

Mathematical Model of HIV-1 Dynamics with T Cell Activation

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Abstract

A deterministic in-host model of HIV-1 that incorporates naive and activated T cells is being investigated. The model represents the dynamics of five subsets of T cells and one class of HIV-1. The virus free and the infection persistent equilibria are found and their stability analysed. With the aid of suitable Lyapunov functionals, we have shown that the model equilibria are globally asymptotically stable under special conditions. The numerical simulation is performed to illustrate both the short term and long term dynamics of HIV-1 infection. The results of simulation are in agreement with published data with regard to CD4+ T cell concentration and the viral load.

Keywords

HIV-1, T Cell, Lyapunov Function, Global Stability

1. Introduction

The most recent global health observatory (GHO, 2014) data of HIV/AIDS published by WHO [1] proclaims that around 78 million people have been infected with the HIV virus and about 39 million people have died of HIV virus. In the current scenario about 35 million people are living with HIV globally and the majority of the cases are in Sub-Saharan Africa where 70% of the total cases are found. The number of people dying from AIDS-related causes like AIDS-related Kaposi's sarcoma has been reduced with the increased access to antiretroviral therapy in low and middle income countries. This accentuates the importance of treatment of HIV through antiretroviral therapy.

The human immunodeficiency virus-1 (HIV-1) is a retrovirus containing two single strands of RNA. It is an enveloped virus that carries its own reverse tran-

scriptase, an enzyme, responsible for transcribing viral RNA. HIV-1 is transmitted via three primary routes: unprotected sexual intercourse, mother to child (vertical transmission), and intravenously. HIV targets immune cells that carry a CD4 receptor. These cells include the CD4+ T cells and monocytes/macrophages. The CD4 receptor binds with the protein gp120 (found on the surface of the virus) in initiating cellular infection. This is a necessary step but not sufficient. A co-receptor is needed for proper infection. The virus uses a cytokine receptor on the surface of the host cell near the CD4 receptor to finish the lock and key entry process. It has been shown that individuals lacking the co-receptor have a natural immunity to infection by HIV-1 [2]. Once inside the host cell, the viral DNA can be inserted into the host cell's genome only upon cellular activation, and new viral particles are created and released.

Many HIV-1 in-host models that seek to elucidate the role of cellular immune response in the pathogenesis of HIV-1 infection have been developed. Some of these models could be reviewed in [3] [4] [5] [6]. Most of these models ignore the activation aspect of the naive T cells. T cells must first get activated to acquire the ability to perform their cytotoxic functions. For instance, CD4+ T cells (helper T cells) are activated upon recognition of their cognate antigen that is bound on major histocompatibility complex class II molecules presented on the surface of an activated antigen presentation cell such as macrophage, dendritic cell etc. For a complete activation process, a second non-specific signal is needed. Once a CD4+ T cell, through a T cell receptor, has recognised its cognate antigen, the next step is to transmit a signal from the surface of the T cell, where the recognition takes place, to the nucleus of the T cell. For the CD4+ T cell to switch from naive state to a state of activation, gene expression must be altered inside the nucleus.

Through the help of activated CD4+ T cells, other immune cells are recruited to the sight of an infection. This is normally done through secretion of chemical messengers (cytokines) by the helper T cells that act in an autocrine or paracrine manner. The activated CD8+ T cells, on the contrary, are only able to recognise their cognate antigen that is loaded on the major histocompatibility complex class I of the activated antigen presenting cells. And the recognition is facilitated through their T cell receptors.

With this background, we are motivated to develop an HIV-1 model that includes the activation of both the naive CD4+ and CD8+ T cells. We assume that the activation process of the CD8+ T cells is enhanced by the action of the activated CD4+ T cells. We further assume that both naive and activated CD4+ T cells are susceptible to HIV-1 infection.

In the current paper, we endeavour to address the following questions.

- 1) Under what conditions does the infection persistent equilibrium point exist?
- 2) What conditions must be satisfied for the model equilibria to remain stable?
- 3) What are the different outcomes in the HIV-1 infection?

Our article is organised as follows: In Section 2, a mathematical model is developed which includes naive T cells, activated T cells, productively infected T cells, and HIV-1 virions. We prove positivity and boundedness of solutions. The equilibria are determined and the basic reproduction number derived. The existence theorem regarding the infection persistent equilibrium is formulated and proved. In Section 3, we establish the local and global stability of the equilibria. Appropriate Lyapunov functionals are formulated in the proof of global stability. In Section 4, we carry out the numerical simulations to validate our mathematical analyses. And lastly, in Section 5 we end with the discussions and conclusion.

2. Model Formulation

In this study, we present a mathematical model of the progression of HIV-1 in the presence of the cellular immune response. We focus on the role of CD4 T cell activation in the pathogenesis of the disease by including the interactions of healthy T cells, activated T cells, HIV-1 infected T cells that are assumed to be productively infected and naive CD8 T cells, activated CD8 T cells or effector cells such as the cytotoxic T lymphocytes (CTLs).

$$\dot{T}_n = \pi_{T_n} - \beta T_n V_1 - d_{T_n} T_n - \alpha_1 T_n T_p, \quad (1)$$

$$\dot{T}_a = \alpha_1 T_n T_p - \beta T_a V_1 - d_{T_a} T_a, \quad (2)$$

$$\dot{T}_p = \beta (T_n + T_a) V_1 - d_{T_p} T_p - \rho E_a T_p, \quad (3)$$

$$\dot{E}_n = \pi_{E_n} - d_{E_n} E_n - \alpha_2 E_n T_a T_p, \quad (4)$$

$$\dot{E}_a = \alpha_2 E_n T_a T_p - d_{E_a} E_a, \quad (5)$$

$$\dot{V}_1 = N_{V_1} d_{T_p} T_p - d_{V_1} V_1. \quad (6)$$

Equation (1) describes the dynamics of naive T-cells subjected to HIV-1 infection. In this study we assume that both the naive and activated CD4 T cells have the same infectivity rate though it is now known that it is mostly the activated CD4 T cells are susceptible to HIV-1 infection. The first term represents the constant source for these cells from the thymus. The second term represents the rate at which the naive CD4 T cells are getting infected by HIV-1. The third term represents the per capita death rate of these cells and the last term represents the removal rate of activated naive CD4 T cells after presented with their cognate antigens by the antigen presenting cells.

Equation (2) represents a class of activated CD4 T cells that are reduced due to HIV-1 infection. This reduction is represented by the second term. And the last term represents the per capita death rate constant.

Equation (3) represents a class of productively infected CD4 T cells. The first term represents the production of these cells from the infection of naive and activated CD4 T cells by HIV-1. The second term is the bursting rate of these cells as they release the HIV-1 virions. And the last term is the rate at which activated effector cells kill the productively infected CD4 T cells. This is the lytic part of

the cellular immune response. We could also consider the nonlytic part in which the cytotoxic T lymphocyte inhibits the viral replication through the release of soluble factors.

