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Hiv Replication Model for The Succeeding Period Of Viral Dynamic Studies In Aids Clinical Trials

R. Lakshmajayam[1] and G.Meenakshi[2]
[1.] Ph.D., Research scholar, [2.] Professor of Statistics
Department of Statistics, Annamalai University, Annamalai Nagar-608002.
Tamil Nadu, India.

ABSTRACT: *Perelson et al. (1993) proposed an ODE model of cell-free viral spread of HIV. Their model consists of four components: uninfected healthy CD_4^+T-cells, latently infected CD_4^+T-cells, actively infected CD_4^+T-cells, and free virus. Rebecca et al. (2000) introduced another model which describes the time between infection of a CD_4^+T-cells and the emission of viral particles on a cellular level. This paper includes HIV replication model for the succeeding period, which is numerically illustrated by David et al. (1995).*

KEYWORDS: *Viral Load, CD_4^+T-Count, HIV-Dynamic Model, Prior Distribution, Posterior Distribution, HIV Replication.*

I. INTRODUCTION:

The study of HIV dynamics is an important recent AIDS research. The recent development of clinical studies on HIV-I dynamics is having a strong impact on HIV/AIDS research. HIV dynamic models are specified by the non-linear mixed effects model, because of the existence of heterogeneity. Most of the existing HIV dynamic models with Anti-viral treatments are considered as ordinary differential equations. The ordinary differential equation cannot be solved analytically. Therefore, most of the researches followed are meant to estimate the parameter using the Bayesian approach with the same prior distribution used. This approach is not suitable for this study. This paper introduces a new model for HIV replication. It is also designed to find out the HIV count of the succeeding period in the plasma.

REVIEW: The virus dynamic data are modeled by Yuh *et al.* (1994) and Wu and Ding (1999). Lee and Nelder (1996) have introduced the hierarchical likelihood for generalized linear models with random effect. Further, Lee and Nelder (2001) and Lee *et al.* (2006) studied non linear models with mixed effects. The authors have revealed difficulties in estimation. Then, Wu and Ding (2002) were evaluated the efficacy of antiviral treatments in HIV dynamics by the Monte Carlo simulations and analytic methods. In this method identification of treatment difference and relative efficiency are very sensitive. Then Putter *et al.* (2002) and Huang *et al.* (2006) have proposed the specific case of HIV dynamic models and parameter estimated by the Bayesian approach.

Bortz and Nelson (2005) have compared six published deterministic models and employed a hierarchical mixed effects modeling approach to characterize the inter and intra-individual variability in the patient population. They used information theory to estimate the population parameter. In this model selection of criteria was based on the ability of patient. Huang *et al.* (2006) proposed special algorithm for computing the likelihood. This method is very difficult and also time consuming. Recently Commenges *et al.* (2010) treated hierarchical approach and penalized likelihood. The maximum h-likelihood estimator (MHLE) of asymptotic distribution of mixed effects is biased. Bias can be neglected if the parametric bootstrap procedure is considered. This is not suitable for analysis of the clinical trial. Nowak and Bangham (1996) proposed a particular HIV dynamics model which is given by

$$\frac{dT^i}{dt} = \lambda^i - \gamma^i T^i V^i - \mu_T^i T^i \quad \rightarrow (1)$$

$$\frac{dT^{*i}}{dt} = \lambda^i - \gamma^i T^i V^i - \mu_{T^*}^i T^{*i} \quad \rightarrow (2)$$

$$\frac{dV^i}{dt} = \pi^i T^{*i} - \mu_V^i V^i \quad \rightarrow (3)$$

Where T^i, T^{*i} represent the concentration of non-infected and infected CD_4^+ respectively and V^i is concentration of virus. HIV dynamic model is a system of differential equation. The analytical solution is not easy to obtain.

