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## MATHEMATICAL ANALYSIS OF HIV INFECTION OF $CD4^+$ T-CELLS WITH DISCRETE DELAYS

A. ANU PRIYADHARSHINI, K. KRISHNAN\*

PG & Research Department of Mathematics, Cardamom Planters' Association College, Bodinayakanur - 625  
513, India

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**Abstract.** In this study, we introduce a discrete time to the model to describe the time delays between infection of a  $CD4^+$  T-cells, and the emission of viral particles on a cellular level. We begin by determining the existence and stability of the equilibrium. Further We investigate the global stability of the infection-free equilibrium and give sufficient condition for the local stability of the infected steady state is asymptotically stable for all delays. Finally, the numerical simulations are presented to illustrate the analytical results.

**Keywords:** stability analysis; HIV-1; discrete delay.

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### 1. INTRODUCTION

In recent years, there has been a lot of interest in mathematical modelling of HIV/AIDS infection, in order to predict the evolution of this modern plague. Since the discovery of the human immunodeficiency virus type 1 (HIV-1) in the early 1980s, the disease has spread in successive waves to most regions around the globe. It is reported that HIV has infected more than 60 million people, and over a third of them subsequently died [1]. Considerable scientific effort has been devoted to the understanding of viral pathogenesis, host/virus interactions, immune

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\*Corresponding author

E-mail address: [drkkmaths@gmail.com](mailto:drkkmaths@gmail.com)

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response to infection, and antiretroviral therapy [2]. HIV primarily attacks a host's  $CD4^+T-$  cells (the main driver of the immune response). The amount of viruses in the blood is a good predictor of the stage of the disease. The amount of  $CD4^+T-$  cells in a typical healthy person's peripheral blood ranges between  $800/mm^3$  and  $1200/mm^3$ . When this value falls below 200, an HIV-positive patient is diagnosed with Acquired Immune Deficiency Syndrome (AIDS). HIV differs from most viruses in that it is a retrovirus: Viruses do not have the ability to reproduce independently, and they must rely on a host to aid reproduction. Most viruses carry copies of their DNA and insert this into the host cell's DNA. Thus, when the host cell is stimulated for reproduction, it reproduces copies of the virus. T cells divide and increase in population once stimulated by antigen or mitogen. Chronic HIV infection causes gradual depletion of the  $CD4^+T-$  cell pool, and thus progressively compromises the host's immune response, leading to humoral and cellular immune function loss (the marker of the onset of AIDS), making the host susceptible to opportunistic infections. In 1993, Perelson, Krischner and De Boer [3] proposed an ODE model of cell-free viral spread of human immunodeficiency virus (HIV) in a well-mixed compartment such as the bloodstream. Their model consists of four components: uninfected healthy  $CD4^+T-$  cells, latently infected  $CD4^+T-$  cells, actively infected  $CD4^+T-$  cells and free virus [4]. This model has been important in the field of mathematical modelling of HIV infection and many other models have been proposed which take the model of Perelson, Krischner and De Boer [3].

In [5] Liming Cai and Xuezhi Li have been simplify their model into one consisting of only three components: the healthy  $CD4^+T-$  cells, infected  $CD4^+T-$  cells and free virus and introduce a discrete time delay to the model to describe the times between infection of a  $CD4^+T-$  cells and the emission of viral particles on a cellular level. Many Mathematical model, used the proliferation process of T-cells have been received in the literature. In addition researchers extend the basic models by adding  $CD4^+$  T- cells simples logistic proliferation term  $rT \left(1 - \frac{T(t)}{T_{max}}\right) CD4^+T$ -cells, full logisitic proliferation term  $rT \left(1 - \frac{T(t)+I(t)}{T_{max}}\right)$ , where r is the maximum proliferation rate of  $CD4^+$  T-cells, T, I respectively represent the concentration of susceptible  $CD4^+T$ -cells, infected  $CD4^+T$ -cells, and  $T_{max}$  is the maximum level of  $CD4^+T$ -cells concentration of the body, and injected T-cells at time t. Inspired by their work, in many authors

have studied stability properties for delay differential equations and applied the results obtained to analyze the stability of the equilibria for the model of HIV-1 infection. To our knowledge, no works are contributed to the analysis for HIV infection of  $CD4^+T$  – cells with two independent delays or two proportional delay terms. Motivated by this situation, we introduce a HIV infection model with independent time delays proposed by Culshaw and Ruan [6]. Here  $\tau_1$  and  $\tau_2$  are two time delays were included in our model. The first delay " $\tau_1$ " is the time between viral entry latent infection. The second delay " $\tau_2$ " is the time between cell infection and viral production. So, we assume that  $CD4^+$  T cells (healthy and infected) are governed by a full Logistic growth term. Therefore, we shall establish a mathematical model as follows

$$(1) \quad \left. \begin{aligned} T'(t) &= s - \mu_1 T(t) + rT(t) \left( 1 - \frac{T(t) + I(t)}{T_{max}} \right) - kT(t)V(t) \\ I'(t) &= kT(t - \tau_1)V(t - \tau_1) + rI(t) \left( 1 - \frac{T(t) + I(t)}{T_{max}} \right) - \mu_2 I(t) \\ V'(t) &= N\mu_2 I(t - \tau_2) - \mu_3 V(t) \end{aligned} \right\}$$

where  $\tau_1$  and  $\tau_2$  are positive.

where  $T(t)$  represents the concentration of healthy  $CD4^+T$  – cells at time  $t$ ,  $I(t)$  represents the concentration of infected  $CD4^+T$  – cells and  $V(t)$  represents the concentration of free HIV at time  $t$ . To explain the parameter, we note that  $s$  is the source of  $CD4^+T$  – cells from precursors,  $r$  is their growth rate of T-cells (thus,  $r > \mu_1$  in general) and  $T_{max}$  is the maximum level of  $CD4^+T$ -cells concentration in the body. The parameter  $k$  represents the rate of infection of T-cells with free virus and so is given as a loss term for both healthy cells and virus, since they are both lost by binding to one another, and is the source term for infected cells.  $\mu_i (i = 1, 2, 3)$  are the nature death rates of the uninfected T-cells, infected T-cells and the virus particles, respectively. It is reasonable to assume that  $\mu_1 \leq \mu_2$ , i.e., the infected T cells have a relatively shorter life than the uninfected T cells due to an HIV viral burden.  $N$  is number of virus produced by infected  $CD4^+$  T-cells during its lifetime. It is clear that according to the viral life cycle. We assume that all parameters are non-negative constant.

The initial conditions of system (1) are

$$(2) \quad T(\theta) = \phi_1(\theta) > 0, \quad I(\theta) = \phi_2(\theta) > 0, \quad V(\theta) = \phi_3(\theta) > 0, \quad (-\tau \leq \theta \leq 0)$$

where functions  $\phi_i \in C([-\tau_1, \tau_2, 0])$ ,  $i = 1, 2, 3$ , and  $C([-\tau_1, \tau_2, 0])$  is the Banach space of continuous function mapping the interval  $[-\tau_1, \tau_2, 0]$  into  $\mathfrak{R}_+^3$ , where  $\mathfrak{R}_+^3 = \{(T, I, V) : T, I, V > 0\}$ . By the fundamental theory of functional differential equations [7], the system (1) has a unique solution  $(T(t), I(t), V(t))$  satisfying the initial condition (2).

The organization of this paper is as follows. In the next section, we verify the boundedness of the solutions and existence of feasible equilibria of the system (1). In Section 3, the local asymptotic stability of feasible equilibria is established. In Section 4, we investigate the global asymptotic stability of feasible equilibria. We also performed numerical simulation to illustrate the main analytical result in the section 5. The paper ends with a conclusion.

## 2. BOUNDEDNESS OF SOLUTIONS AND FEASIBLE EQUILIBRIA

In the following, we first show all solution of the system (1) with (2) are positive and ultimately bounded.

**Proposition 3.1:** *All the solution of system (1) with initial condition (2) are positive and ultimately bounded for all large  $t$ . [?]*

**Proof:**

First, let us prove the positivity by contradiction.

Suppose  $T(t)$  is not always positive. Then, let  $t_0 > 0$  be the first time such that  $T(t_0) = 0$ . (i.e)  $t_0 = \inf\{t/t > 0, T(t) = 0\}$ . From the first equation of (1) we have  $\dot{T}(t_0) = 0$ . By our assumption this means  $T(t) > 0$ , for  $t \in (t_0 - \varepsilon, t_0)$ , where  $\varepsilon$  is an arbitrary small positive constant. This is a contradiction. It follows that  $T(t)$  is always positive.

We now show that  $I(t) > 0$  for all  $t > 0$ . Otherwise if it is not valid, noting that  $T(t) > 0$  and  $I(t) > 0$  ( $-\tau_1 \leq t \leq 0$ ), then there exists a  $t_1$  such that  $I(t_1) = 0$ . Assume that  $t_1$  is the first value which  $T(t_0) = 0$ , that is  $t_1 = \inf\{t > 0 : I(t) = 0\}$  then  $t_1 > 0$ , and from system (1) and (2), we get

$$\dot{I}(t_1) = \begin{cases} \phi_1(t_1 - \tau_1)\phi_3(t_1 - \tau_1) > 0 & \text{if } 0 \leq t_1 \leq \tau_1, \\ T(t_1 - \tau_1)V(t_1 - \tau_1) > 0 & \text{if } t_1 > \tau_1 \end{cases}$$

Thus  $\dot{I}(t_1) > 0$ . Hence, there exists sufficiently small  $\varepsilon_1 > 0$  to make  $I(t) < 0$  for  $t \in (t_1 - \varepsilon, t_1)$ . By the definition of  $t_1$ , this is a contradiction. Therefore,  $I(t) > 0$  for all  $t > 0$ . Similarly, we

easily show that  $V(t)$  is always positive. Thus, we can conclude that all solutions of system (1) with initial conditions (2) remain positive for all  $t > 0$ .

