Persistence of low levels of plasma viremia and of the latent reservoir in patients under ART: a fractional-order approach

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Abstract

Low levels of viral load are found in HIV-infected patients, after many years under successful suppressive anti-retroviral therapy (ART). The factors leading to this persistence are still under debate, but it is now more or less accepted that the latent reservoir may be crucial to the maintenance of this residual viremia. In this paper, we study the role of the latent reservoir in the persistence of the latent reservoir and of the plasma viremia in a fractional-order (FO) model for HIV infection. Our model assumes that (i) the latently infected cells may undergo bystander proliferation, without active viral production, (ii) the latent cell activation rate decreases with time on ART, (iii) the productively infected cells' death rate is a function of the infected cell density. The proposed model provides new insights on the role of the latent reservoir in the persistence of the latent reservoir and of the plasma virus. Moreover, the fractional-order derivative distinguishes distinct velocities in the dynamics of the latent reservoir and of plasma virus. The later may be used to better approximations of HIV-infected patients data. To our best knowledge, this is the first FO model that deals with the role of the latent reservoir in the persistence of low levels of viremia and of the latent reservoir.

Keywords: latent reservoir, long-lived cells, ongoing replication of HIV virus, ART, fractional

1. Introduction

The human immunodeficiency virus (HIV) is a retrovirus that impairs the immune system and leads ultimately to death, when untreated. The Joint United Nations Programme on HIV/AIDS (UNAIDS) reported that 35 million people were estimated to be infected with HIV, by the end of 2013. New infections accounted for 2.1 million in the same year. AIDS-related deaths had declined 35% since 2005, being tuberculosis the main cause of death in HIV infected patients. Nevertheless, 1.5 million people still died from AIDS-related illnesses [34]. UNAIDS report also shows that 19 million people out of the 35 million infected with HIV are unknown of their HIV-positive status. This will likely promote the spread of the infection.

HIV patients on treatment are commonly subjected to a cocktail of three drugs, one protease inhibitor (PIs) and two reverse transcriptase inhibitors (RTIs), known as Highly Active Anti-Retroviral Therapy (HAART). Despite many years of high efficacy of HAART, it is possible to observe, in these patients, the persistence of latently infected cells and of low levels of plasma virus [10, 8]. The decay of the plasma virus in HIV patients under HAART, is characterized by three distinct phases [16]. In the first two weeks of therapy (phase I) there is an initial shoulder stage, due to some delays in the production of progeny virus by infected cells and in pharmacokinetics, followed by a decrease of one to two orders of magnitude in the plasma virus. The later is explained by the immune system response that clears the virus, and by the decline of the short-lived infected $CD4^+$ T cells, with a half-life of less than a day. The second phase of viral decay is slower than the first, with a half-life of 1-4 weeks. In this phase the plasma virus receives contributions from several sources, namely the long-lived HIV infected cells, the infected $CD4^+$ T cells in lower activation states (that allow lower levels of viral replication), and tissues, namely folicular dendritic cells [13]. The last (third) phase has a half-life of months or even years and is distinguished by viral loads below 50 copies/ml.

There is still an open debate concerning the decay properties of the latent reservoir and of plasma viremia in patients under HAART, and their relative contribution. Strain *et al*[31, 32] suggest that the pool of latently infected T cells is heterogeneous, with a half-life of 18 weeks, in the first year of HAART, and of 58 weeks in the subsequent 3 years of HAART. These cells are responsible for competent virus replication. As such, eradication of HIV virus is not fully achieved with complete inhibition of ongoing viral

replication. Dornadula *et al* [10] detect HIV-1 RNA in plasma by ultrasensitive assays, in patients taking suppressive HAART. This finding suggests two important mechanisms of viral persistence: viral latency in quiescent CD4+ T lymphocytes and other cell types, and ongoing low-level viral replication. Perelson and co-workers [16, 7] propose integer-order models to explain the factors that determine the persistence of the latent reservoirs and of low levels of plasma viremia and their relative contributions. In 2006, Kim and Perelson [16] analyse a simple model for HIV that assumes the existence of bystander proliferation of latently infected cells and that the rate of latent cell activation is decreased with time under HAART. They test the role of the T cell bystander proliferation, activation of latent cells, and ongoing viral replication, in the levels of plasma viremia and the stability of the latent reservoir. They find that the proliferation of latent cells contributes to maintain the latent reservoir and influences viral dynamics. On the other hand, ongoing viral replication, for lower drug efficacies, contributed to the persistence of the latent reservoir and the virus. Viral blips, that describe intermittent episodes of detectable viremia, in well supressed patients, were not considered in their work. Conway and Perelson [7] propose simple deterministic and stochastic models to study plasma viremia in HIV treated patients. The model assumes that latent cell activation occurs in patients and that the reproductive ration, during suppressive ART, is less than one. Authors conclude that latent cell activation drives viral dynamics. Moreover, if the effectiveness of therapy is close to 100% then the contribution of ongoing viral replication for persistence of low-levels viremia is very low.

