Global Journal of Pure and Applied Mathematics.
ISSN 0973-1768 Volume 16, Number 5 (2020), pp. 723-739

http://www.ripublication.com/gjpam.htm

A Study of HIV Infection of CD4+ T Cells through Saturated Incidence Rate and Constant Cytokine Effect: A mathematical modelling approach

M.A Haque[1*], **A.K Chakraborty**[1], **M.A Islam**[1],
M.A Rahman[1], **V.C.M Barman**[1]

[1]*Department of Mathematics, Shahjalal University of Science and Technology, Sylhet-3114, Bangladesh.*

Abstract

Human immunodeficiency virus abolishes the body's immune system, damages body organs, and causes death. HIV destroys the immune system by infecting and killing the CD4+ T cells which are known as helper T cells. In this paper, the HIV infection of CD4+ T cells considering the combined effect of nonlinear saturated incidence rate and constant cytokine effect has been studied. A compartmental model through saturated infection rate, cure rate and constant cytokine effect has been proposed. The basic reproduction number has been computed through the next generation matrix method. By using the Jacobin matrix and Ruth- Hurtz criteria, it has been shown that, if the basic reproduction number $R_0 < 1$, the virus-free equilibrium is locally asymptotically stable and if the basic reproduction number $R_0 > 1$, the endemic equilibrium is locally asymptotically stable. The global stability of virus-free equilibrium is shown using the Lyapunov method. In addition, the global stability of endemic equilibrium points are shown through the additive compound matrix method. Numerical simulations are presented to illustrate the results. From the study, it is explored that cytokine has an impact on the dynamics of HIV infection of CD4+ T cells.

Keywords: Human Immune deficiency Virus, Acquired Immune Deficiency Syndrome, cytokines effect, basic reproduction number, Stability analysis.

*Corresponding author: aminul202@yahoo.com

1. INTRODUCTION

Acquired Immunodeficiency Syndrome (AIDS) is triggered by a virus which is known as Human Immunodeficiency Virus (HIV). From the last three decades, it has been a major challenge throughout the world to overcome HIV. The devastating impact of HIV infections mostly affected people of Sub-Saharan Africa. In the early 1980s, around 36 million people are infected and 25 million people are died due to the cause of HIV/AIDS [1]. It is one of the major public health concerns because of the extreme mortality rate of the virus. HIV models are studied by several authors which can be categorically classified into population-level-models and within-host-models [2–10]. Many researchers studied and tried to analyze the mechanism of the virus [11–14]. Viruses do not have the capability to replicate independently and it depends on a host for the aid of reproduction. Viruses usually copies of their DNA and put this into the DNA of the host cells [15]. Therefore, the host cell is infected when it is in contact with the virus, and when the infected host cell is enthused to replicate, it replicates copies of the virus. Since CD4+ T cells play a key role in the human body's immune system, the destruction of these cells is the main cause of the devastating impact of HIV. When HIV infects the body of a person, its main goal is to infect the CD4+ T-cells. The reason is that CD4+ T-cells have a protein on its surface which has a high affinity to the protein on the surface of HIV [15]. The virus then reproduces within the host cells which surge releasing more mature virions. Hence, the main attributes of HIV contagion comprise the demolition of helper CD4+ T cells and the consequence is the dropping of immune capability. HIV virions in specific dwindle the cell function by damaging the helper T cells which constructing a robust immune response [16]. The reduction of healthy CD4+ T-cells outcomes in an enfeebled immune system [17]. During the primary stage of HIV infection, viral load and immune response are in stabilizing positions, however, if not treated or controlled properly, after a few years the HIV infection patient progress into AIDS.

In the arena of epidemiology, researchers have developed models to analyze the dynamics of HIV infection. These models have delivered vital perceptions about the behavior of HIV infection and the strategy of controlling the development of AIDS. Until today, mathematical modeling has become an essential technique in understanding the dynamics of HIV and in decision-making processes for monitoring and treatment of the virus in many countries. Ngina et al. [12] investigated in-host model. The results from the study recognized the importance of the CD8+ T-cells in controlling HIV viral progression. Aruda et al. [18] proposed a model for HIV infection with the inclusion of the CD8+ T-cells. Hattaf and Yousfi [19] studied an in vivo HIV model. However, the model only comprised of the CD4+ T-cells and the virus which is omitted the infected CD4+ T-cells. Ngina et al. [16] explored the in vivo dynamics of HIV infection considering wild type and resistance type healthy CD4+ T-cells, and T lymphocyte cells. It has been observed that during the initial stage of HIV infection virus replication is higher [12, 16].

However, literature that is discussed above mostly considered the bilinear transmission

of infections between healthy and infected cells of CD4+ T-cells. In reality, the saturated incidence rate of transmission is more appropriate rather than by linear transmission, as the initial stage of HIV infection, virus replications rate is higher and after that transmission is being saturated and lasting long time in HIV patient. This might be due to the prevention measuring by HIV patients or overcrowding of infected CD4+ T cells. There is some existing literature on HIV dynamics considering the saturated incidence rate of transmission. Perelson and Nelson [8] studied HIV infection considering a saturated linear incidence rate. Ogunlaran and Oukouomi Noutchie [20] studied effective management of HIV infection considering nonlinear incidence rate and two control parameters. Zhou et al. [15] proposed a model of HIV infection with a cure rate as they considered the loss of the infected cell is the cause of death or via cure. In the study, they also considered the proliferation of cells. Wang et al. [21] analyzed the modeling of slow CD4+ T cells decline in HIV infected individuals through a simulation using statistical techniques. They did not find the mathematical stability analysis and the dynamics of HIV based on the basic reproduction number. Doitsh et al. [22, 23] considered the mechanism of HIV infection and explored that when a virus enters a CD4+ T cell which is non-permissive to viral infection, the caspase-1 pathway is generated to induce pyroptosis, which can secrete inflammatory cytokines. These cytokines entice more CD4+ T cells subsequent to enhance more cell infection and cell death. Therefore, cytokine also plays a great role in the acceleration of uninfected CD4+ T cells to be infected, and it is needed to be considered with the transmission coefficient in the mathematical model. Therefore, the goal of this study is that propose a new mathematical model considering the combined effects of nonlinear saturated incidence rate, constant cytokine effect, and cure rate and explore the dynamics of HIV infection of CD4+ T cells.

