A MODEL BASED ANALYSIS OF ANTI-CD4 THERAPY AS ADJUVANT TO HAART INTERRUPTION

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Abstract: Interruption of Highly Active Antiretroviral Therapy - HAART can be for a variety of reasons. The reasons could be salvage therapy, autoimmunization or to reduce the total time that the patient is on therapy. The problem with HAART interruption is that the virus starts to rebound immediately following HAART cessation, and there is an associate decline in $CD4^+$ T cell counts. There is therefore a need to employ other therapeutic options that will slow down the viral rebound and/or $CD4^+$ T cell decline during HAART interruption. This paper presents a model based analysis of how the duration of HAART interruption can be extended by $CD4^+$ T specific therapies, for patients who initiate therapy during the chronic infection stage. For these patients, the purpose of interruptions is primarily to reduce the time on HAART.

Keywords: Treatment interruption, therapy scheduling, immune based therapy, anti-CD4, immune modulation.

1. INTRODUCTION

Immune based therapies for HIV control entail the direct targeting of the immune system as a therapeutic strategy. These therapies can be used to augment Highly Active Antiretroviral Therapy - HAART. The proposed strategies include:

(1) Expansion of the $CD4^+$ T cell pool by direct lymphocyte transfer or Interleukin-2 (Lane, 2002).
(2) Enhancement of HIV specific immunity by structured treatment interruptions, CD8+ lymphocyte transfers, therapeutic immunization or passive immunotherapy (Lane, 2002).
(3) Suppression of immune activation by the use of immunosuppressive drugs such as hydroxyurea or cylosporin (Fumero, Garcia and Gatell, 2004).
(4) Short-term accelerated depletion of the $CD4^+$ T cells by anti-CD4 therapy (De Boer and Boucher, 1996).

Immune based therapies, as opposed to replication cycled based HAART, are attractive as they offer the potential to minimize the emergence of drug resistance (Fumero, Garcia and Gatell, 2004). However, there is an unavoidable overlap between the two types of therapy.

Research into structured treatment interruptions - STI of HAART is vigorous. The problem with HAART interruption is that the virus starts to rebound immediately following HAART cessation, and there is an associate decline in $CD4^+$ T cell counts. The reason for this rapid rebound of plasma viremia is because viral load suppression with HAART does not necessarily imply a recon-

stitution of HIV specific immune responses (Lori and Lisziewicz, 2001). Other reasons for the rapid viral load rebound when HAART is interrupted are the over stimulation of the immune system during infection (Mohri, *etal.*, 2001) and the availability of new target cells due to $CD4^+$ T cell gains incurred during HAART.

Treatment interruption for the purpose of reducing total time on HAART has been tried out primarily on patients with previous viral suppression (Dybul, *etal*, 2001). The intention is to reduce the toxicity associated with antiretroviral drugs, given that one has to use them indefinitely. One such study on Strategies for the Management of Antiretroviral Therapies (NIH, 2002) aims to "strike a balance between adequately aggressive treatment and minimal side effects". This is a long term study that will cover a period of up to nine years with some patients on either STI or continuous HAART.

STI as an immune based therapy for autoimmunization, is meant to allow short bursts of viral replication to augment HIV specific immune responses. The general intention is to use STI to shift the infected individual to a state where one can attain a degree of viral load control without antiretroviral drugs. This state is referred to as long term non-progressor status - LTNP (Zurakowski and Teel, 2003). Clinical studies have been carried out using this approach on patients who had initiated therapy during the acute and chronic infection stages (Hirschel, *etal*, 2002; Rosenburg, Altfeld and Poon, 2000) and had a record of sustained viral suppression to below detectable levels. Results indicate that autoimmunization has more benefit in the acute infection stage than in the chronic stage. Individuals in the acute infection stage are therefore more likely to attain long term non-progressor status, than those who wait to initiate therapy in the asymptomatic and advanced stages.

Rapid viral load rebounds will be observed with each treatment interruption cycle for many patients in the asymptomatic and advanced stages of the HIV infection. For this group of patients, STI will be for the purpose of reducing the total time on HAART, and should focus on estimating the time before the viral load rebounds, monitoring the viral load so that therapy can be resumed before the rebound occurs, and finding alternative ways to extend the duration of viral load suppression during HAART interruption.

For those patients who have virologic failure, treatment interruption can be employed for salvage purposes. The intention is to allow the re-emergence of the virus strain that responds to therapy. This has been tried out in (Mussini, *etal.*, 2002) and results show that more harm than good is done in most cases, as the $CD4^+$ T cell count often drops to very low levels while the resistant virus strains remain.