Wu and Ding (1999) who used the differential equation model have simplified into a bi-exponential model of the viral concentration. This is considered as

$$V(t) = P_1 e^{-d_1 t} + P_2 e^{-d_2 t} \quad , \quad t > t_c \qquad \rightarrow(4)$$

Where P_1 and P_2 are functions of coefficient underlying the differential equations and t_c is the time (1 to 3 days) and $d_1 = [1 - R_1(1 - e_1)]\delta$ and $d_2 = \left(1 - R_2 \frac{1-e_2}{e_1}\right)\mu_1$

Where R_1 and R_2 are the baseline reproduction /clearance ratio of virus from the two infected cell components (Productivity and long-lived / latently infected cells). e_1 and e_2 are treatment effects in these two components, and δ and μ are death rates of productively and long-lived / latently infected cells. The e_1 and e_2 potency cannot be determined directly from d_1 and d_2 because the parametersR_1,R_2, δ and μ are unknown. Wu and Ding (2002) study fits the bi-exponential model of variation in viral level measurement which is given by

$$Y_{ij} = log_{10}(e^{P_{ij} - d_1 t_{ij}} + e^{P_{2i} - d_2 t_{iy}}) + \varepsilon_{ij}, \qquad \rightarrow(5)$$

$$\xi_i/\beta_i \sim (0, R_i(\beta_i, \xi))$$

Where Y_{ij} is the log-transformation of the measurement of total viral load for the i^{th} subject and at the j^{th} time point $t_{ij}, i = 1, \ldots, n, j = 1, \ldots, m_i$. The viral dynamic parameters for the i^{th} subject are denoted by $\beta_i = [P_{1i}, d_{1i}, P_{2i}, d_{2i}]'$. The within-subject error $\xi_i = [\xi_{i1}, \ldots, \xi_{imi}]'$ is assumed to have Mean and variance covariance matrix $R_i(\beta_i, \xi_1)$ and between – subject variation are,

$$P_{1i} + b_{1i}, \qquad P_{2i} = P_2 + b_{2i}, \qquad \rightarrow(6)$$

$$d_{1i} = d_1 + b_{3i}, \qquad d_{2i} = d_2 + b_{4i}, \qquad \rightarrow(7)$$

Where the population parameters are denoted by $\beta = [P_{1i}, d_{1i}, P_{2i}, d_{2i}]'$. Random effect is $b_i = [b_{1i}, \ldots, b_{4i}] \sim (0, D)$.

In a clinical trial design to find out the optional time, the viral change was considered as a marker for treatment potency by using simulation studies. The robustness against parameter values in the viral dynamic models is carried out by a sensitivity analysis.

The bi-exponential model (4) or (5) is an approximation model used to complete viral dynamic model by the approximation in the simulations studies. Therefore it is generate the tri-exponential model from the simulated data, which is more accurate since it includes the "shoulder" effect (Pearson *et al.* (1996), Herz *et al.* (1996), Mittler *et al*. (1998), Wu and Ding (1999)).

$$Y_{ij} = \left(log^{P_{0i} - d_{0i} t_{ij}} + e^{P_{1i} - d_{1i} t_{ij}} + e^{P_{2i} - d_{1i} t_{ij}}\right) + \xi_i \qquad \rightarrow(8)$$

The between- subject variation of parameters is defined in Eqn. (6) and (7). There are too many parameters in the models and the sensitivity analysis is difficult. Therefore they focus an$P_0 - P_1$, $P_2 - P_1$ and d_1 in the sensitivity analysis. (Perelson et al. (1996), Han et al. (2002)) considered the non-linear mixed effects model for HIV dynamics under protease inhibitor monotherapy is

$$Y_{ij}/V_{0i}, c_i, \delta_i, \sigma^2 \overset{ind.}{\sim} N(S(V_{0i}, c_i, \delta_i, c_j), \sigma^2), \qquad \rightarrow(9)$$

$$(logV_{0i}, log\, C_i, log\, \delta_i)^T/V_0, c, \delta, \Sigma \overset{\text{i.i.d}}{\sim} N(\mu, \Sigma) \qquad \rightarrow(10)$$

Where $\mu = (logV_0 \quad logC \quad log\delta)^T$ and

$$S(V_{0i}, c_i, \delta_i, t_j) = logV_{0i} + log\left[\frac{c_i^2}{(c_i - \delta_i)^2} e^{-\delta_i t_j} - \frac{c_i^2 - (c_i - \delta_i)^2}{(c_i - \delta_i)^2} e^{-c_i t_j} - \frac{c_i \delta_i t_j}{(c_i - \delta_i)} e^{-c_i t_j}\right]$$

