Global stability for a Multistage stem cells transplantation model on HIV1 patient

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Abstract

This paper considers a mathematical model to study the effect of stem cell transplantation on HIV-1 patients. The model was recently proposed by the author. The viral dynamics is described by three ordinary differential equations covering three populations: uninfected T-cells, infected cells and free virus, but, stem cells lineage passes through many stages to become specialized T- cells. The stability of the equilibrium points has been previously analyzed locally. Here we study the global stability. The proposed analysis can help medicine make the right decision about the proposed therapy

1 | INTRODUCTION

HIV-1 is a retrovirus discovered in 1984 Montagnier [1], that targets the helper CD+T cells of the immune system, making people more vulnerable to diseases and infections. According to the World Health Organization's guidelines, there is no viable cure or vaccine for HIV, but treatments can improve patients' quality of life. Understanding the dynamics of HIV-1 by mathematical modeling plays an important role in medicine. The basic mathematical model that describes the interaction of the immune system with HIV considers three populations: uninfected T cells, infected T cells, and free virus [2-6]

$$\begin{cases} \frac{\mathrm{dT}}{\mathrm{dt}} = \lambda - dT - kTV \\ \frac{dT_i}{\mathrm{dt}} = kTV - \rho T_i \qquad amp; \\ \frac{\mathrm{dV}}{\mathrm{dt}} = \sigma T_i - \mathrm{cV} \end{cases} \tag{1}$$

Inside any organism, damaged cells need to be regenerated by new ones. The new cells need a source, which requires a continuous role to replace the older cells. In each organ stem cells are planning this important role to replace the older cells. 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 [7]. The author and coworkers recently proposed a new mathematical model to treat HIV-1 patients by engraftment of the type of cells able to transform to

T-cells (CD4+T)[8,9] :

$$\begin{cases} \frac{dS_1}{\mathrm{dt}} = (2a_1 - 1)\, p_1 S_1 - \ \ \mu_1 S_1 = F_1(S) \\ \frac{dS_2}{\mathrm{dt}} = (2a_2 - 1)\, p_2 S_2 + 2\,(1 - a_1)\, p_1 S_1 - \ \ \mu_2 S_2 = F_2(S) \\ \vdots \\ \frac{dS_{n-1}}{\mathrm{dt}} = (2a_{n-1} - 1)\, p_{n-1} S_{n-1} + 2\,(1 - a_{n-2})\, p_{n-2} S_{n-2} - \ \ \mu_{n-1} S_{n-1} = F_{n-1}(S) \quad amp; \\ \frac{\mathrm{dT}}{\mathrm{dt}} = \lambda - (d + \ \mu_n)\, T - kTV + 2\,(1 - a_{n-1})\, p_{n-1} S_{n-1} = G_1(S, T, T_i, T_i) \\ \frac{dT_i}{\mathrm{dt}} = kTV - \rho T_i = G_2(S, T, T_i, T_i) \\ \frac{\mathrm{dV}}{\mathrm{dt}} = \sigma T_i - cV = G_3(S, T, T_i, T_i) \end{cases} \tag{2}$$

Where S_i denotes the density of stem cells at thei^{th} stage of differentiation, for$i \ = 1, \ 2, \ \ldots, \ n - \ 1$, p_i denotes the proliferation rate, a_i denotes the fraction of self-renewal, and $\mu_i$denotes the death rate. S_{n-1} transforms to mature T-cells. These T-cells, The T cells transformed from S_{n-1} cells, die at a rate μ_n. The T cells produced by the thymus are generated at rate λ and die at a rate d. T cells become infected by free virus at rate k. Infected cells, T_i, die at rate ρ. Virus particles V are produced at rate σ and are cleared at rate c. S is the vector with components$S_1, \ldots, \ S_{n-1}$

Different numbers of compartment n for the lineage with different systems were chosen in previous stem cell models [10- 15] .

