ON ATTAINING MAXIMAL AND DURABLE SUPPRESSION OF THE VIRAL LOAD

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Abstract: Steady state and transient response analysis for an HIV/AIDS model will be conducted in order to determine the extent to which the viral load is suppressible. Results indicate that viral dynamics, before and after the initiation of therapy, are oscillatory, and as such, the viral load will transiently oscillate before settling to some on treatment steady state. Conditions that are conducive to the attainment of "maximal and durable suppression of viral load" will be outlined. This study also provides some insight on the issue of recurrent viral load blips. The effect of treatment when initialized at various stages of the infection progression will be demonstrated.

Keywords: HIV therapy, mathematical model, maximal suppression, durable suppression, steady state, transient response, viral blip.

1. INTRODUCTION

According to the United States Public Health Services (USPHS) guidelines on the use of antiretroviral agents in HIV infected adults and adolescents (USPHS Guidelines, 2003), therapy is considered effective if it can reduce the viral load by 90% in less than 8 weeks and continue to suppress it to below 50 copies per mL of plasma in less than 6 months. Furthermore, the primary goals of such an effective therapy regimen are stated as: "maximal and durable suppression of the viral load, restoration and/or preservation of immunologic function, improvement of quality of life, and reduction of HIV related morbidity and mortality". The tools that are available for the attainment of these goals are: maintenance of high adherence to potent antiretroviral therapy, rational sequencing of drugs in order to maximize the benefits of antiretroviral therapy and preserve future treatment options, testing for drug resistance and adequate monitoring for predictors of virologic success.

It has been shown clinically that the use of Highly Active Anti-retroviral Therapy (HAART) can effectively suppress the virus to below detectable levels. However, durable suppression has proven to be difficult because of the toxicities associated with HAART. All the foregoing calls for the derivation of an optimal control strategy for HIV therapy that can meet the goals/control objectives of therapy and simultaneously minimize the associated toxicities. Such a control strategy should be initiated while the immune system is still functional or at least repairable.

Viral load and $CD4^+$ T cell dynamics have been addressed from a mathematical modelling approach (Hraba, *et al.*, 1990; Kirschner and Perelson, 1995) as well as clinically (Hoetelmans, *et al.*, 1998; Perelson, *et al.*, 1996). This paper focuses on the attainment of "maximal and durable suppression of the viral load". Steady state and transient response analysis (Nise, 2000) of an HIV/AIDS model will be used to determine the extent to which the viral load is suppressible at different stages of the progression of the HIV/AIDS infec-

tion. Analytic solutions for the expected duration and extent of viral load suppression will be derived.

Results indicate that viral dynamics, before and after the initiation of therapy, are generally oscillatory, and as such, the viral load will transiently oscillate before settling to some on treatment steady state which is determined by the combined drug efficacy. The frequency of oscillation gives an indication of the duration(durability) of viral load suppression and the peak undershoot determines the extent(maximality) of viral load suppression. Furthermore, the steady state, the duration and the extent of viral load suppression are parameter dependent. These time estimates will therefore, vary from one individual to the other, given the same drug efficacy. This time response analysis can be used to determine the minimum drug efficacy required in order to attain some degree of viral load suppression, as well as provide some insight on the issue of recurrent viral load 'blips' (Di Mascio, *et al.*, 2002) after effective suppression of the viral load has been attained.

Simulations are used to show the effect on viral load response of initiating therapy at different stages of the HIV infection. Results show that for a constant or fixed drug regimen, maximal and durable suppression of the viral load is attained when therapy is initiated during the asymptomatic stage of the HIV infection. In addition, there is a strong correlation between viral load suppression and controllability (Jeffrey, *et al.*, 2003)

The layout of the paper is as follows:
Section 2 presents the working model under mono and multi-therapies. Section 3 introduces steady state and transient response analysis of the working model. Section 4 summarizes the results, while Section 5 has the conclusions that are drawn from this study.