Next, we shall discuss the boundedness of solutions of the system (1). In the absence of HIV infection, the dynamics of healthy  $CD4^+$ T-cells are governed by

$$\dot{T}(t) = s - \mu_1 T(t) + rT(t) \left( 1 - \frac{T(t) + I(t)}{T_{max}} \right)$$

It can be shown that, the  $CD4^+$ T-cells concentration stabilizes at a level  $T_0$ , which is given by

$$T_0 = \frac{T_{max}}{2r} \left( r - \mu_1 + \sqrt{(r - \mu_1)^2 + \frac{4sr}{T_{max}}} \right)$$

and  $T_0$  satisfy the following equation,

$$(3) \quad s = \mu_1 T_0 - rT_0 + \frac{rT_0^2}{T_{max}}.$$

By the first equation of system (1), we have

$$\dot{T}(t) \leq s - \mu_1 T + rT \left( 1 - \frac{T}{T_{max}} \right)$$

Thus, if  $T(0) < T_0$ , we obtain

$$(4) \quad \limsup_{t \rightarrow +\infty} T(t) \leq T_0, \forall t \geq 0.$$

Let  $W(t) = k[T(t - \tau_1) + I]$ , then

$$(5) \quad \begin{aligned} \dot{W}(t) &= sk - \mu_1 kT(t - \tau_1) + rkT(t - \tau_1) \left( 1 - \frac{T(t - \tau_1) + I(t - \tau_2)}{T_{max}} \right) \\ &+ rkT \left( 1 - \frac{T + I}{T_{max}} \right) - \mu_1 kT \\ &\leq k \left( s + \frac{rT_{max}}{2} \right) - \mu_1 W(t) \end{aligned}$$

Let  $M_1 = k \left( s + \frac{rT_{max}}{2} \right)$  and solving equation (5), we obtain

$$(6) \quad W(t) \leq \frac{M_1}{\mu_1} T \left( W(0) - \frac{M_1}{\mu_1} \right) e^{-\mu_1 t}$$

According to inequality (6), we get  $W(t) < \frac{2M_1}{\mu_1}$  for sufficiently large  $t$ . Recall that  $T(t) > 0$  and  $I(t) > 0$  combining with inequality (4),  $T(t)$  and  $I(t)$  have ultimately above bound  $M_2 > 0$ .

Similiary, the third equation of system (1), we have

$$(7) \quad \dot{V}(t) = N\mu_2 I(t - \tau_2) - \mu - 3V \leq (N\mu_2 M_2) - \mu_3 V$$

solving inequality (7), we have

$$(8) \quad V(t) \leq \frac{N\mu_2 M_2}{\mu_3} + \left[ V(0) - \frac{N\mu_2 M_2}{\mu_3} \right] e^{-\mu_3 t}$$

It follows from inequality (8), that  $V(t)$  has an ultimately above bound  $M_3 > 0$ , for sufficiently large  $t$ . Hence we proved that all solutions of system (1) are ultimately bounded. Then the proof of Theorem 3.1 is completed.

Let  $\Omega = \{(T, I, V) \in R_+^3 : 0 < T \leq T_0, 0 < I \leq M_2, 0 < V \leq M_3\}$ , then  $\Omega$  is the positive invariant set of system (1).

Next, we shall investigate the existence of equilibrium of system (1). The equilibrium of system (1) satisfy the following equation

$$(9) \quad \left. \begin{aligned} s - \mu_1 T(t) + rT(t) \left( 1 - \frac{T(t) + I(t)}{T_{max}} \right) - kT(t)V(t) &= 0 \\ kT(t)V(t) + rI(t) \left( 1 - \frac{T(t) + I(t)}{T_{max}} \right) - \mu_2 I(t) &= 0 \\ N\mu_2 I - \mu_3 V(t) &= 0 \end{aligned} \right\}$$

Clearly, the system (1) has always the infection free equilibrium  $E_0(T_0, 0, 0)$ . From the third equation of (9), we have

$$(10) \quad I = \frac{\mu_3 V}{N\mu_2}$$

Substituting this expression into the second equation of (9) and solving for  $T$  results in,

$$(11) \quad T = \left[ \frac{\mu_3 T_m ((\mu_2 - r))}{N\mu_2 k T_m - r\mu_3} + \frac{r^2 \mu_3}{N\mu_2 (N\mu_2 k T_m - r\mu_3)} \right] V$$

Rewriting the first equation of (9) as

$$(12) \quad s = T \left[ \mu_1 - r \left( 1 - \frac{T + I}{T_{max}} \right) + kV \right]$$

substituting (10) and (11) into (12), we obtain

$$s = (A + BV)(C + DV)$$

where

$$\begin{aligned}
 A &= \frac{\mu_3 T_m (\mu_2 - r)}{N \mu_2 k T_m - r \mu_3} \\
 B &= \frac{r \mu_3^2}{N \mu_2 (N \mu_2 k T_m - r \mu_3)} \\
 C &= (\mu_1 - r) + \frac{\mu_3 r (\mu_2 - r)}{N \mu_2 k T_m - r \mu_3} \\
 D &= \frac{N \mu_3 k^2 T_m + r k (N \mu_2 I - \mu_3)}{N \mu_2 k T_m - r \mu_3}
 \end{aligned}$$

The critical number  $N_{crit}$  is defined by,

$$N_{crit} = \frac{\mu_3}{k \mu_2 T_0} \left( \frac{s}{T_0} + \mu_2 - \mu_1 \right) > 0$$

It is easy to verify that the equation  $s = (A + BV)(C + DV)$  has a unique positive root if and only if  $N > N_{crit}$ . Thus, we also obtain

$$T^* = A + BV^* > 0 \quad \& \quad I^* = \frac{\mu_3}{N \mu_2} V^*.$$

### 3. LOCAL STABILITY ANALYSIS

In this section, we study the local stability of the infection - free equilibrium and the infected equilibrium points.

**Theorem 3.2:** *If  $N \leq N_{crit}$ , then system (1) has only the uninfected equilibrium  $E_0(T_0, 0, 0)$ ; if  $N > N_{crit}$ , the system (1) has the two equilibria; the infected free equilibria  $E_0$  and the chronic infection equilibrium  $E^*(T^*, I^*, V^*)$ .*

**Proof:**

Let  $E^*(T^*, I^*, V^*)$  be an arbitrary equilibrium. Thus, linearizing the system (1) at the equilibrium  $E^*(T^*, I^*, V^*)$ , we obtain the characteristic equation about  $E^*$  as follows

$$\begin{vmatrix}
 \lambda + M_1 & \frac{rT^*}{T_{max}} & kT^* \\
 rT^* - kV^* e^{-\lambda \tau_1} + \frac{rT^*}{T_m} & \lambda + M_2 & -kT^* e^{-\lambda \tau_1} \\
 0 & -N \mu_2 e^{-\lambda \tau_2} & \lambda + \mu_3
 \end{vmatrix} = 0$$

where,

$$M_1 = \left( \mu_1 + \frac{rI^* + 2rT^*}{T_{max}} + kV^* - r \right), \quad M_2 = \left( \mu_2 + \frac{2rI^* + rT^*}{T_{max}} - r \right)$$

Thus, for the uninfected equilibrium  $E_0(T_0, 0, 0)$ , the characteristic equation has been reduces to

$$(13) \quad \left( \lambda + \frac{s}{T_0} + \frac{rT_0}{T_{max}} \right) \left[ \lambda^2 + A_0\lambda + B_0 - C_0e^{-\lambda(\tau_1+\tau_2)} \right] = 0$$

where

$$A_0 = \left( \mu_2 - r + \frac{rT_0}{T_m} + \mu_3 \right) = \frac{s}{T_0} - \mu_1 + \mu_3 + \mu_2 > 0$$

$$B_0 = \left( \mu_2 - r + \frac{rT_0}{T_m} \right) \mu_3 = \mu_3 \left( \frac{s}{T_0} + \mu_2 - \mu_1 \right) > 0$$

$$C_0 = N\mu_3kT_0 > 0$$

Clearly, the equation (13) has a characteristic root  $\lambda_1 = \left( r - \mu_1 + \frac{2rT_0}{T_{max}} \right) = \left( \frac{-s}{T_0} - \frac{rT_0}{T_{max}} < 0 \right)$ , and the rest characteristic roots of equation (13) satisfy the following equation,

$$(14) \quad \left[ \lambda^2 + A_0\lambda + B_0 - C_0e^{-\lambda(\tau_1+\tau_2)} \right] = 0$$

when  $\tau_1 = \tau_2 = 0$ , if  $N < N_{crit}$ , then  $B_0 - C_0e^{-\lambda(\tau_1+\tau_2)} = B_0 - C_0 > 0$ . By Routh-Hurwitz Criterion,  $E_0$  is locally asymptotically stable. If  $N = N_{crit}$ , one eigenvalue is zero, and it is simple., So  $E_0$  is stable. If  $N > N_{crit}$ , then  $B_0 - C_0e^{-\lambda(\tau_1+\tau_2)} < 0$ . Thus  $E_0$  is a saddle with point  $\dim W^s(E_0) = 2$  and  $\dim W^u(E_0) = 1$ .

For the time delays  $\tau_1, \tau_2 > 0$ , we can show that equation (13) has no root with positive real part as  $N < N_{crit}$ . In fact, assume  $\lambda = (u_1 \pm iv_1)$ , where  $V_1 > 0$  and  $i = \sqrt{-1}$ . Substituting  $\lambda = (u_1 \pm v_1i)$  into equation (13) and seperating the real and imaginary parts, we obtain

$$(15) \quad \left. \begin{aligned} u_1^2 - v_1^2 + A_0u_1 + B_0 &= \left( C_0e^{-u_1(\tau_1+\tau_2)} \cos v_1^{(\tau_1+\tau_2)} \right) \\ 2u_1v_1 + A_0V_1 &= \left( -C_0e^{-u_1(\tau_1+\tau_2)} \sin v_1^{(\tau_1+\tau_2)} \right) \end{aligned} \right\}$$

Squaring and adding both equations (15), we have

(16)

$$v_1^2 (v_1^2 + 2u_1^2 + 2A_0u_1 + A_0^2 - 2B_0) + u_1^4 + A_0^2u_1^2 + 2A_0B_0u_1 + 2A_0u_1^3 + 2B_0u_1^2 = C_0^2e^{-2u_1\tau} - B_0^2.$$

Since  $A_0^2 - 2B_0 = \left( \frac{s}{T_0} + \beta - \alpha \right)^2 + d^2 > 0$ . The left side of equation (16) is larger than zero, while the right side of equation (16) is less than zero (since  $u_1 \geq 0$ , and if  $N < N_{crit}$ , then  $B_0 > C_0$ ). This results in contradiction. Therefore,  $u_1 < 0$ , and  $E_0$  is locally asymptotically stable. When  $N > N_{crit}$ , let  $F_1(\lambda) = \left[ \lambda^2 + A_0\lambda + B_0 - C_0e^{-\lambda(\tau_1+\tau_2)} \right]$ , and note that  $F_1(0) =$



$B_0 - C_0 < 0$  and  $\lim_{\lambda \rightarrow +\infty} = +\infty$ . It follows from the continuity of the function  $F_1(\lambda)$  on  $[0, +\infty)$  that the equation (14) has at least one positive real root. Hence, the characteristic equation (13) has at least one positive real root. Hence,  $E_0$  is unstable. This complete the proof.  $\square$

Thus, We obtain the following theorem.

