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МАТЕМАТИЧЕСКАЯ МОДЕЛЬ ДИНАМИКИ РАСПРОСТРАНЕНИЯ ВИЧ-ИНФЕКЦИИ БЕЗ ЛЕЧЕНИЯ

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В данной статье рассматривается математическое и численное моделирование иммунной системы в процессе заболевания без лечения. На сегодняшний день много научных работ посвящено изученнию этой проблемы. Тем не менее, вирус ВИЧ-инфекции обладает достаточно высокой устойчивостью и не существует по мнению многих авторов эффективных лекарств, способных вылечить от данного вируса, так как ВИЧ обладает способностью мутироваться и размножаться в присутствии химических препаратов, которые предназначены для его лечения. Математические модели, используемые в данной статье имеют исследовательский характер. Предлагаемые математические модели позволяют получить описание динамики ВИЧ-инфекции, дают понимание механизма прогрессии заболевания СПИДом. Результаты проведенного численного решения системы дифференциальных уравнений, в данной работе показывают что: болезнь развивается и при малых концентрациях вируса; определённая стабильность уровня вируса не зависит от начальной концетрации инвазии.При отсутствии лечения,при воздействии между вирусом и $CD4^+T$ клетками, вызываемый иммунный ответ должен быть значительно больше, чем скорость размножения вируса в крови; коэффициент скорости размножения неинфицированных $CD4^+T$ клеток должен быть строго больше, чем коэффициент скорости гибели неинфицированных клеток $CD4^+T$

Ключевые слова: МАТЕМАТИЧЕСКОЕ МОДЕЛИРОВАНИЕ, ВЗАИМОДЕЙСТВИЕ, $CD4^+T$ -КЛЕТКИ, ВИЧ, ЛЕКАРСТВО, ИММУНИТЕТ, ИНФЕКЦИИ, СОПРОТИВЛЕНИЕ, РЕМИССИЯ, БОЛЕЗНЬ

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Mathematical and Computer Sciences

MATHEMATICAL MODEL OF THE DYNAMICS OF HIV INFECTION WITHOUT TREATMENT

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This article discusses the mathematical and numerical modeling of the immune system of the course of HIV infection without treatment. Presently a significant number of scientific papers are devoted to the study of this problem. However, HIV infection is highly volatile and there is no effective drug, in that HIV has the ability to mutate and reproduce itself in the presence of chemical substances that are meant to inhibit or destroy it. The mathematical models used in this paper are conceptual and exploratory in nature. The proposed mathematical model allow us to obtain a complete description of the dynamics of HIV infection, and also an understanding of the progression to AIDS.
Thus, the results of the numerical solution of differential equations in this work show that: the disease develops, and at low concentration of the virus, a certain level of stability does not depend on the initial concentration of infestation. In the absence of treatment, for interesting competition between virus and $CD4^+T$ the loss of virus caused by immune response should be strictly greater than the rate of multiplication of the virus in the blood; the reproduction rate of the uninfected $CD4^+T$ cells should be stricly greater than the mortality rate of the uninfected $CD4^+T$ cells.

Keywords: MATHEMATICAL MODELING, INTERACTION, $CD4^+T$ -CELLS, HIV, DRUG, IMMUNITY, INFECTION, RESISTANCE, REMISSION, DISEASE

1. INTRODUCTION

HIV infection is a slowly progresive disease [1] caused by the human immunodeficiency virus (HIV) [2,3].In the literature are mathematical models that describe the complex dynamics of the reaction of the immune system with the viruses present in it [4,5,6,7,8,]. These include infections, replications and mutations of viruses, antigen recognitions, activations and proliferations of lymphocytes, encounters and interactions of virions and lymphocytes.When a body is infected with HIV, the response against the pathogen gradually disrupts the immune system as the lymphocytes cells are infectecd and this makes the immune system not to function to its optimum capacity. However, most of the models make a simplifying assumption concerning the location of the infection (blood). The reason is to ensure that the equations are all scaled appropriately and there is no flow to or from outside compartments [9]. On the contrary, other body compartments also play important roles in disease progression. It has been shown that damage in the lymphoid tissue as a consequence of an infection leads to limited construction of T cells after antiretroviral therapy [10]. Most interesting in these models was the behaviour of the uninfected $CD4^{+}T$ clls in the course of the disease.This variable rapidly declines within the first few days after infection has taken place. This steep decline was ascribed to a sudden increase in the prevalence of apoptosis. Management of diseases arising from HIV infection includes the use of antiretroviral therapy. There are works that attempt to predict effects of these drugs on the disease [11,12,13]. However, the HIV disease is highly volatile and there are no effective drugs [13,14], in that HIV has the ability to mutate, evolve and reproduce itself in the presence of chemical substances that are meant to inhibit or destroy it. In this situation the virus, makes copies of itself that are not sensitive to the chemical substance (resistance effect) [12,15]. HIV undergoes a continual process of evolution after primary infection, and it seems that the balance between evolutionary pressures on HIV and the success of the virus population in adapting to these pressures are

