A Competing Risk Approach to Studying AIDS/TB Mortality Consequence of Migration in rural South Africa

by

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1.0 Introduction

A plethora of evidence has indicated that migration connotes grave implication for the transmission of HIV/AIDS with TB being one of its major opportunistic infections (Watts 1987; Quinn 1994; Decosas, Kane et al. 1995; Brockerhoff and Biddlecom 1999; Bouare 2007; Coffee, Lurie et al. 2007). This engenders concerns in communities with high oscillatory form of migration and HIV prevalence such as South Africa. Sub-Saharan Africa is a home to around 15% of the world population but more than 65% of the people infected with HIV lives there as at 2009 with South Africa contributing about 25% (UNAIDS 2010). In 2009, about 5.3 million adults aged 15 years and above in South Africa were estimated to be living with HIV (UNAIDS 2010). In the same year, about 0.3 million adults died of AIDS, that is, a quarter of the total AIDS-related deaths reported in sub-Saharan Africa where most deaths occurred globally (UNAIDS 2010).

In linking migration with HIV infection, the focus of the earlier studies was on the roles of the mobile population in the geographical spread of the infection (Carswell, Lloyd et al. 1989; Hunt 1989; Quinn 1994). This was seemingly based on the premise that “HIV, like any other infections (that) spread from person to person, will follow the movement of people” (Decosas, Kane et al. 1995). This assertion provides a rather simplistic rationalisation of the complex relationship between migration and HIV. In the words Lalou and Piché (2004), perceiving "the body of migrant as an infected and contagious body, a vehicle for a virus looking to conquer other bodies and territories, separate the body from its social and cultural reality”. However , the emerging studies reveal a shift in the previously prevailing perception of the link between migration □ AIDS/TB infection and this entails the consideration of the relationship between migration and HIV transmission at the macro-social context level (Lalou and Piché 2004; Crush, Williams et al. 2005); the socio-familial disruption characterising certain type of migration (Decosas, Kane et al. 1995; Bouare 2007); socio-behavioural mechanisms rendering migrants vulnerable (Brockerhoff and Biddlecom 1999); certain conditions initiating migration (Colvin, Karim et al. 1995); migration type and structure (Lalou and Piché 2004); bi-directionality of the disease transmission (Lurie, Williams et al. 2003; Lurie 2006).

On the other hand, only few studies have attempted to investigate the mortality consequence of migration and they indicate that migrants have higher probability of dying of AIDS/TB compared to their non-migrant counterparts when they return to their places of origin (Clark, Collinson et al. 2007; Welaga, Hosegood et al. 2009). Although some of the past studies adopted event history analytical approaches as methods of data analysis on the subject matter, there seems to be no evidence of them including other causes of death (non-AIDS/TB) in their analysis. In event history analysis, it has been noted that apart from the outcome event of primary interest (e.g. death due to AIDS), that an individual can experience another event (e.g. non-AIDS death) that can either preclude or alter the probability of the event of interest occurring (Gooley, Leisenring et al. 1999). Mell and Jeong (2010) corroborated this assertion stating that "in competing risk settings, precision in estimating the probability of occurrence of primary events of interest is reduced, statistical power is (also) reduced and inferences on the basis of composite end points are prone to error". Hence, this study takes further step in linking migration with AIDS/TB by investigating how the migrants' risk of dying from other causes compete with their risk of dying of AIDS/TB by employing Fine and Gray (1999) model, an extension of Cox proportional hazard model suitable in event history analysis when competing risk outcomes are involved (Satagopan, Ben-Porat et al. 2004; Pintilie 2006; Mell and Jeong 2010; Pintilie 2011). This is with the intention of discovering a category of disease that is evolving into an epidemic in addition to AIDS/TB.

