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In-Vivo Models of HIV with Reversion of Resting Infected $CD4^+$ Cells

Emmanuella N. Mbazulike, Sunday S. Isah and Chinwendu E. Madubueze

Department of Mathematics/Statistics/Computer Science, University of Agriculture, P.M.B. 2373, Makurdi, Nigeria.

Abstract

Over the years, the use of mathematical models as an aid in understanding features of HIV infection dynamics has been substantial. This paper considered two mathematical models of the viral dynamics of HIV with reversion rate and immune response. The first model used the saturated function as mode of transmission while the second model used the mass action mode of transmission and captured the latently infected $CD4^+$ cells and the productively infected $CD4^+$. The basic properties of the two models such as positivity, existence and uniqueness of the solution of the two models are proven. The basic reproduction number of the models are computed and the models are further analyzed for the stability of the equilibrium states. In addition, numerical simulations are carried out to show the effect of reversion rate and mode of transmission on the dynamics of an in-vivo HIV model. It is observed from numerical results that capturing the latently infected $CD4^+$ cells and the productively infected $CD4^+$ cells using mass action mode of transmission have great impact in reducing basic reproduction number and also reduced the viral load in the body of the infected HIV person. Finally, the sensitivity analysis of the model parameters for the two models are carried out to support the numerical simulation.

Keywords: HIV; Infected $CD4^+$ cells; Reversion state of infected $CD4^+$ cells; Equilibrium states; Sensitivity analysis.

1.0 Introduction

HIV (Human Immunodeficiency Virus) is a member of lentiviruses that has two known types, HIV-1 and HIV- 2 [1]. It infects vital cells in the human immune system such as helper T cells (specifically $CD4^+$cells), macrophages, and dendritic cells [2]. HIV infection leads to low levels of $CD4^+$ cells through a number of mechanisms that include apoptosis of infected T cells [3], apoptosis of uninfected bystander cells [4], direct viral killing of infected cells, and killing of infected $CD4^+$ cells by CD8 cytotoxic lymphocytes [5]. When $CD4^+$cell number declines below a critical level, cell-mediated immunity is lost, and the body becomes progressively more susceptible to opportunistic infections. HIV cannot reproduce itself on its own. It can only replicate inside the cells of host organism and copies its RNA (Ribonucleic acid) genome into healthy cells using an enzyme. This enzyme is called reverse transcriptase and it transcribes viral RNA into DNA which can then be integrated into the host genome which then replicates the virus[6].

According to [6], HIV has a long latency period that is, the time it takes the body's immune system to lose its ability to generate the immune response required to suppress the virus. This leads to an intensified replication of the virus. Without treatment, the average survival is estimated to be 9 to 11 years depending on the HIV subtype [7]. Like any other pathogen, invasion of the body by HIV stimulates an immune response. Although there is a wide range of immune responses, we will focus on $CD4^+$ cells and CD8 cells. CD8 cells control the virus by either lysing the infected cell or inhibiting HIV replication and entry into target cells [8].

The dynamics between virus infections and the immune system involve many different components and are multi–factorial.

Corresponding author: Emmanuella N. Mbazulike, E-mail: emmanuellambazulike@gmail.com, Tel.: +2348165817253

HIV infects $CD4^+$cells, which are a central component orchestrating the generation of specific immune responses that fight the virus [9]. Therefore, the interactions between HIV and the immune system are more complex compared to most other infections

A good number of studies have been conducted to highlight the dynamics of HIV within the host. Ball *et al.* [10] and Perelson and Riberiro [11] reviewed developments in HIV modeling using mass action mode of transmissionwithoutemphasizing the important of immune response and reversion rate.Perelson and Riberiro [11] considered the quantitative findings about HIV by studying acute infection, the response to drug therapy and the rate of generation of HIV variants that escape immune responses.Mugwagwa [8] further worked on the role of CD8 immune responses in HIV. In his work, he showed that a strong cytotoxic lymphocyte (CTL) response can control the viral load while in some cases the virus may persist regardless of the immune response. Hattaf and Yousfi [12]presented a delay – differential equation model with mass action mode of transmission and immune response. They used optimal control approach to describe the interaction between HIV, $CD4^+$cells and cell – mediated immune response. These authors [8] and[12]concluded that the immune response plays a crucial role in reducing the incidence of HIV infection. However, few studies such as Rong *et al.* [13], Yang *et al* [14], Srivastava and Chandra [15], and Arafa *et al* [16] consideredthe reversion of resting infected $CD4^+$cells to uninfected statewithin the host dynamics of HIV without emphasizing the importance of immune responses as stated in [8] and [12]. The reversion of resting infected $CD4^+$ cells to uninfected $CD4^+$ cells is due to non-completion of reverse transcription. Hence, this research work is meant to address the importance of immune responses and reversion of resting infected $CD4^+$cells to uninfected cells on the dynamics of HIV within host.

2.0 Model Formulation

The model is formulated by considering the population of interest, the total cell population and is divided into four mutually exclusive compartments namely: uninfected $CD4^+$ cells, $x(t)$, Infected $CD4^+$cells, $y(t)$, Free virus particle, $v(t)$, and CD8 cells, $z(t)$. Following Sun and Min [17], we assume a saturated infection rate and that some fraction of infected $CD4^+$ cells return to the uninfected classdue to non-completion of reverse transcription. We also assume that infected $CD4^+$ cells have a high death rate compared to uninfected $CD4^+$ cells so that $\mu_2 > \mu_1$. Furthermore, immune responses is incorporated in the model based on the result from [8] and [12]. Hence, below is tabular description of the parameters of the model and the flow diagram.