the major determinants of the rate of disease progression. In the body as a whole, this ongoing struggle is reflected in the level of viral load and the $CD4^{+}T$ cell count, but within the virus population this struggle is evident in changes in the genetic characteristics of viruses [5]. Another problem is that all chemical substances capable of destroying the HIV virus are highly toxic and harmful even though they are meant to reduce infection in the body[16, 17].

In this article, we consider the well-known model of Webb and Kirschner [15], which simulates the human immune system; however, attention is given to a more detailed study of the behaviour at large time intervals. The problem of investigating the stability of the computational scheme to the initial data is considered.

The ability of an organism to defend itself against pathogens and toxins and to avoid infections and diseases is called immunity. This is basically provided by the immune system, which is composed primarily of individual cells spread throughout the body, rather than forming into organs. They are two broad branches of the immune system; innate and adaptive immunity. Adaptive immunity otherwise known as the specific immunity provides pathogen- specific immunity in vertebrates. It is basically composed of T-lymphocyte and B-lymphocyte cells. According to the composition of the adaptive system, it can be further divided into two categories; humoral immunity and cell-mediated immunity. The adaptive immunity is very special as it is present only in vertebrates, and is able to recognize different antigens in a very precise way[18].

2. THE CLONAL SELECTION THEORY

In response to specific antegens invading the body, the clonal selection theory has been used to explain the functions of cells (lymphocytes) of the immune system. This concept which was introduced by an Australian doctor, Frank Burnet in 1957 in an attempt to explain the formation of diversity of antibodies during initiation of the immune system, has become widely accepted model for how the immune system responds to infection, and how cirtain types

of *B* and *T* lymphocytes are selected for destruction of specific antigen [9]. The *B* and *T* lymphocytes are cells that originate from a common limphoid progenitor in the bone marrow. The theory is an explanation of the mechanism of antibody specifity [9].

Each lymphocyte has a unique receptor (antibody) on its surface. These antibodies are proteins that bind with harmful foreign bodies to neutralize them. If the cells receptors matches with that of the antigens then they bind together and the antigen is destroyed. Clonal selection is part of the primary immune response. A primary immune response takes place when a foreign substance enters the body and the body evokes an immune response in order to get rid of the substance. While traveling through the body the antigen will meet the lymphocyte that has on its body the receptor that matches that of the antigen.

A chemical change is triggered as the lymphocyte and the antigen connect. Being activated, the lymphocyte is caused to rapidly proliferate and create many clones of itself. The body will keep multiplying prolific amounts of the lymphocyte cells in order to inhibit the antigen and prevent infection.

The lymphocyte in the course of proliferation create two types of cells. These are the effector cells and the memory cells. Created for immediate immunological defence, the effector or B and T lymphocytes are short lived cells. However, the memory cells which are not active during the primary immune response play a very important role during the secondary immue response.

Effector cells are cells that are created to perform a specific function in response to a particular stimulus. Effector B cells are called plasma cells and secrete antibodies. Effector T cells are divided into helper T cells and Cytotoxic T cells. Helper T cells produce cytokynes. These are protein molecules produced when an antigen is detected to aid in cell to cell communication during immune response. Cytotoxic T cells destroy the cells that are infected or cells that have been damaged by the antigen in question. The memory cells are composed of

some of the B and T cells created.They retain knowledge of the particular antigen. If that same antigen enters the body again, a secondary response is triggered and the action is very swift. A schematic diagram of an immune response is shown below.

