

# Resistance Risk Management in HIV Therapy Switching with Explicit Quiescent T-Cell Modeling

Rutao Luo\* Ryan Zurakowski\*\*

\* *Department of Electrical and Computer Engineering, University of Delaware, Newark, DE 19713 rutao1uo@udel.edu*

\*\* *Department of Electrical and Computer Engineering, University of Delaware, Newark, DE 19713 ryanz@udel.edu*

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**Abstract:** Highly Active Antiretroviral Therapy (HAART) has proven remarkably effective in controlling the development of HIV. However, drug resistance may compromise these benefits. During the use of HAART, drug-resistant strains can 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. Drug resistance is therefore a critical problem for HIV treatment. In this paper, we explicitly model one known reservoir compartment, the quiescent infected CD4+ T cells, and explore the effects of this reservoir on a drug-switching strategy designed to minimize the further development of drug-resistant virus.

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## 1. INTRODUCTION

HIV replication is a complex process, and involves one particularly error-prone step called reverse-transcription. Reverse transcription is the process of copying RNA into DNA. It has been estimated that during each round of HIV-1 replication, 10 point mutations occur on average. This high error rate corresponds to very rapid evolution. As of 2002, twenty antiretroviral drugs belonging to four classes were approved for treatment of the infection Yeni et al. [2002]. Usually combinations consist of two nucleoside-analogue RTIs and either one non-nucleoside-analogue RTI or one protease inhibitor. However, treatment success, even of HAART, is limited. Antiretroviral therapy is not able to eradicate HIV. If the viral replication is not durably suppressed below the detectable limits, the continued replication almost inevitably leads to resistance. Drug resistance is the major reason for treatment failures.

Although a successful HAART regimen reduces the possibility of the emergence of resistant strains, drug-resistant virus may still emerge. There are two possible reasons: 1. pre-existence, 2. poor adherence to the treatment regimen Bonhoeffer and Nowak [1997]. If a patient becomes resistant to all available combinations, the patient may die. Structured Treatment Interruptions, which are planned interruptions in a given therapy, have been used in the past to try to reverse the effect of resistance emergence Ananworanich et al. [2003, 2006], Benson et al. [2006], Deeks et al. [2005], Ghosn et al. [2005], Katlama et al. [2004], Lawrence et al. [2003]. The purpose of these studies was to increase the sensitivity of HIV to antiretroviral drugs. Unfortunately, the reversion to wild-type caused by the interruptions was shown to only be temporary, and the increased viral replication during the interruptions led to disease progression in most studies.

The two types of drugs used in HIV either interfere with the infection of uninfected cells or the successful

production of virus from infected cells. Neither increases the rate at which infected cells are cleared from the body, so long-lived infected cells provide an untouchable reservoir from which a patient may be "re-seeded" with virus no matter how long or how durably the virus has been suppressed. There are many cell types known to make up this reservoir. However, the primary cell type of the long-lived reservoir is most likely CD4 T cells with a quiescent phenotype Chun et al. [1997], Pierson et al. [2000]. In a companion paper Luo and Zurakowski [2008] we have broadly modeled the entire reservoir by neglecting all the unique characteristics of the various reservoir components. In this paper, we focus solely on the quiescent infected T cells, allowing us to model and explore this cell type and its effects in greater depth. This builds on earlier work Zurakowski and Wodarz [2007] which neglected the effect of viral reservoirs.

This paper is organized as follows: In Section 2, a mathematical model of HIV infection with persistent viral reservoirs is introduced. In Section 3, we show simulation results for five different cases and present some therapeutic implications based on them. In Section 4, we discuss the results and the implications of the model for HIV treatment.

