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MATHEMATICAL MODEL FOR AN EFFECTIVE MANAGEMENT OF HIV INFECTION WITH A VIEW OF WINDOW PERIOD

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Abstract:In this study, a mathematical model of Human Immunodeficiency Virus with a view of infection at window period is studied. The model was characterized through optimal control approach and it was established that minimum medications could be used to maximize uninfected CD4+T cells concentration, while the efficacy of drug therapy could be used to prevent the new cells from being infected in the human body system . Finally Gauss Siedel-like finite difference method was employed to carry out the numerical simulation using real life data to validate the reality of the model studied.

Keywords*: Mathematical Model, Window period, Infection, Optimal control, drug therapy*

1. INTRODUCTION

Human Immunodeficiency Virus (HIV) is a deadly virus which attacks the body's immune system, specifically the CD4+T cells resulting into an illness that attacks the body ability to resist infections and usually causes death known as Acquired Immunodeficiency Syndrome (AIDS). The virus can be transmitted by Heterosexual contact, mother-to-child transmission, blood transfusion, homosexual contact, sharing of sharp objects like blades, clippers, unsterilized injection, needles, manicuring and pedicuring etc. Inability of people with HIV to get treatment develops into three stages known as an Acute HIV infection, Clinical latency and Acquired immunodeficiency sydrome. The time between exposure to infection and the accurate test result is known as Window Period. That is a period when an infected and very infectious individual with HIV test negative. It can be categorize into the Window Period of a fourth generational antigen/antibody and a window period after exposure, [1], [2], [14], [18].
Several studies have been carried out on HIV by Biologists and Mathematicians aimed at gaining deeper understanding into the transmission of the HIV pathogenesis infection. [5]" worked on a differential equation model of HIV infection of CD4+T cells. [12]" obtained a model which allows an infected individual to progress from late stages of development to a less advance stage of infection. [8]" examined the optimal control of combined therapy in a single strain HIV-1 model. [11]" investigated the optimal methodology for administering anti-viral medication therapies. [10]" evaluated optimal control of treatment in a basic virus infection model. [16]" analyzed the recruitment effects of HIV susceptible and infected individuals. [7]" worked on treatment control of TB-HIV co-infection model. [3]" analysed the approximate solutions of HIV-I model with arbitrary order. [9]" studied the degree of HIV- I during typical course of infection. [15]" looked at the Mathematical model with control variables following the logistic growth function. [17]" conducted an investigation into vivo Dynamics of HIV infection with the influence of Cytotoxic T Lymphocyte cells. [4]" studied the modelling and optimal control of HIV/AIDS prevention through prEP by determined the prEP strategy that satisfies the optimal control associated with prEP. [13]" modelled HIV dynamics under combined anti-retroviral treatment. [6]" carried out research on the effect of HIV-1 infection and anti-retroviral drug therapy in patient. However, Little or less have been done as regards HIV infection at window Period, in this work, the interest is on mathematical model of effective management of HIV infection at window period using optimal control approach.

2. MODEL FORMULATION

In this section, the HIV model is formulated at window period. The logistic growth function is assumed to consists of the constant recruitment numbers of new and dead uninfected cells. And probably because of overcrowding of free virions or protective measures being used by the HIV patient the rate of infection of $CD4^+T$ cells by free virions is saturated with the view of window period.
The Model is partitioned into four compartments with total population of N(t). Let T(t), I(t), $V_1(t)$, and $V_2(t)$ respectively be the concentration of uninfected CD4+T/ white blood cells, infected cells, infected persons not yet detected at window period and persons who have been confirmed to be HIV positive.

Let $\pi = rT\left(1 - \frac{T}{T_{max}}\right)$ denotes the rate of recruitment of uninfected white blood cell and $\xi = \frac{\beta(V_1+V_2)T}{1+\alpha(V_1+V_2)}$ denotes the force of infection, [9] during and after window period. The transition of disease are represented by the flow diagram in Figure 1 followed by the description of the parameters in Table 1.