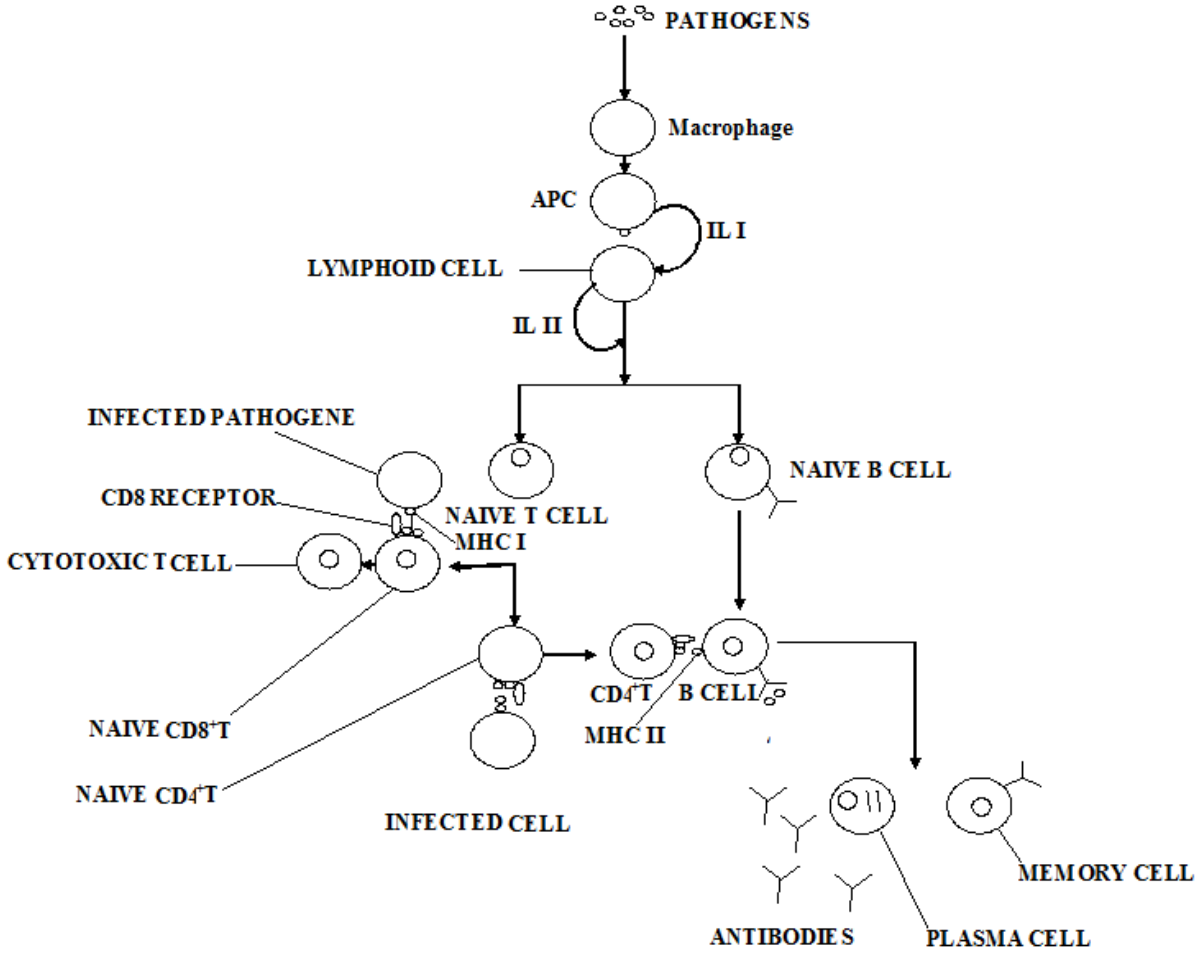


Figure 1: Schematic diagram of an immune response

3. GENERAL PRESENTATION OF HIV INFECTION

HIV Human immunodeficiency virus (HIV) infection has now spread to every country in the world. According to estimates by WHO and UNAIDS, 35million people were living with HIV globally at the end of 2013. That same year, some 2.1 million people became newly infected, and 1.5 million died of AIDS-related causes [14, 19].The scourge of HIV has been particularly devastating in sub-Saharan Africa and South Africa, but infection rates in other

countries remain high. In the United States, approximately 1 million people are currently infected [20].

