THE COST, CAUSE AND PLACE OF DEATH IN PATIENTS DYING WITH HIV/AIDS AND WHO HAVE ACCESS TO ART

Degree: M Phil Palliative Medicine

Principal Researcher: Dr Lize Hellström

Supervisor: Dr Andrew Boulle

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Abstract

THE COST, CAUSE AND PLACE OF DEATH IN PATIENTS DYING WITH HIV/AIDS AND WHO HAVE ACCESS TO ART.

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Introduction

There is still no cure for HIV/AIDS and at present very few patients in Sub-Saharan African (SSA) countries have access to ART. It is therefore not surprising that no studies could be found depicting the cause of death after treatment with ART in SSA. ART will be more freely available in the public sector from 2004 and it is therefore important within the realms of a restricted health budget that the diagnosis, cost and level of care of terminal patients dying in SA during ART should be explored.

More information especially in the African setting is needed to understand how the use of ART has altered the clinical course of HIV/AIDS and changed the cause of death, especially in a TB-endemic country, and how this can be translated into interventions targeted at the redefinition of end-of –life care for persons living with HIV/AIDS.

Methods

This study involved screening the records of both the AfA and Medscheme databases of all patients registered with Aid for Aids (AfA) as part of Option 020, Bonitas Medical Aid in South Africa and included all patients receiving antiretroviral treatment (ART), patients not eligible for ART (CD4 > 250 cells/μL) and patients who elected not to start treatment at the time of their death. The study aimed to explore the causes of death, the costs involved in these deaths as well as the places where these deaths occurred.

Results and Conclusions

It is clear from this study that the fast progression to death was due to:

1. The low initial CD4 counts (median = 63 cells/μL) and

2. The high proportion of WHO stage 4 diagnoses at the time of registration. A significant finding in this study was the large proportion of men dying at home (35.6%) in comparison to women (27%), By comparison more women died in ICU.

A significant percentage of patients did experience high technology biomedicine at the time of death, evident from the 20% of patients dying either in ICU or High Care. A total of 63% of patients died in hospital, whilst those patients who seemed to opt out of care, died at home. Choice as a form of autonomy in palliative care seemed absent in terms of the place of death.

Patients presented very late in the disease process and therefore the cause of death in the SA setting is predominantly due to ADE and ART related causes in compliant patients who have responded immunologically and virologically prior to death. The 3.2% of causes of death related to ART is significant, especially since 2.2% of patients died due to lactic acidosis and received both d4T and ddI. TB was found to be a secondary diagnosis in 38% of patients where a diagnosis of TB was confirmed as either positive or negative.

Costs were raised in the last six months prior to death, with a 700% increase in the last month of life in comparison to the average costs. This increase is predominantly due to increased hospitalization. In the case of HIV/AIDS hospitalization in the acutely terminal stage therefore amounts to a much higher increase in average costs than that seen in cancer-related deaths, which amounted to an average increase of 300% in the last month of life. Using hospitalization cost effectively in terminal HIV/AIDS is therefore a high priority.

Recommendations

1. *Identify patients earlier in the disease process and provide active rehabilitation and urgent preparation to start ART.*
2. *Clinical guidelines are needed for effective end-of-life-care.* Good palliative care should be provided as part of holistic patient care and not instead of hospitalization in ensuring a good death
3. *Accurate diagnosis and treatment of ART related side-effects should be a priority when caring for patients accessing ART.*
4. *Cost effective and accurate diagnosis and management of ADE, IRIS and TB early within the disease process is crucial to reduce cost, in-effective care and mortality at the end of life.*

