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Applying a Deterministic Mathematical Model to the HIV Virus Attacking the Cd4+T Cells: A Deliberation on the Interaction

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ABSTRACT The CD4+T cells are the most abundant white blood cells of the immune system which fight viruses. The CD4+T cells are used as indicators in the laboratory for the disease stage when HIV attacks these cells and thus weakens the immune system. A deterministic mathematical model of the HIV virus attacking the CD4+T cells was studied in terms of virions, uninfected cells and infected cells concentrations. The model assumed a non-responsive immune system to the virus over a short space of time. The study used three CD4+T cells initial states viz., 1000,500 and 300 cells per cubic mm.The default values used for the mathematical model parameters establish a reproductive ratio R_o which is less than one indicating a non-infectious system. The mathematical model graphical solution indicates that rate of decrease of the CD4+T cells are rapid at the initial stage of the 1000 virus and relatively slow rate of increase when the cells are below 300. Furthermore the system attains equilibrium at 500. At the equilibrium rate of change of the un-infected cells is zero but the infected cells decreases rapidly in time. The study recommends administration of drugs after CD4+T cell count measures below 500. The mathematical model estimation may help guide physicians and patients in deciding when to start treatment.

INTRODUCTION

The HIV virus enters the human body via several routes of transmission such as sexually, mother to child transmission and blood or body fluids contact. After entering the body the virus will look for specific cells more specifically CD4 cells because this forms the base of white blood cells for protection of the human body against infection. (Alberts et al. 1995) When the viral nuclei have matured they go out outside the CD4cell and destroy it. (Alberts et al.1995) The virus produces two billion viruses in one day hence the infected person will gradually have high viral load and low CD4 count. HIV virus reduces the quantity of CD4+T cells in the immune system. Elimination of these viruses must be performed timeously and at a very high rate. The virus increases exponentially and then there is a burst of viruses. The productively infected cell has a lifespan of one day. Daily production of infected cells $=5x10^4$virions per infected cells.With healthy immune system the number of CD4+T cells comprise 800 to 1200$\frac{cells}{mm^3}$.These cells fight against diseases. However HIV targets and kills these cells before the immune system has a time to respond or recognise the virus. Consequently the immune system is weakened. (Roy et al. 2013).

In South Africa HIV remains an epidemic crisis. The HSRC (2012) survey estimates the infection rate to be at 6.4 million people (Shisana 2014). This constitutes 12.2 percent of the South African population. HIV stigmatization contributes to under-reporting of cases. (Beaulieu et al. 2014). Early detection is important to prevent the spread of HIV (Ramathuba et al. 2015). Further there is a difference in self-concept of adolescents affected by HIV and those who are not (Asikhia and Mohangi 2014).

The rate of HIV infections among adult population (25 years and more) seems to be increasing. Young woman are still infected at a higher rate. Young people rate of infections is a third of the total infections. Higher treatment levels have reduced viral load in the population. The prevalence (total % of the population that is infected) is highest among females aged between 30 to 34 and it is highest among males 35 to 49 (Shisana 2014). The survey suggests researchers in HIV develop new strategies. One of the new strategies maybe the development of HIV mathematical models. (Johnson 2004)

The CD4 cell count at which combination of antiretroviral therapy should be started is central, unresolved issue in the case of HIV-1-infected patients. Sterne (2001) advocates 350 cells mm^{-3} as the minimum threshold for initiation of antiretroviral therapy. In his study patients receiving antiretroviral therapy vary between 130-330 cells. The results indicate 8 percent of the cohort develops aids, 3 percent results in death

and 10 percent results in aids and death. It is therefore necessary to determine accurately at what CD4+T cells count stage the drug is administered.

A difficult decision is to determine at what stage the physician administer the antiretroviral drugs. Experiments are limited to population groups and samples. Against this background HIV virus attacking the CD4+T cells was investigated using the model by Britton (2003).

