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

A. Ida[a], Y. Oharu[b,*], O. Sankey[b]

[a]*Project Development Department, VINAS Co., Ltd. Osaka, Japan*
[b]*Department of Physics and Astronomy, Arizona State University, USA*

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.
© 2006 Elsevier B.V. All rights reserved.

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

---

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

therapies. In order to formulate a mathematical model which describes HIV infection dynamics under the mth therapy, we employ the following parameters:

Symbols T, T_{I,s_m}, T_{I,r_m}, T_{IR,s_m} and T_{IR,r_m} denote population of healthy $CD4^+T$ cells, that of T cells infected with virus which are all sensitive to the mth therapy, T cells infected with virus which are partly or totally resistant to the mth therapy, T cells infected with drug-sensitive virus only but in the resting phase under the mth therapy, and T cells infected with drug-resistant virus but in the resting phase under the mth therapy. Moreover, V_{s_m} and V_{r_m} stand for the population of drug-sensitive virus and that of drug-resistant virus under the mth therapy, respectively. In particular, V_{s_0} evoluted at the initial time $t = 0$ stands for the original virus which first invaded into the human body. Also, V_{r_m} are generated from V_{s_m} through mutation with mutation rate μ_m under the mth therapy, although V_{r_m} may be changed to a part of $V_{s_{m+1}}$ under the $(m + 1)$th therapy.

In the case that the mth therapy is judged to become ineffective for suppressing the disease progression and extensive mutation of virus at some time $t = t_{m+1}$, the therapy is changed to a new therapy called the $(m + 1)$th therapy which is supposed to be more effective against the disease. In this case it is crucial to formulate suitable initial conditions at time $t = t_{m+1}$ for the $(m + 1)$th therapy. For this purpose we suppose that two (drug sensitivity) rates κ_m and ν_m can be specified in the following way: sensitive virus under the mth therapy remain to be sensitive under the $(m + 1)$th therapy with the rate of ν_m. Also, resistant virus under the mth therapy remain to be resistant under the $(m + 1)$th therapy with the rate of κ_m. Hence, the initial conditions at time $t = t_{m+1}$ take the following forms:

$$V_{s_{m+1}}(t_{m+1}) = (1 - \kappa_m)V_{r_m}(t_{m+1}) + \nu_m V_{s_m}(t_{m+1}),$$

$$V_{r_{m+1}}(t_{m+1}) = \kappa_m V_{r_m}(t_{m+1}) + (1 - \nu_m)V_{s_m}(t_{m+1}).$$

(1) The population dynamics of healthy $CD4^+T$ cells may be described by the following equation:

$$(\partial/\partial t)T = d_T\nabla^2 T - \mathbf{v}_f \cdot \nabla T + S + p_{1,m}(V_{\text{total},m}) - \alpha T$$
$$- [\eta_{1m}\gamma_{s_m} V_{s_m} + \gamma_{r_m} V_{r_m}]T - [\eta_{1m}\bar{\gamma}_{s_m} + \bar{\gamma}_{r_m}]T - [\gamma_{R,s_m} + \gamma_{R,r_m}]T.$$

In the above equation, the first two terms on the right-hand side represent diffusion and transportation along the (blood or lymph) flow field $\mathbf{v}_f$. The second three terms mean natural supply, supply due to immune response depending upon the total population

$$V_{\text{total},m} = V_{s_m} + V_{r_m},$$

and natural mortality, respectively. Also, the third two terms stand for infection of T with drug-sensitive and resistant virus with infection rates $\eta_{1m}\gamma_{s_m}$ and γ_{r_m}, respectively. Further, the fourth two terms express infection of T with drug-sensitive and resistant virus generated from T_{IR,s_m} and T_{IR,r_m} with infection rates $\bar{\gamma}_{s_m}$ and $\bar{\gamma}_{r_m}$, respectively. Finally, the fifth two terms represent transition from infected T cells to infected T cells, T_{IR,s_m} and T_{IR,r_m}, in the resting phase with transition rates γ_{R,s_m} and γ_{R,r_m}, respectively. The transition rates γ_{R,s_m} and γ_{R,r_m} should be measured, although it should be mentioned that these rates are linked with the population of T_{IR,s_m} and T_{IR,r_m} in the following way: it is reasonable to assume that the transition rates γ_{R,s_m} and γ_{R,r_m} are products of pure transition rates ζ_{R,s_m} and ζ_{R,r_m} and infection rates in such a way that

$$\gamma_{R,s_m} = \zeta_{R,s_m}\gamma_{s_m} \quad \text{and} \quad \gamma_{R,r_m} = \zeta_{R,r_m}\gamma_{r_m}.$$

