Hindawi
Discrete Dynamics in Nature and Society
Volume 2019, Article ID 6379142, 8 pages
https://doi.org/10.1155/2019/6379142

Research Article

Mathematical Modeling to Study Multistage Stem Cell Transplantation in HIV-1 Patients

Manar A. Al Qudah,[1] **Sana'a A. Zarea**,[1] **and Saoussan A. Kallel-Jallouli**[2]

[1]*Mathematical Science Department, Princess Nourah bint Abdulrahman University, P.O. Box 84428, Riyadh 11671, Saudi Arabia*
[2]*Université de Tunis El Manar, LR03ES04, Faculté des Sciences de Tunis, 2092, Tunis, Tunisia*

Correspondence should be addressed to Manar A. Al Qudah; manarqudah@yahoo.com

Received 10 June 2019; Accepted 30 July 2019; Published 19 August 2019

Academic Editor: Miguel Ángel López

Stem cells as a therapeutic measure for the treatment of different diseases have a great potential to give rise to different mature cells as they could be used to treat HIV-1 patients when provided with the convenient factors. Thus, this paper proposes a new mathematical model, represented by a system of ODEs, to study the effect of stem cell transplantation for HIV-1 patients. Since stem cells lineage passes through many stages to become more specialized cell types, investigating (theorizing) the best stage for these cells to be engrafted was needed. The proposed system of ODEs can help medicine make the right decision about the proposed therapy.

1. Introduction

A virus called HIV (human immunodeficiency virus) causes AIDS (acquired immunodeficiency syndrome). HIV is a retrovirus that attacks the vital organs and the cells of the human immune system, making people more vulnerable to diseases and infections. Without treatment, HIV can develop into AIDS in many cases. In the absence of therapy the virus progresses. The developing rate of the virus differs between individuals and changes according to many factors. These factors include ability of the body to fight against HIV, the age of the individual, access to healthcare, the individual's genetic inheritance, the presence of other infections, and the resistance to certain strains of HIV.

According to the World Health Organization's guidelines issued in June 2018, there is no viable cure or vaccine for HIV, but treatments can improve patients' quality of life.

When given the right treatment, some patients can live with HIV and reduce their viral load to such a degree that it is not discoverable. Studies by the CDC (Centers for Disease Control and Prevention) proved that in individuals who have no discoverable viral load "through sex there is effectively no risk of transmitting HIV to an HIV-negative partner." Generally, people who live with HIV take a composition of medications called HAART (highly active antiretroviral therapy) or CART (combination antiretroviral therapy) [1]. This antiretroviral therapy (ART) prevents or slows the virus from developing.

We can find two types of HIV: HIV-1 and HIV-2. HIV-1 is more infective and more dangerous than HIV-2 as mentioned in [2]. Also HIV-1 concretes both lymphadenopathy associated virus (LAV) and human T-lymphotropic virus-3 (HTLV-III). HIV-2 is largely found in West Africa [3], according to its relatively poor capacity for transmission.

Understanding the dynamics of HIV-1 by mathematical modeling plays a basic role in medicine. All mathematical models of HIV-1 are based on the model in [4] where they considered the interaction between four components: uninfected CD4 + T-cells, latent infected CD4 + T-cells, infected CD4 + T-cells, and the free virus. Then, many researchers modified this model such as in [5] where they presented the same model without the latent infected CD4 + T-cells. The models that are studied in [6–10] focused on models interested in the dynamics of HIV and a hope for a cure for the infection.

Stem Cell Therapy. Nowadays, stem cell studies are a field of much interest, and within this area there is a need for mathematical model representation of the dynamics growth for stem cells. Inside any organism the new cells need a

source, which requires a continuous role to replace the older cells, to keep the balance of homeostasis for tissue, and to react to the external ecological stresses. In each organ adult stem cells [11, 12] are planning this important role to replace the older cells. Through its niche in the organism and its special nature, the stem cell is able to renew itself. The daughter cells are generated from the stem cells through cell divisions and will differentiate into one of any number of organ specific cell types; in this process of differentiation, they lose their initial capacity for self-renewal. Lie and Xie [13] discussed an accurate equilibrium between stem cell self-renewal and differentiation; also they studied the way stem cells regulate the body and treat human disease. A lot of interest has also been focused on embryonic stem cells [14, 15], a kind of stem cell from earlier in human development, and it is a smart cell that can be differentiated into any type of cells within the body.

Adult stem and embryonic cells have the same properties of proliferation, differentiation, and self-renewal. Hence, thinking about their transplantation in the patient can be a good idea to replace injured cells and help in restoring the function of damaged cells. Recent studies have shown the efficacy of this technique to regenerate some body organs [16]. All of the abovementioned properties are a critical field within the research of stem cells. According to the recent researches that studied proliferation of stem cells, this paper introduces a mathematical model. As discussed in Henrigou et al. [17] and Bonab et al. [18], many therapies of stem cells depend on the availability of the number of the stem cells to transfer. Therefore, the representation of the rate of growth for a population of stem cells as a mathematical model will be very useful. Several models applied to stem cell proliferation as in Loeffler and Wichman [19] and as in Cowan and Morris [20] have been reviewed and accordingly this paper's mathematical model was constructed.

