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Stochastic modeling of HIV viral load by Harris Discrete Uniform Distribution

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Abstract

The viral load monitoring is very important in Anti Retroviral Therapy (ART). Viral load is the measurement of HIV from one ml of blood. In this paper the stochastic nature of viral load is studied and a model of Harris Discrete Uniform (HDU) distribution is fitted to the viral load. The characteristic of the Distribution is studied based on simulation. Here the viral replication is considered as a branching process. The factors influencing the viral load are considered as parameters of the distribution. The changes in the parameters are studied in this paper and from this, the relation among the viral load and parameters are elicited. A comparison between Marshall Olkin and Harris Uniform (MODU) Distribution is also done in this paper. The nature of Hazard function is also mentioned.

Key words: Viral load, branching process, Stochastic Process, Marshall Olkin Distribution, Survival function, Hazard Function.

Introduction

In early stages of HIV infection, rapid growth in viral load is visible. The target cells remain approximately constant level in the second phase of infection, ie., after starting the ART. The stochastic nature of early HIV infection is described in a series of models, each of which captures the aspects of HIV during the early stages of infection. The description of the stochastic nature of HIV we will use the tools of stochastic models and especially at the part of simulation. Here in this paper, a basic viral growth model based on a time dependent branching process is used to describe the growth of HIV infected cells. The role of the immune response to HIV and HIV infected cells is used to describe the movement of the infection to a disease of infected CD4+ T. The aim of this paper is to illustrate modeling HIV growth in the infected cells using branching process model. The parameters for growth depend on the state and nature of the virus in the body. The body environment is decided through the overall health of the body of the individual. This affects the condition and rising of the immune system. Many other factors also play a role on the immune system. The necessity of using stochastic models to describe viral growth was suggested in a series of papers. The ability to answer questions in a context of randomness of the process makes a strong statement for using stochastic models—especially in at early stages of a viral infection. The diversity involved in the genetic heterogeneity in host is a strong weapon of HIV. This will allow the virus to overcome immunity of host and the effects of drugs and vaccines.

In connection with HIV, Viral load is a measure of the amount or quantity of HIV present in one ml of Blood. This is used to monitor the effectiveness of therapy when a person is taking Anti Retroviral Therapy for HIV. During the period of therapy, the viral load will become un-detectable. At this time, the person become safe and also will not transmit HIV to others. An alternate measure for monitoring the well being of an HIV positive person is the CD4 Count. This indirectly measures the immunity of a person to fight against infections.

The primary aim of ART is to inhibit the viral replication and reduce viral load. Most have assumed that ART is able to completely and indefinitely suppress all replication. In spite of taking all types of ART drugs, the virus will persist for decades and will be recrudescent when a positive environment arises at least in some individuals [1]. Cell to cell spread of virus during ART is inherent despite of the treatment. These spread of virus lead to death of CD4+ cells. Figure (1) shows the development of viruses during the period of ART. Variability is the most powerful weapon of HIV, which allows the virus to overcome host immunity and the effects of drugs interventions. HIV variability is a consequence of at least three peculiar features: 1) the “error-prone” mechanism of virus 2) the rapid viral replication, and 3) the occurrence of recombination processes between two or more different HIV Viruses [2].

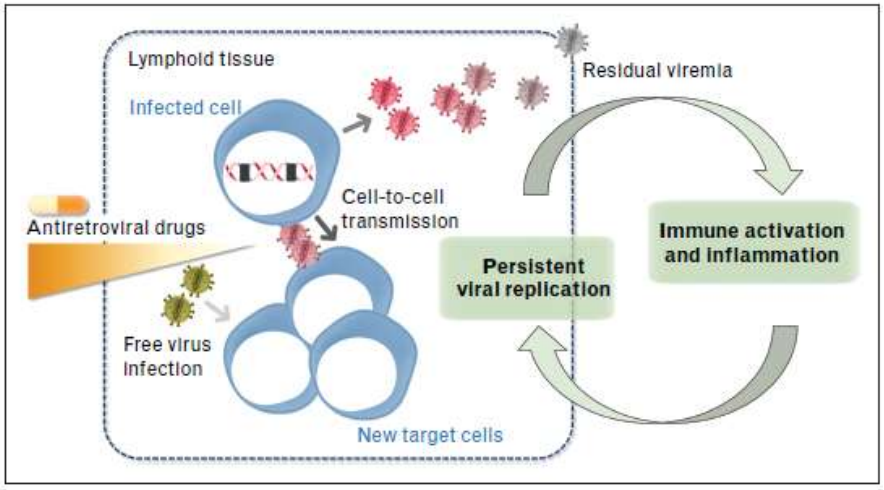


Figure 1. Residual replication during ART.

The viral replication can be considered as a branching stochastic process that give rise to more objects of same types. The objects produced can then produce more and the system develops according to some probability [3,4]. Viral load monitoring remains the most reliable indicator of treatment response. Measurements of viral load changes during therapy analysis using statistic model of viral dynamics. Here we are fitting branching process model to data and a study on simulation of data has been done. The medical data is not available in these days we are depending on simulated data. Consider stochastic model for the interaction of HIV Virus and immune system in an HIV infected individual undergoing a combination therapeutic treatment. A stochastic process is defined by the probabilities, in which, different events happen within a small time interval.

