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A new strategy to decrease risk of resistance emerging during therapy switching in HIV treatment

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Abstract— **Although Highly Active Antiretroviral Therapy (HAART) provides a powerful strategy for HIV treatment, it has been shown that HAART cannot eradicate all viruses in patients because of the existence of long-term reservoir. With the use of HAART, resistant strains develop and become the dominant species. Because the number of independent treatment regimens is limited, once resistance to all available drug classes arises, the patient will die. In this paper, we propose a drug switching strategy to minimize resistance risk of resistance and preserve long-term control of the HIV infection based on a simple model of HIV infection with persistent viral reservoirs.**

I. INTRODUCTION

Among the drugs available for the treatment of HIV, no individual drug has been shown to suppress HIV infection in the long term. In 1996, multi-drug regimens for HIV, called Highly Active Antiretroviral Therapy, or HAART, were introduced and the development of HIV treatment has made a remarkable progress in the last decade. Combinations of antiretroviral drugs provide multiple ways to inhibit HIV replication and also reduce the possibility of escape mutations. If one resistance to one drug being taken emerges, the other drugs can still suppress the replication of that mutant. As of 2002, twenty antiretroviral drugs belonging to four classes have been approved for treatment of the infection [1]. Usually combinations consist of two nucleoside-analogue RTIs and either one non-nucleoside-analogue RTI or protease inhibitor.

Although HAART provides a powerful strategy for HIV treatment, there is a general agreement that HAART cannot cure the HIV infection completely. The primary reason is that the HIV virus can persist in long-lived cellular reservoirs. HIV also infects a subtype of myeloid dendritic cells [2], which probably constitute a reservoir that maintains infection when CD4+ T cell numbers have declined to extremely low levels. In 1997, Finzi et al. showed that a reservoir of latently infected CD4 cells is established at the beginning of infection [3]. Another substantial reservoir consists of resting CD4 cells with a memory phenotype [4], [5]. The long-lived reservoirs provide a critical mechanism for virus persistence during antiretroviral therapy even though active replication is suppressed by drugs.

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Although a successful HAART regimen reduces the possibility of the emergence of resistant strains of the virus, it does not completely block the emergence of the drug-resistance virus. The possible reasons may be either pre-existence or poor adherence to the treatment regimen [6]. If a patient becomes resistant to all HAART options, treatment becomes more complicated and the patient may deteriorate. Recently, a treatment strategy, named ”structured treatment interruptions”, was introduced. The purpose of this kind of study is to increase the sensitivity of HIV to antiretroviral drugs. The interruptions attempt to change the selection pressure from the drug-resistance virus back toward wild-type virus, thus increasing sensitivity of drugs and reducing resistance risk.

Some research exists on how to choose a new drug combination if the resistance to the previous one occurs. However, just few studies have been done on how the timing of the therapy switch influences the risk of resistance. In 1998, D'Amato et al. proposed a stochastic model which predicts a reduced risk of resistance [7]. An early study by Zurakowski and Wodarz suggested that a pattern of structured treatment interruptions using the failing regimen preceding the introduction of the new regimen can significantly decrease the risk of resistance emerging to the new regimen [8]. Building on these two studies, we will present a new drug switching strategy for HIV infection which explicitly accounts for the effect of persistent viral reservoirs.

This paper is organized as follows: In Section II, a simple model of HIV infection with persistent viral reservoirs is introduced. In Section III, we show some simulation results for several different cased and present some therapeutic implications based on the simulation results. In Section IV, we discuss the results, the implications of the model for HIV treatment, as well as the future works.

II. MODEL

A. Mathematical model

We adapted the mathematical model used in [8] to describe the dynamics of target and infected cells during HAART, adding the influence of long-lived reservoirs.

