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A stochastic approach to determine time to cross antigenic diversty threshold of HIV transmission under alertness

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Abstract

The use of stochastic model in the study of HIV infection, the estimation of the likely time at which the seroconversion takes place is an important aspect. An individual takes some precautionary measures with due to avoid the HIV getting transmitted and this called alertness. The use of preventive strategy gives rise to the concept of alertness on the part of individual who has sexual contact with unknown partner. In this paper the stochastic model for the estimation of time to cross the antigenic diversity threshold and variance are derived under the assumption that the threshold level of antigenic diversity is a random variable which follows a Exponentiated Exponential Distribution. The expression for E(T) and variance are derived and Numerical Illustrations are provided.

Key words: Acquired Immuno Deficiency Syndrome, Antigenic Diversity Threshold, Human Immuno Deficiency Virus, Preventive Strategy, Seroconversion.

Notations :

X_i : A random variable denoting the increase in the antigenic diversity arising due to the HIV transmitted during the i^{th} contact $X_1, X_2, \ldots, X_k$ are continuous i.i.d. random variables, with p.d.f. g(.) and c.d.f. G(.).

Y : A random variable representing antigenic diversity threshold and follows exponentiated exponential distribution with parameters α and λ, the p.d.f. being h(.) and c.d.f H(.).

U_i : A continuous random variable denoting the inter-arrival times between successive contacts with p.d.f *f*(.) and c.d.f F(.).

Z : The random variable representing the time between damages.

$g_k(.)$: the p.d.f of random variable $\sum_{i=1}^{k} X_i$

$F_k(.)$: the convoluton of F(.)

T : a continuous random variable denoting the time to seroconversion with p.d.f. $l(.)$ and c.d.f. L(.).

$V_k(.)$: Probability of exactly k contacts in (o, t].

$l^*(s)$: is the Laplace transform of $l(t)$.

$f^*(s)$: is the Laplace transform of $f(t)$.

Introduction

The incidence and spread of Human Immuno Deficiency Virus (HIV) infection and the consequent Acquired Immuno Deficiency Syndrome (AIDS) has created a pandemic situation in the world all over. In the study of HIV infection, the estimation of likely time at which the seroconversion takes place is an important aspect. In doing so the time to seroconversion is taken to be a random variable T. It is quite natural that a person who has homo (or) hetero sexual contacts with an infected person continues to have successive contacts at random time intervals. The infected person acquires more and more of HIV in successive contacts and this contribute to what is called the antigenic diversity of the HIV. The contribution to the antigenic diversity on successive contacts may be interpreted as damages to the immune system. Every individual has a threshold level of antigenic diversity. If the cumulative contribution on successive contacts crosses this random level of threshold then the seroconversion takes place for a detailed study of antigenic diversity threshold and its estimation one can refer to Nowak and May[6], Stilianakis *et al.*[7]. In the present model, the shock model and cumulative process as discussed by Esary *et al.*[1] is used. In doing so, it is interpreted that at every contact the infected person receives a random amount of contribution to the antigenic diversity and when the total contribution crosses the random threshold level the seroconversion takes place.

An effective and also a powerful method or strategy against the HIV infection used to adopted preventive measures, so that the possibility of getting infected is completely ruled out. This gives rise to the concept of alertness on the part of the individuals before the he (or) she is exposed to the risk. A universally recommended strategy to avoid the possible infection is the use condemns by any person. In deriving this model it is assumed that a person with alert uses the prevention strategy and if the person is in–alert then there is a risk of transmission.

A stochastic model for the HIV transmission under alertness under the assumption that the threshold level of antigenic diversity is a random variable which follows a Gamma distribution and mixed exponential distribution has been discussed Kannan *et al.*[2], Kannan *et al.*[3] and Kannan *et al.*[4]. In this paper using the concept of alertness and preventive strategy the stochastic model for the estimation of expected time to seroconversion and its variance are derived under the assumption that the threshold level of antigenic diversity is a random variable which follows an Exponentiated Exponential Distribution. In this study the theoretical results widely are substantiated using numerical data simulated.

