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Analysis of the dynamics of a mathematical model for HIV infection

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Abstract

Mathematical models are essential tools in the study of different infectious diseases. Researchers have developed other in-host models to investigate HIV dynamics in the human body. In this paper, a mathematical model for the HIV infection of $CD4^+$ T cells is analyzed. We consider the proliferation of T cells in this study. It is found that there exist two equilibrium states for this model: Infection-free equilibrium state and infected equilibrium state. Local stability is discussed for both infection-free and infected equilibrium states using Routh–Hurwitz criteria. Also, we calculate the basic reproduction number (R_0) for the model with the help of next generation matrix method. The global stability of the infection-free equilibrium point is discussed using Lyapunov's second method. From the stability analysis, it is found that if basic reproduction number $R_0 \leqslant 1$, infection of HIV is cleared out, and if $R_0 > 1$, infection of HIV persists. The conditions for global stability of the infected equilibrium point are derived using a geometric approach. We find a parameter region where the infected equilibrium point is globally stable. We carry out numerical simulations to verify the results. Also, the effects of the proliferation rate of uninfected $CD4^+$ T cells and recovery rate of infected $CD4^+$ T cells in dynamics of the T cells and free virus are studied using numerical simulations. It is found that small variations of these parameters can change the model's whole dynamics, and infection can be controlled by controlling the proliferation rate and improving the recovery rate.

Keywords: HIV infection, global stability, $CD4^+$ T cells, basic reproduction number.

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1. Introduction

According to the information updated by World Health Organization (WHO) on November 2019, there were approximately 37.9 million people living with HIV at the end of 2018 [19]. HIV has claimed more than 32 million lives so far and it continues to be a major global public health issue. Though AIDS is not fully curable, but with increasing access to effective HIV prevention, diagnosis, treatment with anti-retroviral drugs, HIV infection has become a manageable health condition which enable people living with HIV to enjoy long and healthy lives [19]. The Human Immunodeficiency Virus (HIV) mainly targets the immune system of the host which weakens host's defense system against other opportunistic

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infections. Immune function is measured by $CD4^+$T cells count, which are the most abundant in white blood cells of the immune system. For a normal person, $CD4^+$ T cells count is between 800 and 1200 mm^{-3}. When this cell count reaches 200 mm^{-3} or below in an HIV-infected patient, then the person is classified as having AIDS [12], which is the most advanced stage of HIV infection.

Many researchers have been working in the field of HIV for over three decades. A large number of mathematical models have been developed to understand the dynamical behaviors of HIV and $CD4^+$ T cells, progression of the disease and effect of the antiretroviral treatment [1, 2, 6, 15, 10, 11, 12, 13, 14, 16, 18, 17]. In most of the models where dynamics of HIV and $CD4^+$ T cells are discussed, three populations are mainly considered: uninfected $CD4^+$ T cells, infected $CD4^+$ T cells and free virus population. In these models, they considered that the infected $CD4^+$ T cells start producing virus after they get infected. With this three population, a basic mathematical model to define the dynamics of $CD4^+$ T cells and HIV is

$$\begin{aligned}\frac{dT}{dt} &= s - dT - kVT,\\ \frac{dT^*}{dt} &= kVT - \delta T^*,\\ \frac{dV}{dt} &= pT^* - cV,\end{aligned}$$

where $T(t), T^*(t)$ and $V(t)$ represents the concentrations of uninfected $CD4^+$ T cells, infected $CD4^+$ T cells and free virus respectively. s is the natural production rate and d is the natural death rate of the healthy $CD4^+$ T cells and k is the rate at which they become infected. δ is the death rate of infected T cells. Also, the virus population are produced from infected cells at rate p and dies at rate c.

In the above model, it is considered that $CD4^+$ T cells are created at rate s from the source like precursors in thymus and bone marrow. But literature of Biology indicate that T cells can be also produced by the proliferation of the existing T cells when roused by antigen or mitogen [13]. Considering that the proliferation of healthy $CD4^+$ T cells follows logistic growth term $rT\left(1-\frac{T}{T_{max}}\right)$, Perelson and Nelson proposed a model in [13]. Srivastava and Chanda proposed a model in [18] considering that a proportion of resting cells revert to the uninfected cells [5]. They also discussed global stability of the model. But in the model [18], production of $CD4^+$ T cells through proliferation was not considered.

In this paper, we adapt the model in [18] and develop a model that includes production of new $CD4^+$ T cells through proliferation of existing $CD4^+$ T cells. Here, we consider that proliferation follows logistic growth [13]. The whole paper is distributed as: In Section 2, we discuss our model, basic properties and the equilibrium points of the model. Local stability of both infection-free and infected equilibrium points are discussed in Section 3. Local stability of the infected equilibrium point E^* is discussed in terms of the proliferation rate r. Section 4 contains global stability analysis of both equilibrium points. We find a range of the parameter r for global stability of E^*. Also a condition for global stability of E^* is derived. Numerical simulations are done in Section 5 to verify the analytical results of the model. Also sensitivity of certain parameters of the system are discussed. Finally, Section 6 contains the concluding remarks of the study.

2. The HIV infection model

2.1. Description of the model

In order to construct our model, we have considered the three populations: uninfected $CD4^+$T cell $T(t)$, infected $CD4^+$T cell $T^*(t)$ and the virus population $V(t)$. Here, we have modified the model of Srivastava and Chandra [18] following Rong et al. [14] and Essunger and Perelson [5] with the assumption that uninfected CD^+T cell, $T(t)$ can also be created by proliferation of existing $T(t)$ cells [13]. In view of

this, our proposed model is given by following system of differential equations:

$$\frac{dT}{dt} = s + rT\left(1 - \frac{T}{T_{max}}\right) - kVT + bT^* - dT, \tag{2.1}$$

$$\frac{dT^*}{dt} = kVT - (b+\delta)\,T^*, \tag{2.2}$$

$$\frac{dV}{dt} = N\delta T^* - cV, \tag{2.3}$$

with $T(0) > 0, T^*(0) \geqslant 0$ and $V(0) \geqslant 0$.

In this model, parameters d, δ and c represent usual death frequencies of uninfected $CD4^+T$ cells, infected $CD4^+T$ cells and the virus population respectively. Due to the virus burden of HIV infected T cells, assumption $d \leqslant \delta$ is considered. Also, s represents inflow rate of $CD4^+T$ cells from source, the mass-action term kVT in (2.1) defines the incidence of infection of uninfected $CD4^+$ T cells where $k > 0$ represents rate of infection of T cells. In this model, we have considered that healthy CD^+T cells can also be created by proliferation. Consider, this proliferation follows simplified logistic growth $rT\left(1 - \frac{T}{T_{max}}\right)$ as proposed in Perelson and Nelson [13]. b is the rate at which infected cells return to uninfected class [18, 14]. N is average number of free virus particles produced by an infected cell.