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$$\begin{aligned} \dot{x} &= \lambda - dx - \beta_w(1-u_1)(1-u_2)xy_w \\ &\quad -\beta_r(1-u_2)xy_r \\ \dot{y_w} &= \beta_w(1-u_1)(1-u_2)xy_w - a_w y_w + \lambda_w \\ \dot{y_r} &= \beta_r(1-u_2)xy_r - a_r y_r + \lambda_r \end{aligned} \quad (1)$$

As for previous mathematical models that describe various aspects of HIV-1 dynamics [7], [8], this model's states include x, the CD4+ T cells that are susceptible to infection (target cells); y_w, CD4+ T cells infected by wide-type virus; and y_r, the CD4+ T cells infected by resistant virus. The parameters are λ, the generation rate of the target cells; d, the natural death rate of target cells; β_w and β_r, the infection rates of wild-type and resistant virus respectively; a_w and a_r, the death rates of cells infected by wild-type and resistant-type virus respectively; λ_w and λ_r, the two virus types' respective generation rate from long-lived reservoirs. u_1 and u_2 represent the drug efficacies. The values of u_1, u_2 , may be applied between 0 and 1. Because of the excessive toxicity, we do not apply the both regimens at the same time.

B. The steady state analysis

The proposed system (1) has three steady states. We calculated them theoretically. However, the results are too complicated to represent in this paper. We list their approximations as follows:

1. The first steady state is:

$$\begin{aligned} x_0 &= \tfrac{\lambda}{d} - \xi_1 \\ y_{w0} &= \xi_{1w} \\ y_{r0} &= \xi_{1r} \end{aligned} \quad (2)$$

where ξ_1, ξ_{1w}, ξ_{1r} respresent three small numbers. This equilibrium point is stable if $\frac{\lambda\beta_w(1-u_1)(1-u_2)}{a_w d} < 1$ and $\frac{\lambda\beta_r(1-u_2)}{a_r d} < 1$.

2. The second steady state is:

$$\begin{aligned} x_1 &= \tfrac{a_w}{\beta_w(1-u_1)(1-u_2)} - \xi_2 \\ y_{w1} &= \tfrac{\lambda}{a_w} - \tfrac{d}{\beta_w(1-u_1)(1-u_2)} + \xi_{2w} \\ y_{r1} &= \xi_{2r} \end{aligned} \quad (3)$$

where ξ_2, ξ_{2w}, ξ_{2r} respresent three small numbers and which is stable if $\beta_w(1-u_1)(1-u_2) > \beta_r(1-u_2)$.

3. The third steady state is:

$$\begin{aligned} x_2 &= \tfrac{a_r}{\beta_r(1-u_2)} - \xi_3 \\ y_{w2} &= \xi_{3w} \\ y_{r2} &= \tfrac{\lambda}{a_r} - \tfrac{d}{\beta_r(1-u_2)} + \xi_{3r} \end{aligned} \quad (4)$$

where ξ_3, ξ_{3w}, ξ_{3r} respresent three small numbers and which is stable if $\beta_w(1-u_1)(1-u_2) < \beta_r(1-u_2)$.

C. Drug Switching Strategy

In biology, a sudden change in a gene or unit of hereditary material will result in a new inheritable characteristic. Drug resistance occurs as a result of changes, or mutations, in HIV's genetic structure. HIV replication is a complex process, called reverse transcriptase. Reverse transcription is the opposite process of Transcription: copying RNA into DNA. Reverse transcriptase is not an very good copier. It has been estimated that during each round of HIV-1 replication, 10 mistakes are incorporated. This is a lot worse than an ordinary cell's transcription process These mistakes in HIV's genetic structure are called mutations.

Most mutations that can influence the effectiveness of combination therapy occur before a patient begins treatment. Normally, at the beginning of antiretroviral treatment, the amount of HIV in a patient's body goes down dramatically. The reason for this is that most of the virus is the wild-type. Just as the wild-type virus is most fit and most able to replicate without any treatment, it is also the most sensitive to antiretroviral treatment. On the other hand, there is a strong likelihood that there are viruses with certain mutations in the reverse transcriptase or protease enzymes that give them a survival advantage. The drug cannot stop these kinds of viruses from reproducing, and the drug-resistant virus is able to replicate despite the presence of the drug and will become the dominant strain over time. Mutations almost always occur before treatment begins. It has been shown that for any sufficiently potent antiviral therapy, the number of mutation events occurring after the start of anti-viral therapy is insignificant compared to the genetic diversity present at the start of anti-viral therapy [6], [9]. The reason for this reduced chance is that the therapy reduces the chance of mutation by lowering the virus reproduction rate. Therefore, the risk of resistance emerging to a new regimen is proportional to the amount of virus present at the start of application of this regimen [6], [9].

