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Mathematical Model on the Viral Load/Burden of HIV/AIDS in the Body of a Host

G.C.E. Mbah* and T.I. Chinebu
University Of Nigeria, Nsukka.

Abstract

We analyze a non-linear model of the human immunodeficiency virus (HIV) infection that considers the interaction between a replicating virus, $CD4^+$ T cell and the cytotoxic-T-Lymphocytes (CTL) i.e. $CD8^+$ T cell. The non-negative steady state of the model equation were obtained when $P_4 \le 1$ and $P_4 > 1$, and further analyzed for stability. We observe that the steady state of the model equation when $P_4 \le 1$ is asymptotically stable if $P_4 < 1$ and unstable if $P_4 > 1$. Also, we observe that the steady state of the mode equation when $P_4 > 1$ is asymptotically stable.

Keywords: Viral load/burden, $CD4^+$ T cell count, the HIV infection and immune control.

1.0 Introduction

In recent time, mathematical models have proven to be valuable in understanding the dynamic of the HIV infection. Many sample mathematical approaches have been developed to explore the relation between antiviral immune responses, viral load (the amount of HIV in the body of the host that constantly reproduces more viruses) and virus diversity infections with HIV.

World Bank [19] stated that there are three stages of HIV infection i.e. acute stage, latency (Asymptomatic) stage and clinical AIDS stage. Due to the progressive nature of development of AIDS, [17] and [18] divided the clinical AIDS stage into persistent generalized lymphadenopathy (PGL), AIDS related complex (ARC) and full-blown AIDS. These phases show progressive increase in the intensity of the signs and symptoms.

The effect of HIV infection has been mentioned by the works of [31] and [32]. According to them, HIV's disruption make infected people susceptible to illness that do not normally occur or that are usually not serious. These illnesses are called opportunistic illnesses because they take advantage of the damage to the immune system.

Lippincott [30] showed that HIV transmission system has biologic and social determinants. Biologic determinants include characteristics of the pathogen, the host and biomedical interventions. Social determinants include individual-level, pairwise and community level processes that affect behviour and thus the structure and dynamics of the transmission network.

Jacquez [20] were the first to use mathematical models to emphasis the importance of primary stage transmission using a computational deterministic model. They showed that an interval of high contagiousness during primary infection followed by a large decline in infectiousness was consistent with the pattern of epidemic seen in cohorts of man who have sex with men (MSM) in the early years of the epidemic.

To estimate the effect of change of human immunodeficiency virus (HIV) dynamics (drug regimens, T-cell count and viral load) on HIV progression, many top-down mathematical model based on the solution of a set of ordinary differential equation (ODE) have been proposed ([13], [34], [35] and [38]). One drawback of this approach is that it is restricted by the ODE's ability to estimate temporal but not spatial change of system variable.

Another possible approach to stimulate HIV progression is the bottom up approach based on Agent-Based (AB) model [39] and Cellular Automata (CA) model [36]. This approach can be used to construct and understand the components of complex system by assigning different agents (proto types) developed in different ways to simulate a considered model (such as an HIV progressive model). During the development process, agents cooperate to reward successful agents. Although this approach can be used to study HIV progression and at the population level [39], it has not been implemented at the cellular level since it is very difficult to keep up-dating agents and their spatial connections when the system dynamic rapidly changes during acute phase of HIV progression [33].

Graziano [4] formulated mathematical models which explicitly represents the effect of special distribution of T cells and HIV load in HIV progression. In constructing the governing differential equation, he considers the Eulerian conservative form of the continuity equation to preserve mesh size and dimensions.

*Corresponding author: E-mail; godwin.mbah@unn.edu.ng, Tel. +2348034198454

In a study carried out by [40], they formulated and studied a mathematical model for the transmission of HIV/AIDS considering Counseling and Antiretroviral Therapy (ART). Here the population is partitioned into three compartment of susceptible S(t), infected I(t) and Removed R(t). A mathematical model to investigate the effect of treatment and vaccination on the spread of HIV/AIDS can be found, for example in [21], [22], [23] and [24]. Models for the control of HIV using condom can be found for example in [25], [26], [27] and [28].

In [29], Simple models were developed taking into account the essential non-linearity of HIV dynamics. In this paper, we provide a detailed analytical study of a mathematical model of the interaction between infective virus, $CD4^+$ T cells, and CTL ($CD8^+$ T cells) thereby estimating the viral load/burden. Specifically, we consider the existence and stability of the infected steady state of the system.

2. Background

- In this section, we discuss the biological background of the problem to be studied. It is a well-known fact that human immunodeficiency virus (HIV) is different in structure from other retroviruses. It is roughly spherical with a diameter of about 120nm, around 60 times smaller than a red blood cell, yet large for a virus. It is composed of two copies of positive single stranded RNA that codes for the virus' nine genes which are (gag, pol, and env, tat, rev, nef, vif, vpr, vpu and tev) encoding 19 proteins. Three of these genes, gag, pol and env, contains information needed to make the structural proteins for new virus particles.

gag, pol and env are general retroviral gene while tat, rev, vif, vpr, nef and vpu are specific HIV genes. The major factors in this model is the rate at which human immunodeficiency virus (HIV) is reproduced in the body of the host. This is a determining factor because it has been proposed that during the non asymptomatic stage of HIV infection, the virus has a relatively low affinity towards T cell (and has a high affinity for macrophages resulting in a low kill rate of $CD4^+$ T cells by the immune system. This implies that the number of functional $CD4^+$ T cells falls in an HIV infected person. When certain number of $CD4^+$ T cells has been eliminated by the HIV cells as was stated above, this is initially compensated for through the production of new helper T cells from the thymus (originally from the bone marrow). Once the virus becomes lymphotropic (or T-tropic), however, it begins to infect $CD4^+$ T cells far more efficiently (likely due to a charge in the co-receptors it binds to during infection), and the immune system is overwhelmed.