## 2. MODEL

### 2.1 Mathematical model

We use an ordinary differential equation model to describe the dynamics of target cells, actively infected cells and quiescent infected cells during HAART:

$$\begin{aligned}
 \dot{\mathbf{x}} &= \lambda - d\mathbf{x} - \beta_w(1-u_1)(1-u_2)\mathbf{x}\mathbf{y}_w \\
 &\quad - \beta_r(1-u_2)\mathbf{x}\mathbf{y}_r \\
 \dot{\mathbf{y}}_w &= (1-f_w)\beta_w(1-u_1)(1-u_2)\mathbf{x}\mathbf{y}_w \\
 &\quad - a_w\mathbf{y}_w + \alpha_w\mathbf{l}_w \\
 \dot{\mathbf{y}}_r &= (1-f_r)\beta_r(1-u_2)\mathbf{x}\mathbf{y}_r \\
 &\quad - a_r\mathbf{y}_r + \alpha_r\mathbf{l}_r \\
 \dot{\mathbf{l}}_w &= f_w\beta_w(1-u_1)(1-u_2)\mathbf{x}\mathbf{y}_w \\
 &\quad + r_w\mathbf{l}_w - \alpha_w\mathbf{l}_w \\
 \dot{\mathbf{l}}_r &= f_r\beta_r(1-u_2)\mathbf{x}\mathbf{y}_r - a_r\mathbf{y}_r + r_r\mathbf{l}_r - \alpha_r\mathbf{l}_r
 \end{aligned} \tag{1}$$

As in previous mathematical models that describe various aspects of HIV-1 dynamics D'Amato et al. [1998], Zurakowski and Wodarz [2007], this model's states include  $\mathbf{x}$ , the CD4+ T cells that are susceptible to infection (target cells);  $\mathbf{y}_w$ , CD4+ T cells infected by wild-type virus;  $\mathbf{y}_r$ , CD4+ T cells infected by resistant virus;  $\mathbf{l}_w$ , the quiescent T-cells infected with wild-type virus; and  $\mathbf{l}_r$ , the quiescent T-cells infected with resistant virus. The parameters are:  $\lambda$ , the generation rate of the target cells;  $d$ , the natural death rate of target cells;  $\beta_w$  and  $\beta_r$ , the infection rates of wild-type and resistant virus respectively;  $a_w$ ,  $a_r$ , the death rates of cells infected by wild-type and resistant-type virus respectively;  $r_w$  and  $r_r$ , the clonal expansion rate of quiescent cells for two virus types;  $f_w$  and  $f_r$ , the formation fractions of two infected cell types' quiescent reservoirs; and  $\alpha_w$  and  $\alpha_r$ , the two cell types' activation rate from quiescence.  $u_1$  and  $u_2$  represent the drug efficacy of two epitope-independent multidrug antiviral regimens. 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.

The proposed system (1) has three steady states. We have calculated them analytically; however, the results are too complicated to present in this paper. Briefly, the steady states are:

1. The trivial, uninfected state, where there are no infected cells,
2. The case where wild-type virus outcompetes resistant virus in the main compartment,
3. The case where resistant virus outcompetes wild-type in the main compartment.

### 2.2 Drug Switching Strategy

Most mutations that can influence the effectiveness of combination therapy occur before a patient begins treatment. It has been shown that for any sufficiently potent antiviral therapy, the number of replication events occurring after the start of anti-viral therapy is insignificant compared to the genetic diversity present at the start of anti-viral therapy. Therefore, the risk of resistance emerging to a new regimen is roughly proportional to the amount of virus present at the start of the regimen Bonhoeffer and Nowak [1997], Ribeiro and Bonhoeffer [2000].

We observe that if virus resistant to drug combination  $\mathbf{u}_1$  is present when  $\mathbf{u}_1$  is applied, the system approaches the third steady state. In the absence of suppressive therapy, wild-type virus outcompetes this resistant strain. Therefore, if the patient temporarily removed from therapy, the wild-type virus will grow exponentially and the resistant virus will decay exponentially. Our strategy is to choose

