A Model Based Analysis Of Aids Treatment

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Abstract

This work compares the results for $CD4^+T$ cells count and viral load obtained from HIV sero-positive patients with results from numerical simulations by computer. The quantitative analysis compares the standard administration of drugs anti HIV (HAART schemes) using constant doses with the alternative sub optimal treatment, by the use of variable drug dosage according to the evolution of a quantitative measure of the side effects. The sub optimal schemes for treatments are obtained from a mathematical model and depend on a quantitative index. The alternative scheme showed that it is possible the same results of actual data using variable dosage having less side effects.

INTRODUCTION

Mathematical models of dynamical systems have been used extensively in studying biological phenomena. Recent increase in cases of AIDS have lead to new mathematical models that have been developed to describe the dynamic behaviour of viral load on $CD4^+T$ cells counts and to analyse the effects of treatment strategies [1-3]. On the other hand new treatment schemes has helped many sero-positives patients to have a normal life. The specialised literature reports on success achieved by highly active antiretroviral therapy (HAART) that has prolonged the life of patients from 1-3 years [4]. However, long-term use of HAART could have adverse effects, such as metabolic abnormalities and irreversible fat redistribution syndromes. Other fact is the eventual intolerance against HAART, leading to treatment interruptions by some patients. These interruptions have also been object of study and, in some instances [4-5] 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.

Quantitative descriptions of the dynamics exhibited by AIDS are now available as a consequence of intense clinical research, together with advances in the mathematical modelling methods: [6-9]. These mathematical models can be used to optimise the drug doses required in the treatment. The model used in this work was originally proposed by Tan and Wu in [9] and is similar to the one proposed by Perelson in [8].

Caetano & Yoneyama have shown, in a previous work [10], that it is possible to improve the treatment effectiveness by using closed loop drugs administration strategy. It was shown 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. It was also shown (by computer simulation) that it is possible to use the optimal control theory to reduce the side effects during a short-term treatment scheme [11] while adequate therapeutic results are obtained. Caetano & Yoneyama also carried out a comparative study and two optimisation methods [12]. Responses corresponding to the actual observed data and simulation data were compared in terms of long period and short period drug administration strategies.

The objective of the present work is to analyse the dynamics of viral load and $CD4^+T$ cells counts with a dynamic model fitted to match the actual data and considering the sub optimisation 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 one of the selected cases 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 adopted mathematical model comprises four differential equations representing the uninfected $CD4^+T$ cells, active infected $CD4^+T$ cells and free viruses. A performance index was developed to try to describe the side effects in a quantitative way. Then a numerical technique from the optimal control theory was introduced to solve and also to provide a prognosis related to the strategies for control of viraemia

METHODS

The model in Tan [9] describes the HIV pathogenesis under treatment by antiviral drugs. The model 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 mathematical model used in this work is a simplified version of a more general model that includes stochastic terms, as originally presented by Tan. The dynamics is described by the differential equations

$$\begin{cases} \dot{x}_1 = S(x_4) + \lambda(x_1, x_2, x_3)x_1 - x_1\left[\mu_1 + k_1(m_1)x_4\right] \\ \dot{x}_2 = \omega k_1(m_1)x_4 x_1 - x_2\left[\mu_2 + k_2(m_2)\right] \\ \dot{x}_3 = (1-\omega)k_1(m_1)x_4 x_1 + k_2(m_2)x_2 - \mu_3 x_3 \\ \dot{x}_4 = N(t)\mu_3 x_3 - x_4\left[k_1(m_1)x_1 + \mu_v\right] \end{cases} \quad (1)$$

where $\dot{x} = dx/dt$ represents the time derivative and the values from parameters of dynamic system are obtained by relations:

$$S(x_4) = \frac{s\theta}{\theta + x_4} \quad (2)$$

$$\lambda(x_1, x_2, x_3) = r\left[1 - (x_1 + x_2 + x_3)/T_{\max}\right] \quad (3)$$