Of great importance is the death rate of the $CD4^+$ T cell. Usually the $CD4^+$ T cells are reduced in most HIV + person by about 30 to 100 cells per year. There exist a period when HIV (i.e. the virus) is undetected in the blood. This simply indicates that there is battle between the HIV and the immune system. This is achieved through the two signal activation (i.e. recognition and verification). During this period, the T-helper cells then allows itself to proliferate by releasing a potent T cell growth factor called interleukin-2 (IL-2) which acts upon itself on an autocrime fashion. Proliferating helper T cells can differentiate into two major subtypes of cells known as type 1 and type 2 helper T cells respectively. These types are defined on the basis of the specific cytokines they produce. T_H 1 cells produces interferon gamma (or IF $N-\gamma$) and lymphotoxin (also known as tumor necrosis factor beta $(orTNF-\beta)$, while T_H 2 cells produces interleukin-3 $(IL-3)$, among numerous other cytokines.

Actually, HIV can survive even when all the detectable virons in the blood (viremia) are eliminated. It integrates itself into the DNA of the host cell and can stay there for years, lying dormant, immuned to all kinds of therapy because it is just DNA. When the cell divides and DNA is copied the virus is copied too. After years, the virus can become active again, seize the cells machinery and replicate.

3. Governing Equation

The model includes the interaction of infective HIV, $CD4^+$ T cells and cytotoxic T lymphocytes, CTL's ($CD8^+$ T cells). We use V, I and C to denote the population densities of infective HIV, $CD4^+$ T cells and CTLs, respectively. Then $\frac{dv}{dt}, \frac{dI}{dt}, \text{and } \frac{dc}{dt}$ denote the rate of change in population densities of infective HIV, $CD4^+$ T cells and CTLs ($CD8^+$ T cells), respectively at time t.

From the assumptions made in the study, the following equations are derived

*Corresponding author: E-mail; godwin.mbah@unn.edu.ng, Tel. +2348034198454

$$\frac{dv}{dt} = \psi^{\gamma} IV - \beta V - \zeta VC \qquad (3.1)$$

$$\frac{dI}{dt} = (\mu + \delta) - \alpha I - \xi IV \qquad (3.2)$$

$$\frac{dc}{dt} = \phi V - \theta C \qquad (3.3)$$

Where the parameter are;

ψ^{γ} is the production rate of the virus which indicate geometrical reproduction,and ψ is a constant while $\gamma = 0,1,2,3,\ldots.$ (β) is the death rate of virus , ζ is the clearance per virus in the body of the host through the destruction of infected cells before they release a fresh crop of viruses and is assume to be in complex, $(\mu+\delta)$ is the quantity of $CD4^+$ T cells, but μ is the newly produced $CD4^+$ T cells from source within the body of the host while δ is the rate of production of $CD4^+$T cells from proliferating cells, α is the death rate of $CD4^+$ T cells, ξ is the death rate per $CD4^+$ T cells due to the number of the viral infected cells, ϕ is the rate of stimulation of cytotoxic T lymphocytes (CTLs), $CD8^+$ T cells by the $CD4^+$ T cells due to presence of infective virus and θ represents the death rate of cytotoxic T lymphocyte (CTLs) $CD8^+$ T cells.

We now introduce new parameters by letting

$$P_1 = \beta, P_2 = \alpha, P_3 = \theta, P_4 = \frac{(\mu+\delta)\psi^{\gamma}}{\alpha\beta},$$

$$P_5 = \frac{\alpha\zeta\phi}{\xi\theta}$$

where the parameters P_4 and P_5 respectively represents, the basic reproduction ratio for the virus and the death rate of virus due to the immune response. By using the new parameters and introducing new variable so that the system will be non-dimensionalized, we have that the new variables introduce are:

$$x = \frac{\xi IV}{\alpha I} \Rightarrow V = \frac{x\alpha}{\xi}$$

$$y = \frac{\alpha I}{(\mu+\delta)} \Rightarrow I = \frac{y(\mu+\delta)}{\alpha}$$

$$z = \frac{\xi IV\theta C}{\alpha I\phi V} \Rightarrow C = \frac{Z\alpha\phi}{\xi\theta}$$

Substituting the new variables into equations (3.1), (3.2) and (3.3), we have:

$$\frac{dx}{dt} = P_1(P_4 xy - x) - P_5 xz \qquad (3.4)$$

$$\frac{dy}{dt} = P_2(1 - y - xy) \qquad (3.5)$$

$$\frac{dz}{dt} = P_3(x - z) \qquad (3.6)$$

By defining three non-linear functions

$$f_1(x,y,z) = P_1(P_4 xy - x) - P_5 xz$$
$$f_2(x,y,z) = P_2(1 - y - xy)$$

*Corresponding author: E-mail; godwin.mbah@unn.edu.ng, Tel. +2348034198454

$$f_3(x,y,z) = P_3(x-z)$$

Equations (3.4), (3.5) and (3.6) becomes respectively

$$\frac{dx}{dt} = f_1(x,y,z) \tag{3.7}$$

$$\frac{dy}{dt} = f_2(x,y,z) \tag{3.8}$$

$$\frac{dz}{dt} = f_3(x,y,z) \tag{3.9}$$

A point $(\hat{x},\hat{y},\hat{z})$ is called a steady state of the system (3.7), (3.8) and (3.9) if it is a constant solution of the equations.