Review of Literature

The process of viral production in the infected cell begins, when an infected cell is stimulated. As a result, so many viremia are released from an infected cell, each taking a piece of the cell membrane. The process of viremia production will be assumed to involve two independent processes, host cell death and batch release [5]. We can easily able to describe the pattern of the process when we consider the batch releasing process as a branching process [6]. A model that describes the relation among infected cells, number of viremia and healthy cells will explain the importance of viral load during ART [7]. The death rate, infectivity rate etc are explained in detail in the paper mentioned above. This death rate of viruses suggested from above mentioned two papers is taken for death rate calculation of this paper. These periods of development of virus and death rates are also considered here.

The structure and cycle of viral replication is studied to get the nature and pattern of viral load and its decaying manner. The viral replication in each stage of HIV is different for different individuals. According to their age, health conditions and set point time the viral replication and its impacts are different [8,9]. Keeping all these matters in consideration, we developed a model by considering the nature of viral load as branching process. In [10] a MODU distribution approach to HIV -1 is done. In this paper we are trying to do a discrete uniform distribution approach using Harris approximation to viral load of HIV -1 [11,12, 13].

Modeling

As stated earlier, the viral load is affected by many factors. If 'Λ' indicates the virons produced, 'K' is the number of generation before extinction of virons produced and 'θ' is the death rate of CD+4 cells, by studying the viral load pattern and CD+4 count life length, we can assume that the distribution as Harris Uniform Distribution (discussed in earlier paper). Let X follows the discrete uniform distribution with distribution function,

F (x) = x/Λ
and

$$\bar{F}(x) = 1 - F(x) = 1 - \frac{x}{\Lambda}, x = 1,2,3 \ldots\ldots \Lambda$$

The parameters discussed above are the total effect of viral load expansion. If the random variable 'X' indicates the viral load and f(x) is the probability mass function, $\bar{F}(x)$ is the Survival function, then we can write the new distribution by substituting $\bar{F}(x)$ to get a new Harris family of survival function by adding a new parameter 'Λ', as

$$\bar{H}(x, \Lambda, k) = \left\{\frac{\Lambda.\bar{F}^k(x)}{[1-(1-\Lambda)(\bar{F}^k(x))]}\right\}^{1/k}, k>0, 0<\Lambda<\infty$$

Then by adding new parameter 'θ' and 'k', we get the new distribution function as follows

$$\bar{H}(x,\theta,k)=\left\{\frac{\theta.\left(1-\frac{x}{\Lambda}\right)^{k}}{1-(1-\theta)\left(1-\frac{x}{\Lambda}\right)^{k}}\right\}^{1/k} \quad ,x=1,2,3,\dots\Lambda,0<\theta<\infty,k\in N$$

$$\bar{H}(x,\theta,k)=\frac{\theta^{\frac{1}{k}}.(\Lambda-x)}{\{\Lambda^{k}-(1-\theta)(\Lambda-x)^{k}\}^{\frac{1}{k}}},$$

$$Where\ x=1,2,3,\dots\Lambda,0<\theta<\infty,k\in N,\ \text{N is set of positive integers.}$$

The probability Mass function of HDU distribution is given by

$$\mathrm{h}(\Lambda,\theta,\mathrm{k})=\bar{\mathrm{H}}(\mathrm{x},\theta,\mathrm{k})-\bar{\mathrm{H}}((\mathrm{x}-1),\theta,\mathrm{k})$$

$$\mathrm{h}(\Lambda,\theta,\mathrm{k})=\frac{\theta^{\frac{1}{k}}.(\Lambda-x+1)}{\{\Lambda^{k}-(1-\theta)(\Lambda-x+1)^{k}\}^{\frac{1}{k}}}-\frac{\theta^{\frac{1}{k}}.(\Lambda-x)}{\{\Lambda^{k}-(1-\theta)(\Lambda-x)^{k}\}^{\frac{1}{k}}},\mathrm{x}=1,2,3\dots\Lambda$$

Possible values for θ, ʎ and k are simulated based on previous studies to get corresponding probabilities. The generated table can be used as reference table for the doctors or persons dealing with prolonged patients with HIV.