We employ the saturation functions

$$p_{k,m}(\xi) = p_{k,m}^*\xi/(c_{k,m} + \xi) \quad \text{for } \xi \geqslant 0 \text{ and } k = 1, \ldots, 4,$$

$$p_{5,m}(\xi) = p_{5,m}^*\xi/(c_{5,m} + \xi) \text{ for } \xi \geqslant \Xi, \quad = 0 \text{ for } \xi < \Xi,$$

and the treatment function

$$\eta_{1m}(x, t) = \exp(-d_1(x)t), \quad t \geqslant 0, \quad x \in \Omega,$$

which is a rapidly decaying positive function on $[0, \infty]$ for each $x \in \Omega$.

(2) Secondly, the population dynamics of drug-sensitive virus may be described through the equation:

$$(\partial/\partial t)V_{S_m} = d_{V_s}\nabla^2 V_{S_m} - \mathbf{v}_f \cdot \nabla V_{S_m} + (1 - \mu_m)p_{3,m}(V_{\text{total},m})V_{S_m}$$

$$+ \eta_{1m}\bar{\gamma}_{S_m}V_{S_m} + \eta_{2m}p_{4,m}(V_{total,m})V_{S_m} - \varepsilon_m(t)V_{S_m}.$$

In the above equation, the first two terms on the right-hand side represent diffusion and advection along the flow field $\mathbf{v}_f$ generated by the circulation system. The second term means that drug-sensitiveness is remained under the mth therapy. Also, the third two terms stand for the restriction (by η_{1m} and η_{2m}) of regeneration of drug-sensitive virus. Finally, the last term represents the decay effect due to the immune system under the mth therapy.

Here the function $\varepsilon_m(t)$ represents the immune response induced by the immune system. In the normal state, the count of $CD4^+T$ lymphocytes is about 1000 per 1 ml. In six weeks after the primary infection, it goes down up to 500 per milliliter. Then the immune system is activated and the amount recovers to 800 per 1 ml, although it decreases about 50–100 counts per 1 ml every year and $CD4^+T$ cell count turns out to decline below the threshold 250 per 1 ml. This process takes place on the primary stage of infection. Under antiretroviral therapy, the immune system is again activated to recover the population of $CD4^+T$ cells. Therefore the function $\varepsilon_m(t)$ may be illustrated as a function of the form:
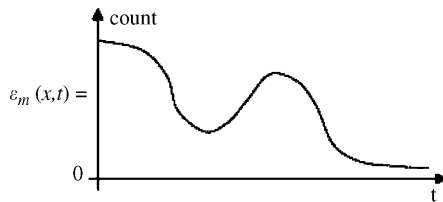
Also, we have employed the two treatment functions of the forms:

$$\eta_{1m}(x,t) = \exp(-d_{1m}(x)t), \quad \eta_{2m}(x,t) = \max\{\exp(-d_{2m}(x)t), d_{3m}(x)\},$$

where d_{1m}, d_{2m} and d_{3m} are bounded positive measurable functions.

(3) Thirdly, the population dynamics of drug-resistant virus may be described by the equation below:

$$(\partial/\partial t)V_{r_m} = d_{V_r}\nabla^2 V_{r_m} - \mathbf{v}_f \cdot \nabla V_{r_m} + p_{3,m}(V_{\text{total},m})[\mu_m V_{S_m} + V_{r_m}] + \bar{\gamma}_{r_m}V_{r_m} - \varepsilon_m(t)V_{r_m}.$$

In the above equation, the first two terms on the right-hand side represent diffusion and advection along the flow field $\mathbf{v}_f$ generated by the (blood and lymph) circulation system. The second two terms mean generation of drug-resistant virus and regeneration of drug-resistant virus due to mutation, respectively. Finally, the third two terms stand for regeneration of drug-resistant virus and immune response of the immune system under the mth therapy.

Here the function $\varepsilon_m(t)$ is supposed to be same as in Item (2). Since all the virus involved in this equation are drug-resistant under the mth therapy, treatment functions of the forms η_{1m} and η_{2m} as introduced in Item (2) are not included in this equation. It is understood that the above equation may be linked with T_{I,s_m} in the sense that

$$V_{S_m} = \text{Kamp}, s_m \cdot T_{I,S_m}, \quad V_{r_m} = \text{Kamp}, r_m \cdot T_{I,r_m},$$

where Kamp,s_m and Kamp,r_m mean the amplification rates of V_{S_m} and V_{r_m} in $CD4^+T$ cells, respectively. It is known that if an HIV virus individual V_{S_m} or V_{r_m} invade into a $CD4^+T$ cell, then over 500 HIV copies are generated.