2. MODEL DESCRIPTION

For the formulation of HIV infection of CD4+ T cells model, we have considered here mainly three compartments, the concentration of healthy that is the uninfected CD4+ T cells (T), infected CD4+T cells (I), and the viral load of virions (V). When the uninfected CD4+ T cells interact with the virus, it becomes infected. Here the rate of infection is given by $\frac{\beta(1+\delta_c)}{1+\alpha_1 V}$. We have considered the saturated incidence rate instead of the bilinear incidence rate of infection. Because saturated incidence rate of transmission is more appropriate rather than by linear transmission. Here the saturated incidence rate factor is $(1 + \alpha_1 V)$. This happened due to the protection measuring by HIV patients or overcrowding of infected CD4+T cells. Besides, we have considered the constant rate of cytokine effect, as it enhances more T cells to be infected, and the cure rate as well. Thereafter, uninfected T cells become infected when these meet with the virus. A portion of infected T cells is also cured either by body immunity or drug. Based on the above-mentioned assumptions, the following system of nonlinear differential equations

is developed to describe the model.

$$\begin{aligned}
\frac{dT}{dt} &= \lambda - \frac{\beta(1+\delta_c)}{1+\alpha_1 V}TV + \eta I - d_1 T \\
\frac{dI}{dt} &= \frac{\beta(1+\delta_c)}{1+\alpha_1 V}TV - \eta I - d_2 I \\
\frac{dV}{dt} &= \alpha_2 I - d_3 V
\end{aligned} \tag{2.1}$$

Table-1 describes the parameters of the model (2.1).

Table 1: List of parameters

Parameter	Description
β	The rate of infection of CD4+T cell by virus
δ_c	The constant rate of cytokine effect which attract more uninfected CD4+T cells and make it infected
λ	The rate at which new T cells are created from sources
α_1	The saturation factor
α_2	The average rate of virus production by per infected CD4+ T cell
η	The cure rate
d_1	The death rate of the healthy T cell
d_2	The death rate of the infected CD4+T cell
d_3	The death rate of the virus cell

In the next section we will discuss about the equilibrium points and the basic reproduction number of the proposed model.

3. MATHEMATICAL STABILITY

In this section the equilibrium points of the model (2.1) have been presented and the basic reproduction number will be introduced. Equilibrium points are calculated from the set of equations in which the variables do not change with time. To find the equilibrium points of the proposed model, we set $\frac{dT}{dt} = \frac{dI}{dt} = \frac{dV}{dt} = 0$ in (2.1). Which implies,

$$\begin{aligned}
&\lambda - \frac{\beta(1+\delta_c)}{1+\alpha_1 V}TV + \eta I - d_1 T = 0 \\
&\frac{\beta(1+\delta_c)}{1+\alpha_1 V}TV - \eta I - d_2 I = 0 \\
&\alpha_2 I - d_3 V = 0
\end{aligned} \tag{3.2}$$

The system of equations (3.2) will be used to find the disease free and endemic

equilibrium points.

3.1. Disease Free Equilibrium Point

The disease free equilibrium (DFE) exist in the case of absence of disease among the populations. Using $I = 0$, and $V = 0$ in (3.2), the virus free equilibrium point of the model (2.1) is found to be $E^0(T^0, I^0, V^0) = \left(\frac{\lambda}{d_1}, 0, 0\right)$.

3.2. Basic Reproduction Number

The basic reproduction number is a dimensionless number and an important threshold quantity in every infectious disease. It is defined as the expected number of secondary cases produced by a single infection case into a complete susceptible population [24]. To find out the basic reproduction number of the model (2.1), the method of next generation matrix is used. This method is introduced by Dirkmann et al [25], which is generally used in such cases where the population is divided into discrete and disjoint classes. In next generation matrix method, the basic reproduction number (R_0) is defined as the spectral radius or dominant eigenvalue of the next generation operator [24]. According to this method it is necessary to identify the infection classes of the model. For the model (2.1), there are two infection class which are,

$$\begin{aligned} \frac{dI}{dt} &= \frac{\beta(1+\delta_c)}{1+\alpha_1 V} TV - \eta I - d_2 I \\ \frac{dV}{dt} &= \alpha_2 I - d_3 V \end{aligned} \tag{3.3}$$

Using the method of next generation matrix (the details calculation of the method is omitted here and refer [26] to the interested reader), the basic reproduction number is found to be,

$$R_0 = \frac{\lambda\beta\alpha_2(1+\delta_c)}{d_1 d_3(\eta + d_2)} \tag{3.4}$$

The basic reproduction number is a very useful quantity to determine the status of an uninfected and infected and CD4+ T-cells. In the next section we are going to discuss about the stability analysis of our proposed model.

3.3. Endemic Equilibrium point

When the viruses are present among the population, the endemic equilibrium points (EEP) are found. For this case the infection compartments are nonzero. There may be several critical points present in this case. Denoting the endemic equilibrium point by $E^*(T^*, I^*, V^*)$, where T^*, I^*, and V^* are the positive solutions of the system (3.2) and using nonzero infection class in the system (3.2), the following endemic equilibrium

points are found.

$$T^* = \frac{(d_2+\eta)(d_2d_3+\alpha_1\alpha_2\lambda)}{\alpha_2(d_1d_2\alpha_1+d_2\beta(1+\delta_c)+d_1\alpha_1\eta)}, I^* = \frac{-d_1d_2d_3-d_1d_3\eta+\alpha_2\beta\lambda+\alpha_2\beta\delta_c\lambda}{\alpha_2(d_1d_2\alpha_1+d_2\beta(1+\delta_c)+d_1\alpha_1\eta)},$$
$$V^* = \frac{-d_1d_2d_3-d_1d_3\eta+\alpha_2\beta\lambda+\alpha_2\beta\delta_c\lambda}{d_3(d_1d_2\alpha_1+d_2\beta(1+\delta_c)+d_1\alpha_1\eta)}$$

Here in the above expressions it is observed that T^* is positive since the parameters of the model are non negative. I^* and V^* are positive if,

$$\begin{aligned} &\alpha_2\beta\lambda+\alpha_2\beta\delta_c\lambda-d_1d_2d_3-d_1d_3\eta>0 \\ =>&d_1d_3(\eta+d_2)\left[R_0-1\right]>0 \end{aligned} \tag{3.5}$$

This condition is true for $R_0 > 1$. Thus, it is concluded that the system (2.1) has a unique positive endemic equilibrium if $R_0 > 1$. In the next section we are going to discuss about the stability analysis of the proposed model.

