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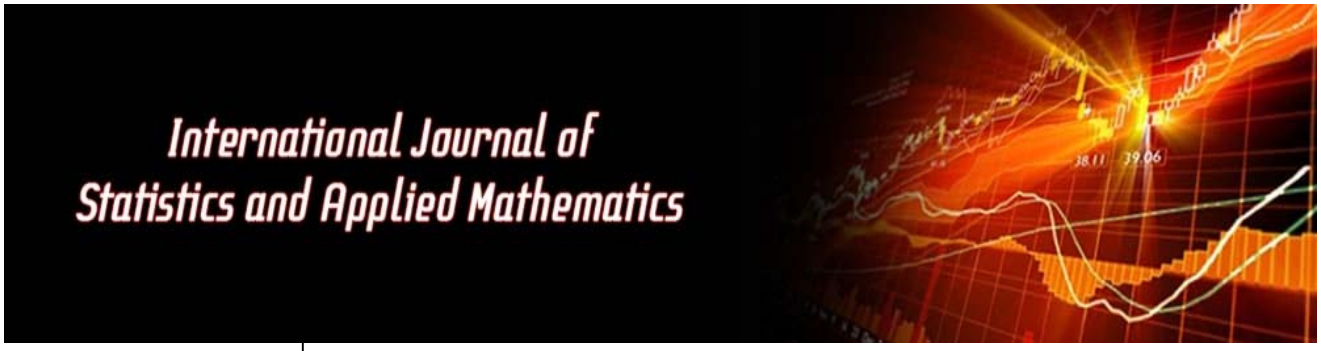

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A statistical modelling for viral replication in the CD_4^+T cells dynamic by bayesian methodology

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Abstract
A proper treatment or effective vaccine for HIV positive patients is still a dream to the doctors and Scientist although several drugs have been used for the chemotherapy of HIV infections. Monitoring the patients CD_4^+T count and viral load for every period is expensive and also has some practical difficulties. For avoiding this kind of problem, the prediction of viral load is very much essential for the treatment of patients. In the existing HIV Replication models, most of them are non- linear mixed effects models. Some of the models are developed by the differential equations. From these models finding the solution of the parameters are very difficult. Some of the researchers used the Bayesian methodology in which selection of prior distribution is improper. So, an attempt has been made in this research, finding the predictive distribution of viral load for the future period using Exponential Distribution as Prior by the Bayesian methodology.

Keywords: Viral replication, CD_4^+T cells dynamic, exponential distribution and predictive distribution

Introduction
In the HIV infection, immune power variation in the blood plasma is indicated by the changes of $CD_4{}^+T$ lymphocyte counts and viral load. These $CD_4{}^+T$ lymphocyte counts and viral load of infected patient are commonly used to guide clinical decisions regarding drug theraphy. The random fluctuations of these indicators create the significant change in the clinical trials. In the clinical trials, normally reconstitution of the $CD_4{}^+T$ cells pool, happened a substantial proportion of patients. Obtaining long term reconstitution of the $CD_4{}^+T$ cells pool and its efficiency is very difficult, when followed the co-adjustant treatment, the effect of clinical trials only measured by expected variation between the $CD_4{}^+T$-cell count and plasma RNA levels. The number of $CD_4{}^+T$ cells expressing the ki67 proliferation marker hereafter called $CD_4{}^+T$ count and ki67 count respectively. Measurements of $CD_4{}^+T$ counts were made every 3 months while ki67 counts were measured at weekly patients $CD_4{}^+T$ cells count between 100 – 350 cells/μL and (100 – 400 cells/ μL) their age ≥ 18 years. As year 2015 reference, approximately 285 million people living with HIV are eligible for treatment ($CD_4{}^+T < 500$), but currently have no access to antiretroviral therapy. Reduced serum level of micronutrients is common in HIV disease. Micronutrients supplementation may mitigate disease progression and mortality. General assumption that peripheral blood $CD_4{}^+T$ counts (1000/mm^3) are a good indicator for $CD_4{}^+T$ densities. At the pretreatment, $CD_4{}^+T$ lymphocyte counts from 36 to 490 per mm^3 and viral levels from 15 x 10^3 to 554 x 10^3 virions per ml respectively David. D. Ho. *et al.* (1995) [18]. Human immune deficiency virus (HIV) infection and treatment with anti retroviral nucleoside analogues (nucleoside reverse transcriptase inhibitors or NRTIs) affect mitochondrial DNA content and its function. A number of important clinical syndromes observed in HIV- infected persons relate to mitochondrial dysfunction, including lactic acidosis, myopathy, cardio myopathy, pancreatitis, peripheral neuropathy and possibly lipodystrophy.

