

Criteria for Annihilation of HIV-1 During HAART Therapy

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Abstract - HAART therapy of HIV-1 induced AIDS is modeled by a system of non-linear deterministic differential equations. The clinically plausible patho-physiological 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 criteria for the existence of clinically desirable therapeutic outcomes are presented. In particular, the necessary and sufficient conditions for the annihilation of HIV-1 virions are clearly exhibited in terms of the model physiological parameters. Computer simulations are presented illustrating patho-physiodynamics of HIV-1 induced AIDS. In this paper, HAART protocols with constant continuous or periodic transdermal and intravenous drug infusions are used in our mathematical model.

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

1 Introduction

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. As a result of these physiological events, a host of opportunistic bacterial and viral infections overwhelm the HIV-1 positive person [12]. Highly active anti-retroviral therapy (HAART) protocols have been approved as an efficacious treatment of HIV-1 induced AIDS. This 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 [14].

HAART therapy is responsible for the reduction of viral load in $CD4^+$ T cells and production of measurable reconstitution of the patients' immune system [17]. However, HAART protocols have limited therapeutic efficacy due to extreme toxicity, non-compliance, intermittent scheduling, biochemical/clinical drug resistance, short drug half-life and low bio-availability.

Many mathematical models of HAART therapy have been developed in an attempt to demonstrate the existence of efficacious and optimal therapies that will minimize side effects [8, 9, 10, 11, 13, 14, 15, 16]. 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 [18]. Stengel in [14] presented a mathematical model of HIV-1 infection and HAART which demonstrated the efficacy of a mathematically optimal therapy. Using the LQR, Scheme, Caetano and Yoneyama in [2] 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.

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. Several authors investigated the consequences of structured long-term and short-term treatment interruptions during HAART [1, 2, 4, 8]. The current model will discuss these consequences by means of simulations.

The current paper will be divided into five 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 this section. In Section 4, clinically plausible computer simulations will be exhibited. Section 5 will be the summary and discussion of the basic results of the paper.

2 Parameters

The model parameters, constants, and variables are listed 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 metabolic rate constants associated with HAART drug elimination

(σ_i, λ_i) : Michaelis-Menten 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⁺ T₄ helper cells ($i = 1, 2$)

k_i : constant depicting degradation, loss of clonogenicity or “death” ($i = 1, 2, 3, 4$)

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⁺ T₄ cells by CD8⁺ T₈ cytotoxic lymphocytes ($i = 1, 2$)

All the parameters are positive.

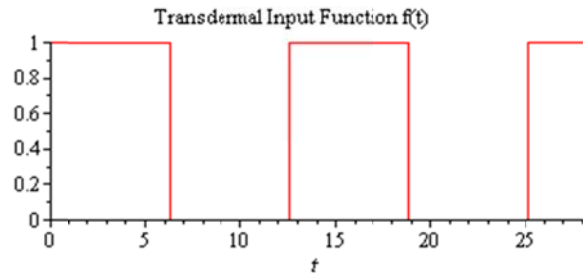
$$\left\{ \begin{array}{l} \dot{x}_1 = S_1 + a_1 x_1^2 e^{-b_1 x_1} - \alpha_1 x_1 x_3 - q_1 x_1 x_2 - k_1 x_1 - e_{10} \\ \dot{x}_2 = S_2 + a_2 x_1 x_2 e^{-b_2 x_1} + \alpha_2 x_1 x_3 - q_2 x_1 x_2 - k_2 x_2 - \beta_1 x_3 \\ \quad - K_1 x_2 x_4 - e_{20} - \frac{\xi_2 \sigma_2 x_2 x_5}{\lambda_2 + x_5}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

The model includes the following clinical improvement:

- (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 [6]. 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 $f(t) = \lceil \lceil \sin(5t) \rceil \rceil$ can be depicted by the following plot:



3 Model Equations and Analyses

3.1 Model equations

The HIV-1 patho-physiological dynamics during HAART therapy can be modeled using the following system of non-linear ordinary differential equations:

3.2 Criteria for Annihilation of HIV-1 Virions

In this subsection, the necessary and sufficient criteria will be presented for the cure of an AIDS patient through

annihilation of the HIV-1 infected CD4⁺ T cells and plasma viremia. This criterion is derived for the scenario for which $f(t) \equiv 1$, which corresponds to constant continuous application of HAART drug either by transdermal delivery or intravenous infusion.

