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RESEARCH ARTICLE

A STATISTICAL MODEL FOR HIV REPLICATION IN THE INFECTED CD_4^+ T - CELLS

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ABSTRACT

Plenty of literatures proposed various models for the viral dynamics. Most of these models consist of four components of CD_4^+ T -cells as infected CD_4^+ T -cells, non-infected CD_4^+ T –cells, blanket CD_4^+ T -cells and free virus. This paper describes the model for HIV replication in the infected CD_4^+ T -cells, under the assumption of law of mass action by using truncated logistic distribution and numerically illustrated the replication of viral load for the future period.

INTRODUCTION

The dynamics between viral infection and immune system involves many different components. The outcomes of dynamic cannot be understood only by verbal or graphical reasoning. Mathematical model provides set of assumptions and to generate new hypotheses, suggest experiments and measures crucial parameters and get logical conclusion. The interaction between HIV and immune system is more complex compared to other infections. While immune responses have the potential to fight the virus, HIV infections CD_4^+ T helper cell, which are central components orchestrating (Planning) the generation of specific immune response. Depending on co-receptor usage, HIV can infect other immune cells, such as macrophages and dendrite cells that are also involved in the generation of antiviral immunity. Thus the suboptimal immune responses develop early during the cute phase of infection and can contribute to viral persistence and to the ability of the virus to mutate and evolve.

The infection remains asymptomatic for years before the viral load sufficiently increases and the population CD_4^+ T helper cell falls to low level leading to the development of AIDS. Diseases progression is associated with the evolution of specific viral variant that are more virulent and pathogenic. HIV has a physiological impact on the immune system. It targets and infects white blood cells known as CD_4^+ T -cells which are part of the immune system. CD_4^+ T -cells are helper cells produced from precursors in bone marrow and thymus. When a person has chronic HIV infection, it causes gradual depletion of the CD_4^+ T -cell pools. In a normal human being the level of CD_4^+ T -cells in the peripheral blood is regulated at a level between $800mm^3$ to $1200mm^3$. When the CD_4^+ T -cell counts falls below $200mm^3$, a person becomes vulnerable to opportunistic infections.

Many mathematical and computational models have been developed to investigate the complexity of HIV dynamics, immune response and drug therapy. However, there are only few models which consider the dynamics of virus intercellular replication at a single level. This Proposed HIV intercellular replication model where infected cells undergo a single cycle of virus replication. This model is validated by comparing simulation results with available experimental data. Simulation results give insights about the details of HIV replication dynamic inside the cell at the protein level. Therefore the model can be used for future studies of HIV intercellular replication in vivo and drug treatment.

The findings of this research will be of great benefit to the public health sector, community, NGOs and other end users of such epidemiological results. It will help in policy formulation, planning, budgeting, resource allocation and making appropriate decisions in tandem with control of the diseases by critically taking into account the aspect of treatment of HIV.

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REVIEW OF LITERATURE

Perelson *et.al.* (1993) proposed models of viral spread in the blood stream. The models consist of four components, such as un - infected CD_4^+ T -cells, latently infected CD_4^+ T-cells, actively infected CD_4^+ T -cells and free virus.
The models are considered as,

$$\frac{dT^*}{dt} = kTv_I - \delta T^*$$
$$\frac{dv_I}{dt} = -Cv_I$$
$$\frac{dV_{NI}}{dt} = N\delta T^* - CV_{NI}$$

Where

T– HIV virions infect target T- cells, T^* – productively infected T- cells, V_I – infection virions produced before initiation of the drug, V_{NI} - non infected virions, C – decay rate of non – infectious virus. N – productively infected T -cell assumed to produce N virions in its life time.

The parameters of this models are estimated by non-linear least square regression method. The estimated parameters of this models are baised, because assumption of imperfect drug. The estimated life time productively infected T- cells, and plasma virions are 1.6 days and 0.24 days respectively.

Perelson *et.al.* (1993); D Schenzle (1994) a deterministic logistic growth model was used to generation of T- cell growth. Theoretically derived the probabiliy distribution of the number of T- cells and HIV. Analytical solution is extremely difficult. Then extensive Monte Carlo simulation of study the distributions of the T- cells and the free virus. Simulation study showed that the HIV progression might be partitioned in two three periods as infection period (first 2 years) the transition period (2-5 years) and the steady – state period. After 7 years the infection process has reached the steady state. The earlier stage of the infection the probability distribution of the CD_4^+ T- cells and free virus are skewed and then finally became Gaussian distribution after several years.

Ho *et.al.* (1995) showed that the infection pathogenesis was a rapidly varying viral dynamical process, about twelve billon viral particles per day were being produced in a infected individuals.

The data from twently patients were used in the following model.

$$V^*(t) = P - CV(t)$$

Where

$V^*(t)$ – reproduced the rate of change viral concentration at time t, V(t) - viral concentration, P – the daily production rate, C – viral clearance rate.

Perelson *et.al.* (1996) extended the Ho *et.al.* (1995) model as

$$T^*(t) - K\,T_O\,V_I(t) - \delta\,T^*(t)$$
$$V_I(t) = (1- n_p)\,N\,\delta\,T^* - C\,V_I(t)$$
$$V_{NI}(t) = n_p\,N\,\delta\,T^*(t) - C\,V_{NI}(t)$$

Where

δ – T- cells decay rate, n_p – efficacy of the protease inhibitor is between 0 and 1, T_O – incapable of infecting target T- cells. (un - infected T- cells), K – constant rate HIV infect the target cells. Then viral decay is considered as exponential $V_I(t) = V_O \exp(-ct)$.

Where

t = 0 at which the drug takes effect of the phamacokinetic decays. Where V_O – initial viral load. From the above model, estimated average a life – span productively infected cells and plasma virions are 2.2 days and 3 days respectively. The estimated average total HIV-1 production was 10.3×10^9 virions per day. (Ho *et.al.* 1995; Perelson *et.al.* 1996; Wei *et.al.* 1995) provided strong support for existence of a high rate of HIV replication and clearence infected individuals.

Wai.yuan Tan and Hulin wu (1998) proposed a stochastic model for interaction between T- cells and free HIV virus absence of treatment by antiviral [drugs in the cellular level]. The model having four – dimentional stochastic process on

$X = \{T_1(t), T_2(t), T_3(t), V(t)\}$ consists
$T_1(t)$ – un - infected T- cells
$T_2(t)$ – latently infected T- cells
$T_3(t)$ – actively infected T- cell and free virus at a time t. The T- cells generation consider in this model a possion process (or) pure – birth process.

$$V(t) = P_1 e^{-d_1 t} + P_2 e^{-d_2 t}$$

Where

$$d_1 = [1 - R_1(1 - e_1)]\delta$$
$$d_2 = \left[1 - R_1\left(\frac{1-e_2}{e_1}\right)\right]\mu$$

are called the first and second phase (before and after treatment effect) and R_1 and R_2 one baseline reproduction / clearance rate of virus from productively and long – lived / latently infected cells. e_1 and e_2 are treatment effects productively infected / latently infected cells, δ and μ are death rates of productively long lived /latently infected cells.