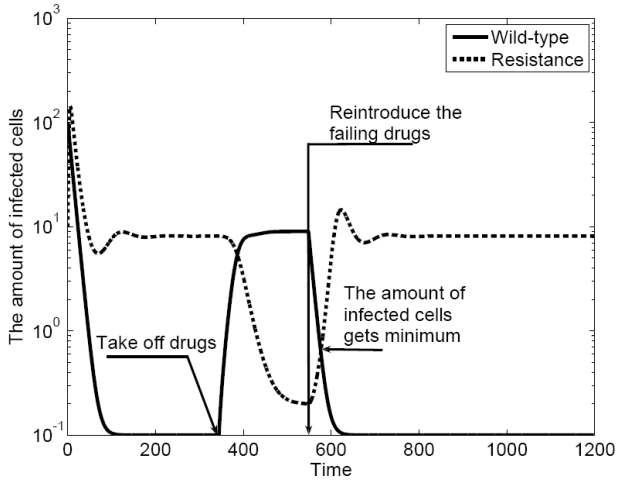

Fig. 1. **Dynamics of infected cells by using our drug-switch strategy**

Our concern in this paper is to manage a switching therapy, which minimizing the risk of resistance emergence. In other words, the purpose of this approach is to find a drug-switching schedule that yields the minimum total amount of infected cells for starting a new regimen.

While intermittent therapy has been used for other purposes with little effect, our approach uses the technique for an entirely different purpose. Based on the model (1), when the fist drug combination is failing, the system approaches the third steady state. We notice that the wild-type virus outcompetes all resistant viruses in the absence of suppres-

sive therapy. Therefore, if the patient is taken off the drugs, the wild-type virus will grow exponentially and the resistant virus will decay exponentially. Our strategy is to choose the best time to reintroduce the failing drugs, resulting in the deepest drop in the number of all infected cells (both wild-type and resistant) will get a temporary dig, as shown in Fig.1. Therefore, if a new regimen starts at this time, the risk of resistance emergence will be minimized.

III. SIMULATION

In this section, we shows how death rates of infected cells (a_w, a_r) and generation rates from long-lived reservoirs (λ_w, λ_r) influence the drug switch strategy by representing the simulation results for five different cases. In the following figures, T1 represents the time for waiting before the failing therapy is reintroduced; T2 represents the time to get the minimum resistance risk from the failing therapy is reintroduced; M point means the moment for getting the minimum resistance risk.

Case I: Resistant strain has the same properties with wild-type strain except the infection rates ($\beta_w = 0.01$, $\beta_r = 0.005$). Parameter values: $\lambda = 1$, $\lambda_w = 0.01$, $\lambda_r = 0.01$, $d = 0.01$, $\beta_w = 0.01$, $\beta_r = 0.005$, $a_w = 0.1$, $a_r = 0.1$. The simulation results are shown in Fig.2 and Fig.3.

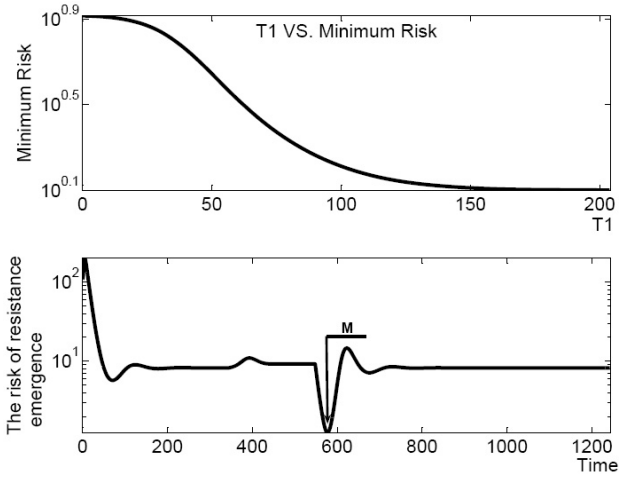

Fig. 2. **(A) T1 VS. Minimum Risk; (B) The dynamics of total amount of infected cells by reintroducing the failing therapy**

From Fig.2(A), we see that the longer we wait before reintroducing the failing therapy, the smaller risk we get. The reason is that the increasing rate of the cells infected by wild-type virus is much faster than the decay rate of the cells infected by resistant virus after the patient take off the therapy. Therefore, the minimum amount of total infected cells occurs at the moment which the system reaches its steady state.

