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Quantitative analysis of viral persistence and transient viral load rebound from HIV clinical data

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Abstract

Highly active antiretroviral therapy (HAART) suppresses HIV RNA viral load below the limit of detection for many patients. However, clinical data demonstrates that the HIV virus is not eradicated by HAART, even in patients who have had no detectable virus for 7 years [1]. One possible reason is that a stable resting latent reservoir with a long half-life exists in resting memory CD4⁺T cells [2]. In this paper, we propose a mathematical model with a constant contribution of a stable latent reservoir and identified this constant by using one patient's data from AutoVac HAART interruption study [3]. Many patients also have transient rebounds of plasma viral RNA (viral blips) under otherwise successful control of the virus by HAART. Activation of latently infected cells can explain these transient rebounds of viral load. Little quantitative analysis about the activation of reservoir has been done based on any clinical experiment data. Here, we model the activation dynamics of the reservoir by a time-independent activation rate and estimate this rate by using the clinical data from the AutoVac HAART interruption study [3].

I. INTRODUCTION

Highly active antiretroviral therapy (HAART) has proven successful in controlling the virus replication for most HIV-1 patients. It is also clear that current HAART regimens can not eliminate the virus. Researchers believe that two possible reasons can explain why HIV can not be eradicated by current HAART treatments. One is that HAART treatment can not stop the virus replication completely, because of the poor penetrability of drugs into different anatomic compartments. [4] [5]. Another reason is the persistence of long-term latent reservoirs. HIV infects a subtype of myeloid dendritic cells [6], which probably constitute a reservoir that maintains infection when CD4⁺T cell numbers have declined to extremely low levels. In 1997, Finzi et al. showed that a reservoir of latently infected CD4⁺T cells is established at the beginning of infection [7]. Another substantial reservoir consists of resting CD4⁺T cells with a memory phenotype [8], [9]. Siliciano et al. [10] found that the average half-life of the latent reservoir in resting CD4⁺T cells is 44 months, which means it is extremely stable. Therefore, the long-lived reservoirs provide a critical mechanism for virus persistence during antiretroviral therapy even though active replication is successfully suppressed by HAART regimen.

Although people think latent reservoirs is a critical obstacle to the eradication of virus, little research has been done to quantitatively analyze their dynamics based on clinical data. The

main reason is that direct measurement of latent reservoir is hard. Intermittent episodes of low-level viremia are often observed in HAART treated patients [11]. Research in [12] showed that viral blips may be caused by activation of reservoirs. Rong and Perelson proposed a comprehensive model, which includes the dynamics of a stable-class reservoir and an activated-class of reservoir [13] [14]. This model can explain the viral persistence and viral blips. From the experiment being considered, only data of plasma viral RNA concentration is available. The extended model is too complicated to identify from this data. Therefore, a simpler model is proposed.

The importance of a quantitative understanding the dynamics of reservoir activation, transient viremia, and residual viremia is significant. As discussed in [15], [16], these various events may contribute to ongoing viral evolution and mutational escape. Furthermore, understanding the rates at which these events occur will be critical to evaluating strategies to eradicate HIV or effect a functional cure [17].

The paper is organized as follows. In subsection II, we propose a mathematical model, which is identifiable by using the data from AutoVac HAART interruption study. A brief introduction of the clinical data used in this paper is given in subsection II-B. A quantitative analysis of the contribution of stable latent reservoir and reservoir activation is discussed in subsection III-A and III-B. In section IV, we summarize this paper with some discussion and future works.

II. MODEL and DATA

A. Viral dynamics model

We choose an ordinary differential mathematical model to describe the dynamics of target cells, infected cells and free virus.

$$\begin{aligned}\dot{x}(t) &= \lambda - d x(t) - \beta(1-u)x(t)v(t) \\ \dot{y}(t) &= \beta(1-u)x(t)v(t) - a y(t) + \lambda_y \\ \dot{v}(t) &= \gamma y(t) - \omega v(t)\end{aligned}\quad (1)$$

This model's states include x , the CD4⁺T cells that are susceptible to infection (target cells); y , infected CD4⁺T cells; v , the viral load. The parameters are λ , the proliferation rate of the target cells; d , the natural death rate of target cells; β , the infection rates of virus respectively; u , the drug efficacy; $\lambda_y(t)$, the contribution of the long-term stable reservoir to actively infected CD4⁺T cells; γ , the proliferation rate of free virus; ω , the clearance rate for the free virus. Since the mean half-life of stable reservoir is 44 months [10], compared with the half-life of virus (days or weeks) [13], we can assume that the contribution of stable reservoir is approximately constant.

