

ON THE ESTIMATION OF PROBABILITY OF DEATH OF AIDS PATIENTS IN THE PRESENCE OF COMPETING RISKS

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ABSTRACT

This paper aims at identifying and studying the effect of various independent risks that an AIDS patient is exposed to in day to day life. These risks have been identified as Tuberculosis (TB), Hepatitis-B (H.B), Diarrhea (DH), Bacterial Meningitis (B.M.) and others for the collected data of AIDS patients in National Capital territory of Delhi. The Crude, Net (*type – I* and *type – II*) and Partially Crude Probabilities of death for these risks have been computed and a comprehensive analysis of this data reveals that AIDS patients suffering from TB are exposed to the highest risks of death than other prevalent opportunistic infections. Analysis shows that Partially Crude Probabilities of death for TB with respect to other opportunistic infections are highly variable and Partially Crude Probabilities of death for other opportunistic infections in the absence of TB are very much alike. Net Probability of death (*type – I*) for TB is same as the Partially Crude probability of death for TB when all other risks have been eliminated. Also it is found that death due to Tuberculosis is statistically significant ($p - value < 0.001$) as compared to other risks.

1. INTRODUCTION

It has been over two decades since the first case of full-blown Acquired Immuno deficiency syndrome (AIDS) was identified. Currently, Human Immuno deficiency virus (HIV) infection has assumed a magnitude of an international pandemic [Quinn (1996), Mann and Tarantola (1998)] and it's notability is most striking in Asia [Islam et. al. (2002)]. It is believed that nearly 90% of all HIV infected people are living in developing countries [Quinn (1996)]. In 2006, UNAIDS estimated that there were 5.6 million people living with HIV in India, which indicated that there were more people with HIV in India than any other country in the world [UNAIDS (2008)]. However, NACO disputed this estimate, and claimed that the actual figure was lower NACO (April (2006)). In 2007, following the first survey of HIV among the general population, UNAIDS and NACO agreed on a new estimate between 2 million and 3.6 million people living with HIV. The figure was confirmed to be 2.4 million in 2008. This puts India behind South Africa and Nigeria in numbers living with HIV [UNAIDS 2007, 2008].

In terms of AIDS cases, the most recent estimate comes from August 2006, at which stage the total number of AIDS cases reported to NACO was 124,995 in India. Of this number, 88,245(71%) were male and 36,750(29%) were female and (36%) were under the age of 30. These figures are not accurate reflections of the actual situation as large numbers of AIDS cases go unreported [NACO, (August 2006)].

All the above figures indicate the gigantic magnitude of this infection and hence warrant an urgent need to do an in-depth study of the fatality of various diseases to which the HIV patients are exposed to.

Death of an AIDS patient is caused by any opportunistic infection (in biological terms, called "RISKS") prevalent in the population. As we know, AIDS is a syndrome which curbs the immune system of the body and hence leaves the individual vulnerable to the opportunistic infections which on any other day would have been just a passing cloud. A co-infection is another illness one may get while having HIV. People who have HIV can also get these illnesses viz. T.B [Doe, S. (1995), Moses, A.E.,et.al. (2003)], Malaria, Hepatitis-B [Bonacini, M.et.al.(2004)], Hepatitis-C [Swami,O.,et.al(2005)], Diarrhea, Bacterial Meningitis, Measles etc.

Long before HIV, malaria and tuberculosis were causes of significant morbidity and death. Now the specter of co-infection and drug resistance compound the challenge of identifying and treating people with AIDS, TB, or malaria as well as preventing further infection. Strategies that simultaneously address these health problems include building on and strengthening the existing health infrastructure, increasing the number and skills of health care workers, and coordinating and integrating services.

In this paper, we have considered AIDS patients who are exposed to different risks in Delhi and NCT region. We have collected live data of AIDS patients in the Anti Retroviral Therapy (ART) centre located at Ram Manohar Lohia (RML) hospital at Delhi. RML is one of the largest centers in Delhi where patients used to come for their treatment not only from Delhi but also from various regions located nearby this city.