Equation (4) represents the naive CD8 T cells. The first term represents the constant source of the naive CD8 T cells from the thymus. The second term is the per capita death of the naive CD8 T cells. The third term represents the activation rate of these cells upon exposure to the cognate antigen with the help of the activated CD4 T cells.

Equation (5) represents a class of activated CD8 T cells. The first term is a variable source from the activated naive CD8 T cells and the last term is the per capita death rate constant.

Equation (6) represents the concentration of HIV-1. The first term is the source of HIV-1 virions arising from the bursting of productively infected CD4 T cells and the last term is the per capita death rate constant.

The model parameters above with their definitions are summarised in **Table 1**.

3.1. Positivity of Solutions and Boundedness of Solutions

3.1.1. Positivity of Solutions

For the model system above to be immunological meaningful, it is important to prove that all its state variables are non-negative for all times. In other words, solutions of the model above with positive initial data remain positive for all $t > 0$.

Table 1. Model parameters and their definitions.

Parameter	Definitions
π_{s_1}	Source of naive CD4+ T cells
π_{s_4}	Source of naive CD8+ T cells
β	Infection rate of naive CD4+ T cells by HIV-1
d_{s_1}	Death rate of naive CD4+ T cells
d_{s_2}	Death rate of activated CD4+ T cells
d_{s_3}	Death rate of productively infected CD4+ T cells
d_{s_4}	Death rate of naive CD8+ T cells
d_{s_5}	Death rate of activated CD8+ T cells
d_{s_6}	Death rate of HIV-1 virion
α_1	Activation rate of naive CD4+ T cells
α_2	Activation rate of naive CD8+ T cells
N_{s_6}	Maximum carrying capacity of infected CD4+ T cells
ρ	Killing of infected CD4+ T cells by CD8+ T effector cells

We thus show that our model is well posed in the sense that the populations do not become negative, and the populations are bounded. Also, the non-negative orthant is positively invariant, in other words, any trajectory that begins in the non-negative orthant remains there for all time.

For simplicity of notations, we let

$$\begin{aligned} x_1(t) &:= T_n(t), \quad x_2(t) := T_a(t), \quad x_3(t) := T_p(t), \quad x_4(t) := E_n(t), \quad x_5(t) := E_a(t), \\ x_6(t) &:= V_1(t), \quad \pi_{d_{x_1}} := \pi_{T_n}, \quad d_{x_1} := d_{T_n}, \quad d_{x_2} := d_{T_a}, \quad d_{x_3} := d_{T_p}, \quad \pi_{x_4} := \pi_{E_n}, \\ d_{x_4} &:= d_{E_n}, \quad d_{x_5} := d_{E_a}, \quad d_{x_6} := d_{V_1}, \quad N_{x_6} := N_{V_1} \end{aligned}$$

where $:=$ means equal by definition.

Denote by \mathbb{R}_+^6 the set of points

$$x_i = (x_1, x_2, x_3, x_4, x_5, x_6) \in \mathbb{R}^6 \tag{7}$$

with positive coordinates and consider the system with initial values

$$x^0 = (x_0^1, x_0^2, x_0^3, x_0^4, x_0^5, x_0^6) \in \mathbb{R}_+^6 \tag{8}$$

Lemma 1. *Let $x_0^i \geq 0, i = 1, 2, 3, 4, 5, 6$. Then the solution $x_i \in \mathbb{R}_+^6$ for all $t > 0$ in the region*

$$\Gamma^6 = \{(x_1, x_2, x_3, x_4, x_5, x_6) \mid x_i \in \mathbb{R} \ \forall i, i = 1, 2, 3, 4, 5, 6\} \subseteq \mathbb{R}^6.$$

The systems (1)-(6) can be rewritten as follows:

$$\dot{x}_1 = \pi_{x_1} - \beta x_1 x_6 - d_{x_1} x_1 - \alpha_1 x_1 x_3, \tag{9}$$

$$\dot{x}_2 = \alpha_1 x_1 x_3 - \beta x_2 x_6 - d_{x_2} x_2, \tag{10}$$

$$\dot{x}_3 = \beta(x_1 + x_2)x_6 - d_{x_3} x_3 - \rho x_3 x_5, \tag{11}$$

$$\dot{x}_4 = \pi_{x_4} - d_{x_4} x_4 - \alpha_2 x_2 x_3 x_4, \tag{12}$$

$$\dot{x}_5 = \alpha_2 x_2 x_3 x_4 - d_{x_5} x_5, \tag{13}$$

$$\dot{x}_6 = N_{x_6} d_{x_3} x_3 - d_{x_6} x_6. \tag{14}$$

Proof. Under the given initial conditions, it is easy to prove that the solutions of the system (9)-(14) are positive; if not, we assume a contradiction: that there exists a first time $t_i, i = 1, 2, \dots, 6$ such that

$$x_i(t_i) = 0, \quad \dot{x}_i(t_i) < 0, \quad x_j(t) \geq 0, \quad 0 \leq t \leq t_j, \quad i \neq j. \tag{15}$$

In the first case, we have

$$\dot{x}(t_1) = \pi_{x_1} > 0, \tag{16}$$

which is a contradiction. It means that $x_1(t) \geq 0, \forall t \geq 0$.

In the second case, we have

$$\dot{x}(t_2) = \alpha_1 x_1(t_2) x_3(t_2) \geq 0. \tag{17}$$

which is a contradiction. Hence, $x_2(t) \geq 0$ for all $t \geq 0$. In the third case,

$$\dot{x}(t_3) = \beta x_1(t_3) x_6(t_3) + \beta x_2(t_3) x_6(t_3) \geq 0. \tag{18}$$

which is a contradiction. Hence, $x_3(t) \geq 0$ for all $t \geq 0$. Analogously, we can show that the rest of the variables are non-negative.

3.1.2. Boundedness of Solutions

We already have a lower bound given by the above lemma 1 for the solutions of model (9)-(14) with nonnegative initial values. We now show that the solutions are bounded from above.

We denote by $C_b(I)$ the set of all continuous and bounded functions defined on the interval I taking values in \mathbb{R}^6 .

Lemma 2. Let $\varphi: [0, \infty) \rightarrow \mathbb{R}^6$ be a solution of system (9)-(14). If $\varphi(0) \in \mathbb{R}_+^6$, then $\varphi \in C_b[0, \infty)$.