**Theorem 3.3:** *The infection - free equilibrium  $E_0(T_0, 0, 0)$  of the system (1) is locally asymptotically stable when  $N < N_{crit}$  and unstable when  $N > N_{crit}$ .*

**proof:**

For infected equilibrium  $E^* = (T^*, I^*, V^*)$ , then the characteristic equation (13) reduces to  
(17)

$$\Delta(\lambda, \tau_1, \tau_2) = \lambda^3 + a_1\lambda^2 + a_2\lambda + a_3e^{-\lambda\tau_1} + a_4\lambda e^{-\lambda\tau_1} + a_5e^{-\lambda(\tau_1+\tau_2)} + a_6\lambda e^{-\lambda(\tau_1+\tau_2)} + a_7e^{-\lambda\tau_2} + a_8$$

where

$$\begin{aligned} a_1 &= \left( \frac{s}{T^*} + \frac{r(T^* + I^*)}{T_{max}} + \frac{kT^*V^*}{I^*} + \mu_3 \right) > 0 \\ a_2 &= \frac{s}{T^*} \left( \frac{kT^*V^*}{I^*} + \frac{rI^*}{T_{max}} + \mu_3 \right) + (T^* + I^*) \frac{r\mu_3}{T_{max}} + \frac{kT^*V^*\mu_3}{I^*} + \frac{rk(T^*)^2V^*}{I^*T_{max}} \\ a_3 &= \frac{rkT^*V^*\mu_3}{T_{max}} \\ a_4 &= \frac{rkT^*V^*}{T_{max}} \\ a_5 &= \left[ \frac{k^2T^*(V^*)^2\mu_3}{I^*} - \left( \frac{s}{T^*} + \frac{rT^*}{T_{max}} \right) \frac{kT^*V^*\mu_3}{I^*} \right] \\ a_6 &= \left[ \frac{-kT^*V^*\mu_3}{I^*} \right] \\ a_7 &= \left[ \frac{-rkT^*V^*\mu_3}{I^*} \right] \\ a_8 &= \left[ \frac{sr\mu_3I^*}{T^*T_{max}} \right] + \left( \frac{s}{T^*} + \frac{rT^*}{T_{max}} \right) \frac{kT^*V^*\mu_3}{I^*} \end{aligned}$$

when  $\tau_1 = \tau_2 = 0$  in equation (17), we can write as

$$(18) \quad \lambda^3 + a_1\lambda^2 + \bar{a}_2\lambda + \bar{a}_3 = 0$$

where

$$\begin{aligned}\bar{a}_2 &= \frac{s}{T^*} \left( \frac{KT^*V^*}{I^*} + \frac{rI^*}{T_m} + \mu_3 \right) + (T^* + I^*) \left[ \frac{r\mu_3}{T_m} + \frac{rKT^*V^*}{I^*T_m} \right] \\ \bar{a}_3 &= \left[ \frac{K^2T^*(V^*)^2\mu_3}{I^*} + \frac{sr\mu_3I^*}{I^*T_m} \right] > 0\end{aligned}$$

Hence  $a_1 > 0$ ,  $\bar{a}_2 > 0$ ,  $\bar{a}_3 > 0$ , by directly calculating we obtain

$$\begin{aligned}b &= a_1\bar{a}_2 - \bar{a}_3 \\ &= \left( \frac{r\mu_3}{T_m} + \frac{rkT^*V^*}{I^*T_m} \right) a_1(T^* + I^*) + \frac{s}{T^*} \left( \frac{kT^*V^*}{I^*} + \frac{rI^*}{T_m} + \mu_3 \right) \\ &\quad - \frac{k^2T^*(V^*)^2\mu_3}{I^*} + \frac{rs}{T_mT^*} \left[ kT^*V^* + \frac{rI^*}{T_m} \right]\end{aligned}$$

If  $\tau_1 = \tau_2 = 0$ , by Routh-Hurwitz criterion, we have following theorem.

**Theorem 3.4:** *If  $b > 0$ , then the infected equilibrium  $E^*(T^*, I^*, V^*)$  is locally asymptotically stable.*

To show that the infected equilibrium  $E^*(T^*, I^*, V^*)$  of system (1) is locally asymptotically stable for all  $\tau_1$  and  $\tau_2$ . We firstly introduce a lemma (3.1) coming from literature [63].

**Lemma 3.1:** *A set of necessary and sufficient conditions for the equilibrium  $\bar{E}$  to be asymptotically stable for all  $(\tau_1, \tau_2) \geq 0$  is the following.*

- (i) *The real parts of all the roots of  $\Delta(\lambda, 0) = 0$  are negative.*
- (ii) *For all real  $\omega$  and  $(\tau_1, \tau_2) \geq 0$ ,  $\Delta(i\omega, \tau_1, \tau_2) \neq 0$ , where  $i = \sqrt{-1}$ .*

**Proof:**

Here  $\Delta(\lambda, 0) = 0$  has roots whose real parts are negative. Therefore, the condition (i) is easily satisfied. we now verify the condition (ii) of lemma(3.1). Firstly, when  $\omega_0 = 0$ , we have  $\Delta(0, \tau_1, \tau_2) = a_3 + a_5 + a_7 \neq 0$ . Secondly, when  $\omega_0 \neq 0$ , we have

(19)

$$\Delta(\lambda, \tau) = \lambda^3 + a_1\lambda^2 + a_2\lambda + a_3e^{-\lambda\tau_1} + a_4\lambda e^{-\lambda\tau_1} + a_5e^{-\lambda(\tau_1+\tau_2)} + a_6\lambda e^{-\lambda(\tau_1+\tau_2)} + a_7e^{-\lambda\tau_2} + a_8$$

**Case 3.1 :**

$$\boxed{\tau_1 = \tau_2 = 0}$$

Substitute the delay values in (19), the charactersitic equation becomes,

$$\lambda^3 + a_1\lambda^2 + (a_2 + a_4 - a_6)\lambda + (a_3 + a_5 - a_7 + a_8) = 0$$

By Routh-Hurwitz Criterion, that all the eigen values of the characteristic equation has negative real part  $\Leftrightarrow a_1 > 0, (a_2 + a_4 - a_6) > 0, (a_3 + a_5 - a_7 + a_8) > 0$ .

Therefore,  $E^*$  is locally asymptotically stable.

### Case 3.2:

$$\tau_1 \neq 0, \tau_2 = 0 (\tau_1 > 0)$$

The charactersitic equation becomes,

$$(20) \quad \lambda^3 + a_1 \lambda^2 + a_2 \lambda + (a_3 + a_5) e^{-\lambda \tau_2} + (a_4 - a_6) \lambda e^{-\lambda \tau_2} + (a_8 - a_7) = 0$$

Let  $\lambda = i\omega_1$  ( $\omega_1 > 0$ ). From the equation (20), it becomes

$$i\omega_1^3 + a_1 \omega_1^2 - ia_2 \omega_1 - (a_3 - a_5) e^{-i\omega_1 \tau_1} - i\omega_1 \tau_1 (a_4 + a_6) e^{-i\omega_1 \tau_1} - a_8 + a_7 = 0$$

Separate the real and imaginary parts,

$$a_1 \omega_1^2 + a_7 - a_8 = (a_3 - a_5) \cos \omega_1 \tau_1 + (a_4 + a_6) \omega_1 \sin \omega_1 \tau_1$$

$$\omega_1^3 - a_2 \omega_1 = (a_3 - a_5) \sin \omega_1 \tau_1 - (a_4 + a_6) \omega_1 \cos \omega_1 \tau_1$$

Squaring and adding both equation, we obtain

$$(21) \quad \omega_1^6 + (a_1^2 - 2a_2) \omega_1^4 + (a_2^2 - 2a_1 a_7 - a_6^2 - a_6^2 - 2a_4 a_6 - 2a_1 a_8 - a_4^2) \omega_1^2 + (a_7^2 - 2a_3 a_5 - a_3^2 + a_8^2) = 0$$

Let  $\rho = \omega^2$ ;  $b_1 = a_1^2 - 2a_2$ ;  $b_2 = a_2^2 - 2a_1 a_7 - a_6^2 - a_4^2 - 2a_4 a_6 - 2a_1 a_8$ ;  $b_3 = a_7^2 + 2a_3 a_5 - a_3^2 + a_8^2 - 2a_4 a_6 - a_4^2$

Then the equation (21) becomes,

$$(22) \quad g(\rho) = \rho^3 + b_1 \rho^2 + b_2 \rho + b_3 = 0.$$

We claim Equation (22) has no any positive roots for  $b_2, b_3 > 0$ . In fact, we notice that  $\frac{dg(\rho)}{d\rho} = 3\rho^2 + 2b_1 \rho + b_2$ .

Let,

$$(23) \quad \frac{dg(\rho)}{d\rho} = 0 \Rightarrow 3\rho^2 + 2b_1 \rho + b_2 = 0.$$

The roots of Equation (23) are given by

$$\rho_{1,2} = \frac{-b_1 \pm \sqrt{b_1^2 - 3b_2}}{3}.$$

If  $b_2 > 0$ , then  $(b_1^2 - 3b_2) < b_1^2$  (i.e)  $\sqrt{(b_1^2 - 3b_2)} < b_1$ . Hence  $\rho_1, \rho_2$  are both negative, the equation (3.14) has no positive root. Therefore, if  $G(0) = b_3 > 0$ , then equation(3.14) has no positive root. For any time delay  $\tau > 0$ , the infected equilibrium,  $E^* = (T^*, I^*, V^*)$  is locally asymptotically stable for  $\tau_1 > 0, \tau_2 = 0$ .