(4) Fourthly, the following equation may be employed as a governing equation to describe the population dynamics of drug-sensitive infected cells:

$$(\partial/\partial t)T_{I,s_m} = d_{T_{I,S}}\nabla^2 T_{I,s_m} - \mathbf{v}_f \cdot \nabla T_{I,s_m} - p_{2,m}(V_{\text{total},m})T_{I,s_m} - \beta_m T_{I,s_m}$$

$$+ \eta_{1m}\gamma_{s_m}V_{s_m}T + \eta_{1m}\bar{\gamma}_{s_m}T - \gamma_{R,s_m}T_{I,s_m}.$$

In the above equation, the first two terms on the right-hand side represent diffusion and advection along the flow field $\mathbf{v}_f$. The second two terms mean immune response and natural mortality under the mth therapy, respectively. Also, the third two terms stand for restriction (by η_{1m}) of drug-sensitive infection and infection with drug sensitive virus generated from T_{IR,s_m}, respectively. Finally, the last term represents transition from T_{I,s_m} to latently infected cells T_{IR,s_m}.

Here η_{1m} is the treatment function as introduced in Item (2) and the equation is coupled with T_{IR,s_m} through the infection rate $\bar{\gamma}_{r_m}$:

$$\bar{\gamma}_{s_m} = \bar{\bar{\gamma}}_{s_m} \cdot \text{Kamp}, s_m \cdot \delta_{act,s_m} \cdot T_{IR,s_m}$$

for some $\bar{\bar{\gamma}}_{s_m} \in [0,1]$, an amplification rate Kamp,s_m and an activation rate δ_{act,s_m}.

(5) Fifthly, the population dynamics of drug-resistant infected cells may be described by the following equation:

$$(\partial/\partial t)T_{I,r_m} = d_{T_{I,r}}\nabla^2 T_{I,r_m} - \mathbf{v}_f \cdot \nabla T_{I,r_m} - p_{2,m}(V_{\text{total},m})T_{I,r_m} - \hat{\beta}_m T_{I,r_m} + \gamma_{r_m}V_{r_m}T + \bar{\gamma}_{r_m}T - \gamma_{R,r_m}T_{I,r_m}.$$

In the above equation, the first two terms on the right-hand side represent diffusion and advection along the flow field $\mathbf{v}_f$. The second two terms mean immune response depending upon the total population $V_{\text{total},m} = V_{s_m} + V_{r_m}$ and natural mortality, respectively. Also, the third two terms stand for resistant infection and infection with resistant virus generated from T_{IR,r_m}, respectively. Finally, the last term represents transition from T_{I,r_m} to latently infected cells T_{IR,r_m}. This equation is coupled with T_{IR,r_m} through the infection rate:

$$\bar{\gamma}_{r_m} = \bar{\bar{\gamma}}_{r_m} \cdot \text{Kamp}, r_m \cdot \delta_{\text{act},r_m} \cdot T_{IR,r_m}$$

for some weight $\bar{\bar{\gamma}}_{r_m} \in [0,1]$, an amplification rate Kamp, r_m and an activation rate δ_{act,r_m}.

(6) The population dynamics of drug-sensitive latently infected cells may be described by the following equation:

$$(\partial/\partial t)T_{IR,s_m} = d_{T_{IR,s}}\nabla^2 T_{IR,s_m} - \mathbf{v}_f \cdot \nabla T_{IR,s_m} + \gamma_{R,s_m}T_{I,s_m} - \bar{\beta}_m T_{IR,s_m}$$
$$- \eta_{1m}\delta_{\text{act},m}T_{IR,s_m} - p_{2,m}(V_{\text{total},m})\delta_{\text{act},s_m}T_{IR,s_m}.$$

In the above equation, the first two terms on the right-hand side represent diffusion and advection of T_{IR,s_m} along the flow field $\mathbf{v}_f$. The second two terms mean transition from T_{I,s_m} to T_{IR,s_m} and natural mortality, respectively. Also, the fifth term stands for activation of latently infected cells and treatment. Finally, the last term represents immune response to the activated T_{IR,s_m}. The rate γ_{R,s_m} is the transition rate on the mth stage of antiretroviral therapy and $\bar{\beta}_m$ means the mortality rate which is understood to be small since T_{IR,s_m} tend to stay at specific parts of the lymphatic system for a comparatively long period such as several months or even a few years.