Viral Dynamic's Models are based on the following indicators of uninfected cells (T) can become infected by virus (V) to generate productively infected cells (I), long-lived cells (M) or latently infected cells(L). Latent infected cells may divide, sustaining this pool, which leaks to the productive.

Pathogenesis of human immune deficiency virus infection are linked closely to the viral replication. In the best of our knowledge, there is no existing statistical frame work to systematic model and estimate the viral replication. Weekly Monitoring $CD_4{}^+T$ counts and viral load of the infected persons is expensive. Therefore this paper focuses the predictive distribution of viral replication when $CD_4{}^+T$ counts rate is increasing nature due to the anti retroviral therapy. By using Bayesian methodology, joint predictive distribution of viral load, and $CD_4{}^+T$ counts has been derived and obtain marginal distribution of $CD_4{}^+T$ count from the joint predictive distribution. Finally predictive joint and marginal distributions of viral load and $CD_4{}^+T$ counts are illustrated through the graphs.

Review of Literatures about Hiv Models

Rachel Waema1 (2005) Developed HIV/AIDS epidemic models by using Generating functions (GF) and with a conceptual framework which summarizes all the concepts of HIV/AIDS transmission models. Stochastic models based on Mother to child transmission (MTCT), Heterosexual transmission and Combined models were developed. By using the stochastic models formulated, and also demonstrated how various factors affect the expectations of susceptible and infective persons. Onoja Matthew Akpa and Benjamin Agboola Oyejola (2010) [13] reviewed some of the models proposed by various authors for describing the epidemiology as well as the epidemiological consequences of the HIV/AIDS epidemic as they focused on deterministic models. HIV transmission dynamics when the population divided into compartments consisting of those who are susceptible, in each of the infection stages, or in the AIDS phase. Basavarajaiah. D. M. *et al.* (2012) [11] fitted mathematical models, which exhibit two equilibriums namely, the disease-free and the endemic equilibrium. Consider a population of size N (t) at time *t* with constant inflow of susceptible with rate пN. The population size N(t) is divided into five subclasses which are susceptible S(t), infectives I(t) (also assumed to be infectious), pre-AIDS Patients P(t) treated class T(t) and AIDS patients A(t) with natural mortality rate μ in all classes. α is the disease induced death rate in the AIDS patients' class and ϑ the rate at which AIDS patients get treatment. Shane T. Jensen *et al.* (2013) [10] presented a statistical model for quantifies the evolution of HIV populations when exposed to particular therapies. A hierarchical Bayesian approach is used to estimate differences in rates of nucleotide changes between treatment and control group sequences. Each group's rates are allowed to vary spatially along the HIV genome. They employed a coalescent structure to address the sequence diversity within the treatment and control HIV populations. They evaluated the model in simulations and estimate HIV evolution in two different applications: a conventional drug therapy and an antisense gene therapy. R. Lakshmajayam and G.Meenakshi (2014) [6] Explained a mathematical model of HIV replication model for the succeeding period, which is numerically illustrated through David *et al.* (1995) [18] data. Daniela De Angelis *et al.* (2014) [7] estimated HIV prevance through the posterior distribution approach. Navjot Kaur1 *et al.* (2014) [8] The heterosexual transmissions of HIV/AIDS and formulate the mathematical model by dividing the total adult population under consideration into three different classes: male, female and female sex workers. and organized the formulation of nonlinear ODE model, describes the basic properties of the model through the computation of basic reproduction number and the stability analysis the numerical simulations to verify our theoretical. R. Lakshmajayam and G. Meenakshi (2015) [2, 3] described the model for HIV replication in the infected CD4+ 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. R. Lakshmajayam and G.Meenakshi (2015) [2, 3] Explained the determination of average HIV replication in the blood plasma using truncated logistic model. This model can be used for future studies of HIV intracellular replications. Alan S explained the diagram of Viral Dynamics model based on the various components of CD_4^+ T cells. Uninfected cells (T) can become infected by virus (V) to generate productively infected cells (I), long-lived infected cells (M) or latently infected cells (L). Only a small fraction of CD_4^+ T cells in the periphery become infected with HIV and thus identifying the target cells in this model is not straightforward. However, the model is able to describe the kinetics of T-cell depletion. Ioannis Andrianakis *et al.* (2015) [4] fitted complex models to real world data having large numbers of input and output parameters. They presented a present a novel method that has the potential to improve the calibration of complex infectious disease models (hereafter called simulators).They presented this in the form of a tutorial and a case study match a dynamic, event driven, individual based stochastic HIV simulator, using extensive demographic, behavioural and epidemiological data available from Uganda. Khangelani Zuma and Goitseone Mafoko (2015) [5] considered an approach for estimating parameters when infection time is unknown and assumed correlated within an EA (enumerator areas) where dependency is modeled as frailties assuming a normal distribution for frailties and a Weibull distribution for baseline hazards. The data was from a household based population survey that used a multi-stage stratified sample design to randomly select 23,275 interviewed individuals from 10,584 households of whom 15,851 interviewed individuals were further tested for HIV. The existing models are mostly illustrated HIV infection in the classical methodology. In this paper concentrated bayesian methodology for prediction of viral replication.