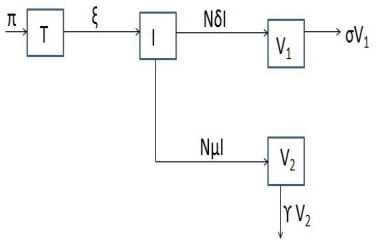

Figure 1: Flow diagram for the spread of the HIV

Table 1: Definition of parameters and values

Parameters	Description	value
$T(t)$	Uninfected $CD4^+T$ cells at time t	1000
$I(t)$	Infected $CD4^+T$ cells	400
$V_1(t)$	HIV of infected persons not yet detected at window period	80
$V_2(t)$	Total free HIV at time t	80
r	Rate of growth	0.03
T_{max}	Maximum $CD4^+T$ cells in the body	1500
β	Infection rate of $CD4^+T$ by virus	0.00024
α	The saturation factor	0.001
μ	Disappearance of infected cells per capital	0.2
δ	Disappearance of infected cells at window period per capital	0.2
	Loss of free virus for the population of the free HIV	2.4
σ	Loss of virus for the population of persons infected but not yet detected	2.4
U_1	Efficacy of drug therapy in blocking the infection of new cells	
U_2	Efficacy of drug therapy in inhibiting the production of virus	
N	Average number of virus particles produce by an infected $CD4^+T$	500
r_1	Weight function of drug therapy (1)	200
r_2	Weight function of drug therapy (2)	250
π, ξ	Recruitment rate, Force of infection rate	

Some of the Parameter values were from [9]. The model is thus presented as;

$$\frac{dT}{dt} = rT\left(1 - \frac{T}{T_{max}}\right) - \frac{\beta(V_1+V_2)T}{1+\alpha(V_1+V_2)} \quad T(0) = T_0 \geq 0 \quad (1)$$

$$\frac{dI}{dt} = \frac{\beta(V_1+V_2)T}{1+\alpha(V_1+V_2)} - N(\delta+\mu)I \quad I(0) = I_0 \geq 0 \quad (2)$$

$$\frac{dV_1}{dt} = N\delta I - \sigma V_1 \quad V_1(0) = V_0 \geq 0 \quad (3)$$

$$\frac{dV_2}{dt} = N\mu I - \gamma V_2 \quad V_2(0) = V_0 \geq 0 \quad (4)$$

Introducing controls $U_1(t)$ and $U_2(t)$ which denotes the efficacy of drug therapy in blocking the infection of new cells and the efficacy of drug therapy in inhibiting the production of virus respectively. Equations(1 - 4) becomes,

$$\frac{dT}{dt} = rT\left(1 - \frac{T}{T_{max}}\right) - \frac{(1-U_1)\beta(V_1+V_2)T}{1+\alpha(V_1+V_2)}, T(0) = T_0 \geq 0 \quad \ldots\ldots\ldots(5)$$

$$\frac{dI}{dt} = \frac{(1-U_1)\beta(V_1+V_2)T}{1+\alpha(V_1+V_2)} - N(\delta+\mu)I \quad I(0) = I_0 \geq 0 \quad \ldots\ldots..(6)$$

$$\frac{dV_1}{dt} = (1-U_2)N\delta I - \sigma V_1 \quad V_1(0) = V_0 \geq 0 \quad \ldots(7)$$

$$\frac{dV_2}{dt} = (1-U_2)N\mu I - \gamma V_2 \quad V_2(0) = V_0 \geq 0 \quad \ldots(8)$$

3. CHARACTERIZATION OF THE MODEL

The optimal control problem is formulated as;
Maximize

$$J(U_1,U_2) = \int_0^{tf}\left(T(t) - \left(\frac{r_1}{2}U_1^2 + \frac{r_2}{2}U_2^2\right)\right)dt \quad ,$$
$$(U_i(t) \in U), 0 \leq t \leq t_f, 0 \leq U_i \leq 1, i = 1,2$$
$\ldots\ldots..(9)$

Subject to (5)-(8), where positive constants r_1 and r_2 are relative weight attached to the drug therapies. The main interest is to maximize (9) by increasing the population of the uninfected $CD4^+T$ cells, reducing the viral load and reducing the cost of treatment as

well. An optimal control pair (U_1^*, U_2^*) is obtained such that

$$J(U_1^*(t), U_2^*(t)) = \max_{(U_1^*(t), U_2^*(t)) \in U} J(U_1(t), U_2(t)) \quad \ldots.(10)$$

