An attempt at the computer-aided management of HIV infection☆

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Abstract

The immune system is a complex and diverse system in the human body and HIV virus disrupts and destroys it through extremely complicated but surprisingly logical process. The purpose of this paper is to make an attempt to present a method for the computer-aided management of HIV infection process by means of a mathematical model describing the dynamics of the host pathogen interaction with HIV-1. Treatments for the AIDS disease must be changed to more efficient ones in accordance with the disease progression and the status of the immune system. The level of progression and the status are represented by parameters which are governed by our mathematical model. It is then exhibited that our model is numerically stable and uniquely solvable. With this knowledge, our mathematical model for HIV disease progression is formulated and physiological interpretations are provided. The results of our numerical simulations are visualized, and it is seen that our results agree with medical aspects from the point of view of antiretroviral therapy. It is then expected that our approach will take to address practical clinical issues and will be applied to the computer-aided management of antiretroviral therapies.
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1. Antiretroviral therapy for HIV infection

Ongoing HIV replication leads to the damage of immune system and progression of AIDS disease, and a goal of therapy is the maximal suppression of viral replication. Combination antiretroviral therapy is the foundation of management of patients with HIV infection. The antiretroviral drugs used in combination regimens need to be used according to optimal schedules of therapies and dosages. Any decision on antiretroviral therapy need to have a long-term impact on future options for the patient. At present, many of the most important questions related to the treatment of HIV disease do not have definite answers. Among them are the questions of when therapy should be started, what the best initial regimen is, when a given regimen should be changed, and what it should be changed to when a change is made. In an effort to facilitate this decision process, the United States Department of Health and Human Services has

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published a series of frequently updated guidelines including the "Principles of Therapy of HIV Infection", "Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescent", and "Guidelines for the Prevention of Opportunistic Infections in Persons Infected with HIV".

Currently licensed drugs for the treatment of HIV infection fall into two main categories as those that inhibit the viral reverse transcriptase enzyme and those that inhibit the viral protease enzyme. There are numerous drug–drug interactions that need to be taken into consideration when using these agents. There are drugs among FDA-approved reverse transcriptase inhibitors which include the nucleoside and the nonnucleoside analogues should not be used as monotherapy for HIV infection. Physicians ensure that the patient is also on additional antiretroviral medication. The reverse transcriptase inhibitors block the HIV replication cycle at the point of RNA-dependent DNA synthesis in the reverse transcription step. While the nonnucleoside reverse transcriptase inhibitors are quite selective for the HIV-1 reverse transcriptase, the nucleoside analogues inhibit a variety of DNA polymerization reaction in addition to these of the HIV-1 reverse transcriptase. See also [1]. For this reason, serious side effects are more common with the nucleoside analogues and include mitochondrial damage that can lead to hepatic steatosis and lactic acidosis as well as peripheral neuropathy and pancreatitis.

The introduction of the HIV-1 protease inhibitors to the therapy is important. When used as part of initial regimens in combination with reverse transcriptase inhibitors, these agents have been shown to be capable of suppressing levels of HIV replication to under 50 copies per milliliter in the majority of patients for a minimum of 3 years. As in the case of reverse transcriptase inhibitors, resistance to protease inhibitors can develop rapidly in the setting of monotherapy, and thus these agents should be used as part of combination regimens of therapy. Treatment decisions are based on the fact that one is dealing with a chronic infection. While early therapy is generally the rule in infectious disease, immediate treatment of every HIV infected individual when diagnosis are made may not give the best results, and decisions in therapy takes the balance between risks and benefits into account. At present, a reasonable course of action is to initiate antiretroviral therapy in anyone with the acute HIV syndrome; patients with symptomatic disease; patients with asymptomatic disease with $CD4^+T$ cell counts < 500 per milliliter or with $> 20,000$ copies of HIV/RNA per milliliter. Once the decision has been made to initiate therapy, the health care providers decide which drugs to use as the first regimen. The decision regarding choice of drugs not only will affect the immediate response to therapy but also will have implications regarding options for future therapy regimens. The initial regimen is usually the most effective as the virus has not developed significant resistance. See [1] for details.

The two options for initial therapy which are most commonly used today are two different three-drug regimens. The first regimen utilizes two nucleoside analogues and a protease inhibitor. The second regimen utilizes two nucleoside analogues and a nonnucleoside reverse transcriptase inhibitor. There are no clear data at present on which to base distinctions between these two approaches. Following the initiation of therapy, a one-log reduction in plasma HIV/RNA levels within 1–2 months and eventually a decline in plasma HIV/RNA levels to < 50 copies per milliliter should be expected. During the same time, there should be a rise in the $CD4^+T$ cell counts of 100–150 per milliliter. Other reasons for a change in therapy include a persistently declining $CD4^+T$ cell count, clinical deterioration, or drug toxicity.

As in the case of initiating therapy, changing therapy may have a lasting impact on future options of therapy. When changing therapy because of clinical progression or worsening laboratory parameters, it is recommended to attempt to provide a regimen with at least two new drugs. In the patient in whom a change is made for reasons of drug toxicity, a replacement of one drug is suggested. Plasma HIV RNA levels and $CD4^+T$ lymphocyte counts are to be monitored every 3–4 months during therapy and more frequently if one is considering a change in regimen or immediately following a change in regimen. HIV resistance profiles should improve outcomes of therapy in patients failing their current antiretroviral regimen. Rates of disease progression differ among individuals, and treatment decisions are to be individualized based on plasma HIV levels and $CD4^+T$ cell counts. See [3].

In view of these aspects, we have performed numerical simulations for monitoring the HIV disease progression and change in time of HIV virus population dynamics. In accordance with the visualized numerical results, it is expected that computer-aided management of antiretroviral therapies may be realized.

2. An HIV infection model

In view of the discussions in Section 1, we may formulate the following mathematical model for describing the HIV disease progression. Let m denote nonnegative integers $m = 0, 1, 2, \ldots$ and represent the mth stages of applied