Objectives

1. Identify a simple HIV mathematical model and find the solution
2. Describe the interaction of the infected virus, uninfected virus and virions graphically
3. At what stage should antiretroviral be administered

METHODOLOGY

Mathematical Models

A mathematical model is a formulation of hypothesis about a disease transmission process (Van den Dreischer 2008). Mathematical model can assist health researchers to make decisions. Conventional methods focus on experimental and statistical results which are narrow and confined to certain population groups. Laboratory experiments are simplified because of the difficulty of the large scale experiments. This implies that virus data maybe skewed. The statistics applied to these data sets maybe biased. The model has a number of advantages because it can provide a language for describing disease spread and reduces the disease phenomenon to factors. It can also be used to recommend effective control, estimate severity and potential scale of epidemic as well as testing hypotheses. Deterministic models generate unique solutions. The parameters are based on average values of random processes. The study uses continuous time models in which events are modelled as events occurring at a point in time (Solomon and Christopher 2001). The goal is to extract as much as possible from available parameters. The graphical solution to the model provides an accurate representation of both the knowledge and uncertainty of the HIV (Solomon and Chrsitopher 2001).

Associated with the model is the reproductive ratio $R_0<1$. The reproductive ratio is defined as the expected number of virions that one virion yields in an uninfected cell population. The system is non-infectious. However, due to the change in the CD4+T cells count the system lends itself to other infectious diseases such as TB. Hence, treatment of the patient at a specified CD4+T cell count is crucial.

Perelson (1993) examines this model for the interaction of HIV with CD4+T cells that considers four populations: viz uninfected T cells, latently infected T cells, actively infected T cells and free virus. As a result it predicts that different viral strains can cause different amounts of T-cell depletion and generate depletion at different rates.

To solve the model with respect to rates a software mathematical 8.0 can be used. Mathematica uses analytical and numerical methods to solve system of equations. Srivastava (2014) applied a dynamic model of HIV infection of CD4+T. The model is solved using numerical methods. The method employs numerical schemes in computational mathematics for nonlinear models. The results are stable and accurate. Mathematica uses these numerical schemes to solve the mathematical model.

Deterministic Model

Briton (2003) advances the following model for HIV virus without the immune system interaction.

- $\frac{dv}{d\tau} = aY - bV$
- $\frac{dx}{d\tau} = c - dX - \beta XV$
- $\frac{dY}{d\tau} = \beta XV - fY$
- where V=number of virions in an organism,X=number of uninfected target cells
- Y=number of infected cells
- b = virions die a specific rate
- c=Rate of production of uninfected cells
- d=Specific rate of death of cells
- $\beta\nu$=Specific rate of infection of cells by virus (linear functional response)
- f=Rate of death of infected cells
- a is the rate constant by cells becoming infected by the virus
- τ = time in seconds

Assumptions of the Model

The Briton model assumes the relationship between virus and the uninfected cells is analogous to the relationship between predator and prey mode. The model further assumes the spread of the virus inside the body is similar to the criterion for the spread of diseases in a population. The model uses the following tabulated default values as sourced from Perelson (1993):

The rate constant of cells becoming infected by virus (a) is 2.4×10^{-5} /mm^3/day, number of virions in an organism (v) is 10^{-3}mm^{-3}, the number of uninfected target cells (X) is 1000 mm^{-3}, Number of infected cells (Y) is 0, rate of production of uninfected cells(c) is 0.03/day, Virion death rate (b) is 2.4/day, specific rate of infection of cells (βv) is, 3x10-^{3} day death rate of infected cells (e) is 0.24/day and specific rate of death of cells (d) is 0.02/day.

The model was tested using three different sets of values based on a studies performed by Sterne (2001) and Shisana (2014).

- TEST1 (Normal CD4+T cells count): Vo=0.01; X=1000;Y=0
- TEST2 (Half of the CD4+T cells count): Vo=0.01; X=500;Y=500
- TEST3 (Antiretroviral treatment stage): Vo=0.01; X=300;Y=700

The reproductive ratio for all initial values yields $R_0<1$. This implies the system is non-infectious. The Briton model was solved using Mathematica 8.0 which employ a simple computational model to solve the mathematical model. The model employs a population consisting of actively infected CD4+T cells by the virus. The model assumes during the time span selected that CD4+T cells do not recognise the virus as a threat.