2.2. *Basic properties of the model*

In absence of HIV infection, dynamics of healthy $CD4^+T$ cells are administrated by the equation [12, 13]

$$\frac{dT}{dt} = s - dT + rT\left(1 - \frac{T}{T_{max}}\right).$$

Thus, for stability at a level T_0 is given by the equation,

$$s + rT_0\left(1 - \frac{T_0}{T_{max}}\right) - dT_0 = 0,$$

solving this equation, we have

$$T_0 = \frac{T_{max}}{2r}\left[(r-d) + \sqrt{(r-d)^2 + \frac{4sr}{T_{max}}}\right].$$

We consider only one value of T_0 as the other is negative. Thus, when there is no infection of HIV, healthy T-cell concentration becomes stable at a level T_0 which is given by,

$$T_0 = \frac{T_{max}}{2r}\left[(r-d) + \sqrt{(r-d)^2 + \frac{4sr}{T_{max}}}\right].$$

2.2.1. *Invariant region*

Lemma 2.1. *The feasible region ϕ defined by*

$$\phi = \{(T(t), T^*(t), V(t)) \in \mathbb{R}^3_+ : T \leqslant T_0, 0 \leqslant T + T^* \leqslant \frac{s + rT_0}{d}, V \leqslant K\},$$

for some $K \geqslant 0$, which is positively invariant with respect to system (2.1)-(2.2)-(2.3).

Proof. From the equation (2.1) of the system, we know $T(t) \leqslant T_0$ if $T(0) \leqslant T_0$. Adding the first two equations of the system gives,

$$T' + T^{*'} = s + rT\left(1 - \frac{T}{T_{max}}\right) - dT - \delta T^* \leqslant s + rT_0 - d(T + T^*), \quad \text{(since } d \leqslant \delta\text{)}.$$

Thus,

$$T + T^* \leqslant \frac{s + rT_0}{d} + Ce^{-dt},$$

where C is any constant. This implies $T + T^* \to \frac{s + rT_0}{d}$ when $t \to \infty$. Therefore, $T + T^*$ is bounded by $\frac{s + rT_0}{d}$. Since T is bounded, therefore both the uninfected and infected T cell populations are always bounded. From Equation (2.3) of the system, it is clear that V is bounded, say by $K \geqslant 0$. So we have a bounded set,

$$\phi = \{(T(t), T^*(t), V(t)) \in \mathbb{R}^3_+ : T \leqslant T_0, 0 \leqslant T + T^* \leqslant \frac{s + rT_0}{d}, V \leqslant K\},$$

which is positively invariant with respect to the system (2.1)–(2.3). □

2.2.2. Positivity of the solutions

Lemma 2.2. *The exact solutions* $(T(t), T^*(t), V(t))$ *of the system* (2.1)–(2.3) *with the initial conditions* $T(0) \geqslant 0$, $T^*(0) \geqslant 0$ *and* $V(0) \geqslant 0$ *are positive for all* $t > 0$.

Proof. With the given initial conditions, we need to prove that the solutions of the system are positive. If not, we assume that there is a contradiction: there exists a first time t_1 such that

$$T(t_1) = 0, \quad T'(t_1) < 0, \quad T^*(t) \geqslant 0, \quad V(t) \geqslant 0, \quad 0 < t < t_1,$$

there exits t_2 such that

$$T^*(t_2) = 0, \quad T^{*'}(t_2) < 0, \quad T(t) \geqslant 0, \quad V(t) \geqslant 0, \quad 0 < t < t_2,$$

and there exits t_3 such that

$$V(t_3) = 0, \quad V'(t_3) < 0, \quad T(t) \geqslant 0, \quad T^*(t) \geqslant 0, \quad 0 < t < t_3.$$

In the first case we have from the equation (2.1) of the system,

$$T'(t_1) = s + bT^*(t_1) > 0,$$

which is a contradiction, we have $T(t) \geqslant 0$ fo all $t > 0$. In the second case from the equation (2.2) of the system we have

$$T^{*'}(t_2) = kV(t_2)T(t_2) \geqslant 0,$$

which is a contradiction, so we have $T^*(t) \geqslant 0$ for all $t > 0$. Similarly it can be shown that $V(t) \geqslant 0$ for all $t > 0$. Thus, the solutions $T(t), T^*(t), V(t)$ of the system are positive for all $t > 0$. □

2.3. Equilibrium points of the model

2.3.1. The infection free equilibrium point and basic reproduction number

It is straightforward that the model always has a infection-free equilibrium point $E_0 = (T_0, 0, 0)$ where

$$T_0 = \frac{T_{max}}{2r}\left[(r - d) + \sqrt{(r - d)^2 + \frac{4sr}{T_{max}}}\right].$$

Now, we calculate the basic reproduction number of the model using next generation matrix method. Biologically, basic reproduction number indicates the number of newly infected $CD4^+$ T cells that arise from any one infected cell when almost all cells are uninfected [2].

Let $X = (T^*, V, T)$, then the system (2.1)–(2.3) can be written as

$$\frac{dX}{dt} = F(X) - V(X),$$

where, $F(X)$ is the rate at which new infections appear, $V(X)$ is the rate at which individuals transfer, and

$$F(X) = \begin{pmatrix} kVT \\ 0 \\ 0 \end{pmatrix} \quad \text{and} \quad V(X) = \begin{pmatrix} (b+\delta)T^* \\ cV - N\delta T^* \\ kVT + dT - bT^* - s - rT + \dfrac{rT^2}{T_{max}} \end{pmatrix}.$$