Model :

A person, when alert, uses the preventive strategy and if the person is in-alert then there is a risk of transmission. The transmission of HIV in successive contacts during which the

person is in-alert, gives rise to a cumulative damage process, which damage results into the human immune mechanism. It results in the change over from seronegative to seropositive status by acquiring more and more HIV in successive contacts.

Assumptions of the Model :

- Sexual contact is the only source of HIV transmission.
- During any contact in which a person is inalert the transmission of HIV is a sure event.
- A person is alert in a single contact with probability p, and inalert with probability q, so that p + q = 1.
- The damage caused to the immune system due to the antigenic diversity is linear and additive.
- The total damage caused when exceed a threshold level Y which itself is a random variable, the seroconversion occurs and a person is recognized as infected.

Results

$$P\left[\sum_{i=1}^{k} X_i < Y\right] = \int_0^{\infty} g_k(x)\,\overline{H}(x)\,dx$$

where $\overline{H}(x) = 1 - H(x)$

Let Y ~ Exponentiated Exponential (λ, α)

$$h(y) = \alpha\lambda\left(1 - e^{-\lambda y}\right)^{\alpha-1} e^{-\lambda y}$$

$$H(y) = \left(1 - e^{-\lambda y}\right)^{\alpha}, \alpha, \lambda, y > 0$$

$$\therefore \overline{H}(y) = 1 - \left(1 - e^{-\lambda y}\right)^{\alpha}$$

Put $\alpha = 2$ then

$$\overline{H}(y) = 1 - \left(1 - e^{-\lambda y}\right)^{2}$$

$$= 2e^{-\lambda y} - e^{-2\lambda y}$$

$$P\left[\sum_{i=1}^{k} X_i < Y\right] = \int_0^{\infty} g_k(x)\left[2e^{-\lambda x} - e^{-2\lambda x}\right]$$

$$= \left[2g^*(\lambda)\right]^k - \left[g^*(2\lambda)\right]^k$$

We define the survival function as S(t) and S(t) = P[T > t]

$$= \sum_{k=0}^{\infty} \Pr\{\text{exactly k contacts in } (0, t]\}$$

$$* \Pr\{\text{the cumulative total of antigenic diversity} < Y\}$$

$$\therefore S(t) = V_k(t)\, P\sum_{i=1}^{k}\left[X_i < Y\right]$$

$$= \sum_{k=0}^{\infty}\left[F_k(t) - F_{k+1}(t)\right]\ \left[\left[2g^*(\lambda)\right]^k - \left[g^*(2\lambda)\right]^k\right]$$

L(t) = 1 – S(t)

$$= 1 - \left\{\sum_{k=0}^{\infty}\left[F_k(t) - F_{k+1}(t)\right]\ \left[\left[2g^*(\lambda)\right]^k - \left[g^*(2\lambda)\right]^k\right]\right\}$$

$$= 2\left[1 - g^*(\lambda)\right]\sum_{k=0}^{\infty} F_k(t)\left[g^*(\lambda)\right]^{k-1}$$

$$- \left[1 - g^*(2\lambda)\right]\sum_{k=0}^{\infty} F_k(t)\left[g^*(2\lambda)\right]^{k-1}$$

On simplification

Taking laplace transform of $l(t)$ we get,

$$l^*(s) = 2\left[1 - g^*(\lambda)\right]\ \sum_{k=0}^{\infty}\left[f^*(s)\right]^k\left[g^*(\lambda)\right]^{k-1}$$

$$- \left[1 - g^*(2\lambda)\right]\ \sum_{k=0}^{\infty}\left[f^*(s)\right]^k\left[g^*(2\lambda)\right]^{k-1}$$

where $\left[f^*(s)\right]^k$ is the laplace transform of $F_k(t)$

$$l^*(s) = \frac{2[1 - g^*(\lambda)] f^*(s)}{[1 - g^*(\lambda) f^*(s)]} - \frac{[1 - g^*(2\lambda)] f^*(s)}{[1 - g^*(2\lambda) f^*(s)]}$$

