Analysis of a sub-optimal scheme of drug dosage in the AIDS treatment

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KEYWORDS

Optimization, direct method, AIDS, treatment.

ABSTRACT

Here the results for $CD4^+T$ cells count and the viral load obtained from HIV sero-positive patients are compared with results from numerical simulations by computer. Also, the standard scheme of administration of drugs anti HIV (HAART schemes) which uses constant doses is compared with an alternative sub-optimal treatment scheme which uses variable drug dosage according to the evolution of a quantitative measure of the side effects. The quantitative analysis done here shows that it is possible to obtain, using the alternative scheme, the same performance of actual data but using variable dosage and having fewer side effects. Optimal control theory is used to solve and also to provide a prognosis related to the strategies for control of viraemia.

1 - INTRODUCTION

Models of dynamical systems have been extensively used in studying biological phenomena. The increase in the number of cases of AIDS have lead to the development of several new mathematical models which describe the dynamical behavior of the viral load on $CD4^+T$ cells counts as well as analyze the effects of treatment strategies [12, 13, 14].

On the other hand new treatment schemes has helped many sero-positives patients to have a normal life. In [9] one can see reports on success achieved by highly active antiretroviral therapy (HAART) that has prolonged the life of patients from 1-3 years.

However, long-term use of HAART could have adverse effects, such as metabolic abnormalities and irreversible fat redistribution syndromes.

Also, the eventual intolerance against HAART by some patients may leads to treatment interruptions. In some instances [8, 9] up to three stops were noted during the treatment.

Remarkably, some cases were related to improvements in $CD4^+T$ counts and decrease of the viral load.

The intense clinical research has made available now several quantitative descriptions of the dynamics of AIDS as well as more advanced mathematical modeling methods [5, 6, 10, 11].

These models can be used to optimize the drug doses required in the treatment. Here we use a model that was originally proposed by Tan and Wu [6] and is similar to Perelson [10].

Caetano & Yoneyama have shown in [1] that it is possible to improve the treatment effectiveness by using closed loop drugs administration strategy.

They showed that closed loop treatment schemes could have advantages when compared to the standard treatment because more information is used for the control of the drug doses. Also, it is possible to use optimal control theory to reduce the side effects during a short-term treatment scheme while adequate therapeutic results are obtained (see [2]).

Caetano & Yoneyama also carried out a comparative study and two optimization methods [3]. Responses corresponding to the actual observed data and simulation data were compared in terms of long-term period and short-term period drug administration strategies.

Here the main objective is to analyze the dynamics of the viral load and the $CD4^+T$ cells counts with a model that is fitted to match the actual data and considering the sub-optimization problem with dynamic constraints for multi-drug treatment case.

The data were provided by *Centro de Referência e Treinamento em DST-AIDS* in São Paulo, Brazil.

In the first case the patient went through the treatment during a period of around 495 days which he received AZT (600 mg) and 3TC (300 mg). Before this period the patient had not received any specific drug for the treatment of AIDS.

The second case is a patient that also received AZT (600 mg) and 3TC (300 mg) for around 340 days before the start of HAART scheme.

The model adopted consists of four differential equations representing the $CD4^+T$ cells (uninfected, latent infected and actively infected) and also the free viruses.
We construct a performance index that tries to describe the side effects in a quantitative way.

2 - THE MODEL

The model in Tan [6] describes the HIV pathogenesis under treatment by antiviral drugs. It has four differential equations and stochastic terms in the variable that represent the number of latent infected T cells. It has also stochastic components on infection free HIV and non-infection free HIV variable.
The model used here is given below by the differential equations in (1). It is a simplified version of a more general model that includes stochastic terms, as originally presented by Tan.

$$\begin{cases} \dot{x}_1 = S(x_4) + l(x_1, x_2, x_3)x_1 - x_1[m_1 + k_1(m_1)x_4] \\ \dot{x}_2 = wk_1(m_1)x_4x_1 - x_2[m_2 + k_2(m_2)] \\ \dot{x}_3 = (1-w)k_1(m_1)x_4x_1 + k_2(m_2)x_2 - m_3x_3 \\ \dot{x}_4 = N(t)m_3x_3 - x_4[k_1(m_1)x_1 + m_4] \end{cases} \quad (1)$$

where

$x_1(t) \equiv$ uninfected $CD4^+T$ cells;

$x_2(t) \equiv$ latent infected $CD4^+T$ cells;

$x_3(t) \equiv$ actively infected $CD4^+T$ cells;

$x_4(t) \equiv$ free virus HIV

s = the rate of generation of x_1;

r = rate of stimulated growth of x_1;

T_{max} = maximum T cells population level;

m_i = death rate of x_i; I = 1,2,3,4.

k_1 = infection rate from x_1 to x_2 by viruses;

k_2 = conversion rate from x_2 to x_3;

N = the number of infectious virions produced by an actively infected T cell;

q = viral concentration needed to decrease s.

and the coefficients k_1 and k_2 are functions of the drug doses m_1 and m_2.

