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ORIGINAL ARTICLE

On Estimating the Time from HIV Infection to AIDS - A Stochastic Modeling Approach

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Abstract

Objectives: To construct a statistical model through which one can estimate the mean time to get AIDS condition in a HIV infected individual. **Methods:** The methodology adopted for the construction of the statistical model for estimating the time to get AIDS condition considers the antigenic diversity threshold and the antigenic diversity induced by the virus entered through every individual infected sexual contact and the antigenic diversity induced by their corresponding quasi – species. A comparison has been made with the existing model in the literature which considers the antigenic diversity developed through sexual contacts only, with reference to the expected time to get AIDS and its variance. **Findings:** On evaluating the model constructed, it is seen that the time to get AIDS is adversely affected by the number of contacts with infected individuals and the antigenic diversity induced by the virus entered through those contacts as well as their quasi-species. It is observed that a person will attains AIDS condition sooner when the number of contacts with the infected individual increases. **Novelty:** Similar types of models developed to estimate the time to get AIDS condition in an infected individual consider only the number of contacts and the amount of virus transmitted. Here an additional factor of Antigenic diversity induced by the quasi-species is also considered.

Keywords: Human Immunodeficiency Virus; AIDS; Viral quasi-species; Antigenic Diversity Threshold

1 Introduction

The HIV virus, which damages the immune system and increases its vulnerability to infections and illnesses, is the cause of AIDS. Numerous antigenic variations are exposed by HIV, the causative agent of AIDS, which makes it challenging for the immune system to identify and react to the antigens. The HIV virus's antigenic diversity has a significant impact on the time at which AIDS develops. The HIV infected person can withstand against it only with a certain level of antigenic diversity, called the Antigenic diversity threshold (ADT) (Nowak and May (1991))[(1)]. Every infected contact attributed with some amount of antigenic diversity and added to that the replication of more and more quasi species promotes increase in the levels of antigenic

diversity. It is thought that an infected person's life expectancy is shortened if the total accumulated antigenic diversity goes beyond the Antigenic Diversity Threshold (ADT).

Several authors have looked into different aspects of antigenic diversity. After a lengthy and varying period of incubation, an HIV infection results in serious immune system damage and, consequently, the illness known as Acquired Immuno-Deficiency Syndrome (AIDS), according to Martin A. Nowak and Robert M. May (1991) [1]. The idea that AIDS develops when the diversity of antigenic variants of HIV in an infected person surpasses a threshold, beyond which immune system cannot continue to survive, is based on the dynamics of the interaction between immune response and antigenic variation in the virus population. Stilianakis et al. (1994) [2] created a model to predict the non-monotonic risk of AIDS transition that is partially characterized by the Antigenic Diversity threshold. Nowak et al. (1997) [3] expanded Stilianakis' model to emphasize that the antigenic diversity threshold is the explanation for the long and variable interval observed between HIV infection and the initiation of AIDS. By all means, estimating the expected time needed to cross the Antigenic Diversity Threshold (ADT) is vital as it reveals the likelihood of developing AIDS symptoms in an infected person. The Antigenic Diversity Threshold (ADT) was taken as a random variable in a stochastic model developed by Jaisankar R. and Sabeurnisha A. (2017) [4] for estimating the time to develop AIDS based on the antigenic diversity generated by each interaction with an infected person. Veena and Kannan (2023) used shock models cumulative damage process to estimate the seroconversion time, assuming the exponential antigenic diversity distribution [5].

In this study, a stochastic model for calculating the time to obtain AIDS an infection is developed, which takes into account both variants of HIV entered through infective contacts and also those associated with viral quasi-species. It is hypothesized that these two mechanisms assisted in the development of AIDS. It is assumed that these are the two processes contribute independently towards the progression to AIDS.

2 Methodology

2.1 Assumptions of the Model

- HIV can only be spread by sexual contacts with infected individuals.
- A person having several number of contacts at random which may include some infective contacts also.
- When an individual is having sexual contacts with HIV infected partners, a random number of HIV is getting transmitted, at each contact. Each contact contributes to Antigenic diversity.
- The quasi species of the viruses developed by the replication of viruses entered through every infective contact also make some contribution to the antigenic diversity.
- The amount of virus entered through every contact follows exponential distribution.
- Every HIV virus replicates its own viral quasi-species after some time period which is also assumed to follow exponential distribution.
- There exists an Antigenic threshold level, say, *Z*, which is assumed to be an exponential random variable.
- Over a time period, say (*0, t*), a person is having *n* number of contacts at random out of which *k* are infected contacts.