2. THE WORKING MODEL

Equations (1)-(4) describe the population dynamics of the immune system cells and the virus and are as presented in (Kirschner, *et al.*, 1997)

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

$$\frac{dT_1}{dt} = q_1 \beta VT - \delta_1 T_1 - kT_1 \quad (2)$$

$$\frac{dT_2}{dt} = q_2 \beta VT - \delta_2 T_2 + kT_1 \quad (3)$$

$$\frac{dV}{dt} = N\delta_2 T_2 - cV \quad (4)$$

The state variables T, T_1, T_2 and V are the concentrations of the uninfected CD4$^+$ T cells, the latently infected CD4$^+$ T cells, the actively infected CD4$^+$ T cells and the free virus particles respectively. Equation (1) shows that uninfected CD4$^+$ T cells are produced from a source at a constant rate s and proliferate to a maximum given by T_m, at a rate that is proportional to their abundance, with p as the proliferation rate constant. Uninfected CD4$^+$ T cells die with a rate constant d_T and 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. Equations (2) and (3) show that infection of healthy CD4$^+$ T cells produces a fraction q_1 of latently infected CD4$^+$ T cells that die with a rate constant δ_1 and a fraction q_2 of actively infected CD4$^+$ T cells that die with a rate constant δ_2. k is the rate constant at which latent cells are activated to produce virus particles. Equation (4) similarly shows that an actively infected CD4$^+$ T cell produces N free virus particles during its lifetime, which die with a rate constant c.

This model does explain the virus dynamics up to the clinical latency stage sufficiently. 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. Model parameter estimates are as presented in Table 1 and are sourced from (Alvarez-Ramirez, *et al.*, 2000; Nowak and May, 2000; Perelson and Nelson, 1999; Perelson, *et al.*, 1996).

Table 1 : Parameter estimates.

Parameter	Value
s	$10 mm^{-3} day^{-1}$
d_T	$0.02 day^{-1}$
β	$7.5 \times 10^{-6} mm^{-3} day^{-1}$
p	$0.03 day^{-1}$
T_m	$1500 mm^{-3}$
q_1	0.05
q_2	0.55
δ_1	$0.02 day^{-1}$
δ_2	$0.5 day^{-1}$
k	0.075
N	2000 virions cell^{-1}
c	$5 day^{-1}$

Figure (1) shows how the plasma concentrations of the uninfected CD4$^+$ T cell, infected CD4$^+$ T cell and free virus particles vary with time from initial infection to the asymptomatic stage. It can be seen that the initial decline of the healthy CD4+ T cells and the increase in viral load are very rapid. All variables however, do eventually

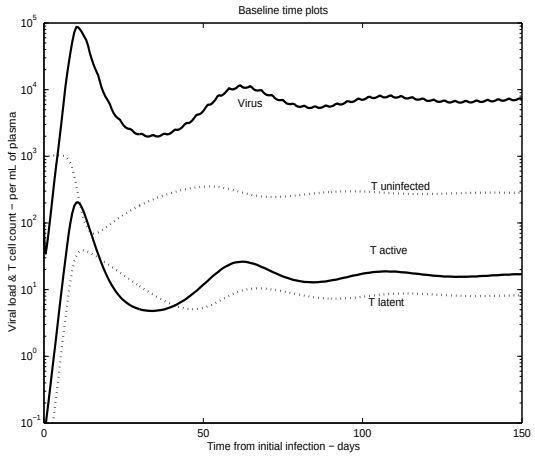

Fig. 1. Plasma concentrations for T, T_1, T_2 and V. Parameters are as in Table 1

settle in damped oscillations to their respective untreated steady state values.

2.1 *Effect of Anti-retroviral Drugs*

The two classes of commonly used anti-retroviral agents are Reverse Transcriptase(RT) Inhibitors and Protease Inhibitors(PI). Both agents work within the CD4$^+$ T cell because they do not prevent the virus from entering the cell. RTs reduce successful infection of the CD4$^+$ T cell by the virus by reducing the values of q_1 and q_2. Perfect inhibition therefore, occurs when $q_1 = q_2 = 0$. In practice however, perfect inhibition is not attainable. Protease Inhibitors on the other hand, block the protease enzyme so that the virus particles that are produced are mostly noninfectious. There are therefore two types of virus particles when protease inhibitors are used. The first type are the infectious virus particles that still continue to infect CD4$^+$ T cells and the other is the noninfectious type. Similarly, perfect inhibition occurs when all virus particles that are produced are noninfectious. Current therapies use a combination of Reverse Transcriptase and Protease Inhibitors and the combined therapy model can be presented as