We considered Competing Risk Theory [Biswas,S.(1993), Chiang, C.L.(1968), David, H. and Moeschberger, M. (1978)] for the a analysis of this data. This theory assumes that several risks compete against each other independently. Ultimately a particular risk succeeds in taking away the life of the patient either in the presence of all the possible risks or in the presence of a particular set of risk.

The live data collected from ART center show that there are many opportunistic infections that are operating on the population of AIDS patients in Delhi and NCT region. Some of these opportunistic infections which also form a part of our present studies can be highlighted as Tuberculosis (TB), Hepatitis-B (Hep-B), Diarrhea (DH), Bacterial Meningitis (BM), etc.

To estimate the probability of death due to any risk, Competing Risk Theory provides several measures such as Crude, Net (*type-I*, *type-II*) and Partially Crude probability of death.

1.1. Crude Probability of Death

It is the probability that an AIDS patient alive at time x_i dies in the interval (x_i, x_{i+1}) due to a specific risk R_δ in the presence of all the risks operating in the population. It is denoted by $Q_{i\delta}$.

1.2. Net Probability Of Death (Type-I)

It is the probability that an AIDS patient alive at time x_i will die in the interval (x_i, x_{i+1}) due to a specific risk R_δ when all other risks are off from the population. It is denoted by $q_{i\delta}$.

1.3 Net Probability Of Death (Type – II)

It is the probability that an AIDS patient alive at time x_i will die in the interval (x_i, x_{i+1}) due to any risk operating in the population when a particular risk R_δ (say) is off from the population (i.e. death due to any risk except R_δ). It is denoted by $q_{i\delta}$.

1.4. Partially Crude Probability Of Death

It is the probability that an AIDS patient alive at time x_i will die in the interval (x_i, x_{i+1}) due to a specific risk R_δ , when any one or more risks ($R_j, j = 1, 2, \dots, n, j \neq \delta$) are off from the population.

We have collected a sample size ($n =$) 1005 of AIDS patients for 4 years (2004 -2007) from RML hospital. Out of which 81 AIDS patients died due to TB, 18 died due to Hep-B, 19 died due to DH, and 29 died due to BM. Rest deaths are due to other diseases that are not much dominant for death of AIDS patients. Year wise reported AIDS patients and deaths are shown in table-1

Let

l_i : Number of AIDS alive at time x_i .

d_i : Number of death of AIDS patients in the interval (x_i, x_{i+1}) .

p_i : Probability of survival of an AIDS patients in the interval (x_i, x_{i+1}) .

q_i : Probability of dying of an AIDS patients in the interval (x_i, x_{i+1}) provided he has survived till x_i .

D_{i1} : Number of deaths of AIDS patients in the interval (x_i, x_{i+1}) due to TB.

D_{i2} : Number of deaths of AIDS patients in the interval (x_i, x_{i+1}) due to HepB.

D_{i3} : Number of deaths of AIDS patients in the interval (x_i, x_{i+1}) due to DH.

D_{i4} : Number of deaths of AIDS patients in the interval (x_i, x_{i+1}) due to BM.

D_{i5} : Number of deaths of AIDS patients in the interval (x_i, x_{i+1}) due to other disease (OD).

Table1: Number of AIDS patients and deaths reported at ART centers in NCT Delhi.

Time interval (x_i, x_{i+1})	No. of AIDS patients surviving at the beginning of the time interval (x_i, x_{i+1}) ' l_i '	Number of Deaths in the time interval (x_i, x_{i+1}) d_i	Deaths due to				
			TB D_{i1}	Hep-B D_{i2}	Diarrhea D_{i3}	Bacterial Meningitis D_{i4}	Other disease D_{i5}
2004-05	124	16	9	2	1	2	2
2005-06	190	30	12	3	3	8	4
2006-07	306	50	26	7	6	7	4
2007-08	385	71	34	6	9	12	10
TOTAL	1005	167	81	18	19	29	20

We obtained the estimate of Crude Probability of Death, Net Probability of Death- (*type - I*), Net Probability of Death- (*type - II*) and Partially Crude Probability of Death of AIDS patients as follows