Basically, x_1 cells are stimulated to proliferate with rate $l(x_1, x_2, x_3)$ in the presence antigen and HIV, that is,

$$l(x_1, x_2, x_3) = r[1 - (x_1 + x_2 + x_3)/T_{max}] \quad (2)$$

Without the presence of HIV the rate of generation is $S(x_4)$, that is,

$$S(x_4) = \frac{sq}{q + x_4} \quad (3)$$

In the presence of free HIV (x_4), uninfected cells x_1 can be infected to become x_2 cells or x_3 cells, depending on the probability of the cells to become actively or latently infected with rate ω.

The x_2 cells can be activated to become x_3 cells. This activation rate is k_2.

The x_3 cells are short living and will normally be killed upon activation with death rate μ_3.

When x_3 cells die free viruses x_4 are released with rate N(t) described by

$$N(t) = b_2 - (b_2 - N_0)e^{-b_1 t} \quad (4)$$

The x_1, x_2 cells and x_4 (free viruses) also have finite life and the death rates in this model are μ_1, μ_2 and μ_v respectively.

The effects of drugs such as reverse transcriptase inhibitors and protease inhibitors are considered via the parameters k_1 and k_2.

3 - THE CONTROL STRATEGY

The standard treatment of sero positive patients includes two classes of drug to block the action of HIV.

The first class includes drugs that blocks *reverse transcriptase* enzyme involved in exchange of viral-RNA and viral-DNA. Some of the available reverse transcriptase inhibitors are: *zidovudine* (AZT), *didanosine* (ddI), *lamivudine* (3TC), zalcitabine (ddc), stavudine (D4T), *Abacavir* (Ziagen), *Viramune* (nevirapine), *Rescriptor* (delavirdine) and *Sustiva* (efavirenz), among others.

The second class includes drugs that inhibit the protease enzyme: *Invirase* (saquinavir), *Norvir* (ritonavir), *Crixivan* (indinavir), *Viracept* (nelfinavir), *Agenerase* (amprenivir) and others.

The administration of these drugs is made according to tables proposed by World Health Organization. The medical staff may change the used drugs when patients develop resistance or present intense side effects.

In the present work the parameters in Tan's model takes the form

$$k_1(m_1) = k_{10}e^{-a_1 m_1} \quad (5)$$

$$k_2(m_2) = k_{20}e^{-a_2 m_2} \quad (6)$$

where k_{10} and k_{20} are natural rate for conversion of uninfected CD4 cells into latently infected CD4 cell and natural rate for conversion of latently infected CD4 cell into actively infected cell, respectively. Also, the parameters a_1 and a_2 are the efficiency of drugs for reverse transcriptase and protease inhibitors, respectively.

The variables $m_1(t)$ and $m_2(t)$ are the doses from drugs administrated to reverse transcriptase and protease inhibitors respectively, while a_1 and a_2 are constants.

In [7,17] one can see other works dealing with the control of the viral load using a mathematical modeling and simulations by computer.

3.1 - The Optimal Control

One possible approach could be the use Pontryagin's Maximum Principle ([15], [16]).

However, in many actual application problems the analytical solutions for optimal control are very difficult to obtain because of the need to solve the TPBVPs (Two Point Boundary Value Problem).

This way of solving the optimal control problem is said to be an indirect method. An alternative is to optimize directly the cost functional (known as performance index) using the parameterization of the control (the input functions m(t)).

In the present case, this involves a subset of the coefficients in a series expansion employing hyperbolic functions.

Those approximations are sub-optimal, in the sense that the cost achieved is generally worse when the higher terms of the series expansion are neglected. However, those sub-optimal inputs were found to be satisfactory in the present problem.

