ASIAN JOURNAL
ISSN: 0976-3376

Available Online at http://www.journalajst.com

ASIAN JOURNAL OF SCIENCE AND TECHNOLOGY

Asian Journal of Science and Technology
Vol. 1, Issue 4, pp.041-043, May, 2011

RESEARCH ARTICLE

EXTREMELY PROLONGED HIV SEROCONVERSION TO ESTIMATE THE EXPECTED TIME THROUGH GENERALIZED RAYLEIGH DISTRIBUTION

Subramanian, C and Rajivgandhi, R*

Department of Statistics, Annamalai University, Tamil Nadu, India - 608 002

Received 7th March, 2011; Received in revised from; 17th April, 2011; Accepted 30th April, 2011; Published online 25th May, 2011

Since the beginning of HIV/AIDS, epidemic mathematicians and statisticians have developed models to describe and predict the course of the infection. Tools were derived from the firmly established theory of epidemic modeling, although some adjustments became necessary, because of specific characteristics of HIV infection. The time to cross antigenic diversity threshold of the infected person is a vital event in seroconversion. The expected time to attain the seroconversion period is calculated by Generalized Rayleigh distribution using shock model approach and cumulative damage process. Numerical examples are given to illustrate various aspects of the model considered for the expected time to seroconversion.

Key words: Antigenic diversity, Generalized Rayleigh distribution, Seroconversion, Threshold

INTRODUCTION

HIV is transmitted through three primary routes; sexual contact with an infected person, significant exposure to infected blood or blood products (including needles shared among intravenous drug users) and parentally from an infected mother to her child Barnett & Whiteside (2002), Barnett & Finkbeiner (1998) and WHO (2001). Laboratory and epidemiological studies have, however shown that HIV is not transmitted by everyday contact, by touching, hugging or kissing, sneezing, through food or water or by mosquitoes and other biting insects McMillan (1992). People infected with HIV, risk of death increases as CD4 cell count declines, and this trend has been noted even in the high CD4 count range. The optimum CD4 cell count at which to start antiretroviral therapy (ART) in individuals infected with HIV is unclear Phillips (1992). Most guidelines state that, in patients without a previous AIDS event, ART should be started when the CD4 count falls to 350 cells per µL. Mathematical model is obtained for the expected time of breakdown point to reach the seroconversion threshold level. In the context of HIV/AIDS, the assumptions that the times between decision period are independent and identically distributed (i.i.d) random variable. The number of outlet at each period of time is i.i.d. random variables and the threshold level is a random variable following Generalized Rayleigh distribution. Graphical illustrations are provided for the support of the model. One can see for more detail in Esary *et al.* (1973), Sathiyamoorthi (1980), Rajivgandhi *et al*. (2010) about the expected time to cross the threshold level of seroconversion period.

***Corresponding author:** statrajiv@gmail.com; manistat@yahoo.co.in*

Assumption

These assumptions are somewhat artificial, but are made because of the lack of detailed real-world information on one hand and in order to illustrate the proceedings on the other hand.

1. Sexual contacts are the only source of HIV infection.
2. The antigenic diversity threshold of any individual is a random variable.
3. If the total damage crosses a threshold level Y which itself is a random variable, the seroconversion occurs and a person is recognized as an infected.
4. The inter-arrival times between successive contacts, the sequence of damage and the threshold are mutually independent.

Notations

X_i : a continuous random variable denoting the amount of contribution to the antigenic diversity due to the HIV transmitted in the i^{th} contact, in other words the damage caused to the immune system in the i^{th} contact, with p.d.f g (.) and c.d.f G (.).

Y : a continuous random variable denoting the threshold which follows Generalized Rayleigh distribution.

U_i : a random variable denoting the inter-arrival times between contact with c.d.f. $F_i(.)$,

$i = 1,2,3 \ldots k.$

$g(.)$: The probability density functions of X_i

$g^*(.)$: Laplace transform of g (.)

