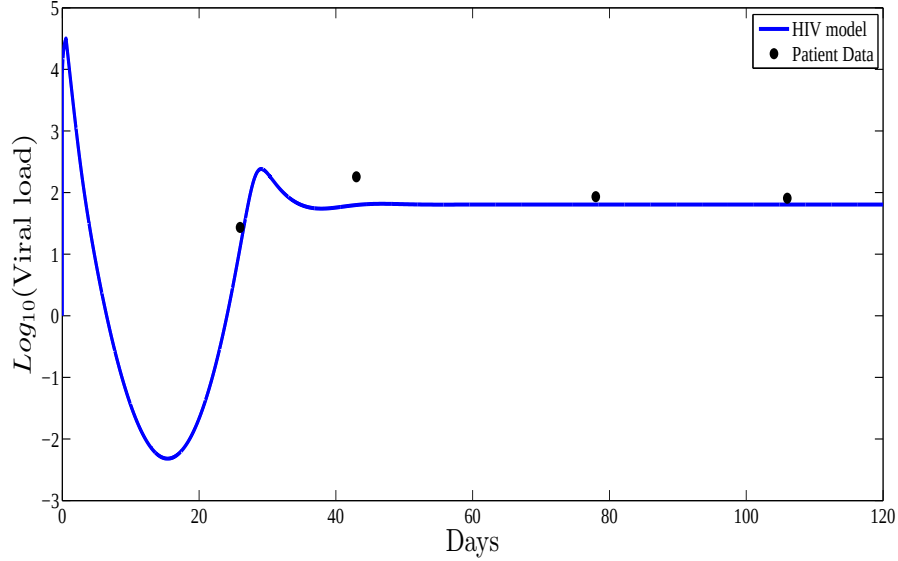


Figure 1: Behavior of the infection for the first patient during the first 120 days for $\lambda = 11.537$, $d_1 = 0.08$, $k_1 = 0.022$, $d_2 = 0.3$, $d_3 = 0.25$, $a = 5000$, $p = 0.04$, $c = 0.25$ and $b = 0.002$.

5 A clinical data based application

Define the following objective function

$$J = \frac{1}{n} \sum_{i=1}^n (\log(v(t_i)) - \log(\hat{v}(t_i)))^2,$$

where $v(t_i)$ represents the virus concentration at time t_i using the mathematical model and $\hat{v}(t_i)$ represents the virus concentration clinical data at time t_i .

The numerical simulations are performed and compared to three first patient data [21]. The authors took data for patients 1 and 2 from the University of Washington study [11].

Figure 1 shows the evolution of the infection during the first 120 days for the first patient when $R_0 = 1.48 \times 10^3 > 1$ and $R_{CTL} = 1.23 > 1$. We remark that the viral replication fit better the clinical data. Indeed the error is approximately $J \approx 2.23 \times 10^{-2}$.

Figure 2 shows the evolution of the infection during the first 150 days for the first patient when $R_0 = 1.22 \times 10^3 > 1$ and $R_{CTL} = 1.07 > 1$. We remark that the viral replication fit better the clinical data. Indeed the error is approximately $J \approx 5.91 \times 10^{-1}$.

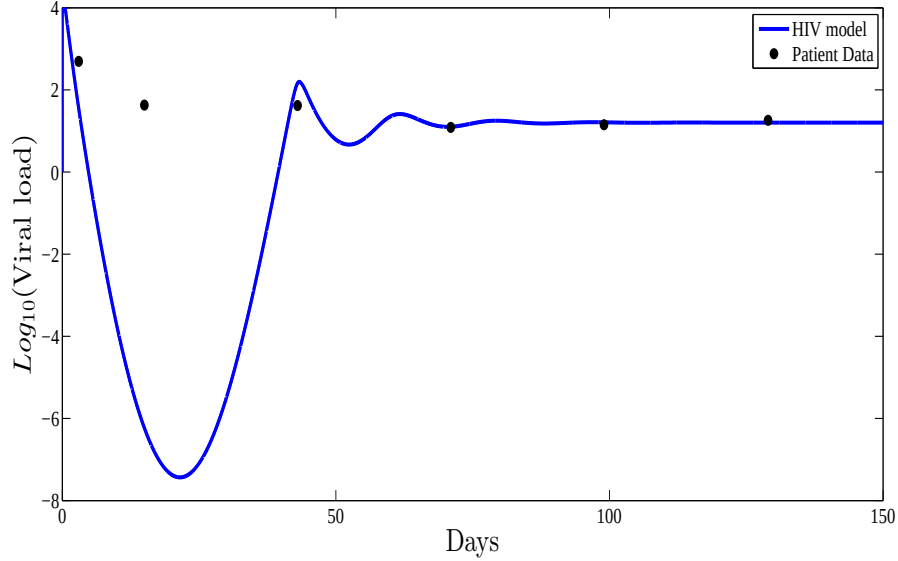


Figure 2: Behavior of the infection for the second patient during the first 150 days for $\lambda = 11.537$, $d_1 = 0.07$, $k_1 = 0.08$, $d_2 = 0.1$, $d_3 = 0.2$, $a = 800$, $p = 0.0024$, $c = 0.0035$ and $b = 0.02$.