Glossary

ADE – AIDS Defining Events

AfA – Aid for AIDS

AFB – Acid Fast Bacilli

AIDS – Acquired Immune Deficiency Syndrome

ADE – AIDS defining Events

ARE – Acute Renal Failure

ARI – AIDS Related Infection

ART – Antiretroviral Therapy

CDC – Centre for Disease Control and Prevention

COD – Cause of Death

H/C – High Care Unit

HIV – Human Immunodeficiency Virus

HRE – HIV related Event

ICU –Intensive Care Unit

IQR – Inter Quartile Range

IRIS – Immune Reconstitution Inflammatory Syndrome

K/S – Kaposi Sarcoma

NHL – Non-Hodgkin Lymphoma

NNRTI – Non- Nucleoside Reverse Transcriptase Inhibitor

NRTI – Nucleoside Reverse Transcriptase Inhibitor

OI – Opportunistic Infection

OTC – Over the Counter

PCP – Pneumocystis Carinii Pneumonia

PI – Protease Inhibitor

PLWHA – People Living with HIV/AIDS

PTB – Pulmonary Tuberculosis

PWA – Person with AIDS

SSA – Sub-Saharan Africa

SA – South Africa

TB – Tuberculosis

TBM – Tuberculous Meningitis

VCT – Voluntary Counseling and Testing

WHO – World Health Organization

WHOQOL - World Health Organization's Quality of Life Instrument

?COD – Unknown/Uncertain Cause of Death

Chapter I

1. *Introduction*

1.1 General

This study involved all patients registered with Aid for Aids (AfA) as part of Option 020, Bonitas Medical Aid in South Africa and included patients receiving antiretroviral treatment (ART), patients not eligible for ART (CD4 > 250 cells/μL) and patients who elected not to start treatment at the time of their death. The study aimed to explore the causes of death, the costs involved in these deaths as well as the places where these deaths occurred.

As all patients had access to ART once registered with the disease management company, AfA, most patients would have received ART, once the criteria for starting treatment were met. The facts that the patient had a choice to register with AfA and had a choice to start treatment were kept in mind as important factors during the research into understanding the stage of the disease at the start of receiving ART.

A quantitative, descriptive study was performed by screening medical records of a group of patients registered with the same Disease Management Company (AfA). This group was chosen as they formed the largest homogenous patient group managed by AfA. Approval to gather data and to do research was received from the Director of Medscheme, the Director of AFA, and the Chairman of the board of trustees at Bonitas Medical Aid. They were satisfied that this analysis would contribute to planning for future provision of services.

There is still no cure for HIV/AIDS and presently very few patients in Sub-Saharan African (SSA) countries have access to ART. It is therefore not surprising that no studies could be found reflecting the cause of death after treatment with ART in SSA. ART has become more freely available in the public sector since 2004 and a restricted health budget therefore necessitates an exploration of the diagnosis, cost and level of care of terminal patients dying in South Africa whilst receiving ART. In addition, specific attention should be focused on those patients who are dying while they undergo seemingly well-controlled treatment with undetectable viral load and raised CD4 counts. The increasing burden of cumulative HIV-related morbidity and treatment-related toxic effects over time within the setting of a developing country needs to be explored. Another question to be answered is what influence the high incidence of tuberculosis has on mortality outcomes.

Many studies confirm that the last months in the life of cancer patients, trauma patients and elderly people are expensive. The last month of life is the most expensive of all. Another general finding is that expenses become less as patients become older. However, the HIV/AIDS patient profile is predominantly that of young economically active people with or without minor dependants. They do not want to die, especially as most illnesses are potentially curable. The assertion that the costs of aggressive medical treatment for dying patients (in the last-year-of-life) are disproportionately high needs to be explored. This should be explored with the following dichotomy in mind: on the one hand there is the need for a "good death" (in palliative terms) and on the other hand, there is the need for disease-specific curative management..

1.2 Clarification of Private Health Care Funding in SA

According to Benatar (2004), privately funded health care in SA cares for approximately 18% of the population at present with an annual budget of 60% of all health care spending. Managed health care is provided to Bonitas by Medscheme and ensures that scheme rules are adhered to, authorization for hospital admission is provided and that case management is applied within the benefit structure for individual illnesses. In order to access ART, all the Bonitas patients who are diagnosed with HIV/AIDS must register with AfA, the disease management company under the auspices of Medscheme Holdings, contracted to provide this service. Registration entails the completion of a medical report with full clinical and laboratory details by the medical provider chosen by the patient, a consent form signed by the patient or legal guardian in the event of a child and a section with contact details of both the patient and the provider. Both the patient and the medical provider are regularly reminded to update information and to forward new results to AfA. This information is stored on a data base which is regularly updated. This is one of the data bases which were used to extract data electronically and was screened manually to further clarify data in this research.

In addition Medscheme has a call centre which provides authorization for hospital admissions. Case managers at the contracted hospitals gather clinical data which is then electronically loaded on to another database for major medical interventions. This is the second database from which data was gathered both electronically and manually for use in this research.

Payment will be made directly to the provider only if all the conditions in terms of authorization, registration and benefit limits have been adhered to. This process facilitates accurate and timeous provision of high quality data.