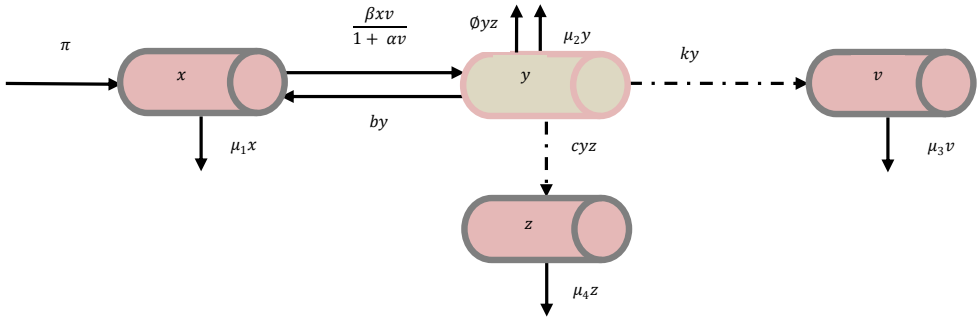

Figure 1: Model diagram showing movements of cells between compartments

Table 1: Model Parameter Values

Parameter	Description
b	Rate at which resting infected $CD4^+$cells revert to uninfected cells
π	Recruitment rate of $CD4^+$cells
μ_3	Natural death rate of the virus
μ_4	Natural death rate of healthy CD8 cells
μ_2	Natural death rate of infected $CD4^+$cells
μ_1	Natural death rate of healthy $CD4^+$cells
β	Effective contact rate between an infected $CD4^+$ cells and a healthy $CD4^+$cells
$\emptyset$	Natural death rate of healthy $CD4^+$cells
k	Virus population
c	Proliferation of CD8 cells

In view of the flow diagram, we obtain the following deterministic system of non-linear ordinary differential equations:

$$\frac{dx}{dt} = \pi - \frac{\beta xv}{1+\alpha v} - \mu_1 x + by$$

$$\frac{dy}{dt} = \frac{\beta xv}{1+\alpha v} - \mu_2 y - \emptyset yz - by$$
$$\frac{dv}{dt} = ky - \mu_3 v \quad (1)$$
$$\frac{dz}{dt} = cyz - \mu_4 z.$$

The nonnegative initial conditions of the model system (1) are $x(0) = x_0,\ y(0) = y_0,\ v(0) = v_0,\ z(0) = z_0$.

2.1 Model Analysis

The Model (1) will be analyzed qualitatively to get insights into the dynamical features of the in-vivo HIV infection considering the reversion state of the infected cells to uninfected state.

The basic properties of the model (1) are very cardinal in the proofs of stability of the equilibrium states. We begin by showing that all solutions of the system (1) are positive for all time $t \geq 0$.

2.1.1 Positivity of Solution

Lemma 1. Let the initial conditions for the model system (1) be $\{x_0, y_0, v_0, z_0 \geq 0\} \in \Omega$, where Ω is the positivity invariant region. Then, the solution set {x(t), y(t), v(t), z(t)} of the system (1) is positive for all $t \geq 0$.

Proof. From the first equation of system (1), we have

$$\frac{dx}{dt} = \pi - \frac{\beta xv}{1+\alpha v} - \mu_1 x + by,$$

Which can be rewrite as

$$\frac{dx}{dt} \geq -\left(\frac{\beta v}{1+\alpha v} + \mu_1\right) x. \quad (2)$$

Now, $\frac{\beta v}{1+\alpha v} < \beta$ since $\frac{\beta}{1+\alpha v} \leq 1$ for $\alpha \geq 1$.Therefore (2) can be written as

$$\frac{dx}{dt} \geq -(\beta + \mu_1)x. \quad (2^*)$$

Integrating (2^*) by separation of variables and applying the initial conditions, yields

$x(t) \geq x_0 e^{-(\beta+\mu_1)t} \geq 0$.

In a similar way, we show the second, third and fourth equations of the model system (1) remain positive.

Thus, the solution set of the model (1) is positive in Ω for all $t \geq 0$.

2.1.2 Existence and Uniqueness of Solution for the Model

For the mathematical model to predict the future of the system from its current state at time t_0, the initial value problem (IVP)

$$x' = f(t,x),\ x(t_0) = x_0 \quad (3)$$

must have a solution that exists and is unique.

In this sub-section, we give conditions for the existence and uniqueness of solution for the system of equations.