Fractional Calculus (FC) is a generalization of integration and differentiation to non-integer orders. Leibniz and Newton were the first mathematicians to propose and develop this new approach to Calculus. In a famous letter exchange, in 1695, Leibniz questioned L'Hôpital about the possibility of generalizing the concept of integer-order derivatives to non-integer orders. L'Hôpital replied concerned about the consequences of considering a $1/2$ order derivative. Leibniz ends with a 'prophecy' saying that a $1/2$ order would lead to useful consequences in the future. More on fractional calculus can be seen in [23, 20, 28, 4]. Fractional-order (FO) derivatives use more information about the system under study than integer-order ones. In other words, fractional operators are 'memory-like operators, in contrast with integer-order ones, that are local operators. Most commonly, in a FO system, the state of the system at a given moment t depends on the states before t, namely $t-1$, $t-2, \cdots$. For the last few years, FC has been applied in many areas of science,

namely electrochemistry, physics, fluid mechanics, mechanical systems, and other areas of engineering, and biology [22, 21, 9, 26, 24, 17, 2, 36, 14, 18, 5]. In [37] the authors study the stability of the disease-free and of the endemic equilibria of a FO model for HIV infection with time delay. They give conditions to ensure the asymptotic stability of the two equilibria under some conditions on the delay. In 2013, Arafa *et al* [3] study the effect of treatment in a FO model for HIV-1 dynamics. The same authors [2], in 2014, compare the numerical results of a FO model for HIV epidemics with data from 10 HIV patients and conclude that the FO model fits better the data of the patients' plasma viral load than the integer-order model. In [25], Pinto *et al*, propose a fractional complex-order model for drug resistance in HIV infection. Distinct growth rates for the $CD4^+$ T helper cells were considered. Results from the FO system reveal rich dynamics and variation of the value of the complex-order derivative sheds new light on the modelling of the intracellular delay. Moreover, sustained oscillations (viral blips) appear as the proliferation rate of $CD4^+$ T cells increases.

In this paper, we study the contribution of the latent reservoir in the persistence of low-level viremia and the latent reservoir in a FO model for HIV infection. We do not consider viral blips. To our best knowledge it is the first FO model that deals with these important issues in HIV dynamics. In Section 2 we present the model. In Section 3 we compute the reproduction number of the model and compute the stability of the disease-free equilibrium. The discussion of the results of the simulations of the model are done in Section 4. Last section is devoted to the conclusions.

2. Model

We propose the following integer-order model to describe the dynamics of the production and clearance of HIV-1 virus during HAART, where latently infected and long-lived chronically infected cells are considered.

$$\dot{T} = \lambda + p\left(1 - \frac{T}{T_{max}}\right) - (1-\epsilon)kVT - \delta_T T \quad (1)$$

$$\dot{L} = f(1-\epsilon)kTV + rL - aL \quad (2)$$

$$\dot{I} = (1-\alpha)(1-f)(1-\epsilon)kTV + aL - mEI - \delta_I I I^{\omega} \quad (3)$$

$$\dot{C} = \alpha(1-f)(1-\epsilon)kVT - mEC - \delta_C C \quad (4)$$

$$\dot{V} = N_s\delta_I I + N_c\delta_C C - cV \quad (5)$$

$$\dot{E} = \lambda_E + \rho_1 IE + \rho_2 CE - \delta_E E \quad (6)$$

$$\dot{a} = -\nu(a - a_{min}) \quad (7)$$

The dynamics of the CD4$^+$ T cells, T, is modelled by equation (1). These cells are generated by thymus at a rate λ and by proliferation of existing cells given by the second term, where p is the maximum proliferation rate, and T_{max} is the target cell density. They die at a rate $\delta_T T$. T cells are infected by HIV at a rate k. Parameter ϵ is the efficacy of combined therapy in blocking the infection, where $\epsilon = (1-\epsilon_{PI})(1-\epsilon_{RTI})$, and ϵ_{PI} is the drug efficacy of PIs, and ϵ_{RTI} is the drug efficacy of RTIs. A 100% effective therapy corresponds to $\epsilon = 1$.

A fraction f of CD4$^+$ T cells becomes latently infected. The latently infected cells, L, may also be regenerated at a rate r, where $r = p_{bs} - \delta_L$, and p_{bs} denotes the rate of bystander proliferation and δ_L is the death rate. The bystander proliferation is defined as an occasional proliferation of (latently infected) memory T cells, which does not induce the cell's activation into viral production. This bystander proliferation was observed in mice and, assuming that exists in humans, could increase the stability of the latent reservoir [16].

The latently infected cells are activated and become productively infected T cells, I, at a rate a (equation (3)). We assume that the activation rate constant decays exponentially in time, from an initial value a_0, to a certain minimum a_{min} (equation (7)). The productively infected cells' death rate is chosen to be a function of infected cell density. In order to do so, we use a power law obtaining $\delta_I I I^{\omega}$.