But the c.d.f of Z is given by

$$F(Z) = q \sum_{n=1}^{\infty} (1-q)^{n-1} G_n(Z)$$

Taking laplace stieltjes transform of F(z) is

$$F^*(s) = \int_0^{\infty} e^{-st} \, dF(Z)$$

$$\int_0^{\infty} e^{-st} \, dF(Z) = q \sum_{n=1}^{\infty} (1-q)^{n-1} \int_0^{\infty} e^{-st} \, d\, G_n(Z)$$

$$F^*(s) = q \sum_{n=1}^{\infty} (1-q)^{n-1} G_n(Z)$$

$$= q \sum_{n=1}^{\infty} (1-q)^{n-1} [G_n(Z)]^n$$

$$= q \left\{ \left[(1-q)^{1-1} [G^*(s)]^1\right] + \left[(1-q)^{2-1} [G^*(s)]^2\right] + \left[(1-q)^{3-1} [G^*(s)]^3\right] + \cdots \right\}$$

Hence,

$$F^*(s) = \frac{qG^*(s)}{[1 - (1-q) G^*(s)]}$$

And

$$f^*(s) = \frac{qg^*(s)}{[1 - (1-q) g^*(s)]}$$

Assuming that g ~ exp(μ), then

$$g^*(s) = \frac{c}{c+s}$$

$$g^{*1}(0) = -\frac{1}{c}$$

and $g^{*11}(0) = \frac{2}{c^2}$

$$\frac{df^*(s)}{ds} = \frac{\{q\, g^{*1}(s)[1 - (1-q) g^*(s)] - [-(1-q) g^{*1}(s)] q\, g^*(s)\}}{[1 - (1-q) g^*(s)]^2}$$

$$= \frac{\{q\, g^{*1}(s)[1 - (1-q) g^*(s)] + (1-q) g^{*1}(s) q\, g^*(s)\}}{[1 - (1-q) g^*(s)]^2}$$

at s = 0

$$= \frac{\{q\, g^{*1}(0) \;\; [1 - (1-q) g^*(0)] + (1-q) g^{*1}(0) q\, g^*(0)\}}{[1 - (1-q) g^*(0)]^2}$$

$$= \left(\frac{q\, g^{*1}(s)}{q^2} \right)$$

$$= \frac{g^{*1}(0)}{q}$$

$$f^{*1}(0) = \frac{-1}{cq}$$

We know that,

$$E(T) = -\frac{dl^*(s)}{ds}\Big|_{S=0}$$

$$l^*(s) = \frac{2[1 - g^*(\lambda)]f^*(s)}{[1 - g^*(\lambda)f^*(s)]} - \frac{[1 - g^*(2\lambda)]f^*(s)}{[1 - g^*(2\lambda)f^*(s)]}$$

$$l^{*t}(s) = \frac{2\{[1 - g^*(\lambda)]f^*(s)\ [1 - g^*(\lambda)]f^{*t}(s) - [1 - g^*(\lambda)]f^*((s)[0 - g^*(\lambda)]f^{*t}(s)\}}{[1 - g^*(\lambda)f^*(s)]^2}$$

$$- \frac{\{[1 - g^*(2\lambda)]f^*(s)[1 - g^*(2\lambda)]f^{*1}(s) - [1 - g^*(2\lambda)]f^*(s)[0 - g^*(2\lambda)]f^{*1}(s)\}}{[1 - g^*(2\lambda)f^*(s)]^2}$$

$$= \frac{2[1 - g^*(\lambda)]f^{*t}(S)f^*(s)}{[1 - g^*(\lambda)f^*(s)]^2} - \frac{[1 - g^*(2\lambda)]f^{*t}(s)f^{*t}(s)}{[1 - g^*(2\lambda)f^*(s)]^2}$$

On simplification

At s = 0

$$l^*(s) = \frac{2[1 - g^*(\lambda)]f^{*t}(0)f(0)}{[1 - g^*(\lambda)f^*(0)]^2} - \frac{[1 - g^*(2\lambda)]f^{*t}(0)f^*(0)}{[1 - g^*(2\lambda)f^*(0)]^2}$$