The Jacobian matrix of $F(X)$ and $V(X)$ at infection-free equilibrium E_0 are respectively,

$$DF(E_0) = \begin{pmatrix} f_{2\times 2} & 0 \\ 0 & 0 \end{pmatrix} \quad \text{and} \quad DV(E_0) = \begin{pmatrix} & \nu_{2\times 2} & 0 \\ & & 0 \\ -b & kT_0 & d - r + \dfrac{rT_0}{T_{max}} \end{pmatrix},$$

where, $f_{2\times 2} = \begin{pmatrix} 0 & kT_0 \\ 0 & 0 \end{pmatrix}$ and $\nu_{2\times 2} = \begin{pmatrix} b+\delta & 0 \\ -N\delta & c \end{pmatrix}$. From Driessche and Watmough [4], $f\nu^{-1}$ is the next generation matrix of the system (2.1)–(2.3) and the basic reproduction number is given by its spectral radius. Thus,

$$f\nu^{-1} = \frac{1}{c(b+\delta)} \begin{pmatrix} kN\delta T_0 & kT_0(b+\delta) \\ 0 & 0 \end{pmatrix},$$

and it follows that spectral radius is

$$\rho(f\nu^{-1}) = \frac{kN\delta T_0}{c(b+\delta)}.$$

Therefore, the basic reproduction number of the model (2.1)–(2.3) is

$$R_0 = \frac{kN\delta T_0}{c(b+\delta)}. \tag{2.4}$$

2.3.2. Infected equilibrium point

Proposition 2.3. *A unique infected equilibrium point* $E^* = (\overline{T}, \overline{T^*}, \overline{V}) \in int(\phi)$, *the interior of* ϕ, *where*

$$\overline{T} = \frac{c(b+\delta)}{Nk\delta}, \quad \overline{T^*} = \frac{c\overline{V}}{N\delta}, \quad \overline{V} = \frac{s\gamma^2 + (r-d)\gamma c(b+\delta) - \dfrac{r}{T_{max}}(b+\delta)^2c^2}{ck\delta\gamma}, \quad \gamma = Nk\delta,$$

exists when $R_0 > 1$.

We know that, infected equilibrium exists when $\overline{V} > 0$

$$\begin{aligned} &\implies s\gamma^2 + (r-d)\gamma c(b+\delta) - \frac{r}{T_{max}}(b+\delta)^2c^2 > 0 \\ &\implies \frac{r}{T_{max}}(b+\delta)^2c^2 - (r-d)\gamma c(b+\delta) - s\gamma^2 < 0 \\ &\implies (x-\alpha_1)(x-\alpha_2) < 0, \end{aligned}$$

where

$$x = c(b+\delta), \alpha_1 = \frac{\gamma T_{max}}{2r}\left[(r-d) + \sqrt{(r-d)^2 + \frac{4rs}{T_{max}}}\right],$$

and

$$\alpha_2 = \frac{\gamma T_{max}}{2r}\left[(r-d) - \sqrt{(r-d)^2 + \frac{4rs}{T_{max}}}\right].$$

Since $x - \alpha_2 > 0$ therefore $x - \alpha_1 < 0$, i.e.,

$$c(b+\delta) < \frac{\gamma T_{max}}{2r}\left[(r-d) + \sqrt{(r-d)^2 + \frac{4rs}{T_{max}}}\right],$$

which implies

$$c(b+\delta) < \gamma T_0 \implies R_0 > 1.$$

3. Local stability

3.1. Local stability of infection-free equilibrium point E_0

Theorem 3.1. *The infection free equilibrium point E_0 is locally asymptotically stable if $R_0 < 1$, locally stable if $R_0 = 1$ and unstable if $R_0 > 1$.*

Proof. The Jacobian matrix of the system (2.1)–(2.3) at E_0 is

$$J(E_0) = \begin{pmatrix} -d + r\left(1 - \frac{T_0}{T_{max}}\right) - \frac{rT_0}{T_{max}} & b & -kT_0 \\ 0 & -(b+\delta) & kT_0 \\ 0 & N\delta & -c \end{pmatrix}.$$

The characteristic equation of $J(E_0)$ is given by

$$(\lambda - a_1)(\lambda^2 + a_2\lambda + a_3) = 0, \tag{3.1}$$

where $a_1 = -d + r\left(1 - \frac{T_0}{T_{max}}\right) - \frac{rT_0}{T_{max}}$, $a_2 = b + \delta + c$ and $a_3 = (b+\delta)c - N\delta kT_0$. One eigen value of $J(E_0)$ is

$$-d + r\left(1 - \frac{T_0}{T_{max}}\right) - \frac{rT_0}{T_{max}} = -\frac{s}{T_0} - \frac{rT_0}{T_{max}} < 0,$$

using the first equation of the system. The real parts of the other two eigen values have negative sign if and only if

$$a_3 = (b+\delta)c - N\delta KT_0 > 0,$$

implies $\frac{N\delta KT_0}{(b+\delta)c} < 1$, i.e., $R_0 < 1$. Thus if $R_0 < 1$, then all eigen values are negative, thus E_0 is asymptotically stable. If $R_0 = 1$, one eigenvalue is 0 and thus E_0 is locally stable. If $R_0 > 1$, one eigenvalue of $J(E_0)$ is positive, thus E_0 is unstable. □

3.2. Local stability of infected equilibrium point E^*

To investigate the persistence of infection of HIV when $R_0 > 1$, we have to inspect the local stability of E^*. The Jacobian matrix of the model (2.1)–(2.3) at E^* is

$$J(E^*) = \begin{pmatrix} -\bar{a} & b & -k\bar{T} \\ k\bar{V} & -(b+\delta) & k\bar{T} \\ 0 & N\delta & -c \end{pmatrix},$$

where

$$\bar{a} = -r\left(1 - \frac{\bar{T}}{T_{max}}\right) + \frac{r\bar{T}}{T_{max}} + k\bar{V} + d = \frac{r\bar{T}}{T_{max}} + \frac{s}{\bar{T}} + \frac{b\overline{T^*}}{\bar{T}} > 0.$$

The characteristic polynomial of $J(E^*)$ is

$$P(\lambda) = \lambda^3 + A\lambda^2 + B\lambda + C,$$

where

$$\begin{aligned}
A &= \overline{a} + b + \delta + c,\\
B &= \left(\frac{r\overline{T}}{T_{max}} + \frac{s}{\overline{T}}\right)(b+\delta+c) + \frac{bc\overline{T^*}}{\overline{T}},\\
C &= \overline{a}(b+\delta)c - \overline{a}N\delta k\overline{T} - bk\overline{V}c + k^2\overline{VT}N\delta\\
&= k\overline{V}c\delta > 0.
\end{aligned}$$

Now,

$$\begin{aligned}
AB - C &= (\overline{a}+b+\delta+c)\left\{\left(\frac{r\overline{T}}{T_{max}} + \frac{s}{\overline{T}}\right)(b+\delta+c) + \frac{bc\overline{T^*}}{\overline{T}}\right\} - k\overline{V}c\delta\\
&= (\overline{a}+b+c)\left\{\left(\frac{r\overline{T}}{T_{max}} + \frac{s}{\overline{T}}\right)(b+\delta+c) + \frac{bc\overline{T^*}}{\overline{T}}\right\}\\
&\quad + \delta\left(\frac{r\overline{T}}{T_{max}} + \frac{s}{\overline{T}}\right)(b+\delta) + c\delta\left(\frac{2r\overline{T}}{T_{max}} + d - r\right).
\end{aligned}$$

Here we observe that $A > 0, B > 0$ and $C > 0$. But $AB - C > 0$ if $\frac{2r\overline{T}}{T_{max}} + d - r \geqslant 0$. Thus, using Routh–Hurwitz criteria we obtain the following stability condition.