$$f_1(\hat{x},\hat{y},\hat{z}) = 0 \tag{3.10}$$

$$f_2(\hat{x},\hat{y},\hat{z}) = 0 \tag{3.11}$$

$$f_3(\hat{x},\hat{y},\hat{z}) = 0 \tag{3.12}$$

Proposition I: Suppose $P_1, P_2, P_3, > 0$

(a) If $P_4 \le 1,$ then the non-negative steady state of the system (3.7), (3.8), and (3.9) is $(\hat{x}_0,\hat{y}_0,\hat{z}_0) = (0,1,0)$

(b) If $P_4 > 1,$ then the non negative steady state of the system (3.7), (3.8) and (3.9) are that given in (a) above and

$$(\hat{x},\hat{y},\hat{z}) = \left(k, \frac{1}{1+k}, k\right)$$

Proof:

From equation (3.8) we have:

$$P_2 = 0 \ or \ \hat{y} = \frac{1}{\hat{x}+1} \tag{3.13}$$

From equation (3.9) we have

$$P_3 = 0 \ or \ \hat{x} = \hat{z} \tag{3.14}$$

Substituting equations (3.13) and (3.14) into system (3.7), we have:

$$\hat{x}\left[P_5\hat{x}^2 + (P_5 + P_1)\hat{x} - P_1(P_4 - 1)\right] = 0 \tag{3.15}$$

Then;

$$\hat{x} = 0 \ or \ \hat{x} = -\tfrac{1}{2}\left(1 + {}^{P_1}\!/_{P_5}\right) + \tfrac{1}{2}\left\{\left(1 + {}^{P_1}\!/_{P_5}\right)^2 + \frac{4P_1(P_4-1)}{P_5}\right\}^{1/2} \tag{3.16}$$

From the proof of proposition I, we have:

(a) $P_4 \le 1,$ then the non negative steady state of the system (3.7), (3.8) and (3.9) is $(\hat{x}_0,\hat{y}_0,\hat{z}_0) = (0,1,0)$ (3.17)

(b) if $P_4 > 1$ then the non-negative steady state of the system (3.7), (3.8), and (3.9) are that given in 3.17 and

$$(\hat{x},\hat{y},\hat{z}) = \left(k, \frac{1}{k+1}, k\right) \tag{3.18}$$

Where

$$k = -\tfrac{1}{2}\left(1 + {}^{P_1}\!/_{P_5}\right) + \tfrac{1}{2}\left\{\left(1 + {}^{P_1}\!/_{P_5}\right)^2 + \frac{4P_1(P_4-1)}{P_5}\right\}^{1/2}$$

Now, we consider a region close to the steady state and let

$$x = \hat{x} + X, \ y = \hat{y} + Y, \ z = \hat{z} + Z$$

*Corresponding author: E-mail; godwin.mbah@unn.edu.ng, Tel. +2348034198454

Expanding f_1, f_2 *and* f_3 in Taylor series expansion about $(\hat{x}, \hat{y}, \hat{z})$ then retaining only the linear terms we obtain the following linear system

$$\begin{bmatrix} \frac{dx}{dt} \\ \frac{dy}{dt} \\ \frac{dz}{dt} \end{bmatrix} = Q \begin{bmatrix} x \\ y \\ z \end{bmatrix} \qquad (3.19)$$

Where Q denote the Jacobian matrix of the model system evaluated at $(\hat{x}, \hat{y}, \hat{z})$ i.e., the Jacobian matrix is thus;

$$Q = \begin{bmatrix} P_1(P_4\hat{y} - 1) - P_5\hat{z} & P_1P_4\hat{x} & -p_5\hat{x} \\ -P_2\hat{y} & -P_2(\hat{x}+1) & 0 \\ P_3 & 0 & -p_3 \end{bmatrix} \qquad (3.20)$$

At this point, the stability of the model is studied in terms of the eigen values of the matrix Q. Based on the theory of differential equation, we know that the steady state of the system (3.19) where det $Q \neq 0$ is stable if no eigen value of Q has positive real part, and is asymptotically stable if all eigen values have negative real part i.e.

If $\lambda_n = a_n + ib_n$

Where a_n is the real part of λ_n then,

$a_n \leq 0 \forall_n \Rightarrow$ stability

$a_n < 0 \forall_n \Rightarrow$ asymptotically stable

$a_n > 0$ if or at least one $n \Rightarrow$ unstable

The characteristic determinant of Q becomes

$$\begin{vmatrix} P_1(P_4\hat{y} - 1) - P_5\hat{z} - \lambda & P_1P_4\hat{x} & -p_5\hat{x} \\ -P_2\hat{y} & -P_2(\hat{x}+1) - \lambda & 0 \\ P_3 & 0 & -p_3 - \lambda \end{vmatrix}$$

The characteristic equation is

$$\Rightarrow \begin{vmatrix} P_1(P_4\hat{y} - 1) - P_5\hat{z} - \lambda & P_1P_4\hat{x} & -p_5\hat{x} \\ -P_2\hat{y} & -P_2(\hat{x}+1) - \lambda & 0 \\ P_3 & 0 & -p_3 - \lambda \end{vmatrix} = 0 \qquad (3.21)$$

