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A STOCHASTIC MODEL FOR SEROCONVERSION TIMES OF HIV TRANSMISSION

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ABSTRACT

This paper focuses on the study of a Stochastic Model for predicting the seroconversion time of HIV transmission. As the immune capacities of an individual vary and also have its own resistance, the antigenic diversity threshold is different for different person. We propose a stochastic model to study the damage process acting on the immune system that is non- linear. The mean of seroconversion time of HIV and its variance are derived. A numerical example is given to illustrate the seroconversion times of HIV transmission.

Key words : Antigenic diversity threshold, T_4, Cells, Seroconversion, Human Immuno deficiency Virus. Acquired lmmuno Deficiency Syndrome. Alpha poisson Process. Mittag–Laffler distribution.

INTRODUCTION

The study of the science of epidemiology has gained great significance to the epidemic diseases, namely, Severe Acute Respiratory Syndrome (SARS) and Acquired Immuno Deficiency Syndrome (AIDS). SARS is a respiratory illness that has recently reported in Asia, North America, and Europe. SARS has rapidly generated a serious worldwide concern within a short span of time. In 1981, AIDS was first reported in USA. From then to till now the AIDS epidemic remains a mysterious phenomenon and intensive research is in progress throughout the world in an effort to understand it and develop therapies and vaccines for this terrifying disease. The causative agent of AIDS disease is the retrovirus HIV (Human Imunodeficiency Virus).

Epidemiological studies (Brook Meyer Ron and Gail Mitchell, 1994) have pointed out that the route of HIV transmission is blood and that the transmission occurs primarily through sexual contacts, sharing of contaminated needles, transfusion of infected blood / blood products, infected mother's breast milk to infants or vertical transmission from mother to fetus in uterus or at delivery. Many authors studied the seroconversion time of HIV transmission by taking sexual contact alone is the only mode of HIV transmission. The sexual contacts are assumed between a seropositive person who is labeled as index case and seronegative counterpart is called as partner. A seroconversion from seronegative to seropositive state takes place after an incubation period due to the contraction of HIV to the partner from the index case by sexual contacts.

Several authors have studied the stochastic models for the projection of number of cases of incidence in futute, rate of spread, etc. Shiboski and Jewel1 (1990) have obtained the expression for hazard rate and prevalence function for the transmission of HIV. They

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also have developed parametric and non-parametric methods of estimation of infectivity on the basis of available data from the partner studies. The concept of antigenic diversity threshold is found in Nowak and May (1991). Stilianakis *el. al.* (1994) discussed the transmission of HIV in successive contacts and its effects on antigenic diversity. Sathiyamoorthy and Kannan (1998) also obtained the expression for the expected time to seroconversion and its variance assuming the inter contact times to be correlated random variables. Sathiyamoorthy and Kannan (2000) derived a stochastic model based on the cumulative damage process with the assumption that the antigenic diversity threshold is a random variable and the damage process acting on the immune system is assumed to be linear. But as the immune capacities of an individual vary and also have its own resistance, the assumption of the antigenic diversity threshold acting on the immune system to be "linear" is not appropriate. In this paper, we propose a stochastic model of Seroconversion time of HIV transmission at time t with contact n (n = 0,1,2 ...) in which the antigenic diversity threshold level is Erlang k=2 distribution with the damage process, acting on the immune system of an infected individual is non linear and cumulative (Esary *et al.,* 1973).

There are certain number of HIV is getting transmitted during every contact and they in turn contribute to the antigenic diversity during the regenerative process. When the total antigenic diversity crosses a threshold level, the seroconversion takes place due to the depleting T_4 cells. The damage caused to the immune system of an individual can be interpreted as the cumulative antigenic diversity in successive contacts.

Assumptions:

i) Sexual contact is the only source of HIV transmission.
ii) An uninfected individual has sexual contacts with a HIV infected partner.
iii) Damages to individuals are caused by transmission of HIV at each contact and the inter arrival time between the contacts are independent identically distributed random variables.
iv) The damage process acting on the immune system of an infected individual non-linear and cumulative.
V) The total damage caused exceeds a threshold level Y is itself a random variable
vi) The process that generates the contacts, the sequence of damages and threshold are mutually independent.

Notations:

X_i -the increase in the antigenic diversity arising due to the HIV transmitted during i^{th} contact.

G (.) -probability distribution function of X_i

g (.) -the probability density function of X^i

gk(.) - the probability function of the random variable $\sum_{i=1}^{k} X_i$ which is the k convolution of g(.)

Y - random variable denoting the antigenic diversity threshold has an Erlang k=2 distribution with parameter μ.

F (.) – the probability density function of threshold.

T – random variable denoting the time to seroconversion.

a – contact rate of the infected partner.

a - intensity of the HIV of the infected partner

$V_k(t)$ – the probability that there are exactly k contacts in (0,t] with intensity represented as a Alpha Poisson process with parameters 'a' and '**a**' is

$$p_{a,\alpha}(n,t) = \sum_{k=0}^{\infty} (-1)^k \binom{k+n}{k} \frac{(at)^{\alpha(k+n)}}{\Gamma(\alpha(k+n)+1)}, \quad a>0, \quad 0<\alpha\le 1, \quad n=0,1,2,\ldots$$

The inter arrival time between the contacts follow Mittag–Leffler (1990,2001) distribution which is given by

$$F_{a,\alpha}(t) = \sum_{k=1}^{\infty} \frac{(-1)^{k-1}}{\Gamma(\alpha k+1)} (at)^{\alpha k}, \quad t\ge 0, \quad a>0, \ 0<\alpha\le 1$$

Now the prevalence function = L (t) = 1 - S (t).