$$\mathrm{N(t)} = \beta_2 - (\beta_2 - N_0)e^{-\beta_1 t} \quad (4)$$

with $x_1 = x_1(t) \equiv$ uninfected CD4$^+$T cells; $x_2 = x_2(t) \equiv$ latent infected CD4$^+$T cells; $x_3 = x_3(t) \equiv$ active infected CD4$^+$T cells; $x_4 = x_4(t) \equiv$ free virus HIV; s = the rate of generation of x_1; $T_1 =$ maximum T cells population level; $\mu_1 =$ death rate of x_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; $\theta =$ viral concentration needed to decrease s. 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 $\lambda(x_1, x_2, x_3)$ in the presence antigen and HIV (equation 3). Without the presence of HIV the rate of generation is $S(x_4)$ (equation 2). 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. The x_1, x_2 cells and also x_4 (free viruses) have finite life and the death rates in this model are μ_1, μ_2 and μ_v respectively. When x_3 cells die free viruses x_4 are released with rate N(t) described by (4).

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

CONTROL STRATEGY

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

$$k_1(m_1) = k_{10}e^{-\alpha_1 m_1} \quad (5)$$

$$k_2(m_2) = k_{20}e^{-\alpha_2 m_2} \quad (6)$$

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 active infected cell, respectively. The parameters α_1 and α_2 are the efficiency of drugs for reverse transcriptase and protease inhibitors, respectively.

The variables m_1 and m_2 are the doses from drugs administrated to reverse transcriptase and protease inhibitors respectively, while α_1 and α_2 are constants. Other works dealing with the control of the viral load using a mathematical modelling and simulations by computer are [13-14].

The Optimal Control

The optimal control theory is widely used by mathematicians and engineers for improvements in the costs of dynamics systems. One approach is to 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 manner of solving the optimal control problem is said to be an indirect method. An alternative is to optimise directly the cost functional (known as performance index) using the parameterisation of control. The parameterisation of the input functions m(t), in the present case, 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.

Direct Method

The numerical method used here was proposed in Jacob [17] 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

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

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

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

that in the specific problem is described by the equations (1)-(6). The performance index tries to make a compromise between the side effects and the therapeutic effects, reflected by the CD4 count and a viral load. The chosen index is the same that has been used before in the literature [12]:

$$\begin{aligned} J(m) = & \frac{\gamma_1}{x_1^2(t_f)} + \gamma_2 x_4^2(t_f) + \\ & \int_{t_o}^{t} \left\{ \phi_1 \left(1 - e^{-\varepsilon_1 m_1^2(t)} \right) + \phi_2 \left(1 - e^{-\varepsilon_2 m_2^2(t)} \right) \right. \\ & \left. + \frac{\gamma_1}{x_1^2(t)} + \gamma_2 x_4^2(t) \right\} dt \end{aligned} \tag{9}$$

The biological interpretation of the proposed cost functional is that the two first terms out of integral represent the target of maximising non-infected CD4 and 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. The terms 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.

The control input m(t) is represented by an expansion over the interval [0 , t_f] with the form (for i= 1, 2)

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

where the coefficients c_{ij} are to be determined by minimizing (9). After fitting the parameters the obtained values are:

$\phi_1 = 100$

$\phi_2 = 0$

$\varepsilon_1 = 7.5\text{E-}9$

$\varepsilon_2 = 0$

$\gamma_1 = 250{,}000$

$\gamma_2 = 1\text{E-}8$

Clinical Data

The values for CD4$^+$T cell counts and viral load were obtained from patients (patient-039 and patient-002) contained in the sample (43 patients) of medical reports at the *Centro de Referência e Treinamento em DST-AIDS* in São Paulo, Brazil. The 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-039) and for 340 days (patient-002) when they switched to the HAART scheme.

RESULTS

The results are shown in Figures 1-7. During the period presented in Figure 1 and Figure 5 the two patients had manifested symptoms of AIDS. The patient-039 (Figure 1) had bacterial pneumonia + herpes + hepatitis C and the patient-002 had advanced stages of herpes. The drugs prescribed for the two patients were Zidovudine (AZT) 600 mg plus Lamivudine (3TC) 300 mg each day.