A fraction η of productively infected cells, I, becomes long-lived chronically infected cells, C (equation (4)). These cells are killed by the immune response at a rate mEC and die at a rate $\delta_C C$.

Equation (5) gives the dynamics of the virus. Virus are produced by

productively infected and long-lived chronically infected cells, I and C, at rates $N_s\delta_I I$ and $N_c\delta_C C$. Their clearance rate is c.

The Cytotoxic T Lymphocytes (CTLs) - equation (6) - proliferate due to infected cells, I and C, at rates $\rho_1 IE$ and $\rho_2 CE$, respectively. Effector cells are assumed to be produced at rate λ_E and are lost at rate $\delta_E E$. The effector cells grow at a rate that depends upon the pre-existence of other effector cells and infected cells. This is motivated by the notion that precursor CTLs encounter infected cells and subsequently proliferate into mature effectors.

We will now consider the fractional derivative of model $(1)-(7)$, used in the Caputo sense, i.e.:

$$\frac{d^\alpha y(t)}{dt^\alpha} = I^{p-\alpha} - y^{(p)}(t), \quad t > 0$$

where α is the order of the fractional derivative, $p = [\alpha]$ is the value of α rounded up to the nearest integer, $y^{(p)}$ is the p-th derivative of $y(r)$, $I^{\star p}$ is the Riemman-Liouville operator of order $\star p > 0$ given by:

$$I^{p^\star} z(t) = \frac{1}{\Gamma(p^\star)} \int_0^t \left(t - t^{'}\right)^{p^\star - 1} z(t^{'}) dt^{'}$$

where $\Gamma(p^\star)$ is the gamma function.
The fractional-order model associated to the integer-order model described by equations $(1)-(7)$ is given by:

$$\frac{d^\alpha T}{dt^\alpha} = \lambda^\alpha + p\left(1 - \frac{T}{T_{max}}\right) - (1-\epsilon)k^\alpha VT - \delta_T^\alpha T \tag{8}$$

$$\frac{d^\alpha L}{dt^\alpha} = f(1-\epsilon)k^\alpha TV + r^\alpha L - aL \tag{9}$$

$$\frac{d^\alpha I}{dt^\alpha} = (1-\eta)(1-f)(1-\epsilon)k^\alpha TV + aL - m^\alpha EI - \delta_I^\alpha II^\omega \tag{10}$$

$$\frac{d^\alpha C}{dt^\alpha} = \eta(1-f)(1-\epsilon)k^\alpha VT - m^\alpha EC - \delta_C^\alpha C \tag{11}$$

$$\frac{d^\alpha V}{dt^\alpha} = N_s\delta_I^\alpha I + N_c\delta_C^\alpha C - c^\alpha V \tag{12}$$

$$\frac{d^\alpha E}{dt^\alpha} = \lambda_E + \rho_1^\alpha IE + \rho_2^\alpha CE - \delta_E^\alpha E \tag{13}$$

$$\frac{d^\alpha a}{dt^\alpha} = -\nu(a - a_{min}) \tag{14}$$

We note that the existence of the fractional-order derivative α on both sides in the equations of the model has to do with considering the same time dimension $(time)^{-\alpha}$ on both sides.

2.1. Model reduction

In this section, we reduce the FO model given by equations $(8)-(14)$, by applying valid clinical assumptions and relations among variables and parameters.

We start by assuming that the number of helper T cells remains constant. This can be explained by the fact that $CD4^+$ T cells increase slowly in patients under suppressive HAART, after an initial transient increase phase [12]. Moreover, the proportion of productively infected cells, of patients in therapy, is small in the peripheral blood T cell population. Thus, we let $T = T_0$, that represents a quasi-steady state value of T. As such, the model described by equations $(8)-(14)$ is reduced to:

$$\frac{d^\alpha L}{dt^\alpha} = f(1-\epsilon)k^\alpha T_0 V + r^\alpha L - aL \tag{15}$$

$$\frac{d^\alpha I}{dt^\alpha} = (1-\eta)(1-f)(1-\epsilon)k^\alpha T_0 V + aL - m^\alpha EI - \delta_I^\alpha I I^\omega \tag{16}$$

$$\frac{d^\alpha C}{dt^\alpha} = \eta(1-f)(1-\epsilon)k^\alpha V T_0 - m^\alpha EC - \delta_C^\alpha C \tag{17}$$

$$\frac{d^\alpha V}{dt^\alpha} = N_s\delta_I^\alpha I + N_c\delta_C^\alpha C - c^\alpha V \tag{18}$$

$$\frac{d^\alpha E}{dt^\alpha} = \lambda_E + \rho_1^\alpha IE + \rho_2^\alpha CE - \delta_E^\alpha E \tag{19}$$

$$\frac{d^\alpha a}{dt^\alpha} = -\nu(a - a_{min}) \tag{20}$$

3. Reproduction number

We compute the reproduction number, R_0, of the FO model described by equations $(15)-(20)$ using the next generation method [35], and the local stabilities of its disease-free equilibrium. R_0 represents the average number of secondary infected cells which will result from a single infected cell in a population of susceptible $CD4^+$ T cells.