### Case 3.3:

$$\tau_1 = 0, \tau_2 \neq 0 (\tau_2 > 0)$$

The charactersitic equation becomes,

$$(24) \quad \lambda^3 + a_1 \lambda^2 + (a_2 + a_4) \lambda + (a_5 + a_7) e^{-\lambda \tau_2} - a_6 \lambda e^{-\lambda \tau_2} + (a_3 + a_2) = 0$$

Let  $\lambda = i\omega_2 (\omega_2 > 0)$

$$i\omega_2^3 + a_1 \omega_2^2 + (a_2 + a_4) i\omega_2 - (a_5 + a_7) e^{-i\omega_2 \tau_2} - i\omega_2 a_6 e^{-i\omega_2 \tau_2} - a_3 + a_8 = 0$$

Separate the real and imaginary parts, we have

$$a_1 \omega_2^2 - (a_3 + a_8) = (a_5 + a_7) \cos \omega_2 \tau_2 + a_6 \omega_2 \sin \omega_2 \tau_2$$

$$\omega_2^3 - (a_2 + a_4) \omega_2 = - (a_5 + a_7) \sin \omega_2 \tau_2 + a_6 \omega_1 \cos \omega_2 \tau_2$$

Squaring and adding both equation, we obtain

(25)

$$\omega_2^6 + (a_1^2 - 2a_2 - 2a_4) \omega_2^2 + [a_2^2 + 2a_2 a_4 + a_4^2 - 2a_1 a_3 - 2a_1 a_8] \omega_2^2 + [a_3^2 - 2a_3 a_8 - a_8^2 + a_7^2 - a_5^2] = 0$$

Let  $\rho = \omega_2^2$ ;  $b_1 = a_1^2 - 2a_2 - 2a_4$ ;  $b_2 = a_2^2 + 2a_2 a_4 + a_4^2 - 2a_1 a_3 - 2a_1 a_8$ ;  $b_3 = a_3^2 + 2a_3 a_8 + a_7^2 + a_8^2 - a_5^2$

Then the equation (25) becomes,

$$(26) \quad g(\rho) = \rho^3 + b_1 \rho^2 + b_2 \rho + b_3 = 0.$$

by case(ii), we get  $\Delta(i\omega_2, \tau_2) \neq 0$ , for any  $\tau_2 > 0, \tau_1 = 0$ . Therefore  $E^* = (T^*, I^*, V^*)$  is locally asymptotically stable for  $\tau_2 > 0, \tau_1 = 0$ .

### Case 3.4:

$$\tau_1 > 0 \text{ \& } \tau_2 > 0$$

The charactersitic equation becomes,

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3e^{-\lambda\tau_1} + a_4\lambda e^{-\lambda\tau_1} + a_5e^{-\lambda(\tau_1+\tau_2)} + a_6\lambda e^{-\lambda(\tau_1+\tau_2)} + a_7e^{-\lambda\tau_2} + a_8 = 0$$

Let  $\tau_1 = \tau_2 > 0$

(27)

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3e^{-\lambda\tau_1} + a_4\lambda e^{-\lambda\tau_1} + a_5e^{-\lambda(\tau_1+\tau_2)} + a_6\lambda e^{-\lambda(\tau_1+\tau_2)} + a_7e^{-\lambda\tau_2} + a_8 = 0$$

Let  $\lambda = i\omega (\omega > 0)$

$$i\omega^3 + a_1\omega^2 - a_2i\omega - a_3e^{-i\omega\tau} - i\omega_4e^{-i\omega\tau} - a_5e^{-i\omega(\tau_1+\tau_2)} - a_6i\omega e^{-i\omega(\tau_1+\tau_2)} + a_7e^{-i\omega\tau} + a_8 = 0$$

Separate the real and imaginary parts, we have

$$a_1\omega^2 - a_8 = a_3 \cos \omega\tau - a_5 \cos \omega(\tau_1 + \tau_2) + a_4 \sin \omega\tau - a_6\omega \sin \omega(\tau_1 + \tau_2) - a_7 \cos \omega\tau$$

$$\omega^3 - a_2\omega = -a_3 \cos \omega\tau - a_5 \sin \omega(\tau_1 + \tau_2) - a_4 \cos \omega\tau + a_6\omega \sin \omega(\tau_1 + \tau_2) + a_7 \cos \omega\tau$$

Squaring and adding both equation, we obtain

$$\begin{aligned} (a_1\omega^2 + a_8)^2 + (\omega^3 - a_2\omega)^2 &= a_3^2 + a_4^2\omega^2 + a_5^2 + a_6^2\omega^2 + a_7^2 \\ (28) \quad &= \omega^6 + (a_1^2 - 2a_2a_8)\omega^4 + (a_2^2 - 2a_1a_8 - a_4^2 - a_6^2)\omega^2 + (a_8^2 - a_3^2 - a_7^2 - a_5^2) \end{aligned}$$

Let  $\rho = \omega^2$ ;  $b_1 = a_1^2 - 2a_2a_8$ ;  $b_2 = a_2^2 + 2a_2a_4 + a_4^2 - 2a_1a_3 - 2a_1a_8$ ;  $b_3 = a_3^2 + 2a_3a_8 + a_7^2 + a_8^2 - a_5^2$

Then the equation (28) becomes,

$$(29) \quad g(\rho) = \rho^3 + b_1\rho^2 + b_2\rho + b_3 = 0.$$

by case(i), we get  $\Delta(i\omega_2, \tau_2) \neq 0$ , for any  $\tau_1, \tau_2 > 0$ . Therefore  $E^* = (T^*, I^*, V^*)$  is locally asymptotically stable for  $\tau_1 > 0$ ,  $\tau_2 > 0$ . Hence the conditions (i) and (ii) of lemma (3.1) are satisfied if the system (1) holds.  $\square$

#### 4. GLOBAL STABILITY ANALYSIS

In this section, we construct a suitable Lyapunov function to study the global dynamics of the infection-free equilibrium and chronic infection equilibrium for system (1).

**Theorem 3.5:** *If  $N \leq N_{crit}$ , then the infection - free equilibrium,  $E_0(T_0, 0, 0)$  of system (1) is globally asymptotically stable in  $\Omega$ .*

**Proof:** Define a Liapunov functional

$W(t) = T(t) - T_0 \ln \frac{T(t)}{T_0} + I(t) - V(t) + K \int_0^{\tau_1} T(t - \omega)V(t - \omega)d\omega + N\mu_2 \int_0^{\tau_2} I(t - \omega)d\omega$ . Here  $W(t)$  is well-defined, continuous and positive defined for all  $(T, I, V) > 0$  and  $\theta \in [0, \rho]$ . Also,

the global minimum  $W(=0)$  occurs at the infection free steady state  $E_0$ . Thus every solutions tends to the viral free steady state  $E_0$ . Further, a function  $W(t)$  along the trajectories of (1) satisfies.

$$\begin{aligned} \frac{dW}{dt} &= (T - T_0) \left[ \frac{s}{T} + r \left( 1 - \frac{T+I}{T_m} \right) - \mu_1 - kV \right] + kT(t - \tau_1)V(t - \tau_1) - \mu_2 I \\ &\quad + rI \left( 1 - \frac{T+I}{T_m} \right) - N\mu_2 I(t - \tau_2) + \mu_3 V - kT(t - \tau_1)V(t - \tau_1) + kTV \\ &\quad - N\mu_2 I + N\mu_2 I(t - \tau_2) \\ &= (T - T_0) \left[ \frac{s}{T} + r \left( 1 - \frac{T+I}{T_m} \right) - \mu_1 \right] + kT_0 V + r \left( 1 - \frac{T+I}{T_m} \right) - \mu_2 I + \mu_3 V - N\mu_2 I \end{aligned}$$

Using the equation;

$$r - \mu_1 = \frac{rT_0}{T_m} - \frac{s}{T_0},$$

we get,

$$\begin{aligned} \frac{dW}{dt} &= -\frac{s(T - T_0)^2}{TT_0} - \frac{r}{T_m} [(T - T_0 + I)]^2 + kT_0 V + rI \left( 1 - \frac{T_0}{T_m} \right) - \mu_2 I + kT_0 V \\ &\quad - \mu_3 V - N\mu_2 I \end{aligned}$$

Using the equation,

$$r \left( 1 - \frac{T_0}{T_m} \right) = \mu_1 - \frac{s}{T_0},$$

we get

$$\begin{aligned} \frac{dW}{dt} &= -\frac{s(T - T_0)^2}{TT_0} - \frac{r}{T_m} [(T - T_0 + I)]^2 - \mu_3 V + kT_0 V - \frac{\mu_2 k T_0}{\mu_3} \\ &\quad \left( \frac{\mu_3}{\mu_2 k T_0} \left[ \frac{s}{T_0} + \mu_2 - \mu_1 \right] + N \right) I \end{aligned}$$

Rewritten  $\frac{dW}{dt}$  interms of the critical number, we get

$$\frac{dW}{dt} = -\frac{s(T - T_0)^2}{TT_0} - \frac{r}{T_m} [(T - T_0 + I)]^2 + kT_0 V - \mu_3 V + kT_0 V - \frac{\mu_2 k T_0}{\mu_3} (N_{crit} - N) I$$

If  $N \leq N_{crit}$ , then  $\frac{dW}{dt} \leq 0$ , from corollary [57],  $E_0$  is asymptotically stable. Also,  $N = N_{crit}$ ,  $\frac{dW}{dt} = 0$  implies that  $T(t) = T_0$  and  $I(t) = 0$ . While in the case  $N < N_{crit}$ ,  $\frac{dW}{dt} = 0$  if and only if  $T(t) = T_0$  and  $I(t) = 0$ . It is easy to show that  $E_0(T_0, 0, 0)$  is the largest invariant set  $\{(T(t), I(t), V(t)) : \frac{dW}{dt} = 0\}$ . By the classical Liapunov - Lasalle invariance principle [58],  $E_0$

is globally asymptotically stable. This complete the proof.  $\square$

In the following, we consider the global asymptotic stability of chronic infection equilibrium  $E^*(T^*, I^*, V^*)$ . We construct an Liapunov functional for chronic infection equilibrium using suitable combinations of the Liapunov functions given by  $g(x) := x - 1 - \ln x$ .

Thus, the function  $g$  has a global minimum at 1 and satisfies  $g(1) = 0$ .