Let

$$f_1(t,x) = \pi - \frac{\beta xv}{1+\alpha v} - \mu_1 x + by \quad (4)$$
$$f_2(t,x) = \frac{\beta xv}{1+\alpha v} - \mu_2 y - \emptyset yz - by \quad (5)$$
$$f_3(t,x) = ky - \mu_3 v \quad (6)$$
$$f_4(t,x) = cyz - \mu_4 z \quad (7)$$

So that

$$x' = f(t,x),\ x(t_0) = x_0 \quad (8)$$

Theorem 1.*Let* Ω *denotes the region*

$$|t - t_0| \leq a, \|x - x_0\| \leq b, x = (x_1, x_2, \dots, x_n), x_0 = (x_1, x_2, \dots, x_n) \quad (9)$$

and suppose that $f(t,x)$ *satisfies the Lipchitz condition*

$$\|f(t,x_1) - f(t,x_2)\| \leq k\|x_1 - x_2\| \quad (10)$$

Whenever the pairs (t, x_1) and (t, x_2) belong to D′,where k is a positive constant. Then, there exists a constant $\delta > 0$such that a unique continuous vector solution x(t) of the system (8) exist in the interval $|t - t_0| \leq \delta$. It is important to note that condition (8) is satisfied by the requirement that $k = \frac{\partial f_i}{\partial x_j}, i, j = 1,2, \dots, n$ be continuous and bounded in Ω.

Lemma 2. If f(t, x) has continuous partial derivative $\frac{\partial f_i}{\partial x_j}$ on a bounded closed convex domain R, then it satisfies a Lipchitz condition in R.

We are interested in the region

$$1 \leq \varepsilon \leq R \quad (11)$$

and for a bounded solution of the form

$$0 < R < \infty \quad (12)$$

We have the following existence theorem.

Theorem 2. Let **Ω** denote the region defined in (9)such that (11) and (12) hold. Then, there exists a solution of model system (4) − (7) which is bounded in the region **Ω**.

Proof. Let $f_1 = \pi - \frac{\beta xv}{1+\alpha v} - \mu_1 x + by$

$f_2 = \frac{\beta xv}{1+\alpha v} - \mu_2 y - \emptyset yz - by$

$f_3 = ky - \mu_3 v$

$f_4 = cyz - \mu_4 z$

It suffices that $\frac{\partial f_i}{\partial x_j}, i,j = 1,2,3,4$ are continuous. Consider the partial derivatives of the first equation of (1) that is

$\frac{\partial f_1}{\partial x} = -\frac{\beta v}{1+\alpha v} - \mu_1, \quad \left|\frac{\partial f_1}{\partial x}\right| = \left|-\frac{\beta v}{1+\alpha v} - \mu_1\right| < \infty$

$\frac{\partial f_1}{\partial y} = b, \quad \left|\frac{\partial f_1}{\partial y}\right| = |b| < \infty$

$\frac{\partial f_1}{\partial v} = \frac{-\beta x(1-v)}{(1+\alpha v)^2}, \quad \left|\frac{\partial f_1}{\partial x}\right| = \left|-\frac{\beta x(1-v)}{(1+\alpha v)^2}\right| < \infty$

$\frac{\partial f_1}{\partial z} = 0, \quad \left|\frac{\partial f_1}{\partial y}\right| = |0| < \infty$

In a similar way, we solve for all the equations of the model. Clearly, all the partial derivatives of (1) are continuous and bounded. Hence, there exists a unique solution of (4) - (7) in the region **Ω** by theorem 2.

2.1.3 Existence and Stability of Equilibrium Points

Let $E(x^*, y^*, v^*, z^*)$ be the equilibrium point of the system (1). The steady state solutions are obtained by equating the right hand side (RHS) of system (2.1) to zero and solve. Thus,

$\frac{dx}{dt} = \pi - \frac{\beta xv}{1+\alpha v} - \mu_1 x + by = 0$ (13)

$\frac{dy}{dt} = \frac{\beta xv}{1+\alpha v} - \mu_2 y - \emptyset yz - by = 0$ (14)

$\frac{dv}{dt} = ky - \mu_3 v = 0$ (15)

$\frac{dz}{dt} = cyz - \mu_4 z = 0$ (16)

2.1.4 The Virus-free Equilibrium, E_0

The virus free equilibrium E_0 is a point where HIV has not yet invaded the cell population, that is $y = v = 0$.

Solving (13)-(16) simultaneously for $y = v = 0$, we have virus free equilibrium (VFE) E_0 given by

$E_0 = (x^*, y^*, v^*, z^*) = (\frac{\pi}{\mu_1}, 0, 0, 0)$ (17)

2.1.5 The Basic Reproduction Number, R_0

The basic reproduction number denoted by R_0, is defined as the average number of secondary infections produced when an infected cell is introduce in a wholly uninfected $CD4^+$ cells during its entire period of infectiousness. We compute R_0 using the next generation operator approach described by [18].

Considering the infective compartments, the associated generation matrices F and V at the VFE E_0 are given by

$F = \begin{bmatrix} 0 & \frac{\beta\pi}{\mu_1} \\ 0 & 0 \end{bmatrix}$ and $V = \begin{bmatrix} \mu_2 + b & 0 \\ -k & \mu_3 \end{bmatrix}$.

while the inverse matrix of V is given by

$V^{-1} = \begin{bmatrix} \frac{1}{\mu_2 + b} & 0 \\ \frac{k}{\mu_3(\mu_2 + b)} & \frac{1}{\mu_3} \end{bmatrix}$

The eigenvalues corresponding to the product matrix, FV^{-1} are $\lambda_1 = \frac{\beta k\pi}{\mu_1\mu_3(\mu_2+b)}$, $\lambda_2 = 0$.

Therefore, the dominant eigenvalue (that is, the spectral radius) is the basic reproduction number, that is $R_0 = \max[|\lambda_1|, |\lambda_2|]$. This gives

$R_0 = \frac{\beta k\pi}{\mu_1\mu_3(\mu_2+b)}$ (18)

According to [18], virus free equilibrium E_0 is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$. Therefore, the following theorem holds.

