Stability of a Modified Mathematical Model of AIDS Epidemic Can Stem cells Offer A new Hope of Cure for HIV1?

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Abstract: We propose a new mathematical model to quantitatively study the effect of stem cell transplantation in the treatment of HIV 1 infection. The analysis indicates that the therapy cannot offer a cure to the infection, but simply offers a better life to the ill person and delay death.
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1. Introduction

CD4+T (T-cells) lymphocytes play a fundamental regulatory role in the immune system. The number of CD4+T cells in the circulation provides important information about the immune competence of an individual [1]. People with CD4+T cell counts above 500 cells/ml generally have relatively normal immune functions and are at low risk for opportunistic infections [2]. The decrease in CD4+T cells under the indicated number can perturb the balance of the normal immune functions of the body [3].

Human immunodeficiency virus (HIV) is a retrovirus discovered in 1984 [4], [5]. The virus mainly affects CD4+Tlymphocytes. These originally healthy cells become infected and transform to factories to produce more HIV. The correlation between increase in viral load with depletion in the concentration of CD4+T and disease progression was observed by many scientists as in [6], [7], [8], [9], and [10]. Without intervention, HIV disease progresses and CD4+T cell counts reduce, typically by about 30-100 cells/ ml per year. [2]. In this process, the immune cells get continuously destroyed weakening the body's ability to flight disease and leading to the development of Acquired Immune Deficiency syndrome (AIDS). The suffering individual will die within 8 to 10 years if left untreated.

Today, living in the 21st century, we are still unable to cure HIV. Some light of hope for the treatment of this incurable disease is the Stem cell therapy. Hematopoietic stem cells are characterized by their ability to self-renew as well as to differentiate, [11] to give rise to a mature healthy specialized cell of the immune system [12], [13], [14] and can then replace diseased cells. It is similar to the principal of organ transplantation. We transplant cells instead of organs.

This paper is organized as follows: In section 2, we introduce the model ofviral dynamics corresponding to the stem cell therapy. In section 3, we analyzethe implicit model, we find out the critical points and we discuss the stability. Finally, in section 4, we discuss the implications withregards to the patienttreatment.

2 Modeling Stem Cells Therapy

A combination of viral load and of the concentration of CD4+T lymphocyte in the blood is considered to be the best indicator in evaluating the stage of the disease in HIV infected individuals, for the determination of T the commencement of a therapy and for monitoring the efficacy of the treatment [15], [3], [16], [17], and [18].

As mentioned in[19],[20],[21],[22], and [23], if uninfected susceptible T cells are produced at rate λ_T, dieat rate d_T and become infected cells T_i at rate $k_T TV$, infected cells are produced at rate $k_T TV$ and dieat rate $\rho_{Ti} T_i$, free visions (V) are produced from infected cells at rate $\pi_{Ti} T_i$ and declines at rate $c_v V$, then the basic model of viral dynamics can be presented by the system of ordinary differential equations:

$$\frac{dT(t)}{dt} = \lambda_T - d_T T - k_T TV$$
$$\frac{dT_i(t)}{dt} = k_T TV - \rho_{Ti} T_i$$
$$\frac{dV(t)}{dt} = \pi_{Ti} T_i - c_v V \quad (1)$$

If normal stem cells in the top of the hierarchy denoted by S divide at rate r, die at rate d and produce terminally differentiated T-cells at rate c, then the dynamic of stem cell transformation can be represented in two variables by[24], [25], and [26].

$$\frac{dS(t)}{dt} = (r-d)S(t)$$
$$\frac{dT(t)}{dt} = cS - dT(t)$$

More precisely, we know there are three possibilities to a stem cell to divide: [27]

- Symmetric self-renewal, where a stem cell can divide to become two stem cells, with probability α_S,

-Asymmetric self-renewal, where one daughter cell remains a stem cell while the other does not inherit this characteristic, with probability α_A,

- Symmetric commitment differentiation, where a stem cell can divide to become two committed cells, with probability α_D.