The parameters were obtained by fitting Tan's mathematical model to the clinical data using several computer simulations until good precision was obtained in terms of CD4 counts and viral load. The Figures 2 and 6 show the results of the fitting process. It is possible to note that the fitting is adequate in both cases. The corresponding parameters that were used in the simulations are presented in tables I-IV. The simple simulations are made using constant control $m_1 = 900$ (AZT = 600 mg + 3TC = 300 mg) and $m_2 = 0$ (none protease inhibitor). The patient-039 have 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 32,000 copies/ml (Figure 3). 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.

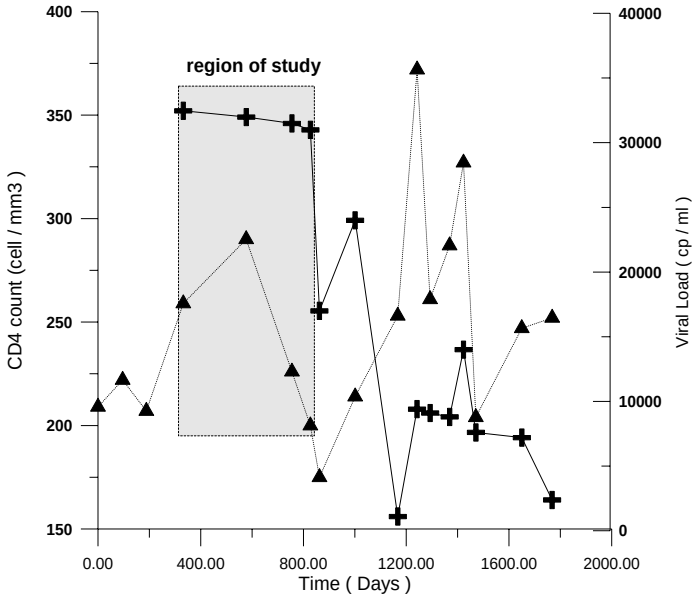

Figure 1. Historical data of patient-039.

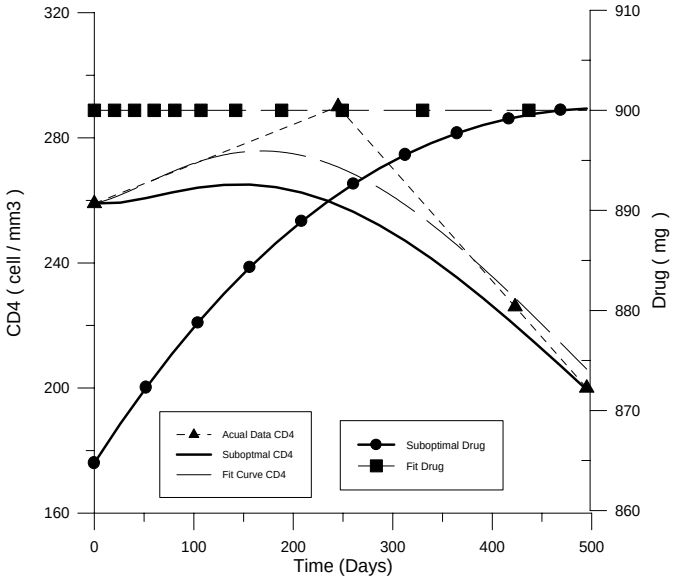

Figure 2. Optimal and fit curves for CD4 count and drug doses for patient-039.

The patient-002 in Figure 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 1000 cells/mm^3.)