2.1. Crude Probability of Death

An estimate of crude probability of death of AIDS patients is obtained by the formula

$$\hat{Q}_{ij} = \frac{D_j}{l_i}, \quad j=1,2,\dots,5 \quad (2.1)$$

2.2. Net probability of death (type-I)

An estimate of Net probability of death (type-I) is obtained by the formula

$$\hat{q}_{ij} = 1 - (\hat{p}_i)^{\frac{D_j}{d_i}}, \quad j=1,2,\dots,5 \quad (2.2)$$

2.3. Net probability of death(type-II):

An estimate Net probability of death(type-II) is obtained by the formula

$$\hat{q}_{i,j} = 1 - (\hat{p}_i)^{1 - \frac{D_{ij}}{d_i}}, \quad j=1,2,\dots,5 \quad (2.3)$$

2.4. Partially Crude probability of death:

An estimate of Partially Crude probability of death is obtained by the formula

$$\hat{Q}_{r \neq j}^{ij.r \dots k} = \frac{D_{ij}}{d_i - \sum_{\substack{m=1 \\ m \neq j}}^k D_{im}} \left(1 - (\hat{p}_i) \frac{d_i - \sum_{\substack{m=1 \\ m \neq j}}^k D_{im}}{d_i} \right), \quad j, k = 1, 2, \dots, 5 \tag{2.4}$$

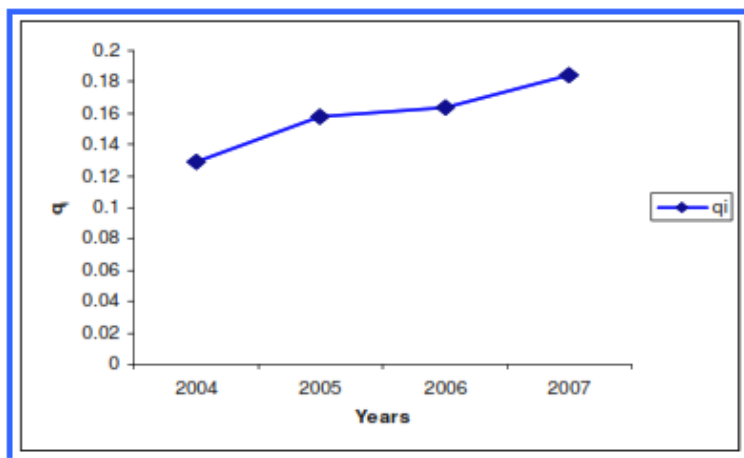
where number 1,2,2,3,4,5 denote the risks TB, Hep-B, DH, BM and OD respectively.

Data was analyzed for the period 2004-2007 and probability of death without specification of cause, Crude probabilities of death, Net probabilities of death (*type-I* and *type-II*) and partially crude probabilities of death have been estimated for each year. These results have been tabulated and represented graphically in the Tables and figures.

Table 2: Yearly Estimates of probability of death of AIDS patients without specification of cause and Yearly Estimates of Crude probability of death of AIDS patients due to a specific cause.

Year	q_i	p_i	Q_{i1}	Q_{i2}	Q_{i3}	Q_{i4}	Q_{i5}
2004	0.12903	0.87097	0.07258	0.016129	0.008065	0.016129	0.032258
2005	0.15789	0.84211	0.06315	0.015789	0.015789	0.042105	0.021053
2006	0.16339	0.83661	0.08497	0.022875	0.019608	0.022876	0.019608
2007	0.18441	0.81558	0.08831	0.015584	0.023377	0.031168	0.018181
Ave.	0.15868	0.841318	0.07725	0.017594	0.01671	0.02807	0.022775

Figure 1: Graphical representation of annual death rate of AIDS patients without specification of cause



As we are aware that over the year the number of AIDS patients are increasing and till date there is no cure for the disease. Thus the probability of death is also increasing with time. However, the rate of increase is gradually smoothing out, the reason probably being better awareness & medical facilities.

From the table-2 we observe that the average of estimated Crude probability of death of AIDS patient due to TB is 10.077254, Hep-B is 0.017394, DH is 0.016709, BM is 0.028069 and OD is 0.022775 in the presence of all other risks. On the basis of these observations, we conclude that Crude probability of death due to TB is highest as compared to other prevalent diseases in the population and thus TB is identified as major risk for AIDS patients in Delhi. Figure 2 clearly shows this fact for the Crude probability of death of AIDS patient

Figure-2: Graphical representation of Crude Probabilities of death of AIDS patients.