Therefore $\alpha_A + \alpha_S + \alpha_D = 1$. We suppose that the stem cells S divide at rate k and die at rate δ_S. T cells die at rate δ_N and they are formed through asymmetric and differentiation division of S cells. We need to introduce an amplification factor A to finally get the simplified ODE [28], [29], [30], [31].

$$\frac{dS(t)}{dt} = [k(\alpha_S - \alpha_D) - \delta_S]S(t)$$
$$\frac{dT(t)}{dt} = \lambda_T - d_T T(t) + (2\alpha_D + \alpha_A)kAS(t) - k_T T(t)V(t) \quad (2)$$

$\alpha = k(\alpha_S - \alpha_D) - \delta_S$ represents the net per-capita growth rate of stem cells [32]

The resulting dynamic of stem cell therapy for HIV can then be represented by the simple ordinary differential equations:

$$\frac{dS(t)}{dt} = [k(\alpha_S - \alpha_D) - \delta_S]S(t)$$
$$\frac{dT(t)}{dt} = \lambda_T - d_T T(t) + (2\alpha_D + \alpha_A)kAS(t) - k_T T(t)V(t)$$
$$\frac{dT_i(t)}{dt} = k_T T(t)V(t) - \rho_{Ti} T_i(t)$$
$$\frac{dV(t)}{dt} = \pi_{Ti} T_i(t) - c_v V(t). \quad (3)$$

We assume all of the parameters $k, \alpha_S, \alpha_D, \ldots$ non-negative and $k(\alpha_S - \alpha_D) - \delta_S$ non-positive.

3. Equilibrium Points and Stability Analysis

In this section we are going to discuss the stability of the model of viral dynamics corresponding to the stem cell therapy given by Eqs. (3). It is clear that system (3) is an almost linear autonomous system and the equilibrium points has the form (S, T, T_i, V). The following theorem gives us the equilibrium points.

Theorem 1 The system (3) has two equilibrium points given by the following: $P_1(S, T, T_i, V) = (0, \frac{\lambda_T}{d_T}, 0, 0)$, corresponding to the free disease case and $P_2(S, T, T_i, V) = (0, \frac{\lambda_T}{d_T}\frac{1}{R_0}, \frac{d_T c_v}{k_T \pi_{Ti}}(R_0 - 1), \frac{d_T}{k_T}(R_0 - 1))$; with $R_0 = \frac{k_T \lambda_T \pi_{Ti}}{c_v \rho_{Ti} d_T}$. (Basic Reproduction Number) corresponding to endemic case.

Proof To find the equilibrium points, we solve the following system for (S, T, T_i, V) using Mathematic a software:

$$[k(\alpha_S - \alpha_D) - \delta_S]S = 0$$
$$\lambda_T - d_T T + (2\alpha_D + \alpha_A)kAS - k_T T V = 0$$
$$k_T T V - \rho_{Ti} T_i = 0$$
$$\pi_{Ti} T_i - c_v V = 0.$$

If the basic reproduction ratio of the viruses given by $R_0 = \frac{k_T \lambda_T \pi_{Ti}}{c_v \rho_{Ti} d_T}$, then we get the following equilibrium points:

$P_1(S, T, T_i, V) = (0, \frac{\lambda_T}{d_T}, 0, 0)$, and

$P_2(S, T, T_i, V) = (0, \frac{\lambda_T}{d_T}\frac{1}{R_0}, \frac{d_T c_v}{k_T \pi_{Ti}}(R_0 - 1), \frac{d_T}{k_T}(R_0 - 1))$.

We shall study the stability of the equilibrium points P_1 and P_2.

Theorem 2 The free disease case P_1 is asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.

