MORTALITY PATTERNS AND THE INFLUENCE OF ANTIRETROVIRAL THERAPY IN MEDICAL PATIENTS AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

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Of

Master of Medicine in the branch of Internal Medicine

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I, Janie Kriel declare that this research report is my own work.

It is being submitted for the degree of Master of Medicine in the branch of Internal Medicine at the University of the Witwatersrand, Johannesburg.

It has not been submitted before for any degree or examination at this or any other University.

Janie Kriel

.....

.....

This research report is lovingly dedicated to the memory of my grandmother

Jacoba Maria Steyn

1932- 2004

ABSTRACT

Background

South Africa has experienced an HIV epidemic that resulted in an increased population mortality rate and decreased life expectancy. Since 2007 these trends have reversed. Antiretroviral therapy has been shown to decrease mortality and increase life expectancy at a community and population level. The impact of antiretroviral therapy at a large healthcare facility level is unclear. Mortality patterns in South Africa are also changing however the method of data collection often underrepresents the burden of HIV.

Aim

To determine the mortality patterns of medical inpatients at CHBAH and to assess if improved access to antiretroviral therapy has decreased mortality and increased age at death over the period 2006 to 2009 when there was a rapid scale-up of antiretroviral therapy in the public sector.

Methods

This is a retrospective, cross-sectional study. Adult mortalities in the medical wards were reviewed between 2006 and 2009. Causes of death were ascertained by medical consultants who reviewed the patient records and results at the time of completing patient death certificates.. The annual mortality rates were determined

and deaths were analysed with respect to age at death, sex and HIV-status.

Results

Data on 16020 deaths were available for analyses. The overall crude mortality rate fell significantly year on year from 113/100000 to 79/100000. The mean age at death for HIV-negative patients was 60in 2006 and showed no significant increase over the study period. The mean age at death of HIV-positive patients increased significantly year on year from 38 in 2006 to 40 years in 2009 .

The peak age category of death for HIV-positive females moved from 30-34 to 35-39 years over the study period. Peak age category at time of death in males remained unchanged at 40-49 years An estimated total of 101478 years of life were lost to HIV disease in females and 65008 years were lost in HIV-positive males during the study period . HIV, tuberculosis and pneumonia were the top three causes of death and their proportional contribution to mortality remained unchanged over the study period. Diseased associated with advanced immunosuppression such as cryptococcal meningitis and infectious diarrhoea decreased over the study period.

The mortality trends seen in this study are similar to those reported at population level. Increases in life expectancy occurred in the HIV-positive population and opportunistic infections as major contributors to death decreased, during the time that antiretroviral therapy was being escalated.

Conclusion

Improvement in mortality patterns within the HIV-positive group at the time that antiretroviral therapy was escalated suggest that cART roll-out had a positive impact on mortality at CHBAH.

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1.0 INTRODUCTION

A country's mortality trends accurately reflect its developmental level. In 2005, a person born in northern, southern or western Europe could expect to live for an average of 78.6 years.[1]

Mortality rates have decreased worldwide over the past twenty years while during the same two decades the mortality rates in South Africa increased.[2] The increasing mortality rates seen in South Africa can be attributed to the delayed response of the South African Health system to the HIV epidemic in the region.

A quarter of all HIV-infected persons in sub-Saharan Africa live in South Africa. South Africa has the highest number of people living with HIV and Acquired Immunodefiecy Syndrome (AIDS) in the world, estimated at 6.2 million individuals. [1,2,3,4]

As a result of HIV, the expected lifespan of a South African was reduced by an estimated 13 years from 64 years in 1990 to 51 years in 2005.[5] It was estimated that during this time period around one thousand people were dying daily in South Africa due to HIV-related disease.[6]

Historically, low income countries have distinct disease profiles characterised by high child mortality, widespread malnutrition and a dominance of communicable disease. This typical mortality pattern evolves

as development progresses and changes to a predominance of noncommunicable diseases.[7]

During the transition developing countries suffer a double burden of disease due to the occurrence of both communicable and non-communicable disease profiles simultaneously, in South Africa the high toll of unnatural, trauma-related deaths and the HIV epidemic resulted in a quadruple disease burden.[7] This quadruple burden means mortality rates in South Africa far exceed those of countries with a similar gross domestic product and health expenditure profiles.[8]

Of the 57 million global deaths reported by the World Health Organisation (WHO) in 2008, 36 million were due to non-communicable diseases with ischaemic heart disease and cerebrovascular disease cited as the leading causes of death in this category in 2004. The highest ranking communicable disease was respiratory tract infections. Globally, HIV/AIDS ranked as the sixth leading cause of death.[9]

In contrast to this, Bradshaw *et a*l found AIDS- related illnesses emerged as the overwhelming number one cause of premature mortality in all nine provinces of South Africa during the same time period.[7]

After HIV/AIDS- related disease, the top twelve causes of years of life lost for South Africans in descending order were homicide and violence, tuberculosis, diarrhoeal diseases, road traffic accidents, lower respiratory tract infections, cerebrovascular events, ischaemic heart disease,

hypertensive heart disease, suicide, septicaemia and complications of diabetes mellitus.[7]

In 2008 it was estimated that 79% of years of life lost were due to communicable diseases with only 15% being attributed to non-communicable diseases. Despite marked economic differences between the nine provinces of South Africa the death rate due to non-communicable diseases was similar.[7]

AIDS-related illness accounted for 14% of total years of life lost in the Western Cape at the low end to 51% of total years of life lost in KwaZulu-Natal, reflecting the distribution of HIV in South Africa.[7] In 2012 the Human Sciences Research Council household survey found that only just over a third of HIV infected adults knew their HIV-status.[10]

According to the WHO South African health profile, the prevalence of HIV in 2009 was 178 per 1000 adults aged 15- 49 years, with a global average of eight persons per 1000.[11]

In 2002-2005 the HIV incidence among women, especially young women aged 15- 24 years was ten times higher than their male counterparts. During the period 2005- 2008, a lower HIV incidence rate of 1.3/100 p.a. was estimated for both men and women aged 15-49 years.[4]

There was a statistically significant decline in incidence of HIV infection among young women between the ages of 15 and 24 years, but overall population incidence did not decrease.[4]

In the age group 25- 49 years the incidence among both men and women in 2005-2008 were similar to the estimated incidence for the 2002-2005 period.[4]

Without therapeutic intervention the majority of individuals living with HIV/AIDS face certain death, Bradi *et al* (2006) showed that without combination antiretroviral therapy (cART) 22.2% of patients with WHO stage IV disease will die within six months of diagnosis.[12]

Mortality statistics and related information on death occurrences between 1997 and 2013 was released in the first quarter of 2014 by Statistics South Africa.[13] This information was based on death reports collected through the South African civil registration system which is maintained by the Department of Home Affairs. The report outlined observed trends over the fifteen year period. Maternal and perinatal deaths were included but stillbirths were excluded from the report.

