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Frank Nani
Fayetteville State University, fnani@uncfsu.edu

Mingxian Jin
Fayetteville State University, mjin@uncfsu.edu

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Frank Nani and Mingxian Jin
Department of Mathematics and Computer Science
Fayetteville State University, Fayetteville, NC 28301, USA

Abstract –*The techniques of mathematical modeling and investigative computer simulations are used to study the qualitative aspects of the patho-physiodynamics of HIV-1 associated Kaposi sarcoma (KS) during Highly Active Anti-Retroviral Therapy (HAART) of AIDS. Using a system of non-linear deterministic differential equations, the model incorporates the biologically measurable and clinically relevant immunological interactions and parameters. In particular, the computer simulations elucidate the role of CD8$^+$ T lymphocyte in the annihilation and persistence of Kaposi sarcoma during HAART.*

Keywords: Kaposi sarcoma, mathematical modeling, HAART efficacy, computer simulations, persistence of Kaposi Sarcoma

1 Introduction

Human Herpes Virus 8 (HHV8) acts in association with HIV-1 to induce lympho-proliferation and Kaposi sarcoma (KS) in AIDS patients. The clinical and histo-pathological aspects of KS have been documented by Kemény et al. [3], Lesbordes et al. [5], and Zhu et al. [11].

The role of CD8$^+$ T lymphocytes in regulating the growth of KS has been investigated by Li et al. [6] and Stebbing et al [8]. The use of adoptive immunotherapy with activated autologous CD8$^+$ T cells with interleukin-2 infusion in treatment of AIDS was described in a paper by Klimas et al. [4], Touloumi et al. [9], and Urassa et al. [10]. The patho-physio-dynamics of KS during HAART has been clinically investigated by Bihl et al. [1], and Dupont et al. [2].

In the current research, we shall present a mathematical model of the patho-physio-dynamics of KS associated with AIDS during HAART. This paper is extension of our earlier mathematical model on HIV-1 AIDS dynamics during latency phase [7]. Investigative computer simulations will be used to elucidate the effect of adoptive transfer of CD8$^+$ T cells on Kaposi sarcoma dynamics during HAART. This research is one of the major attempts to construct a clinically plausible mathematical model which incorporates HAART therapy, HIV-1 induced AIDS dynamics, and Kaposi sarcoma.

2 Parameters

In this section, the model parameters, constants, and variables are presented as modified from [7].

x_1: the number density of non-HIV-1-infected CD4$^+$ helper T-lymphocytes per unit volume at any time t

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

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

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

x_5: the concentration of drug molecules of the HAART treatment protocol at any time t

x_6:The number of Kaposi sarcoma cancer cells in the AIDS patient at any time t during HAART

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

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

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

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

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)

α_i: constant associated with HIV-1 infection of CD4$^+$ T_4 helper cells (i =1, 2, 3)

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

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

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

η_i: constant depicting the rate of which HIV-1 virions incapacitate the CD8$^+$ T_8 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)

(σ_4, λ_4): Michaelis-Menten metabolic rate constants associated with cytolytic action of $CD8^+$ against Kaposi Sarcoma cancer cells

γ_4: constant depicting the cytolytic efficacy of $CD8^+$ T cells against Kaposi sarcoma cancer cells

ξ_i: cytotoxic coefficient where $0 \le \xi_i \le 1$ (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)

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

c_i: kinetic constants depicting logistic tumor growth for Kaposi sarcoma

3 Model Equations

The following system of non-linear deterministic ordinary differential equations models the patho-physiological dynamics of HIV-1 induced AIDS virions and associated Kaposi sarcoma cancer cells, $CD4^+$ (infected and non-infected) T cells, and $CD8^+$ T cells during HAART therapy.