$g_k(.)$: The k- fold convolution of g (.) i.e., p.d.f. of $\sum_{i=1}^{k} X_i$

$f(.)$: p.d.f. of random variable denoting between successive contact with the corresponding c.d.f. F (.)
$F_k(.)$: k-fold convolution of F (.)
$V_k(t)$: Probability of exactly k successive contact.
$S(.)$: Survival function, i.e., $P[T > t]$
$L(t)$: 1 - S (t)

RESULT

Surles and Padgett (2001) introduced two-parameters, Burr Type X distribution and correctly named as the generalized Rayleigh distribution. The two-parameters generalized Rayleigh distribution is a particular member of the generalized Weibull distribution, originally proposed by Mudholkar and Srivastava (1993).

Let Y be the random variable which has the cdf defined as

$$F(x;\alpha,\lambda) = \left(1 - e^{-(\lambda x)^2}\right)^{\alpha}$$

The corresponding survival function is

$$\left(1 - e^{-2\lambda x}\right)^{\alpha} \sim \left(1 - e^{-2\lambda x}\right)^{n} = \sum_{r=0}^{n} (-1)^r \binom{n}{r} \left(e^{-2\lambda x}\right)^r$$

$$\bar{F}(x) = \sum_{r=1}^{n} (-1)^{r+1} \binom{n}{r} \left(e^{-2\lambda x}\right)^r \qquad (1)$$

a) Random Threshold for Cumulative Damage

One is interested in an item for which there is a significant individual variation in ability to withstand shocks. There may be no practical way to inspect an individual item to determine its threshold y. In this case, the threshold must be a random variable.

The shock survival probability are given by

$$P\left(\sum_{i=1}^{k} X_i < Y\right) = \int_0^{\infty} g_k(x)\,\bar{F}(x)\,dx \qquad (2)$$

$$= \int_0^{\infty} g_k(x) \left[\sum_{r=1}^{n} (-1)^{r+1} \binom{n}{r} \left(e^{-2\lambda x}\right)^r\right] dx$$

$$= \sum_{r=1}^{n} (-1)^{r+1} \binom{n}{r} g_k(2\lambda r) \qquad (3)$$

Equation (3) denotes the k^{th} convolution.

Therefore $S(t) = P[T > t]$ is the survival function which gives the probability that the cumulative antigenic diversity will fail only after time t. Survival analysis is a class of statistical methods for studying the occurrence and timing of events. These methods are most often applied to the study of deaths.

$S(t) = P(T > t)$ = Probability that the total damage survives beyond t

$$= \sum_{k=0}^{n} P\{\text{there are exactly k contacts in } (0,t]\} * P\{\text{the total cumulative antigenic diversity } (0,t]\}$$

$$S(t) = P(T > t) = \sum_{k=0}^{\infty} V_k(t) P(X_k < Y) \qquad (4)$$

b) Progressive stage of HIV through renewal process

It may happen that successive shocks become increasingly effective in causing damage, even though they are independent. This means that $V_k(t)$, the distribution function of the k^{th} damage is decreasing in $k = 1,2,\ldots$ for each t.

It is also known from renewal process that

$$P(\text{exactly k policy decesions in } (0,t]) = F_k(t) - F_{k+1}(t) \qquad \text{with} \quad F_0(t) = 1$$

$$= \sum_{k=0}^{\infty} \sum_{r=1}^{n} [F_k(t) - F_{k+1}(t)] \binom{n}{r} (-1)^{r+1} g_k^*(2\lambda r)$$

$$= \sum_{r=1}^{n}{}' \binom{n}{r} (-1)^{r+1} - \sum_{r=1}^{n}{}' \binom{n}{r} (-1)^{r+1} \left(1 - g_k^*(2\lambda r)\right) \sum_{k=1}^{\infty}{}' [F_k(t)]\,[g^*(2\lambda r)]^{k-1}$$

$P(T < t) = L(t)$ = The distribution function of life time (T)

$$L(t) = 1 - S(t)$$

$$= 1 - \sum_{r=1}^{n}{}' \binom{n}{r} (-1)^{r+1} - \sum_{r=1}^{n}{}' \binom{n}{r} (-1)^{r+1} \left(1 - g^*(2\lambda r)\right) \sum_{k=1}^{\infty}{}' [F_k(t)]\,[g^*(2\lambda r)]^{k-1}$$