3.4. Stability Analysis

3.4.1. Local Stability Analysis

The local stability analysis of the model (2.1) has been discussed in this section. From the system of equation (2.1), the Jacobian matrix of our proposed model is,

$$J = \begin{pmatrix} -\frac{\beta(1+\delta_c)}{1+\alpha_1V}V-d_1 & \eta & -\frac{\beta(1+\delta_c)}{(1+\alpha_1V)^2}T \\ \frac{\beta(1+\delta_c)}{1+\alpha_1V}V & -\eta-d_2 & \frac{\beta(1+\delta_c)}{(1+\alpha_1V)^2}T \\ 0 & \alpha_2 & -d_3 \end{pmatrix} \tag{3.6}$$

Lemma 3.1. *The disease free equilibrium E^0 is locally asymptotically stable if $R_0 < 1$.*

Proof. For the disease free equilibrium point, the Jacobian matrix (3.6) is

$$J^0 = \begin{pmatrix} -d_1 & \eta & -\beta(1+\delta_c)T^0 \\ 0 & -\eta-d_2 & \beta(1+\delta_c)T^0 \\ 0 & \alpha_2 & -d_3 \end{pmatrix} \tag{3.7}$$

One of the eigenvalues of (3.7) is $-d_1$, which is negative and the others are found by the equation:

$$\Lambda^2+(\eta+d_2+d_3)\Lambda+(\eta+d_2)d_3-\alpha_2\beta(1+\delta_c)T_0=0 \tag{3.8}$$

The roots of (3.8) are $\Lambda = \frac{-(\eta+d_2+d_3)\pm\sqrt{(\eta+d_2+d_3)^2-4((\eta+d_2)d_3-\alpha_2\beta(1+\delta_c)T_0)}}{2}$ and the real part of the roots are negative if $(\eta+d_2)d_3-\alpha_2\beta(1+\delta_c)T_0>0$, which implies $R_0<1$.

Thus, in case of DFE, the the real part of the roots of characteristic polynomial are negative if $R_0 < 1$ and consequently the DFE is locally asymptotically stable [27]. This concludes for $R_0 < 1$, the disease free equilibrium is locally asymptotically stable.

Lemma 3.2. *The positive endemic equilibrium E^* of the model is locally asymptotically stable if $R_0 > 1$ and $\alpha_1 > 0$.*

Proof. For endemic point the Jacobian (3.6) is

$$J^* = \begin{pmatrix} -\frac{\beta(1+\delta_c)}{1+\alpha_1 V^*}V^* - d_1 & \eta & -\frac{\beta(1+\delta_c)}{(1+\alpha_1 V^*)^2}T^* \\ \frac{\beta(1+\delta_c)}{1+\alpha_1 V^*}V^* & -\eta - d_2 & \frac{\beta(1+\delta_c)}{(1+\alpha_1 V^*)^2}T^* \\ 0 & \alpha_2 & -d_3 \end{pmatrix} \tag{3.9}$$

The characteristic equation of the matrix (3.9) is: $\Lambda^3 + a_1\Lambda^2 + a_2\Lambda + a_3 = 0$
where, $a_1 = \eta + d_2 + d_3 + \frac{\beta(1+\delta_c)V^*}{1+\alpha_1 V^*} + d_1$
$a_2 = d_1(\eta + d_2 + d_3) + (d_2 + d_3)\frac{\beta(1+\delta_c)V^*}{1+\alpha_1 V^*} + d_3(\eta + d_2)\left[1 - \frac{\alpha_2\beta(1+\delta_c)T^*}{d_3(\eta+d_2)(1+\alpha_1 V^*)^2}\right]$
$a_3 = \frac{d_2 d_3\beta(1+\delta_c)V^*}{1+\alpha_1 V^*} + d_1 d_3(\eta + d_2)\left[1 - \frac{\alpha_2\beta(1+\delta_c)T^*}{d_3(\eta+d_2)(1+\alpha_1 V^*)^2}\right]$
From the second and third equation of (3.2) it is found that, $\frac{\alpha_2\beta(1+\delta_c)T^*}{1+\alpha_1 V^*} = d_3(\eta + d_2)$.
Using this value a_2 and a_3 can be written as,
$a_2 = d_1(\eta + d_2 + d_3) + (d_2 + d_3)\frac{\beta(1+\delta_c)V^*}{1+\alpha_1 V^*} + d_3(\eta + d_2)\left[1 - \frac{1}{1+\alpha_1 V^*}\right]$
$a_3 = \frac{d_2 d_3\beta(1+\delta_c)V^*}{1+\alpha_1 V^*} + d_1 d_3(\eta + d_2)\left[1 - \frac{1}{1+\alpha_1 V^*}\right]$
and, $a_1 a_2 - a_3 = (\eta + d_2 + \frac{\beta(1+\delta_c)V^*}{1+\alpha_1 V^*})(d_1(\eta + d_2 + d_3) + (d_2 + d_3)\frac{\beta(1+\delta_c)V^*}{1+\alpha_1 V^*} + d_3(\eta + d_2)\left[1 - \frac{1}{1+\alpha_1 V^*}\right]) + d_3(d_1(\eta + d_2 + d_3) + d_3\frac{\beta(1+\delta_c)V^*}{1+\alpha_1 V^*} + d_3(\eta + d_2)\left[1 - \frac{1}{1+\alpha_1 V^*}\right]) + d_1(d_1(\eta + d_2 + d_3) + (d_2 + d_3)\frac{\beta(1+\delta_c)V^*}{1+\alpha_1 V^*})$

Here $a_1 > 0$. a_2, a_3, and $a_1 a_2 - a_3$ are positive if and only if $1 - \frac{1}{1+\alpha_1 V^*}$ is greater than zero that implies $\alpha_1 V^* > 0$. For endemic equilibrium point $V^* > 0$ for $R_0 > 1$ and if $\alpha_1 > 0$ then all of the coefficients of the characteristic equation of the matrix (3.9) are positive and by Routh-Hurwitz criterion endemic equilibrium point is locally asymptotically stable [28]. This concludes the endemic equilibrium is locally asymptotically stable for $R_0 > 1$ and $\alpha_1 > 0$.