RESULTS

Graphs viz V versus t; X versus t and Y versus t are displayed for the three tests stated above.

Test 1

Figure 1 depicts virions against time. Virions decreases exponentially in time.

Figure 2 depicts uninfected cells versus time. It has a negative gradient straight-line.

Figure 3 depicts infected cells versus time. The graph is similar to a bell shape but skewed to the right

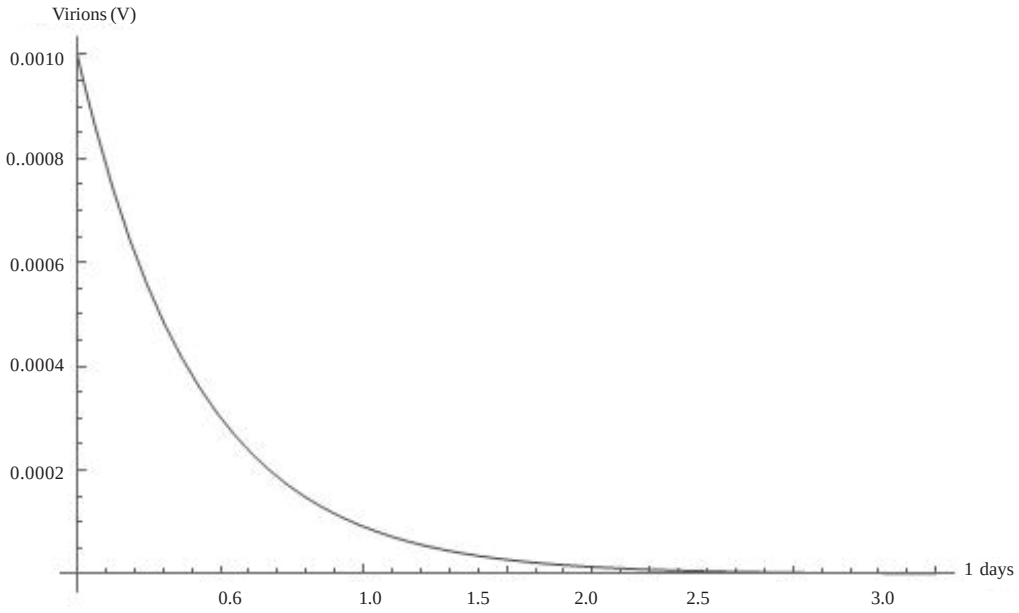

Fig. 1. Virions versus time

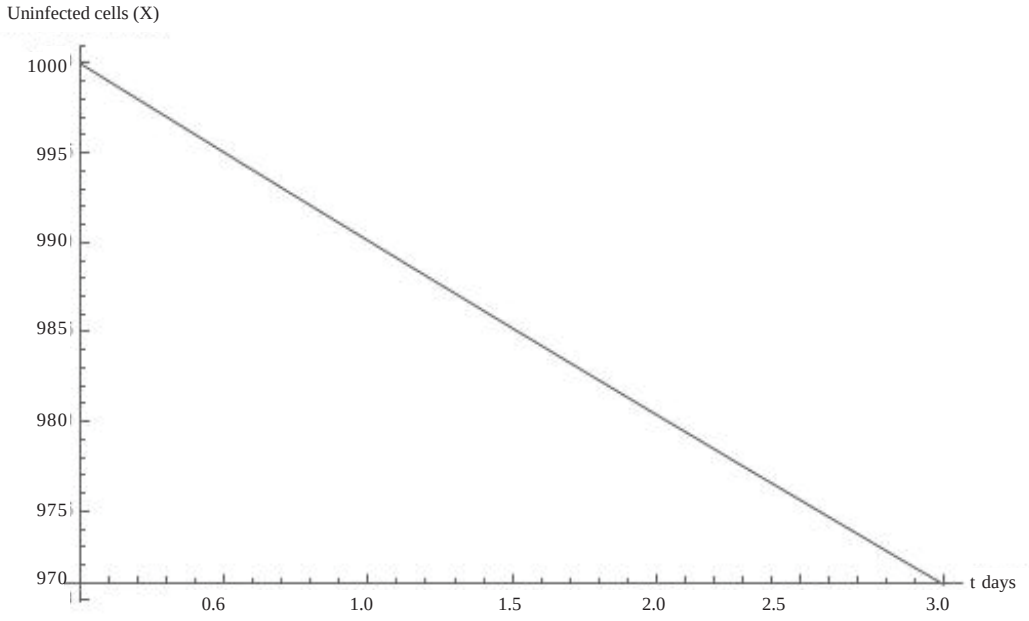

Fig. 2. Uninfected cells versus time

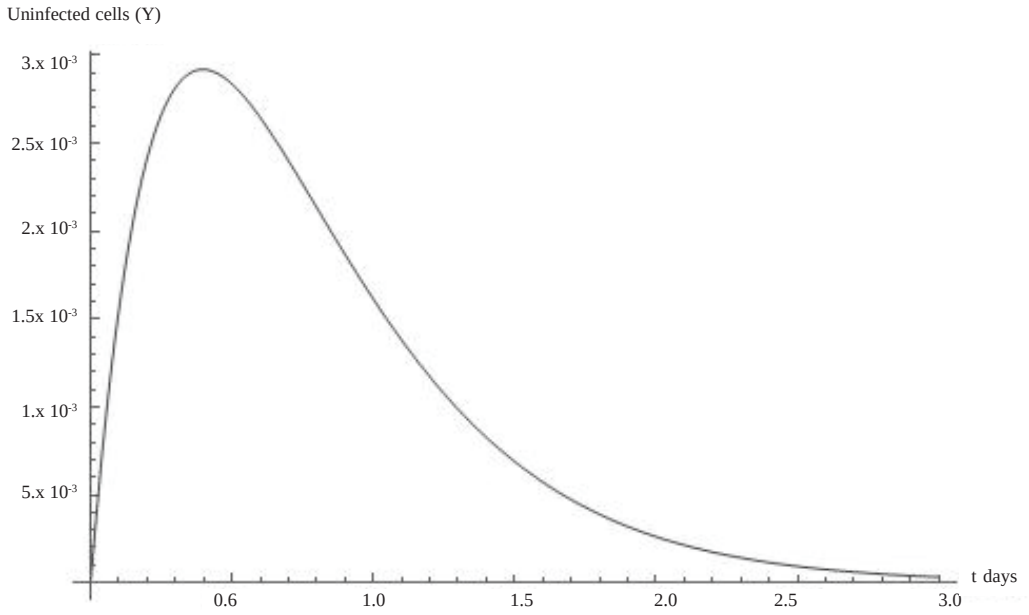

Fig. 3. Infected cells versus time

In Figure 1 the virions decrease exponentially. The Figure 2 indicates a straight line negative gradient graph. The CD4+T cells decrease to 975 from 1000 in three days. The rate of decrease is approximately 8 cells per day per cubic mm. The Figure 3 indicates a skewed to the right. It exhibits a maximum at 0.5 days. Thereafter it decreases gradually. It implies the much of the infected cells take a longer time to be eradicated.

Test 2

Figure 4 depicts Virions against time. The bell shaped graph is skewed to the right.

Figure 5 depicts uninfected cells versus time. The graph is constant

Figure 6 depicts infected cells versus time. The graph is a decreasing exponential curve.

In Figure 4 the virions are distributed normally and seem to be symmetrical. It suggests equilibrium within the virions regime. In Figure 5 it is a constant graph and the uninfected cells seem to be in equilibrium as there is no increase or decrease in the uninfected cells. Figure 6 indicates that the infected cells decrease exponentially with large rates of change.