S (t) = P {T > t}

=Probability that the seroconversion does not take before t

$= \sum_{k=1}^{\infty} P$[No seroconversion before t / exactly k contact in (o, t] with intensity a] x

P [exactly k contacts in (o, t] with intensity **a**]

$$= \sum_{k=1}^{\infty} V_k(t) \ \mathrm{P}\left\{\sum_{i=1}^{k} X_i < Y\right\}$$

where V_k (t) = probability of exactly k contacts in (o, t].

$$\text{Now, P } \{X < Y\} = \int_0^{\infty} G(x) f(x) dx$$

$$= \mu^2 \int_0^{\infty} G(x) x \ e^{-\mu x} dx$$

$$= -\mu^2 \int_0^{\infty} G(x) \frac{d}{d\mu} e^{-\mu x} dx$$

$$= -\mu^2 \frac{d}{d\mu} G^*(\mu)$$

$$= -\mu^2 \frac{d}{d\mu}\left[\frac{g^*(\mu)}{\mu}\right]$$

Then $P\{X_1 + X_2 + ... + X_k < Y\} = -\mu^2 \frac{d}{d\mu}\left[\frac{g_k^*(\mu)}{\mu}\right]$

$$= -\mu^2 \frac{d}{d\mu}\left[\frac{g^*(\mu)^k}{\mu}\right]$$

$$= -\mu k\left[g^*(\mu)\right]^{k-1} g^{*/}(\mu) + \left[g^*(\mu)\right]^k$$

Now S (t) = P {T > t}

$$= \sum_{k=0}^{\infty} \frac{e^{-(at)^{\alpha}}\left[(at)^{\alpha}\right]^k}{(\alpha k)!}\left\{\left[g^*(\mu)\right]^k - \mu k\left[g^*(\mu)\right]^{k-1} g^{*/}(\mu)\right\}$$

$$= \exp\left\{-(at)^{\alpha}[1 - g^*(\mu)]\right\}\left[1 - \frac{(at)^{\alpha}\mu}{\alpha} g^{*/}(\mu)\right]$$

$$L(t) = P\{T \le t\} = 1 - e^{-(at)^{\alpha}[1 - g^*(\mu)]}\left[1 - \frac{(at)^{\alpha}}{\alpha}\mu g^{*/}(\mu)\right]$$

If g (.) has Mittag - Leffler distribution with parameter a and **a,** then

$$g^*(\mu) = \frac{a^{\alpha}}{a^{\alpha} + \mu^{\alpha}} \Rightarrow g^{*/}(\mu) = -\frac{\alpha a^{\alpha}\mu^{\alpha-1}}{(a^{\alpha} + \mu^{\alpha})^2}$$

$$L(t) = P\{T \le t\} = 1 - \exp\left\{-(t)^{\alpha}\left[\frac{a^{\alpha}\mu^{\alpha}}{a^{\alpha} + \mu^{\alpha}}\right]\right\}\left[1 + \frac{a^{2\alpha} t^{\alpha}\mu^{\alpha}}{(a^{\alpha} + \mu^{\alpha})^2}\right]$$

The probability density function of seroconversion time T is

$$\Psi(t) = \frac{\alpha a^{\alpha}\mu^{2\alpha}}{(a^{\alpha} + \mu^{\alpha})^2}\exp\left\{-(t)^{\alpha}\ \frac{a^{\alpha}\mu^{\alpha}}{\mu^{\alpha} + a^{\alpha}}\right\} t^{\alpha-1}\left[1 + \frac{a^{2\alpha} t^{\alpha}}{a^{\alpha} + \mu^{\alpha}}\right]$$

The expected time of seroconversion is given by

$$E(T) = \int_0^\infty t\psi(t)dt = \frac{1}{a^\alpha + \mu^\alpha}\left[\frac{a^\alpha + \mu^\alpha}{a^\alpha \mu^\alpha}\right]^{\frac{1}{\alpha}}\left[\mu^\alpha \Gamma(1/\alpha+1) + a^\alpha \Gamma(1/\alpha+2)\right]$$

$$\text{And } E(T^2) = \frac{1}{a^\alpha + \mu^\alpha}\left[\frac{a^\alpha + \mu^\alpha}{a^\alpha \mu^\alpha}\right]^{\frac{2}{\alpha}}\left[\mu^\alpha \Gamma(2/\alpha+1) + a^\alpha \Gamma(2/\alpha+2)\right]$$

On simplification, we get the variance,

$$V(T) = \frac{(a^\alpha+\mu^\alpha)^{\frac{2}{\alpha}-1}}{a^2\mu^2}\left\{\left[\mu^\alpha\Gamma(2/\alpha+1)+a^\alpha\Gamma(2/\alpha+2)\right]-\left[\frac{1}{a^\alpha+\mu^\alpha}\right]\left[\mu^\alpha\Gamma(1/\alpha+1)+a^\alpha\Gamma(1/\alpha+2)\right]^2\right\}$$

It is interesting to note that when **a** = 1 these results act as a generalised result of the model where the contacts represented as Poisson process with assumption that the damage process acting on the immune system of an infected individual is linear.

Particular case:

Case (i): When k = 1 the mean and variance of the time to seroconversion of HIV transmission becomes

$$E(T) = \left[\frac{a^\alpha + \mu^\alpha}{a^\alpha \mu^\alpha}\right]^{\frac{1}{\alpha}}\Gamma(1/\alpha+1)$$

$$V(T) = \left[\frac{a^\alpha + \mu^\alpha}{a^\alpha \mu^\alpha}\right]^{\frac{2}{\alpha}}\left[\Gamma(2/\alpha+1) - \Gamma(1/\alpha+1)^2\right]$$

This is the Mean and Variance of the seroconversion time of HIV transmission for the contacts as Alpha Poisson Process and the antigenic diversity threshold is exponential distribution

Case (ii): When a = 1, the mean and variance of the time to seroconversion of HIV transmission becomes

$E(T) = (\mu+2a)/a\mu$

$$V(T) = \frac{2a^2+\mu^2+4a\mu}{a^2\mu^2}$$

This is the Mean and Variance of the seroconversion time of HIV transmission for the contact as Poisson Processes and the antigenic diversity threshold is Erlang k=2 distribution.

