

Original Research Article

Generalized Theoretical Criteria for Annihilation of HIV-1 Virions During HAART

ABSTRACT

Aims: This paper is an elaborate and quantitative attempt to construct medically applicable mathematical models and derive criteria for efficacious **Highly Active Anti-Retroviral Therapy (HAART) protocol** for an AIDS patient. The patho-physiological dynamics of Human Immuno-deficiency Virus type 1 (HIV-1) induced AIDS during **HAART** is modeled by a system of non-linear deterministic differential equations. The physiologically relevant and clinically plausible equations depict the dynamics of uninfected CD4⁺ T cells (x_1), HIV-1 infected CD4⁺ T cells (x_2), HIV-1 virions in the blood plasma (x_3), HIV-1 specific CD8⁺ T cells (x_4), and the concentration of HAART drug molecules (x_5). The major objective of this research is to construct an elaborate mathematical model that depicts patho-physiodynamics of HIV-1 virions during **HAART**. The derived therapeutic criteria are expressed in terms of clinically measurable physiological parameters. Investigative computer simulations which describe certain aspects of HIV-1 dynamics during HAART are also presented in the paper.

Study design: The mathematical model is constructed based on contemporary research data condensed from the clinical literature on HAART of AIDS. A system of coupled non-linear deterministic differential equations are used to characterize the patho-physiodynamics of HAART during the post chronic phase. The mathematical analysis of the model equations and the computer simulations are performed with regard to HAART protocols with constant continuous intravenous and transdermal drug infusions. **A syncytium term with stoichiometric coefficient is introduced into the model to account for the formation of large multinucleated gp120 bearing CD4⁺ T cells that are observed in some AIDS patients. By assigning a zero value to the stoichiometric coefficient, the role of syncytium is abrogated.**

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 conducted during the Spring of 2012.

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

Results: The therapeutic outcomes are presented in the form of theoretical criteria which are obtained from mathematical analysis of the model equations. In particular, the critical parameters which govern the dynamics of HIV-1 virions during HAART are clearly identified. Some clinical implications of HAART are elucidated in the computer simulations using hypothetical physiological parametric configurations.

Conclusion: This research has demonstrated the existence of plausible criteria under which HIV-1 virions can be annihilated using HAART. The latent HIV-1 virion reservoirs are implicated in unsuccessful scenarios of HAART. It has also been demonstrated that the rate constants associated with activation of lymphocytes by cytokine interleukin-2 (IL-2) play a significant role in determining the efficacious outcomes of HAART.

Keywords: *HIV-1 patho-physiodynamics, mathematical modeling, HAART therapy, AIDS cure criteria, Michaelis-Menten kinetics*

AMS Subject Classification: 93A30; 93D05; 93D20; 34A34; 92C42; 92C35

1. Introduction

Highly Active Anti-retroviral Therapy (HAART) is currently the most therapeutically efficacious treatment protocol for treating the Acquired Immunodeficiency Syndrome (AIDS). HIV-1 virions induce AIDS by orchestrating an irreversible destruction of the $CD4^+$ T cells which then paralyze the immune system of the HIV-1 positive person. The major objectives of HAART therapy are the prolongation and improvement of the long-term life quality of patients; optimization of therapy such as to suppress the HIV-1 viral load to below 50 copies of HIV-1 RNA; reconstitution of the patients' immune system such that the $CD4^+$ T cells proliferate to carrying capacity; and minimization of drug toxicity. HAART treatment protocol consists of nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, anti-fungals /anti-bacterials and in future, integrase inhibitors. The reverse transcriptase inhibitors prevent reverse transcription of HIV-1 specific DNA. The protease inhibitors are antagonistic to maturation and formation of new HIV-1 virions. The possible role of integrase inhibitors is to prevent the integration of HIV-1 viral DNA into the patients' DNA [1, 2].

In order to achieve the therapeutic goals of HAART, it is plausible to involve the techniques of mathematical modeling. Before the advent of HAART, the primary focus of the mathematical modelers is to quantitatively analyze the observed patho-physio dynamics of HIV-1 infection in the AIDS patients. These earlier research papers involve the pioneering work of Perelson et al. [3], Nowark et al. [4], and other contributors [5, 6].

A recent paper by Nani and Jin [7] provided some physiological criteria under which HIV-1 virions in an AIDS patient can be annihilated during HAART.

Some of the earlier mathematical modeling publications focus on single-drug AIDS therapy using Zidovudine (INN) or azidothymidine (AZT) [8]. Then the advent of Active Retro-viral Therapy (ART) and the associated clinical limitation led to the development of HAART treatment protocols. In spite of the initial success of HAART, there are clinically measurable and observable shortcomings in the treatment of AIDS [9]. In particular, HAART is not successful in about 40% of AIDS patients because of drug-induced toxicity and complications of treatment. HAART protocols have been clinically observed to have limited therapeutic efficacy due to biochemical/clinical drug resistance, short drug half-life, low bio-availability and blood plasma toxicities.

Mathematical modeling provides a quantitative and rational approach to solve the therapeutic efficacy problems associated with HAART. In particular, the models focused on finding optimal therapeutic schedules, the roles of latent viral reservoirs as well as minimizing of toxic side effect [5,6,8,10-14].

Mathematical models which incorporate the explicit computation of the cure rate of HIV-1 induced AIDS during HAART include models by [15-17].

During HAART, the major obstacle to total viral eradication is the existence of viral reservoirs and retroviral latency [18]. Retroviral latency is defined as an integrated pro-virus with no active transcription. This is associated with low-level chronic viral and persistent cryptic HIV-1 replication. These processes lead to viral persistence after initial successful HAART [18]. Mathematical models which demonstrate persistence due to viral reservoirs have been constructed by Nani and Jin [15, 16]. Other models which elegantly address the role of viral reservoirs in persistence include papers by Rong and Perelson in [19], Kim and Perelson in [20], and Sedaghat, Siliciano and Wilke in [21].

Optimal therapies that will minimize side effects have been investigated by many authors in [3-5, 7, 8, 14, 22, 23]. Zaric et al. in 1998 presented a model which was focused on the simulation of protease inhibitors and role of drug resistant HIV-1 virions [24]. Stengel in [22] presented a mathematical model of HIV-1 infection and HAART which demonstrated the efficacy of a mathematically optimal therapy. Caetano and Yoneyama in [11] constructed a HAART model which incorporated the roles of latently infected $CD4^+$ T cells, and discussed how the reverse transcriptase and protease inhibitors affected HIV-1 dynamics during HAART, using the LQR, Scheme. In particular, Hattaf and Yousfi incorporated the basic reproductive number R_0 in determination of optimal HIV therapy in [25]. In a separate paper, the same authors constructed a delayed differential equation model of HIV-1 dynamics during therapy in [26]. They employed a numerical algorithm and Pontryagin's Maximum Principle in determination of the optimal therapies. In a future paper, we will use Pontryagin's Minimal Principle to construct admissible optimal therapies such as to minimize the toxicity of the drug but maximize the therapeutic efficacy of HAART.

In this paper, an elaborate mathematical model will be constructed which will incorporate physiologically plausible effects such as Michaelis-Menten kinetics, role of HIV-1 latent viral reservoirs, continuous transdermal drug delivery, and the implicit lymphocyte proliferation induction by the CD4⁺ T cells. The activation and proliferation is accomplished by a paracrine and autocrine processes which are mediated by the cytokine interleukin-2, secreted by the CD4⁺ T cells. A special feature of the current paper is the inclusion of the syncytium production term to the HIV-1 virion compartment. It has been shown by Koot et. al. in [27] that syncytium inducing HIV-1 variants, occurring 2 years before progression to AIDS, on an average, significantly increase the rate of CD4⁺ declines. The destruction mechanism of CD4⁺ and CD8⁺ T cells due to syncytium formation and other mechanisms has been described by Shut et. al. in [28]. These features are incorporated in the current paper by assigning two separate cell loss rates. The HIV virion can also disintegrate by releasing the soluble HIV-1 envelope protein gp120 into the blood plasma which can attach to uninfected CD4⁺ T cells, causing attack by antibodies thereby increasing the rate of decline of immuno-competent CD4⁺ T cells. Mathematical structures are used in the current model to demonstrate these aspects of HIV-1 and CD4⁺ T cell dynamics.

Several authors investigated the consequences of structured long-term and short-term treatment interruptions during HAART [9-11, 14]. The current model will discuss these consequences by means of simulations.

The current paper will be divided into eight sections. The first section gives the introduction into HAART therapy and provides the basis for current research. This is followed by presentation and discussion of the model parameters in Section 2. In Section 3 the mathematical model of HAART therapy will be constructed. Also the necessary and sufficient criteria for annihilation of HIV-1 virions during HAART will be presented in sections 4, 5, and 6. In Section 7, clinically plausible computer simulations will be exhibited. Section 8 will be the summary and discussion of the basic results of the paper.

2. Parameters

In this section, the physiological variable and parameters of the HAART model equations will be defined and explained. It must be emphasized that some of these parameters are biologically measurable or can be estimated using clinical techniques. In clinical experience, these parameters are different from patient to patient depending on their patho-physiological conditions.

A list of model parameters, constants, and variables is shown as follows.

x_1 : the number density of non-HIV-1-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

x_5 : the concentration of drug molecules of the HAART treatment protocol

S_1 : rate of supply of un-infected CD4⁺ T₄-lymphocytes

S_2 : rate of supply of latently infected CD4⁺ T₄-lymphocytes

S_3 : rate of supply of HIV-1 virions from macrophage, monocytes, microglial cells and other lymphoid tissue different from T₄-lymphocytes

S_4 : rate of supply of CD8⁺ T₈ lymphocytes from the thymus

D : rate of HAART drug infusion by transdermal delivery

a_i, b_i : constant associated with activation of lymphocytes by cytokine interleukin-2 (IL-2) ($i = 1, 2, 3, 4$)

c : rate of HAART drug degradation and excretion

α_i : constant associated with HIV-1 infection of CD4⁺ T₄ helper cells ($i = 1, 2, 3$)

β_1 : the number of HIV-1 virions produced per day by replication and budding in CD4⁺ T₄ helper cells

β_2 : rate constant associated with replication and “budding” of HIV-1 in syncytia CD4⁺ T₄ helper cells per day per microliter (μ l) 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⁺ T₄ helper cells and released into the blood plasma

η_i : constant depicting the rate of which HIV-1 virions incapacitate the CD8⁺ T₈ cytotoxic cells ($i = 1, 2$)

(σ_0, λ_0) : Michaelis-Menten nonlinear metabolic rate constants associated with HAART drug elimination
 (σ_i, λ_i) : Michaelis-Menten nonlinear metabolic rate constants associated with HAART drug pharmacokinetics ($i = 2, 3$)
 ξ_i : cytotoxic coefficient where $0 \leq \xi_i \leq 1$ ($i = 2, 3$)
 q_i : constant depicting competition between infected and un-infected $CD4^+$ T_4 helper cells ($i = 1, 2$)
 k_i : constant depicting degradation, loss of clonogenicity or “death” ($i = 1, 2, 3, 4$)
 k_5 : rate constant depicting exponential drug elimination pharmacokinetics
 e_{i0} : constant depicting death or degradation or removal by apoptosis (programmed cell death) ($i = 1, 2, 3, 4$)
 K_i : constant associated with the killing rate of infected $CD4^+$ T_4 cells by $CD8^+$ T_8 cytotoxic lymphocytes ($i = 1, 2$)
 All the parameters are positive.

3. Model Equations

3.1. Description of the Model Equations

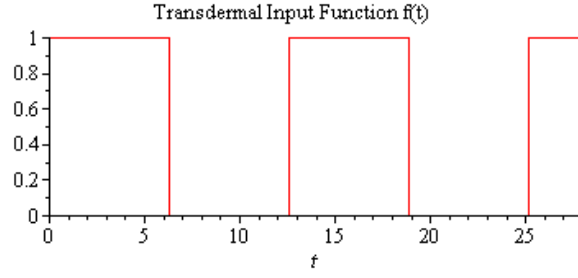
The HIV-1 patho-physiological dynamics during HAART therapy can be modeled using the following system of non-linear ordinary differential equations. A detailed description of the dynamics of the model variables x_1, x_2, x_3 , and x_4 can be found in Nani and Jin [15].

$$\begin{cases}
 \dot{x}_1 = S_1 + a_1 x_1^2 e^{-b_1 x_1} - \alpha_1 x_1 x_3 - q_1 x_1 x_2 - k_1 x_1 - e_{10} \\
 \dot{x}_2 = S_2 + a_2 x_1 x_2 e^{-b_2 x_1} + \alpha_2 x_1 x_3 - q_2 x_1 x_2 - k_2 x_2 - \beta_1 x_3 \\
 \quad - K_1 x_2 x_4 - e_{20} - \frac{\xi_2 \sigma_2 x_2 x_5}{\lambda_2 + x_5} \\
 \dot{x}_3 = S_3 + \beta_2 x_2 x_3 + \beta_3 x_3 - \alpha_3 x_1 x_3 - \eta_1 x_3 x_4 - k_3 x_3 - e_{30} \\
 \quad - \frac{\xi_3 \sigma_3 x_3 x_5}{\lambda_3 + x_5} \\
 \dot{x}_4 = S_4 + a_4 x_1 x_4 e^{-b_4 x_1} - K_2 x_2 x_4 - \eta_2 x_3 x_4 - k_4 x_4 - e_{40} \\
 \dot{x}_5 = Df(t) - \frac{\sigma_0 x_5}{\lambda_0 + x_5} - \frac{\sigma_2 x_2 x_5}{\lambda_2 + x_5} - \frac{\sigma_3 x_3 x_5}{\lambda_3 + x_5} - k_5 x_5 \\
 f(t) = \begin{cases} 1 & \text{for constant continuous input} \\ |\lceil \sin nt \rceil| & \text{for periodic input} \end{cases} \\
 x_i(t_0) = x_{i0} \quad \text{for } i = \{1, 2, 3, 4, 5\}
 \end{cases} \quad (3.1)$$

The model includes the following clinical improvements:

- (i) The drug delivery uses transdermal, stealth-liposome encapsulated drug delivery, instead of the matrix tablet form because of improved therapeutic efficacy and reduced gastro-intestinal toxicity [12]. It is also assumed that elastic liposomes are formulated and selectively targeted such as to reduce toxicity to non-HIV-1-infected $CD4^+$ T cells (x_1) and $CD8^+$ cytotoxic T cells (x_4).
- (ii) The HAART drug is such that each renal excretion and body clearance rate follows Michaelis-Menten kinetics.
- (iii) $g(x_1, x_j) = a_j x_1 x_j e^{-b_j x_1}$ for $j = (1, 2, 4)$
 This function depicts the process of lymphocyte activation which is mediated by x_1 ($CD 4^+$) T helper cells. These cells secrete a cytokine called interleukin-2.

(iv) The periodic input function $f(t) = |\text{ceil}(\sin(5t))|$ can be depicted by the following plot:



3.2. Boundedness and Invariance of Non-negativity of Solutions

In this subsection theoretical conditions will be constructed under which solutions to the HAART mathematical model equations are well-posed, ultimately bounded, and exhibit invariance of non-negativity for all $t \in [t_0, T] \subset \mathfrak{R}_+ = [0, \infty)$. In this case, t_0 , and T are defined respectively as times at which HAART therapy begins and terminates.

