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Behavioral Analysis of HIV Epidemic Model in a Post- Eclipse Stage

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ABSTRACT

In this works, Human Immunodeficiency Virus (HIV) epidemic model including an eclipse stage of infected cells with latently infected cells was considered. The local and global stability of the system were established using the associated basic reproduction number R_0 . Bifurcation analysis was used to establish conditions for the local stability of the endemic equilibrium using the centre manifold theorem. The result shows that the disease free equilibrium is locally and globally asymptotically stable, when the associated disease threshold parameter is less than unity, and the system exhibit backward bifurcation. Numerical Simulations carried out for the analytical result suggest that the attack to the latently infected cells cannot be ignored because some quicker cells from this stage will move with time to productively infected class/cells.

1.0 Introduction

Following the advances in immunology over the years, researchers are able to understand the dynamics of infection at the cellular-level and considerable attention has been paid to study the dynamics of HIV infection mode [1].This Lentivirus (slowly replicating retrovirus) which can lead to Acquired Immunodeficiency Syndrome (AIDS); has become a hazard infectious disease in both developed and developing nations. It is a fatal disease, which breaks down the body immune system. Leaving the victim vulnerable to a host life threatening opportunistic infections, neurological disorders or unusual malignancies, it has caused mortality of millions of people and expenditure of enormous amount of money in health care and disease control [2]. In literatures, many mathematical models have been developed in order to understand the dynamics of HIV infection with $CD4^+T$ cells [3]. And the description of the virus infection process has three populations: uninfected target cells, productively infected cells, and free viral particles [4].

Follow the model proposed in [4], infected cells are assumed to produce new virions immediately after target cells are infected by a free virus. However, there are many biological steps between viral infections of target cell production of HIV-1 virions. In 2007. [5] Studied an extension of the basic model of HIV-1 infection, The main feature of their model is that an eclipse stage for the infected cells is included and a portion of these cells are reverted to the uninfected class .This kind of model was early presented by [6]. [7] Performed the global stability analysis of this model. [8] put forward another model in 1997. He divided infected cells into two kinds: long-lived productively infected cells and latently infected cells. Latently infected cells are also activated into productively infected cells. In this papers the Cytotoxic T Lymphocytes (CTL) immune response was taken into account with the progression of infected cells from the eclipse phase to the productive and latently infected to productively infected cell, and a portion of this cells are reverted to the uninfected cells/class or be latent down in the body can express HIV immune response and with time can cause immune response by CTLs .The role of CTL is universal and necessary to eliminate or control the disease during viral infections. In particular, as a part of innate response, it gives antiviral defense by attacking infected cells. The basic HIV infection model which takes into consideration the CTL immune response has been proposed by [4] as follows:

$$\left.\begin{aligned} \frac{dx}{dt} &= s - \beta xy - dx + \delta w \\ \frac{dw}{dt} &= \beta xy - (\delta + \eta + q)w \\ \frac{dy}{dt} &= qw - pyz - \alpha y \\ \frac{dz}{dt} &= f(x, y, z) - rz \end{aligned}\right\} \tag{1}$$

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Where $x, w, y \text{ and } z$ represent the concentration of uninfected target cells, concentration of infected cells in the eclipse stage at time t, productively infected cells, CTLs at time t respectively. Parameter s and d are the birth and death rate of uninfected cells, respectively. The uninfected cells become infected at the rate of βxy. Productively infected cells are produced at the rate βxy, infected cells in the eclipse phase revert to the uninfected class at a constant rate δ, and they may alternatively progress to the productively infected class at the rate q or die at the rate η. α is the death rate of productively infected cells, p is the strength of the lytic component, and r is the death rate of CTLs.

Function $f(x, y, z)$ describes the rate immune response activated by the infected cells. [9], [10] assumed that the production of CTLs depends only on the population of infected cells and gives $f(x, y, z) = cy$ and $f(x, y, z) = cyz$ respectively. [4] in their studied , also choose meanwhile, their model include an eclipse stage of infected cells. After the eclipse stage, some quicker infected cells which become productively infected cells are obviously attacked by CTLs. Other infected cells which will be reverted to the uninfected class or be latent down in the body do not have the ability to express HIV and will not cause CTL immune response. Therefore they only take the immune response to productively infected cells into account and ignored the attack to latently infected cells by CTLs.

This present study therefore aims at Improving on the model stated above by [4] incorporating the latently infected class / cells in the model. Motivated by the work of [4].We are now concern with the progression of infected cells from the eclipse stage to the productively and latently to productively cells. A portion of these cells are reverted to the uninfected class or be latent down in the body, do have the ability to express HIV and can cause CTL immune response. Therefore, the present study takes into account the immune response to productively infected cells and do not ignore the attack to latently infected cells, because with time some portion of this cell will progress to the productively infected class. Thus our new models are as follows:

2.0 Model formation

$$\begin{aligned}
\frac{dx}{dt} &= s - (\beta_1 xy + \beta_2 xb) - dx + \delta w + k_2 b, \\
\frac{dw}{dt} &= \beta_1 xy + \beta_2 xb - (\delta + \eta + q + k) w, \\
\frac{db}{dt} &= kw - k_1 bz - (k_3 + \gamma + k_2) b, \\
\frac{dy}{dt} &= qw - pyz - \alpha y + k_3 b, \\
\frac{dz}{dt} &= f(x, y, z) - rz
\end{aligned} \tag{2}$$

Where k_1 represent the strength of the lytic component in the latently stages/cells. γ Is death rate of the latently infected cells, k_3 the rate at which the latently infected cells becomes productivity, and k_2 the rate at which the latently infected cells is reverted to the uninfected cells while b represent the concentration of the latently infected cells at time t. The uninfected cells become infected at the rate of $\beta_1 xy + \beta_2 xb$. Productively infected cells are produced at rate $\beta_1 xy + \beta_2 xb$ and also consider the dynamics of HIV infection with CTL response and give $f(x, y, z) = cyz + c_1 bz$.