Which solves out to

$$\lambda^3 + \left[P_2(\hat{x}+1) + P_1 + P_3 + P_5\hat{z} - P_1P_4\hat{y}\right]\lambda^2$$
$$+ \left[P_2P_3(\hat{x}+1) + P_1P_2(\hat{x}+1) + P_2P_5(\hat{x}+1)\hat{z} + P_1P_3 + P_3P_5\hat{z} + P_3P_5\hat{x} - P_1P_2P_4\hat{y} - P_1P_3P_4\hat{y}\right]\lambda$$
$$+ \left[P_1P_2P_3(\hat{x}+1) + P_2P_3P_5(\hat{x}+1)\hat{z} + P_2P_3P_5\hat{x}(\hat{x}+1) - P_iP_2P_3P_4\hat{y}\right] = 0 \qquad (3.22)$$

We then let

*Corresponding author: E-mail; godwin.mbah@unn.edu.ng, Tel. +2348034198454

$$\left.\begin{aligned} P_2(\hat{x}+1)+P_1+P_3+P_5\hat{z} &= r_1 \\ -P_1P_4\hat{y} &= s_1 \\ P_2(\hat{x}+1)(P_1+P_3+P_5\hat{z})+P_3(P_1+P_5(\hat{x}+\hat{z})) &= r_2 \\ -P_1P_4(P_2+P_3)\hat{y} &= s_2 \\ P_2P_3(\hat{x}+1)(P_1+P_5(\hat{x}+\hat{z})) &= r_3 \\ -P_1P_2P_3P_4\hat{y} &= s_3 \end{aligned}\right\} \quad (3.23)$$

Then the characteristic equation of the matrix Q is given by

$$U_0(\lambda_n)=\lambda^3+(r_1+s_1)\lambda^2+(r_2+s_2)\lambda+r_3+s_3=0 \quad (3.24)$$

Preposition 2:

(a) Suppose $P_1,P_2,P_3,P_4>0$. The steady state of equation (3.17) of the system (3.19) is asymptotically stable if $P_4<1$, and unstable if $P_4>1$.

(b) $P_1,P_2,P_3,P_5>0$ *and* $P_4>1$, then the steady state (3.18) of the system (3.19) is asymptotically stable.

Proof:

We first remark that the characteristic equation of matrix Q is given by

$$U_0(\lambda_n)=\lambda^3+(r_1+s_1)\lambda^2+(r_2+s_2)\lambda+r_3+s_3=0 \quad (3.24)$$

Substituting equation (3.23) into (3.24) we obtain (3.22).Also, Substituting (3.17) into equation (3.22) we obtain

$$\lambda^3+[P_1+P_2+P_3-P_1P_4]\lambda^2+[P_1P_2+P_2P_3+P_1P_3-P_1P_2P_4-P_1P_3P_4]\lambda$$
$$+P_1P_2P_3-P_1P_2P_3P_4=0 \quad (3.25)$$

We solved for λ and obtain the following

$$\lambda_1=-P_2,\lambda_2=-P_3,\lambda_3=-P_1(1-P_4)$$

From the proof we have:

(a) After substituting the steady state (3.17) into the system (3.19) we obtain that the characteristic equation is in the form

$$(\lambda+P_2)(\lambda+P_3)(\lambda+P_1-P_1P_4)=0$$

This shows that the eigenvalues of matrix Q are

$$\lambda_1=-P_2,\lambda_2=-P_3,\lambda_3=-P_1(1-P_4)$$

This implies that the eigenvalues $\lambda_1<0$ and $\lambda_2<0$. If $P_4<1$, clearly λ_3 will be less than 0 $(\lambda_3<0)$, which means that the steady state (3.17) is asymptotically stable. If $P_4>1$, then λ_3 will be greater than $0(\lambda_3>0)$, we conclude that the steady state (3.17) is unstable.

(b) Since $P_4>1$, the steady state (3.18) exist and k>0. By Routh-Hurwitz criterion, it follows that all roots of the characteristic equation (3.24) have negative real parts if and only if

$$\left.\begin{aligned} &r_1+s_1>0, r_3+s_3>0 \\ &(r_1+s_1)(r_2+s_2)-(r_3+s_3)>0 \end{aligned}\right\} \quad (3.26)$$

Verifying condition (3.26) we substitute system (3.18) into equation (3.23) and we obtain

$$r_1-s_1=P_3+P_2(k+1)$$

$$r_3+s_3=P_2P_3k(P_1+P_5(2k+1))$$

*Corresponding author: E-mail; godwin.mbah@unn.edu.ng, Tel. +2348034198454

$$(r_1 + s_1)(r_2 + s_2) - (r_3 + s_3) = W$$

$$= P_2 P_3^2 (k+1) + P_5 P_3^2 k + P_2^2 (k+1)\left(P_5 k^2 + P_1 k + P_3 (k+1)\right)$$

This means that condition (3.26) is satisfied. Thus, steady state (3.18) is asymptotically stable.

4. Analysis of Result

In formulating these mathematical models on HIV/AIDS, for the estimation of viral load/burden in the body of a host, many variables as stated earlier were appropriately built in and thus we had a fairly good model. Of particular importance to be mentioned among the parameters here are the production ratio of virus and the death rate of virus due to the immune response because they determine the rate at which the virus increases and decreases respectively in the body of a host.

We conduct numerical simulations to confirm the theoretical predications discussed in section 3. We first use the values of parameters P_1, P_2, P_3, P_4, P_5 that are suggested by Verotta and Schaedeli (2002). We show the qualitative behaviour of the three variables HIV (x), $CD4^+$ T cell (y) and CTL(z) when the basic reproductive rate of the virus is under control level i.e. P_4 is less than one $(P_4 < 1)$. We numerically solve the system (3.7), (3.8) and (3.9) by using the fourth order Runge-Kutta-Fehlberg method with

$P_1 = 0.85$, $P_2 = 0.133$, $P_3 = 1.22$, $P_4 = 0.278$ and $P_5 = 4.56$.