Theorem 3.1 Consider

(i) $\Omega = \{(x_1, x_2, x_3, x_4, x_5) \in \mathfrak{R}_+^5 \mid 0 \leq x_i \leq \Phi_i, i = 1, 2, 3, 4, 5\}$

Let

(ii)
$$\begin{aligned} \Phi_i &= \max \left\{ (x_{i0}, \frac{S_i + C_i - e_{i0}}{k_i}), i = 1, 2, 3, 4 \right\} \\ \Phi_5 &= \max \{ x_{50}, \frac{D}{\delta} \} \end{aligned} \quad (3.2)$$

where

$$\delta_i = \inf_{t \in [t_0, T]} \left[\frac{\sigma_i x_i}{\lambda_i + x_5} \right] \quad \text{for } i = \{0, 2, 3\}$$

and

$$\delta = \min \{ \delta_0 + \delta_2 + \delta_3, k_5 \},$$

Then there exists a $T_0 > 0$ such that for $T_0 < t < \infty$, all solutions to the HAART model equations (3.1) with initial values $x_{i0} \in \mathfrak{R}_+^5 = \{x_i \in \mathfrak{R} \mid x_i \geq 0, i = (1, 2, 3, 4, 5)\}$ are ultimately bounded, dissipative, and will eventually enter the non-negatively invariant region Ω . In particular, the solutions are trapped in the region Ω for all $t > T_0 \subset \mathfrak{R}_+$

Proof. Using the result from Nani and Jin in [7], let

$$C_j = \sup_{t \in [t_0, T]} [a_j x_1 x_j e^{-b_j x_1}] \quad \text{for } j = \{1, 2, 4\} \quad (3.3)$$

$$C_3 = \sup_{t \in [t_0, T]} [\beta_2 x_2 x_3 + \beta_3 x_3]$$

The non-linear system (4.1) can be converted to the following non-linear differential inequalities:

$$\begin{cases} \dot{x}_1 \leq S_1 + C_1 - k_1 x_1 - e_{10} \\ \dot{x}_2 \leq S_2 + C_2 - k_2 x_2 - e_{20} \\ \dot{x}_3 \leq S_3 + C_3 - k_3 x_3 - e_{30} \\ \dot{x}_4 \leq S_4 + C_4 - k_4 x_4 - e_{40} \\ \dot{x}_5 \leq D - \delta x_5 \\ x_i(t_0) = x_{i0} \text{ where } i = \{1, 2, 3, 4, 5\} \end{cases} \quad (3.4)$$

Theorem [[Kamke: (ref. [29] Theorem. 2.6.3)]]

Consider the differential inequality

$$\begin{cases} \frac{dx_i}{dt} \leq f_i(x_1, x_2, \dots, x_n) & \text{with } f : C(R^n, R) \\ x_i(t_0) = x_{i0} \end{cases}$$

where $t \in [t_0, b]$, $b \in R_+ = (0, \infty)$

Suppose

$$\begin{cases} \frac{du_i}{dt} = f_i(u_1, u_2, \dots, u_n) \\ u_i(t_0) = u_{i0} \end{cases}$$

such that $x_{i0} \leq u_{i0}$

Then $x_i(t) \leq u_i(t)$

Applying Kamke theorem to the system (3.4), the following inequalities hold.

$$\begin{cases} x_i \leq \frac{S_i + C_i - e_{i0}}{k_i} + \gamma_i e^{-k_i t} & \text{for } i = \{1, 2, 3, 4\}, \quad \text{where } S_i + C_i - e_{i0} > 0 \\ x_5 \leq \frac{D}{\delta} + \gamma_5 e^{-\delta t} & \text{and } \gamma_i \in R_+ = (0, \infty) \text{ and } i = \{1, 2, 3, 4, 5\} \end{cases} \quad (3.5)$$

In particular, the following results can be obtained.

$$\begin{aligned} \limsup_{t \rightarrow \infty} x_i(t) &\leq \frac{S_i + C_i - e_{i0}}{k_i}, \quad i = \{1, 2, 3, 4\} \\ \limsup_{t \rightarrow \infty} x_5(t) &\leq \frac{D}{\delta} \end{aligned} \quad (3.6)$$

Thus, Ω is non-negatively invariant and the system is ultimately bounded, dissipative, with the bounds defined by the following equations.

$$\begin{aligned} \sup_{t \in [t_0, T]} x_i(t) &= \max_{t \in [t_L, t_P]} \left\{ x_{i0}, \frac{S_i + C_i - e_{i0}}{k_i} \right\}, \quad i = \{1, 2, 3, 4\} \\ \sup_{t \in [t_0, T]} x_5(t) &= \max_{t \in [t_0, T]} \left\{ x_{50}, \frac{D}{\delta} \right\} \end{aligned} \quad (3.7)$$

As a consequence of (3.7), the orbits of $x_i(t)$ are uniformly bounded.

This completes the proof. $\square$

4. The Equilibria and Computation of the Jacobian Matrices

In this section, the model equations will be restricted to the case for which the drug input function has the form $f(t) = 1$. Thus, (3.1) reduces to a system (4.1) of deterministic, non-linear, and autonomous ordinary differential equations.

$$\begin{cases}
\dot{x}_1 = S_1 + a_1 x_1^2 e^{-b_1 x_1} - \alpha_1 x_1 x_3 - q_1 x_1 x_2 - k_1 x_1 - e_{10} \\
\dot{x}_2 = S_2 + a_2 x_1 x_2 e^{-b_2 x_1} + \alpha_2 x_1 x_3 - q_2 x_1 x_2 - k_2 x_2 - \beta_1 x_3 - K_1 x_2 x_4 - e_{20} - \frac{\xi_2 \sigma_2 x_2 x_5}{\lambda_2 + x_5} \\
\dot{x}_3 = S_3 + \beta_2 x_2 x_3 + \beta_3 x_3 - \alpha_3 x_1 x_3 - \eta_1 x_3 x_4 - k_3 x_3 - e_{30} - \frac{\xi_3 \sigma_3 x_3 x_5}{\lambda_3 + x_5} \\
\dot{x}_4 = S_4 + a_4 x_1 x_4 e^{-b_4 x_1} - K_2 x_2 x_4 - \eta_2 x_3 x_4 - k_4 x_4 - e_{40} \\
\dot{x}_5 = D - \frac{\sigma_0 x_5}{\lambda_0 + x_5} - \frac{\sigma_2 x_2 x_5}{\lambda_2 + x_5} - \frac{\sigma_3 x_3 x_5}{\lambda_3 + x_5} - k_5 x_5 \\
x_i(t_0) = x_{i0} \quad \text{for } i = \{1, 2, 3, 4, 5\}
\end{cases} \quad (4.1)$$

The physiological outcomes or the equilibria during constant continuous transdermal HAART therapy occur when $\dot{x}_i = 0$ for $i=1,2,3,4,5$.

4.1 Local existence criteria for clinically relevant steady states of HAART

In this subsection, a subset of clinically relevant states or the possible patho-physiological outcomes from constant continuous transdermal HAART therapy are listed and analyzed. These outcomes are labelled E_i for $i = 1, 2, \dots, 10$. The local existence criteria are labelled C_i .

(i) $E_1 = [0, 0, 0, 0, x_5]$

$$C_1: \begin{cases} S_i - e_{i0} = 0 & i = \{1, 2, 3, 4\} \\ D - \frac{\sigma_0 x_5}{\lambda_0 + x_5} - k_5 x_5 = 0 & \text{for } x_5 \in \Omega \end{cases}$$

This equilibrium represents the scenario in which HAART annihilates the HIV-1 virions, the non-infected CD4+, the infected CD4+, and CD8+ T cells. The immuno-compromised patient may become incapacitated with opportunistic infections.

(ii) $E_2 = [0, 0, 0, x_4, x_5]$

$$C_2: \begin{cases} S_i - e_{i0} = 0 & i = \{1, 2, 3\} \\ D - \frac{\sigma_0 x_5}{\lambda_0 + x_5} - k_5 x_5 = 0 & \text{for } x_5 \in \Omega \end{cases}$$

This equilibrium is similar to case (i) except that HIV-1 specific CD8+ cells are now present in the steady state.

(iii) $E_3 = [x_1, 0, 0, x_4, x_5]$

$$C_3: \begin{cases} S_1 + a_1 x_1^2 e^{-b_1 x_1} - k_1 x_1 - e_{10} = 0 \\ S_i - e_{i0} = 0 & i = \{2, 3\} \\ S_4 + a_4 x_1 x_4 e^{-b_4 x_1} - k_4 x_4 - e_{40} = 0 \\ D - \frac{\sigma_0 x_5}{\lambda_0 + x_5} - k_5 x_5 = 0 & \text{for } x_1, x_4, x_5 \in \Omega \end{cases}$$

This equilibrium corresponds to a scenario of successful HAART protocol in which the steady state consists of some uninfected CD4+ T cells, HIV-1 specific CD8+ T cells, and some drug residue.

(iv) $E_4 = [x_1, 0, 0, 0, x_5]$

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$$C_4: \begin{cases} S_1 + a_1 x_1^2 e^{-b_1 x_1} - k_1 x_1 - e_{i0} = 0 \\ S_i - e_{i0} = 0 \quad i = \{2,3,4\} \\ D - \frac{\sigma_0 x_5}{\lambda_0 + x_5} - k_5 x_5 = 0 \quad \text{for } x_1, x_5 \in \Omega \end{cases}$$

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This equilibrium also corresponds to a scenario of successful HAART protocol in which the steady state consists of some uninfected CD4+ T cells and some drug residue but no HIV-1 specific CD8+ T cells.

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(v) $E_5 = [0, x_2, x_3, 0, x_5]$

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$$C_5: \begin{cases} S_i - e_{i0} = 0 \quad i = \{1,4\} \\ S_2 - k_2 x_2 - \beta_1 x_3 - e_{20} - \frac{\xi_2 \sigma_2 x_2 x_5}{\lambda_2 + x_5} = 0 \\ S_3 + \beta_2 x_2 x_3 + \beta_3 x_3 - k_3 x_3 - e_{30} - \frac{\xi_3 \sigma_3 x_3 x_5}{\lambda_3 + x_5} = 0 \\ D - \frac{\sigma_0 x_5}{\lambda_0 + x_5} - \frac{\sigma_2 x_2 x_5}{\lambda_2 + x_5} - \frac{\sigma_3 x_3 x_5}{\lambda_3 + x_5} - k_5 x_5 = 0 \quad \text{for } x_2, x_3, x_5 \in \Omega \end{cases}$$

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This equilibrium exhibits a failure of HAART protocol. In particular, the HIV-1 infected CD4+ T cells and HIV-1 virions populate the steady state in addition to some drug residue whereas the non-infected CD4+ and CD8+ T cells are annihilated.

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(vi) $E_6 = [0, 0, x_3, 0, x_5]$

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$$C_6: \begin{cases} S_i - e_{i0} = 0 \quad i = \{1,2,4\} \\ S_3 + \beta_3 x_3 - k_3 x_3 - e_{30} - \frac{\xi_3 \sigma_3 x_3 x_5}{\lambda_3 + x_5} = 0 \\ D - \frac{\sigma_0 x_5}{\lambda_0 + x_5} - \frac{\sigma_3 x_3 x_5}{\lambda_3 + x_5} - k_5 x_5 = 0 \quad \text{for } x_3, x_5 \in \Omega \end{cases}$$

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This equilibrium also depicts a case of therapeutic failure of HAART because HIV-1 virions still remain in the blood plasma of the patient.

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(vii) $E_7 = [0, x_2, 0, 0, x_5]$

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$$C_7: \begin{cases} S_i - e_{i0} = 0 \quad i = \{1,3,4\} \\ S_2 - k_2 x_2 - e_{20} - \frac{\xi_2 \sigma_2 x_2 x_5}{\lambda_2 + x_5} = 0 \\ D - \frac{\sigma_0 x_5}{\lambda_0 + x_5} - \frac{\sigma_2 x_2 x_5}{\lambda_2 + x_5} - k_5 x_5 = 0 \quad \text{for } x_2, x_5 \in \Omega \end{cases}$$

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This equilibrium represents another a scenario of unsuccessful HAART protocol because HIV-1 infected CD4+ T cells and drug residue populate the steady state.

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(viii) $E_8 = [x_1, x_2, 0, 0, x_5]$

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$$C_8: \begin{cases} S_i - e_{i0} = 0 \quad i = \{3,4\} \\ S_1 + a_1 x_1^2 e^{-b_1 x_1} - k_1 x_1 - q_1 x_1 x_2 - e_{i0} = 0 \\ S_2 + a_2 x_1 x_2 e^{-b_2 x_1} - q_2 x_1 x_2 - k_2 x_2 - e_{20} - \frac{\xi_2 \sigma_2 x_2 x_5}{\lambda_2 + x_5} = 0 \\ D - \frac{\sigma_0 x_5}{\lambda_0 + x_5} - \frac{\sigma_2 x_2 x_5}{\lambda_2 + x_5} - k_5 x_5 = 0 \quad \text{for } x_1, x_2, x_5 \in \Omega \end{cases}$$

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This equilibrium is not clinically desirable because of existence of HIV-1 infected CD4+ T cells.

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(ix) $E_9 = [x_1, x_2, 0, x_4, x_5]$

C₉:

$$\begin{cases} S_1 + a_1 x_1^2 e^{-b_1 x_1} - q_1 x_1 x_2 - k_1 x_1 - e_{10} = 0 \\ S_2 + a_2 x_1 x_2 e^{-b_2 x_1} - q_2 x_1 x_2 - k_2 x_2 - K_1 x_2 x_4 - e_{20} - \frac{\xi_2 \sigma_2 x_2 x_5}{\lambda_2 + x_5} = 0 \\ S_3 - e_{30} = 0 \\ S_4 + a_4 x_1 x_4 e^{-b_4 x_1} - K_2 x_2 x_4 - k_4 x_4 - e_{40} = 0 \\ D - \frac{\sigma_0 x_5}{\lambda_0 + x_5} - \frac{\sigma_2 x_2 x_5}{\lambda_2 + x_5} - k_5 x_5 \quad \text{for } x_1, x_2, x_3, x_5 \in \Omega \end{cases}$$

This equilibrium is another scenario of therapeutic failure of HAART protocol because HIV-1 infected CD4+ T cells are all present.

(x) $E_{10} = [x_1, x_2, x_3, x_4, x_5]$

The steady state E_{10} depicts a person who is living with AIDS. In this case, the model exhibits persistence and the viral titer is not sufficient to annihilate the immune system. The criteria for persistence of HIV-1 AIDS during HAART will be discussed in Theorem 5.5.

There are some other steady states which are not listed because they are less clinically interesting.

4.2 Computation of the Jacobian Matrices

Using the Hartman-Grobman theorem, it is possible to investigate the therapeutic efficacy of HAART and the physiological stability of HIV-1 AIDS disease dynamics associated with the model equations, by linearizing the system (4.1) in the neighborhood of the equilibria.