3.4.2. Global Stability Analysis

The property of global stability for both disease free and endemic equilibrium has been discussed in this section by using the following Lemmas and Theorems.

Lemma 3.3. *The disease free equilibrium point E^0 of the model (2.1) is globally asymptotically stable is Ω if $R_0 \leq 1$.*

Proof. Consider the following positive defined Lyapunov function

$$\begin{aligned} L &= d_1 d_3 I + \lambda\beta(1+\delta_c)V \\ \Rightarrow L' &= d_1 d_3 \left[\frac{\beta(1+\delta_c)}{1+\alpha_1 V}TV - \eta I - d_2 I\right] + \lambda\beta(1+\delta_c)\left[\alpha_2 I - d_3 V\right] \\ &\leq d_1 d_3 \left[\beta(1+\delta_c)\frac{\lambda}{d_1}V - \eta I - d_2 I\right] + \lambda\beta(1+\delta_c)\left[\alpha_2 I - d_3 V\right] \\ &= -d_1 d_3(\eta + d_2)I + \lambda\beta\alpha_2(1+\delta_c)I \\ &= d_1 d_3(\eta + d_2)\left[R_0 - 1\right] I \end{aligned}$$

Therefore $L' \leq 0$ for $R_0 \leq 1$ and $L' = 0$ if and only if $I = 0$. Furthermore $(T, I, V) \to \left(\frac{\lambda}{d_1}, 0, 0\right)$ as $t \to \infty$, since $I \to 0$ as $t \to \infty$. Consequently, the largest compact invariant set in $\{(T, I, V) \in \Omega : L' = 0\}$ is the singleton $\{E^0\}$, where E^0 is the virus free equilibrium point. Hence by Lasalle's invariance principle [29], E^0 is globally asymptotically stable in Ω if $R_0 \leq 1$.This completes the proof.

It has been shown in section (3.3) that for $R_0 > 1$ the model has a unique endemic equilibrium E^*. To establish the global stability of E^*, we will use the geometric approach proposed by Li and Muldowney [30]. For the details process of the method we refer [31, 32] to the interested readers. Here only the brief introduction of the method have been introduced from [32]. Assume that $x \mapsto f(x) \in R^n$ be a C^1 map for x in an open set $D \subset R^n$. Consider the differential equation,

$$x' = f(x) \tag{3.10}$$

It is considered that the solution of (3.10) is denoted by $x(t, x_0)$ such that $x(0, x_0) = x_0$. We have the following two assumptions [31].

(H1) There exits a compact absorbing set $K \subset D$.

(H2) Equation (3.10) has a unique equilibrium x^* in D.

Let $P : x \mapsto P(x)$ be a non singular $\binom{n}{2} \times \binom{n}{2}$ matrix-valued function, which is C^1 in D and a vector norm $|\cdot|$ on R^N, where $N = \binom{n}{2}$. Let μ be the Lozinskii measure with respect to the $|\cdot|$ [32]. Define a quantity,

$$q = \limsup_{t\to\infty} \sup \frac{1}{t}\int_0^t \mu(B(x(s, x_0)))ds \tag{3.11}$$

Where $B = P_f P^{-1} + PJ^{[2]}P^{-1}$ in which P_f and $J^{[2]}$ are described in [31]. The following criteria for global stability has been established by Li and Muldowney [30].

Lemma 3.4. *[30] Assume that the conditions (H1) and (H2) holds. Then x^* is globally asymptotically stable in D provide that a function $P(x)$ and Lozinskii measure μ exists such that $q < 0$.*

Lemma 3.5. *[32] The system (2.1) is uniformly persistent in Ω if $R_0 > 1$, that is, there exists $c > 0$ such that $\liminf_{t\to\infty} T(t) \geq c$, $\liminf_{t\to\infty} I(t) \geq c$, and $\liminf_{t\to\infty} V(t) \geq c$.*

Proof. From the global stability of virus free equilibrium it is found that E^0 is unstable when $R > 1$. Following [33] the uniform persistence can be proved for the model (2.1). That is, the uniform persistent implies from the instability of E^0 together with $E^0 \in \partial\Omega$, that means there exists a $c > 0$ such that $\liminf_{t\to\infty} T(t) \geq c$, $\liminf_{t\to\infty} I(t) \geq c$, and $\liminf_{t\to\infty} V(t) \geq c$. The existence of a compact set in the interior of Ω which is equivalent to the uniform persistence that is absorbing for (2.1). This verifies assumption (H1). Furthermore, in the previous section we have shown that E^* is the only equilibrium in the interior of Ω. This verifies assumption (H2).

Lemma 3.6. *Under the condition $R_0 > 1$, the unique endemic equilibrium E^* is globally asymptotically stable in Ω.*

Proof. From (3.6) the Jacobian matrix of the model is,

$$J = \begin{pmatrix} -\frac{\beta(1+\delta_c)}{1+\alpha_1 V}V - d_1 & \eta & -\frac{\beta(1+\delta_c)}{(1+\alpha_1 V)^2}T \\ \frac{\beta(1+\delta_c)}{1+\alpha_1 V}V & -\eta - d_2 & \frac{\beta(1+\delta_c)}{(1+\alpha_1 V)^2}T \\ 0 & \alpha_2 & -d_3 \end{pmatrix}$$

and its second additive compound matrix is:

$$J^{[2]} = \begin{pmatrix} -\frac{\beta(1+\delta_c)}{1+\alpha_1 V}V - d_1 - d_2 - \eta & \frac{\beta(1+\delta_c)}{(1+\alpha_1 V)^2}T & \frac{\beta(1+\delta_c)}{(1+\alpha_1 V)^2}T \\ \alpha_2\frac{I}{V} & -\frac{\beta(1+\delta_c)}{1+\alpha_1 V}V - d_1 - d_3 & \eta \\ 0 & \frac{\beta(1+\delta_c)}{1+\alpha_1 V}V & -\eta - d_2 - d_3 \end{pmatrix}$$

