7-7-2012

Mathematical Modeling and Simulation of 1 Acute and Chronic Phase HIV-1 Dynamics

Frank Nani
Fayetteville State University, fnani@uncfsu.edu

Mingxian Jin
Fayetteville State University, mjin@uncfsu.edu

Mathematical Modeling and Simulation of Acute and Chronic Phase HIV-1 Dynamics.

Frank K. Nani[1*], Mingxian Jin[2]

[1]*Fayetteville State University, 1200 Murchison Road Fayetteville NC 28301*

[2]*Fayetteville State University, 1200 Murchison Road Fayetteville NC 28301*

ABSTRACT

Aims: To construct a clinically plausible mathematical model of the patho-physiological dynamics of HIV-1 induced AIDS during the acute and chronic phases which incorporates the interactions between uninfected CD4+ T cells, HIV-1 infected CD4+ T cells, HIV-1 virions in the blood plasma, and specific cytotoxic CD8+ T cells. In particular, the model describes quantitatively the time evolution of AIDS in the patient during the acute phase and the asymptomatic chronic clinical latency phase and elucidates the effect of latent HIV-1 reservoirs on the prognosis of AIDS. The major objective is to derive mathematical criteria depicting the necessary and sufficient conditions under which the HIV-1 virions can be maintained definitely at the subclinical viral blood plasma level such that the HIV-1 seropositive person does not develop full-blown AIDS..

Study design: The model is based on contemporary published patho-physiological data on acute and clinical chronic phase HIV-1 induced AIDS. These data are meticulously condensed into a clinically plausible four compartmental mathematical model that incorporates the dynamics and interactions between non-HIV-1 infected CD4+ T lymphocytes. HiV-1 infected lymphocytes, free HIV-1 virions in the blood plasma, and HIV-1 specific cytotoxic CD8+ T lymphocytes. The relevant stoichiometric interaction rate constants, apoptotic rate constants ,rate constats for viral recruitment from latent reservoirs, and other relevant parameters are clearly exhibited in the mathematical model.

Place and Duration of Study: This research was done at Fayetteville State University, North Carolina USA, and is sponsored by the FSU Mini-Grant Award and the HBCU Graduate STEM Grant. The research was done during the Spring of 2012.

Methodology:. The deterministic nonlinear HIV-1 AIDS patho-physio-dynamical equations are analyzed using the techniques of dynamical system theory, principles of linearized stability, Hartman-Grobman theory, and other relevant mathematical techniques. The clinically desirable equilibrium states are and their local existence and global stability are analyzed. Investigative computer simulations are performed illustrating some physiological outcomes.

Results: Mathematical criteria are derived under which the clinically desired outcomes can occur. Investigative computer simulations are presented which elucidate a number of physiological scenarios of primary HIV-1 infection, involving the annihilation, and persistence of HIV-1 in the absence of AIDS Pharmacotherapy

Conclusion: Mathematical modeling can be a useful technique in the derivation of prognostic criteria and quantitative analysis of AIDS during the acute and chronic phases.

Keywords: HIV-1 annihilation criterias, mathematical model, computer simulations, acute and chronic phase

* Tel.: +001 910 672 1793; fax: +001 910 672 1070.
E-mail address: fnani@uncfsu.edu.

1. INTRODUCTION

Human Immunodeficiency Virus (HIV) belongs to a family of ribonucleic (RNA) lenti-viruses. In particular, the epidemiologically common subtype called HIV-1 is implicated for causing the Human Acquired Immunodeficiency Syndrome (AIDS). The pathogenesis of AIDS can be divided into three main phases called the acute phase, the clinical latency phase, and the full-blown AIDS phase.

The HIV-1 virion uses the glycoprotein *gp*120 to locate the CD4 surface molecules and the host cells. By means of CCR5 or CXCR4, the HIV-1 virions fuses to the host cell surfaces and eventually enter the cell. The CD4+ T cells are the major targets for the HIV-1 virions. But macrophages, monocytes, neurons, astrocytes, and microglia cells in the central nervous system (CNS) possess CCR5 chemokine co-receptors and hence are targets of HIV-1 virions. The pathogenesis of HIV-1 infection comprises the virus life cycle, the host cellular environment, and the viral load in the infected person. There exist strains of HIV-1 virus known as T-tropic and M-tropic which interact respectively with the CXCR4 and CCR5 chemokine co-receptors .

During the acute phase of HIV-1 infection, the person is seropositive after exposure and immunological reaction to the initial viral inoculum. The person experiences transient infection resembling mononucleosis for 1-12 weeks. The symptomatic primary HIV-1 infection is usually characterized by fever, lymphadenopathy, pharyngitis, arthralgia, rash, and lethargy. This is called acute retroviral syndrome (ARS) and is experienced by most but not all of the HIV-1 infected persons. During this phase, large amount of HIV-1 virions are produced inside the patient body. Inside the patient body, the HIV-1 viral envelope decoates and HIV RNA, reverse transcriptase, integrase, and other viral protein enter the host cell leading to formation of a pre-integration complex inside the host cell such as the CD4+ T cells. Then reverse transcriptase is used to produce HIV-1 viral DNA. The viral DNA is transported across the nucleus of the host cell and integrates into the host DNA. The next step is the production of new HIV-1 viral proteins using the HIV-1 viral RNA as genomic RNA. HIV proteases cleave newly synthesized polyproteins at the appropriate places to create the mature protein components of an infectious HIV virion. Then the new viral RNA and viral proteins migrate to the host surface and form a new immature HIV-1provirus. The mature newly formed HIV-1 virions exit the host cell by a process called budding. In particular, several millions of virus RNA copies may be released into the blood plasma of the patient.

After 3 months, the chronic clinical latency phase starts. During this phase, the rate of HIV-1 replication in the host cell decreases as the CD4+ T cells numbers increases as a result of the cytotoxic intervention of the body's immune system mounted by the CD8+ T cells. In particular, it is possible at this stage for the blood plasma HIV-1 viral titre to be subclinical and plunge to undetectable levels. This may continue up to 8 years or longer. Pantaleo, G (1993); Siliciano, R. F. (1998); Wasef, N. M.(2003).

The third phase of HIV-1 dynamics is characterized by a rapid exponential increase in the number of HIV-1 virions in the blood plasma, increase in the number of HIV-1 infected CD_4+ T cells, and a rapid decrease of uninfected CD4+ T cells to a level below 200 cells per microliter and a complete failure of the anti-HIV cytotoxic activity of CD8+ T cells. Walker, C. M. et al. (1986)

Several mathematical models of HIV-1 dynamics have been constructed by many authors including Pantaleo et al (1993); Essunger, P., Perelson, A.S. (1994); Perelson, A.S., Nelson, P. (1999); Kirschner, D., Webb, G.F. (1996); Wodarz, D. et al. (1999); Wodarz, D. (2001); Wodarz, D., Nowark, M. (1999). These authors proposed various mathematical models which describe certain aspects of HIV-1 life cycle with the aim of finding criteria for cure of AIDS or present a quantitative analysis of the dynamics of the HIV-1 virus. Ciupe, M.S., Bivort, B.L., Bortz, D.M. and Nelson, P.W. (2006) presented a detailed analysis of three different mathematical models with regard to local and global stability of infected and uninfected equilibrium (steady) states of HIV-1 infection. Their analysis also included the dynamics of time delay models. Li, M.Y. and Shu, H. (2011) performed an elaborate analysis of the global dynamics of a mathematical model for HTLV-1 infection of CD4+ T cells with delayed CTL response. In particular, they demonstrated that the time delay can destabilize the system equilibrium leading to Hopf bifurcations and stable periodic oscillations. Similar analysis of the global dynamics of HIV-1 infection of CD4+ T cells was done by Wang, L. and Li, M.Y. (2006). They obtained some interesting results on the stability of infected and non-infected equilibrium states of AIDS infection. A stochastic model for HIV-1 population dynamics has been presented and analyzed by Tuckwell and Corfec (1998). In particular, they analyzed the random fluctuations associated with HIV-1 infection and dynamics. In the forthcoming paper, we will present a stochastic model of HIV-1 dynamics which incorporates viral contributions from latent reservoirs and also accounts for apoptosis.

In this paper, new mathematical models for the acute phase and the asymptomatic clinical latency phase are proposed and analyzed. In particular, elaborate and robust mathematical criteria will be presented elucidating the conditions under which the chronic clinical latency phase can be maintained indefinitely in the seropositive HIV-1 infected person.

2.DEFINITION AND DESCRIPTION OF MODEL PARAMETERS.

The model of HIV-1 patho-physio- dynamics presented in this paper contains many variables and constant parameters. These parameters include stoichiometric interaction coefficients, cellular degradation rate constants, apoptotic rate constants, rate constants for production of immune cells from the thymus gland via haematopoietic progenitors, rate constants for recruitment of HIV-1 virions from latent reservoirs, intra-specific competition rate constants between infected / uninfected CD4+ T cells, and activation constants for CD4+/CD8+ T cells. The catalogue of constants is presented as follows

x_1: the number density of un-infected $CD4^+$ helper T-lymphocytes per unit volume

x_2: the number density of HIV-1 infected $CD4^+$ helper T-lymphocytes per unit volume

x_3: the number density of HIV-1 virions in the blood plasma per unit volume

x_4: the number density of HIV-1 specific $CD8^+$ cytotoxic T-lymphocytes per unit volume

S_1: rate of supply of un-infected $CD4^+$ T_4-lymphocytes

S_2: rate of supply of latency infected $CD4^+$ T_4-lymphocytes

S_3: rate of supply of HIV-1 virions from macrophage, monocytes, microglial cells and other lymphoid tissue different from T_4-lymphocytes

S_4: rate of supply of $CD8^+$ T_8-lymphocytes from the thymus

a_i, b_i: constant associated with activation of lymphocytes by cytokine interleukin-2 (IL-2)

α_i: constant associated with HIV-1 infection of $CD4^+$ T_4 helper cells

β_1: the number of HIV-1 virions produced per day by replication and budding in $CD4^+$ T_4 helper cells

β_2: rate constant associated with replication and "budding" of HIV-1 in syncytia $CD4^+$ T_4 helper cells per day per micro liter (μl) and released into the blood plasma

β_3: the number of HIV-1 virions produced per day by replication and "budding" in non-syncytia $CD4^+$ T_4 helper cells and released into the blood plasma

q_i: constant depicting competition between infected and un-infected $CD4^+$ T_4 helper cells

k_i: constant depicting degradation, loss of clonogenicity or "death"

e_{i0}: constant depicting death or degradation or removal by apoptosis (programmed cell death)

K_i: constant associated with the killing rate of infected $CD4^+$ T_4 cells by $CD8^+$ T_8 cytotoxic lymphocytes

..