2.0 Methods

2.1 The Study Area

The data that was used for the analysis came from a health and demographic surveillance system site (HDSS) established in 1992 and situated in Agincourt sub-district, rural northeast area of South Africa. It is a home to more than 80,000 black Africans (mostly Shangan by f6tribe) who occupy about 15,000 households defined as "group of people who reside and eat together, the plus the linked temporary migrants who would eat with them on return" (Collinson 2010). Also, it consists of 21 villages spanning about 400 square kilometres of land area. Furthermore, the study area is located in one of the former apartheid “homelands", a place that the black Africans were forcefully restricted to during the apartheid era that now acts as a migrant sending community.

2.2 Data

The HDSS data collection process is “…through comprehensive registration system starting with a baseline enumeration of the whole population in 1992 and followed by a routine update of the events (e.g. birth, death and migration) by repeated returns to all households in the population on annual basis ” by the field workers with questionnaires. The site also collects information on health and socio-economic status of the Agincourt residents. In this paper, we defined migrants as those who were away from their usual place of residence within the site for at least 6 months. This definition is commonly used in studies on migration (Lalou and Piché 2004; Beguy, Bocquier et al. 2010).

The outcome variable of this study is *Cause of Death* (CoD). It is important to note that in establishing the CoD, that the Agincourt HDSS uses verbal autopsy (VA) approach, which involves "obtaining information on the terminal illness from a family member after the death, and then 'clinically' assessing it to determine the cause" (Kahn, Tollman et al. 1999). These causes are later classified using the ICD 10 codes. Studies originating from the developing countries have shown that the causes of mortality sourced through the VA are more consistent than the CoDs sourced through the traditional death certificate approach (Chandramohan, Maude et al. 1998; Gajalakshmi, Peto et al. 2002; Setel, Rao et al. 2006). We derived the CoD variable by grouping the mortality causes that we obtained from the HDSS database into the following categories i.e. deaths due to: (i) AIDS/TB (ii) other infectious diseases e.g. malaria; (iii) non-communicable diseases (NCDs) e.g. stroke, diabetes, cancer; (iv) unnatural causes e.g. accident, suicide, homicide and (v) unknown (or unspecified).

We created an independent variable named migrant status comprising two categories namely: resident and migrant. Migrant in this study refers to those who returned back to their households between 6 months and 5 years. In order to capture the socio-economic status (SES) of the respondents, we adopted an SES index technique used by Collinson, Gerristen et al. (2009) in their study titled "The Dynamics of Migration, Health and Livelihoods: INDEPTH network perspectives" using the Agincourt HDSS data. This is useful as Agincourt collects an array of data which ranges from household assets, dwelling structure, livestock to water accessibility, sanitation and electricity supply which need to be harmonised with the intention of deriving an indicator of individual SES standing. The description of the approach is follows:

> Each asset variable was coded with the same valence (i.e. increasing values correspond to greater SES) and effectively given equal weight by rescaling so that all values of a given asset variable fall within the range (0,1). Assets were then categorised into five broad groups - 'modern assets', 'livestock assets', 'power supply', 'water and sanitation' and 'dwelling structure'. For each household within each asset group, the rescaled asset values were summed and then rescaled again to yield a group-specific value in the range (0, 1). Finally for each household these five group-specific scaled values were summed to yield an overall asset score whose value could theoretically fall in the range (0, 5). The final overall score effectively gives equal weight to the five asset groupings and within each group to each of the individual assets. A number of other more complex asset indicators were constructed and compared to one another and to the individual asset values. This indicator is highly correlated with the others and more correlated with the individual asset values and since it is far easier to calculate and explicate it was chosen for our final analysis.

Education is another variable used in the study and it is made up of four categories namely: (i) none, (ii) primary (1-6 years of schooling) (iii) secondary (7-12 years) and (iv) tertiary (13 years and above). We divided the year of analyses into four categories which seemingly play significant role in the transition of HIV/AIDS, 1994-1997 (when death due to AIDS was relatively low in South Africa), 1998-2002 (when the disease started emerging as an epidemic) and 2003-2007 (a period of denial by the ruling government of HIV reaching a pandemic stage in the country and thereby failing to create a policy for the distribution of anti-retroviral (ART drugs). Other variables include sex and age, which ranges between 15-49 years. The age group is consistent with what certain international organisation (e.g. World Health Organisation) use in defining the adult population (WHO 2011).