Hulin wu and A. Adam Ding (1999) proposed a mathematical model for HIV dynamics as a mixed effect models consists of target cells, mysterious infected cells, long – lived infected cells, latently infected cells, productively infected cells, infection virus, non – infection virus under the assumption of anti viral therapy of RTI (Reverse Transcriptase Inhibitor) drugs effects. The effect of RTI drugs model followed (Herz *et. al* 1996) by reducing the infection rate k_0 *to* $(1 - v)k_0$

where $0 \le v \le 1$. Parameter v reflects the RTI drug efficacy (Bonhoeffer *et.al.* 1997) in the viral decay model is simplified inform of bi – exponential and fitted the clinical data. But their biological interpretation may not be valid.

Rebeco *et.al.* (2000) reduced the perelson *et.al.* (1993) ordinary differential equation model of viral spread in the blood stream as only three components of the healthy CD_4^+ T - cells, infected CD_4^+ T -cells and free virus. Their model described the discrete time decay between infection of a CD_4^+ T - cells and emission of viral particles on a cellular level and also determine how the intercellular decay affects overall disease progression and mathematically measure how the decay effects of the dynamics in the system.

Where the infected equilibrium is asymptotically stable for all decay. The intercellular decay can cause the cell and virus population to fluctuate in the early stage of infection and in a longer term, infection is steady states are conforming by their simulation study.

Hulin wu and A.Adam Ding (2002) focused viral decay model as the non – linear mixed effect model in which within – subject variation and between – subject variation in viral load measurement are considered. The rate of viral decay before and after potency of antiviral therapies are measured. To fit the bi – exponential model by non - linear regression method and non - linear mixed effect model have been proposed (Wu *et.al.*1998; Wu and Ding,1999; Ding and Wu 2001). They generated the simulation data from the tri - exponential model of (Perelson *et.al.* 1996; Herz *et.al.* 1996; Mittler *et.al.* 1998; Ding and Wu 1999) as

$$y_{ij} = \log\left(e^{P_{0i}-d_{0i}t_{ij}} + e^{P_{1i}-d_{1i}t_{ij}} + e^{P_{2i}-d_{2i}t_{ij}}\right) + e_{ij}$$

and fitted the simulated data in the bi – exponential model of,

$$y_{ij} = \log_{10}\left(e^{P_{1i}-d_{1i}t_{ij}} + e^{P_{2i}-d_{2i}t_{ij}}\right) + e_{ij}$$

Finally the estimated d_1 and d_2 with between – subject variance was followed (Ho *et.al.* 1995; Wei *et.al* 1995; Perelson *et.al* 1996 and 1997; Wu and Ding 1999). The estimated parameter d_1 range from 0.2 to 1.2, and d_2 range from 0.0001 to 0.2. (Mittler *et.al.* 1999; Perelson *et.al.*1997; Ramratnam *et.al.*1999) believed that in vivo; on the order of 10^{10} virions are created and then destroyed every day by the immune system.

Louied *et.al* (2003) proposed the random as well as deterministic model and HIV patient data was illustrated. It is crucial to include target cell dynamics with density dependent growth but that a latent cell component is not needed over this shorter time scale

$$T^*(t) = (1 - n_{rt})\,kv(t)T_{(t)} - \delta T^*(t),$$
$$VT^*(t) = N\,\delta T^*(t) - CV(t)$$
$$T^*(t) = \delta PT(t)\left(1 - \frac{T(t) + T^*(t)}{T_{max}}\right) - d_T T(t) - (1 - n_{rt})\,kv(t)T_{(t)}$$
$$-(1 - n_{rt})\,kv(t)T_{(t)}$$

Where

n_{rt} is the efficacy of the reverse transcriptase (RT) inhibitor mono –therapy N-is the average number of virions produced per-productively infected T-cells.

D.M Bortz and P.W. Nelson (2004) illustrated the wide range of C and a small range for δ undergoing protease inhibitor therapy by sensitivity methodology in which principle component analysis is used.

D.M. Bortz and P.W. Nelson (2005) created a statistical model. A hierarchical mixed-effects modeling approach is employed to characterize the inter-and intra- individual variability in the patient population. Straight forward characterization, of t5he inherent within and between- patient variability by the mixed-effect modeling, for patient, log transform of the n_i-dimensional vector of viral load measurements v_i and n_i time-points is modeled by

$l_n v_t = l_n\, f(\beta + b_i) + \epsilon_i$ Where vector value function represents the solution to the differential equation evaluated at n_i time points and ϵ_i is a vector random variable observation describing the measurement equation in observing viral loads. β - viral clearance rates and CD_4^+ T - cells, death rates and illustrated sample variances for maximum likelihood best fit values of the parameters $(C \ and \ \delta)$

Yangxin Huang and Hulin Wu (2006). Introduced a dynamic model for characteristizing long-term viral dynamic with antiretroviral therapy as a set of non linear differential equations without closed form solutions. So they investigated a Bayesian approach. For estimating the unknown dynamic parameters. But is not suitable of unbalance longitudinal data from individual subjects: Therefore they presented a simulation methodology to implement the proposed approach.

J.Guedj *et.al* (2007) used the fisher information matrix (FIM) to check and to measure the practical identifiability of parameters estimated by Maximum Likelihood Estimation (MLE) and described the following an HIV dynamics model based on five non linear differential

$$dQ = \tau + PT - \alpha Q - \mu_Q Q$$
$$\frac{dT}{dt} = \alpha Q - (1 - \eta)\gamma\, TV_I - PT - \mu_T T$$
$$\frac{dT^*}{dt} = (1 - \eta)\,\gamma\, TV_I - \mu_{T^*} T^*$$
$$\frac{dV_I}{dt} = w\mu_{T^*}\,\pi T^* - \mu_V V_I$$
$$\frac{dV_{NI}}{dt} = (1 - w)\mu_{T^*}\,\pi T^* - \mu_{T^*}\,\pi$$

Where

Q – Quiescent cells. In this model, the activation process is probability one of the major cause of CD4 depletion during HIV infection (Grossman *et.al* 2000). In the steady stale assumption, the treatment effects are initiated with η = 0 is introduced (Ho *et.al* 1995; Ribeiro *et.al* 2002).