We consider the following function $P = P(T, I, V) = \text{diag}(1, I/V, I/V)$; then $P_f = \text{diag}\Big(0, \frac{VI'-IV'}{V^2}, \frac{VI'-IV'}{V^2}\Big)$ and $P_f P^{-1} = \text{diag}\Big(0, \frac{I'}{I} - \frac{V'}{V}, \frac{I'}{I} - \frac{V'}{V}\Big)$. Now,

$$PJ^{[2]}P^{-1} = \begin{pmatrix} -\frac{\beta(1+\delta_c)}{1+\alpha_1 V}V - d_1 - d_2 - \eta & \frac{\beta(1+\delta_c)}{(1+\alpha_1 V)^2}\frac{TV}{I} & \frac{\beta(1+\delta_c)}{(1+\alpha_1 V)^2}\frac{TV}{I} \\ \alpha_2\frac{I}{V} & -\frac{\beta(1+\delta_c)}{1+\alpha_1 V}V - d_1 - d_3 & \eta \\ 0 & \frac{\beta(1+\delta_c)}{1+\alpha_1 V}V & -\eta - d_2 - d_3 \end{pmatrix}$$

The matrix $B = P_f P^{-1} + PJ^{[2]}P^{-1}$ can be written in matrix form:

$$B = \begin{pmatrix} B_{11} & B_{12} \\ B_{21} & B_{22} \end{pmatrix}$$

Where, $B_{11} = -\frac{\beta(1+\delta_c)}{1+\alpha_1 V}V - d_1 - d_2 - \eta$, $B_{12} = \left(\frac{\beta(1+\delta_c)}{(1+\alpha_1 V)^2}\frac{TV}{I}, \frac{\beta(1+\delta_c)}{(1+\alpha_1 V)^2}\frac{TV}{I}\right)$, $B_{21} = \left(\alpha_2\frac{I}{V}, 0\right)^T$, and

$$B_{22} = \begin{pmatrix} \frac{I'}{I} - \frac{V'}{V} - \frac{\beta(1+\delta_c)}{1+\alpha_1 V}V - d_1 - d_3 & \eta \\ \frac{\beta(1+\delta_c)}{1+\alpha_1 V}V & \frac{I'}{I} - \frac{V'}{V} - \eta - d_2 - d_3 \end{pmatrix}$$

Consider the norm in R^3 as $|(u, v, w)|$ =max$(|u|, |v| + |w|)$ where (u, v, w) denotes the vector in R^3. The Lozinskii measure with respect to this norm is defined as $\mu(B) \leq$ sup $\{g_1, g_2\}$. Where, $g_1 = \mu_1(B_{11}) + |B_{12}|$ and $g_2 = \mu_1(B_{22}) + |B_{21}|$ are matrix norms with respect to l_1 vector norm, and μ_1 denotes the Lozinskii measure with respect to this l_1 norm. More specifically,

$$\mu_1(B_{11}) = -\frac{\beta(1+\delta_c)}{1+\alpha_1 V}V - d_1 - d_2 - \eta$$
$$|B_{12}| = \frac{\beta(1+\delta_c)}{(1+\alpha_1 V)^2}\frac{TV}{I}, |B_{21}| = \alpha_2\frac{I}{V}$$

To calculate $\mu_1(B_{22})$, taking the off-diagonal elements of each column of B_{22} in absolute value, then adding to the corresponding columns of the diagonal elements, and then take the maximum of two sums. This leads to,

$$\mu_1(B_{22}) = max\left\{\frac{I'}{I} - \frac{V'}{V} - d_1 - d_3, \frac{I'}{I} - \frac{V'}{V} - d_2 - d_3\right\} = \frac{I'}{I} - \frac{V'}{V} - d_3 + max\{-d_1, -d_2\}$$

Therefore, we have,

$$g_1 = \mu_1(B_{11}) + |B_{12}| = \frac{\beta(1+\delta_c)}{(1+\alpha_1 V)^2}\frac{TV}{I} - \frac{\beta(1+\delta_c)}{1+\alpha_1 V}V - d_1 - d_2 - \eta$$

$$g_2 = \mu_1(B_{22}) + |B_{21}| = \alpha_2\frac{I}{V} + \frac{I'}{I} - \frac{V'}{V} - d_3 + max\{-d_1, -d_2\}$$

From (2.1) we have,

$$\begin{aligned} \frac{I'}{I} &= \frac{\beta(1+\delta_c)}{1+\alpha_1 V}\frac{TV}{I} - \eta - d_2 \\ \frac{V'}{V} &= \alpha_2\frac{I}{V} - d_3 \end{aligned} \tag{3.12}$$

By choosing $\tau = max\{-d_1, -d_2\}$, it is obvious that $\tau < 0$ and using (3.12) we have,

$$g_1 = \frac{\beta(1+\delta_c)}{(1+\alpha_1 V)^2}\frac{TV}{I} - \frac{\beta(1+\delta_c)}{1+\alpha_1 V}V - d_1 - d_2 - \eta \leq \frac{\beta(1+\delta_c)}{(1+\alpha_1 V)}\frac{TV}{I} - d_1 - d_2 - \eta = \frac{I'}{I} - d_1$$

$$g_2 = \mu_1(B_{22}) + |B_{21}| = \alpha_2 \frac{I}{V} + \frac{I'}{I} - \frac{V'}{V} - d_3 + z \leq \frac{I^{'}}{I} + \tau$$

Furthermore, we have,

$$\mu(B) \leq sup\{g_1, g_2\} \leq \frac{I^{'}}{I} + \psi$$

Here, $\psi = max\{-d_1, \tau\} < 0$. By integrating both sides at the same time, we obtain

$$\begin{aligned} &\frac{1}{t}\int_0^t \mu(B)ds \leq \frac{1}{t}\ln\frac{I(t)}{I(0)} + \psi \\ &q = \limsup_{t\to\infty}\sup\frac{1}{t}\int_0^t \mu(B)ds \leq \psi < 0 \end{aligned} \tag{3.13}$$

According to Lemma-3.4 the endemic equilibrium E^* of the model is globally asymptotically stable in Ω if $R > 1$. This completes the proof.