All the constants in system (2) are non negative. We also suppose the following biologically relevant assumptions [16-17] :

$$\begin{cases} S_i\,(0) \geq 0, \ for \ i = 1, \ldots, n \\ \mu_n > 0, \ \mu_i \geq 0, \ for \ i = 1, \ldots, n-1 \\ c > 0, \rho > 0, d > 0, p_i > 0, \ for \ i = 1, \ldots, n-1 \quad amp; \\ a_i \in \left[\ 0, \frac{1}{2}\right), \quad for \ i = 1, \ldots, n-1 \\ (2a_i - 1)\, p_i < \mu_i \ , \quad for \ i = 1, \ldots, n-1 \end{cases} \tag{3}$$

For simplicity, let

$d + \mu_n = d' \ (4)$

$R_0 = \frac{k}{cd'} \ (5)$

We will study, in this article, the global dynamics of (2). In section 2, we shall state the fundamental results concerning the stability of the system. In section 3, we present some lemmas, useful for the study of the global stability that we prove in section 4. We then conclude in the last section and discuss the biological significance of our results

2 | FUNDAMENTAL RESULTS

Theorem 2.1 | Theorem 1 , Alqudah [9]

The system (2) has two equilibrium points given by the following:

$P_u\left(S_1, S_2, \ldots, S_{n-1}, T, T_i, V\right) = (0, 0, \ldots, 0, \frac{\lambda}{d'}, 0, 0)$, corresponding to the uninfected case, and

$P_e\left(S_1, S_2, \ldots, S_{n-1}, T, T_i, V\right) = \left(0, 0, \ldots, 0, \ \frac{\lambda}{d'}\frac{1}{R_0}, \ \frac{d'c}{\varkappa\sigma}\,(R_0 - 1), \ \frac{d'}{k}\,(R_0 - 1)\right)$, corresponding to endemic case.

R_0 is the basic reproduction ratio of the viruses, given by (5)

Remark | 2.2

1- If $R_0 = 1, \ \text{then} \ P_u = P_e$.

2- If $R_0 < 1$, *then* P_e *is impossible.*

Theorem | 2.3

If $R_0 > 1$, then the endemic point P_e is globally asymptotically stable in $\mathbb{R}_+^{n+2}$.

Theorem | 2.4

If $R_0 \leq 1$, then the uninfected point P_u is globally asymptotically stable in $\mathbb{R}_+^{n+2}$.

Corollary | 2.5

The free disease case P_u is unstable if $R_0 > 1$. The endemic point P_e is unstable if $R_0 \leq 1$.

3 | PRELIMINARY LEMMAS

Lemma | 3.1 (classical differential version of Gronwall lemma).

We assume that Θ [?] C^1([0, T); R), T [?] (0, [?]), satisfies the differential inequality

$\dot{\Theta}(t) \leq b(t) + \varphi(t)\,\Theta(t)$on (0, T) (6)

for some φ, b [?] C (0, T),

Then, Θ satisfies the estimate

$\Theta(t) \leq \Theta(0)\, e^{\Phi(t)} + \int_0^t b(\zeta)\, e^{\Phi(t)-\Phi(\zeta)} d\zeta, \qquad \forall t \in [0, t\ )$(7)

where we have defined the primitive function $\Phi(t) := \int_0^t \varphi(\zeta)\,\delta\zeta$

Proof

Let$\chi(t) = \ \Theta(t)\, e^{-\Phi(t)} + \int_0^t b(s)\, e^{-\Phi(s)} \mathrm{ds}$

Then χ is differentiable, and an application of the chain rule shows that

$\dot{\chi}(t) = \left(\dot{\Theta}(t) - \Theta(t)\varphi(t)\right) e^{-\Phi(t)} + b(t)\, e^{-\Phi(t)} = (\dot{\Theta}(t) - \varphi(t)\,\Theta(t) - b(t))e^{-\Phi(t)} \ \leq 0$

The differential inequality (6) means in particular,$\chi(t) \leq \chi(0)\ , \quad \forall t \in [0, t\ )$

and the claim follows.