For subject i, Y_{ij} is the natural logarithm of the plasma concentration of HIV particles at time t_j after the pharmacologic delay of the drug effects, V_{0i} is the plasma concentration of HIV particles at treatment initiation; c_i is the virion clearance rate; and δ_i is the rate at which the infected cells die. The expression $\delta(V_{oi}, c_i, \delta_i, t_j)$ is obtained by solving differential equations that describe the transactions among virus particles target cells and infected cells.Putter *et al.* (2002) described a model in that the population dynamic of HIV and its target cells in plasma are used extensively by a number of authors like McLean et al (1991) and Nowak *et al.* (1997).It is seen that the problem of solving the differential equations analytically is very difficult. So, the parameter $\theta = (\lambda, \rho, \beta, \delta, k, \gamma, \eta, \omega)^T$ estimation was discussed a Bayesian modeling approach to a non-linear random effect by Lee and Nelder (1996) ,Lee and Nelder (2001) and Lee *et al.* (2006).Whereas,

$$\mu_{ij} = f_2(\vec{\theta}_i; t_{ij}), \qquad \tilde{w}_{ij} = log_{10}(HIV - RNA)_{ij}$$

$$V_{ij} = f_1(\vec{\theta}_i; t_{ij}), \qquad z_{ij} = (CD_4)_{ij}$$

The basic reproductive ratio $R_0's$ median is estimated from the derived posterior distribution and density of the predictive distribution of $R_0 = \exp(\hat{\lambda} + \hat{\beta})$ using Gibbs sampling procedure.Bayesian optimal

design for non-linear mixed- effects models has been studied by Stroud *et al.* (2001) who assume that the same prior distribution is used for estimation and prediction. Cong and Kathryn (2004) showed the existence of the posterior risk for the parameter estimator in the Bayesian analysis of non-linear mixed effects model of HIV dynamic. This is considered when the same prior distribution is used. A quadratic loss function is used for the estimation of μ the population mean of the random effect in the mean function $L(\mu - a) = (\mu - a)^T(\mu - a)$. The Bayes estimator of μ is $E(\mu/y)$. The posterior variance is obtained by MCMC method. [Han, Chalonar and Perelson (2002)]

Bortz and Nelson (2005) compared six existing deterministic models with respect to their ability to represent HIV infected patients undergoing reverse transcriptase mono-therapy. In creation of statistical model, a hierarchical mixed effect modeling approach is employed to characterize the inter and intra individual variability in the patient population. Information theory (Akaike (1973)) is used for the model selection and estimated the population parameters from the data which is reported in an experiment by Louie *et al.* (2003).

A Bayesian analysis for a population HIV dynamic model was investigated by Han *et al.* (2002) and Putter *et al.* (2002) in which they used short-term viral load data to estimate the parameters and they also assumed that the drug efficacy was constant over time. Huang et al. (2006), proposed a mechanism - based dynamic model for characterizing long- term viral dynamics with antiretroviral therapy, described by a set of nonlinear differential equations without closed form solutions.In this model they directly incorporate drug concentration, adherence and drug susceptibility into a function of treatment efficacy defined as inhibition rate of virus replication (Molla *et al*. (1996)) Drugs had perfect effect in blocking viral replication (David *et al.* (1995), Perelson *et al.*(1997), Putter *et al*. (2002). They combined a Bayesian approach with mixed effects modeling techniques to estimate both population and individual parameters. This model included the within-subject variations and between variations via hierarchical model framework and these model are flexible in dealing with both is parse and unbalanced longitudinal data from individual subjects by borrowing information from all subjects. The MCMC methods can be employed for easy computation and get closed form solutions to the model. Huang and Wu (2008) focused on design issues evaluated under the setting of a hierarchical Bayesian nonlinear model. They compared a finite number of feasible candidate designs numerically, which are used currently in AIDS clinical trials from different perspectives and provide guidance on how a design might be closer in practice.

MODEL FOR VIRAL DYNAMIC IN BAYESIAN APPROACH: After identification of the HIV infection, the persons were monitoring every period their CD_4^+ lymphocytes count and viral load of plasma per (*ml*) under the treatment conditions (period may be considered three days only. Ref: David *et al.* (1995) and Wu and Ding (1999).Exponential distribution plays an important part in life testing problems. Rate of HIV multiplication may be increasing, therefore, the exponential distribution suitable for this study.Let us assume that numbers of virus released by infected cells are distributed as the exponential with parameter θ_i. The sample information $(x_1, x_2, ..., x_n)$ is the number of virus released by infected cells of n HIV infected persons with various parameters $\theta_i (i = 1, 2, ..., n)$. The likelihood function of the sample information is given by

$$L(x_1, x_2, ..., x_n / \theta_1, \theta_2, ..., \theta_n) = \prod_{i=1}^{n} \theta_i e^{-\theta_i x_i}$$