The course of HIV infection follows a general partten, eventhough they can be variation from patient to patient [6, 19]. The central component orchestrating the generation of the immune response $CD4^+T$ helper cells is the target of HIV. Macrophages and the dendritic cells which are also involve in the generation of specific immune response are also infected by HIV. In the first three to six weeks after infection, the viral load increases exponentially [5, 6, 14]. After one to two weeks following infection, the cellular immune response kicks in , there after the humoral response for between four to eight weeks. Commonly referred to as the primary infection or the initial phase, the early phase shares many similarities with acute infections. The viral load decreases and settles to a more or less constant value for several years with the onset of the cellular immune response. This asymptomatic or chronic phase is referred to as the second phase. During this time, it may appear as if the virus is resting in this phase, but there is a rapid turnover of infected cells and it is the cellular and humoral immune response that keep the viral loads to a constant level. This level is referred to as the set point viral load [5]. The infection remains asymptomatic for years before the virus within host sufficiently increases [21] and the population of host $CD4^+T$ cells decreases because they are the primary target of the virus. The third stage which is characterized by a dramatic loss of $CD4^+T$ cells and a strong increase in the viral load leads to the development of AIDS. The onset of AIDS has been clinically defined as the point at which the $CD4^+T$ cells count in the blood falls below 200 per μl. Disease progression is associated with the evolution of specific variants that are more virulent and pathogenic. To significantly suppress viral replication and to delay disease progression in many patients antiretroviral drug therapy has successfully been used. The mechenism by which these drugs act is two fold: reverse transcriptase inhibitors interfer with the process of reverse transcription

and prevent the virus from infecting a cell; protease inhibitors prevent the assembly of new infectious virus by an infected cell. However, the infected cell remains unaffected and provide a viral reservoir because HIV integrates into the host genome. While most productively infected cells have a relatively short lifspan, many cells are latently infected and are long lived. Thus virus eradication by drug therapy is not possible during the life time of the host. A scematic diagram of HIV live circle is shown in figure 2.

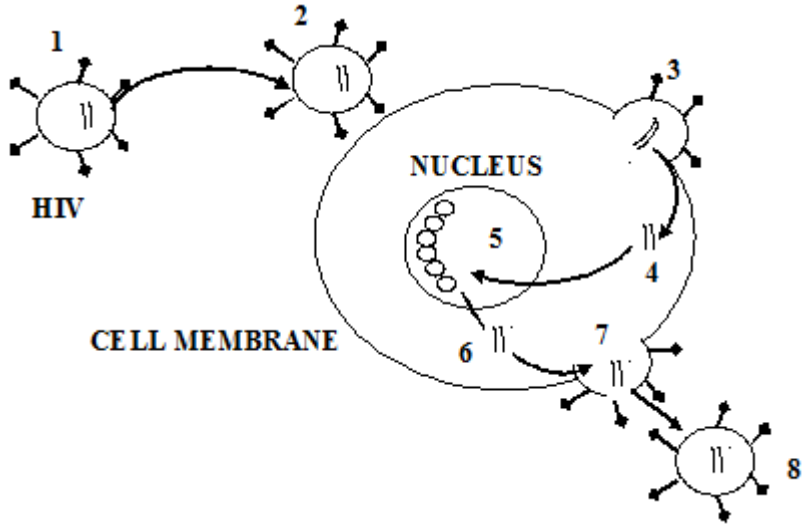


Figure 2.HIV life cycle

However, they have been new insight into the dynamics of this population during HIV infection [3, 15, 21]. These studies identified the turnover rates and life spans of both $CD4^+T$ cells and virus by measuring their rate changes in patients subjected to strong antiviral agents. The simulations indicate that to preclude resistance, antiretroviral drugs must be strong enough and act fast enough to drive viral population below a threshold level. Below the threshold level, remission takes place. These studies have led to a new conceptual view of the HIV infected immune system as a hyper-dynamic process [15]. The model we present here derives from [15] in that it assumes certain terms in the differential equations representing population interaction.

4. CYTOTOXIC T LYMPHOCYTE (CTL) FACTOR IN

REMISSION.

As mentioned above, while successful therapy can suppress virus load, complete virus eradication is not possible under normal circumstaces because of long-lived latent infected cells. If antiretroviral therapy is strong enough and act fast enough to drive the viral load below a threshold level, remission occurs. It is therefore necessary to consider factors that could result in long term immune - mediated control of HIV in the absence of drugs.