Depending on the ability of stem cells to differentiate into some of the specialized phenotypes in response to appropriate signals [21], this paper proposes to treat HIV-1 patients by engraftment of the type of cells able to transform to T-cells (CD4+T). Other varieties of cells were tested for restoring the heart [22–26], the cornea [27], and pancreatic functions [28, 29].

This paper begins by recalling a known mathematical model for multilineage stem cells, which was used to formulate a new mathematical model of the viral dynamic of HIV-1 treatment by stem cell therapy. The study of the model enables us to choose the best stage in the lineage to engraft these cells and help medicine make the good decision.

2. Mathematical Modeling of n-Multistage Stem Cell Maturation

Let s_i be the density of stem cells at the ith stage for $i = 1, 2, \ldots, n-1$, of differentiation and the density of mature cells for $i = n$. Let $h(t)$ be the concentration of signaling molecules which depends only on the density of mature cells s_n; thus the dynamics of a cytokine (a protein, polypeptide, or glycoprotein that are used in signaling and intracellular signaling and also aid in cell-to-cell communication in immune responses and stimulate the movement of cells towards sites of inflammation and infection) can be represented as a first-order differential equation:$dh/dt = \mu(1 - h - \gamma h s_n(t))$, where μ is the death rate of a mature stem cell population and γ is a +ve constant; solving this equation using the approximation of the quasi-steady state we get $h = h_\gamma(t) = 1/(1 + \gamma s_n(t))$. The stem cell lineage can be expressed as an ODEs system [30]:

$$\begin{aligned}
\frac{ds_1}{dt} &= f_1\left(h(t), s_1(t)\right),\\
\frac{ds_2}{dt} &= f_2\left(h(t), s_2(t)\right) + g_1\left(h(t), s_1(t)\right),\\
&\vdots\\
\frac{ds_n}{dt} &= f_n\left(h(t), s_n(t)\right) + g_{n-1}\left(h(t), s_{n-1}(t)\right).
\end{aligned} \tag{1}$$

Here $f_i(h(t), s_i(t))$ is the change of $s_i(t)$ that is caused by processes at the ith stage of maturation. If gain cells caused by the loss of differentiation or death are more weakened than the self-renewal and proliferation, then $f_i(h(t), s_i(t)) > 0$; otherwise $f_i(h(t), s_i(t)) < 0$. But if we suppose that mature cells are postmitotic (they cannot proliferate), then since f_n is accounted only for cell death, we have $f_n(h(t), s_n(t)) < 0$. We denote $g_i(h(t), s_i(t)) \geq 0$ to be the flux of cells from the maturation stage i to maturation stage $i + 1$ due to differentiation.

Let $p_i(t)$ denote the proliferation rate of the subpopulation of type i at time t, $a_i(t)$ denote the fraction of self-renewal, and $\mu_i(t)$ denote the death rate. Then, the flux to mitosis at time t will be $p_i(t)s_i(t)$. The fraction $a_i(t)$ of daughter cells dose not differentiate. Thus, the influx to cell population i after cell division is $2a_i(t)p_i(t)s_i(t)$ and the flux to the next cell compartment is $2(1 - a_i(t))p_i(t)s_i(t)$. The flux to death at time t is given by $\mu_i(t)s_i(t)$. Hence we obtain

$$\begin{aligned}
f_i(t) &= \left(2a_i(t) - 1\right) p_i(t)\, s_i(t) - \mu_i(t)\, s_i(t), \quad \text{for } i < n,\\
g_i(t) &= 2\left(1 - a_{i-1}(t)\right) p_{i-1}(t)\, s_{i-1}(t), \quad \text{for } 1 < i < n,\\
f_n(t) &= -\mu_n(t)\, s_n(t).
\end{aligned} \tag{2}$$

Assume that the proliferation rates and the death rates are constant with time, and self-renewal fractions are controlled by the signal feedback,$a_i(t) = a_i(h(s_i(t))) = a_{i,max}(h(s_i(t)))$, where $a_{i,max} = a_i$ is the maximal fraction of self-renewal. Therefore, system (1) can be written as

$$\begin{aligned}
\frac{ds_1}{dt} &= \left(2a_1h - 1\right) p_1 s_1 - \mu_1 s_1,\\
\frac{ds_2}{dt} &= \left(2a_2h - 1\right) p_2 s_2 + 2\left(1 - a_1h\right) p_1 s_1 - \mu_2 s_2,\\
&\vdots\\
\frac{ds_{\mathrm{i}}}{dt} &= \left(2a_{\mathrm{i}}h - 1\right) p_{\mathrm{i}} s_{\mathrm{i}} + 2\left(1 - a_{\mathrm{i}-1}h\right) p_{\mathrm{i}-1} s_{\mathrm{i}-1} - \mu_{\mathrm{i}} s_{\mathrm{i}},\\
&\vdots\\
\frac{ds_n}{dt} &= 2\left(1 - a_{n-1}h\right) p_{n-1} s_{n-1} - \mu_n s_n.
\end{aligned} \tag{3}$$

