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Computer Simulation of a Mathematical Model of HAART Therapy for HIV-1 AIDS

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Abstract - A clinically plausible mathematical model is constructed to describe the patho-physiological dynamics of HIV-1 induced AIDS during HAART therapy. The model equations incorporate physiological interactions between non-infected helper T cells, HIV-1 infected helper T cells, HIV-1 virions in the blood plasma, HIV-1 specific cytotoxic T cells and drug molecules of the HAART protocol. Investigative computer simulations are performed to elucidate some therapeutic scenarios such as viral annihilation and efficacious HAART therapy. In particular, some mathematical criteria are derived for therapeutic outcomes such as viral persistence and viral annihilation.

Keywords: HAART therapy, computer simulations, mathematical modeling, HIV-1 dynamics, AIDS cure criteria

I. INTRODUCTION

In a previous publication [11], we presented a mathematical model describing the patho-physiological dynamics of the HIV-1 virions during the asymptomatic latency phase. As the HIV-1 virions increase in the blood plasma, the number density of the $CD4^+$ helper T cells decrease and the patient eventually develops AIDS. Currently, the most efficacious method for inducing a decline in number of HIV-1 virions and effecting immune system reconstitution, is by using highly active antiretroviral therapy (HAART) [10, 15]. A typical HAART treatment protocol consists of combinations of protease inhibitors (PIs), and types of reverse transcriptase inhibitors (RTIs), which are fabricated as a compact matrix tablet [1, 2, 10]. It is clinically observed that the HAART treatment regimen has associated side effects such as gastro-intestinal toxicity, lipodystrophy, anemia, thrombocytopenia, and renal failure [3, 9, 10].

Several mathematical models have been developed to describe therapy of HIV-1 induced AIDS [4, 5, 12, 13]. The authors Kirschner and Webb [4, 5] constructed models that described viral dynamics and drug resistance during monotherapy of HIV-1 infection. Perelson et al. [12] described the decay characteristics of HIV-1 infected compartments during combination therapy. In [15], Ye, Kourtis and Kirschner constructed an elaborate mathematical model which described the reconstitution of thymic function in HIV-1 patients during HAART therapy. Recent models, which involve optimal control therapies of HAART, include those by Stengel [14], Joshi [8], Adams et al. [1], Caetano and Yoneyama [2], and Joly [7].

In this paper, an elaborate clinically plausible mathematical model is constructed to describe HAART therapy of HIV-1 induced AIDS. This model incorporates constant continuous and periodic transdermal delivery, Michaelis-Menten drug absorption and clearance kinetics, and effects of viral latent reservoirs. Mathematical analyses of the model persistence are performed and viral persistence criteria are calculated. Investigative computer simulations are performed using hypothetical AIDS patients' physiological parameters.

The major contribution of the current research is the formulation of robust criteria under which the HIV-1 virions will persist or be annihilated during the HAART drug therapy.

II. 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 (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⁺ 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.

III. MODEL EQUATIONS AND ANALYSES

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

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

The model includes the following clinical 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 (CD4⁺) helper T cells. These cells secrete a lymphokine called interleukin-2.

A. Invariance of Non-Negativity of Solutions

In this subsection, conditions will be derived under which solutions curves to the model initial values problem for HAART AIDS therapy will remain non-negative and bounded for all $t \in \mathbb{R}_+$.

Let t_0 be the time at which the HAART therapy begins.

Set

$$\begin{aligned} C_j &= \sup_{t \in [t_0, T]} [a_j x_1 x_j e^{-b_j x_1}] \quad \text{for } j = \{1, 2, 4\} \\ C_3 &= \sup_{t \in [t_0, T]} [\beta_2 x_2 x_3 + \beta_3 x_3] \end{aligned} \quad (3.2)$$

here T is the time at which the HAART is discontinued.