The prior distributions of the $\theta_i^{'}$ are considered as the Poisson with same parameter λ where $\lambda > 0$ sum of Poisson random variables are the incomplete gamma function (Ref: Fundamentals of Mathematical Statistics S. C. Gupta). Hence the prior distributions of θ_is are taken as the sum of Poisson random variable as the gamma function of the form $\frac{1}{\theta_i!}\int_{\lambda}^{\infty} e^{-t} t^{\theta_i} dt$

(i.e.)
$$g(\theta_i) = \frac{1}{\theta_i!}\int_{\lambda}^{\infty} e^{-t} t^{\theta_i} dt$$
$$= \sum_{\theta_i = 0}^{n} \frac{e^{-\lambda}\lambda^{\theta_i}}{\theta_i!}$$

Then the posterior distribution of θ_i is given by

$$L(\theta_i / x_1, x_2, ..., x_n) = L(x_1, x_2, ..., x_n / \theta_1, \theta_2, ..., \theta_n) g(\theta_i)$$

$$= \frac{\prod_{i=1}^{n} \theta_i e^{-\theta_i x_i} \sum_{\theta_i = 0}^{n} \frac{e^{-\lambda} \lambda^{\theta_i}}{\theta_i!}}{k}, \qquad 0 < \theta_i < \infty \text{ and } \lambda > 0.$$

Where $k = \int_0^{\infty} \theta_i e^{-\theta_i x_i} \sum_{i=0}^{n} \frac{e^{-\lambda} \lambda^{\theta_i}}{\theta_i!} d\theta_i$

Therefore posterior distribution of θ_i.

$$= \frac{\prod_{i=1}^{n} \theta_i e^{-\theta_i x_i} \sum_{\theta_i = 1}^{n} \frac{e^{-\lambda} \lambda^{\theta_i}}{\theta_i!}}{\int_0^{\infty} \prod_{i=1}^{n} \theta_i e^{-\theta_i x_i} \sum_{\theta_i = 1}^{n} \frac{e^{-\lambda} \lambda^{\theta_i}}{\theta_i!} d\theta_i}, \qquad 0 < \theta_i < \infty, \qquad \lambda > 0$$

Let $k = \int_0^{\infty} \prod_{i=1}^{n} \theta_i e^{-\theta_i x_i} \sum_{\theta_i = 1}^{n} \frac{e^{-\lambda} \lambda^{\theta_i}}{\theta_i!} d\theta_i$

θ_i are integers values (i.e.) number virus released by the infected cells. In the prior distribution of the parameters are treated as Pre-treatment stage of the infected persons. At the initial stage, numbers of virus released by the infected cells are minimum. Hence consider only finite number virus released in the Pre-treatment stage.

Therefore $\sum_{\theta_i = 0}^{\infty} \frac{e^{-\lambda} \lambda^{\theta_i}}{\theta_i!} = \sum_{\theta_i = 0}^{n} \frac{\lambda^{\theta_i}}{\theta_i!} + \sum_{\theta_i = n}^{\infty} \frac{\lambda^{\theta_i}}{\theta_i!}$

Since $\sum_{\theta_i = n}^{\infty} \frac{e^{-\lambda} \lambda^{\theta_i}}{\theta_i!} = 0,$ the pretreatment stages average number of HIV replications not considering the infinite number of cells.

Hence $\sum_{\theta_i = 1}^{n} \frac{e^{-\lambda} \lambda^{\theta_i}}{\theta_i!} = e^{-\lambda} \sum_{i=1}^{n} \frac{\lambda^{\theta_i}}{\theta_i},$ where θ_i are only the integer values.