2.1 The Existence of the Equilibrium state of equation (2)

From equation (2)

Set, $\frac{dx}{dt} = \frac{dw}{dt} = \frac{db}{dt} = \frac{dy}{dt} = \frac{dz}{dt} = 0$

Hence, Infection–free equilibrium $\varepsilon_0 = \left(\frac{s}{d}, 0, 0, 0, 0 \right)$ (3)

And, the endemic Equilibrium: CTL-free

$$E_c = \left(x = \frac{s}{dR_0}, w = w, b = k\frac{w}{(k_3 + \gamma + k_2)}, y = w\frac{(qk_3 + q\gamma + qk_2 + kk_3)}{\alpha(k_3 + \gamma + k_2)}, z = 0 \right) \tag{4}$$

Where

$$w = \frac{[(\alpha d(\delta + \gamma + q + k) - S\beta_1 q)](k_3 + \gamma + k_2) - (Sk\beta_1 k_2 + KS\beta_2 \alpha)](k_3 + \gamma + k_2)}{(\beta_1 q\gamma + k\beta_1 k_3 + \beta_1 qk_3 + \beta_1 qk_2 + k\beta_2 \alpha)(\gamma q + \gamma k + \gamma\eta + qk_3 + qk_2 + \eta k_2 + k_3\eta + kk_3)}.$$

2.2 The Dynamics of the System of Equation (2)

Let $N(t) = x(t) + w(t) + b(t) + y(t) + z(t)$,where $N(t)$ is the total cell population at any time t, the total population cells is subdivided into sub-population namely; Susceptible $x(t)$,who are not yet infected but can be infected by HIV, Concentration of infection at the Eclipse stage $w(t)$,Concentration of latently infected cells $b(t)$,Concentration of productively infected cell y(t) and the Concentration of CTL $z(t)$. Thus,

$$N(t) = x(t) + w(t) + b(t) + y(t) + z(t) \tag{5}$$

Differentiating (5) with respect to time (t), and simplifying by letting $d = \eta = \gamma = \alpha = r$ which represent the death rates of the respective classes gives,

$\dot{N}(t) = s - d(x + w + b + y + z) - (k_1 b + py + cy + c_1 b)z$. If there is no infection it implies $b = y = 0$ then,

$\dot{N}(t) = s - d(N(t))$

$N^*(t) + d(N(t)) = s \Rightarrow \frac{d}{dt}\left(e^{dt} N\right) = se^{dt}$

$N = \frac{s}{d} e^{dt} e^{-dt} + ce^{-dt} = \frac{s}{d} + ce^{-dt}$

$\therefore$ As t $t \to \infty$

$N = \frac{S}{d}$

2.3 Positivity of Solutions

For the system of equations (2) to be epidemiologically well posed, it is important to prove that all solution with non-negative initial conditions will remain non – negative, for all $t \geq 0$.

Theorem1: Let $\Psi = \Psi_c \subset R_+^5$ with $\Psi_c = \left\{(x, w, b, y, z) \in R_+^5 : x + w + b + y + z \leq \frac{s}{d}\right\}$, and then the solutions $\{x(t), w(t), b(t), y(t), z(t)\}$ of the system (2) are positive $\forall t \geq 0$.

Proof

From the first differential equation of system (2),

$$\left.\begin{aligned} \frac{dx}{dt} &\geq -(d + \beta b + \beta y)x \\ \frac{dx}{x} &\geq -(d + \beta b + \beta y)dt \end{aligned}\right\} \tag{6}$$

Integrating both sides

$$\int \frac{dx}{x} \geq -\int_0^t (d + \beta b + \beta y)dt$$

To obtain

$x(t) \geq Ce^{-\int_0^t [(d+\beta b+\beta y)]dt}$

$at\ t = 0$

$x(0) = Ce^0$

Therefore $C = x(0)$

Hence $x(t) \geq x(0)e^{-\int_0^t [(d+\beta b+\beta y)]dt} \geq 0$ (7)

For all, $t > 0$.

Similar reasoning can be used for other differential equations of equation (2), hence, it follows that the system is positive and bounded with a unique solution.

3.0 Basic Reproduction Number

The computation of the basic reproduction number is essential. The basic reproduction number R_0 is defined as the effective number of secondary infections caused by infected cells/individual during his entire period of infectiousness [11]. This definition is given for the model that represents the spread of infection in a population. It is obtained by taking the largest (dominant) Eigen-value (spectral radius) of the matrix FV^{-1}.

$$R_0 = \left[\frac{\partial F_i(x_0)}{\partial(x_j)}\right]\left[\frac{\partial V_i(x_0)}{\partial(x_j)}\right]^{-1} \tag{8}$$

Where F_i is the rate of appearance of new infection in the compartment $F = \left[\frac{\partial F_i(x_0)}{\partial(x_j)}\right]$

V_i , be the transfer of cells out of the compartment by all (means) $V = \left[\frac{\partial V_i(x_0)}{\partial(x_j)}\right]$

ε_0 , be the disease - free equilibrium. Using the next generation matrix, It can be shown that is the largest (dominant) Eigen-value of FV^{-1} is R_0 , which is the basic reproduction number

$$R_0 = \frac{s(\beta_1 qk_3 + \beta_1 qk_2 + \beta_1 q\gamma + \beta_1 kk_3 + \beta_2 \alpha k)}{\alpha d(\delta + \eta + q + k)(k_3 + \gamma + k_2)} \tag{9}$$

3.1 Local Stability of the equilibrium

Theorem 2: The disease free equilibrium of system (2) is locally asymptotically stable if the coefficient of $\lambda^3 + A\lambda^2 + B\lambda + \alpha(\delta + \mathrm{q} + \mathrm{k} + \mathrm{k})(\mathrm{k}_3 + \mathrm{k}_2 + \gamma)[1 - \mathrm{R}_0] = f(\lambda)$, are positive if $A > 0$, $B > 0$ And $R_0 < 1$ otherwise unstable

Proof:

The Jacobian matrix of equations (2) at the disease-free equilibrium point E_O is

$$|J(E_0) - \lambda I| = 0 \tag{10}$$

Then equation (10) reduces to

$(-d - \lambda)(-r - \lambda)f(\lambda) = 0$

Where $f(\lambda) = \lambda^3 + A\lambda^2 + B\lambda + \alpha(\delta + \mathrm{q} + \mathrm{k} + \mathrm{k})(\mathrm{k}_3 + \mathrm{k}_2 + \gamma)(1 - \mathrm{R}_0)$