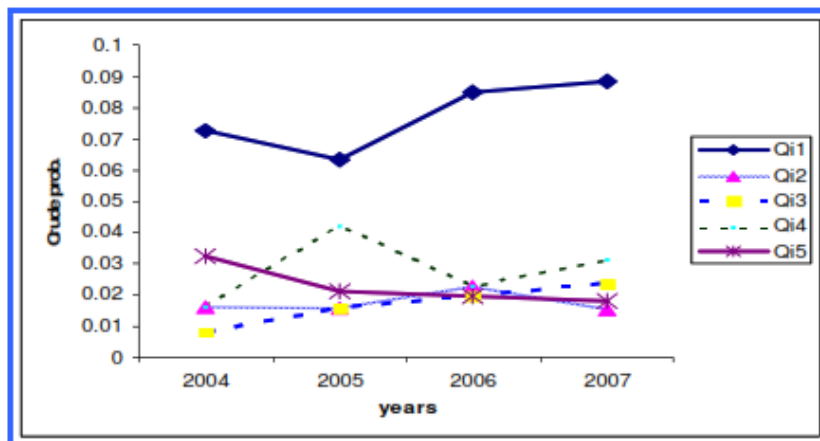


Table-3: t-test for equality of means

	Q_{i1}	Q_{i2}	Q_{i3}	Q_{i4}	Q_{i5}
Q_{i1}	-	0.0000315	0.0000493	0.0004396	0.00009
Q_{i2}		-	0.4098971	0.0622945	0.103716389
Q_{i3}			-	0.0651781	0.11711528
Q_{i4}				-	0.221756937
Q_{i5}					-

The t-test for equality of means shows that the average probability of death due to TB for AIDS patients is significantly higher than others (i.e. p -value < 0.001); however, the average probability of death of AIDS patient due to other risks does not differ significantly.

Table-4: Yearly Estimate of Net probability of death (*type – I*) of AIDS patients

Year	q_{i1}	q_{i2}	q_{i3}	q_{i4}	q_{i5}
2004	0.074766	0.01712	0.008597	0.01712	0.01712
2005	0.066431	0.017038	0.017038	0.044793	0.022647
2006	0.088599	0.024667	0.021182	0.024667	0.014171
2007	0.093012	0.017078	0.025517	0.033865	0.019899
Average	0.080702	0.018976	0.018084	0.030111	0.018459

From table-4 we observe that the average estimate of Net probability of death (*type – I*) due to TB when others are eliminated is 0.080702, Hep-B when others are eliminated is 0.0189758, DH when others are eliminated is 0.018084, BM when others are eliminated is 0.030111 and OD when others are eliminated is 0.018459. By this we conclude that average of the estimated Net probability of death (*type – I*) is highest for the opportunistic infection TB. This means TB has much higher impact on survivability of AIDS patient as compared to other risks. This interpretation can be shown in the figure 3.

Figure 3: Graphical representation of Net probability of death (*type – I*) of AIDS patients due to TB, Hep-B, DH, BM and OD.

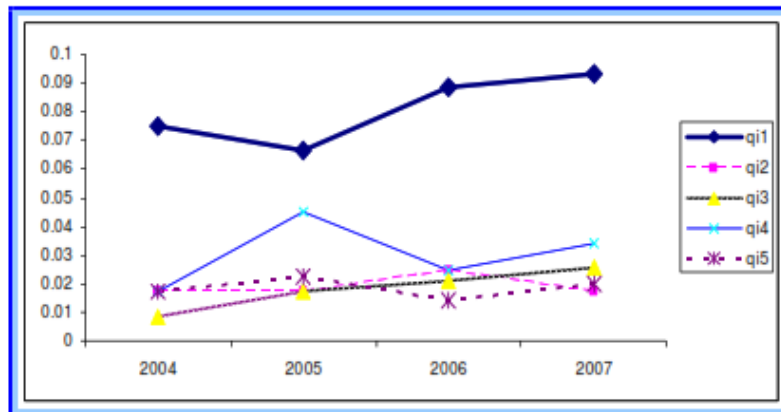


Table-5: Yearly Estimate of Net probability of death *type – II* of AIDS patients