$$\frac{dT}{dt} = s + pT(1 - T/T_m) - d_T T - \beta VT \quad (5)$$

$$\frac{dT_1}{dt} = u_{RT} q_1 \beta VT - \delta_1 T_1 - kT_1 \quad (6)$$

$$\frac{dT_2}{dt} = u_{RT} q_2 \beta VT - \delta_2 T_2 + kT_1 \quad (7)$$

$$\frac{dV_I}{dt} = u_{PI} N \delta_2 T_2 - cV_I \quad (8)$$

$$\frac{dV_N}{dt} = (1 - u_{PI}) N \delta_2 T_2 - cV_N \quad (9)$$

where, $u_{RT} = 1 - \eta_{RT}$ and $u_{PI} = 1 - \eta_{PI}$ are the respective control inputs for the reverse transcriptase and protease inhibitors. η_{RT}, $0 \leq \eta_{RT} \leq 1$ is the combined effectiveness of all the reverse transcriptase inhibitors used and η_{PI}, $0 \leq \eta_{PI} \leq 1$ is the combined effectiveness of all the protease inhibitors used. State variables V_I and V_N are the infectious and noninfectious virus particles respectively. It is assumed that both types of virus particles have the same death rate constant c. A point worth noting is that, in current practice, the measured viral load is the total of the noninfectious and infectious virus particles.

3. MODEL ANALYSIS

3.1 *Steady State Analysis*

The viral load steady state without treatment for equations (1 - 4) is given by

$$V_{ss} = \frac{Nsq}{c} + \frac{p - d_T}{\beta} - \frac{pc}{N\beta^2 q T_m} \quad (10)$$

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

Variations in steady state set points from one individual to the other are due to inter-individual variations in model parameters, whereas the transition from the asymptomatic stage to the advanced stage of the disease could be due to intra-individual changes in parameters over time (Kramer, 1999). When therapy is on, the steady states for the infectious, non infectious and total measured virus are given by

$$V_{Iss} = \frac{a_{CO} Nsq}{c} + \frac{p - d_T}{\beta} - \frac{pc}{a_{CO} N\beta^2 q T_m} \quad (11)$$

$$V_{Nss} = \frac{1 - a_{PI}}{a_{PI}} V_{Iss} \quad (12)$$

$$V_{Tss} = V_{Iss} + V_{Nss} \quad (13)$$

where a_{RT} and a_{PI} are the control input averages for the reverse transcriptase and protease inhibitors respectively. $a_{CO} = a_{RT} a_{PI}$ is the combined effect of the two inhibitors. It is apparent therefore, that therapy reduces the set point and that the new on treatment steady state is determined by the drug(s) efficacy. Conversely, the drug(s) efficacy required can be determined, given the desired treatment steady state. Therapy therefore, moves the states from one point to another. Initiating therapy when the viral load is below this treatment steady state will result in an increasing viral load, which is interpreted as failure to control the viral load. Initiating therapy when the viral load is higher than this treatment steady state will result in some degree of viral load control even though the viral load will eventually settle to the same steady state, given the same drug efficacy.

One can solve Equation (11) for a_{CO} to determine the minimum drug efficacy ($\eta = 1 - a_{co}$) that is

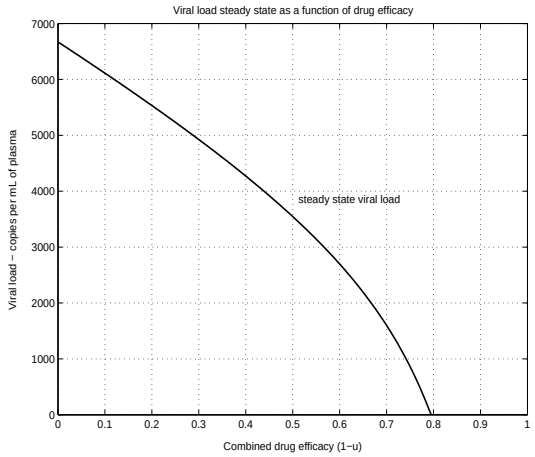

Fig. 2. Viral load steady state as determined by the combined drug efficacy. Parameters are as in Table 1.

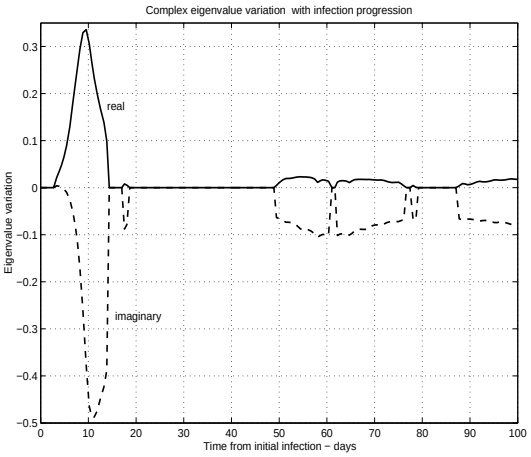

Fig. 3. Complex eigenvalue variation for a fixed drug dosage as infection progresses.