Clearly, $\lambda_1 = -d, \quad \lambda_2 = -r$ and

$f(\lambda) = \lambda^3 + A\lambda^2 + B\lambda + \alpha(\delta + \mathrm{q} + \mathrm{k} + \mathrm{k})(\mathrm{k}_3 + \mathrm{k}_2 + \gamma)(1 - \mathrm{R}_0) = 0$

Where A= $\alpha + (k_3 + \gamma + k_2) + (\delta + \eta + q + k)$

And

B= $\left(\alpha(\delta + \eta + q + k) + (\delta + \eta + q + k)(k_3 + \gamma + k_2) + \alpha(k_3 + \gamma + k_2) - \beta_2 \frac{s}{d}k - \beta_1 \frac{s}{d}q\right)$

Using Descartes rule of positive sign in $f(\lambda)$, the eigenvalues are negative, whenever $A > 0, B > 0$ and R_0 <1. Then disease free equilibrium $E_0 = \left(\frac{s}{d},0,0,0,0\right)$, is locally asymptotically stable.

3.2 Global Stability of the Disease Free Equilibrium

Theorem: 4: The HIV free equilibrium E_0 of system (2) is globally asymptotically stable if $R_0 < 1$, unstable if $R_0 > 1$.

Proof:

Using comparison theorem as implemented in [12], that the rate of change of the infected compartment of equation (2) can be written as

$$\begin{bmatrix} \frac{dw}{dt} \\ \frac{db}{dt} \\ \frac{dy}{dt} \\ \frac{dz}{dt} \end{bmatrix} = (F - V)\begin{bmatrix} w \\ b \\ y \\ z \end{bmatrix} - F_i\begin{bmatrix} w \\ b \\ y \\ z \end{bmatrix}$$

At disease free, w=0, b=0, y=0, z=0 which implies that

$$\begin{bmatrix} \frac{dw}{dt} \\ \frac{db}{dt} \\ \frac{dy}{dt} \\ \frac{dz}{dt} \end{bmatrix} \leq \begin{pmatrix} -(\delta+\eta+q+k) & \beta_2\frac{s}{d} & \beta_1\frac{s}{d} & 0 \\ k & -(k_3+\gamma+k_2) & 0 & 0 \\ q & k_3 & -\alpha & 0 \\ 0 & 0 & 0 & -r \end{pmatrix} \begin{bmatrix} w \\ b \\ y \\ z \end{bmatrix} \tag{11}$$

Then corresponding eigenvalues of (F-V) are all negative i.e.

$$\begin{pmatrix} -(\delta+\eta+q+k)-\lambda & \beta_2\frac{s}{d} & \beta_1\frac{s}{d} & 0 \\ k & -(k_3+\gamma+k_2)-\lambda & 0 & 0 \\ q & k_3 & -\alpha-\lambda & 0 \\ 0 & 0 & 0 & -r-\lambda \end{pmatrix} = 0 \tag{12}$$

Simplifies to give $\lambda_1 = -r$

and

$$\lambda^3 + A\lambda^2 + B\lambda + \alpha(\delta+\eta+q+k)(k_3+\gamma+k_2)[1-R_0] = 0 \tag{13}$$

Where A = $\alpha + (k_3+\gamma+k_2) + (\delta+\eta+q+k)$,

B = $\left(\alpha(\delta+\eta+q+k) + (\delta+\eta+q+k)(k_3+\gamma+k_2) + \alpha(k_3+\gamma+k_2) - \beta_2\frac{s}{d}k - \beta_1\frac{s}{d}q \right)$,

Using Descartes rule of positive sign , 3 signs change which implies that there are 3 negatives root of λ and since all eigenvalue are negative then it follows that equation (2) is stable whenever , $R_0 \prec 1$, $A \succ 0$ $B \succ 0$. Then by [13], and [14].we have that the DFE (E_0) is Globally Asymptotically Stable (GAS), for $R_0 < 1$.

3.3 Local Stability of Endemic Equilibrium Point

Here we study the local stability of the endemic equilibrium around the disease free equilibrium using bifurcation analysis. It is necessary and good to study critically what happened around the disease free equilibrium E_0 because the condition for when $R_0 < 1$ is usually a necessary and sufficient condition for disease eradication, whereas it is no longer sufficient when a backward bifurcation occurs. In fact, the backward bifurcation scenario involves the existence of a subcritical bifurcation at $R_0 = 1$ and of a saddle node bifurcation at $R_0 = R_0^* < 1$. The scenario of backward bifurcation can be describe qualitatively as follows, in the neighborhood of 1, for $R_0 < 1$, a stable disease-free equilibrium coexists with two endemic equilibrium: a smaller equilibrium (i.e., with a smaller number of infective individuals) which is unstable and a larger one (i.e. ., with a larger number of infective individuals) which is stable [15] .which simply implies the appearance and disappearance of diseases.

We make use of the centre manifold theorem, which prescribes the role of the coefficients of a and b of the normal form representing the system dynamics on the central manifold. These coefficient 'decide' the direction of the transcritical bifurcation

Let $\beta_1 = \beta^*$ and if we consider the case R_o =1.So that

$$R_o = \frac{s(\beta_1 q k_3 + \beta_1 q k_2 + \beta_1 q\gamma + \beta_1 k k_3 + \beta_2 \alpha k s)}{\alpha d(\delta+\eta+q+k)(k_3+\gamma+k_2)} = 1 \tag{14}$$

$$\therefore \quad \beta_1 = \beta^* = \frac{\alpha d(\delta+\eta+q+k)(k_3+\gamma+k_2)}{s(qk_3+qk_2+q\gamma+kk_3)} - s\beta_2\alpha k$$

If $\beta_1 < \beta^*$ and $\beta_1 > \beta^*$

We apply the center manifold theorem to show that the system may exhibit backward bifurcation when

$$\beta_1 = \beta^* = \frac{\alpha d(\delta+\eta+q+k)(k_3+\gamma+k_2)}{s(qk_3+qk_2+q\gamma+kk_3)} - s\beta_2\alpha k .$$

First of all, observe that the eigenvalues of the equation (2) at the disease free has a simple zero eigenvalue while other eigenvalues are negatives.