Theorem 3 The virus-free equilibrium point of the in-vivo HIV model described by the system (1) is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.

2.1.6 Global Stability of the Virus Free Equilibrium, E^*

We shall use Lyapunov function to establish the global stability of the virus free equilibrium.

Theorem 4. If $R_0 < 1$, the virus free equilibrium E_0 is globally asymptotically stable in Ω.

Consider the Lyapunov function

$$L = y + \frac{(\mu_2 + b)}{k} v.$$

The derivative of L is given by

$$L' = y' + \frac{(\mu_2 + b)}{k} v' \qquad (19)$$

Where prime' denote the derivative. Substituting y' and v' at the virus-free equilibrium E_0in (19), we have

$$L' = \frac{\mu_3 (\mu_2 + b)}{k}\left(\frac{k\beta\pi}{\mu_1\mu_3 (\mu_2 + b)} - 1\right) v \leq \frac{\mu_3 (\mu_2 + b)}{k}(R_0 - 1)v$$

Therefore, if $R_0 \leq 1$, then $L'(t) \leq 0$. Also, $L'(t) = 0$ if and only if $x = x^*, y = 0, v = 0$, and $z = 0$. Thus, the maximum invariant set in $\{(x, y, v, z) \in \Omega. : L'(t) = 0\}$ is the singleton$\{E_0\}$, where E_0 is the virus free equilibrium state. By LaSalle's invariant principle, every solutions of the model (1) with initial conditions in Ω tends to DFE E_0 as $t \longrightarrow \infty$. Hence, the virus free equilibrium point E_0 is globally asymptotically stable in Ωif $R_0 \leq 1$.

2.1.7 Existence and Stability of the Endemic Equilibrium State

Endemic equilibrium state E^* is a steady state solution where the virus persists in the population, that is $v \neq 0$.

Solving (13)-(16) simultaneously for $y \neq 0$ and $v \neq 0$. We have endemic equilibrium point (EEP)$E^* = (x^*, y^*, v^*, z^*)$

where$x^* = \frac{(c\pi + b\mu_4)(c\mu_3 + \alpha k\mu_4)}{\beta k\mu_4 + \mu_1(c\mu_3 + \alpha k\mu_4)}, y^* = \frac{\mu_4}{c}, v^* = \frac{k\mu_4}{\mu_3 c}, z^* = \frac{\beta x^* v^* - (\mu_2 + b)y^*(1+\alpha v^*)}{(1+\alpha v^*)\emptyset y^*}$ provided$\beta x^* v^* > (\mu_2 + b)y^*(1 + \alpha v^*)$.

2.1.8 Local Stability of the Endemic Equilibrium, E^*

The local stability of the endemic equilibrium is determined using linearization method. The Jacobian matrix, J_{E^*} of model (1) at the endemic equilibrium E^* is given as

$$J_{E^*} = \begin{bmatrix} -\frac{\beta v^*}{1+\alpha v^*} - \mu_1 & b & -\frac{\beta x^*(1-v^*)}{(1+\alpha v^*)^2} & 0 \\ \frac{\beta v^*}{1+\alpha v^*} & -(\mu_2 + b) - \emptyset z^* & \frac{\beta x^*(1-v^*)}{(1+\alpha v^*)^2} & \emptyset y^* \\ 0 & k & -\mu_3 & 0 \\ 0 & cz^* & 0 & cy^* - \mu_4 \end{bmatrix} \qquad (20)$$

The characteristic equation of the Jacobian matrix J_{E^*} (20) is

$$\lambda^4 - \lambda^3\left(cy^* - \mu_4 - \mu_3 - (\mu_2 + \emptyset z^* + b) - \frac{\beta v^*}{1+\alpha v^*} - \mu_1\right) - \lambda^2\left[\left((cy^* - \mu_4) - (\mu_2 + \emptyset z^* + b) - \mu_3\right)\left(\frac{\beta v^*}{1+\alpha v^*} - \mu_1\right) - (\mu_3 - (cy^* - \mu_4)(\mu_2 + \emptyset z^* + b) + \mu_3(cy^* - \mu_4) + (\emptyset y^*)(cz^*) + b\right] - \lambda\left[\left((cy^* - \mu_4 - \mu_3)(\mu_2 + \emptyset z^* + b) + (\emptyset y^*)(cz^*) + \mu_3(cy^* - \mu_4)\right)\left(\frac{\beta v^*}{1+\alpha v^*} - \mu_1\right) - \left((cy^* - \mu_4)(\mu_2 + \emptyset z^* + b) - (\emptyset y^*)(cz^*) - b\right)\mu_3 - (cy^* - \mu_4)b\right] - \left(\mu_3(cy^* - \mu_4)(\mu_2 + \emptyset z^* + b) - \left(\frac{\beta x^*(1-v^*)}{(1+\alpha v^*)^2}\right)(cy^* - \mu_4) + (\emptyset y^*)(cz^*)\mu_3\right)\left[\left(\frac{\beta v^*}{1+\alpha v^*} - \mu_1\right) + \left(\frac{\beta v^*}{1+\alpha v^*}\right)b\mu_3 + \left(\frac{\beta v^*}{1+\alpha v^*}\right)\left(\frac{\beta x^*(1-v^*)}{(1+\alpha v^*)^2}\right)\right](cy^* - \mu_4) = 0 \qquad (21)$$

Using the Routh Hurwitz criteria of stability for (21), the endemic equilibrium is locally asymptotically stable for $R_0 > 1$.