The number of natural deaths steadily increased from 1997 and peaked in 2006 with 560415 deaths for all ages then declined from 2007 to 2011 with 467531 deaths reported in 2011and further declined to 411714 in 2013.[13] The highest percentage of deaths in 2011 occurred amongst age group 35-39 years (7.8%) followed by the age group 30-34 years (7.3%). The percentage of deaths in the 30-34 year age group declined from 9.5% in 2007 to 7.3% in 2011.[13]

It was noted that the trend in the age pattern of deaths showed increases in the proportion of deaths occurring in older age groups and decreases in younger age groups, death distributions by sex and year of death from 1997 to 2011 showed the proportion of male deaths were consistently higher than female deaths. Between 2006 and 2011 the proportion of female deaths decreased from 49.3% to 48.3%.[99]

Male deaths were the highest in the age group 35-39 years (8.4% of all male deaths) and female deaths peaked at 30-34 years (7.2%) Notably the differences between deaths in males and females were minimal at younger ages (0-24 years).[99]

Non-communicable diseases of the circulatory system causing death increased from 14.7% in 2009 to just over 16.0% in 2011 and cerebrovascular diseases was noted as the leading cause of death in persons older than 65 years followed by unspecified other forms of heart disease. Tuberculosis was ranked at number eight in this elderly population group.[99]

Most deaths were reported by health care facilities (46.3%) followed by deaths that occurred at home (26.0%) reported by family members.[99]

cART became available in public clinics on the 1st April 2004, prior to this, access to cART was limited to a few patients on clinical trials and those with financial means to fund their own treatment. All cause mortality in South Africa increased by 79% between 1997 and 2004, this increase was mainly due to natural causes.[14]

Despite the introduction of state funded antiretroviral therapy in 2004, national rollout was hesitant at the outset and aggressive widespread initiation and escalation only started in late 2007 with increased political will and international funding. The landmark National HIV&AIDS and STI Strategic Plan 2007–2011 began to address the monumental challenge. The two primary goals of the HIV/AIDS and STI Strategic plan were to reduce the HIV incidence rate by 50% and to expand the access to cART to include 80% of newly ART-eligible persons by 2011.[15]

South Africa's cART roll-out programme resulted in a rapid increase in the number of HIV-infected patients on antiretroviral therapy.In mid-2005 a total of 60 600 public sector patients were receiving cART , by July 2009 this number had increased to 748 000.[16] A 2012 South African National HIV Survey reported that 2 002 350 patients were on cART with 6.4 million persons living with HIV/AIDS at the time.[10]

The vast majority (85%) of these patients received treatment through the public healthcare sector. Just over 10% were treated within disease management programmes in the private sector with the remaining four percent of patients cared for by NGO's managing community treatment programmes.[10]

Around 61% of all who benefitted from cART were women with men accounting for a third of patients and children 8% of those with sustained

access to cART. Gauteng and KwaZulu Natal provided care to more than 56% of all patients receiving antiretroviral therapy.[16]

The question of cART efficacy in the South African context has been answered as multiple observational studies have clearly shown that cART is as effective in resource- restricted communities as it is in developed countries.[17]

Yet despite the advances made in the era of cART and the considerable decline in the incidence of AIDS- defining illnesses among persons living with HIV, these patients still continue to have excess mortality compared with the general population in the same age and sex groups.[18]

The possible causes for the noted excess mortality was investigated by Wong *et al*(2012) at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) during the period January to December 2009 in which 39 HIV-reactive adult patients on cART who died during admission to CMJAH were enrolled in a prospective post- mortem study.[19]

The study showed that tuberculosis was the leading cause of death in both the study (76%) and control (57%) groups of patients. Tuberculosis was diagnosed microbiologically or histologically in 30% of deceased patients with no clinical findings suggestive of mycobacterial infection. The high incidence of unsuspected tuberculosis in this study suggests tuberculosis may be an under reported major cause of death in this population.[19]

In the recent 2014 Statistics South Africa report, infectious diseases were cited as the main cause of death from 2009 to 2011 with 25% of deaths in 2009 attributed to this main group of causes. A steady decline in deaths from Infectious diseases was noted over the three year period with just over 23% reported in 2011.[13]

Tuberculosis was cited as the leading cause of death for persons between 15 and 49 years. This is not surprising as South Africa carries an enormous burden of tuberculosis-infections. Among the 22 countries with the highest burden of TB (81% of all TB cases globally) South Africa has the highest incidence and prevalence of tuberculosis after adjusting for population size.[20] South Africa has the second highest number of patients diagnosed with multidrug-resistant TB cases and the largest number of HIV-associated TB cases globally.[21] The incidence of tuberculosis was 300 per 100 000 people in the early 1990's to more than 600 cases per 100 000 people in early 2000 and more than 860 per 100 000 people in 2013.[20]

HIV-disease was noted as the third leading cause of death (6.6%) for persons between 24- 49 years and this was the only age group where HIV –disease was among the top ten underlying causes of death according to Statistics South Africa.[99]

The finding by Wong *et al* that tuberculosis contributed to the majority of deaths correlates with studies from India and Sub-Saharan Africa.[19]

In India, Mumbai, tuberculosis was named as the chief cause of death in 63% of HIV- infected but antiretroviral -naive persons in a series of 236 patients[22] and furthermore in a 2010 meta-analysis of post-mortem studies of HIV-reactive adults in Sub-Saharan Africa over the past twenty years, tuberculosis was considered the number one cause of death in 45% of adults.[19]

The study by Wong *et al* (2012) found that in those who died, Immune Reconstitution and Inflammatory Syndrome (IRIS) was an important contributing factor in the deaths of 74% (11/15) of patients initiated early on antiretroviral therapy.[19]

Ingle *et al* (2010) assessed the differences in access and subsequent patient outcomes across antiretroviral treatment clinics in the Free State, South Africa, found that a significant number of the sickest patients in their cohort died before cART could be initiated. Of all deaths over the four year study period, 83% occurred in eligible patients not receiving cART.[23] In those who received antiretroviral therapy the mortality ranged from 8.1% to 32.8%

A study by Herbst *et al* (2009) conducted in rural KwaZulu-Natal showed that the widespread roll-out of cART significantly impacted on the adult population mortality in a secluded community with both a high prevalence of HIV infection and an equally high mortality rate related to HIV with a subsequent significant mortality rate reduction of 22% in females and 29% in males in the study population.[24]

Mortality from tuberculosis in pregnant women has also been shown to decrease with improved cART coverage in both KwaZulu Natal and the city

of Johannesburg (Personal correspondence A Black 2014).[25] The roll-out of antiretroviral therapy can be expected to result in a decline in mortality rates throughout sub-Saharan Africa.

A report from the Soweto area suggested a high incidence of both HIV-disease and HIV-treatment related mortality.[27]

Studies from South Africa and Cambodia have shown that improved cART coverage decreases mortality from infectious diseases and TB in particular[28,29] Improved antiretroviral therapy coverage has also been shown to increase the mean age at time of death. HIV-positive adults in South Africa have near normal life expectancy provided that they start ART before their CD4 count drops below 200 cells per cubic millimeter.[30] cART coverage has been reported to have increased in adults 21.5% in 2006 to 68.2% in 2009 in Gauteng provence.[31]

The Statistics South Africa Data is derived from Death Notification forms (DHA 1663 or BI-1663) the accuracy of the cause of death reported on these forms has been shown to be poor. The inclusion of HIV related causes of death is often misclassified due to reasons beyond poor quality such as concerns around confidentiality and possible litigation by the family of the deceased. REF Nojilana and Birnbaum J

The Statistics South Africa data is population based and no large facility data was found to see if inpatient hospital mortality patterns were reflective of the available population data.

No published reports to date have reviewed the impact of the cART scaling-up process on the adult medical patient mortality patterns in the Soweto area which consists of a large urban population whose health needs are largely served by a single 2700 bed university- supported hospital, the Chris Hani Baragwanath Academic Hospital (CHBAH) which also maintains a confidential mortality data base with cause of death collected independent of the official Death notification forms.

1.1 AIM OF THE STUDY

The aims of this study are to describe the mortality patterns of medical inpatients at CHBAH over the time period 2006 to 2009 and to assess if escalated access to antiretroviral therapy in the Soweto community has altered mortality patterns over this period.

1.2 OBJECTIVES

a. To describe the demographics of deaths of medical in-patients who died at CHBAH during the period 2006 to 2009.

b. To identify the diagnoses responsible for more than 75% of deaths of medical in- patients who died at CHBAH during the period 2006 to 2009.

c. To determine if there is any association between HIV status, sex, age of death and infectious versus non-infectious cause of death.

d. To determine if any changes in the pattern of mortality regarding age and sex of deceased occurred during the period of intensified roll-out of antiretroviral therapy.

2.0 METHODS

2.1 Study design

This is a retrospective, cross sectional study with descriptive and comparative analysis.

