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RESEARCH ARTICLE

ON THE ESTIMATION OF TIME TO GET AIDS SYMPTOMS – A STOCHASTIC APPROACH

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ABSTRACT

Antigenic diversity is an important determinant of outcome of infection with HIV. Successive invasion through various modes of HIV transmission may contribute to the increase in the antigenic diversity of HIV. There it is assumed that there exists antigenic diversity threshold level, beyond which the immune system cannot sustain against the HIV which leads to almost complete breakdown of the immune system. At this point, the onset of AIDS symptoms starts with a HIV infected person. This paper narrates a stochastic model used for estimating the expected time to get AIDS through various modes of transmission of HIV. Numerical illustrations are provided using simulation technique to substantiate the results.

INTRODUCTION

As HIV is a retrovirus, antigenic diversity imposed by the HIV is one of the important factors, of determining the outcome of the infection. Nowak and May (1991) and Stilianakis (1994) have studied the concept of antigenic diversity threshold in the immune system. The immune system is able to mount an effective immune response only against a viral quasi – species whose diversity is below some threshold value. If the total population of viral quasi-species exceeds the "diversity threshold", the immune system is liable to collapse, being unable to regulate viral replication and CD4 cell destruction. On the crossing the antigenic diversity threshold it is believed that the on set of AIDS symptoms in infected person.

It is a known fact that people get HIV infection through four different modes namely homo, hetero sexual contacts, needle sharing and mother's breast feeding. People with random behavior like Hippies may get involved with homosexual contacts, hetero sexual contacts and sharing of unsteriled needles for drug abuse and hence there is a possibility of getting infection in all of these modes.

A person may get increase in the HIV viral load when he is having subsequent contacts/needles sharing with an infected partner. Barbara Bittner *et al.* (1997) have established that there is a positive correlation exists between the viral load and antigenic diversity of HIV especially for the patients with stronger strain specific component for the immune system. Hence it is assumed that homo, hetero sexual contacts with an infected person or sharing of unsteriled needles will make a due contribution to the accumulation of antigenic diversity and when the total antigenic diversity crosses the antigenic diversity threshold the infected person begins to show AIDS symptoms . The time to cross the antigenic diversity threshold or in other words the time to get AIDS symptoms after the infection is investigated here using shock model cumulative damage process. Numerical illustrations are provided using a Monte-Carlo simulation study to substantiate the results.

Assumptions of the Model

An uninfected partner has homo and hetero sexual contacts with an infected person and also shares unsterile needles for drug abuse. On every occasion of homo and hetero sexual contact and sharing of unsterile needle, there is a random amount of transmission of HIV which in-turn contributes to the increase in antigenic diversity level. The consequences due to the three events namely, sharing of needles and homo and heterosexual contacts are statistically independent .Also the process that generates, the random amount of damage is terms of antigenic diversity to the immune system, the inter arrival times between heterosexual, homosexual contacts and sharing of needles are all statistically independent.

Notations

X_i - a continuous random variable denoting the amount of damage caused to the immune system due to the i^{th} homosexual contacts and X_i's are assumed to be i.i.d

Y_i - a continuous random variable denoting the amount of damage caused to the immune system due to the i^{th} needle sharing events and Y_i's are assumed to be i.i.d

Z_i - a continuous random variable denoting the amount of damage caused to the immune system due to the i^{th} heterosexual contacts and Z_i's are assumed to be i.i.d

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$\widetilde{X} = \sum_{i=1}^{p} X_i$

$\widetilde{Y} = \sum_{i=1}^{q} Y_i$

$\widetilde{Z} = \sum_{i=1}^{r} Z_i$

T - A random variable representing the time to Cross the Antigenic Diversity Threshold (CADT)

$g^*(.)$ - The Laplace transform of $g(.)$,where $g(.)$ is the p.d.f of X_i with c.d.f of $G(.)$

$h^*(.)$ -The Laplace transform of $h(.)$, where $h(.)$ is the p.d.f of Y_i with c.d.f of $H(.)$

$k^*(.)$ -The Laplace transform of $k(.)$, where $k(.)$ is the p.d.f of Z_i with c.d.f of $K(.)$