The disease-free equilibrium of the fractional-order model is given by:

$$P_0 = (L_0, I_0, C_0, V_0, E_0, a_0) = \left(0, 0, 0, 0, \frac{\lambda_E}{d_E}, a_{min}\right) \quad (21)$$

The matrix of the new infections terms, F, is given by:

$$F = \begin{bmatrix} 0 & 0 & 0 & f(1-\epsilon)k^\alpha T_0 \\ 0 & 0 & 0 & (1-\eta)(1-f)(1-\epsilon)k^\alpha T_0 \\ 0 & 0 & 0 & \eta(1-f)(1-\epsilon)k^\alpha T_0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

The matrix of the other terms, V, is computed to be:

$$V = \begin{bmatrix} a-r & 0 & 0 & 0 \\ a & m^\alpha E_0 & 0 & 0 \\ 0 & 0 & m^\alpha E_0 + \delta_C^\alpha & 0 \\ 0 & -N_s\delta_I^\alpha & -N_c\delta_C^\alpha & c^\alpha \end{bmatrix}$$

The associative basic reproduction number is thus:

$$R_0 = T_0 k(1-\epsilon)\frac{1}{E_0 c^\alpha m^\alpha (a_{min}-r)(\delta_C^\alpha + E_0 m^\alpha)}\Bigg(N_s\delta_C^\alpha\delta_I^\alpha\left[(a_{min}-r)(1-\eta-f-\eta f)-a\right] +$$

$$+ E_0 N_s \delta_I^\alpha m^\alpha \left[(a_{min}-r)(1-\eta-f)-a\right] + E_0 N_c \delta_C^\alpha \eta m^\alpha \left[(a_{min}-r)(1-f)\right]\Bigg)$$

where ρ indicates the spectral radius of FV^{-1}.

Lemma 1. *[19] The disease-free equilibrium P_0 is locally asymptotically stable if all eigenvalues λ_i of the linearization matrix of the fractional-order model described by equations* $(15)-(20)$*, satisfy* $|arg(\lambda_i)| > \alpha\frac{\pi}{2}$.

Proof. The matrix of the linearization of the fractional-order model described by equations $(15)-(20)$, around the disease-free equilibrium P_0, is given by:

$$M = \begin{bmatrix} r-a_{min} & 0 & 0 & f(1-\epsilon)k^\alpha T_0 & 0 & 0 \\ a_{min} & -m^\alpha E_0 & 0 & (1-\eta)(1-f)(1-\epsilon)k^\alpha T_0 & 0 & 0 \\ 0 & 0 & -(m^\alpha E_0 + \delta_C^\alpha) & \eta(1-f)(1-\epsilon)k^\alpha T_0 & 0 & 0 \\ 0 & N_s\delta_I^\alpha & N_c\delta_C^\alpha & -c^\alpha & 0 & 0 \\ 0 & \rho_1^\alpha E_0 & \rho_2^\alpha E_0 & 0 & -\delta_E^\alpha & 0 \\ 0 & 0 & 0 & 0 & 0 & -\nu \end{bmatrix}$$

The following eigenvalues are easily obtained and are real and negative:

$$-\nu,\ -\delta_E^\alpha$$

The remaining eigenvalues are the roots of the characteristic equation of the 4×4 matrix given below:

$$M_1 = \begin{bmatrix} r - a_{min} & 0 & 0 & f(1-\epsilon)k^\alpha T_0 \\ a_{min} & -m^\alpha E_0 & 0 & (1-\eta)(1-f)(1-\epsilon)k^\alpha T_0 \\ 0 & 0 & -(m^\alpha E_0 + \delta_C^\alpha) & \eta(1-f)(1-\epsilon)k^\alpha T_0 \\ 0 & N_s\delta_I^\alpha & N_c\delta_C^\alpha & -c^\alpha \end{bmatrix}$$

The characteristic polynomial, of order $n = 4$, associated with matrix M_1 is written as:

$$P(\lambda) = \lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4$$

where

$$\begin{aligned}
a_1 &= a_{min} - r + \delta_C^\alpha + c^\alpha + 2E_0m^\alpha \\
a_2 &= a_{min}(c^\alpha + \delta_C^\alpha) + c^\alpha\delta_C^\alpha - c^\alpha r - \delta_C^\alpha r + E_0^2m^{2\alpha} - BN_s\delta_I^\alpha + 2E_0a_{min}m^\alpha + \\
&\quad +2E_0c^\alpha m^\alpha + E_0\delta_C^\alpha m^\alpha - 2E_0m^\alpha r - BN_c\delta_C^\alpha\eta + BN_s\delta_I^\alpha f + BN_c\delta_C^\alpha\eta f - \\
&\quad -BN_s\delta_I^\alpha\eta f \\
a_3 &= E_0^2a_{min}m^{2\alpha} + E_0^2c^\alpha m^{2\alpha} - E_0^2m^{2\alpha}r + a_{min}c^\alpha\delta_C^\alpha - c^\alpha\delta_C^\alpha r - BN_sa_{min}\delta_I^\alpha - \\
&\quad -BN_s\delta_C^\alpha\delta_I + BN_s\delta_I^\alpha r + 2E_0a_{min}c^\alpha m^\alpha + E_0a_{min}\delta_C^\alpha m^\alpha + E_0c^\alpha\delta_C^\alpha m^\alpha - \\
&\quad 2E_0c^\alpha m^\alpha r - E_0\delta_C^\alpha m^\alpha r - BE_0N_s\delta_I^\alpha m - BN_ca_{min}\delta_C^\alpha\eta + BN_sa_{min}\delta_I^\alpha\eta + \\
&\quad BN_s\delta_C^\alpha\delta_dI^\alpha\eta + BN_s\delta_C^\alpha\delta_I^\alpha f + BN_c\delta_C^\alpha\eta r - BN_s\delta_I^\alpha\eta r - BN_s\delta_I^\alpha fr - \\
&\quad -BE_0N_c\delta_C^\alpha\eta m^\alpha + BE_0N_s\delta_I^\alpha\eta m^\alpha + BE_0N_s\delta_I^\alpha fm^\alpha + BN_c^\alpha a_{min}\delta_C^\alpha\eta f - \\
&\quad -BN_sa_{min}\delta_I^\alpha\eta f - BN_s\delta_C\delta_I^\alpha\eta f - BN_c\delta_C^\alpha\eta fr + BN_s\delta_I^\alpha\eta fr + \\
&\quad +BE_0N_c\delta_C^\alpha\eta fm^\alpha - BE_0N_s\delta_I^\alpha\eta fm^\alpha \\
a_4 &= E_0^2a_{min}c^\alpha m^{2\alpha} - E_0^2c^\alpha m^{2\alpha}r - BN_sa_{min}\delta_C^\alpha\delta_I^\alpha + BN_s\delta_C^\alpha\delta_I^\alpha r + E_0a_{min}c^\alpha\delta_C^\alpha m^\alpha - \\
&\quad -E_0c^\alpha\delta_C^\alpha m^\alpha r - BE_0N_sa_{min}\delta_I^\alpha m^\alpha + BE_0N_s\delta_I^\alpha m^\alpha r + BN_sa_{min}\delta_C^\alpha\delta_I^\alpha\eta - \\
&\quad -BN_s\delta_C^\alpha\delta_I^\alpha\eta r - BN_s\delta_C^\alpha\delta_I^\alpha fr - BE_0N_ca_{min}\delta_C^\alpha\eta m^\alpha + BE_0N_sa_{min}\delta_I^\alpha\eta m^\alpha + \\
&\quad +BE_0N_c\delta_C^\alpha\eta m^\alpha r - BE_0N_s\delta_I\eta m^\alpha r - BE_0N_s\delta_I^\alpha fm^\alpha r - BN_sa_{min}\delta_C^\alpha\delta_I^\alpha\eta f + \\
&\quad +BN_s\delta_C\delta_I\eta fr + BE_0N_ca_{min}\delta_C^\alpha\eta fm^\alpha - BE_0N_sa_{min}\delta_I^\alpha\eta fm^\alpha - \\
&\quad -BE_0N_c\delta_C^\alpha\eta fm^\alpha r + BE_0N_s\delta_I^\alpha\eta fm^\alpha r
\end{aligned}$$

where $B = (1-\epsilon)kT_0$.

The Routh-Hurwitz (RH) conditions for $\alpha = 1$ and $n = 4$ are [1]:

$$\Delta_1 = a_1 > 0; \quad \Delta_2 = \begin{vmatrix} a_1 & 1 \\ a_3 & a_2 \end{vmatrix} > 0; \quad \Delta_3 = \begin{vmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ a_5 & a_4 & a_3 \end{vmatrix} > 0 \tag{22}$$

We have computed the first-order derivatives of a_1, Δ_2 and Δ_3 with respect to α. For the biologically reasonable parameter values considered in this study (see Section 4), the three derivatives are negative for all values of $\alpha \in [0, 1]$, which means a_1, Δ_2 and Δ_3 are decreasing functions of α. Since the minimum values of a_1, Δ_2 and Δ_3 are positive, then the later are always positive for all values of $\alpha \in [0, 1]$. In this sense, we do not need to relax the RH conditions of the integer-order case for the fractional-order one. Thus, we proved that the roots of the polynomial $P(\lambda)$ are all negative. We conclude that the disease-free equilibrium P_0 is locally asymptotically stable for all $\alpha \in [0, 1]$.

4. Numerical simulations

In this section we present and discuss the results of the simulations of the reduced FO model (15)-(20). We apply the Grünwald-Letnikov approximation described in [30], that consists of applying finite differences schemes. The order of the approximation is $O(h)$, where h is the step used in the simulations, in this case $h = 0.001$.