3. MODEL DESCRIPTION AND ANALYSIS

In this section, the mathematical formulation for the acute and chronic phase of HIV-1 patho-physio-dynamics will be presented.

3.1. The description of the mathematical model

3.1.1 The CD4+ T cell dynamics:

$$\dot{x}_1 = S_1 + a_1 x_1^2 e^{-b_1 x_1} - \alpha_1 x_1 x_3 - q_1 x_1 x_2 - k_1 x_1 - e_{10} \qquad (3.1)$$

The instantaneous number of uninfected CD4+ T cells in the blood plasma of the patient at any time during the acute or chronic phase is equal to the rate of supply of uninfected CD4+ T cells from the thymus via hematopoietic progenitor cells (S_1); plus the activation/proliferative recruitment of antigen activated and interleukin-2 stimulated CD4+ T cells ($a_1 x_1^2 e^{-b_1 x_1}$); less the number of CD4+ cells recruited into the pool of HIV-1 infected CD4+ T cells by infection with HIV-1 virions ($\alpha_1 x_1 x_3$); less the number of CD4+ T cells lost by intra-

specific competition with HIV-1 infected CD4+ T cells($q_1 x_1 x_2$); less the number of CD4+ T cell lost by enzymatic degradation($k_1 x_1$); and less the number of CD4+ T cells lost by apoptosis/exfoliative cytolytic death(e_{10}).

3.1.2 The HIV-1 infected CD4+ dynamics:

$$\dot{x}_2 = S_2 + a_2 x_1 x_2 e^{-b_2 x_1} + \alpha_2 x_1 x_3 - q_2 x_1 x_2 - k_2 x_2 - \beta_1 x_3 - K_1 x_2 x_4 - e_{20} \quad (3.2)$$

The instantaneous number of HIV-1 infected CD4+ T cells in the blood plasma of the patient during the acute or chronic phase is equal to the rate of supply of HIV infected CD4+ T cells from resting CD4+ T cells (S_2); plus the activation/proliferative recruitment of antigen activated and interleukin-2 stimulated HIV-1 infected CD4+ T cells ($a_2 x_1 x_2 e^{-b_2 x_1}$); plus the addition of the HIV-1 infected CD4+ T cells ($\alpha_2 x_1 x_3$);less the number of CD4+ T cells lost by intra-specific competition with HIV-1 uninfected CD4+ T cells($q_2 x_1 x_2$); less the number of HIV-1 infected CD4+ T cell lost by enzymatic degradation($k_2 x_2$); and less the number of HIV-1 infected CD4+ T cells lost as a result of budding of newly produced virions ($\beta_1 x_3$); less the number of HIV-1 infected CD4+ T cells lost by cytolytic action by HIV-1 specific CD8+ T cells($K_1 x_2 x_4$); and less the number of HIV-1 infected CD4+ T cells lost by apoptosis/exfoliative cytolytic death(e_{20}).

3.1.3 The blood plasma HIV-1 virion dynamics:

$$\dot{x}_3 = S_3 + \beta_2 x_2 x_3 + \beta_3 x_3 - \alpha_3 x_1 x_3 - k_3 x_3 - e_{30} \quad (3.3)$$

The instantaneous number of HIV-1 virions in the blood plasma of the patient is equal to the rate of supply of HIV-1 virions from the latently infected viral reservoirs (S_3); plus the number of HIV-1 virions released from the syncytia of CD4+ T cells/dendritic cells/macrophages ($\beta_2 x_2 x_3$); plus the number of HIV-1 virions released from budding HIV-1 infected CD4+ T cells ($\beta_3 x_3$); less the number of HIV-1 virions lost during infection of CD4+ T cells ($\alpha_3 x_1 x_3$); less the number of HIV-1 virions lost by enzymatic degradation/catabolism($k_3 x_3$); and less the number of HIV-1 virions lost in the form of unintegrated HIV-1 DNA molecules per provirus (e_{30}).

3.1.4 The CD8+ T cells dynamics:

$$\dot{x}_4 = S_4 + a_4 x_1 x_4 e^{-b_4 x_1} - K_2 x_2 x_4 - k_4 x_4 - e_{40} \quad (3.4)$$

The instantaneous number of HIV-1 specific CD8+ T cells is equal to the rate of supply the thymus via hematopoietic progenitor cells; plus activation/proliferative recruitment of antigen activated and interleukin-2 stimulated HIV-1 specific CD8+ T cells ($a_4 x_1 x_4 e^{-b_4 x_1}$); less the number of CD8+ T cells lost during cytolysis of HIV-1 infected CD4+ T cells ();less the number of HIV-1 specific CD8+ T cell lost by enzymatic degradation($k_4 x_4$); less the number of HIV-1 specific CD8+ lost by apoptosis/exfoliative cytolytic death(e_{40}).

3.2 The Cauchy problem for dynamics of HIV-1 during the acute and chronic phases

In this section, the initial value problem (Cauchy problem) for HIV-1 dynamics during the acute and chronic phases will be mathematically analyzed and discussed with regard to well - posedness, dissipativity of solutions, and invariance of non-negativity.

From the previous section, the mathematical model for HIV-1 dynamics during the acute and chronic phases can be described in terms of the following deterministic, non-linear, and coupled ordinary differential equations. It is assumed that within certain biological limits the environment of the interactions between the uninfected CD4+ T cells, HIV-1 infected CD4+ T cells, HIV-1 virions in the blood plasma, and HIV-1 specific CD8+ T cells is homogeneous, isotropic, and hence space independent. Thus ordinary differential equations can be used in the modeling. In the future, mathematical models using partial differential equations, stochastic differential equations, and delay differential equations will be presented. Thus that Cauchy problem is described by the following system of equations:

$$\begin{cases} \dot{x}_1 = S_1 + a_1 x_1^2 e^{-b_1 x_1} - \alpha_1 x_1 x_3 - q_1 x_1 x_2 - k_1 x_1 - e_{10} \\ \dot{x}_2 = S_2 + a_2 x_1 x_2 e^{-b_2 x_1} + \alpha_2 x_1 x_3 - q_2 x_1 x_2 - k_2 x_2 - \beta_1 x_3 - K_1 x_2 x_4 - e_{20} \\ \dot{x}_3 = S_3 + \beta_2 x_2 x_3 + \beta_3 x_3 - \alpha_3 x_1 x_3 - k_3 x_3 - e_{30} \\ \dot{x}_4 = S_4 + a_4 x_1 x_4 e^{-b_4 x_1} - K_2 x_2 x_4 - k_4 x_4 - e_{40} \\ x_i(t_0) = x_{i0} \quad for \quad i = \{1, 2, 3, 4\} \end{cases} \tag{3.5}$$

Let t_0 be the time of the initial HIV-1 infection; and define t_L, t_P, repectively, as the time at which the latency phase begins and the time at which the post latency phase of HIV-1 dynamics commences in a patient. In particular, the phases $[t_0, t_L]$, $[t_L, t_P]$ depict respectively the acute phase and the chronic phase of primary HIV-1 induced AIDS.

3.3 Dissipativity and boundedness of solutions

In this subsection, the dissipativity of the model equations will be discussed.

Definition: Consider the autonomous system of ordinary differential equations:

$$\begin{aligned} &\dot{x} = F(x) \quad x(t_0) = x_0 \\ &where \quad x_0, x \in \Re^n \quad and \quad F \in C(\Re_+^n, \Re^n) \\ &\Re_+^n = \{x_i \in \Re^n \mid x_i \geq 0, i = 1, 2, \ldots, n\} \end{aligned} \tag{3.6}$$

Then the system (3.6) is dissipative if

$$\lim_{t \to \infty} Sup\, x_i(t) < M_i \quad where\ M_i \in \Re_+ \ is\ bounded$$

The invariance of non-negativity , ultimate boundedness of solutions and dissipativity of the model equations will be shown as follows:

Let
$$C_j = \underset{t\in[t_0,t_P]}{Sup}\left[a_j x_1 x_j e^{-b_j x_1}\right] \quad for\ j=\{1,2,4\}$$
$$C_3 = \underset{t\in[t_0,t_P]}{Sup}\left[\beta_2 x_2 x_3 + \beta_3 x_3\right] \tag{3.7}$$

Where t_L is the time at which the latency phase begins. Similarly, t_P is the time at which the post latency phase of HIV-1 dynamics commences in a patient and the time beyond which full-blown AIDS occurs.

The system of differential equations (3.5) reduce to the following differential inequalities, for $t\in[t_0,t_p]$:

$$\begin{cases} \dot{x}_1 \le S_1 + C_1 - k_1 x_1 - e_{10} \\ \dot{x}_2 \le S_2 + C_2 - k_2 x_2 - e_{20} \\ \dot{x}_3 \le S_3 + C_3 - k_3 x_3 - e_{30} \\ \dot{x}_4 \le S_4 + C_4 - k_4 x_4 - e_{40} \end{cases} \tag{3.8}$$

Using the Kamke comparison technique (cf Nani, F., Freedman, H.I. (2000)), the differential inequalities lead to the following theorem.

Theorem 3.1

Let
$$m_i = \underset{t\in[t_0,t_P]}{Max}\left\{x_{iL}, \frac{S_i + C_i - e_{i0}}{k_i}\right\}$$
$$for \quad i=\{1,2,3,4\} \tag{3.9}$$

where $\begin{cases} x_1(t_0) = x_{10} \\ x_2(t_0) = x_{20} \\ x_3(t_0) = x_{30} \\ x_4(t_0) = x_{40} \end{cases}$

Consider the set
$$A = \left\{(x_1,x_2,x_3,x_4)\in \Re_+^4 \,\middle|\, 0 \le x_i < m_i\right\}$$

Then all solutions of the initial value problem (3.5) that originate in int $\Re_+^4$ will eventually enter the set of *A*, such that the solution will be non-negative, ultimately bounded and remain in *A* for all $t\in\Re_+$.