Using that $h = 1/(1 + \gamma s_n)$, then system (3) becomes

$$\begin{aligned}
\frac{ds_1}{dt} &= \left(\frac{2a_1}{1 + \gamma s_n} - 1\right) p_1 s_1 - \mu_1 s_1,\\
\frac{ds_2}{dt} &= \left(\frac{2a_2}{1 + \gamma s_n} - 1\right) p_2 s_2 + 2\left(1 - \frac{a_1}{1 + \gamma s_n}\right) p_1 s_1\\
&\quad - \mu_2 s_2,\\
&\vdots\\
\frac{ds_{\mathrm{i}}}{dt} &= \left(\frac{2a_{\mathrm{i}}}{1 + \gamma s_n} - 1\right) p_{\mathrm{i}} s_{\mathrm{i}} + 2\left(1 - \frac{a_{\mathrm{i}-1}}{1 + \gamma s_n}\right) p_{\mathrm{i}-1} s_{\mathrm{i}-1}\\
&\quad - \mu_{\mathrm{i}} s_{\mathrm{i}},\\
&\vdots\\
\frac{ds_n}{dt} &= 2\left(1 - \frac{a_{n-1}}{1 + \gamma s_n}\right) p_{n-1} s_{n-1} - \mu_n s_n.
\end{aligned} \tag{4}$$

For the initial data and the model parameters, we add the following biologically relevant assumptions as in [30]:

$$\begin{aligned}
&t \epsilon [0, \infty).\\
&s_i(0) \geq 0, \quad for\ i = 1, \ldots, n,\\
&\mu_i \geq 0, \quad for\ i = 1, \ldots, n-1,\\
&\mu_n > 0,\\
&p_i > 0, \quad for\ i = 1, \ldots, n-1,\\
&a_{i,max} \epsilon [0, 1), \quad for\ i = 1, \ldots, n-1,\\
&\gamma > 0.
\end{aligned} \tag{5}$$

3. Mathematical Modeling of the n-Multistage Stem Cell Therapy for HIV-1 Patients

In our previous work [31], we proposed for the first time in literature a model that explains the effect of stem cell transplantation on HIV-1 viral dynamics. The basic model structure that describes the therapy uses four state variables: stem cells (S), healthy T-cells (T), infected T-cells ($\mathrm{T_i}$), and the virus (V):

$$\begin{aligned}
\frac{dS}{dt} &= \left[b\left(\alpha_S - \alpha_D\right) - \delta_S\right] S\\
\frac{dT}{dt} &= \lambda_T - d_T T - k_T \mathrm{TV} + \left(2\alpha_D + \alpha_A\right) bAS\\
\frac{dT_i}{dt} &= k_T \mathrm{TV} - \rho_{T_i} T_i\\
\frac{dV}{dt} &= \pi_{T_i} T_i - cV,
\end{aligned} \tag{6}$$

where the parameters b, α_S, α_D are nonnegative and $b(\alpha_S - \alpha_D) - \delta_S$ are nonpositive. We know there are three possibilities for a stem cell to divide [32]:

(i) Symmetric self-renewal, where a stem cell can divide to become two stem cells, with probability α_s

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

(iii) 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 b and die at rate δ_S. We need to introduce an amplification factor A to finally get the simplified ODE: $dS/dt = [b(\alpha_S - \alpha_D) - \delta_S]S$, such that $b(\alpha_S - \alpha_D) - \delta_S$ represents the net per-capita growth rate of stem cells [33]; for the uninfected susceptible T cells the production rate is λ_T, and the death rate is d_T and they become infected cells (T_i) at rate k_T; the infected cells are produced and die at the rates k_T and ρ_{T_i}, respectively; free virions (V) are produced from infected cells at rate π_{T_i} and decline at rate c.

Since stem cells $S = S_1$ need many stages to transform to mature cells $\mathrm{S_n} = \mathrm{T}$, in this paper we shall perform our previous work [31] by including the stages of the lineage of stem cells given by system (4). Our system (6) can then transform to a new system that describes the n-multistage stem cells transformation in the therapy of HIV-1 patients. This new model describes the dynamics of stem cell transplantation on the virus using $(n + 2)$ state variables ($(n + 2)$ ODEs):

$$\begin{aligned}
\frac{dS_1}{dt} &= \left(\frac{2a_1}{1 + \gamma T} - 1\right) p_1 S_1 - \mu_1 S_1,\\
\frac{dS_2}{dt} &= \left(\frac{2a_2}{1 + \gamma T} - 1\right) p_2 S_2 + 2\left(1 - \frac{a_1}{1 + \gamma \mathrm{T}}\right) p_1 S_1\\
&\quad - \mu_2 S_2,\\
&\vdots\\
\frac{dS_{\mathrm{i}}}{dt} &= \left(\frac{2a_{\mathrm{i}}}{1 + \gamma \mathrm{T}} - 1\right) p_{\mathrm{i}} S_{\mathrm{i}} + 2\left(1 - \frac{a_{\mathrm{i}-1}}{1 + \gamma \mathrm{T}}\right) p_{\mathrm{i}-1} S_{\mathrm{i}-1}
\end{aligned}$$