2.1.9 Sensitivity Analysis of the Model

Sensitivity analysis is a mathematical tool used to determine the robustness of the model predictions to parameter values, since data collection and presumed parameter values have errors [19]. Sensitivity analysis is performed in order to determine the relative importance of model parameters on the virus transmission. This helps to investigate which parameters of the model (1) have highest impact on theR_0. The normalized forward sensitivity index is used in this work.

Definition 1. The normalized forward sensitivity index of a variable τ that depends differentiable on the index of a parameter p is defined as

$$r_\tau^p = \frac{\partial p}{\partial \tau} \times \frac{\tau}{p}$$

We derive analytical expression for the sensitivity of R_0 as $r_\tau^{R_0} = \frac{\partial R_0}{\partial \tau} \times \frac{\tau}{R_0}$, where τ denoting the model parameters. We compute the sensitive indices of the model (1) for each parameter involves in R_0 . The indices with positive signs show that the value of R_0 increases when the corresponding parameters are increased and those with negative signs indicate that the value of R_0 decreases when the parameters are increased.

The sensitivity index of R_0 with respect to β is given by

$$r_\beta^{R_0} = \frac{\partial R_0}{\partial \beta} \times \frac{\beta}{R_0} = 1.$$

In a similar way, we get the sensitivity index of R_0 with respect to all parameters in R_0 , and the sensitivity indices results are given in Table 2.

Interpretation of Sensitivity Indices

In interpreting the sensitivity indices, we keep all factors constant. Table 2 shows that the parameters β, k, π increase the value of R_0 when they are increased. This implies that the in-vivo HIV virus will continue to grow in the cell population when these parameters are increased. However when these parameters b, μ_1, μ_2 and μ_3 are increased, the value of R_0 decreases. This means that the in-vivo HIV virus will die out of growth in the cell population. The most sensitive parameters are the effective contact rate, β, followed by the virus population rate, k, and the recruitment rate of the $CD4^+$ cells, π. Increasing or decreasing the values of β, k, π leads to the increase or decrease in the value of R_0 with the same proportion since the sensitivity index is equal to one. Therefore, β, k, π increase as R_0 increases. The reversion rate of infected $CD4^+$ cells to uninfected $CD4^+$ cells, b is also sensitive. When b is increased, R_0 decreases. This implies that the number of the infected cells will reduce when the reversion rate is increased and hence increases the healthy $CD4^+$ cells.

Table 2: Numerical values of sensitivity indices of R_0 for the Model 1

Parameter	Value	Sensitivity index	Parameter	Value	Sensitivity index
b	0.2day^{-1}	-0.4545455	β	$2.4\times10^{-8}\text{day}^{-1}$	$+1.000000000$
π	$10\text{day}^{-1}\text{mm}^{-3}$	$+1.000000000$	k	4000day^{-1}	$+1.000000000$
μ_3	0.167day^{-1}	-1.000000000	μ_2	0.24day^{-1}	-0.5454545
			μ_1	0.01day^{-1}	-1.000000000

2.2 Modified Model Formulation

We consider mass action term that is βxv as mode of transmission since the virus infecting x cells depends on the number of healthy cells. Following Arafa *et al.* [16], the infected cells are divided into two infected classes namely latently infected $CD4^+$ cells, y_1, and productively infected $CD4^+$ cells, y_2. Definitions of the parameters variables remain the same as the previous model except α, which is progress rate from latently infected $CD4^+$ cells to productively infected $CD4^+$ cells. The flow diagram is given in Figure 2.

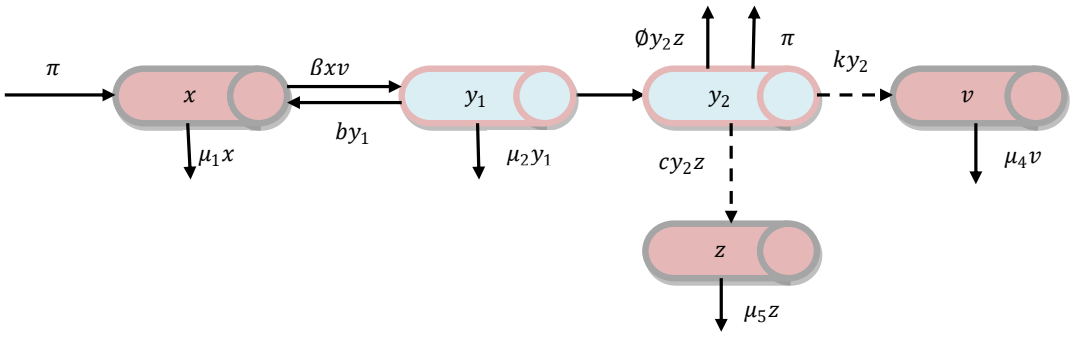

Figure 2: Flow diagram showing movement of cells between Compartments in the Modified Model of the in-vivo HIV Model.