Where $[f^*(s)]^k$ is Laplace transform of $V_k(t)$ since the inter-arrival times are i.i.d. The above equation can be rewritten as,

$$-\sum_{r=1}^{n}{}' \binom{n}{r} (-1)^{r-1} \left(1 - g^*(2\lambda r)\right) \sum_{k=1}^{\infty}{}' [F_k(t)]\,[g^*(2\lambda r)]^{k-1} \qquad (5)$$

$$E(T) = -\frac{d}{ds} L^*(s) \quad \text{given} \quad s = 0$$

$$E(T^2) - \frac{d^2 L^*(s)}{ds^2}$$

From which $V(T)$ can be obtained.

Let the random variable U denoting inter arrival time which follows exponential with parameter c. Now $f^*(s) = \left(\frac{c}{c+s}\right)$, substituting in the below equation (6) we get,

$$L^*(s) = \sum_{r=1}^{n}{}' \binom{n}{r} (-1)^{r+1} \frac{\left(1 - g^*(2\lambda r)\right) f^*(s)}{\left(1 - g^*(2\lambda r) f^*(s)\right)} \qquad (6)$$

$$= \sum_{r=1}^{n}{}' \binom{n}{r} (-1)^{r+1} \frac{c\left(1 - g^*(2\lambda r)\right)}{\left(c + s - g^*(2\lambda r)\,c\right)} \qquad (7)$$

The mean and variance of the time to antigenic diversity to cross seroconversion is derived.

$$E(T) = \sum_{r=1}^{n}{}' \binom{n}{r} (-1)^{r+1} \frac{1}{c\left(1 - g^*(2\lambda r)\right)} \qquad \text{on simplification} \qquad (8)$$

$$E(T^2) = \sum_{r=1}^{n}{}' \binom{n}{r} (-1)^{r-1} \frac{2}{c^2\left(1 \quad g^*(2\lambda r)\right)^2} \qquad \text{on simplification} \qquad (9)$$

$$V(T) = E(T^2) - [E(T)]^2$$

The inter-arrival time of the antigenic diversity follows exponential distribution. The Laplace transformation of the exponential is given by $\left[\mu/\mu + \lambda\right]$.

$$g^*(\,) \sim exp(\mu), \quad g^*(2\lambda r) = \left[\frac{\mu}{\mu + 2\lambda r}\right]$$

$$E(T) = \sum_{r=1}^{n} \binom{n}{r} (-1)^{r+1} \left(\frac{1}{c}\right) \left[\frac{(\mu + 2\lambda r)}{2\lambda r}\right] \qquad (10)$$

$$E(T^2) = \sum_{r=1}^{n} \binom{n}{r} (-1)^{r+1} \left(\frac{2}{c^2}\right) \left[\frac{(\mu + 2\lambda r)}{2\lambda r}\right]^2$$

$$V(T) = \left[\sum_{r=1}^{n} \binom{n}{r} (-1)^{r-1} \left(\frac{2}{c^2}\right) \left[\frac{(\mu + 2\lambda r)}{2\lambda r}\right]^2\right] - \left[\sum_{r=1}^{n} \binom{n}{r} (-1)^{r+1} \left(\frac{1}{c}\right) \left[\frac{(\mu + 2\lambda r)}{2\lambda r}\right]\right]^2 \qquad (11)$$

Special case $(\mu - 1)$

The shape parameter of the generalized Rayleigh distribution α is kept fixed i.e. $\alpha = 1$. We obtained the following

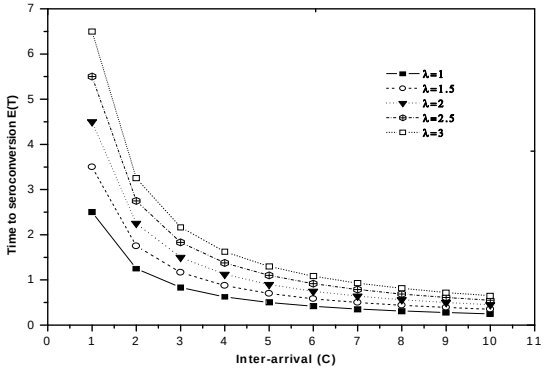
equation (12) and (13) as the expected time to antigenic diversity E (T) and variance V (T).