Year	q_{i1}	q_{i2}	q_{i3}	q_{i4}	q_{i5}
2004	0.058649	0.011386	0.121477	0.113859	0.113859
2005	0.097973	0.143298	0.143298	0.118401	0.138367
2006	0.082072	0.142241	0.145296	0.142241	0.151373
2007	0.100782	0.170249	0.163063	0.155832	0.167793
Average	0.084869	0.116794	0.143284	0.132583	0.142848

Table-5 shows that Net probability of death (*type-II*) of AIDS patients i.e. death of AIDS patients due to any other disease when a particular risk is eliminated from the population. The average of the estimated Net probability (*type-II*) is 0.084869 when TB is eliminated, when Hep-B eliminated is 0.116794, when DH eliminated is 0.143284, when BM is eliminated 0.132583 and OD eliminated is 0.142848. Hence we conclude that when risk TB is eliminated the average of estimated Net probability of death (*type-II*) is least. This again points towards TB as a major risk for AIDS patients. Figure 4 shows the graphical representation of Net probability of death (*type-II*) of AIDS patients when TB, Hep-B, DH, BM and OD eliminated respectively.

Figure 4: Graphical representation of Net probability of death (*type-II*) of AIDS patients when each of opportunistic infection viz. TB, Hep-B, DH, BM and OD eliminated.

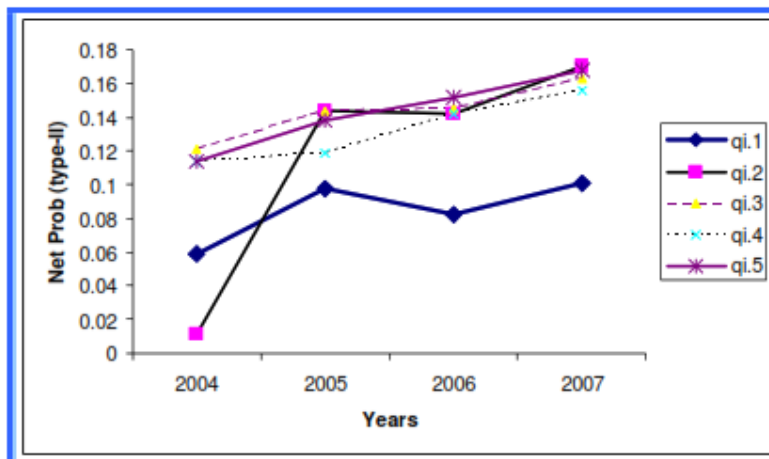


Table 6 & 7 :Yearly Estimate of Partially Crude probability of death of AIDS patients when one and more risks eliminated respectively.

Year	$Q_{i1.2}$	$Q_{i1.3}$	$Q_{i1.4}$	$Q_{i1.5}$	$Q_{i1.23}$	$Q_{i1.24}$	$Q_{i1.25}$
2004	0.073195	0.072886	0.073195	0.073195	0.073505	0.073817	0.073824
2005	0.063688	0.063688	0.064558	0.063869	0.064225	0.065099	0.064431
2006	0.085857	0.085857	0.086006	0.085559	0.085411	0.085559	0.086607
2007	0.089802	0.089122	0.089802	0.090478	0.090205	0.090502	0.089935
Ave	0.078135	0.077888	0.07839	0.078275	0.078336	0.078744	0.078699

Year	$Q_{i1.34}$	$Q_{i1.35}$	$Q_{i1.45}$	$Q_{i1.234}$	$Q_{i1.235}$	$Q_{i1.345}$	$Q_{i1.2345}$
2004	0.073505	0.073506	0.073824	0.074131	0.074131	0.074131	0.074765
2005	0.065099	0.064431	0.065315	0.063889	0.064979	0.064021	0.066431
2006	0.08691	0.086456	0.086607	0.08798	0.087519	0.087519	0.088599
2007	0.09091	0.089797	0.090638	0.091607	0.091464	0.091888	0.093012
Ave	0.079106	0.078547	0.079096	0.079402	0.079523	0.07939	0.080702

Figure-8: Graphical representation of Partially Crude probability of death of AIDS patients due to TB when all other four risks eliminated.