One approach to treatment interruption strategies is to monitor either the viral load or T cell count. Therapy is interrupted or resumed when the monitored variable rises above or falls below predetermined upper and lower bounds. In essence, it entails keeping the variable between an upper and lower bound by on/off control. Another approach to treatment interruption is to have predetermined time periods for when therapy is on and when it is interrupted. The former approach is more difficult to implement when compared to treatment interruption with predetermined on/of periods, as it requires more frequent measurements in order to check if the variable is above or below the cut off points.

Rapid viral load rebounds and $CD4^+$ T cell declines during HAART interruption are considered as undesirable, especially when the T cell count did not rebound adequately while one was still on HAART. Outside the acute infection stage then, potential use of treatment interruption should be explored for patients with reasonably high $CD4^+$ T cell counts. Alternatively, there is a need for other therapeutic options that will slow down the viral rebound and/or $CD4^+$ T cell decline during HAART interruption.

This paper deals specifically with investigating the use of $CD4^+$ T cell specific immune based therapies as adjuvant to HAART interruptions, for patients who initiate therapy during the chronic infection stage. For these patients, the purpose of STI will primarily be to reduce the time on HAART, as they will most likely fail to attain long term non-progressor status. The possibility of extending the duration of HAART interruption by anti-CD4 therapy or immune response suppressing therapy is explored. Anti-CD4 therapy, in this paper, refers to therapies that accelerate the destruction of both the infected and the uninfected target $CD4^+$ T cells. This can be attained by induced cell apoptosis or programmed self destruction (HIV/ATIS, 2002).

The layout of the paper is as follows: Section 2 presents the working model. Section 3 presents the approaches that can be used to extend the duration of HAART interruption and the simulation results are in section 4. Section 5 has the conclusions that are drawn from this study.

2. THE WORKING MODEL

The mathematical model as presented by (Perelson and Nelson, 1999) was adopted and modified for

this paper and the following is a summary of that model.

$$\frac{T}{dt} = s + pT(1 - \frac{T}{T_m}) - dT - \beta TV \quad (1)$$

$$\frac{T_l}{dt} = (1 - \eta_{rt})q_1\beta TV - \delta_1 T_l - kT_l \quad (2)$$

$$\frac{T_a}{dt} = (1 - \eta_{rt})q_2\beta TV - \delta_2 T_a + kT_l \quad (3)$$

$$\frac{V}{dt} = rT_a - cV \quad (4)$$

The state variables T, T_l and T_a are the plasma concentrations of the uninfected, latently infected and actively infected CD4$^+$ T cells, respectively, while V represents the free virus particles.

Equation (1) shows that uninfected CD4$^+$ T cells are produced from a source at a rate s and die with a rate constant d. The source term s is taken as constant, but since HIV may be able to infect cells in the thymus and bone marrow and thus lead to a reduced production of new immunocompetent T cells, it is believed that the source term s is a decreasing function of the viral load (Kirschner and Webb, 1996). T cells are activated and proliferate in HIV infection (Mohri, *etal.*, 2001). The T cell proliferation rate is density dependent with the rate of proliferation slowing as the T cell count gets high. Parameter p is the proliferation rate constant and T_m is the T cell population density at which proliferation shuts off.

Uninfected CD4$^+$ T cells are infected by the virus at a rate that is proportional to the product of their abundance and the amount of free virus particles. The proportionality constant β is an indication of the effectiveness of the infection process and includes the rate at which virus particles find uninfected cells and the rate of virus entry.

Parameters q_1 and q_2 in equations (2) and (3) are the probabilities that upon infection, a CD4$^+$ T cell will become either latent or actively produce virus. Latently infected cells harbour HIV proviral DNA and do not produce virus until they are activated, and the parameter k is the activation rate constant. Parameters δ_1 and δ_2 are the death rate constants for the respective infected cell pool. Equations (4) shows that an actively infected CD4$^+$ T cell produces free virus particles with a rate constant r, which are cleared from plasma with a rate constant c.

η_{rt}, $0 \leq \eta_{rt} < 1$ is the combined effectiveness (inhibitory effect) of all the reverse transcriptase inhibitors used. A point to note is that this model reflects the fact that reverse transcriptase inhibitors do not directly prevent CD4$^+$ T cell infection. Rather, the inhibitors reduce the probability of the infected cell becoming latent or active.