Case (iii): When **a** = 1 and k = 1, the Mean and Variance of the seroconversion time of HIV transmission becomes,

$$E(T) = (\mu + a)/a\mu$$

$$V(T) = \frac{(a+\mu)^2}{a^2\mu^2}$$

which coincides with (Sathiyamoorthi and Kannan, 2001 ; p.26)

For the model with threshold level distributed as Erlang k=2 with parameter μ, a numerical example is given to illustrate the mean and variance of seroconversion time for different a and the same are given in the Tables 1.1 to1.6 and Tables 2.1 to 2.6 respectively.

Table 1.1 : Mean of Seroconversion Time with **a** = 0.1

	μ				
a	0.2	0.4	0.6	0.8	1.0
1	8582122341	5.94E+09	4.81E+09	4.16E+09	3.72E+09
2	6276997383	4.29E+09	3.45E+09	2.97E +09	2.64E+09
3	5256270821	3.57E+09	2.86E+09	2.45E+09	2.18E+09
4	4645753045	3.14E+09	2.51E+09	2.15E+09	1.9E+09
5	4227360316	2.85E+09	2.27E+09	1.94E+09	1.72E+09
6	3917163902	2.63E+09	2.09E+09	1.78E+09	1.58E+09
7	3675037800	2.46E+09	1.95E+09	1.67E+09	1.47E+09
8	3479048508	2.32E+09	1.84E+09	1.57E+09	1.39E+09
9	3316053948	2.21E+09	1.75E+09	1.49E+09	1.32E+09
10	3177632618	2.11E+09	1.67E+09	1.42E+09	1.26E+09

Table 1.2 : Mean of Seroconversion Time with **a** = 0.2

	μ				
a	0.2	0.4	0.6	0.8	1.0
1	9158.39488	6200.179	4989.850	4298.598	3840.000
2	6924.11487	4579.197	3634.469	3100.089	2748.075
3	5941.87999	3877.267	3052.798	2589.041	2284.802
4	5355.51455	3462.057	2710.627	2289.599	2014.191
5	4953.76634	3179.469	2478.670	2087.189	1831.679
6	4655.76134	2970.940	2308.038	1938.629	1697.959
7	4422.95176	2808.725	2175.645	1823.573	1594.547
8	4234.30708	2677.757	2068.986	1731.029	1511.471
9	4077.24182	2569.054	1980.627	1654.466	1442.815
10	3943.69757	2476.883	1905.831	1589.734	1384.823

Table 1.3 : Mean of Seroconversion Time with **a** = 0.3

	μ				
a	0.2	0.4	0.6	0.8	1.0
1	229.792658	152.289453	121.685556	104.552607	93.340276
2	179.358505	114.896329	89.9412003	76.1447267	67.199293
3	157.500107	98.9952454	76.5975526	64.3030144	56.373701
4	137.254690	89.6782523	68.8340873	57.4481645	50.131973
5	144.548160	83.3783903	63.6093104	52.8516018	45.958531
6	129.190567	78.7500537	59.7861682	49.4976227	42.920088
7	124.105789	75.1623936	56.8319176	46.9118620	40.581862
8	119.994974	72.2740801	54.4597861	44.8396261	38.710881
9	116.578848	69.8824850	52.5000358	43.1304875	37.169779
10	113.679062	67.8587414	50.8449903	41.6891951	35.871700

Table 1.4 : Mean of Seroconversion Time with **a** = 0.4

	μ				
a	0.2	0.4	0.6	0.8	1.0
1	47.7461487	30.99214	24.5885	21.07109	18.79971
2	38.405849	23.87307	18.43901	15.49607	13.61557
3	34.4425423	20.91372	15.91538	13.22965	11.52367
4	32.1240896	19.20292	14.46745	11.93654	10.33544
5	30.5581383	18.05685	13.50258	11.07823	9.549230
6	29.409333	17.22127	12.80195	10.45686	8.981434
7	28.5199286	16.57756	12.26393	9.980867	8.547339
8	27.8047444	16.06204	11.83422	9.601462	8.201895
9	27.2132323	15.63715	11.48085	9.289997	7.918706
10	26.7132561	15.27907	11.18363	9.028424	7.681170

Table 1.5 : Mean of Seroconversion Time with **a** = 0.5

	μ				
a	0.2	0.4	0.6	0.8	1.0
1	20.944273	13.324555	10.497311	8.972136	8.000000
2	17.324555	10.472136	7.9848170	6.6622776	5.828442
3	15.830644	9.3182503	6.9814239	5.7486555	4.976067
4	14. 972136	8.6622776	6.4153222	5.2360679	4.500000
5	14.400000	8.2284271	6. 0427344	4.9000000	4.188854
6	13.984817	7.9153222	5.7748517	4.6590751	3.966326
7	13.666331	7.6761715	5.5708477	4.4760227	3.797572
8	13.412277	7.4860679	5.4090751	4.3311388	3.664213
9	13.203646	7.3304073	5.2768814	4.2129342	3.555555
10	13.028427	7.2000000	5.1663264	4.1142135	3.464911

Table 1.6 : Mean of Seroconversion Time with **a** = 1.0

	μ				
a	0.2	0.4	0.6	0.8	1.0
1	6.000000	3.500000	2.666667	2.250000	2.000000
2	5.500000	3.000000	2.166667	1.750000	1.500000
3	5.333333	2.833333	2.000000	1.583333	1.333333
4	5.250000	2.750000	1.916667	1.500000	1.250000
5	5.200000	2.700000	1.866667	1.450000	1.200000
6	5.166666	2.666667	1.833333	1.416667	1.166667
7	5.142857	2.6462857	1.809524	1.392857	1.142857
8	5.125000	2.6250000	1.791667	1.375000	1.125000
9	5.111111	2.6111111	1.777778	1.361111	1.111111
10	5.100000	2.6000000	1.766667	1.350000	1.100000