$$
\begin{aligned}
&- \mu_1 S_1,\\
&\vdots\\
\frac{dS_{n-1}}{dt} &= \left(\frac{2a_{n-1}}{1+\gamma T} - 1\right) p_{n-1} S_{n-1}\\
&+ 2\left(1 - \frac{a_{n-2}}{1+\gamma T}\right) p_{n-2} S_{n-2} - \mu_{n-1} S_{n-1},\\
\frac{dT}{dt} &= \lambda_T - d_T T - k_T TV + 2\left(1 - \frac{a_{n-1}}{1+\gamma T}\right) p_{n-1} S_{n-1}\\
&- \mu_n T,\\
\frac{dT_i}{dt} &= k_T TV - \rho_{T_i} T_i,\\
\frac{dV}{dt} &= \pi_{T_i} T_i - cV.
\end{aligned}
\tag{7}
$$

Different numbers of compartment n were chosen in previous researches, as mentioned in [34]. By n=8 we mean that the direct reflection of the biological case of differentiation of white blood stem cells into neutrophilic granulocytes [35]; in this case we treat all immature and mature cells as separated populations so they might be understood as stem cells and their direct progeny. The compartment n=6 corresponds to short- and long-term repopulating stem cells, multipotent progenitor cells, committed progenitor cells, precursors, and mature cells, so it is related to the properties of division cells. For simplicity we consider $n = 2$. The nth compartment is the population of mature cells, which we suppose, for simplicity, do not divide any more. In the next section, we will study the following 5-dimensional version extracted from model (7):

$$
\begin{aligned}
\frac{dS_1}{dt} &= \left(\frac{2a_1}{1+\gamma T} - 1\right) p_1 S_1 - \mu_1 S_1,\\
\frac{dS_2}{dt} &= \left(\frac{2a_2}{1+\gamma T} - 1\right) p_2 S_2 + 2\left(1 - \frac{a_1}{1+\gamma T}\right) p_1 S_1\\
&- \mu_2 S_2,\\
\frac{dT}{dt} &= \lambda_T - (d_T + \mu_3) T - k_T TV\\
&+ 2\left(1 - \frac{a_2}{1+\gamma T}\right) p_2 S_2,\\
\frac{dT_i}{dt} &= k_T TV - \rho_{T_i} T_i,\\
\frac{dV}{dt} &= \pi_{T_i} T_i - cV.
\end{aligned}
\tag{8}
$$

Here μ_3 is the death rate of T-cells that come out from the final stage of the stem cell maturation, so for simplicity let $d_T + \mu_3 = \beta$.

4. Study of the Mathematical Model of the 2-Multistage Stem Cell Therapy for HIV-1 Patients

In this section, we are going to discuss the stability of the model of viral dynamics corresponding to the stem cell therapy given by system (8). We shall try to find out equilibrium points of system (8) in the form (S_1, S_2, T, T_i, V). As in [36] we take γ to be very small; therefore we replace $a_i/(1+\gamma T)$ by a_i, for $i = 1, 2, \ldots, n-1$, which is equivalent to choosing $h = 1/(1+\gamma T)\epsilon(0,1)$ as in [37].

The following theorem gives us the equilibrium points for the following system:

$$
\begin{aligned}
\frac{dS_1}{dt} &= (2a_1 - 1) p_1 S_1 - \mu_1 S_1,\\
\frac{dS_2}{dt} &= (2a_2 - 1) p_2 S_2 + 2(1 - a_1) p_1 S_1 - \mu_2 S_2,\\
\frac{dT}{dt} &= \lambda_T - \beta T - k_T TV + 2(1 - a_2) p_2 s_2,\\
\frac{dT_i}{dt} &= k_T TV - \rho_{T_i} T_i,\\
\frac{dV}{dt} &= \pi_{T_i} T_i - cV.
\end{aligned}
\tag{9}
$$

If the basic reproduction ratio of the viruses is given by $R_0 = k_T \lambda_T \pi_{T_i} / c\rho_{T_i}\beta$, then we get the following theorem.

Theorem 1. *System (9) has two equilibrium points given by* $P_1(S_1, S_2, T, T_i, V) = (0, 0, \lambda_T/\beta, 0, 0)$ *corresponding to the free disease case and* $P_2(S_1, S_2, T, T_i, V) = (0, 0, (\lambda_T/\beta)(1/R_0), (\beta c/k_T \pi_{T_i})(R_0 - 1), (\beta/k_T)(R_0 - 1))$ *corresponding to the endemic case.*

Proof. To find the equilibrium points, we solve the following system for (S_1, S_2, T, T_i, V):

$$
\begin{aligned}
(2a_1 - 1) p_1 S_1 - \mu_1 S_1 &= 0\\
(2a_2 - 1) p_2 S_2 + 2(1 - a_1) p_1 S_1 - \mu_2 S_2 &= 0\\
\lambda_T - \beta T - k_T TV + 2(1 - a_2) p_2 s_2 &= 0\\
k_T TV - \rho_{T_i} T_i &= 0\\
\pi_{T_i} T_i - cV &= 0.
\end{aligned}
\tag{10}
$$