The desired physiological steady states during HAART therapy, are $E_1 = [\hat{x}_1, 0, 0, 0, \hat{x}_5]$ and $E_2 = [\bar{x}_1, 0, 0, \bar{x}_4, \bar{x}_5]$. In each of these, the HIV-1 infected CD4⁺ T cells (x_2) and plasma HIV-1 virions (x_3) are annihilated. In particular, $E_2 = [\bar{x}_1, 0, 0, \bar{x}_4, \bar{x}_5]$ is plausibly physiologically easily attainable in an AIDS patient since some HIV-1 specific CD8⁺ (cytotoxic T) cells usually persist during HAART as memory T cells.

Thus the criteria for annihilation of HIV-1 virions will be derived using $E_2 = [\bar{x}_1, 0, 0, \bar{x}_4, \bar{x}_5]$ as a target steady state. In $R_+^{x_1, x_4, x_5} = [x_1, x_4, x_5 \mid x_1 \geq 0, x_4 \geq 0, x_5 \geq 0]$, the model equations reduce to (3.2).

$$\begin{cases} \dot{x}_1 = S_1 + a_1 x_1^2 e^{-b_1 x_1} - k_1 x_1 - e_{10} \\ \dot{x}_4 = S_4 + a_4 x_1 x_4 e^{-b_4 x_1} - k_4 x_4 - e_{40} \\ \dot{x}_5 = Df(t) - \frac{\sigma_0 x_5}{\lambda_0 + x_5} \\ f(t) = 1 \\ x_i(t_0) = x_{i0} \quad \text{for } i = \{1, 4, 5\} \end{cases} \quad (3.2)$$

Consider the Liapnnov functional:

$$V := \sum \frac{1}{2} c_i (x_i - \bar{x}_i)^2 \quad (3.3)$$

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

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

$$\dot{V} = c_1 (x_1 - \bar{x}_1) \dot{x}_1 + c_4 (x_4 - \bar{x}_4) \dot{x}_4 + c_5 (x_5 - \bar{x}_5) \dot{x}_5$$

At a steady state $f(t) = 1$, the following equations hold.

$$\begin{cases} S_1 - e_{10} = k_1 \bar{x}_1 - a_1 \bar{x}_1^2 e^{-b_1 \bar{x}_1} \\ S_4 - e_{40} = k_4 \bar{x}_4 - a_4 \bar{x}_1 \bar{x}_4 e^{-b_4 \bar{x}_1} \\ D = \frac{\sigma_0 \bar{x}_5}{\lambda_0 + \bar{x}_5} \end{cases} \quad (3.4)$$

Thus

$$\begin{aligned} \dot{V} &= c_1 k_1 (x_1 - \bar{x}_1) (\bar{x}_1 - x_1) \\ &\quad + a_1 c_1 (x_1 - \bar{x}_1) [G(\bar{x}_1) - G(x_1)] \\ &\quad + c_4 k_4 (x_4 - \bar{x}_4) (\bar{x}_4 - x_4) \\ &\quad + a_4 c_4 (x_4 - \bar{x}_4) [F(\bar{x}_1, \bar{x}_4) - F(x_1, x_4)] \\ &\quad + c_5 \sigma_0 [L(\bar{x}_5) - L(x_5)] \end{aligned}$$

where

$$\begin{aligned} G(x_1) &= x_1^2 e^{-b_1 x_1} \\ F(x_1, x_4) &= x_1 x_4 e^{-b_4 x_1} \\ L(x_5) &= \frac{x_5}{\lambda_0 + x_5} \end{aligned} \quad (3.5)$$

such that G, F, L are continuous, differentiable, and have bounded, derivatives.