Comparison between MODU and HDU

We can define a new survival function w.r.to MODU Prasanth and Sandhya (2014)

$$g(x,\Upsilon)=\frac{\Upsilon\bar{F}^{k}(x)}{1-\bar{\Upsilon}\,\bar{F}^{k}(x)},k\geq 1$$

When k =1, this reduces to MO scheme

$$g(x,\Upsilon)=\frac{\Upsilon\bar{F}\ \ (x)}{1-\bar{\Upsilon}\,\bar{F}\ \ (x)}$$

Now if X follows HDU distribution, then its survival function is

$$\bar{H}(x,\theta,k)=\frac{\theta^{\frac{1}{k}}.(\Lambda-x)}{\{\Lambda^{k}-(1-\theta)(\Lambda-x)^{k}\}^{\frac{1}{k}}}$$

When K=1, this survival function becomes

$$P(X>x)\ =\frac{\theta(\Lambda-x)}{\Lambda-(1-\theta).(\Lambda-x)}$$

which is the survival function of MODU (ʎ, θ)

The hazard function (also called the force of mortality, instantaneous failure rate, instantaneous death rate, or age-specific failure rate) is a way to model data distribution in survival analysis. The hazard rate refers to the rate of death for an item of a given life time or age (x). The hazard function analyzes the likelihood that an item will survive to a certain point in time based on its survival to an earlier time (t).

The Hazard function corresponding to the HDU(λ,θ,k) function is given by

$$\mathrm{R}(\mathrm{x})=\frac{\mathrm{h}(\mathrm{x})}{\bar{\mathrm{H}}(\mathrm{x})}$$

$$R(x)=\frac{\frac{\theta^{\frac{1}{k}}.(\Lambda-x+1)}{\{\Lambda^{k}-(1-\theta)(\Lambda-x+1)^{k}\}^{\frac{1}{k}}}-\frac{\theta^{\frac{1}{k}}.(\Lambda-x)}{\{\Lambda^{k}-(1-\theta)(\Lambda-x)^{k}\}^{\frac{1}{k}}}}{\frac{\theta^{\frac{1}{k}}.(\Lambda-x)}{\{\Lambda^{k}-(1-\theta)(\Lambda-x)^{k}\}^{\frac{1}{k}}}}$$

$$R(x) = \frac{\frac{\theta^{\frac{1}{k}}.(\Lambda - x + 1)}{\{\Lambda^k - (1-\theta)(\Lambda - x + 1)^k\}^{\frac{1}{k}}}}{\frac{\theta^{\frac{1}{k}}.(\Lambda - x)}{\{\Lambda^k - (1-\theta)(\Lambda - x)^k\}^{\frac{1}{k}}}} - 1$$

$$\mathrm{R(x)} = \left[\frac{(\lambda - \mathrm{x} + 1)}{(\lambda - \mathrm{x})}\right].\left[\frac{\lambda^{\mathrm{k}} - (1-\theta)(\lambda - \mathrm{x})^{\mathrm{k}}}{\lambda^{\mathrm{k}} - (1-\theta)(\lambda - \mathrm{x} + 1)^{\mathrm{k}}}\right]^{\frac{1}{\mathrm{k}}} - 1$$

Analysis

For different values of k, λ, θ, and x, the figures of probability mass function are drawn for comparison. The probabilities which are insignificant are kept as blank. Table 1 shows different probabilities for different values of x and λ.

Table 1 Probabilities of X for different values of λ, K=2 and θ =0.24.

θ= 0.24			k = 2, θ= 0.24					
x\ λ	30	50	100	150	200	250	300	350
10	0.031535	0.027612	0.021123	0.016982	0.014160	0.012128	0.010601	0.009412
20	0.018911	0.016134	0.013552	0.011799	0.010417	0.009307	0.008400	0.007649
30	0.016337	0.012028	0.009981	0.008980	0.008178	0.007498	0.006914	0.006408
40		0.010312	0.007989	0.007252	0.006715	0.006257	0.005853	0.005494
50		0.009799	0.006768	0.006107	0.005697	0.005362	0.005066	0.004800
60			0.005982	0.005309	0.004958	0.004692	0.004463	0.004256
70			0.005469	0.004731	0.004403	0.004176	0.003989	0.003822
80			0.005143	0.004303	0.003975	0.003770	0.003609	0.003469
90			0.004961	0.003981	0.003639	0.003443	0.003298	0.003177
100			0.004899	0.003739	0.003372	0.003177	0.003042	0.002933
110				0.003558	0.003157	0.002958	0.002827	0.002726
120				0.003426	0.002983	0.002775	0.002646	0.002550
130				0.003337	0.002842	0.002623	0.002492	0.002398
140				0.003284	0.002729	0.002494	0.002359	0.002267
150				0.003266	0.002639	0.002385	0.002245	0.002152
160					0.002569	0.002294	0.002147	0.002052
170					0.002516	0.002216	0.002061	0.001964
180					0.002479	0.002152	0.001987	0.001886
190					0.002457	0.002098	0.001923	0.001818
200					0.002450	0.002054	0.001867	0.001757
210						0.002020	0.001818	0.001703
220						0.001993	0.001777	0.001655
230						0.001975	0.001741	0.001613
240						0.001964	0.001712	0.001575
250						0.001960	0.001687	0.001542
260							0.001668	0.001514
270							0.001652	0.001489
280							0.001642	0.001467
290							0.001635	0.001449
300							0.001633	0.001434
310								0.001421
320								0.001412
330								0.001405
340								0.001401
350								0.001400