i.e. $\left| J(E_0, \beta^*) - \lambda I \right| = 0$

$$\begin{vmatrix} -d-\lambda & \delta & -\frac{(\beta_2 s+k_2)}{d} & -\beta^*\frac{s}{d} & 0 \\ 0 & -(\delta+\eta+q+k)-\lambda & \frac{\beta_2 s}{d} & \beta^*\frac{s}{d} & 0 \\ 0 & k & -(k_3+\gamma+k_2)-\lambda & 0 & 0 \\ 0 & q & k_3 & -\alpha-\lambda & 0 \\ 0 & 0 & 0 & 0 & -r-\lambda \end{vmatrix} = 0 \tag{15}$$

Solving, equation (15)gives

$$\left\{\lambda_1 = 0, \lambda_2 = -d, \lambda_3 = -r, \lambda_4 = \frac{-B-\sqrt{B^2-4AC}}{2A}, \lambda_5 = -\left(\frac{B-\sqrt{B^2-4AC}}{2A}\right)\right\} \tag{16}$$

Where the values of A, B and C. are given in Appendix A.1.

Thus $\lambda_1 = 0$ is a simple zero eigenvalue and the other eigenvalues are real and negatives. Hence, when $\beta_1 = \beta^*$ (or equivalently when $R_0 = 1$), the disease-free equilibrium E_0 is nonhyperbolic equilibrium: the assumption 1 of the theorem in appendix A is then verified.

Now denote W = $(w_1, w_2, w_3, w_4, w_5)^T$ to be the right eigenvector associated with the zero eigenvalue $\lambda_1 = 0$. It follows that

$$J(E_0, \beta^*)\begin{pmatrix} w_1 \\ w_2 \\ w_3 \\ w_4 \\ w_5 \end{pmatrix} = \begin{pmatrix} -d & \delta & -\frac{(\beta_2 s+k_2)}{d} & -\beta^*\frac{s}{d} & 0 \\ 0 & -(\delta+\eta+q+k) & \frac{\beta_2 s}{d} & \beta^*\frac{s}{d} & 0 \\ 0 & k & -(k_3+\gamma+k_2) & 0 & 0 \\ 0 & q & k_3 & -\alpha & 0 \\ 0 & 0 & 0 & 0 & -r \end{pmatrix}\begin{pmatrix} w_1 \\ w_2 \\ w_3 \\ w_4 \\ w_5 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} \tag{17}$$

Hence, equation (17) result to,

$$w = \begin{pmatrix} \left[\frac{1}{d}\left(\frac{\delta}{k}\right)(k_3+\gamma+k_2) - \beta_2\frac{s}{d} - k_2 - \frac{\beta^* s}{\alpha k d}\left(q(k_3+\gamma+k_2)+kk_3\right)\right]w_3, \\ \frac{(k_3+\gamma+k_2)}{k}w_3, w_3, \frac{(q(k_3+\gamma+k_2)+kk_3)w_3}{\alpha k}, 0 \end{pmatrix} \tag{18}$$

Where $w_3 > 0$ is a free right positive eigenvector.

Furthermore, the left eigenvector, $v = (v_1, v_2, v_3, v_4, v_5,)$ given by:

$$(v_1, v_2, v_3, v_4, v_5)\begin{pmatrix} -d & \delta & -\frac{\beta_2 s}{d} & -\beta^* \frac{s}{d} & 0 \\ 0 & -(\delta+\eta+q+k) & \frac{\beta_2 s}{d} & \beta^* \frac{s}{d} & 0 \\ 0 & k & -(k_3+\gamma+k_2) & 0 & 0 \\ 0 & q & k_3 & -\alpha & 0 \\ 0 & 0 & 0 & 0 & -r \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} \tag{19}$$

The solution of (19) yield

$$v = \left(0,\ \frac{\alpha d}{s\beta^*}\ v_4,\ \left[v_4\left[\frac{\alpha d}{s\beta^*}+k_3\right]\left(\frac{1}{(k_3+\gamma+k_2)}\right)\right]v_4,\ v_4,\ 0\right) \tag{20}$$

Where $v_4 > 0$ is a free positive variable (eigenvector) i.e. $v_4 > 0$.

Furthermore, let

$$\left.\begin{aligned} \frac{dx_1}{dt} &= f_1 = s-(\beta_1 x_1 x_4 + \beta_2 x_1 x_3) - dx_1 + \delta x_2 + k_2 x_3 \\ \frac{dx_2}{dt} &= f_2 = \beta_1 x_1 x_4 + \beta_2 x_1 x_3 - (\delta+\eta+q+k)x_2 \\ \frac{dx_3}{dt} &= f_3 = kx_2 - k_1 x_3 x_5 - (k_3+\gamma+k_2)x_3 \\ \frac{dx_4}{dt} &= f_4 = qx_2 - px_4 x_5 - \alpha x_4 + k_3 x_3 \\ \frac{dx_5}{dt} &= f_5 = Cx_4 x_5 + C_1 x_3 x_5 - rx_5 \end{aligned}\right\} \tag{21}$$

Where $x = x_1, w = x_2, b = x_3, y = x_4, z = x_5$,

Then Computation of a and b defined in appendix A, may be computed as

$$a = \sum_{k,i,i=1}^{5} \frac{v_k\, w_i\, w_j\, \partial^2 f_k}{\partial x_i\, \partial x_j}\left(E_o, \beta^*\right) \tag{22}$$

$$b = \sum_{k,i,j=1}^{5} v_k w_i \frac{\partial^2 fk}{\partial_{xi}\beta_1}\left(E_o, \beta^*\right). \tag{23}$$

Taking in to account of equation (2) and considering non-zero components of the left eigenvector v it follows that;

$$a = \sum_{k,i,j=1}^{5} v_k w_i w_j \frac{\partial^2 fk}{\partial x_i \partial x_j}\left(E_o, \beta^*\right) = 2 v_2\, w_1\, w_3\, \beta_2 \tag{25}$$

$$a = \left(2\left(\frac{\alpha d}{s\beta^*}\right)v_4\right)\times\left(\left(\frac{\delta(k_3+\delta+k_2)}{dk} - \frac{\beta^*}{\alpha k d}\left(q(k_3+\gamma+k_2)+kk_3\right) - \beta_\alpha \frac{s}{d} - k_2\right)\right) w_3^2 \times \beta_2$$