Let

$$\begin{aligned} u_1 &= x_1 - \bar{x}_1 \\ u_2 &= x_4 - \bar{x}_4 \\ u_3 &= x_5 - \bar{x}_5 \end{aligned} \quad (3.6)$$

and let

$$X = \begin{bmatrix} u_1 \\ u_2 \\ u_3 \end{bmatrix} \in R_+^3 \quad (3.7)$$

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

$$A = \begin{bmatrix} a_{11} & \frac{1}{2} a_{12} & \frac{1}{2} a_{13} \\ \frac{1}{2} a_{12} & a_{22} & \frac{1}{2} a_{23} \\ \frac{1}{2} a_{13} & \frac{1}{2} a_{23} & \frac{1}{2} a_{33} \end{bmatrix} \quad (3.8)$$

Now

$$\begin{aligned} \dot{V} &:= a_{11} u_1^2 + \frac{1}{2} a_{12} u_1 u_2 + \frac{1}{2} a_{13} u_1 u_3 \\ &\quad + \frac{1}{2} a_{12} u_2 u_1 + a_{22} u_2^2 + \frac{1}{2} a_{23} u_2 u_3 \\ &\quad + \frac{1}{2} a_{13} u_3 u_1 + \frac{1}{2} a_{23} u_3 u_2 + a_{33} u_3^2 \\ &= -c_1 k_1 (x_1 - \bar{x}_1)^2 - a_1 c_1 (x_1 - \bar{x}_1) [G(x_1) - G(\bar{x}_1)] \\ &\quad - c_4 k_4 (x_4 - \bar{x}_4)^2 - a_4 c_4 (x_4 - \bar{x}_4) [F(x_1, x_4) - F(\bar{x}_1, \bar{x}_4)] \\ &\quad - c_5 \sigma_0 (x_5 - \bar{x}_5) [L(x_5) - L(\bar{x}_5)] \end{aligned} \quad (3.9)$$

In particular, the $[a_{ij}]_{3 \times 3}$ are defined as follows:

$$\begin{cases} a_{11} := -[c_1 k_1 + a_1 c_1 \left(\frac{G(x_1) - G(\bar{x}_1)}{x_1 - \bar{x}_1} \right)] \\ a_{12} := -a_4 c_4 \left[\frac{F(x_1, x_4) - F(\bar{x}_1, \bar{x}_4)}{x_4 - \bar{x}_4} \right] = a_{21} \\ a_{13} = a_{31} = 0 \\ a_{22} = -c_4 k_4 \\ a_{23} = a_{32} = 0 \\ a_{33} := -c_5 \sigma_0 \left[\frac{L(x_5) - L(\bar{x}_5)}{x_5 - \bar{x}_5} \right] \end{cases} \quad (3.10)$$

As the flow associated with the model equations approaches $E_2 = [\bar{x}_1, 0, 0, \bar{x}_4, \bar{x}_5]$, the matrix entries $[a_{ij}]_{3 \times 3}$ have the following form:

$$\begin{aligned} a_{11} &\rightarrow -[c_1 k_1 + a_1 c_1 G'(\bar{x}_1)] \\ a_{12} &\rightarrow -a_4 c_4 \frac{\partial}{\partial x_1} [F(\bar{x}_1, \bar{x}_4)] \\ a_{22} &= -c_4 k_4 \\ a_{33} &\rightarrow -c_5 \sigma_0 L'(\bar{x}_5) \end{aligned} \quad (3.11)$$

In particular, it can be shown that

$$\begin{aligned} \frac{\partial}{\partial x_1} F(\bar{x}_1, \bar{x}_4) \Big|_{x_1 = \bar{x}_1} &= \bar{x}_4 e^{-b_4 \bar{x}_1} (1 - \bar{x}_1 b_4) \\ G'(\bar{x}_1) &= \bar{x}_1 e^{-b_1 \bar{x}_1} (2 - \bar{x}_1 b_1) \\ L'(\bar{x}_5) &= \frac{\lambda_0}{(\lambda_0 + \bar{x}_5)^2} > 0 \end{aligned} \quad (3.12)$$