The model adequately explains the virus and target cell dynamics up to the clinical latency stage. The limitation of this model is that it does not account for the later stages of the disease when the CD4$^+$ T cell count does go down towards zero and the associated rapid increase in the viral load. This later or advanced stage of the disease is when the patient is said to have AIDS.

3. CANDIDATE THERAPIES TO AUGMENT HAART INTERRUPTION

The system given by equations (1) to (4) is identifiable (Xia and Moog, 2003). That is, it is possible to estimate the model parameters from viral load and CD4$^+$ T cell count measurements. However, parameters $\eta_{rt}q_1$ and $\eta_{rt}q_2$ will vary with drug dosage. If one assumes linear drug pharmacokinetic and pharmacodynamic effects, then the variation of these parameters with dosage can be assumed also to be linear (Joshi, *et al*, 1999; Jeffrey, Xia and Craig, 2003).

The viral load will rebound during HAART interruptions. This is because HAART interruptions "induce sudden antigenic activation with high peaks of viral load, up to a set-point of viral load or higher, which infects new populations of activated CD4 T cells .." (Fumero, Garcia and Gatell, 2004). Strategies that reduce cell activation or limit the population of available target cells can therefore be used to slow down the rebound rate. These immune based CD4$^+$ T cell specific therapies could entail:

(1) Reducing T cell proliferation rate p, hence referred to as proliferation suppressive therapy.
(2) Reducing T cell source rate s, hence referred to as source limiting therapy.
(3) Accelerating T cell death rates d, δ_1 and δ_2, hence referred to as anti-CD4 therapy.

Source rate limiting therapy would entail an interference with the thymus, and has the potential to cause more harm than good. Its potential use will not be considered in this paper.

The steady states for the viral load and uninfected CD4$^+$ T cell count for the system given by equations (1)-(4) are:

$$T_{ss} = \frac{c\delta_2}{(1 - \eta_{rt})q\beta r} \quad (5)$$

$$V_{ss} = \frac{(1 - \eta_{rt})qrs}{c\delta_2} - \frac{d}{\beta} + \frac{p}{\beta}(1 - \frac{c\delta_2}{(1 - \eta_{rt})q\beta r T_m}) \quad (6)$$

where $q = q_2 + q_1(\frac{k}{k+\delta_1})$.

It is clear from the above equations, why and how HAART reduces the viral load and increases $CD4^+$ T cell counts.

The following notation will be adopted:
For proliferation suppressive therapy, η_{ps}, $0 \leq \eta_{ps} < 1$ is the effectiveness (inhibitory effect) of the proliferation suppressing drugs used.
For anti-CD4 therapy, η_{af}, $0 \leq \eta_{af} \leq 1$ is percentage rate at which $CD4^+$ T cell death rate is increased, or the death acceleration factor.

When HAART is interrupted, the steady states will change. When proliferation suppressive therapy is used during this period, then the steady states will be :

$$T_{ss} = \frac{c\delta_2}{q\beta r} \tag{7}$$

$$V_{ss} = \frac{qrs}{c\delta_2} - \frac{d}{\beta} + \frac{(1-\eta_{ps})p}{\beta}(1 - \frac{c\delta_2}{q\beta r T_m}) \tag{8}$$

Similarly, the steady states when Anti-CD4 therapy is used will be:

$$T_{ss} = \frac{(1+\eta_{af})c\delta_2}{q_{af}\beta r} \tag{9}$$

$$V_{ss} = \frac{q_{af}rs}{(1+\eta_{af})c\delta_2} - \frac{(1+\eta_{af})d}{\beta} + \frac{p}{\beta}(1 - \frac{(1+\eta_{af})c\delta_2}{q_{af}\beta r T_m}) \tag{10}$$

where $q_{af} = q_2 + q_1(\frac{k}{k+(1+\eta_{af})\delta_1})$.

A point to note is that, T_{ss}, unlike V_{ss}, does not depend on parameters p and d. Reducing p, or increasing d in the absence of HAART will effectively reduce the viral load set point V_{ss}, but will have no effect on the $CD4^+$ T cell steady state T_{ss}, as depicted by equations (9) and (10). However, increasing the infected cell death rates δ_1 and δ_2 will increase the $CD4^+$ T cell steady state as well as reduce the viral load set point. So the above considered $CD4^+$ T cell specific therapies will reduce the viral load, but unlike HAART, may not comparably increase the $CD4^+$ T cell count.