Where $\beta^* = \dfrac{\alpha d(\delta+\eta+q+k)(k_3+\gamma+k_2)-s\beta_2\alpha k}{s(qk_3+qk_2+q\gamma+kk_3)}$

Now considering only the non-zero components of the eigenvector v at virus free equilibrium it follows that:

$$a = \frac{v_4 w_3^2 \beta_2}{k}(qk_3+qk_2+q\gamma+kk_3) > 0 \quad (26)$$

$v_4, w_3 > 0$

Next is the computation of the coefficient b; as follows:

$$b = v_2w_1\frac{\partial^2 f_2}{\partial x_1\partial\beta_1} + v_2w_2\frac{\partial^2 f_2}{\partial x_1\partial\beta_1} + v_2w_3\frac{\partial^2 f_2}{\partial x_3\partial\beta_1} + v_2w_4\frac{\partial^2 f_2}{\partial x_4\partial\beta_1} + v_2w_5\frac{\partial^2 f_2}{\partial x_5\partial\beta_1} + v_3w_1\frac{\partial^2 f_3}{\partial x_1\partial\beta_1} +$$
$$v_3w_2\frac{\partial^2 f_3}{\partial x_2\partial\beta_1} + v_3w_3\frac{\partial^2 f_3}{\partial x_3\partial\beta_1} + v_3w_4\frac{\partial^2 f_3}{\partial x_4\partial\beta_1} + v_3w_5\frac{\partial^2 f_3}{\partial x_5\partial\beta_1} + v_4w_1\frac{\partial^2 f_4}{\partial x_1\partial\beta_1} + v_4w_2\frac{\partial^2 f_4}{\partial x_2\partial\beta_1} +$$
$$v_4w_3\frac{\partial^2 f_4}{\partial x_3\partial\beta_1} + v_4w_4\frac{\partial^2 f_4}{\partial x_4\partial\beta_1} + v_4w_5\frac{\partial^2 f_4}{\partial x_5\partial\beta_1}$$

In view of (w) and (v), we the get

$$a = \frac{v_4 w_3^2 \beta_2}{k}(qk_3+qk_2+q\gamma+kk_3) > 0, \text{ and } b = \frac{v_2w_4s}{d} > 0 \quad (27)$$

The coefficient b is always positive so that, according to appendix A, it is the sign of the coefficient a which will decides the local dynamics around the disease- free equilibrium for $\beta_1 = \beta^*$. And it is clearly seen above that the coefficient a is positive which implies that the system exhibits backward bifurcation i.e. hopf in nature.

3.4 The Sensitivity Analysis

In determining how best to reduce the reproduction rate of virus in the blood cells, There is need to know the relative importance of the different factors responsible for its transmission and prevalence [16]. Initial disease transmission is directly related to R_0 and disease prevalence is directly related to the endemic equilibrium point, specifically to the magnitudes of x, w, b, y and z.

Definition: The normalized forward sensitivity index of a variable, U, that depends differentiable on a parameter, η is defined as

$$\gamma_\eta^U := \frac{\partial U}{\partial\eta}\times\frac{\eta}{U}$$

From equation (9), $R_0 = \dfrac{s(\beta_1qk_3+\beta_1qk_2+\beta_1q\gamma+\beta_1kk_3+\beta_2\alpha k)}{\alpha d(\delta+\eta+q+k)(k_3+\gamma+k_2)}$, and derive an analytical expression for the sensitivity of R_0, as $\gamma_\eta^{R_0} = \dfrac{\partial R_0}{\partial\eta}\times\dfrac{\eta}{R_0}$, to each of the twelve below as different parameters for example.

The sensitivity index of R_0 with respect to β_1.

$$\beta_1 = \gamma_{\beta_1}^{R_0} = \frac{\partial R_0}{\partial\beta_1}\times\frac{\beta_1}{R_0} = 0.9936407839.$$

Therefore we have the sensitivity indices of R_0 to parameters of the human immunodeficiency virus (HIV) model with CTL's cells (2), which was evaluated based on some assumed parameter values given in table below:

Table. 3.1

Parameter	Value	Parameter	Value
s	1.5	σ	0.002
k	0.00022	ρ	0.0004
q	1.5	δ	0.00005
φ	0.002	α	0.4
$\varepsilon = \beta_1$	0.005	d	0.0022
$\tau = \beta_2$	0.0024	η	0.0004

Then the analysis;

$$S = \gamma_S^{R_0} = \frac{\partial R_0}{\partial S}\times\frac{S}{R_0} = 1,$$

$$q = \gamma_q^{R_0} = \frac{\partial R_0}{\partial q} \times \frac{q}{R_0} = -0.005925998039$$

$$\varepsilon = \beta_1 = \gamma_\varepsilon^{R_0} = \frac{\partial R_0}{\partial \varepsilon} \times \frac{\varepsilon}{R_0} = 0.9936407839,$$

$$\tau = \beta_2 = \gamma_\tau^{R_0} = \frac{\partial R_0}{\partial \tau} \times \frac{\tau}{R_0} = 0.006359216229$$

$$\rho = \gamma_\rho^{R_0} = \frac{\partial R_0}{\partial \rho} \times \frac{\rho}{R_0} = -0.0005660665790,$$

$$\sigma = \gamma_\sigma^{R_0} = \frac{\partial R_0}{\partial \sigma} \times \frac{\sigma}{R_0} = -0.0028965747730$$

$$\varphi = \gamma_\varphi^{R_0} = \frac{\partial R_0}{\partial \varphi} \times \frac{\delta\varphi}{R_0} = -0.002896574730,$$

$$\delta = \gamma_\delta^{R_0} = \frac{\partial R_0}{\partial \delta} \times \frac{\delta}{R_0} = -0.00003331845109$$

$$\alpha = \gamma_S^{R_0} = \frac{\partial R_0}{\partial \alpha} \times \frac{\alpha}{R_0} = -0.09936407837,$$

$$d = \gamma_d^{R_0} = \frac{\partial R_0}{\partial d} \times \frac{d}{R_0} = -1$$

$$K = \gamma_K^{R_0} = \frac{\partial R_0}{\partial k} \times \frac{k}{R_0} = 0.006225863411.$$

The analysis shows that β_1, β_2, k are positive values of the sensitivity analysis, which implies that any increase in any of these parameters, will definitely trigger the rate of infection in both the eclipse stage and latently stage of infections. And with this it shows that the attack to latently infected cells cannot be ignore at any time t, and s =1 is the birth rate of the uninfected cells which is normal

4.0 Discussion of Results

In this study, Human Immunodeficiency Virus (HIV) epidemic model including an eclipse stage of infected cells incorporated with latently infected stage of infection, with CTLs immune response was presented. Numerical simulations were presented using a set of reasonable values and show the effect of some parameters on system of equation (2).