The initial conditions and the parameter values used in the simulations of the reduced FO model are set as follows. We consider that the third phase viral decay (viral load below 50 $copies/ml$) started 3 months after initiation of ART. Thus, we set $T_0 = 595$ $cells/ml$. This is derived from [32], where it is calculated a median value of T cell count before treatment to be 486 $cells/ml$. We assume there is an increase of 109 $cells/ml$ during the first 3 months of therapy. The total number of latently infected cells capable of replicate virus is $L_0 = 10^5$ cells. This is justified by the fact that there is approximately a total of 1.2×10^{11} T cells after 3 months under ART. We let $V_0 = 50$ $copies/ml$, which gives in a typical 70-kg individual a total of 7.5×10^5 HIV-1 RNA copies. The death rate of productively infected cells is $\delta_I = 1/day$, and of chronically infected cells is $\delta_C = 0.07/day$. The virus clearance rate is $23/day$. The fraction of latently new infected cells is considered to be $f = 3 \times 10^{-6}$. The viral infectivity is taken to be $k = 8 \times 10^{-6} \mu l/RNA\ copy \cdot day$. The death rate of effector cells (CTLs) is

$\delta_E = 0.05$ and the production rate is $\lambda_E = 1 cell/mL/day$. Parameter values are taken from [6, 16, 7].

4.1. Decay dynamics of the latent reservoir and of the plasma viral load - effect of bystander proliferation

In Figs 1-4 we show the effect of the bystander proliferation of the latent reservoir on the plasma viremia and on the pool of latently infected cells, for $\alpha = 0.5, 0.7, 0.9, 1.0$. We omit similar results for $\alpha < 0.5$.

These simulations consider results from [32], where it is estimated that the latent reservoir has a median half-life of 18 weeks, during the first year under ART. In the subsequent three years, the decay slows with a median-life of 58 weeks. We consider $\epsilon = 1$ (100% effectiveness), such that the decay profile of the latent reservoir is justified uniquely by the effects of the cell activation, a, and the cell regeneration, r.

The results for $\alpha = 1$, $r = -0.00171$ and $\nu = 0.00939$ represent the best fit curve for the data studied in [32]. For other values of α, we notice that there is a 'delay' in the solution to reach similar outputs. This delay is attributable to the memory effect of the FO model. The results obtained for $\alpha < 1$ may be adjusted to other patients' data, since there is a considerable variety of studies in which the half-life of latently infected cells is different from the one computed in [32], varying from 6 months to 44 months [11, 27, 7]. The present work can also be extended for values of $\alpha > 1$.

We notice that the value of the plasma viremia goes to zero in all cases studied. This can be explained by solving the equations of the fractional-order model (15)-(20) for the parameter values used in the simulations, namely $\nu > 0$, $a_{min} = 0$ and $\epsilon = 1$. These could mean that with a zero (close to) value of the latent reservoir minimum activation rate, a_{min}, the only way to obtain a non-zero steady state viral load would be through ongoing viral replication. Nevertheless, several studies demonstrate that plasma viruses originate from latently infected cells, and as such the minimum activation rate must be greater than zero [33].

4.2. Effect of persistent low level activation on the pool of latently infected cells and on the plasma viremia

In this set of figures (Figs. 5-7) we want to further analyse the effect of the activation rate of the latent reservoir, $a_{min} > 0$, on the persistence of the latent reservoir and plasma virus, in the absence of ongoing viral replication.

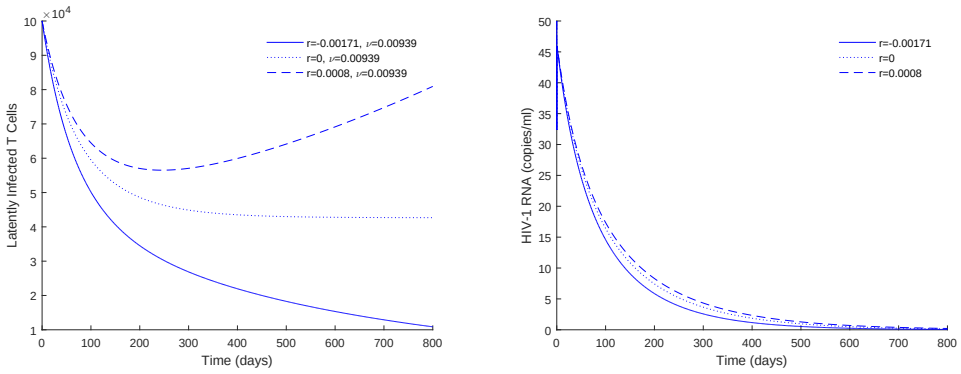

Figure 1: Effect of the bystander proliferation of the latent reservoir on the pool of latently infected cells and on the plasma viremia for $\alpha = 1.0$.