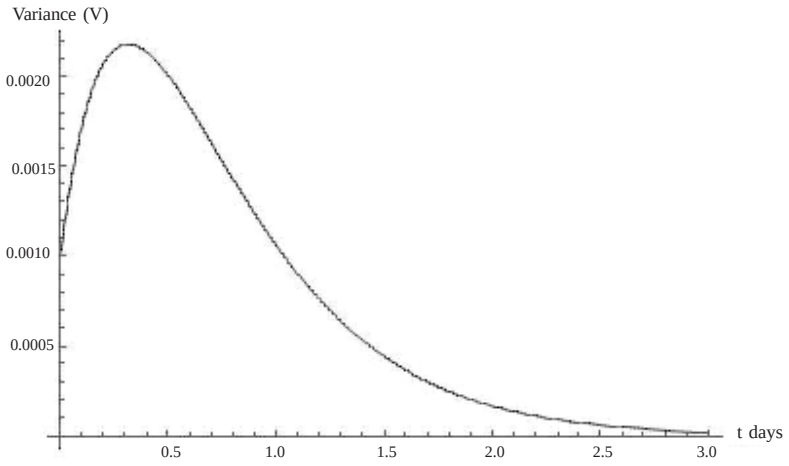

Fig. 4. Virions versus time

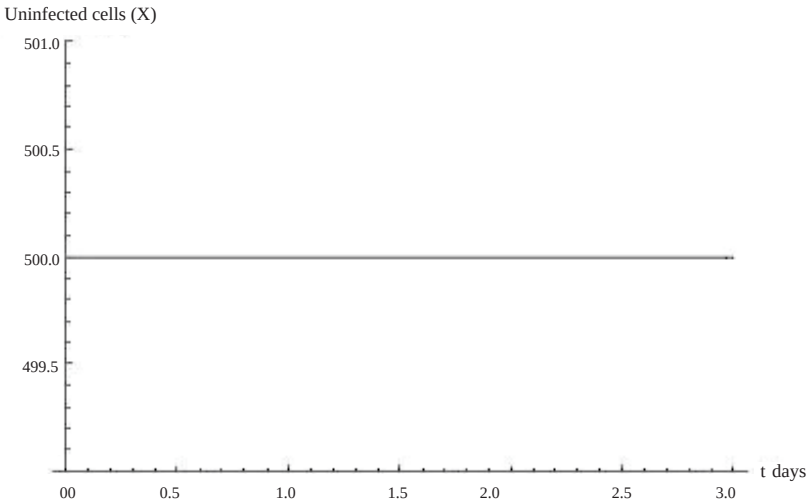

Fig. 5. Uninfected cells versus time

Test 3

Figure 7 depicts virions versus time. The graph is bell shaped with skew to the right.

The Figure 8 depicts uninfected cells versus time. The graph is a positive straight line.

Figure 9 depicts uninfected cells versus time. The graph is a decreasing exponential curve**.**

Test 3

In Figure 7 the virions form a bell shape curve and achieve a maximum at 0.5 days and decreases to zero. In Figure 8 the uninfected cells increases proportionally positively. The rate of increase is 4 cells per day per cubic mm. In Fig-