Proof. Because of Lemma 1, it only remains to prove the existence of an upper bound to the nonnegative solutions of system (9)-(14). Let $y(t) = \sum_{i=1}^5 x_i$ be the total concentration of the T cells. Then,

$$y(t) \leq y(0) + \frac{\pi_{x_1} + \pi_{x_4}}{\Lambda_k}, \text{ where } \Lambda_k = \min \{d_{x_j}\}, j = 1, 2, 3, 4, 5. \quad (19)$$

Hence, we obtain

$$x_6(t) \leq \frac{N_{x_6} d_{x_3}}{d_{x_6}} \left(y(0) + \frac{\pi_{x_1} + \pi_{x_4}}{\Lambda_k} \right). \quad (20)$$

3.2. Equilibria

To find the steady states of the model system (9)-(14), we set each differential equation to solve and solve the resulting system simultaneously from which we obtain two equilibria. These are infection free equilibrium, ε^0 and the infection persistent equilibrium ε^* in which are the coordinates are strictly positive.

$$\varepsilon^0 = (x_1^0, x_2^0, x_3^0, x_4^0, x_5^0, x_6^0), \text{ where } x_1^0 = \frac{\pi_{x_1}}{d_{x_1}}, x_4^0 = \frac{\pi_{x_4}}{d_{x_4}}, x_i^0 = 0, i = 2, 3, 5, 6. \quad (21)$$

Derivation of the Basic Reproduction Number, \mathcal{R}_0

The method of Castillo-Chavez *et al.* [7] is used to compute the reproductive number for the model (9)-(14) and representing the total number of newly infected CD4 T cells arising out of one infected CD4 T cell.

Heterogeneity is defined using groups defined by fixed characteristics:

$$\begin{cases} \frac{dX}{dt} = f(X, Y, Z), \\ \frac{dY}{dt} = g(X, Y, Z), \\ \frac{dZ}{dt} = h(X, Y, Z). \end{cases} \quad (22)$$

where $X \in \mathbb{R}^5, Y \in \mathbb{R}, Z \in \mathbb{R}$, and $h(X, 0, 0) = 0$. Assuming that $g(X^*, Y, Z) = 0$ implicitly determines a function $Y = \tilde{g}(X^*, Z)$. Let $A = D_Z h(X^*, \tilde{g}(X^*, 0), 0)$ and further assume that A can be written in the form $A = M - D$, with $M \geq 0$ (that is $m_{ij} \geq 0$) and $D > 0$, a diagonal matrix. The reproduction numbers are then evaluated from the matrix MD^{-1} .

The cell population subgroups are divided between X non-infected cells, Y infected but not infectious cells and Z infectious class. Then,

$X = (x_1, x_2, x_4, x_5), Y = x_3$ and $Z = x_6$.

Let $U_0 = (X^*, 0, 0)$ denote the virus free equilibrium, that is, $f(X^*, 0, 0) = g(X^*, 0, 0) = h(X^*, 0, 0) = 0$ and $Y = \tilde{g}(X^*, Z)$, where

$$\tilde{g}(X^*, Z) = \frac{\beta \pi_{x_1} Z + \beta d_{x_1} x_2^0 Z}{d_{x_1} (d_{x_1 + \rho x_5^0})} \tag{23}$$

Computing $A = D_Z h(X^*, \tilde{g}(X^*, 0), 0)$ gives

$$\frac{N_{x_6} \beta \pi_{x_1}}{d_{x_1}} - d_{x_6}, \tag{24}$$

Therefore,

$$\mathcal{R}_0 = \frac{N_{x_6} \pi_{x_1} \beta}{d_{x_1} d_{x_6}}. \tag{25}$$

Let us now state the infection persistent equilibrium, ε^* .

$$\varepsilon^* = (x_1^*, x_2^*, x_3^*, x_4^*, x_5^*, x_6^*), \tag{26}$$

where

$$\begin{cases} x_1^* = \frac{\pi_{x_1}}{\beta x_6^* + d_{x_1} + \alpha_1 x_3^*}, \\ x_2^* = \frac{\alpha_1 x_3^* \pi_{x_1}}{\beta x_6^* + d_{x_2} \beta x_6^* + d_{x_1} + \alpha_1 x_3^*}, \\ x_4^* = \frac{\Pi_{x_4} (d_{x_2} + \beta x_6^*) (d_{x_1} + \alpha_1 x_3^* + \beta x_6^*)}{d_{x_4} (d_{x_2} + \beta x_6^*) (d_{x_1} + \alpha_1 x_3^* + \beta x_6^*) + \Pi_{x_1} \alpha_1 \alpha_2 x_3^{*2}}, \\ x_5^* = \frac{\Pi_{x_1} \Pi_{x_4} \alpha_1 \alpha_2 x_3^{*2}}{d_{x_5} (d_{x_4} (d_{x_2} + \beta x_6^*) (d_{x_1} + \alpha_1 x_3^* + \beta x_6^*) + \Pi_{x_1} \alpha_1 \alpha_2 x_3^{*2})}, \\ x_6^* = \frac{N_{x_6} d_{x_3} x_3^*}{d_{x_6}}. \end{cases} \tag{27}$$

Theorem 1. (Existence of the infection persistence equilibrium)

Consider the system (9)-(14). The infection persistent equilibrium, ε^* , exists if $\mathcal{R}_0 > 1$, where x_3^* is positive solution to the quintic equation

$$Q_1(x_3) = A_5 x_3^5 + A_4 x_3^4 + A_3 x_3^3 + A_2 x_3^2 + A_1 x_3 = 0 \tag{28}$$

with

$$\begin{cases} A_5 = \frac{N_{x_6} \beta d_{x_3}^2 d_{x_5} \varphi_4 \varphi_5}{d_{x_6}} + \frac{N_{x_6} \Pi_{x_1} \pi_{x_4} \alpha_1 \alpha_2 \beta d_{x_3} \rho \varphi_5}{d_{x_6}} > 0, \\ A_4 = d_{x_5} \varphi_2 \varphi_4 + \frac{N_{x_6} \beta d_{x_3}^2 d_{x_5} \varphi_3 \varphi_5}{d_{x_6}} + \pi_{x_1} \pi_{x_4} \alpha_1 \alpha_2 d_{x_2} \rho \varphi_5 + \frac{N_{x_6} \pi_{x_1} \pi_{x_4} \alpha_1 \alpha_2 \beta d_{x_1} d_{x_3} \rho}{d_{x_6}}, \\ A_3 = d_{x_5} \varphi_1 \varphi_4 + d_{x_5} \varphi_2 \varphi_3 + \pi_{x_1} \pi_{x_4} \alpha_1 \alpha_2 d_{x_1} d_{x_2} \rho + \frac{N_{x_6} \beta d_{x_1} d_{x_2} d_{x_3}^2 d_{x_4} d_{x_5} \varphi_5}{d_{x_6}}, \\ A_2 = d_{x_5} \varphi_1 \varphi_3 + d_{x_1} d_{x_2} d_{x_4} d_{x_5} \varphi_4, \\ A_1 = d_{x_1} d_{x_2} d_{x_4} d_{x_5} \varphi_1, \end{cases} \tag{29}$$

and

$$\left\{ \begin{aligned} \varphi_1 &= d_{x_1} d_{x_2} d_{x_3} (1 - \mathcal{R}_0) < 0, \\ \varphi_2 &= d_{x_2} d_{x_3} \varphi_5 - \frac{N_{x_6}^2 \pi_{x_1} \beta^2 d_{x_3}^2}{d_{x_6}^2} + \frac{N_{x_6} \beta d_{x_1} d_{x_3}^2}{d_{x_6}} - \frac{N_{x_6} \pi_{x_1} \alpha_1 \beta d_{x_3}}{d_{x_6}}, \\ \varphi_3 &= d_{x_2} d_{x_4} \varphi_5 + \frac{N_{x_6} \beta d_{x_1} d_{x_3} d_{x_4}}{d_{x_6}}, \\ \varphi_4 &= \pi_{x_1} \alpha_1 \alpha_2 + \frac{N_{x_6} \beta d_{x_3} d_{x_4} \varphi_5}{d_{x_6}} > 0, \\ \varphi_5 &= \alpha_1 + \frac{N_{x_6} \beta d_{x_3}}{d_{x_6}} > 0. \end{aligned} \right. \tag{30}$$

Proof. From (28), $Q_1(x_3) = 0 \Rightarrow x_3^* = 0$ (which results in the virus free steady state, ε^0), or

$$Q_2(x_3) = A_5 x_3^4 + A_4 x_3^3 + A_3 x_3^2 + A_2 x_3 + A_1 = 0, \tag{31}$$

To establish the existence of a positive solution of $Q_2(x_3)$, we argue as follows.