Also set

$$\delta_i = \sup_{t \in [t_0, T]} \left[\frac{1}{\lambda_i + x_5} \right] \quad \text{for } i = \{0, 2, 3\} \quad (3.3)$$

The system of non-linear model equations exhibited in (3.1) can be converted to the following system of differential inequalities using (3.2) and (3.3). Let $f(t) = 1$.

$$\begin{cases} \dot{x}_1 \leq S_1 + C_1 - k_1 x_1 - e_{10} \\ \dot{x}_2 \leq S_2 + C_2 - k_2 x_2 - e_{20} \\ \dot{x}_3 \leq S_3 + C_3 - k_3 x_3 - e_{30} \\ \dot{x}_4 \leq S_4 + C_4 - k_4 x_4 - e_{40} \\ \dot{x}_5 \leq D - \delta x_5 \\ \text{where } \delta = \delta_0 + \delta_2 + \delta_3 \\ x_i(t_0) = x_{i0} \quad \text{where } i = \{1, 2, 3, 4, 5\} \end{cases} \quad (3.4)$$

The Kamke comparison technique [11] can be used to obtain the following system of non-linear inequalities.

$$\begin{cases} x_i \leq \frac{S_i + C_i - e_{i0}}{k_i} + \gamma_i e^{-k_i t} \quad \text{for } i = \{1, 2, 3, 4\} \\ x_5 \leq \frac{D}{\delta} + \gamma_5 e^{-\delta t} \quad \text{where } \delta = \delta_0 + \delta_2 + \delta_3 \\ \text{and } \gamma_i \in \mathbb{R}_+ = (0, \infty) \text{ and } i = \{1, 2, 3, 4, 5\} \end{cases} \quad (3.5)$$

The preceding analyses lead to the following conclusions.

C1. The solutions to the HAART model are ultimately bounded.

C2. The system is dissipative as implied by the inequalities

$$\limsup x_i(t) \leq \frac{S_i + C_i - e_{i0}}{k_i}, \quad i = \{1, 2, 3, 4\}$$

$$\limsup x_5(t) \leq \frac{D}{\delta}$$

C3.

$$\sup_{t \in [t_0, T]} x_i(t) = \max_{t \in [t_0, T]} \left\{ x_{i0}, \frac{S_i + C_i - e_{i0}}{k_i} \right\}, \quad i = \{1, 2, 3, 4\}$$

$$\sup_{t \in [t_0, T]} x_5(t) = \max_{t \in [t_0, T]} \left\{ x_{50}, \frac{D}{\delta} \right\}$$

Therefore, we have the following theorem.

Theorem 1 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 $x_{i0} \in \mathbb{R}_+^5 = \{x_i \in \mathbb{R} \mid x_i \geq 0, i = \{1, 2, 3, 4, 5\}\}$ will eventually enter the positive invariant region.

$$A = \{(x_1, x_2, x_3, x_4, x_5) \in \mathbb{R}_+^5 \mid 0 \leq x_i < B_i\}$$

where $B_i = \sup_{t \in [t_0, T]} x_i$

In particular, the solutions are trapped in the region A for all $t \in \mathbb{R}_+$.

B. Persistence of AIDS during HAART

In this subsection, criteria will be derived under which the HIV-1 virions will persist under HAART therapeutic protocols, with constant continuous infusion with rate D .

$$m_i = \inf_{t \in [t_0, T]} \{a_i x_1 x_i e^{-b_i x_i}\} \quad \text{where } i = \{1, 2, 4\}$$

$$L_1 = \sup_{t \in [t_0, T]} \{\alpha_1 x_3 + q_1 x_2 + k_1\}$$

$$L_2 = \sup_{t \in [t_0, T]} \left\{ q_2 x_1 + k_2 + K_1 x_4 + \frac{\xi_2 \sigma_2 x_2 x_5}{\lambda_2 + x_5} \right\}$$

$$U_1 = \sup_{t \in [t_0, T]} \{\beta_1 x_3\}$$

$$L_3 = \sup_{t \in [t_0, T]} \left\{ \alpha_3 x_1 + \eta_1 x_4 + k_3 + \frac{\xi_3 \sigma_3}{\lambda_3 + x_5} \right\}$$

$$m_3 = \inf_{t \in [t_0, T]} \{\beta_2 x_2 x_3 + \beta_3 x_3\}$$

$$L_4 = \inf_{t \in [t_0, T]} \{K_2 x_2 + \eta_2 x_3 + k_4\}$$

$$L_5 = \inf_{t \in [t_0, T]} \left\{ \frac{\sigma_0}{\lambda_0 + x_5} + \frac{\sigma_2 x_2}{\lambda_2 + x_5} + \frac{\sigma_3 x_3}{\lambda_3 + x_5} \right\}$$