τ_i - Inter arrival times between homosexual contacts which are assumed to be i.i.d random variables

η_i - Inter arrival times between needles sharing which are also assumed to be i.i.d random variables

δ_i - Inter arrival times between heterosexual contacts which are assumed to be i.i.d random variables

$E_P(.)$ - c.d.f of $\sum_{i=1}^{p} \tau_i$

$F_q(.)$ - c.d.f of $\sum_{i=1}^{q} \eta_i$

$J_r(.)'$ - c.d.f of $\sum_{i=1}^{r} \delta_i$

U - a random variable represents the antigenic diversity threshold (ADT) level which is assumed to follow Exponential distribution with parameter θ

RESULTS

The probability that the total antigenic diversity induced by p homosexual contacts, q occasions of needle sharing and r heterosexual contacts does not exceed the threshold U is given by,

$$P(\widetilde{X} + \widetilde{Y} + \widetilde{Z} < U) = \int_0^{\infty} (G_P H_q K_r)(u)\theta . e^{-\theta u}\, du$$

$$= \frac{\theta(g_p{}^* h^*{}_q k^*{}_r)}{\theta}(\theta)$$

$$= g^{*p} h^{*q} k^{*r}(\theta)$$

$P[T > t] = \sum_{p=0}^{\infty} \sum_{q=0}^{\infty} \sum_{r=0}^{\infty}$ P[That there are p homosexual contacts, q occasions of needle sharing and r heterosexual contacts in (0, t)]. Pr [the threshold is not crossed]

$$= \left[\sum_{p=0}^{\infty} [E(t)_P - E(t)_{p+1}] \, g^{*}(\theta) \right] * \left[\sum_{q=0}^{\infty} [F(t)_q - F(t)_{q+1}] \, h^{*}(\theta) \right]$$

$$* \left[\sum_{r=0}^{\infty} [J(t)_r - J(t)_{r+1}] \, k^{*}(\theta) \right]$$

$$= \left[\left(1-(1-g^{*}(\theta)) \right) * \left(\sum_{p=0}^{\infty} E_p(t) g^{*}(\theta)^{p-1}(\theta) \right) \right] * \left[\left(1-(1-k^{*}(\theta)) \right) * \left(\sum_{q=0}^{\infty} F_k(t) h^{*}(\theta)^{q-1}(\theta) \right) \right]$$

$$* \left[\left(1-(1-h^{*}(\theta)) \right) * \left(\sum_{r=0}^{\infty} J_r(t) k^{*}(\theta)^{r-1}(\theta) \right) \right]$$

As a particular case, if we assume that the inter-arrival times between homosexual contacts, heterosexual contacts and needle sharing follow exponential distributions with parameters λ_1, λ_2 and λ_3 respectively, we have

$$P[T > t] = \left[1-\left(1-e^{-\lambda_1 t(1-g^{*}(\theta))} \right) \right] * \left[1-\left(1-e^{-\lambda_2 t(1-h^{*}(\theta))} \right) \right] * \left[1-\left(1-e^{-\lambda_3 t(1-k^{*}(\theta))} \right) \right]$$

$$= e^{-t[\lambda_1(1-g^{*}(\theta))+\lambda_2(1-h^{*}(\theta))+\lambda_3(1-k^{*}(\theta))]}$$

Now,

$$L(t) = P[T \le t] = 1 - P[T > t]$$

$$= 1 - e^{-t[\lambda_1(1-g^{*}(\theta))+\lambda_2(1-h^{*}(\theta))+\lambda_3(1-k^{*}(\theta))]}$$

The p.d.f of T is given by,

$$l(t) = [\lambda_1(1-g^{*}(\theta)) + \lambda_2(1-h^{*}(\theta)) + \lambda_3(1-k^{*}(\theta))$$

$$* e^{-t[\lambda_1(1-g^{*}(\theta))+\lambda_2(1-h^{*}(\theta))+\lambda_3(1-k^{*}(\theta))]}$$