**Theorem 3.6:** *If  $N > N_{crit}$  and  $r \leq \mu_1 + \frac{r}{T_{max}}[T^* + I^*]$ , then the unique chronic infection equilibrium  $E^*(T^*, I^*, V^*)$  of system (1) is globally asymptotically stable for any  $\tau_1, \tau_2 \geq 0$ .*

**Proof:**

We define a Liapunov function as follows:

$$L(t) = L_1(t) + kT^*V^*L_2(t) + kT^*V^*L_3(t)$$

where

$$(30) \quad L_1(t) = \left( T(t) - T^* \ln \frac{T(t)}{T^*} \right) + \left( I(t) - I^* \ln \frac{I(t)}{I^*} \right) + \frac{kT^*V^*}{N\mu_2 I^*} \left( V(t) - V^* \ln \frac{V(t)}{V^*} \right)$$

$$(31) \quad L_2(t) = \int_0^{\tau_1} \left( \frac{T(t-\omega)V(t-\omega)}{T^*V^*} - 1 - \ln \frac{T(t-\omega)V(t-\omega)}{T^*V^*} \right) d\omega$$

$$(32) \quad L_3(t) = \int_0^{\tau_2} \left( \frac{I(t-\omega)}{I^*} - 1 - \ln \frac{I(t-\omega)}{I^*} \right) d\omega$$

At infected steady state, we have

$$(33) \quad \left. \begin{aligned} r - \mu_1 &= \frac{-s}{T^*} + kV^* + \frac{r}{T_m} (T^* + I^*) \\ r - \mu_2 &= \frac{-kT^*V^*}{I^*} + \frac{r}{T_m} (T^* + I^*) \\ \mu_3 V^* &= N\mu_2 I^* \end{aligned} \right\}$$

The derivative of  $U_1(t)$  with respect to 't' along the solution of (30), we get

$$\begin{aligned} \frac{dL_1}{dt} &= \left( \frac{T - T^*}{T} \right) \frac{dT}{dt} + \left( \frac{I - I^*}{I} \right) \frac{dI}{dt} + \frac{kT^*V^*}{N\mu_2 I^*} \left( \frac{V - V^*}{V} \right) \frac{dV}{dt} \\ &= (T - T^*) \left( \frac{s}{T} - \frac{r}{T_m} (T + I) - kV + r - \mu_1 \right) \\ &\quad + (I - I^*) \left( \frac{kT(t - \tau_1)V(t - \tau_1)}{I} - \frac{r}{T_m} (T + I) + r - \mu_2 \right) \end{aligned}$$

$$+ \frac{kT^*V^*}{N\mu_2I^*} \left(1 - \frac{V^*}{V}\right) \{N\mu_2I(t - \tau_2) - \mu_3V\}$$

Using the equation (33), we get

$$\begin{aligned} &= \left\{ \left( \frac{-s}{TT^*} (T - T^*)^2 \right) - \frac{r}{T_m} [(T - T^*) + (I - I^*)]^2 \right\} + \{-kTV + kTV^*\} \\ &+ kT^*V^* \left( 1 + \frac{T(t - \tau_1)V(t - \tau_1)}{T^*V^*} - \frac{I}{I^*} - \frac{T(t - \tau_1)V(t - \tau_1)I^*}{T^*V^*I} + \frac{T}{T^*} - \frac{TV}{T^*V^*} \right) \\ &+ \frac{kT^*V^*}{N\mu_2I^*} N\mu_2I(t - \tau_2) - \frac{kT^*V^*}{N\mu_2I^*} \left( \frac{V^*}{V} \right) N\mu_2I(t - \tau_2) \end{aligned}$$

We can rewritten  $\frac{dL_1}{dt}$  as,

$$\begin{aligned} &= -(s - kT^*V^*) \left[ \frac{(T - T^*)^2}{TT^*} \right] - \frac{r}{T_m} [(T - T^*) + (I - I^*)]^2 \\ &+ kT^*V^* \left[ \left( 3 - \frac{T^*}{T} - \frac{TV}{T^*V^*} + \frac{T(t - \tau_1)V(t - \tau_1)}{T^*V^*} - \frac{I}{I^*} - \frac{T(t - \tau_1)V(t - \tau_1)I^*}{T^*V^*I} \right) \right] \\ &+ kT^*V^* \left[ \left( \frac{T}{T^*} + \frac{T^*}{T} - 2 \right) \right] + \frac{kT^*V^*}{N\mu_2I^*} N\mu_2I(t - \tau_2) - \frac{kT^*V^*}{N\mu_2I^*} \left( \frac{V^*}{V} \right) N\mu_2I(t - \tau_2) \end{aligned}$$

Using the equation,

$$\left( \frac{s - kT^*V^*}{T^*} \right) = (\mu_1 - r) + \frac{r}{T_m} (T^* + I^*)$$

We get

$$\begin{aligned} \frac{dL_1}{dt} &= - \left\{ (\mu_1 - r) + \frac{r}{T_m} (T^* + I^*) \right\} \left[ \frac{(T - T^*)^2}{T} \right] - \frac{r}{T_m} [(T - T^*) + (I - I^*)]^2 \\ &+ kT^*V^* \left[ \left( 3 - \frac{T^*}{T} - \frac{TV}{T^*V^*} + \frac{T(t - \tau_1)V(t - \tau_1)}{T^*V^*} - \frac{I}{I^*} - \frac{T(t - \tau_1)V(t - \tau_1)I^*}{T^*V^*I} \right) \right] \\ &+ \frac{kT^*V^*}{N\mu_2I^*} N\mu_2I(t - \tau_2) - \frac{kT^*V^*}{N\mu_2I^*} \left( \frac{V^*}{V} \right) N\mu_2I(t - \tau_2) \end{aligned}$$

Since the  $L_2(t)$  equation,

$$L_2(t) = kT^*V^* \int_0^{\tau_1} \left( \left[ \frac{T(t - \omega)V(t - \omega)}{T^*V^*} - 1 - \ln \frac{T(t - \omega)V(t - \omega)}{T^*V^*} \right] \right) d\omega$$

It is easy to see that, the derivative of  $L_2(t)$

$$\begin{aligned} \frac{dL_2}{dt} &= \frac{d}{dt} \left\{ \int_0^{\tau_1} \left[ \frac{T(t - \omega)V(t - \omega)}{T^*V^*} - 1 - \ln \frac{T(t - \omega)V(t - \omega)}{T^*V^*} \right] d\omega \right\} \\ &= \left[ - \frac{T(t - \tau_1)V(t - \tau_1)}{T^*V^*} + \frac{TV}{T^*V^*} + \ln \frac{T(t - \tau_1)V(t - \tau_1)}{T^*V^*} - \ln \frac{TV}{T^*V^*} \right] \end{aligned}$$



Consider

$$\ln \frac{T(t-s)V(t-s)}{T^*V^*} + \ln \frac{T^*V^*}{TV} = \ln \left( \frac{T(t-s)V(t-s)I^*}{T^*V^*I} \right) + \ln \frac{T^*}{V^*} + \ln \left( \frac{IV^*}{I^*V} \right)$$

$$\frac{dL_2}{dt} = \left[ -\frac{T(t-\tau_1)V(t-\tau_1)}{T^*V^*} + \frac{TV}{T^*V^*} + \ln \frac{T(t-\tau_1)V(t-\tau_1)I^*}{T^*V^*I} + \ln \frac{IV^*}{I^*V} + \ln \frac{T^*}{T} \right]$$

Since  $L_3(t)$  the equation,

$$L_3(t) = \int_0^{\tau_1} \left( \frac{I(t-\omega)}{I^*} - 1 - \ln \frac{I(t-\omega)}{I^*} \right) d\omega$$

The derivative of  $L_3(t)$  along solution of system (32), we get,

$$\begin{aligned} \frac{dL_3}{dt} &= \frac{d}{dt} \left[ \int_0^{\tau_2} \left( \frac{I(t-\omega)}{I^*} - 1 - \ln \frac{I(t-\omega)}{I^*} \right) \omega \right] \\ &= \left\{ -\frac{I(t-\tau_2)}{I^*} + \frac{I}{I^*} + \ln \frac{I(t-\tau_2)}{I^*} - \ln \frac{I}{I^*} \right\} \end{aligned}$$

Consider,

$$\ln \frac{I(t-\tau_2)}{I^*} - \ln \frac{I}{I^*} = \ln \frac{I(t-\tau_2)V^*}{I^*V} - \ln \frac{IV^*}{I^*V}$$

$$\frac{dL_3}{dt} = \left[ -\frac{I(t-\tau_2)}{I^*} + \frac{I}{I^*} + \ln \frac{I(t-\tau_2)V^*}{I^*V} - \ln \frac{IV^*}{I^*V} \right]$$

Since

$$\frac{dL}{dt} = \frac{dL_1}{dt} + kT^*V^* \frac{dL_2}{dt} + kT^*V^* \frac{dL_3}{dt}$$

We obtain,

$$\begin{aligned} \frac{dL}{dt} &= - \left\{ (\mu_1 - r) + \frac{r}{T_m} (T^* + I^*) \right\} \left[ \frac{(T - T^*)^2}{T} \right] - \frac{r}{T_m} [(T - T^*) + (I - I^*)]^2 \\ &+ kT^*V^* \left[ \left( 3 - \frac{T^*}{T} - \frac{TV}{T^*V^*} + \frac{T(t-\tau_1)V(t-\tau_1)}{T^*V^*} - \frac{I}{I^*} - \frac{T(t-\tau_1)V(t-\tau_1)I^*}{T^*V^*I} \right) \right] \\ &+ \frac{kT^*V^*}{N\mu_2I^*} N\mu_2I(t-\tau_2) - \frac{kT^*V^*}{N\mu_2I^*} \left( \frac{V^*}{V} \right) N\mu_2I(t-\tau_2) \\ &+ kT^*V^* \left[ -\frac{T(t-\tau_1)V(t-\tau_1)}{T^*V^*} + \frac{TV}{T^*V^*} + \ln \frac{T(t-\tau_1)V(t-\tau_1)I^*}{T^*V^*I} + \ln \frac{IV^*}{I^*V} + \ln \frac{T^*}{T} \right] \end{aligned}$$

$$+ kT^*V^* \left[ -\frac{I(t-\tau_2)}{I^*} + \frac{I}{I^*} + \ln \frac{I(t-\tau_2)V^*}{I^*V} - \ln \frac{IV^*}{I^*V} \right]$$

$$\begin{aligned} \frac{dL}{dt} = & - \left\{ (\mu_1 - r) + \frac{r}{T_m} (T^* + I^*) \left[ \frac{(T - T^*)^2}{T} \right] \right\} - \frac{r}{T_m} [(T - T^*) + (I - I^*)]^2 \\ & - kT^*V^* \left[ \left( \frac{T^*}{T} - 1 - \ln \frac{T^*}{T} \right) \right] - kT^*V^* \\ & \left[ \left( \frac{T(t-\tau_1)I^*V(t-\tau_1)}{T^*V^*I} - 1 - \ln \frac{T(t-\tau_1)I^*V(t-\tau_1)}{T^*V^*I} \right) \right] \\ & - kT^*V^* \left[ \left( \frac{I(t-\tau_2)V^*}{I^*V} - 1 - \frac{I(t-\tau_2)V^*}{I^*V} \right) \right] \end{aligned}$$

$$(34) \quad \begin{aligned} \frac{dL}{dt} = & - \left\{ (\mu_1 - r) + \frac{r}{T_m} (T^* + I^*) \left[ \frac{(T - T^*)^2}{T} \right] \right\} - \frac{r}{T_m} [(T - T^*) + (I - I^*)]^2 \\ & - kT^*V^* \left[ g \left( \frac{T^*}{T} \right) \right] - kT^*V^* \left[ g \left( \frac{T(t-\tau_1)I^*V(t-\tau_1)}{T^*V^*I} \right) \right] ds \\ & - kT^*V^* \left[ g \left( \frac{I(t-\tau_2)V^*}{I^*V} \right) \right] ds \end{aligned}$$