Table 2.1 : Variance of Seroconversion time with **a** = 0.1

	μ				
a	0.2	0.4	0.6	0.8	1.0
1	1.6061E+26	7.46228E+25	4.81679E+25	3.54767E+25	2.80614E+25
2	8.8417E+25	4.01524E+25	2.55723E+25	1.86557E+25	1.46474E+25
3	6.30181E+25	2.82402E+25	1.78455E+25	1.29466E+25	1.01211E+25
4	4.97911E+25	2.21042E+25	1.38911E+25	1.00381E+25	7.82341E+24
5	4.15863E+25	1.83282E+25	1.14689E+25	8.26259E+24	6.42439E+24
6	3.59586E+25	1.57545E+25	9.82411E+24	7.06005E+24	5.47879E+24
7	3.18373E+25	1.38795E+25	8.62945E+24	6.18853E+24	4.79464E+24
8	2.86766E+25	1.24478E+25	7.71967E+24	5.52606E+24	4.27535E+24
9	2.61681E+25	1.13159E+25	7.00201E+24	5.00434E+24	3.8669E+24
10	2.41237E+25	1.03966E+25	6.42031E+24	4.58206E+24	3.53668E+24

Table 2.2 : Variance of Seroconversion time with **a** = 0.2

	μ				
A	0.2	0.4	0.6	0.8	1.0
1	1.4241E+11	62016116137	3892022286	28224463736	2211471355
2	85366760266	35602396678	2177610878	15504029034	1197114307
3	64532106711	26255665001	1582328742	11146774164	8538519908
4	53367493966	21341690067	1272924673	8900599169	6778307421
5	46277805260	18263787041	1080720921	7513532972	5696383468
6	41316900462	16133026678	9485195585	6563916250	4958373393
7	37619790577	14558956028	8513738321	5868772698	4419750306
8	34739862919	13341873492	9485195585	5335422517	4007541539
9	32421725409	14368479548	8513738321	4911710246	3680790815
10	30508051533	11569451315	6682890712	4565946760	3414670411

Table 2.3 : Variance of Seroconversion time with **a** = 0.3

	μ				
a	0.2	0.4	0.6	0.8	1.0
1	7686053.038	3164452.141	1939107.729	1388428.733	1079834.668
2	4959857.006	1921513.259	1134751.210	791113.0352	602559.8801
3	3942770.199	1476563.947	854005.8931	586430.3358	441360.8537
4	3388660.443	1239964.251	706942.3810	480378.3149	358558.1332
5	3032006.402	1090262.643	614877.8361	414503.9356	307442.1215
6	2779572.809	985692.5496	551095.2229	369140.9866	272410.7036
7	2589571.471	907818.2996	503911.5646	335747.9475	246723.6194
8	2440264.074	847165.1108	467367.0421	309991.0629	226975.5806
9	2319135.251	798332.5228	438085.5776	289426.4023	211253.0549
10	2218427.454	758001.6004	414003.2713	272565.6608	198394.2802

Table 2.4 : Variance of Seroconversion time with **a** = 0.4

	μ				
a	0.2	0.4	0.6	0.8	1.0
1	90085.13100	35363.10347	21246.33847	15061.22453	11650.7764
2	61872.68922	22521.28275	12908.27946	8840.775868	6655.65120
3	51279.97000	17921.48933	10009.45900	6725.289881	4986.37377
4	45477.18298	15468.17231	8489.697484	5630.320687	4131.17391
5	41725.45018	13910.96739	7536.512338	4949.692625	3603.40524
6	39060.22741	12819.99251	6874.743247	4480.372332	3241.49087
7	37047.95621	12005.34190	6384.159209	4134.358750	2975.84666
8	35462.49323	11369.29574	6003.423634	3867.043076	2771.37841
9	34173.32092	10856.07827	5697.774448	3653276301	2608.38415
10	33099.35684	10431.36255	5445.945529	3477.741847	2474.90756

Table 2.5 : Variance of Seroconversion time with **a** = 0.5

	μ				
a	0.2	0.4	0.6	0.8	1.0
1	7417.708763	2796.40217	1652.903114	1162.627674	895.9999990
2	5368.331020	1854.42719	1036.207720	699.1005425	521.2152954
3	4603.440598	1519.84240	824.1898625	543.6110749	397.9577807
4	4185.940303	1342.08275	713.5752232	463.6067977	335.2500000
5	3916.799999	1229.54429	644.4033377	414.0499999	296.7083505
6	3726.099585	1150.86015	596.4812246	379.9606018	270.3510176
7	3582046238	1092.20736	561.0154196	354.8734063	251.0439766
8	3469.543845	1046.48507	533.5302322	335.5206888	236.2069443
9	3377.921427	1009.64550	511.4933998	320.0641566	224.3950617
10	3301.747473	979.199999	493.3578187	307.3860748	214.7332408

Table 2.6 : Variance of Seroconversion time with **a** = 1.0

	μ				
a	0.2	0.4	0.6	0.8	1:0
1	71.000000	23.500000	13.222222	9.125000	7.000000
2	60.250000	17.750000	9.138889	5.875000	4.250000
3	56.777778	15.944444	7.888889	4.902778	3.444444
4	55.062500	15.062500	7.284722	4.437500	3.062500
5	54.040000	14.540000	6.928889	4.165000	2.840000
6	53.361111	14.194444	6.694444	3.986111	2.694444
7	52.877551	13.948980	6.528345	3.859694	2.591837
8	52.515625	13.765630	6.404514	3.765625	2.515625
9	52.234567	13.623460	6.308642	3.692901	2.456790
10	52.010000	13.510000	6.232222	3.635000	2.410000