By introducing $R_0 = k_T \lambda_T \pi_{T_i} / c\rho_{T_i}\beta$, we get the result. □

In the next theorems we study the stability at 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 (9) is given by

$$J = \begin{bmatrix} (2a_1 - 1)\, p_1 - \mu_1 & 0 & 0 & 0 & 0 \\ 2(1 - a_1)\, p_1 & (2a_2 - 1)\, p_2 - \mu_2 & 0 & 0 & 0 \\ 0 & 2(1 - a_2)\, p_2 & -\beta - k_T V & 0 & -k_T T \\ 0 & 0 & k_T V & -\rho_{T_i} & k_T T \\ 0 & 0 & 0 & \pi_{T_i} & -c \end{bmatrix}. \tag{11}$$

At the health point P_1 the Jacobian matrix becomes

$$J_1 = \begin{bmatrix} (2a_1 - 1)\, p_1 - \mu_1 & 0 & 0 & 0 & 0 \\ 2(1 - a_1)\, p_1 & (2a_2 - 1)\, p_2 - \mu_2 & 0 & 0 & 0 \\ 0 & 2(1 - a_2)\, p_2 & -\beta & 0 & -k_T \dfrac{\lambda_T}{\beta} \\ 0 & 0 & 0 & -\rho_{T_i} & k_T \dfrac{\lambda_T}{\beta} \\ 0 & 0 & 0 & \pi_{T_i} & -c \end{bmatrix}. \tag{12}$$

So the characteristic equation $\det(J_1 - rI) = 0$ has the eigenvalues

$$\begin{aligned} r_1 &= (2a_1 - 1)\, p_1 - \mu_1, \\ r_2 &= (2a_2 - 1)\, p_2 - \mu_2, \\ r_3 &= -\beta, \\ r_{4,5} &= \frac{-\beta\left(c + \rho_{T_i}\right) \pm \sqrt{\left[\beta\left(c + \rho_{T_i}\right)\right]^2 - 4\beta\left[\beta c \rho_{T_i} - k_T \lambda_T \pi_{T_i}\right]}}{2\beta} \\ &= \frac{-\beta\left(c + \rho_{T_i}\right) \pm \sqrt{\beta}\sqrt{\beta c^2 - 2\beta c \rho_{T_i} + 4k_T \lambda_T \pi_{T_i} + \beta {\rho^2}_{T_i}}}{2\beta}. \end{aligned} \tag{13}$$

□

To get the asymptotically stable case for the free disease equilibrium point we shall have for the first and the second roots $(2a_1 - 1)p_1 < \mu_1$ and $(2a_2 - 1)p_2 < \mu_2$ which are true and agree with [30, 31, 36]; since the population of mature cells S_3 reaches some value, then the term $(2a_i(t) - 1)p_i(t)S_i(t) < 0$, for $i < n$, and the number of cells at stage i decreases, while the lowness of the density for the mature cells causes $(2a_i(t) - 1)p_i(t)s_i(t) > 0$, for $i < n$, and if the death rates are not too high, then the number of cells at stage i increases. These show how the level of mature cells affects the dynamics of each cell subpopulation. Also it is clear that $r_3 = -\beta < 0$, and if $R_0 = k_T \lambda_T \pi_{T_i} / c\rho_{T_i}\beta < 1$, then $c\rho_{T_i}\beta^2 > k_T \lambda_T \pi_{T_i}\beta$, so $(\beta(c+\rho_{T_i}))^2 > \beta(\beta c^2 - 2\beta c\rho_{T_i} + 4k_T\lambda_T\pi_{T_i} + \beta{\rho^2}_{T_i})$; then $r_{4,5} < 0$.

If $R_0 = k_T \lambda_T \pi_{T_i} / c\rho_{T_i}\beta > 1$, then $c\rho_{T_i}\beta^2 < k_T\lambda_T\pi_{T_i}\beta$, so $(\beta(c+\rho_{T_i}))^2 < \beta(\beta c^2 - 2\beta c\rho_{T_i} + 4k_T\lambda_T\pi_{T_i} + \beta{\rho^2}_{T_i})$; then $r_{4,5} > 0$. Thus, we get the result.

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

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

To study the endemic point P_2, we need the following lemma.

Lemma 4 (see [37]). *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:

$$r = \frac{1}{3}\left(-a_1 + \sqrt{{a_1}^2 - 3a_2}\right) \tag{14}$$

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

Proof. At the point $(0, 0, (\lambda_T/\beta)(1/R_0), (\beta c/k_T\pi_{T_i})(R_0 - 1), (\beta/k_T)(R_0 - 1))$ the Jacobian matrix becomes

$$J_2 = \begin{bmatrix} (2a_1 - 1)\, p_1 - \mu_1 & 0 & 0 & 0 & 0 \\ 2(1 - a_1)\, p_1 & (2a_2 - 1)\, p_2 - \mu_2 & 0 & 0 & 0 \\ 0 & 2(1 - a_2)\, p_2 & -\beta R_0 & 0 & -k_T \dfrac{\lambda_T}{\beta R_0} \\ 0 & 0 & \beta(R_0 - 1) & -\rho_{T_i} & k_T \dfrac{\lambda_T}{\beta R_0} \\ 0 & 0 & 0 & \pi_{T_i} & -c \end{bmatrix}. \tag{15}$$