3.2 - Direct Method

The numerical method used here was proposed by Jacob in [4] and is available in the form of a computer program called EXTREM. The objective is to find a control input

$$m(t) = [m_1(t) \quad m_2(t)]^T$$

that minimizes the cost function

$$J(m) = h(x(t_f), t_f) + \int_{t_0}^{tf} g(x(t), m(t), t)dt \qquad (7)$$

where t_o and t_f are the initial and final instants of time, fixed *a priori*.

The functions h and g are constrained by the state equation

$$\dot{x} = f(x(t), m(t)) \qquad (8)$$

that in the specific problem is described by the equations (1)-(6).

The chosen performance index tries to make a compromise between the side effects and the therapeutic effects, reflected by the CD4 count and a the viral load and it has been used before in [3]:

$$J(m) = \frac{g_1}{x_1^2(t_f)} + g_2 x_4^2(t_f) + \int_{t_0}^{tf} \left\{ f_1\left(1 - e^{-e_1 m_1^2(t)}\right) + f_2\left(1 - e^{-e_2 m_2^2(t)}\right) + g_2 x_4^2(t) \right\} dt \qquad (9)$$

The biological interpretation of the proposed cost functional is that the two first terms out of integral represent the target of maximizing non-infected CD4 cells and also to minimize the viral load after a pre-specified time horizon.

The coefficients ϕ_1 and ϕ_2 of the terms in the integrand are weights that reflect the dose-related side effects of the two drugs ($m_1(t)$ and $m_2(t)$) which must be adequately balanced.

The two last terms are included to force x_1 (uninfected $CD4^+T$ cells) to increase and x_4 (viral load) to decrease with treatment.

Finally, ε_1 and ε_2 are sensibilities of the patient with respect to reverse transcriptase inhibitors and protease inhibitors respectively. To fit these parameters is very difficult and only are possible with a controlled experiment.

In this optimization method (see [4]) the control input m(t) is represented by an expansion over the interval [0 , t_f] with the form (for i= 1, 2)

$$m_i(t) = \frac{c_{i1} - c_{i4}}{2} \tanh\left(\frac{0.08(t - c_{i3})}{|c_{i2}|}\right) + \frac{c_{i1} + c_{i4}}{2} + \frac{c_{i4} - c_{i7}}{2} \tanh\left(\frac{0.08(t - c_{i5})}{|c_{i6}|}\right) - \frac{c_{i4} - c_{i7}}{2} + \frac{c_{i7} - c_{i10}}{2} \tanh\left(\frac{0.08(t - c_{i9})}{|c_{i8}|}\right) - \frac{c_{i7} - c_{i10}}{2} \qquad (10)$$

where the coefficients c_{ij} are to be determined by minimizing (9).

Here, after fitting the parameters the obtained values were:

f_1 = 100 $\quad e_1$ = 7.5E-9 $\quad g_1$ = 250,000

f_2 = 0 $\quad e_2$ = 0 $\quad g_2$ = 1E-8

Table I - Parameters fitted, *Patient*-A.

s	r	T_{max}	μ_1	μ_2	μ_3	μ_v	k_{10}
0.4	0.01	1850	0.0022	0.02	1E-6	7E-5	1E-6

k_{20}	N_0	θ	ω	β_1	β_2	α_1	α_2
0.0001	2,000	10,000	0.01	0.05	1,000	0.002	0

Table II - Initial conditions, *Patient*-A.

x_1	x_2	x_3	x_4	t_f
259	200	10	32,473	495

Table III - Parameters fitted, *Patient*-B.

s	r	T_{max}	μ_1	μ_2	μ_3	μ_v	k_{10}
0.01	0.102	700	0.05	0.14	0.006	1E-6	3E-7

k_{20}	N_0	θ	ω	β_1	β_2	α_1	α_2
0.007	1,000	10,000	0.97	0.01	1,000	0.002	0

Table IV - Initial conditions, *Patient*-B.

x_1	x_2	x_3	x_4	t_f
28	300	110	40,700	340

3.3 Clinical Data

The values for $CD4^+T$ cell counts and the viral load were obtained from two patients in a sample of 43 patients of medical reports at the *Centro de Referência e Treinamento em DST-AIDS* in São Paulo, Brazil.

They were patient-039 in the sample, to whom we shall call *Patient*-A, and patient-002 in the sample, to whom we shall call *Patient*-B.