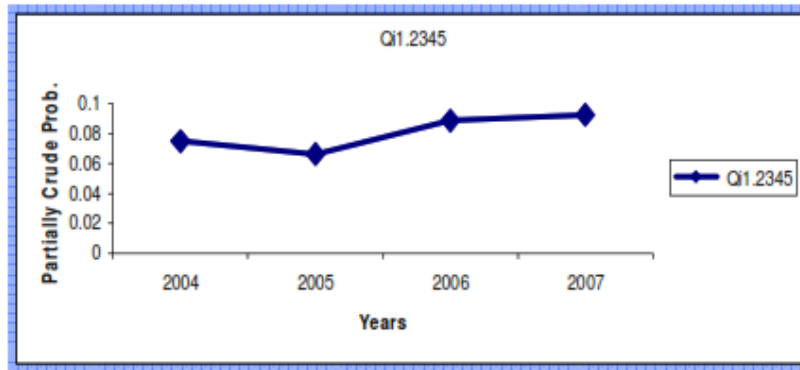


Table 8 : Yearly Estimate of Partially Crude probability of death of AIDS patients due to TB(2),Hep-B(3),DH(3),BM(4) and OD(5) when one and more risks eliminated respectively.

Year	$Q_{i1.2}$	$Q_{i1.3}$	$Q_{i1.4}$	$Q_{i1.5}$	$Q_{i1.23}$	$Q_{i1.24}$	$Q_{i1.25}$
2004	0.073195	0.072886	0.073195	0.073195	0.073505	0.073817	0.073824
2005	0.063688	0.063688	0.064558	0.063869	0.064225	0.065099	0.064431
2006	0.085857	0.085857	0.086006	0.085559	0.085411	0.085559	0.086607
2007	0.089802	0.089122	0.089802	0.090478	0.090205	0.090502	0.089935
Ave	0.078135	0.077888	0.07839	0.078275	0.078336	0.078744	0.078699

Table 8 : Yearly Estimate of Partially Crude probability of death of AIDS patients due to TB(2),Hep-B(3),DH(3),BM(4) and OD(5) when one and more risks eliminated respectively.

Year	$Q_{i2.1}$	$Q_{i2.3}$	$Q_{i2.4}$	$Q_{i2.5}$	$Q_{i2.13}$	$Q_{i2.14}$	$Q_{i2.15}$	$Q_{i2.34}$
2004	0.016757	0.016197	0.016266	0.016266	0.016829	0.016901	0.016901	0.016335
2005	0.016328	0.015922	0.016146	0.015966	0.016467	0.016702	0.016513	0.016282
2006	0.023936	0.023114	0.023154	0.023034	0.024191	0.024233	0.024105	0.023397
2007	0.016344	0.015781	0.015847	0.015803	0.016553	0.016623	0.016576	0.016048
AVE.	0.018341	0.017753	0.017853	0.017767	0.01851	0.018615	0.018524	0.018015
Year	$Q_{i2.35}$	$Q_{i2.45}$	$Q_{i2.134}$	$Q_{i2.35}$	$Q_{i2.345}$	$Q_{i2.1345}$	$Q_{i3.5}$	$Q_{i3.12}$
2004	0.016335	0.016404	0.016974	0.016974	0.016474	0.01712	0.008133	0.008451
2005	0.016101	0.016328	0.016844	0.016654	0.016467	0.017038	0.015966	0.016467