Applying the Pontryagin's maximum principle, the Hamiltonian function associated with the system (5) - (8) is defined by

$$H(t, U, T, I, V_1, V_2, \lambda_1, \lambda_2, \lambda_3, \lambda_4) = L(T, U, t) + \lambda_1 \frac{dT(t)}{dt} + \lambda_2 \frac{dI(t)}{dt} + \lambda_3 \frac{dV_1(t)}{dt} + \lambda_4 \frac{dV_2(t)}{dt}$$

$$= T - \left(\frac{r_1}{2}\right) U_1^2(t) + \left(\frac{r_2}{2}\right) U_2^2(t) + \lambda_1 \left[rT\left(1 - \frac{T}{T_{max}}\right) - \frac{(1-U_1)\beta(V_1+V_2)T}{1+\alpha(V_1+V_2)}\right] + .$$

$$\lambda_2 \left[\frac{(1-U_1)\beta(V_1+V_2)T}{1+\alpha(V_1+V_2)} - N(\delta+\mu)I\right]$$

$$+\lambda_3[(1-U_2)N\delta I - \sigma V_1] + \lambda_4[(1-U_2)N\mu I - \gamma V_2] \quad \ldots.(11)$$

Theorem: Let $T^*(t), I^*(t), V_1^*(t)$, and $V_2^*(t)$ represents the optimal state solutions while U_1^*, U_2^* represents the associated optimal controls for the problem (5-8). Then there exist adjoint variables $\lambda_1, \lambda_2, \lambda_3$ and λ_4 that satisfies the adjoint conditions:

$$\frac{d\lambda_1}{dt} = -1 - \lambda_1\left[r\left(1 - \frac{2T}{T_{max}}\right) - \lambda_1 \frac{(1-U_1)\beta(V_1+V_2)}{1+\alpha(V_1+V_2)} - \lambda_2 \frac{(1-U_1)\beta(V_1+V_2)}{1+\alpha(V_1+V_2)}\right] \quad \ldots.(12)$$

$$\frac{d\lambda_2}{dt} = \lambda_2 N(\delta+\mu) - \lambda_3(1-U_1)N\delta - \lambda_4(1-U_1)N\mu \quad \ldots..(13)$$

$$\frac{d\lambda_3}{dt} = \lambda_1(1-U_1)\beta V_2 T\left(1 - \frac{\alpha(V_1+V_2)}{1+\alpha(V_1+V_2)}\right) - \lambda_2(1-U_1)\beta V_2 T\left(1 - \frac{\alpha(V_1+V_2)}{1+\alpha(V_1+V_2)}\right) + \lambda_3\sigma \quad \ldots.(14)$$

$$\frac{d\lambda_4}{dt} = \lambda_1(1-U_1)\beta V_1 T\left(1 - \frac{\alpha(V_1+V_2)}{1+\alpha(V_1+V_2)}\right) - \lambda_2(1-U_1)\beta V_1 T\left(1 - \frac{\alpha(V_1+V_2)}{1+\alpha(V_1+V_2)}\right) + \lambda_4\sigma \quad \ldots.(15)$$

Proof

The Hamiltonian is differentiated with respect to λ_1, λ_2, λ_3, λ_4, to obtain the adjoint equations as

$$\frac{d\lambda_1}{dt} = -\frac{\partial H}{\partial T} = -1 - \lambda_1\left[r\left(1 - \frac{2T}{T_{max}}\right) - \lambda_1 \frac{(1-U_1)\beta(V_1+V_2)}{1+\alpha(V_1+V_2)} - \lambda_2 \frac{(1-U_1)\beta(V_1+V_2)}{1+\alpha(V_1+V_2)}\right]$$

$$\frac{d\lambda_2}{dt} = -\frac{\partial H}{\partial I} = \lambda_2 N(\delta+\mu) - \lambda_3(1-U_1)N\delta - \lambda_4(1-U_1)N\mu$$

$$\frac{d\lambda_3}{dt} = -\frac{\partial H}{\partial V_1} = \lambda_1(1-U_1)\beta V_2 T\left(1 - \frac{\alpha(V_1+V_2)}{1+\alpha(V_1+V_2)}\right) - \lambda_2(1-U_1)\beta V_2 T\left(1 - \frac{\alpha(V_1+V_2)}{1+\alpha(V_1+V_2)}\right) + \lambda_3\sigma$$

$$\frac{d\lambda_4}{dt} = -\frac{\partial H}{\partial V_2} = \lambda_1(1-U_1)\beta V_1 T\left(1 - \frac{\alpha(V_1+V_2)}{1+\alpha(V_1+V_2)}\right) - \lambda_2(1-U_1)\beta V_1 T\left(1 - \frac{\alpha(V_1+V_2)}{1+\alpha(V_1+V_2)}\right) + \lambda_4\sigma$$