Theorem 3.2. *The infected equilibrium point* E^* *whenever it exists is locally asymptotically stable if*

$$\frac{2r\overline{T}}{T_{max}} + d - r \geqslant 0.$$

4. Global stability

4.1. Global stability of infection-free equilibrium point E_0

Now, we will discuss the global stability for the infection-free equilibrium E_0 by Lyapunov's second method.

Theorem 4.1. *If* $R_0 \leqslant 1$, *then infection-free equilibrium point* E_0 *is globally asymptotically stable in* ϕ *and if* $R_0 > 1$, *then* E_0 *is unstable.*

Proof. Let, we define the Lyapunov function for the system (2.1)–(2.3)

$$L = \frac{N\delta}{(b+\delta)}T^* + V.$$

Finding derivative of L we have

$$\frac{dL}{dt} = \frac{N\delta}{(b+\delta)}\frac{dT^*}{dt} + \frac{dV}{dt}.$$

With the help of Equations (2.2) and (2.3) of the system,

$$\begin{aligned}
\frac{dL}{dt} &= Vc\left(\frac{N\delta kT}{c(b+\delta)} - 1\right)\\
&\leqslant Vc\left(\frac{N\delta kT_0}{c(b+\delta)} - 1\right)\\
&= Vc(R_0 - 1),
\end{aligned}$$

since, $T \leqslant T_0$ in ϕ. Thus it is clear that $\frac{dL}{dt} \leqslant 0$ if $R_0 \leqslant 1$. Also, $\frac{dL}{dt} = 0$ if and only if $V = 0$ or if $R_0 = 1$ and $T = T_0$. If S is the set of solutions of the model where $\frac{dL}{dt} = 0$, i.e., $S = \{(T, T^*, V) \in \phi : \frac{dL}{dt} = 0\}$, in this

case the Lyapunov–Lasalle theorem [7] implies that all paths in ϕ move towards the leading positively invariant subset of S, where S represents the set of population in where free virus is absent. On the boundary of ϕ where $V = 0$ we have, $\frac{dT}{dt} = s + rT\left(1 - \frac{T}{T_{max}}\right) - dT$. Thus, $T \to T_0$ as $t \to \infty$. Thus, all the solutions in ϕ converges to E_0 when $R_0 \leqslant 1$.

When $R_0 > 1$, it is observed from the Jacobian matrix of the model at E_0 that the characteristic equation (3.1) has one positive eigen value. Thus, infection-free equilibrium point E_0 is unstable when $R_0 > 1$. □

4.2. Global stability of the infected equilibrium point E^*

Now, we are interested to discuss the global stability of infected equilibrium point E^* of the model (2.1)–(2.3). Our main focus is to find the range of r for which E^* is globally asymptotically stable. For this purpose, we apply the approach developed by Li and Muldowney [8], which is summarized below:

Let the mapping $f : x \rightarrowtail f(x) \in \mathbb{R}^n$ be C^1 for $x \in G$ where $G \subset \mathbb{R}^n$ be an open set. Consider the solution $x(t)$ to the differential equation

$$x^{'} = f(x), \tag{4.1}$$

is uniquely determined by its initial value $x(0) = x_0$ and denote the solution to (4.1) by $x(0, x_0) = x_0$. A set E is said to be absorbing set in G for the system (4.1) if $x(t, E_1) \subset E$ for each compact set $E_1 \subset G$ when t is sufficiently large. The following assumptions are made by Li and Muldowney [8]:

(H_1) There is a unique equilibrium $\bar{x}$ of the system (4.1) in G.

(H_2) There exists a compact absorbing set $E \subset G$.

For any $n \times n$ matrix M, the second additive compound matrix of M, denoted by $M^{[2]}$, is an $\binom{n}{2} \times \binom{n}{2}$ matrix. If $M = (m_{ij})$ is a 3×3 matrix, then

$$M^{[2]} = \begin{pmatrix} m_{11} + m_{22} & m_{23} & -m_{13} \\ m_{32} & m_{11} + m_{33} & m_{12} \\ -m_{31} & m_{21} & m_{22} + m_{33} \end{pmatrix}. \tag{4.2}$$

For a square matrix M, the Lozinskii measure [3] with respect to the induced norm $|.|$ is defined as

$$\mu(M) = \lim_{h \to 0} \frac{|I + hM| - 1}{h}.$$

For $x \in G$, consider $Q : x \rightarrowtail Q(x)$ be an $\binom{n}{2} \times \binom{n}{2}$ matrix-valued function that is C^1 and $Q^{-1}(x)$ exists. Define

$$M = Q_f Q^{-1} + Q J^{[2]} Q^{-1}.$$

Here, we obtain the matrix Q_f by replacing all entries q_{ij} of Q by their respective derivatives in the direction of f. Also, $J^{[2]}$ is second additive compound matrix of the Jacobian matrix J of the system (4.1) and let μ be a Lozinskii measure on $\mathbb{R}^{l \times l}$ where $l = \binom{n}{2}$, then define the quantity $\bar{q}_2$ as follow

$$\bar{q}_2 = \lim_{t \to \infty} \sup \sup_{x_0 \in E} \frac{1}{t} \int_0^t \mu(M(x(s, x_0)))ds.$$

We have the following result established by Li and Muldowney [8].

Theorem 4.2. *For the system (4.1), consider that the set G is simply connected and the assumptions (H_1) and (H_2) are satisfied. Then the unique equilibrium point $\bar{x}$ is globally asymptotically stable in G if there exists a function $Q(x)$ and a Lozinskii measure μ which satisfy the condition $\bar{q}_2 < 0$.*

Theorem 4.3. *When* $R_0 > 1$, *the infected equilibrium point* E^* *is globally asymptotically stable in* $\mathrm{int}(\phi)$ *if* r *satisfies* $r < \frac{d}{1-p}$, *where* $0 < p < 1$ *such that* $T > pT_{max}$. *Thus, a range of* r *where the infected equilibrium point* E^* *is stable is* $d \leqslant r < \min\left\{\frac{d}{1-p}, \delta\right\}$.