The use of anti-CD4 therapies at first sight may appear counter intuitive because current focus of therapy is to increase $CD4^+$ T cell counts. However, anti-CD4 therapies will not 'harm' the immune system. Their ability to reduce the viral load set point could imply that their use during HAART interruptions could reduce the peak viral load. This in turn could imply that the rate of viral load rebound is reduced, and consequently prolong the duration of HAART interruption.

Table 1. Parameter estimates

Parameter	Value
s	10 mm^{-3} day^{-1}
p	0.03 day^{-1}
T_m	1000 mm^{-3}
d	0.01 day^{-1}
β	4×10^{-8} mL^{-1} day^{-1}
q_1	0.005
q_2	0.55
δ_1	0.01 day^{-1}
δ_2	0.5 day^{-1}
k	0.025
r	240 cell^{-1} day^{-1}
c	5 day^{-1}
η_{rt}	0.7 for 300 days

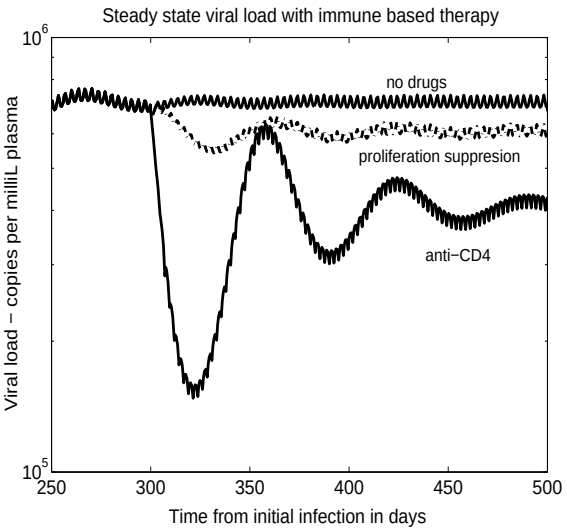

Fig. 1. Untreated viral load set point and set point adjustment by immune therapies, when initiated at day 300. Parameters are in Table 1. Efficacy : $\eta_{ps} = \eta_{af} = 0.25$

4. RESULTS

Model parameter estimates used in simulations are as presented in Table 1. (Perelson and Nelson, 1999; Kirschner, Lenhart and Serbin, 1997; Nowak and May, 2000; Kirschner and Webb, 1996; Ho, *etal.*, 1995).

Figures 1 and 2 show that, from an end point drug efficacy perspective, anti-CD4 therapy, that is, accelerating T cell death rates, is better than proliferation suppressive therapy at reducing the viral load, given the same drug efficacy. Furthermore, anti-CD4 therapy has an added advantage of being able to also increase the $CD4^+$ T cell count. Care should be taken though, not to confuse a lower drug efficacy to automatically imply a lower pill intake.

Given that anti-CD4 therapy is better than proliferation suppressive therapy, figure 3 shows how one could expect viral load rebound to be slowed

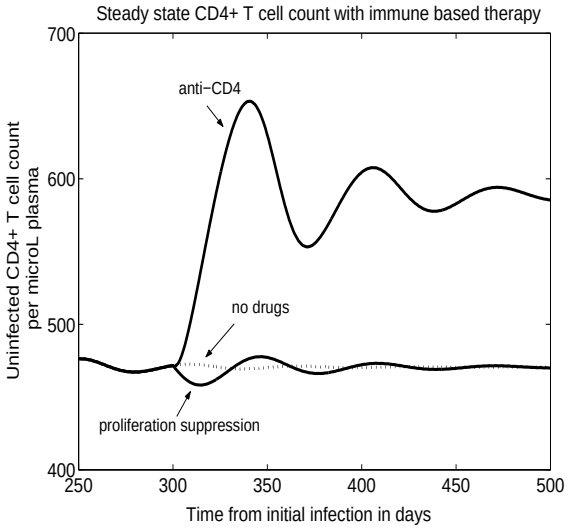

Fig. 2. Uninfected $CD4^+$ T cell set point with no treatment and set point adjustment by immune therapies, when initiated at day 300. Parameters are in Table 1. Efficacy : $\eta_{ps} = \eta_{af} = 0.25$