2006	0.023275	0.023316	0.024492	0.024362	0.023561	0.024666	0.019743	0.020771
2007	0.016003	0.01607	0.016838	0.01679	0.016275	0.01708	0.023704	0.024724
AVE.	0.017928	0.01803	0.018787	0.018695	0.018194	0.018976	0.016887	0.017603
Year	$Q_{i3.14}$	$Q_{i3.15}$	$Q_{i3.24}$	$Q_{i3.25}$	$Q_{i3.45}$	$Q_{i3.124}$	$Q_{i3.245}$	$Q_{i3.245}$
2004	0.008451	0.008451	0.008202	0.008202	0.008202	0.008523	0.008523	0.008272
2005	0.016702	0.016513	0.016282	0.016101	0.016328	0.016844	0.016654	0.016467
2006	0.020771	0.020662	0.02009	0.019985	0.019985	0.02103	0.020919	0.020231
2007	0.024935	0.024865	0.023971	0.023904	0.024105	0.025149	0.025077	0.024309
AVE.	0.017715	0.017623	0.017136	0.017048	0.017155	0.017887	0.017793	0.01732
Year	$Q_{i2.1245}$	$Q_{i4.5}$	$Q_{i4.13}$	$Q_{i4.12}$	$Q_{i4.15}$	$Q_{i4.32}$	$Q_{i4.35}$	$Q_{i4.25}$
2004	0.008597	0.016266	0.016829	0.016901	0.016901	0.016335	0.016335	0.016404
2005	0.017038	0.042576	0.043912	0.043912	0.044036	0.042815	0.042935	0.042935
2006	0.02118	0.023034	0.024191	0.024233	0.024105	0.023397	0.023275	0.023316
2007	0.02551	0.031606	0.033106	0.032966	0.033153	0.031827	0.032006	0.031872
AVE.	0.018081	0.02837	0.029509	0.029503	0.029549	0.028593	0.028638	0.028632
Year	$Q_{i4.132}$	$Q_{i4.135}$	$Q_{i4.325}$	$Q_{i4.1325}$	$Q_{i5.2}$	$Q_{i5.13}$	$Q_{i5.14}$	$Q_{i5.12}$
2004	0.016974	0.016974	0.016474	0.01712	0.016266	0.016829	0.016901	0.016901
2005	0.044286	0.044411	0.043298	0.044791	0.021229	0.021956	0.022269	0.021956
2006	0.024492	0.024362	0.023561	0.024666	0.013231	0.013823	0.013848	0.013848
2007	0.033389	0.033579	0.032276	0.033868	0.026192	0.027588	0.027706	0.027471
AVE.	0.029785	0.029832	0.028902	0.030111	0.019229	0.020049	0.020181	0.020044
Year	$Q_{i5.34}$	$Q_{i5.32}$	$Q_{i5.42}$	$Q_{i5.135}$	$Q_{i5.132}$	$Q_{i5.342}$	$Q_{i5.1342}$	
2004	0.016335	0.016335	0.016404	0.016974	0.016974	0.016474	0.01712	
2005	0.02171	0.021407	0.02171	0.022459	0.022143	0.021894	0.022652	
2006	0.01337	0.01337	0.013393	0.013995	0.013995	0.013535	0.01417	
2007	0.026746	0.026523	0.026634	0.028063	0.027824	0.026972	0.028304	
AVE.	0.01954	0.019409	0.019535	0.020373	0.020234	0.019719	0.020562	

In Table 8, The partially Crude probability of death due to other risks (apart from TB) have been calculated and it is seen that for each risks, elimination of other risks has approximately no impact on the probability of death due to that particular risk.

Figure 9: Graphical representation of Partially crude probability of death of AIDS patients due to Hep-B and DH, when other one or more risks eliminated respectively.

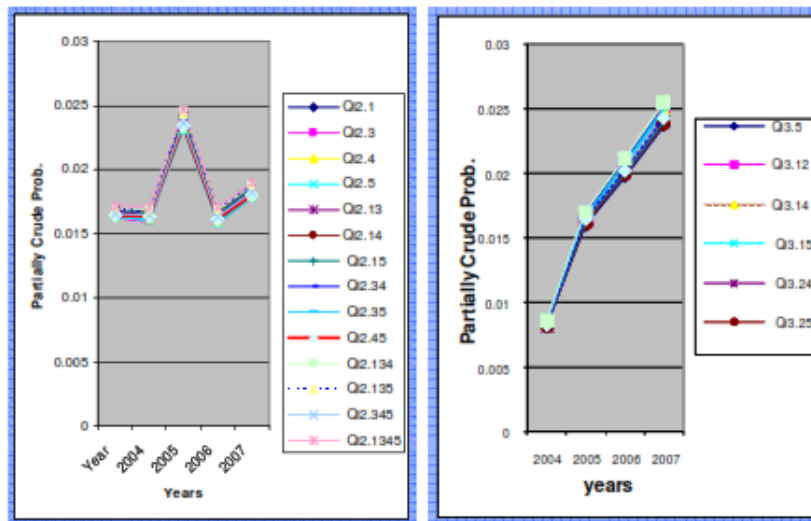


Figure 10: Graphical representation of Partially crude probability of death of AIDS patients due to BM and OD when other one or more risks eliminated respectively.