required to obtain a treatment steady state viral load of zero as depicted in Figure (2). It should be noted that increasing the drug efficacy above this value will have no further suppression of the virus that is produced from the $CD4^+$ T cells. This means that any circulating or detectable plasma viremia is from alternate sources such as Follicular Dendritic Cells (FDC), macrophages, resting memory T cells and others that are known to harbour pro-viral DNA (Ngo-Giang-Huong, *et al.*, 2001). This combined drug efficacy for zero steady state is parameter dependant, varies from one individual to another and can get as high as $95\%(u = 0.05)$ for some parameter combinations. This explains why some individuals experience virologic failure on therapy that is highly effective on others. The zero solution to Equation (11) for a_{CO} is also the minimum drug efficacy, from a vaccination point of view, that is required to prevent the initial virus inoculation from successfully replicating. This, however, is so if one assumes that virus replication starts in the $CD4^+$ T cells before spreading to other compartments.

3.2 *Transient Response Analysis*

When therapy is initiated, the transition of the viral load from the pre-treatment value to the on treatment steady state is what's of interest to the doctors. Issues that are of concern are the suppression of the viral load to below 50mL of plasma and the ability of the drugs to maintain such suppression once attained. An approximate analysis by linearizing the nonlinear equations in (5–8) at the points when therapy is initiated can be obtained. The Jacobians when evaluated at an operating point (T^o, V^o) are given by

$$\mathbf{A} = \begin{bmatrix} \kappa_1 & 0 & 0 & -\beta T^o \\ u_{RT} q_1 \beta V^o & -(\delta_1 + k) & 0 & u_{RT} q_1 \beta T^o \\ u_{RT} q_2 \beta V^o & k & -\delta_2 & u_{RT} q_2 \beta T^o \\ 0 & 0 & u_{PI} N \delta_2 & -c \end{bmatrix}$$

where $\kappa_1 = p(1 - 2T_o/T_m) - d_T - \beta V_o$

The eigenvalues of matrix $\mathbf{A}$ are either all real or have a complex pair depending on the stage of the infection progression and the drug efficacy. When a complex eigenvalue pair is encountered, this means that when therapy is initiated, the response will oscillate about the treatment steady state before settling. The viral load transient response therefore, will have the form,

$$\tilde{v}(t) = A_1 e^{\lambda_1 t} + A_2 e^{\lambda_2 t} + A_3 e^{\sigma t} \cos(\omega t + \phi) \quad (14)$$

Given the initial conditions then, the period of oscillation and the duration of viral load suppression to below either the treatment steady state or 50 copies per mL of plasma, can be determined by solving Equation (14). Figure (3) shows how, for a fixed drug dosage, the imaginary component (frequency ω) and the real part (transient decay rate σ) of the complex eigenvalue, varies as the infection progresses. Initiating therapy at some infection stages then, can be expected to result in a more oscillatory transition to the steady state than at other stages. This analysis is consistent with the often observed 'viral load blips' under HAART, where viral load blips are defined as transient rebounds of plasma viremia after effective suppression of the viral load has been attained. When the drug efficacy is fixed, analysis of the eigenvalues shows that, except for the very early stages of the HIV infection, the values of λ_1 and λ_2 remain fairly constant as the HIV infection progresses. This implies that the variation in response is mainly due to the variation in the complex eigenvalue parameters σ and ω.

Inspection of the eigenvalue variation in Figure (3) also gives an indication of how the duration of viral load suppression is expected to vary as the infection progresses. It can be seen that very early

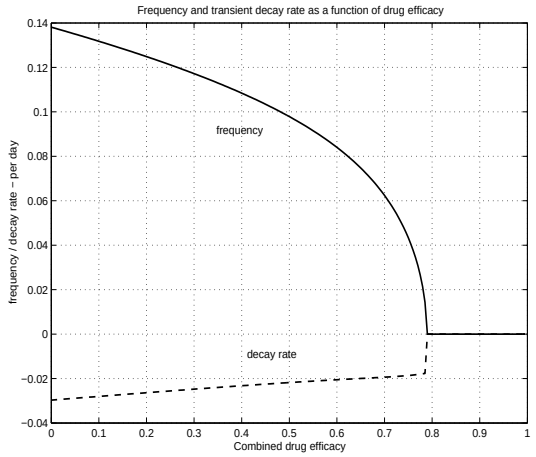

Fig. 4. Relative frequency for varying drug efficacy when therapy is initiated at the asymptomatic stage.