Proof

The differential inequalities (3.8) can be used to obtain the following expressions:

$$x_i \leq \frac{S_i + C_i - e_{i0}}{k_i} + \sigma_{i0} e^{-k_i t} \tag{3.10}$$

where $\sigma_{i0} \in \Re^+ \; and \; i = \{1, 2, 3, 4\}$

Hence, for $i = \{1, 2, 3, 4\}$,

$$\lim Sup\, x_i(t) \leq \frac{S_i + C_i - e_{i0}}{k_i}$$

and

$$x_i(t) \in \underset{A}{Sup} \left\{ x_{i0}, \frac{S_i + C_i - e_{i0}}{k_i} \right\} \tag{3.11}$$

Thus the flow associated with the system (3.5) is dissipative, and non-negatively invariant if $S_i + C_i - e_{i0} > 0$. In particular, the flow associated with the model equations (3.5) will eventually enter the set A and remains trapped in A for $t \in \Re^+$, if $x_{i0} \in \text{int}\, \Re_+^4$. □

3.4 Criteria for persistence of HIV-1 virions in the chronic phase

In this section, the criteria for the persistence of HIV-1 virions during the chronic phase will be derived.

The differential equation for the HIV-1 patho- physiodynamics during the clinical chronic phase is:

$$\dot{x}_3(t) = S_3 + \beta_2 x_3 - \alpha_3 x_1 x_3 - k_3 x_3 - e_{30}$$

where S_3 is the reflux and repopulation rate of the plasma HIV-1 virions from the lymphoid tissue, microgial cells, reticules-endothelial cells, monocytes/macrophages and other sanctuaries. e_{30} is a constant degradation rate of HIV-1 virions. β_2 is the "budding" rate constant of HIV-1 virions.

Let

$$\overline{L}_1 = \inf_{t \in [t_L, t_P]} x_1(t) \tag{3.12}$$

and

$$S_3 - e_{30} \geq 0$$

$$\dot{x}_3(t) \geq S_3 + \beta_2 x_3 - \alpha_3 \overline{L}_1 x_3 - k_3 x_3 - e_{30} \tag{3.13}$$

By solving (3.13) using Kamke's comparison technique [1, 12], the following inequality is obtained:

$$x_3(t) \geq \frac{S_3 - e_{30}}{k_3 + \alpha_3 \overline{L}_1 - \beta_2} + k e^{-(k_3 + \alpha_3 \overline{L}_1 - \beta_2)t} \tag{3.14}$$

where k is a positive constant.

In particular, the following theorems arise immediately:

Theorem 3.2. Suppose

(i) $S_3 - e_{30} > 0$

(ii) $k_3 + \alpha_3 L_1 - \beta_2 > 0$

Then

$$\liminf x_3(t) \geq \frac{S_3 - e_{30}}{k_3 + \alpha_3 \bar{L}_1 - \beta_2} > \mathrm{H} > 0 \tag{3.15}$$

where H is a bounded positive number of subclinical value. As a consequence, the number of HIV-1 virions in the blood plasma of the AIDS patient during the chronic phase will exhibit persistence. The patient will not develop full-blown AIDS if the value of H is such that the patient does not experience immune system paralysis.

Theorem 3.3. Suppose

(i) $S_3 - e_{30} = 0$

(ii) $k_3 + \alpha_3 L_1 - \beta_2 > 0$ (3.16)

(iii) $0 < \frac{S_3 - e_{30}}{k_3 + \alpha_3 L_1 - \beta_2} < \varepsilon$

where ε is a small positive number.

Then the blood plasma HIV-1 viral titre is negligibly subclinical and the AIDS patient has insignificant HIV-1 RNA copies in the blood plasma during the chronic phase.

Theorem 3.4. Suppose

(i) $k_3 + \alpha_3 L_1 - \beta_2 < 0$

(ii) $S_3 - e_{30} > 0$ (3.17)

Then the number of HIV-1 virions in the blood plasma increases exponentially. The HIV-1 positive patient will develop full-blown AIDS. Consequently, the patient will ultimately loose immuno-competency and eventually die as a result of opportunistic infections.

4. ANALYSES OF THE PHYSIOLOGICAL OUTCOMES

The clinically significant equilibrium patho-physiological outcomes of HIV-1 dynamics during the acute and chronic phases will be analyzed in this section using the principles of linearized stability. The outcomes are called equilibrium points or rest points of the model equations. The analyses will involve five clinically interesting equilibrium outcomes labeled {E_i: i =1, 2, 3, 4, 5}.

4.1 Criteria for existence of physiological outcomes

(i) E_1 = [0, 0, 0, 0]: this represents the case in which uninfected $CD4^+$ T cells, infected $CD4^+$ T cells, HIV-1 virions in blood plasma, and HIV-1 specific CD8+ T cells are all destroyed. This leads to the immune system paralysis in which the patient dies of opportunistic bacteria or viral infection. This case is clinically feasible if S_i - e_{i0} =0.

(ii) E_2 = [$\hat{x}_1$, 0, 0, $\hat{x}_4$]: this represents the case in which infected $CD4^+$ T cells and HIV-1 virions in blood plasma are all destroyed. Clinical doctors working with HIV-1 infected patients would like to achieve this outcome. This equilibrium point is clinically possible under the following necessary conditions:

$$\begin{cases} S_1 + a_1 \hat{x}_1^2 e^{-b_1 \hat{x}_2} - k_1 \hat{x}_1 - e_{10} = 0 \\ S_2 - e_{20} = 0 \\ S_3 - e_{30} = 0 \\ S_4 + a_4 \hat{x}_1 \hat{x}_4 e^{-b_4 \hat{x}_1} - k_4 \hat{x}_4 - e_{40} = 0 \end{cases} \tag{4.1}$$

(iii) E_3 = [0, $\bar{x}_2$, $\bar{x}_3$, 0]: this depicts a clinically worst case situation in which both uninfected $CD4^+$ T cells and HIV-1 specific $CD8^+$ T cells are destroyed. This equilibrium point is clinically possible under the following necessary conditions:

$$\begin{cases} S_1 - e_{10} = 0 \\ S_2 - \beta_1 \bar{x}_3 - k_2 \bar{x}_2 - e_{20} = 0 \\ S_3 - \beta_2 \bar{x}_3 - k_3 \bar{x}_3 - e_{30} = 0 \\ S_4 - e_{40} = 0 \end{cases} \tag{4.2}$$

(iv) E_4 = [$\tilde{x}_1$, 0, 0, 0]: this is the most clinically desirable equilibrium point in which infected CD4+ T cells, plasma HIV-1 virions, and HIV-1 specific cytotoxic CD8+ T cells are all annihilated. The necessary conditions for the existence of this equilibrium point are:

$$\begin{cases} S_1 + a_1 \tilde{x}_1^2 e^{-b_1 \tilde{x}_2} - k_1 \tilde{x}_1 - e_{10} = 0 \\ S_2 - e_{20} = 0 \\ S_3 - e_{30} = 0 \\ S_4 - e_{40} = 0 \end{cases} \tag{4.3}$$

(v) E_5 = [$\breve{x}_1, \breve{x}_2, \breve{x}_3, \breve{x}_4$]: this case can only exist if the equation (3.0) exhibits persistence in which all the four factors co-exist. The details of showing persistence in nonlinear systems of differential equations have been discussed by Nani, F., Freedman, H.I. (2000).

There are other equilibrium points such as $E[x_1, x_2, 0, 0]$, $E[0, 0, x_3, x_4]$ and many planar or axial points. These are clinically uninteresting and are not considered in this paper, but will be analyzed in a future paper.

4.2. Linearized stability analysis of physiological outcomes

The Hartman-Grobman theorem can be used to investigate the local physiological stability of HIV-1 AIDS disease dynamics associated with the model equations, in the neighborhood of the physiological outcomes (equilibrium states). The mathematical model is nonlinear and as such it is difficult to obtain any meaningful quantitative criteria about the model. Fortunately, the Hartman-Grobman theorem guarantees that the information contained in the linearized system and the information contained the nonlinear system are equivalent in the neighborhood of the rest points.

The Jacobian matrix of linearization near any physiological outcome is denoted symbolically by

$$J[E_k] := \{a_{ij}\} \in M_{4x4}(\Re) \quad where\ k = 1, 2, 3, ...$$

$$\begin{aligned}
a_{11} &:= a_1 x_1 (2 - b_1 x_1) e^{-b_1 x_1} - \alpha_1 x_3 - q_1 x_2 - k_1 \\
a_{12} &:= -q_1 x_1 \\
a_{13} &:= -\alpha_1 x_1 \\
a_{14} &:= 0 \\
a_{21} &:= a_2 x_2 (1 - b_2 x_1) e^{-b_2 x_1} - q_2 x_2 \\
a_{22} &:= a_2 x_1 e^{-b_2 x_1} - q_2 x_1 - k_2 - K_1 x_4 \\
a_{23} &:= \alpha_2 x_1 - \beta_1 \\
a_{24} &:= -K_1 x_2 \\
a_{31} &:= -\alpha_3 x_3 \\
a_{32} &:= \beta_2 x_3 \\
a_{33} &:= \beta_2 x_2 + \beta_3 - \alpha_3 x_1 - k_3 \\
a_{34} &:= 0 \\
a_{41} &:= a_4 x_4 (1 - b_4 x_1) e^{-b_4 x_1} \\
a_{42} &:= -K_2 x_4 \\
a_{43} &:= 0 \\
a_{44} &:= a_4 x_1 e^{-b_4 x_1} - K_2 x_2 - k_4
\end{aligned} \tag{4.4}$$

