ABSTRACT

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Title of the Thesis: Disease Dynamics and Its Optimal Control

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Human immunodeficiency virus type-1 (HIV-1) is a deadly pathogen that infects $CD4^+T$ cells, one type of immune cell. A gradual decline of $CD4^+T$ cells in blood plasma is a signature of HIV-1 infection. HIV infection causes AIDS (Acquired Immunodeficiency Syndrome) when the $CD4^+T$ cells count drops to 200 cells per µl from its normal value of 1000 cells per µl. The immune system cannot function properly in a reduced level of $CD4^+T$ cells. As a result, an HIV-infected individual becomes susceptible to various opportunistic infections. Basic HIV-1 in-host models consider dissemination of infection through cell-free mode, where the free plasma virus infects the healthy $CD4^+T$ cells. Recent in vitro studies, however, show that infection can spread from one infected cell to another uninfected cell. This cell-to-cell viral spread through virological synapses is the predominant mode of HIV-1 infection. Antiretroviral therapy significantly reduces the viral load and increases the $CD4^+T$ cell count, thus preventing the onset of AIDS and increasing the life span of HIV-1 infected patients.

Previous studies on HIV-1 infection with mono or multi-blockers consider the mode of infection through a single pathway, which is the cell-free mode. So, the question is, what would be the control strategy in cell-to-cell transmission mode? To the best of our knowledge, no work has considered such controls in a multi-pathways HIV-1 infection model. Therefore, the main objective of this thesis is to gain insights into the effect of single and multi-blockers drugs on the dynamics of an HIV-1 infection model in the presence of both cell-to-cell and cell-free infection modes.

Most models of HIV-1 infection assume that the transmission process follows a mass action or bilinear law. This law says that the infection rate at any time is proportional to the product of viral and host cell numbers. But, the mass action law has some unrealistic properties, e.g., the number of newly infected $CD4^+T$ cells produced by a single virus may be unbounded. Some authors have used a saturated infection rate to prevent this unboundedness of the contact rate. 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 occur to make the cell productively infectious. The time required for transforming a healthy cell into an infectious cell is known as the intercellular delay. We considered a multi-pathways in-host HIV-1 infection model with saturated infection rates and intracellular delay using three controls to explore the viremia.

HIV-1 mathematical models usually consider the interaction between the host cells (i.e., $CD4^+T$) and plasma free-virus. However, the activated $CD8^+T$ of CTL cells can kill the infected host cells and thus reduce the production of the free virus through the infected cell lysis. It is to be mentioned that the activation of CTL is not instantaneous. It takes some time for stimulation by our immune cells. It is of utmost importance to know how far

different antiretroviral therapies can control viremia in the presence of delay. We, therefore, studied a multi-pathways HIV-1 infection model with CTL delay in the presence of treatments. The main objective is to explore how immune response delay affects the plasma viral load in the presence and absence of the blockers and to determine the optimal dose.

We analyzed our considered models in all cases under two cases: (i) the controls are constant or (ii) the controls are time-dependent. We prove that the proposed model's unique solutions exist and are bounded. We demonstrate the local and global stabilities of the disease-free and infected steady states in the constant control case. It is shown for the delay-induced model that there exists some critical value (τ^*) of the delay parameter below which the system is stable and above which it is unstable. The stability switching occurs through a Hopf bifurcation. In the time-dependent control, we define a suitable optimal control problem. An objective function is characterized based on maximizing the healthy $CD4^+T$ cell counts and minimizing the count of infected $CD4^+T$ cells along with other systemic costs of drug therapy. We derived the necessary conditions for optimal infection control by applying Pontryagin's minimum principle. It is analytically shown that an optimal control triplet exists that maximizes the objective functional. Using extensive simulation results, we have demonstrated the effect of different control measures with mono-drug and multi-drug therapies with different delays. It is shown that removing the infection is not possible, and the infected cells persist in all three mono-drug protocols using any mono-drug treatment. However, virus counts go below the detection level of a protease inhibitor but infected $CD4^+T$ cells persist. This, however, does not happen in the case of an RTI inhibitor or synapse-forming inhibitor. Infected $CD4^+T$ cells persist, but the non-zero virus count may be possible due to cell-to-cell infection dissemination and protease inhibitor use. Such a result has not been shown in any previous study. In the case of a multi-drug therapy, we observed that infection could be removed in all options which contain the protease inhibitor. Our study deciphers that immune response delay significantly affects the system dynamics. If CTL's response is quicker, then $CD4^+T$ cell count may remain stable but fails to do so if response time increases.

The Covid-19 pandemic has put the world under immeasurable stress. Initially, no specific drug or vaccine was used to prevent the coronavirus infection. Therefore, in the absence of a vaccine or specific drug, we proposed a mathematical Covid-19 epidemic control model using the repurposing drugs and non-pharmaceutical interventions. A case study with the Indian Covid-19 epidemic data is presented to visualize and illustrate the effects of lockdown, maintaining personal hygiene & safe distancing, and repurposing drugs. It is shown that India significantly improved the overall Covid-19 epidemic burden through the combined use of NPIs and repurposing drugs.

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