6 Conclusion

In this paper, we have studied the model of the Human Immunodeficiency Virus (HIV) dynamics in the presence of the immune response which is represented by the cytotoxic T lymphocytes (CTL) cells. The model includes a saturated infection rate in order to better describe the viral infection. The positiveness and the boundedness of solutions are proved; which is consistent with biological studies. Also, we have studied the stability of both disease-free and endemic steady states. The disease free steady state is globally asymptotically stable when the basic reproduction number is less than unity ($R_0 < 1$). The existence of two other infection steady states when $R_0 > 1$ is established. The global stability of these infection steady states depend on the basic reproduction number R_0 , the CTL immune response reproduction number R_{CTL} . Numerical simulations are performed in order to show the behavior of infection during the days of observation. It was shown that the model can fit the clinical data.

7 Open problems

There are some open problems that can be considered as future directions of this present work. For example, one can consider a logistic growth for the

uninfected cells and study the stability of each steady state and to perform the numerical simulations. Also, one can consider the same problems with spatial diffusion of the free viruses. This latter can be studied by some suitable Lyapunov functional and the numerical study can also be interesting.

References

- [1] R.A. Weiss, How does HIV cause AIDS?, *Science* **260** (1993) 1273–1279.
- [2] W. Blanttner, R.C. Gallo and H.M. Temin, HIV causes aids, *Science* **241** (1988) 515–516.
- [3] A. Saez-Cirion, C. Lacabartz, O. Lambotte, P. Versmisse, A. Urrutia, F. Boufassa, F. Barre-Sinoussi, J.F. Delfraissy, M. Sinet, G. Pancino and A. Venet, HIV controllers exhibit potent CD8 T cell capacity to suppress HIV infection ex vivo and peculiar cytotoxic T-lymphocyte activation phenotype, *Proceedings of the National Academy of Sciences* **104** (2007) 6776–6781.
- [4] M.R. Betts, M.C. Nason, S.M. West, S.C. De Rosa, S.A. Migueles, J. Abraham, M.M. Lederman, J.M. Benito, P.A. Goepfert, M. Connors, M. Roederer and R.A. Koup RA, HIV nonprogressors preferentially maintain highly functional HIV-specific CD8+ T-cells, *Blood* **107** (2006) 4781–4789.
- [5] M.A. Nowak and C.R.M. Bangham C.R.M., Population dynamics of immune responses to persistent viruses; *Science*, **272** (1996) 74–79.
- [6] A. Korobeinikov, Global properties of basic virus dynamics models. *Bulletin of Mathematical Biology*, **66** (2004) 879–883.
- [7] H. L. Smith, P. De Leenheer, Virus dynamics: a global analysis, *SIAM Journal on Applied Mathematics* **63** (2003), 1313–1327.
- [8] E.S. Daar, T. Moudgil, R.D. Meyer and D.D. Ho, Transient highlevels of viremia in patients with primary human immunodeficiency virus type 1, *New Engl. J. Med.* **324** (1991) 961–964.
- [9] J.O. Kahn and B.D. Walker, Acute human immunodeficiency virus type 1 infection, *New Engl. J. Med.*, **339** (1998) 33–39.
- [10] G.R. Kaufmann, P. Cunningham, A.D. Kelleher, J. Zauders, A. Carr, J. Vizzard, M. Law and D.A. Cooper, Patterns of viral dynamics during primary human immunodeficiency virus type 1 infection, The Sydney Primary HIV Infection Study Group, *J. Infec. Dis.* **178** (1998) 1812–1815.

- [11] T. Schacker, A. Collier, J. Hughes, T. Shea and L. Corey, Clinical and epidemiologic features of primary HIV infection, *Ann. Int. Med.* **125** (1996) 257–264.
- [12] X. Wang, A. Elaiw and X. Song, Global properties of a delayed HIV infection model with CTL immune response, *Applied Mathematics and Computation* **218** (2012) 9405–9414.
- [13] X. Wang, Y. Tao and X. Song, Global stability of a virus dynamics model with Beddington-DeAngelis incidence rate and CTL immune response, *Nonlinear Dynamics* **66** (2011) 825–830.
- [14] Q. Sun and L. Min, Dynamics Analysis and Simulation of a Modified HIV Infection Model with a Saturated Infection Rate, *Computational and mathematical methods in medicine*, **2014** (2014) Article ID 145162, 14 pages.
- [15] Y. Kuang, Delay Differential Equations with Applications in Population Dynamics, Academic Press, San Diego, 1993.
- [16] R.V. Culshaw, S. Ruan, A delay-differential equation model of HIV infection of D4+ T-cells, *Math. Biosci.* 165(2000) 27-39.
- [17] R.V. Culshaw, S. Ruan, G. Webb, A mathematical model of cell-to-cell HIV-1 that include a time delay, *J. Math.Biol.* 46 (2003) 425-444.
- [18] J.E. Mittler, B. Markowitz, D.D. Ho, A.S. Perelson, Improved estimates for HIV-1 clearance rate and intracellular delay, *AIDS* 13 (1999) 1415-1417.
- [19] Allali, K., Danane, J. and Kuang, Y., 2017. Global Analysis for an HIV Infection Model with CTL Immune Response and Infected Cells in Eclipse Phase. *Applied Sciences* (2076-3417), 7(8).
- [20] Q. Sun, L. Min, and Y. Kuang, Global stability of infection-free state and endemic infection state of a modified human immunodeficiency virus infection model, *IET systems biology* **9** (2015) 95–103.
- [21] M.A Stafford, L. Corey, Y. Cao, E.S. Daar, D.D. Ho and A.S. Perelson, Modeling plasma virus concentration during primary HIV infection, *Journal of theoretical biology* **203** (2000) 285–301.