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

$$J[E_k] := \{a_{ij}\}_{5 \times 5} \in M_{5 \times 5}(\mathfrak{R}) \quad k = 3, 4, 5$$

In particular, the a_{ij} entries are defined as follows:

$$\begin{aligned}
a_{11} &:= a_1 x_1 (2 - b_1 x_1) e^{-b_1 x_1} - \alpha_1 x_3 - q_1 x_2 - k_1 \\
a_{12} &:= -q_1 x_1 \\
a_{13} &:= -\alpha_1 x_1 \\
a_{14} &:= 0 \\
a_{15} &:= 0 \\
a_{21} &:= a_2 x_2 (1 - b_2 x_1) e^{-b_2 x_1} - q_2 x_2 \\
a_{22} &:= a_2 x_1 e^{-b_2 x_1} - q_2 x_1 - k_2 - K_1 x_4 - \frac{\xi_2 \sigma_2 x_5}{\lambda_2 + x_5} \\
a_{23} &:= \alpha_2 x_1 - \beta_1 \\
a_{24} &:= -K_1 x_2 \\
a_{25} &:= -\frac{\xi_2 \lambda_2 \sigma_2 x_2}{(\lambda_2 + x_5)^2} \\
a_{31} &:= -\alpha_3 x_3 \\
a_{32} &:= \beta_2 x_3 \\
a_{33} &:= \beta_2 x_2 + \beta_3 - \alpha_3 x_1 - \eta_1 x_4 - k_3 - \frac{\xi_3 \sigma_3 x_5}{\lambda_3 + x_5} \\
a_{34} &:= -\eta_1 x_3 \\
a_{35} &:= -\frac{\xi_3 \sigma_3 \lambda_3}{(\lambda_3 + x_5)^2} \\
a_{41} &:= a_4 x_4 (1 - b_4 x_1) e^{-b_4 x_1} \\
a_{42} &:= -K_2 x_4 \\
a_{43} &:= -\eta_2 x_4 \\
a_{44} &:= a_4 x_1 e^{-b_4 x_1} - K_2 x_2 - \eta_2 x_3 - k_4 \\
a_{45} &:= 0 \\
a_{51} &:= 0 \\
a_{52} &:= -\frac{\sigma_2 x_5}{\lambda_2 + x_5} \\
a_{53} &:= -\frac{\sigma_3 x_5}{\lambda_3 + x_5} \\
a_{54} &:= 0 \\
a_{55} &:= -\frac{\sigma_0 \lambda_0}{(\lambda_0 + x_5)^2} - \frac{\sigma_2 \lambda_2 x_2}{(\lambda_2 + x_5)^2} - \frac{\sigma_3 \lambda_3 x_3}{(\lambda_3 + x_5)^2} - k_5
\end{aligned} \tag{4.2}$$

The Jacobian matrices for the steady states E_3, E_4, E_5 are respectively listed as follows:

$$J\{E_1[0, 0, 0, 0, x_5]\} =$$

$$\begin{bmatrix}
-k_1 & 0 & 0 & 0 & 0 \\
0 & -k_2 - \frac{\xi_2 \sigma_2 x_5}{\lambda_2 + x_5} & -\beta_1 & 0 & 0 \\
0 & 0 & \beta_3 - k_3 - \frac{\xi_3 \sigma_3 x_5}{\lambda_3 + x_5} & 0 & -\frac{\xi_3 \sigma_3 \lambda_3}{(\lambda_3 + x_5)^2} \\
0 & 0 & 0 & -k_4 & 0 \\
0 & -\frac{\sigma_2 x_5}{\lambda_2 + x_5} & -\frac{\sigma_3 x_5}{\lambda_3 + x_5} & 0 & -\frac{\sigma_0 \lambda_0}{(\lambda_0 + x_5)^2} - k_5
\end{bmatrix} \tag{4.3}$$

$$\begin{aligned}
& J\{E_2[0, 0, 0, x_4, x_5]\} = \\
& \begin{bmatrix} -k_1 & 0 & 0 & 0 & 0 \\ 0 & -k_2 - K_1 x_4 - \frac{\xi_2 \sigma_2 x_5}{\lambda_2 + x_5} & -\beta_1 & 0 & 0 \\ 0 & 0 & \beta_3 - \eta_1 x_4 - k_3 - \frac{\xi_3 \sigma_3 x_5}{\lambda_3 + x_5} & 0 & -\frac{\xi_3 \sigma_3 \lambda_3}{(\lambda_3 + x_5)^2} \\ a_4 x_4 & -K_2 x_4 & -\eta_2 x_4 & -k_4 & 0 \\ 0 & -\frac{\sigma_2 x_5}{\lambda_2 + x_5} & -\frac{\sigma_3 x_5}{\lambda_3 + x_5} & 0 & -\frac{\sigma_0 \lambda_0}{(\lambda_0 + x_5)^2} - k_5 \end{bmatrix}
\end{aligned} \tag{4.4}$$

$$\begin{aligned}
& J\{E_3[x_1, 0, 0, x_4, x_5]\} = \\
& \begin{bmatrix} a_1 x_1 (2 - b_1 x_1) e^{-b_1 x_1} - k_1 & -q_1 x_1 & -\alpha_1 x_1 & 0 & 0 \\ 0 & a_2 x_1 e^{-b_2 x_1} - q_2 x_1 - k_2 - K_1 x_4 - \frac{\xi_2 \sigma_2 x_5}{\lambda_2 + x_5} & \alpha_2 x_1 - \beta_1 & 0 & 0 \\ 0 & 0 & \beta_3 - \alpha_3 x_1 - \eta_1 x_4 - k_3 - \frac{\xi_3 \sigma_3 x_5}{\lambda_3 + x_5} & 0 & -\frac{\xi_3 \sigma_3 \lambda_3}{(\lambda_3 + x_5)^2} \\ a_4 x_4 (1 - b_4 x_1) e^{-b_4 x_1} & -K_2 x_4 & -\eta_2 x_4 & a_4 x_1 e^{-b_4 x_1} - k_4 & 0 \\ 0 & -\frac{\sigma_2 x_5}{\lambda_2 + x_5} & -\frac{\sigma_3 x_5}{\lambda_3 + x_5} & 0 & -\frac{\sigma_0 \lambda_0}{(\lambda_0 + x_5)^2} - k_5 \end{bmatrix}
\end{aligned} \tag{4.5}$$

$$\begin{aligned}
& J\{E_4[x_1, 0, 0, 0, x_5]\} = \\
& \begin{bmatrix} a_1 x_1 (2 - b_1 x_1) e^{-b_1 x_1} - k_1 & -q_1 x_1 & -\alpha_1 x_1 & 0 & 0 \\ 0 & a_2 x_1 e^{-b_2 x_1} - q_2 x_1 - k_2 - \frac{\xi_2 \sigma_2 x_5}{\lambda_2 + x_5} & \alpha_2 x_1 - \beta_1 & 0 & 0 \\ 0 & 0 & \beta_3 - \alpha_3 x_1 - k_3 - \frac{\xi_3 \sigma_3 x_5}{\lambda_3 + x_5} & 0 & -\frac{\xi_3 \sigma_3 \lambda_3}{(\lambda_3 + x_5)^2} \\ 0 & 0 & 0 & a_4 x_1 e^{-b_4 x_1} - k_4 & 0 \\ 0 & -\frac{\sigma_2 x_5}{\lambda_2 + x_5} & -\frac{\sigma_3 x_5}{\lambda_3 + x_5} & 0 & -\frac{\sigma_0 \lambda_0}{(\lambda_0 + x_5)^2} - k_5 \end{bmatrix}
\end{aligned} \tag{4.6}$$

$$\begin{aligned}
& J\{E_5[0, x_2, x_3, 0, x_5]\} = \\
& \begin{bmatrix} -q_1 x_2 - k_1 - \alpha_1 x_3 & 0 & 0 & 0 & 0 \\ a_2 x_2 - q_2 x_2 & -k_2 - \frac{\xi_2 \sigma_2 x_5}{\lambda_2 + x_5} & -\beta_1 & -K_1 x_2 & -\frac{\xi_2 \lambda_2 \sigma_2 x_2}{(\lambda_2 + x_5)^2} \\ -\alpha_3 x_3 & \beta_2 x_3 & \beta_2 x_2 + \beta_3 - k_3 - \frac{\xi_3 \sigma_3 x_5}{\lambda_3 + x_5} & -\eta_1 x_3 & -\frac{\xi_3 \sigma_3 \lambda_3}{(\lambda_3 + x_5)^2} \\ 0 & 0 & 0 & -K_2 x_2 - \eta_2 x_3 - k_4 & 0 \\ 0 & -\frac{\sigma_2 x_5}{\lambda_2 + x_5} & -\frac{\sigma_3 x_5}{\lambda_3 + x_5} & 0 & -\frac{\sigma_0 \lambda_0}{(\lambda_0 + x_5)^2} - \frac{\sigma_2 \lambda_2 x_2}{(\lambda_2 + x_5)^2} - \frac{\sigma_3 \lambda_3 x_3}{(\lambda_3 + x_5)^2} - k_5 \end{bmatrix}
\end{aligned} \tag{4.7}$$

$$\begin{aligned}
& J\{E_7[0, x_2, 0, 0, x_5]\} = \\
& \begin{bmatrix} -q_1x_2 - k_1 & 0 & 0 & 0 & 0 \\ a_2x_2 - q_2x_2 & -k_2 - \frac{\xi_2\sigma_2x_5}{\lambda_2 + x_5} & -\beta_1 & -K_1x_2 & -\frac{\xi_2\lambda_2\sigma_2x_2}{(\lambda_2 + x_5)^2} \\ 0 & 0 & \beta_2x_2 + \beta_3 - k_3 - \frac{\xi_3\sigma_3x_5}{\lambda_3 + x_5} & 0 & -\frac{\xi_3\sigma_3\lambda_3}{(\lambda_3 + x_5)^2} \\ 0 & 0 & 0 & -K_2x_2 - k_4 & 0 \\ 0 & -\frac{\sigma_2x_5}{\lambda_2 + x_5} & -\frac{\sigma_3x_5}{\lambda_3 + x_5} & 0 & -\frac{\sigma_0\lambda_0}{(\lambda_0 + x_5)^2} - \frac{\sigma_2\lambda_2x_2}{(\lambda_2 + x_5)^2} - k_5 \end{bmatrix} \\
& \tag{4.8}
\end{aligned}$$

$$\begin{aligned}
& J\{E_9[x_1, x_2, 0, x_4, x_5]\} = \\
& \begin{bmatrix} a_1x_1(2 - b_1x_1)e^{-b_1x_1} + q_1x_2 - k_1 & -q_1x_1 & -\alpha_1x_1 & 0 & 0 \\ a_2x_2(1 - b_2x_1)e^{-b_2x_1} + q_2x_2 & a_2x_1e^{-b_2x_1} - q_2x_1 - k_2 - K_1x_4 - \frac{\xi_2\sigma_2x_5}{\lambda_2 + x_5} & \alpha_2x_1 - \beta_1 & -K_1x_2 & -\frac{\xi_2\sigma_2\lambda_2x_2}{(\lambda_2 + x_5)^2} \\ 0 & 0 & \beta_2x_2 + \beta_3 - \alpha_3x_1 & 0 & -\frac{\xi_3\sigma_3\lambda_3}{(\lambda_3 + x_5)^2} \\ a_4x_4(1 - b_4x_1)e^{-b_4x_1} & -K_2x_4 & -\eta_1x_4 - k_3 - \frac{\xi_3\sigma_3x_5}{\lambda_3 + x_5} & 0 & 0 \\ 0 & -\frac{\sigma_2x_5}{\lambda_2 + x_5} & -\frac{\sigma_3x_5}{\lambda_3 + x_5} & a_4x_1e^{-b_4x_1} + K_2x_2 - k_4 & -\frac{\sigma_0\lambda_0}{(\lambda_0 + x_5)^2} - \frac{\sigma_2\lambda_2x_2}{(\lambda_2 + x_5)^2} - k_5 \end{bmatrix} \\
& \tag{4.9}
\end{aligned}$$

5. Necessary Criteria for Local Stability of Equilibria during HAART

Let $E = \{E_1, E_2, \dots, E_{10}\}$ denote the set of some clinically relevant equilibria of model equations (4.1). In this section, the local stability of E_4, E_5, E_1 , and E_3 will be analyzed using the principles of linearized stability of autonomous ordinary differential equations. In particular, the necessary mathematical criteria for certain therapeutic outcomes during HAART are computed and presented in the form of theorems.

5.1 Local Stability of $E_4 = [\hat{x}_1, 0, 0, 0, \hat{x}_5]$

The Jacobian matrix associated with $E_4 = [\hat{x}_1, 0, 0, 0, \hat{x}_5]$ is defined as

$$J\{E_4[\hat{x}_1, 0, 0, 0, \hat{x}_5]\} := \begin{bmatrix} \hat{a}_{11} & \hat{a}_{12} & \hat{a}_{13} & 0 & 0 \\ 0 & \hat{a}_{22} & \hat{a}_{23} & 0 & 0 \\ 0 & 0 & \hat{a}_{33} & 0 & \hat{a}_{35} \\ 0 & 0 & 0 & \hat{a}_{44} & 0 \\ 0 & \hat{a}_{52} & \hat{a}_{53} & 0 & \hat{a}_{55} \end{bmatrix}$$

If the condition $\hat{x}_1 = \frac{\beta_1}{\alpha_2}$ is imposed on the Jacobian matrix above, then $\hat{a}_{23} = 0$. The eigen-spectrum

associated with the Jacobian matrix is defined as

$$\sigma(J\{E_4[\hat{x}_1, 0, 0, 0, \hat{x}_5]\}) = \{\lambda_i \mid \lambda^2 + \hat{a}_1\lambda + \hat{a}_2 = 0, i = 1, 2\} \cup \{\lambda_3, \lambda_4, \lambda_5\}$$

where

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$$\begin{cases} \hat{a}_1 = -(\hat{a}_{33} + \hat{a}_{55}) \\ \hat{a}_2 = \hat{a}_{33}\hat{a}_{55} - \hat{a}_{35}\hat{a}_{53} \\ \lambda_3 = \hat{a}_{11} \\ \lambda_4 = \hat{a}_{22} \\ \lambda_5 = \hat{a}_{44} \end{cases}$$

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Theorem 5.1. Suppose C_4 in Section 4.1 holds, and:

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$$(i) \quad \begin{cases} \hat{a}_1 > 0 \\ \hat{a}_2 > 0 \\ \hat{x}_1 = \frac{\beta_1}{\alpha_2} \end{cases} \quad (5.1)$$

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$$(ii) \quad \begin{cases} \hat{a}_{11} = a_1 \hat{x}_1 (2 - b_1 \hat{x}_1) e^{-b_1 \hat{x}_1} - k_1 < 0 \\ \hat{a}_{22} = a_2 \hat{x}_1 e^{-b_2 \hat{x}_1} - q_2 \hat{x}_1 - k_2 - \frac{\xi_2 \sigma_2 \hat{x}_5}{\lambda_2 + \hat{x}_5} < 0 \\ \hat{a}_{44} = a_4 \hat{x}_1 e^{-b_4 \hat{x}_1} - k_4 < 0 \end{cases} \quad (5.2)$$

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Then the HAART therapeutic outcome $E_4 = [\hat{x}_1, 0, 0, 0, \hat{x}_5]$ exists and it is a local attractor.

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Proof. The eigen-values of $J\{E_4[\hat{x}_1, 0, 0, 0, \hat{x}_5]\}$ satisfy the determinantal equations:

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$$\det | J\{E_4[\hat{x}_1, 0, 0, 0, \hat{x}_5]\} - \lambda I | =$$

$$\det \begin{vmatrix} \hat{a}_{11} - \lambda & \hat{a}_{12} & \hat{a}_{13} & 0 & 0 \\ 0 & \hat{a}_{22} - \lambda & \hat{a}_{23} & 0 & 0 \\ 0 & 0 & \hat{a}_{33} - \lambda & 0 & \hat{a}_{35} \\ 0 & 0 & 0 & \hat{a}_{44} - \lambda & 0 \\ 0 & \hat{a}_{52} & \hat{a}_{53} & 0 & \hat{a}_{55} - \lambda \end{vmatrix} = 0$$

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Using the Laplace expansion technique for determinant, the characteristic eigen-value polynomial is given by

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$$p(\lambda, J(E_4)) = (\hat{a}_{11} - \lambda)(\hat{a}_{22} - \lambda)(\hat{a}_{44} - \lambda) \det \begin{vmatrix} \hat{a}_{33} - \lambda & \hat{a}_{35} \\ \hat{a}_{53} & \hat{a}_{55} - \lambda \end{vmatrix} = 0$$

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But

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$$\det \begin{vmatrix} \hat{a}_{33} - \lambda & \hat{a}_{35} \\ \hat{a}_{53} & \hat{a}_{55} - \lambda \end{vmatrix} := \lambda^2 - (\hat{a}_{33} + \hat{a}_{55})\lambda + \det \begin{vmatrix} \hat{a}_{33} & \hat{a}_{35} \\ \hat{a}_{53} & \hat{a}_{55} \end{vmatrix}$$

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Let

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$$\begin{aligned} \hat{a}_1 &= -(\hat{a}_{33} + \hat{a}_{55}) \\ \hat{a}_2 &= \det \begin{vmatrix} \hat{a}_{33} & \hat{a}_{35} \\ \hat{a}_{53} & \hat{a}_{55} \end{vmatrix} \end{aligned} \quad (5.3)$$

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The eigen-spectrum is therefore given by

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$$\sigma(J\{E_4[\hat{x}_1, 0, 0, 0, \hat{x}_5]\}) = \{\lambda_i \mid \lambda^2 + \hat{a}_1 \lambda + \hat{a}_2 = 0, i = 1, 2\} \cup \{\lambda_3, \lambda_4, \lambda_5\}$$

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where

$$\lambda_1 = \frac{1}{2}(-\hat{a}_1 - \sqrt{\hat{a}_1^2 - 4\hat{a}_2})$$

$$\lambda_2 = \frac{1}{2}(-\hat{a}_1 + \sqrt{\hat{a}_1^2 - 4\hat{a}_2})$$

$$\lambda_3 = \hat{a}_{11}$$

$$\lambda_4 = \hat{a}_{22}$$

$$\lambda_5 = \hat{a}_{44}$$

The conditions (5.1) and (5.2) guarantee that the eigen-values associated with the equilibrium E_4 have negative real part by virtue of Routh-Hurwitz criteria [7]. Hence, the equilibrium is locally asymptotically stable and a local attractor as well as a hyperbolic sink. This theorem establishes the local existence and local stability of a clinically desirable physiological outcome of HAART protocol. $\square$

Clinical Implication 5.1. The criteria (5.1) and (5.2) guarantee a temporary cure for the AIDS patient. There will be a finite time interval during which the HIV-1 virions will be annihilated from the patient's blood plasma. This will however be short-lived because the rest point $E_4[x_1, 0, 0, 0, x_5]$ may become unstable and the criteria for temporal cure are violated. It is possible for therapeutic criteria to be derived to maintain the patient to be permanently free of AIDS, which we shall discuss in Theorem 5.5.