2.3 Statistical Analysis

In order to investigate the likelihood of a migrant dying of AIDS/TB in the context of competing risk causes, we employed Fine and Gray (1999) model of mortality differential. This model is based on the assumption that competing risk event are independent of each other and it allows for semi-parametric distribution of the data. Unlike Cox proportional hazard model, it retains "the competing risk observations in the risk set with a diminishing weight" (Pintilie 2011). The period of observation was between 1st January, 1994 and 31st December, 2007. It should be noted that the analysis accommodated those that started residing in the study site after the start date (i.e. 1st January, 1994). The individuals that did not experience the event of interest as at the end date or left the study area before the end date, were treated as censored observations. This is inclusive of those whose CoD indicates unknown or unspecified. We limited the analysis to individuals aged 15 to 49 years.

All analyses were performed using a software program called Stata version 11. We used the *stsplit* command in stata to split the event history data into the following time period i.e. 1994-1997, 1998-2002 and 2003-2007. Also, we installed and used *stcompet*, an additional procedure developed by Coviello and Boggess (2004) that is available as a Stata add-on to estimate the cumulative incidence function (CIF). With the aid of *stcompet*, we computed the CIF of AIDS/TB related mortality by taking deaths due to NCDs, other infectious diseases and unnatural causes as competing risk events. The CIF of AIDS/TB mortality is the probability of an individual dying of the disease at a particular time in the presence of other causes. Afterwards, we used the *stcrreg* command to fit competing-risk model, based on the definition of Fine and Gray (1999). For comparison purpose, we also fitted a Cox's proportional hazard model.

3.0 Results and Discussion

A total of 4,351 people, out of 102,495 that were exposed, died during the period of observation starting from 1st January, 1994 to 31st December, 2007. The characteristics of these people as at the time of their death are shown in Table 1. Apart from period 1994-97, more than half of the people died of AIDS/TB compared with other causes in period 1998-02 (42%) and 2003-07 (57%). NCDs came second in the rating of the causes of death with 29% in 1994-97, 24% in

1998-02 and 18% in 2003-07 with unnatural and other infection causes of mortality coming third and fourth respectively and both following trend in relation to the period of analysis. The mean age of the subjects at death 34 and this is the same for the three period with the youngest person being 15years and the oldest 49 years at death. More than half of the deceased are male with the period 1994-97 having the highest proportion, 62% while period 1998-02 had the lowest percentage.

Table 1. Characteristics of the respondents at death

Characteristics	**1994-1997** (**n**=386)	**1998-2002** (n=1049)	**2003-2007** (n=2049)
Causes of death			
AIDS/TB	84(22)	441(42)	1160(57)
NCDs	112(29)	249(24)	371(18)
Other Infections	25(6)	67(6)	125(6)
Unnatural	89(23)	159(15)	196(10)
Unspecified*	76(20)	133(13)	197(10)
Age± (mean)	34	34	34
Sex			
Male	241(62)	540(51)	1062(52)
Female	145(38)	509(49)	987(48)
Education Status			
None	136(36)	254(26)	347(18)
Primary	111(29)	271(27)	420(22)
Secondary	125(33)	436(44)	1050(55)
Tertiary	10(3)	31(3)	82(4)
Migrant Status			
Resident	283(73)	433(41)	592(29)
Migrant	101(27)	616(59)	1456(71)
SES¥ (mean)	2.45	2.44	2.46

NB: The values are presented in "n(%)" format
*The "unspecified" category was treated as censored observation.
± Age (in years) ranges from 15 to 49 years
¥ The SES values are between 0.94 and 3.76.