2.2 Notations

- U_i - A random variable that represents Antigenic Diversity caused or induced by the i^{th} contact with a HIV-infected person which follows an exponential distribution, say, g(.) with parameter γ.
- V_i – A random variable representing the Antigenic diversity induced by the quasi-species of U_i after some time period which is assumed to follow exponential distribution, say, h(.) with parameter λ.
- I (.) – The probability distribution of the antigenic diversity produced through the i^{th} contact and its corresponding quasi-species respectively.
- $\widetilde{U}$ - Total antigenic diversity induced by k contacts
- $\widetilde{V}$ - Total antigenic diversity induced by the quasi-species of U_i
- Z – A random variable representing the stochastic Antigenic Diversity Threshold (ADT), which is assumed to follow an exponential distribution with parameter μ.
- T – Stochastic time at which Antigenic diversity threshold Z is passed.

2.3 The Proposed Model

Suppose that an individual has having *n* contacts at random over the time period (*0, t*) and let the number of infected contacts out of *n* contacts be *k*.Now the probability of having *n* contacts during the interval *(0, t)* is described by a Poisson process with

parameter, say, α, which is given by,

$$P(N=n/t)=\sum_{n=0}^{\infty}\frac{e^{-\alpha t}(\alpha t)^n}{n!}$$

The Probability that out of *n* randomly chosen partners *k* are infected is described by Binomial (*n, p*).

$$P(N=k/n)=\sum_{k=0}^{n}\left(\begin{array}{c} n \\ k \end{array}\right)p^k q^{n-k}$$

The probability that the antigenic diversity, developed through *k* sexual contacts with infected individuals and their viral quasi-species after a certain time period, does not cross the threshold level (CADT) is given by,

$$\begin{aligned} P\left[\left(\widetilde{U}+\widetilde{V}\right)<Z\right] &= \int_0^{\infty} I(z)\mu e^{-\mu z}dz \\ &= \left[g^*(\mu)\right]^k\left[h^*(\mu)\right]^k \end{aligned}$$

Where $g^*(.)$ is the Laplace transform of $g(.)$ and $h^*(.)$ is the Laplace transform of $h(.)$

The probability that the total Antigenic diversity does not cross the threshold level in *n* contacts out of which *k* are infectious is given by

$$\begin{aligned} P(T>t) &= \sum_{n=0}^{\infty}\frac{e^{-\alpha t}(\alpha t)^n}{n!}*\sum_{k=0}^{n}\left(\begin{array}{c} n \\ k \end{array}\right)q^{n-k}(1-q)^k*[g^*(\mu)]^k[h^*(\mu)]^k \\ P(T>t) &= \sum_{n=0}^{\infty}\frac{e^{-\alpha t}(\alpha t)^n}{n!}*\sum_{k=0}^{n}\left(\begin{array}{c} n \\ k \end{array}\right)\left((1-q)g^*(\mu)h^*(\mu)\right)^k q^{n-k} \\ P(T>t) &= \sum_{n=0}^{\infty}\frac{e^{-\alpha t}(\alpha t)^n}{n!}*[q+(1-q)g^*(\mu)h^*(\mu)]^n \\ P(T>t) &= \sum_{n=0}^{\infty}\frac{e^{-\alpha t}\alpha t^n}{n!}\left(q+(1-q)g^*(\mu)h^*(\mu)\right)^n \end{aligned}$$

Taking, $A=(q+(1-q)g^*(\mu)(h^*(\mu))$

$$\begin{aligned} P(T>t) &= \sum_{n=0}^{\infty}\frac{e^{-\alpha t}\alpha t^n}{n!}(A)^n \\ P(T\le t) &= 1-P(T>t) \\ P(T\le t) &= 1-\sum_{n=0}^{\infty}\frac{e^{-\alpha t}(\alpha t)^n}{n!}(A)^n \\ f(t) &= \sum_{n=0}^{\infty}\frac{e^{-\alpha t}\alpha^n A^n}{n!}\left[(\alpha t^n-nt^{n-1})\right] \end{aligned}$$