Case II: Resistant strain has the same properties with wild-type strain except the infection rates ($\beta_w = 0.01$, $\beta_r = 0.005$) and the death rate ($a_w = 0.1$, $a_r = 0.3$). Parameter values: $\lambda = 1$, $\lambda_w = 0.01$, $\lambda_r = 0.01$, $d = 0.01$, $\beta_w = 0.01$, $\beta_r = 0.005$, $a_w = 0.1$, $a_r = 0.3$. The simulation results are shown in Fig.4 and Fig.5.

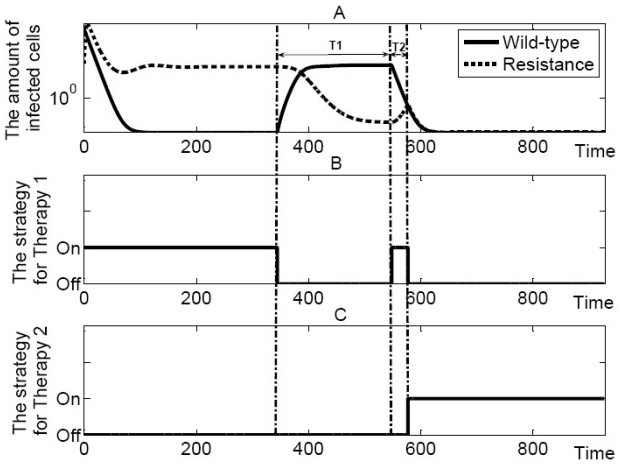

Fig. 3. **(A) The dynamics of infected cells under our strategy; (B) The schedule of Therapy 1; (C) The schedule of Therapy 2;**

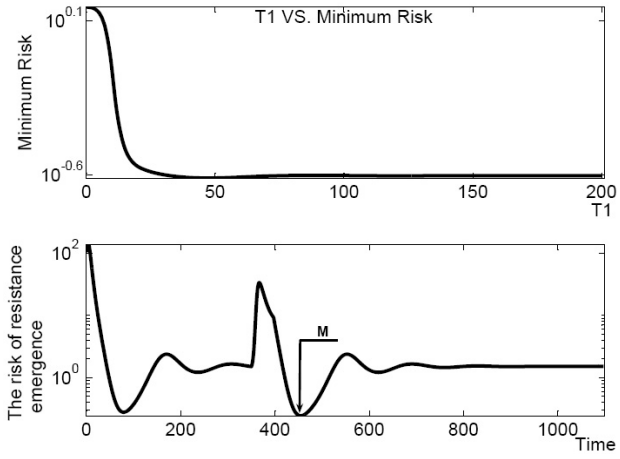

Fig. 4. **(A) T1 VS. Minimum Risk; (B) The dynamics of total amount of infected cells by reintroducing the failing therapy**

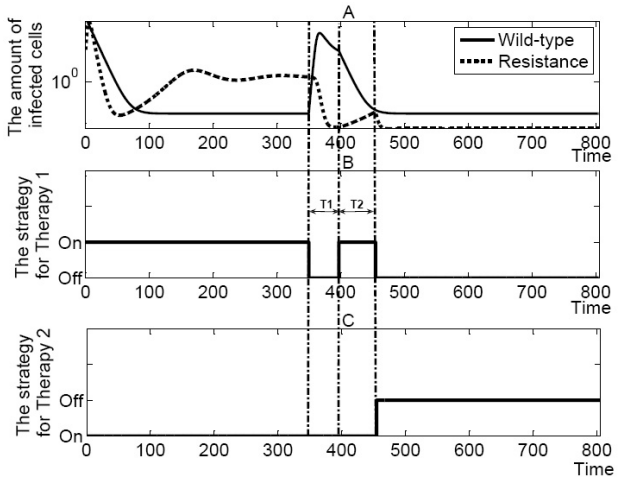

Fig. 5. **(A) The dynamics of infected cells under our strategy; (B) The schedule of Therapy 1; (C) The schedule of Therapy 2;**

Fig.4(A) gives us the following important information: for this case, we can control the minimum resistance risk by manipulating how long we wait before reintroducing the failing therapy (T1). In this case, because the death rate of the cells infected by resistant virus is larger than that of the cells infected by wild-type virus, after the patient take off the therapy, the increasing rate of the cells infected by wild-type virus and the decay rate of the cells infected by resistant virus are almost in the same level. The minimum total amount of infected cells occurs before the system reaches its steady state.