5.2 Local Stability of $E_5 = [0, \bar{x}_2, \bar{x}_3, 0, \bar{x}_5]$

In this subsection, the local existence and stability of $E_5 = [0, \bar{x}_2, \bar{x}_3, 0, \bar{x}_5]$ will be analyzed. The results are summarized in the following theorem.

Theorem 5.2. Suppose

(i) Existence criteria C_5 for equilibrium $E_5 = [0, \bar{x}_2, \bar{x}_3, 0, \bar{x}_5]$ holds. (5.4)

(ii) Let $\sigma(J\{E_5[0, \bar{x}_2, \bar{x}_3, 0, \bar{x}_5]\})$ be the eigen-spectrum of

$$J\{E_5[0, \bar{x}_2, \bar{x}_3, 0, \bar{x}_5]\} := \begin{vmatrix} \bar{a}_{11} & 0 & 0 & 0 & 0 \\ \bar{a}_{21} & \bar{a}_{22} & \bar{a}_{23} & \bar{a}_{24} & \bar{a}_{25} \\ \bar{a}_{31} & \bar{a}_{32} & \bar{a}_{33} & \bar{a}_{34} & \bar{a}_{35} \\ 0 & 0 & 0 & \bar{a}_{44} & 0 \\ 0 & \bar{a}_{52} & \bar{a}_{53} & 0 & \bar{a}_{55} \end{vmatrix} \quad (5.5)$$

With the $\bar{a}_{ij}$ are depicted by (4.7).

Such that

$$\sigma(J\{E_5[0, \bar{x}_2, \bar{x}_3, 0, \bar{x}_5]\}) = \{\lambda_i \mid \lambda^3 + \bar{a}_1\lambda^2 + \bar{a}_2\lambda + \bar{a}_3 = 0, i = 1, 2, 3\} \cup \{\lambda_4, \lambda_5\} \quad (5.6)$$

Where

$$\begin{aligned} \bar{a}_1 &= -\text{Trace} \begin{bmatrix} a_{22} & a_{23} & a_{25} \\ a_{32} & a_{33} & a_{35} \\ a_{52} & a_{53} & a_{55} \end{bmatrix} \\ \bar{a}_2 &= \det \begin{vmatrix} \bar{a}_{33} & \bar{a}_{35} \\ \bar{a}_{53} & \bar{a}_{55} \end{vmatrix} + \det \begin{vmatrix} \bar{a}_{22} & \bar{a}_{25} \\ \bar{a}_{31} & \bar{a}_{33} \end{vmatrix} + \det \begin{vmatrix} \bar{a}_{22} & \bar{a}_{23} \\ \bar{a}_{32} & \bar{a}_{33} \end{vmatrix} \\ \bar{a}_3 &= -\det \begin{vmatrix} \bar{a}_{22} & \bar{a}_{23} & \bar{a}_{25} \\ \bar{a}_{32} & \bar{a}_{33} & \bar{a}_{35} \\ \bar{a}_{52} & \bar{a}_{53} & \bar{a}_{55} \end{vmatrix} \\ \lambda_4 &= \bar{a}_{11} \\ \lambda_5 &= \bar{a}_{44} \end{aligned} \quad (5.7)$$

Then the rest point $E_5[0, \tilde{x}_2, \tilde{x}_3, 0, \tilde{x}_5]$ is locally asymptotically stable hyperbolic sink and a local attractor if

$$\tilde{a}_1 > 0, \tilde{a}_3 > 0, \tilde{a}_1 \tilde{a}_2 > \tilde{a}_3 \quad (5.8)$$

Proof. The eigen-values associated with $E_5[0, \tilde{x}_2, \tilde{x}_3, 0, \tilde{x}_5]$ satisfy

$$\det |J\{E_5[0, \tilde{x}_2, \tilde{x}_3, 0, \tilde{x}_5]\} - \lambda I_5| = 0$$

Using the Laplace expansion technique of determinants leads to (5.6) with the Routh-Hurwitz coefficients depicted by (5.7). The conditions specified in (5.8) guarantee that the equilibrium is locally asymptotically stable and a local attractor. $\square$

Clinical Implication 5.2. This theorem depicts the conditions for one of the worst scenarios during AIDS therapy using continuous infusion HAART. If the conditions (5.4) and (5.8) hold, then the HAART therapy annihilated all the uninfected $CD4^+$ T cells, and HIV-1 specific cytotoxic $CD8^+$ T cells. Consequently, the immune system of the AIDS patient becomes incapacitated and the patient becomes the target of opportunistic infections. However, this situation may not last very long but could be fatal.

5.3 Local Stability of $E_1 = [0, 0, 0, 0, \tilde{x}_5]$

In this subsection, the local existence and local stability of the non-clinically efficacious equilibrium E_1 will be discussed. Theoretical criteria under which $E_1 = [0, 0, 0, 0, \tilde{x}_5]$ is locally stable will be derived. The results are summarized in the following theorem.

Theorem 5.3. Suppose

- (i) The criterion C_5 holds for the local existence of $E_1 = [0, 0, 0, 0, \tilde{x}_5]$
- (ii) Let

$$\tilde{M} = \begin{bmatrix} \tilde{a}_{22} & \tilde{a}_{23} & 0 \\ 0 & \tilde{a}_{33} & \tilde{a}_{35} \\ \tilde{a}_{52} & \tilde{a}_{53} & \tilde{a}_{55} \end{bmatrix}$$

Such that

$$\begin{aligned} \tilde{a}_1 &= -\text{Trace}(\tilde{M}) \\ \tilde{a}_2 &= \det \begin{bmatrix} \tilde{a}_{33} & \tilde{a}_{35} \\ \tilde{a}_{53} & \tilde{a}_{55} \end{bmatrix} + \tilde{a}_{22}(\tilde{a}_{33} + \tilde{a}_{55}) \\ \tilde{a}_3 &= -\det \tilde{M} \end{aligned} \quad (5.9)$$

Then the equilibrium E_1 is hyperbolic sink, locally asymptotically stable, and a local attractor if

$$\tilde{a}_1 > 0, \tilde{a}_2 > 0, \tilde{a}_3 > 0, \tilde{a}_1 \tilde{a}_2 > \tilde{a}_3$$

Proof. Let λ_i for $i = \{1, 2, 3, 4, 5\}$ denote the eigen-values corresponding to the Jacobian matrix $J\{E_1[0, 0, 0, 0, \tilde{x}_5]\}$ given by (4.3). Then the corresponding eigen-spectrum is given by the equation:

$$\sigma(J\{E_1[0, 0, 0, 0, \tilde{x}_5]\}) = \{\lambda_i \mid \lambda^3 + \tilde{a}_1 \lambda^2 + \tilde{a}_2 \lambda + \tilde{a}_3 = 0, i = 1, 2, 3\} \cup \{\lambda_4, \lambda_5\}$$

where $\tilde{a}_1, \tilde{a}_2, \tilde{a}_3$ are specified in (5.9). But $\lambda_4 = \tilde{a}_{11} = -k_1 < 0$ and $\lambda_5 = \tilde{a}_{44} = -k_4 < 0$.

The conclusion of the theorem follows immediately after application of the Routh-Hurwitz criteria. $\square$

Clinical Implication 5.3. If the HAART protocol used for the AIDS patient is such that condition (5.9) is satisfied, then the patient experiences extreme immune system cytotoxicity in which the uninfected $CD4^+$ T cells, HIV-1 specific cytotoxic $CD8^+$ T cells, HIV-1 virions, and HIV-1 infected $CD4^+$ T cells are all decimated. This is not a

therapeutically desirable clinical outcome, because the patient may become severely incapacitated. To avoid this scenario, the HAART therapy must implemented in such a way that criterion (5.9) is violated.

5.4 Local stability of $E_3 = [\bar{x}_1, 0, 0, \bar{x}_4, \bar{x}_5]$

The local existence and local stability of the equilibrium $E_3 = [\bar{x}_1, 0, 0, \bar{x}_4, \bar{x}_5]$ will be analyzed in this subsection. The clinical relevance of the theoretical therapeutic criteria will be discussed.

Let $\sigma(J\{E_3[\bar{x}_1, 0, 0, \bar{x}_4, \bar{x}_5]\})$ be the eigen-spectrum for the Jacobian matrix $(J\{E_3[\bar{x}_1, 0, 0, \bar{x}_4, \bar{x}_5]\})$ such that $\sigma(J\{E_3[\bar{x}_1, 0, 0, \bar{x}_4, \bar{x}_5]\}) = \{\lambda_i \mid \det |J(E_3) - \lambda I| = 0, i = 1, 2, 3, 4, 5\}$

Theorem 5.4. Suppose

(i) The local existence criteria C_3 holds for E_3

(ii) $\bar{x}_1 = \frac{\beta_1}{\alpha_2} = \frac{1}{b_4}$

(iii)
$$\begin{cases} a_1 \bar{x}_1 (2 - b_1 \bar{x}_1) e^{-b_1 \bar{x}_1} - k_1 < 0 \\ a_2 \bar{x}_1 e^{-b_2 \bar{x}_1} - q_2 \bar{x}_1 - k_2 - K_1 \bar{x}_4 - \frac{\xi_2 \sigma_2 \bar{x}_5}{\lambda_2 + \bar{x}_5} < 0 \end{cases}$$

(iv)
$$\bar{M} = \begin{bmatrix} \bar{a}_{33} & 0 & \bar{a}_{35} \\ \bar{a}_{43} & \bar{a}_{44} & 0 \\ \bar{a}_{53} & 0 & \bar{a}_{55} \end{bmatrix}$$

with

$$\sigma(J(E_3)) = [\lambda_i \mid \lambda^3 + \bar{a}_1 \lambda^2 + \bar{a}_2 \lambda + \bar{a}_3 = 0, i = 1, 2, 3] \cup [\lambda_4, \lambda_5]$$

where

$$\begin{aligned} \bar{a}_1 &= -\text{Trace}(\bar{M}) \\ \bar{a}_2 &= \det \begin{vmatrix} \bar{a}_{44} & 0 \\ 0 & \bar{a}_{55} \end{vmatrix} + \det \begin{vmatrix} \bar{a}_{33} & \bar{a}_{35} \\ \bar{a}_{53} & \bar{a}_{55} \end{vmatrix} + \det \begin{vmatrix} \bar{a}_{33} & 0 \\ \bar{a}_{43} & \bar{a}_{44} \end{vmatrix} \\ \bar{a}_3 &= -\det \bar{M} \\ \lambda_4 &= \bar{a}_{11} < 0 \\ \lambda_5 &= \bar{a}_{22} < 0 \end{aligned}$$

Then the equilibrium E_3 exists locally and is a local attractor if

$$\bar{a}_1 > 0, \bar{a}_2 > 0, \bar{a}_3 > 0, \bar{a}_1 \bar{a}_2 > \bar{a}_3 \quad (5.10)$$

Proof. Consider the Jacobian matrix (4.5) associated with the equilibrium E_3 . By imposing the condition (ii) of the theorem and computing the eigen-values using the Laplace expansion technique, it can be observed that the eigen-values satisfy equation (5.10). The Routh-Hurwitz criteria when applied to the matrix $\bar{M}$ together with the conditions in (5.10) guarantees the local existence of E_3 as a local attractor. $\square$

5.5 Persistence analysis of HAART

The pathophysiology of HIV-1 persistence during HAART is described elaborately in the paper by Pomerantz in [18]. In this subsection, the mathematical criteria for viral persistence during HAART will be derived. The interior

rest point E_{10} exists if and only if the system (4.1) exhibits persistence. This describes a situation in which the patient survives for a long time with AIDS. It is possible during HAART that, the HIV-1 virions cannot be annihilated but instead the system persists in a chronic configuration in which the blood plasma levels of the HIV-1 virions co-exist with the other clinically measurable parameters such as uninfected $CD4^+$ T cells, the HIV-1 infected $CD4^+$ T cells, HIV-1 specific $CD8^+$ T cells, and HAART drug molecules. The criteria for existence of E_{10} are listed in the following theorem.

Theorem 5.5. Let

$$(i) \quad \begin{cases} m_i = \inf_{t \in [t_0, T]} \{a_i \bar{x}_1 \bar{x}_i e^{-b_i \bar{x}_i}\} \quad \text{where } i = \{1, 2, 4\} \\ L_1 = \sup_{t \in [t_0, T]} \{\alpha_1 \bar{x}_3 + q_1 \bar{x}_2 + k_1\} \\ L_2 = \sup_{t \in [t_0, T]} \left\{ q_2 \bar{x}_1 + k_2 + K_1 \bar{x}_4 + \frac{\xi_2 \sigma_2 \bar{x}_2 \bar{x}_5}{\lambda_2 + \bar{x}_5} \right\} \\ U_1 = \sup_{t \in [t_0, T]} \{\beta_1 \bar{x}_3\} \\ L_3 = \sup_{t \in [t_0, T]} \left\{ \alpha_3 \bar{x}_1 + \eta_1 \bar{x}_4 + k_3 + \frac{\xi_3 \sigma_3}{\lambda_3 + \bar{x}_5} \right\} \\ m_3 = \inf_{t \in [t_0, T]} \{\beta_2 \bar{x}_2 \bar{x}_3 + \beta_3 \bar{x}_3\} \\ L_4 = \sup_{t \in [t_0, T]} \{K_2 \bar{x}_2 + \eta_2 \bar{x}_3 + k_4\} \\ L_5 = \sup_{t \in [t_0, T]} \left\{ \frac{\sigma_0}{\lambda_0 + \bar{x}_5} + \frac{\sigma_2 \bar{x}_2}{\lambda_2 + \bar{x}_5} + \frac{\sigma_3 \bar{x}_3}{\lambda_3 + \bar{x}_5} + k_5 \bar{x}_5 \right\} \end{cases} \quad (5.11)$$

$$(ii) \quad \begin{cases} \liminf x_1 \geq \frac{S_1 + m_1 - e_{10}}{L_1} > 0 \\ \liminf x_2 \geq \frac{S_2 + m_2 - U_1 - e_{20}}{L_2} > 0 \\ \liminf x_3 \geq \frac{S_3 + m_3 - e_{30}}{L_3} > 0 \\ \liminf x_4 \geq \frac{S_4 + m_4 - e_{40}}{L_4} > 0 \\ \liminf x_5 \geq \frac{D}{L_5} > 0 \end{cases} \quad (5.12)$$

Then the system $[x_1, x_2, x_3, x_4, x_5]$ will persist and the HAART therapeutic outcome $E_{10} = [\bar{x}_1, \bar{x}_2, \bar{x}_3, \bar{x}_4, \bar{x}_5]$ exists.