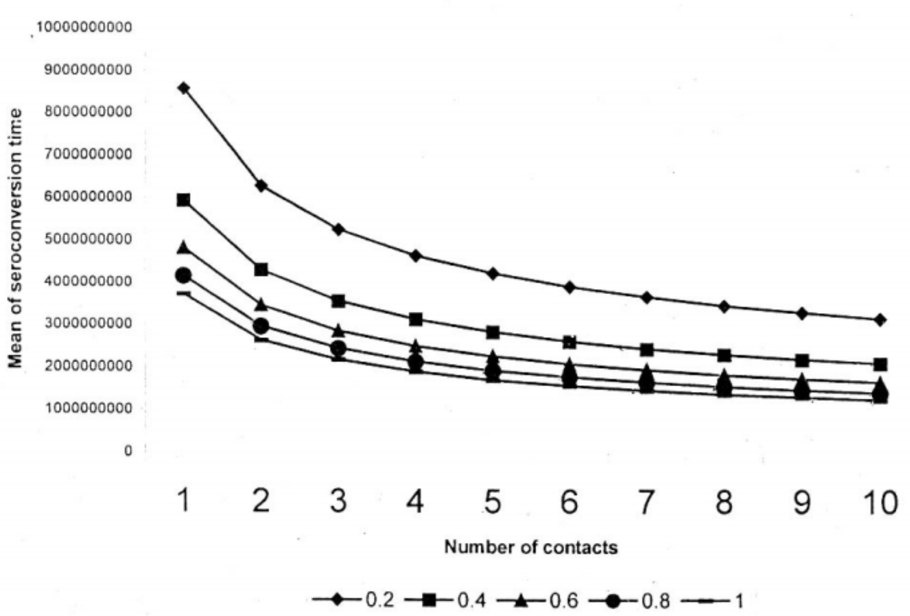

Fig. 1.1 : Mean of Seroconversion Time with **a** = 0.1

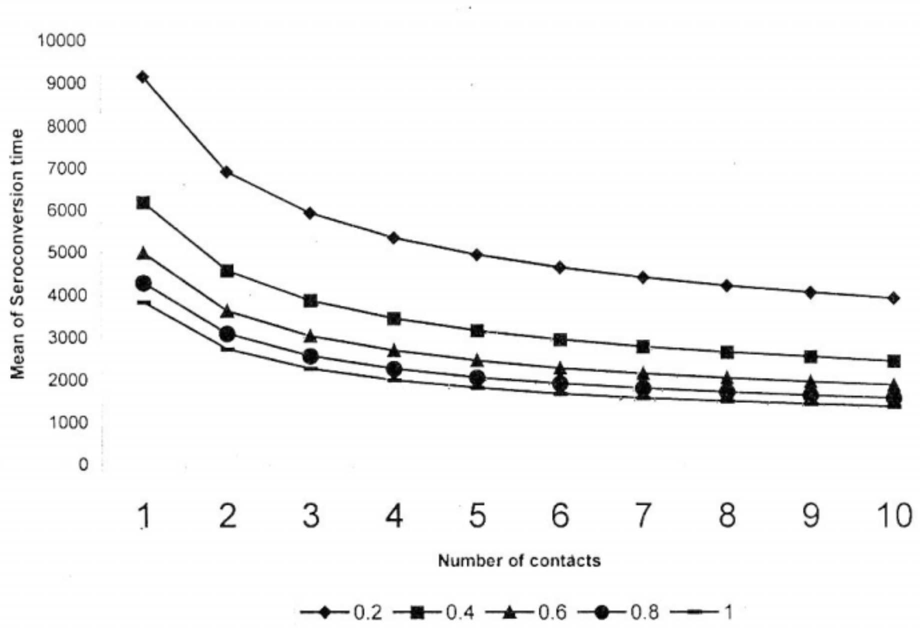

Fig. 1.2 : Mean of Seroconversion Time with **a** = 0 2

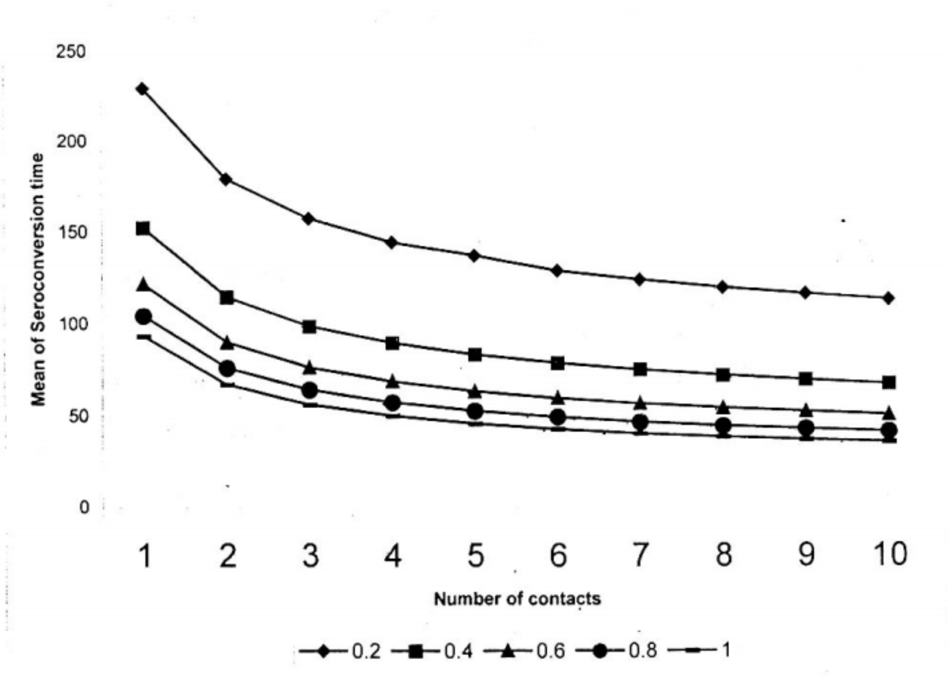

Fig. 1.3 : Mean of Seroconversion Time with **a** = 0.3

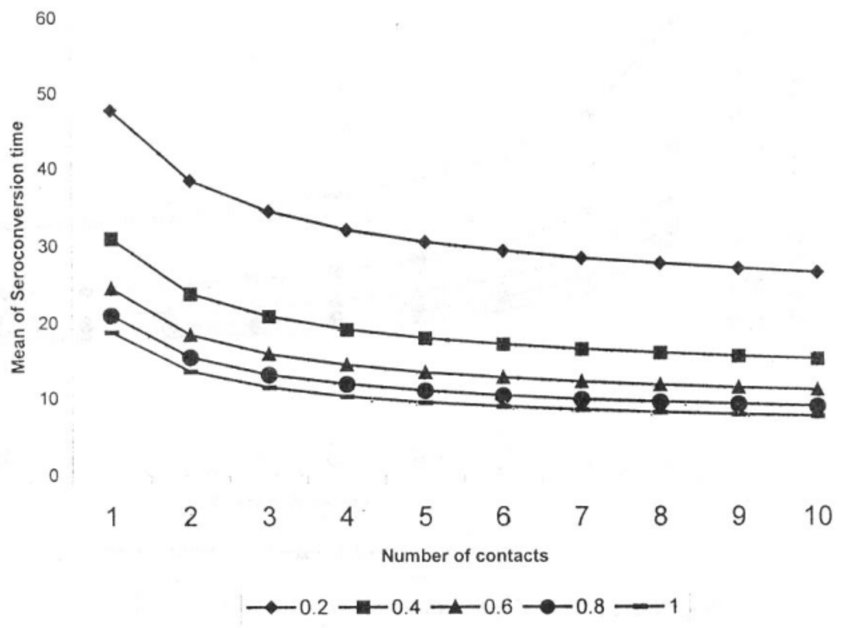

Fig. 1.4 : Mean of Seroconversion Time with **a** = 0.4

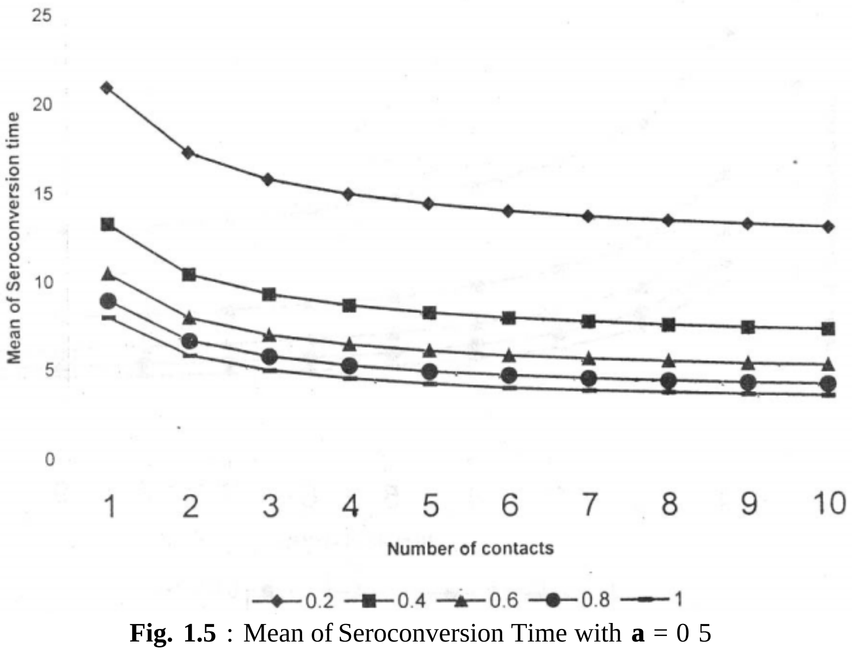

Fig. 1.5 : Mean of Seroconversion Time with **a** = 0 5