2.2 Study population

The population of Soweto in 2005 comprised of approximately 1.12 million predominantly black urban South Africans. CHBAH is a public hospital that serves approximately ninety percent of Sowetan residents, with the remaining 10% using private healthcare. CHBAH is a large facility with 2700 beds. Although CHBAH is an Academic hospital it caters for all levels of patients requiring hospitalisation

from the Soweto area, and at the time of the study was the only public inpatient facility for the area.

The reported prevalence of HIV in Gauteng between 2005 and 2009 was 24.9 % in adults.[31] cART coverage in adults has been reported to have increased from 21.5% in 2005 to 68.2% in 2009.[16]

The earliest available HIV roll-out programme data for the Soweto area is from 2008, when it was reported that a cumulative 15 373 persons had been started on cART and by 2010 this number had increased to a cumulative 74 864 persons. The National Department of Health District Health information system reported 563 508 patients remained on cART at the end of 2013 in the Soweto area (City of Johannesburg, Region D).[32]

2.3 Data collection

In 2006 in order to enable monitoring of deaths at CHBAH a data sheet was developed to serve as a paper based mortality tool. The data form is completed by a medical consultant at the time of signing the patients' death certificate. Cause of death is ascertained by the medical consultant by reviewing the patient file, cause of death reported on the sheet need not be the same as that reported on the death certificate (due to stigma surrounding HIV- status this and HIV-related diseases are not always stated on the death certificate which is made available to patients families at CHBAH)

HIV status is reported as known positive, known negative, not known or clinically suspected because of AIDS-defining illness, categorising a patient as clinically suspected HIV infection was at the discretion of the consultant and no fixed guidelines were provided for this classification.

If the HIV-status is not available in the patient records a search of the hospital laboratory records is done and the data sheet updated by an investigator.

The CD_4- cell count reported is the last available result on the hospital laboratory system, the vast majority being taken during final admission. Antiretroviral therapy status is determined from patient records.

All death certificates of deceased patients from within the Department of Medicine are meant to be signed by a Medical Consultant however Medical Registrars may sign death certificates after hours if requested to by mortuary staff, in these instances the death data collection sheet was not completed. All deaths occurring at CHBAH were recorded on a Medicom data base, number of deaths reported as having occurred in all of the Medical wards was retrieved from the Medicom system to give the closest approximation available of the true number of Medical deaths occurring at CHBAH during the time period 2006-2009.

Data management

The data was captured into Microsoft Excel 2007 (Microsoft, Redmond, WA). Cause of death was coded using the tenth International Classification of Diseases codes(ICD-10), by a person trained in ICD-10 coding. Where queries arose a consultant assisted in assigning the code.

Primary cause and possible secondary causes of death were coded for; only primary cause of death was used for this analysis.

The number and sex of medical admissions were collected daily from the medical admission ward register by Dr A Black and entered into a separate medical database for medical admissions.

Both data bases were started in 2006 as operational data bases within the Department of Medicine. The data used for analysis was delinked from patient identifiers, and the data sheets were filed in a locked filing cabinet within the Department of Medicine.

2.4 Inclusion criteria

Records of all adults who died in the adult medical wards at CHBAH, of a medical cause between 2006 and 2009.

2.5 Exclusion criteria

All non-medical deaths including antenatal and perinatal deaths even if they died in an adult medical ward.

2.6 Ethical considerations

Ethical approval has been granted by The University of the Witwatersrand Human Research Ethics Committee.

Clearance number **M111103** (Appendix X)

2.6 Methodology

Systematic review of the Department of Medicine database constructed over the period 2006- 2009.

Variables captured:

Age, sex, cause(s) of death, HIV- status, CD_4-cell count, cART status.

2.7 Statistical analysis

Descriptive statistics were presented with 95% confidence intervals, standard deviations for means and inter-quartile range for median values. Comparisons between discrete data categories were done using Chi-square test for large numbers and Fisher's exact test for sparse data. Crude mortality rates were determined and expressed as a rate per 100 000. The total number of medical admissions for each year was used as the denominator for the population.

For comparative statistics, continuous data were analysed using the two-tailed unpaired t test. A p-value of <0.05 was considered significant. Two-tailed Pearson's Correlation Co-efficient test was computed at a 0.01 level of confidence to determine any correlation

between HIV-status, sex, decreased age at death and infectious versus non-infectious causes of death. A probability result < 0.05 was considered significant. While only the primary cause of death was included in the analysis, consultants completing the data sheets could assign multiple causes of death to a single patient such as renal failure and diabetes. As the data collected included other contributors to death other than just the primary cause of death a principle components analysis using all contributing causes of death was done to determine if any contributing factors of death stood out as playing a significant role in the mortality of this population.

For cause of death conditions listed as the primary cause of death falling within the top 75% of causes of death were analysed. Using the top 75% of causes allowed for a manageable number of causes to be listed and provided more data for analysis than if the report was restricted to only the top 10 causes of death..

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Statistical package:

Intercooled STATA version 10 (Stata-Corp, LP, College Station.TX)

2 RESULTS

The department of Medicine data base contained 16020 deaths for the review period 2006-2009. These deaths were all captured from the data sheets. The number of Medical deaths recorded in the Hospital Medicom data base for the same time period was 22668.

3.1

The number of annual admissions for both Medicom and the Department of Medicine database together with the annual number of medical admissions are shown in table 1. Annual crude mortality rates with differences between years for both the Medicom and Department of Medicine database are included in table 1. The difference the annual number of deaths reported in Medicom and those reported in the Department of Medicine database represents possible missing data.

Table 1 Crude mortality rates by year

	Number of admissions	Number of deaths	Crude mortality rates per 100 000 admissions	P value for difference between previous year
2006 Dept Med	44055	4997	113	–
Medicom		5758	131	
Difference		761 (13%)		
2007 Dept Med	39079	4303	110	0.13
Medicom		6218	159	<0.05
Difference		1915 (31%)		

2008 Dept Med Medicom Difference	38971	3951 5437 1486 (27%)	101 140	<0.05 <0.05
2009 Dept Med Medicom Difference	40828	3216 5255 2039 (39%)	79 130	<0.05 <0.05

3.3 DEMOGRAPHICS

3.3.1 Age:

From an initial sample size of 16020, 15800 cases were included in the analysis as 220 cases were missing..

The distribution of age and death appears bimodal and skewed to the left, in the histogram shown as graph 4. Testing for normality gave a kurtosis value of -0.193.

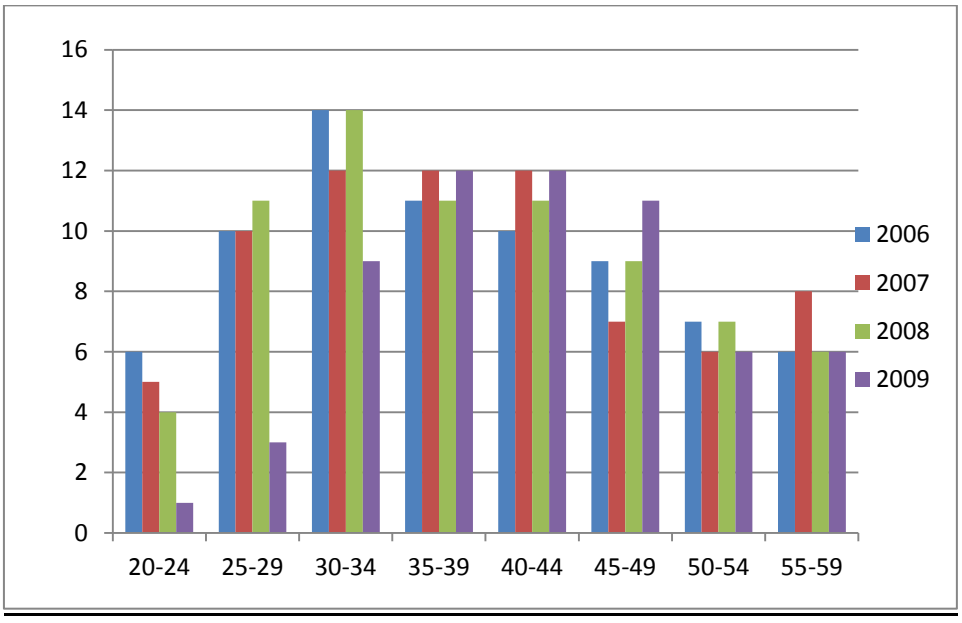
Graph 4: Age distribution of the sample

The statistical test for normality allowed for parametric analysis and the age of the entire mortality database is described in table 1 by year.