Then $k = \int_0^{\infty} \prod_{i=1}^{n} \theta_i e^{-\theta_i x_i} e^{-\lambda} \sum_{\theta_i = 1}^{n} \frac{\lambda^{\theta_i}}{\theta_i!} d\theta_i$

The conditional distribution of θ_i given $(x_1, x_2, ..., x_n)$ is given by

Hence $P(\theta_i / x_1, x_2, ..., x_n) = \frac{\prod_{i=1}^{n} \theta_i e^{-\theta_i x_i} \sum_{\theta_i = 1}^{n} \frac{e^{-\lambda} \lambda^{\theta_i}}{\theta_i!}}{k}, \qquad 0 < \theta_i < \infty, \lambda > 0$

Finally the Bayes estimator of the θ is given by

$$E(\theta / x_1, x_2, ..., x_n) = \int_0^{\infty} \theta_i P(\theta_i / x_1, x_2, ..., x_n) d\theta_i$$

$$= \int_0^{\infty} \theta_i k^{-1} \prod_{i=1}^{n} \theta_i e^{-\theta_i x_i} \sum_{\theta_i=1}^{n} \frac{e^{-\lambda}\lambda^{\theta_i}}{\theta_i!} d\theta_i$$

$$= k^{-1} \int_0^{\infty} \prod_{i-0}^{n} \theta_i^{\,2} e^{-\theta_i x_i} \sum_{\theta_i=1}^{n} \frac{e^{-\lambda}\lambda^{\theta_i}}{\theta_i!} d\theta_i$$

Sinha (1986) in his book "Reliability and Life testing" the random variables have been treated as a independent and identically distributed as exponential with equal parameter and hence the Fishers information of $\theta = \frac{1}{\theta^2}$. Hence the prior distribution is considered as improper i.e. $g(\theta) = \frac{1}{\theta}$, Therefore $\int_0^{\infty} g(\theta) \neq 1$. In this situation the Bayes estimator of $\hat{\theta} = \frac{n\bar{x}}{(n-1)}$, $g(\theta) = \frac{1}{\theta^2}$. Bayes estimator of $\hat{\theta} = \bar{x}$ .Which is the maximum likelihood as well as uniformly minimum variance unbiased estimator of θ. That assumption is not suitable for infected persons HIV replication rate. Here random variables are independent but not identically distributed. Therefore the researcher decided to fit the HIV replication in the model of the following which is illustrated by the two diagrams of CD_4^+T infection and HIV replication. It is also decided to see the multiplicated number virious for the succeeding periods, which are denoted by $H_1(t)$ and $H_2(t)$, where assumed that CD_4^+T counts at the two periods are constant by using the data David et.al (1995).

II. THE MODEL FOR HIV REPLICATION:

The model is given by

$$H(t_1) = H(t) - d_1 x(t) - (1 - d_1)x(t) - d_2 y(t) + R_2(t) - R_3(t) + e$$

Where

$H(t_1)$ – is denoted by the number of virus plasma per (***ml***^{3})in the next period (Period may be three days only)

$H(t)$ – Existing number of virus in the plasma at the current period.

$x(t)$ – Number of powerful virus to infect the CD_4^+T cells.

$y(t)$ – Number of non-infectious virus of infection.

$R(t)$ – Number of blanket CD_4^+T cells.

$R_2(t)$ –Total Number of multiplicated virus at the end stage of the current period.

$R_3(t)$ –Number of blanket cells dead due to the ART medicines.

$I(t)$ – Number of infected CD_4^+T cells at the current period (susceptible CD_4^+T cells).

$N(t)$ – Number of un-infected CD_4^+T cells at the current period.

e – Error which is distributed as $N(0, \sigma^2)$(measurement error).

Where $H(t) = a\,x(t) + (1 - a)y(t)$

$R(t) = (1 - \delta_1)I(t)$

Where $I(t) = (1 - d_1)\,C$

$R_1(t) = (1 - \delta_3)R(t)$

$R_2(t) = [\delta_4\, R_1(t)] \times P$

$R_3(t) = \delta_5 R_2(t)$

Where δ_5 is the replicative rate of infected CD_4^+T - cells.

The assumptions of the above model are

[1] After identification of HIV infection the patient who has not affected by any other diseases.

[2] Generation of CD_4^+T- cells (growth rate) in the every period (three days) are considered as uniform.

[3] Number of virus released per CD_4^+T are constant per period (three days).

[4] $0 < (a, d_1, d_2, \delta_1, \delta_2, \delta_3, \delta_4, \delta_5) < 1$

Where a –is rate of powerful virus to infect the CD_4^+T cells (per/mm^{-3} plasma).

d_1 – Rate of natural death of powerful virus per period.

d_2 – Death rate of non-infectious virus (per mm^3) per period (three days).

δ_1 – Death rate of infected CD_4^+T cells period (three days) per mm^3.