The availability of assays able to distinguish infected and non-infected cells Perelson *et.al.* (1998) as well as infectious and non-infectious viruses (Ruset *et.al* 2004). May useful to improve the identifiability of model parameters and thus

usefulness of HIV dynamic model to analyze the real data. The estimation of the free virions clearance and the number of virus produced by an infected cell are very difficult by means of rapid dynamics of these components.

Yong Sheng Ding *et.al* (2008) introduced a stochastic model for AIDS transmission. This model is based on the concepts of birth rate (B) independent on the total population; C contact rate (C) between individuals; death rate (α) sufficiency from AIDS; P vertical distribution pobability 0< P <1; β is the constant transmission rate. The proportion of the population infected with HIV agaist total population Z statistics the ordinary diffential equation

$$\frac{dz}{dt} = (p-1)\,BZ + (\beta c - \alpha)(1-Z)Z$$

β should be a stochastic process by the considency the environmental effect:

Samira Khalili *et.al* (2010) employed the stochastic modeling in which the resistance of the nucleoside – analogue reverse transcriptase inhibitors machanisms.pue to the fact that mutation rate of HIV is quite high and resistance to treatments decreases the effect of treatment. The intra cellular model of HIV infection provides the opportunity to investigate the combined effects of different class of HIV drugs such as protease inhibitors fusion inhibitors and integrate inhibitors.

Model of HIV replication for the future period in the viral dynamic study

Davide Verotta (2005) described the model of HIV-I dynamic through the clinical HIV-I data. The model of viral dynamic is function of the (1). Non- infected T-cells, (2). Infected T-cells, (3). Infective Virus, (4). Cytotoic T- lymphocytes and their interactions, explains in the form of differential equation. This method is concentrated a bases of no viral load, no immune response, and response of ART. The parameter estimation of this type of non-linear mixed effect model is not easy. Avoiding this kind of problem latest literatures follows the Bayesian approach. In this approach prior selection of multi parameter is more difficult in the viral dynamic studies. The present paper simplified form of a new model is developed for HIV replication for the future period.

Viral dynamic model is considered as function of the (1). Infected CD_4^+ T-cells, (2). Blanket CD_4^+ T -cells, (3). Lysing CD_4^+ T -cells, (4). Non - Infected CD_4^+ T -cells, (5). Viral Load. The rate of change in the viral replication per period is given by

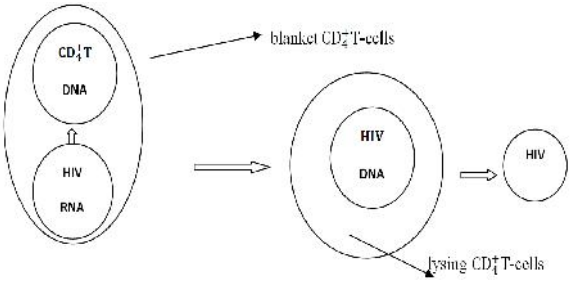
$$\frac{dH(t)}{dt} = H_1(t) = y(t) + R_2(t) - v(t) + e$$

Where

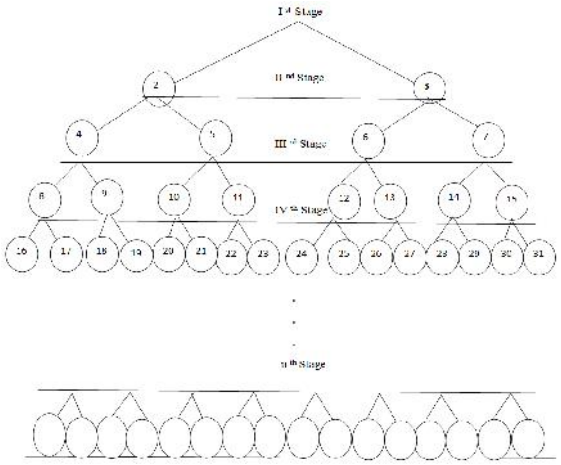
$y(t)$ – is number of non infected virus per period, $R_2(t)$ - is number of virus released by lysing CD_4^+ T –cells per period, $v(t)$ – is number of cleared virons, $e \sim N(0, \sigma^2)$ is random error affected by various biological aspects during the viral dynamic.

Method of viral replication CD_4^+ T –cells

When stimulated the CD_4^+ T-cells react with HIV RNA, CD_4^+ T -cells DNA finally become a CD_4^+ T-cell receptor access the HIV RNA and CD_4^+ T -cells become HIV RNA, this interaction takes some period of time such as called a window period or seroconversion and such as type of CD_4^+ T-cells called as blanket CD_4^+ T-cells. After the seroconversion HIV RNA becomes HIV DNA due to the auto catalytic reaction between CD_4^+ T - DNA and HIV RNA. HIV DNA replicated more and more within the blanket CD_4^+ T -cells. If replication of HIV DNA concentration more than the CD_4^+T-cells DNA concentration. At this stage blanket cell may be broken cut and release more number of virus by the method of law of mass action such a type of CD_4^+ T -cells called as lysing CD_4^+ T -cells.



Where blanket CD_4^+ T - is function of viral RNA and lysing CD_4^+ T -cell is function of viral DNA. During the period of seroconversion the each viral DNA split in multiples of 2 at each stage. That can be illustrated by the following tree diagram and assume that n stages viral DNA split in a CD_4^+ T –cell. HIV-1 infected model time delay is used to describe the time between infection of un-infected target cells and the emission of viral particles as proposed by Herz *et.al* (1996). This process is carry on when HIV construction more than the CD_4^+ T –cell DNA. At this stage the cell is going to lyses and release new virus.



Number of replicated virus per period in a blanket CD_4^+ T –cells

At the lytic stage of blanket CD_4^+ T–cell become a lysing CD_4^+ T–cell, that will be leased the number of HIV at a time is measured by the formula.

$1 + i + \sum_{j=1}^{n-2} 2i^j, \qquad j = 1,2,\dots,n-2$

where j's are number of stages and i = 2.