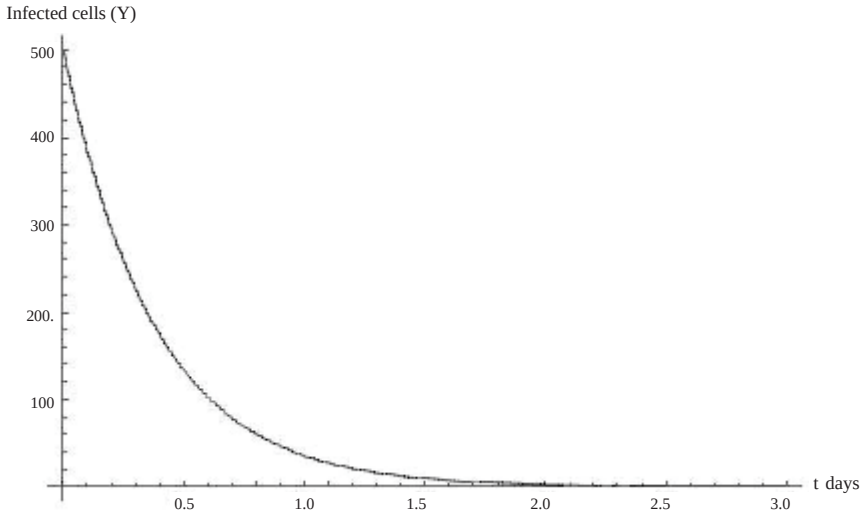

Fig. 6. Infected cells versus time

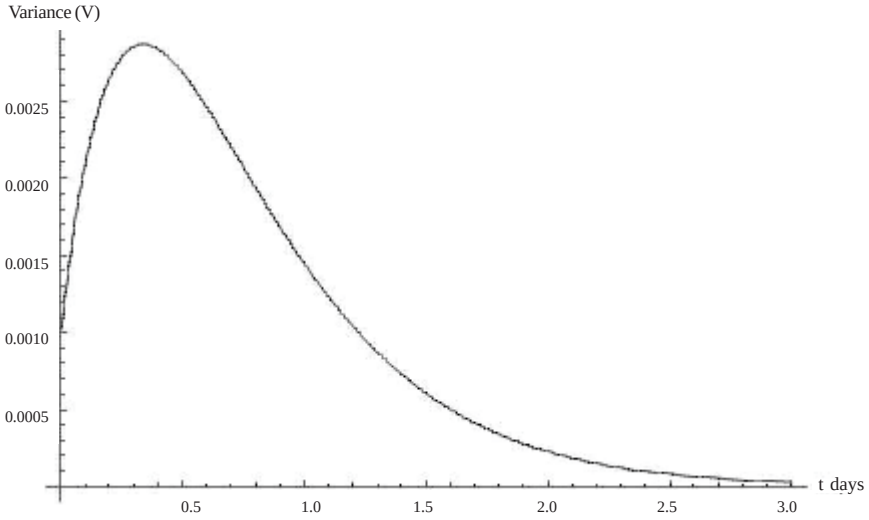

Fig. 7. Virions versus time

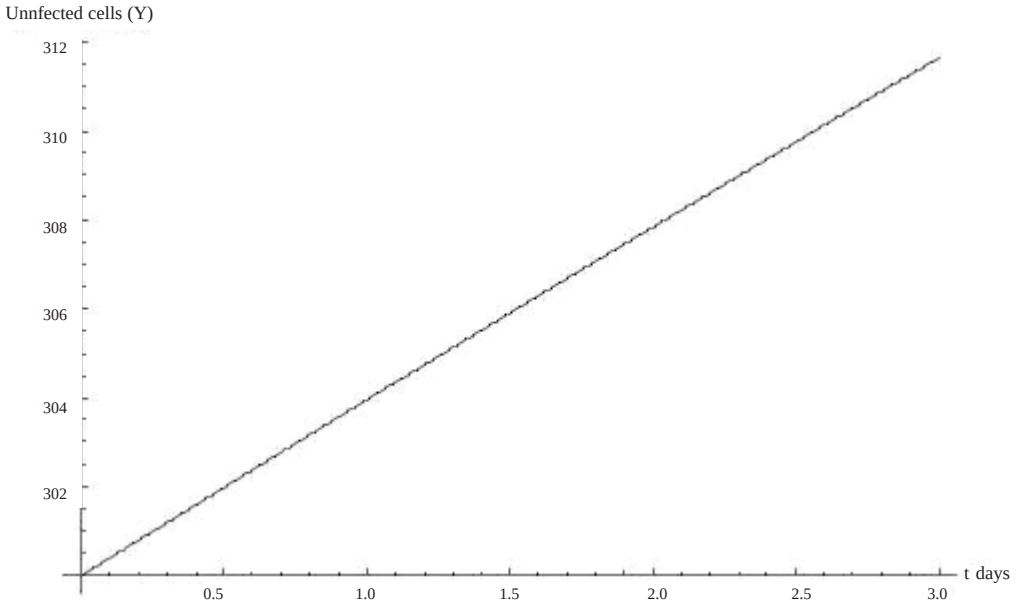

Fig. 8. Uninfected cells versus time

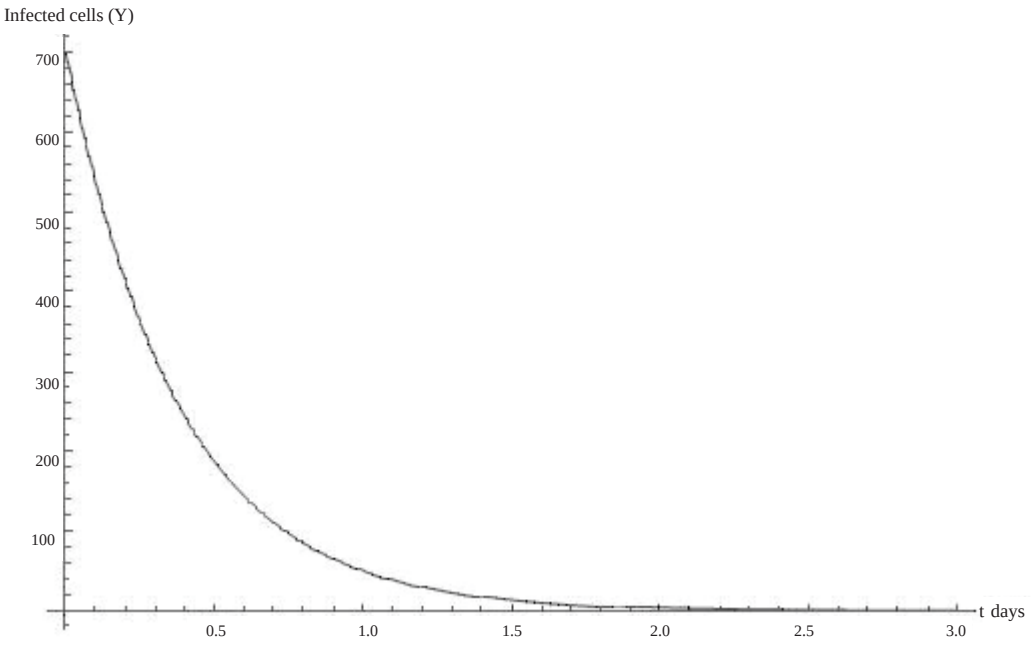

Fig. 9. Infected cells versus time

ure 9 the infected cells deceases exponentially with large rates of change.

DISCUSSION

The South African survey study (Shishana 2014), Stigmatizing study (Beaulieu et al. 2014) and Self-concept and Academic Performance studies (Asikhia and Mohangi 2014) indicates that researchers needed quick strategy for intervention. The mathematical model provided the accuracy for intervention in terms of time lines.

The Britton (2003) deterministic model with the default and initial values explained the behaviour of the virions, infected and uninfected cells and their interaction relatively accurately using graphical solution method as suggested by Johnson (2004), Solomon and Christopher (2001), Perelson (1993), Srivastava (2014) and van den Dreisher (2008).

It seems that when the system has a maximum supply of CD4+T cells (1000) the virions tend to destroy the uninfected cells at a negative rate. The rate of decrease is 8 cells per day per cubic mm. The infected cells distribution forms a skewed bell shaped curve. Since the percentage skewness is small it seems that the cells are attacked randomly. The infected cells graph exhibit skewness to the right. This indicates longer survival and infection periods.

The system establishes equilibrium at the 500 CD4+T cells concentration. This implies there is no increase or decrease in the uninfected cells and rate of change is zero. The concentration of virions decreases gradually. The infected cells decrease exponentially with large rates of change.

After further depletion the CD4+T cells (300) the system tend to increase the CD4+T cells but it increases very slowly approximately 4 cells per day per cubic mm. At this stage it will be difficult for the immune system block other diseases from entering the system.

CONCLUSION

The mathematical model describes the interaction between the infected cell, uninfected cells and virions effectively. It is recommended that at the 500 count antiretroviral drugs should be administered to protect the system from other infections as drugs administered at 350 maybe too late. This may be late as the system improves its cell count very slowly and consequently other diseases could be entering the system.

This study advocates the use of a mathematical model as a guide for such decision. Further it is recommended that the model can be used to test various hypotheses of the disease. Therefore public health should use it as a form of measurement.

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