1.3 Palliative Care and HIV/AIDS

Although this study cannot provide guidelines for the implementation of effective palliative care, it is important to understand why, where and at which cost patients are dying with HIV/AIDS. This knowledge will enable facilities to plan, develop expertise and implement interventions for future provision of palliative care as defined by the WHO definition (short version) by Doyle (2001):"*The active total care of patients whose disease is not responding to curative treatment.*" Van Niekerk (2003) stated "*...the provision of ART is the most important palliative care treatment!*" It is within this context that this study will explore the medical aspects of care preceding death.

Chapter 2

2. *Literature Search*

2.1 Cause of Death

The natural course of HIV/AIDS - when anti-retroviral therapy (ART) is not affordable - is well known. Where people do receive ART however, we do not know yet at what stage and from what cause they would die in the African setting. ART has changed the cause of death, although the disease still remains incurable.

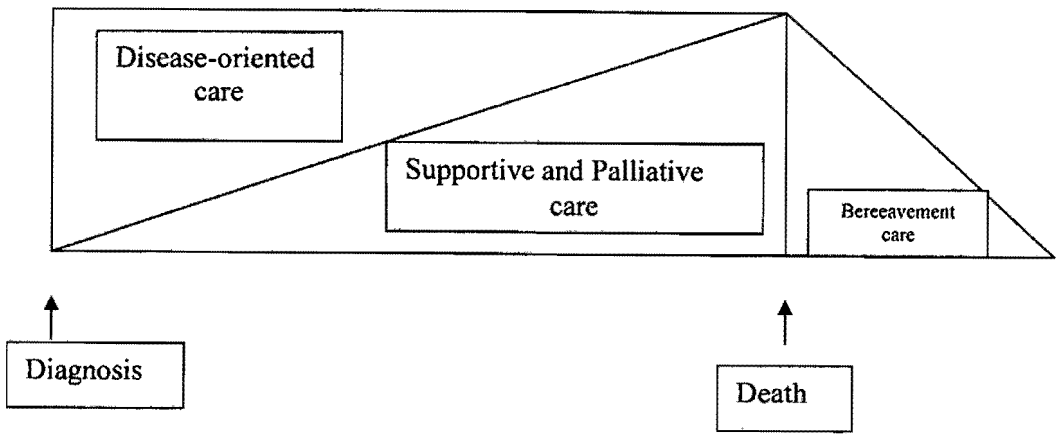
Five studies done in the northern hemisphere: New York by Sansone (2000), Europe by Mocroft (2002), France by Bonnet (2002), ATHENA by Van Sighem (2003) and Baltimore-USA by Moore (1999), found that the overall mortality rate declined and that the number of treated patients who had died because of sepsis and opportunistic infections, decreased significantly. These studies also showed that deaths due to hepatic-related problems and myocardial infarcts increased significantly. Non-Hodgkin Lymphoma (NHL) is the only HIV-related cause of death (HRE), which remains a major cause of death in all 5 studies mentioned above. Intravenous drug users have a higher incidence of death than the other transmission groups predominantly related to hepatic problems and specifically Hepatitis C, as described by Rosenthal (2003).

More information, especially in the African setting, is needed to understand how the use of ART alters the clinical course of AIDS and how it changes the cause of death. This information is especially needed in TB-endemic countries before end-of-life care for persons living with AIDS can be redefined.

2.2 Palliative Care

The WHO defines palliative care as the active total care of patients who suffer from a disease that is not responsive to curative treatment. (Van Niekerk, 2003). The goal of palliative care is to ensure quality of life. ART is essentially the best palliative treatment available to people living with HIV/AIDS. AIDS patients who are terminally ill and who do not have access to ART are sometimes inappropriately treated or denied investigations or treatment when they present with potentially reversible disease. Deeks (2001) found that patients treated with ART will also present with further complications of HIV disease, especially where drug resistance has occurred and the goal of therapy changes from viral

suppression to salvage therapy. Maartens (2001) concluded that these patients will still benefit from ART, in part because the mutations which confer resistance render the virus less fit. Guidelines proposed by Maartens (2001) on instituting palliative care apply to patients with a CD4< 50, a poor quality of life (Karnofsky scale < 4) and no reversible illness and for whom ART is not a treatment option. Another article on palliative care in HIV/AIDS by Dinat (2003) suggests that the palliative component of care should be incorporated at diagnosis and not only at the physical end of life. An integrated model for chronic progressive illness which includes both curative and palliative care from diagnosis and onwards is displayed below. (Source: WHO. Publication #1100804)



Van Der Loeff (2002) also report that the Karnofsky scale is a good predictor of mortality where patients are not on ART. It is, however, evident form the studies by Sansone (2000), Mocroft (2002), Bonnet (2002), Van Sighem (2003) and Moore (1999), that the rate of deaths caused by AIDS-defining events (ADE) is much lower where patients do receive ART. It is uncertain if these guidelines apply to end-stage ART patients as well, or what is meant by the diagnosis of end-stage AIDS in the context of ART?