Model of HIV replication in the lysing CD_4^+ T–Cells

$$H(t) = h_1 \left(HC + \frac{c_1}{h_1} C_0\right)\left\{\left(HC + \frac{c_1}{h_1} C_0\right) - [H]_0 + \frac{c_1}{h_1} C_0\right\} \quad \dots (1)$$

Where

c_1 is the catalytic constant of CD_4^+ T–cells h_1 is the catalytic constant of HIV, C_0 is the CD_4^+ T–cells DNA concentration, H_0 is the HIV RNA concentration, HC is common concentration RNA and DNA of HIV and CD_4^+ T–cells. The rate of change of common concentration is considered as,

$$\frac{d\,HC}{dt} = c_1 C_0 (H_0 - HC) + h_1\, HC\,(C_0 - HC)$$

by equation of the law of mass action. If $h_1 > c_1$ the rate of change in the viral replication, (the number of replication of HIV (viral load) per period as $\left(\frac{dH(t)}{dt}\right)$ It is the function of HIV RNA and CD_4^+ T -cells DNA concentration. Assumption of infected number of CD_4^+ T -cells as n. The expected number of viral replication for the succeeding period denoted as

$$\sum_{i=1}^{n} \frac{dH(t_i)}{dt} = \sum_{i=1}^{n} h_i \left(HC + \frac{c_i}{h_i} C_0\right)\left\{HC + \frac{c_i}{h_i} C_0 - H_0 + \frac{c_i}{h_i} C_0\right\}$$

i = 1,2, … , n ... (2)

The following table shows that HIV replication per cell, by the assumption of various set of sample observations of CD_4^+ T–cells DNA concentration and HIV RNA concentration.

$C_0 = 10$, 12,14,16,18 (m.g), H_0 = 10.2, 12.2, 14.2, 16.2, 18.2 (m.g) $c_1 =$ 5,7,9,11,13 (m.g) h_1 = 6, 8,10,12,14 (m.g) $HC = (C_0)(H_0)$

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
							HIV concentration
c_1	h_1	HC	$\frac{c_1}{h_1} C_0 + HC$	$\frac{c_1}{h_1} C_0 + H_0$	(4) - (5)	(4) (h_1) (5)	(7) (3)
5	6	102	110.33	18.53	91.84	12266.48	120.25
7	8	146.1	156.9	17.7	139.2	22217.01	151.75
9	10	198.8	211.4	26.8	184.6	56655.2	284.98
11	12	259.2	273.76	30.76	243.0	101050.29	259.2
13	14	327.6	344.16	34.76	309.4	309.4	327.6

Total number of HIV replication for succeeding period is sum of HIV concentration for the above sample observation is 1458.06.

Model for HIV replication per period

The rate of change of viral load for the future period is denoted by

$$\frac{dH(t)}{dt} = H_1(t) = y(t) + R_2(t) - v(t) + e \quad \dots (3)$$

Where

$y(t) = H(t) - \alpha[x(t)]$, $R_2(t) = \delta_4 p R_1(t)$, $x(t)$ is powerful virus, $R_1(t)$-is number of virus replicated at the current period, $H(t)$ – is existing virus in the plasma, $v(t)$- is number of blanket cell death (cleared virion). The equation (3) can be modified as function of plasma virus by using the law of mass action that is

$$H_1(t) = [H(t) - \alpha(x(t))][\delta_4 p R_1(t) - \delta_3 R(t)] \quad \dots (4)$$

Where

δ_3 - death rate of blanket CD_4^+ T-cells per mm^3, δ_4 - death rate of lysing CD_4^+ T-cells per mm^3, p – number of virus released from the each lysing CD_4^+ T-cells, α - rate of powerful virus per mm^{-3} and $0 < \alpha_1, \delta_3, \delta_4 < 1$, $R(t)$ - is number of blanket CD_4^+ T-cells. The equation (4) can be written as

$$H_1(t) = C\,[H(t) - A][B - H(t)], \; C>0 \quad \dots (5)$$

Where

$A = \alpha(x(t))$ - is existing virus in the plasma, B= $\delta_4 p R_1(t)$ – is maximum number of viral replication at the current period. $\delta_3 R(t) -$ is the function of $H(t)$ referred from R. Lakshmajayam and G. Meenakshi (2014),

$$[P(H_1(t)) / P(H_1(t) > 0)] = \frac{BDe^{\frac{H_1(t)}{C}} + A}{De^{\frac{H_1(t)}{C}} + 1},$$

Since $H_1(t)$ is the random variable which is distributed as the truncated logistic distribution. The equation (5) interpreted as rate of growth (excess over initial) of viral replication when C > 0, B > 0.

$P(H_1(t)) = \frac{BDe^{\frac{1}{C}} + A}{De^{\frac{1}{C}} + 1}$ as $H_1(t) \to 1$, A$\to$ 0, as existing plasma virus is zero and when $H_1(t) \to r$, r = 1,2, … , and D > 0 the distribution of viral replication is given by

$$P(H_1(t)) = \frac{BDe^{\frac{r}{C}} + A}{De^{\frac{r}{C}} + 1} \text{ as } H_1(t) \to r,$$

$$P(H_1(t)) = \frac{De^{\frac{r}{C}}\left(B + ADe^{\frac{r}{C}}\right)}{De^{\frac{r}{C}}\left(1 + De^{\frac{r}{C}}\right)}$$

$$P(H_1(t)) = \frac{\left(B + ADe^{\frac{r}{C}}\right)}{\left(1 + De^{\frac{r}{C}}\right)},$$

$$P(H_1(t)) = \frac{1}{\left(1 + De^{\frac{r}{C}}\right)} \quad \text{, as } B \to 1 \text{ and } A \to 0$$

Where

C is fixed constant (average construction of RNA), D is fixed constant (average construction of DNA

The following table shows that HIV replication of various counts and the corresponding probability of changes. Viral load increases are calculated by the C ++ Programme.

C ++ **Programme for viral load and its corresponding probability**

```
#include<iostream.h>
#include<conio.h>
#include<math.h>
Void main ()
{
long double re1,re2,result[100],r,i,n,x[50],d,c;
clrscr();
cout<<“enter the value for n,d,c”<<endl;
cin>>n;
cin>>d;
cin>>c;
             for(i=1;i<=n;++)
             {
             cout<<“enter the value for x”;
             cin>>x[i];
             re 1=exp(x[i]/c);
             re 2=(1+(d*re 1));
             result[i]=(1/re 2);
             cout<<result[i]<<endl;
             }
cout<<“----------------------------------------------------------------------
-”<<endl;
Cout<<“ x[i]”<< “/t”<< “p [x]”<<endl;
             for (i=1;i<=n;i++)
             {
            cout<<“ x[i]”<< “/t”;
            cout<<result[i]<<endl;
            }
}
getch();
```

Table.1 $P(H_1(t)) = \frac{1}{\left(1 + De^{\frac{H_1(t)}{C}}\right)}$ when C = 2(m.g) D = 5 (m.g) and r = 1,2,3, … , If C < D,