Taking Laplace transforms we get,

$$\begin{aligned}
L[f(t)] &= L\left(\sum_{n=0}^{\infty}\frac{\alpha^n A^n}{n!}e^{-\alpha t}(-\alpha t^n)+\sum_{n=0}^{\infty}\frac{\alpha^n A^n}{n!}e^{-\alpha t}(nt^{n-1})\right)\\
&= \sum_{n=0}^{\infty}\frac{\alpha^n A^n}{n!}\left(-\alpha\frac{n!}{(s+\alpha)^{n+1}}\right)+\sum_{n=1}^{\infty}\frac{\alpha^n A^n}{n!}\left(\frac{n(n-1)!}{(s+\alpha)^n}\right)\\
&= \sum_{n=0}^{\infty}\alpha^n A^n\left(\frac{-\alpha}{(s+\alpha)^{n+1}}\right)+\sum_{n=1}^{\infty}\alpha^n A^n\left(\frac{1}{(s+\alpha)^n}\right)\\
&= \frac{-\alpha}{(s+a)}\sum_{n=0}^{\infty}\left(\frac{\alpha A}{s+a}\right)^n+\sum_{n=1}^{\infty}\left(\frac{\alpha A}{s+a}\right)^n\\
&= \frac{-\alpha}{(s+\alpha)}*\frac{1}{1-\frac{\alpha A}{s+\alpha}}+\frac{\alpha A}{s+\alpha}*\frac{1}{1-\frac{\alpha A}{s+\alpha}}\\
&= \frac{-\alpha}{(s+\alpha)}*\frac{\alpha+s}{\alpha+s-\alpha A}+\frac{\alpha A}{s+\alpha}*\frac{\alpha+s}{\alpha+s-\alpha A}\\
&= \frac{-\alpha}{\alpha+s-\alpha A}+\frac{\alpha A}{\alpha+s-\alpha A}\\
&= \frac{\alpha(A-1)}{\alpha(1-A)+s}\\
E(T) &= -\frac{d}{ds}\left(\frac{\alpha(A-1)}{\alpha(1-A)+s}\right)_{s=0}\\
&= \left(\frac{\alpha(A-1)}{(\alpha(1-A)+s)^2}\right)_{s=0}\\
&= \frac{1}{\alpha(1-A)}
\end{aligned}$$

Using $A=(q+(1-q)g^*(\mu)(h^*(\mu))$

As a special case if we assume that $g(.)$ and $h(.)$ are exponential distributions with parameters γ and λ respectively, we have,

$$E(T)=\frac{(\gamma+\mu)(\lambda+\mu)}{\alpha\left(1-\lambda\gamma p+q(\lambda+\mu)(\gamma+\mu)\right)}$$

$$E\left(T^2\right)=\frac{2}{\alpha^2(1-A)^2}$$

And hence the Variance is,

$$V(T)=\frac{(\gamma+\mu)^2(\lambda+\mu)^2}{\alpha^2\left(1-\lambda\gamma p+q(\lambda+\mu)(\gamma+\mu)\right)^2}$$

3 Results and Discussion

A simulation approach is used to assess the behavior of the developed model, and random numbers simulated for the distributions in question for different parameter combinations are used to calculate the sample mean and variance of the time to exceed the antigenic diversity threshold. Fig 1 to 3 shows the behavior of $E(T)$ and $V(T)$ for various combinations of parameter values.

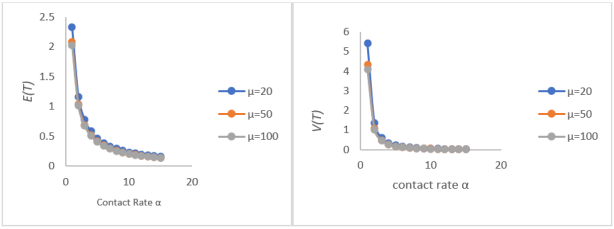

Fig 1. a- Mean Time to Cross ADT, b- Variance Time to Cross ADT

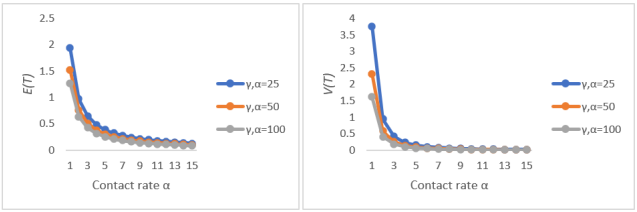

Fig 2. a- Mean Time to Cross ADT, b- Variance Time to Cross ADT

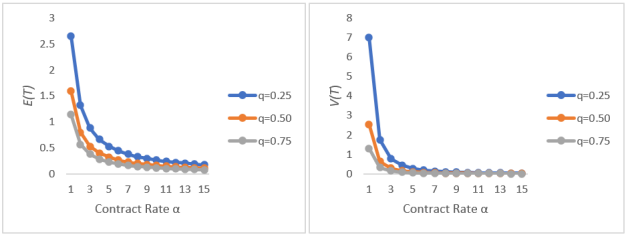

Fig 3. a- Mean Time to Cross ADT, b- Varianace Time to Crosss ADT

Figure 1a & Figure 1b shows the expected values of T and the associated variance for various values of μ while holding q, λ, and γ as constants. Both $E(T)$ and $V(T)$ are observed to decrease as μ increases. This could mean that if an infected individual has a higher ADT level, their risk of moving to AIDS may decrease.