And with respect to U_1 and U_2 as:

$$\frac{\partial H}{\partial U_1} = U_1 r_1 + \lambda_1 \frac{\beta(V_1+V_2)}{1+\alpha(V_1+V_2)} - \lambda_2 \frac{\beta(V_1+V_2)}{1+\alpha(V_1+V_2)}$$

$$\frac{\partial H}{\partial U_2} = U_2 r_2 - \lambda_3 N\delta I - \lambda_4 N\mu I$$

Hence, the optimal controls becomes

$$U_1^* = \min\left(\max\left(\frac{\lambda_1(t) - \lambda_2(t)\beta(V_2^* + V_2^*)T}{r_1(1+\alpha(V_1^*+V_2^*))}, 0\right), 1\right) \quad \ldots.(16)$$

$$U_2^* = \min\left(\max\left(\frac{\lambda_3(t)[-N\delta I^*(t)] - [N\mu I^*]\lambda_4(t)}{r_2}, 0\right), 1\right) \quad (17)$$

Equations (16) and (17) is incoporated into systems (5) –(15) and the resulting optimal system was solved numerically.

4. NUMERICAL SIMULATION

In this section Gauss-Siedel-Like implicit finite difference method was employed to solve the optimality system using the data presented on Table 1. The state system wass solved with forward difference in time and the adjoint system was solved with the backward difference in time using MATLAB Mathematical software. And to validate the effectiveness of the studied model numerical simulations was carried out for a period of 100 days based on the disease progression before and after the introduction of treatments. Some of the parameter values were from [9] and contained in Table 1. The results were presented in Tables 2 – 3 and Figures 2-7.

5 RESULTS AND DISCUSSION

From the results obtained it was observed that with the use of control (drugs therapy), HIV viral load reduces drastically and patients with HIV positive can relatively enjoy good health with long life expectancy. Figure 2 shows that without control the number of uninfected cells reduces drastically while the concentration of cells is maintained from the beginning to the end of the period with treatments. Figure 3 indicates that the number of infected cells reduces rapidly from the beginning to the end while the infected cells grows at the beginning and become more stable toward the end of the period without treatment.

Figure 4 and 5 shows that at window period the viral load increases without treatments while no increase in the virus is recorded with treatments.

Figures 6 and 7 shows that the optimality controls $U_1(t)$ and $U_2(t)$ (treatments) are required to stop new infection of cells and guide against viral creation with less side effects.

Table 2: Effect of zero % function immune system

Time(Days)	$CD4^+T$	Viral load
0	1000	0.001
2	985	0.5
4	934	307
6	748	526953
10	602	1001723
20	183	2136528
40	0	3534682
50	0	4111373

Table 3: Effect of anti-HIV immune response

boundary condition	Viral load with control effect
0	291193
0.2	233041
0.4	174889
0.6	116737
0.8	58586
1	434