$$
\begin{cases}
\dot{x}_1 = S_1 + a_1 x_1^2 e^{-b_1 x_1} - \alpha_1 x_1 x_3 - q_1 x_1 x_2 - k_1 x_1 - e_{10} \\
\dot{x}_2 = S_2 + a_2 x_1 x_2 e^{-b_2 x_1} + \alpha_2 x_1 x_3 - q_2 x_1 x_2 - k_2 x_2 - \beta_1 x_3 \\
\qquad - K_1 x_2 x_4 - e_{20} - \dfrac{\xi_2 \sigma_2 x_2 x_5}{\lambda_2 + x_5} \\
\dot{x}_3 = S_3 + \beta_2 x_2 x_3 + \beta_3 x_3 - \alpha_3 x_1 x_3 - \eta_1 x_3 x_4 - k_3 x_3 - e_{30} \\
\qquad - \dfrac{\xi_3 \sigma_3 x_3 x_5}{\lambda_3 + x_5} \\
\dot{x}_4 = S_4 + a_4 x_1 x_4 e^{-b_4 x_1} - K_2 x_2 x_4 - \eta_2 x_3 x_4 - \gamma_4 \dfrac{\sigma_4 x_4 x_6}{\lambda_4 + x_4} \\
\qquad - k_4 x_4 - e_{40} \\
\dot{x}_5 = D\left|\lceil \sin nt \rceil\right| - \dfrac{\sigma_0 x_5}{\lambda_0 + x_5} - \dfrac{\sigma_2 x_2 x_5}{\lambda_2 + x_5} - \dfrac{\sigma_3 x_3 x_5}{\lambda_3 + x_5} \\
\dot{x}_6 = c_1 x_6 - c_2 x_5^2 - \dfrac{\sigma_4 x_4 x_6}{\lambda_4 + x_4} \\
x_i(t_0) = x_{i0} \quad for \quad i = \{1, 2, 3, 4, 5, 6\}
\end{cases}
\tag{3.1}
$$

4 Simulation results and discussion

A brief summary of the simulation results will be presented in this section. Figure 1 and Figure 2 correspond respectively to hypothetical HIV-1 KS patient's physiological parametric configurations P_1 (Table 1) and P_2 (Table 2).

(i) Hypothetical clinical case #1[Figure 1, P_1]:
It is observed that HAART treatment successfully annihilates the HIV-1 virions in the blood plasma and reduces the number density of HIV-1 infected $CD4^+$ T cells, whereas the non-infected $CD4^+$ T cells proliferate to clinically efficacious levels. On the other hand, the HIV-1 specific $CD8^+$ T cells are eliminated and consequently the Kaposi sarcoma proliferates out of control.

(ii) Hypothetical clinical case #2 [Figure 1, P_1']:
In this scenario, the physiological parametric configuration is the same as that of P_1 except that there is an adoptive transfer of 2000 units of ex-vivo interlenkin-2 activated $CD8^+$ cytotoxic T cells. In P_1', the S_4 value is now assigned to a value of 2000 instead of 10 as in P_1. The therapeutic outcome is clinically efficacious because the Kaposi sarcoma is annihilated.

(iii) Hypothetical clinical case #3[Figure 2, P_2]:
This scenario discusses the effect of HIV-1 latent viral reservoirs on the treatment outcome. In particular, S_3 is set to a value of 1000, depicting the influx of 1000 HIV-1 virions from reservoirs such as microglial cells, macrophages and dendritic cells. It is observed that even though the HAART dose rate D is increased to 4000 units, there is a subsequent therapeutic failure because the non-infected $CD4^+$ cell number plummets as HIV-1 virions overwhelm the immune system. On the other hand, the adoptive transferred 2000 units of $CD8^+$ cells are able to keep the Kaposi sarcoma cancer cells under the clinically detectable level of 1000 cells.

(iv) Hypothetical clinical case #4 [Figure 2, P_2']:
The physiological parametric configuration is the same as that of P_2 except for the fact that the HAART drug dose rate D is increased to 5000 units, and the non-infected $CD4^+$ T cells (x_1) are given an extra boost of interleukin-2 (IL-2) dose and as such the value of a1 is now 0.45. The outcome is clinically efficacious because the plasma HIV-1 virions (x_3), the HIV-1 infected $CD4^+$ T cells (x_2), and the KS cancer cells are kept under the clinically detectable level of 1000 cells, whereas the non-HIV-1 infected $CD4^+$ T cells (x_1) repopulate to clinically efficacious level.

5 Summary

Our research can be summarized in the following statements:

(i) It is possible for HAART therapy to annihilate the HIV virions without necessarily eliminating KS.

(ii) Adoptive transfer of $CD8^+$ T cells at a predetermined dose rate can annihilate KS cancer cells.

(iii) It will require both HAART and adoptive transfer $CD8^+$ T cells incubated with IL-2 to decimate both HIV-1 virions and the Kaposi sarcoma cancer cells.