When HAART regimens successfully suppress the replication of virus, the proposed system (1) has the steady state as follows:

$$\begin{aligned}\bar{x} &= \frac{\lambda}{d} \\ \bar{y} &= \frac{\lambda_y}{d} \\ \bar{v} &= \frac{\lambda_y \gamma}{d \omega}\end{aligned}\quad (2)$$

From the steady state, our model suggests that the virus can not be eradicate, even HAART regimens stop the replication of virus efficiently.

B. Clinical data

The clinical data from the AutoVac study at IrsiCaixa HIV research foundation is used to identify the model. The AutoVac study is a structured treatment interruptions (STI) study. STI are defined as one or more planned, timing pre-specified, cyclical interruptions in ART. The study enrolled 26 HIV patients on standard cART, whose viral load had been undetectable for at least two years. 14 patients were randomized to a control group, and 12 patients to the experimental group. Informed consent was obtained from all study participants. The 12 patients in the experimental group interrupted their cART regimens, remaining off therapy until two consecutive viral load measurements above 3000 copies/ml were obtained, or for a maximum of 30 days. cART was reinitiated for 90 days, and then the interruption was repeated. Viral load measurements were obtained 3 times weekly during the interruptions. Each patient underwent at least three cycles of interruptions. In 10 patients, viral rebound was observed during all three interruptions. Shown in Fig.1 is a plot of the logarithm of the viral load versus time in days for Patient 4 in this study. For this particular patient, there are 3 interruptions in treatment, followed by reinstatement. In this paper, this patient's data is discussed and used for identifying the model 1.

III. Results

A. Contribution of stable latent reservoir

In the AutoVac study, only viral load data are available. In this situation, not all parameters in Equations 1 can be identified independently [18], [19]; all parameters except γ and λ in Equations 1 are uniquely identifiable by differential algebra. More details concerning identifiability are found in [20], [21], [22]. Therefore, we fix the value of γ as 500 copies/cell and estimate the other 6 parameters, λ , d , β , a , ω , and λ_y .

For the purpose of fitting the data, the first 2 pulses of Patient 4 are used for parameter estimation. Nonlinear least-square error method in [23] is implemented to solve this identification problem. The estimates of each parameter in Equation 1 for this patient are shown in Table. I and the viral load fitted by this identified model is shown in Fig. 2.

B. Dynamics of latent reservoir activation

As shown in Fig. 2, the identified model does not track the data well in the decay phase of each treatment intervention. The reason is that Equations 1 does not include the dynamics of latent cell activation induced by infection, which explains the transient low-level viral rebound and viremia [12]. Rong et al. developed a five-state ODE model which include the dynamics for reservoir decay and replenishment [13]. However, direct measurement of the reservoir's contribution is difficult. This model is not identifiable by using the viral load data from the AutoVac study. A simplified model is developed:

$$\begin{aligned}\dot{x}(t) &= \lambda - d x(t) - \beta(1-u)x(t)v(t) \\ \dot{y}(t) &= \beta(1-u)x(t)v(t) - a y(t) + f(t)acti(t) + \lambda_y \\ \dot{v}(t) &= \gamma y(t) - \omega v(t)\end{aligned}\quad (3)$$

Where $acti(t)$ is the time-dependent contribution of reservoir activation; $f(t)$ is the switch function for reservoir activation. We assume that the value of $acti(t)$ between two consecutive measurement is invariant. Because latent cell activation is usually caused by infection events, the activation time can not be predicted. An antigen-dependent switch function for the activation of latent cell, $f(t)$, is proposed as in [13]. $f(t)$ is defined as:

$$f(t) = \begin{cases} 0 & \text{if } t < T_{start} \\ 1 & \text{if } T_{start} \leq t < T_{stop} \\ 0 & \text{if } t \geq T_{stop} \end{cases}$$

Where T_{start} is the starting time of reservoir activation; T_{stop} is the ending time of reservoir activation. In our case, T_{start} is chosen as the measurement time during the viral load decay phase, which was followed by a higher viral load measurement. T_{stop} is the measurement time following which all measurements are less than 50 copies/mL.

The non-linear least-square error method in [23] is applied for estimation the activation rate of reservoir. The estimation and simulation results are shown in Fig.3. This patient appear to have large, frequent transient rebounds in the viral load below 1000 copies/mL. The simulation results fit these rebounds and intermittent viremia in the data accurately, because a large amount of active infected cells are generated in a short time by the stochastic activation of reservoirs. From identification results of $acti(t)$, the decay of latent reservoir during each activation is observed. The latent reservoir is replenished when the reservoir is not activated, because the first value of $acti(t)$ in the each activation session is always larger than the last value of $acti(t)$ in the preceding session, assuming that the activation rate is a constant.