During immune response, cytotoxic T cell (CTL) play an important pathogenic role. They are in particular effective at fighting HIV replication [22]. HIV specific helper cells are targeted at the dominant viral variant and their emergence is associated with a rapid fall in viral load before the development of an antibody response. [23]

In the absence of helper T - cells, which slowly decreases during HIV disease, the cytotoxic T cells are unable to keepup with the increasig diverse population of HIV inside the body. As HIV mutates in the body, due to several factors including pressure from antiretroviral medication, these cytotoxic T cells become increasinly irrelevant.

Mathematical models have identified two parameters that influence the dynamics between HIV and specific CTL responses. In the first instnce, CTL activation / proliferation in response to antigen is important for limiting virus load [5] and this has been shown in persistent HIV infection [24]. However, in addition, virus clearance or efficient long term CTL - mediated control also requires antigen independent long - term persistence of memory cytotoxic T lymphocyte pressure (CTLp) [1]. This ensures that immune pressure is maintained on the declining virus population and this drives the virus extinct and remission is maintained. If CTLp are short - lived in the absence of antigen, they will decline after virus load has been reduced to a low level following CD8 - mediated activity. This enables the virus to regrow, resulting in an equilibrium describing persistent virus infection in the presence of anongoing CTL response,

maintained by the persisting antigen. Hence, antigen - independent persistence of memory CTLp is required for clearance of infection.

5. THE MODEL

We consider the model of the dynamics of infection in the absence of treatment, and the use of several drugs of intensive care . The model of interaction of the immune system with HIV are described in the following state variables:

T - concentration of uninfected $CD4^+T$ cells;

T_s - the concentration of $CD4^+T$ cells infected with HIV;

V_s - concentration of HIV virus.

We note that the model describes the processes in the blood, the replication of the virus and mortality of cells occuring in the limphatic system, as a result the model describes the dynamics observed in the blood variables rather than operating characteristics of infection.

The derivatives with respect to time of these variables satisfy the system of differential equations:

$$\frac{dT(t)}{dt} = S(t) - mT(t) + l_1(t)T(t)V_S(t) - k_sV_S(t)T(t) \qquad (1)$$

$$\frac{dT_s(t)}{dt} = k_sV_s(t)T(t) - m_1T_s(t) - l_2(t)T_s(t)V_s(t) \qquad (2)$$

$$\frac{dV_S(t)}{dt} = l_3T_s(t)V_s(t) - k_vT(t)V_s(t) - G_s(t) \qquad (3)$$

The system of equation has the initial conditions:

$T(0) = 600\,units/mm^3;\ T_S(0) = 1unit/mm^3;\ V_S(0) = 10units/mm^3.$

The expressions on the right sides of equations (1)-(3) indicate the following:In equation (1), $S(t) = S_1 - \frac{S_2V_S(t)}{B_S + V_S(t)}$ is a function, which represents the source of, uninfected $CD4^+T$ - cells from the thymus and other compartments. Here S_1 and S_2 are constants, B_s is a saturation constant (saturation ratios

introduced into the model to adjust the parameters of growth under great changes in populations during the course of infection and treatment). m - is the mortality rate of uninfected $CD4^+T$ - cells (birth rate = $\frac{1}{m}$); $l_1(t)T(t)V_S(t)$ where $l_1(t)=\frac{l_1}{C+V_s(t)}$ and C describes the proliferation rate of $CD4^+T$ – cells in the plasma eliciting an immune response, due to the effect of stimulating the immune system antigen; this explains the increased turnover member of $CD4^+T$ – cells;

k_s - is the infection rate of $CD4^+T$ - cells by the virus.

In equation (2): $k_sV_s(t)T(t)$ - the growth rate of infected $CD4^+T$ - cells as the virus infects T - cells; $m_1T_s(t)$ – a loss due to mortality of the infected cells;

$l_2(t)T_s(t)V_s(t)$ where $l_2(t)=\frac{l_2}{C_i+V_s(t)}$ is a saturation coefficient) describes the death of infected cells owing to the presence of virus.