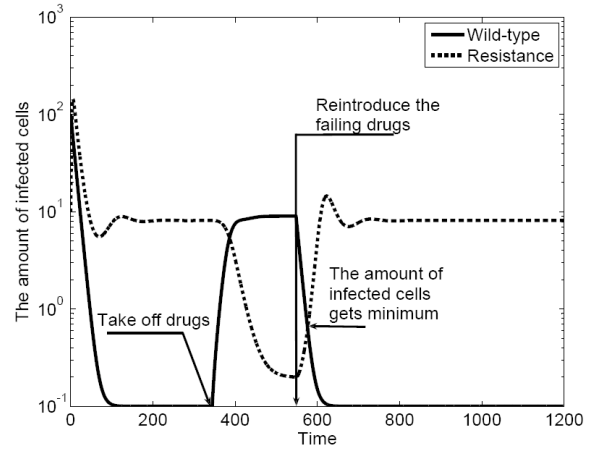


Fig. 1. Illustration of the drug-switching strategy

the best time to reintroduce the failing drug regimen  $\mathbf{u}_1$ , resulting in the deepest drop in the total number of infected cells as shown in Fig.1. If we introduce regimen  $\mathbf{u}_2$  at this point, the risk of virus resistant to  $\mathbf{u}_2$  emerging can be thus minimized.

### 3. SIMULATION

In this section, we show how the death rates of infected cells ( $a_w$ ,  $a_r$ ) and the initial number of long-lived reservoir cells ( $\mathbf{l}_{w-ini}$ ,  $\mathbf{l}_{r-ini}$ ) influence the drug switch strategy by representing the simulation results for five different cases. In the following figures, T1 represents the wait time before  $\mathbf{u}_1$  is reintroduced; T2 is the reintroduction period for  $\mathbf{u}_1$  which achieves the minimum resistance risk; M is the time at which minimum resistance risk is achieved. Risk of resistance emergence is calculated as being proportional to the total infected cell count at the point of introduction.

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:  $\lambda = 1$ ,  $d = 0.01$ ,  $\beta_w = 0.01$ ,  $\beta_r = 0.005$ ,  $a_w = 0.1$ ,  $a_r = 0.1$ ,  $r_w = 0.1$ ,  $r_r = 0.1$ ,  $f_w = 0.1$ ,  $f_r = 0.1$ ,  $\alpha_w = 0.0008$ ,  $\alpha_r = 0.0008$ . The initial conditions:  $\mathbf{x}_{ini} = 200$ ,  $\mathbf{y}_{w-ini} = 100$ ,  $\mathbf{y}_{r-ini} = 10$ ,  $\mathbf{l}_{w-ini} = 1$ ,  $\mathbf{l}_{r-ini} = 1$ . The simulation results are shown in Fig.2 and Fig.3.

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 takes off the therapy. Therefore, the minimum amount of total infected cells occurs at the moment which the system reaches its steady state.

Case II: Parameters and initial conditions as for Case I except the death rates ( $a_w = 0.1$ ,  $a_r = 0.3$ ). The simulation results are shown in Fig.4 and Fig.5.

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, there is a point at which the residual growth of wild-type infected cells becomes more important than the continued decay of resistant infected cells. Therefore, T1 can be found which yields a true minimum in the

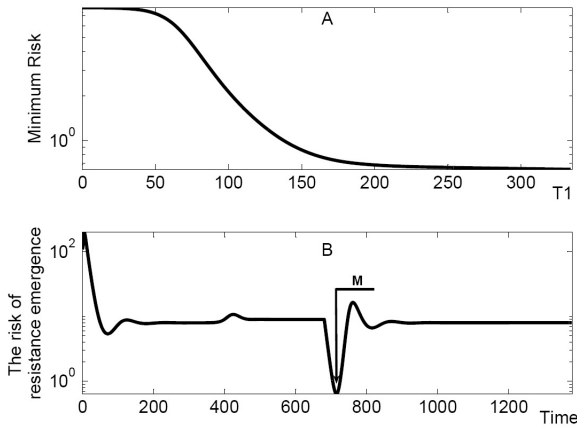


Fig. 2. (A) T1 VS. Minimum Risk; (B) The dynamics of total amount of infected cells by reintroducing the failing therapy