δ_2 – Natural death rate of non-infected cells per mm^3.

δ_3 – Death rate of blanket CD_4^+T cells per period per mm^3.

δ_4 – Death rate of lysing cells per mm^3.

p – Number of virus released from the each lysing CD_4^+T - cells.

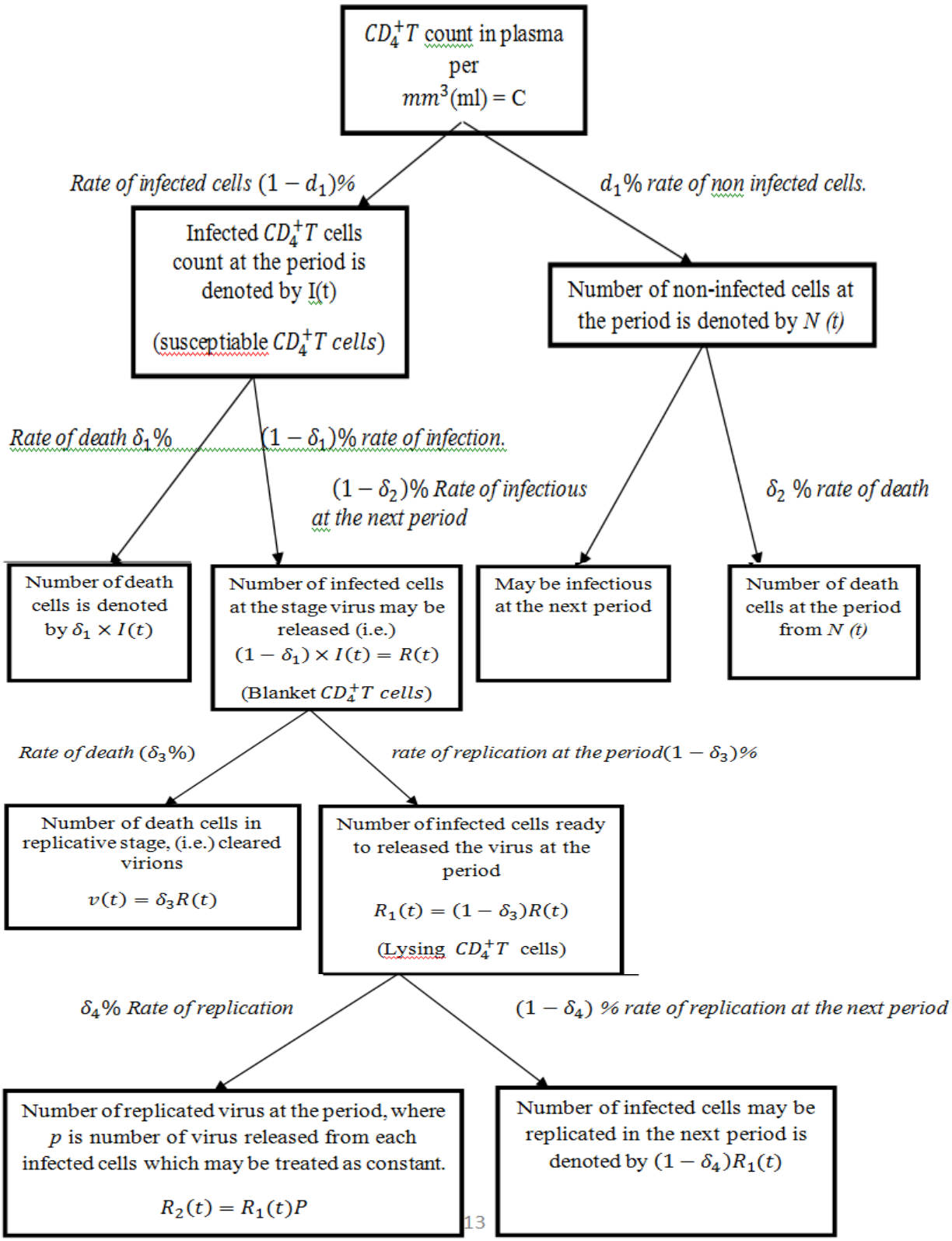


Diagram: 2 **Flow chart of HIV replication**

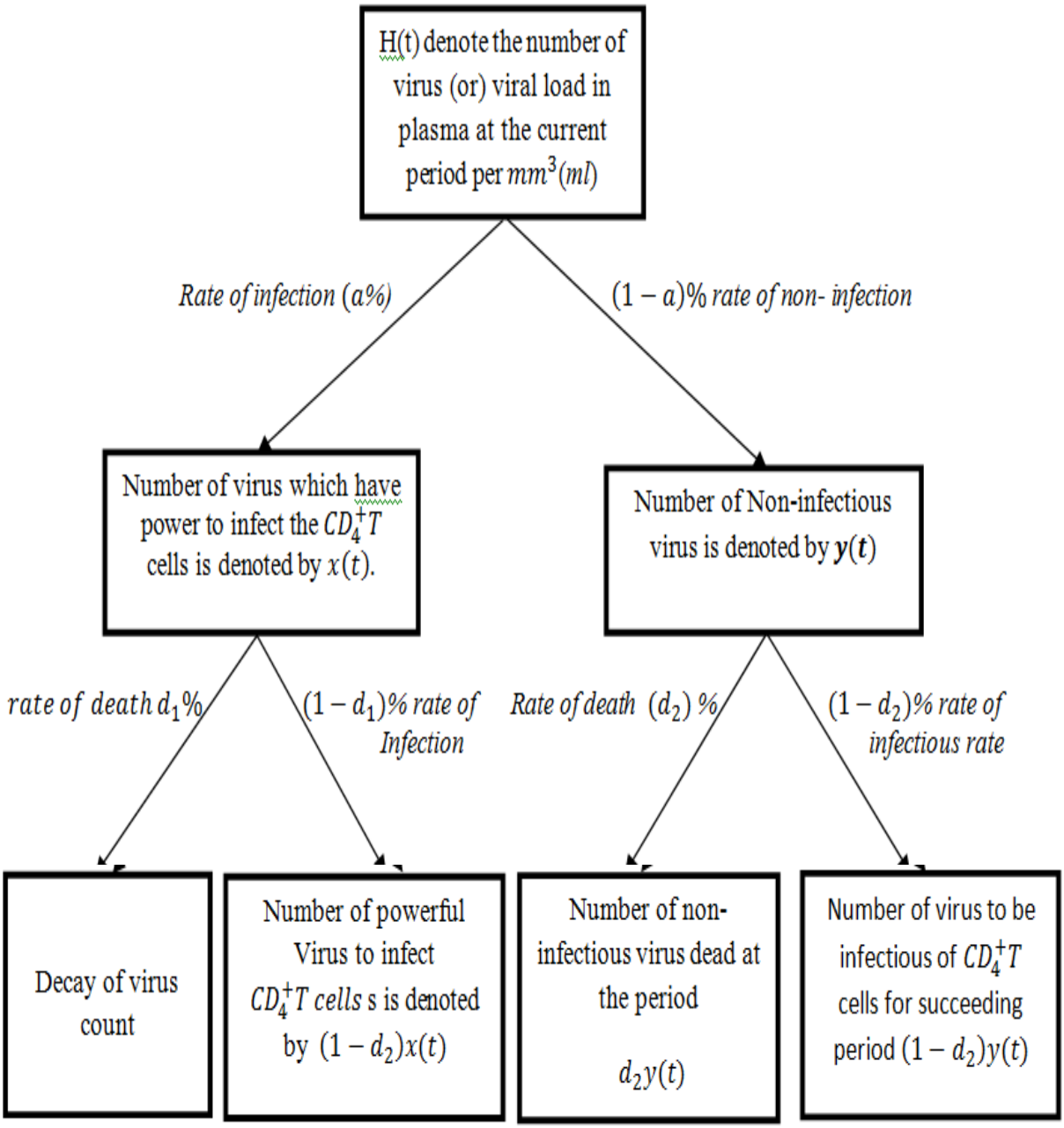


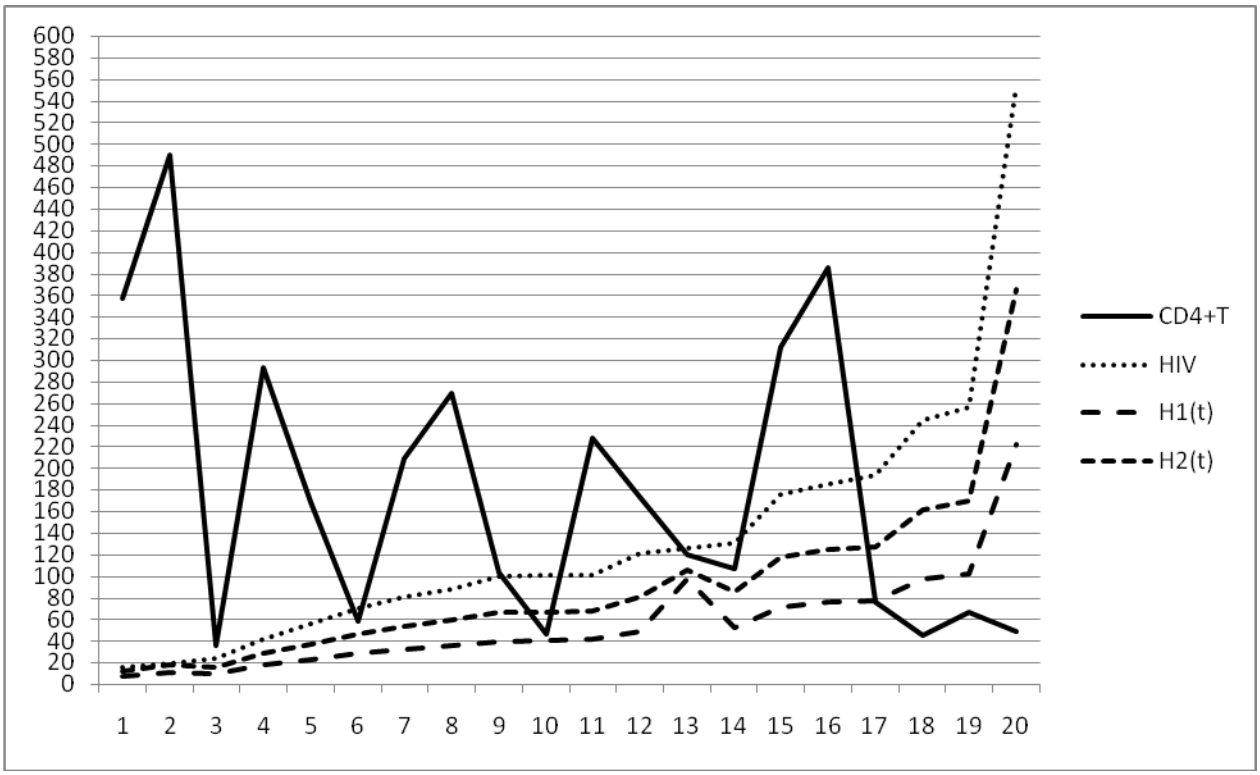
Table of HIV replication for succeeding periods:

CD4 Count	Current Period HIV Count	I st Succeeding Period HIV Count $H_1(t)$	II nd Succeeding Period HIV Count $H_2(t)$
357	15	7	12
490	18	11	18
36	23	9	15
293	41	18	29
169	55	23	37
59	70	28	46
209	80	33	54
269	88	36	59