In equation (3): The virus population increases due to the term $l_3(t)T_S(t)V_s(t)$ where $l_3(t)=\frac{l_3}{C_I+V_s(t)}$ This term describes the increase in the population of virus in the blood. The dependence of this term on $T_S(t)$ takes into account the reduction in the proliferation of the virus in the plasma when the concentration of infected $CD4^+T$ cells in the plasma decreases. Since most virus enters into the plasma from the external source of lymph,the plasma viral population during the final stage of the infection grows rapidly; $k_V(t)T(t)V_S(t)$ - describes the destruction of the virus by the immune system; $G_S(t)=\frac{G_SV_S(t)}{B+V_S(t)}$ (where B isaturation constant) takes into account the entry of the virus from the lymphoid system. This term is a major contributor to the population of virus in the blood.

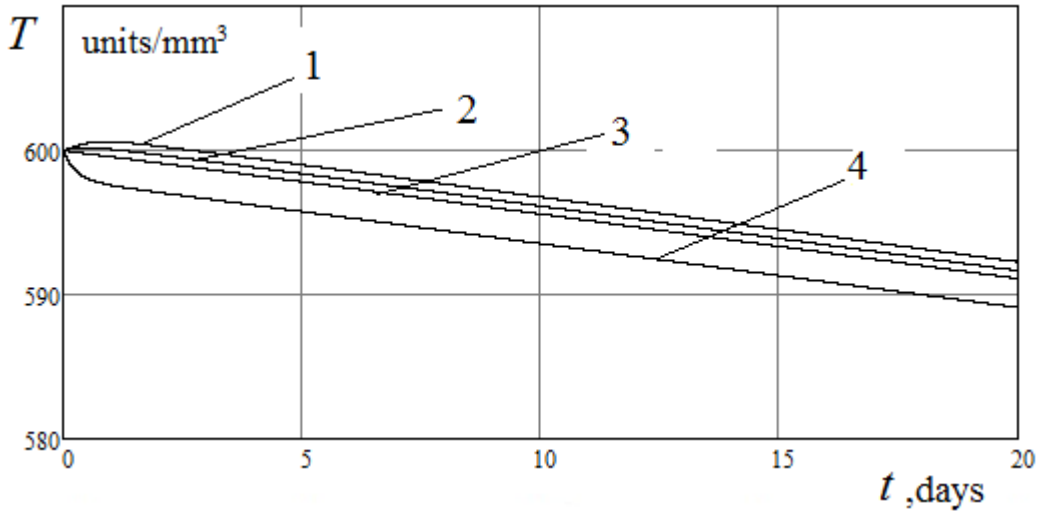
Table1: List of Constants and Parameters

Symbol	Description	Value
m	Mortality rate of uninfected $CD4^+T$ cells	$0.005/day$
m_1	Mortality rate of infected $CD4^+T$ cells	$0.25/day$
k_s	The rate at which $CD4^+T$ cells are infected by sensitive virus	$0.0005mm^3/day$
k_r	The rate at which $CD4^+T$ cells are affected by resistant virus	$0.0005mm^3/day$
k_v	Loss of virus caused by immune response	$0.0062mm^3/day$
l_1	The rate of reproduction of uninfected $CD4^+T$ cells	$0.025/day$
l_2	The rate of reproduction of infected $CD4^+T$ cells	$0.25/day$
l_3	The rate of reproduction of virus in the blood	$0.8/day$
G_s	External parameter of lymphoid sensitivity virus	$41.2mm^3/day$
G_r	External parameter oflymphoid resistivity virus	$41.2mm^3/day$
V_0	Threshold resistance	$0.5/mm^3$
q	The proportion of resistance virus obtained as a result of normal reproduction of virus	10^{-7}
C	Saturation ratio of uninfected $CD4^+T$ cells	$47.0/mm^3$
C_i	Saturation ratio of infected $CD4^+T$ cells	$47.0/mm^3$
B	Saturation ratio of external virus source	$2.0/mm^3$
B_s	Saturation ratio of $CD4^+T$ cell source	$13.8/mm^3$
S_1	Influx of $CD4^+T$ cells in the absence of virus	$4.0mm^3day$
S_2	Decrease of influx of $CD4^+T$ cells	$2.8mm^3day$
c_1	Treatment parameter inhibiting the rate of distribution of $CD4^+T$ cells by the virus	0.5
c_2	Treatment parameter inhibiting the rate of inflow	0.25
c_3	Treatment parameter, the maximum inhibition rate of inflow of the virus from an external source of lymphoid.	0.15

6. NUMERICAL SIMULATION AND ANALYSIS

Using MathCAD, we employed Runge Kuta method of order 4 to obtain our simulations. With the initial condions as given above, we investigate the influence of Vs(0) at the initial time. Figures 3a, b, and c show the results of numerical integration of the model equations (3.1) - (3.3), reflecting the course of infection in the absence of treatment.Our calculations with identical initial

conditions showed an exact match with the calculations of the authors in the model [15, 25]. This fact serves for us as check of correctness of our computing work with models from [15, 25]. Below are the results of our simulations.