Proof. For a proof refer to Nani and Jin [7, 15, 16]. $\square$

Clinical Implication 5.5 If uninfected $CD4^+$ T cells, infected $CD4^+$ T cells, the HIV-1 viral mRNA copies in the blood plasma, HIV-1 specific cytotoxic $CD8^+$ T cells, and the HAART drug concentration are within certain thresholds, then the AIDS patient will live with AIDS. If any of the conditions listed in (5.11) are violated, the patient will experience unpredictable therapeutic outcomes including full-blown AIDS or spontaneous elimination of HIV-1 virions.

6. Sufficient Criteria for Permanent Cure of AIDS during HAART

In this section, the sufficient criteria for permanent annihilation of HIV-1 virions during HAART will be derived. The clinically desirable physiological outcomes are $E_4[x_1, 0, 0, 0, x_5]$ and $E_3 = [x_1, 0, 0, x_4, x_5]$. It must be recalled that E_4 corresponds to the physiological outcome in which HIV-1 infected $CD4^+$ T cells, the HIV-1 virions in the blood plasma and HIV-1 specific $CD8^+$ T cells are eliminated in the blood plasma of the AIDS patient. The sufficient criteria for E_4 will be discussed first.

6.1 Global stability of $E_4 = [\hat{x}_1, 0, 0, 0, \hat{x}_5]$

In this subsection, the global stability of $E_4 = [\hat{x}_1, 0, 0, 0, \hat{x}_5]$ will be established in the space

$$\Omega = \{(x_1, x_2, x_3, x_4, x_5) \in \mathfrak{R}_+^5 \mid 0 \leq x_i \leq \Phi_i \quad i = 1, 2, 3, 4, 5\} \quad \text{with } \Phi_i \text{ defined in (3.2).}$$

Let

$$S_+^{x_1 x_5} = \{(x_1, x_5) \in \mathfrak{R}_+^2 \mid 0 \leq x_i \leq \Phi_i \quad i = 1, 5\} \subset \Omega$$

The global asymptotic stability of E_4 in Ω will be established respect to the flow emanating from $\text{int } S_+^{x_1 x_5} \subset \text{int } R_+^{x_1 x_5}$.

The model equations (4.1) correspondingly reduce to the following:

$$\begin{cases} \dot{x}_1 = S_1 + a_1 x_1^2 e^{-b_1 x_1} - k_1 x_1 - e_{10} \\ \dot{x}_5 = D - \frac{\sigma_0 x_5}{\lambda_0 + x_5} - k_5 x_5 \\ x_i(t_0) = x_{i0} \quad \text{for } i = \{1, 5\} \end{cases} \quad (6.1)$$

Let N be a neighborhood of a point in $\text{int } S_+^{x_1 x_5} \subset \Omega$. Choose a functional V on N such that

- (i) V is positive definite with respect to E_4
- (ii) $V \rightarrow \infty$ as $\|x_i\| \rightarrow \partial R_+^{x_1 x_5} \quad i = \{1, 5\}$
- (iii) $V \in C^1(R_+^2, R)$ and bounded below
- (iv) V is a Liapunov functional for (6.1)
- (v) $V(E_4) = 0$
- (vi) $\exists \eta > 0$ such that $V(x_i) > 0$ wherever $x_i \in B_\eta(E_4)$ for $\hat{x} \neq x$ where

$$B_\eta(x_i) = \{x \in R_+^{x_1 x_5} \mid \|x - \bar{x}_i\| < \eta\}$$

- (v) $\dot{V} \leq 0$ along the solution trajectories of (6.1)

Consider the Liapunov functional:

$$V := \sum \frac{1}{2} \hat{c}_i (x_i - \hat{x}_i)^2 \quad (6.2)$$

where $i = \{1, 5\}$ and $\hat{c}_i \in R_+ = (0, \infty)$

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

$$\begin{aligned} \dot{V} &= \hat{c}_1 (x_1 - \hat{x}_1) \dot{x}_1 + \hat{c}_5 (x_5 - \hat{x}_5) \dot{x}_5 \\ &= \hat{c}_1 (x_1 - \hat{x}_1) (S_1 + a_1 x_1^2 e^{-b_1 x_1} - k_1 x_1 - e_{10}) + \\ &\quad \hat{c}_5 (x_5 - \hat{x}_5) (D - \frac{\sigma_0 x_5}{\lambda_0 + x_5} - k_5 x_5) \end{aligned} \quad (6.3)$$

But at a steady state, the following equations hold.

$$\begin{cases} S_1 - e_{10} = k_1 \hat{x}_1 - a_1 \hat{x}_1^2 e^{-b_1 \hat{x}_1} \\ D = \frac{\sigma_0 \hat{x}_5}{\lambda_0 + \hat{x}_5} - k_5 \hat{x}_5 \end{cases} \quad (6.4)$$

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

$$G(x_1) = a_1 x_1^2 e^{-b_1 x_1} \quad (6.5)$$

$$L(x_5) = \frac{\sigma_0 x_5}{\lambda_0 + x_5}$$

$$\begin{aligned} V^* &= \hat{c}_1 (x_1 - \hat{x}_1) \dot{x}_1 + \hat{c}_5 (x_5 - \hat{x}_5) \dot{x}_5 \\ &= \hat{c}_1 (x_1 - \hat{x}_1) (-a_1 \hat{x}_1^2 e^{-b_1 x_1} + k_1 \hat{x}_1 + a_1 x_1^2 e^{-b_1 x_1} - k_1 x_1) + \hat{c}_5 (x_5 - \hat{x}_5) \left(\frac{\sigma_0 \hat{x}_5}{\lambda_0 + \hat{x}_5} - \frac{\sigma_0 x_5}{\lambda_0 + x_5} \right) \\ &\quad + \hat{c}_5 k_5 (x_5 - \hat{x}_5) (\hat{x}_5 - x_5) \\ &= \hat{c}_1 (x_1 - \hat{x}_1) [G(x_1) - G(\hat{x}_1)] + \hat{c}_1 (x_1 - \hat{x}_1) (k_1 \hat{x}_1 - k_1 x_1) \\ &\quad + \hat{c}_5 (x_5 - \hat{x}_5) [L(\hat{x}_5) - L(x_5)] - \hat{c}_5 k_5 (x_5 - \hat{x}_5)^2 \end{aligned} \quad (6.6)$$

$$V^* = -\hat{c}_1 k_1 (x_1 - \hat{x}_1)^2 + \hat{c}_1 (x_1 - \hat{x}_1) [G(x_1) - G(\hat{x}_1)] - \hat{c}_5 (x_5 - \hat{x}_5) [L(x_5) - L(\hat{x}_5)] - \hat{c}_5 k_5 (x_5 - \hat{x}_5)^2 \quad (6.7)$$

Let

$$\begin{aligned} v_1 &= x_1 - \hat{x}_1 \\ v_2 &= x_5 - \hat{x}_5 \end{aligned} \quad (6.8)$$

and

$$X = \begin{bmatrix} v_1 \\ v_2 \end{bmatrix} \in \mathbf{R}_+^2 \quad (6.9)$$

and define $M = \{m_{ij}\} \in M_{2 \times 2}(\mathbf{R})$ such that

$$M = \begin{bmatrix} m_{11} & \frac{1}{2} m_{12} \\ \frac{1}{2} m_{21} & m_{22} \end{bmatrix}$$

then

$$\begin{aligned} V^* &:= m_{11} v_1^2 + \frac{1}{2} m_{12} v_1 v_2 + \frac{1}{2} m_{21} v_2 v_1 + m_{22} v_2^2 \\ &= X^T M X \end{aligned} \quad (6.10)$$

where X^T denotes the transpose of X and V^* is negative definite if satisfy the conditions of $m_{11} < 0$ and $\det(M) > 0$.

In particular, the $[m_{ij}]_{2 \times 2}$ are defined as follows:

$$\begin{cases} m_{11} := -[\hat{c}_1 k_1 - \hat{c}_1 \left(\frac{G(x_1) - G(\hat{x}_1)}{x_1 - \hat{x}_1} \right)] \\ m_{12} = m_{21} = 0 \\ m_{22} := -\hat{c}_5 \left[\frac{L(x_5) - L(\hat{x}_5)}{x_5 - \hat{x}_5} \right] - \hat{c}_5 k_5 \end{cases} \quad (6.11)$$

As the flow dynamics approaches the steady state $E_4 = [\hat{x}_1, 0, 0, 0, \hat{x}_5]$, the following conditions hold:

$$\begin{aligned} \lim_{x_1 \rightarrow \hat{x}_1} m_{11} &= -[\hat{c}_1 (k_1 - G'_1(\hat{x}_1))] \\ \lim_{x_2 \rightarrow \hat{x}_2} m_{22} &= -\hat{c}_5 (L'(\hat{x}_5) - k_5) \end{aligned} \quad (6.12)$$

where

$$G'(\hat{x}_1) = a_1 \hat{x}_1 e^{-b_1 \hat{x}_1} (2 - b_1 \hat{x}_1)$$

$$L'(\hat{x}_5) = \frac{\sigma_0 \lambda_0}{(\lambda_0 + \hat{x}_5)^2} > 0$$

In particular,

$$G'(\hat{x}_1) \begin{cases} > 0 \text{ if } \hat{x}_1 < \frac{2}{b_1} \\ = 0 \text{ if } \hat{x}_1 = \frac{2}{b_1} \\ < 0 \text{ if } \hat{x}_1 > \frac{2}{b_1} \end{cases}$$

The sufficient criteria for the global asymptotic stability of E_4 are specified in the following theorem.

Theorem 6.1 Let

(i) Conditions of Theorem 5.1 holds

$$(ii) \hat{x}_1 \leq \frac{2}{b_1} \text{ and } k_1 > G'(\hat{x}_1)$$

Then the equilibrium E_4 is a globally asymptotically stable with respect to the flow emanating from $\text{int } S_+^{x_1 x_5} \subset \Omega$.

Proof. The condition (i) of the theorem guarantees the local existence of E_4 and establishes that E_4 is a local attractor. The global asymptotic stability of E_4 can be shown by invoking the Gantmacher criteria [30] for negative definiteness of matrix M as defined in (6.10). In particular, V^* is negative definite if $m_{11} < 0$ and $\det M > 0$. But $m_{11} = -\hat{c}_1[k_1 - G'(\hat{x}_1)]$ is less than zero if condition (ii) of the theorem hypothesis holds. However, $\det M > 0$ since the product $m_{11}m_{22} > 0$. Thus, $V^* < 0$ and hence E_4 is a global attractor. This completes the proof. $\square$

Comments on Theorem 6.1

(i) If $G(\hat{x}_1) > 0$ then $k_1 > G(\hat{x}_1)$ and $\hat{x}_1 > \frac{2}{b_1}$ constitute sufficient condition for global asymptotic stability of E_4 .

(ii) If $G(\hat{x}_1) < 0$, then $\hat{x}_1 > \frac{2}{b_1}$ is a sufficient condition for global asymptotic stability of E_4 .

(iii) If $G(\hat{x}_1) = 0$ then $\hat{x}_1 = \frac{2}{b_1}$ is a sufficient condition for global asymptotic stability of E_4 .

Clinical Implication 6.1

(i) The function $G(\hat{x}_1)$ is a measure of the rate at which the $CD4^+$ T cells (x_1) are activated by interleukin-2 (IL-2) in an autocrine process when the physiological flow during HAART tends to E_4 . It is possible to attach a biochemical measure to coefficient a_1 and b_1 of $G(\hat{x}_1)$. This can be done as follows:

$$G(\hat{x}_1) = a_1 \hat{x}_1^2 e^{-b_1 \hat{x}_1} = \frac{a_1 \hat{x}_1^2}{e^{b_1 \hat{x}_1}} = \frac{a_1 \hat{x}_1 \hat{x}_1}{1 + b_1 \hat{x}_1 + \frac{(b_1 \hat{x}_1)^2}{2!} + \dots} \approx \frac{a_1 \hat{x}_1 \hat{x}_1}{1 + b_1 \hat{x}_1} = \frac{\frac{a_1}{b_1} \hat{x}_1 \hat{x}_1}{\frac{1}{b_1} + \hat{x}_1} = \frac{V_{\max} \hat{x}_1 \hat{x}_1}{K_m + \hat{x}_1}$$

where $K_m = \frac{1}{b_1}$ is approximately equal to the Michaelis-Menten constant of the CD4⁺ T cells activation reaction by

interleukin-2, and $V_{\max} = \frac{a_1}{b_1}$ represents the maximal velocity of the CD4⁺ T cells IL-2 activation reaction.

(ii) Note that k_1 is the rate of degradation and decay of the CD4⁺ T cells during AIDS. Thus the theorem implies that if the rate of degradation of CD4⁺ T cells is greater than the rate of IL-2 activation of T cells and if in addition, the number of the CD4⁺ T cells are such that $\hat{x}_1 < 2K_m$, then the patient will be cured of AIDS.

6.2 Global stability analysis for $E_3 = [\bar{x}_1, 0, 0, \bar{x}_4, \bar{x}_5]$

In this subsection, the other clinical desirable equilibrium $E_3 = [\bar{x}_1, 0, 0, \bar{x}_4, \bar{x}_5]$ is analyzed. The aim is to find the sufficient criteria under which the HIV-1 virions in the blood plasma, the HIV-1 infected CD4⁺ T cells are annihilated but the HIV-1 specific CD8⁺ T cells will persist as memory T cells as well as the CD4⁺ T cells and some drug residues will remain in the AIDS patient. It is expected that the CD4⁺ T cells will eventually repopulate to their carrying capacity whereas the drug residues will ultimately dissipate. The analysis will be similar to the preceding one for E_4 .

The restriction of the model equations (4.1) to the space

$S_+^{x_1, x_4, x_5} = \{(x_1, x_4, x_5) \in \mathfrak{R}_+^3 \mid 0 \leq x_i \leq \Phi_i \quad i = 1, 4, 5\} \subset \Omega$ leads to the following equations.

$$\begin{cases} \dot{x}_1 = S_1 + a_1 x_1^2 e^{-b_1 x_1} - k_1 x_1 - e_{10} \\ \dot{x}_4 = S_4 + a_4 x_1 x_4 e^{-b_4 x_1} - k_4 x_4 - e_{40} \\ \dot{x}_5 = D - \frac{\sigma_0 x_5}{\lambda_0 + x_5} - k_5 x_5 \\ x_i(t_0) = x_{i0} \quad \text{for } i = \{1, 4, 5\} \end{cases} \quad (6.13)$$

The global stability of $E_3 = [\bar{x}_1, 0, 0, \bar{x}_4, \bar{x}_5]$ will be established with respect to the flow emanating from $\text{int } S_+^{x_1, x_4, x_5} \subset \Omega$.

Consider the Liapnnov functional:

$$V := \sum \frac{1}{2} \bar{c}_i (x_i - \bar{x}_i)^2 \quad (6.14)$$

where $i = \{1, 4, 5\}$ and $\bar{c}_i \in R_+ = (0, \infty)$

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

$$V^* = \bar{c}_1 (x_1 - \bar{x}_1) \dot{x}_1 + \bar{c}_4 (x_4 - \bar{x}_4) \dot{x}_4 + \bar{c}_5 (x_5 - \bar{x}_5) \dot{x}_5$$

Thus a steady state, $\dot{x}_i = 0$ and the following equations hold.

$$\begin{cases} S_1 - e_{10} = k_1 \bar{x}_1 - a_1 \bar{x}_1^2 e^{-b_1 \bar{x}_1} \\ S_4 - e_{40} = k_4 \bar{x}_4 - a_4 \bar{x}_1 \bar{x}_4 e^{-b_4 \bar{x}_1} \\ D = \frac{\sigma_0 \bar{x}_5}{\lambda_0 + \bar{x}_5} + k_5 \bar{x}_5 \end{cases} \quad (6.15)$$

Thus

$$\begin{aligned} V^* = & \bar{c}_1 k_1 (x_1 - \bar{x}_1)(\bar{x}_1 - x_1) \\ & + \bar{c}_1 (x_1 - \bar{x}_1)[G(\bar{x}_1) - G(x_1)] \\ & + \bar{c}_4 k_4 (x_4 - \bar{x}_4)(\bar{x}_4 - x_4) \\ & + \bar{c}_4 (x_4 - \bar{x}_4)[F(\bar{x}_1, \bar{x}_4) - F(x_1, x_4)] \\ & + \bar{c}_5 \sigma_0 [L(\bar{x}_5) - L(x_5)] \end{aligned}$$

where

$$\begin{aligned} G(x_1) &= a_1 x_1^2 e^{-b_1 x_1} \\ F(x_1, x_4) &= a_4 x_1 x_4 e^{-b_4 x_1} \\ L(x_5) &= \frac{\sigma_0 x_5}{\lambda_0 + x_5} \end{aligned}$$

(6.16)

The functions G, F, L are continuous, Lebesgue measurable, and of bounded variations.