4. NUMERICAL SIMULATIONS

To investigate the effect of constant cytokine and the dynamical behaviour of the compartments, the numerical simulations of the model (2.1) have been performed. MATLAB programming code has been developed to perform the numerical simulations. Due to the lack of availability and limitations of the experimental values of the parameters, in this paper, some of the parameter values are taken from [21, 34] and others are assumed for the purpose of simulations. Two different set of initial conditions, $I_1 = (100, 0, 0.001)$ and $I_2 = (100, 10, 10)$ are used in the simulations for the study of the dynamics by differing the initial number of the infected and virus cell. Here, two different values of the cytokine parameter, $\delta_c = 0$ and $\delta_c = 0.5$, are considered in generating each of the figures. For figure-1 and 2, the other parameters are,

$$\lambda = 6, \alpha_1 = 0.01, \beta = 0.25, \eta = 0.1, d_1 = 0.1, d_2 = 0.1, d_3 = 0.1, \alpha_2 = 0.00079 \tag{4.14}$$

Using the parameter set (4.14) and $\delta_c = 0$, it is obtained from the expression (3.4) that the reproduction number is $R_0 = 0.5925$. However, when the value of $\delta_c = 0.5$ and the parameter set (4.14) are considered , it is found that $R_0 = 0.8887$. For both of the cases the reproduction number is less than one. According to lemma-3.3, the global stability of the model is asymptotically stable for disease free equilibrium E^0 if $R_0 < 1$.

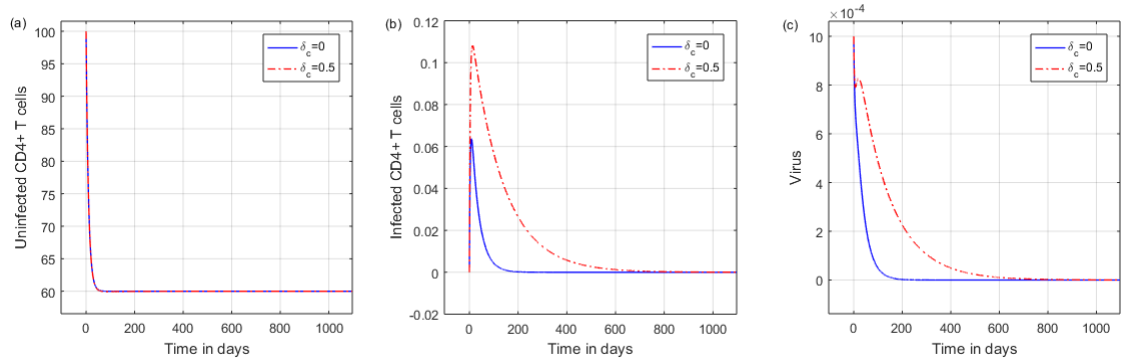

Figure 1: using I_1 and parameter (4.14)

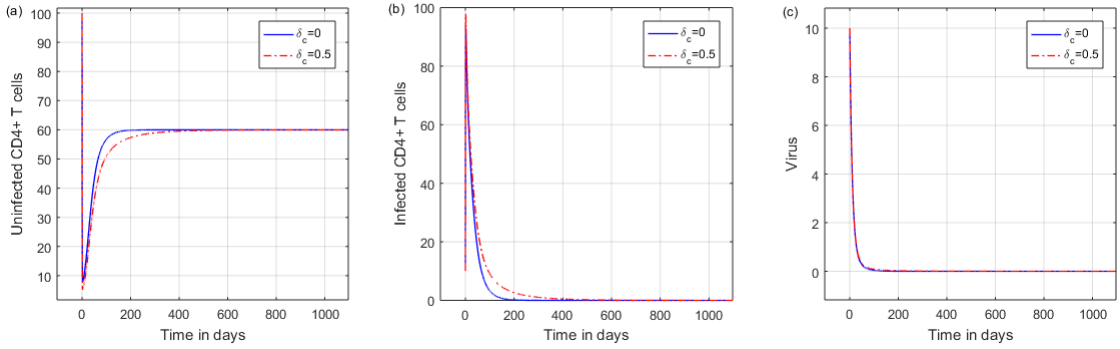

Figure 2: using I_2 and parameter (4.14)

Figure-1 & 2 validates the result of lemma-3.3. It can be seen from figure-1 that starting from initial value 100, the uninfected CD4+ T cell has been in the equilibrium point T^0 after 80 days. There is no remarkable effect of the constant cytokine parameter δ_c in figure-1(a). From figure-1(b) and 1(c), it can be observed that without cytokine effect the infected and virus cells are reached at the disease free equilibrium state after 250 days. However, when the value of $\delta_c = 0.5$, it took 1000 days to reach the equilibrium. In the figure-2, the initial value for uninfected cell was 100 and initial value for infected and virus cell was 10. Within a short period of time uninfected CD4+ T cell decreased and then again started increasing which reached in the equilibrium point in 250 days for $\delta_c = 0$. It took 1000 days to reach equilibrium point for $\delta_c = 0.5$. In figure-2(b), the infected CD4+ T cell started increasing from 10 and reached a peak of 98 within very short time. It took same time as figure-1(a) to reach the equilibrium point. The close view of figure-2(c) gives a similar phenomenon as in figure-1(c). In both of the figures when the cytokine effect is absent it took maximum 250 days to reach the equilibrium point E^0. However, for $\delta_c = 0.5$ it took four times more days to reach the equilibrium regardless of initial conditions.

To generate the next figures we have changed the value of the parameter λ from 6 to 15. This has to be done to increase the value of R_0. The new set of parameters are,

$$\lambda = 15, \alpha_1 = 0.01, \beta = 0.25, \eta = 0.1, d_1 = 0.1, d_2 = 0.1, d_3 = 0.1, \alpha_2 = 0.00079 \tag{4.15}$$

We found $R_0 = 1.4812$ by using parameter set (4.15) and $\delta_c = 0$, however, we found $R_0 = 2.2219$ using $\delta_c = 0.5$ and parameter set (4.15). In both of the cases, R_0 is greater than one. Lemma 3.6 states the endemic equilibrium is globally stable if $R_0 > 1$. Figure-3 & 4 validates lemma 3.6.