Notice that  $T^*, I^*, V^* > 0$ , we have that  $\frac{dL}{dt} \leq 0$ . By theorem 5.3.1 in [4], solutions limit to  $\mu$ , the largest invariant subset  $L'(t) = 0$ . Using the similar argument as that in [34] and by Lasealle's on variable principle, the global asymptotic stability of  $E^*$  follows. Therefore,  $E^*(T^*, I^*, V^*)$  is globally asymptotically stable for any  $\tau_1, \tau_2 \geq 0$ . This complete the proof.  $\square$

## 5. NUMERICAL SIMULATION

In order to check the main results of this paper, we use Matlab software to carry out some numerical simulations. For the simulations, we use a similar set of parameter values as those in [64].

TABLE 1. **Variables and Parameters for viral spread**

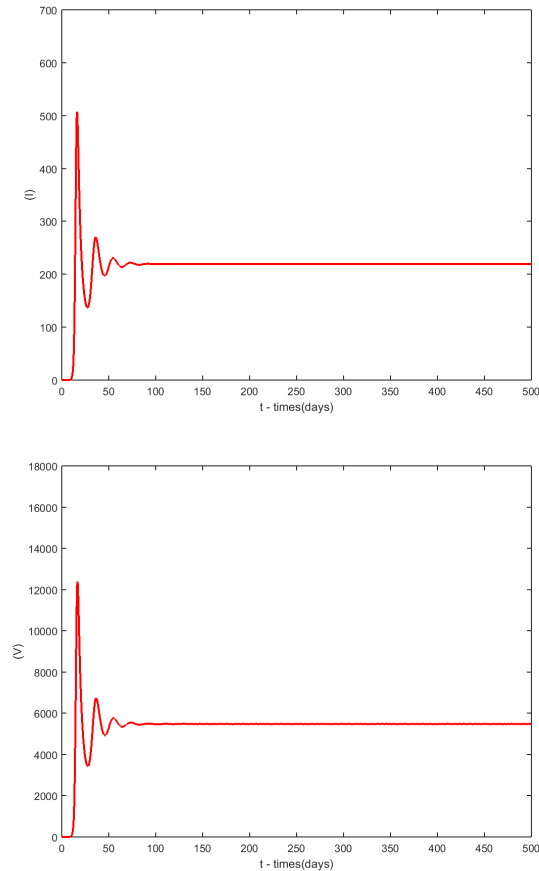
Parameter	Expansion	Values
T	Uninfected $CD4^+$ T cell population size	$1000mm^{-3}$
I	Infected $CD4^+$ T cell density	0
V	Initial density of HIV RNA	$10^{-3} mm^{-3}$
$\mu_1$	Natural death rate of $CD4^+$ T cells	$0.2 day^{-1}$
$\mu_2$	Blanket death rate of infected $CD4^+$ T cells	$1 day^{-1}$
$\mu_3$	Death rate of free virus	$2.4 day^{-1}$
$k$	Rate $CD4^+$ T cells become infected with virus	$1 \times 10^{-4}mm^3 day^{-1}$
$r$	Growth rate of $CD4^+$ T cell population	$0.95day^{-1}$
$N$	Number of virions produced by infected $CD4^+$ T cells	Varies
$T_{max}$	Maximal population level of $CD4^+$ T cells	$1500mm^{-3}$
$s$	Source term for uninfected $CD4^+$ T cells	$0.1 day^{-1} mm^{-3}$
$T_0$	$CD4^+$ T cell population for HIV-negative persons	$1000 mm^{-3}$

Analytical studies can never completed without numerical verification of the results. In this section, to verify the validity of the theoretical result of this chapter, we perform numerical simulation. Beside verification of our analytical findings these numerical solutions are very important from practical point of view.

In order to illustrate the system dynamics we have used the default parameter values in Table 1. The average  $CD4^+$ T- cells count in healthy human body is 1000 cells  $mm^3$  [53] which is taken as its initial value. Since there is no infected  $CD4^+$ T- cells immediately after first effective contact between a healthy  $CD4^+$ T- cells and a human immunodeficiency virus, so that the initial value of infected  $CD4^+$ T- cells is taken to be zero. The initial viral load is considered as  $1 \times 10^{-3}mm^3$ . We therefore fix the initial value for each iteration as  $(1000,0,1 \times 10^{-3})$ . Thus, the parameter values and initial condition of the system relate to real world scenarios.

First we have simulated the non - delayed system (1) with  $\tau_1 = \tau_2 = 0$ . For the parameter values given in Table 1. The number of infectious viruses released N, varies in the literature, here we first take  $N = 60$ . From the ODE model, then all the conditions of lemma (3.1) are

satisfied and the infected steady state  $\bar{E}$  is asymptotically stable. Figure 4 show that trajectories of system (1) approach to steady state. If we increase the value of  $N$ , then the numbers of uninfected  $CD4^+T$ - cells and vir uses are decreases and the number of infected cells increases substantially, but the stability of the steady state does not change. We note that though the dynamics of system (1) are very similar to that of Perelson, Krichner and De Boer model [3], the actual steady state values in our model (1) are different. Our bifurcation value  $N_{crit}$  is lower, the equilibrium level of healthy  $CD4^+T$ - cells is lower and the equilibrium level of free virus is higher than that in Perelson Krichner and De Boer model [3]. Thus the infected steady state  $\bar{E}$  is asymptotically stable for all  $\tau_1, \tau_2 > 0$ . Take  $N = 60, \tau_1 = \tau_2 = 0.1$  and other parameter values given in Table 1. Numerical solution show that the infected steady state  $\bar{E}$  is asymptotically stable (Figure 1).



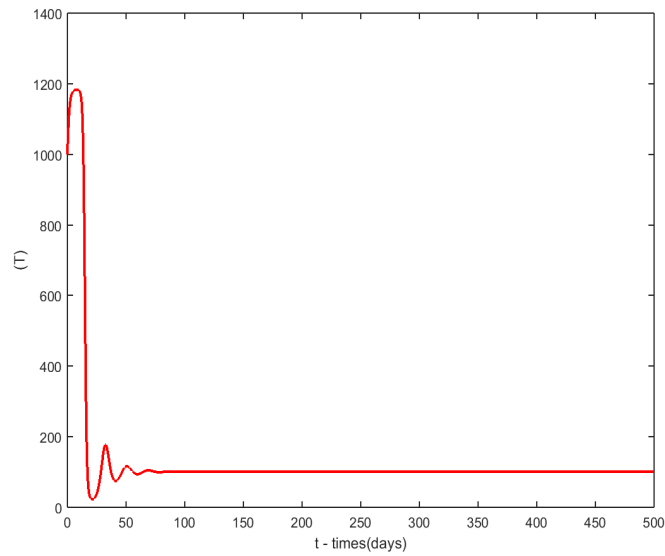
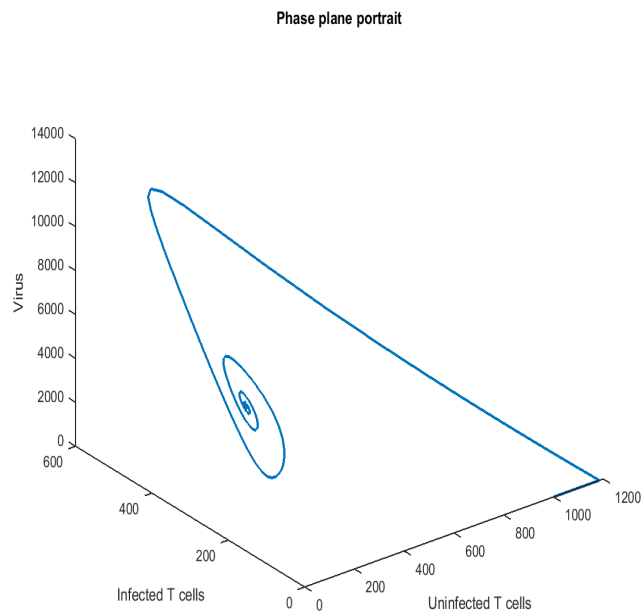
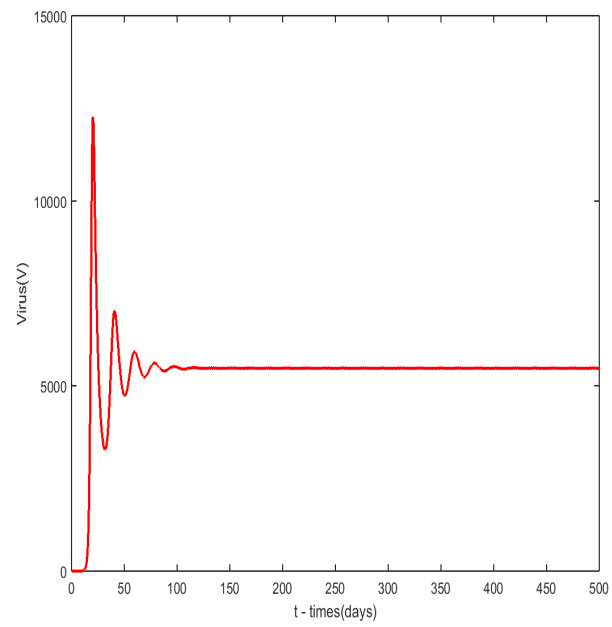
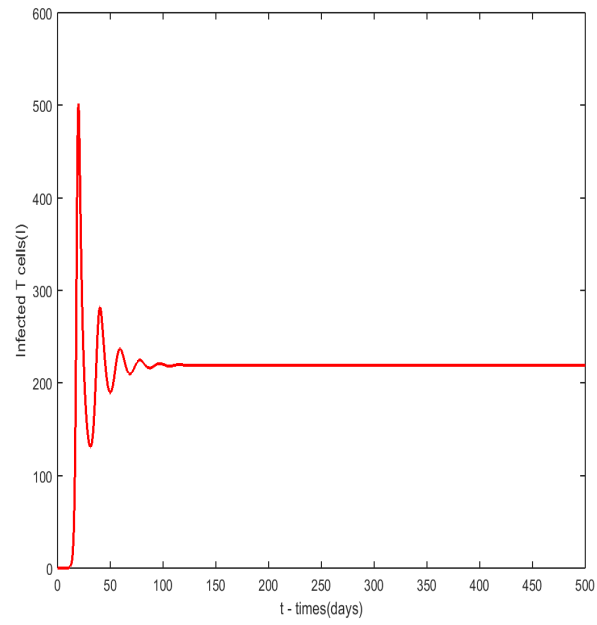