Thus

$$F_{x_1}(\bar{x}_1, \bar{x}_4) = \begin{cases} > 0 \text{ if } \bar{x}_1 < \frac{1}{b_4} \\ = 0 \text{ if } \bar{x}_1 = \frac{1}{b_4} \\ < 0 \text{ if } \bar{x}_1 > \frac{1}{b_4} \end{cases} \quad (3.13)$$

Similarly,

$$G'(\bar{x}_1) = \begin{cases} > 0 \text{ if } \bar{x}_1 < \frac{2}{b_1} \\ = 0 \text{ if } \bar{x}_1 = \frac{2}{b_1} \\ < 0 \text{ if } \bar{x}_1 > \frac{2}{b_1} \end{cases} \quad (3.14)$$

Since $F(x_1, x_4)$, $G(x_1)$, and $L(x_5)$ are continuous and differentiable functions in each variable, the matrix entries a_{11} , a_{12} , a_{22} , a_{33} exist and remain bounded in the space: $R_+^{x_1 x_4 x_5}$, as $[x_1, 0, 0, x_4, x_5] \rightarrow [\bar{x}_1, 0, 0, \bar{x}_4, \bar{x}_5]$.

Hence, \bar{V} can be written in the form

$$\bar{V} = X^T A X$$

where

$$A = \begin{bmatrix} a_{11} & \frac{1}{2} a_{12} & 0 \\ \frac{1}{2} a_{12} & a_{22} & 0 \\ 0 & 0 & a_{33} \end{bmatrix} \quad (3.15)$$

The matrix A is negative definite if the following criteria hold:

$$A_1 = \det a_{11} < 0 \quad \text{or} \quad a_{11} < 0$$

$$A_2 = \det \begin{vmatrix} a_{11} & \frac{1}{2} a_{12} \\ \frac{1}{2} a_{12} & a_{22} \end{vmatrix} > 0 \quad \text{or} \quad a_{11} a_{22} - \frac{1}{4} (a_{12})^2 > 0$$

$$A_3 = \det \begin{vmatrix} a_{11} & \frac{1}{2} a_{12} & 0 \\ \frac{1}{2} a_{12} & a_{22} & 0 \\ 0 & 0 & a_{33} \end{vmatrix} < 0 \quad \text{or} \quad a_{33} [a_{11} a_{22} - \frac{1}{4} (a_{12})^2] < 0 \quad (3.16)$$

Theorem 3.1: Suppose

$$(i) \quad G'(\bar{x}_1) > 0$$

$$(ii) \quad c_4 k_4 [c_1 k_1 + a_1 G'(\bar{x}_1)] < \frac{1}{4} [a_4 c_4 F_{x_1}(\bar{x}_1, \bar{x}_4)]^2$$

Then the physiological steady state $E_2 = [\bar{x}_1, 0, 0, \bar{x}_4, \bar{x}_5]$ is globally asymptotically stable, and hence the HIV-1 virions are annihilated in the $CD4^+$ T cells and the blood plasma. Thus $E_2 = [\bar{x}_1, 0, 0, \bar{x}_4, \bar{x}_5]$ is a global attractor.

Proof. The result follows immediately from the negative definite criteria on A_1 , A_2 , and A_3 . It is noted that $a_{33} < 0$, and $a_{11} < 0$ if $G'(\bar{x}_1) > 0$. If a_{11} and a_{33} are both negative, then the restriction on A_3 is satisfied if condition (ii) of the theorem holds. Thus \bar{V} is negative definite and the theorem holds. \square

4 Simulation results and discussion

In this section, the simulation results are presented. The computer programming code for the simulations was written in C++. Transdermal delivery was simulated as a rectangular periodic function $f(t)$ such that $f := |\text{ceil}(\sin(5t))|$.