Now,

$$E(T) = \int_0^{\infty} t \left[\lambda_1(1-g^{*}(\theta)) + \lambda_2(1-h^{*}(\theta)) + \lambda_3(1-k^{*}(\theta)) \right]$$

$$e^{-[\lambda_1(1-g^{*}(\theta))+\lambda_2(1-h^{*}(\theta))+\lambda_3(1-k^{*}(\theta))]t} \, dt$$

$$= [-t \exp[(\lambda_1(1-g^{*}(\theta)) + (\lambda_2(1-h^{*}(\theta)) + (\lambda_3(1-k^{*}(\theta))]t]_0^{\infty}$$

$$+ \int_0^{\infty} \exp[(\lambda_1(1-g^{*}(\theta)) + (\lambda_2(1-h^{*}(\theta)) + (\lambda_3(1-k^{*}(\theta))]t \; dt$$

$$= [-te^{-[\lambda_1(1-g^{*}(\theta))+\lambda_2(1-h^{*}(\theta))+\lambda_3(1-k^{*}(\theta))]}]_0^{\infty} + \int_0^{\infty} e^{-[\lambda_1(1-g^{*}(\theta))+\lambda_2(1-h^{*}(\theta))+\lambda_3(1-k^{*}(\theta))]t} \, dt$$

$$e^{-[\lambda_1(1-g^{*}(\theta))+\lambda_2(1-h^{*}(\theta))+\lambda_3(1-k^{*}(\theta))]t} \, dt$$

$$E(T) = \frac{1}{[\lambda_1(1-g^{*}(\theta)) + \lambda_2(1-h^{*}(\theta)) + \lambda_3(1-k^{*}(\theta))]}$$

$$E(T^2) = \int_0^{\infty} t^2 [\lambda_1(1-g^{*}(\theta)) + \lambda_2(1-h^{*}(\theta)) + \lambda_3(1-k^{*}(\theta))] e^{-[\lambda_1(1-g^{*}(\theta))+\lambda_2(1-h^{*}(\theta))+\lambda_3(1-k^{*}(\theta))]t} \, dt$$

$$= \frac{2}{\lambda_1(1-g^*(\theta)) + \lambda_2(1-h^*(\theta)) + \lambda_3(1-k^*(\theta))]^2}$$

Variance of the time to CADT is given by,

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

$$= \frac{1}{[\lambda_1(1-g^*(\theta)) + \lambda_2(1-h^*(\theta)) + \lambda_3(1-k^*(\theta))]^2}$$

As a special case if we assume that *g(.)* and *h(.)* and *k(.)* are exponential with mean β_1, β_2 and β_3 respectively, we have

$$g^*(\theta) = \frac{1}{1+\beta_1\theta},\ h^*(\theta) = \frac{1}{1+\beta_2\theta},\ k^*(\theta) = \frac{1}{1+\beta_3\theta}$$

Now, the mean time to cross the ADT is given by,

$$E(T) = \frac{1}{\lambda_1\left(\frac{\beta_1\theta}{1+\beta_1\theta}\right) + \lambda_2\left(\frac{\beta_2\theta}{1+\beta_2\theta}\right) + \lambda_3\left(\frac{\beta_3\theta}{1+\beta_3\theta}\right)}$$

and the variance is

$$V(T) = \frac{1}{\left[\lambda_1\left(\frac{\beta_1\theta}{1+\beta_1\theta}\right) + \lambda_2\left(\frac{\beta_2\theta}{1+\beta_2\theta}\right) + \lambda_3\left(\frac{\beta_3\theta}{1+\beta_3\theta}\right)\right]^2}$$

A Monte-Carlo simulation study for the estimation of mean time to cross the ADT and its variance for this mode has been carried out. For this purpose ten thousands random numbers for various combinations of parameters based on the density of *T* have been generated .First it is decided to make a comparative study in the time to cross the antigenic diversity threshold (CADT) when three modes of transmission are considered with only one model. For this purpose the comparison in the mean and variance of time to CADT based on the simulated values are tabulated in Tables 1 and 2 and the curves corresponding to these values are given in Figures 1.1 and 1.2

Table 1. Time to Cross the ADT (one source)