Inmodified model of the in-vivo HIV

The modified model equations is derived with aid of the flow diagram in figure 2 as

$$\frac{dx}{dt} = \pi - \beta xv - \mu_1 x + by_1$$
$$\frac{dy_1}{dt} = \beta xv - \mu_2 y_1 - by_1 - \alpha y_1$$
$$\frac{dy_2}{dt} = \alpha y_1 - \mu_3 y_2 - \emptyset y_2 z \qquad (22)$$
$$\frac{dv}{dt} = ky_2 - \mu_4 v$$
$$\frac{dz}{dt} = cy_2 z - \mu_5 z \ .$$

The nonnegative initial conditions of the modified model (22) are $x(0) = x_0$, $y_1(0) = y_{1_0}$, $y_2(0) = y_{2_0}$, $v(0) = v_0$, $z(0) = z_0$.

2.3 Modified Model Analysis

2.3.1 Positivity of the solutions of the Modified Model

The positivity of the solutions of the modified model is stated in the following lemma.

Lemma 3. Let the initial conditions for the model system (21) be$\{x(0), y_1(0), y_2(0), v(0), z(0) \geq 0\} \in \Psi$, where Ψ is the positivity invariant region. The solution set $\{x(t), y_1(t), y_2(t), v(t), z(t)\}$ of the system (22) is positive for all time, $t \geq 0$.

Proof. From the first equation of modified model(22), which is given as

$\frac{dx}{dt} = \pi - \beta xv - \mu_1 x + by_1.$

We have

$\frac{dx}{dt} = \pi + by_1 - (\beta v + \mu_1)x \geq -(\beta v + \mu_1)x.$ (23)

Integrating (23) by separation of variables and applying the initial conditions, yields

$x(t) \geq x(0)e^{-\int_0^t (\beta v + \mu_1)dt} \geq 0.$

In a similar way, we show that all the solutions of the modified model remains positive in the domain Ω. Therefore, the solution set of the modified model (22) is positive in Ψ for all time $t \geq 0$.

2.3.2 Existence and Uniqueness of Solution for the Modified Model

The theorem 2 is used to proof the existence and uniqueness of the solution of the modified model as it is done in model (1). Let

$\frac{dx}{dt} = f_1(t,x) = \pi - \beta xv - \mu_1 x + by_1$ (24)

$\frac{dy_1}{dt} = f_2(t,x) = \beta xv - \mu_2 y_1 - by_1 - \alpha y_1$ (25)

$\frac{dy_2}{dt} = f_3(t,x) = \alpha y_1 - \mu_3 y_2 - \emptyset y_2 z$ (26)

$\frac{dv}{dt} = f_4(t,x) = ky_2 - \mu_4 v$ (27)

$\frac{dz}{dt} = f_5(t,x) = cy_2 z - \mu_5 z$ (28)

So that

$x' = f(t,x),\ x(t_0) = x_0.$

It suffices that $\frac{\partial f_i}{\partial x_j}, i,j = 1,2,3,4,5$ are continuous and bounded. Consider the partial derivatives of $f_1(t,x)$

$\frac{\partial f_1}{\partial x} = -\beta v - \mu_1, \left|\frac{\partial f_1}{\partial x}\right| = |-\beta v - \mu_1| < \infty$

$\frac{\partial f_1}{\partial y_1} = b, \quad \left|\frac{\partial f_1}{\partial y_1}\right| = |b| < \infty$

$\frac{\partial f_1}{\partial y_2} = 0, \quad \left|\frac{\partial f_1}{\partial y_2}\right| = |0| < \infty$

$\frac{\partial f_1}{\partial v} = -\beta x, \quad \left|\frac{\partial f_1}{\partial x}\right| = |-\beta x| < \infty$

$\frac{\partial f_1}{\partial z} = 0, \quad \left|\frac{\partial f_1}{\partial z}\right| = |0| < \infty$

The other equations of the modified model are solved in a similar way and this shows that all the partial derivatives of modified model (22) are continuous and bounded. Hence, by theorem (2), there exist a unique solution of model (22) in the region Ψ.

2.4.3 Existence and Stability of Virus-free Equilibrium State of the Modified Model

In this sub-section, the model is qualitatively analyzed to investigate the condition of existence of the virus-free equilibrium state of the model (22). The procedure to find E_0 and R_0 has been explained in model (1).

Thus, the virus-free equilibrium state (VFE) E_0 and the basic reproduction number, R_0, of the modified model are given by $E_0 = (\frac{\pi}{\mu_1}, 0, 0, 0, 0)$ and $R_0 = \frac{\beta\pi\alpha k}{\mu_1\mu_3\mu_4(\mu_2+b+\alpha)}$ respectively.

The following theorem gives the local stability of the virus free equilibrium state of the modified model.

Theorem 5*The virus-free equilibrium state of the modified model is locally asymptotically stable if* $R_0 < 1$ *and unstable if* $R_0 > 1$.

2.4.4 Sensitivity Analysis of the Modified Model

The sensitivity analysis of the modified model parameters are given in Table 3 below and the interpretation is done as model (1).

Table 3: Numerical values of sensitivity indices of R_0 for the modified Model.