In particular, the drug input is continuous for 6 months and off for another 6 months until HAART is discontinued. Figure 1 presents an unsuccessful HAART therapy for a hypothetical AIDS patient with the patho-physiological parametric configuration P_1 in Table 1. 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 (x_2) exhibit periodic dynamics and the prognosis for the hypothetical patient is unwholesome.

Figure 2 depicts a successful HAART outcome in which the plasma HIV-1 virions (x_3) are annihilated using the hypothetical patient parameter configuration P_2 in Table 2. Also the HIV-1 infected $CD4^+$ T helper cells (x_2) are

drastically reduced to below 100 cells/ μ l. The non-infected $CD4^+$ T helper cells (x_1) are repopulated in this simulation. This outcome has been clinically observed and discussed by Ye et al. [17].

TABLE 1. Hypothetical AIDS Patient Parametric Configuration P_1

$S_1 = 400$ /day/ μ l $a_1 = 0.09$ /day/cell/ μ l $b_1 = 0.01$ /cell/ μ l $\alpha_1 = 0.5$ /day/virion/ μ l $k_1 = 0.0005$ /day/ μ l $q_1 =$ 0.00045 /day/ μ l/cell $e_{10} =$ 0.0025 cells/day/ μ l $x_{10} = 800$ cells/ μ l	$S_2 = 800$ /day/ μ l $a_2 = 0.03$ /day/cell/ μ l $b_2 = 0.004$ /cell/ μ l $\alpha_2 = 0.5$ /day/virion/ μ l $k_2 = 0.005$ /day/ μ l $q_2 = 0.00001$ /day/ μ l/cell $\beta_1 = 1.5$ virions/ $CD4^+$ /day $K_1 = 0.0001$ /day/ μ l $e_{20} = 0.0005$ cells/day/ μ l $\xi_2 = 0.85$ $x_{20} = 400$ cells/ μ l	$S_3 = 10$ /day/ μ l $\beta_2 =$ 0.0015 virions/ $CD4^+$ /day/ μ l $\beta_3 = 1.05$ virions/ $CD4^+$ /day $\alpha_3 = 0.027$ /day/virion/ μ l $k_3 = 0.0001$ /day $e_{30} = 0.0001$ /day $\eta_1 = 0.25$ $\xi_3 = 0.001$ $x_{30} = 500$ cells/ μ l	$S_4 = 10$ /day/ μ l $a_4 = 0.35$ /day/cell/ μ l $b_4 = 0.01$ /cell/ μ l $K_2 = 0.0024$ /day/ μ l $k_4 = 0.08$ /day/ μ l $e_{40} = 0.0002$ cells/day/ μ l $\eta_2 = 0.45$ $x_{40} = 730$ cells/ μ l	$D = 3000$ units $\sigma_0 = 0.5$ mg/day $\sigma_2 = 30$ mg/day $\sigma_3 = 5$ mg/day $\lambda_0 = 5$ mg/L $\lambda_2 = 10$ mg/L $\lambda_3 = 0.025$ mg/L $x_{50} = 1500$ cells/ μ l $n = 5$
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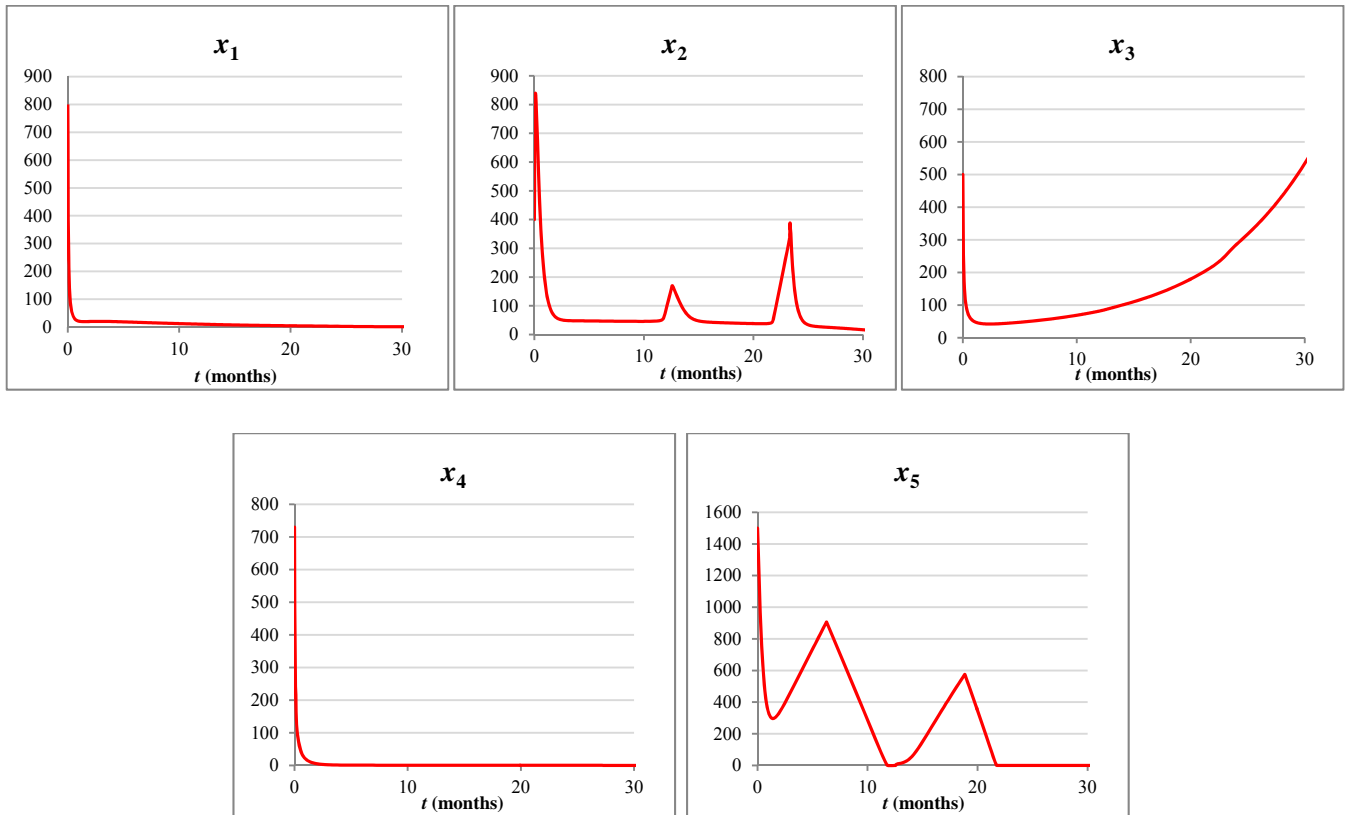