3a) Graphical simulations of uninfected $CD4^{+}T$ cells against time for the equations (1-3)

In Figure 3a, b, and c the curves

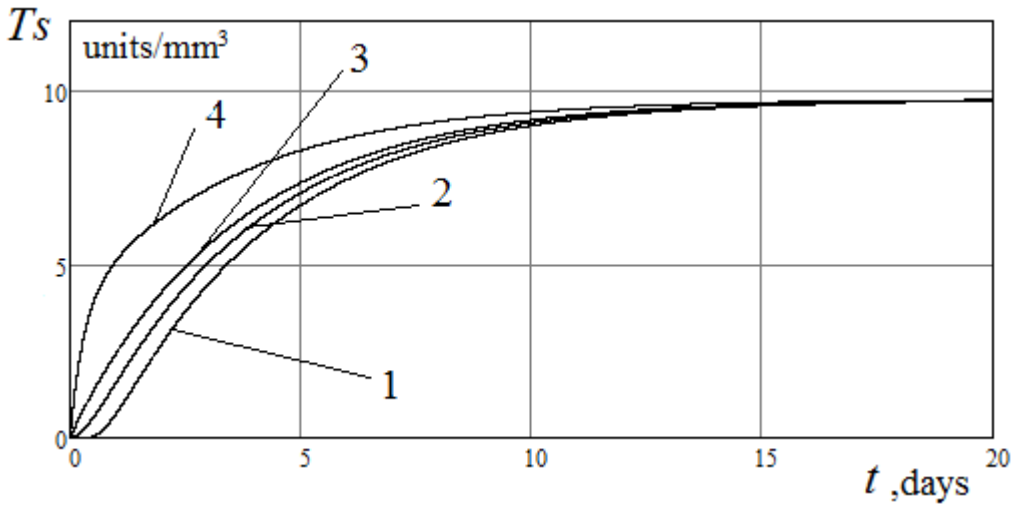
"1" represents the instance at which Vs(0) = 0.001

"2" represents the instance at which Vs(0) = 0.1

"3" represents the instance at which Vs(0) = 10

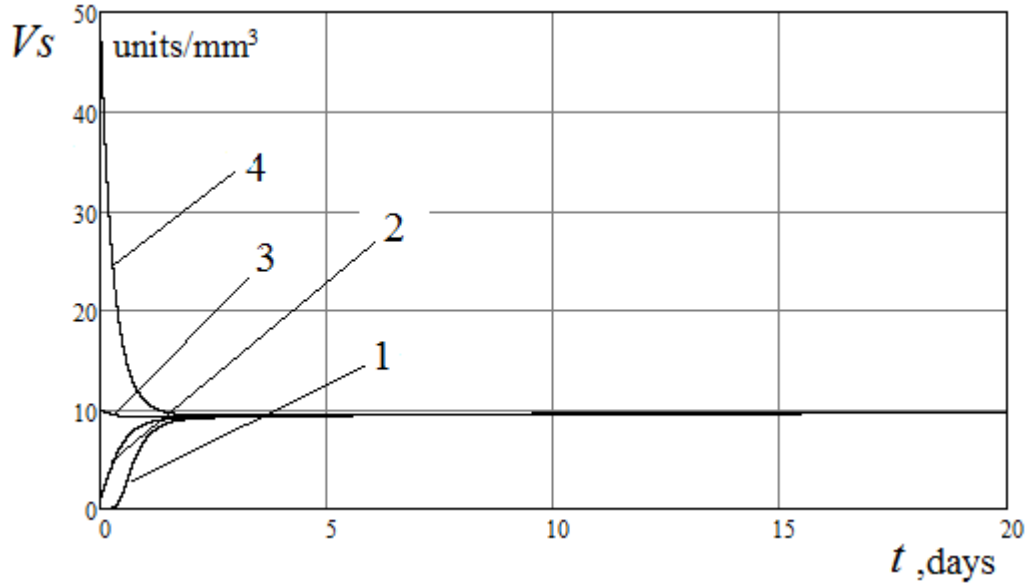
"4" represents the instance at which Vs(0) = 50

In figure 3a, all the curves show depletion of the T cells after acute viremia in the first few days following seroconversion. However, the figure shows that "4" progresses faster than "3", "2" and "1" respectively. Furthermore "4" shows a sharp decent before progressing steadily as *t*increases. In contrast however, "1" shows an increase turnover before making a downward steady decline. Thus Figure 3a shows that they could be remission in the immune system if V(0) is reduced considerably, that is making the external source very low since it is the main source of the viral load.