Note

$$Q_2(0) = A_1 = d_{x_1}^2 d_{x_2}^2 d_{x_3} d_{x_4} d_{x_5} (1 - \mathcal{R}_0) < 0. \tag{32}$$

Due to continuity of $Q_2(x_3)$ we note that

$$\begin{aligned} \lim_{x_3 \rightarrow \infty} Q_2(x_3) &= +\infty, \text{ there exists a positive value of } x_3, \text{ say, } x_3^* \in (0, +\infty) \\ \text{such that } Q_2(x_3^*) &= 0. \end{aligned} \tag{33}$$

Observation 1

$$\lim_{x_3^* \rightarrow 0} x_1^* = \frac{\pi_{x_1}}{d_{x_1}}, \lim_{x_3^* \rightarrow \infty} x_1^* = 0, \tag{34}$$

$$\lim_{x_3^* \rightarrow 0} x_j^* = 0, \lim_{x_3^* \rightarrow \infty} x_j^* = 0, j = 2, 5 \tag{35}$$

$$\lim_{x_3^* \rightarrow 0} x_4^* = \frac{\pi_{x_4}}{d_{x_4}}, \tag{36}$$

$$\lim_{x_3^* \rightarrow \infty} x_4^* = \frac{\pi_{x_4}}{d_{x_4} + \Psi}, \text{ where } \Psi = \frac{\alpha_1 \alpha_2 d_{x_6}^2 \pi_{x_1}}{\beta N_{x_6} d_{x_3} (\beta N_{x_6} d_{x_3} + \alpha_1 d_{x_6})} \tag{37}$$

$$\lim_{x_3^* \rightarrow \infty} x_5^* = \frac{\Psi \pi_{x_4}}{d_{x_4} d_{x_5} + \Psi}. \tag{38}$$

4. Stability Analysis of Equilibria

4.1. Local Stability of Virus Free Equilibrium Point, ε^0

Theorem 2. For system (9)-(14), if $\mathcal{R}_0 < 1$, then the infection free equilibrium, ε^0 , is locally asymptotically stable and unstable otherwise.

Proof. Consider the Jacobian matrix, $J(\varepsilon^0)$, evaluated at ε^0 , of the system (9)-(14).

$$J(\varepsilon^0) = \begin{pmatrix} -d_{x_1} & 0 & -\alpha_1 x_1^0 & 0 & 0 & -\beta x_1^0 \\ 0 & -d_{x_2} & \alpha_1 x_1^0 & 0 & 0 & 0 \\ 0 & 0 & -d_{x_3} & 0 & 0 & \beta x_1^0 \\ 0 & 0 & 0 & -d_{x_4} & 0 & 0 \\ 0 & 0 & 0 & 0 & -d_{x_5} & 0 \\ 0 & 0 & N_{x_6} d_{x_3} & 0 & 0 & -d_{x_6} \end{pmatrix} \tag{39}$$

The corresponding characteristic equation has the following eigenvalues

$$\lambda_1 = -d_{x_1}, \lambda_2 = -d_{x_2}, \lambda_3 = -d_{x_4}, \lambda_4 = -d_{x_5}$$

and the other two eigenvalues are obtained from the following reduced matrix, J_1

$$J_1 = \begin{pmatrix} -d_{x_3} & \beta x_1^0 \\ N_{x_6} d_{x_3} & -d_{x_6} \end{pmatrix} \tag{40}$$

From (40), we investigate the nature of eigenvalues by noting the following.

$$\text{Trace}(J_1) = -(d_{x_3} + d_{x_6}) < 0, \tag{41}$$

$$\text{Det}(J_1) = d_{x_3} d_{x_6} (1 - \mathcal{R}_0) > 0, \text{ since } \mathcal{R}_0 < 1. \tag{42}$$

By (41) and (42), we see that all the eigenvalues are negative and thus the infection free equilibrium, ε^0 , is locally asymptotically stable.

If $\mathcal{R}_0 > 1$, then the corresponding eigenvalues of the sub-matrix (40) are

$$\lambda^- = \frac{-(d_{x_3} + d_{x_6}) - \sqrt{(d_{x_3} + d_{x_6})^2 - 4d_{x_3} d_{x_6} (1 - \mathcal{R}_0)}}{2} < 0, \tag{43}$$

$$\lambda^+ = \frac{-(d_{x_3} + d_{x_6}) + \sqrt{(d_{x_3} + d_{x_6})^2 - 4d_{x_3} d_{x_6} (1 - \mathcal{R}_0)}}{2} > 0, \tag{44}$$

where the discriminant, Δ , is

$$\Delta = (d_{x_3} + d_{x_6})^2 - 4d_{x_3} d_{x_6} (1 - \mathcal{R}_0) = (d_{x_3} - d_{x_6})^2 + 4d_{x_3} d_{x_6} \mathcal{R}_0 > 0. \tag{45}$$

4.2. Global Stability of Infection Free Equilibrium, ε^0

Theorem 3. Consider the system (9)-(14). The infection free equilibrium, ε^0 , is globally asymptotically stable if $\alpha_i = 0, i = 1, 2$ and $\mathcal{R}_0 < 1$.