Parameter	Value	Sensitivity index	Parameter	Value	Sensitivity index
b	0.2day^{-1}	-0.7639419402	β	$2.4\times10^{-8}\text{day}^{-1}$	$+1.000000000$
π	$10\text{day}^{-1}\text{mm}^{-3}$	$+1.000000000$	k	4000day^{-1}	$+1.000000000$
α	0.0608day^{-1}	$+0.7677616499$	μ_2	0.001day^{-1}	-0.0038197097
μ_4	0.1day^{-1}	-1.000000000	μ_1	0.01day^{-1}	-1.000000000
μ_3	0.24day^{-1}	-1.000000000			

3.0 Numerical Simulation

The numerical simulations of the model are carried out using a set of reasonable parameter values given in Table 4. Some parameter values are from different literatures and some are assumed. The initial conditions $x(0) = 1000000ml^{-1}$, $y_1(0) = 0, y_2(0) = 0,\ v(0) = 100ml^{-1}$, $z(0) = 10ml^{-1}$ are used for the simulation.

Table 4: Model Parameter Values

Parameter	Value	Source	Parameter	Value	Source
π	$10\text{day}^{-1}\text{mm}^{-3}$	Estimated	β	$2.4 \times 10^{-8}\text{day}^{-1}$	[13]
α	0.0608day^{-1}	"	$\emptyset$	1day^{-1}	"
b	0.2day^{-1}	"	k	4000day^{-1}	"
$\mu_4 z$	0.1day^{-1}	"	$\mu_2 y$	0.24day^{-1}	[8]
$\mu_5 z$	0.1day^{-1}	"	$\mu_2 y_1$	0.001day^{-1}	"
$\mu_3 y_2$	0.24day^{-1}	"	c	0.005day^{-1}	"
$\mu_3 v$	0.167day^{-1}	"	μ_1	0.01day^{-1}	[10]

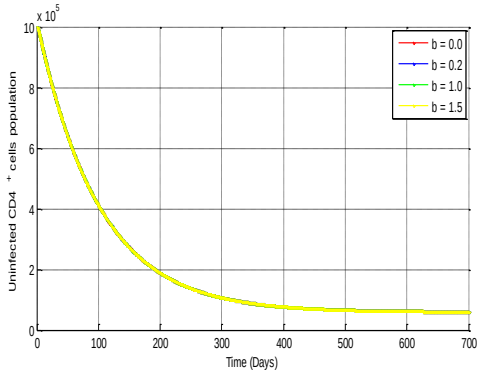

Fig. 3(a)

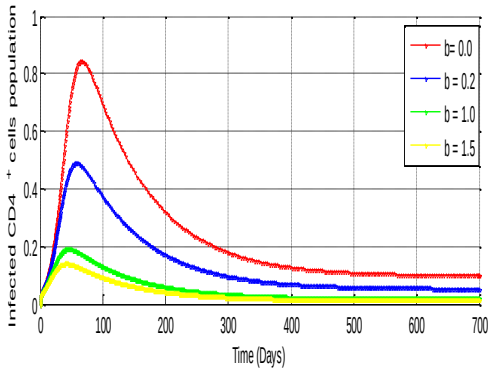

Fig. 3(b)

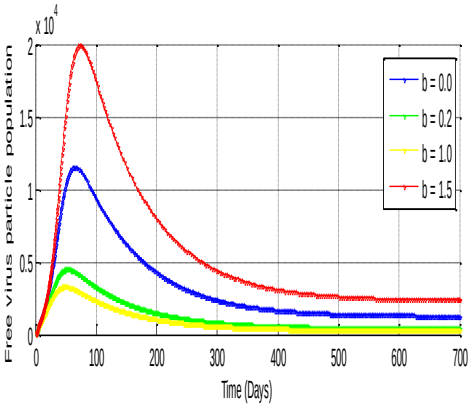

Fig. 3(c)

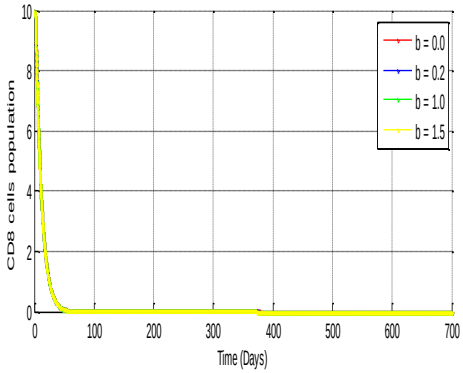

Fig. 3(d)

Simulation result for the uninfected $CD4^+$ cells, infected $CD4^+$ cells, free virus particle and CD8 cells populations against time for model (1).

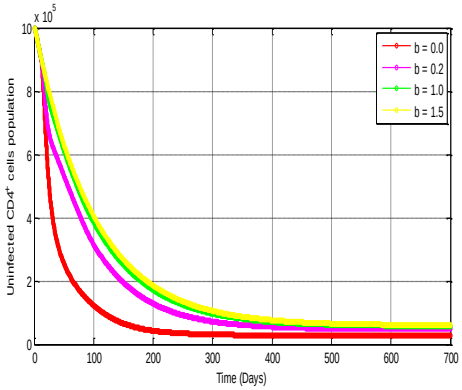

Fig. 4(a)

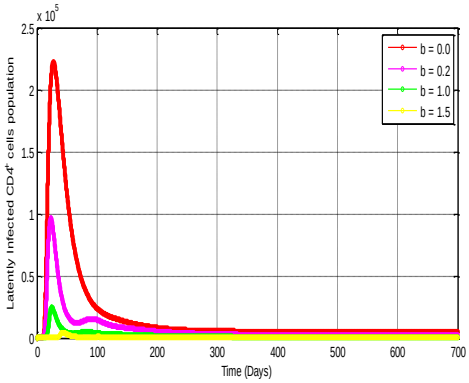

Fig. 4(b)