Table 1 also shows that a higher proportion of the dead as at the time of their death had secondary education most especially in the second and third period - 44% and 55% respectively. On migrant status, the proportion of resident who died decreased consistently from the first to the third period i.e. from 73% in 1994-97 to 29% in 2003-07. On the other hand, there was an increase in percentage of death observed among the migrants at the time of their death from 27%

in 1994-97 to 71% in 2003-07. This is consistent with the previous studies which show that migrants are returning back to their rural homes to receive health care and later died of terminal diseases mostly AIDS (Clark, Collinson et al. 2007; Welaga, Hosegood et al. 2009). The mean SES at death varies little between 2.45 in 1994-97 to 2.46 in 2003-0 with the highest and lowest values being 0.94 and 3.76 respectively.

Figure 1 shows the cumulative incidence function of dying of AIDS/TB in the presence of other competing causes namely: NCDs, other infectious diseases and unnatural causes. It can be seen that the CIF of dying of AIDS/TB between the age of 15 and 49 years was less than 10% in the first period, 1994-97 and this is the same for the other diseases. In period 1998-2002, the CIF of AIDS/TB rose steadily from less than 10% among those aged 14-37 years and followed the same pattern until it peaked at 15% for those aged 49 years with the NCDs showing the similar pattern of ascent in the latter age groups and eventually peaked at 11% at age 49 while the other causes (i.e. other infections and unnatural causes) remained below 10%. However, in period 2003-2007, the CIF AIDS/TB rose sharply from about 2% among those aged 23 to it reached a peak of 35% among those aged 49 years. This increase is more than double of the highest CIF recorded for AIDS/TB in 1998-02 period and it is the highest among the four period under consideration. The CIF of NCDs in this period is similar to that of 1998-2002 and peaking almost at the same height of 11% among the 49 years old. Similarly, the CIFs of other causes still remains under 10% for the entire age group in 2003-07.

Table 2 shows a multi-adjusted risk for AIDS/TB mortality by period of analysis in the presence of the following competing causes of interest: NCDs, other infections and unnatural causes. The risks were estimated by performing Fine and Gray (1999) competing-risk regression analysis. The SHR denotes sub-hazard ratio which can be interpreted the same way as the Cox's hazard ratio. The results are also display graphically in Figure 2. The table shows that in period 1994-07 that migrants had a 3.73 times higher risk (P for trend < 0.001) of dying of AIDS/TB compared with their non-migrants counterparts with all the competing causes present. This risk is similar to the one estimated for period 1998-02 whose risk stood at 3.63. Although, the risk of AIDS/TB death went down in 2003-07 in comparison with the earlier period yet it was still 1.97 times greater than that of the residents. Nevertheless, the results suggests that HIV/TB infection might