FIGURE 1. The ODE Model: Local asymptotic stability of the infected steady state  $\bar{E}$ ,  $\tau_1, \tau_2 = 0$ ,  $N = 60$  and all other parameters are given in Table 1





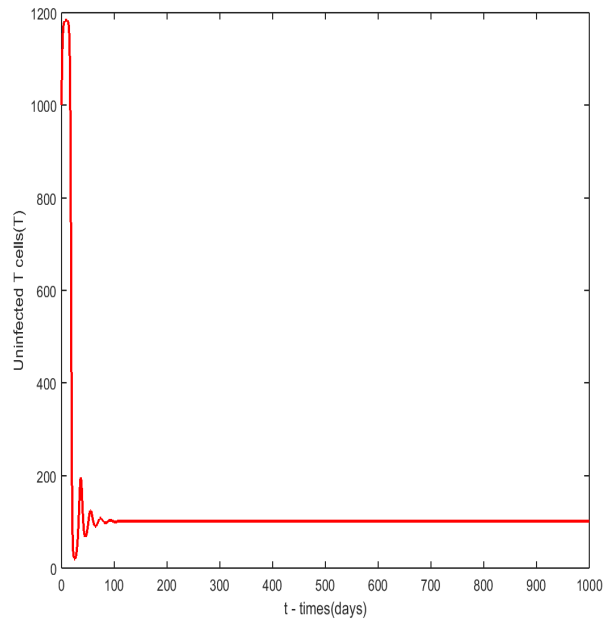
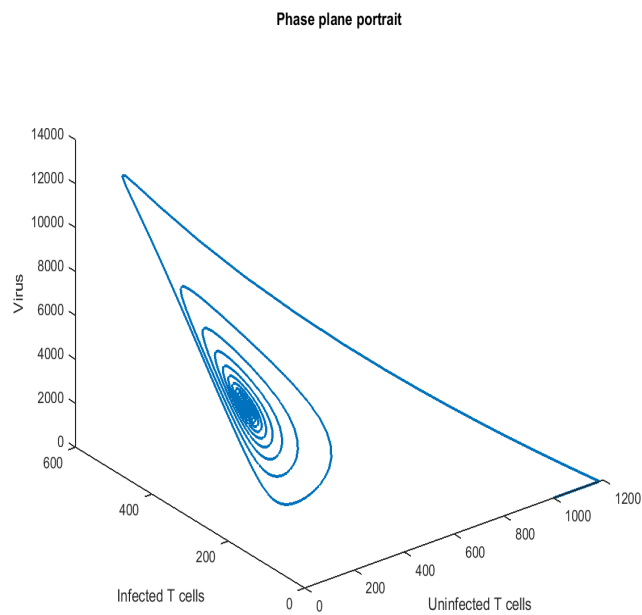
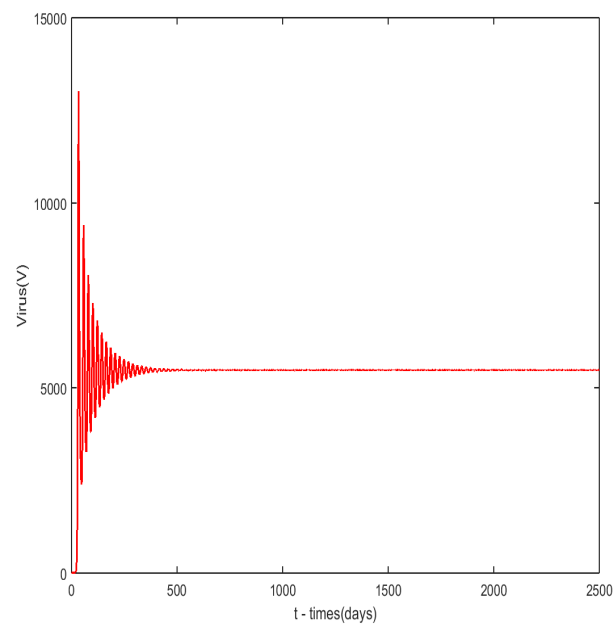
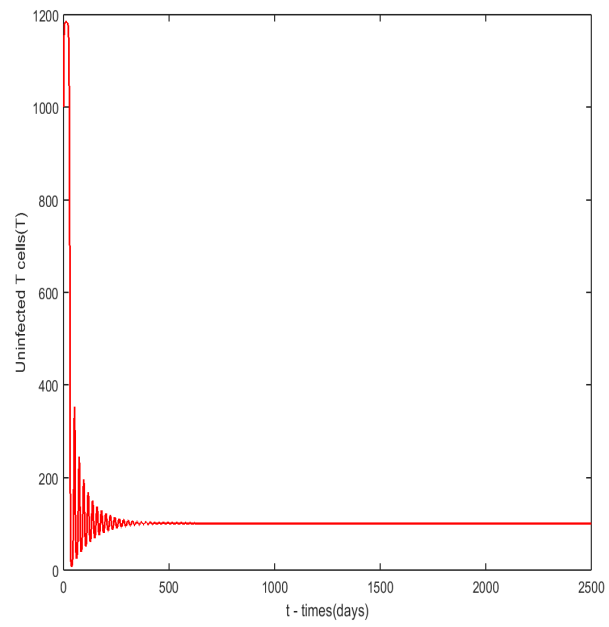


FIGURE 2. Local asymptotic stability of the infected steady state  $\bar{E}$ ,  $\tau_1 = \tau_2 = 0.1$ ,  $N = 60$  and all other parameters are given in Table 1







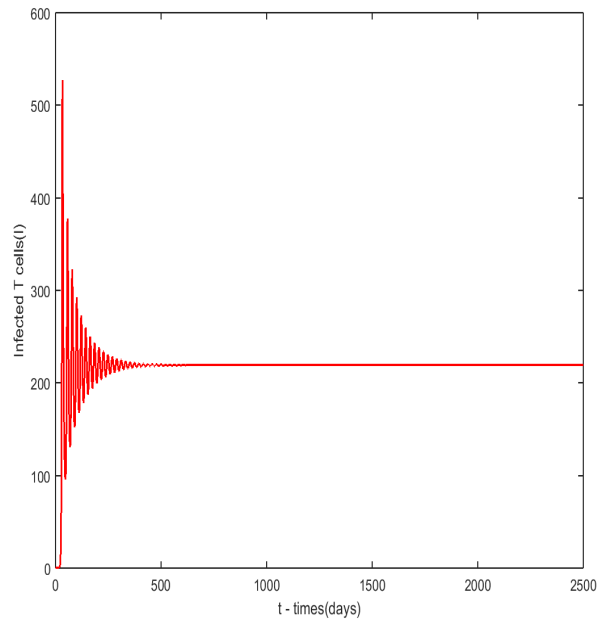
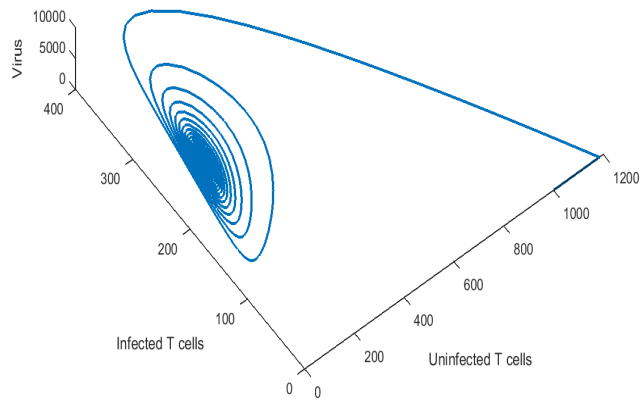
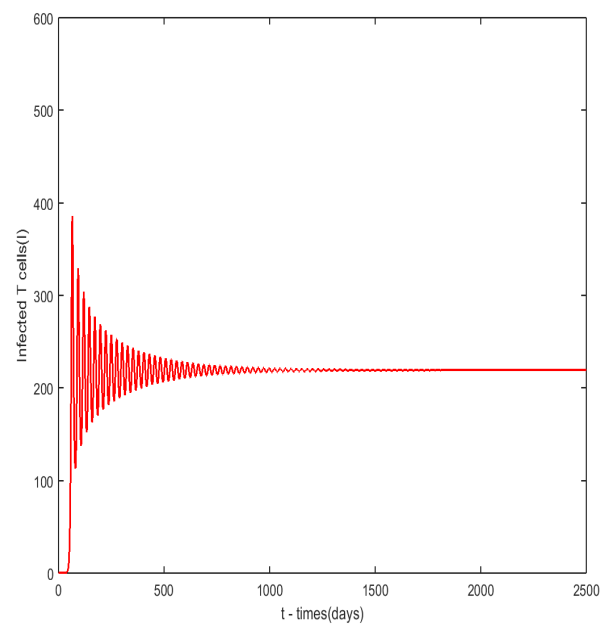
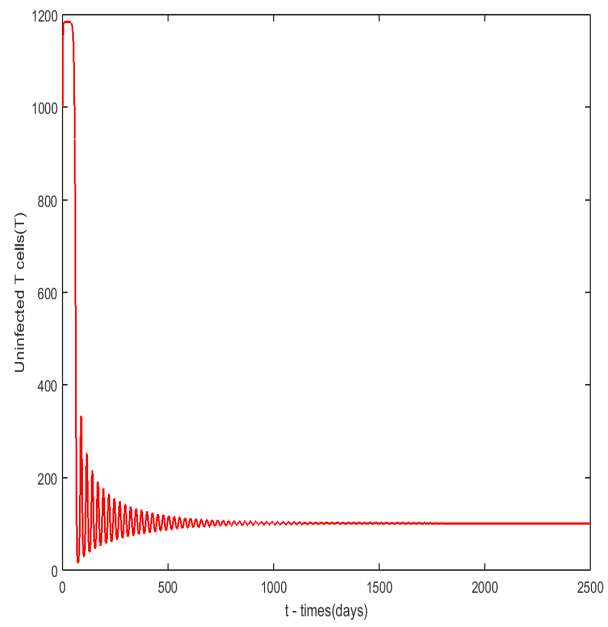