So the characteristic equation $\det(J_2 - rI) = 0$ has the eigenvalues $r_1 = (2a_1 - 1)p_1 - \mu_1$, $r_2 = (2a_2 - 1)p_2 - \mu_2$, and the other eigenvalues are roots of the polynomial $f(r) = r^3 + a_1 r^2 + a_2 r + a_3 = 0$, where $a_1 = c + \rho_{T_i} + \beta R_0$, $a_2 = \beta R_0(c + \rho_{T_i})$, and $a_3 = c\rho_{T_i}\beta(R_0 - 1)$. □

Since $R_0 \geq 1$, then $\beta R_0(c + \rho_{T_i}) \geq 0$, and $c\rho_{T_i}\beta(R_0 - 1) \geq 0$. Then, according to Lemma 4, we deduce that P_2 is asymptotically stable.

5. Study of the Mathematical Model of the n-Multistage Stem Cell Therapy for HIV-1 Patients

In this section, we will consider previously given $(n + 2)$-dimensional system (7). As mentioned in the previous section, we can replace $a_i/(1 + \gamma T)$ by a_i for $i = 1, 2, \ldots, n - 1$. Then (7) can be written as

$$\begin{aligned}
\frac{dS_1}{dt} &= (2a_1 - 1)\, p_1 S_1 - \mu_1 S_1,\\
\frac{dS_2}{dt} &= (2a_2 - 1)\, p_2 S_2 + 2(1 - a_1)\, p_1 S_1 - \mu_2 S_2,\\
&\vdots\\
\frac{dS_{n-1}}{dt} &= (2a_{n-1} - 1)\, p_{n-1} S_{n-1} + 2(1 - a_{n-2})\, p_{n-2} S_{n-2}\\
&\quad - \mu_{n-1} S_{n-1},\\
\frac{dT}{dt} &= \lambda_T - (d_T + \mu_n)\, T - k_T \mathrm{TV}\\
&\quad + 2(1 - a_{n-1})\, p_{n-1} S_{n-1},\\
\frac{dT_i}{dt} &= k_T \mathrm{TV} - \rho_{T_i} T_i,\\
\frac{dV}{dt} &= \pi_{T_i} T_i - cV.
\end{aligned} \tag{16}$$

Assume that $d_T + \mu_n = \beta'$. If the basic reproduction ratio of the viruses (that depends on the patient) is given by $R_0 = k_T \lambda_T \pi_{T_i}/c\rho_{T_i}\beta'$, then, using mathematical induction, we can deduce the following theorem.

Theorem 6. *System (16) has two equilibrium points given by the following:*

$P_1(S_1, S_2, \ldots, S_{n-1} T, T_i, V) = (0, 0, \ldots, 0, \lambda_T/\beta', 0, 0)$, *corresponding to the free disease case, and*

$$\begin{aligned}
P_2(S_1, S_2, \ldots, S_{n-1} T, T_i, V) = \Bigg(&0, 0, \ldots, 0, \frac{\lambda_T}{\beta'}\\
&\cdot \frac{1}{R_0}, \frac{\beta' c}{k_T \pi_{T_i}}(R_0 - 1), \frac{\beta'}{k_T}(R_0 - 1)\Bigg),
\end{aligned} \tag{17}$$

corresponding to the endemic case.

Theorem 7. *The free disease case P_1 is asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.*

Remark 8. (1) If $R_0 = 1$, then $P_1 = P_2$

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

Theorem 9. *If $R_0 \geq 1$, then the endemic point P_2 is asymptotically stable.*

6. Conclusion

We have formulated an n-multistage system of ODEs model to study the influence of the treatment of HIV-1 infection with stem cell transplantation. Evidently the effect of the therapy on the viral dynamics depends on the patient (depends on R_0).

(i) If $R_0 \leq 1$, we have only one equilibrium point corresponding to the free disease case $P_1(S_1, S_2, \ldots, S_{n-1}, T, T_i, V) = (0, 0, \ldots, 0, \lambda_T/d_T, 0, 0)$, which is asymptotically stable. We can then conclude that the infected T-cells and virus particles will be cleared and the stem cells exhausted. In this case, the patient is healed

Here we can also add a comment on the best stage we can choose for the mutant cells to be transplanted on the patient.

Since all the components $S_1, S_2, \ldots, S_{n-1}$ of the point P_1 are equal to zero, then it is better to transplant the stem cells when they are nearly transformed to mature T-cells. This result is known in the cases of corneal transplantation, skin transplantation, and cardiac disease.