Case III: Resistant strain has the same properties with wild-type strain except the death rate ($a_w = 0.1$, $a_r = 0.3$). Parameter values: $\lambda = 1$, $\lambda_w = 0.01$, $\lambda_r = 0.01$, $d = 0.01$, $\beta_w = 0.01$, $\beta_r = 0.01$, $a_w = 0.1$, $a_r = 0.3$. The simulation results are shown in Fig.6 and Fig.7.

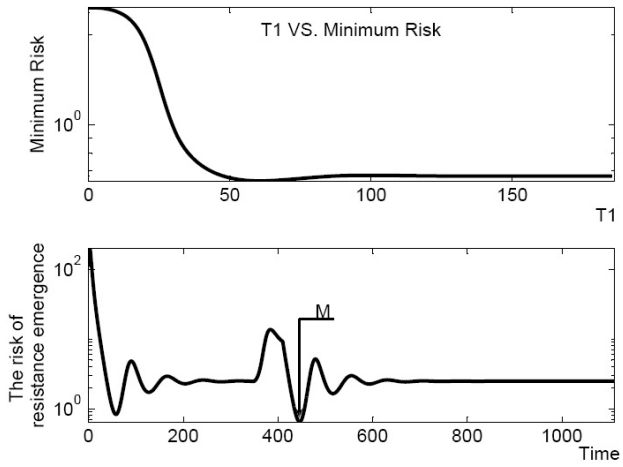

Fig. 6. **(A) T1 VS. Minimum Risk; (B) The dynamics of total amount of infected cells by reintroducing the failing therapy**

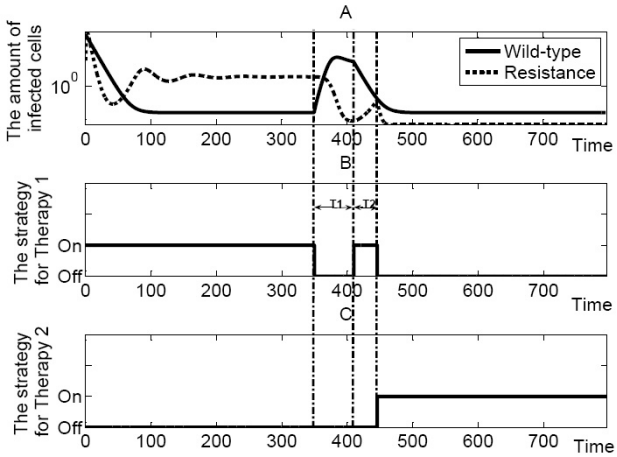

Fig. 7. **(A) The dynamics of infected cells under our strategy; (B) The schedule of Therapy 1; (C) The schedule of Therapy 2;**

The simulation results of this case are similar with Case II. The point of minimum risk occurs before the systems approaches its steady state. Therefore, for this case, the resistance risk can be minimized by choosing a proper time for reintroducing the failing therapy.

Case IV: Resistant strain has the same properties with wild-type strain except the infection rates ($\beta_w = 0.01$, $\beta_r = 0.005$) and and generation rate from long-lived reservoirs ($\lambda_w = 0.20$, $\lambda_r = 0.01$). Parameter values: $\lambda = 1$, $\lambda_w = 0.20$, $\lambda_r = 0.01$, $d = 0.01$, $\beta_w = 0.01$, $\beta_r = 0.005$, $a_w = 0.1$, $a_r = 0.1$. The simulation results are shown in Fig.8 and Fig.9.