TABLE 1. Hypothetical AIDS Patient Parametric Configuration P_1

$S_1 = 800$ /day/μl $a_1 = 0.15$ /day/cell/μl $b_1 = 0.01$ /cell/μl $\alpha_1 =$ 0.5/day/virions/μl $k_1 = 0.0005$/day/μl $q_1 =$ 0.00045/day/μl/cell $e_{10} =$ 0.0025 cells/day/μl $x_{10} = 500$ cells/μl	$S_2 = 800$ /day/μl $a_2 = 0.11$ /day/cell/μl $b_2 = 0.004$/cell/μl $\alpha_2 = 0.5$/day/virions/μl $k_2 = 0.005$/day/μl $q_2 = 0.00001$/day/μl/cell $\beta_1 = 1.5$ virions/$CD4^+$/day $K_1 = 0.0001$/day/μl $e_{20} = 0.0005$ cells/day/μl $x_{20} = 400$ cells/μl	$S_3 = 10$ /day/μl $\beta_2 =$ 0.0085virions/$CD4^+$/day/μl $\beta_3 = 2.75$ virions/$CD4^+$/day $\alpha_3 = 0.027$ /day/virions/μl $k_3 = 0.0001$/day $e_{30} = 0.0001$ /day $\eta_1 = 0.055$ $\xi_2 = 0.85$ $\xi_3 = 0.0001$ $x_{30} = 1000$ virions/μl	$S_4 = 10$ /day/μl $a_4 = 0.35$ /day/cell/μl $b_4 = 0.01$/cell/μl $K_2 = 0.0024$ /day/μl $k_4 = 0.08$/day/μl $e_{40} = 0.0002$ cells/day/μl $\eta_2 = 0.055$ $\gamma_4 = 0.15$ $x_{40} = 1500$ cells/μl	D = 4000 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* $\lambda_3 = 0.015$ *mg/L* $x_{50} = 1500$ cells/μl $n = 5$	$c_1 = 6.405$ $c_2 = 0.00075$ $\sigma_4 = 7$ *mg*/day $\lambda_4 = 5.5$ *mg/L* $x_{60} =$ 2500cells

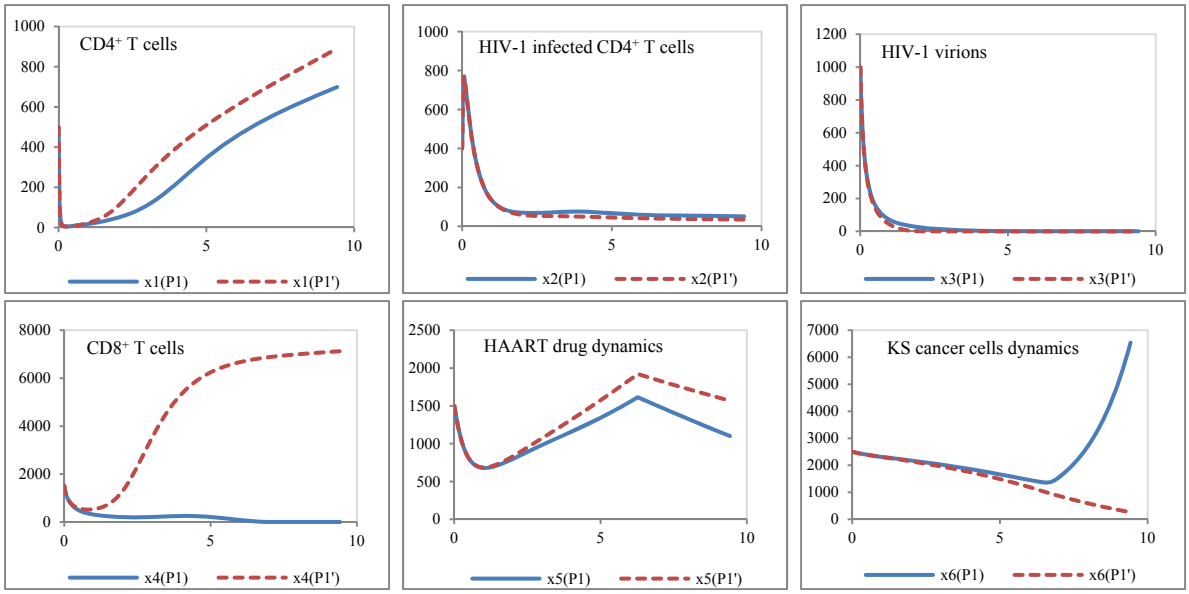

Figure 1 Simulation results using parametric configurations P_1 vs. P_1'
(P_1' is the modified P_1: same as P_1 except $S_4 = 2000$. The time axis unit is months.)