Proof. From the discussion, we have $\mathrm{int}(\phi)$ is simply connected and if $R_0 > 1$ then E^* is the unique equilibrium in $\mathrm{int}(\phi)$. Thus our model satisfies assumption (H_1). Also from Theorem 4.1, we can say there exists an absorbing compact set $E \subset \phi$ for our model. Therefore, assumption (H_2) is satisfied by our model. Now set the function

$$Q = Q(T, T^*, V) = \mathrm{diag}\left(1, \frac{T^*}{V}, \frac{T^*}{V}\right).$$

Let f denote the vector field on the model, then

$$Q_f Q^{-1} = \mathrm{diag}\left(0, \frac{T^{*'}}{T^*} - \frac{V'}{V}, \frac{T^{*'}}{T^*} - \frac{V'}{V}\right).$$

The Jacobian matrix J related to the general solution $(T(t), T^*(t), V(t))$ of the model is

$$\begin{pmatrix} -a & b & -kT \\ kV & -b-\delta & kT \\ 0 & N\delta & -c \end{pmatrix},$$

and its second compound matrix $J^{[2]}$ as defined in (4.2) is below

$$\begin{pmatrix} -a-b-\delta & kT & kT \\ N\delta & -a-c & b \\ 0 & kV & -b-\delta-c \end{pmatrix},$$

where $a = -rT\left(1 - \frac{T}{T_{max}}\right) + \frac{rT}{T_{max}} + kV + d$. Now,

$$M = Q_f Q^{-1} + QJ^{[2]}Q^{-1} = \begin{pmatrix} -a-b-\delta & kT\frac{V}{T^*} & kT\frac{V}{T^*} \\ N\delta\frac{T^*}{V} & \frac{T^{*'}}{T^*} - \frac{V'}{V} - a - c & b \\ 0 & kV & \frac{T^{*'}}{T^*} - \frac{V'}{V} - b - \delta - c \end{pmatrix} = \begin{pmatrix} M_{11} & M_{12} \\ M_{21} & M_{22} \end{pmatrix},$$

where

$$M_{11} = (-a-b-\delta), \quad M_{12} = \begin{pmatrix} kT\frac{V}{T^*} & kT\frac{V}{T^*} \end{pmatrix}, \quad M_{21} = \begin{pmatrix} N\delta\frac{T^*}{V} \\ 0 \end{pmatrix},$$

and

$$M_{22} = \begin{pmatrix} \frac{T^{*'}}{T^*} - \frac{V'}{V} - a - c & b \\ kV & \frac{T^{*'}}{T^*} - \frac{V'}{V} - b - \delta - c \end{pmatrix}.$$

Let (u, v, w) denote vectors in $\mathbb{R}^3$, choose a norm in $\mathbb{R}^3$ as $|(u, v, w)| = \max\{|u|, |v| + |w|\}$ and let μ be the corresponding Lozinskii measure. Then we have following approximation [9]

$$\mu(M) \leqslant \max\{g_1, g_2\}, \tag{4.3}$$

where $g_1 = \mu_1(M_{11}) + |M_{12}|$ and $g_2 = |M_{21}| + \mu_1(M_{22})$, here $|M_{12}|$, $|M_{21}|$ are matrix norm and μ_1 is Lozinskii measure with respect to l_1 norm. Therefore, $\mu_1(M_{11}) = -a-b-\delta, |M_{12}| = kT\frac{V}{T^*}, |M_{21}| = N\delta\frac{T^*}{V}$ and $\mu_1(M_{22})$ can be calculated as follows:

$$\begin{aligned}\mu_1(M_{22}) &= \max\left\{\frac{T^{*'}}{T^*} - \frac{V'}{V} - a - c + kV, \frac{T^{*'}}{T^*} - \frac{V'}{V} - b - \delta - c + b\right\} \\ &= \frac{T^{*'}}{T^*} - \frac{V'}{V} - c + \max\{-z, -\delta\},\end{aligned}$$

where

$$z = a - kV = d - r\left(1 - \frac{T}{T_{max}}\right) + \frac{rT}{T_{max}}. \tag{4.4}$$

We know that, when there is no HIV infection, the population size of T cells, remain below the maximum capacity T_{max}. Thus $T < T_{max}$ for all t. Consider we have $0 < p < 1$ which satisfies $T > pT_{max}$ for large t. Using this

$$z = a - kV = d - r\left(1 - \frac{T}{T_{max}}\right) + \frac{rT}{T_{max}} > d - r(1-p). \tag{4.5}$$

From the equations of the model,

$$\frac{T^{*'}}{T^*} = \frac{kVT}{T^*} - b - \delta, \frac{V'}{V} = \frac{N\delta T^*}{V} - c.$$

Substituting these in the expressions for g_1 and g_2, we get

$$g_1 = -a - b - \delta + \frac{kTV}{T^*} = \frac{T^{*'}}{T^*} - a < \frac{T^{*'}}{T^*} - z, \tag{4.6}$$

$$g_2 = N\delta\frac{T^*}{V} + \frac{T^{*'}}{T^*} - \frac{V'}{V} - c + \max\{-z, -\delta\} = \frac{T^{*'}}{T^*} - \min\{z, \delta\}. \tag{4.7}$$

For sufficiently large t, using (4.3), (4.5), (4.6) and (4.7), we have

$$\mu(M) \leqslant \frac{T^{*'}}{T^*} - \zeta,$$

where

$$\zeta = \min\{d - r(1-p), \delta\} > 0.$$

Now, let $(T(t), T^*(t), V(t))$ be any solution starting in the compact absorbing set $E \subset \phi$ and let $\bar{t}$ be sufficiently large such that $(T(t), T^*(t), V(t)) \in E$ for all $t \geqslant \bar{t}$. Then along each solution $(T(t), T^*(t), V(t))$ such that $(T(0), T^*(0), V(0)) \in E$ we have for $t > \bar{t}$,

$$\frac{1}{t}\int_0^t \mu(M)ds \leqslant \frac{1}{t}\int_0^{\bar{t}} \mu(M)ds + \frac{1}{t}\ln\frac{T^*(t)}{T^*(\bar{t})} - \left(\frac{t-\bar{t}}{t}\right)\zeta.$$

The boundedness of T^* and definition of $\bar{q}_2$ implies $\bar{q}_2 < 0$.