These patients were chosen because they had not used specific drugs to combat HIV up to the moment that the first symptoms of AIDS appeared. Then they used the

combination AZT (600 mg) + 3TC (300 mg) (constant doses) for 495 days (*Patient*-A) and for 340 days (*Patient*-B) when they switched to the HAART scheme.

4 - NUMERICAL RESULTS

The results are shown in figures 1-7. During the period presented in Fig-1 and Fig-5 the two patients had manifested symptoms of AIDS. In those figures the CD4 count and the viral load are represented by the "*triangles*" and the "*plus signs*", respectively.

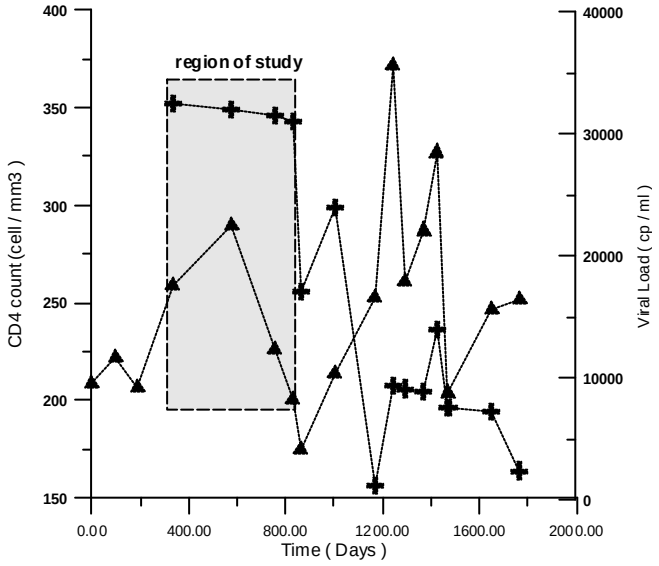

Fig-1 - Historical data of *Patient*-A.

The *Patient*-A had bacterial pneumonia + herpes + hepatitis C and the *Patient*-B had advanced stages of herpes. The drugs prescribed for the two patients were Zidovudine (AZT) 600 mg plus Lamivudine (3TC) 300 mg each day.

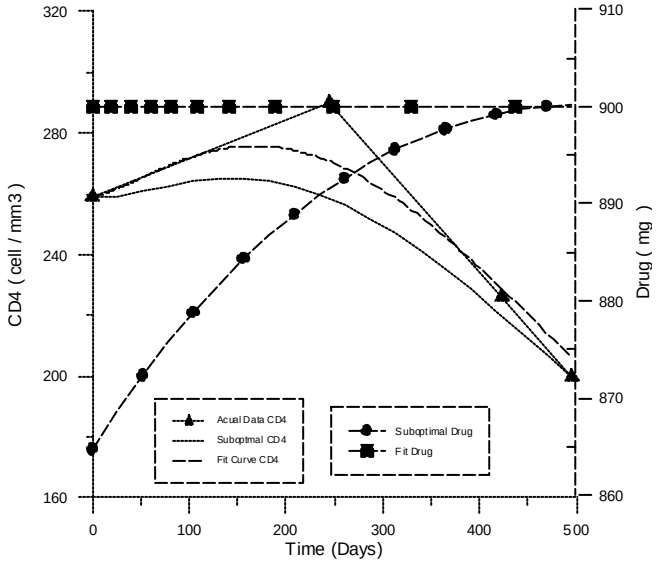

Fig-2 - Optimal and fit curves for CD4 count and drug doses for *Patient*-A.

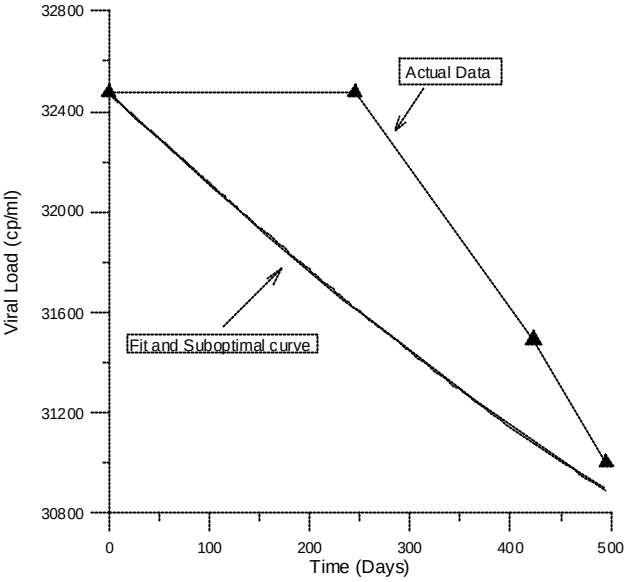

Fig-3 - Viral load (optimal and fitted) for *Patient*-A.