4.2.1 Criteria for annihilation of HIV-1 virions during the acute and chronic phases

The Jacobian matrix of linearization in the neighborhood of E_2 is given by the following matrix:

$$J\{E_2[\hat{x}_1,0,0,\hat{x}_4]\} = \begin{bmatrix} a_1\hat{x}_1(2-b_1\hat{x}_1)e^{-b_1\hat{x}_1} - k_1 & -q_1\hat{x}_1 & -\alpha_1\hat{x}_1 & 0 \\ 0 & a_2\hat{x}_1e^{-b_2\hat{x}_1} - q_2\hat{x}_1 - k_2 - K_1\hat{x}_4 & \alpha_2\hat{x}_1 - \beta_1 & 0 \\ 0 & 0 & \beta_3 - \alpha_3\hat{x}_1 - k_3 & 0 \\ a_4\hat{x}_4(1-b_4\hat{x}_1)e^{-b_4\hat{x}_1} & -K_2\hat{x}_4 & 0 & a_4\hat{x}_1e^{-b_4\hat{x}_1} - k_4 \end{bmatrix} \quad (4.5)$$

The application of the principle of linearized stability and local stability theorems lead to the following:

Theorem 4.1. Suppose

(i) $a_1\hat{x}_1(2-b_1\hat{x}_1)e^{-b_1\hat{x}_1} - k_1 < 0$

(ii) $a_2\hat{x}_1e^{-b_2\hat{x}_1} - q_2\hat{x}_1 - k_2 - K_1\hat{x}_4 < 0$

(iii) $\beta_3 - \alpha_3\hat{x}_1 - k_3$ (4.6)

(iv) $a_4\hat{x}_1e^{-b_4\hat{x}_1} - k_4 < 0$

Then the rest point $E_2[\hat{x}_1,0,0,\hat{x}_4]$ is local attractor. In particular, the HIV-1 infected CD4+ T cells and the HIV-1 virions in the blood plasma of the AIDS patient are temporarily annihilated during the acute and chronic phases in the absence of the pharmacotherapy.

Theorem 4.2. Suppose the conditions of Theorem 4.1 hold, and the following additional conditions hold:

(i) $\hat{x}_1 = \frac{2}{b_1} = \frac{\beta_3}{\alpha_3}$

(ii) $\hat{x}_4 = \frac{a_2\hat{x}_1e^{-b_2\hat{x}_1}}{K_1}$ (4.7)

(iii) $a_4\hat{x}_1e^{-b_4\hat{x}_1} < k_4$

Then the local attractor E_2 can be written in the following form:

$$E_2 = [\frac{2}{b_1}, 0, 0, \frac{2a_2e^{-\frac{2b_2}{b_1}}}{b_1K_1}] \quad (4.8)$$

The clinical implication of this result is that the transient annihilation of the HIV-1 virions and HIV-1 infected CD4+ T cells occurs during the acute and chronic phases if CD4+ T cells and CD8+ T cells number densities are given respectively by $\frac{2}{b_1}$ and $\frac{2a_2 e^{-\frac{2b_2}{b_1}}}{b_1 K_1}$.

4.2.2 The criteria for transient immune system paralysis during the acute and chronic phases of AIDS

One of the rest points corresponding the immune system paralysis during primary AIDS infection is E_3. The Jacobian matrix of the linearization of the model equations in the neighborhood of E_3 is given as follows:

$$J\{E_3[0, \bar{x}_2, \bar{x}_3, 0]\} = \begin{bmatrix} -\alpha_1\bar{x}_3 - q_1\bar{x}_2 - k_1 & 0 & 0 & 0 \\ a_2\bar{x}_2 - q_2\bar{x}_2 & -k_2 & -\beta_1 & -K_1\bar{x}_2 \\ \alpha_3\bar{x}_3 & \beta_2\bar{x}_3 & \beta_2\bar{x}_2 + \beta_3 - k_3 & 0 \\ 0 & 0 & 0 & -K_2\bar{x}_2 - k_4 \end{bmatrix} \quad (4.9)$$

The application of the principles of linearized stability gives the following result:

Theorem 4.3. Let

(i) $\beta_2\bar{x}_2 + \beta_3 - k_3 - k_2 < 0$

(ii) $\beta_1\beta_2\bar{x}_3 - k_2(\beta_2\bar{x}_2 + \beta_3 - k_3) > 0$ (4.10)

Then the rest point E_3 is local attractor.

The clinical implication of Theorem 4.3 is that the immune system of the AIDS patient suffices transient paralysis when the conditions (4.10) hold.

Theorem 4.4. Suppose the conditions of Theorem 4.1 hold, and the following additional conditions hold:

(i) $\hat{x}_1 > \frac{2}{b_1}$

(ii) $\hat{x}_1 = \frac{\beta_3}{\alpha_3}$

$a_2\hat{x}_1 e^{-b_2\hat{x}_1} - K_1\hat{x}_4 = 0 \quad or$

(iii) $a_2\hat{x}_1 e^{-b_2\hat{x}_1} = q_2\hat{x}_1 \quad or$ (4.11)

$a_2\hat{x}_1 e^{-b_2\hat{x}_1} - k_2 = 0$

(iv) $a_4\hat{x}_1 e^{-b_4\hat{x}_1} < k_4$

Then E_2 is a local attractor.

The analysis of other rest points will be done in a future publication.

4.3. Global stability analysis of physiological outcomes

In this section, theoretical criteria will be presented for global stability of the clinically desirable physiological outcome $E_2[\hat{x}_1, 0, 0, \hat{x}_4]$.

Consider space $R_+^{x_1 x_4} = [x_1, x_4 \mid x_1 \geq 0, x_4 \geq 0]$ (4.12)

The model equations (3.5) correspondingly reduce to the following:

$$\begin{cases} \dot{x}_1 = S_1 + a_1 x_1^2 e^{-b_1 x_1} - k_1 x_1 - e_{10} \\ \dot{x}_4 = S_4 + a_4 x_1 x_4 e^{-b_4 x_1} - k_4 x_4 - e_{40} \\ x_i(t_0) = x_{i0} \quad for \quad i = \{1,\ 4\} \end{cases} \tag{4.13}$$

Consider the Liapunov functional [1, 12]:

$$V := \sum \frac{1}{2} \hat{c}_i (x_i - \hat{x}_i)^2$$
$$where\ i = \{1, 4\}\ and\ \hat{c}_i \in R_+ = (0, \infty) \tag{4.14}$$

The derivative of V along the solution curves of the model equations yields the result:

$$\begin{aligned} \overset{*}{V} &= \hat{c}_1(x_1 - \hat{x}_1)\dot{x}_1 + \hat{c}_4(x_4 - \hat{x}_4)\dot{x}_4 \\ &= \hat{c}_1(x_1 - \hat{x}_1)(S_1 + a_1 x_1^2 e^{-b_1 x_1} - k_1 x_1 - e_{10}) + \\ &\quad \hat{c}_4(x_4 - \hat{x}_4)(S_4 + a_4 x_1 x_4 e^{-b_4 \hat{x}_1} - k_4 x_4 - e_{40}) \end{aligned} \tag{4.15}$$

Define the following Lebesgue measurable, functions which are of bounded variation:

$$\begin{aligned} G(x_1) &= a_1 x_1^2 e^{-b_1 x_1} \\ F(x_1, x_4) &= a_4 x_1 x_4 e^{-b_4 x_1} \end{aligned} \tag{4.16}$$

$$\begin{aligned} \overset{*}{V} &= \hat{c}_1(x_1 - \hat{x}_1)\dot{x}_1 + \hat{c}_4(x_4 - \hat{x}_4)\dot{x}_4 \\ &= \hat{c}_1(x_1 - \hat{x}_1)(-a_1 \hat{x}_1^2 e^{-b_1 x_1} + k_1 \hat{x}_1 + a_1 x_1^2 e^{-b_1 x_1} - k_1 x_1) + \\ &\quad \hat{c}_4(x_4 - \hat{x}_4)(-a_4 \hat{x}_1 \hat{x}_4 e^{-b_4 \hat{x}_1} + k_4 \hat{x}_4 + a_4 x_1 x_4 e^{-b_4 x_1} - k_4 x_4) \\ &= \hat{c}_1(x_1 - \hat{x}_1)[G(x_1) - G(\hat{x}_1)] + \hat{c}_1(x_1 - \hat{x}_1)(k_1 \hat{x}_1 - k_1 x_1)] + \\ &\quad \hat{c}_4(x_4 - \hat{x}_4)[F(x_1, x_4) - F(\hat{x}_1, \hat{x}_4)] + \hat{c}_4(x_4 - \hat{x}_4)(k_4 \hat{x}_4 - k_4 x_4)] \end{aligned} \tag{4.17}$$

$$\begin{aligned} \overset{*}{V} &= -\hat{c}_1 k_1 (x_1 - \hat{x}_1)^2 + \hat{c}_1(x_1 - \hat{x}_1)[G(x_1) - G(\hat{x}_1)] + \\ &\quad \hat{c}_4(x_4 - \hat{x}_4)[F(x_1, x_4) - F(\hat{x}_1, \hat{x}_4)] - \hat{c}_4 k_4 (x_4 - \hat{x}_4)^2 \end{aligned} \tag{4.18}$$

Let

$$\begin{aligned} v_1 &= x_1 - \hat{x}_1 \\ v_2 &= x_4 - \hat{x}_4 \end{aligned} \tag{4.19}$$

and

$$X = \begin{bmatrix} v_1 \\ v_2 \end{bmatrix} \in R_+^2$$

and define define $A=\{a_{ij}\} \in M_{2X2}(R)$ such that

$$A = \begin{bmatrix} a_{11} & \frac{1}{2}a_{12} \\ \frac{1}{2}a_{21} & a_{22} \end{bmatrix} \tag{4.20}$$

then

$$\begin{aligned} \overset{*}{V} &:= a_{11}v_1^2 + \frac{1}{2}a_{12}v_1v_2 + \frac{1}{2}a_{21}v_2v_1 + a_{22}v_2^2 \\ &= X^T AX \end{aligned} \tag{4.21}$$

Where X^T denotes the transpose of X and $\overset{*}{V}$ is negative definite if the eigen-values of A have negative real parts.