$H_1(t)$	$P\{H_1(t)\}$	$H_1(t)$	$P\{H_1(t)\}$
1	0.108183	11	0.000817
2	0.068533	12	0.000496
3	0.04272	13	0.000301
4	0.026354	14	0.000182
5	0.016152	15	0.000111
6	0.0098959	16	6.708802e-05
7	0.006003	17	4.069202e-05
8	0.00365	18	2.468135e-05
9	0.002217	19	1.497014e-05
10	0.001346	20	9.079904e-06

$H_1(t)$	$P\{H_1(t)\}$	$H_1(t)$	$P\{H_1(t)\}$
21	5.50726e-06	20	9.079904e-06
22	3.340329e-06	30	6.118046e-08
23	2.026015e-06	40	4.122307e-10
24	1.228841e-07	50	2.777589e-12
25	7.453301e-07	60	1.871525e-14
26	4.420657e-07	70	1.261023e-16
27	2.741917e-07	80	8.496709e-19
28	1.663057e-07	90	5.725037e-21
29	1.008695e-07	100	3.8575e-23
30	6.118046e-08	110	5.357274e-34

$H_1(t)$	$P\{H_1(t)\}$	$H_1(t)$	$P\{H_1(t)\}$
150	5.357274e-34	650	1.429958e-142
200	7.440152e-45	700	1.985918e-153
250	1.033284e-55	750	2.758032e-164
300	1.435019e-66	800	3.830339e-175
350	1.992947e-77	850	5.319554e-186
400	2.767793e-88	900	7.387766e-197
450	3.843895e-99	950	1.026009e-207
500	5.33838e-110	1000	1.424915e-218
550	7.413913e-121	1050	1.978414e-229
600	1.02964e-131	1100	2.748305e-204

$H_1(t)$	$P\{H_1(t)\}$
1200	5.300793e-262
1400	1.971935e-305
1600	1.112537e-309
1800	1.112537e-309
2000	1.112537e-309

Revised from of table (1)

Table 1

$H_1(t)$	1	2	3	4	5	6	7	8	9	10
$P\{H_1(t)\}$	0.108	0.068	0.042	0.026	0.016	0.009	0.006	0.003	0.002	0.001

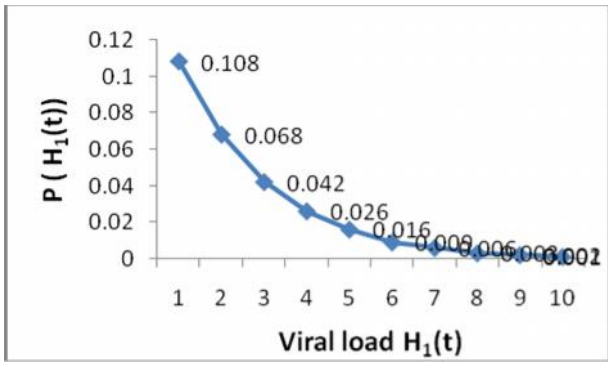


Figure1

Table 2

$H_1(t)$	11	12	13	14	15	16	17	18	19	20
$P\{H_1(t)\}$	0.000	0.000	0.000	0.000	0.000	0.670	0.406	0.246	0.149	0.907

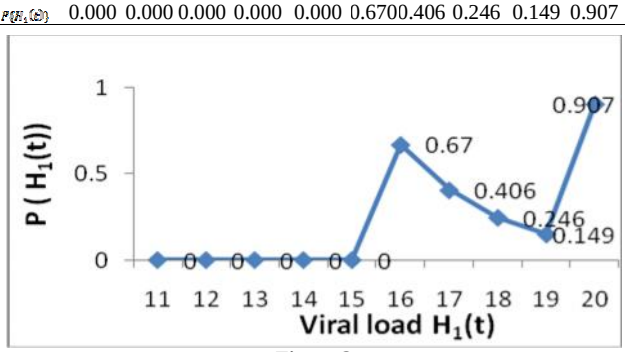


Figure 2

Table3

$H_1(t)$	21	22	23	24	25	26	27	28	29	30
$P\{H_1(t)\}$	0.550	0.334	0.202	0.122	0.745	0.442	0.272	0.161	0.101	0.616

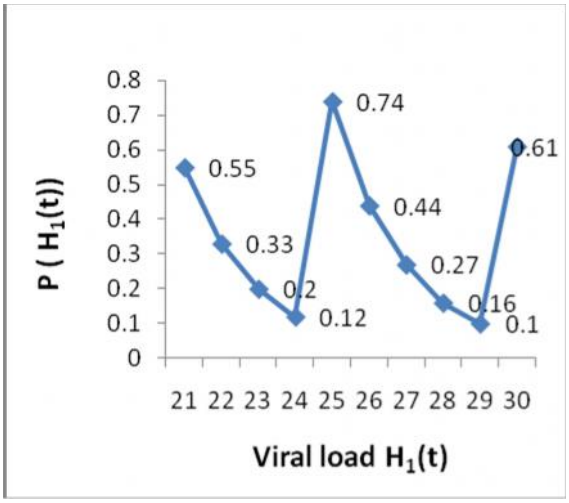


Figure 3

Table4

$H_1(t)$	20	30	40	50	60	70	80	90	100	110
$P\{H_1(t)\}$	0.909	0.616	0.414	0.272	0.181	0.121	0.848	0.575	0.383	0.535

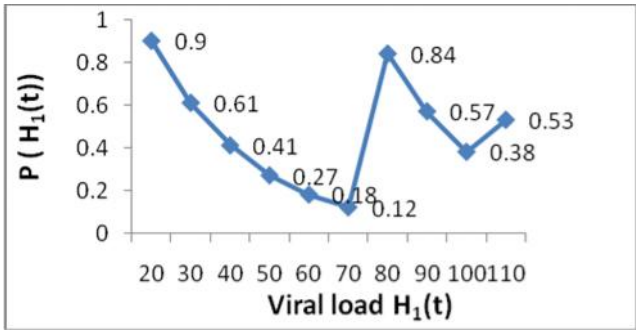


Figure 4

Table 5

$H_1(t)$	150	200	250	300	350	400	450	500	550	600
$P\{H_1(t)\}$	0.535	0.747	0.101	0.141	0.191	0.272	0.383	0.535	0.747	0.101

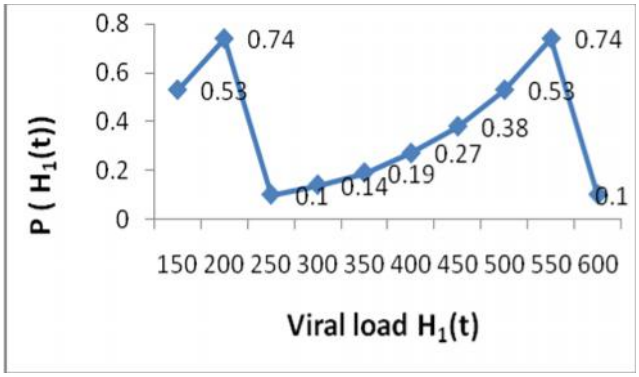


Figure 5

Table 6

$H_1(t)$	650	700	750	800	850	900	950	1000	1050	1100
$P\{H_1(t)\}$	0.141	0.198	0.275	0.383	0.531	0.738	0.102	0.142	0.197	0.274