Let $g^*(\lambda) = \frac{\mu}{\mu + \lambda}, g^*(2\lambda) = \frac{\mu}{\mu + 2\lambda}$

$$E(T) = \frac{2\left[1 - \frac{\mu}{\mu + \lambda}\right]\left[\frac{-1}{cq}\right]}{\left[1 - \frac{\mu}{\mu + \lambda}\right]^2} - \frac{\left[1 - \frac{\mu}{\mu + 2\lambda}\right]\left[\frac{-1}{cq}\right]}{\left[1 - \frac{\mu}{\mu + 2\lambda}\right]^2}$$

On simplification

$$E(T) = \frac{3\mu + 2\lambda}{2cq\lambda}$$

$$= \frac{[1 - (1 - q)g^*(s)]^2[1 - (1 - q)g^*(s)]}{[1 - (1 - q)g^*(s)]^2}$$

At s = 0

$$= \frac{g^{*\prime\prime}(0)}{q} + \frac{2(1-q)\ [g^{*\prime}(0)]^2}{q^2}$$

$$g^{*\prime\prime}(0) = \frac{2}{c^2} \qquad g^{*\prime}(0) = \frac{-1}{c}$$

$$= \frac{2}{c^2 q} + \frac{2(1-q)}{(cq)^2}$$

$$E(T^2) = \left.\frac{d^2 l^*(s)}{ds^2}\right|_{S=0}$$

$$= \frac{2\left\{ \begin{array}{l} [1-g^*(\lambda)]f^*(s)\ \ [1-g^*(\lambda)]f^{*\prime\prime}(s) + 2[1-g^*(\lambda)]f^*(s)[0-g^*(\lambda)]f^{*\prime\prime}(s)[-g^*(\lambda)]f^{*\prime}(s) \\ \qquad\qquad [1-g^*(\lambda)]f^{*\prime}(s) \end{array} \right\}}{[1-g^*(\lambda)f^*(s)]^4}$$

$$- \frac{\left\{ [1-g^*(2\lambda)]f^*(s)[1-g^*(2\lambda)]f^{*\prime\prime}(s) + 2[1-g^*(2\lambda)]\ \ [-g^*(2\lambda)]f^{*\prime\prime}(s)[1-g^*(2\lambda)]f^{*\prime}(s) \right\}}{[1-g^*(2\lambda)f^*(s)]^4}$$

At s = 0

$$= \frac{2\left\{ \begin{array}{l} [1-g^*(\lambda)]f^*(0)[1-g^*(\lambda)]f^{*\prime\prime}(0) + 2[1-g^*(\lambda)]f^*(0)[g^*(\lambda)]f^{*\prime\prime}(0)[-g^*(\lambda)]f^{*\prime}(0) \\ \qquad\qquad [1-g^*(\lambda)]f^{*\prime}(0) \end{array} \right\}}{[1-g^*(\lambda)f^*(0)]^4}$$

$$- \frac{\left\{ [1-g^*(2\lambda)]f^*(0)[1-g^*(2\lambda)]f^{*\prime\prime}(0) + 2[1-g^*(2\lambda)]f^*(0)[-g^*(2\lambda)]f^{*\prime\prime}(0)[1-g^*(2\lambda)]f^{*\prime}(0) \right\}}{[1-g^*(2\lambda)f^*(0)]^4}$$

$$= 2\left\{ \frac{[1-g^*(\lambda)]^2[1-g^*(\lambda)]\left\{\left[\frac{g^{*\prime\prime}(0)}{q} + \frac{2(1-q)\ \left((g^{*\prime}(0))^2\right)}{(q)^2}\right] + 2[1-g^*(\lambda)]^2\left[\frac{g^{*1}(0)}{q}\right]^2 g^*(\lambda)\right\}}{[1-g^*(\lambda)]^4} \right\}$$

$$- \left\{ \frac{[1-g^*(2\lambda)]^2[1-g^*(2\lambda)]\left\{\left[\frac{g^{*\prime\prime}(0)}{q} + \frac{2(1-q)\left((g^{*1}(0))^2\right)}{(q)^2}\right] + 2[1-g^*(2\lambda)]^2\left[\frac{g^{*\prime}(0)}{2}\right]^2 g^*(2\lambda)\right\}}{[1-g^*(2\lambda)]^4} \right\}$$