Corollary | 3.2

If $c_1 \neq 0$ and c_2 are constants, then,

{\displaystyle u'(t)\leq \beta (t)\,u(t),\qquad t\in I^{\circ },}$\dot{\Theta}(t) \leq c_2 + c_1\Theta(t) \Rightarrow \Theta(t) \leq \Theta(0)\, e^{c_1 t} + \frac{c_2}{c_1}(e^{c_1 t} - 1)$

Lemma | 3.3

Consider the triangular system in $\mathbb{R}^n$

$$(\mathrm{TS}) \begin{cases} \dot{X} = F(X), \\ \dot{Y} = G(X, Y) \end{cases}$$

With $X \in \mathbb{R}^{n-k}$, $Y \in \mathbb{R}^k$, F and G C^1 functions. Moreover, we assume

A_1: $X = 0$ is a globally asymptotically stable fixed point for $\dot{X} = F(X)$

A_2: $Y = Y_o$ is a globally asymptotically stable fixed point for $\dot{Y} = G(0, Y)$

A_3: Every forward orbit of (TS) is bounded.

Then, $(0, Y_o)$ is a globally asymptotically stable point for (TS).

Proof

This lemma is known in the case $Y_o = 0$ (see Seibert[17-18])

Suppose now, $Y_o \neq 0$, then take $Z = Y - Y_o$,$g(X, Z) = G(X, Z + Y_o)$,

and apply the known result for the new system

$$\begin{cases} \dot{X} = F(X), \\ \dot{Z} = G(X, Z + Y_o) \end{cases}$$

Lemma | 3.4 (see for example Farina ; Luenberger[19, 20])

The nonnegative octant$\mathbb{R}^n_+ = \{x = (x_1, \ldots, x_i, \ldots, x_n) \in \mathbb{R}^n / x \geq 0\}$is a positively invariant region (i.e. a trajectory that starts in the nonnegative orthant remains there for t≥ 0) for the dynamical system

$$\dot{x}_i = f_i(x_1, \ldots, x_i, \ldots, x_n), \ i = 1, 2, \ldots, n$$

if and only if:

$f_i(x_1 \geq 0, \ldots x_i = 0, \ldots, x_n \geq 0) \geq 0, \forall i \in [1, n]$

4 | GLOBAL STABILITY

4. 1 | Useful Simplification

Let us begin by noticing that, our system (2) can be written in the triangular form in $\mathbb{R}^{n+2}$:

$$(\mathrm{TS}) \begin{cases} \dot{X} = F(X), \\ \dot{Y} = G(X, Y) \end{cases}$$

with$X = S = (S_1, S_2, \ldots, S_{n-1}) \in \mathbb{R}^{n-1}$,$F(S) = MS$

So,

$\dot{S} = F(S) = MS$ (8)

Where M is the triangular matrix

$$\begin{pmatrix} (2a_1 - 1)p_1 - & \mu_1 & amp;0 & amp;0 & amp;\ldots & amp;0 \\ 2(1 - a_1)p_1 & amp;(2a_2 - 1)p_2 - & \mu_2 & amp;0 & amp;\ldots & amp;0 \\ 0 & amp;2(1 - a_2)p_2 & amp;(2a_3 - 1)p_3 - & \mu_3 & amp;\cdots & amp;0 \\ \vdots & amp;\vdots & amp;\vdots & amp;\ddots & amp;\vdots \\ 0 & amp;0 & amp;0 & amp;\cdots & amp;(2a_{n-1} - 1)p_{n-1} - & \mu_{n-1} \end{pmatrix}$$
(9)

and

$Y = (T, T_i, V)$,

$G(S, T, T_i, V) =$

$$\begin{pmatrix} \lambda - (d + \ \mu_n)T - kTV + 2\,(1 - a_{n-1})\,p_{n-1}S_{n-1} \\ kTV - \rho T_i \\ \sigma T_i - \mathrm{cV} \end{pmatrix},$$

$$G\,(0, T, T_i, V) = \begin{pmatrix} \lambda - (d + \ \mu_n)T - k\mathrm{TV} \\ kTV - \rho T_i \\ \sigma T_i - \mathrm{cV} \end{pmatrix}$$

$$\dot{Y} = G\,(0, T, T_i, V) \Leftrightarrow \textit{system}\ \ (1)\,,\ \textit{with "}d\textit{" replaced by "}d' = (d + \ \mu_n)\textit{"}$$

So, we need to study the global stability of the system (1)

Let us begin by proving the boundedness of the solutions of system (2)

4. 2 | Positivity and boundedness

Since in our model (2), we study the evolution of cells, we need the following result:

Theorem | 4.1

The nonnegative octant $\mathbb{R}_+^{n+2}$ is positively invariant by system (2)