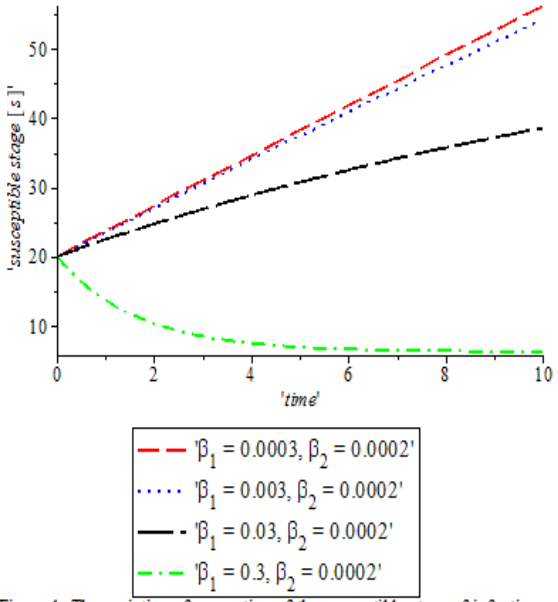

Figure 1: The variation of proportion of the susceptible stage of infection for different values of beta[1]

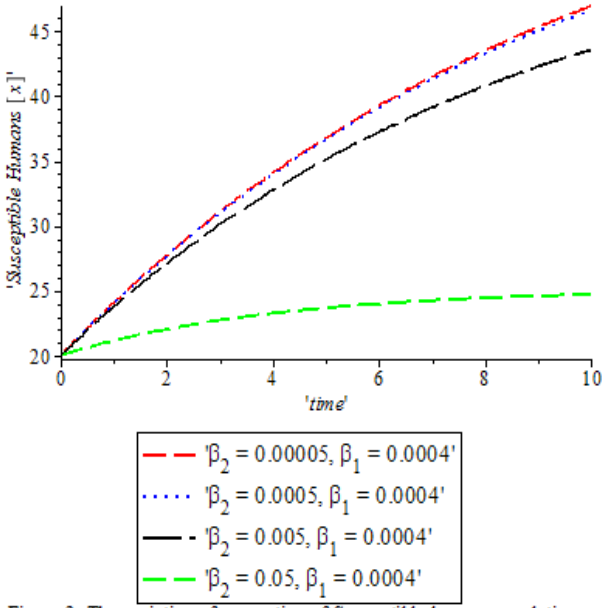

Figure 2: The variation of proportion of Susceptible human population for different values of beta[2]

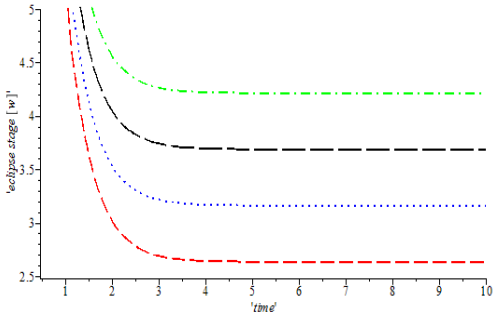

Figure 3: The variation of proportion of the eclipse stage of infection for different values of beta[1]

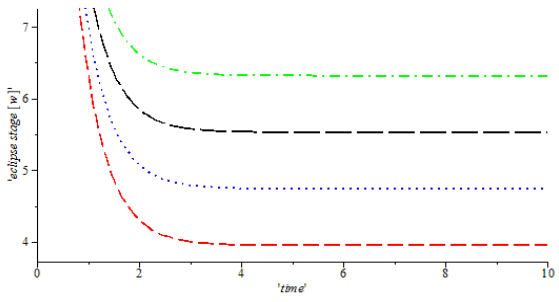

Figure 4: The variation of proportion of the eclipse stage of infection for different values of beta[2]

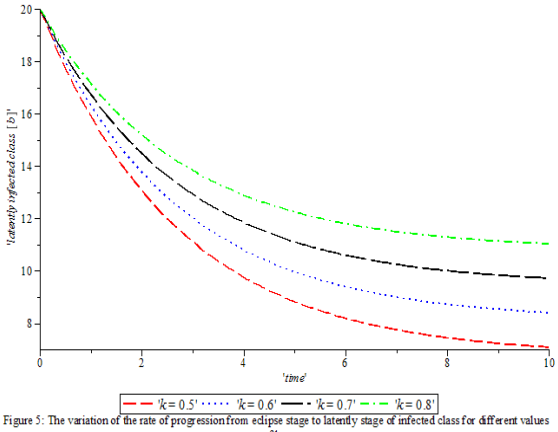

Figure 5: The variation of the rate of progression from eclipse stage to latently stage of infected class for different values of k.

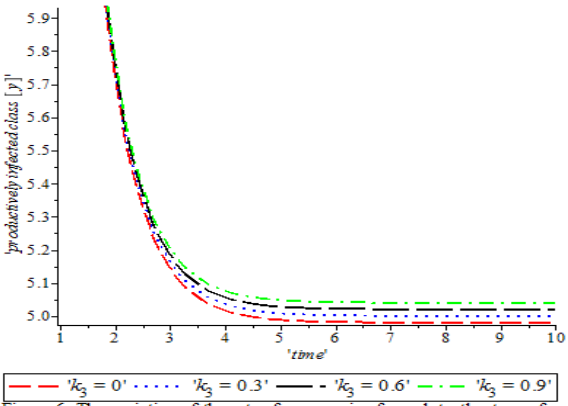

Figure 6: The variation of the rate of progression from latently stage of infectedto productively class for different values k[3]

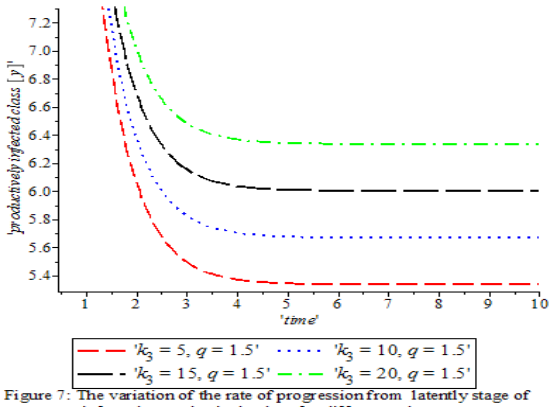

Figure 7: The variation of the rate of progression from latently stage of infectedto productively class for different values .