Proof. Consider the Lyapunov function, V , defined by

$$V = \left(x_1 - x_1^* - x_1^* \ln \frac{x_1}{x_1^*} \right) + x_2 + x_3 + \left(x_4 - x_4^* - x_4^* \ln \frac{x_4}{x_4^*} \right) + x_5 + \frac{\beta \pi_{x_1}}{d_{x_1} d_{x_6}} x_6. \tag{46}$$

Differentiating with respect to time, t , we get

$$\begin{aligned} \dot{V} = & \left(1 - \frac{x_1^0}{x_1} \right) \left[\pi_{x_1} - \beta x_1 x_6 - d_{x_1} x_1 - \alpha_1 x_1 x_3 \right] + \alpha_1 x_1 x_3 - \beta x_2 x_6 - d_{x_2} x_2 \\ & + \beta x_1 x_6 + \beta x_2 x_6 - d_{x_3} x_3 - \rho x_3 x_5 + \left(1 - \frac{x_4^0}{x_4} \right) \left[\pi_{x_4} - d_{x_4} x_4 - \alpha_2 x_2 x_3 x_4 \right] \\ & + \alpha_2 x_2 x_3 x_4 - d_{x_5} x_5 + \frac{\beta \pi_{x_1}}{d_{x_1} d_{x_6}} \left[N_{x_6} d_{x_3} x_3 - d_{x_6} x_6 \right] \end{aligned} \tag{47}$$

Using the conditions satisfied by system (9)-(14) at ε^0 and rearranging the terms, we obtain

$$\begin{aligned} \dot{V} = & d_{x_1} x_1^0 \left(2 - \frac{x_1^0}{x_1} - \frac{x_1}{x_1^0} \right) + d_{x_4} x_4^0 \left(2 - \frac{x_4^0}{x_4} - \frac{x_4}{x_4^0} \right) \\ & + d_{x_3} (\mathcal{R}_0 - 1) x_3 - d_{x_2} x_2 - \rho x_3 x_5 - d_{x_5} x_5 \leq 0. \end{aligned} \tag{48}$$

Since the arithmetic mean is greater than or equal to the geometrical mean, the first two terms of (48) are less than or equal to zero. And the global stability of ε^0 follows from LaSalle’s Invariance principle [8].

4.3. Local Stability of Infection Persistent Equilibrium, ε^*

Theorem 4. For system (9)-(14), if $\mathcal{R}_0 > 1$, then the infection persistent equilibrium, ε^* , is locally asymptotically stable and unstable otherwise.

Proof. Consider the Jacobian matrix, $J(\varepsilon^0)$, evaluated at ε^0 , of the system (9)-(14).

$$J(\varepsilon^0, \beta^*) = \begin{pmatrix} -d_{x_1} & 0 & -\alpha_1 x_1^0 & 0 & 0 & -\beta^* x_1^0 \\ 0 & -d_{x_2} & \alpha_1 x_1^0 & 0 & 0 & 0 \\ 0 & 0 & -d_{x_3} & 0 & 0 & \beta^* x_1^0 \\ 0 & 0 & 0 & -d_{x_4} & 0 & 0 \\ 0 & 0 & 0 & 0 & -d_{x_5} & 0 \\ 0 & 0 & N_{x_6} d_{x_3} & 0 & 0 & -d_{x_6} \end{pmatrix} \tag{49}$$

with β chosen as our bifurcation parameter where $\beta = \beta^* = \frac{d_{x_1} d_{x_6}}{N_{x_6} \pi_{x_1}}$.

The corresponding characteristic equation of the matrix, (49), has the following eigenvalues

$$\lambda_1 = -d_{x_1}, \lambda_2 = -d_{x_2}, \lambda_3 = -d_{x_4}, \lambda_4 = -d_{x_5}$$

and the other two eigenvalues are obtained from the following reduced matrix, J_1^*

$$J_1^* = \begin{pmatrix} -d_{x_3} & \beta^* x_1^0 \\ N_{x_6} & -d_{x_6} \end{pmatrix} \tag{50}$$

From which we get the eigenvalues

$$\lambda_5 = 0 \text{ and } \lambda_6 = -(d_{x_3} + d_{x_6}) \tag{51}$$

Note that we have a simple zero eigenvalue and the rest of the eigenvalues are negative. Therefore, we can now apply the center manifold theory to prove the local stability of the infection persistent equilibrium, ε^* . The left eigenvector associated with the zero eigenvalue of $J(\varepsilon^*, \beta^*)$ is $v = (v_1, v_2, v_3, v_4, v_5, v_6)$ where

$$v_i = 0, \quad i = 1, 2, 4, 5; \quad v_3 = N_{x_6} x_6, \quad v_6 = v_6 > 0. \tag{52}$$

and the corresponding right eigenvector is $w^T = (w_1, w_2, w_3, w_4, w_5, w_6)^T$ where

$$\begin{cases} w_1 = \frac{-d_{x_6} (\alpha_1 \pi_{x_1} + d_{x_1} d_{x_3})}{N_{x_6} d_{x_1}^2 d_{x_3}} w_6, \\ w_2 = \frac{\alpha_1 \pi_{x_1}}{N_{x_6} d_{x_1} d_{x_3}} w_6, \\ w_3 = \frac{d_{x_6}}{N_{x_6} d_{x_3}} w_6, \\ w_j = 0, \quad j = 4, 5, \\ w_6 = w_6 > 0 \end{cases} \tag{53}$$

According to coefficients **a** and **b** defined in Theorem 4.1 of Castillo-Chavez and Song [9], it follows that

$$\begin{aligned} \mathbf{a} &= \sum_{k,i,j=1}^6 v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j} (\varepsilon^0, \beta^*) \\ &= v_3 \left[2w_1 w_6 \frac{\partial^2 f_3}{\partial x_1 \partial x_6} + 2w_2 w_6 \frac{\partial^2 f_3}{\partial x_2 \partial x_6} \right] \\ &= -\frac{2N_{x_6} \beta^{*2} w_6^2 x_1^0 v_6}{d_{x_1}} < 0. \end{aligned} \tag{54}$$

and

$$\begin{aligned} \mathbf{b} &= \sum_{k,i=1}^6 v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \beta^*} \\ &= N_{x_6} v_6 \left[w_1 \frac{\partial^2 f_3}{\partial x_1 \partial \beta^*} + w_2 \frac{\partial^2 f_3}{\partial x_2 \partial \beta^*} + w_3 \frac{\partial^2 f_3}{\partial x_3 \partial \beta^*} + w_6 \frac{\partial^2 f_3}{\partial x_6 \partial \beta^*} \right] \\ &= N_{x_6} (x_1^0 + x_2^0) v_6 w_6 > 0. \end{aligned} \tag{55}$$

We now use the following theorem whose proof is found in Castillo-Chavez and Song [9].

Theorem 5. Consider the following general system of ordinary differential equations with a parameter ϕ

$$\frac{dx}{dt} = f(x, \phi), \quad f : \mathbb{R}^n \times \mathbb{R} \rightarrow \mathbb{R} \text{ and } f \in C^2(\mathbb{R}^n \times \mathbb{R}), \tag{56}$$

where 0 is an equilibrium of the system, that is $f(0, \phi) = 0$ for all ϕ and assume

A1: $A = D_x f(0, 0) = \frac{\partial f_i}{\partial x_j}(0, 0)$ is the linearization of system (9)-(14) around the equilibrium 0 with ϕ evaluated at 0. Zero is a simple eigenvalue of A and other eigenvalues of A have negative real parts;

A2: Matrix A has a right eigenvector w and a left eigenvector v corresponding to the zero eigenvalue. Let f_k be the k^{th} component of f and

$$\begin{aligned} a &= \sum_{k,i,j}^n v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0, 0), \\ b &= \sum_{k,i}^n v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0, 0), \end{aligned} \tag{57}$$

The local dynamics of system (9)-(14) around 0 are totally governed by a and b.