***in above table, probabilities which are not significant are kept as blank.**

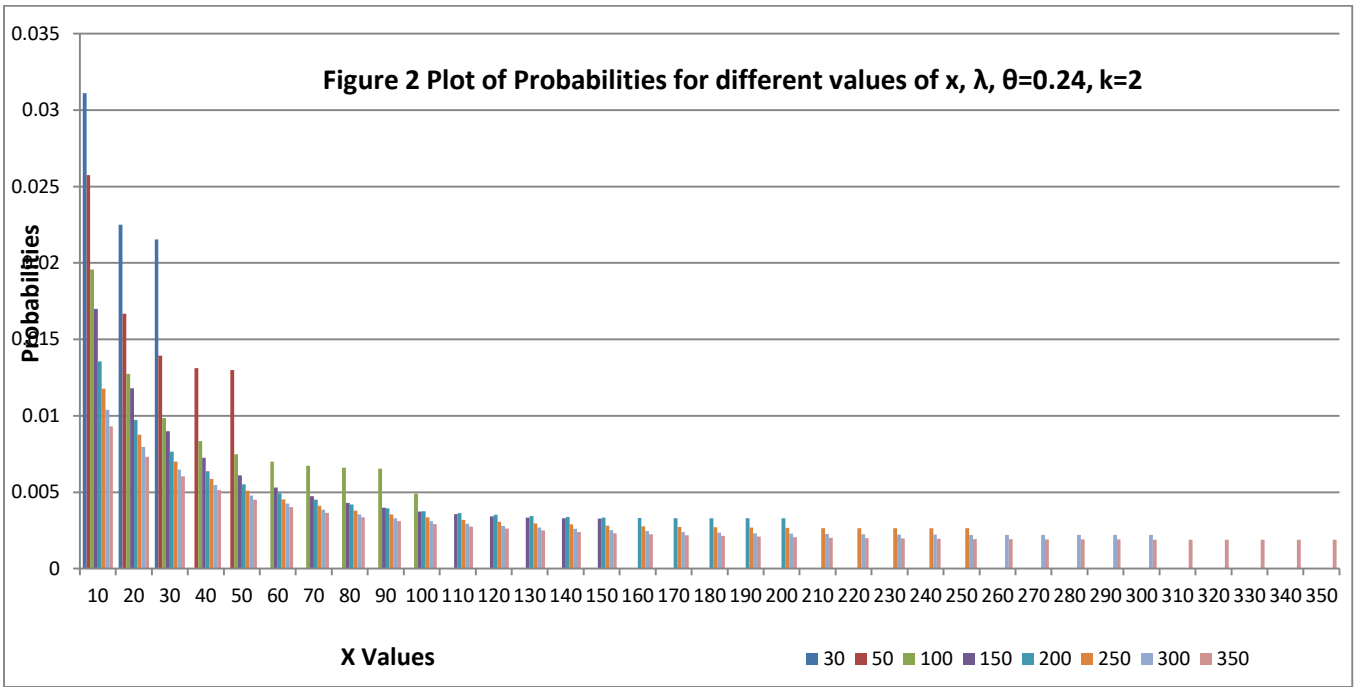


Table 2 Gives different probabilities for k=3

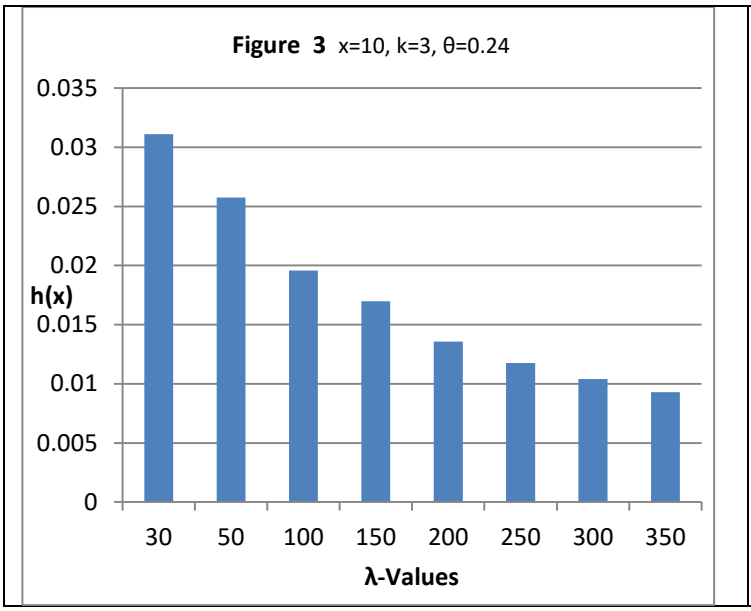
Figures 3, Figure 4 and Figure 6 clarifies the relation and variation among the X values and their probabilities