Let $g^*(\lambda) = \frac{\mu}{\mu+\lambda}$ $g^*(2\lambda) = \frac{\mu}{\mu+2\lambda}$

$$= 2\left\{\frac{\left[1-\frac{\mu}{\mu+\lambda}\right]\left[\frac{2}{qc^2}+2(1-q)\frac{1}{(qc)^2}\right]+\frac{2}{(qc)^2}\left[\frac{\mu}{\mu+\lambda}\right]}{\left(\frac{\mu}{\mu+\lambda}\right)^2}\right\}$$

$$-\left\{\frac{\left[1-\frac{\mu}{\mu+2\lambda}\right]\left[\frac{2}{qc^2}+2(1-q)\frac{1}{(qc)^2}+\frac{2}{(qc)^2}\left[\frac{2\mu}{\mu+2\lambda}\right]\right]}{\left(\frac{2\mu}{\mu+2\lambda}\right)^2}\right\}$$

$$E(T^2) = \frac{8\lambda^2+14\mu^2+24\mu\lambda}{4\lambda^2c^2q^2}$$

$$V(T) = \frac{8\lambda^2+14\mu^2+24\mu\lambda}{4\lambda^2c^2q^2} - \left[\frac{3\mu+2\lambda}{2\lambda cq}\right]^2$$

$$V(T) = \frac{5\mu^2+4\lambda^2+12\lambda\mu}{4\lambda^2c^2q^2}$$

Special case :

When there is no alertness, then q = 1, so

$$\mu_t = \frac{3\mu+2\lambda}{2c\lambda}$$

In the case alertness

$$\mu_{ta} = \frac{3\mu+2\lambda}{2c\lambda q}$$

Therefore $\mu_{ta} > \mu_t$ and this implies that the mean time to seroconversion is larger in the case of alertness, which is inversely proportional to the probability of alertness of which is an interesting result.

$$\sigma_{ta}^2 = \frac{5\mu^2+4\lambda^2+12\lambda\mu}{4\lambda^2c^2q^2}$$

When q =1, if there is no alertness the variance is

$$\sigma_t^2 = \frac{5\mu^2+4\lambda^2+12\lambda\mu}{4\lambda^2c^2}$$

Which are the results obtained by Kannan *et al*.[5]

Numerical Illustration :

Table 1

c	λ = 0.1, μ = 0.5, q = 0.5	
	E(T)	V(T)
1	17.00	189.00
2	8.50	47.25
3	5.67	21.00
4	4.25	11.81
5	3.40	7.56
6	2.83	5.25
7	2.43	3.86
8	2.13	2.95
9	1.89	2.33
10	1.70	1.89

Table 2

μ	c = 1, λ = 0.1, q = 0.5	
	E(T)	V(T)
0.1	5.0	21.00
0.2	8.00	48.00
0.3	11.00	85.00
0.4	14.00	132.00
0.5	17.00	189.00
0.6	20.00	256.00
0.7	23.00	333.00
0.8	26.00	420.00
0.9	29.00	517.00