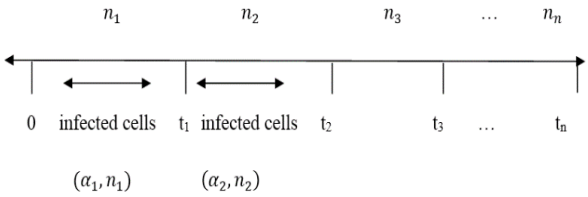
Modeling of viral replication

- Initially viral infection take place is binding of a viral RNA with CD_4^+ T cell's DNA, such a type of binding CD_4^+ T cell is called as blanket cells. Finally the blanket cells broken out and released number of the replicated virus after during the period of seroconversion. The period of seroconversion may be varied according to the infected person's immune power.

Assumptions of the model

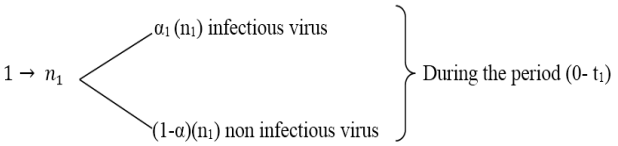
- Initially assume that a virus is bind with a CD_4^+ T cell.
- α is the probability that virus becomes infectious.
- A certain time interval [0,t] can be divided into n periods, assumed to be $(0 - t_1)$, $(t_1 - t_2)\ldots (t_{n-1} - t_n)$.
- In first stage time $(0,t_1)$ there are n_1 number of cells released. From this (n_1,α_1) will be infectious virus, remaining $(1-\alpha_1)$ n_1 may be non infectious virus.
- In the second stage, there are $1+(1-\alpha_1)n_1$ viruses denoted by n_2, among these n_2 viruses α_2 will be infectious, remaining $(1-\alpha_2)n_2$ are non infectious.
- The following is illustrated for the various stages of HIV replications during the period $[0,t_n]$.

Number of virus released for n stages

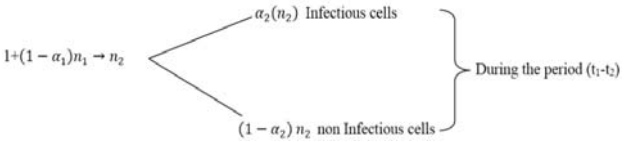


Period of infection

In the I[st] stage: (sero conversion period) $(0,t_1)$



In the II stage number of infected virus is $(1-\alpha_1)\ n_1$ over the period (t_1,t_2)



In the III stage number of infectious virus is denoted by $(1-\alpha_2)\ n_2$, where α_1 and α_2 are the percentage of the infected HIV number from the previous stages.