Thus, if $R_0 > 1$ then the infected equilibrium point E^* is globally asymptotically stable if

$$\min\{d - r(1-p), \delta\} > 0,$$

i.e., if $r < \frac{d}{1-p}$, where $0 < p < 1$ such that $T > pT_{max}$ and $\delta > 0$ (which is obvious). Also in absence of HIV infection, T-cell concentration is stabilize at T_0. Therefore, naturally $r \geqslant d$. Thus, we have the range of r for which the infected equilibrium point E^* is globally stable as

$$d \leqslant r < \min\left\{\frac{d}{1-p}, \delta\right\}. \qquad \square$$

Here, Theorem 4.3 provides complete description of the global stability of E^* in terms of the range of parameter r, but we can have another simpler sufficient condition for the stability of E^*. For this purpose, we have to see the last part of the above proof. For sufficiently large t, using (4.3), (4.4), (4.6) and (4.7), we have

$$\mu(M) \leqslant \frac{T^{*'}}{T^*} - \zeta_1,$$

where

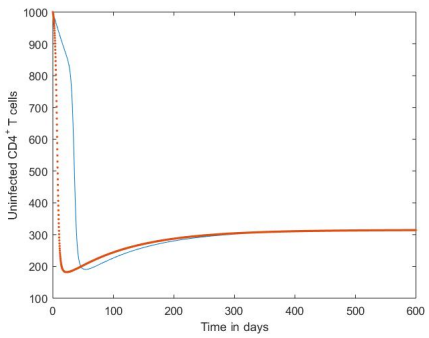
$$\zeta_1 = \min\{d - r\left(1 - \frac{T}{T_{max}}\right) + \frac{rT}{T_{max}}, \delta\} > 0.$$

The remaining part is same as the above proof. Thus we obtain the following stability condition:

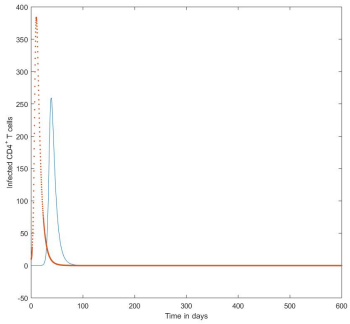
Theorem 4.4. *The infected equilibrium point* E^* *when exists is globally asymptotically stable if* $d - r + \frac{2rT}{T_{max}} > 0$.

5. Numerical simulations

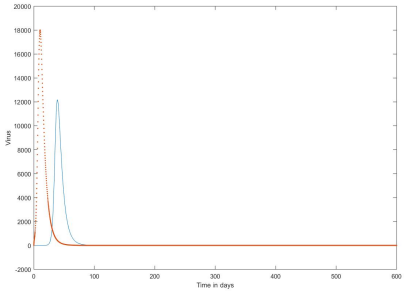
In this section, we have carried out numerical simulations with the help of Matlab software. For this purpose we have used the following data set which are also used in [18]. Specifically, $s = 10 mm^{-3} day^{-1}$, $k = 0.000024 mm^{-3} day^{-1}$, $d = 0.01 day^{-1}$, $b = 0.2 day^{-1}$, $\delta = 0.16 day^{-1}$, $c = 3.4 day^{-1}$ and $N = 1000$. The parameter r is not used in [18] and also from Theorem 4.3 we have observed that the stability of E^* is dependent on the value of r. Therefore in our simulations we vary the value of r to see the behavior of the system at its different value. Consider $T_{max} = 1500$. The results are demonstrated in the figure for two different sets of initial values $I_1 = (1000, 0, 0.001)$ and $I_2 = (1000, 10, 10)$.



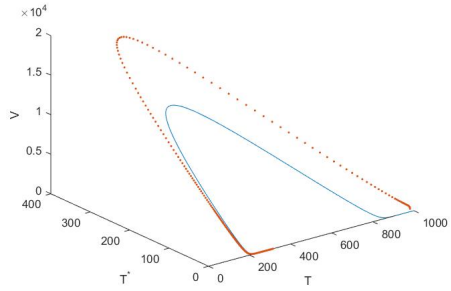
(a) Uninfected $CD4^+$ T cells vs. Time in days.



(b) Infected $CD4^+$ T cells vs. Time in days.



(c) Virus vs. Time in days.



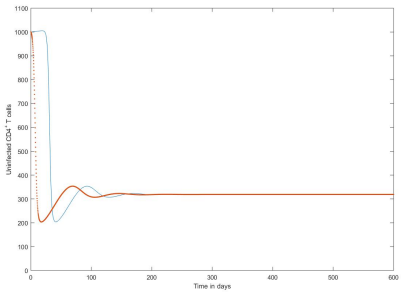
(d) Stability of the infection-free equilibrium.

Figure 1: Global stability of the infection free equilibrium E_0 for the initial values $I_1 = (1000, 0, 0.001)$ (Solid lines) and $I_2 = (1000, 10, 10)$ (Dotted lines).

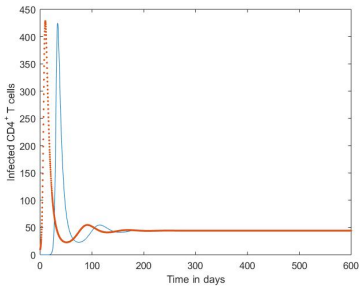
First we choose, $s = 2.9$, $r = 0.001$, $k = 0.000024 mm^{-3} day^{-1}$, $d = 0.01 day^{-1}4$, $b = 0.2 day^{-1}$, $\delta = 0.16 day^{-1}$, $c = 3.4 day^{-1}$, $T_{max} = 1500$ and $N = 1000$. So from (2.4), we have basic reproduction

number, $R_0 = 0.988 < 1$. Thus according to the Theorem 4.1, disease dies out. Figure 1a–1c in solid lines for the initial values $I_1 = (1000, 0, 0.001)$ and in dotted lines for the initial values $I_2 = (1000, 10, 10)$ have confirmed this result. Also, Figure 1d shows that the infection-free equilibrium point $E_0(314.878, 0, 0)$ for these set of parameters is asymptotically stable.

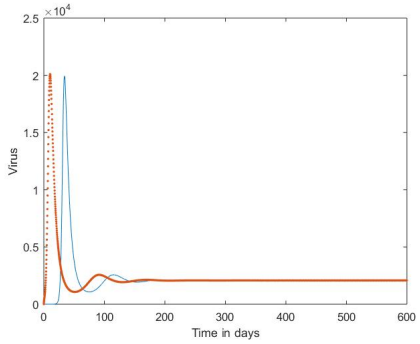
Now, we choose $s = 10mm^{-3}day^{-1}$, $r = 0.001$, $k = 0.000024mm^{-3}day^{-1}$, $d = 0.01day^{-1}$, $b = 0.2day^{-1}$, $\delta = 0.16day^{-1}$, $c = 3.4day^{-1}$, $T_{max} = 1500, N = 1000$, then for this set of data we have $R_0 = 3.238 > 1$. In this case, system goes to the infected steady state. It also satisfies the condition in Theorem 4.4 for global stability of infected equilibrium point. Thus according to Theorem 4.4 disease will persist. Figure 2a–2c confirms this result. Also, Figure 2d shows that the infected equilibrium point $E^*(318.75, 44.147, 2077.5)$ for this set of parameter is asymptotically stable.



