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Immuno-modulatory strategies for reduction of HIV reservoir cells

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HIGHLIGHTS

- We investigate possible strategies to eradicate the reservoir via a validated model.
- Reactivating latently infected cells is not sufficient to eradicate the reservoir.
- Raising the efficacy of CD8+ T cells is essential to make activation strategy work.
- A proper suppression of the immune system may assist in eradicating the reservoir.

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ABSTRACT

Antiretroviral therapy is able to suppress the viral load to below the detection limit, but it is not able to eradicate HIV reservoirs. Thus, there is a critical need for a novel treatment to eradicate (or reduce) the reservoir in order to eliminate the need for a lifelong adherence to antiretroviral therapy, which is expensive and potentially toxic. In this paper, we investigate the possible pharmacological strategies or combinations of strategies that may be beneficial to reduce or possibly eradicate the latent reservoir. We do this via studies with a validated mathematical model, where the parameter values are obtained with newly acquired clinical data for HIV patients. Our findings indicate that the strategy of reactivating the reservoir combined with enhancement of the killing rate of HIV-specific CD8+ T cells is able to eradicate the reservoir. In addition, our analysis shows that a targeted suppression of the immune system is also a possible strategy to eradicate the reservoir.

1. Introduction

Antiretroviral therapy (ART) for HIV infection typically consists of several antiretroviral drugs that each targets a specific stage of the HIV life cycle and is effective in suppressing the viral load to below the detection limit. However, HIV can persist at undetectable levels in the presence of ART and cessation of ART leads to a viral rebound within 3–4 weeks (e.g., see Shirakawa et al., 2013 and references therein). Thus, the majority of HIV patients must adhere to a lifelong ART regimen in order to control the HIV infection.

It has been found that the persistence of HIV is due to several potential viral reservoirs, including resting CD4+ T cells that contain integrated HIV DNA as well as anatomical sanctuaries that are not reached by the antiretroviral drugs (see Shirakawa et al., 2013 for details). We remark that resting CD4+ T cells with replication competent HIV DNA integrated into their host genomes, i.e., latently infected CD4+ T cells, refer to those resting CD4+ T cells that contain integrated HIV DNA and are capable of producing virus *only upon activation*. The size of this latent reservoir is extremely stable. However, the mechanisms for maintaining this stability remain unclear. Several explanations have been proposed and tested through mathematical modeling (see the review in Rong and Perelson, 2009). These include homostatic proliferation of latently infected CD4+ T cells (Rong and Perelson, 2009) that has been confirmed experimentally (Chomont et al., 2009) and asymmetric cell division (Rong and Perelson, 2009) wherein it was assumed that latently infected cells generate two daughter cells with one in the latent state and the other in the productive state. Recently, it was shown in Wang and Rong (2014) that latently infected cells with intermediate transcription activities may maintain their size through a high level of homeostatic proliferation, while the ones with low transcriptional activities are likely to be maintained through the reversion from infected cells with intermediate transcription.

Due to the stability of latent reservoir size, reactivation of latently infected CD4+ T cells serves as a major source of viral rebound upon treatment failure, and hence they are considered to

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be the most challenging obstacle to HIV eradication (e.g., see Donahue and Wainberg, 2013 and references therein). Thus, there is a critical need for a novel treatment to eradicate this latent reservoir in order to eliminate the need for lifelong adherence to ART, which is not only expensive and toxic (Abdella et al., 2011; Max and Sherer, 2000), but also leaves HIV patients at risk for developing Acquired Immunodeficiency Syndrome (AIDS) (Egger et al., 2002). Throughout our discussion we will use the term "eradication" to mean that state where viral load levels are suppressed to very low levels in the absence of continuous therapy. More specifically, we shall mean that state where removal of therapy will result in a low level of viral load which is in the neighborhood of an asymptotically stable set point of viral load.

To have a better understanding of latency, we give a brief introduction to the replication and transcription of HIV and refer the interested reader to Buzon et al. (2010), Friedrich et al. (2010), Sharkey et al. (2000) and references therein for more information. Following binding to the main receptor of CD4+ T cells, HIV fuses with the cell membrane and releases its contents into the cytoplasm. Once inside the cell, reverse transcriptase converts HIV RNA into a double-stranded DNA molecule (linear cDNA) with long terminal repeats (LTRs), which contain upstream regulatory regions that serve as binding sites for transcription factors which can upregulate virus production. The cDNA is then transported into the nucleus and integrated into the host chromosome with an integrase enzyme. The integrated HIV DNA, i.e., provirus, may then either lie dormant or be transcribed into viral RNA. We remark that if the cDNA fails to integrate, then the cDNA circularizes to form a 2-long terminal repeat (2-LTR) circle. Several mechanisms have been proposed that contribute to the establishment of latently infected CD4+ T cells. Two possible sources of latency are the activated CD4+ T cells that transition to a resting state following infection, and direct infection of a resting CD4+ T cell.