Figure 1 Simulation results using parametric configuration P_1

TABLE 2. Hypothetical AIDS Patient Parametric Configuration P_2

$S_1 = 800 \text{ /day/}\mu\text{l}$ $a_1 = 0.15 \text{ /day/cell/}\mu\text{l}$ $b_1 = 0.01 \text{ /cell/}\mu\text{l}$ $\alpha_1 = 0.5 \text{ /day/virion/}\mu\text{l}$ $k_1 = 0.0005 \text{ /day/}\mu\text{l}$ $q_1 = 0.00045 \text{ /day/}\mu\text{l/cell}$ $e_{10} = 0.0025 \text{ cells/day/}\mu\text{l}$ $x_{10} = 500 \text{ cells/}\mu\text{l}$	$S_2 = 800 \text{ /day/}\mu\text{l}$ $a_2 = 0.03 \text{ /day/cell/}\mu\text{l}$ $b_2 = 0.004 \text{ /cell/}\mu\text{l}$ $\alpha_2 = 0.5 \text{ /day/virion/}\mu\text{l}$ $k_2 = 0.005 \text{ /day/}\mu\text{l}$ $q_2 = 0.00001 \text{ /day/}\mu\text{l/cell}$ $\beta_1 = 1.5 \text{ virions/CD4}^+ \text{ /day}$ $K_1 = 0.0001 \text{ /day/}\mu\text{l}$ $e_{20} = 0.0005 \text{ cells/day/}\mu\text{l}$ $\xi_2 = 0.85$ $x_{20} = 400 \text{ cells/}\mu\text{l}$	$S_3 = 10 \text{ /day/}\mu\text{l}$ $\beta_2 = 0.0015$ $\text{virions/CD4}^+ \text{ /day/}\mu\text{l}$ $\beta_3 = 1.05 \text{ virions/CD4}^+ \text{ /day}$ $\alpha_3 = 0.027 \text{ /day/virion/}\mu\text{l}$ $k_3 = 0.0001 \text{ /day}$ $e_{30} = 0.0001 \text{ /day}$ $\eta_1 = 0.25$ $\xi_3 = 0.001$ $x_{30} = 500 \text{ cells/}\mu\text{l}$	$S_4 = 10 \text{ /day/}\mu\text{l}$ $a_4 = 0.35 \text{ /day/cell/}\mu\text{l}$ $b_4 = 0.01 \text{ /cell/}\mu\text{l}$ $K_2 = 0.0024 \text{ /day/}\mu\text{l}$ $k_4 = 0.08 \text{ /day/}\mu\text{l}$ $e_{40} = 0.0002 \text{ cells/day/}\mu\text{l}$ $\eta_2 = 0.45$ $x_{40} = 730 \text{ cells/}\mu\text{l}$	$D = 4000 \text{ units}$ $\sigma_0 = 0.5 \text{ mg/day}$ $\sigma_2 = 30 \text{ mg/day}$ $\sigma_3 = 5 \text{ mg/day}$ $\lambda_0 = 5 \text{ mg/L}$ $\lambda_2 = 10 \text{ mg/L}$ $\lambda_3 = 0.025 \text{ mg/L}$ $x_{50} = 1500 \text{ cells/}\mu\text{l}$ $n = 5$
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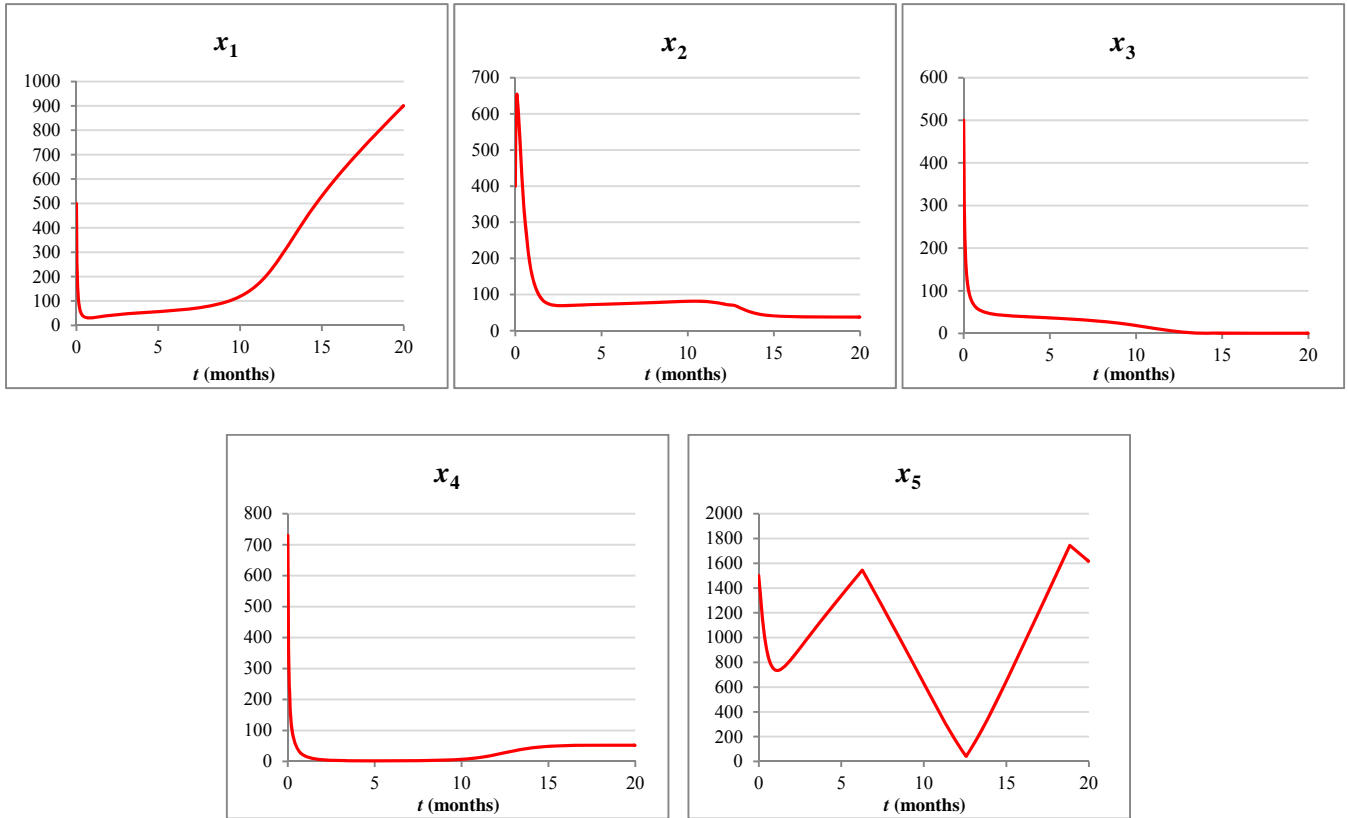