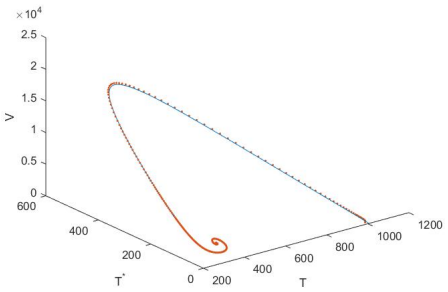
(a) Uninfected $CD4^+$ T cells vs. Time in days.



(b) Infected $CD4^+$ T cells vs. Time in days.



(c) Virus vs. Time in days.

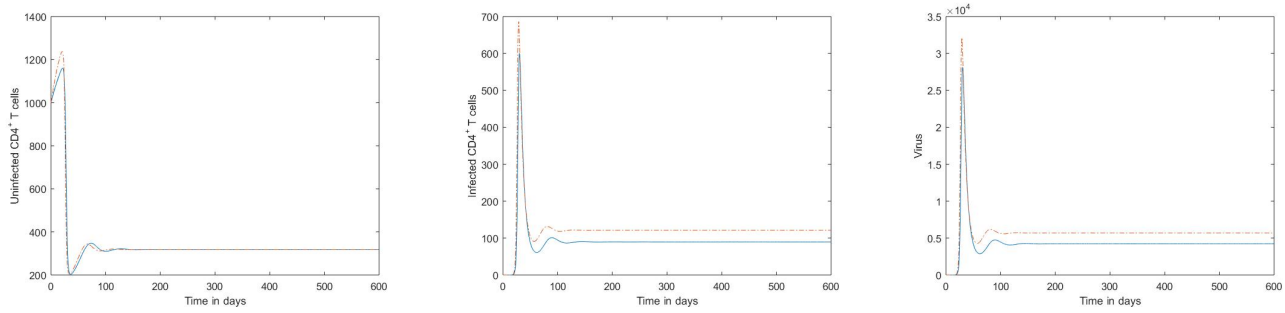


(d) Stability of the infected equilibrium.

Figure 2: Global stability of the infected equilibrium E^* for the initial values $I_1 = (1000, 0, 0.001)$ (Solid lines) and $I_2 = (1000, 10, 10)$ (Dotted lines).

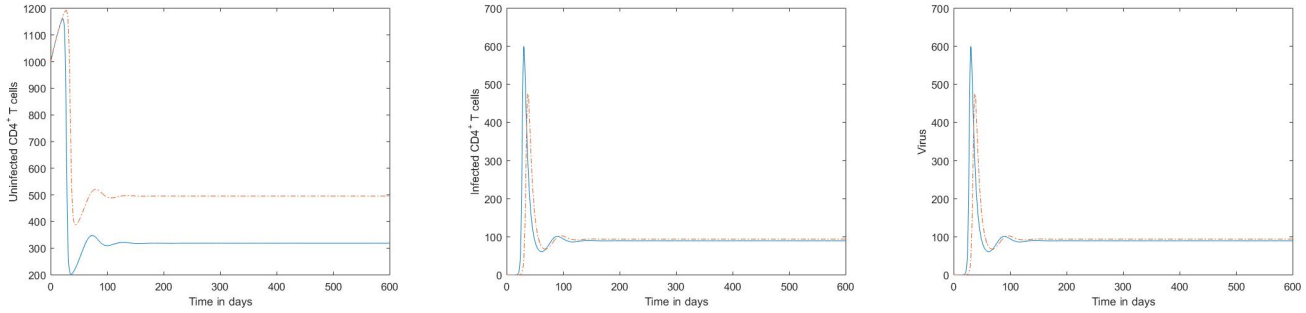
We know choosing parameter values for model is difficult. In the above numerical simulation we considered the values of parameters used in [18]. But in our model we consider that uninfected T cells can be also produced by proliferation of existing uninfected $CD4^+$ T cells. In [12], they have discussed about biologically realistic choices for the parameters r, d, s and T_{max}. But it is also mentioned that other set of parameters can be used. Here we investigate the sensitivity of certain parameters of the model (2.1)–(2.3) on HIV infection of a host.

From Figure 3, it is seen that when r increases proportion of infected $CD4^+$ T cells and virus population increases. This proliferation occurs due to the stimulation of antigen and mitogen. Thus, if r value can be controlled by applying drug the infected $CD4^+$ T cell and virus population will remain under control. Figure 4 shows that when b increases propotion of healthy $CD4^+$T cells increases while increase in the infected $CD4^+$ T cells and virus population slow down. Thus disease can be controlled by applying drug which can increase the rate of reverting infected $CD4^+$ T cells.



(a) Uninfected $CD4^+$ T cells vs. Time in days. (b) Infected $CD4^+$ T cells vs. Time in days. (c) Virus population vs. Time in days.

Figure 3: Variation of population for $r = 0.03$ (Solid lines) and $r = 0.05$ (Dotted lines).



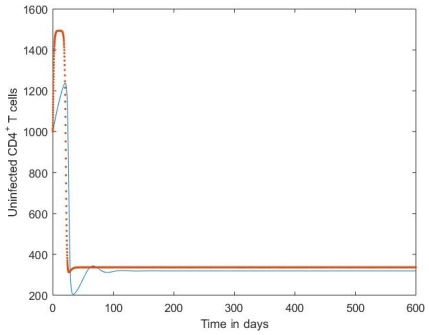
(a) Uninfected $CD4^+$ T cells vs. Time in days. (b) Infected $CD4^+$ T cells vs. Time in days. (c) Virus population vs. Time in days.

Figure 4: Variation of population for $b = 0.2$ (Solid lines) and $b = 0.4$ (Dotted lines).