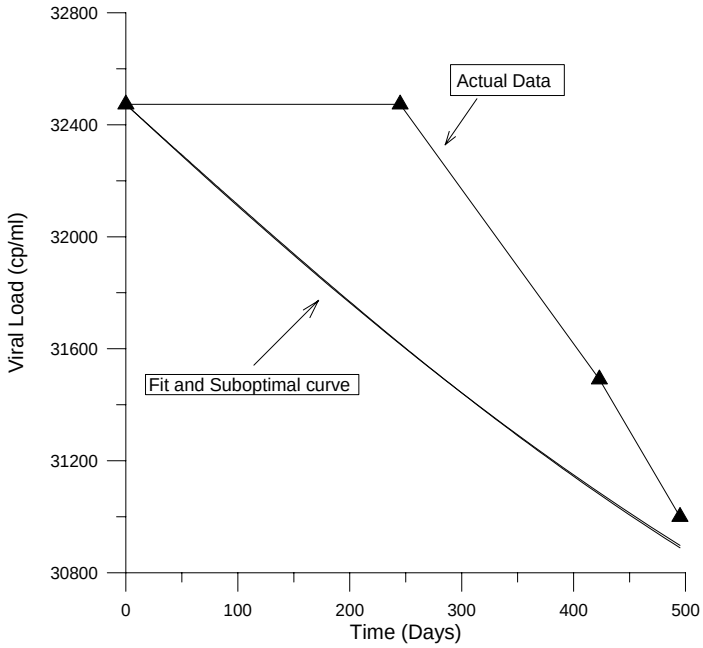

Figure 3. Viral load (optimal and fitted) for patient-039.

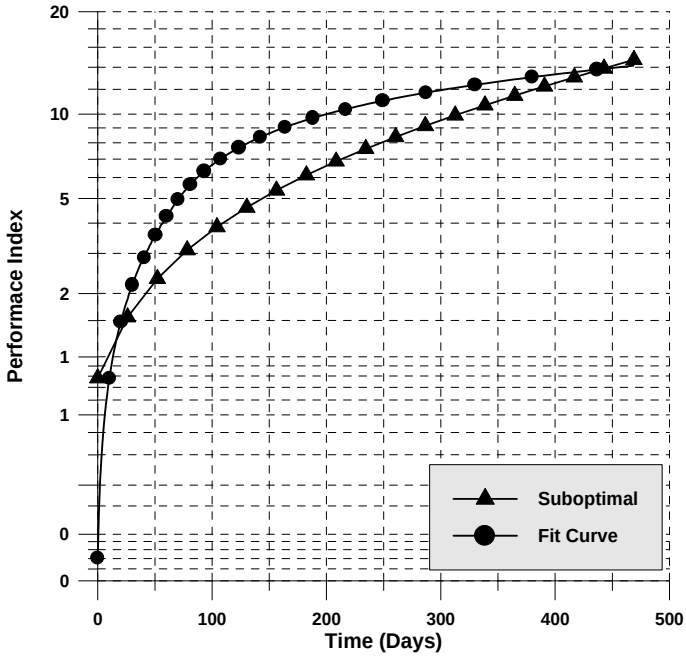

Figure 4. Performance index for patient-039.

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.

It is possible to note that for patient-039 the optimal treatment will yield smaller doses in the initial period, but increasing until the final. He could start the treatment with 865 mg and 495 days later with 900 mg of drugs. The advantage in this case is observed in Figure 2.

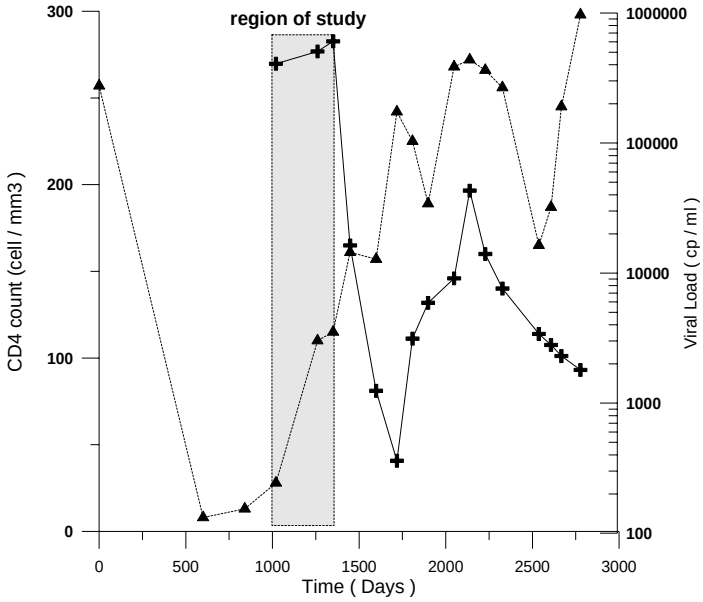

Figure 5. Historical data of patient-002.

