HIV Treatment in Resource-Limited Environments:
An Approximate Dynamic Programming Approach

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Acquired Immune Deficiency Syndrome (AIDS) and its cause, the Human Immunodeficiency Virus (HIV), are significant public health concerns. By the end of 2005, there were 40 million people infected with HIV, 5 million new cases, and 3 million deaths from AIDS worldwide [6]. HIV attacks the CD4 white blood cells, damaging the immune system. As the virus depletes the patients CD4 count, the immune system deteriorates, and patients become more susceptible to opportunistic infections, such as pneumonia and malaria [5]. The transition from HIV to AIDS generally occurs when the patients CD4 count falls below 200 cells/mm$^3$ of blood, or approximately 15% of normal levels.

The only treatment option for chronic HIV is antiretroviral therapy (ART). ART can halt virus replication, decrease transmission rates, and subsequently increase the patients lifetime. In patients infected with HIV, the virus attacks the immune system at a rate that is approximately proportional to the amount of virus in the body [4]. For patients in the chronic stage of HIV, the rate of damage to the body increases if the virus grows unchecked. The only option patients have to reduce this rate of damage is to take ART. Upon initiating therapy, the amount of virus in the body (viral load or VL, measured in the number of copies/mL of blood decreases rapidly and the immune system (measured by the CD4 count) recovers in a similar fashion. The CD4 level at the initiation of ART has been shown to be a significant prognostic variable for the patients survival [1]. If a patient waits too long to initiate ART, she risks suffering irreparable damage to her immune functions, thus reducing the benefit provided by the drugs. Finally, ARVs cannot indefinitely improve a patients health; eventually the virus will develop resistance to the drugs, rendering them less effective.

In the past 20 years, HIV has globally claimed over 20 million lives and is one of the biggest public health concerns in the developing world. The area impacted the most by the HIV epidemic has been sub-Saharan Africa, where more than 28 million people are reported to be infected. Given the large number of patients and the broader socio-economic conditions of the region, the demand for ART drugs far exceeds the supply. It is estimated that there are 6 million patients are currently in need of treatment with fewer than 8% having access to it [2]. To combat the

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effects of drug scarcity, the World Health Organization (WHO) developed the 3 by 5 Initiative whose goal was to provide access to 3 million people by 2005. The WHO succeeded in more than doubling the drug supply in these countries (400,000 in 2003 to 1 million in 2005) but still fell short of their goal. While the amount of drugs available to patients has steadily risen over the course of the last 20 years, the number of new HIV cases has continued to rise and significantly compromised the progress made toward universal access to treatment.

Under such resource constraints, the question of efficient allocation of HIV treatment becomes relevant. We consider a decision maker who must make allocation decisions so as to maximize the societal benefit. In particular, the decision maker must maximize the total lifetime expectancy or quality-adjusted expectancy of the considered infected population. The need to explore such trade-offs is further strengthened by the fact that, HIV tends to develop resistant ART mutations that gradually undermine the benefits of the provided therapy. Hence, given the spread of the HIV epidemic and the shortage of drugs, decision makers are called to optimize the societal impact of their resources by deciding (i) a profiling of patients and priority rules for allocating available treatments, and, (ii) the criteria under which a patient must be removed from treatment in order for that resource to be released for another qualified patient.

The first part of this work concerns the development of a simulation model that will provide insights and explore the dynamics underlying the problem of optimal HIV treatment allocation. Towards this direction, we implement the HIV progression model developed in [1] that models the uncertainty of the CD4 and VL progression for individual patients before, during, and after an ART treatment. The progression model is capable of simulating important events (mutations, non-adherence, death) that influence the individual patient’s HIV progression and life expectancy. The model has been clinically validated and a reliable tool to answer HIV related pharmacoeconomic questions. Subsequently, we implement a simulation of patient cohorts with different coverage levels, ranging from 1 to 100%, where patients health statuses are updated according to the aforementioned HIV progression model. We use this simulation tool to evaluate different treatment allocation policies and quantify their effect on the average expected lifetime of the considered patient population. As a concrete example, we evaluate the performance of different WHO guidelines that concern the distribution of available ART doses based on the health statuses of the considered patient population. Our simulation model provides numerical evidence that there are significant performance differences among the WHO guidelines across varying coverage levels with survival gaps of up to 1.3 years. Furthermore, our simulation model provides with additional insights on those structural properties of the WHO guidelines that make their performance differ, for example, we have numerical evidence that in low coverage levels, guidelines inducing short treatment durations are preferred over guidelines with longer treatment durations.

The next part of this work seeks to model the aforementioned problem as a sequential stochastic control problem where the decision maker observes the patients health progression, and makes decisions regarding the re-allocation of treatment resources with the objective of maximizing the average expected lifetime of the considered population. We provide a Markov Decision Process (MDP) formulation, but the state space of this formulation grows exponentially with respect to the problem parameters. Furthermore, an exact mathematical model is hard to construct since the system transition probabilities depend on the parallel evolution of multiple HIV progression models. In order to alleviate those difficulties and develop algorithmic solutions that balance performance and computational tractability, we explore and implement ideas drawn from the
area of *Approximate Dynamic Programming* (ADP) [3]. We consider value function approximations that attempt to capture the problem dynamics and the non-linearities incurred by the complex HIV progression model that drives the evolution of the system. Our approximations depend on a set of parameters that are estimated using separate simulation trajectories. Subsequently, we design a series of suboptimal policies of different implementation complexities and provide evidence of substantial improvement over the WHO guidelines. In particular, we where able to numerically demonstrate improved average survival rates and quality-adjusted life expectancies of up to 8% over the best WHO guideline for varying coverage levels.

References