Figure 2 Simulation results using parametric configuration P_2

5 Summarizing remarks

In this research, we presented a mathematical model which describes the patho-physiological dynamics of HIV-1 induced AIDS during HAART therapy. This model incorporates several physiological aspects of HIV-1 patho-physiology. These include the recruitment of virions from latent HIV-1 reservoirs (S_3) such as macrophages, microglial cells and lymphoid tissues. The model also includes autocrine and paracrine activation of $CD4^+$ and

$CD8^+$ T cells. Michaelis-Menten pharmacokinetics is used to describe the dynamics of the HAART drug in the AIDS patient. The simulations used a blend of estimated and literature based [3, 10, 13] hypothetical patient parametric configurations. The simulation results depict respectively scenarios for efficacious and non-efficacious HAART therapeutic outcomes.

The necessary conditions for existence of a plausible physiological outcome $E_2 = [\bar{x}_1, 0, 0, \bar{x}_4, \bar{x}_5]$ are

$$\begin{cases} S_1 + a_1 \bar{x}_1^2 e^{-b_1 \bar{x}_1} - k_1 \bar{x}_1 - e_{10} = 0 \\ S_2 - e_{20} = 0 \\ S_4 + a_4 \bar{x}_1 \bar{x}_4 e^{-b_4 \bar{x}_1} - k_4 \bar{x}_4 - e_{40} = 0 \\ D - \frac{\sigma_0 \bar{x}_5}{\lambda_0 + \bar{x}_5} = 0 \end{cases} \quad (5.1)$$

The sufficient conditions for successful HAART therapy and cure of AIDS are

$$\begin{cases} G'(\bar{x}_1) > 0 \\ c_4 k_4 [c_1 k_1 + a_1 G'(\bar{x}_1)] < \frac{1}{4} [a_4 c_4 F_{x_1}(\bar{x}_1, \bar{x}_4)]^2 \end{cases} \quad (5.2)$$

It is possible to refine (5.2) to

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

where K_m denotes the Michaelis-Menten constant. In a future publication, more necessary and sufficient criteria for the cure of HIV-1 induced AIDS will be presented and discussed.

6 References

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