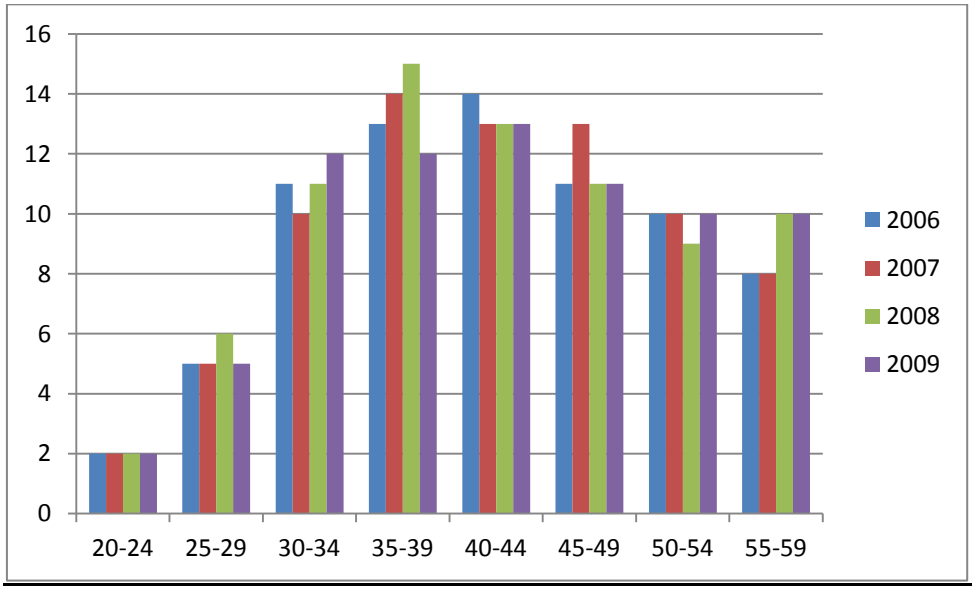
Table 1: Age description of all deaths by year 2006-2009

	2006	2007	2008	2009
N	4499	4257	3871	3121
Mean age in years	48.00	48.90	47.82	49.39
Standard deviation	17.31	17.09	16.80	17.59
95% CI	47.6-48.6	47.9-49.0	47.2-48.3	48.7-50.0
Range	14-105	14-99	14-99	19-108

Proportion of deaths between the age of 20 and 60 years is represented by graph 5 for the percentage of females and graph 6 for percentage of males.



Graph 5: Females, age at time of death by age category expressed in percentage on Y-axis from(20-60 years) 2006-2009



Graphs 6: Males, age at time of death by age category (20-60 years) 2006-2009 expressed in percentage contribution.

Age analysis by HIV-status:

HIV-negative status was significantly corrrelated to Age: r = 0.378; as age increase the probability of being HIV-negative increases. HIV-positive status was significantly correlated to Age: r = -0.048: as age decreases the probability of being HIV-positive increases.

Sub analysis was done only on patients with confirmed HIV-status. Sample size was sufficient to detect a two year difference at $\alpha < 0.05$ and $\beta > 0.9$ for all the sub-analysis.

The age of death of confirmed HIV-positive patients is described year in table 2.

Table 2: Age description of confirmed HIV-positive deaths

	2006	2007	2008	2009
n	2346	1982	1915	1533
Median	38.8	38	38	39
Mean	38	39.1	39.1	40
Standard deviation	10.2	10.1	10.1	10.8
95% Confidence Interval	32.9- 43.0	32.6-43.3	32.6-43.3	35.7-42.2
Range	16-83	14- 80	14-79	14-91

The age of death of confirmed HIV-negative patients is described year in table 3.

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Table 3: Age description of confirmed HIV-negative deaths

	2006	2007	2008	2009
N	824	620	602	407
Median	60	63	62	63
Mean	60	61.6	59.6	61.5
SD	17.3	16.8	18.0	17.8
95% CI	51.5-68.5	55.1-70.9	52.5-71.4	52.5-70.9
Range	16-98	17-97	14-99	15-104

Table 4: Comparison of difference in mean age at death of HIV-positive patients 2006-2009

	2006-2007	2007-2008	2008-2009

Difference in means (95% CI)	1.1(0. 5-1.7)	0.0 (-0.6-0.6)	0.9 (0.2-1.6)
p	< 0.0001		0.01

Table 5: Comparison of difference in mean age at death of HIV-negative patients 2006-2009

	2006-2007	2007-2008	2008-2009
Difference in means (95%CI)	1.6 (0.2-3.4)	-2.0 (-4.0—0.0)	1.9(0.4-4.2)
p	0.08	0.05	0.1

Table 6: Mean age at time of death by sex, irrespective of HIV-status.

	Females	Males
2006	47.5 years	48.7 years
2007	44.0 years	46.0 years

2008	44.5 years	46.4 years
2009	46.2 years	46.9 years

Table 7: Difference in mean age at death between males and females by HIV-status

		Females mean age (years)	**n**	**Males mean age (years)**	**n**	**Difference in mean (95%CI)**	**p**
HIV +	2006	37.2	1272	40.8	1074	3.6(2.8-4.5)	<0.05
	2007	37.6	1045	40.8	937	3.2(2.3-4.1)	<0.05
	2008	35.9	933	41	922	5.0(4.2-5.8)	<0.05
	2009	38.7	788	41.5	751	2.8(1.7-3.8)	<0.05
HIV -	2006	61.8	434	58.0	391	3.81.5-6.2)	<0.05
	2007	63.7	337	59.1	283	4.6(2.0-7.2)	<0.05
	2008	60.7	302	58.8	295	1.9(-1.0-4.8)	0.21

	2009	63.9	214	58.8	196	5.1(1.6-8.5)	<0.05

Table 8: Difference in means of age at time of death of HIV-negative females compared to HIV-positive females and difference in mean age at death of HIV-negative males compared to HIV-positive males.

	HIV- Females vs HIV+ Females Difference in mean (95%CI)	**HIV - Males vs HIV+ Males Difference in mean (95%CI)**
2006	**Δ24.6(23.2-26.0) p<0.0001**	**Δ17.1(15.818.5) p<0.0001**
2007	**Δ26.1(24.6-27.7) p<0.0001**	**Δ18.3(16.8-19.9) p<0.0001**
2008	**Δ24.7(23.2-26.3) p<0.0001**	**Δ17.9(16.3-19.5) p<0.0001**

2009	**∆25.2(23.2-27.1)** **p<0.0001**	**∆17.3(15.4-19.2)** **p<0.0001**

A crude estimate of years of life lost due to HIV infection was made by multiplying the difference in age at death between HIV negative and HIV positive deaths by the number of HIV positive deaths (Table X)