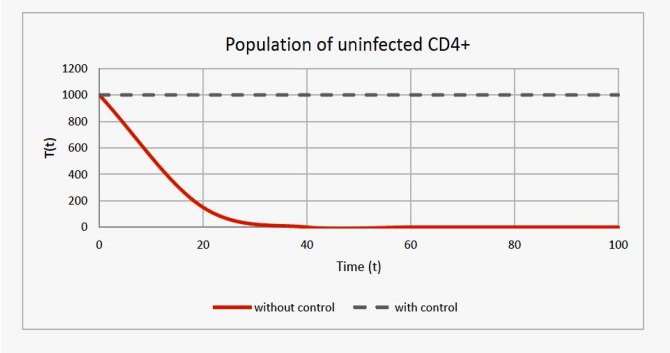

Figure 2: Population of Uninfected CD4+T cells

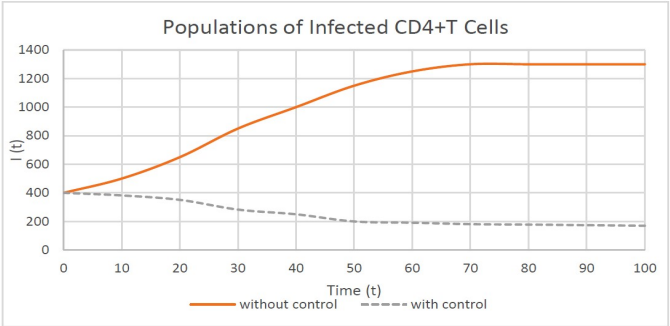

Figure 3: Population of Infected CD4+T cells

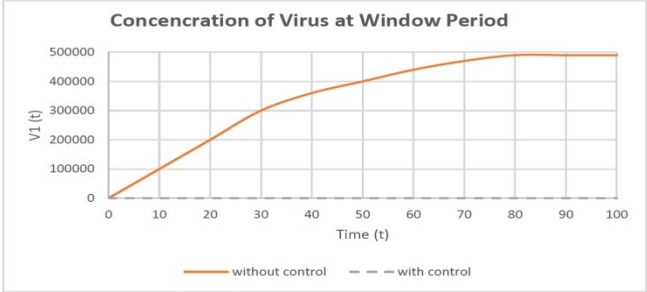

Figure 4: Concentration of Virus at Window Period

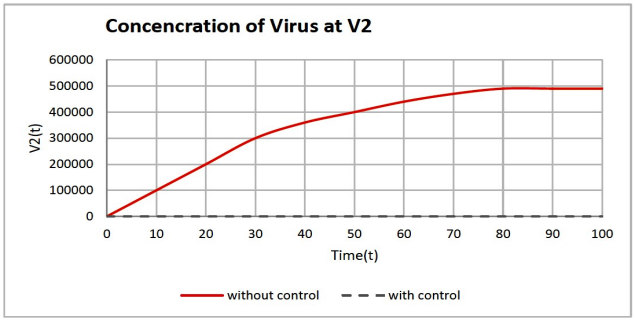

Figure 5: Concentration of Free HIV at V2

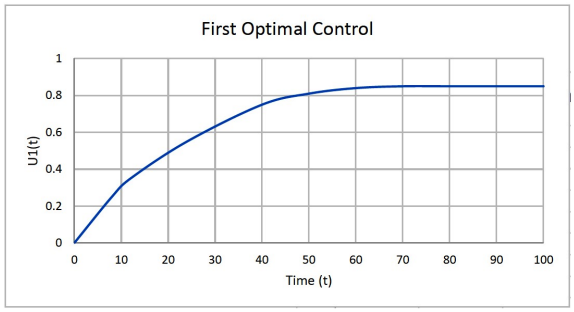

Figure 6: Optimal control I

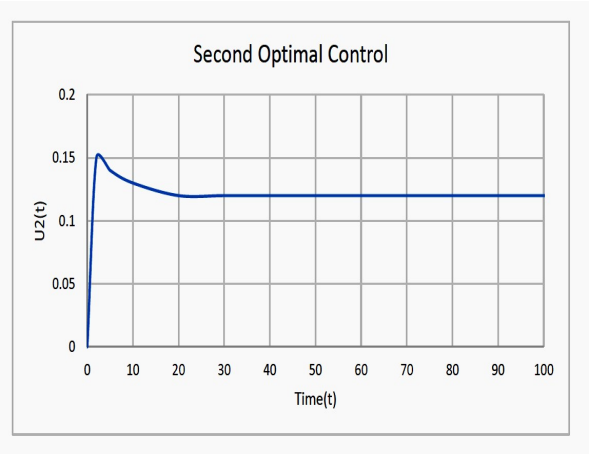

Figure 7: Optimal control II

6. CONCLUSION

This study presented a mathematical model with controls in order to effectively manage HIV with a view of window period. Optimal control approach was used to optimize the concentration of virus in the body by maximize the number of uninfected CD4+T cells and minimize the virus using minimum medication therapies. The model were finally solved numerically to validate the effectiveness of the model.

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