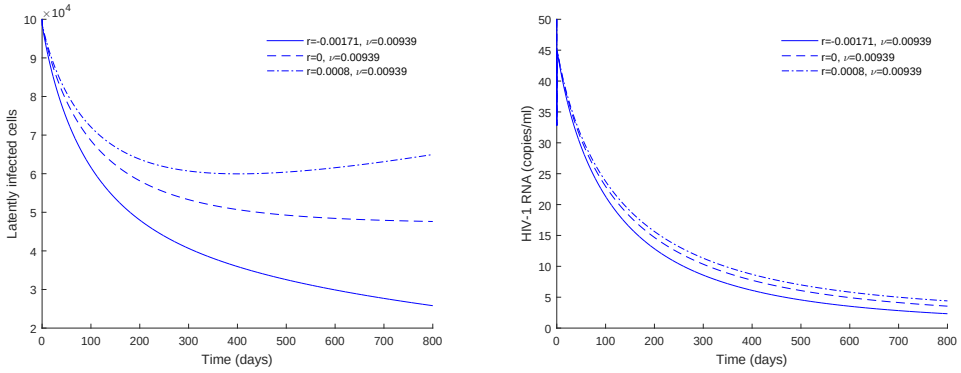

Figure 2: Effect of the bystander proliferation of the latent reservoir on the pool of latently infected cells and on the plasma viremia for $\alpha = 0.9$.

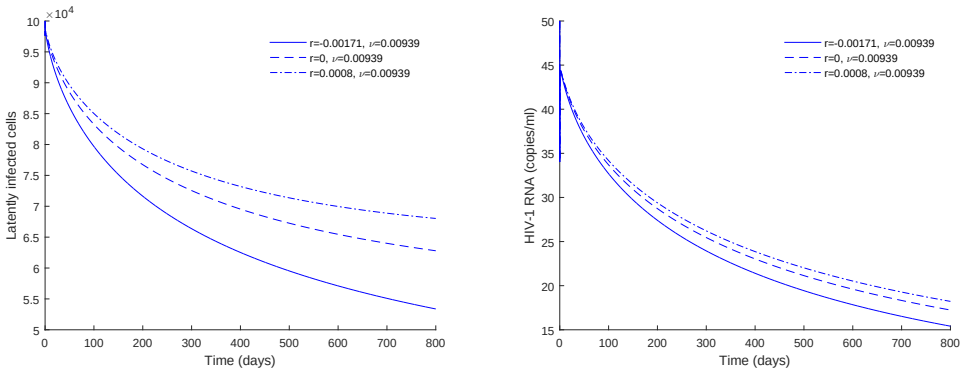

Figure 3: Effect of the bystander proliferation of the latent reservoir on the pool of latently infected cells and on the plasma viremia for $\alpha = 0.7$.

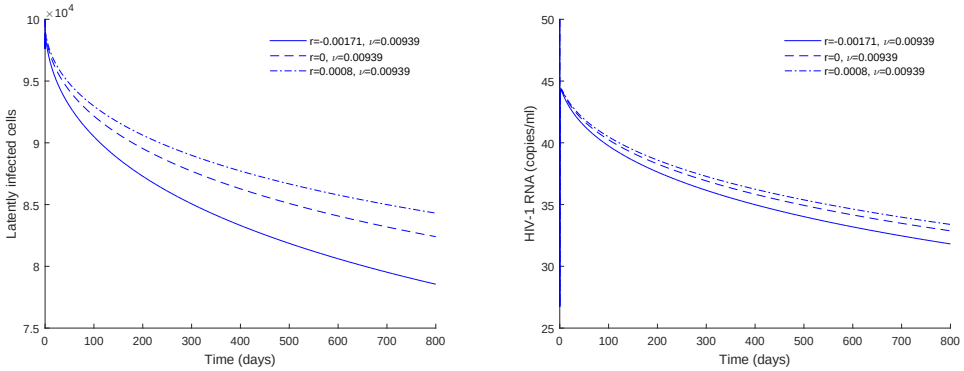

Figure 4: Effect of the bystander proliferation of the latent reservoir on the pool of latently infected cells and on the plasma viremia for $\alpha = 0.5$.

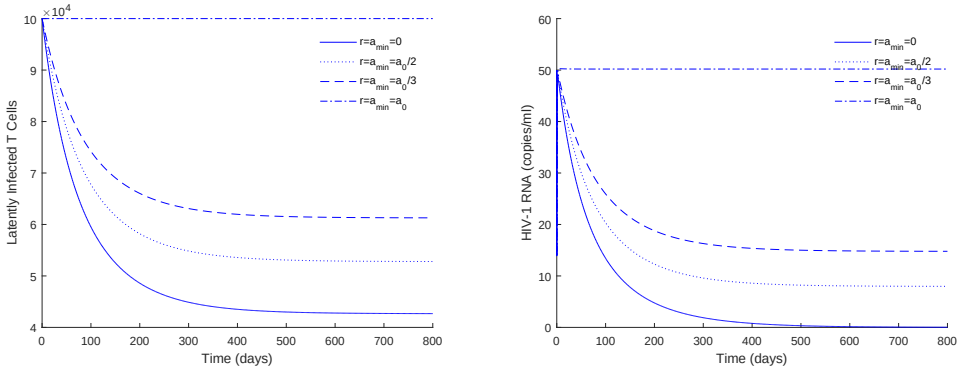

Figure 5: Effect of persistent low level activation on the pool of latently infected cells and on the plasma viremia for $\alpha = 1.0$.