Then the following differential inequalities are obtained:

$$\begin{cases} \dot{x}_1 \geq S_1 + m_1 - L_1 x_1 - e_{10} \\ \dot{x}_2 \geq S_2 + m_2 - L_2 x_2 - U_1 - e_{20} \\ \dot{x}_3 \geq S_3 + m_3 - L_3 x_3 - e_{30} \\ \dot{x}_4 \geq S_4 + m_4 - L_4 x_4 - e_{40} \\ \dot{x}_5 \geq D - L_5 x_5 \\ x_i(t_0) = x_{i0} \quad \text{where } i = \{1, 2, 3, 4, 5\} \end{cases} \quad (3.6)$$

Therefore, the following inequalities are obtained:

$$\begin{cases} x_1 \geq \frac{S_1 + m_1 - e_{10}}{L_1} + d_1 e^{-L_1 t} \\ x_2 \geq \frac{S_2 + m_2 - U_1 - e_{20}}{L_2} + d_2 e^{-L_2 t} \\ x_3 \geq \frac{S_3 + m_3 - e_{30}}{L_3} + d_3 e^{-L_3 t} \\ x_4 \geq \frac{S_4 + m_4 - e_{40}}{L_4} + d_4 e^{-L_4 t} \\ x_5 \geq \frac{D}{L_5} + d_5 e^{-L_5 t} \end{cases} \quad (3.7)$$

The system will exhibit persistence if

$$\begin{cases} \liminf x_1 \geq \frac{S_1 + m_1 - e_{10}}{L_1} > 0 \\ \liminf x_2 \geq \frac{S_2 + m_2 - U_1 - e_{20}}{L_2} > 0 \\ \liminf x_3 \geq \frac{S_3 + m_3 - e_{30}}{L_3} > 0 \\ \liminf x_4 \geq \frac{S_4 + m_4 - e_{40}}{L_4} > 0 \\ \liminf x_5 \geq \frac{D}{L_5} > 0 \end{cases} \quad (3.8)$$

C. Necessary Criteria for cure of AIDS during HAART

One of the desired physiological steady states during HAART therapy is $E = [\hat{x}_1, 0, 0, 0, \hat{x}_5]$. In this configuration, the HIV-1 infected T_4 helper cells (x_2), and HIV-1 virions (x_3), and HIV-1 specific cytotoxic T_8 cells (x_4) are annihilated by the HAART therapy.

The necessary conditions for the cure of AIDS using constant continuous transdermal infusion HAART therapy include:

$$\begin{cases} S_1 + a_1 \hat{x}_1^2 e^{-b_1 \hat{x}_1} - k_1 \hat{x}_1 - e_{10} = 0 \\ S_2 - e_{20} = 0 \\ S_3 - e_{30} = 0 \\ S_4 + a_4 \hat{x}_1 \hat{x}_4 e^{-b_4 \hat{x}_1} - k_4 \hat{x}_4 - e_{40} = 0 \\ D - \frac{\sigma_0 \hat{x}_5}{\lambda_0 + \hat{x}_5} = 0 \end{cases} \quad (3.9)$$

The sufficient conditions for the cure of AIDS can be obtained using a Liapunov functional, to guarantee that $E=[\hat{x}_1, 0, 0, 0, \hat{x}_5]$ is globally asymptotically stable. This will be done in a future publication.