103	99	40	66
47	100	40	67
228	101	41	68
174	121	49	81
120	126	98	106
107	130	52	86
312	175	71	117
386	185	76	124
76	193	78	127
46	244	98	161
67	256	103	169
49	554	222	365

$a = 0.2,\quad d_1 = 0.3,\quad d_2 = 0.5,\quad \delta_1 = 0.4,\quad \delta_3 = 0.2,\quad \delta_4 = 0.5,\quad \delta_5 = 0.5,\quad p = 5\%$

Graph of HIV replication for succeeding periods and CD$^+$4 cells damages:



III. CONCLUSION:

$H_1(t)$ is calculated by taking current period HIV count (H(t) per(ml)Plasma) and $H_2(t)$ is calculated by HIV count as $HIV + H_1(t)$ and when CD_4^+T count is stable based on the model discussed in this paper. Find out first two succeeding periods HIV multiplication (Viral Load) of rounded values. This is shown in the Table and Graph referring the data given in David.D.Ho, (1995). From the above information it is concluded that, every period HIV replication count is increased the patient who has the less number of CD_4^+T counts. At this stage the prescription of medicine by doctor is critical. Monitoring the patients CD_4^+T count and viral load for every period is expensive and arise some practical difficulties. For avoiding this kind of problem the prediction of viral load is very much essential. Therefore the proposed model is used for prediction count.

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