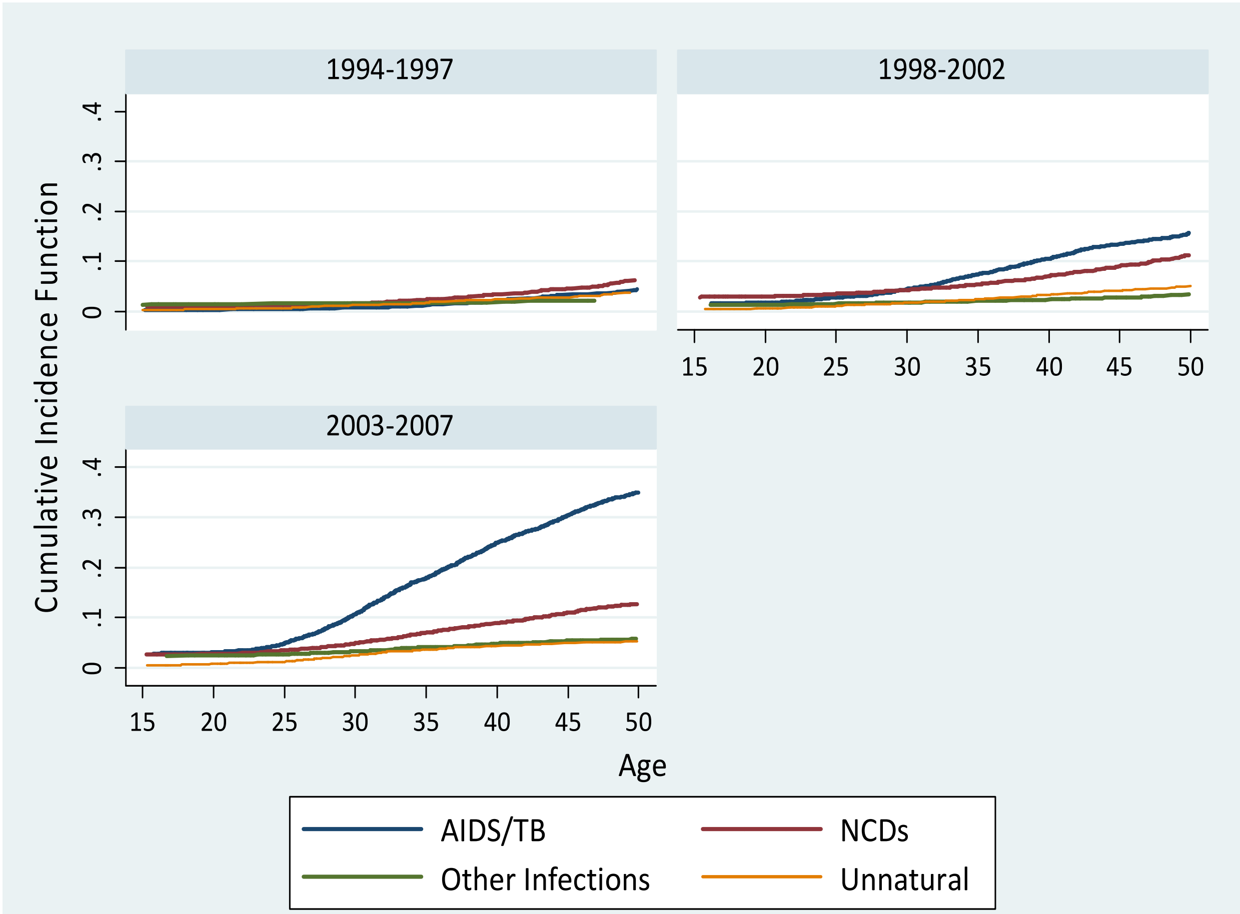


Figure 1. Cumulative incidence of dying of AIDS/TB and the competing causes (NCDs, other infections and unnatural cause) by period of analysis

have reached a stage of saturation in the rural area thereby implying that non-migrants have almost the same risk of dying of the disease. In fact, studies have shown that HIV transmission route could be bi-directional and that migration that entails leaving one's spouse behind can create not only social disruption but emotional instability which can make either partner to engage in extra-marital sexual relationships (Decosas, Kane et al. 1995; Lurie, Williams et al. 2003; Clark, Collinson et al. 2007). In the earlier years of HIV, there was a belief that the mobile population were responsible for the spread of the disease. In the words of Quinn (1994), "One hypothesis is that the migration of individuals from areas of low endemicity to new uninfected areas was eventually responsible for dissemination of HIV throughout the world." This assertion may not be unlikely as the results of the analysis show migrants to possess higher risk of dying in period 1994-97 and 1998-02.

In period 1994-97, the table shows an increase in the hazard of AIDS/TB death from 3.73 (when all competing causes were controlled for in the analysis) to 4.57 when only NCDs were considered as a competing cause. This could be interpreted that migrants have 4.57 risk (*P* for trend < 0.001) times greater risk of dying of AIDS/TB in the presence of NCDS. It is interesting to note that the risk rose when only NCDs were treated as competing cause meaning that all the causes combined suppressed the chance of AIDS/TB mortality. The same trend was observed in period 1998-02 and 2003-07 where the SHR stood at 4.18 (*P* for trend < 0.001) and 2.37 ((*P* for trend < 0.001) respectively. Considering the other causes (other infections and unnatural) individually, we did not see these causes competing with the risk AIDS/TB like the NCDs. but their combination saw the SHR coming down. It can be seen that having them individually in existence, the AIDS/TB had greater chance.