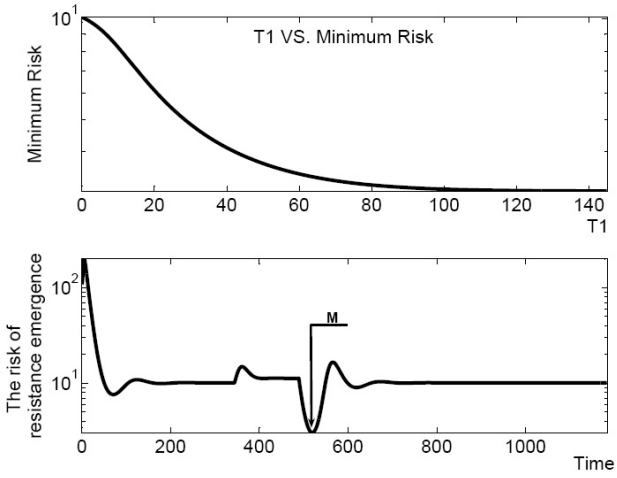

Fig. 8. **(A) T1 VS. Minimum Risk; (B) The dynamics of total amount of infected cells by reintroducing the failing therapy**

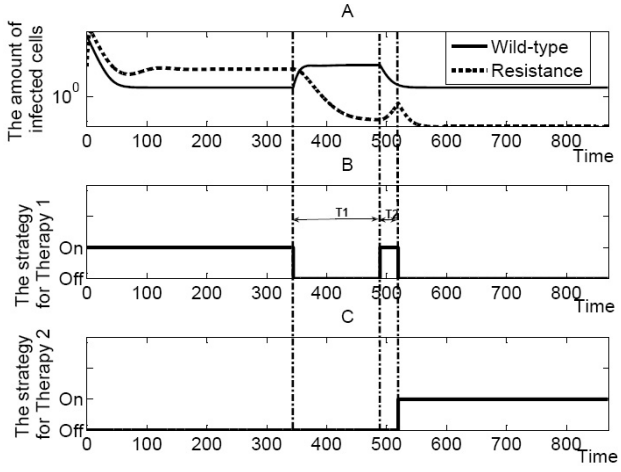

Fig. 9. **(A) The dynamics of infected cells under our strategy; (B) The schedule of Therapy 1; (C) The schedule of Therapy 2;**

The purpose of this case and the following case is to test how it influences our strategy if the two kinds of infected cells have different generation rates from long-lived reservoirs influence. From Fig.8(A), we can see that in order to get the best result, we need to wait as long as possible for reintroducing the failing therapy.

Case V: Resistant strain has the same properties with wild-type strain except the infection rates ($\beta_w = 0.01$, $\beta_r = 0.005$) and and generation rate from long-lived reservoirs ($\lambda_w = 0.01$, $\lambda_r = 0.20$). Parameter values: $\lambda = 1$, $\lambda_w = 0.01$, $\lambda_r = 0.20$, $d = 0.01$, $\beta_w = 0.01$, $\beta_r = 0.005$, $a_w = 0.1$, $a_r = 0.1$. The simulation results are shown in Fig.10 and Fig.11.

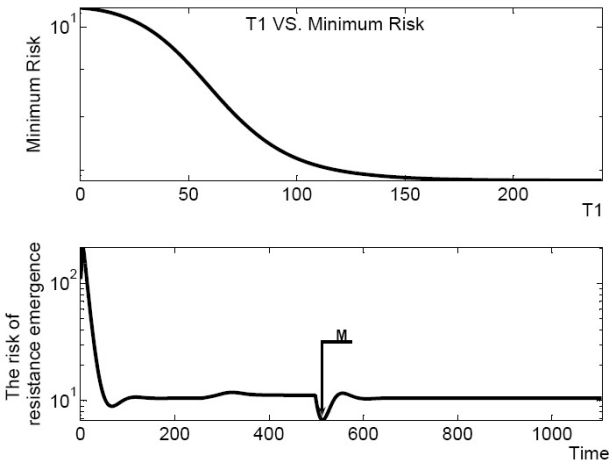

Fig. 10. **(A) T1 VS. Minimum Risk; (B) The dynamics of total amount of infected cells by reintroducing the failing therapy**

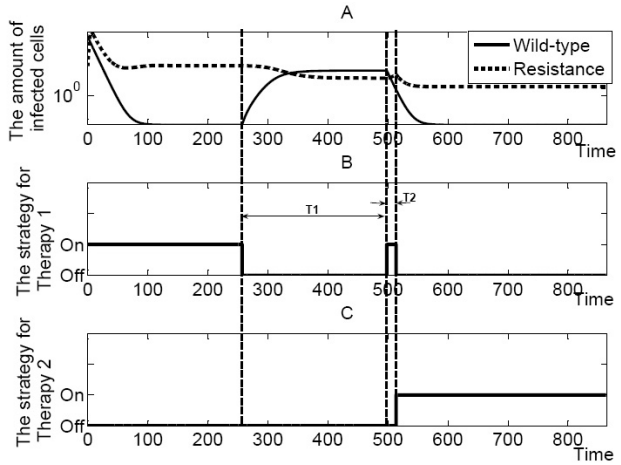

Fig. 11. **(A) The dynamics of infected cells under our strategy; (B) The schedule of Therapy 1; (C) The schedule of Therapy 2;**