The results of the fitting process are shown in Fig-2 and Fig-6. The parameters were obtained by fitting Tan's model to the clinical data using several computer simulations until good precision was obtained in terms of CD4 counts and the viral load.

It is possible to note (Fig. 3) that the fitting is adequate in both cases.

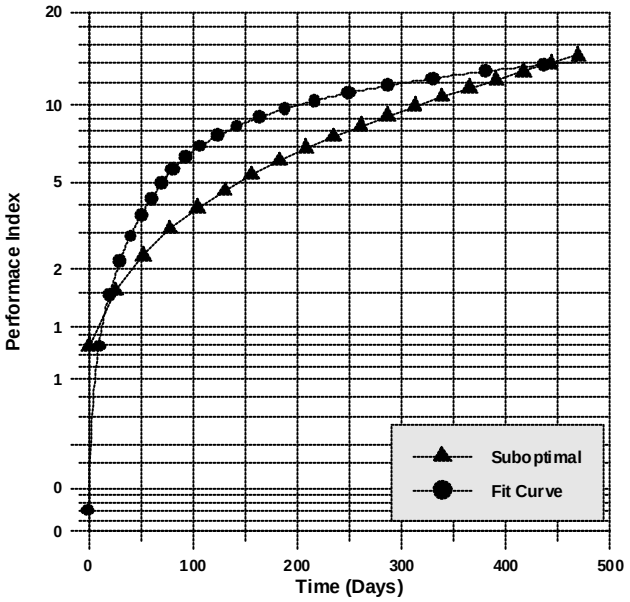

Fig-4 - Performance index for *Patient*-A.

The corresponding parameters that were used in the simulations are presented in Tables I-IV.

For this simulations it was used the constant control

m_1 = 900 (AZT = 600 mg plus 3TC = 300 mg)

m_2 = 0 (none protease inhibitor).

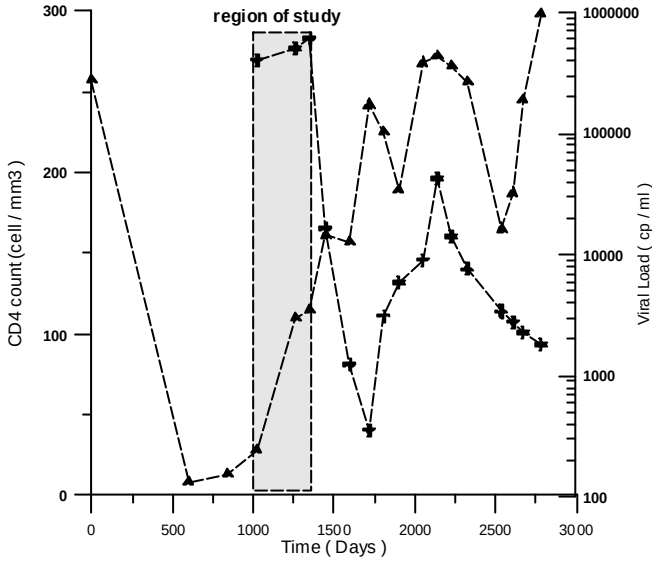

Fig-5 - Historical data of *Patient*-B.

The *Patient*-A had an increase in $CD4^+$T cells count until mid-period but after that he presented a typical picture of immunological resistance with the viral load tending to be very high, around 32000 copies/ml (Fig-2). After 495 days he started a HAART scheme and it is possible to observe the decrease of the viral load and increase of CD4 count.

The *Patient*-B (Fig-5) also has a typical immunological resistance with the viral load increase in this period (340 days). The initial $CD4^+$T cells count was 30 cells/mm^3 and in the final period was around 110 cells/mm^3 (healthy individuals have CD4 cells counts about 1,000 cells/mm^3).