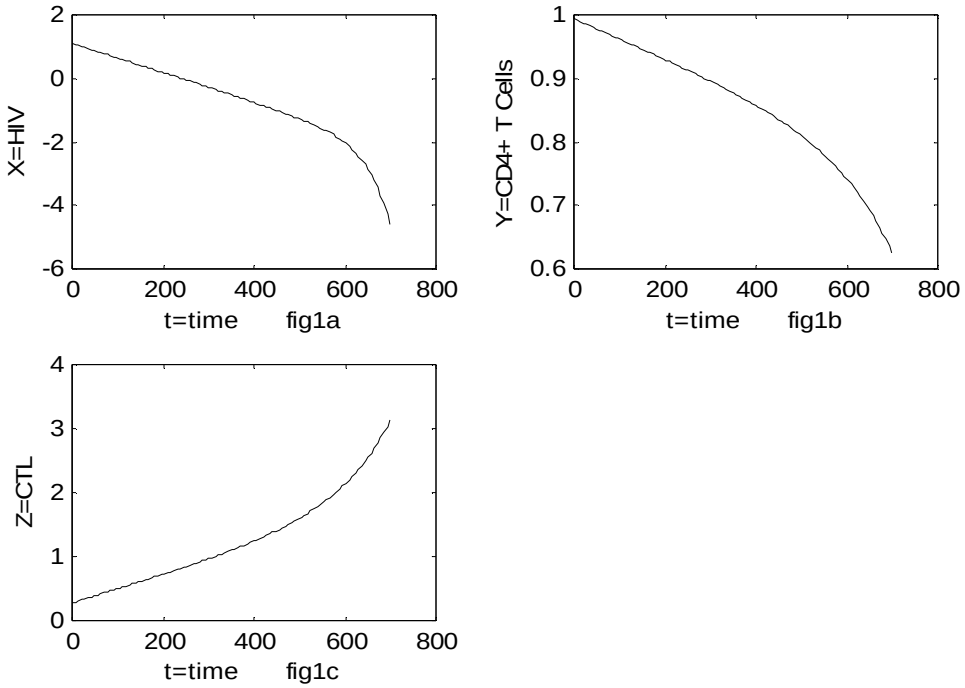

FIG: 1a – 1c; (t=0.0:7.0:700)

In figures (1a – 1c), we show the time series for the density of HIV in the blood, the density of the $CD4^+$ T Cells in the blood and that of the CTL in the blood respectively. Both HIV and $CD4^+$ T Cells density decreases while the CTL density increases.

*Corresponding author: E-mail; godwin.mbah@unn.edu.ng, Tel. +2348034198454

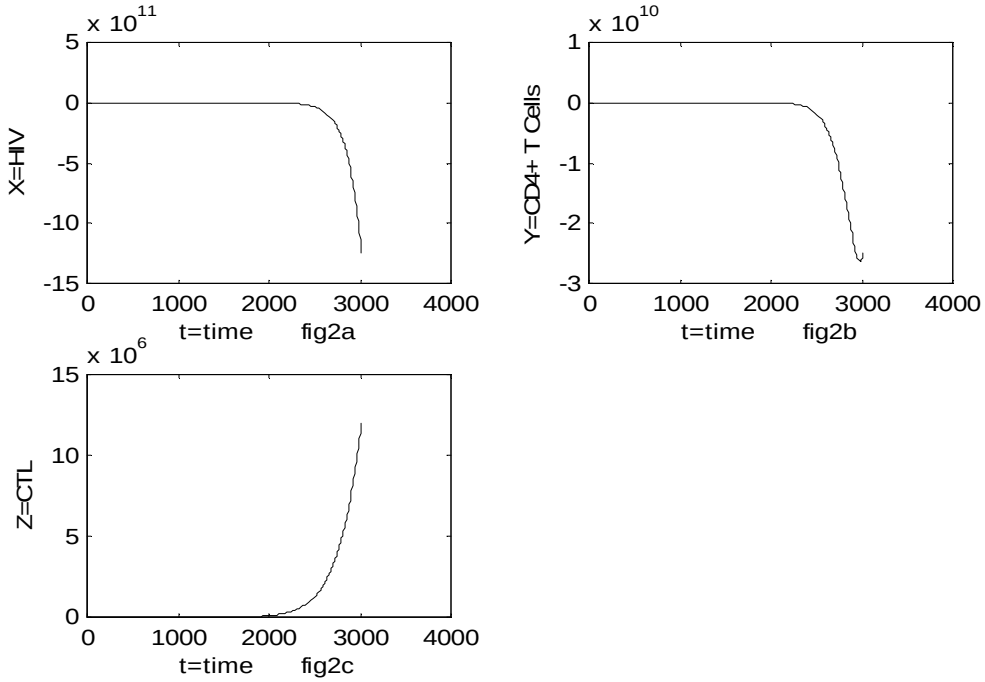

FIG:2a – 2c; (t=0.0:7.0:3020)

From figures (2a – 2c), it shows that as time passes, the density of HIV, continue to decrease, the density of $CD4^+$ T Cells(y) start to increase while that of CTL(z) continuously increases. This can only be possible if the physical parameters $(\psi^{\gamma}, \beta, \mu+\delta, \alpha)$ can be maintained through vaccination and post-exposure immunization so that the condition $P_4 < 1$ is satisfied.