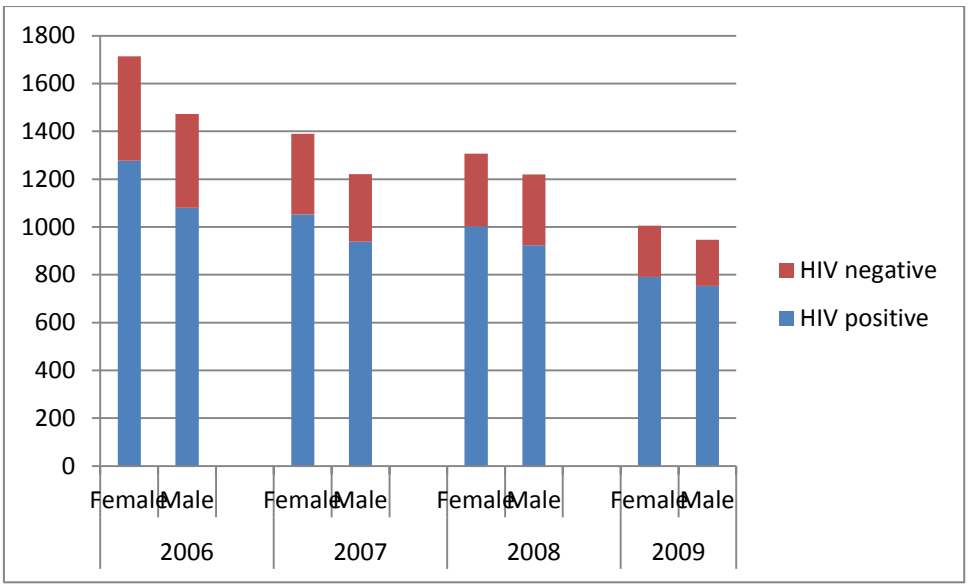
Table X

	HIV-positive females	**HIV-positive males**
2006	**31291**	**18365**
2007	**27274**	**17147**
2008	**23045**	**16504**
2009	**19857**	**12992**
Total	**101478**	**65008**

3.3.2 Sex:

While a sample of 16020 was available 178 did not have their sex documented.The dataset indicated that 50.8% of the sample was female and 48% male. The sex split is consistent with the demographics of South Africa according to the Census (2011) report for South Africa and falls within their 95% confidence interval, suggesting that the sex distribution of my sample of deceased patients is similar to the general living population.

HIV status and sex:



Graph 8: HIV-status and sex distribution of deceased patients 2006-2009

There was no significant difference between HIV-status and sex when testing the entire sample, however sub-analysis on confirmed HIV status showed significant correlation between female sex and

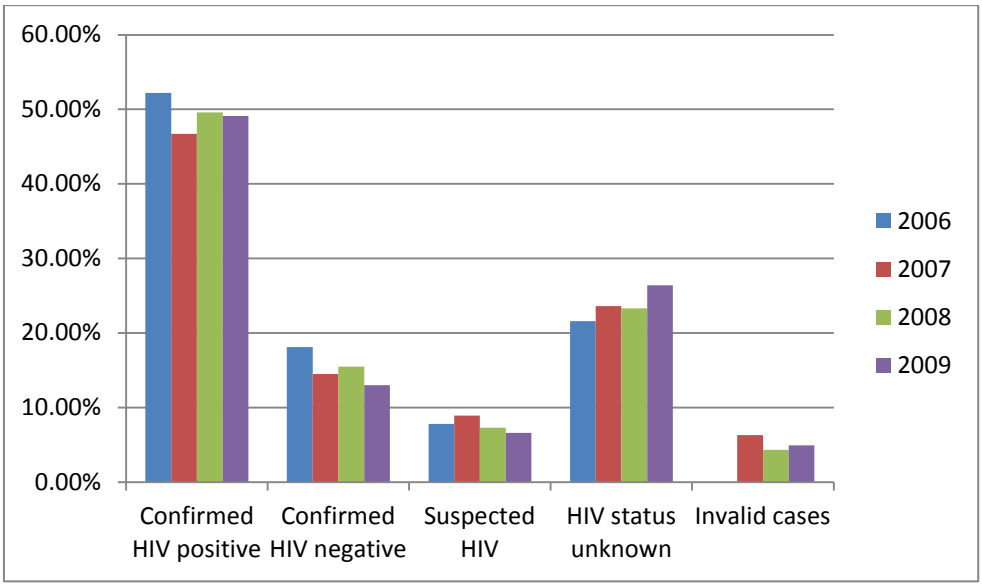
HIV status r=0,03; females were more likely to be HIV positive than males (p >0.001)

3.4 HIV- Status:

The HIV status as classified by the dataset included analysis of HIV-positive, HIV- negative, HIV suspected, and HIV unknown.

HIV- positive*:*

From the dataset, 49.5% of the cases were HIV- positive, 15.5% were HIV- negative, 7.7% of the cases had suspected HIV, and 24.4% HIV status unknown. 2.9% of the values indicative of the HIV status were missing from the dataset.



Graph 9: HIV-status of deceased patients 2006-2009

2006: 52.2% of patients were HIV- positive; 18.4% of patients were HIV-negative; 7.8% of patients were suspected of being HIV-infected; and 21.6% of patients presented with an unknown HIV status.

2007: 46.7% of patients were HIV- positive; 14.5% of patients were HIV -negative; 8.9% of patients presented being suspected of HIV; and 23.6% of patients presented with unknown HIV status.

6.3% of the cases in 2007 were invalid.

2008: 49.6% of patients were HIV -positive; 15.5% of patients were HIV- negative; 7.3% of patients were suspected of being HIV-positive and 23.3% of patients presented with unknown HIV status.

4.3% of the cases in 2008 were invalid.

2009: 49.1% of patients were HIV- positive; 13% of patients were HIV- negative; 6.6% of patients were suspected of being HIV-positive; and 26.4% of patients presented with unknown HIV status. 4.9% of the cases in 2009 were invalid.

There was no significant trend for the presentation of HIV- positive patients. However, there was a clear decrease in the number of patients presenting with a confirmed HIV-negative status over the four year period.

Unknown HIV- status increased over the four year period.

3.5 CD_4-count:

From the dataset, 12050 cases representing 75.2% of the data were elegible for a CD_4 –count under the South African HIV Guidelines; however only 4005 CD4 counts were available for analysis.

Median CD_4-count is 44 cells/mm^3 IQR 16-104

Table 9: CD_4 - count and frequency by categories

CD4 Count	Frequency

<1	10
<10	83
<50	482
<100	**532**
<150	462
<200	340
<250	373
<300	196
<350	283
<400	280
<450	118
<500	66
>500 aggregated	780

3.6 Antiretroviral therapy:

Table 10: cART-eligibility by CD_4 -criteria and cART coverage

	Number of confirmed HIV positive patients	Patients on ART at time of death irrespective of CD_4-cell count	Patients eligible for cART by CD4 criteria alone not receiving treatment (CD_4<200 cells/mm^3)
2006	2381	226	1101
2007	2008	238	758
2008	1961	284	733
2009	1578	281	556

In 2006 of the 2381 HIV-positive confirmed patients 226 received ART at time of death (9.49%). The average CD_4-count for those on cART was 110 cells/mm. A total of 1101 patients (46% of total HIV-positive patients) with a documented CD_4-count of less than 200 cells/mm^3 were not receiving cART at time of death.

In 2007 of the 2008 HIV-positive confirmed patients 238 received ART at time of death (11.8%). The average CD_4-count for those on cART was 98 cells/mm. A total of 758 patients (37% of total HIV-positive patients) with a documented CD_4-count of less than 200 cells/mm^3 were not receiving cART at time of death.

In 2008 of the 1961 HIV-positive confirmed patients 284 received ART at time of death (14.5%). The average CD_4-count for those on cART was 102 cells/mm. A total of 857 patients (43% of total HIV-positive patients) with a documented CD_4-count of less than 200 cells/mm^3 were not receiving cART at time of death.

In 2009 of the 1578 HIV-positive confirmed patients 281 received cART at time of death (17.8%). The average CD_4-count for those on cART was 106 cells/mm. A total of 556 patients (35% of total HIV-positive patients) with a documented CD_4-count of less than 200 cells/mm^3 were not receiving cART at time of death.

The data sheet did not account for timing of ART initiation, we therefore are unable to comment on the timing of ART initiation and subsequent death.