Proof

We have just to apply lemma 3.4

$F_1(S_1 = 0, S_2 \geq 0, \ldots, S_{n-1} \geq 0) = 0 \geq 0,$

$F_2\left(S_1 \geq 0, S_2 = 0, \ldots, S_{n-1} \geq 0\right) = 2\,(1 - a_1)\,p_1 S_1 \geq 0, \quad since \quad a_1 \leq 1$

$\vdots$

$$F_{n-1}\left(S_1 \geq 0, \ldots, S_{n-1} = 0\right) = 2\,(1 - a_{n-2})\,p_{n-2}S_{n-2} \geq 0, \quad since \quad a_{n-2} \leq 1$$

$$G_1\,(S \geq 0,\ T = 0, T_i \geq 0,\ \ V \geq 0) = \lambda + 2\,(1 - a_{n-1})\,p_{n-1}S_{n-1} \geq 0,\ since\ \ a_{n-1} \leq 1$$
$$G_2\,(S \geq 0,\ T \geq 0, T_i = 0,\ \ V \geq 0) = \mathrm{kTV} \geq 0$$
$$G_3\,(S \geq 0,\ T \geq 0, T_i \geq 0,\ V = 0) = \sigma T_i \geq 0$$

Theorem | 4.2

Every forward orbit of (2) inside $\mathbb{R}_+^{n+2}$ is bounded.

Proof

The simple integration of the equation (8) gives the solution$S\,(t) = e^{\mathrm{tM}}S\,(0)$, which is bounded, since the eigenvalues of the matrix M (given by (9) are negative)

Let $W\,(t) = T + T_i$, then,

$\dot{W}(t) = \lambda - d'T - kTV + 2\,(1 - a_{n-1})\,p_{n-1}S_{n-1} + kTV - \rho T_i$

$$= \lambda + 2\,(1 - a_{n-1})\,p_{n-1}S_{n-1} - d'T - \rho T_i \leq \lambda' - \min\,(d', \rho)\,W\,(t)$$

and,

$$\dot{W}(t) \leq a - \mathrm{bW}\,(t)$$

we deduce, by corollary 3.2,

$W(t) \leq \frac{a}{b} + (W(0) - \frac{a}{b})e^{-bt} \leq \frac{2a}{b} + \mathrm{W}(0) = c_1$

Finally,

$$\dot{V}(t) = \sigma T_i - \mathrm{cV} \leq \sigma c_1 - cV$$

and we conclude by corollary 3.2, in a similar way.

4. 3 | Stability of system (1), with d replaced by d'

We need to remark that if (T, T_i, V) is a solution for (1), then (0, T, T_i, V) is also a solution for (2), so, will remain in the positive octant, and bounded.

For simplicity, we drop the prime from d'

Theorem 4.3

1. If R_0 [?] 1, then the infection free-equilibrium$P_u{}^* = (\frac{\lambda}{d}, 0, 0)$ is globally asymptotically stable for (1) in the positive octant $\mathbb{R}^3_+$.
2. If $R_0 > 1$, then, the endemic equilibrium point$P_e{}^* = (\frac{\lambda}{d}\frac{1}{R_0},\ \frac{dc}{\varkappa\sigma}(R_0 - 1),\ \frac{d}{k}(R_0 - 1))$ is globally asymptotically stable for the system (1) in the positive octant $\mathbb{R}^3_+$

Where R_0 is the basic reproduction ratio, given by (5)

Proof

We use the Lyapunov method. Let

$L = \frac{\sigma}{\rho}\int_{\frac{\lambda}{d}}^{T} \frac{\xi - \frac{\lambda}{d}}{\xi}\mathrm{d}\ \xi + \frac{\sigma}{\rho}T_i + V$

on $\mathbb{R}^3_+$

Evidently, $L(P_u{}^*) = 0$ and $L > 0$, in$\mathbb{R}^3_+ \setminus \{P_u{}^*\}$