In particular, the $[a_{ij}]_{2x2}$ are defined as follows:

$$\begin{cases} a_{11} := -\hat{c}_1 k_1 + \hat{c}_1\left(\dfrac{G(x_1) - G(\hat{x}_1)}{x_1 - \hat{x}_1}\right) \\ a_{12} = a_{21} = 0 \\ a_{22} := -\hat{c}_4 k_4 + \hat{c}_4\left[\dfrac{F(x_1, x_4) - F(\hat{x}_1, \hat{x}_4)}{x_4 - \hat{x}_4}\right] \end{cases} \tag{4.22}$$

As the flow dynamics approaches the steady state $E_2[x_1, 0, 0, x_4]$, the following conditions hold:

$$\begin{aligned} a_{11} &\to -\hat{c}_1 k_1 + G_1'(\hat{x}_1)] \\ a_{22} &\to -\hat{c}_4 k_4 + \hat{c}_4 F_{x_4}(\hat{x}_1, \hat{x}_4) \end{aligned} \tag{4.23}$$

but

$$\begin{aligned} G'(\hat{x}_1) &= a_1 \hat{x}_1 e^{-b_1 \hat{x}_1}(2 - b_1 \hat{x}_1) \\ F_{x_4}(\hat{x}_4) &= a_4 \hat{x}_4 e^{-b_4 \hat{x}_1}(1 - b_4 \hat{x}_4) \end{aligned} \tag{4.24}$$

Hence, the sufficient criteria for the global asymptotic stability of E_2 are specified in the following theorem.

Theorem 4.5. Suppose the following conditions hold:

(i) Criterion (4.1)

(ii) $\hat{x}_1 \geq \frac{2}{b_1}$

(iii)) $\hat{x}_4 \geq \frac{1}{b_4}$

Then the clinically desirable rest point E_2 is a global attractor.

The clinical implication of Theorem 4.5 is that the AIDS patient will experience permanent annihilation of the infected CD4+ T cells and HIV-1 virions in the blood plasma if the patient's patho-physio-dynamics conforms to the conditions specified in the theorem.

5. COMPUTER SIMULATION RESULTS AND DISCUSSION

In this section, investigative computer simulations are performed under specific parametric configurations. It must be stated emphatically that Theorems 4.1 – 4.4 are applicable only to the equilibrium configurations $\{E_i: i = 1, 2, 3, 4, \ldots, n\}$. of the patho-physiodynamics of HIV-1 virus in the AIDS patient. These theorems are "if…then…" theorems and as such are fulfilled only when the AIDS dynamics attains the equilibrium configuration in the patient. In particular, there exist certain sufficient but not necessary criteria under which the AIDS patient can experience clinically favorable outcomes. On the other hand, under the specified conditions of Theorems 4.1-4.4 the predicted results are valid. The simulation results are presented in Sections 5.1 through 5.4. The time profile for the simulation is measured in years.

The problem of parameter estimation in mathematical modeling of physiological systems is a non-trivial one. There is a quasi-uniqueness of patho-physio-dynamics of disease in the patient and as such no two persons have identical physiological parametric configurations for a given disease. These phenomena have been discussed in the publication by Wu, H. et al. (1999). Several techniques concerning parameter estimation have been discussed by many authors including Ciupe, M.S. et al. (2006), Perelson, A.S., et al. (1996); Perelson, A.S., and Nelson, P. (1999); Han, C. et al. (2002); Graziosi, C. et al. (1993); Chun, T.W., et al. (1996); Wodarz, D., et al. (1999); Wodarz, D., and Nowark, M. (1999).

Theorems 4.1-4.4, however, are based on equilibrium configurations of patho-physio-dynamics of AIDS. Thus, the techniques presented in the above references must be modified in order to obtain relevant estimates of the dynamical variables presented in this paper. In particular, in vitro and in vivo experiments as well as human biopsies from the peripheral blood of the AIDS patient are required in order to accurately determine most of the dynamical variables and constants of the model. Simulations based on equilibrium dynamics of AIDS using ACSL (Advanced Continuous Simulation Language) will be presented in a forthcoming paper.

5.1 Simulation results for hypothetical AIDS patient #1

The hypothetical patient #1 possesses a non-equilibrium patho-physio-dynamics parametric configuration P_1 presented in Table 1. The HIV-1 dynamics in this patient represents the classic profile for the acute and clinically chronic phases of AIDS. The simulation results for patient #1 are exhibited in Figure 1. It can observed that the HIV-1 infected CD4+ T cells and the blood plasmas HIV-1 virions are completely eradicated in this patient without the use of anti-AIDS pharmaco-therapeutic drug protocols. In addition, patient #1 experiences immune system reconstitution as the uninfected CD4+ T cells repopulate and proliferate towards their pre-HIV-1 infection carrying capacities.

Table 1 Parametric Configuration P_1

$S_1 = 1.5$ /day/μl	$S_2 = 0.85$ /day/μl	$S_3 = 0.0$ /day/μl	$S_4 = 0.272$ /day/μl
$a_1 = 0.009$ /day/cell/μl	$a_2 = 0.004$ /day/cell/μl	$\beta_2 = 0$ virons/CD4$^+$/day/μl	$a_4 = 0.0075$ /day/cell/μl
$b_1 = 0.001$ /cell/μl	$b_2 = 0.004$/cell/μl	$\beta_3 = 50$ virons/CD4$^+$/day	$b_4 = 0.001$/cell/μl
$\alpha_1 = 0.05$/day/virion/μl	$\alpha_2 = 0.1$/day/virion/μl	$\alpha_3 = 0.0027$/day/virion/μl	$K_2 = 0.0024$ /day/μl
$k_1 = 0.005$/day/μl	$k_2 = 0.05$/day/μl	$k_3 = 0.0001$/day	$k_4 = 0.001$/day/μl
$q_1 = 0.0045$/day/μl/cell	$q_2 = 0.0001$/day/μl/cell	$e_{30} = 0.0001$ /day	$e_{40} = 7.75$ cells/day/μl
$e_{10} = 8.8$ cells/day/μl	$\beta_1 = 50$ virons/CD4$^+$/day	$x_{30} = 0.01$ cells/μl	$x_{40} = 800$ cells/μl
$x_{10} = 703$ cells/μl	$K_1 = 0.001$/day/μl		
	$e_{20} = 0.005$ cells/day/μl		
	$x_{20} = 100$ cells/μl		

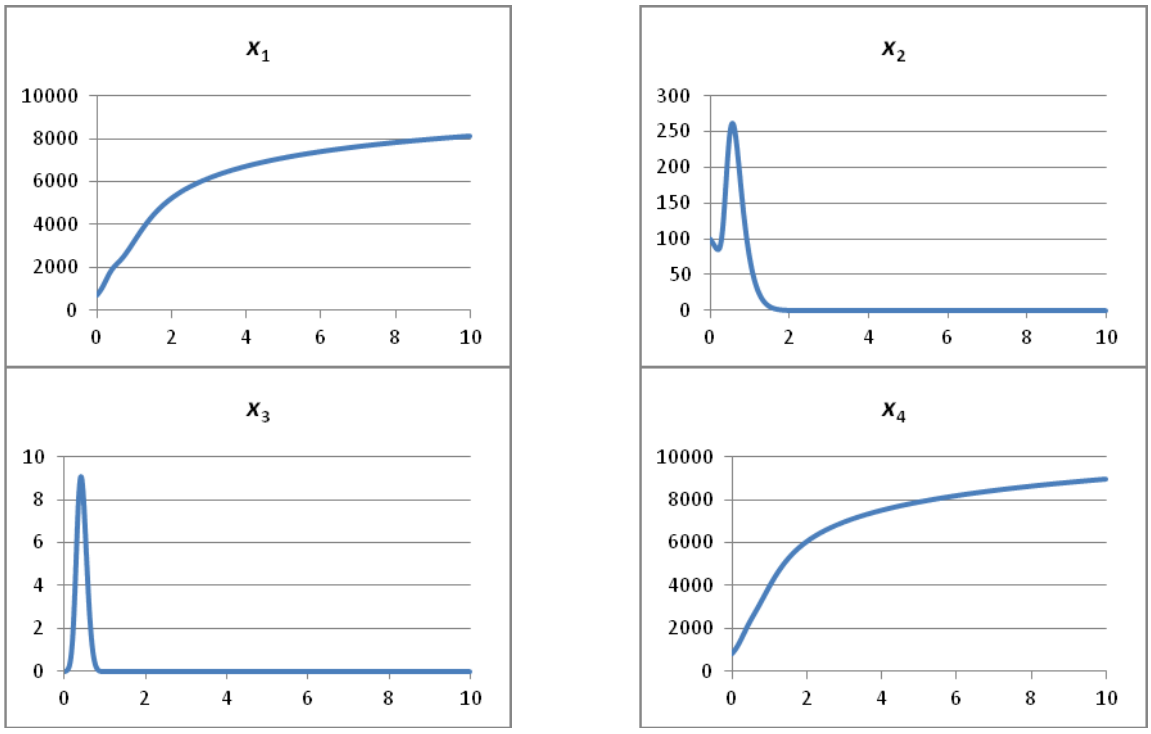

Figure 1 Simulation results using parametric configuration P_1

5.2 Simulation results for hypothetical AIDS patient #2

For this simulation, the hypothetical AIDS patient #2 is assigned the patho-physiological parameter configuration presented in Table 2. As in the previous simulation, the configuration P2 does not depict an equilibrium configuration. The simulation results are exhibited in Figure 2. It can be observed that the patient does not have a clinically favorable prognosis. Because the disease has apparently progressed beyond the time point characterized as t_p, which is defined as the threshold time for full-blown AIDS. As presented in Figure 2, the patient undergoes immune system paralysis in which the CD4+ T cells transiently destroyed. On the other hand, the cytotoxic activity of CD8+ T cells appears to be potent as observed in the eradication of the HIV-1 infected CD4+ T cells. Paradoxically the plasma HIV-1 viremia increases exponentially in the patient resulting in a more morbid AIDS outcome.