IV. CONCLUSIONS AND FUTURE WORKS

A. CONCLUSIONS

The long-term latent reservoir in resting memory CD4 cells is believed to be the main reason for that the HIV infection is intrinsically incurable. Due to the limited clinical data about latent reservoir, we still lack quantitative understanding about the mechanism and dynamics of this reservoirs. The clinical data of multiple interruptions in the AutoVac study had a high measurement frequency (one measurement every 2–5 days), which is fast enough to observe the transient viral load rebound and intermittent viral blips. Therefore, these patient data provided the opportunity to quantify the contribution of viral reservoirs to the active infected cell compartment. Based on these data, the stable contribution, which is characterized in terms of number of productively infected cells produced per day, from reservoir was estimated. This contribution explains the persistence of HIV virus under successfully suppressed HAART regimen. Our model and the identification results also support that the intermittent low-level viral load rebound and blips are caused by spontaneous reactivation of quiescent cells. The identified activation rate curves are consistent with the theoretical predictions in [13], [14].

B. FUTURE WORKS

The estimation of reservoir activation in this paper is based on a single patient's data and neglects measurement uncertainty inherent in viral load assays. In order to get a better quantification of viral reservoir dynamics, Bayesian estimation approaches will be adapted to a model incorporating reservoir activation events. The approach used in this paper requires a qualitative analysis of regions including reservoir activation, creating the potential for operator bias; in the future, we plan to develop an algorithmic approach to automatically identify candidate activation regions.

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References

1. Siliciano J, Kajdas J, Finzi D, Quinn T, Chadwick K, Margolick J, Kovacs C, Gange S, Siliciano R. Long-term follow-up studies confirm the stability of the latent reservoir for HIV-1 in resting CD4+ T cells. *Nature medicine*. 2003; 9(6):727–728.
2. Chun T-W, Carruth L, Finzi D, Shen X, DiGiuseppe JA, Taylor H, Hermankova M, Chadwick K, Margolick J, Quinn TC, Kuoparallel Y-H, Brookmeyerparallel R, Zeiger MA, Barditch-Crovo P, Siliciano RF. Quantification of latent tissue reservoirs and total body viral load in HIV-1 infection. *Nature*. 1997; 387:183–188. [PubMed: 9144289]
3. Ruiz L, Carcelain G, Martinez-Picado J, Frost S, Marfil S, Paredes R, Romeu J, Ferrer E, Morales-Lopetegi K, Autran B, Clotet B. HIV dynamics and T-cell immunity after three structured treatment interruptions in chronic HIV-1 infection. *AIDS*. Jun; 2001 15(9):F19–F27. [PubMed: 11416734]
4. Gunthard H, Havlir D, Fiscus S, Zhang Z, Eron J, Mellors J, Gulick R, Frost S, Brown A, Schleif W, et al. Residual human immunodeficiency virus (HIV) type 1 RNA and DNA in lymph nodes and HIV RNA in genital secretions and in cerebrospinal fluid after suppression of viremia for 2 years. *Journal of Infectious Diseases*. 2001; 183(9):1318. [PubMed: 11294662]
5. Smith D, Wong J, Shao H, Hightower G, Mai S, Moreno J, Ignacio C, Frost S, Richman D, Little S. Long-term persistence of transmitted HIV drug resistance in male genital tract secretions: implications for secondary transmission. *Journal of Infectious Diseases*. 2007; 196(3):356. [PubMed: 17597449]
6. Knight SC, Macatonia SE, Patterson S. HIV I infection of dendritic cells. *Int Rev Immunol*. 1990; 6(2–3):163–175. [PubMed: 2152500]
7. Finzi D, Hermankova M, Pierson T, Carruth LM, Buck C, Chaisson RE, Quinn TC, Chadwick K, Margolick J, Brookmeyer R, Gallant J, Markowitz M, Ho DD, Richman DD, Siliciano RF. Identification of a reservoir for HIV-1 in patients on highly active antiretroviral therapy. *Science*. Nov; 1997 278(5341):1295–1300. [PubMed: 9360927]
8. Chun TW, Carruth L, Finzi D, Shen X, DiGiuseppe JA, Taylor H, Hermankova M, Chadwick K, Margolick J, Quinn TC, Kuo YH, Brookmeyer R, Zeiger MA, Barditch-Crovo P, Siliciano RF. Quantification of latent tissue reservoirs and total body viral load in HIV-1 infection. *Nature*. May; 1997 387(6629):183–188. [Online]. Available: <http://dx.doi.org/10.1038/387183a0>. [PubMed: 9144289]
9. Pierson T, Hoffman TL, Blankson J, Finzi D, Chadwick K, Margolick JB, Buck C, Siliciano JD, Doms RW, Siliciano RF. Characterization of chemokine receptor utilization of viruses in the latent reservoir for human immunodeficiency virus type 1. *J Virol*. Sep; 2000 74(17):7824–7833. [PubMed: 10933689]
10. Siliciano JD, Kajdas J, Finzi D, Quinn TC, Chadwick K, Margolick JB, Kovacs C, Gange SJ, Siliciano RF. Long-term follow-up studies confirm the stability of the latent reservoir for HIV-1 in resting CD4+ T cells. *Nat Med*. Jun; 2003 9(6):727–728. [Online]. Available: <http://dx.doi.org/10.1038/nm880>. [PubMed: 12754504]
11. Di Mascio M, Markowitz M, Louie M, Hogan C, Hurley A, Chung C, Ho D, Perelson A. Viral blip dynamics during highly active antiretroviral therapy. *Journal of virology*. 2003; 77(22):12165. [PubMed: 14581553]
12. Jones L, Perelson A. Transient viremia, plasma viral load, and reservoir replenishment in HIV-infected patients on antiretroviral therapy. *Journal of acquired immune deficiency syndromes (1999)*. 2007; 45(5):483. [PubMed: 17496565]
13. Rong L, Perelson AS. Modeling latently infected cell activation: viral and latent reservoir persistence, and viral blips in HIV-infected patients on potent therapy. *PLoS Comput Biol*. Oct. 2009 5(10):e1000533. [Online]. Available: <http://dx.doi.org/10.1371/journal.pcbi.1000533>. [PubMed: 19834532]
14. Rong L, Perelson AS. Modeling HIV persistence, the latent reservoir, and viral blips. *Journal of Theoretical Biology*. 2009; 260(2):308–331. [Online]. Available: <http://www.sciencedirect.com/science/article/B6WMD-4WJBC3M-1/2/b3a9c53da2826f0dfa78e593121c57e7>. [PubMed: 19539630]
15. Siliciano JD, Siliciano RF. Biomarkers of HIV replication. *Current opinion in HIV and AIDS*. Nov; 2010 5(6):491–497. [PubMed: 20978392]