The high prevalence of HIV and tuberculosis in South Africa has probably led to the diversion of attention and resources from the control and treatment of the NCDs such as diabetes, heart disease, cancer etc. Apart from this study showing that NCDs compete better than other causes on the risk of AIDS/TB, the emerging line of evidence (from other publication) has revealed that the prevalence of NCDs is not only on the increase but also has the tendency of making substantial contribution to the burden of diseases in the country most especially among the rural dwellers (Tollman, Kahn et al. 2008; Mayosi, Flisher et al. 2009).

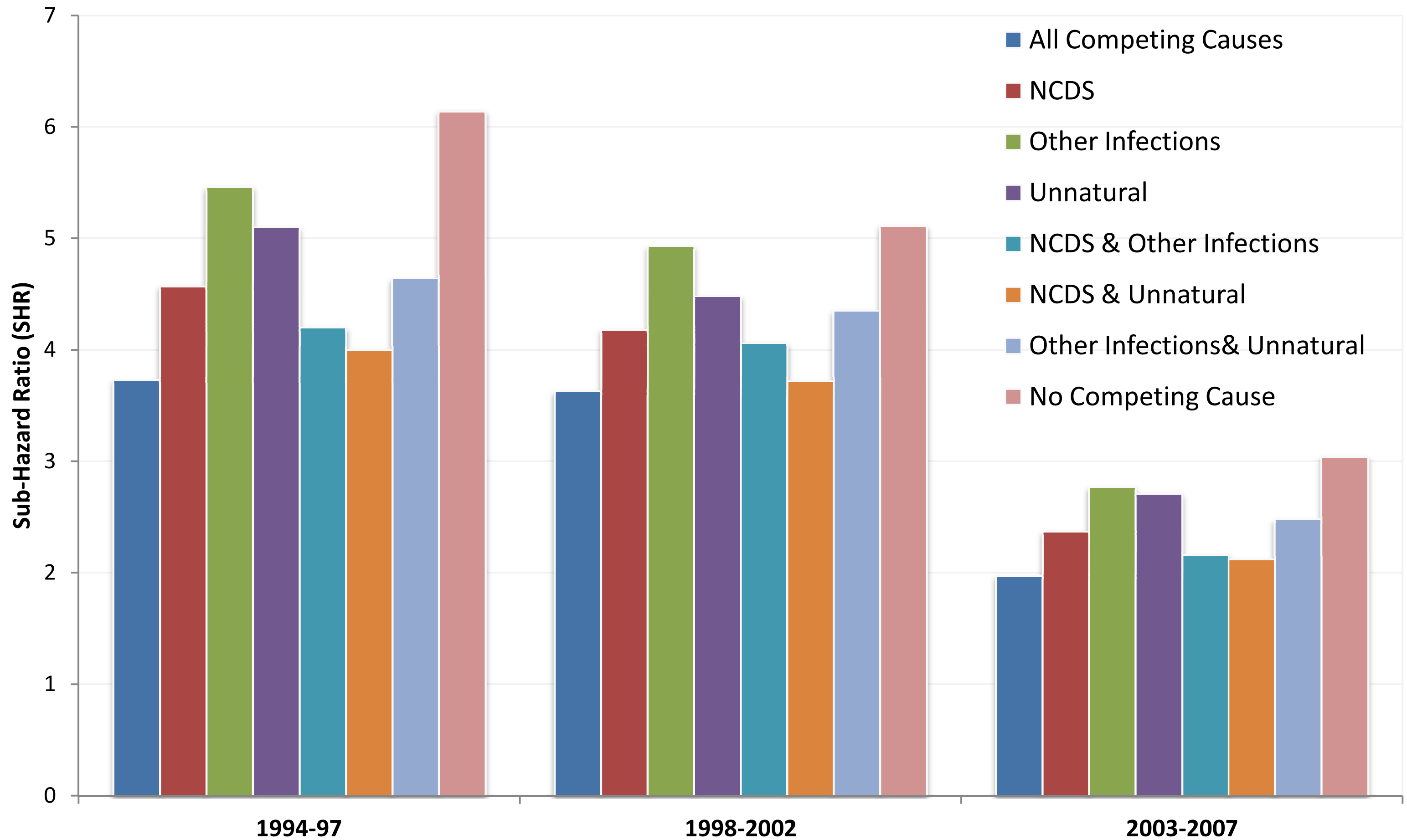
Table 2 also shows the hazard ratio of AIDS/TB estimated without the inclusion of other causes. From the first to the last period, the risk of a migrant dying of AIDS/TB was higher than that of the resident in the absence of competing causes - 6.14 times (*P* for trend < 0.001) in 1994-97, 5.11 times (*P* for trend < 0.001) in 1998-02; and 3.04 times (*P* for trend < 0.001) in 2003-07. These values were greater than the respective values estimated from fitting competing risk model. This highlights the concern of the previous authors on the importance of not using Cox's model when competing causes are in existence ((Satagopan, Ben-Porat et al. 2004; Pintilie 2006; Mell and Jeong 2010; Pintilie 2011).

