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Modeling Influence of Raltegravir Intensification on Viral Dynamics: Stability and Hopf Bifurcation*

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Abstract In this paper, we propose an ordinary differential equation model with logistic target cell growth to describe influence of raltegravir intensification on viral dynamics. The basic reproduction number R_0 is established. The infection-free equilibrium E_0 is globally attractive if $R_0 < 1$, while virus is uniformly persistent if $R_0 > 1$. In addition, we find that Hopf bifurcation can occur at around the positive equilibrium within certain parameter ranges. Numerical simulations are performed to illustrate theoretical results.

Keywords Multi-stage models, Logistic target cell growth, Stability, Hopf bifurcation.

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1. Introduction

It is widely known that CD4+ T cells have been considered as the primary target cells for human immunodefficiency virus (HIV) infection. However, as yet AIDS is still an illness for which there is no vaccine since some latent viruses can reside in memory CD4+ T cells. In recent years, HIV infection is treated with a combination therapy, known as highly active anti-retroviral therapy (HAART) (see, e.g. [1, 2]), which can effectively control HIV replication in infected individuals by stopping the virus from replicating and restore their immune system [3] and reduced the number of AIDS deaths reported from potent antiretroviral medications. In the absence of antiretroviral therapy, the viral load in infected individuals soared to the peak level, followed by a decline to reach an viral set-point level during chronic infection, and thereby infect the susceptible CD4+ T cells [4].

New drug classes result from investigation of up-and-coming drug targets for the treatment of HIV infection. The integrase inhibitor raltegravir was authorized for the treatment of HIV infection [5]. More drugs such as entry inhibitor, reverse-transcriptase (RT) inhibitor, integrase inhibitor(II), and protease inhibitor(PI) have been developed to act at specific stages for clinical development [6]. For instance,

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RT inhibitor can block the process of reverse transcription. II can block process of virus DNA integrate into the host cell's DNA.

The study of dynamics for viral infection dynamical models have made excellent insights into the pathogenesis and treatment of diseases [7–14]. In [8, 9, 11], some basic three-dimensional viral dynamical models with drug treatment were proposed. Then in [4, 9, 15], some researchers have incorporated the effect of latently infected stage into the mathematical model since latently infected stage of cells can be activated by related enzymes to become the productively infected. Lloyd proposed a comprehensive model including multiple stages with treatment from different classes drug approach to analyze the dynamics of HIV decay [16, 17]. Sedaghat et al. developed a mathematical model including two stages employed to study the question of the viral load decay with RT inhibitor or integrase inhibitor in patients under treatment [18]. A number of models discussing the efficacy of antiviral treatment by insights of time-varying can be found in [19–21]. Several other models were developed to analyze the question of the rapid decay of plasma viral load after application of integrase inhibitors (see, e.g. [4, 22–25]).

In recent years, to explore the effect influence of raltegravir intensification, Wang et al. [26] established a mathematical model, in which CD4+ T cells are unlimited growth. In biology, it is more realistic to assume that the population of the CD4+ T cell has a logistic growth function [27, 28]. Motivated by the aforementioned works, in this paper, we propose an HIV infection dynamical model with logistic target cell growth to explore the effect influence of raltegravir intensification:

$$\begin{cases} \dfrac{dT}{dt} = sT(t)\left[1 - \dfrac{T(t)+I_1(t)}{T_M}\right] - (1-\varepsilon_{RT})\beta V_I(t)T(t), \\ \dfrac{dI_1}{dt} = (1-\varepsilon_{RT})\beta V_I(t)T(t) - d_1 I_1(t) - (1-\varepsilon_{II})k_1 I_1(t) - k_2 I_1(t), \\ \dfrac{dI_2}{dt} = (1-f)(1-\varepsilon_{II})k_1 I_1(t) - \delta I_2(t) + aL(t), \\ \dfrac{dI_3}{dt} = k_2 I_1(t) - d_3 I_3(t), \\ \dfrac{dL}{dt} = f(1-\varepsilon_{II})k_1 I_1(t) - d_L L(t) - aL(t), \\ \dfrac{dV_I}{dt} = (1-\varepsilon_{PI})N\delta I_2(t) - cV_I(t), \\ \dfrac{dV_{NI}}{dt} = \varepsilon_{PI} N\delta I_2(t) - cV_I(t). \end{cases} \tag{1.1}$$

Detailed biological considerations of the parameters of the model (1.1) can be found in Table 1. We observe that variables I_3 and V_{NI} are decoupled from the other equations of model (1.1). Therefore, we only need to analyze the dynamical behavior