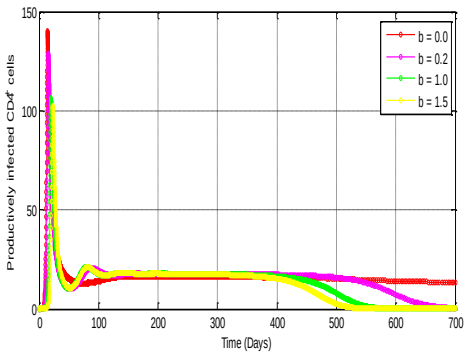

Fig. 4(c)

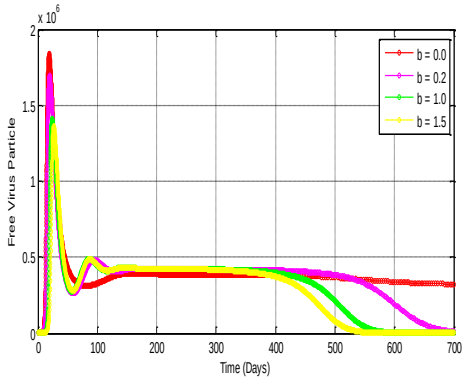

Fig. 4(d)

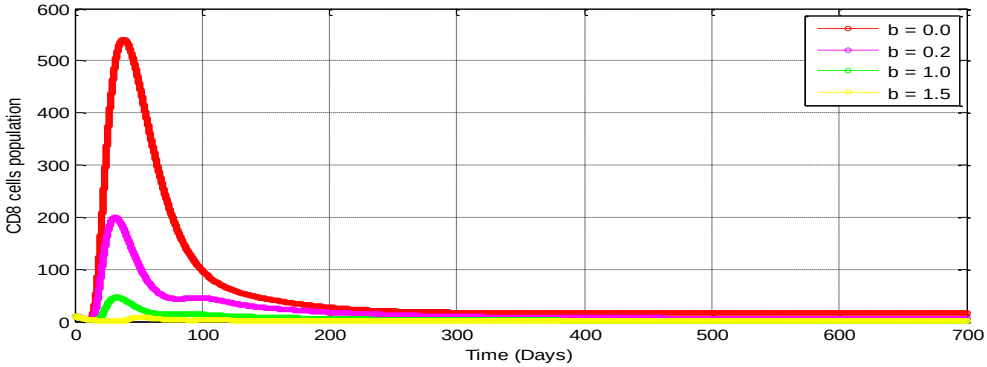

Fig. 4(e)

Simulation result foruninfected $CD4^+$ cells, latently infected $CD4^+$ cells, productively infected $CD4^+$ cells, **f**ree virus particles and CD8 cells against time for the modified model.

4.0 Discussion

The mass action mode of infection is very important in the formulation of the in-vivo HIV model. This is shown in Figures 3(a), 3(b), 4(a) and 4(b). In these figures, we expected the number of the uninfected cells to increase and the number of CD8 cell to decrease (Figures 4(a) and 4(e)) when the rate of reversion of resting infected cells to uninfected state is gradually increased (Figures 3(a) and 3(d)). But, this is not so because of the mode of infection used for the model 1 that is saturated infection. In addition, the effect of the reversion of resting infected cells to uninfected state for the model 1 is shown in Figures 3(b) and 3(c). Before the integration of the viral genome into the genome of the $CD4^+$cells, a relative size of resting infected cells revert to the uninfected cells. This implies that the more resting infected cells continue to revert to uninfected cells, the lesser the number of infected $CD4^+$ cells. Meanwhile, the model (1) has a basic reproduction number R_0= 0.99005 which shows that the virus will die out with time as long as resting infected $CD4^+$cells continue to revert to uninfected cells. Furthermore, the importance of the reversion rate in reducing the number of $CD4^+$ cells in the body of HIV infected person is shown in Figures 4(b) –4(d). It indicates that the number of infected cells (latently and productively infected) and free virus particles decreases as the rate of the reversion of infected cells to uninfected state gradually increases. The basic reproduction number for the modified model is $R_0 = 0.4219$ and this connotes that the virus will die out faster with time when compare with the basic reproduction number of model (1). Although, it is already established that CD8 cells reduces number of infected $CD4^+$ cells [8], we have found from the result that the reversion of resting infected to uninfected cells will further reduce the number of $CD4^+$ cells.

5.0 Conclusion

In this paper, two models of an in-vivo HIV incorporating the reversion state of the infected $CD4^+$ cells to uninfected $CD4^+$ cells are considered. The virus dynamics is described by non-linear ODES. The solution set of the two models are shown to be positive for all time and have unique solution that exists. The basic reproduction numbers, R_0, of the two models are computed using the next generation method [18]. The models are further analyzed for the existence and stability of the equilibrium states. Additionally, numerical simulation of the two models are carried out to examine the effect of the reversion state of the infected $CD4^+$ cells to uninfected $CD4^+$ cells on the dynamics of an in-vivo HIV. The second model shows that capturing the latently infected $CD4^+$ cells and the productively infected $CD4^+$ cells using mass action mode of transmission

have great impact in reducing R_0 and also reduces the viral load in the body of the infected HIV person. Finally, the sensitivity analysis of the model parameters for the two models are carried out to support the numerical simulation.

6.0 References

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