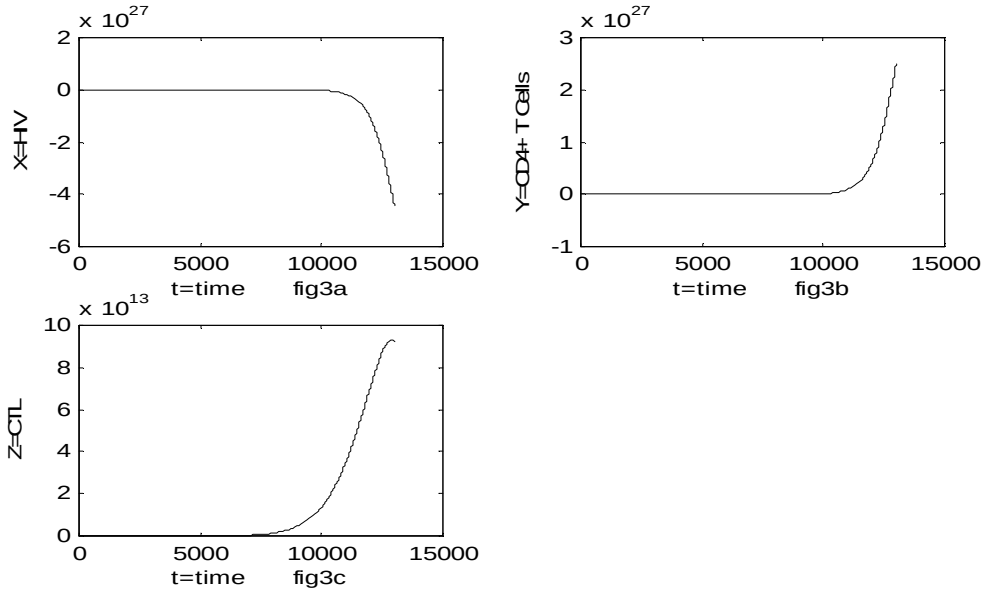

FIG: 3a – 3c; (t=0.0:7.0:13000)

Also figures 3a – 3c, show that as time continues to pass, the density of the $CD4^+$ T cells continuously increase while that of the HIV decreases. Viewing this biologically, it will be seen that when, the basic reproductive rate of the virus is under the control, then at the beginning of the infection, each virus cell produces on the average less than its decline rate. Hence the infection cannot spread and the $CD4^+$ T cells density continue to increase at $(\mu+\delta)/\alpha$.

*Corresponding author: E-mail; godwin.mbah@unn.edu.ng, Tel. +2348034198454

Also to show the qualitative behaviour of the three variables HIV(x), $CD4^+$ T cells (y) and CTL (z) when the basic reproductive rate of the virus is not under control level i.e. greater than one, we numerically solve the system (3.7), (3.8) and (3.9) by using the fourth order Runge-Kutta-Fehlberg method with

$P_1 = 0.2$, $P_2 = 0.005$, $P_3 = 0.03$, $P_4 = 7.0$ and $P_5 = 0.5$.

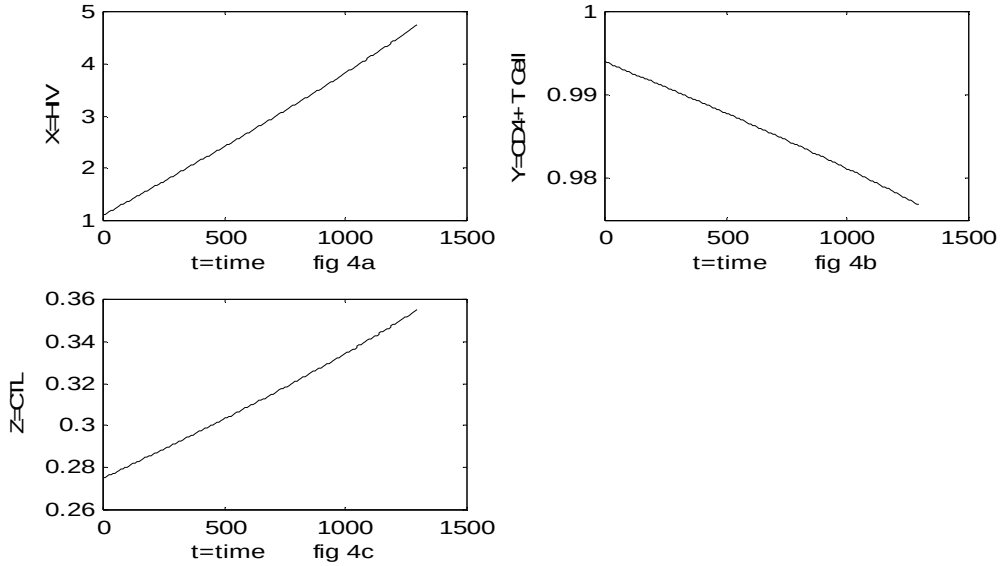

fig 4a -4c; (t=0.0:7.0:1300)

From figures (4a-4c), we show the time series of the density of HIV, $CD4^+$ T cells and CTL in the blood which shows a continuous increase in the density of HIV and CTL, and a decrease in density of $CD4^+$ T cells. This is because after HIV infection, the tRNA picked from the former host cell facilitates the immediate conversion of viral RNA to double-stranded DNA by the action of reverse transcriptase. As the host DNA divides, the virus is also copied to divide and in this way the virus continues to multiply.