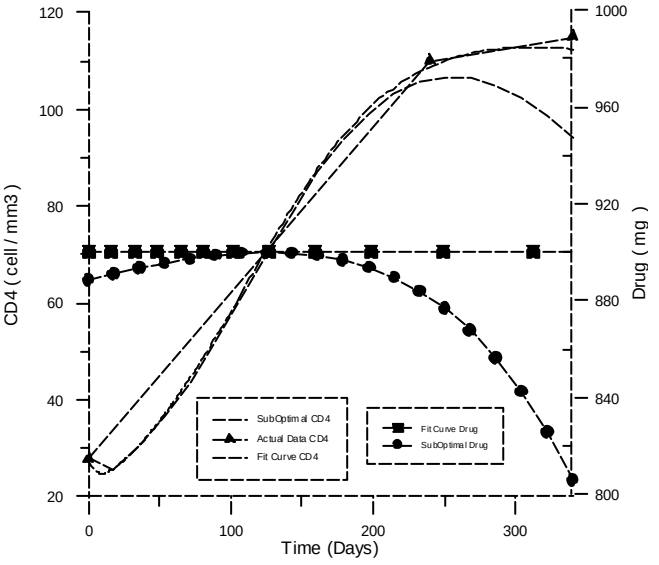

Fig-6 - Optimal and standard treatment for *Patient*-B.

After the fitting of curves to the actual data the direct method described in the last section is used to solve the optimal control problem for the two patients.

In Fig-2 it is possible to see that for *Patient*-A the optimal treatment will yield smaller doses in the initial period, but this should be gradually increased until the final period. He could start the treatment with 865 mg and 495 days later would be reaching 900 mg of drugs.

4.1 - Optimal treatment for *Patient*-A

During this simulated treatment the sub-optimal values of side effects would be less than with the standard treatment.

We can observe a comparison between the simulated results and actual values for *Patient*-A in Fig-4. When the actual values are inserted into equation (9), the performance index, one can see that it has higher values than the sub-optimal control solution.

4.2 - Optimal treatment for *Patient*-B

In Fig-6 it is possible to see that for *Patient*-B the optimal treatment would be improved by starting using around 880 mg of drugs and gradually decreased until the final period (340 days) to end up around 800 mg.

The results for CD4 are similar to the actual data (also in Fig-6) and to HIV the curves had undetectable differences of the same type of Fig-3 for *Patient*-A.

Also in this case it is possible to observe the better results for sub-optimal control than the actual data (Fig-7). But the solution is almost the same for constant use of drugs.

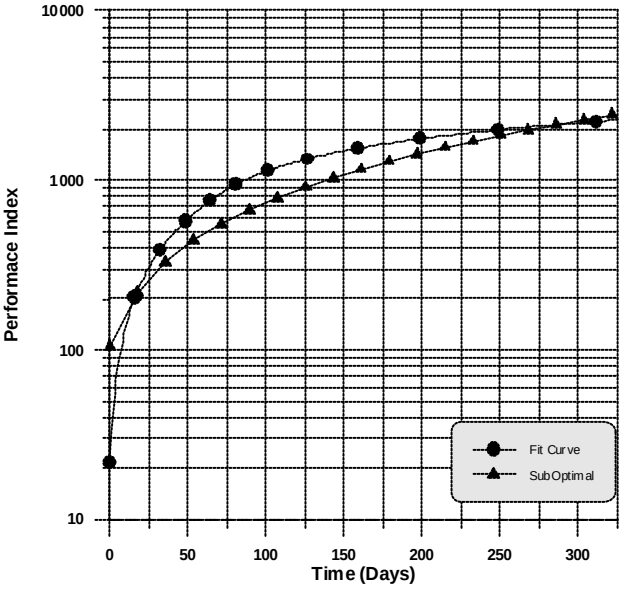

Fig-7 - Performance index for *Patient*-B.

5 - DISCUSSION AND CONCLUSION

Here we have seen an application of the optimal control theory for improving the administration strategy of drugs for the treatment of AIDS.

The work includes comparisons of theoretical solutions obtained using computer simulations based on mathematical model with actual clinical data from two cases: *Patient*-A and *Patient*-B from the *Centro de Referência e Treinamento em DST-AIDS* in São Paulo city, Brazil.

The optimal control problem was solved with a numerical direct method. The mathematical solutions show that treatments can be improved in terms of side effects, although further studies are required to establish the adequacy of the therapeutic results.

An important fact related to the use of the optimal (sub-optimal) strategy lies in the probability of CD4 infected cells transforming from latent to active forms. For *Patient*-A this probability was

$$\omega = 0.01 \ (1\%)$$

and for *Patient*-B was

$$\omega = 0.97 \ (97\%).$$

It is interesting to observe that the chance of infected CD4 cells to become latent under the optimal control is almost 50% smaller than HAART scheme.