When comparing the period of 2006 and 2007 with the period 2008 and 2009, the number of cART eligible patients on cART increased significantly (p=0.0001)

The above is limited in that only those patients who were documented HIV-positive with known CD_4-counts were included in the 2-tailed Fischer exact test analysis

3.7 Causes of death:

	2006		2007		2008		2009

This section ranks the top(>75%) primary causes of death. These are based on the ICD-10 codes assigned to the causes of death recorded on the data sheet

Percentage of cause of death represented:

2006: 78%

2007: 88.58%

2008: 84.85%

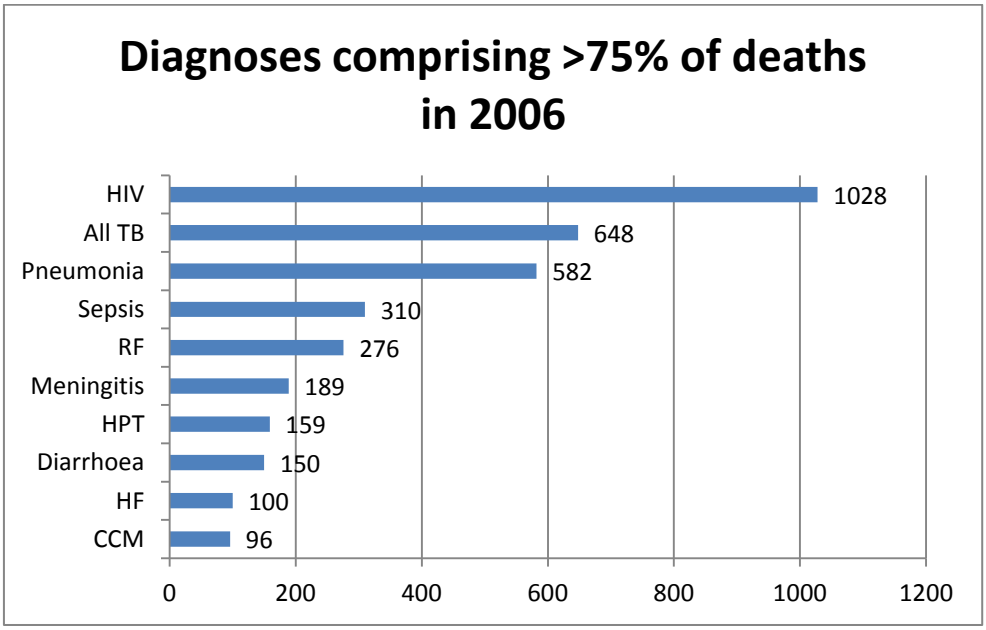
2009: 80.89%.

Table 11: Diagnoses representing >75% causes of death by year 2006-2009

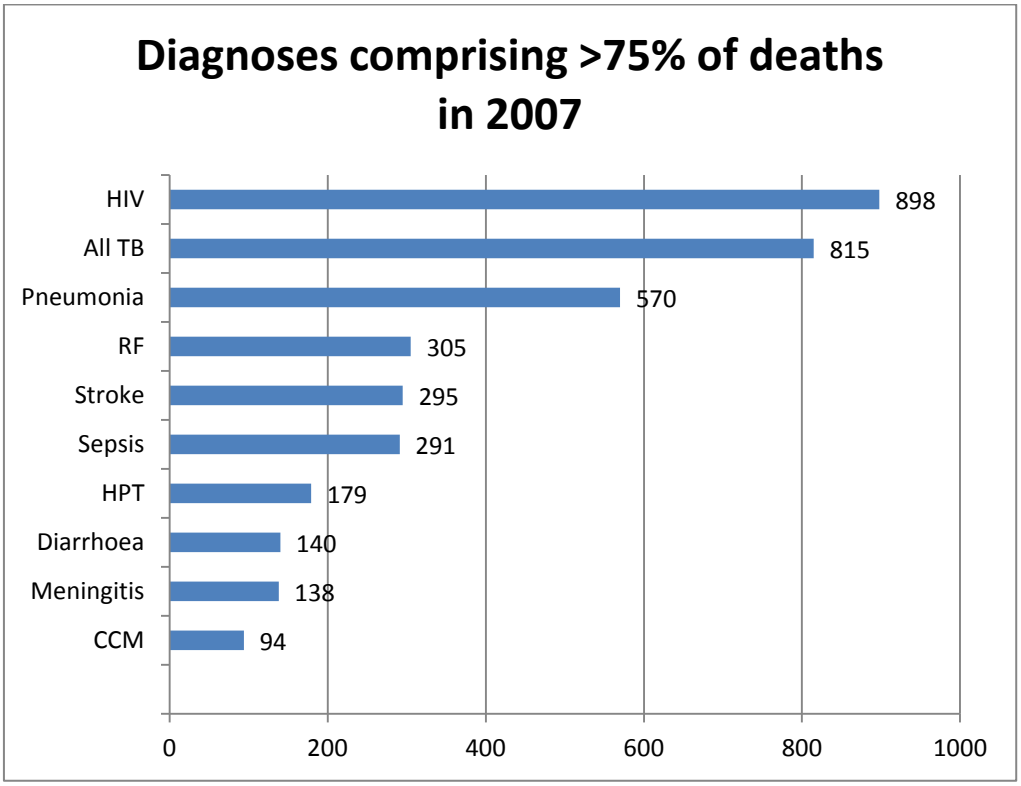
1	HIV unspecified 20.6%(n=1028)	1	HIV unspecified 20.9% (n=898)	1	HIV unspecified 21.7% (n=858)	1	HIV unspecified 20.1% (n=675)
2	Pneumonia unspecified 11.6% (n=582)	2	Pneumonia unspecified 13.2% (n=570)	2	Pneumonia unspecified 13.2% (n=520)	2	Pneumonia unspecified 13.4% (n=431)
3	PTB confirmed 6.5% (n=325)	3	Renal failure unspecified 7.1% (n=305)	3	Septicaemia 7.5% (n=298)	3	Septicaemia 9.4% (n=302)
4	PTB unspecified 6.2% (n=310)	4	Stroke unspecified 6.9% (n=295)	4	PTB confirmed 7.0% (n=277)	4	Renal failure unspecified 7.9% (n=255)
5	Septicaemia 6.2% (n=310)	5	PTB unspecified 6.8% (n=293)	5	Acute gastroenteritis 6.0% (n=237)	5	PTB confirmed 6.9% (n=222)
6	Renal failure unspecified 5.5% (n=276)	6	Septicaemia 6.8% (n=291)	6	Stroke unspecified 5.2% (n=207)	6	Stroke unspecified 6.1% (n=196)
7	Meningitis unspecified 3.8% (n=189)	7	PTB confirmed 6.5% (n=279)	7	Renal failure unspecified 4.8% (n=190)	7	TB of other organs 4.9% (n=156)
8	Hypertension 3.2% (n=159)	8	Hypertension 4.2% (n=179)	8	Meningitis unspecified 4.5% (n=177)	8	Hypertension 4.2% (n=134)
9	Acute gastroeneritis 3.0% (n=150)	9	Acute gastroenteritis 3.3% (n=140)	9	PTB unspecified 4.2% (n=167)	9	PTB unspecified 4.0% (n=130)

10	Heart failure 2.0% (n=100)	10	Meningitis unspecified 3.2% (n=138)	10	Hypertension 3.2% (n=128)	10	Meningitis unspecified 3.0% (n=98)
11	Cryptococcal meningitis 1.9%(n=96)	11	TB of other organs 3.0% (n=129)	11	TB of other organs 2.7% (n=108)		
		12	TB of CNS 2.6% (n=114)	12	Cryptococcal meningitis 2.4% (n=93)		
		13	Cryptococcal mengitits 2.2% (n=94)	13	TB of the CNS 2.3% (n=90)		