Contacts/ Rate(λ_i) β=1000	Mean		Variance	
	Actual	Simulated	Actual	Simulated
1	0.334	0.32011	0.11156	0.09085
2	0.167	0.16906	0.02789	0.02733
3	0.11133	0.10782	0.0124	0.0111
4	0.0835	0.08151	0.00697	0.00743
5	0.0668	0.07073	0.00446	0.00494
6	0.05894	0.05896	0.00347	0.00363
7	0.04771	0.04799	0.00228	0.00261
8	0.06262	0.06681	0.00392	0.00452
9	0.03711	0.03636	0.00138	0.00139
10	0.0334	0.03271	0.00112	0.0011

Table 2. Time to Cross the ADT (Three sources)

Contacts/ Needle Sharing Rates(λ_i)	Mean		Variance	
	Actual	Simulated	Actual	Simulated
1	0.34667	0.34727	0.1218	0.13088
2	0.1733	0.1741	0.03004	0.03185
3	0.11556	0.1147	0.01335	0.01302
4	0.08667	0.08632	0.00751	0.00716
5	0.06933	0.0658	0.00481	0.00445
6	0.05778	0.067	0.00334	0.00406
7	0.04952	0.04856	0.0243	0.00255
8	0.04333	0.04231	0.00188	0.00187
9	0.03852	0.03819	0.00148	0.00137
10	0.03476	0.03457	0.0012	0.00113

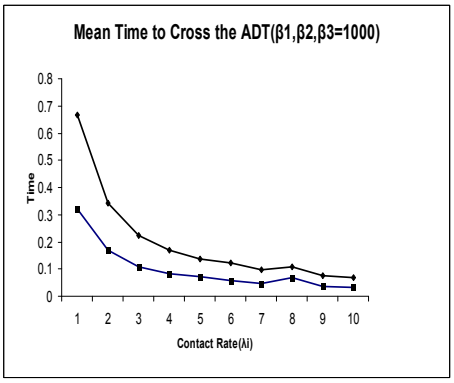

Fig. 1.1. Mean Time to Cross the ADT $(\beta_1, \beta_2, \beta_3 = 1000)$

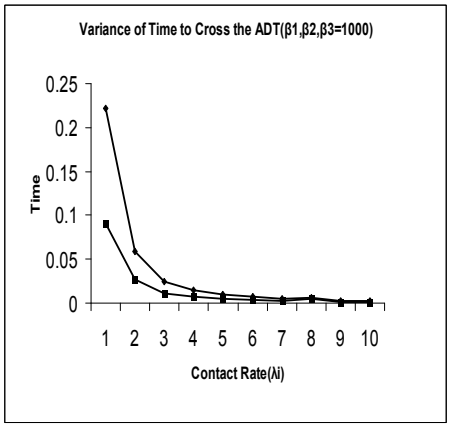

Fig. 1. 2. Variance of Time to Cross the ADT $(\beta_1, \beta_2, \beta_3 = 1000)$

From these figures it is observed that the expected time to Cross the Antigenic Diversity Threshold (CADT) as well as its variance gets increased when we have only one mode of transmission as compared with three modes. It shows that avoiding further needles sharing, homo sexual, hetero sexual contacts with infected persons, the time to get AIDS symptoms may be extended. Also it is seen that the expected time to CADT and its variance becomes shorter with the increase in the contact rates (homo,hetero sexual contacts and needles sharing),which shows when the frequency of needles sharing /contacts increases, the time to get AIDS symptoms decreases.

The behavior of the expected time to CADT and its variance for various values of β_i's are shown in Table 3. The corresponding values are plotted against contact rates and presented in Figure 3.1, 3.2. It could be observed that as β_i's get increased expected time to CADT and its variance are getting decreased. It shows that when the partner is more infectious, the damage caused by him to the immune system is more and therefore the index case will reach to the level of getting AIDS symptoms soon.