Table 2 Parametric Configuration P_2

$S_1 = 1.5$ /day/μl $a_1 = 0.009$ /day/cell/μl $b_1 = 0.001$ /cell/μl $\alpha_1 = 0.05$/day/virion/μl $k_1 = 0.005$/day/μl $q_1 = 0.0045$/day/μl/cell $e_{10} = 8.8$ cells/day/μl $x_{10} = 703$ cells/μl	$S_2 = 0.85$ /day/μl $a_2 = 0.004$ /day/cell/μl $b_2 = 0.004$/cell/μl $\alpha_2 = 0.1$/day/virion/μl $k_2 = 0.05$/day/μl $q_2 = 0.0001$/day/μl/cell $\beta_1 = 51$ virons/CD4$^+$/day $K_1 = 0.001$/day/μl $e_{20} = 0.005$ cells/day/μl $x_{20} = 200$ cells/μl	$S_3 = 10.5$ /day/μl $\beta_2 = 0.025$ virons/CD4$^+$/day/μl $\beta_3 = 51$ virons/CD4$^+$/day $\alpha_3 = 0.027$/day/virion/μl $k_3 = 0.0001$/day $e_{30} = 0.0001$ /day $x_{30} = 5.5$ cells/μl	$S_4 = 0.272$ /day/μl $a_4 = 0.0075$ /day/cell/μl $b_4 = 0.001$/cell/μl $K_2 = 0.0024$ /day/μl $k_4 = 0.08$/day/μl $e_{40} = 10.75$ cells/day/μl $x_{40} = 800$ cells/μl

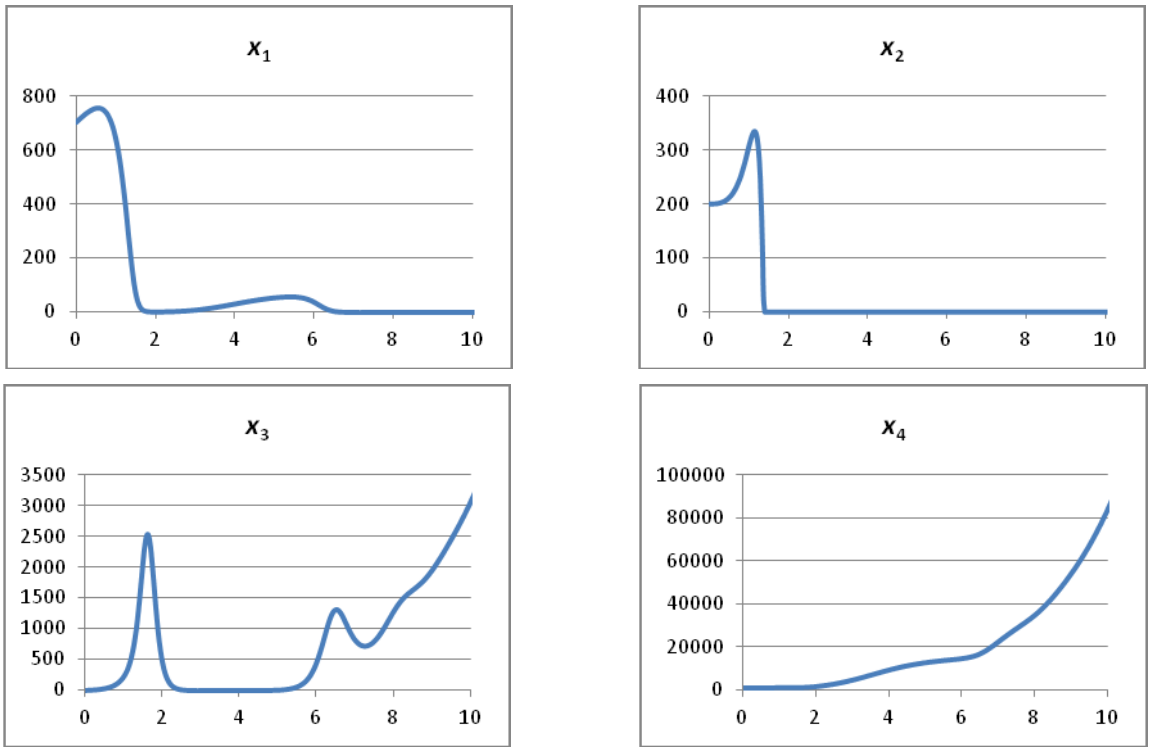

Figure 2 Simulation results using parametric configuration P_2

5.3 Simulation results for hypothetical AIDS patient #3

The patho-physiological parametric configuration of patient #3 is shown in Table 3. It must be noted that the AIDS in this patient is in the acute phase and as such the simulation results span a time period lasting up to one year. The results of the simulation are in Figure 3. This is a non-equilibrium AIDS configuration simulation as it is evident by the simulation time profile. The simulation results show that at the end of the acute phase, the AIDS patient experiences annihilation of uninfected CD4+ T cells. In addition, the HIV-1 specific CD8+ T cells eradicate successfully the HIV-1 infected CD4+ T cells. Unfortunately the immune system paralysis, which occurs as a consequence of the low CD4+ T cell number density, eventually leads to an exponential increase of the blood plasma HIV-1 viremia. This simulation represents an unfavorable AIDS outcome during the acute phase.

Table 3 Parametric Configuration P_3

$S_1 = 1.5$ /day/μl $a_1 = 0.009$ /day/cell/μl $b_1 = 0.001$ /cell/μl $\alpha_1 = 0.05$/day/virion/μl $k_1 = 0.005$/day/μl $q_1 = 0.0045$/day/μl/cell $e_{10} = 8.8$ cells/day/μl $x_{10} = 703$ cells/μl	$S_2 = 0.0$ /day/μl $a_2 = 0.004$ /day/cell/μl $b_2 = 0.004$/cell/μl $\alpha_2 = 0.1$/day/virion/μl $k_2 = 0.05$/day/μl $q_2 = 0.0001$/day/μl/cell $\beta_1 = 10$ virons/CD4$^+$/day $K_1 = 0.001$/day/μl $e_{20} = 0.005$ cells/day/μl $x_{20} = 100$ cells/μl	$S_3 = 0.0$ /day/μl $\beta_2 = 0.0$ virons/CD4$^+$/day/μl $\beta_3 = 10$ virons/CD4$^+$/day $\alpha_3 = 0$ /day/virion/μl $k_3 = 0.0001$/day $e_{30} = 0.0001$ /day $x_{30} = 0.01$ cells/μl	$S_4 = 0.272$ /day/μl $a_4 = 0.0075$ /day/cell/μl $b_4 = 0.001$/cell/μl $K_2 = 0.0024$ /day/μl $k_4 = 0.001$/day/μl $e_{40} = 7.75$ cells/day/μl $x_{40} = 800$ cells/μl

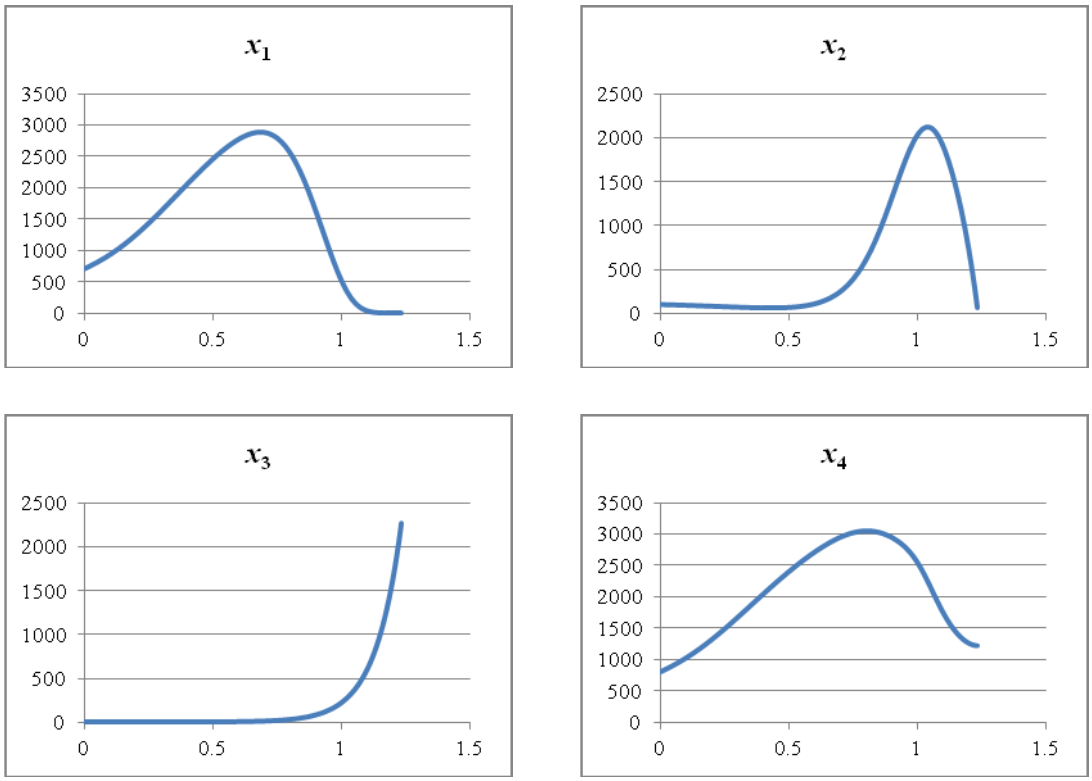

Figure 3 Simulation results using parametric configuration P_3

5.4 Simulation results for hypothetical AIDS patient #4

The simulation results for hypothetical patient #4 are exhibited in Figure 4. These simulation results are based on the patho-physiological parametric configuration P4. In this patient the AIDS disease progresses from the acute phase into a 6 year clinically chronic phase before the development of full-blown AIDS.