The derivative of L along the solutions of (1) is

$$\dot{L} = \frac{\sigma}{\rho}(\lambda - dT - kTV)\frac{T - \frac{\lambda}{d}}{T} + \frac{\sigma}{\rho}(kTV - \rho T_i) + \sigma T_i - \mathrm{cV}$$

$$= \frac{\sigma}{\rho}(\lambda - dT - kTV)\frac{T - \frac{\lambda}{d}}{T} + \frac{\sigma}{\rho}(\mathrm{kTV}) - \mathrm{cV}$$

$$= \frac{-\sigma}{\delta\mathrm{T}\rho}(\lambda - dT)^2 - \frac{\sigma\varkappa}{}$$

greekdTV(d+-$\lambda\frac{}{T)+\frac{\sigma k}{\rho}TV - \mathrm{cV}}$

$$= \frac{-\sigma}{\delta\mathrm{T}\rho}(\lambda - dT)^2 + \left(\frac{\mathrm{k}}{\mathrm{d}} + c\right)V = \frac{-\sigma}{\delta\mathrm{T}\rho}(\lambda - dT)^2 + \left(\frac{\mathrm{k}}{\mathrm{dc}} - 1\right)\mathrm{cV}$$

$$\dot{L} = \frac{-\sigma}{d'\mathrm{T}\rho}(\lambda - dT)^2 + (R_0 - 1)\,\mathrm{cV}$$

And $\dot{L} < 0$ in$\mathbb{R}^3_+ \setminus \{P_u{}^*\}$ if and only if $R_0 \leq 1$

Now, for the endemic point, we use LaSalle's principle. let$T^* = \frac{\lambda}{d}\frac{1}{R_0}$,$T_i{}^* = \frac{dc}{\varkappa\sigma}(R_0 - 1)$, $V^* = \frac{d}{k}(R_0 - 1)$, and

$L = \int_{T^*}^{T} \frac{\xi - T^*}{\xi}\mathrm{d}\,\xi + \int_{T_i{}^*}^{T_i} \frac{\xi - T_i{}^*}{\xi}\mathrm{d}\,\xi + \frac{\rho}{\sigma}\int_{V^*}^{V} \frac{\xi - V^*}{\xi}\mathrm{d}\,\xi$

The derivative of L along the solutions of (1) is

$\dot{L} = (\lambda - dT - kTV)\frac{T - T^*}{T} + \frac{T_i - T_i{}^*}{T_i}(kTV - \rho T_i) + \frac{\rho}{\sigma}\frac{V - V^*}{V}(\sigma T_i - \mathrm{cV})$

$= (\lambda - dT) - (\lambda - dT - kTV)\frac{T^*}{T} - \frac{T_i{}^*}{T_i}(kTV - \rho T_i) + \frac{\rho}{\sigma}(-\mathrm{cV}) - \frac{\rho}{\sigma}\frac{V^*}{V}(\sigma T_i - \mathrm{cV})$

$=\lambda - dT\ - \lambda\frac{T^*}{T} + dT^* - \mathrm{kTV}\frac{T_i{}^*}{T_i} - \rho T_i\frac{V^*}{V} + \frac{\varsigma\rho}{\sigma}V^* + \rho T_i{}^*$

$= \mathrm{d}T^*\left[2 - \frac{T^*}{T} - \frac{T}{T^*}\right] + \rho T_i{}^*\left[3 - \frac{k}{\rho}\frac{\mathrm{TV}}{T_i} - \frac{\rho}{k}\frac{T_i{}^*}{TV^*} - \frac{V^*T_i}{VT_i{}^*}\right]$

Since

$x + \frac{1}{x} - 2$ and $x + y + \frac{1}{\mathrm{xy}} - 3$

are non negative for all x, y positive, we deduce $\dot{L} \leq 0$

$$\dot{L} = 0 \Leftrightarrow \left[2 - \frac{T^*}{T} - \frac{T}{T^*}\right] = \left[3 - \frac{k}{\rho}\frac{\mathrm{TV}}{T_i} - \frac{\rho}{k}\frac{T_i{}^*}{TV^*} - \frac{V^*T_i}{VT_i{}^*}\right] = 0$$

$$\Leftrightarrow (T - T^*)^2 = \left[3 - \frac{k}{\rho}\frac{\mathrm{TV}}{T_i} - \frac{\rho}{k}\frac{T_i{}^*}{TV^*} - \frac{V^*T_i}{VT_i{}^*}\right] = 0$$

$$\Leftrightarrow T = T^* \text{and}\left[2 - \frac{c}{\sigma}\frac{V}{T_i} - \frac{\sigma T_i}{\mathrm{cV}}\right] = 0$$

$$\Leftrightarrow T = T^* \text{ and } (cV - \sigma T_i)^2 = 0$$

$\Leftrightarrow T = T^*$ and$V = \frac{\sigma}{c}T_i$

The largest invariant subset of $\left\{\dot{L} = 0\right\}$ by (1) in the positive octant, satisfies $T = T^*$, then $\dot{T} = 0$and $\lambda - d^{'}T^* - kT^*V = 0 \Leftrightarrow V = V^*$