(ii) If $R_0 > 1$, the free disease case P_1 is unstable, and the infected state $P_2(S_1, S_2, \ldots, S_{n-1}, T, T_i, V) = (0, 0, \ldots, 0, (\lambda_T/d_T)(1/R_0), (d_T c_V/k_T \pi_{T_i})(R_0 - 1), (d_T/k_T)(R_0 - 1))$ is asymptotically stable, which means that any HIV-1 infection for that patient will progress to chronic infection after stem cell exhaustion

Therefore, stem cell therapy will not offer a cure to that infected person ($R_0 > 1$) but simply will help delay progression to the chronic stage. If we repeat the transplantation of stem cells in a manner to prevent its exhaustion from the patient, we can prevent AIDS.

We advise medicine to try to replace the chemical drug therapy with the apparently safe stem cell therapy. But will clinical experiments meet the expectations?

7. Future Works

For more interest we will study a fractional order of mathematical modeling to study multistage stem cell transplantation on HIV-1 patients based on [38, 39]. The presence of a fractional differential order in differential equations can lead to more consistency and more accuracy to real life than the integer-order models because the fractional derivatives enable the description of the memory and hereditary properties inherent in various processes and materials. The most important property of these models is their nonlocal property which does not exist in the integer-order differential operators. We mean by this property that the next state of a model depends not only on its current state but also on all of its historical states.

Data Availability

No data were used to support this study.

Conflicts of Interest

The authors declare that they have no conflicts of interest regarding the publication of this paper.

Acknowledgments

This research was funded by the Deanship of Scientific Research at Princess Nourah bint Abdulrahman University through the Fast-track Research Funding Program.

References

[1] https://commons.wikimedia.org/wiki/User:Splette-Thomas_Splettstoesser, https://www.scistyle.com.

[2] P. B. Gilbert, I. W. McKeague, G. Eisen et al., "Comparison of HIV-1 and HIV-2 infectivity from a prospective cohort study in Senegal," *Statistics in Medicine*, vol. 22, no. 4, pp. 573–593, 2003.

[3] R. W. Doms and J. D. Reeves, "Human immunodeficiency virus type 2," *Journal of General Virology*, vol. 83, no. 6, pp. 1253–1265, 2002.

[4] A. S. Perelson, D. E. Kirschner, and R. D. Boer, "Dynamics of HIV infection of CD4+ T cells," *Mathematical Biosciences*, vol. 114, no. 1, pp. 81–125, 1993.

[5] R. P. Duffin and R. H. Tullis, "Mathematical models of the complete course of HIV infection and AIDS," *Journal of Theoretical Medicine*, vol. 4, no. 4, pp. 215–221, 2002.

[6] R. V. Culshaw and S. Ruan, "A delay-differential equation model of HIV infection of CD4+ T-cells," *Mathematical Biosciences*, vol. 165, no. 1, pp. 27–39, 2000.

[7] D. Kirschner, "Using mathematics to understand HIV immune dynamics," *Notices*, vol. 43, no. 2, pp. 191–202, 1996.

[8] A. S. Perelson and P. W. Nelson, "Mathematical analysis of HIV-1 dynamics in vivo," *SIAM Review*, vol. 41, no. 1, pp. 3–44, 1999.

[9] P. W. Nelson and A. S. Perelson, "Mathematical analysis of delay differential equation models of HIV-1 infection," *Mathematical Biosciences*, vol. 179, no. 1, pp. 73–94, 2002.

[10] O. M. Ogunlaran and S. C. O. Noutchie, "Mathematical model for an effective management of HIV infection," *BioMed Research International*, vol. 2016, Article ID 4217548, 6 pages, 2016.

[11] C. Mora, M. Serzanti, A. Consiglio, M. Memo, and P. Dell'Era, "Clinical potentials of human pluripotent stem cells," *Cell Biology and Toxicology*, vol. 33, no. 4, pp. 351–360, 2017.

[12] M. Nishio, "Human pluripotent stem cells: towards therapeutic development for the treatment of lifestyle diseases," *World Journal of Stem Cells*, vol. 8, no. 2, p. 56, 2016.

[13] L. Li and T. Xie, "Stem cell niche: Structure and function," *Annual Review of Cell and Developmental Biology*, vol. 21, pp. 605–631, 2005.

[14] J. A. Thomson, J. Itskovitz-Eldor, S. S. Shapiro et al., "Embryonic stem cell lines derived from human blastocysts," *Science*, vol. 282, no. 5391, pp. 1145–1147, 1998.

[15] L. M. Hoffman and M. K. Carpenter, "Characterization and culture of human embryonic stem cells," *Nature Biotechnology*, vol. 23, no. 6, pp. 699–708, 2005.

[16] P. K. Nguyen, D. Nag, and J. C. Wu, "Methods to assess stem cell lineage, fate and function," *Advanced Drug Delivery Reviews*, vol. 62, no. 12, pp. 1175–1186, 2010.

[17] P. Hernigou and F. Beaujean, "Treatment of osteonecrosis with autologous bone marrow grafting," *Clinical Orthopaedics and Related Research*, vol. 405, pp. 14–23, 2002.

[18] M. M. Bonab, K. Alimoghaddam, F. Talebian, S. H. Ghaffari, A. Ghavamzadeh, and B. Nikbin, "Aging of mesenchymal stem cells in vitro," *BMC Cell Biology*, vol. 7, no. 14, 2006.