IV. SIMULATION RESULTS AND DISCUSSION

The computer simulations are performed using hypothetical AIDS patients' configuration P_1 and P_2 , as

exhibited in Table I and Table II. It should be stressed that the data values are estimates and some are from the literature values listed in [4, 5, 11, 12]. Realistic parameters can only be obtained from actual AIDS patients under clinical conditions. Several investigative computer simulations are performed depicting the scenarios of viral persistence and viral annihilation. Two samples of the simulations are exhibited in Figure 1 for constant continuous transdermal infusion and Figure 2 for periodic transdermal infusion.

TABLE I. CONSTANT CONTINUOUS TRANSDERMAL INFUSION PARAMETRIC CONFIGURATION P_1

$S_1 = 400 \text{ /day/}\mu\text{l}$ $a_1 = 0.03 \text{ /day/cell/}\mu\text{l}$ $b_1 = 0.1 \text{ /cell/}\mu\text{l}$ $\alpha_1 = 0.5 \text{ /day/virion/}\mu\text{l}$ $k_1 = 0.0005 \text{ /day/}\mu\text{l}$ $q_1 = 0.00045 \text{ /day/}\mu\text{l/cell}$ $e_{10} = 1.9 \text{ cells/day/}\mu\text{l}$ $x_{10} = 200 \text{ cells/}\mu\text{l}$	$S_2 = 800 \text{ /day/}\mu\text{l}$ $a_2 = 0.03 \text{ /day/cell/}\mu\text{l}$ $b_2 = 0.004 \text{ /cell/}\mu\text{l}$ $\alpha_2 = 0.5 \text{ /day/virion/}\mu\text{l}$ $k_2 = 0.005 \text{ /day/}\mu\text{l}$ $q_2 = 0.00001 \text{ /day/}\mu\text{l/cell}$ $\beta_1 = 1.5 \text{ virions/CD4}^+ \text{ /day}$ $K_1 = 0.0001 \text{ /day/}\mu\text{l}$ $e_{20} = 0.0005 \text{ cells/day/}\mu\text{l}$ $x_{20} = 400 \text{ cells/}\mu\text{l}$	$S_3 = 1000 \text{ /day/}\mu\text{l}$ $\beta_2 = 0.025 \text{ virions/CD4}^+ \text{ /day/}\mu\text{l}$ $\beta_3 = 1.5 \text{ virions/CD4}^+ \text{ /day}$ $\alpha_3 = 0.027 \text{ /day/virion/}\mu\text{l}$ $k_3 = 0.0001 \text{ /day}$ $e_{30} = 0.0001 \text{ /day}$ $\eta_1 = 0.25$ $\xi_2 = 0.85$ $\xi_3 = 0.001$ $x_{30} = 500 \text{ cells/}\mu\text{l}$	$S_4 = 0.272 \text{ /day/}\mu\text{l}$ $a_4 = 0.03 \text{ /day/cell/}\mu\text{l}$ $b_4 = 0.01 \text{ /cell/}\mu\text{l}$ $K_2 = 0.0024 \text{ /day/}\mu\text{l}$ $k_4 = 0.008 \text{ /day/}\mu\text{l}$ $e_{40} = 0.0002 \text{ cells/day/}\mu\text{l}$ $\eta_2 = 0.45$ $x_{40} = 800 \text{ cells/}\mu\text{l}$	$D = 1000 \text{ units}$ $\sigma_0 = 50 \text{ mg/day}$ $\sigma_2 = 50.98 \text{ mg/day}$ $\sigma_3 = 10 \text{ mg/day}$ $\lambda_0 = 5 \text{ mg/L}$ $\lambda_2 = 5.5 \text{ mg/L}$ $\lambda_3 = 2.5 \text{ mg/L}$ $x_{50} = 1000 \text{ cells/}\mu\text{l}$