Table 3. Time to Cross the ADT for different values of β

	Contact Rate(λ_i)	Mean		Variance	
		Actual	Simulated	Actual	Simulated
β_i=0.1	1	0.40000	0.41396	0.16000	0.16811
	2	0.20000	0.20359	0.04000	0.04073
	3	0.13333	1.13303	0.01777	0.01588
	4	0.10000	0.10244	0.01000	0.01184
	5	0.08000	0.07563	0.00640	0.00536
	6	0.06667	0.06764	0.00444	0.00384
	7	0.05714	0.05856	0.00327	0.00344
	8	0.05000	0.05224	0.00250	0.00259
	9	0.04444	0.04535	0.00198	0.00184
	10	0.04000	0.03876	0.00160	0.00152
β_i=0.01	1	0.34000	0.34464	0.11560	0.11794
	2	0.17000	0.16222	0.02890	0.02603
	3	0.11333	0.11289	0.01284	0.01191
	4	0.08500	0.08711	0.00722	0.00804
	5	0.06800	0.06782	0.00462	0.00463
	6	0.05667	0.05337	0.00321	0.00288
	7	0.04857	0.04720	0.00236	0.00233
	8	0.04250	0.04263	0.00181	0.00182
	9	0.03778	0.03744	0.00143	0.00144
	10	0.03400	0.03314	0.00116	0.00106
β_i=0.001	1	0.33400	0.35377	0.11156	0.12964
	2	0.16700	0.15629	0.02789	0.02595
	3	0.11133	0.10370	0.01240	0.01092
	4	0.08350	0.08312	0.00697	0.00694
	5	0.06680	0.62750	0.00446	0.00412
	6	0.05567	0.05570	0.00310	0.00341
	7	0.04771	0.04775	0.00228	0.00247
	8	0.04175	0.04006	0.00174	0.00153
	9	0.03711	0.03505	0.00138	0.00118
	10	0.03340	0.03316	0.00112	0.00113

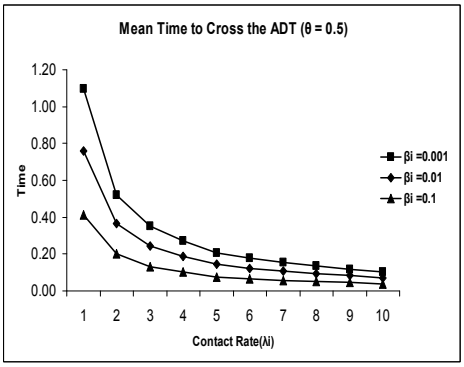

Fig. 3.1. Mean Time to Cross the ADT $(\theta = 0.5)$

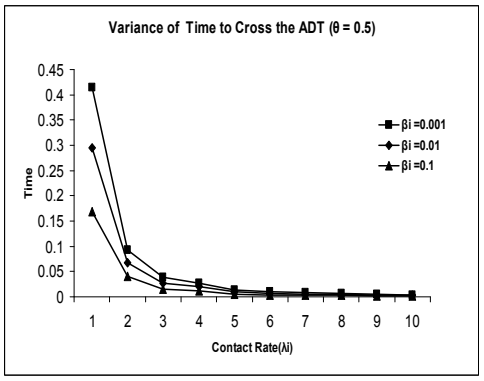

Fig. 3.2. Variance of Time to Cross the ADT $(\theta = 0.5)$

Table 4. Time to Cross the ADT for different values of θ

Contact Rate(λ_i)	Mean		Variance	
	Actual	Simulated	Actual	Simulated
θ=10.0, β_i=0.01				
1	0.33367	0.3288	0.11133	0.1047
2	0.16683	0.17133	0.02788	0.02915
3	0.11122	0.10794	0.01237	0.01221
4	0.08342	0.08674	0.00696	0.00832
5	0.06673	0.06566	0.00445	0.00393
6	0.05561	0.05423	0.00309	0.00302
7	0.04767	0.04683	0.00227	0.00227
8	0.04171	0.0403	0.00174	0.00161
9	0.03707	0.03516	0.00137	0.00126
10	0.03337	0.03359	0.00111	0.00097
θ=100				
1	0.33337	0.33917	0.11113	0.11611
2	0.16668	0.17301	0.02778	0.02888
3	0.11112	0.11362	0.01235	0.01187
4	0.08334	0.08795	0.00695	0.00789
5	0.06667	0.0717	0.00445	0.00559
6	0.05556	0.0536	0.00309	0.00274
7	0.04762	0.04861	0.00227	0.0025
8	0.04167	0.0414	0.00174	0.0018
9	0.03704	0.0378	0.00137	0.00144
10	0.03334	0.03355	0.00111	0.00109
θ=1000				
1	0.33334	0.34479	0.11111	0.1215
2	0.16667	0.17888	0.02778	0.03303
3	0.11111	0.11015	0.01235	0.012
4	0.08333	0.08481	0.00694	0.00682
5	0.06667	0.07302	0.00444	0.00606
6	0.05556	0.05397	0.00309	0.00306
7	0.04762	0.05033	0.00227	0.00278
8	0.04167	0.04191	0.00174	0.00168
9	0.03704	0.03777	0.00137	0.00146
10	0.0333	0.03326	0.00111	0.00114