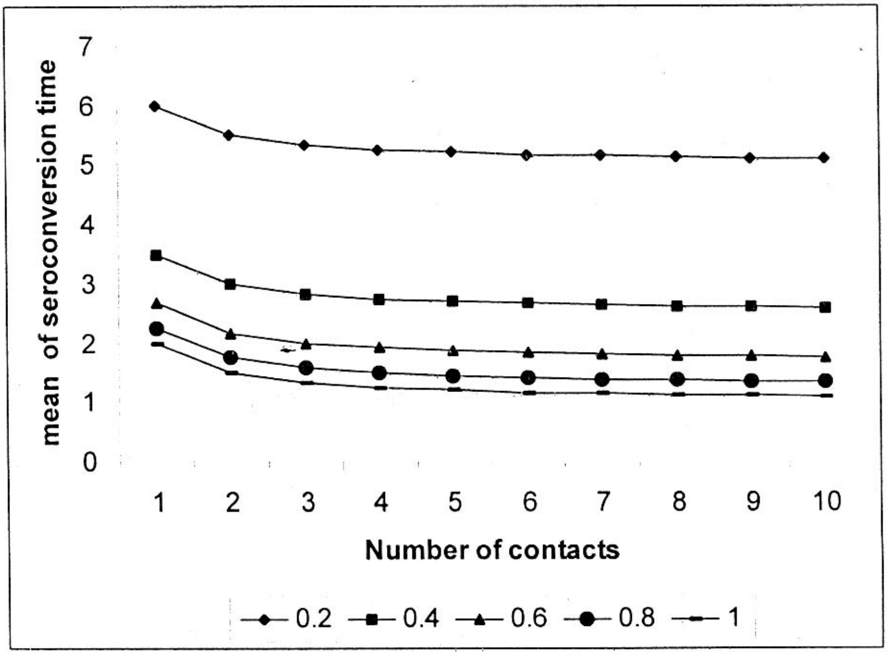

Fig. 1.6 : Mean of Seroconversion Time with **a** = 1.0

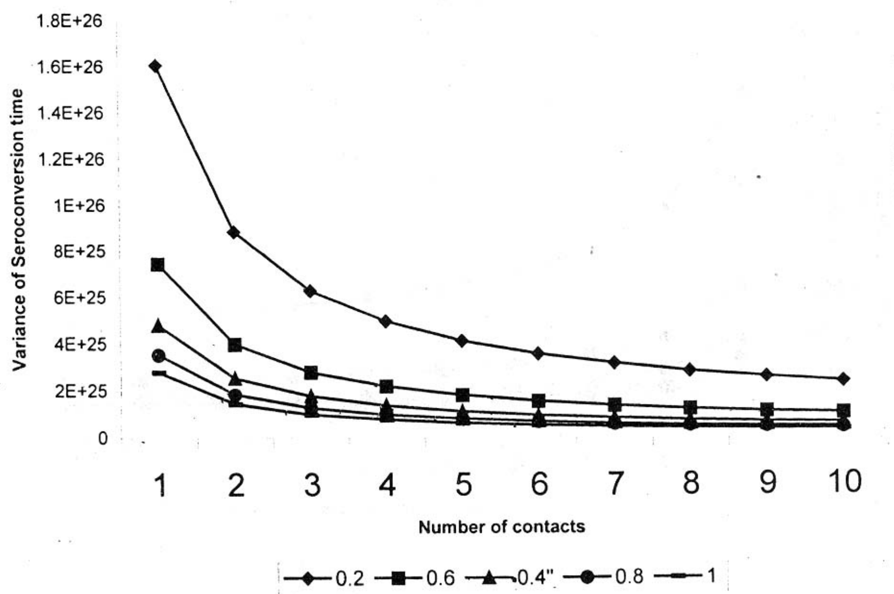

Fig. 2.1 : Variance of Seroconversion Time with **a** = 0.1

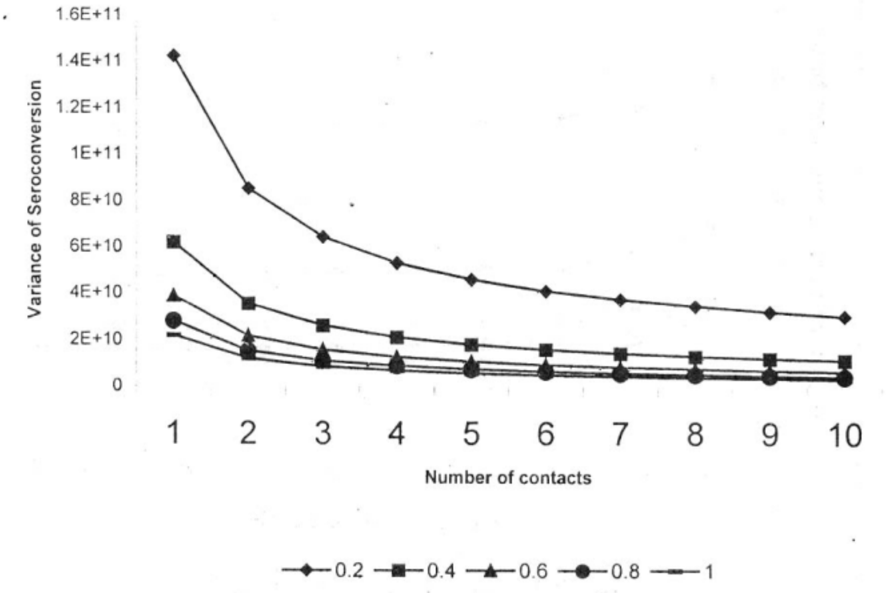

Fig. 2.2 : Variance of Seroconversion Time with **a** = 0.2

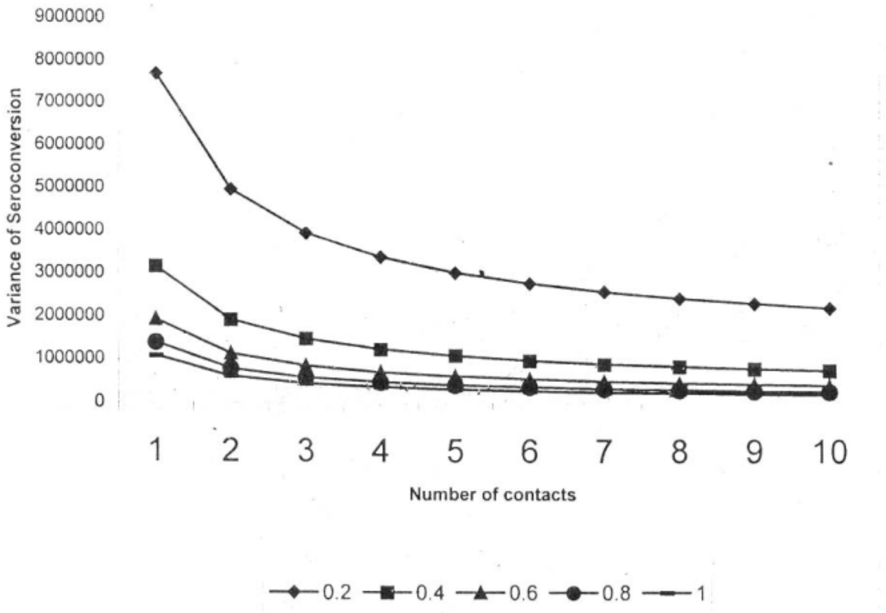

Fig. 2.3 : Variance of Seroconversion Time with **a** = 0.3

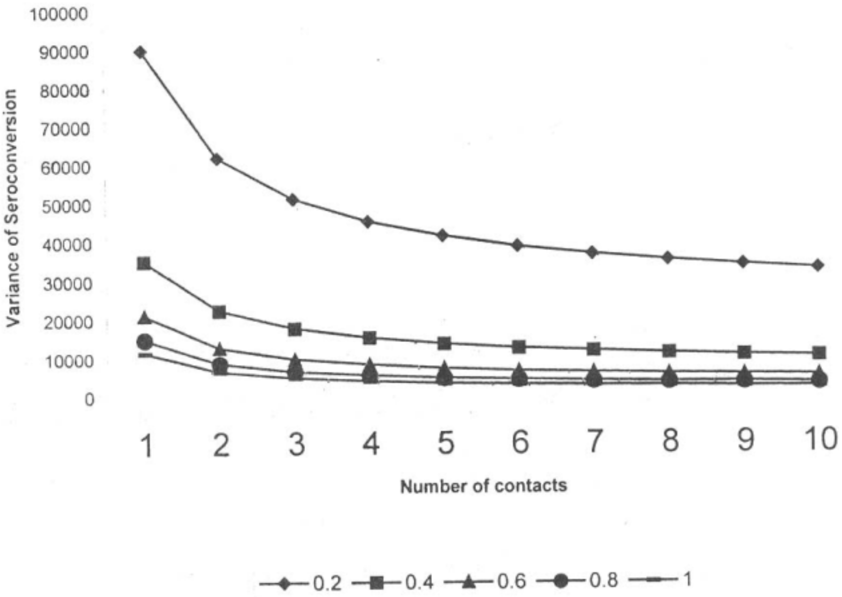