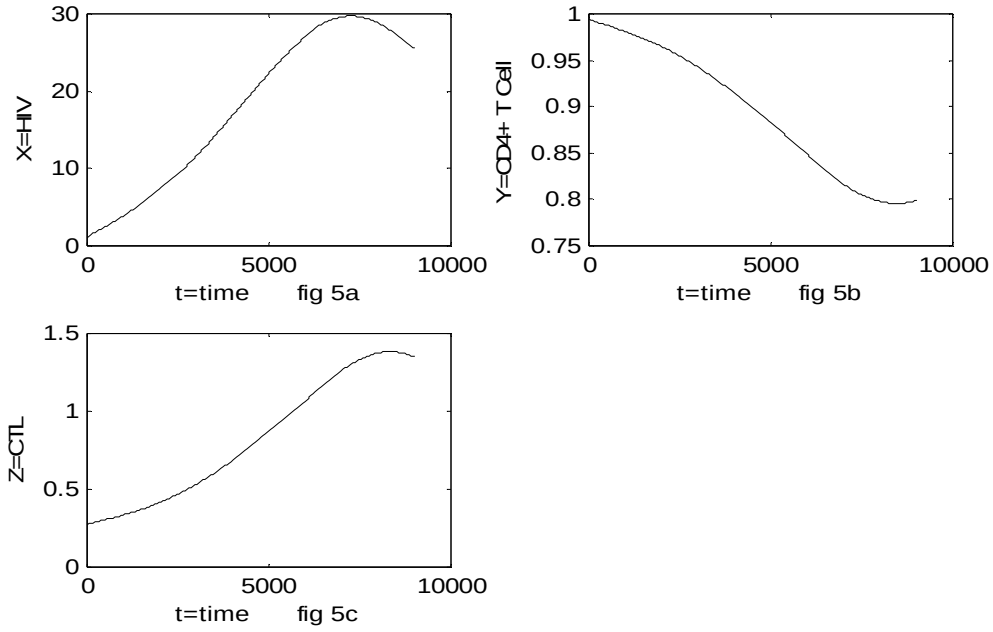

FIG:5a – 5c; (t=0.0:7.0:9000)

Figures (5a-5c), shows that as time passes, i.e. at t = 9000, the density of HIV and CTL starts decreasing while that of $CD4^+$ T cells start increasing. This is because a strong immune defense reduces the number of viral particles on the blood stream making the start of the infection's clinical latency stage.

*Corresponding author: E-mail; godwin.mbah@unn.edu.ng, Tel. +2348034198454

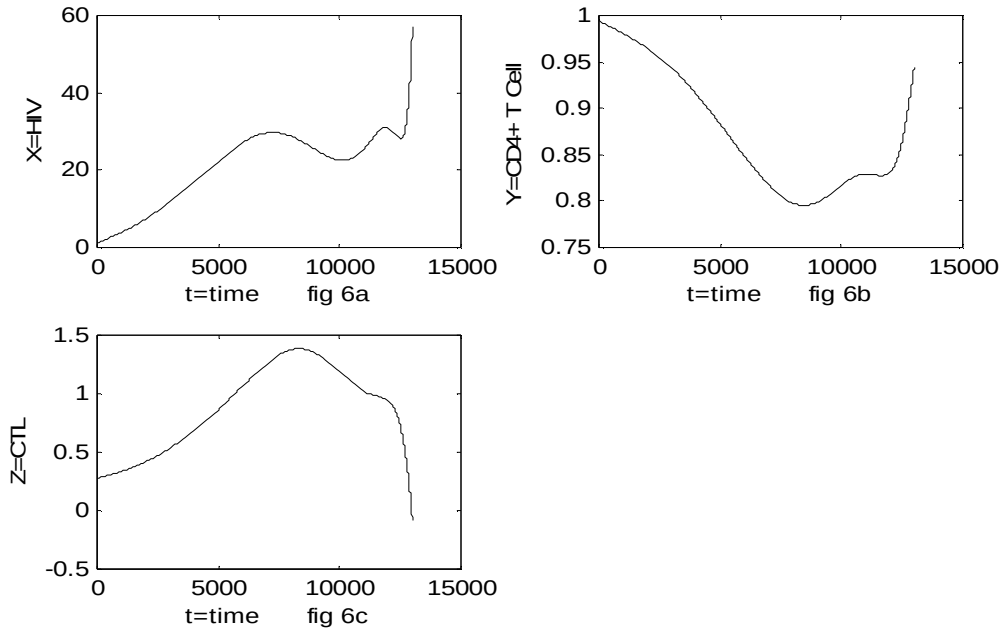

FIG: 6a – 6c; (t=0.0:7.0:13000)

Figures 6a-6c, show that as time continue to pass, both the density of HIV and $CD4^+$ T cells oscillate for a while before increasing. This verifies the fact that cases abound where the pro-viral DNA becomes integrated into the host cells DNA, the cell will be fully infected but not actively producing HIV proteins. This is the latent stage of HIV infection during which the infected cells can be an "unexploded bomb" for potentially a long time. Once the host cell starts to produce proteins from the pro-viral DNA, the HIV supplied protase enzyme must cleave the nascent HIV proteins in order for them to be assembled into HIV virons. The virons leave the cell by budding through cholesterol rafts on the host cell surface [8].