We depict the graphs for $\alpha = 1.0, 0.9, 0.7$. We obtain analogous results for $\alpha \leq 0.5$.

From the observation of the figures, we conclude that there are values of a_{min} for which both the latent reservoir and the plasma virus tend to a non-zero steady state, with non-negligible magnitude, within the period of interest. This means that the plasma viremia is maintained without exhausting the latent reservoir and with non-existing ongoing viral replication, as long as the regeneration rate r is approximately a_{min}. This behaviour is observed for all values of α. Since we are dealing with a memory-like system, the dynamics of the latent reservoir and of plasma viremia 'slow down' as α is decreased from one.

5. Conclusions

In this paper we give more insight on the dynamics of the latent reservoir and of the plasma virus, in a FO model for HIV infection. We show that both latent reservoir and plasma viremia may be maintained at non-negligible magnitudes for positive values of the activation rate of the latent reservoir, and without ongoing viral replication. This phenomenon is seen for all values of the FO derivative α. Moreover, the derivative α may be used to further explore and understand data from HIV-infected patients under ART, whose latently infected cells may have a panoply of half-lives, which may range from 6 to 44 months. This diversity deeply influences the type and time of

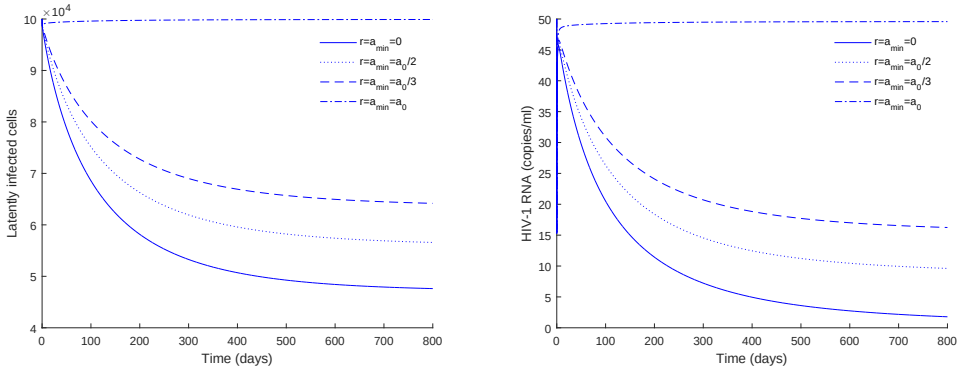

Figure 6: Effect of persistent low level activation on the pool of latently infected cells and on the plasma viremia for $\alpha = 0.9$.

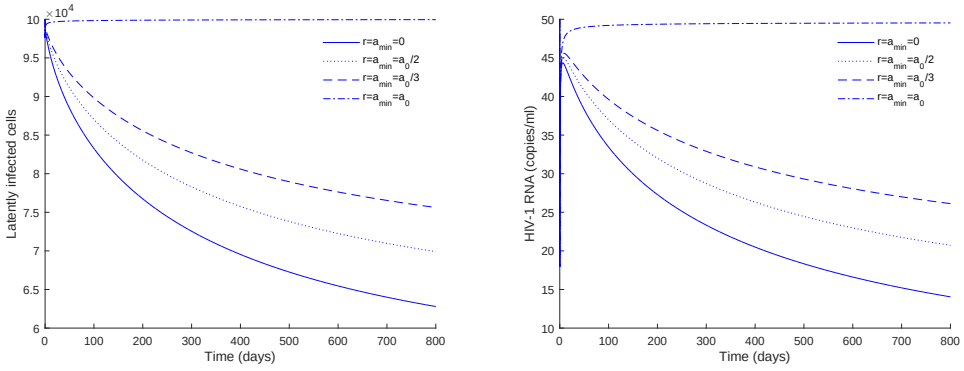

Figure 7: Effect of persistent low level activation on the pool of latently infected cells and on the plasma viremia for $\alpha = 0.7$.

antiretroviral therapy. A 'better' (i.e., more adjusted to the patient's health status) therapeutic regimen lessens the secondary effects of the drugs and may improve the patients' quality of life, as well as increase their longevity. Furthermore, optimal therapies may also reduce the considerable costs involved in ART. To conclude, presently, the therapeutic strategies to achieve a functional cure for HIV focus on the eradication of the latent reservoirs. Our model suggests such approach to be effective. In fact, very recent studies are in accordance with this path. Kaminski *et al* [15] show that gene editing using CRISPR/Cas9 can be used to eliminate HIV-1 DNA from $CD4^+$ T cells and thus be a valid contribution to the cure of AIDS.

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