

ON THE ESTIMATION OF TIME TO GET AIDS ON THE BASIS OF ANTIGENIC DIVERSITY AND VIRULENCE THRESHOLD

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ABSTRACT

In the study of HIV infection, several stochastic models were developed to describe the spread and progression of AIDS. It is quite impossible for a HIV infected individual to get rid of the infection and the ultimate end is the progression to the condition of AIDS and hence death. Hence the studies relating to the estimation of time to cross Antigenic Diversity Threshold of HIV infected is an important aspect. In this paper we propose a stochastic model under the assumption that the time interval between contacts with follows exponential distribution. The concept of cumulative process is used for describing the accumulated antigenic diversity and virulence due to the contacts with the infected. Numerical illustrations are provided for different combinations of parameters involved in the model for substantiation.

Keywords: Antigenic diversity threshold, Virulence threshold, HIV, AIDS.

INTRODUCTION

HIV infection and its progression to AIDS is a matter of great concern because it is not only relating to the health of an individual but also is a social problem of the community. Several studies were made by the medical experts to study the infection from different aspects. In an infected individual, the intensity of progression to AIDS may depend on the extent of exposure to this virus. The antigens accumulated due to successive contacts contribute to the progression towards AIDS. It is believed that when the total antigenic diversity induced by the invaded viruses goes beyond certain level, called the Antigenic diversity threshold (ADT) the condition of AIDS begins to occur in an infected individual. The concept of antigenic diversity and virulence thresholds has been discussed by Nowak, *et. al.*(1994).

In the process of getting AIDS condition in an infected Individual, a significant role is played by the antigenic diversity and the virulence developed by the invading antigens. Virulence is defined as the ability of an agent of infection to produce disease. The virulence of a microorganism is a measure of the severity of the disease it causes.

Virulence, a term that is often used interchangeably with pathogenicity, refers to the degree of disease caused by the organism. The extent of virulence is generally related to the ability of the pathogen to multiply within the host and can be influenced by other factors. According to Karen Z. Lancaster and Julie K. Pfeiffer (2012), viral factors and host barriers influence virus-induced disease and asymptomatic infection with symptomatic infection is regulated by a "virulence threshold". Understanding the modulation of virulence thresholds could give an idea of the outcome of the disease and help in the design of the therapeutic and rational vaccine.

In HIV infection it is reasonable to assume that the condition of AIDS begins to occur in an infected if the virulence threshold is crossed. Sabastian Bonho effer and Nowak (1994) have discussed the concept of mutation and evolution of virulence. For some highly mutating parasites, virulence may be a random by product of intra-host evolution. In this paper a stochastic model to estimate the time to get AIDS is discussed taking into consideration the two thresholds namely antigenic diversity threshold and the virulence threshold. In doing so it is assumed that the AIDS takes place if either one of the thresholds is crossed due to the accumulation of either the antigenic diversity or the virulence.

ASSUMPTIONS OF THE MODEL

1. Sexual contact is the only source of transmission of HIV.
2. Over a time period, a person is assumed to have a number of sexual contacts with persons at random which includes HIV infected partners.
3. It is assumed that every contact with an infected contributes to the increase in antigenic diversity as well as the virulence.

4. The antigenic diversity threshold and virulence threshold of an individual is assumed to be a random variable, follows exponential distribution.
5. The inter arrival times between successive contacts are assumed to be independent and identically distributed random variables.
6. Over a period of time say $(0,t)$ an infected individual is having contacts with ' m ' persons at random and out of which n are infected and q is the probability that his random partner is being infected by HIV.
7. The times between any two successive contacts are assumed to be independent.

NOTATIONS

X_i - a random variable denoting the contribution to antigenic diversity on the i^{th} contact $i = 1,2,3, \dots m$ and with p.d.f $g(.)$ with c.d.f $G(.)$
 Y_i - The increase in the virulence due to the i^{th} contact, $i = 1,2,3, \dots m$ with p.d.f $q(.)$ and c.d.f $Q(.)$.
 Z_1 - A random variable representing the antigenic diversity threshold level, which has p.d.f $h(.)$ and c.d.f $H(.)$.
 Z_2 - A random variable representing the virulence threshold level, which has p.d.f $k(.)$ and c.d.f $K(.)$.
 $f^*(.)$ - Laplace transform of $f(.)$.
 U_i - A continuous random variable denoting the inter-arrival times between successive contacts, with probability distribution function $W(.)$ and the density function $w(.)$.
 $W_m(.)$ - Cumulative distribution function of $\sum_{i=0}^m U_i$
 $w^*(.)$ - Laplace transform of $w(.)$.