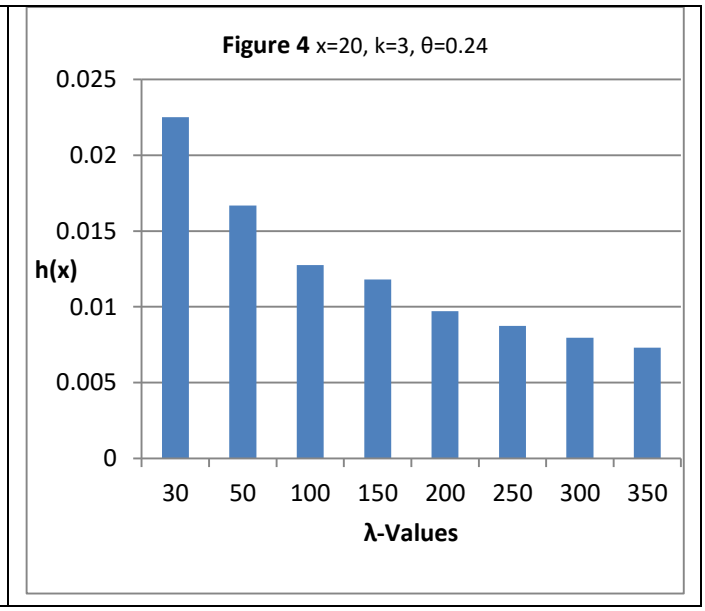
Table 2. Probabilities of X for different values of λ, K=3 and θ =0.24.

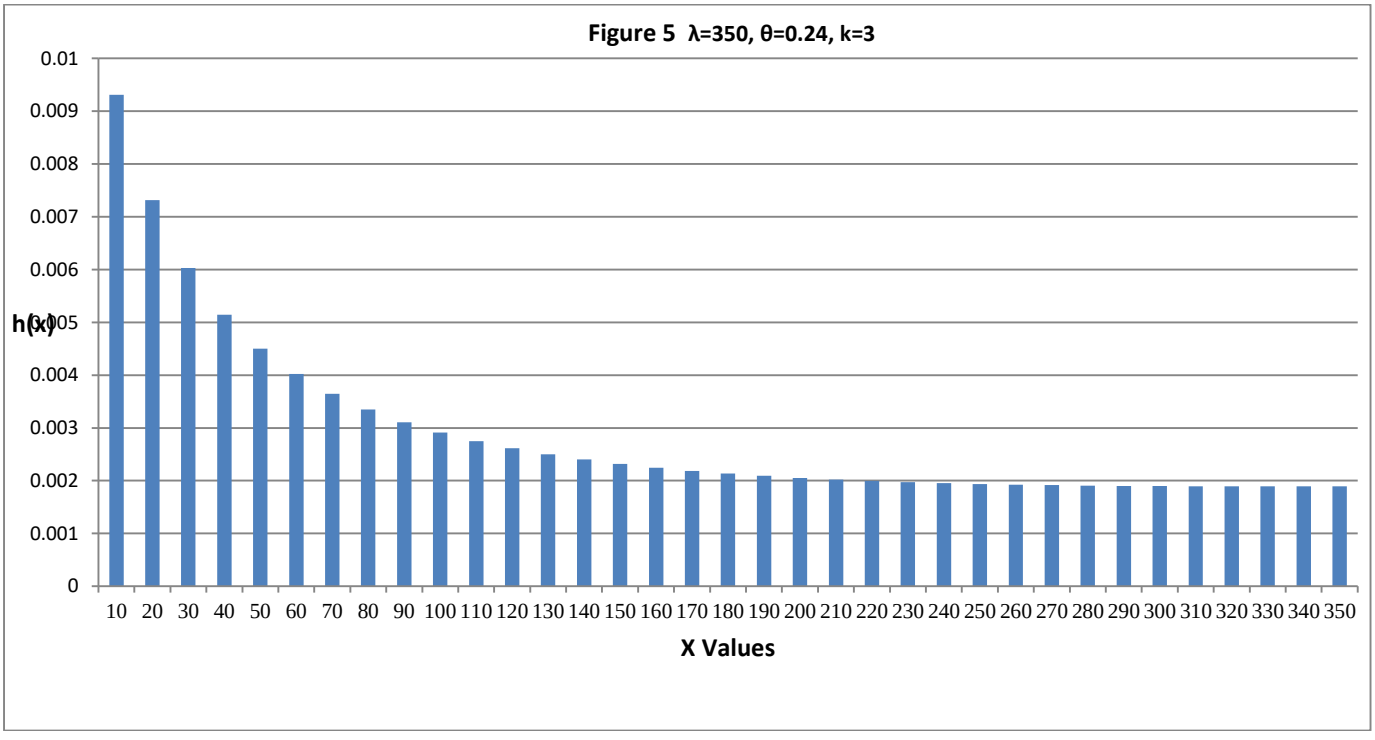
θ= 0.24			k = 3, θ= 0.24					
x\ λ	30	50	100	150	200	250	300	350
10	0.031097	0.025749	0.019576	0.016982	0.013561	0.011767	0.010393	0.009307
20	0.022499	0.016679	0.012748	0.011799	0.009717	0.008749	0.007965	0.007312
30	0.021534	0.013943	0.009845	0.00898	0.00764	0.006998	0.006474	0.00603
40		0.013108	0.008341	0.007252	0.006367	0.005871	0.005477	0.005146
50		0.012986	0.007491	0.006107	0.005522	0.005096	0.004771	0.004504
60			0.007001	0.005309	0.004931	0.004537	0.00425	0.00402
70			0.006729	0.004731	0.004503	0.00412	0.003853	0.003646
80			0.006595	0.004303	0.004185	0.0038	0.003542	0.003349
90			0.006546	0.003981	0.003946	0.003551	0.003295	0.003109
100			0.004899	0.003739	0.003764	0.003354	0.003096	0.002913
110				0.003558	0.003625	0.003196	0.002933	0.00275
120				0.003426	0.00352	0.00307	0.002799	0.002614
130				0.003337	0.003442	0.002968	0.002687	0.002499
140				0.003284	0.003386	0.002887	0.002595	0.002402
150				0.003266	0.003346	0.002822	0.002518	0.002319
160					0.00332	0.002771	0.002453	0.002248
170					0.003304	0.002731	0.0024	0.002188
180					0.003295	0.0027	0.002355	0.002136
190					0.003292	0.002677	0.002319	0.002092
200					0.003292	0.002661	0.002289	0.002054
210						0.002651	0.002266	0.002022
220						0.002644	0.002247	0.001995
230						0.002641	0.002233	0.001972
240						0.00264	0.002222	0.001953
250						0.002639	0.002214	0.001938