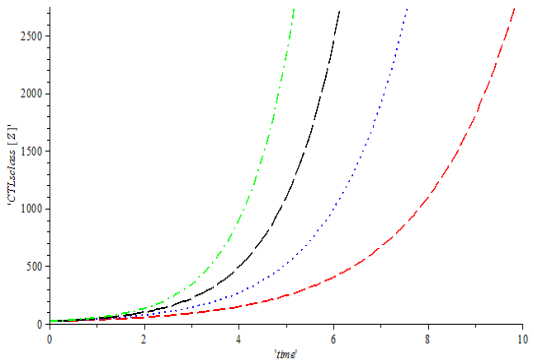

Figure 8: The variation of the rate of ctl class for different values of c.

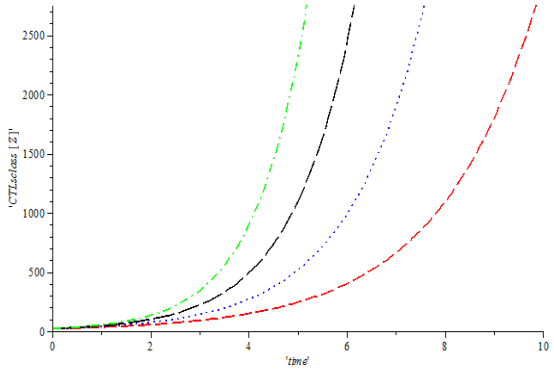

Figure 9: The variation of the rate of ctl class for different values of c.

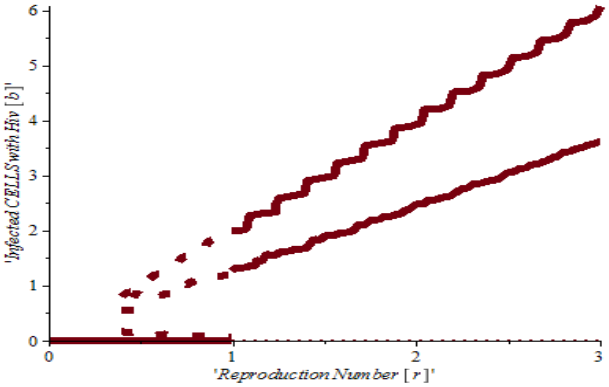

Figure 10: The backward bifurcation diagram for the HIV infection with parameter values subs β[1]=0.5 ,q=0.1, δ=0.02, p=0.003,s=10,k[2]= 0.002, k[3]=0.1, β[2]=0.0002, k[1]=0.01,c[1] =0.5, d=0.002,γ=0.1, α= 0.01, η=20,

Discussion of simulation

Figure 1 and 2: shows that as the transmission parameter β_1, β_2 increases there's movement out of the susceptible cells/uninfected to the infected.

Figure 3 and 4: shows that as β_1, β_2 increases there's increment in the proportion of the cells that are infected at the eclipse stage of infection.

Figure.5 and 6: Shows that increase in k and k_3 will cause corresponding increase in the progression of cells from the eclipse stage to the latently stage of infection.

Figure .7: Shows that any increase in k_3 will leads to the increase in the progression of cells from the latently stage of infection to productively stage.

Figure .8 and .9: Shows that increase in the CTLs immune response, will lead to the reverse of some cells to the susceptible cells.

Figure 10: The appearance and disappearance of disease, this established that the disease free co-exists will the endemic. And this also establish that the disease can only be eradicated at a particular point that is less than 1 , which shows what happens when $R = 1$: apart from when $R_0 < 1, R_0 > 1$.That is there exist $R^* < R_0 < 1$

Conclusion

In this work, we have studied HIV epidemic model in a Post – Eclipse stage with CTL immune response. The local and global stability of the uninfected equilibrium E_0 have been proved to be asymptotically stable if the basic reproduction number $R_0 < 1$ and unstable if $R_0 > 1$ Descartes' rule, and comparison theorem. When the basic reproduction number $R_0 < 1$ it shows that the disease will be controlled when compared with earlier model.

However further analysis shows that the condition for when $R_0 < 1$ is not sufficient for the diseases to be eradicated, because of the phenomenon called bifurcation. The bifurcation analysis reveals that R_0 must be brought below a certain critical threshold number R^*, so that total disease eradication is achieved if $R_0 < R^* < 1.$ The bifurcation analysis reveals latently infected cells should not be ignored because there are many biological steps between viral infection of target cells and the production of HIV virions i.e. the time interval between infection and the first detection of viral RNA in the plasma, and the time interval between invasion of the body by an infecting organism and the appearance of the first sign/symptom.

Appendix: A:

Theorem A. Bifurcation theorem: Assume:

Consider the following general system of ordinary differential equations with parameter ϕ such that:

$$\frac{dx}{dt} = f(x,\phi),\ f : R^n \times R \to R^n \text{ and } f \in c^2(R \to R^n).$$

Without loss of generality, we assume that $x = 0$, is equilibrium for

(a) A= $D_x f(0,0)$ is the linearization matrix of system (B) around the equilibrium $x = 0$ with ϕ evaluated at 0. zero is a simple Eigenvalue of A and all other eigenvalues of A have negative real parts;

(b) Matrix A has a (nonnegative) right eigenvector w and a left-eigenvector v corresponding to the zero eigenvalue.