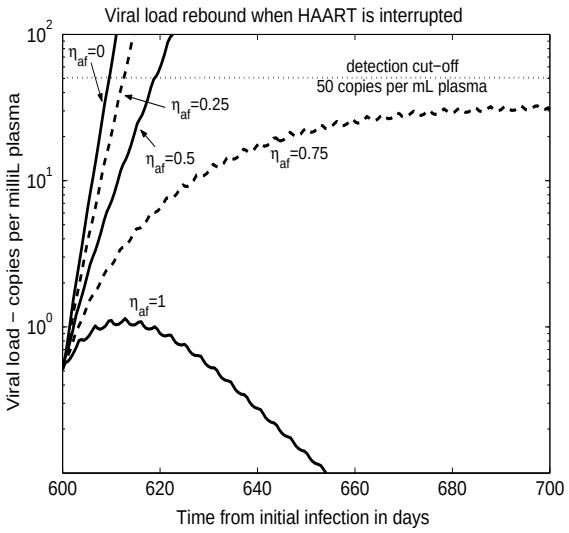

Fig. 3. Viral load rebound when anti-CD4 therapy is used during HAART interruption. η_{af}: death rate acceleration factor. HAART was previously ON for 300 days from day 300 : $\eta_{rt} = 0.7$.

down when anti-CD4 therapy is used during HAART interruption. For this individual case, viral load suppression at below detectable levels can be maintained for almost 10 days without drugs ($\eta_{af} = 0$). Also, significantly longer HAART interruption periods can be attained by the use of anti-CD4 therapy. One however, needs to weigh the advantages of increasing OFF HAART periods against the sacrifice of having no drug free days.

Figure 4 shows that using anti-CD4 therapy results in a much more rapid initial decline in $CD4^+$ T cell counts than when no drugs are used during HAART interruption. This is followed by a much slower decline as the $CD4^+$ T cell counts eventually settle at a value that is higher than when no drugs are used. When considering the sacrifice of having no drug free days then, one should also consider the benefits of long term $CD4^+$ T cell gains.

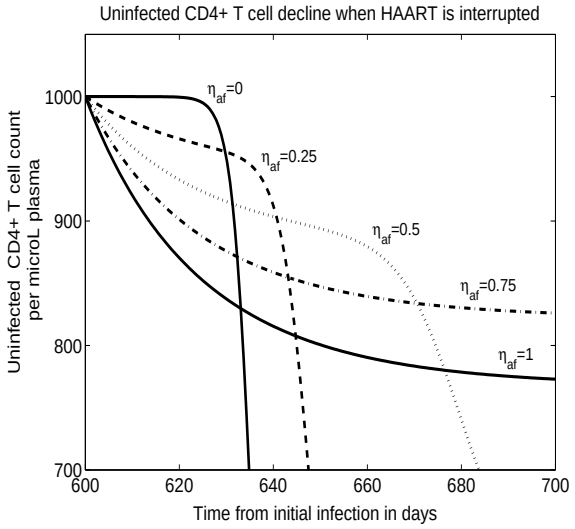

Fig. 4. Uninfected $CD4^+$ T cell decline when anti-CD4 therapy is used during HAART interruption. η_{af}: death rate acceleration factor. HAART was previously ON for 300 days from day 300 : $\eta_{rt} = 0.7$

What remains then, is to determine the efficacy of the anti-CD4 therapy required for pre-determined ON/OFF HAART periods. Conversely, if the efficacy is known, then the ON/OFF HAART period can be determined. The optimal ON/OFF HAART periods also need to be determined.

5. CONCLUSIONS

It is not possible for some HIV infected individuals to attain long term viral load control when HAART is interrupted. A possible way to prolong OFF HAART periods for these individuals is to alternate HAART with anti-CD4 immune based therapies.

The use of anti-CD4 therapies at first sight may appear counter intuitive because current focus of therapy is to increase $CD4^+$ T cell counts. However, anti-CD4 therapy has a potential to prolong the duration of HAART interruptions without excessive reduction in $CD4^+$ T cell counts. Even though anti-CD4 therapy initially accelerates $CD4^+$ T cell depletion, it does not necessarily, in the long term harm the immune system in so far as $CD4^+$ T cell counts are concerned.

Anti-CD4 immune based therapy issues that need to be addressed are whether any further benefit can be gained from its concomitant use during ON HAART periods, or if its use should be restricted to HAART interruption periods. Also, for the regimen considered in this paper, the individual is either ON HAART, or ON anti-CD4 therapy. The possibility of whether anti-CD4 therapy use can be limited to include schedules with drug holidays where the individual is either ON HAART, or ON anti-CD4 therapy, or completely OFF all drugs, needs to be explored.

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