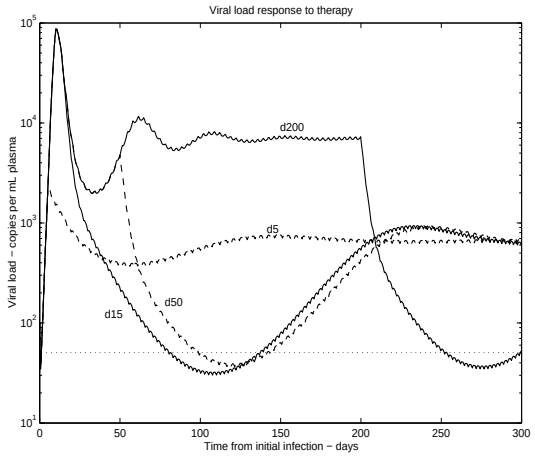

Fig. 5. Response to therapy when initiated at days 5, 15, 50 and 200 of the HIV infection.

initiation of therapy will result in a shorter viral load suppression period, which is indicated by the relatively higher value of ω. Late therapy during the asymptomatic stage will most likely result in a prolonged viral load suppression period.

Figure (4) similarly, shows how the expected duration of viral load suppression varies with drug efficacy, when therapy is initiated at the asymptomatic stage. It can be seen that higher drug doses (lower control u) result in a longer period of viral load suppression, which is indicated by the decreasing value of ω.

4. RESULTS

4.1 *Durable Suppression*

The best way to ensure durable suppression of the viral load to below 50 copies is to select a drug dosage that has a treatment steady state of at most 50 copies per mL of plasma. As this is usually not possible, durable viral load suppression can be attained when therapy is initiated at a time when the associated complex eigenvalues have a lower frequency component. If any viral load suppression to below the treatment steady state is attained, then it will be long lived as the virus slowly rebounds and settles. Figure (5) shows how viral load suppression depends on when therapy is initiated, given a constant drug dosage. It can be seen that a fixed drug dosage can be suppressive at one stage of the infection, but fail when therapy is initiated too early.

4.2 *Maximal Suppression*

Viral load suppression is considered to be maximal when the viral load reaches below levels of detection by the currently available assays. An estimation of the minimum value that the viral load can reach is useful in determining whether viral load suppression to below detectable levels is possible. This minimum value can be obtained by differentiating and solving Equation (14) and depends on both the drug efficacy and when therapy is initiated. It is also reasonable to assume that the longer the viral load suppression period is, the lower below 50 copies the viral load can be reduced to.

4.3 *Viral load blips*

Since a viral load blip is a transient rebound of the viral load to above some set value after suppressive therapy has been attained, this means that blips are more likely to occur when drug doses with steady states that are higher than that set value are used. Blips also may depend on the frequency ω and the rate σ, at which the sinusoidal transient dies out. For a fixed drug dosage and a constant ω, blips will be more likely to occur when therapy is initiated at a stage where σ is lower.

5. CONCLUSIONS

The following conclusions can be drawn from this study.

(1) The end result of HIV therapy is to move the pre-treatment viral load to a treatment steady state value, that is determined by the individuals parameters and the drug efficacy. Initiating therapy when the viral load is below this treatment steady state will result in an increasing viral load, which will be perceived as failure to control the viral load.
(2) If a drug is capable of driving the viral load to a particular steady state value, then the

duration of viral load suppression to below this steady state value can be maximized by choosing the right time to initiate therapy.

(3) Initiating therapy during the early stages of the infection when the viral load is very high, results in a faster transition to the treatment steady state. This however, implies a shorter viral load suppression period.

(4) Initiating therapy during the asymptomatic stage of the infection will result in a more durable suppression of the viral load. One can also assume that maximal suppression will also be attained.

(5) Viral load blips will most probably occur whenever the drug efficacy is such that the viral load treatment steady state is higher than the figure that is set as indicative for a blip. The stage of the infection process where viral load blips are most likely to occur, given a fixed drug efficacy is really not clear.

(6) If individual parameters are known, it is then possible to anticipate the duration of viral load suppression, as well as the magnitude and timing of the viral load blip. This study therefore, puts emphasis on the need to estimate parameters and individualize antiretroviral therapy.

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