The same way the replication may be carried out over the n period, and every period is considered as 3 months. Over the n period number of virus released is considered as random variable, which is distributed as logistic. Therefore the following Bayesian methodology is developed for the predictive distribution of largest replication over the n period, and find the distribution of n[th] order statistic (highest replication over the period) is obtain by the following method

$$f(y/\mu,\tau) = \frac{e^{-\left(\frac{(y-\mu)}{\tau}\right)}}{\tau\left[1+\ e^{-\left(\frac{(y-\mu)}{\tau}\right)}\right]^2}, \quad \mu > 0, \tau > 0$$

Where μ is the average viral replication per period and τ^2 is the variation among the replication over the period.

$$F(y/\mu,\tau) = \frac{1}{\left[1+\ e^{-\left(\frac{(y-\mu)}{\tau}\right)}\right]^2}, \quad \mu > 0, \tau > 0$$

Then the joint density function of $y_1, y_2, y_3, \ldots, y_n$ is given by

$$\prod_{i=1}^{n} f(y/\mu,\tau) = \prod_{i=1}^{n} \frac{e^{-z}}{(1+e^{-z})^2},$$

where $z = \left(\frac{y-\mu}{\tau}\right)$

Let $y_1, y_2, \ldots, y_n$ are number of viral replication over the n period of a HIV infected person. Over the n[th] period, the number of virus released as random variable which is largest number n^{th} order statistics as considered $y_1 < y_2 < y_3 \ldots < y_n$ and its density is given by

$$f_y(y_n) = n\left[f_y(y_n)\right]^{n-1} f_y(y_n)\backslash$$

$$= n\left[\frac{1}{(1+e^{-z})^2}\right]^{n-1} \frac{e^{-z}}{\tau(1+e^{-z})^2}$$

On simplification

$$= \frac{n}{\tau}\frac{e^{-z}}{(1+\ e^{-z})^{2n}}$$

where $z = \frac{y_n-\mu}{\tau}$ and μ is the average of HIV replication over the period.

The prior density of the parameter μ is assumed to be exponential with parameter θ *and* α.

$$p(\mu) = \theta e^{-\theta(\mu-\alpha)}, \alpha > 0, \theta > 0, \mu > 0$$

The posterior density of the largest replication is given by,

$$p(\mu/y_n) \propto f_y(y_n).p(\mu)$$

$$\propto \frac{\mathrm{n}}{\tau}\ (1+\mathrm{e}^{-z})^{-2n}\mathrm{e}^{-z}\theta\mathrm{e}^{-\theta\,(\mu-\alpha)}$$

On simplification

$$= \frac{\mathrm{n}\theta\ \mathrm{e}^{-\theta(\mathrm{y_n}-\alpha)}}{\tau}\ \frac{e^{-az}}{(1+e^{-z})^{2n}}$$

where $z = \frac{y_n-\mu}{\tau}$, $z\tau - y_n = -\mu$ and $(\ 1-\ \tau\theta) = a$

The normalizing constant is given by

$$\frac{n\theta}{\tau}\int_{y_n/\tau}^{\infty} \frac{\mathrm{e}^{-\theta(\mathrm{y_n}-\alpha)}\ e^{-az}}{(1+e^{-z})^{2n}}dz = d.$$

$$\frac{n\theta\ \mathrm{e}^{-\theta(\mathrm{y_n}-\alpha)}}{\tau}\int_{y_n/\tau}^{\infty} \frac{e^{-az}}{(1+e^{-z})^{2n}}dz = d.$$

let $u = e^{-za}$, $dv = (1+e^{-z})^{-2n}$

$du = -ae^{-za}$, $v = \frac{(1+e^{-z})^{-2n+1}}{-2n+1}e^{-z}(-1)$

On simplification

$$d = e^{-a\left(y_n/\tau\right)}.$$

The posterior density is given by

$$p(\mu/y_n) = \frac{1}{d}\ f_y(y_n).p(\mu)$$

$$= \frac{1}{d}\frac{(e^{-z})^a}{(1+e^{-z})^{2n}}$$

Where $a = (1-\theta\tau)$

The predictive density is obtained by averaging out the parameter μ from the posterior density. It is given by

$$g(y_n/\mu) = \int_0^\infty p(\mu/y_n) f_y(y_n/\mu) d\mu$$

$$= \frac{1}{d} \int_0^\infty \frac{e^{-az}}{(1+e^{-z})^{2n}} \frac{e^{-z}}{(1+e^{-z})^2} d\mu$$