16. Maldarelli F. Targeting viral reservoirs: ability of antiretroviral therapy to stop viral replication. *Current opinion in HIV and AIDS*. Jan; 2011 6(1):49–56. [PubMed: 21228755]
17. Josefsson L, Dahl V, Palmer S. Can HIV infection be eradicated through use of potent antiviral agents? *Curr Opin Infect Dis*. Dec; 2010 23(6):628–632. [PubMed: 20847693]
18. Stafford MA, Corey L, Cao Y, Daar ES, Ho DD, Perelson AS. Modeling plasma virus concentration during primary HIV infection. *J Theor Biol*. Apr; 2000 203(3):285–301. [Online]. Available: <http://dx.doi.org/10.1006/jtbi.2000.1076>. [PubMed: 10716909]
19. Wu H, Zhu H, Miao H, Perelson AS. Parameter identifiability and estimation of HIV/AIDS dynamic models. *Bull Math Biol*. Apr; 2008 70(3):785–799. [Online]. Available: <http://dx.doi.org/10.1007/s11538-007-9279-9>. [PubMed: 18247096]
20. Ritt, JF. *Differential algebra*. American Mathematical Society; 1950.
21. Saccomani MP, Audoly S, D'Angio L. Parameter identifiability of nonlinear systems: the role of initial conditions. *Automatica*. 2003; 39(4):619–632. [Online]. Available: <http://www.sciencedirect.com/science/article/B6V21-47VS0K7-2/2/38b82139821c47f0b043469853e8e2a7>.
22. Saccomani MP, Audoly S, Bellu G, Angi LD. Examples of testing global identifiability of biological and biomedical models with the daisy software. *Computers in Biology and Medicine*. 2010; 40(4):402–407. [Online]. Available: <http://www.sciencedirect.com/science/article/B6T5N-4YGI89-2/2/544bc66b12f8d5c969a472e305e19ae9>. [PubMed: 20185123]
23. Luo R, Piovoso MJ, Martinez-Picado J, Zurakowski R. HIV model parameter estimates from clinical data including reservoir dynamics. *PLoS One*. Submitted.

Fig. 1.
The clinical data from the AutoVac study for Patient 4

Fig. 2. Model fitting for Patient 4

Red star: experimental data (detection limit: 50 copies/mL); solid line: estimate.

Fig. 3. The identification and simulation results (Equations 3) for Patient 4 in the AutoVac study
 A. The switch function; B. The activation rate vs. time; C. Model fitting for the identified patients.

TABLE I

The identified parameter's value for Patient 4.

Patient 4		
Parameter	Unit	Value
λ	$cells * \mu L^{-1} * d^{-1}$	76.5162
d	d^{-1}	0.0769
β	$copies^{-1} * mL * d^{-1}$	4.1766×10^{-6}
u	NA	93%
a	d^{-1}	0.7183
λ_y	$cells * \mu L^{-1} * d^{-1}$	2.5×10^{-4}
γ	$copies * cells^{-1}$	500
ω	d^{-1}	1.0681