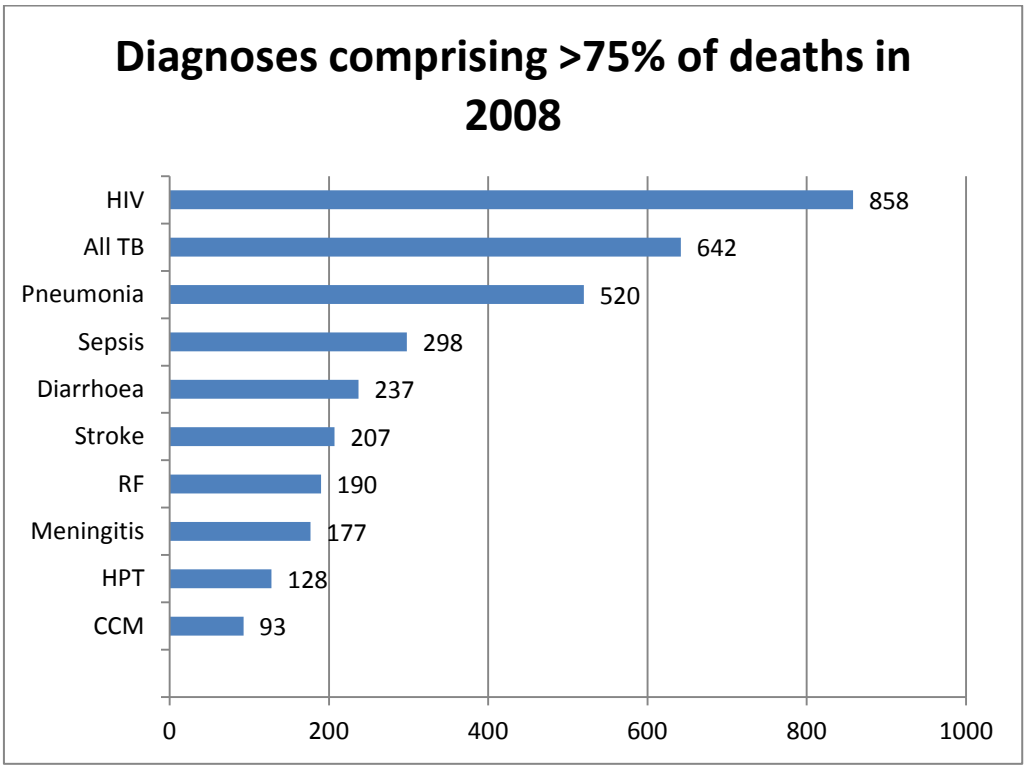
Graph 10 to 13 shows the causes of 75% of deaths with all TB aggregated into single category.



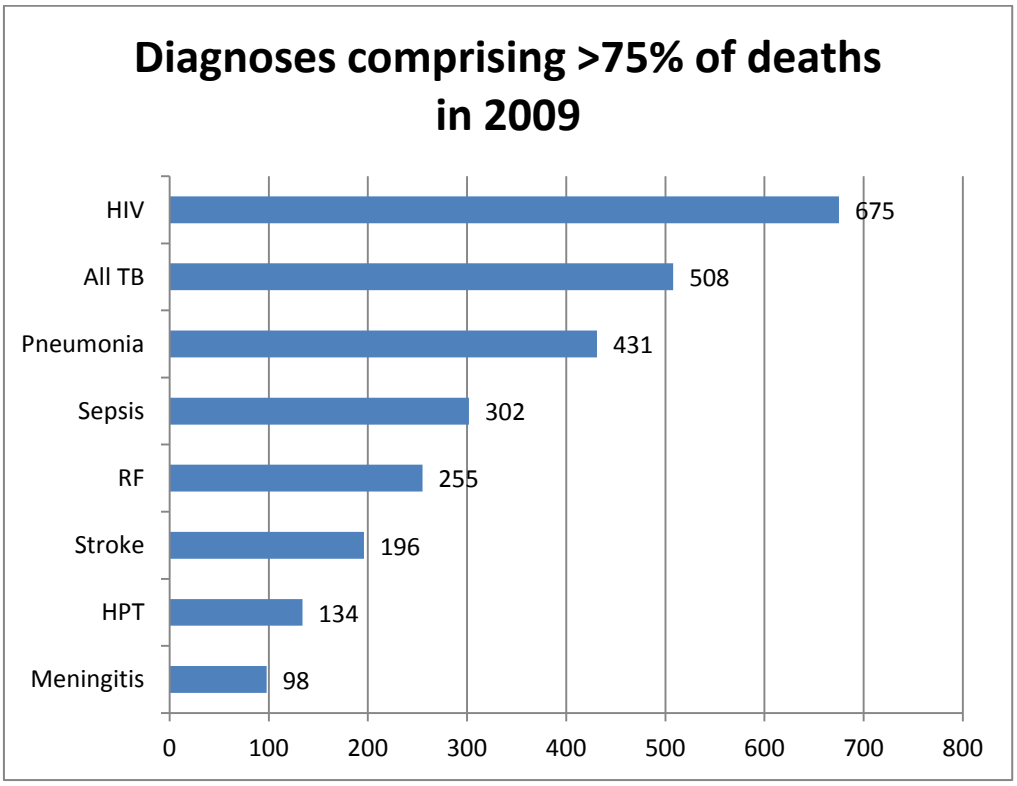
Graph 10: Causes responsible for >75% of deaths in 2006



Graph 11: Causes responsible for >75% of deaths in 2006



Graph 12: Causes responsible for >75% of deaths in 2008



Graph 13: Causes responsible for >75% of deaths in 2009

As the database included both primary as well as contributory or secondary causes of death for each individual patient, a principle components analysis (PCA) was conducted at a 0.05 significance level, to determine the loadings of numerous causes of death and to isolate the highest contributing cause to the primary listed causes of death from the period 2006-2009. From 2006 to 2009, where not reported as the primary cause of death, the only conditions found to be significant ($p<0.05$) contributors to the primary reported causes of death were: Unspecified HIV-disease (ICD-10 code B24) and tuberculosis.After non-specific HIV-disease, tuberculosis contributed significantly as a cause of

death. No contributory causes of death as recorded in the data base were identified as significant contributors to mortality.

Correlation coefficients and cause of death:

HIV positive: Infectious r = 0.112 p> 0.0001

Non-infectious r = -0.83 p= 0.579

The probability of a non-infectious cause of death decreased non- significantly with a positive HIV status.

HIV negative: Infectious r=0.083 p=0.74

Non-infectious r = 0.298 p=0.001

HIV-negative status is significantly associated with non-infectious cause of death.

HIV status and age were confounders when analysing association between sex and cause of death. When controlling for HIV status and age no association was found between sex and cause of death.

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4 LIMITATIONS

The data collection relied on the medical consultants completing the data sheet at the time of issuing death certificates, this is done routinely every weekday morning, the death certificates for patients who die on weekends are usually completed on the following Monday. At times death certificates may be completed by registrars at the request of family or the mortuary staff, registrars do not complete the data sheet, thus not all deaths were captured, the practice of registrars completing death certificates increased in 2009 and may be a contributing factor to the lower number of deaths reported in The Department of Medicine data base when compared to the data from Medicom. The number of medical admissions used as the denominator for the crude mortality rate is accurate and the high mortality

rate seen suggests that it is unlikely that a large number of deaths were excluded. The cause of death was assigned by a medical consultant and determined by reviewing the patient file and results, different consultants may have put in a varying amount of effort in trying to determine the most likely cause of death. Not all results such as microbiological cultures and histology were available at the time of completing the data sheets and the only outstanding results that were followed up and later entered into the data base were HIV and CD_4 cell count results. This may have led to an under- representation of diagnoses that are dependent on results of outstanding investigations.

While only the primary cause of death was included in the analysis, consultants completing the data sheets could assign multiple causes of death to a single patient such as renal failure and diabetes. A principle components analysis using all contributing causes of death did however not identify any other major contributors to cause of death, analysis was thus restricted to the primary cause of death as assigned on the data sheet.

5 STRENGTHS

CHBAH was the only public inpatient health facility for the Soweto population during the study period. The deaths occurring at CHBAH is thus representative of a large urban population in South Africa.

The paper-based post mortem diagnoses were determined by Internal Medicine consultants. The datasheet was not an official document removing the limitations of Death Certificates when it came to recording HIV status and HIV related causes of death.

The study period was of a four year duration which is sufficiently long enough to sufficient duration to allow for the benefits of cART to be demonstrated if they existed.