On simplification

$$= \frac{\sum_{i=1}^{\infty}(a+1)^i \sum_{i=1}^{2n+3}(-1)^i}{d\tau \sum_{i=1}^{2n+3}\binom{2n+3}{j}} \int_{y_n/\tau}^{\infty} \frac{z^i}{(z^i)^j} dz$$

$$= A \int_{y_n/\tau}^{\infty} z^i (z^i)^{-j} \, dz$$

$where\ z = \frac{y_n - \mu}{\tau}$ and $A = \frac{\sum_{i=1}^{\infty}(a+1)^i \sum_{i=1}^{2n+3}(-1)^i}{d\tau \sum_{j=1}^{2n+3}\binom{2n+3}{j}}$

$$= A \int_{y_n/\tau}^{\infty} z^i \, z^{-ij} dz$$

$$= \left[\frac{z^{i(1-i)}}{i(1-j)+1}\right]_{y_n/\tau}^{\infty}$$

$$= \frac{\sum_{i=1}^{2n+3}(-1)^i}{d\tau \sum_{j=1}^{2n+3}\binom{2n+3}{j}} \left[\frac{\sum_{i=1}^{\infty}(a+1)^i z^{i(1-j)}}{i(1-j)+1}\right]$$

$on\ simplification$

$$= \frac{e^{-(a+1)\, y_n/\tau}}{e^{-a\ y_n/\tau}\ \tau\left(\sum_{j=1}^{2n+3}\binom{2n+3}{j}\right)},$$

$$g(y_n/\mu) = \frac{e^{-y_n/\tau}}{\tau s}$$

Where

$$s = \sum_{j=1}^{2n+3}\binom{2n+3}{j}$$

$$d = e^{-a\, y_n/\tau}$$

Let CD_4^+T cells depletion is considered as random variable. It may be naturally decreasing after the HIV infection of the patients. Therefore consider its density function is the following form

$$f(x) = \frac{a^x e^{-x}}{b^x}\ if\ 0 < x < \infty, a, b > 0, a < b.$$

and its distribution function is given by

$$F_X(x) = \frac{e^{-x}\left(a/b\right)^x}{\log\left(a/b\right)+1}\ a < b, x \in [50,500]$$

Where

$$\int_0^\infty \frac{e^{-x}a^x}{b^x} dx = \int_0^\infty \left(\frac{a}{b}\right)^x e^{-x}\, dx$$

$on\ simplification$

$$= \frac{P^x e^{-x}}{(L+1)}$$

$$= \frac{e^{-x}(a/b)^x}{\log\left(\frac{a}{b}\right)+1}$$

Where $L = \log\left(\frac{a}{b}\right)$

The predictive distribution of largest HIV replication and corresponding depletion density is given by

$$g(x,y) = \left(e^{-x}\left(a/b\right)^x . c\right)\frac{e^{-y/\tau}}{\tau s}$$

$$g(x,y) = e^{-x}\left(a/b\right)^x e^{-y} w$$

$$= we^{-(x+y)}\left(a/b\right)^x$$

$$= we^{-z}\left(a/b\right)^v |J|$$

$$= we^{-v}\left(a/b\right)^v e^{-y}$$

$$= we^{-y}\left(a/b\right)^v$$

$$= we^{-v}\left(a/b\right)^v e^{-y}$$

since $|J| = 1$, $where\ y_n = y\ and\ \frac{c}{\tau s} = w$

$$s = \sum_{j=1}^{n+1}(n+1)c_j, c = \frac{1}{L+1}$$

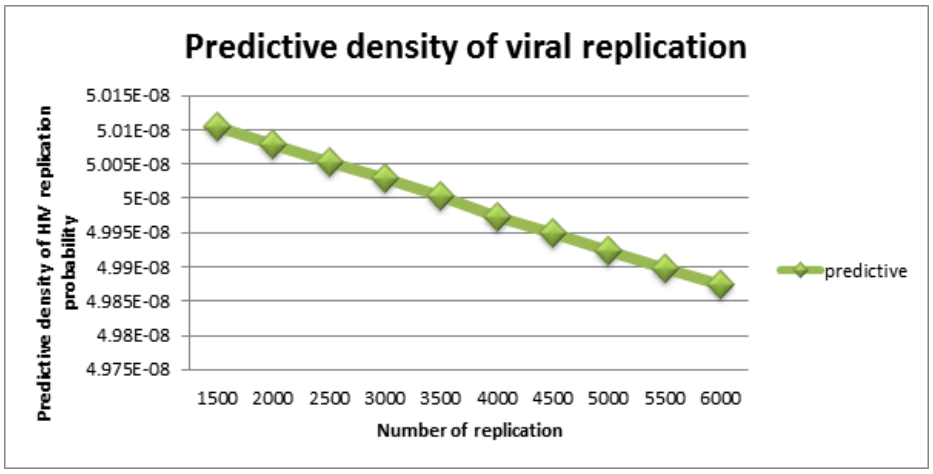
$L = \log\left(a/b\right)$, J $>$ 0 and $b > a$.

a and b the integers and y_n is the largest HIV replication over the period.