Proof The Jacobian matrix corresponding to system (3) is given by:

$$J = \begin{bmatrix} k(\alpha_S - \alpha_D) - \delta_S & 0 & 0 & 0 \\ (2\alpha_D + \alpha_A)kA & -d_T - k_T V & 0 & -k_T T \\ 0 & k_T V & -\rho_{Ti} & k_T T \\ 0 & 0 & \pi_{Ti} & -c_v \end{bmatrix}.$$

At the health point P_1 the Jacobian matrix becomes

$$J_1 = \begin{bmatrix} k(\alpha_S - \alpha_D) - \delta_S & 0 & 0 & 0 \\ (2\alpha_D + \alpha_A)kA & -d_T & 0 & -k_T \frac{\lambda_T}{d_T} \\ 0 & 0 & -\rho_{Ti} & k_T \frac{\lambda_T}{d_T} \\ 0 & 0 & \pi_{Ti} & -c_v \end{bmatrix},$$

and the characteristic equation is:

$$det(J_1 - rI) = [(-d_T - r)([k(\alpha_S - \alpha_D) - \delta_S] - r)$$
$$(r^2 + (c_v + \rho_{Ti})r - \frac{k_T \lambda_T \pi_{Ti}}{d_T} + c_v \rho_{Ti})] = 0,$$

then using Mathematic a software the eigen values are given by:

$r_1 = -d_T$, $r_2 = k(\alpha_S - \alpha_D) - \delta_S$,

$$r_3 = \frac{1}{2d_T}(-d_T(c_v + \rho_{Ti}) + \sqrt{d_T}$$
$$\sqrt{c_v^2 d_T + 4k_T \lambda_T \pi_{Ti} - 2c_v \rho_{Ti} d_T + d_T \rho_{Ti}^2})$$

and

$$r_4 = \frac{1}{2d_T}(-d_T(c_v + \rho_{Ti}) - \sqrt{d_T}$$
$$\sqrt{c_v^2 d_T + 4k_T \lambda_T \pi_{Ti} - 2c_v \rho_{Ti} d_T + d_T \rho_{Ti}^2}).$$

Since $k(\alpha_S - \alpha_D) - \delta_S < 0$, then the first and the second roots are negative. If $R_0 = \frac{k_T \lambda_T \pi_{Ti}}{c_v \rho_{Ti} d_T} < 1$, then $4c_v \rho_{Ti} d_T^2 > 4k_T \lambda_T \pi_{Ti} d_T$, so

$$(-d_T(c_v + \rho_{Ti}))^2 >$$
$$d_T(c_v^2 d_T + 4k_T \lambda_T \pi_{Ti} - 2c_v \rho_{Ti} d_T + d_T \rho_{Ti}^2),$$ which means that $r_3 < 0$ and $r_4 < 0$.

If $R_0 = \frac{k_T \lambda_T \pi_{Ti}}{c_v \rho_{Ti} d_T} > 1$, then $4c_v \rho_{Ti} d_T^2 < 4k_T \lambda_T \pi_{Ti} d_T$,

$$(-d_T(c_v + \rho_{Ti}))^2 <$$
$$d_T(c_v^2 d_T + 4k_T \lambda_T \pi_{Ti} - 2c_v \rho_{Ti} d_T + d_T \rho_{Ti}^2),$$ which means that $r_3 > 0$ and $r_4 > 0$ Thus, we get the result.

Remark 3 1) If $R_0 = 1$, then $P_2 = P_1$.

2) If $R_0 < 1$, then P_2 is impossible.

To study the point P_2, we need the following lemma:

Lemma 4 As in [33], the polynomial $f(r) = r^3 + a_1 r^2 + a_2 r + a_3$, has the following results:

(i) If $a_3 < 0$, then $f(r)$ has at least one positive root.

(ii) If $a_1 > 0$, $a_3 \geq 0$, and $a_2 \geq 0$, then $f(r)$ has no positive root.

(iii) If $a_1 > 0$, $a_3 \geq 0$, and $a_2 < 0$, then $f(r)$ has a positive root: $r = \frac{1}{3}(-a_1 + \sqrt{a_1^2 - 3a_2}$.

Theorem 5 If $R_0 \geq 1$, then the endemic point P_2 is asymptotically stable.