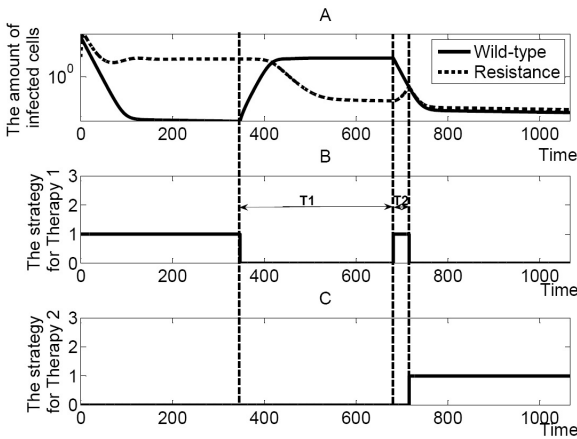


Fig. 3. (A) Infected Cell Dynamics; (B) Optimal  $u_1$  schedule; (C) Optimal  $u_2$  schedule.

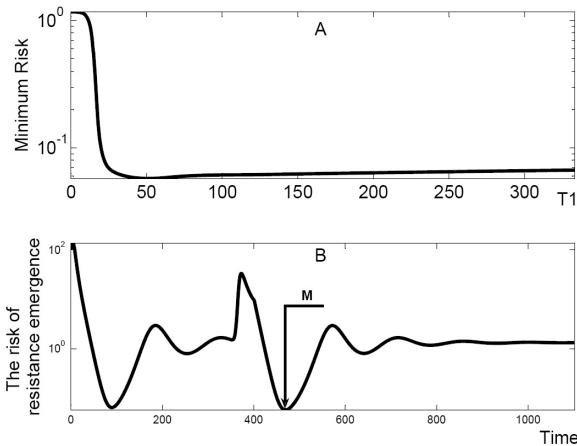


Fig. 4. (A) T1 VS. Minimum Risk; (B) The dynamics of total amount of infected cells by reintroducing the failing therapy

resistance risk (as opposed to Case I, where T1 should be as long as possible).

Case III: Parameters and initial conditions are as in Case II, except the initial size of long-lived reservoirs

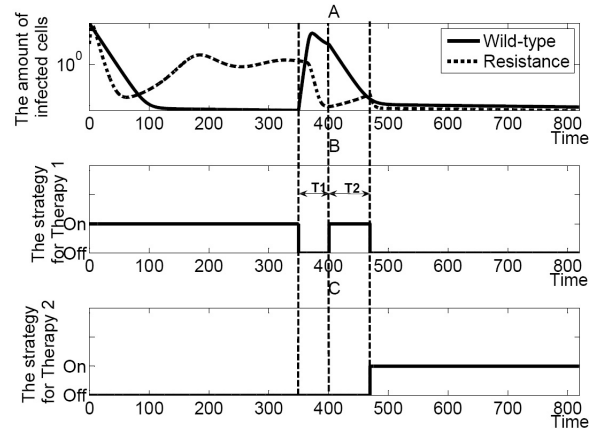


Fig. 5. (A) Infected Cell Dynamics; (B) Optimal  $u_1$  schedule; (C) Optimal  $u_2$  schedule.

( $l_w-ini, l_r-ini$ ) is increased from 1 to 10. The simulation results are shown in Fig.6 and Fig.7.

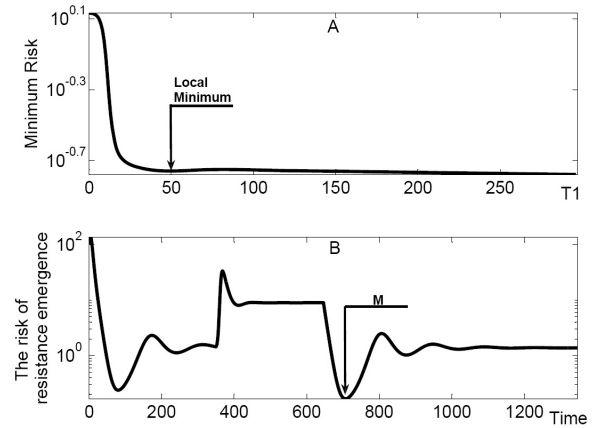


Fig. 6. (A) T1 VS. Minimum Risk; (B) The dynamics of total amount of infected cells by reintroducing the failing therapy