Let $V^* = X^T C X$ (6.17)

where

$$X = \begin{bmatrix} u_1 \\ u_2 \\ u_3 \end{bmatrix} \in R_+^3$$

and

$$\begin{aligned} u_1 &= x_1 - \bar{x}_1 \\ u_2 &= x_4 - \bar{x}_4 \\ u_3 &= x_5 - \bar{x}_5 \end{aligned} \quad (6.18)$$

such that X^T denotes the transpose of X . Define $C \in M_{3 \times 3}(R)$ such that

$$C = \begin{bmatrix} c_{11} & \frac{1}{2} c_{12} & \frac{1}{2} c_{13} \\ \frac{1}{2} c_{12} & c_{22} & \frac{1}{2} c_{23} \\ \frac{1}{2} c_{13} & \frac{1}{2} c_{23} & c_{33} \end{bmatrix} \quad (6.19)$$

Now

$$\begin{aligned} V^* := & c_{11} u_1^2 + \frac{1}{2} c_{12} u_1 u_2 + \frac{1}{2} c_{13} u_1 u_3 \\ & + \frac{1}{2} c_{12} u_2 u_1 + c_{22} u_2^2 + \frac{1}{2} c_{23} u_2 u_3 \\ & + \frac{1}{2} c_{13} u_3 u_1 + \frac{1}{2} c_{23} u_3 u_2 + c_{33} u_3^2 \end{aligned} \quad (6.20)$$

Where the $[c_{ij}]_{3 \times 3}$ are defined as follows:

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$$\begin{cases} c_{11} := -[\bar{c}_1 k_1 - \bar{c}_1 (\frac{G(x_1) - G(\bar{x}_1)}{x_1 - \bar{x}_1})] \\ c_{12} := -\bar{c}_4 [\frac{F(x_1, x_4) - F(\bar{x}_1, \bar{x}_4)}{x_1 - \bar{x}_1}] = c_{21} \\ c_{13} = c_{31} = 0 \\ c_{22} = -\bar{c}_4 k_4 \\ c_{23} = c_{32} = 0 \\ c_{33} := -\bar{c}_5 [\frac{L(x_5) - L(\bar{x}_5)}{x_5 - \bar{x}_5}] - \bar{c}_5 k_5 \end{cases} \quad (6.21)$$

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As the flow associated with the model equations approaches $E_3 = [\bar{x}_1, 0, 0, \bar{x}_4, \bar{x}_5]$, the matrix entries $[c_{ij}]_{3 \times 3}$ have the following form:

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$$\begin{aligned} \lim_{x_1 \rightarrow \bar{x}_1} c_{11} &= -[\bar{c}_1 k_1 - \bar{c}_1 G'(\bar{x}_1)] \\ \lim_{x_1 \rightarrow \bar{x}_1} c_{12} &= -\bar{c}_4 [F_{x_1}(\bar{x}_1, \bar{x}_4)] \\ \lim_{x_4 \rightarrow \bar{x}_4} c_{22} &= -\bar{c}_4 k_4 \\ \lim_{x_5 \rightarrow \bar{x}_5} c_{33} &= -\bar{c}_5 L'(\bar{x}_5) - \bar{c}_5 k_5 \end{aligned} \quad (6.22)$$

671 But it can be shown that

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In particular, (cf. Nani and Jin [7, 15, 16])

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Similarly,

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$$F_{x_1}(\bar{x}_1, \bar{x}_4) = \begin{cases} > 0 \text{ if } \bar{x}_1 < \frac{1}{b_4} \\ = 0 \text{ if } \bar{x}_1 = \frac{1}{b_4} \\ < 0 \text{ if } \bar{x}_1 > \frac{1}{b_4} \end{cases} \quad (6.24)$$

$$G'(\bar{x}_1) = \begin{cases} > 0 \text{ if } \bar{x}_1 < \frac{2}{b_1} \\ = 0 \text{ if } \bar{x}_1 = \frac{2}{b_1} \\ < 0 \text{ if } \bar{x}_1 > \frac{2}{b_1} \end{cases} \quad (6.25)$$

685 Using the specifications in (4.31), the matrix C has the form

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$$C = \begin{bmatrix} c_{11} & \frac{1}{2} c_{12} & 0 \\ \frac{1}{2} c_{12} & c_{22} & 0 \\ 0 & 0 & c_{33} \end{bmatrix} \quad (6.26)$$

690 The matrix C is negative definite if the following criteria hold:

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$$\begin{aligned}
& (i) \quad \det c_{11} < 0 \quad \text{or} \quad c_{11} < 0 \\
& (ii) \quad \det \begin{vmatrix} c_{11} & \frac{1}{2}c_{12} \\ \frac{1}{2}c_{12} & c_{22} \end{vmatrix} > 0 \quad \text{or} \quad c_{11}c_{22} - \frac{1}{4}(c_{12})^2 > 0 \\
& (iii) \quad \det \begin{vmatrix} c_{11} & \frac{1}{2}c_{12} & 0 \\ \frac{1}{2}c_{12} & c_{22} & 0 \\ 0 & 0 & c_{33} \end{vmatrix} < 0 \quad \text{or} \quad c_{33}[c_{11}c_{22} - \frac{1}{4}(c_{12})^2] < 0
\end{aligned} \tag{6.27}$$

Theorem 6.2 Let $\{x_1, x_4, x_5\} \in S_+^{x_1 x_4 x_5} \subset \Omega$. Consider the patho-physiological equilibrium $E_3 = [\bar{x}_1, 0, 0, \bar{x}_4, \bar{x}_5]$ such that

$$\begin{aligned}
& (i) \quad \bar{x}_1 = \frac{1}{b_4} < \frac{2}{b_1} \\
& (ii) \quad k_1 > G'(\bar{x}_1) > 0
\end{aligned}$$

Then $E_3 = [\bar{x}_1, 0, 0, \bar{x}_4, \bar{x}_5]$ is globally asymptotically stable with respect to the flow emanating from $S_+^{x_1 x_4 x_5} \subset \Omega$. In particular E_3 is a global attractor. Consequently, all the HIV-1 virions will be permanently annihilated in the AIDS patient.

Proof. The patho-physiological equilibrium E_3 is a global attractor if $\dot{V} = X^T CX$ is negative definite, or equivalently if the matrix C is negative definite. But C is negative definite if conditions (6.27) (i), (ii), (iii) hold (cf. Gantmacher [30]). Note that (6.27) (i) holds if $k_1 > G'(\bar{x}_1)$ and $\bar{x}_1 < \frac{2}{b_1}$. If $\bar{x}_1 = \frac{1}{b_4}$, then $c_{12} = 0$, which leads to the fulfillment of (6.27) (ii). But $c_{33} < 0$ and $c_{12} = 0$ whereas $c_{11} c_{22} > 0$. Thus condition (6.27) (iii) is satisfied. As a result, $\dot{V}$ is negative definite. Therefore, E_3 becomes a global attractor and hence the theorem follows. $\square$

Clinical Implications 6.2

(i) Theorem 6.2 gives the sufficient theoretical criteria for the HIV-1 infected CD4⁺ T cells and HIV-1 virions in the blood plasma to be eradicated during HAART. This theorem also provides the conditions under which HIV-1 specific CD8⁺ T cells will persist as memory cells after the HAART therapy.

(ii) It is possible to express the conditions of Theorem 6.2 in terms of clinically measurable biophysical parameters. By using Taylor expansions of $e^{-b_4 \bar{x}_1}$ and $e^{-b_1 \bar{x}_1}$, the condition $\bar{x}_1 = \frac{1}{b_4} < \frac{2}{b_1}$ is approximately equivalent to the expression

$$\bar{x}_1 = K_m^{CD8^+} < 2K_m^{CD4^+} \tag{6.28}$$

This can be interpreted to mean that HAART will cure the AIDS patient if the number density of uninfected CD4⁺ T cells is equal to the Michaelis-Menten constant of the IL-2 activation of the CD8⁺ T cells, which in turn has to be less than twice Michaelis-Menten constant of the IL-2 activation of the CD4⁺ T cells.

Corollary 6.2 Suppose $\bar{x}_1 = \frac{1}{b_4} = \frac{2}{b_1}$

Then the physiological steady state $E_3 = [\bar{x}_1, 0, 0, \bar{x}_4, \bar{x}_5]$ is a global attractor.

Proof. The conditions (6.27) (i), (ii), (iii) hold if the theorem hypothesis is satisfied. This makes the matrix C in (6.19) negative definite. Consequently, the equilibrium becomes global attractor. $\square$

It is possible to combine Theorem 6.2 and Corollary 6.2 to obtain the combined criteria:

$$\bar{x}_1 = \frac{1}{b_4} \leq \frac{2}{b_1}$$

$$\bar{x}_1 \approx K_m^{CD8+} \leq 2K_m^{CD4+}$$

7. Simulations and Discussion of Results

Investigative computer simulations will be presented and discussed. These simulations are performed using clinically plausible hypothetical patient patho-physiological parametric configurations. In particular, the simulations executed for the non-autonomous version of the model equations as displayed in (7.1).

$$\begin{cases} \dot{x}_1 = S_1 + a_1 x_1^2 e^{-b_1 x_1} - \alpha_1 x_1 x_3 - q_1 x_1 x_2 - k_1 x_1 - e_{10} \\ \dot{x}_2 = S_2 + a_2 x_1 x_2 e^{-b_2 x_1} + \alpha_2 x_1 x_3 - q_2 x_1 x_2 - k_2 x_2 - \beta_1 x_3 - K_1 x_2 x_4 - e_{20} - \frac{\xi_2 \sigma_2 x_2 x_5}{\lambda_2 + x_5} \\ \dot{x}_3 = S_3 + \beta_2 x_2 x_3 + \beta_3 x_3 - \alpha_3 x_1 x_3 - \eta_1 x_3 x_4 - k_3 x_3 - e_{30} - \frac{\xi_3 \sigma_3 x_3 x_5}{\lambda_3 + x_5} \\ \dot{x}_4 = S_4 + a_4 x_1 x_4 e^{-b_4 x_1} - K_2 x_2 x_4 - \eta_2 x_3 x_4 - k_4 x_4 - e_{40} \\ \dot{x}_5 = Df(t) - \frac{\sigma_0 x_5}{\lambda_0 + x_5} - \frac{\sigma_2 x_2 x_5}{\lambda_2 + x_5} - \frac{\sigma_3 x_3 x_5}{\lambda_3 + x_5} - k_5 x_5 \\ f(t) = \lceil \sin 5t \rceil \\ x_i(t_0) = x_{i0} \quad \text{for } i = \{1, 2, 3, 4, 5\} \end{cases} \quad (7.1)$$

The drug input function $f(t)$ is a technical construct such as to generate the rectangle pulse function as shown in Section 3.1. It represents a periodically calibrated transdermal or intra-venous or caplet drug matrix input with period ω . In particular,

$$f(t) = f(t + \omega) \quad \text{where } \omega = 6.25 \text{ days}$$

It should be noted that the system (4.1) represents HAART during constant continuous caplet drug matrix input which is different from the scenarios used in the simulations of this section.

The complete mathematical analysis of the non-autonomous system (7.1) using Floquet Theory and Theory of non-linear periodic Dynamical Systems will be done in a future publication.

The numerical estimates used are variations of estimates published in the references: [3, 4, 11, 19, 20, 23]. Some techniques for estimating HIV-I dynamical parameters include Monte Carlo simulation and polynomial regression analysis. The investigative computer simulations elucidate several dynamical aspects of HIV-1 AIDS dynamics which are based on the respective parametric configurations. The x-axis of the simulation graphs is calibrated in months.

7.1 Simulation results for hypothetical AIDS patient #1

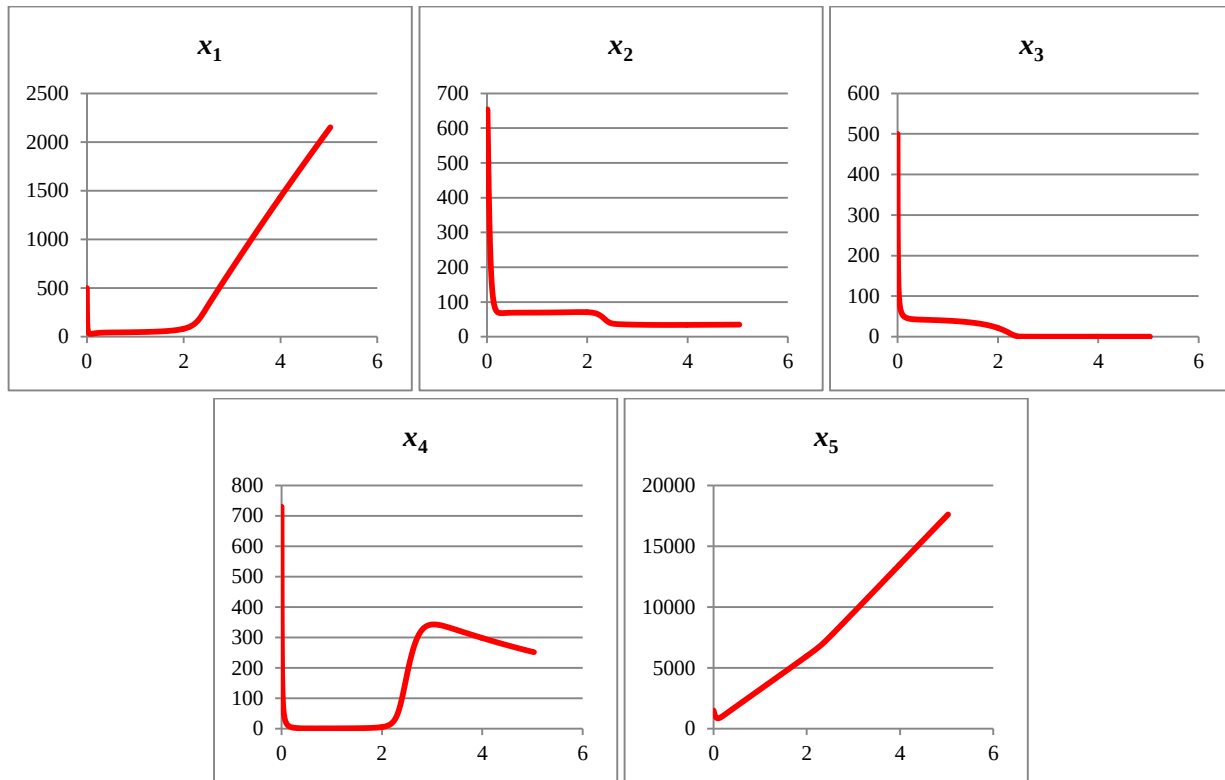
The AIDS patho-physiological parametric configuration of hypothetical patient #1 is denoted by P_1 and exhibited in Table 1. The simulation results show that the HAART protocol impairs HIV-1 dynamics in this patient leading to eradication of plasma HIV-1 viremia. The simulation results for patient #1 are exhibited in Figure 1. It can be observed that the HIV-1 infected $CD4^+$ T cells are eradicated in this patient with the use of anti-AIDS pharmacotherapeutic drug protocols. In addition, patient #1 experiences HAART-induced immune system reconstitution as the uninfected $CD4^+$ T cells and HIV-1 specific $CD8^+$ T cells repopulate.