260							0.002209	0.001925
270							0.002206	0.001915
280							0.002204	0.001907
290							0.002204	0.001902
300							0.002204	0.001897
310								0.001895
320								0.001893
330								0.001892
340								0.001892
350								0.001892

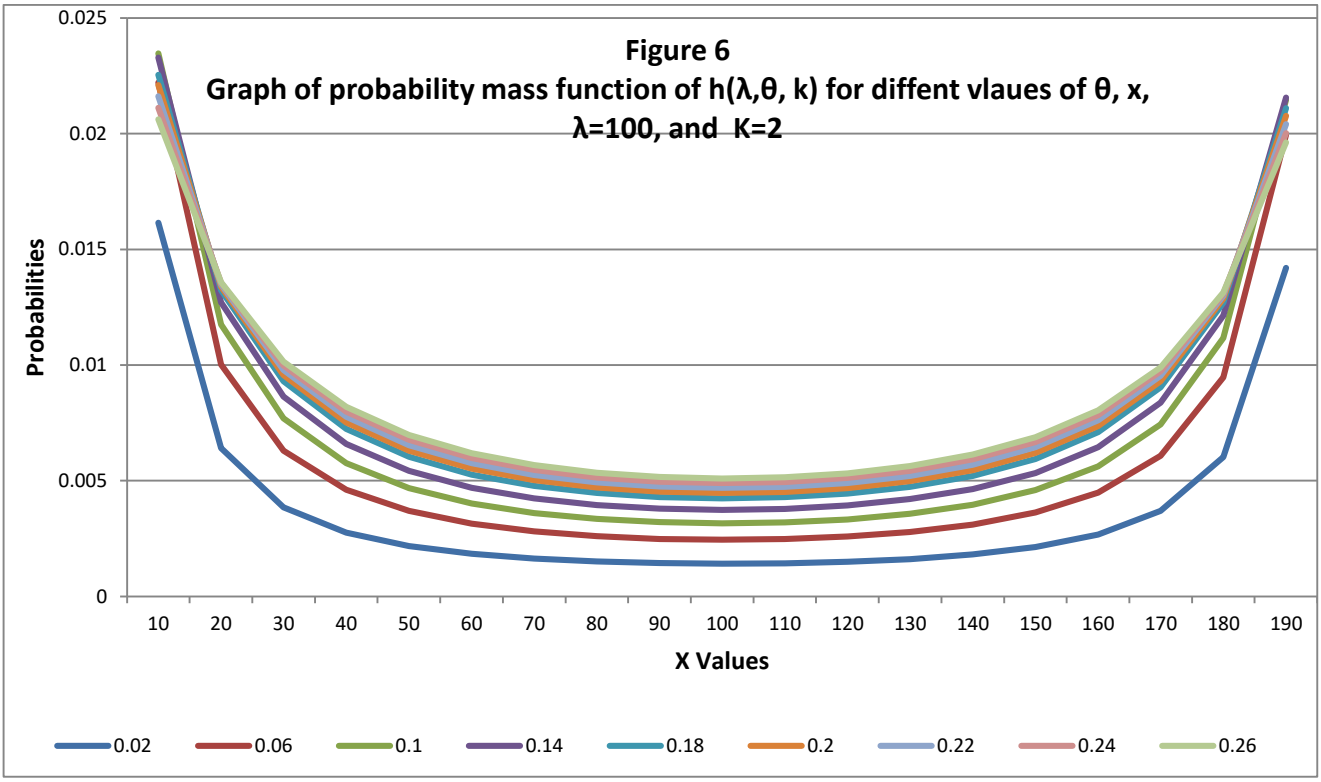
***in above table, probabilities which are not significant are kept as blank.**







By analyzing the figures corresponding to different values of x, θ, λ and k the probabilities are decreasing and approach to a consistent probability.