When more infected cells become latent their actions may have a longer time horizon and hence, more difficult to combat.

The initial viral load was 32,473 copies/ml for *Patient*-A and 407,000 copies/ml for *Patient*-B. While the viral load decreases for *Patient*-A, it (slowly) increases for *Patient*-B (more than 500,000 copies/ml).

6 - ACKNOWLEDGEMENTS

The authors are grateful to the *Centro de Referência e Treinamento em DST-AIDS* in São Paulo city, Brazil, in particular to Dr. Mylva Fonsi for her help in providing the actual data used in this work.

REFERENCES

[1] Caetano, M. A. L. & Yoneyama, T. 1999. Comparative evaluation of open loop and closed loop drug administration strategies in the treatment of AIDS. Anais da Academia Brasileira de Ciências. V. 71. No. 4-I. 589-597.

[2] Caetano, M. A. L. & Yoneyama, T. 1999. Optimal control theory applied to the anti-viral treatment of AIDS. *Theory and Mathematics in Biology and Medicine Conference*. Amsterdam. Netherlands.

[3] Caetano & Yoneyama. 2002. Short and Long Period Optimization of Drugs Doses in the Treatment of AIDS. Anais da Academia Brasileira de Ciências. V. 74. No. 3/4 (to be edited).

[4] Jacob, H. G., 1972. An engineering optimization method with application to STOL aircraft approach and landing trajectories. NASA. TN-D 6978. Langley.

[5] Nowak M. A. & C. R. M. Bangham 1996. Population Dynamics of Immune Responses to Persistent Viruses. *Science*. V. 272. 74-79.

[6] Tan, W. Y. & Wu, H. 1998. Stochastic modelling of the dynamics of $CD4^+$T-cell infection by HIV and some Monte Carlo studies. *Mathematical Biosciences*. 147. 173-205.

[7] Wein, L. D., D'Amato, R. M., Perelson, A. S., 1998. Mathematical analysis of antiretroviral therapy aimed at HIV-1 eradication or maintenance of low viral loads. *J. Theor. Biol*. V. 192. 81-98.

[8] Taffé, M. Rickenbach, B. Hirschel, M. Opravil, H. Furrer. P. Janin, F. Bugnon, B. Ledergerber, T. Wagels, P. Sudre. 2002. Impact of occasiona short interruptions of HAART on the progression of HIV infection: results from a cohort study. *AIDS*. V. 16. No. 5. 747-755.

[9] Garcia, M. Plana, G. M. Ortiz, S. Bonhoeffer, A. Soriano, C. Vidal, A. Cruceta, M. Arnedo, C. Gil, G. Pantaleo, T. Pumarola, T. Gallart, D. F. Nixon, J. J. Miró, J. M. Gatell. 2001. The virological and immunological consequences of structured treatment interruptions in chronic HIV-1 infection. *AIDS*. V. 15. No. 9. F29-F40.

[10] Perelson, A. S., D. E. Kirshner, R. DeBoer. 1993. Dynamics of HIV-infection of CD4+T-cells. *Mathematical Biosciences*. V. 114. 81-125.

[11] Phillips, A. 1996. Reduction of HIV concentration during acute infection, independence from a specific immune response. *Science*. V. 271. 497-499.

[12] Mittler, J.E., Sulzer, B., Neumann, A. U., Perelson, A. S., 1998. Influence of delayed viral production on viral dynamics in HIV-1 infected patients. *Mathematical Biosciences*. 152. 143-163.

[13] Murray, J. M.., Kaufmann, G.; Kelleher, A. D., Cooper, D. A., 1998. A model of primary HIV-1 infection. *Mathematical Biosciences*. 154. 57-85.

[14] Wick, D. 1999. On T-cell dynamics and hyperactivation theory of AIDS pathogenesis. *Mathematical Biosciences*. 158. 127-144.

[15] Kirk, D. E., 1970. *Optimal Control Theory; An Introduction*. Prentice-Hall. New Jersey, 452 p.

[16] Lewis, F. L., 1986. *Optimal Control*. New York. 362 p.

[17} Perelson, A. S., P. W. Nelson. 1999. Mathematical Analysis of HIV-1 Dynamics in Vtvo, *SIAM Review*. V. 41. No. 1. 3-44.