Table 4 Parametric Configuration P_4

$S_1 = 1.5$ /day/μl $a_1 = 0..5$ /day/cell/μl $b_1 = 0.001$ /cell/μl $\alpha_1 = 0.05$/day/virion/μl $k_1 = 0.005$/day/μl $q_1 = 0.0045$/day/μl/cell $e_{10} = 8.8$ cells/day/μl $x_{10} = 703$ cells/μl	$S_2 = 0.0$ /day/μl $a_2 = 0.05$ /day/cell/μl $b_2 = 0.004$/cell/μl $\alpha_2 = 0.5$/day/virion/μl $k_2 = 0.05$/day/μl $q_2 = 0.0001$/day/μl/cell $\beta_1 = 2$ virons/CD4$^+$/day $K_1 = 0.001$/day/μl $e_{20} = 0.005$ cells/day/μl $x_{20} = 100$ cells/μl	$S_3 = 0.0$ /day/μl $\beta_2 = 0.0001$ virons/CD4$^+$/day/μl $\beta_3 = 2$ virons/CD4$^+$/day $\alpha_3 = 0.0001$/day/virion/μl $k_3 = 0.0001$/day $e_{30} = 0.0001$ /day $x_{30} = 0.01$ cells/μl	$S_4 = 0.272$ /day/μl $a_4 = 0.0075$ /day/cell/μl $b_4 = 0.001$/cell/μl $K_2 = 0.0024$ /day/μl $k_4 = 0.08$/day/μl $e_{40} = 7.75$ cells/day/μl $x_{40} = 800$ cells/μl

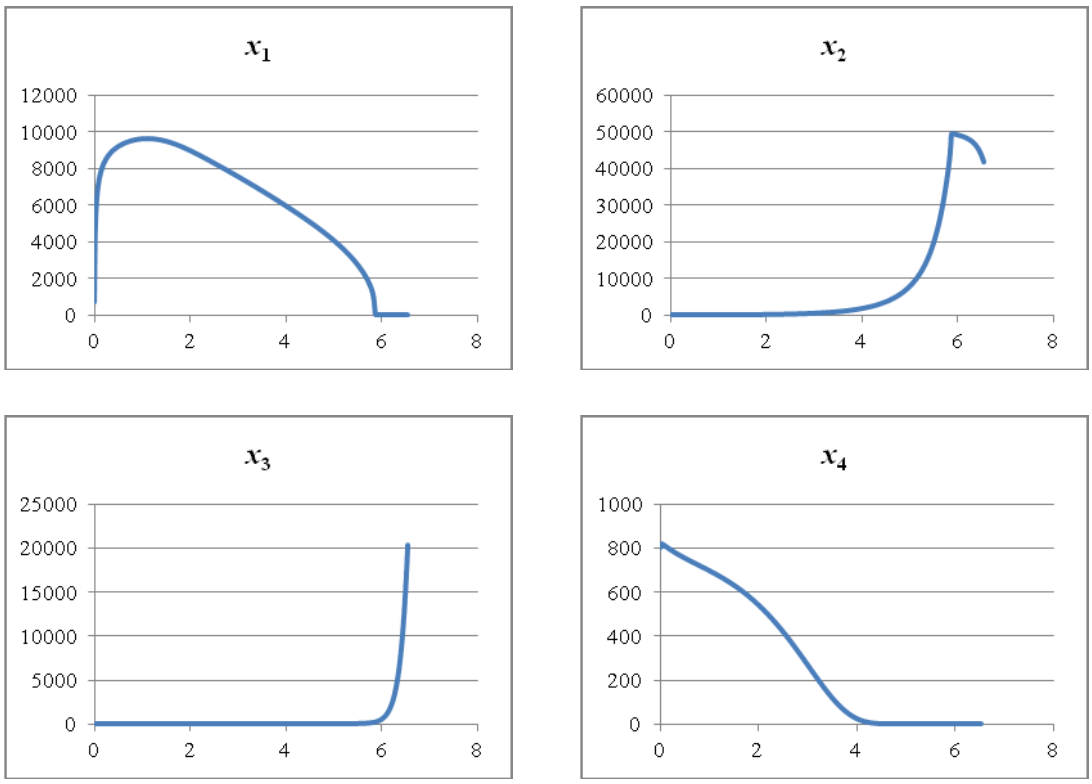

Figure 4 Simulation results using parametric configuration P_4

5.5 Simulation results for hypothetical AIDS patient #5

This scenario represents a relatively favorable progression of AIDS in hypothetical patient #5. The data for the simulation results are given in Table 5 and the simulation results are displayed in Figure 5. The patho-physiological parametric configuration of this patient does not represent an equilibrium configuration and as such the condition of theorems 4.1-4.4 are not applicable. It can be observed from the simulation results that the patient would develop full-blown AIDS approximately after 10 years. On the other hand, the patient experiences relatively good immune-competency from the beginning of the initial infection up to approximately 10 years before the onset of full-blown AIDS.

Table 5 Parametric Configuration P_5

$S_1 = 1.5$ /day/μl $a_1 = 2.5$ /day/cell/μl $b_1 = 0.001$ /cell/μl $\alpha_1 = 0.05$/day/virion/μl $k_1 = 0.005$/day/μl $q_1 = 0.0045$/day/μl/cell $e_{10} = 8.8$ cells/day/μl $x_{10} = 703$ cells/μl	$S_2 = 0.0$ /day/μl $a_2 = 0.05$ /day/cell/μl $b_2 = 0.004$/cell/μl $\alpha_2 = 0.5$/day/virion/μl $k_2 = 0.05$/day/μl $q_2 = 0.0001$/day/μl/cell $\beta_1 = 2$ virons/CD4$^+$/day $K_1 = 0.001$/day/μl $e_{20} = 0.005$ cells/day/μl $x_{20} = 100$ cells/μl	$S_3 = 0.0$ /day/μl $\beta_2 = 0.0001$ virons/CD4$^+$/day/μl $\beta_3 = 2$ virons/CD4$^+$/day $\alpha_3 = 0.0001$/day/virion/μl $k_3 = 0.0001$/day $e_{30} = 0.0001$ /day $x_{30} = 0.01$ cells/μl	$S_4 = 0.272$ /day/μl $a_4 = 4.0$ /day/cell/μl $b_4 = 0.001$/cell/μl $K_2 = 0.0024$ /day/μl $k_4 = 0.001$/day/μl $e_{40} = 7.75$ cells/day/μl $x_{40} = 800$ cells/μl

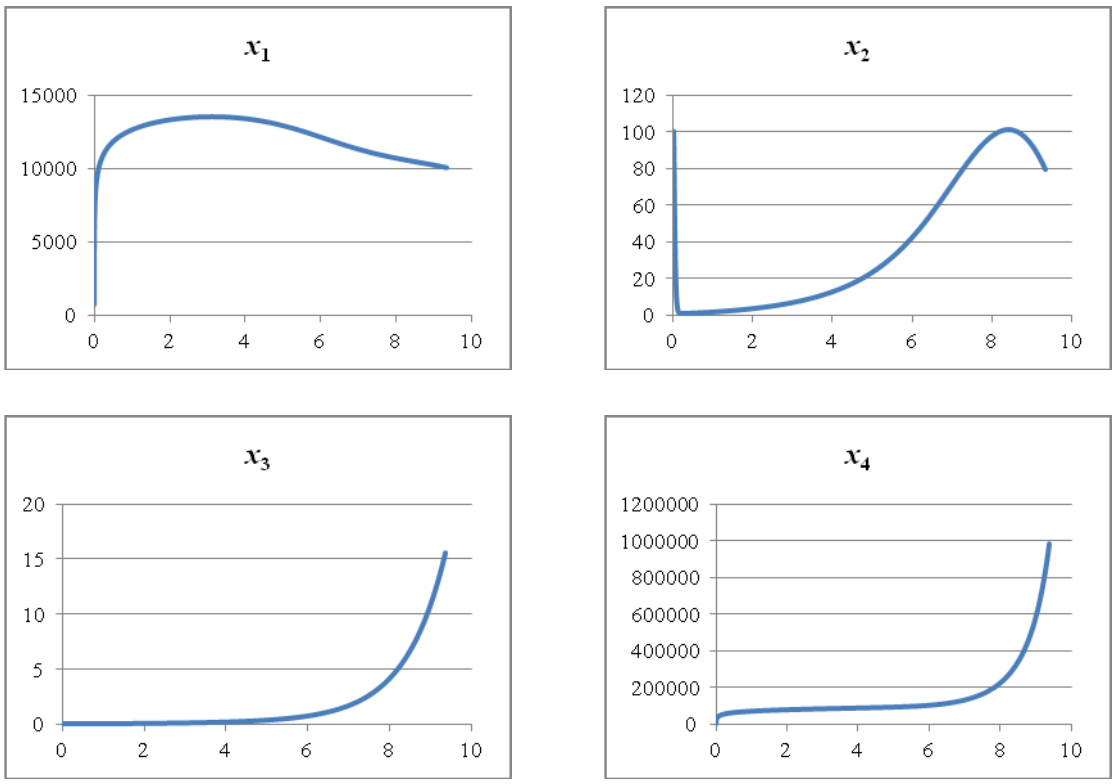

Figure 5 Simulation results using parametric configuration P_5

5.6 Simulation results for hypothetical AIDS patient #6

The patho-physiological configuration of hypothetical patient #6 is given in Table 6. The simulation results depict an AIDS scenario which progresses from the acute phase through a relatively short chronic phase and heading towards the development of full-blown AIDS, as shown in Figure 6. It can be observed also that from the time period between 0 to 4 years the patient has sufficient immuno-competency as it is evident in the relatively higher dynamic number density of the CD4+ T cells and the HIV-1 specific CD8+ T cells as compared to the low dynamic number density of the HIV-1 infected CD4+ T cells and the blood plasma HIV-1 virions. Beyond the period of 6 years, then blood plasma HIV-1 virion and the HIV-1 infected CD4+ T cells number densities begin to rise as the patient heads towards the development of full-blown AIDS.