Strategies for eradication of HIV have been proposed in the literature (e.g., see Katlama et al., 2013; Pace et al., 2011; Shirakawa et al., 2013; Smith et al., 2012 and references therein), including gene therapy to make cells resistant to HIV and pharmacological approaches to eliminate the reservoirs. Specifically, efforts to eradicate the latent reservoir to date have focused on reactivating the latently infected CD4+ T cells in the presence of ART. In theory, this reactivation strategy could induce virus production and subsequent cell death in latently infected CD4+ T cells either from direct cytopathic effects or immune clearance, while, simultaneously, ART could block new infection from the released virus. For example, histone deacetylase (HDAC) inhibitors have emerged as the lead drug candidate for reactivation of the latently infected CD4+ T cells. However, as suggested in Katlama et al. (2013) and Shan et al. (2012), simple reactivation of latently infected CD4+ T cells may not be sufficient for eradication of latent reservoir. We propose that a data-driven systems modeling approach can be used to quantitatively estimate the effect of adjuvant therapies, given in addition to ART, on patient viral load and latent reservoir levels. Thereby, the potential for adjuvant drug candidates to eradicate or significantly reduce HIV reservoirs can be evaluated *in silico* based on previously obtained patient data to inform the design of future clinical trials.

In this paper, we use a mathematical model to elucidate immunomodulatory strategies that could be used in addition to ART to assist in eradicating the latent reservoir by inducing a stable virus-free or virus-undetectable state. The model we used is adopted from Banks et al. (2008), and it includes both previously mentioned sources of establishing latently infected cells. It was found in Banks et al. (2008) that this model provides reasonable fits to patients enrolled in a clinical trial that tested the efficacy of ART regimens. The model fit the data for all of the 14 patients considered from that trial, and the clinical data in Banks et al. (2008) were from patients that all underwent ART and had at least one treatment interruption. The available clinical data analyzed in Banks et al. (2008) included the total number of CD4+ T cells and censored viral load. In addition, the model from Banks et al. (2008) was found to have impressive predictive capability when comparing model simulations (with parameters estimated using only half of the longitudinal observations) to the corresponding full longitudinal data sets. Recently, we obtained new clinical data from a study performed at Massachusetts General Hospital in which all patients in the study have never gone off ART after ART was initiated. This newly acquired data includes the amount of integrated HIV DNA, a novel measurement that has not previously been used in mathematical modeling of HIV, in addition to the usual measurements for the total number of CD4+ T cells and the censored viral load. In the following, we use these new data to obtain estimates for the parameters in the model. We then investigate the possible eradication strategies by varying the estimated values of a number of model parameters.

2. Mathematical model

We use the model from Banks et al. (2008) to evaluate different strategies that may eradicate the latent reservoir. Descriptions of the state variables are given in Table 1 and the schematic in Fig. 1. We allow the differentiation rate from T_1 to T_2 to be different from the one from T_1^* to T_2^* and the activation rate of T_2^* to be different from that of T_2.

The corresponding compartmental ordinary differential equation (ODE) model is given by

$$\dot{T}_1 = -d_1 T_1 - (1-\xi_1) k_1 V_I T_1 - \gamma_T T_1 + p_T \left(\frac{a_T V_I}{V_I + K_V} + a_A \right) T_2, \tag{2.1}$$

$$\dot{T}_1^* = (1-\xi_1) k_1 V_I T_1 - \delta T_1^* - m E_1 T_1^* - \gamma_{Ts} T_1^* + p_T \left(\frac{a_{Ts} V_I}{V_I + K_V} + a_{As} \right) T_2^*, \tag{2.2}$$

$$\dot{T}_2 = \lambda_T \frac{K_s}{V_I + K_s} + \gamma_T T_1 - d_2 T_2 - (1 - f\xi_1) k_2 V_I T_2 - \left(\frac{a_T V_I}{V_I + K_V} + a_A \right) T_2, \tag{2.3}$$

Table 1
Model states.

States	Unit	Description
T_1	cells/μl-blood	Uninfected activated CD4+ T cells
T_1^*	cells/μl-blood	Infected activated CD4+ T cells
T_2	cells/μl-blood	Uninfected Resting CD4+ T cells
T_2^*	cells/μl-blood	infected resting (or latently infected) CD4+ T cells
V_I	RNA copies/ml-plasma	Free infectious virus
V_{NI}	RNA copies/ml-plasma	Free noninfectious virus
E_1	cells/μl-blood	HIV-specific effector CD8+ T cells
E_2	cells/μl-blood	HIV-specific memory CD8+ T cells