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Table 1 Hypothetical AIDS Patient Parametric Configuration P_1

$S_1 = 800 \text{ /day/}\mu\text{l}$ $a_1 = 0.15 \text{ /day/cell/}\mu\text{l}$ $b_1 = 0.019 \text{ /cell/}\mu\text{l}$ $\alpha_1 =$ $0.5 \text{ /day/virion/}\mu\text{l}$ $k_1 = 0.0005 \text{ /day/}\mu\text{l}$ $q_1 =$ $0.00045 \text{ /day/}\mu\text{l/cell}$ $e_{10} =$ $0.0025 \text{ cells/day/}\mu\text{l}$ $x_{10} = 500 \text{ cells/}\mu\text{l}$	$S_2 = 800 \text{ /day/}\mu\text{l}$ $a_2 = 0.03 \text{ /day/cell/}\mu\text{l}$ $b_2 = 0.004 \text{ /cell/}\mu\text{l}$ $\alpha_2 = 0.5 \text{ /day/virion/}\mu\text{l}$ $k_2 = 0.005 \text{ /day/}\mu\text{l}$ $q_2 =$ $0.00001 \text{ /day/}\mu\text{l/cell}$ $\beta_1 = 1.05$ $\text{virions/CD4}^+ \text{ /day}$ $K_1 = 0.0001 \text{ /day/}\mu\text{l}$ $e_{20} = 0.005 \text{ cells/day/}\mu\text{l}$ $\xi_2 = 0.85$ $x_{20} = 400 \text{ cells/}\mu\text{l}$	$S_3 = 10 \text{ /day/}\mu\text{l}$ $\beta_2 = 0.0015$ $\text{virions/CD4}^+ \text{ /day/}\mu\text{l}$ $\beta_3 = 1.05$ $\text{virions/CD4}^+ \text{ /day}$ $\alpha_3 = 0.027$ $\text{/day/virion/}\mu\text{l}$ $k_3 = 0.0001 \text{ /day/}\mu\text{l}$ $e_{30} = 0.0001 \text{ /day}$ $\eta_1 = 0.25$ $\xi_3 = 0.001$ $x_{30} = 500 \text{ cells/}\mu\text{l}$	$S_4 = 10 \text{ /day/}\mu\text{l}$ $a_4 = 0.35$ $\text{/day/cell/}\mu\text{l}$ $b_4 = 0.01 \text{ /cell/}\mu\text{l}$ $K_2 = 0.0024$ $\text{/day/}\mu\text{l}$ $k_4 = 0.08 \text{ /day/}\mu\text{l}$ $e_{40} = 0.0002$ $\text{cells/day/}\mu\text{l}$ $\eta_2 = 0.45$ $x_{40} = 730 \text{ cells/}\mu\text{l}$	$D = 5000 \text{ units}$ $\sigma_0 = 0.5 \text{ mg/day}$ $\sigma_2 = 30 \text{ mg/day}$ $\sigma_3 = 5 \text{ mg/day}$ $\lambda_0 = 5 \text{ mg/L}$ $\lambda_2 = 15 \text{ mg/L}$ $\lambda_3 = 0.025 \text{ mg/L}$ $x_{50} = 1500$ $\text{cells/}\mu\text{l}$ $k_5 = 0.0 \text{ /day}$ constant infusion
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Figure 1 Simulation results using parametric configuration P_1

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7.2 Simulation results for hypothetical AIDS patient #2

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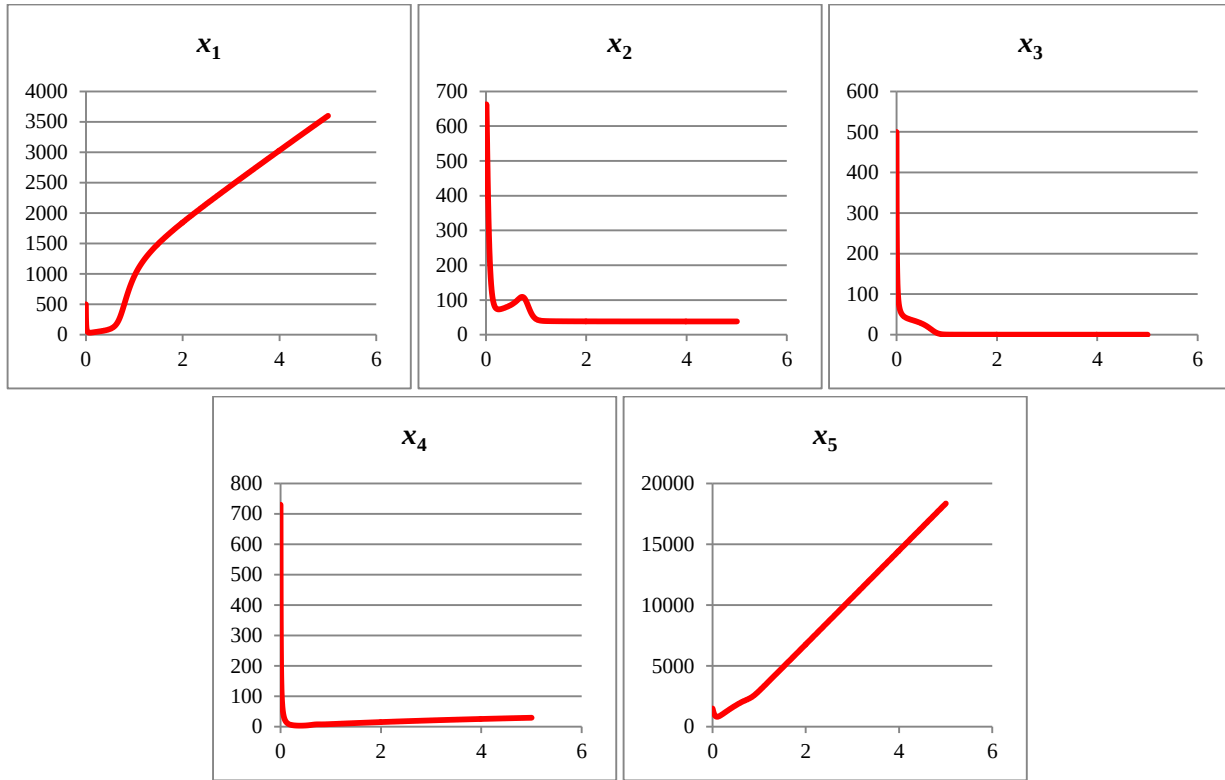
The hypothetical AIDS patient #2 is assigned the patho-physiological parametric configuration P_2 as presented in Table 2. The simulation results are exhibited in Figure 2. It can be observed that this patient does have a clinically favorable prognosis under HAART treatment protocol. The AIDS patho - physiodynamics during the given HAART protocol is similar to that for patient #1, as the patient #2 also undergoes immune system reconstitution in which the CD4^+ T cells repopulate. On the other hand, the proliferative activity of the HIV-1 specific CD8^+ T cells appears to be down-regulated.

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Table 2 Hypothetical AIDS Patient Parametric Configuration P_2

$S_1 = 800 \text{ /day/}\mu\text{l}$ $a_1 = 0.15 \text{ /day/cell/}\mu\text{l}$ $b_1 = 0.005 \text{ /cell/}\mu\text{l}$ $\alpha_1 = 0.5 \text{ /day/virion/}\mu\text{l}$ $k_1 = 0.0005 \text{ /day/}\mu\text{l}$ $q_1 =$ $0.00045 \text{ /day/}\mu\text{l/cell}$ $e_{10} = 0.0025$ $\text{cells/day/}\mu\text{l}$ $x_{10} = 500 \text{ cells/}\mu\text{l}$	$S_2 = 800 \text{ /day/}\mu\text{l}$ $a_2 = 0.03 \text{ /day/cell/}\mu\text{l}$ $b_2 = 0.004 \text{ /cell/}\mu\text{l}$ $\alpha_2 = 0.5 \text{ /day/virion/}\mu\text{l}$ $k_2 = 0.005 \text{ /day/}\mu\text{l}$ $q_2 =$ $0.00001 \text{ /day/}\mu\text{l/cell}$ $\beta_1 = 1.05$ $\text{virions/CD4}^+ \text{ /day}$ $K_1 = 0.0001 \text{ /day/}\mu\text{l}$ $e_{20} = 0.005 \text{ cells/day/}\mu\text{l}$ $\xi_2 = 0.85$ $x_{20} = 400 \text{ cells/}\mu\text{l}$	$S_3 = 10 \text{ /day/}\mu\text{l}$ $\beta_2 = 0.0015$ $\text{virions/CD4}^+ \text{ /day/}\mu\text{l}$ $\beta_3 = 1.05$ $\text{virions/CD4}^+ \text{ /day}$ $\alpha_3 = 0.027 \text{ /day/virion/}\mu\text{l}$ $k_3 = 0.0001 \text{ /day/}\mu\text{l}$ $e_{30} = 0.0001 \text{ /day}$ $\eta_1 = 0.25$ $\xi_3 = 0.001$ $x_{30} = 500 \text{ cells/}\mu\text{l}$	$S_4 = 10 \text{ /day/}\mu\text{l}$ $a_4 = 0.35 \text{ /day/cell/}\mu\text{l}$ $b_4 = 0.01 \text{ /cell/}\mu\text{l}$ $K_2 = 0.0024 \text{ /day/}\mu\text{l}$ $k_4 = 0.08 \text{ /day/}\mu\text{l}$ $e_{40} = 0.0002$ $\text{cells/day/}\mu\text{l}$ $\eta_2 = 0.45$ $x_{40} = 730 \text{ cells/}\mu\text{l}$	$D = 5000 \text{ units}$ $\sigma_0 = 0.5 \text{ mg/day}$ $\sigma_2 = 30 \text{ mg/day}$ $\sigma_3 = 5 \text{ mg/day}$ $\lambda_0 = 5 \text{ mg/L}$ $\lambda_2 = 15 \text{ mg/L}$ $\lambda_3 = 0.025 \text{ mg/L}$ $x_{50} = 1500 \text{ cells/}\mu\text{l}$ $k_5 = 0.0 \text{ /day}$ constant infusion
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Figure 2 Simulation results using parametric configuration P_2

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7.3 Simulation results for hypothetical AIDS patient #3

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For this scenario, the patho-physiological parametric configuration of hypothetical patient #3 is as shown in Table 3. It must be noted that HIV-1 AIDS dynamics during HAART treatment protocol in this patient is exacerbated by contributions from latent reservoirs in contrast to the other hypothetical patients. The results of the simulation are shown in Figure 3. This is a non-equilibrium AIDS configuration simulation as it is evident parametric configuration and by the simulation time profile. The simulation results show that during the given HAART protocol, the hypothetical AIDS patient #3 experiences annihilation of uninfected $CD4^+$ T cells and the HIV-1 specific $CD8^+$ T cells. Consequently, immune system paralysis occurs as a consequence of the low $CD4^+$ T

cell number density, leading to an exponential increase of the blood plasma HIV-1 viremia. This simulation represents an unfavorable AIDS outcome during HAART.

Table 3 Hypothetical AIDS Patient Parametric Configuration P_3

$S_1 = 800 \text{ /day/}\mu\text{l}$ $a_1 = 0.15 \text{ /day/cell/}\mu\text{l}$ $b_1 = 0.003 \text{ /cell/}\mu\text{l}$ $\alpha_1 = 0.5 \text{ /day/virion/}\mu\text{l}$ $k_1 = 0.0005 \text{ /day/}\mu\text{l}$ $q_1 = 0.00045 \text{ /day/}\mu\text{l/cell}$ $e_{10} = 0.0025 \text{ cells/day/}\mu\text{l}$ $x_{10} = 250 \text{ cells/}\mu\text{l}$	$S_2 = 800 \text{ /day/}\mu\text{l}$ $a_2 = 0.03 \text{ /day/cell/}\mu\text{l}$ $b_2 = 0.004 \text{ /cell/}\mu\text{l}$ $\alpha_2 = 0.5 \text{ /day/virion/}\mu\text{l}$ $k_2 = 0.005 \text{ /day/}\mu\text{l}$ $q_2 = 0.00001 \text{ /day/}\mu\text{l/cell}$ $\beta_1 = 1.05 \text{ virions/CD4}^+ \text{ /day}$ $K_1 = 0.0001 \text{ /day/}\mu\text{l}$ $e_{20} = 0.005 \text{ cells/day/}\mu\text{l}$ $\xi_2 = 0.85$ $x_{20} = 400 \text{ cells/}\mu\text{l}$	$S_3 = 10 \text{ /day/}\mu\text{l}$ $\beta_2 = 0.0015 \text{ virions/CD4}^+ \text{ /day/}\mu\text{l}$ $\beta_3 = 1.05 \text{ virions/CD4}^+ \text{ /day}$ $\alpha_3 = 0.027 \text{ /day/virion/}\mu\text{l}$ $k_3 = 0.0001 \text{ /day/}\mu\text{l}$ $e_{30} = 0.0001 \text{ /day}$ $\eta_1 = 0.25$ $\xi_3 = 0.001$ $x_{30} = 500 \text{ cells/}\mu\text{l}$	$S_4 = 10 \text{ /day/}\mu\text{l}$ $a_4 = 0.35 \text{ /day/cell/}\mu\text{l}$ $b_4 = 0.002 \text{ /cell/}\mu\text{l}$ $K_2 = 0.095 \text{ /day/}\mu\text{l}$ $k_4 = 0.08 \text{ /day/}\mu\text{l}$ $e_{40} = 0.0002 \text{ cells/day/}\mu\text{l}$ $\eta_2 = 0.45$ $x_{40} = 730 \text{ cells/}\mu\text{l}$	$D = 5000 \text{ units}$ $\sigma_0 = 1.0 \text{ mg/day}$ $\sigma_2 = 30 \text{ mg/day}$ $\sigma_3 = 5 \text{ mg/day}$ $\lambda_0 = 5 \text{ mg/L}$ $\lambda_2 = 15 \text{ mg/L}$ $\lambda_3 = 0.025 \text{ mg/L}$ $x_{50} = 3000 \text{ cells/}\mu\text{l}$ $k_5 = 0.0 \text{ /day}$ Constant Infusion
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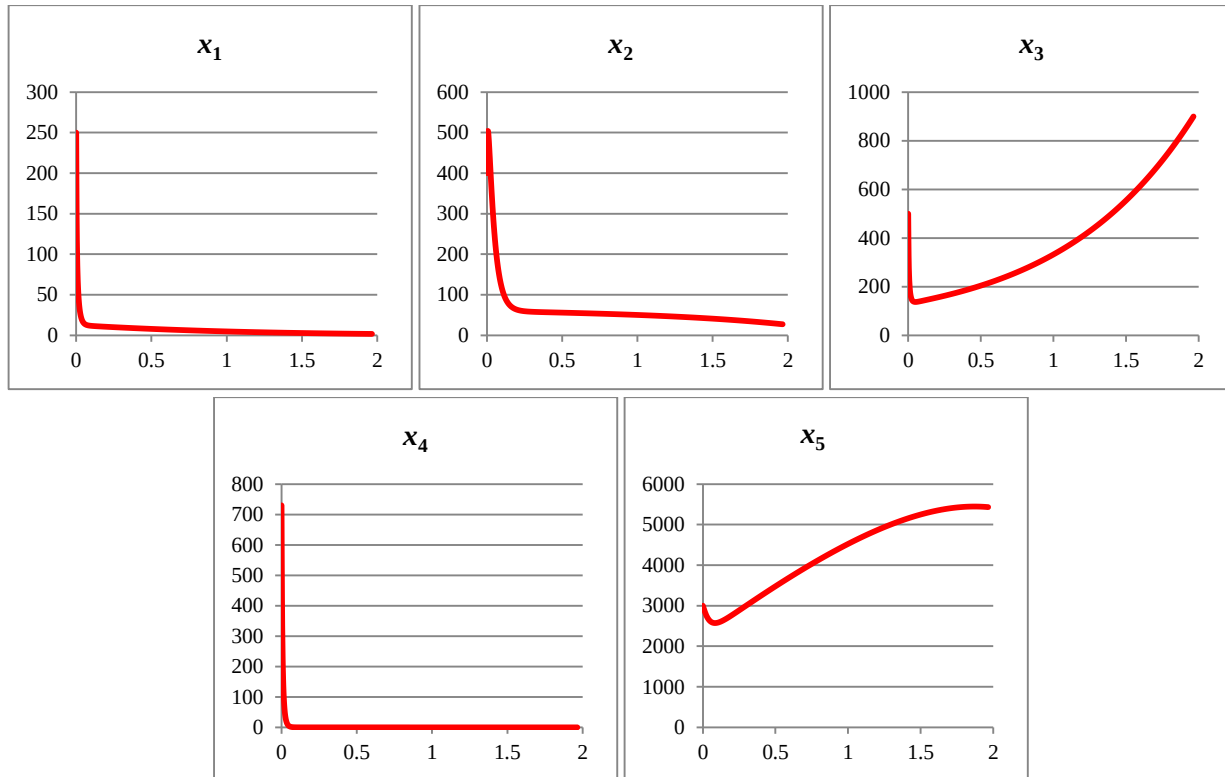