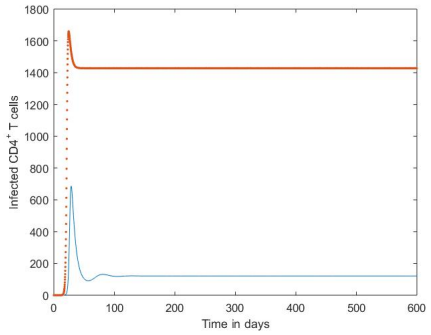
Now, we consider, for one case $r = 0.05, b = 0.2$ and for the other case $r = 0.85, b = 0.22$, all the other parameters are considered same as Figure 2. Basic reproduction number for these cases are $R_0 = 4.431$ and 4.441 respectively. The simulations are shown in the Figure 5. From, Figure 5, it is clear that though the value of basic reproduction number R_0 are very much close to each other for these cases, but the dynamics of the system are different. Here, Figure 5a demonstrate the behavior of uninfected $CD4^+$ T cells with time. If $r = 0.05, b = 0.2$, the uninfected $CD4^+$ T cell population first increases and on around 20 days it reaches maximum level then it decreases and and on around 34 days it will be at minimum level. After this it again increases and around 68 days again it decreases. This behavior will continue with time until it reaches its equilibrium point. For $r = 0.85, b = 0.22$, the uninfected $CD4^+$ T cell population increases rapidly and around 7-8 days it reaches maximum level then it will be constant for some days, around 14 days again it decreases and and around 26 days it will be at minimum level. Then it increases with time until it reaches its equilibrium point.

From, the Figure 5a, it is also clear that in the later case the uninfected cell population reaches the equilibrium state faster than the earlier case. Figure 5b depicts that, if $r = 0.05, b = 0.2$, initially there is no change in the infected $CD4^+$T cells for the first 15 days, then from around 16 days it increases rapidly and around 29 days it reaches maximum level. Then it starts deceasing and around 58 days it reaches minimum level, after that again it increases up to 80 days and then again decreases. This continues until it reaches the equilibrium level. For $r = 0.85, b = 0.22$, initially there is no change in the infected $CD4^+$T cells for the first 12-13 days, then from around 14 days it increases rapidly and around 25 days it reaches maximum level. After that it decreases until it reaches its equilibrium level. Also it is clear that for infected population also, in the later case reaches the equilibrium state faster than the earlier case. At the same time, Figure 5c shows that for $r = 0.05, b = 0.2$ initially there is no change in the virus population

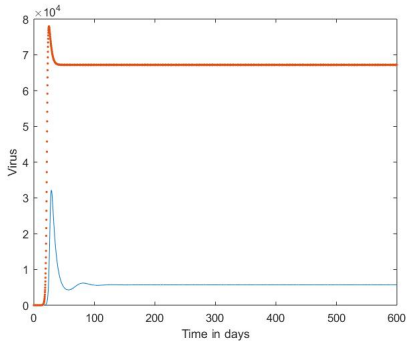
for first 15 days and then it increases rapidly and around 30 days reaches its maximum level. Then it decreases and around 58 days it reaches its minimum level, after that it increases and around 80 days it starts decreasing. This process continues until it reaches its equilibrium level. Again, for $r = 0.85, b = 0.22$, there is no change in the virus population for the first 15 days, then starts increasing rapidly and around 25 days reaches maximum level. After that, it decreases until it reaches equilibrium level. For virus population also, it reaches equilibrium level faster in the later case than the earlier case. Thus it is clear that though basic reproduction number, R_0 of both cases are almost equal but dynamics of T cells and virus population are different.



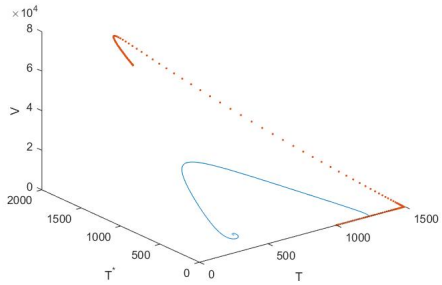
(a) Uninfected $CD4^+$ T cells vs. Time in days.



(b) Infected $CD4^+$ T cells vs. Time in days.



(c) Virus vs. Time in days.



(d) Stability of the infected equilibrium.

Figure 5: Global stability of the infected equilibria for two different set of parameters $r = 0.05, b = 0.2$ (Solid lines) and $r = 0.85, b = 0.22$ (Dotted lines), other parameters are same and for the initial value $I_1 = (1000, 0, 0.001)$.

6. Conclusion

In this study, on the basis of the HIV infection model in [18], we have considered a modified model by considering that healthy $CD4^+T$ cells can also be created by proliferation. Also, we have considered that this proliferation follows simplified logistic growth $rT\left(1 - \frac{T}{T_{max}}\right)$ as anticipated in Perelson and Nelson [13]. The basic reproduction number, R_0 of our model is calculated by next generation matrix method. From (2.4), it is clear that basic reproduction number, R_0 is dependent on r. It is also found that the basic reproduction number is also dependent on b, rate at which infected $CD4^+$ T cells get recovered to the healthy $CD4^+$ T cell population.

Here, we have also dicussed local as well as global stability of the model. Theorem 4.1 indicates that infection-free equilibrium point is globally stable if $R_0 \leqslant 1$, otherwise it is unstable. Biologically, it implies that if the number of newly infected $CD4^+$ T cell raised from an infected $CD4^+$ T cell is less than or equal to one then the infected $CD4^+T$ cells and the virus particles are cleared out from the T cell population

and thus the disease dies out. Thus, if basic reproduction number, R_0 of an infected person is less than or equal to one, then the person can recover automatically provided the person is infected by any amount of viruses. If basic reproduction number, R_0 of the infected person is greater than one but if any treatment can reduce this number below one, then the person will be cured from HIV. Therefore, we can focus on a treatment policy which can control the number of new infections of healthy $CD4^+$ T cells to control the HIV infection.

From [18], we find that if logistic term for proliferation is not considered then the infected equilibrium is globally asymptotically stable if it exists i.e. when $R_0 > 1$. But in model (2.1)–(2.3), it is observed that the stability of the infected equilibrium depends on r as well as R_0. Thus, finding a range of r where infected equilibrium point is globally stable is important. In Theorem 4.3, we have calculated a range of r, where infected equilibrium point, if it exists is globally stable. In the proof of Theorem 4.3, we have considered $0 < p < 1$ which satisfies $T > pT_{max}$. Calculation of such biologically feasible p's will give different ranges of r where infected equilibrium point E^* is globally stable. Also sensitivity of the parameters r and b in the system are checked by varying these parameters as parameter r may also vary with age [12] and b can vary by using drug. It is found that HIV infection can be controlled by applying drugs which can decrease r and increase b, i.e., the rate of reverting infected $CD4^+$ T cells to uninfected $CD4^+$ T cells. Numerical simulations have confirmed that these results are acceptable. Also comparing our results with [18], we get proliferation of healthy $CD4^+$ T cells has large impact on the dynamics of HIV and $CD4^+$ T cells.

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