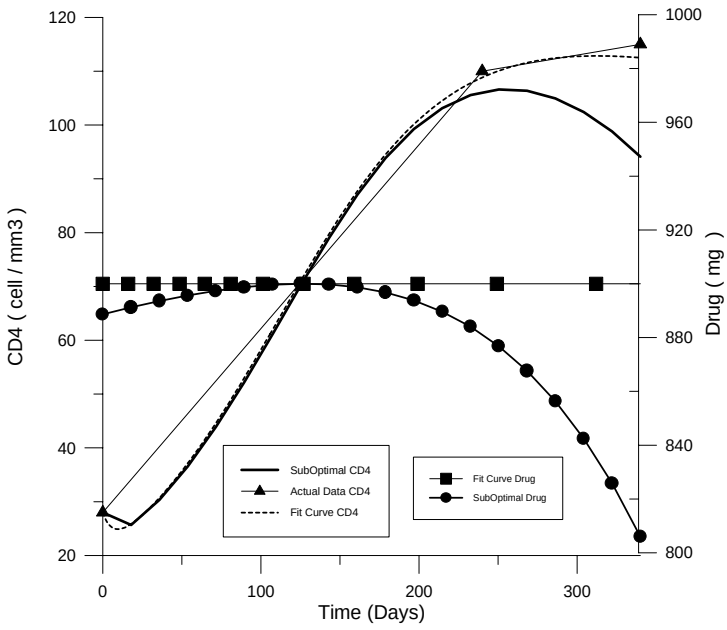

Figure 6. Optimal and standard treatment for patient-002.

During this simulated treatment the sub optimal values of side effects would be less than with the standard treatment. In Figure 4 one can see a comparison between the simulated results and actual values of the patient.

The actual results are inserted into equation (9) and compared with simulated data. The actual data presents values for performance index that are greater than optimal control solution.

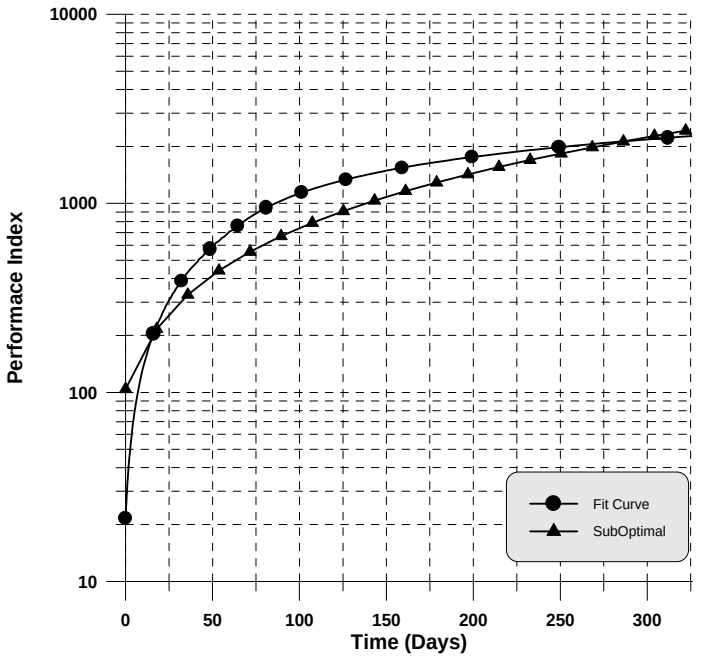

Figure 7. Performance index for patient-002.

For the patient-002 the optimal treatment would be improved by starting using around 880 mg of drugs and after that (340 days) finish with 800 mg. The results for CD4 are similar to the actual data (Figure 6) and to HIV the curves had undetectable differences the same type of Figure 3 for patient-039. Also in this case it is possible to observe the better results for optimal control. But the solution is almost the same for constant use of drugs (Figure 7).

DISCUSSION

This work presented two cases of an application of the optimal control theory in 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 of patient-039 and patient-002 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-039 this probability was $\omega = 0.01$ (1%) and for patient-002 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 for patient-039 was 32,473 copies/ml and patient-002 was 407,000 copies/ml. While the viral load decrease for patient-039, it (slowly) increases for patient-002 (more than 500,000 copies/ml).

Table I - Parameters fitted, patient-039.

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-039.

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

Table III - Parameters fitted, patient-002.

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-002.

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

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