3b) Graphical simulations of infected T cells against time for the equations (1-3)

In Figure 3b we investigate the effects of Vs(0) on the infected T cells. The curves show that at the beginnig Ts(0) = Vs(0) = 0. Following primary viremia, the infected T cells progress in direct proportion with respect to time. The graphs however show that the infected T cells irrespective of initial viral load, grows and stabilizes at a certain point. Thus, curves 1, 2,3,and 4 converge after some numberof days and become steady as t increases.



3c) Graphical simulations of virus cells against time for the equations (1-3)

In Figure 3c the simulations "1" and "2" show the capacity of the virus to grow very quickly from extremly low levels. This means that 0 viral level is unstable since they is a large viral influx from the limph system . "4" shows that the immune system is able to respond and bring down the viral load. We observe that "1", "2" and "4" converge to "3" as t increases. This observation is consistent with recent clinical findings that disease prognoses is correlated to a set point of viral level established in each patient soon after initial viremia and viral levels and replication remain relatively stable after the set point.

As shown in [15], the curves of Fig. 3a,b,c are consistent with the results of clinical trials of HIV [26, 6, 27, 28]. After a period of acute infection during the first few weeks after seroconversion, the number of $CD4^+T$ cells gradually decline from approximately from $600-800 units/mm^3$ to zero over a period of time equal to approximately 10years (normal number of $CD4^+T$ cells varies in the range of $800-1000 units/mm^3$) [6, 28]. The decline of T is more rapid in the early stage of infection [27] (wherein infected $CD4^+T$ cells (Ts) constitute up to 4% of the total number of $CD4^+T$ cells T [26]). The life expectancy of infected $CD4^+T\ Ts$ cells is approximately equal to two days [18]. After an initial period of acute infection, virus increases from below $50 units/mm^3$ to $1000 units/mm^3$ or more during the variable course of infection with a sharp increase towards the end of the symptomatic phase [6].The life span of a virus outside the cell is about 7.2hrs [21].

In order to gain insight into the immune response to the replicating virus in the model, we herein examine some of the parameters. In this model, the rate of multiplication of the uninfected $CD4^+T-$ cells and virus is govern by the given differentials equations. The response by the immune system which brings about an interesting competition between the populations can be effective only if $k_V > l_3$ and $l_1 > m$. This means that the reproduction of the uninfected $CD4^+T$-cells (l_1)(the rate of reproduction of the virus) (l_3) becomes arbitrary large as the

concentration of the virus(uninfected $CD4^+T$ - cells) become large. We remark that in the model, it is not possible to totally eliminate the virus, that is to make the virus concentration go to zero. However, it is possible to reduce the virus concentration to a very low level. If $k_V = l_1 = 0.25$, periodic fluctuation of virus and the uninfected $CD4^+T$ - cells are observed; if $l_1 > k_V$, both populations execute damp oscilations and approach a steady state, in which it could be said that virus is present but prevented from multiplying by the $CD4^+T$ - cells, if $k_V < l_1$ both concentration execute oscilation of increasing amplitude. The term G_S which is the external inpute of virus from compartments outside the blood exerts a major influence upon the virus population. As the parameter G_S increases, the qualitative behaviour of the system changes. Thus, if the parameter G_s is kept very low the system can eradicate infection.

7. Conclusion

In this paper, we sought numerical solutions of a system of differential equations which explains the dynamics of the immune system and HIV in the absence of treatment. Our simulation results are in agrement with the results in typical HIV course. Eradication is made difficult because persistent infection is maintained in reservoirs including the lymph system. Furthermore, it was shown that as the disease develops, a certain level of stability does not depend on the initial concentration of infestation. Our simulation results show that if the viral load is kept very low remission will occur.

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