[19] M. Loeffler and H. E. Wichmann, "A comprehensive mathematical model of stem cell proliferation which reproduces most of the published experimental results," *Cell Proliferation*, vol. 13, no. 5, pp. 543–561, 1980.

[20] R. Cowan and V. B. Morris, "Determination of proliferative parameters from growth curves," *Cell Proliferation*, vol. 20, no. 2, pp. 153–159, 1987.

[21] M. Körbling and Z. Estrov, "Adult stem cells for tissue repair—a new therapeutic concept?" *The New England Journal of Medicine*, vol. 349, no. 6, pp. 570–582, 2003.

[22] S. L. M. A. Beeres, F. M. Bengel, J. Bartunek et al., "Role of imaging in cardiac stem cell therapy," *Journal of the American College of Cardiology*, vol. 49, no. 11, pp. 1137–1148, 2007.

[23] J. C. Wu, I. Y. Chen, G. Sundaresan et al., "Molecular imaging of cardiac cell transplantation in living animals using optical bioluminescence and positron emission tomography," *Circulation*, vol. 108, no. 11, pp. 1302–1305, 2003.

[24] O. Lindvall and Z. Kokaia, "Review stem cells for the treatment of neurological disorders," *Nature*, vol. 441, no. 7097, pp. 1094–1096, 2006.

[25] S. U. Kim, I. H. Park, T. H. Kim et al., "Brain transplantation of human neural stem cells transduced with tyrosine hydroxylase and GTP cyclohydrolase 1 provides functional improvement in animal models of Parkinson disease," *Neuropathology*, vol. 26, no. 2, pp. 129–140, 2006.

[26] P. Hagell and P. Brundin, "Cell survival and clinical outcome following intrastriatal transplantation in parkinson disease," *Journal of Neuropathology & Experimental Neurology*, vol. 60, no. 8, pp. 741–752, 2001.

[27] K. Chakrabarty, R. Shetty, and A. Ghosh, "Corneal cell therapy: with iPSCs, it is no more a far-sight," *Stem Cell Research and Therapy*, vol. 9, no. 287, 2018.

[28] C. E. Couri, M. C. Oliveira, A. B. Stracieri et al., "C-peptide levels and insulin independence following autologous non-myeloablative hematopoietic stem cell transplantation in newly diagnosed type 1 diabetes mellitus," *Journal of the American Medical Association*, vol. 301, no. 15, pp. 1573–1579, 2009.

[29] K. A. D'Amour, A. G. Bang, S. Eliazer et al., "Production of pancreatic hormone-expressing endocrine cells from human embryonic stem cells," *Nature Biotechnology*, vol. 24, no. 11, pp. 1392–1401, 2006.

[30] T. Stiehl and A. Marciniak-Czochra, "Characterization of stem cells using mathematical models of multistage cell lineages," *Mathematical and Computer Modelling*, vol. 53, no. 7-8, pp. 1505–1517, 2011.

[31] M. A. Alqudah, S. A. Kallel, and S. Zarea, "Stability of a modified mathematical model of AIDS epidemic can stem cells offer a new hope of cure for HIV1?" *Life Science Journal*, vol. 13, no. 11, 2016.

[32] M. Wu, H. Y. Kwon, F. Rattis, J. Blum, C. Zhao, R. Ashkenazi et al., "Imaging hematopoietic precursor division in real time," *Cell Stem Cell*, vol. 1, no. 5, pp. 541–554, 2007.

[33] M. D. Johnston, C. M. Edwards, W. F. Bodmer, P. K. Maini, and S. J. Chapman, "Examples of mathematical modeling," *Cell Cycle*, vol. 6, no. 17, pp. 2106–2112, 2007.

[34] T. Stiehl and A. Marciniak-Czochra, "Mathematical modeling of leukemogenesis and cancer stem cell dynamics," *Mathematical Modelling of Natural Phenomena*, vol. 7, no. 1, pp. 166–202, 2012.

[35] A. Marciniak-Czochra, T. Stiehl, A. D. Ho, W. Jäger, and W. Wagner, "Modeling of asymmetric cell division in hematopoietic stem cells—regulation of self-renewal is essential for efficient repopulation," *Stem Cells and Development*, vol. 18, no. 3, pp. 377–386, 2009.

[36] P. R. Paździorek, "Mathematical model of stem cell differentiation and tissue regeneration with stochastic noise," *Bulletin of Mathematical Biology*, vol. 76, no. 7, pp. 1642–1669, 2014.

[37] R. Naresh, A. Tripathi, and D. Sharma, "A nonlinear AIDS epidemic model with screening and time delay," *Applied Mathematics and Computation*, vol. 217, no. 9, pp. 4416–4426, 2011.

[38] Y. Ding and H. Ye, "A fractional-order differential equation model of HIV infection of CD4+ T-cells," *Mathematical and Computer Modelling*, vol. 50, no. 3-4, pp. 386–392, 2009.

[39] A. A. Arafa, S. Z. Rida, and M. Khalil, "A fractional-order model of HIV infection with drug therapy effect," *Journal of the Egyptian Mathematical Society*, vol. 22, no. 3, pp. 538–543, 2014.