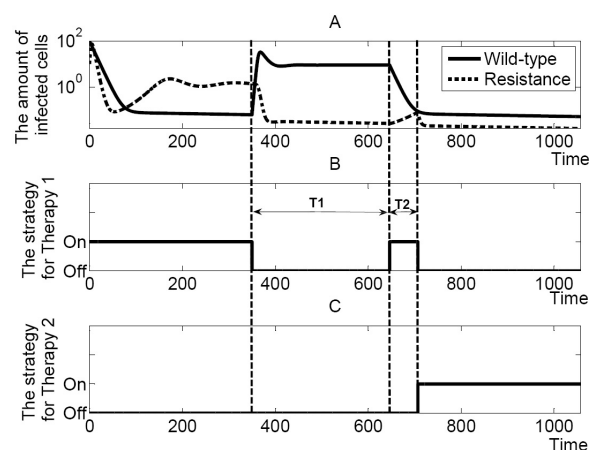


Fig. 7. (A) Infected Cell Dynamics; (B) Optimal  $u_1$  schedule; (C) Optimal  $u_2$  schedule.

In this case, we notice an interesting phenomenon: Fig.6 shows that the risk of resistance reaches a local minimum first and then goes up. After some time, the risk goes down again. The local minimum occurs for the reasons

discussed in Case II; the possibility in this case of further draining the reservoirs by waiting longer make it a local minimum (as opposed to a global minimum in Case II).

Case IV: Parameters and initial conditions are as in Case I, except the death rates are as in Case II ( $a_w = 0.1$ ,  $a_r = 0.3$ ). The simulation results are shown in Fig.8 and Fig.9.

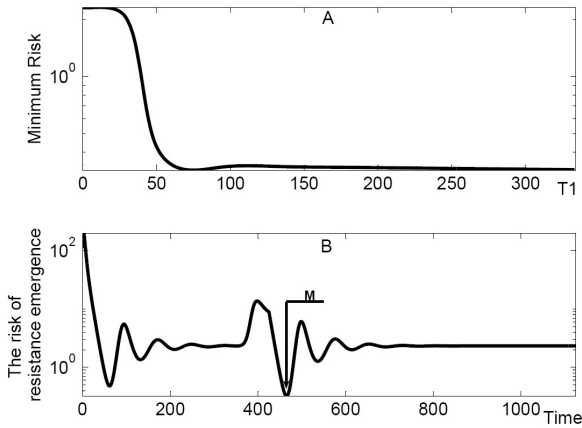


Fig. 8. (A)  $T_1$  VS. Minimum Risk; (B) The dynamics of total amount of infected cells by reintroducing the failing therapy

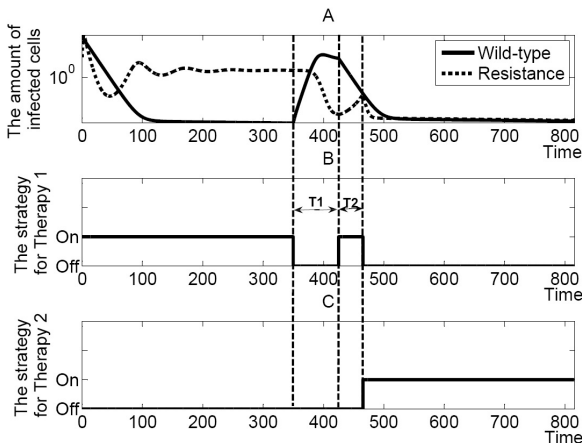


Fig. 9. (A) Infected Cell Dynamics; (B) Optimal  $u_1$  schedule; (C) Optimal  $u_2$  schedule.

The shape of Fig.8 (A). is very similar to Case III. The risk of resistance reaches a local minimum first, and then goes up, and finally, goes down.

Case V: Parameters and initial conditions are as in Case I, except we increase the initial value of long-lived reservoirs ( $l_{w-ini}, l_{r-ini}$ ) from 1 to 10. The simulation results are shown in Fig.10 and Fig.11.