Proof: At the point P_2, the Jacobian matrix becomes:

$$J_2 = \begin{bmatrix} k(\alpha_S - \alpha_D) - \delta_S & 0 & 0 & 0 \\ (2\alpha_D + \alpha_A)kA & -d_T R_0 & 0 & -k_T \frac{\lambda_T}{d_T}\frac{1}{R_0} \\ 0 & d_T(R_0 - 1) & -\rho_{Ti} & k_T \frac{\lambda_T}{d_T}\frac{1}{R_0} \\ 0 & 0 & \pi_{Ti} & -c_v \end{bmatrix},$$ so:

the characteristic equation is given by

$$det(J_2 - rI) = (r - (k(\alpha_S - \alpha_D) - \delta_S))$$
$$(-r^3 - (c_v + d_T R_0 + \rho_{Ti})r^2 - c_v d_T R_0$$
$$+ d_T \rho_{Ti} R_0 - \frac{k_T \pi_{Ti} \lambda_T}{d_T R_0} + c_v \rho_{Ti})r + 2k_T \pi_{Ti} \lambda_T$$
$$- \frac{k_T \pi_{Ti} \lambda_T}{R_0} - c_v \rho_{Ti} d_T R_0) = 0, \qquad (5)$$

, then $r_1 = k(\alpha_S - \alpha_D) - \delta_S$, is the eigen-value of the characteristic equation (5), to find the other eigen values we solve

asymptotically stable.

$$det(J_2 - rI) = (r - (k(\alpha_S - \alpha_D) - \delta_S))$$
$$(-r^3 - (c_v + d_T R_0 + \rho_{Ti})r^2 - c_v d_T R_0$$
$$+ d_T \rho_{Ti} R_0 - \frac{k_T \pi_{Ti} \lambda_T}{d_T R_0} + c_v \rho_{Ti})r + 2k_T \pi_{Ti} \lambda_T$$
$$- \frac{k_T \pi_{Ti} \lambda_T}{R_0} - c_v \rho_{Ti} d_T R_0) = 0, \qquad (5)$$

then $r_1 = k(\alpha_S - \alpha_D) - \delta_S$, is the eigen value of the characteristic equation (5), to find the other eigen values we solve

$$f(r) = r^3 + a_1 r^2 + a_2 r + a_3 = 0, \qquad (6)$$

such that:

$a_1 = c_v + d_T R_0 + \rho_{Ti}$,

$a_2 = c_v d_T R_0 + d_T \rho_{Ti} R_0 - \frac{k_T \pi_{Ti} \lambda_T}{d_T R_0} + c_v \rho_{Ti}$,

$a_3 = 2 k_T \pi_{Ti} \lambda_T - \frac{k_T \pi_{Ti} \lambda_T}{R_0} - c_v \rho_{Ti} d_T R_0$, and , since $R_0 \geq 1$, then $c_v d_T R_0 + d_T \rho_{Ti} R_0 - \frac{k_T \pi_{Ti} \lambda_T}{d_T R_0} + c_v \rho_{Ti} \geq 0$ and $2 k_T \pi_{Ti} \lambda_T - \frac{k_T \pi_{Ti} \lambda_T}{R_0} - c_v \rho_{Ti} d_T R_0 \geq 0$, then, according to **Lemma 1**, we deduced that P_2 is asymptotically stable.

4. Conclusion

We have formulated a model for HIV 1 infection with stem cell treatment to study the influence of the therapy on viral dynamics. We have found the same basic reproductive ratio $R_0 = \frac{k_T \lambda_T \pi_{Ti}}{c_v \rho_{Ti} d_T}$ as the system (1) before introducing the stem cells [34], [35], [36]. This ratio was shown to determine the asymptotic stability of the free-disease steady state when $R_0 < 1$ (the infected T cells and virus particles will be cleared) and the infected steady state when $R_0 > 1$ (anyinitial HIV infection will progress to chronic infection).

So, stem cell therapy will not offer a cure to the infected person, but simply will help delay progression to the chronic stage.

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