Integrate with respect to x to get the marginal density of y is we^{-y}.

Predictive density table for viral replication

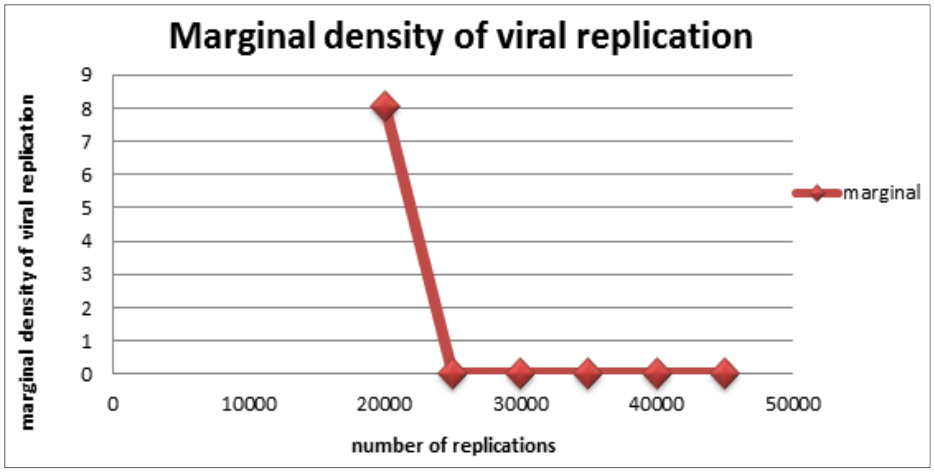
Viral Replication Per Period / µL Y in $(10)^2$	$e^{-y_n/\tau}$	$\frac{e^{-y_n/\tau}}{\tau s}$
1500	0.9984	$5.010384365\times 10^{-8}$
2000	0.9979	$5.007875158\times 10^{-8}$
2500	0.9974	$5.005365952\times 10^{-8}$
3000	0.9969	$5.002856745\times 10^{-8}$
3500	0.9964	$5.000347538\times 10^{-8}$
4000	0.9958	$4.997336489\times 10^{-8}$
4500	0.9953	$4.994827282\times 10^{-8}$
5000	0.9948	$4.992318076\times 10^{-8}$
5500	0.9943	$4.989808869\times 10^{-8}$
6000	0.9938	$4.987299662\times 10^{-8}$



From the above graph, when the viral replication increases in certain stage corresponding predictive density is decreasing. From this it is observed that replication is very much crucial condition to the patients for his life time is questionable.

Marginal density table for viral replication

Viral Replication Per Period / µL Y	Marginal Density of Viral Replication we^{-y}
20000	8.055054716
25000	$6.004376057\times 10^{-2}$
30000	$4.229875079\times 10^{-4}$
35000	$2.922504595\times 10^{-6}$
40000	$2.001785963\times 10^{-8}$
45000	$1.364220855\times 10^{-10}$

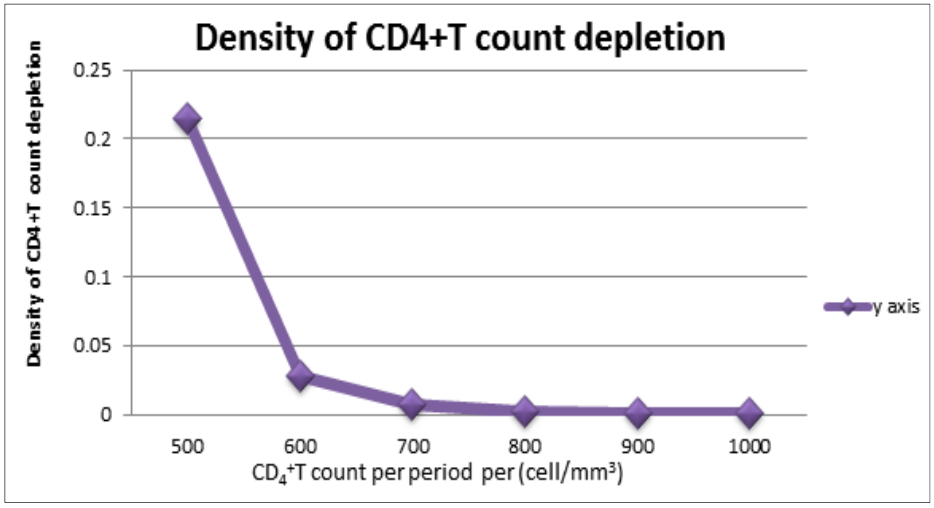


From the above graph, Marginal density of viral replication goes to negligible when rapid growth of virus at that stage patient may be going to die.