Let f_k denotes the k^{th} component of f, and a = $\sum_{k,i,j=1} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0), \quad b = \sum_{k,i=1} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0,0).$

Then the local dynamics of system in (B) around $x = 0$ are totally determined by a and b. Assume that b>0, then:

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

(ii) $a < 0, b < 0. when\ \phi < 0, with\ |\phi| << 1,\ x = 0$ is unstable; when 0 $< \phi <<1$, $x = 0$ is locally asymptotically stable and there exists a positive unstable equilibrium;

(iii) $a > 0, b > 0. when\ \phi < 0, with\ |\phi| << 1,\ x = 0$ is unstable stable and there exists a locally asymptotically stable negative equilibrium ; when 0 $< \phi <<1$, $x = 0$ is stable and appositive unstable equilibrium appears;

(iv) $a \prec 0, b \succ 0.$ When ϕ changes from negative to positive, $x = 0$ changes its stability from stable to unstable. Correspondently, a negative unstable equilibrium becomes positive and locally asymptotically stable

Appendix: A.1

$$+\lambda\begin{pmatrix}\left[-\delta q\beta_2\alpha+\beta_2 sk^2k_3-d\delta\gamma^2q-2dq^2k_3\gamma-2dq^2\gamma k_2-dk^2\gamma k_3-d\gamma^2\alpha q-dk\gamma^2q\right.\\ -d\eta\gamma^2q-dk^2\alpha k_3-dk_3^2\alpha q-dk_3^2\alpha k-2dqk_3^2k-dkk_2^2q-dk^2k_3-d\delta k_2^2q\\ -dk_2^2\alpha q-d\delta k_3^2q-d\delta k_3^2k-d\eta k_3k-d\eta k_2^2q-2dq^2k_3k_2-d\eta k_3{}^2q-dq^2k_3^2\\ -dq^2k_2^2-dq^2\gamma^2-dk^2k_3^2-2d\delta k_3qk_2-d\delta k_2kk_3-d\delta kk_3-2d\eta k_3-d\eta k_2kk_3\\ -d\eta\alpha kk_3-3dqk_2kk_3-dq\alpha kk_3-2dk_3\alpha kk_3+\beta_2\delta kqk_3+\beta_2\delta kqk_2+\beta_2\delta kq\gamma\\ -2d\delta qk_2-d\delta\gamma kk_3-2d\eta k_3q\gamma-2d\eta\gamma qk_2-d\eta\gamma kk_3-3dq\gamma kk_3-2dk\gamma qk_2\\ -2dk_3\alpha q\gamma-2d\gamma\alpha qk_2-d\gamma\alpha kk_3-dkk_3(\alpha kk_3+\delta\gamma\alpha+\delta\gamma\alpha+\eta\gamma\alpha+\eta k_2\alpha+q\gamma\alpha\\ +qk_2\alpha-\alpha\delta k_3-\alpha\delta\gamma-\alpha\delta k_2-\alpha\eta k_3-\alpha\eta\gamma-\alpha\eta k_2-\alpha qk_3-\alpha q\gamma-\alpha qk_2+qk_3\alpha\\ \left.+k\gamma\alpha+\alpha kk_2+\delta k_3\alpha+\eta k_3\alpha-\alpha kk_3-\alpha k\gamma-\alpha kk_2\right)\end{pmatrix}=0$$

Where A = $\left(-dkk_3-dqk_3-dqk_2-dq\gamma\right)$, B= $\begin{pmatrix}-d\eta qk_2-d\delta qk_3-d\delta k_2-2dk_3qk_2-dk_2kk_3\\ -d\alpha qk_3-d\eta kk_3-2dqkk_3-dkqk_2-d\alpha qk_2\\ -d\gamma^2q-dk^2k_3-dq^2k_3-dk_3^2k-dq^2\gamma-dq^2k_2\\ -dk_3^2q-dk_2^2q-d\alpha kk_3--2d\gamma qk_2-d\eta q\delta-d\gamma kk_3\\ -d\delta q\gamma-dkq\delta-2dk_3q\gamma-d\delta kk_3-d\alpha q\gamma-d\eta qk_3\end{pmatrix}$

And C= $\begin{pmatrix}\left[-\delta q\beta_2\alpha+\beta_2 sk^2k_3-d\delta\gamma^2q-2dq^2k_3\gamma-2dq^2\gamma k_2-dk^2\gamma k_3-d\gamma^2\alpha q-dk\gamma^2q\right.\\ -d\eta\gamma^2q-dk^2\alpha k_3-dk_3^2\alpha q-dk_3^2\alpha k-2dqk_3^2k-dkk_2^2q-dk^2k_3-d\delta k_2^2q\\ -dk_2^2\alpha q-d\delta k_3^2q-d\delta k_3^2k-d\eta k_3k-d\eta k_2^2q-2dq^2k_3k_2-d\eta k_3{}^2q-dq^2k_3^2\\ -dq^2k_2^2-dq^2\gamma^2-dk^2k_3^2-2d\delta k_3qk_2-d\delta k_2kk_3-d\delta kk_3-2d\eta k_3-d\eta k_2kk_3\\ -d\eta\alpha kk_3-3dqk_2kk_3-dq\alpha kk_3-2dk_3\alpha kk_3+\beta_2\delta kqk_3+\beta_2\delta kqk_2+\beta_2\delta kq\gamma\\ -2d\delta qk_2-d\delta\gamma kk_3-2d\eta k_3q\gamma-2d\eta\gamma qk_2-d\eta\gamma kk_3-3dq\gamma kk_3-2dk\gamma qk_2\\ -2dk_3\alpha q\gamma-2d\gamma\alpha qk_2-d\gamma\alpha kk_3-dkk_3(\alpha kk_3+\delta\gamma\alpha+\delta\gamma\alpha+\eta\gamma\alpha+\eta k_2\alpha+q\gamma\alpha\\ +qk_2\alpha-\alpha\delta k_3-\alpha\delta\gamma-\alpha\delta k_2-\alpha\eta k_3-\alpha\eta\gamma-\alpha\eta k_2-\alpha qk_3-\alpha q\gamma-\alpha qk_2+qk_3\alpha\\ \left.+k\gamma\alpha+\alpha kk_2+\delta k_3\alpha+\eta k_3\alpha-\alpha kk_3-\alpha k\gamma-\alpha kk_2\right)\end{pmatrix}$

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