6 DISCUSSION

The HIV epidemic in South Africa resulted in an increase in mortality and a decreased median age of death for the population. This pattern changed after the introduction of antiretroviral therapy to the public sector. Median age of death reached its nadir of 42.6 years in 2004 and thereafter steadily started to increase year on year and mortality started to decrease from 2007. This analysis from the largest hospital in the Southern hemisphere covers a critical time period in the

changing epidemiology of mortality in South Africa. The data presented in this study showed a significant year on year decrease in crude mortality in medical inpatients from 113/100000 admissions in 2006 to 79/100000 admission in 2009. Department of Medicine database only captured a possible 61% of deaths in 2009 and the low crude mortality rate for this year may reflect missing data, however, when using the maximum possible number of deaths from the Medicom database, a significant year on year reduction in mortality rate from 159/100000 in 2007 to 130/100000 in 2009 is still seen. This decrease occurred in medical patients alone and suggests that the improved death rate seen at a population level is due to improved survival in medical patients, this may have been due to the introduction of cART or other changes that occurred at CHBAH during this time period such as the introduction of reviews of possible preventable causes of death and the opening of a dedicated medical highcare area in the admissions ward.

Twenty five percent of all the ages were below 34 years, 50% of all the ages were below 45 years, and 75% of ages below 60 years.

Thus, 75% of all the cases analysed were below 60 years of age, while 25% of the cases were above 60 years.

Half of the deceased were HIV-positive and the results clearly indicates that the greatest burden of HIV deaths occurred in people younger than 40

years of age, the economically most active part of society with three quarters of deaths occurring in persons younger than 60 years.

The mean age of death for the entire study population was 47.7 years, which is lower than the average life expectancy of South Africans in 2005. This is unexpected as the dataset excluded maternity and trauma-related deaths which occured at a younger age, this was also unexpeced as Soweto is an an urban population in the wealthiest province of South Africa with excellent access to healthcare.

The peak age of death for females moved from the age category 30-34 years in 2006 to 35-44 years in 2009 which is consistent with the changes seen at the population level. There was no change in the peak age category at death for males over the study period and probably reflects the low numbers of males within the HIV programme, making this an important group to target for future HIV campaigns. When disaggregating the data by HIV-status, mean age at death for HIV-positive patients showed a significant increase from 38 to 40 years. No significant increase in the mean age for HIV-negative patients was seen suggesting that the increase of age at death in this study was likely due to interventions in the HIV-positive group of which the most important was the roll-out of cART.

Throughout the study period HIV-positive females died at a significantly younger age than HIV-positive males reflecting the younger age of HIV-acquisition in females. In the HIV-negative group

females died at a significantly older age than males in 2006 and 2007, whilst no significant difference was observed in 2008 and 2009. The reversal of the normal sex-mortality pattern could not be explained and requires further investigation.

Both HIV-positive males and females died at a significantly younger age than the HIV-negative group. An estimated 101478 years of life were lost due to HIV in females of this population and 65008 years of life were lost in HIV-positive males despite the roll-out of cART which was delayed in South Africa.

Within the study being female increased the likelihood of being HIV-positive, once again this follows the epidemiology of HIV-infection in sub-Saharan African.

Of concern in this study is that over time while the proportion of confirmed HIV-status remained constant, there was an increase in the proportion of patients with an unknown HIV status, this despite a widespread campaign by the Department of Health to promote HIV counselling and testing during this period. This may be due to stigma of HIV-positive status with widespread public testing only gathering momentum after President J Zuma publically tested for HIV in April 2010. The percentage of known HIV-status in the study population is however higher than the 30% found in KZN at this time.[24] This study population comprised of medical inpatients and was not a population-based cohort and the levels of known HIV-status are surprisingly low given the fact that HIV-testing could be considered an important part of the medical workup of a patient in Southern Africa. The decrease in HIV-testing in this study

population over the four year period may reflect changing patterns of healthcare worker testing in the inpatient population.

Or this may represent a group of patients unwilling to test for HIV both in their pre- and postmorbid state, now presenting to the healthcare facility with HIV-associated disease. If this trend is seen to continue in future analysis it requires in root cause analysis and appropriate interventions.

When looking at the immunological status of the HIV-positive deaths while a large number died with CD4-counts greater than 500 cells/mm^3 the low median CD4- count of 44 cells/mm^3 shows that the majority of HIV-positive patients who died presented with advanced HIV-disease.

South African Antiretroviral guidelines at the time advocated initiation of cART when the CD_4- count was less than 200 cells/mm^3 or if the patient presented with an AIDS-defining illness.

In this study the most frequently occurring CD_4-count at time of death was less than 100 CD_4 cells per cubic millimeter.

Although when comparing the period of 2006 and 2007 with the period 2008 and 2009, the number of cART- eligible patients on ART increased

significantly with only nine percent eligible patients receiving ART in 2006 which increased to 17% by 2009 (Table 10). Patients initiated on cART are expected to have better survival and a sample of deaths may result in bias towards patients that are HIV-positive and not receiving cART. A further bias is that patients may have presented too ill to give a history of cART, the medical attendant may not have taken previous medical history and the patient may not have disclosed the history of antiretroviral use.

The data sheet did not account for timing of ART initiation, we therefore are unable to comment on the timing of ART initiation and subsequent death.

A country's mortality patterns reflects its developmental status, Population level data suggest that South Africa is in a period of transition with non-communicable disease-related mortality increasing and communicable disease-mortality decreasing. However due to the HIV epidemic this picture is mixed with HIV and tuberculosis remaining important contributors to mortality.

At a population level the top two causes of death in South Africa in 2009 were TB(12%), pneumonia(7.5%) with HIV only ranking at seventh and comprising 3.1% of deaths. This study showed HIV to be the number one cause of death at 20% followed by tuberculosis then pneumonia. The higher rate of HIV-deaths is probably due to underreporting at population

level where HIV-status is often omitted from death certificates. These results are closer to estimated HIV deaths.[300]

Causes of death that featured prominently in this study and not at a population level was septicaemia, renal failure and meningitis. This may be due to the sicker patients being more likely to be admitted to a healthcare facility. Over the four year period the top three causes of death: HIV, tuberculosis and pneumonia did not change in neither ranking nor the proportion contribution to mortality. Patterns that may reflect an increased in population cART coverage were diarrhoea and cryptococcal meningitis moving out of the list of conditions contributing 75% of deaths. The only evidence of an increase in non-communicable disease was an increase in cerebrovascular disease-related deaths in this study period. While diabetes is a prominent disease in this population and ranked fifth at a population level it did not enter into the list of major contributors to mortality and was not identified as an underlying or secondary cause either. The reason for could not be ascertained.

7 The causes of death identified in this study suggest that HIV continued to have a significant impact on mortality and that the population was not yet going through epidemiologic transition to a pattern suggesting improved developmental status.CONCLUSION

To my knowledge, this is the largest analysis of mortality in South Africa to date that has not relied on death certificates with their known inaccuracies

but rather used confidential record- based post mortem analysis by medical consultants.

This study showed a decrease in mortality for medical patients over the time period 2006-2009. Age of death increased significantly in the HIV-positive group of patients with no change observed in the HIV-negative population. While infectious diseases remained the major contributors to death, the decrease is diseases associated with decreased immunity suggests that increased access to cART has impacted positively on the mortality patterns in this population.

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9 ABBREVIATIONS

AIDS	Acquired Immune Deficiency Syndrome
cART	Combination Antiretroviral therapy
CD_4- count	Cluster of Differentiation Count
CHBAH	Chris Hani Baragwanath Academic Hospital
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
HIV	Human Immunodeficiency Virus
ICD-10	International Classification of Disease
IRIS	Immune Reconstitution and Inflammatory Syndrome
MAC	Mycobacterium Avium Complex
WHO	World Health Organization
NGO	Nongovernment Organisation
p/a	Per annum
STI	Sexually Transmitted Infection
TB	Tuberculosis