Fig. 2.4 : Variance of Seroconversion Time with **a** = 0.4

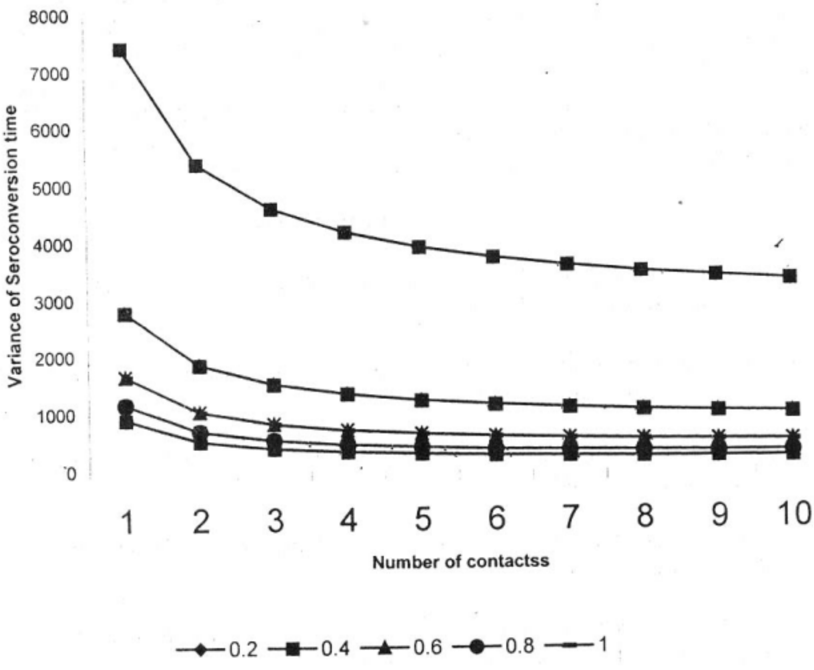

Fig. 2.5 : Variance of Seroconversion Time with **a** = 0.5

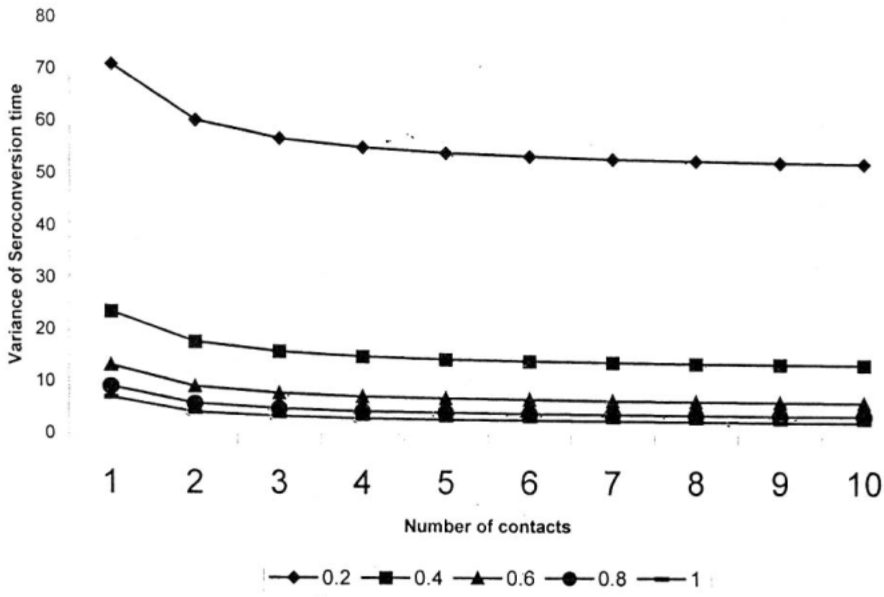

Fig. 2.6 : Variance of Seroconversion Time with **a** = 1.0

From the Figures 1.1 to 1.6 and Figures 2.1 to 2.6, we observed that for fixed ' μ ' when 'a' (contact rate) increases, the mean of seroconversion time decreases. Also if 'a' is fixed and 'μ' (Antigenic diversity threshold) is allowed to increase then the mean time to seroconversion decreases. The same tendency is also noticed on the variances of the seroconversion time of HIV transmission. Also the intensity of the HIV of the infected partner increases, the Mean and Variance of seroconversion time decreases. The practical implication of the result is that the spread of HIV is faster as the intensity of the immune system is lower.

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