THE MODEL

The probability that the antigenic diversity developed by the n sexual contacts with infected individuals that does not cross the threshold level is given by,

$$\begin{aligned}
 P(X_1 + X_2 + \dots + X_n \leq Z_1) &= \int_0^\infty H(x)g(x)dx \\
 &= \int_0^\infty H(x)\mu e^{-\mu x} dx \\
 &= \mu H^*(\mu) \\
 &= [f^*(\mu)]^n
 \end{aligned}$$

The probability that the virulence developed by the n sexual contacts with infected individuals that does not cross the threshold level is given by,

$$\begin{aligned}
 P(Y_1 + Y_2 + \dots + Y_n \leq Z_2) &= \int_0^\infty Q(y)k(y) dy \\
 &= \int_0^\infty Q(y)\lambda e^{-\lambda x} dx \\
 &= \lambda Q^*(\lambda) \\
 &= [g^*(\lambda)]^n
 \end{aligned}$$

Now, the probability of having m contacts during the interval $(0, t)$ is

$$P(M = m|t) = \sum_{m=0}^\infty [W_m(t) - W_{m+1}(t)]$$

The probability that out of ' m ' randomly chosen partners ' n ' are infected is

$$P(N = n|m) = \binom{m}{n} q^n (1 - q)^{m-n}$$

Then the probability that threshold has not passed at time ' t ' becomes

$$P(T > t) = \sum_{m=0}^\infty [W_m(t) - W_{m+1}(t)] * \sum_{n=0}^m \binom{m}{n} q^n (1 - q)^{m-n} * P[\sum_{i=1}^m x_i < Z_1 \cup \sum_{i=1}^m y_i < Z_2]$$

$$\begin{aligned}
 &= \sum_{m=0}^\infty [W_m(t) - W_{m+1}(t)] * \sum_{n=0}^m \binom{m}{n} q^n (1 - q)^{m-n} * [\int_0^\infty g_m(x)H(x) dx + \\
 &\hspace{15em} \int_0^\infty q_m(y)K(y) dy]
 \end{aligned}$$

$$P(T > t) = \sum_{m=0}^\infty [W_m(t) - W_{m+1}(t)] * \sum_{n=0}^m \binom{m}{n} q^n (1 - q)^{m-n} * [f^*(\mu) + g^*(\lambda)]^n$$

$$= \sum_{m=0}^\infty [W_m(t) - W_{m+1}(t)] * (1 - q)^m \sum_{n=0}^m \binom{m}{n} q^n (1 - q)^{-n} * [f^*(\mu) + g^*(\lambda)]^n$$

$$= \sum_{m=0}^\infty [W_m(t) - W_{m+1}(t)] * (1 - q)^m \sum_{n=0}^m \binom{m}{n} * \left(\frac{(f^*(\mu) + g^*(\lambda))q}{(1-q)} \right)^n$$

$$= \sum_{m=0}^{\infty} [W_m(t) - W_{m+1}(t)] * [1 - q(1 - (f^*(\mu) + g^*(\lambda)))]^m$$

$$= \sum_{m=0}^{\infty} [W_m(t) - W_{m+1}(t)] * A^m,$$

Where $A = [1 - q(1 - (f^*(\mu) + g^*(\lambda)))]$

$$P(T \leq t) = (1 - A) \sum_{m=1}^{\infty} [W_m(t)] A^{m-1}$$

Taking Laplace transform and Differentiating the above equation with respect to t and we get

$$l^*(s) = (1 - A) \sum_{m=1}^{\infty} [w_m(s)] A^{m-1}$$

$$= (1 - A) w^*(s) \sum_{m=1}^{\infty} [w^*(s)]^{m-1} A^{m-1}$$

$$= (1 - A) \left[\frac{1}{w^*(s)} - A \right]^{-1}$$

$$\frac{d}{ds} l^*(s) = (1 - A) \frac{d}{ds} \left[\frac{1}{w^*(s)} - A \right]^{-1}$$

$$= (1 - A) \left[\frac{1}{w^*(s)} - A \right]^{-2} \left[\frac{1}{(w^*(s))^2} \right] w^{*'}(s)$$

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

$$= -(1 - A) \left[\frac{1}{w^*(0)} - A \right]^{-2} \left[\frac{1}{(w^*(0))^2} \right] w^{*'}(0)$$

$$E(T) = \frac{1}{\theta q((1 - (f^*(\mu) + g^*(\lambda))))}$$

In particular, if we assume that the random variable U denoting inter arrival times between successive contacts follows exponential distribution with parameter ' θ ' and if the damage caused to the immune system due to a sexual contacts follows exponential distribution with parameter β , then $w^*(s) = \theta/(\theta + s)$. The mean and the variance of the time to cross the ADT can be obtained as,

$$E(T^2) = -\frac{d^2}{ds^2} l^*(s) \Big|_{s=0}$$

$$= (1 - A) \frac{d^2}{ds^2} \left[\frac{1}{w^*(s)} - A \right]^{-2} \left[\frac{1}{(w^*(s))^2} \right] w^{*'}(s)$$

$$= -\frac{2A(w^{*'}(0))^2}{(1 - w^*(s)A)^3} - \frac{w^{*''}(0)}{(1 - w^*(s)A)^2}$$

$$E(T^2) = \frac{1}{(\theta q)^2((1 - (f^*(\mu) + g^*(\lambda))))^2}$$

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

$$V(T) = \frac{2}{(\eta q)^2((1 - (f^*(\mu) + g^*(\lambda))))^2} - \left[\frac{1}{\eta q((1 - (f^*(\mu) + g^*(\lambda))))} \right]^2$$

$$V(T) = \frac{1}{(\theta q)^2(1 - (f^*(\mu) + g^*(\lambda)))^2}$$

A simulation study for the estimation of mean time to CADT and its variance under these models has been done with the assumption that the distribution of damage is exponential with parameter β . The random deviates of sizes n from the distribution of threshold, inter-arrival times, and the damage have been

generated and the estimates for μ, λ and β have been obtained. The estimates for $E(T)$ and $V(T)$ under these models are obtained by substituting estimated values for the corresponding parameters.