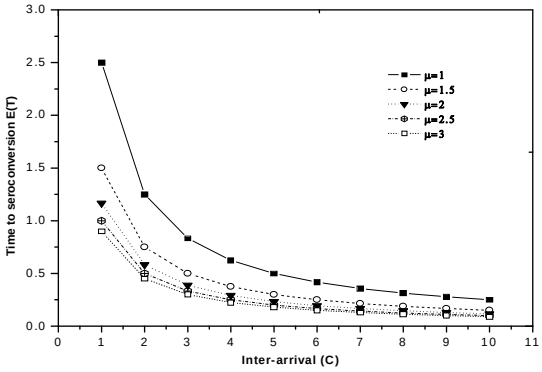
$$E(T) = \left[\frac{\mu + 2\lambda}{2\lambda c}\right] \quad (12)$$

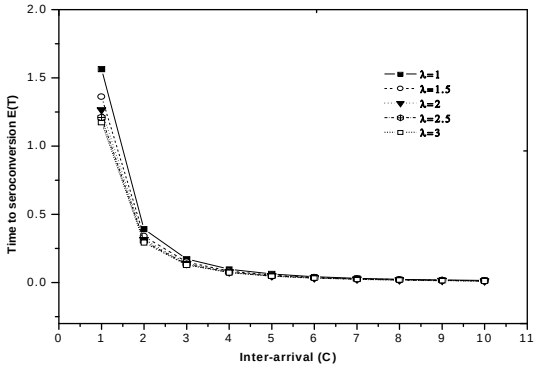
$$V(T) = \left[\frac{(\mu + 2\lambda)^2}{4c^2\lambda^2}\right] \quad (13)$$

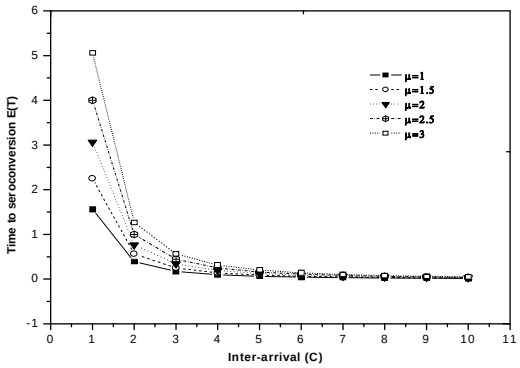
Numerical Illustration

The theory developed was tested using stimulated data in MathCAD software. To illustrate the method described in this paper (special case), we give some limited simulation results. The expected time and variance from the above equation (12) and (13) is found out with the changes in parameters and with increasing parameters which is observed in the given figures below.









Conclusion

When λ is kept fixed the inter-arrival time 'c' which follows exponential distribution, is an increasing case by the process of renewal theory. Therefore, the value of the expected time $E(T)$ to cross the antigenic diversity of seroconversion is found to be decreasing, in all the cases of the parameter value $\lambda = 1, 1.5, 2, 2.5, 3$. When the value of the parameter λ increases, the expected time is also found decreasing, this is observed in Figure 1. The same case is found in Variance V (T) which is observed in Figure 3. When μ is kept fixed and the inter-arrival time 'c' increases, the value of the expected time E (T) to cross the antigenic diversity of seroconversion is found to be decreasing, in all the cases of the parameter value $\mu = 1, 1.5, 2, 2.5, 3$. When the value of the parameter μ increases, the expected time is found increasing, this is indicated in Figure 2. The same case is observed in the antigenic diversity of seroconversion of Variance V (T) which is observed in Figure 4.

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