FIGURE 3. Local asymptotic stability of the infected steady state  $\bar{E}$ ,  $\tau_1 = 1$ ,  $\tau_2 = 0.1$ ,  $N = 60$  and all other parameters are given in Table 1

Phase plane portrait





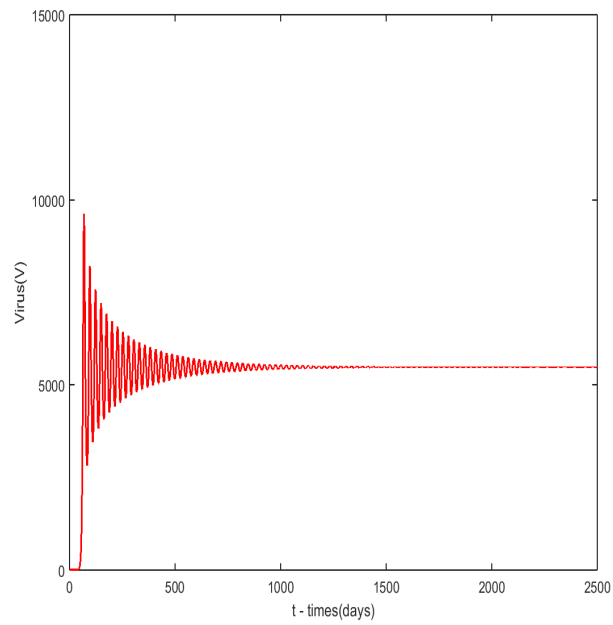
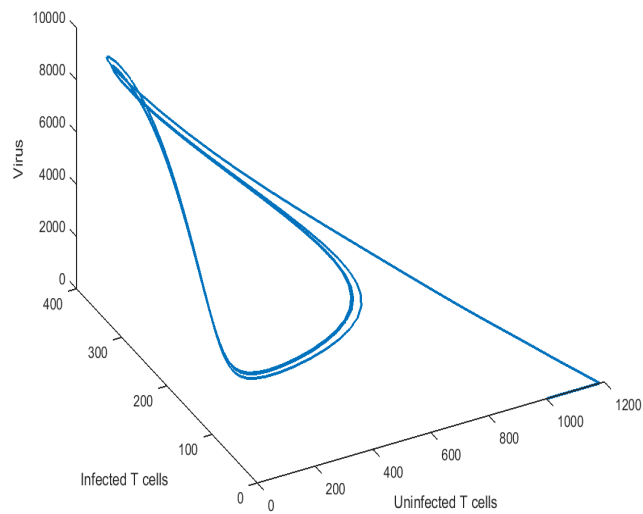
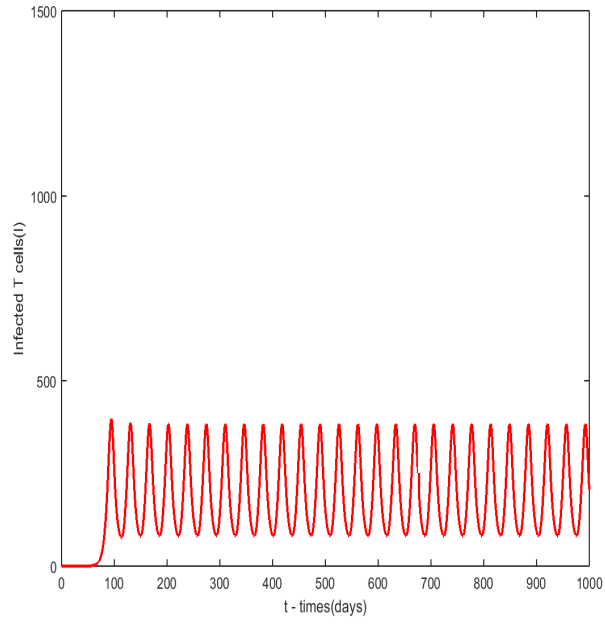
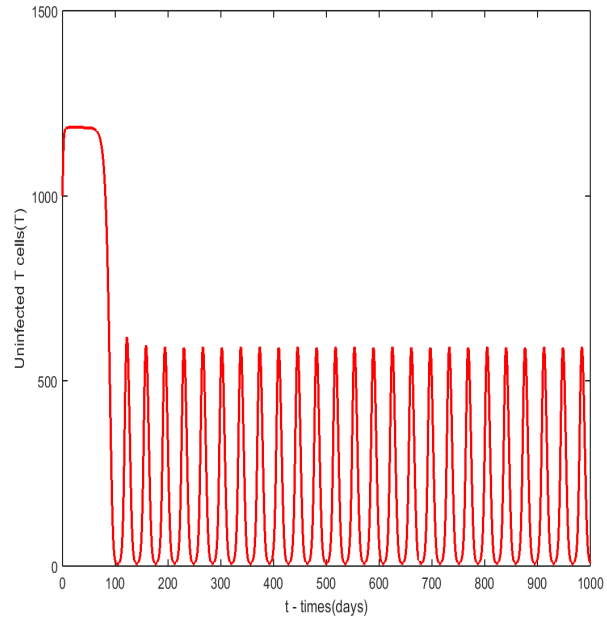


FIGURE 4. Local asymptotic stability of the infected steady state  $\bar{E}$ ,  $\tau_1 = 0.1$ ,  $\tau_2 = 3$ ,  $N = 60$  and all other parameters are given in Table 1

Phase plane portrait





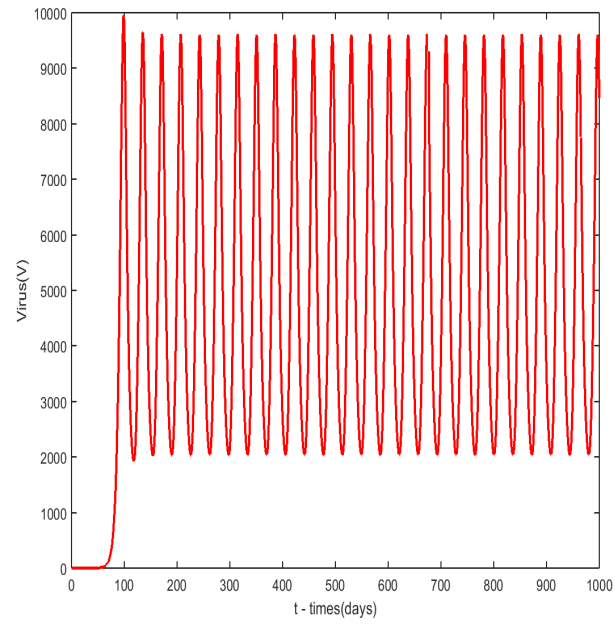


FIGURE 5. Periodic solution bifurcated from the infected steady state  $\bar{E}$ ,  $\tau_1 = 1.5$ ,  $\tau_2 = 3$  and all other parameters are given in Table 1

In Figure 3, we plot the time series solution of the delayed system (2) for  $\tau_1 = 0.1$  &  $\tau_2 = 3$ , with  $N = 60$  (Figure 3). Following the analytical results, we observe that the larger delay  $\tau_2$  can not produce any oscillations and the system populations remain stable for all values of  $\tau_1 < \tau_2$ . The only difference between the two cases is that the viral blip occurs earlier with high peak when  $\tau_2$  is smaller and it occurs later with low peak if the delay is higher ( $\tau_2 = 3$ ). Further under the condition of  $\tau_1 = 1$  when  $\tau_2 = 0.1$ ,  $\bar{E}$  is asymptotically stable (see Figure 2). while at  $\tau_1 = 1.21$  and  $\tau_2 = 0.1$ ,  $\bar{E}$  loses stability and the Hopf bifurcation occurs. From Figure 3.5, the periodic solution bifurcated from the infected steady state  $\bar{E}$ , when  $\tau_1 .5$ ,  $\tau_3 > 0$ . Take  $N = 60$ , and other parameter values given in table 1. Numerical solution show that the infected steady state  $\bar{E}$  is asymptotically unstable.

## 6. CONCLUSIONS

In this work, we have proposed a delayed model to describe the dynamics of HIV infection of  $CD4^+$  T-cells by taking two independent delays, we first proved that proposed model is mathematically and virologically well-posed. In addition, we have proved that the disease-free equilibrium  $E_0$  is globally asymptotically stable. If the critical number  $N_{crit} \leq N$ , which means that the HIV particals are eradicated. When  $N_{crit} > N$ ,  $E_0$  become unstable and there occurs the HIV infection equilibrium  $E^*$  which is globally asymptotically stable.

Finally we investigate the delay induced oscillations could occur via instability. Numerical simulations shows that the bifurcation is super critical and the bifurcating periodic solution is absolutely asymptotically stable. Sufficient conditions are established for the local asymptotic stability of the uninfected steady state and the infected steady state. The influence of the time delays in the stability of equilibrium states is discussed. We shared that the local stability of the uninfected steady state is discrete of the size of the delay; on the other hand, we proved that increasing the delay can destabilize the infected steady state leading to a Hopf bifurcation periodic solutions.

## CONFLICT OF INTERESTS

The author(s) declare that there is no conflict of interests.

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