$CD^{+}{}_{4}T$ Count Per Period of a Patient

$CD^{+}{}_{4}T$count/ µL x	*a*	*b*	$e^{-x}\left(a/b\right)^{x}$
500	*10*	*5*	0.2144
600	*15*	*10*	0.0273
700	*20*	*15*	0.0067
800	*25*	*20*	0.0017
900	*30*	*25*	0.0005
1000	*35*	*30*	0.0001

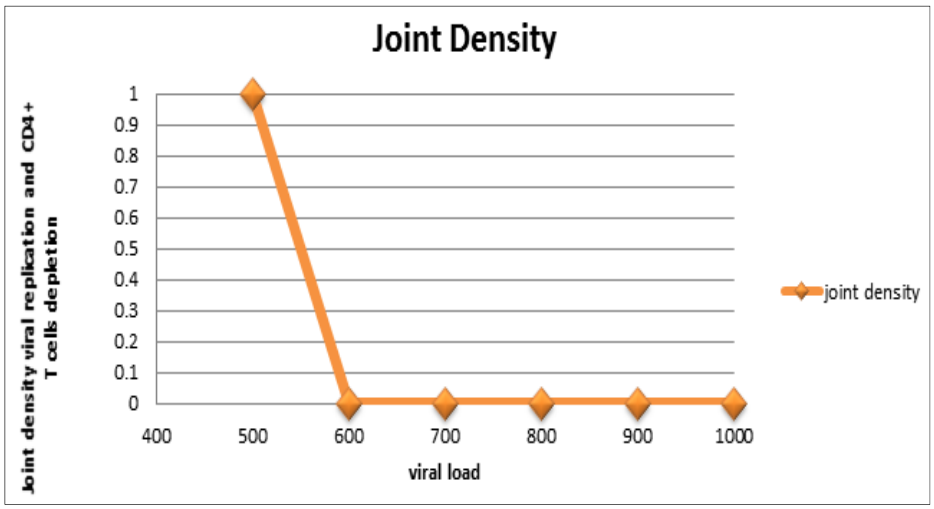
Density of $CD_4{}^{+}$ T count Depletion



When depletion of the $CD_4{}^{+}T$ count is raising after certain stages, the probability of $CD_4{}^{+}T$ count depilation is stable goes to zero. From this period the $CD_4{}^{+}T$ count generation is maximum (1000) may be damaged.

Joint density table for viral replication and $CD_4{}^{+}$ T cell depletion

Viral Replication Per Period / µL Y	$we^{-y}e^{-v}\left(a/b\right)^{v}$
1000	$1.364220855\times 10^{-14}$
900	$1.000892982\times 10^{-11}$
800	$4.968257812\times 10^{-9}$
700	$2.833681303\times 10^{-6}$
600	$1.639194664\times 10^{-3}$
500	1.000000



When $CD_4{}^{+}T$ cells depletion, viral replication also decreases. Their joint density is gradually increasing at the stage of minimum $CD_4{}^{+}T$ cells count at 600.

4. Conclusion

When the HIV infected person's viral load is gradually increases at the stage of depliation of CD_4^+T-cells count, In this stages the measuring viral load and damaged $CD_4{}^+T$ -cells for future period is very much essential to suggest the medicine for further period to prolong the human life time. The Doctors and Scientists combat to treat HIV positive patients prediction of viral load very much essential. Still, there is no a proper treatment or effective vaccine for HIV positive patients. The only way to extend their life time by, the determination of viral load for the future period. The researcher has developed a HIV replication model for the succeeding period for the viral dynamics. The proposed model is used for prediction of viral load for succeeding period.In this research the predictive density of viral replication and the joint density of viral replication and $CD_4{}^+T$ depliation gradually ofter the certain stage.This model will very of much useful for prediction of drug to the department of Drug production, the policy makers, Insurance Department, Bio Statistics Department and all departments deal with epidemic.

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