1) $a > 0, b > 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is locally asymptotically stable, and there exists a positive unstable equilibrium; when $0 < \phi \ll 1$, 0 is unstable and there exists a negative and locally asymptotically stable equilibrium;

2) $a < 0, b < 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is unstable; when $0 < \phi \ll 1$, 0 is locally asymptotically stable, and there exists a positive unstable equilibrium;

3) $a > 0, b < 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is unstable, and there exists a locally asymptotically stable negative equilibrium; when $0 < \phi \ll 1$, 0 is stable and a positive unstable equilibrium appears;

4) $a < 0, b > 0$. When ϕ changes from negative to positive, 0 changes its stability from stable to unstable. Correspondingly a negative unstable equilibrium becomes positive and locally asymptotically stable.

Thus, $a < 0$ and $b > 0$. Using Theorem 5 item (4), we have established the following result which only holds for $\mathcal{R}_0 > 1$ but close to 1:

Theorem 6. The unique virus present equilibrium state guaranteed by Theorem 5 is locally asymptotically stable for \mathcal{R}_0 near 1.

4.4. Global Stability of Infection Persistent Equilibrium, ε^*

Theorem 7. Consider the system (9)-(14). If $\alpha_1 = \rho = 0$ and $\mathcal{R}_0 > 1$, then the infection persistent equilibrium, ε^* , is globally asymptotically stable (GAS).

Define a Lyapunov function, L , as follows

$$L = \left(x_1 - x_1^* - x_1^* \ln \left(\frac{x_1}{x_1^*} \right) \right) + \left(x_2 - x_2^* - x_2^* \ln \left(\frac{x_2}{x_2^*} \right) \right) + \left(x_3 - x_3^* - x_3^* \ln \left(\frac{x_3}{x_3^*} \right) \right) + \frac{1}{N_{x_6}} \left(x_6 - x_6^* - x_6^* \ln \left(\frac{x_6}{x_6^*} \right) \right) \tag{58}$$

Differentiating along the solutions of system (9)-(14), we get

$$L = \left(1 - \frac{x_1^*}{x_1} \right) \dot{x}_1 + \left(1 - \frac{x_2^*}{x_2} \right) \dot{x}_2 + \left(1 - \frac{x_3^*}{x_3} \right) \dot{x}_3 + \frac{1}{N_{x_6}} \left(1 - \frac{x_6^*}{x_6} \right) \dot{x}_6, \tag{59}$$

Using the conditions of the infection persistent equilibrium point, ε^* we obtain

$$L = \left(1 - \frac{x_1^*}{x_1} \right) \left[\beta x_1^* x_6^* + d_{x_1} x_1^* - \beta x_1 x_6 - d_{x_1 x_1} \right] + \left(1 - \frac{x_2^*}{x_2} \right) \left[-\beta x_2 x_6 + \beta x_2^* x_6^* \frac{x_2}{x_2^*} \right] + \left(1 - \frac{x_3^*}{x_3} \right) \left[\beta x_1 x_6 + \beta x_2 x_6 - \beta x_1^* x_6^* \frac{x_3}{x_3^*} - \beta x_2^* x_6^* \frac{x_3}{x_3^*} \right] + \frac{1}{N_{x_6}} \left(1 - \frac{x_6^*}{x_6} \right) \left[N_{x_6} d_{x_3} x_3 - N_{x_6} d_{x_3} x_3^* \frac{x_6}{x_6^*} \right] \tag{60}$$

We now implement the following transformation

$$y_i = \frac{x_i}{x_i^*}, \quad i = 1, 2, \dots, 6 \tag{61}$$

$$\begin{aligned} L &= \beta x_1^* x_6^* \left(1 - \frac{1}{y_1}\right) (1 - y_1 y_6) + d_{x_1} x_1^* \left(1 - \frac{1}{y_1}\right) (1 - y_1) \\ &\quad + \beta x_2^* x_6^* \left(1 - \frac{1}{y_2}\right) (y_2 - y_2 y_6) + \beta x_1^* x_6^* \left(1 - \frac{1}{y_3}\right) (y_1 y_6 - y_3) \\ &\quad + \beta x_2^* x_6^* \left(1 - \frac{1}{y_3}\right) (y_2 y_6 - y_3) + d_{x_3} x_3^* \left(1 - \frac{1}{y_6}\right) (y_3 - y_6) \\ &= \beta x_1^* x_6^* \left(3 - \frac{1}{y_1} - \frac{y_3}{y_6} - \frac{y_1 y_6}{y_3}\right) + d_{x_1} x_1^* \left(2 - \frac{1}{y_1} - y_1\right) \\ &\quad + \beta x_2^* x_6^* \left(1 - \frac{y_3}{y_6} - \frac{y_2 y_6}{y_3} + y_2\right) \end{aligned} \tag{62}$$

Since the arithmetic mean is greater than or equal to the geometrical mean, all the three terms of (62) are less than or equal to zero. And the global stability of ε^* follows from LaSalle’s Invariance principle [8].

5. Numerical Simulations

To illustrate the analytic results obtained above, we give some simulations using the parameter values in **Table 2** and **Table 3**. Numerical results are displayed in the following figures.

In the following **Figure 1** we demonstrate the existence of the virus free equilibrium point, ε^0 . This signifies the case when there is no infection present. In other words, it is a scenario where the pathogen that had initially invaded the host has been cleared either through the action of the immune response or treatment (or both). Of course in our case, there is no treatment. So this clearance is all attributed to the immune response. In **Figure 2(a)** we simulate the dynamics of naive CD4+ T cells and productively infected cells. The naive CD4+ T cells are assumed to have an initial concentration of 10^6 cells per mL. We also assume that the productively infected CD4+ T cell population is initially zero. We observe from the figure that the naive CD4+ T cell population declines from its maximum value and attains its minimum value after about one and half years

Table 2. Model parameters and their definitions.

Variable	Definitions	Value	Source
$x_1(0)$	Initial naive CD4+ T cells	10^6 cells ml^{-1}	[10]
$x_2(0)$	Initial activated CD4+ T cells	0 cells ml^{-1}	[11]
$x_3(0)$	Initial productively infected CD4+ T cells	0 cells ml^{-1}	[11]
$x_4(0)$	Initial naive CD8+ T cells	5×10^5 cells ml^{-1}	[11]
$x_5(0)$	Initial activated CD8+ T cells	0	[11]
$x_6(0)$	Initial HIV-1 virions	3 virions ml^{-1}	[12]

Table 3. Model parameters and their definitions.