The pictorial representation of probability mass function for simulated values of x, shows that the distribution is a bathtub shaped one, and the function indicates a decreasing failure rate at the value of x< λ and increasing failure rate for values of x>λ. The values for x<10 and X>190 are outliers of X values, for λ =100.

While drawing graph for different values of λ and for different values of θ (ranging from 0.02 to 0.26), we are getting the same bathtub shaped curves and the outliers for λ values are as following

λ = 50 outliers are X<5 and X> 95

λ =100 outliers are X<10 and X> 190

λ = 200 outliers are X<20 and X>380

Here also we are getting the similar IFR and DFR that we have obtained in the graph for λ =100.

At turning points of Figure 6, the probabilities at point X= (λ-x) is approximately equal to Probabilities at the point X=(x-λ).

In Table 3, the turning points (Approximate Values of X) of bath tub curve at a decreasing point are given.

Table 3 Turning Points and Standard Error for different values of θ at decreasing point of survival function.

θ	0.02	0.06	0.1	0.14	0.18	0.2	0.22	0.24	0.26	
X	22	28	32	35	40	42	44	44.5	45	Mean =36.944
$(X=\mu)^2$	223.32	79.99	24.44	3.78	9.34	25.56	49.79	57.09	64.9	Total = 538.22
							SE	7.733206	Variance	59.803

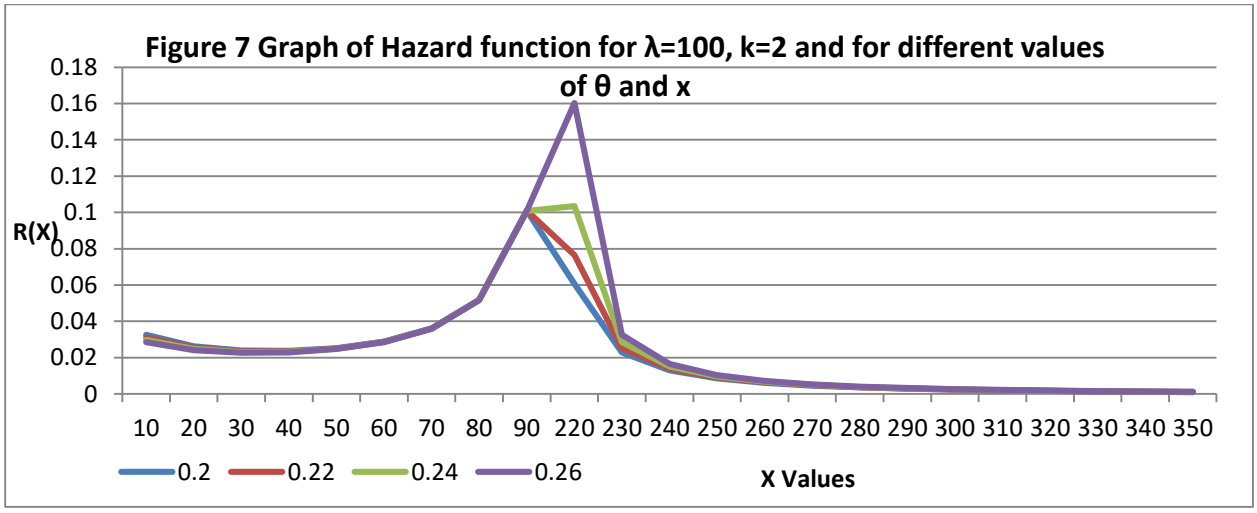
Standard Error is SE =7.73 the Standard Error shows a less variation at the corner turning point of bathtub curve.