Figure 3 Simulation results using parametric configuration P_3

7.4 Simulation results for hypothetical AIDS patient #4

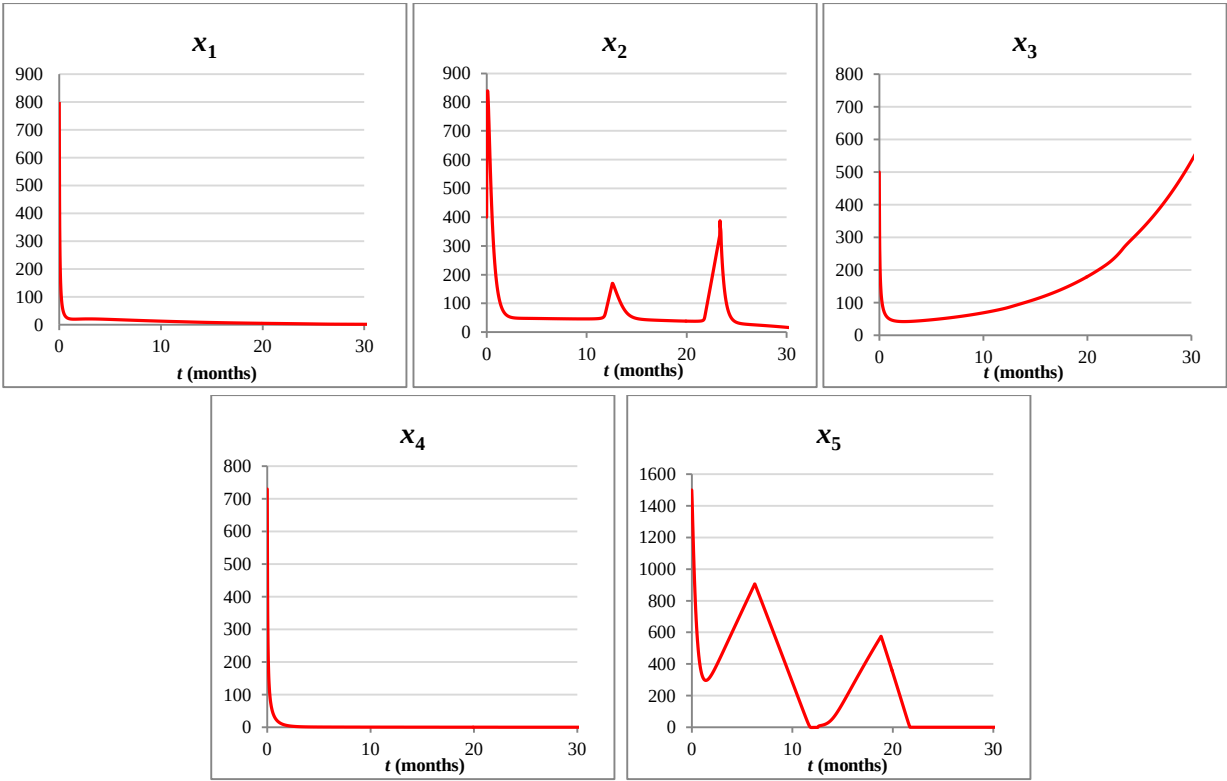
In this scenario, the drug input is continuous for 6 months and off for another 6 months until HAART is discontinued. Figure 4 presents an unsuccessful HAART therapy for a hypothetical AIDS patient with the patho-physiological parametric configuration P_4 in Table 4. In this HAART scenario, the plasma HIV-1 virions (x_3) completely overwhelmed the non-infected $CD4^+$ T helper cells (x_1) and the HIV-1 specific $CD8^+$ cytotoxic T cells (x_4). The HIV-1 infected $CD4^+$ T cells exhibit periodic dynamics and the prognosis for the hypothetical patient is unwholesome (see Nani and Jin [15, 16]).

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Table 4 Hypothetical AIDS Patient Parametric Configuration P_4

$S_1 = 400 \text{ /day/}\mu\text{l}$ $a_1 = 0.09 \text{ /day/cell/}\mu\text{l}$ $b_1 = 0.01 \text{ /cell/}\mu\text{l}$ $\alpha_1 = 0.5 \text{ /day/virion/}\mu\text{l}$ $k_1 = 0.0005 \text{ /day/}\mu\text{l}$ $q_1 = 0.00045 \text{ /day/}\mu\text{l/cell}$ $e_{10} = 0.0025 \text{ cells/day/}\mu\text{l}$ $x_{10} = 800 \text{ cells/}\mu\text{l}$	$S_2 = 800 \text{ /day/}\mu\text{l}$ $a_2 = 0.03 \text{ /day/cell/}\mu\text{l}$ $b_2 = 0.004 \text{ /cell/}\mu\text{l}$ $\alpha_2 = 0.5 \text{ /day/virion/}\mu\text{l}$ $k_2 = 0.005 \text{ /day/}\mu\text{l}$ $q_2 = 0.00001 \text{ /day/}\mu\text{l/cell}$ $\beta_1 = 1.5 \text{ virions/CD4}^+ \text{ /day}$ $K_1 = 0.0001 \text{ /day/}\mu\text{l}$ $e_{20} = 0.0005 \text{ cells/day/}\mu\text{l}$ $\xi_2 = 0.85$ $x_{20} = 400 \text{ cells/}\mu\text{l}$	$S_3 = 10 \text{ /day/}\mu\text{l}$ $\beta_2 = 0.0015 \text{ virions/CD4}^+ \text{ /day/}\mu\text{l}$ $\beta_3 = 1.05 \text{ virions/CD4}^+ \text{ /day}$ $\alpha_3 = 0.027 \text{ /day/virion/}\mu\text{l}$ $k_3 = 0.0001 \text{ /day}$ $e_{30} = 0.0001 \text{ /day}$ $\eta_1 = 0.25$ $\xi_3 = 0.001$ $x_{30} = 500 \text{ cells/}\mu\text{l}$	$S_4 = 10 \text{ /day/}\mu\text{l}$ $a_4 = 0.35 \text{ /day/cell/}\mu\text{l}$ $b_4 = 0.01 \text{ /cell/}\mu\text{l}$ $K_2 = 0.0024 \text{ /day/}\mu\text{l}$ $k_4 = 0.08 \text{ /day/}\mu\text{l}$ $e_{40} = 0.0002 \text{ cells/day/}\mu\text{l}$ $\eta_2 = 0.45$ $x_{40} = 730 \text{ cells/}\mu\text{l}$	$D = 3000 \text{ units}$ $\sigma = 0.5 \text{ mg/day}$ $\sigma_2 = 30 \text{ mg/day}$ $\sigma_3 = 5 \text{ mg/day}$ $\lambda_0 = 5 \text{ mg/L}$ $\lambda_2 = 10 \text{ mg/L}$ $\lambda_3 = 0.025 \text{ mg/L}$ $x_{50} = 1500 \text{ cells/}\mu\text{l}$ $n = 5$
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Figure 4 Simulation results using parametric configuration P_4

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8. Summary, Discussion and Future Work

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The current paper is elaborate and quantitative attempt to construct medically applicable mathematic models and derive criteria for efficacious HAART protocol for an AIDS patient. The mathematical equations presented in Section 3 are a generalization of the models by Perelson et al[3], Wodarz and Nowak [5], and Tan et al. [23], and many other authors by incorporating more clinically relevant parameters of HIV-1 patho-physiodynamics. In particular, interleukin-2 activation of both $CD4^+$ T cells and $CD8^+$ T cells are implicitly incorporated into the model. In this paper, it has been demonstrated that the parameters (a_1, b_1) and (a_4, b_4) play a significant role in determining

the efficacious outcomes of HAART. Clearly, the clinically desirable outcomes are the rest points E_4 and E_3 . The criteria for the existence of E_4 and E_3 are listed respectively in Theorem 5.1, and Theorem 5.4. These theorems give the conditions under which both E_4 and E_3 can be temporarily or transiently attained. The criteria for E_4 and E_3 to become global attractors are listed in Theorem 6.1 and Theorem 6.2. These theorems, expressed in terms of simple clinically attainable and measurable parameters, give the sufficient conditions for the cure of AIDS. It will be emphasized that there exist other therapeutic criteria but these are intractable and extremely arduous to achieve in a clinical setting.

One essential feature of this research is that the HAART protocol is implemented by using the constant continuous intravenous infusion or constant continuous transdermal infusion of the drug. As such, the criteria derived in this paper are applies to these settings. The mathematical model for intermittent caplet or matrix tablet per oral drug administration can be derived using the non-autonomous version of the model equations involving the drug input function $f(t)$ discussed by Nani and Jin in [7].

The scenarios for clinical failure during HAART due to extreme drug toxicity are represented by the rest points E_1 and E_5 . The criteria for these therapeutic outcomes are described by Theorem 5.3 and Theorem 5.2, respectively.

The future work will involve the construction of mathematical models which will describe an AIDS therapy using HAART in addition to ACI (Active Cellular Immunotherapy) involving interleukin-2. Also, in the future, the mathematical model for HAART will include the roles of mutations such as the delta32 CCR5 on therapeutic outcomes.

References

- [1] Hess C. et al., HIV-1 specific CD8⁺ T cells with an effector phenotype and control of viral replication, *Lancet* 362, 2004:863-866.
- [2] Pantaleo G. and Fauci AS, New concepts in the immunopathogenesis of HIV infection, *Annual Review of Immunology*, 13, 1995:487-512.
- [3] Perelson AS et al., Decay characteristics of HIV-1 infected compartments during combination therapy, *Nature*, vol. 387, 1997:188-191.
- [4] Nowak MA, Bonhoeffer S., Shaw GM, May RM, Anti-viral drug treatment: dynamics of resistance of free virus and infected cell population, *J. Theor. Biol.* 184, 1997:203-217.
- [5] Wodarz D., M.A. Nowak, Specific therapy regimes could lead to long-term immunological control of HIV, *Proc. National Acad. Sci. USA*, 96, 1999:14464-14469.
- [6] Ye P., Kourtis AP, and Kirschner DE, Reconstitution of thymic function in HIV-1 patients treated with highly active antiretroviral therapy, *Clinical Immunology*, vol. 106, 2003:95-105.
- [7] Nani F. and Jin M., Computer Simulation of a Mathematical Model of HAART Therapy for HIV-1 AIDS, in *Proceedings of the International Conference on BioMedical Engineering and Informatics (BMEI'11)*, Shanghai, China, October 2011
- [8] Lowe SH, J.M. Prins, J.M. Lange, Anti-retroviral therapy in previously untreated adults infected with the human immunodeficiency virus type 1: established and potential determinants of virological outcome, *Neth. J. Med.*, 62, 2004:424-440.
- [9] Doepel LK, International HIV/AIDS trial finds continuous antiretroviral therapy superior to episodic Therapy, *NIH News*, National Institute of Health, Jan 18 (2006) Available from <http://www.nih.gov/news/pr/jan2006/niald-18.htm>
- [10] Bajaria, SH, Webb G, Kirschner ED, Predicting differential responses to structured treatment interruptions during HAART, *Bulletin of Mathematical Biology*, 66, 2004:1093–1118.
- [11] Caetano MAL, Yoneyama T, Short and long period optimization of drug doses in the treatment of AIDS, *Anais de Academia Brasileira de Ciências*, September año/vol 74, número 003, 2002:379-392.
- [12] Jain S, Tiwary AK, Jain NK, Transdermal delivery of an anti-HIV agent using elastic liposomes: mechanism of action, *Current Drug Delivery*, vol. 3(2), 2006:157-166.

- 882 [13] Jin X. et al., An antigenic threshold for maintaining human immunodeficiency virus type 1-specific
883 cytotoxic T lymphocytes, *Mol. Med.* 6, 2000:803-809.
- 884 [14] Lisziewicz J. and Lori F., Structured treatment interruptions in HIV/AIDS therapy, *Microbes and Infection* 4,
885 2002:207-214.
- 886 [15] Nani F. and Jin M., Criteria for Annihilation of HIV-1 During HAART Therapy, *Proceedings of the*
887 *International Conference on Bioinformatics and Computational Biology 2011 (BIOCOMP'11)*, Las Vegas,
888 NV, July 2011
- 889 [16] Nani F. and Jin M., Theoretical Analysis and Simulation of Acute and Chronic Phase HIV-1 Dynamics,
890 *British Journal of Mathematics & Computer Science*, 4(11), 2014:1450-1479.
- 891 [17] Hattaf K. and Yousfi N., Dynamics of HIV infection model with therapy and cure rate, *International Journal*
892 *of Tomography and Statistics*, 16 (W11), 2011:74-80.
- 893 [18] Pomerantz RJ, Reservoirs of Human immunodeficiency virus Type 1: the main obstacles to viral eradication,
894 *Clinical Infectious Diseases*, 34, 2002:91-97.
- 895 [19] Rong L. and Perelson A., Modeling latency infected cell activation: viral and latent reservoir persistence,
896 and viral blips in HIV-infected patients on potent therapy, *PLoS Computational Biology*, 5(10), Oct 2009:
897 e1000533.
- 898 [20] Kim H. and Perelson A., Viral and latent reservoir persistence in HIV-1 infected patients on therapy, *PLoS*
899 *Computational Biology*, 2(10), Oct 2006:e135.
- 900 [21] Sedaghat AR, Siliciano RF, and Wilke CO, Low-level HIV-1 replication and the dynamics of the resting
901 CD4+ T cells reservoir for HIV-1 in the setting of HAART, *BMC Infectious Diseases*. 2008, 8:2.
- 902 [22] Stengel RF, Mutation and control of the human immunodeficiency virus, *Mathematical Biosciences*, vol.
903 231, 2008:93-102.
- 904 [23] Tan WY and Xiang Z., Some state space models of HIV pathogenesis under treatment by anti-viral drugs in
905 HIV-infected individuals, *Mathematical Biosciences*, 156, 1999:69-94.
- 906 [24] Zaric GS, Bayoumi AM, Brandean ML, and Owens DK, Effects of protease inhibitors on the spread of HIV
907 strains, a simulation study, *Simulation*, 1998:262-275.
- 908 [25] Hattaf K. and Yousfi N., Two optimal treatments of HIV infection model, *World Journal of Modelling and*
909 *Simulation*, 8, 2012:27-35.
- 910 [26] Hattaf K. and Yousfi N., Optimal control of a delayed HIV infection model with immune response using an
911 efficient numerical method, *ISRN Biomathematics*, 2012.
- 912 [27] Koot M, Keet PM, Vos A, Goede R, et al., Prognostic value of HIV-1 syncytium-inducing Phenotype for
913 rate of CD4+ cell depletion and prognosis to AIDS., *Ann Intern. Med*, 118(9), 1993:681-688.
- 914 [28] Shutt DC, Jenkins LM, Carolan EJ, Stapelton J., Daniels KJ, Kennedy RC, and Soll DR, T cell syncytia
915 induced by HIV release, *Journal of Cell Science*, 111, 1998:99-109.
- 916 [29] Hsu SB, Ordinary Differential equations with applications, *Series on Applied Mathematics*, Vol. 21, 2nd
917 Edition, World Scientific Press, London, UK, 2013:34-35
- 918 [30] Gantmacher FR, The theory of matrices, Chelsea Publishing Co., New York, NY, 1995:300-308.