The estimates of time to CADT for various values of θ are plotted against contact rates and presented in Figure.4.1 & 4.2. It could be observed that as θ increases the expected time to CADT and the variance are increased. It shows that when ADT increases the immune system is able to withstand long against the viral population.

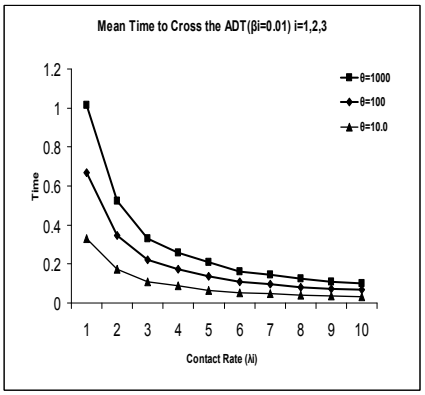

Fig. 4.1: Mean Time to Cross the ADT $(\beta_i = 0.01)$

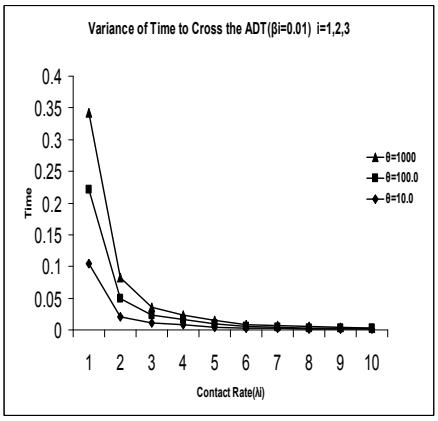

Fig. 4.2. Variance of Time to Cross the ADT $(\beta_i = 0.01)$

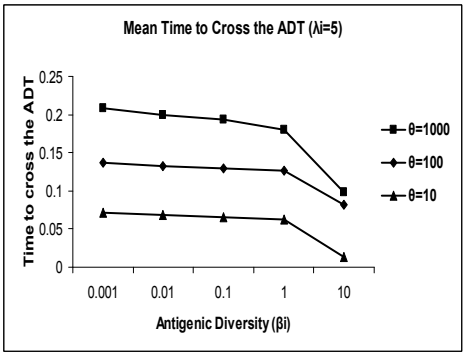

Fig. 5.1. Mean Time to Cross the ADT $(\lambda_i = 5)$

In the Figures 5.1 and 5.2 the antigenic diversity (amount of damages) β_i's is plotted against the time to cross the antigenic diversity threshold (CADT) assuming that all the β_i's are equal $(i = 1,2,3)$.

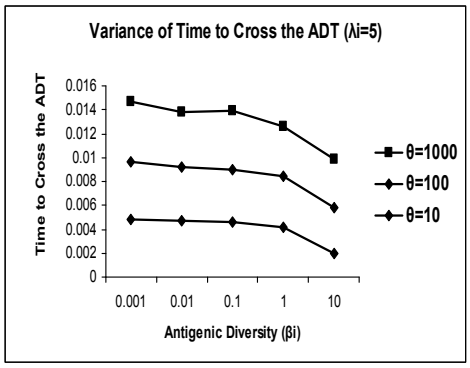

Fig. 5.2. Variance of Time to Cross the ADT $(\lambda_i = 5)$

The corresponding data are given in table 5. From this figure 5.1 and 5.2 it is observed that when antigenic diversity β_i's increases the expected time to Cross the Antigenic diversity threshold (CADT) decreases, but it depends on the individual's antigenic diversity threshold level. If an infected person possesses a high ADT level he will get AIDS symptoms later when compared to person with low ADT level.

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