Figures 2a & Figure 2b shows how the mean and variation of time it takes to cross ADT for various γ and λ values. As the antigenic diversity induced by viruses entered through the infected contacts and their corresponding quasi-species increase, the immune system becomes more weaken with viruses and hence, AIDS symptoms could appear sooner rather than gradually. It is also clear that more frequent contacts with an infected individual lead to the development AIDS symptoms sooner.

Figure 3a & Figure 3b shows the mean and variance for the time to cross the ADT for a values of q. Therefore, having random sex with a group that is more vulnerable to HIV infection will cause the person to develop AIDS symptoms rapidly.

While making comparison of our model with that of the model developed by Jaisankar and Saberunnisa (2017) which considers only the antigenic diversity developed through sexual contacts for the same set of parameters the following results are observed.

It can be noticed that the inclusion of antigenic diversity developed by the quasi species has an impact on both the mean time to get AIDS and its variance; the infected individual attains AIDS condition sooner. The model taken for the comparison was developed with similar assumptions of the proposed model except that the consideration of the antigenic diversity developed by quasi-species.

4 Conclusion

It is to be noted that all the models that are developed so far in the literature considered the antigenic diversity induced by the sexual contacts with the infected persons only. But this article actively incorporate the Antigenic diversity induced by the

Table 1. Results of the Proposed Model

	$\gamma = 10\ \lambda = 15\ p = 0.5\ q = 0.5$					
Contact rate A	**Mean**			**Variance**		
	$\mu = 20$	$\mu = 50$	$\mu = 100$	$\mu = 20$	$\mu = 50$	$\mu = 100$
1	2.32816	2.078891	2.023676	5.420327	4.321789	4.095265
2	1.16408	1.039446	1.011838	1.355082	1.080447	1.023816
3	0.776053	0.692964	0.674559	0.602259	0.480199	0.455029
4	0.58204	0.519723	0.505919	0.33877	0.270112	0.255954
5	0.465632	0.415778	0.404735	0.216813	0.172872	0.163811
6	0.388027	0.346482	0.337279	0.150565	0.12005	0.113757
7	0.332594	0.296984	0.289097	0.110619	0.0882	0.083577
8	0.29102	0.259861	0.25296	0.084693	0.067528	0.063989
9	0.258684	0.230988	0.224853	0.066918	0.053355	0.050559
10	0.232816	0.207889	0.202368	0.054203	0.043218	0.040953
11	0.211651	0.18899	0.183971	0.044796	0.035717	0.033845
12	0.194013	0.173241	0.16864	0.037641	0.030012	0.028439
13	0.179089	0.159915	0.155667	0.032073	0.025573	0.024232
14	0.166297	0.148492	0.144548	0.027655	0.02205	0.020894
15	0.155211	0.138593	0.134912	0.02409	0.019208	0.018201

Table 2. Results of the Model developed by Jaisankar and Saberunnisa (2017) [4]

	$\beta = 15\ q = 0.5$					
Contact rate A	**Mean**			**Variance**		
	$\mu = 20$	$\mu = 50$	$\mu = 100$	$\mu = 20$	$\mu = 50$	$\mu = 100$
1	3.10985	2.10108	1.76483	14.4916	5.18582	3.30743
2	1.55493	1.05054	0.88241	3.6229	1.29645	0.82686
3	1.03662	0.70036	0.58828	1.61018	0.5762	0.36749
4	0.77746	0.52527	0.44121	0.90572	0.32411	0.20672
5	0.62197	0.42022	0.35297	0.57966	0.20743	0.1323
6	0.51831	0.35018	0.29414	0.40254	0.14405	0.09187
7	0.44426	0.30016	0.25212	0.29575	0.10583	0.0675
8	0.38873	0.26264	0.2206	0.22643	0.08103	0.05168
9	0.34554	0.23345	0.19609	0.17891	0.06402	0.04083
10	0.31099	0.21011	0.17648	0.14492	0.05186	0.03307
11	0.28271	0.19101	0.16044	0.11977	0.04286	0.02733
12	0.25915	0.17509	0.14707	0.10064	0.03601	0.02297
13	0.23922	0.16162	0.13576	0.08575	0.03069	0.01957
14	0.22213	0.15008	0.12606	0.07394	0.02646	0.01688
15	0.20732	0.14007	0.11766	0.06441	0.02305	0.0147

quasi-species of the viruses entered through every infected contact. As it is the fact the expected time to CADT would be sooner when compared with all the models which does not consider the antigenic diversity induced by the quasi-species of the HIV. However, the following may be taken as the limitations of the model.

The model is based on assumption of exponential distribution that may not fully capture real-world variability. No empirical validation with clinical or epidemiological data is given. Also, the model does not account for antiretroviral therapy (ART) or other medical interventions.

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