(7) The following equation may be employed as a governing equation for the population dynamics of latently infected drug-resistant cells:

$$(\partial/\partial t)T_{IR,r_m} = d_{T_{IR,r}}\nabla^2 T_{IR,r_m} - \mathbf{v}_f \cdot \nabla T_{IR,r_m} + \gamma_{R,r_m}T_{I,r_m} - \bar{\beta}_m T_{IR,r_m} - p_{2,m}(V_{\text{total},m})\delta_{\text{act},r_m}T_{IR,r_m}.$$

In the above equation, the first two terms on the right-hand side represent diffusion and advection along the flow field $\mathbf{v}_f$. The second two terms mean transition from T_{I,r_m} to T_{IR,r_m} and natural mortality, respectively. Finally, the last term stands for immune response to the activated T_{IR,r_m}.

In the mathematical model as mentioned above, we have employed the following rates and coefficients: the rates γ_{s_m} and γ_{r_m} denote the rates of infection of T cells with virus which are sensitive and resistant to the mth therapy, respectively. γ_{R,s_m} and γ_{R,r_m} mean the rates of transition from infected T cells with drug-sensitive and drug-resistant virus to the infected cells in the resting phase under the mth therapy. The rates δ_{act,s_m} and δ_{act,r_m} represent the rates of activation of T_{IR,s_m} and T_{IR,r_m} which are transitional to T_{I,s_m} and T_{I,r_m}, respectively. Kamp,s_m and Kamp,r_m denote the rates of amplification of V_{s_m} and V_{r_m} generated in T_{I,s_m} and T_{I,r_m}, respectively. β_{s_m}, $\bar{\beta}_{s_m}$, β_{r_m} and $\bar{\beta}_{r_m}$ mean the natural mortality rates of T_{I,s_m}, T_{IR,s_m}, T_{I,r_m} and T_{IR,r_m}, respectively. Finally, μ_m stands for the mutation rate under the mth therapy.

Stable solvability of the above mathematical model is verified by applying the so-called semi-implicit product formula. The numerical solvability is also treated via the same approach. See [2,4] for detailed verifications.

3. Numerical simulations

The primary purpose of the numerical simulation is to analyze change in time of the levels of virus and states of disease progression, the rates of viral turnover, the relationship between immune system activation and viral replication, and the time at which drug resistance start appearing by mutation. The $CD4^+T$ cell count is understood to be the best
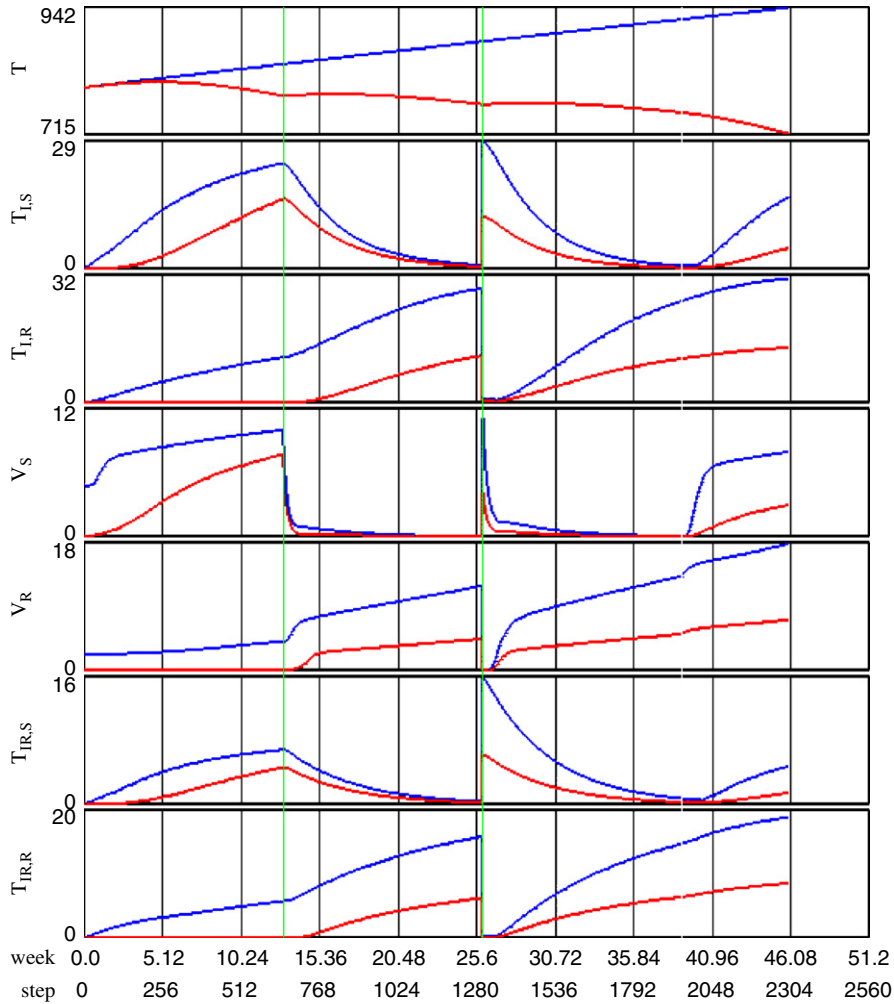
Fig. 1. Simulation results.