Parameter	Value	Source
π_{x_3}	$10^4 \text{ mL}^{-1} \text{ day}^{-1}$	[11]
π_{x_4}	$2 \times 10^4 \text{ mL}^{-1} \text{ day}^{-1}$	[11]
β	$[2.4 \times 10^{-8}, 2.5 \times 10^{-7}] \text{ mL virus}^{-1} \text{ day}^{-1}$	[11]
d_{x_3}	0.01 day^{-1}	[11]
d_{x_2}	0.21 day^{-1}	[11]
d_{x_3}	0.24 day^{-1}	[11]
d_{x_4}	0.03 day^{-1}	[11]
d_{x_5}	0.0047 day^{-1}	[11]
d_{x_6}	3 day^{-1}	[11]
α_1	$1.4 \times 10^{-4} \text{ cell}^{-1} \text{ day}^{-1}$	[13]
α_2	$2.3 \times 10^{-6} \text{ cell}^{-2} \text{ day}^{-1}$	[13]
N_{x_6}	$10 - 1000 \text{ virions}^{-1} \text{ cell}^{-1}$	[14]
ρ	$5.47 \times 10^{-5} \text{ mL cell}^{-1} \text{ day}^{-1}$	[13]

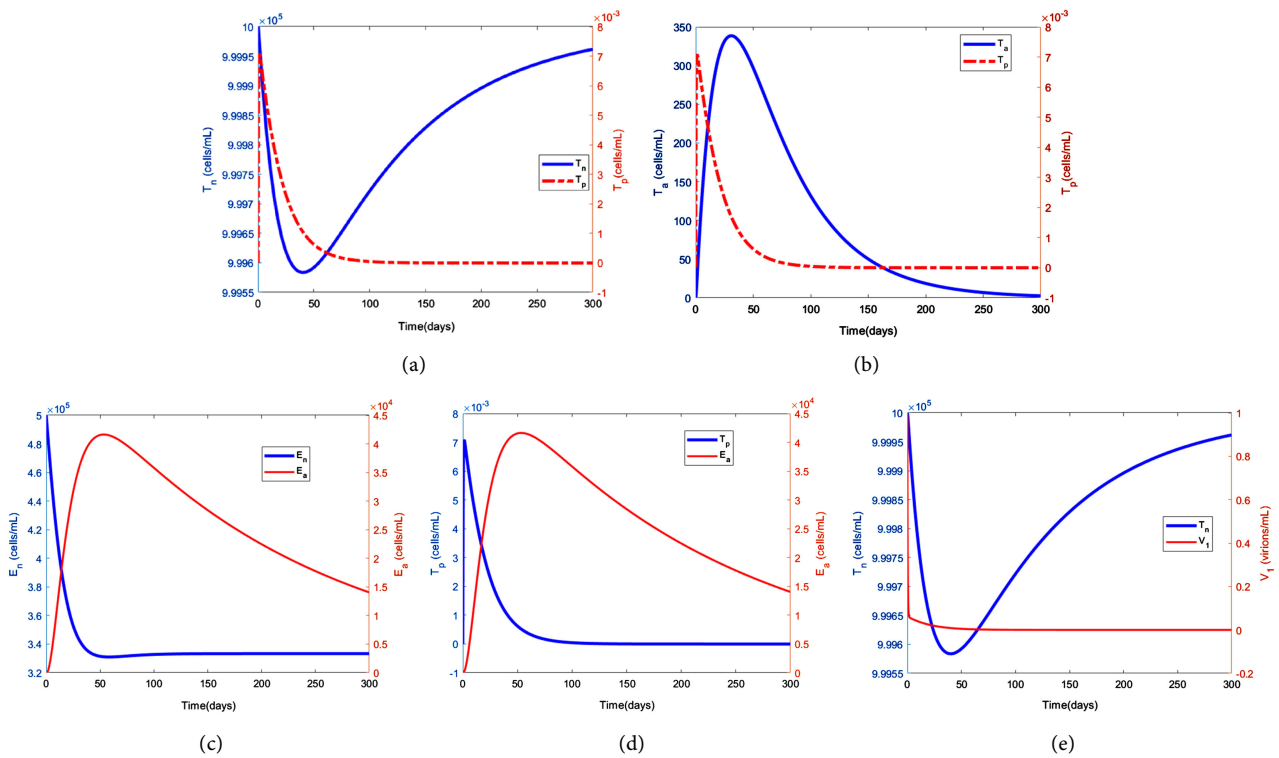


Figure 1. Existence of virus free equilibrium point, ε^0 . (a) Naive and productively infected CD4+ T cell dynamics; (b) Productively infected and activated CD4+ T cell dynamics; (c) Naive and activated CD8+ T cell dynamics; (d) Activated CD8+ T and productively infected CD4+ T cell dynamics; (e) Naive CD4+ T cell and HIV-1 dynamics.

before reaching a steady state value in about two and half years. This is quite typical of HIV-1 infection for those patients who do not access highly active antiretroviral therapy (HAART).

In the following **Figure 2** we demonstrate the existence of an infection persistent equilibrium point, ε^* . This represents a scenario when the host is invaded by a pathogen, herein referred to as HIV-1, and the infection is established. We simulate our model with $\mathcal{R}_0 = 1.1667$, where the basic reproduction number, \mathcal{R}_0 , results from utilising the data in **Table 1**. In **Figure 3**, we simulate the long term dynamics of HIV-1 infection. In **Figure 3(c)**, naive CD4+ T cells and HIV-1 dynamics are simulated. It is assumed, in this study, that the initial inoculum is 3 virions. It is interesting to observe that after about five years, the viral load reduces to about 200 cells per microlitre. It is at this level when a patient is said to have acquired immune deficiency syndrome (AIDS). It is a condition when a patient's immunity is weakened to a point where it can hardly fight off any opportunistic infection. Note that in about eight and half years the HIV-1 virus grows unboundedly and the CD4 count declines to zero.

In **Figure 3**, we simulate the long term dynamics of HIV-1 infection over a period of 3500 days.

6. Discussion and Conclusion

From the analysis of the infection persistent steady state equilibrium point, ε^* ,