Figure 1.1

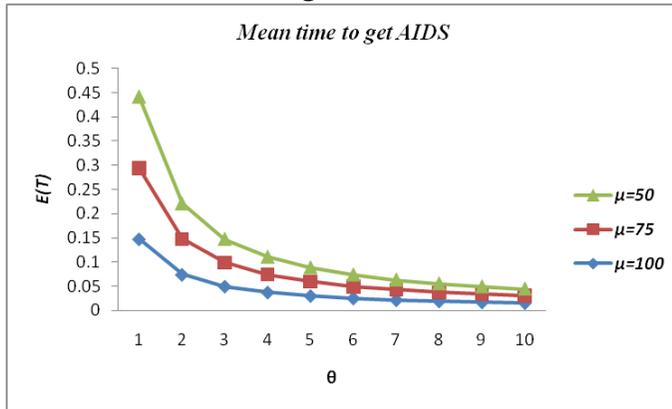


Figure 1.2

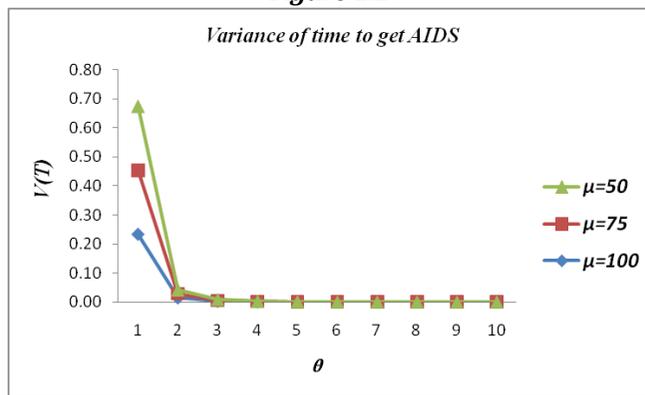


Figure 2.1

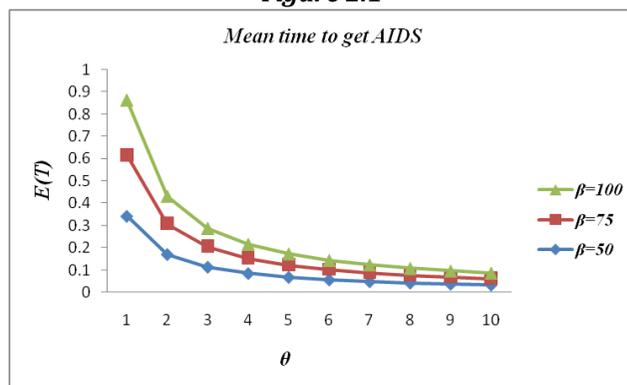
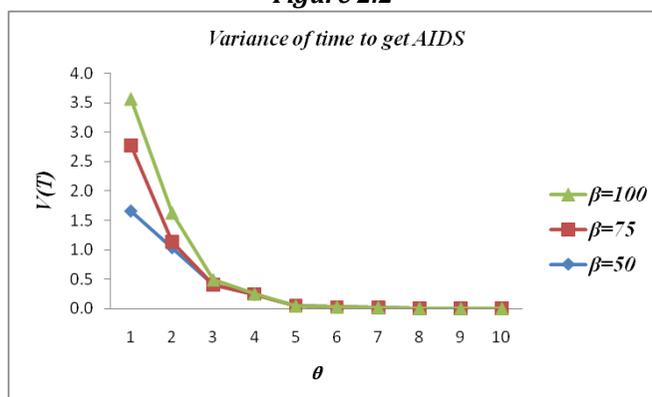


Figure 2.2



CONCLUSION

1. In figures 1.1. and 1.2, the curves show the expected value of T and the corresponding variance for different values of μ keeping β, q and λ as constants. It is seen that when μ is higher, both $E(T)$ and $V(T)$ are decreasing. This may be interpreted as if an infected person's ADT and virulence threshold levels are higher, then the time to get AIDS may get extended. Also it can be noticed that when the contacts are more frequent with infected persons the symptoms of AIDS will occur soon.

2. In figures 2.1 and 2.2, the behavior of time to cross ADT for various values of mean β has been observed. From this, it can be observed that when the immune system gets more infected with accumulated antigenic diversity and virulence due to several contacts with infected individuals, the symptoms of AIDS may be developed soon in an infected individual. Also if a person is having contacts with more infected individuals, he may get the condition of AIDS soon.

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