indicator of the state of immunologic competence of the patient with HIV infection. Our mathematical model of HIV infection process encompasses a spectrum ranging from an acute syndrome associated with primary infection to a prolonged asymptomatic state to advanced disease. An attempt has been made to simulate the following four stages of the HIV infection processes: the early and later stages of HIV infection, the most crucial stage after the first antiretroviral therapy has started, the second stage after the first therapy was changed to a new therapy, and states in the case that treatment stops. These results of our numerical simulations agree with medical and physiological aspects. More detailed and other important physiological aspects will be taken into account in the subsequent studies. See [2].

We depict our simulation results in Fig. 1 which consists of seven graphs. In each graph, the lower curve represents the change in time of the L^1-norm of (nonnegative) parameter and illustrates the infection process in the primary stage, the change in time of disease progression under the second therapy and the last state after all the therapies have been stopped. The upper curve in each graph shows the change in time of the L^∞-norm of (nonnegative) parameter. These L^∞-curves may also be useful for investigating the stability of numerical computation.

The first part from step 0 to step 640 illustrates a period of the primary stage to the stage after infection has been established. It is observed that treatment-sensitive cells are much more prolific than resistant cells. Treatment-resistant cells are still not as prolific as sensitive cells. This eventually evolves into a stable state. As mentioned previously, it is expected that mutation of sensitive virus occurs in the next stage after the establishment of chronic infection. The second part of the graph from step 640 to step 1280 depicts the change in time of disease progression which takes

place after the first antiretroviral therapy has been started. A stable state is quickly reached for each case. The treatment seems to be effective in the sense that it results in the almost complete destruction of sensitive virus, but this allows the resistant virus to flourish without strong competition with the immune system. The third part of the graph between step 1280–step 1980 illustrates the change in time of disease progression after the first therapy was changed to the second therapy. At step 1280 we necessitate imposing a new initial condition as mentioned in the first part of Section 2. It is seen from the numerical results that a change in time of disease progression similar to the second stage is repeated. The last part between step 1280–step 2300 suggests a state after all the treatments have been stopped. This result is obtained by means of the same model with no treatments. When treatment stops, resistant virus are present and sensitive virus increase rapidly. Thus it is likely to reach a state in which both types of cells coexist, and this may cause further treatment by some more effective therapy to be less effective. These results of our numerical simulations agree with medical and physiological aspects.

It is best to regard HIV disease as beginning at the time of primary infection and progressing through various stages. Active virus replication and progressive immunological impairment occur throughout the course of HIV disease progression in most patients. It should be our next plan to develop a new extended model such that these aspects can be taken into account, and it is anticipated that our approach could take to address practical clinical issues and applied to the computer-aided management of antiretroviral therapies.

References

[1] Fauci, et al., in: E. Braunwald, et al. (Eds.), Harrison's Principles of Internal Medicine, 15th ed., McGraw-Hill, New York, pp. 1852–1913.
[2] A. Ida, S. Oharu, Y. Oharu, A mathematical approach to HIV infection dynamics, 2006, this issue.
[3] D.E. Kirschner, G.F. Webb, Resistance, remission, and qualitative differences in HIV chemotherapy, Emerging Infect. Dis. 3 (3) (1997) 273–283.
[4] D. Tebbs, On the product formula approach to a class of quasilinear evolution systems, Tokyo J. Math. 26 (2) (2003) 423–445.