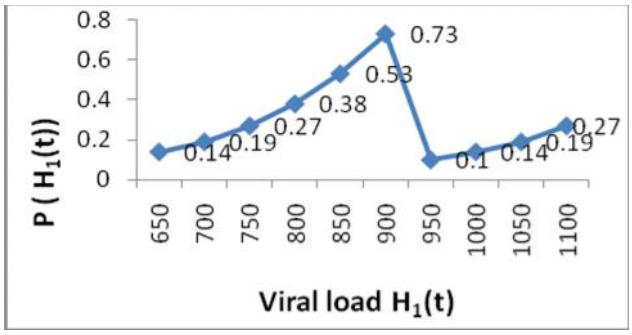


Figure 6

Table 7

$H_1(t)$	1200	1400	1600	1800	2000	4000	5000	10000	100000	1000000
$P\{H_1(t)\}$	0.530	0.197	0.112	0.112	0.112	0.112	0.112	0.112	0.112	0.112

Figure 7

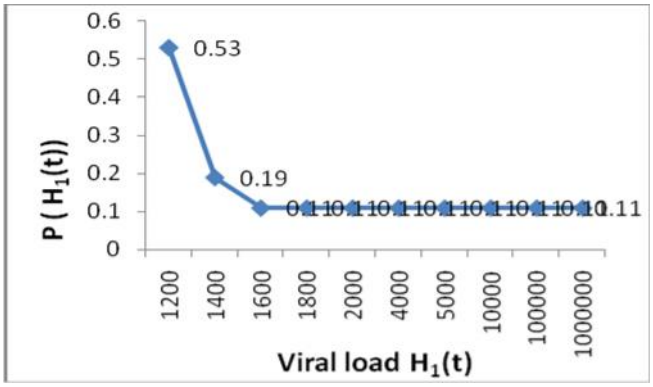


Table 8

$H_1(t)$	16	20	24	30	40	50	60	70	80	90	100	110
$[P(H_1$	0.670	0.909	0.121	0.616	0.414	0.272	0.181	0.121	0.848	0.575	0.383	0.535

$H_1(t)$	200	250	300	350	400	450	500	600	900	1000	1200	1600	10000
$[P(H_1$	0.747	0.101	0.141	0.191	0.127	0.383	0.535	0.101	0.737	0.141	0.535	0.111	0.111

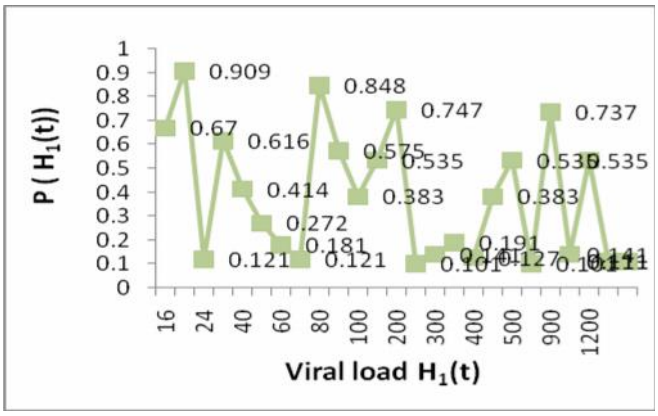


Figure 8

Table 9

$H_1(t)$	1	100	200	300	400	500	600	700	800	900	1000	1200
$[P(H_1$	0.108	0.383	0.747	0.141	0.272	0.535	0.101	0.198	0.383	0.738	0.142	0.53

$H_1(t)$	1400	1600	1800	2000	5000	10000	100000	1000000
$[P(H_1(t)$	0.197	0.112	0.112	0.112	0.112	0.112	0.112	0.112

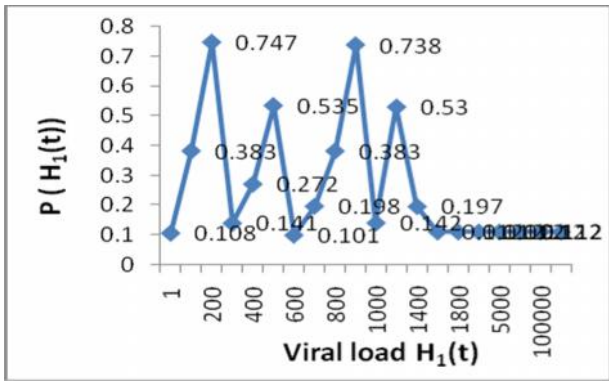


Figure 9

Table 2

$P(H_1(t)) = \frac{1}{\left(1+De^{\frac{H_1(t)}{C}}\right)}$ when C = 7(m.g) D = 5 (m.g) and r = 1,2,3, … , If D < C,

$H_1(t)$	$P\{H_1(t)\}$	$H_1(t)$	$P\{H_1(t)\}$
1	0.147758	11	0.039892
2	0.130658	12	0.034766
3	0.11527	13	0.030278
4	0.101482	14	0.026354
5	0.089177	15	0.022926
6	0.078234	16	0.019938
7	0.068533	17	0.017327
8	0.059957	18	0.15055
9	0.052394	19	0.013077
10	0.045738	20	0.011356

$H_1(t)$	$P\{H_1(t)\}$	$H_1(t)$	$P\{H_1(t)\}$
21	0.009859	40	0.000659
22	0.008558	50	0.000158
23	0.007427	60	3.788693e-05
24	0.006445	70	9.079904e-06
25	0.005592	80	2.176023e-06
26	0.004851	90	5.214871e-07
27	0.004208	100	1.24975e-07
28	0.00365	110	2.995039e-08
29	0.0013165	120	7.177641e-09
30	0.002745	130	1.720129e-09

$H_1(t)$	$P\{H_1(t)\}$	$H_1(t)$	$P\{H_1(t)\}$
150	9.879152e-11	650	9.412072e-42
200	7.809374e-14	700	7.440152e-45
250	6.173235e-17	750	5.881368e-48
300	4.879882e-20	800	4.649165e-51
350	3.8575e-23	850	3.61512e-54
400	3.049316e-27	900	2.90512e-57
450	2.410455e-29	950	2.29649e-60
500	1.905441e-32	1000	1.815353e-63
550	1.190663e-35	1050	1.435019e-66
600	1.190663e-38	1100	1.134369e-69

