Applied Mathematics and Computation 266 (2015) 119–134

Contents lists available at ScienceDirect

Applied Mathematics and Computation

journal homepage: www.elsevier.com/locate/amc

A within-host virus model with multiple infected stages under time-varying environments

Xia Wang [a,b], Shengqiang Liu [c,*], Xinyu Song [b]

[a] School of Mathematics and Information Sciences, Shaanxi Normal University, Xi'an, 710062, China
[b] College of Mathematics and Information Science, Xinyang Normal University, Xinyang, 464000, China
[c] The Academy of Fundamental and Interdisciplinary Science, Harbin Institute of Technology, 3041#, 2 Yi-Kuang Street, Harbin, 150080, China

ARTICLE INFO

MSC:
34C25
34D40
92C45
92C60

Keywords:
Time-varying
Multiple infected stages
Within-host virus model
Permanence and extinction
Viral load

ABSTRACT

HIV-1 infection and treatment may occur in the non-constant environment due to the time-varying drug susceptibility and growth of target cells. In this paper, we propose a within-host virus model with multiple stages for infected cells under time-varying environments, to study how the multiple infected stages affect on the counts of viral load and $CD4^+$-T cells. We establish the sufficient conditions for both persistent HIV infection and clearance of HIV infection based on two positive constants R_*, R^*. When the system is under persistent infection, we further obtained detailed estimates of both the lower and upper bounds of the viral load and the counts of $CD4^+$-T cells. Furthermore, numerical simulations are carried out to verify our analytical results and demonstrate the combined effects of multiple infected stages and non-constant environments, and reflect that both persistence and clearance of infection are possible when $R_* < 1 < R^*$ holds. In particular, the numerical results exhibit the viral load of system with multiple infected stages may be less than that with single infected stage, and simulate the effect of time-varying environment of the autonomous system with multiple infected stages. We expect that our theoretical and simulation results can provide guidance for clinical therapy for HIV infections.

1. Introduction

Over the last two decades there has been extensive research on modeling and analysis of the human immunodeficiency virus (HIV) infection ([1–4,5–9]). Most HIV infection models focus on the single-infected stage for infected cells. The standard technique for developing mathematical descriptions of HIV infection between virus particles and uninfected $CD4^+$ T-cells is to model the system with single-infected stage as a set of autonomous ordinary differential equations. This approach has led to many insights into the factors that affect HIV infection and control. The infection remains asymptomatic for years, the population of $CD4^+$-T cells falls to low levels and the virus load sufficiently increases leading to the development of AIDS. However, it is very important to establish an appropriate HIV model for HIV antiviral therapy and control, thus consideration of following factors should attract more attention.

Firstly, multiple infected stages and treatment for infected cells are more interesting. As noted in [11–21], they investigated that an infected individual enters the first infectious stages at the moment of infection and then progresses through all these stages until the last one, with the infectiousness of a person depending upon his current disease stage. In [17], Hyman et al.

* Corresponding author. Tel.: +0086 45186402848.
E-mail address: lsqmath@gmail.com, sqliu@hit.edu.cn (S. Liu).

http://dx.doi.org/10.1016/j.amc.2015.05.033
0096-3003/

suggested that some infected individuals could pass through four infection stages: (1) the highly infectious acute stage in the first few weeks; (2) the low infectivity early chronic stage; (3) the high infectivity late chronic stage; (4) the AIDS stage. And Sedaghat et al. [21] established two-stages infection model based on three different kinds of levels of virus during the chronic phase of infection. Samanta [20] investigated a non-autonomous stage-structured HIV/AIDS epidemic model with two stages between HIV/AIDS patients not the host cells in the body, established some sufficient conditions on the permanence and extinction of the disease, and obtained the explicit formula of the eventual lower bounds of infected individuals. Thus, additional multiple infected stages and treatment for infected cells are important and realistic to model for HIV-1 pathogenesis and drug treatment dynamics.

On the other hand, the non-autonomous phenomenon, are familiar features in virus infection models, such as varying infection rate (see [22–29]), and especially the periodic drug therapy and periodic drug effectiveness, occur in many realistic within-host models, relevant to our study here are the works [30–34] and so on.

Motivated by these factors above, especially multiple infected stages were introduced in the non-autonomous HIV infection model, to give a more appropriate model and better understanding of the antiretroviral drug during HIV-1 virus infection. Our primary goals of this paper are to establish such precise estimates of the viral load using the lower and upper bounds of coefficients, and to investigate what happens if the model including multiple infected stages.