So, the largest invariant subset of $\left\{\dot{L} = 0\right\}$ by (1) is reduced to $\{{P_e}^*\}$

then from LaSalle's invariance principal, we conclude the global asymptotic stability.

4. 4 | Proof of the principle results

Let us prove the free disease case$P_u = (0, 0, \ldots, 0, \frac{\lambda}{d}, 0, 0)$ is globally asymptotically stable in $\mathbb{R}_+^{n+2}$ if $R_0 \leq 1$

If $R_0 \leq 1$, we have just to apply lemma 3.3. Since A_3 is already done in subsection 4.2, we have to verify A_1 and A_2

$\mathrm{A}_{1:}$ The global stability of $S = 0$ for the liner system $\dot{S} = MS$, where M is the matrix given by (9), is insured by the negativity of the eigenvalues of the matrix M.

$\mathrm{A}_{2:}$ $X_o = (\frac{\lambda}{d}, 0, 0)$ is globally asymptotically stable in $\mathbb{R}_+^3$, for the equation

$$\dot{X} = G(X, 0) \Longleftrightarrow (1), \text{"}d\text{" } \textit{replaced by } \text{"}d' = (d + \ \mu_n)\text{"}$$

This is already given by part (i) of theorem 4.3

If $R_0 > 1$, then, let us prove the endemic point P_e is globally asymptotically stable for (2) in the positive octant$\mathbb{R}_+^{n+2}$. Like for the previous paragraph, we have just to apply lemma 3.3, so,

we have just to verify A_1, since A_2 and A_3 have been already done.

$A_2 : X_o = (\frac{\lambda}{d}\frac{1}{R_0},\ \frac{dc}{\varkappa\sigma}(R_0 - 1),\ \frac{d}{k}(R_0 - 1))$ is a globally asymptotically stable point for

$$\dot{X} = G(X, 0) \Longleftrightarrow (1), "d" \textit{ replaced by } "d' = (d + \ \mu_n)"$$

This is already given by part (ii) of theorem 4.3

5 | NUMERICAL SIMULATIONS

5.1 | Before infection: system1

1-Patient 1 ($R_0 > 1$)

TABLE 1 Estimates of parameters values

Parameter	Biological Meaning	Normal Value
$T[0]$	The concentrations of uninfected $CD4^+T$ cells at time t=0	$10ml^{-1}$ [21]
$T_i[0]$	Infected cells at time t=0	0 ml^{-1} [21]
$V[0]$	free virus particles at time t=0	10^{-6} ml^{-1} [21]
λ	The recruitment rate of uninfected T cells from the body	$0.17ml^{-1}$ day^{-1} [22]
d	The death rate of T cells produced by the body	0.017 day^{-1} [22]
K	Infection rate of T cells by free viruses	6.3X 10^{-4} ml day^{-1} [22]
ρ	The death rate of cells	0.39 ml^{-1} day^{-1} [22]
σ	The rate of production of virions by infected cells	870 day^{-1} [22]
c	The clearance rate of free virus	3 day^{-1} [22]

a b

c

FIGURE 1 Numerical solutions to model (1) for a patient with parameters given by table 1, R_0= 4.68

2- **Patient 2** ($R_0 < 1$)