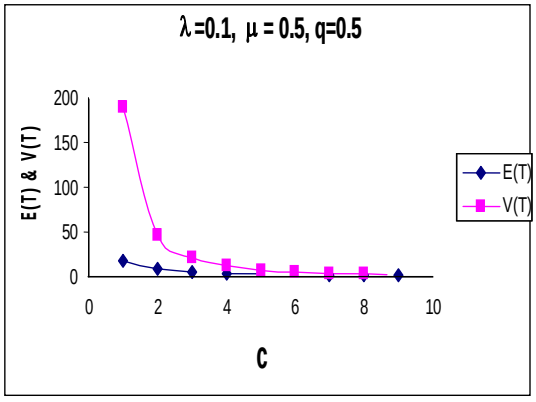

Figure 1

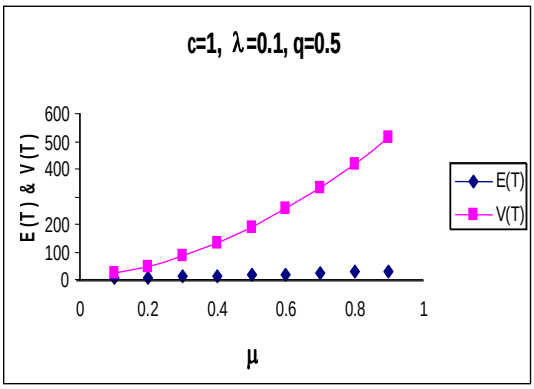

Figure 2

As the value c namely the parameter of the random variable denoting interarrival time increases then under alertness the expected time increases then under alertness the expected time seroconversion decreases and also variance time to seroconversion decreases.

As the value of μ which is namely the parameter of the random variable X_i denoting the contribution to the antigenic diversity increases then, the expected time to seroconversion and variance of seroconversion increases. This is due to the fact that g(.) is the distribution of $X_{(i)}$, the magnitude of contribution to antigenic

diversity. Since $E(X)=\frac{1}{\mu}$, as μ increase there is a decrease in the contribution of antigenic diversity. Hence mean time to seroconversion increases, so also the value of variance of seroconversion time.

Table 3

λ	c = 1, μ = 0.5 q = 0.5	
	E(T)	V(T)
0.5	5.00	21.00
1	3.50	11.25
1.5	3.00	8.56
2	2.75	7.31
2.5	2.60	6.60
3	2.50	6.14
3.5	2.43	5.82
4	2.38	5.58
4.5	2.33	5.40
5	2.30	5.25

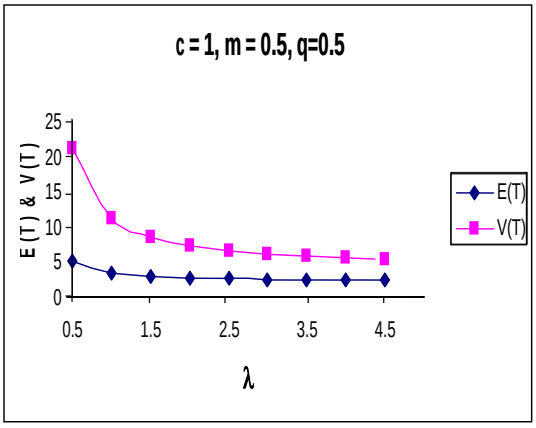

Figure 3

As the parameter of the threshold distribution λ increases the mean time to seroconversion as well as the variance time to seroconversion decrases.

Table 4

q	C = 1, μ = 0.5, λ = 0.1	
	E(T)	V(T)
0.1	85.00	4752.00
0.2	42.50	1181.25
0.3	28.30	525.00
0.4	21.25	295.31
0.5	17.00	189.00
0.6	14.17	131.25
0.7	12.14	96.43
0.8	10.63	73.83
0.9	9.44	58.33

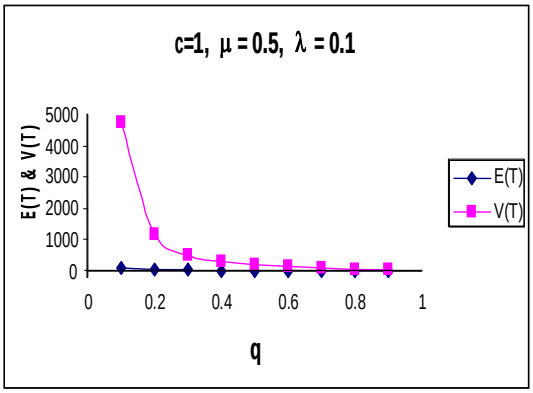

Figure 4

If 'q' the probability of in alertness increases the contribution to the antigenic diversity in successive contacts will be more and hence there is a decrease in mean time to seroconversion and also it variance.

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