Table 2: Multi-adjusted risk of migrants vs residents dying of AIDS/TB mortality by period of analysis with and without the presence of other causes.

	1994-1997			1998-2002			2003-2007		
	SHR	**95% CI**	***P*-value**	**SHR**	**95% CI**	***P*-value**	**SHR**	**95% CI**	***P*-value**
All Competing Causes	3.73	2.21-6.31	<0.001	3.63	2.92-4.51	<0.001	1.97	1.70-2.28	<0.001
NCDS	4.57	2.72-7.68	<0.001	4.18	3.38-5.16	<0.001	2.37	2.05-2.69	<0.001
Other Infections	5.46	3.25-9.17	<0.001	4.93	4.01-6.07	<0.001	2.77	2.44-3.14	<0.001
Unnatural	5.10	3.02-8.60	<0.001	4.48	3.63-5.52	<0.001	2.71	2.38 - 3.08	<0.001
NCDS & Other Infections	4.20	2.50-7.09	<0.001	4.06	3.28-5.01	<0.001	2.16	1.88-.249	<0.001
NCDS & Unnatural	4.00	2.37-6.75	<0.001	3.72	3.00-4.61	<0.001	2.12	1.84-2.45	<0.001
Other Infections& Unnatural	4.64	2.74-7.85	<0.001	4.35	3.52-5.38	<0.001	2.48	2.17-2.83	<0.001
No Competing Cause	6.14*	3.37-11.16	<0.001	5.11*	4.14 - 6.32	<0.001	3.04	2.65 -3.48	<0.001

NB: SHR -Sub-hazard ratio
CI - Confidence Interval

Figure 2: Multi-adjusted risk of migrants vs residents dying of AIDS/TB mortality by period of analysis with and without the presence of other causes.



4.0 Conclusion

Migration is an important risk factor in the AIDS/TB mortality of people living in South Africa. HIV intervention efforts should not only be geared towards the migrants (at their various places of destination) but to their left behind partners in the migrant sending communities as HIV prevalence has seemingly reached a stage of saturation in the country with the possibility of either partner being the source of HIV/TB that eventually terminate the live of the other partner. Nonetheless, migrants still have the greater chance of contributing to the demise of their partners. Other diseases should not however be neglected as this study has shown that the risk of mortality due to AIDS/TB is being reduced in the presence of other causes of death. Hence, efforts should be made to reducing the mortality consequence of NCDs such as cardiovascular (lifestyle) diseases as well as the unnatural causes and other infectious diseases.

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