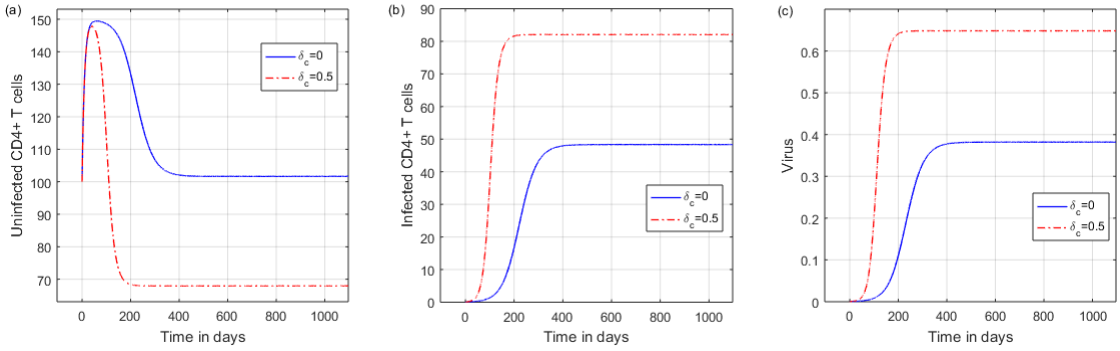

Figure 3: using I_1 and parameter (4.15)

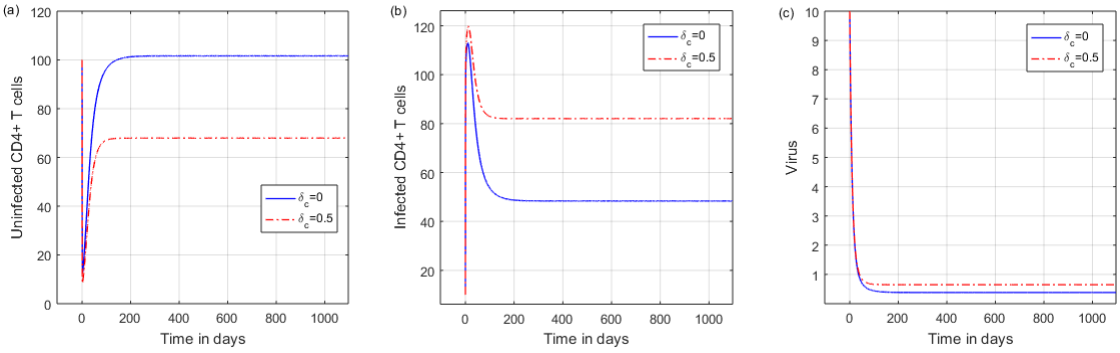

Figure 4: using I_2 and parameter (4.15)

Using parameter (4.15) and $\delta_c = 0$, the endemic equilibrium point is found to be, $E^* = (101.65, 48.34, 0.38)$. Also for (4.15) and $\delta_c = 0.5$, the value is $E^* = (67.95, 82.05, 0.65)$. From figure-3 & 4, it can be seen that in case of $\delta_c = 0$, maximum 300 days is taken for the compartments to reach the equilibrium point E^*, while for $\delta_c = 0.5$ the required time is 500 days. The indices of the graphs for the compartment of infected and virus CD4+ T cell are higher for $\delta_c = 0.5$ rather than $\delta_c = 0$. As it is known

that when the infected and virus cell increases, the uninfected cell decreases. We can see from figure-3(a) & 4(a) that the level of the curve for $\delta_c = 0$ is high compare to $\delta_c = 0.5$. From the simulations it can be concluded that the figures support the theoretical results obtained from section (3) and the constant cytokine parameter enhances the infection level and decreases the healthy CD4+ T cell.

5. CONCLUSION

In this paper, to study the effect of cytokine of HIV infection on CD4+T cells, a realistic mathematical model has been developed and analyzed using the concept of compartmental modelling. In order to make the model more appropriate, the nonlinear saturated incidence rate and the cure rate have been considered. It is found that the model has a unique endemic equilibrium point for $R_0 > 1$. The conditions for which the equilibrium points are stable or unstable are identified. By constructing Liaponov function, we have shown that the disease free equilibrium point of the model is globally asymptotically stable for $R_0 \leq 1$. Furthermore, the endemic equilibrium point is shown globally stable for $R_0 > 1$ using matrix additive method. Simulations are performed to validate the analytical result that gives a rigorous view of the dynamics of the compartments as well as an insight of the effect of the cytokine parameter. The dynamics of the compartments have been studied using different initial conditions and the cytokine parameter. From the simulation it has been observed that due to the inclusion of constant cytokine effect there is a change in the dynamics of uninfected and infected CD4+T cells and virus cell as well. From figures it can be concluded that, for both of the initial conditions the infection level increases for a positive value of the cytokine parameter. In presence of the cytokine effect the healthy cell decreases, whereas the infected and virus cell increases, which supports biological intuition. For the case of the disease free equilibrium, it took four times more days to reach the equilibrium point for the compartments when the value of cytokine parameter increases from 0 to 0.5. On the other hand, it took two times for the case of the endemic equilibrium. Through the mathematical modeling approach with stability analysis and numerical simulations, it has been shown that the cytokine has a great impact on the dynamics of HIV infection of CD4+ T cells.

REFERENCES

[1] Organization, W. H. *World health statistics 2015* (World Health Organization, 2015).

[2] Bonhoeffer, S., Coffin, J. M. & Nowak, M. A. Human immunodeficiency virus drug therapy and virus load. *Journal of Virology* **71**, 3275–3278 (1997).

[3] Bonhoeffer, S., May, R. M., Shaw, G. M. & Nowak, M. A. Virus dynamics and drug therapy. *Proceedings of the National Academy of Sciences* **94**, 6971–6976 (1997).