In this paper, we will provide some sufficient conditions on the permanence and extinction of system (1), which are different from the popular technique of uniform persistence theory to address the virus dynamic system in a periodic environment [38]. To our best knowledge, if the system is a periodic system, we can obtain the threshold values by using the theory of uniform persistence for periodic systems developed by Prof. Xiaoqiang Zhao (see [10,25]); if the system is almost periodic without delay, then the conditions of the threshold values may be weakened, as shown in [28]. Our system is a general non-autonomous model (not necessarily periodic) with multiple infected stages. The standard techniques to address periodic (or almost periodic) systems, such as the basic reproduction ratio derivation and the persistence theory of periodic (or almost periodic) systems, are not applicable here. Fortunately, the analysis techniques in [34] (with single-infected stage) provided a tool so that one can do this simple non-autonomous HIV infection model, which make it possible for us to consider the model with multi-stage infection and treatment. Thereupon, the research of non-autonomous HIV infection model multiple infected stages is not only interesting but also necessary, and more challenging than the single-infected stage [34].

This article is organized as follows. The next section presents a non-autonomous HIV-1 model with multiple infected stages and gives some preliminaries lemmas. Our main results on permanence and extinction of system (1) are completely determined by the threshold values and obtained in Section 3. In Section 4, numerical simulations are considered to illustrate our main results. We also investigate the impact of multiple infected stages on HIV infection through the sensitivity analysis of R_* and comparisons between delayed non-autonomous HIV-1 models with single-infected stage and three infected stages. A brief conclusion is given in Section 5.

2. Model formulation and preliminaries

HIV replication cycle may contain much stages, such as reverse transcription, integration, assembly and viral release and so on. Different drug classes act on specific stages. A comprehensive model including multiple stages may be more accurate in studying the dynamics of HIV decay under treatment from different drug classes. There are some clinical and experimental data that show that drugs acting on later stages of viral replication cycle may lead to a more rapid viral load decline. A model including two stages have been developed to study the dynamics under treatment in Sedaghat et al. [21]. They showed that the stage in the HIV-1 life cycle at which a drug acts may affect the observed decay dynamics, which is the later in the life cycle an inhibitor acts, the more rapid the decay in viremia. In this section, based on the works of [11,17,21,35–37], we formulate a general multistage infection progression model between uninfected $CD4^+$ T-cells and virus particles which traverses n different stages during its life-cycle. We distinguish the host populations into the following compartments: uninfected cells $x(t)$, a succession of infected cells $y_i(t)$, $i = 1, 2, \ldots, n$, whose members are in the ith stage of the infection progression, and virus particles $v(t)$. Based on the above assumptions and Section 1, a non-autonomous HIV-1 model with multiple stages for infected cells can be considered as follows:

$$\begin{cases} \dot{x}(t) = \lambda(t) - \mu(t)x(t) - \beta(t)x(t)v(t), \\ \dot{y}_1(t) = \beta(t)x(t)v(t) - k_1(t)y_1(t), \\ \dot{y}_2(t) = \widetilde{k}_1(t)y_1(t) - k_2(t)y_2(t), \\ \dot{y}_3(t) = \widetilde{k}_2(t)y_2(t) - k_3(t)y_3(t), \\ \qquad \cdots \\ \dot{y}_n(t) = \widetilde{k}_{n-1}(t)y_{n-1}(t) - k_n(t)y_n(t), \\ \dot{v}(t) = \widetilde{k}_n(t)y_n(t) - \delta(t)v(t), \end{cases} \tag{1}$$

where

$$\begin{aligned} &k_i(t) = \widetilde{k}_i(t) + \delta_i(t), \quad \widetilde{k}_i(t) = (1 - \varepsilon_{II}(t))k_i(t), \quad i = 1, \ldots, n-1, \\ &\widetilde{k}_n(t) = (1 - \varepsilon_{PI}(t))N(t)k_n(t), \quad \beta(t) = (1 - \varepsilon_{RT}(t))k(t), \end{aligned} \tag{2}$$

and the meanings of functions $\lambda(t)$, $\mu(t)$, $k_i(t)$, $\delta_i(t)$ $(i = 0, 1, \ldots, n)$, $k(t)$, $\delta(t)$, $N(t)$, $\varepsilon_{RT}(t)$, $\varepsilon_{II}(t)$ and $\varepsilon_{PI}(t)$ appeared in (2) are in accordance with the corresponding autonomous system parameters λ, μ, k_j, k, δ, N, ε_{RT}, ε_{II} and ε_{PI}, respectively.