$H_1(t)$	$P\{H_1(t)\}$
1200	7.088356e-76
1400	2.767793e-88
1600	1.080737e-100
1800	4.219938e-113
2000	1.647754e-125
4000	1.357546e-249
5000	1.112537e-309
10000	1.112537e-309
100000	1.112537e-309
1000000	1.112537e-309

Revised from of table (2)

Table 1

$H_1(t)$	1	2	3	4	5	6	7	8	9	10
$P\{H_1(t)\}$	0.147	0.130	0.115	0.101	0.089	0.078	0.068	0.059	0.052	0.045

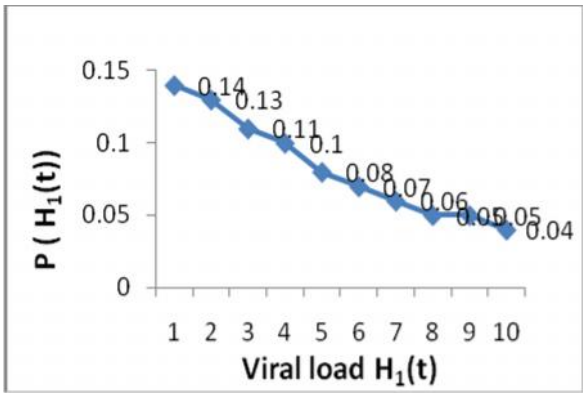


Figure1

Table 2

$H_1(t)$	11	12	13	14	15	16	17	18	19	20
$P\{H_1(t)\}$	0.039	0.034	0.030	0.026	0.022	0.019	0.017	0.015	0.013	0.011

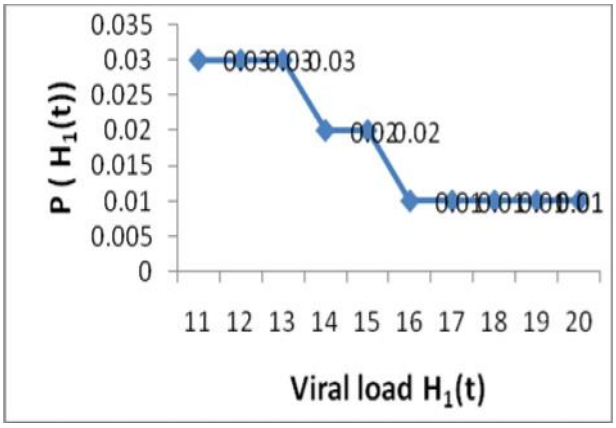


Figure 2

Table 3

$H_1(t)$	21	22	23	24	25	26	27	28	29	30
$P\{H_1(t)\}$	0.009	0.008	0.007	0.006	0.005	0.004	0.003	0.001	0.001	0.002

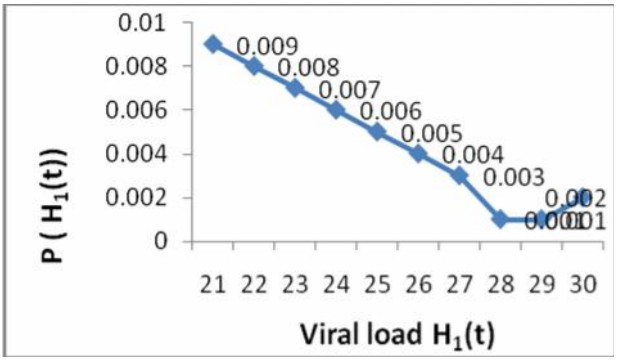


Figure 3

Table 4

$H_1(t)$	40	50	60	70	80	90	100	110	120	130
$P\{H_1(t)\}$	0.00	0.00	0.378	0.907	0.217	0.521	0.124	0.299	0.717	0.172

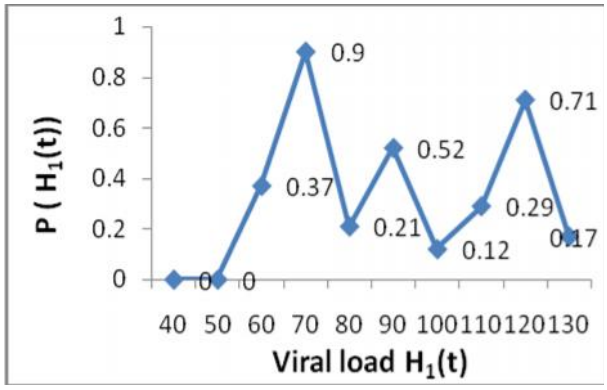


Figure 4

Table5

$H_1(t)$	150	200	250	300	350	400	450	500	550	600
$P\{H_1(t)\}$	0.987	0.780	0.617	0.487	0.385	0.304	0.241	0.190	0.150	0.119

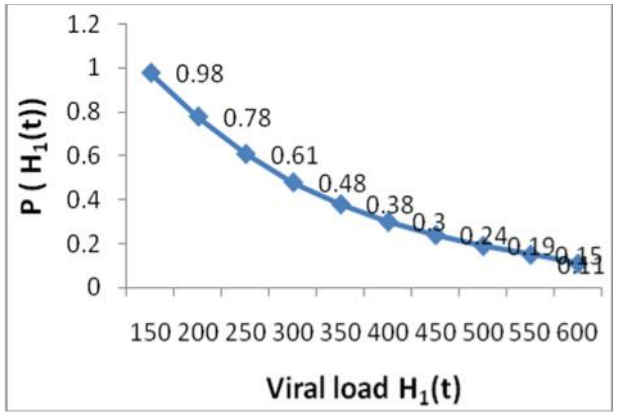


Figure 5

Table 6

$H_1(t)$	650	700	750	800	850	900	950	1000	1050	1100
$P\{H_1(t)\}$	0.941	0.744	0.588	0.464	0.367	0.290	0.229	0.181	0.143	0.113

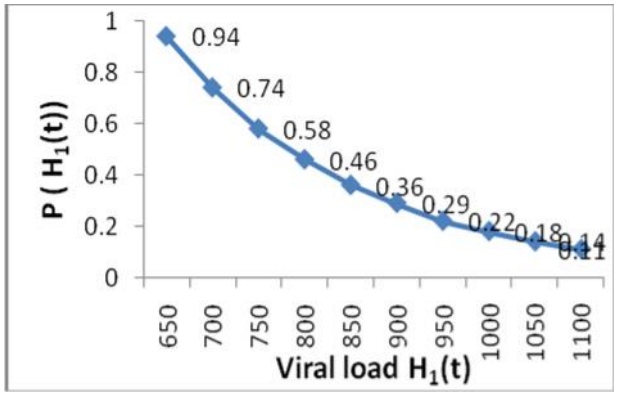


Figure 6

Table7

$H_1(t)$	1200	1400	1600	1800	2000	4000	5000	10000	100000	1000000
$P\{H_1(t)\}$	0.708	0.276	0.108	0.421	0.164	0.135	0.111	0.111	0.111	0.111