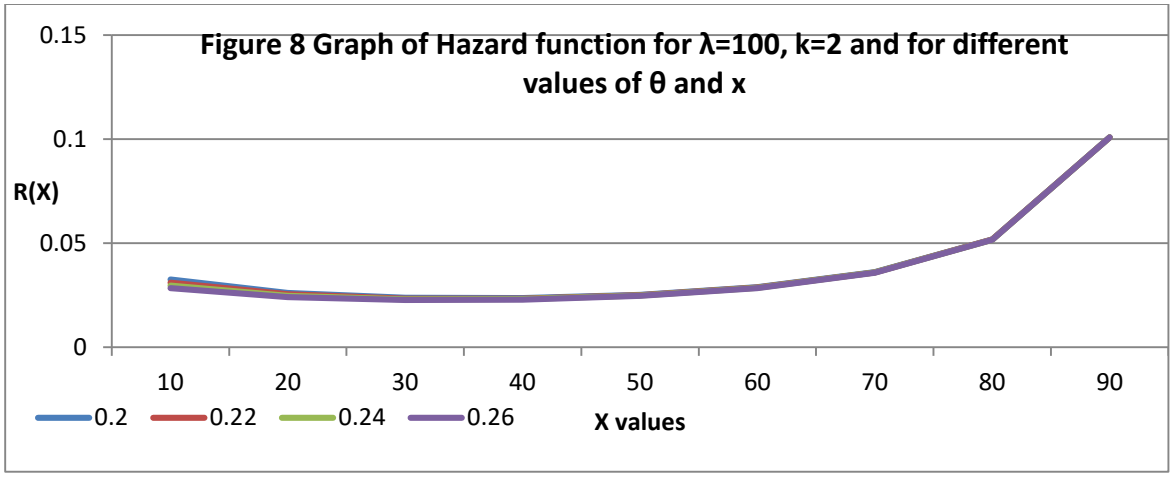
Now considering the hazard function, $R(x) = \left[\frac{(\lambda-x+1)}{(\lambda-x)}\right].\left[\frac{\lambda^k-(1-\theta)(\lambda-x)^k}{\lambda^k-(1-\theta)(\lambda-x+1)^k}\right]^{\frac{1}{k}} - 1$ we arrive at following conclusions.

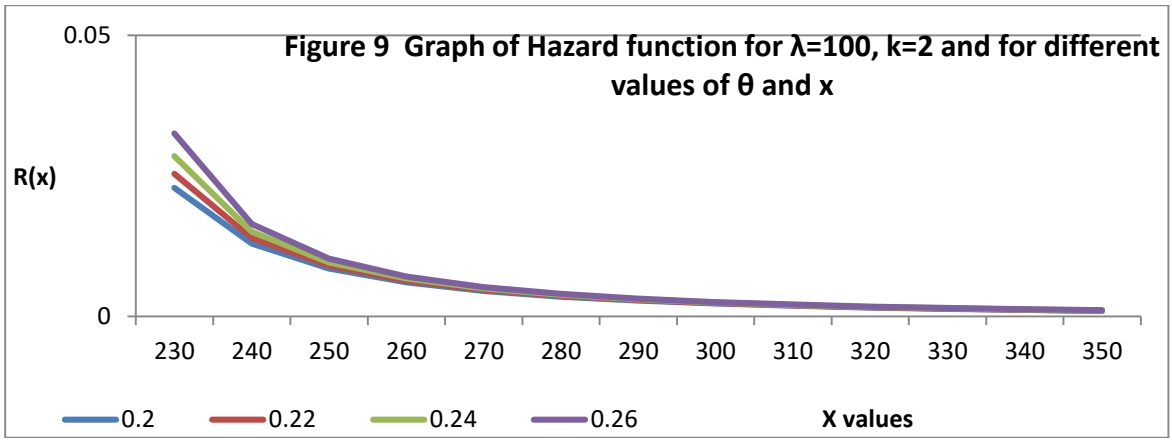
Using the above mentioned hazard function, a table is created and comparison of hazard rate based on the graphs corresponding to them is explained.

Table 4 Hazard function for different values of k,λ,θ

	k=2	λ =100		
θ	0.2	0.22	0.24	0.26
X				
10	0.032572	0.031072	0.029703	0.02845
20	0.026132	0.025439	0.024781	0.024156
30	0.023828	0.023436	0.023057	0.022691
40	0.023649	0.023404	0.023164	0.022929
50	0.02519	0.025028	0.024868	0.024709
60	0.02883	0.02872	0.028611	0.028502
70	0.036061	0.035987	0.035914	0.035841
80	0.051783	0.051737	0.051691	0.051645
90	0.100933	0.100909	0.100886	0.100862
220	0.060615	0.076446	0.103498	0.160343
230	0.022869	0.025392	0.02854	0.032579
240	0.012959	0.01394	0.015081	0.016427
250	0.008525	0.00904	0.009622	0.010283
260	0.006075	0.00639	0.00674	0.00713
270	0.004554	0.004766	0.004998	0.005253
280	0.003538	0.003689	0.003853	0.004033
290	0.002822	0.002934	0.003057	0.003189
300	0.002298	0.002385	0.002479	0.00258
310	0.001903	0.001972	0.002046	0.002126
320	0.001597	0.001653	0.001713	0.001778
330	0.001357	0.001403	0.001452	0.001505
340	0.001164	0.001203	0.001244	0.001288
350	0.001008	0.00104	0.001075	0.001112







From the figures depicted above, the hazard rate shows an increasing tendency for smaller value of 'X' and also, from a specific value of x, the distribution shows a decreasing hazard rate.

Conclusion

The paper provides an idea about the distributional structure of viral growth of HIV during the period of ART. The pattern of viral load at different stages of HIV can be easily referred from the tables constructed in this paper. Also this paper will be a guide for further estimation in viral load. The evidence of persistent replication in many HIV -1 infected individual on ART argues for development and evaluation of novel strategies in medical therapy that will fully suppress viral replication. A new development in technologies is essential to facilitate the detection and study of viral dynamics.

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