Figure 1. Simulation results using parametric configuration P_1

TABLE II. PERIODIC TRANSDERMAL INFUSION PARAMETRIC CONFIGURATION P_2

$S_1 = 400 \text{ /day/}\mu\text{l}$ $a_1 = 0.03 \text{ /day/cell/}\mu\text{l}$ $b_1 = 0.01 \text{ /cell/}\mu\text{l}$ $\alpha_1 = 0.5 \text{ /day/virion/}\mu\text{l}$ $k_1 = 0.0005 \text{ /day/}\mu\text{l}$ $q_1 = 0.00045 \text{ /day/}\mu\text{l/cell}$ $e_{10} = 0.0025 \text{ cells/day/}\mu\text{l}$ $x_{10} = 200 \text{ cells/}\mu\text{l}$	$S_2 = 800 \text{ /day/}\mu\text{l}$ $a_2 = 0.03 \text{ /day/cell/}\mu\text{l}$ $b_2 = 0.004 \text{ /cell/}\mu\text{l}$ $\alpha_2 = 0.5 \text{ /day/virion/}\mu\text{l}$ $k_2 = 0.005 \text{ /day/}\mu\text{l}$ $q_2 = 0.00001 \text{ /day/}\mu\text{l/cell}$ $\beta_1 = 1.5 \text{ virions/CD4}^+ \text{ /day}$ $K_1 = 0.0001 \text{ /day/}\mu\text{l}$ $e_{20} = 0.0005 \text{ cells/day/}\mu\text{l}$ $x_{20} = 400 \text{ cells/}\mu\text{l}$	$S_3 = 10 \text{ /day/}\mu\text{l}$ $\beta_2 = 0.025 \text{ virions/CD4}^+ \text{ /day/}\mu\text{l}$ $\beta_3 = 1.5 \text{ virions/CD4}^+ \text{ /day}$ $\alpha_3 = 0.027 \text{ /day/virion/}\mu\text{l}$ $k_3 = 0.0001 \text{ /day}$ $e_{30} = 0.0001 \text{ /day}$ $\eta_1 = 0.25$ $\xi_2 = 0.85$ $\xi_3 = 0.001$ $x_{30} = 500 \text{ cells/}\mu\text{l}$	$S_4 = 10 \text{ /day/}\mu\text{l}$ $a_4 = 0.75 \text{ /day/cell/}\mu\text{l}$ $b_4 = 0.01 \text{ /cell/}\mu\text{l}$ $K_2 = 0.00024 \text{ /day/}\mu\text{l}$ $k_4 = 0.08 \text{ /day/}\mu\text{l}$ $e_{40} = 0.0002 \text{ cells/day/}\mu\text{l}$ $\eta_2 = 0.45$ $x_{40} = 750 \text{ cells/}\mu\text{l}$	$D = 1000 \text{ units}$ $\sigma_0 = 10 \text{ mg/day}$ $\sigma_2 = 100 \text{ mg/day}$ $\sigma_3 = 10 \text{ mg/day}$ $\lambda_0 = 5 \text{ mg/L}$ $\lambda_2 = 10 \text{ mg/L}$ $\lambda_3 = 2.5 \text{ mg/L}$ $x_{50} = 1500 \text{ cells/}\mu\text{l}$ $n = 4$

Figure 2. Simulation results using parametric configuration P_2

It is observed that, in principle, AIDS can be cured. In particular, using parametric configuration P_1 for constant continuous transdermal infusion, the HAART therapy was unsuccessful because the HIV-1 virions increased dramatically during the therapy, whereas the $CD4^+$ helper T cells were eliminated. In Figure 2, using periodic transdermal infusion with parametric configuration P_2 , it is observed that the HAART therapy was successful because the HIV-1 virions were annihilated, whereas the $CD4^+$ helper T cells and the $CD8^+$ HIV-1 specific cytotoxic T cells repopulated.

It should be mentioned that there are other simulation scenarios in which the constant continuous transdermal infusion were successful and the periodic transdermal infusion were unsuccessful. Those scenarios will be presented in a future paper.

V. SUMMARIZING REMARKS

In this paper, a clinically plausible mathematical model for HAART therapy is presented which incorporates the patho-physiological dynamics of HIV-1 virions. The novel transdermal route of drug delivery which minimizes drug toxicity is utilized. The simulations of the model show that for some given AIDS patients' parametric configurations, it is possible to cure AIDS. The necessary mathematical criteria for these scenarios have been presented in the paper. The next step in the research towards the cure for AIDS is to investigate whether these results can be achieved *in vivo* as well as in the human AIDS patients.

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