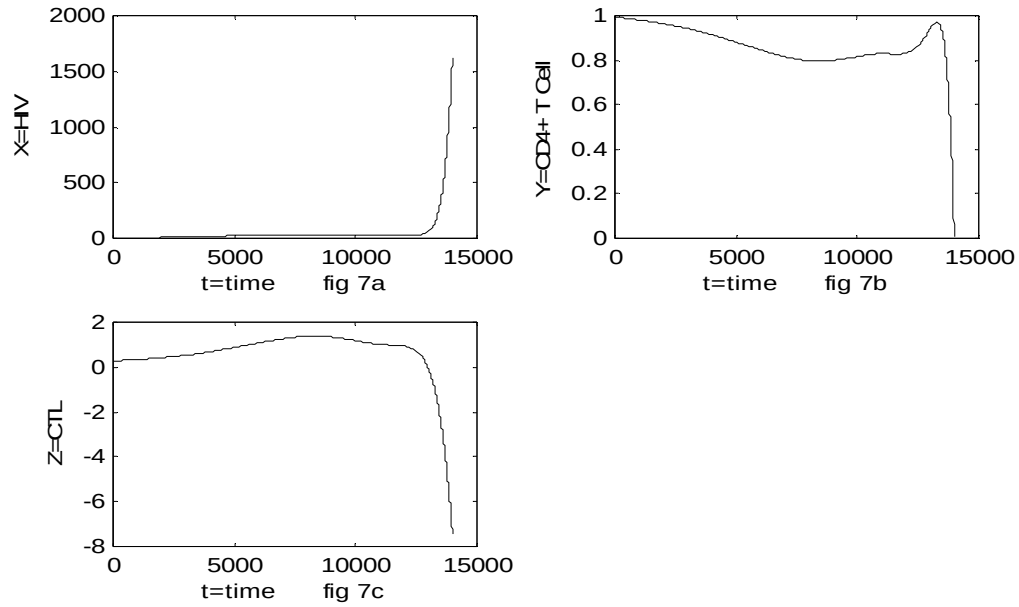

FIG: 7a – 7c; (t=0.0:7.0:13990)

Figure (7a-7c), shows that at $t \geq 12,650$ the viral load increases until it results to a full blown AIDS. Also at $t \geq 13,400$, the $CD4^+$ T cells count start decreasing until it is too low i.e. less than about 200 cells per cubic milliliter of blood.

*Corresponding author: E-mail; godwin.mbah@unn.edu.ng, Tel. +2348034198454

From the biological point of view, when $(P_4 > 1,)$ the basic productive rate of the virus is not under control level, each virus cell produces on the average more that its loss rate. In this case, the virus can establish an infection since its death rate due to the immune response is low.

Here, even if the immune response is maintained, virus persists. However the virus may persist without causing disease for sometime if the immune system is strongly responsive. This is the clinical latency stage of the infection. During this stage, HIV is active within the lymphoid organs, where large amount of virus becomes trapped in the follicular dendrite cells (FDC) network. The surrounding tissues that are rich in $CD4^+$ T cells may also become infected cells and as free virus. During this time, $CD4^+$ $CD45RO^+$ T cell carry most of the pro-viral load.

Also, HIV can survive even when all detectable virons in the blood (Viremia) are eliminated. It integrates itself into the DNA of the host cell and can stay there for years, lying dormant, immune to all kinds of therapy because it is just DNA. When the cell divides and the DNA is copied, the virus is copied too. After years, the virus can become active again seize the cells machinery and replicate.

5. Summary and Conclusion

Interpreting the result of proposition (2) in the biological sense, we have that, when $p_4 < 1$ the basic reproduction ratio for the virus is at a control level which means the virus is unsuccessful in escaping from the specific immune response, CTL, which produces a protein kown as CAML (Calcium-Modulating Cyclophilin Ligand), that inhibits the release of the HIV-1 virus from human cells. Part (a) of proposition (2) ensures that $p_4 < 1$, then the virus is unable to maintain the infection for a more longer period of time. The $CD4^+$ T cells population will converge to the ratio $(\mu + \delta)/\alpha$.

Changes in the basic reproduction ratio P_4 can have an influential effect on virus load/burden even if the virus is close to maintaining the infection because a strong CTL response results in a low virus load/burden. If the virus load/burden (V) is sufficiently small, then the total death rate of $CD4^+$ T cells due to the infection (ξIV) is small compared to the total loss of $CD4^+$ T cell (αI). Thus, the virus weakly affects the steady state density of $CD4^+$ T cell. By this model, patients with strong CTL ($CD8^+$ T cell) responses should have a greater reduction in steady state viral load/burden than those with weak CTL ($CD8^+$ T cells) response. According to the above reasons, if the physical parameters $(\psi^{\gamma}, \beta, \mu + \delta, \alpha)$ can be maintained so that the condition $P_4 < 1$ in proposition (2a) is satisfied, for example through vaccination and post-exposure immunization, then it may be possible to prevent progression towards AIDS.

However, by the second statement of part (a) and part (b) of proposition (2), if $P_4 > 1,$ that is, the basic reproduction ratio for the virus is not in a controlled range, then the virus can establish an infection and the uninfected steady state (3.17) loses its stability while the infected steady state (3.18) comes into existence and is stable. The long asymptomatic period between infection and collapse of the immune system is the duration required for the virus population to evolve into full blown AIDS since the $CD4^+$ T cell count has been reduced to less than about 200 cells per cubic millilitre of blood. This can be attributed to the fact that the HIV coating proteins readily detaches from virus particles. The blood becomes filled with these proteins, which can stick to the $CD4^+$ T cells, gluing them together. In addition, they are recognized by the immune system causing the immune cells to attack their own $CD4^+$ T cells [8]. This is then the case in which progression to full blown AIDS can be expected, and the patient can succumb to opportunistic infections.

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*Corresponding author: E-mail; godwin.mbah@unn.edu.ng, Tel. +2348034198454

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*Corresponding author: E-mail; godwin.mbah@unn.edu.ng, Tel. +2348034198454