TABLE 2 Estimates of parameters values

Parameter	Biological Meaning	Normal Value
$T[0]$	The concentrations of uninfected $CD4^+T$ cells at time t=0	$10ml^{-1}$ [21]
$T_i[0]$	Infected cells at time t=0	0 ml^{-1} [21]
$V[0]$	free virus particles at time t=0	10^{-6} ml^{-1} [21]
λ	The recruitment rate of uninfected T cells from the body	$30ml^{-1}$ day^{-1} [23]

d	The death rate of T cells produced by the body	0.01 day^{-1} [23]
K	Infection rate of T cells by free viruses	0.001 ml day^{-1} [23]
ρ	The death rate of cells	0.8 ml^{-1} day^{-1} [23]
σ	The rate of production of virions by infected cells	5 day^{-1} [23]
c	The clearance rate of free virus	23 day^{-1} [23]

a b

c

FIGURE 2 Numerical solutions to model (1) for a patient with parameters given by tables 1,R_0= 0.815

5.2 | After treatment: system 2

System(2) with n=2 becomes

$$\begin{cases} \frac{dS_1}{\mathrm{dt}} = (2a_1 - 1)\, p_1 S_1 - \ \mu_1 S_1 = F_1(S) \\ \frac{\mathrm{dT}}{\mathrm{dt}} = \lambda - (d + \ \mu_2)\, T - kTV + 2\,(1 - a_1)\, p_1 S_1 = G_1(S, T, T_i, T_i) \\ \frac{dT_i}{\mathrm{dt}} = kTV - \rho T_i = G_2(S, T, T_i, T_i) \\ \frac{\mathrm{dV}}{\mathrm{dt}} = \sigma T_i - cV = G_3(S, T, T_i, T_i) \end{cases} amp; \quad (2)$$

TABLE 3 Estimates of parameters values for the stem cell division model

$(2a_1 - 1)\, p_1 - \ \mu_1$	-0.222	[24,25]
$(d + \ \mu_2)$	1.397	[24,25]
$2\,(1 - a_1)\, p_1$	1.0836	[24,25]

a b

c d

FIGURE 3 Numerical solutions to model (2) for a patient with parameters given by tables 3, ($R_0 = 0.0341$).

6 | CONCLUSION AND DISCUSSION

This paper presents a study on the global stability of a system of ODEs, recently introduced [8]. The system represents a new model to study the influence of the treatment of HIV-1 infection with stem cell transplantation, with multistage stem cell lineage. The results show that the basic reproduction number of virus$R_0 = \frac{k}{c(d+\mu_n)}$ is a sharp number that decreases with increasing μ_n, a constant that depends on the flux to death of the final stage of stem cell lineage.

If $R_0 > 1$, then we found that the endemic point P_e is globally asymptotically stable in $\mathbb{R}_+^{n+2}$.

If $R_0 \leq 1$, then we proved that the uninfected point $P_u$is globally asymptotically stable in $\mathbb{R}_+^{n+2}$.

So, a person with $R_0 = \frac{k}{cd} < 1$ (before stem cell injection, corresponding to equation (1)), do not need to be treated, since the uninfected point ${P_u}^*$ is globally asymptotically stable for the system (1). The ill person will be automatically healed after a certain time, without any need to the therapy.

Contrariwise, for a person with$R_0 = \frac{k}{cd} > 1$ (before stem cell injection), there are two possibilities:

If biologically, it is possible to inject stem cells to lower the reproduction number $R_0 = \frac{k}{c(d+\mu_n)}$ to make it smaller than 1, then, the patient will be healed after a certain time of therapy, since P_u is globally asymptotically stable for the system (2).

If medically, it is not possible to lower the reproduction number $R_0 = \frac{k}{c(d+\mu_n)}$, to make it smaller than 1, then, the patient will never be healed.

Moreover, since the endemic point

$$P_e\left(S_1, S_2, \ldots, S_{n-1}, T, T_I, V\right) = \left(0, 0, \ldots, 0,\ \frac{\lambda}{d'}\frac{1}{R_0},\ \frac{d'c}{\varkappa\sigma}\left(R_0 - 1\right),\ \frac{d'}{k}\left(R_0 - 1\right)\right)$$

of our stem cell therapy (2), in the case $R_0 > 1$, is globally asymptotically stable , and has all its first components$S_1,\ S_2, \ldots, S_{n-1}$ (corresponding to stem cell stages) equal to zero, then, either in the case when stem cell therapy can not offer a cure to that infected person with very high reproduction number, if we repeat the transplantation of stem cells in a manner to prevent its exhaustion from the patient, we delay progression to the chronic stage, and can prevent AIDS.

Conflict of Interest Statement: no conflict

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