The results of this case is the same as the first one. we need to wait as late as possible for reintroducing the failing therapy. It is reasonable, because the long-lived reservoirs only have a little influence on the increasing rate of the cells infected by wild-type virus and the decay rate of the cells infected by resistant virus when the patient take off the therapy. Therefore, they hardly change the system's transient response.

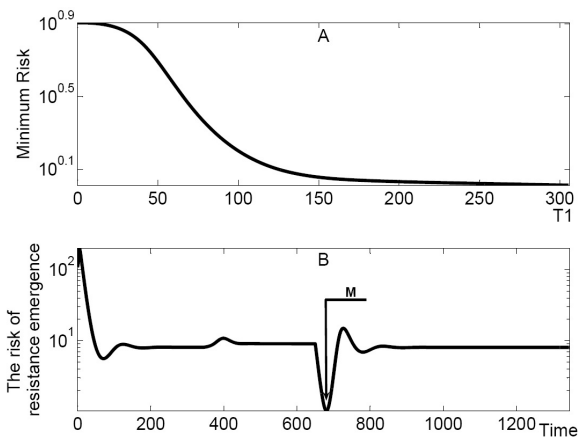


Fig. 10. (A)  $T_1$  VS. Minimum Risk; (B) The dynamics of total amount of infected cells by reintroducing the failing therapy

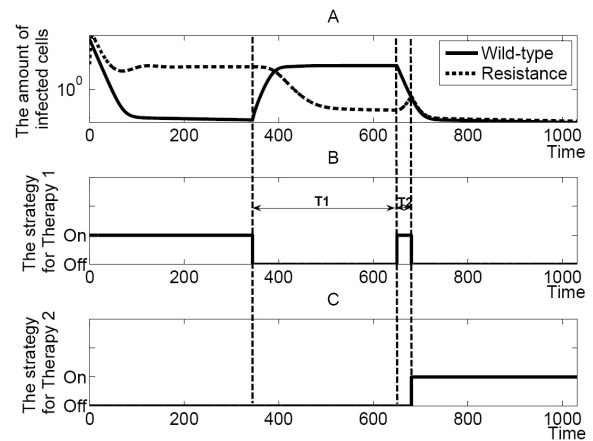


Fig. 11. (A) Infected Cell Dynamics; (B) Optimal  $u_1$  schedule; (C) Optimal  $u_2$  schedule.

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 also 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 Case I and V, the reintroduction time should be as late as possible. However, a long treatment interruption may damage the organs irreversibly Aiuti and Mezzaroma [2006], as the long-term uncontrolled infection will allow the HIV disease to develop to the point.

In Case II, when the death rate of resistant strain is large enough the initial amount of latent reservoirs is relatively small, the reintroduction of the failing therapy should happen before the system reaches its steady state. As we can see in Fig.4 , 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. In Case III and IV, although the simulation results shows that the global minimum lies at  $T_1 = \infty$ , allowing the disease to progress uncontrolled that long

would be unacceptable. A better solution switches at the point where the resistance risk reaches a local minimum.

#### 4. CONCLUSIONS

The issue of HIV resistance emergence impacts the treatment for HIV and AIDS patient greatly. The solutions to overcome HIV resistance exist not only in inventing new drugs, but also in developing proper therapeutic strategies.

The new approach to interrupted therapy introduced in Zurakowski and Wodarz [2007], Luo and Zurakowski [2008] suggests that treatment interruptions in the failing therapy could provide a chance to minimize the resistance risk to a new therapy, if the failing therapy was reintroduced properly. In this paper, we showed that this approach is robust to more accurate modeling of the dynamics of quiescent infected T cells for a wide range of parameter values. The simulation results also show how the parameters and the initial conditions influence the schedule of therapy switching. A knee in the benefit of continued interruption suggests a natural trade-off point between increased benefit and increased disease progression. Under certain circumstances, there may also be a local or even a global minimum at this point.

Future work in the area will be focused on permutation cocktails of previously failed drugs, which will yield better short-term control of the virus.

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