TABLE 2. Hypothetical AIDS Patient Parametric Configuration P_2

$S_1 = 800$ /day/μl $a_1 = 0.15$ /day/cell/μl $b_1 = 0.01$ /cell/μl $\alpha_1 =$ 0.5/day/virions/μl $k_1 = 0.0005$/day/μl $q_1 =$ 0.00045/day/μl/cell $e_{10} = 0.0025$ cells/day/μl $x_{10} = 500$ cells/μl	$S_2 = 800$ /day/μl $a_2 = 0.11$ /day/cell/μl $b_2 = 0.004$/cell/μl $\alpha_2 = 0.5$/day/virions/μl $k_2 = 0.005$/day/μl $q_2 = 0.00001$/day/μl/cell $\beta_1 = 1.5$ virons/$CD4^+$/day $K_1 = 0.0001$/day/μl $e_{20} = 0.0005$ cells/day/μl $x_{20} = 400$ cells/μl	$S_3 = 1000$ /day/μl $\beta_2 = 0.0085$ virons/$CD4^+$/day/μl $\beta_3 = 2.75$ virions/$CD4^+$/day $\alpha_3 = 0.027$/day/virions/μl $k_3 = 0.0001$/day $e_{30} = 0.0001$ /day $\eta_1 = 0.055$ $\xi_2 = 0.85$ $\xi_3 = 0.0001$ $x_{30} = 1000$ virions/μl	$S_4 = 2000$ /day/μl $a_4 = 0.35$ /day/cell/μl $b_4 = 0.01$/cell/μl $K_2 = 0.0024$ /day/μl $k_4 = 0.08$/day/μl $e_{40} = 0.0002$ cells/day/μl $\eta_2 = 0.055$ $\gamma_4 = 0.15$ $x_{40} = 1500$ cells/μl	D = 4000 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* $\lambda_3 = 0.015$ *mg/L* $x_{50} = 1500$ cells/μl $n = 5$	$c_1 = 6.405$ $c_2 = 0.00075$ $\sigma_4 = 7$ *mg*/day $\lambda_4 = 5.5$ *mg/L* $x_{60} =$ 2500cells

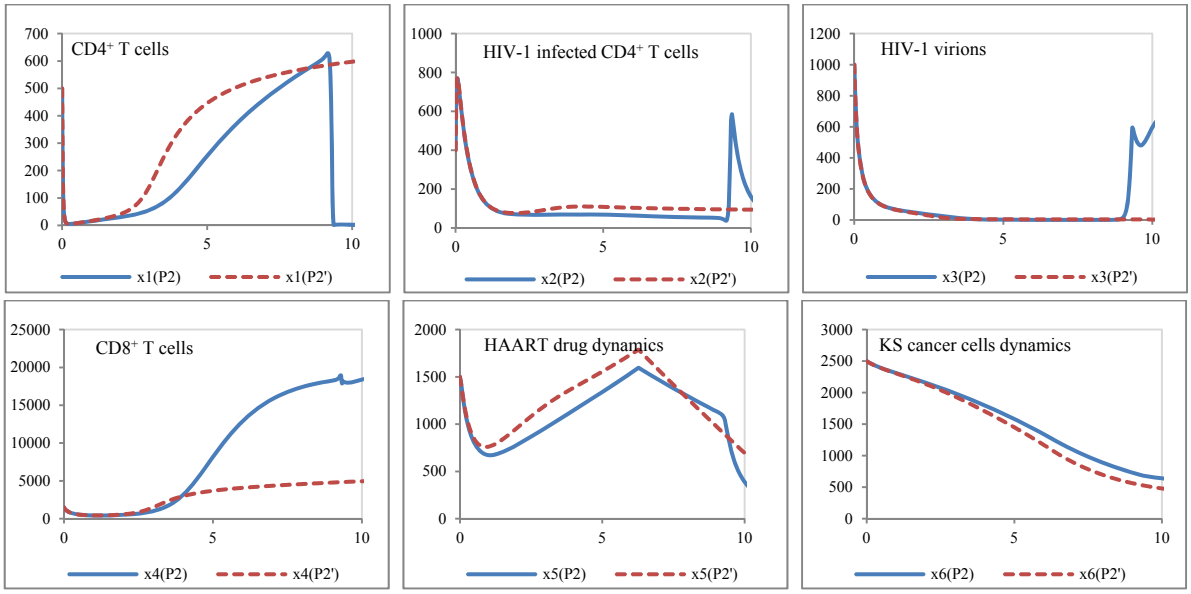

Figure 2 Simulation results using parametric configurations P_2 vs. P_2'
(P_2' is the modified P_2: same as P_2 except a_1=0.45, D=5000.The time axis unit is months.)

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