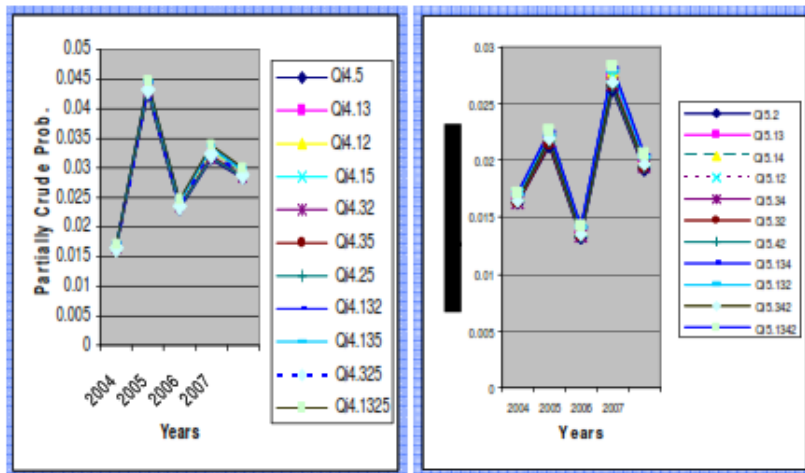


Figure-9 and 10 shows the graphical behavior of Partially crude probability of death of AIDS patients due to Hepatitis-B , Diarrhea, Bacterial Meningitis and other deceases when other one or more risks eliminated respectively.

4. DISCUSSION

The probability of death of AIDS patients without any specification of cause is highest in the year (2007-08) while lowest in the year (2004-05) and has the tendency of increasing as time increases. We also observe that the rate of increase is lower in the years 2005-06 and 2006-07 as compared to other years. The average of estimated Crude probability of death of AIDS patients due to TB in the presence of all the risks is approximately 10 times more than the average of Crude probability of death due to Hep-B. It is approximately 6 times more than the average of Crude probability of death due to DH and BM and for OD it is approximately 7 times. It is found that on the average, probability of death due to opportunistic infection TB is significantly higher (i.e. p -value < 0.001) than any other opportunistic infections. However the average probability of death for other opportunistic infections is not very significant.

The average of Net probability of death (*type - I*) and Net probability of death (*type - II*) show that opportunistic infection TB has higher impact on survivability of AIDS patients as compared to other opportunistic infections. The estimate of Partially Crude probability of death of AIDS patient due to TB when one, two or more risks are eliminated is very much alike. It is also observed that for this data the Partially Crude probability of death due to TB when all prevalent risks have been eliminated is same as the Net probability (*type - I*) of death due to TB.

This shows that survivability of AIDS patients is significantly affected by the opportunistic infection TB and presence or absence of other risks has approximately no effect on probability of death due to TB for AIDS patients.

Finally, it can be concluded that chance of death of AIDS patient due to opportunistic infection TB is the highest in National Capital Territory, Delhi.

5. FUTURE TRAJECTORIES

The global burden of TB has risen dramatically in the past ten years due to the HIV epidemic. TB is the leading infectious killer of people living with HIV, and accounts for an estimated 13% of AIDS deaths worldwide. HIV and TB are so closely connected that they are often referred to as co-epidemics or dual epidemics. The epidemics drive and reinforce one another. HIV activates dormant TB in a person, who then becomes infectious and able to spread the TB bacillus to others.

We may now look to explore the effect of other common opportunistic infections on the AIDS patients to carry this research further. Also the larger population (more than one state) may be considered for AIDS patients suffering with other dreaded opportunistic infections.

The occurrence of tuberculosis (TB), Human immunodeficiency virus (HIV) and Hepatitis infections in the same patient poses unique clinical and public health challenges because medication to treat TB and HIV are hepatotoxic⁽¹⁵⁾ and need for further epidemiologic and clinical studies to optimize the magnitude of this complicated medical condition.

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