Table 6 Parametric Configuration P_6

$S_1 = 1.5$ /day/μl $a_1 = 1.5$ /day/cell/μl $b_1 = 0.001$ /cell/μl $\alpha_1 = 0.05$/day/virion/μl $k_1 = 0.005$/day/μl $q_1 = 0.0045$/day/μl/cell $e_{10} = 8.8$ cells/day/μl $x_{10} = 703$ cells/μl	$S_2 = 0.0$ /day/μl $a_2 = 0.05$ /day/cell/μl $b_2 = 0.004$/cell/μl $\alpha_2 = 0.5$/day/virion/μl $k_2 = 0.05$/day/μl $q_2 = 0.0001$/day/μl/cell $\beta_1 = 2$ virons/CD4$^+$/day $K_1 = 0.001$/day/μl $e_{20} = 0.005$ cells/day/μl $x_{20} = 100$ cells/μl	$S_3 = 0.0$ /day/μl $\beta_2 = 0.0001$ virons/CD4$^+$/day/μl $\beta_3 = 2$ virons/CD4$^+$/day $\alpha_3 = 0.0001$/day/virion/μl $k_3 = 0.0001$/day $e_{30} = 0.0001$ /day $x_{30} = 0.01$ cells/μl	$S_4 = 0.272$ /day/μl $a_4 = 3.0$ /day/cell/μl $b_4 = 0.001$/cell/μl $K_2 = 0.0024$ /day/μl $k_4 = 0.001$/day/μl $e_{40} = 7.75$ cells/day/μl $x_{40} = 800$ cells/μl

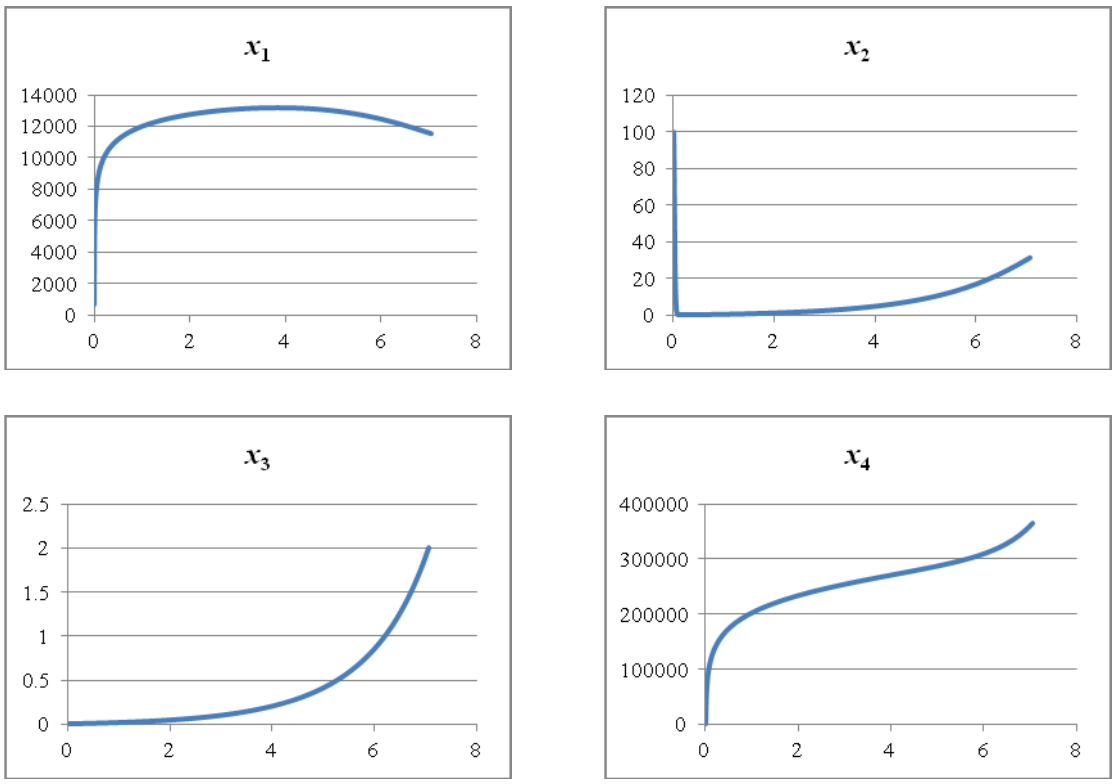

Figure 6 Simulation results using parametric configuration P_6

6. SUMMARIZING REMARKS

In this paper, we have presented a novel and robust approach to the study of HIV-1 dynamics during the acute and chronic phases. The special contribution of this model includes an explicit role of source terms S_1, S_2, S_3, S_4, which depict recruitment from the thymus gland and the HIV-1 viral reservoirs. Clinically relevant activation functions describing the action of IL-2 on the T cells are also included in the model equations. The clinical outcomes are clearly exhibited together with the associated criteria for existence. In particular, the simulation results depict the scenario of chronic asymptomatic HIV-1 infection during chronic latency phase in which the infected $CD4^+$ T cells and the plasma, viremia are annihilated. The results elucidate and exhibit additional details of HIV-1 dynamics than the cited literature. In a future publication, investigative computer simulation results will be presented elucidating Theorems 4.1-4.4. In particular, the simulation software ACSL (Advanced Continuous Simulation Language) will be used in the simulation of time delay versions of model equations (3.5).

7. REFERENCES

[1] Amann, H., (1990). Ordinary Differential Equations, An Introduction to Nonlinear Analysis, Walter de Gruyter & Co, Berlin., pp. 209

[2] Chun, T., Engel, D., Berrey, M., Shea, T., Corey, L., and Fauci, A., (1998). Early establishment of a pool of latently infected, resting CD4+ T cells during primary HIV-1 infection, *Proc. Natl. Acad. Sci.* USA, Vol. 95, pp. 8869–8873.

[3] Chun, T.W., Finzi D, Margolick, J. (1996). Fate of HIV-1 infected T-cells in vivo: Rates of transition to stable latency. *Nat Med* 1996; 334:1222-1330.

[4] Ciupe, M.S., Bivort, B.L., Bortz, D.M.,, and Nelson, P.W., (2006). Estimating kinetic parameters from HIV primary infection data through the eyes of three different mathematical models, Mathematical Biosciences 200 pp. 1–27

[5] Clark, S.J., Shaw, G.M. (1993). The acute retroviral syndrome and the patho-genesis of HIV-1 infection, *Semin Immunology*; 5:149

[6] Daar, E.S. (1991). Transient high levels of viremia in patients with primary human immunodeficiency virus type I infection. *New Engl. J. Med*; 324:961

[7] Essunger, P., Perelson, A. S. (1994). Modeling HIV infection of CD 4+ T-cell subpopulations. *J. thero. Biol.* 170(4):367-91

[8] Graziosi, C. (1993). Kinetics of human immunodeficiency virus type 1 (HIV-1) DNA and RNA synthesis during primary HIV-1 infection. *Proc Natl Acad Sci. USA*, 90:6405

[9] Han, C., Chaloner, K., Perelson, A.S., (2002). Bayesian analysis of a population HIV dynamic model. *Case Studies in Bayesian Statistics*, Vol.6, Springer-Verlag: New York,

[10] Kirschner, D., Webb, G.F.(1996). A model for treatment strategy in the chemotherapy of AIDS. *Bull. Math. Biol.* 58, 367-390.

[11] Li, M.Y., Shu, H.(2011). Global dynamics of a mathematical model for HTLV-1 infection of CD4+ T cells with delayed CTL response, Nonlinear Analysis: Real World Applications doi:10.1016/j.nonrwa.2011.02.026

[12] Nani, F. Freedman, H.I.(2000). A mathematical model of cancer treatment by immunotherapy. *Mathematical Biosciences* 163 159-199.

[13] Nowark, M.A, Bangham, C.R.M. (1996). Population dynamics of immune responses to persistent viruses. *Science* 272, 74-79, 1996.

[14] Pantaleo, G., Graziosi. C., Demarest, J.F. (1993). HIV infection is active and progressing in lymphoid tissue during the clinically latent stage of disease. *Nature*, 362:355-358.

[15] Perelson, A.S., Neumann, A.U., Markwitz, M. (1996). Viral dynamics in vivo: virion clearance rate, infected cell life-span, viral generation time. *Science*, 271:1582-1586.

[16] Perelson, A.S., Nelson, P. (1999) Mathematical analysis of HIV-1 dynamics in vivo, SIAM Rev. 41(1), 3-44.

[17] Reddy, Y.S., Kashuba, A. (2003). Importance of antiretroviral drug concentration in sanctuary sites and viral reservoirs. *AIDS Research and Human Retroviruses*, Vol. 19 (11), pp. 167-176.

[18] Rubbert, A. (2002). Course of HIV RNA in CD4+ and CD8+ lymphocytes in HIV-infected patients undergoing HAART as determined by ultrasensitive fluorescence in Situ hybridization (UFISH). *Proc. of the 9th Conf. on Retroviruses and Opportunistic Infections*.

[19] Siliciano, R.F. (1998). Immunodeficiency in HIV-1 infection in: *AIDS and Other Manifestations of HIV Infection, 3rd ed.* Wormser,G. (Ed.) pp.257-278, Lippincott-Raven Publishers, Philadelphia.

[20] Sonza, S., Crowe, S. (2001). Reservoirs for HIV infection and their persistence in the face of undetectable viral load. *AIDS Patient Care and STDs*; 15(10).

[21] Suspène, R., Meyerhans, A. (2012). Quantification of Unintegrated HIV-1 DNA at the Single Cell Level In Vivo. PLoS ONE 7(5): e36246. doi:10.1371/journal.pone.0036246.

[22] Tuckwell, H.C., Corfec, E.L., (1998). A stochastic model for early HIV-1 population dynamics. *J. theor. Biol.* 195, 451-463.

[23] Walker, C.M., Moody, D.J., Stites, D.P., Levy, J.A. (1986). $CD8^+$ lymphocytes can control HIV infection in vitro by suppressing virus replication. *Science*, 234:1563-1566.

[24] Wang, L, Li MY, Mathematical analysis of the global dynamics of a model for HIV infection of CD4+ T cells. Math Biosci 200:44–57, 2006

[25] Wassef, N. M., Young, J. Miller, R. (2003). Viral reservoirs/transient infection in HIV/AIDS: where are we now and where should we go? *AIDS Research and Human Retroviruses*, Vol. 19 (11), pp. 333-344.

[26] Wodarz, D., Lloyd, A. (1999). Dynamics of macrophage and T cell infection by HIV. *J. theor. Biol.* 196, 101-113.

[27] Wodarz, D. (2001). Helper-dependent vs. helper-independent CTL responses in HIV infection: implications for drug therapy and resistance. *J.theor. Biol.* 213, 447-459.

[28] Wodarz, D., Nowark, M. (1999). Specific therapy regimes could lead to long-term immunological control of HIV. *Pro. Natl. Acad. Sci. USA* 96(25), 14464-14469.

[29] Wu, H., Ding, A., DeGruttola, V. (1999). Why are the decay rates in plasma HIV-1 different for different treatments and in different patient populations? *AIDS,* 13(3): 429-430.