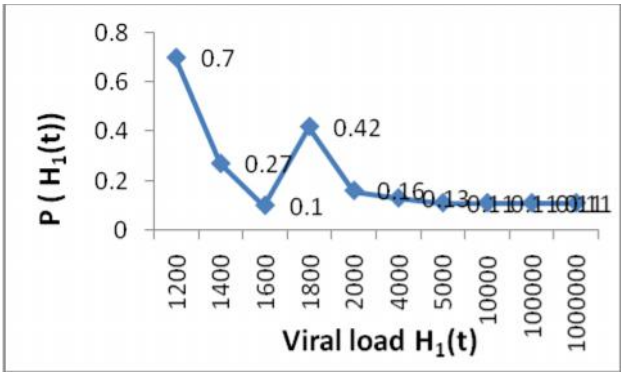


Figure7

Table 8

$H_1(t)$	60	90	110	130	150	200	250	300	350	400	450	500
$P\{H_1(t)\}$	0.378	0.521	0.229	0.122	0.987	0.780	0.617	0.487	0.385	0.304	0.241	0.290

$H_1(t)$	550	600	650	700	750	800	850	900	950	1000	2000	5000
$P\{H_1(t)\}$	0.150	0.119	0.941	0.744	0.558	0.464	0.367	0.290	0.229	0.181	0.164	0.111

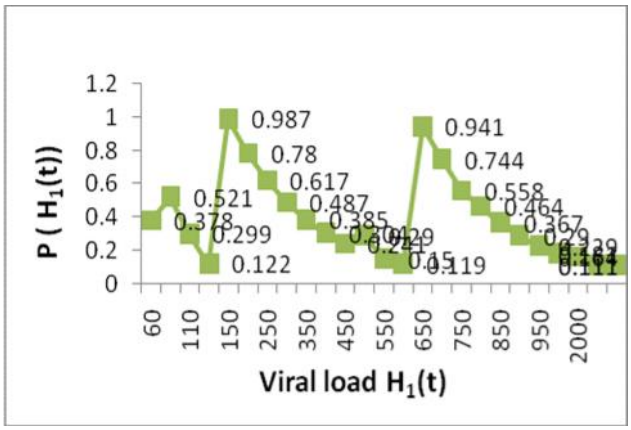


Figure 8

Table 9

$H_1(t)$	1	100	200	300	400	500	600	700	800	900	1000	1200
$P\{H_1(t)\}$	0.147	0.124	0.78	0.487	0.301	0.19	0.119	0.744	0.464	0.29	0.181	0.708

$H_1(t)$	1400	1600	1800	2000	5000	10000	100000
$P\{H_1(t)\}$	0.276	0.108	0.421	0.164	0.111	0.111	0.111

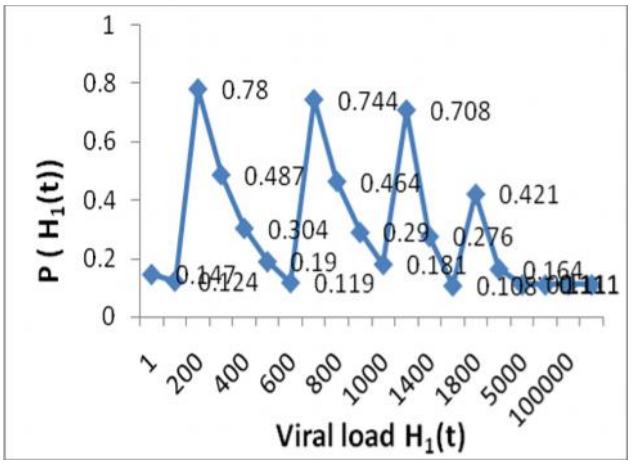


Figure 9

CONCLUSION

It is concluded that from the tables and corresponding graphs that when HIV counts increases, there is a changes of replication of virus increases. Therefore the HIV infected persons viral load is gradually increases at this stage CD_4^+T - cells count will be reduced from this we concluded that life time of HIV infected persons may be very short after the stage of rapid growth of viral load.

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A delay- differential equation model of HIV infection of CD_4^+T-cells. Rebecca *et. al* (2000).

Variable and Parameters for viral spread

Table-1

	Parameters and Variables	Values
	Dependent Variables	
T	Un-infected CD_4^+T-cell population size	1000 mm^{-3}
I	Infected CD_4^+T-cell density	0
V	Initial density of HIV RNA	10^{-3} mm^{-3}
	Parameters and Constants	
μ_T	Natural death rate of CD_4^+T-cells	0.02 day^{-1}
μ_1	Blanket death rate of infected CD_4^+T-cells	0.26 day^{-1}
μ_B	Lytic death rate for infected cells	0.24 day^{-1}
μ_V	Death rate of free virus	2.4 day^{-1}
K_1	Rate CD_4^+T-cells become infected with virus	2.4 X $10^{-5}mm^{-3}$ day^{-1}
K'_1	Rate infected cells becomes active	2 X $10^{-5}mm^{-3}$ day^{-1}
R	Growth rate of CD_4^+T-cell population	0.03 day^{-1}
N	Number of virions produced by infected CD_4^+T-cells	Varies
T_{max}	Aximum population level of CD_4^+T-cells	1500 mm^{-3}
S	Source term for uninfected CD_4^+T-cells	$10(day)^{-1}$ mm^{-3}

Parameter values	Description source
n_{rt} : 0.8	Reverse transcriptase(RT) efficacy : Nelson *et al* (2001)
P: 0.03 (hr^{-1})	T-cell growth rate : Perelson *et al* (1993)
T_o: from data (cells/ mm^3)	Initial target cell population: Louie et al(2003)
N: 480 (virion mm^3/ (cell ml))	Virions per lysing cell : Perelson and Nelson (1999)
V_o: from data (virions/ml)	Initial viral load : Louie *et al* (2003)
d_T : 0.02 (hr^{-1})	Natural T-Cells death rate : Perelson *et al* (1993)
f: 0.03	Efficacy of latent infection : Perelson *et al* (1997)
k_2 : 0.01(hr^{-1})	Latent cell activation rate : Perelson *et al* (1997)
T_{max}: 1500 (mm^{-3})	Maximum T-Cell density : Perelson *et al* (1993)

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