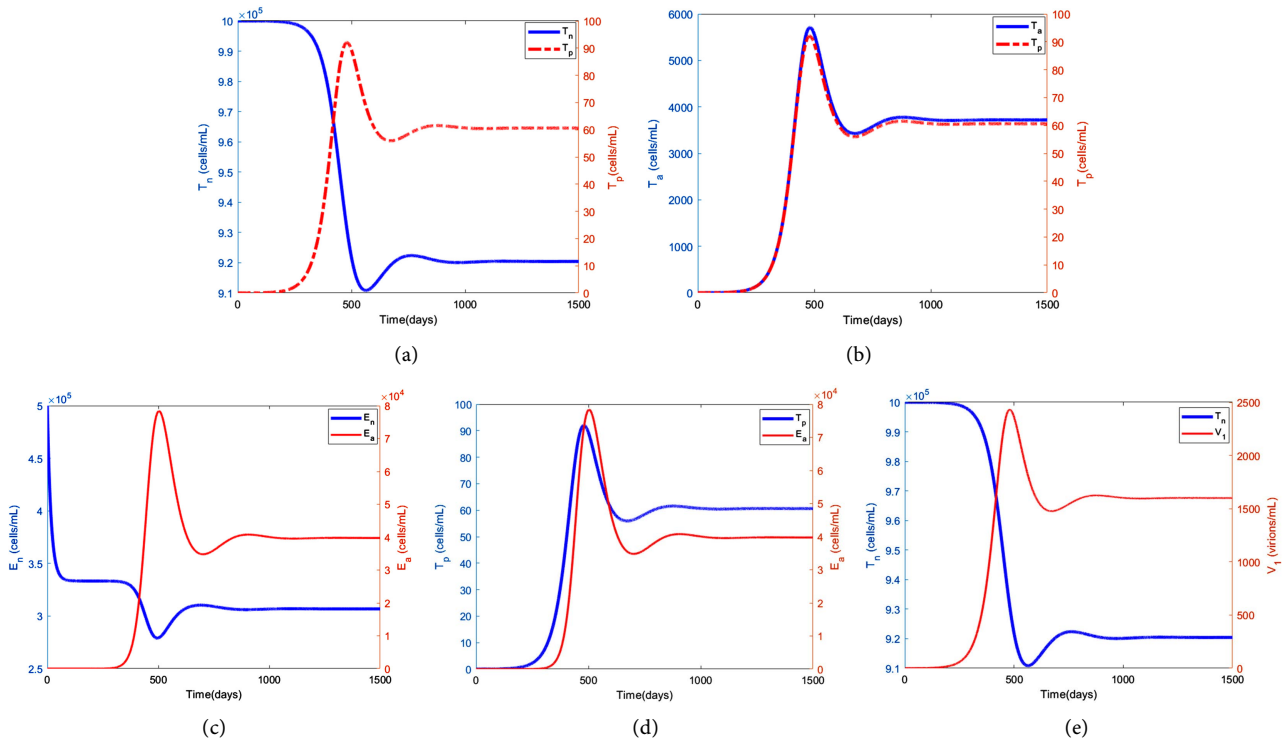


Figure 2. Existence of infection persistent equilibrium point, ε^* . (a) Naive and productively infected CD4+ T cell dynamics; (b) Productively infected and activated CD4+ T cell dynamics; (c) Naive and activated CD8+ T cell dynamics; (d) Activated CD8+ T and productively infected CD4+ T cell dynamics; (e) Naive CD4+ T cell and HIV-1 dynamics.

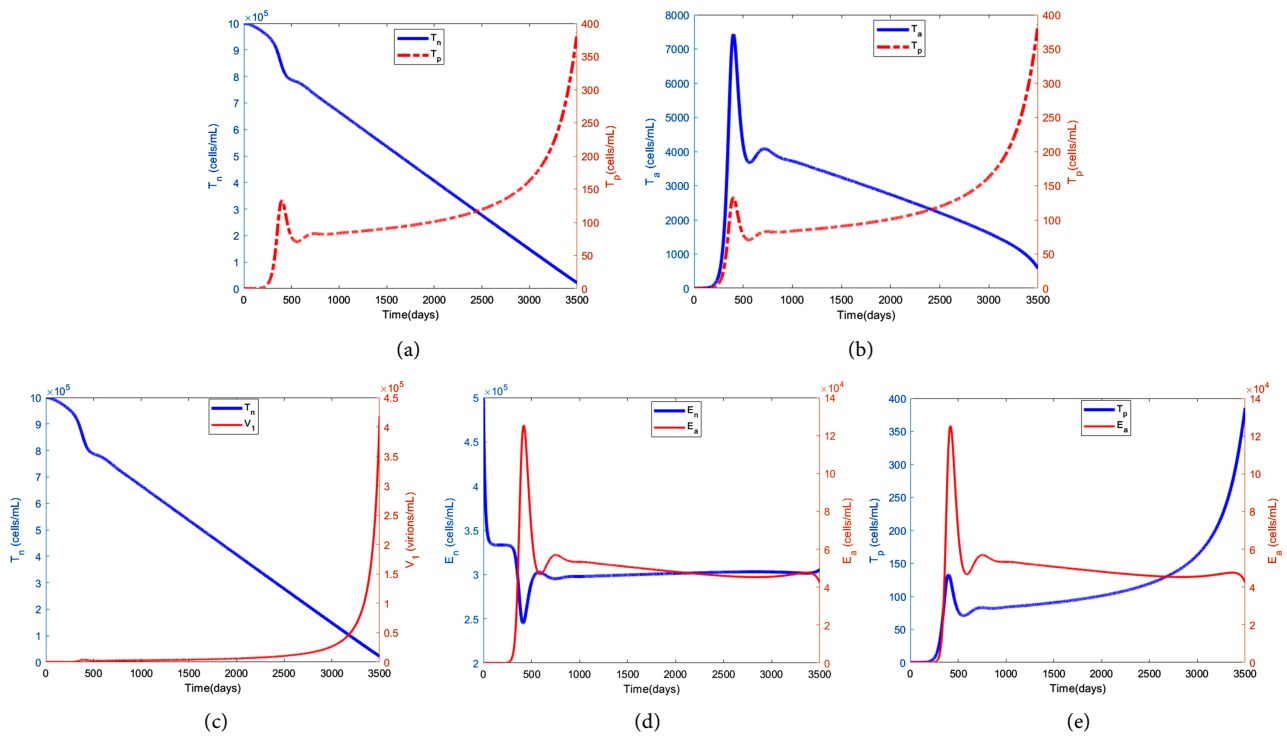


Figure 3. Evolution of HIV infection over a period of 3500 days. (a) Naive and productively infected CD4+ T cell dynamics; (b) Productively infected and activated CD4+ T cell dynamics; (c) Naive CD4+ T cell and HIV-1 dynamics; (d) Naive and activated CD8+ T cell dynamics; (e) Activated CD8+ T and productively infected CD4+ T cell dynamics.

we observe from (34) that when the population of productively infected CD4+ T cells at steady state approaches zero, the population of the uninfected naive CD4+ T cells, in the long run, rebounds to the non-infected steady state. The numerical simulation attests to this observation in **Figure 1(a)**. And as expected when the productively infected CD4+ T cells increase in number substantially, the population of uninfected CD4+ T cells declines to very low levels before attaining its steady state value. This is illustrated in **Figure 2(a)**.

In Equation (35) we note that when the level of infected CD4+ T cells approaches zero, then the steady state values, x_j^* , $j = 2, 5$ also approach zero due to low levels of antigenic stimulation. Note that when the number of infected CD4+ T cells increases unboundedly it may result in exhaustion which may ultimately impair the activation mechanism of precursors. From Equation (36), we observe that when the steady state value of infected CD4+ T cells approaches zero, the steady state value of the naive CD8+ T cells approaches the non-infected steady state. This is due to the fact that there are now a small number of activated CD4+ T cells available to aid in the activation of these precursors. Hence, there will be less number of activated CD8+ T cells. From (37), we see that the non-infected steady state value, $\frac{\pi_{x_4}}{d_{x_4}}$, of the naive CD8+ T cells is

decreased due to the activation mechanism. Also, from (37) and (38) we see that when the activation rates approach zero, the steady state of the naive CD8+ T

cells rebounds to its non-infected state and that of activated CD8+ T cells approaches zero. Hence, there will be a small number of cytotoxic T cells to kill the infected CD4+ T cells.

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Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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