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Transmission dynamics and optimal control strategies in a multi-pathways delayed HIV infection model with multi-drug therapy

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Abstract In this article, we develop and study an optimal control in a multi-pathways in-host HIV infection model with saturated incidence, intracellular delay, and self-proliferation of the host cells. In the first phase, all three controls are assumed to be constant; in the second phase, controls are considered time-dependent. We determine the infected steady state's local stability conditions and discuss the delay-induced bifurcation. In the time-dependent case, we define a suitable objective function to maximize the cell counts of healthy $CD4^+T$ cells. We apply Pontryagin's minimum principle to give the conditions for optimal control. PRCC-based sensitivity analyses are performed to identify the system's sensitive parameters and cost function. In addition, cost-effectiveness analyses are carried out to recognize the most cost-effective strategy. We validate and compare the effect of different drug therapies for various intracellular delays through numerical simulation. It is observed that the infection can be removed by all multi-drug treatments, including cell-to-cell blockers, for any delay. The cost-effectiveness analysis suggests that protease inhibitors and cell-to-cell blockers are a comparatively better strategy for relieving HIV-1 infection using a multi-drug therapeutic scheme. The study also indicates that the treatment duration depends on delay, i.e., if the delay is shorter, the treatment period is also faster.

1 Introduction

Mathematical models are used to analyze and predict the evolution of disease dynamics. In developing HIV-infected mathematical models to know the disease dynamics, it is essential to express the disease transmission term mathematically to understand the dynamics of viral load, healthy and infected $CD4^+T$ cells. Most of HIV-1 infection mathematical models assume that the transmission process follows a mass action or bilinear law [1–7]. This law says that the infection rate at any time is proportional to the product of viral and host cell numbers [8]. However, the mass action law has some unrealistic properties, e.g., the number of newly infected $CD4^+T$ cells produced by a single virus depends on x and becomes very high when x is large [9]. To prevent this unboundedness of the contact rate, some authors [10–13] used saturated infection rate $\frac{\beta_1 x(t)v(t)}{1+v(t)}$, where $x(t)$ and $v(t)$ are concentrations of healthy $CD4^+T$ cells and virus particles at time t, respectively, and $\beta_1(>0)$ is the proportionality constant and is known as the cell-free transmission coefficient. On the other hand, [14] considered the saturation effect on x population as $\frac{\beta_1 x(t)v(t)}{a+x(t)}$ to understand the failure of $CD8^+T$ cells vaccination against Simian/Human Immunodeficiency Virus and a is the half-saturation constant. A generalized Hill-type function $\frac{\beta_1 x^n v}{a^n+x^n}$ was considered in [15] to observe the dynamics of HIV-1 infection models. Most authors [1, 2, 16–19] used the mass action form to represent the of cell-to-cell incidence function $\beta_2 x(t)y(t)$, where $y(t)$ is the concentration of productively infected $CD4^+T$ cells at time t and $\beta_2(>0)$ is the proportionality constant and known as cell-to-cell transmission coefficient. In a very recent study, [13, 20] considered incidence function $\frac{\beta_2 x(t)y(t)}{1+ly(t)}$ to prevent the unboundedness of the contact rate and l is a positive parameter.

Time delay is crucial for a realistic representation of biological phenomena [21–23]. In the epidemic model, the intracellular delay is an obvious event to be considered to make the epidemic model more realistic [15, 24]. In the case of HIV, the process between the first effective contact of a virus/ infected cell with a healthy $CD4^+T$ cell and the latter becoming productively infectious is not instantaneous. After entering a virus into the healthy cell, many intracellular mechanisms make the cell productively contagious, i.e., can infect a healthy cell and produce new virus through cell lysis. The time required for transforming a healthy cell into an infectious cell is known as the intercellular delay. However, a time delay is needed between initial viral entry into a host cell and subsequent viral production. We refer to two classic books [25, 26] for a general idea of incorporating various delays into a biological model

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