[4] Butler, S., Kirschner, D. & Lenhart, S. Optimal control of chemotherapy affecting the infectivity of hiv. *Advances in Mathematical Population Dynamics: Molecules, Cells, Man. World Scientific Publishing* 104–120 (1997).

[5] Culshaw, R. V. & Ruan, S. A delay-differential equation model of hiv infection of cd4+ t-cells. *Mathematical biosciences* **165**, 27–39 (2000).

[6] Magnus, C. & Regoes, R. R. Restricted occupancy models for neutralization of hiv virions and populations. *Journal of Theoretical Biology* **283**, 192–202 (2011).

[7] Nowak, M. A., Bonhoeffer, S., Shaw, G. M. & May, R. M. Anti-viral drug treatment: dynamics of resistance in free virus and infected cell populations. *Journal of theoretical biology* **184**, 203–217 (1997).

[8] Perelson, A. S. & Nelson, P. W. Mathematical analysis of hiv-1 dynamics in vivo. *SIAM review* **41**, 3–44 (1999).

[9] Perelson, A. S., Neumann, A. U., Markowitz, M., Leonard, J. M. & Ho, D. D. Hiv-1 dynamics in vivo: virion clearance rate, infected cell life-span, and viral generation time. *Science* **271**, 1582–1586 (1996).

[10] Wodarz, D. & Hamer, D. H. Infection dynamics in hiv-specific cd4 t cells: Does a cd4 t cell boost benefit the host or the virus? *Mathematical Biosciences* **209**, 14–29 (2007).

[11] Attarian, A. & Tran, H. An optimal control approach to structured treatment interruptions for hiv patients: a personalized medicine perspective. Tech. Rep., North Carolina State University. Center for Research in Scientific Computation (2017).

[12] Ngina, P. M., Mbogo, R. W. & Luboobi, L. S. Mathematical modelling of in-vivo dynamics of hiv subject to the influence of the cd8+ t-cells. *Applied Mathematics* **8**, 1153–1179 (2017).

[13] Paterson, D. L. *et al.* Adherence to protease inhibitor therapy and outcomes in patients with hiv infection. *Annals of internal medicine* **133**, 21–30 (2000).

[14] Waema, R. & Olowofeso, O. E. Mathematical modeling for human immunodeficiency virus (hiv) transmission using generating function approach. *Kragujevac Journal of Science* 115–130 (2005).

[15] Zhou, X., Song, X. & Shi, X. A differential equation model of hiv infection of cd4+ t-cells with cure rate. *Journal of Mathematical Analysis and Applications* **342**, 1342–1355 (2008).

[16] Ngina, P., Mbogo, R. W. & Luboobi, L. S. The in vivo dynamics of hiv infection with the influence of cytotoxic t lymphocyte cells. *International scholarly research notices* **2017** (2017).

[17] Assone, T., Paiva, A., Fonseca, L. A. M. & Casseb, J. Genetic markers of the host in persons living with htlv-1, hiv and hcv infections. *Viruses* **8**, 38 (2016).

[18] Arruda, E. F. *et al.* An optimal control approach to hiv immunology. *Applied Mathematics* **6**, 1115 (2015).

[19] Hattaf, K. & Yousfi, N. Dynamics of hiv infection model with therapy and cure rate. *International Journal of Tomography & Statistics* **16**, 74–80 (2011).

[20] Ogunlaran, O. M. & Oukouomi Noutchie, S. C. Mathematical model for an effective management of hiv infection. *BioMed Research International* **2016** (2016).

[21] Wang, S., Hottz, P., Schechter, M. & Rong, L. Modeling the slow cd4+ t cell decline in hiv-infected individuals. *PLoS computational biology* **11**, e1004665 (2015).

[22] Doitsh, G. *et al.* Cell death by pyroptosis drives cd4 t-cell depletion in hiv-1 infection. *Nature* **505**, 509–514 (2014).

[23] Doitsh, G. *et al.* Abortive hiv infection mediates cd4 t cell depletion and inflammation in human lymphoid tissue. *Cell* **143**, 789–801 (2010).

[24] Van den Driessche, P. & Watmough, J. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Mathematical biosciences* **180**, 29–48 (2002).

[25] Diekmann, O., Heesterbeek, J. A. P. & Metz, J. A. On the definition and the computation of the basic reproduction ratio r 0 in models for infectious diseases in heterogeneous populations. *Journal of mathematical biology* **28**, 365–382 (1990).

[26] Paul, S. C., Haque, M. A., Islam, M. A. & Chakraborty, A. K. Mathematical modeling and analyzing of transmission dynamics of influenza with carrier. *International Journal of Applied Mathematics & Statistics* **57**, 26–40 (2018).

[27] Shahrear, P., Chakraborty, A. K., Islam, M. A. & Habiba, U. Analysis of computer virus propagation based on compartmental model. *Applied and Computational Mathematics* **7**, 12–21 (2018).

[28] Dutta, A. & Gupta, P. K. A mathematical model for transmission dynamics of hiv/aids with effect of weak cd4+ t cells. *Chinese journal of physics* **56**, 1045–1056 (2018).

[29] La Salle, J. P. *The stability of dynamical systems* (SIAM, 1976).

[30] Li, M. Y. & Muldowney, J. S. A geometric approach to global-stability problems. *SIAM Journal on Mathematical Analysis* **27**, 1070–1083 (1996).

[31] Zhang, J., Jia, J. & Song, X. Analysis of an seir epidemic model with saturated incidence and saturated treatment function. *The Scientific World Journal* **2014** (2014).

[32] Ozair, M., Lashari, A. A., Jung, I. H. & Okosun, K. O. Stability analysis and optimal control of a vector-borne disease with nonlinear incidence. *Discrete Dynamics in Nature and Society* **2012** (2012).

[33] Guo, S.-M., Li, X.-Z. & Ghosh, M. Analysis of a dengue disease model with nonlinear incidence. *Discrete Dynamics in Nature and Society* **2013** (2013).

[34] Shi, X., Li, G., Zhou, X. & Song, X. Analysis of a differential equation model of hiv infection of cd4+ t-cells with saturated reverse function. *Turkish Journal of Mathematics* **35**, 649–666 (2011).