The results of this case is the same as last one. we need to wait as late as possible for reintroducing the failing therapy. It is reasonable, because from long-lived reservoirs influence only have a little influence on the dynamics of the both kinds of infected cells. In other words, the influence is not large enough to change the following fact: the increasing rate of the cells infected by wild-type virus is much faster than the decay rate of the cells infected by resistant virus when the patient take off the therapy. Therefore, the point of minimum resistance risk occurs at the time which the system reaches its steady state.

From the simulation results, we see that after we reintroduce the failing therapy, there is always a minimum value for the total amount of infected cells, which means if new therapy is introduced at this moment, we minimize the risk for resistance emerging to the new therapy. We can manipulate the size of this this minimum according to how long we wait before reintroducing our failing therapy. The time for reintroducing the failing therapy will depend on the initial conditions and parameters. In all tested cases except Case II and III, the reintroduction time should be as late as possible. However, a long treatment interruption may damage the organs irreversiblely [10], as the long-term uncontrolled infection will allow the HIV disease to develop to the point.

In Case II and III, if the death rate of resistant strain is large enough, in order to minimize the risk, the reintroduction of the failing therapy should happen before the system reaches its steady state. As we can see in Fig.4 and Fig.6, there is a clear point of minimizing the resistance risk. With this in mind, this knee point becomes a natural switching point for reintroducing the failing therapy.

IV. CONCLUSIONS AND FUTURE WORKS

A. Conclusions

The issue of HIV resistance emergence impacts the treatment for HIV and AIDS patient greatly. The solutions to overcome HIV resistance exit not only in inventing new drugs, but also in developing proper therapeutic strategies. This paper suggests that current switching strategies do not optimally utilize failing therapies, and that optimal use of failing therapies dramatically increases the chances of future therapies succeeding.

Although some clinical data show that treatment interruptions in HIV treatment increase the risk of the resistance emergence, Zurakowski and Wodarz [8] suggested that treatment interruptions could provide a chance for minimize the resistance risk to a new therapy, if the failing therapy was reintroduced properly. This paper has expanded on their research, and proposed a simple mathematical model which accounts for the effects of long-lived reservoirs and shows how to minimize the risk of resistance emergence by proper therapy switching. The results also explore how changing parameters influence the optimal schedule of therapy switching. For some cases, as when the resistant virus is more cytotoxic than the wild type (yielding a larger death rate of infected cells) , there exists a time point for reintroducing the failing therapy at which a true minimum is reached in the resistance risk.

B. Future Works

In this paper, we use a simple mathematical model and also used some assumptions, which may not be hold in practice. Firstly, in the model of this paper, we assume that the efficacy of drug is 100% to non-resistant virus or 0 to resistant virus. In fact, the maximum efficacy of antiretroviral drugs lies somewhere inbetween 0 and 1 (close to 1). Furthermore, the resistance profile of a virus is never all or nothing; even resistant virus is usually partially suppressed by a given HAART cocktail. Future works will explore the importance of this partial suppression, using data from the Stanford HIV database.

Secondly,this model is a deterministic system and does not include any representation of mutations between different virus strains. Mutation is fundamentally a stochastic process, and deterministic models will only yield average behavior. Therefore, a more accurate stochastic mathematical model which depicts the mutations will be explored in future works.

During the process of treatment, it is possible to distinguish between the wild-type and resistant virus, but extremely expensive under the current biological technologies, as it involves genotyping samples. Measuring the total virus load is inexpensive, and should provide enough information for state estimation. Future works will explore the use of nonlinear state estimation techniques to overcome implementation problems with this technique.

In this paper, we assume the influence of each virus on the resistance risk is the same. However, different strains have different probabilities of producing a given resistant strain, based on their true genetic distances. In the future, a cost function which describes the resistance risk will be built and our optimization will be made based on the cost function.

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