2.3 Risk Factors

The ATHENA study by Van Sighem (2003) showed in accordance with previous findings that clinical markers associated with a higher survival probability and a slower progression to AIDS, are

- high baseline CD4 cell count
- absence of CDC category–C or ADE before the start of ART and
- no or limited prior treatment with antiretroviral drugs.

Age and intravenous drug use are significant predictors for progression towards death, although these do not signify progression towards AIDS. In addition Van Sighem (2003) showed that continuous ART is associated with slower progression to death and AIDS in comparison with interrupted ART.

Studies by Van Der Loeff (2002) and Morgan (2002) reported higher mortality rates pre-ART, as well as those of inpatients on ART, in older patients. Women die of ADE more often than men. According to studies by Van Der Loeff (2002) and Bonnet (2002) women also had a lower CD4 count at the time of diagnosis.

2.4 Place of Death

According to the Bordeaux study by Bonnet (2002), 61% of deaths occur in the general ward, 14% in ICU, 10% in a palliative ward and 15% at home. A study by Uys (2003) on the aspects of care in PWA who do not have access to ART, reported that 52% of patients died at home. Good deaths are correlated to the place where patients die and the largest percentage of clients whose deaths were reported to have been 'good deaths', had died at home (61% of deaths).

The reason for admission of patients in this group to hospital is one of three:

- the care became too difficult for the caregiver
- the family believed that they had not done enough if they did not take the patient to hospital or
- there were certain symptoms that the family could not control such as difficulty in breathing, intense pain and multiple fistulas and wounds.

2.4.1 Prognostication related to the place of death

Drought (2002) stated that it is becoming exceedingly difficult to leave this life without encountering biomedicine. Today, as opposed to 30 years ago, we can choose the approach to care at the end of life if the following three assumptions are met:

- if the timing of death can be predicted
- if patients and providers recognize choice as a component of treatment and
- if individuals can confront and consider their own mortality and their physical decline in an engaged and rational manner.

Mak (1999) identified the following elements of a good death: comfort, openness, completion, control, optimism, readiness and choice of location. Even with the use of ART,

AIDS remains an incurable disease. Furthermore, the role of palliative intervention - where patients do not respond to ART any more - is not clear. Better communication might diminish the contradiction between wanting everything that can be done (expensive), and wanting an idealized good death (preferably at home).

Prognostication in terminal HIV/AIDS is difficult. The majority of patients is young and pursue more aggressive curative treatment late in the disease process. HIV/AIDS is furthermore a multi-system disorder with variable presentation and curable components within a progressive and fatal disease process, leading to uncertainty and indistinct boundaries between care and palliation. The following biomedical markers as documented by Afessa (2000) for hospitalized patients relate to poor prognosis in terminal AIDS:

- Aids-defining illness e.g. PCP
- Need for ventilation
- Low serum albumin level
- High Apache 2 score
- Pneumothorax complicating ventilation
- Multiple organ Failure >= 3 organs > 3 days

Predicting end of life is difficult. In the context of ART it is important to understand the extent to which palliative options are considered with the consequent rational use of resources and opportunities for a good death. Van Niekerk (2003) stated that in accordance with the World Health Organization's (WHO) definition of palliative care, providing ART is the most important palliative care treatment in addition to good pain and symptom management for patients with late stage HIV/AIDS. It is within this context that the palliative care principle needs further development within the South African context.

2.5 Costs

The costs related to ART and early interventions are well known, but the costs involved in the caring of a patient during the last months of his or her life (after having benefited from ART) are not well studied, especially not in SSA. Gebo (1999) found that consistent with findings in other studies by Decock (2001), Torti (2003) and Krentz (2003), the costs related to hospital inpatient and community care were significantly lower after the introduction of HAART, but offset by the higher costs of the drugs and outpatient costs. Total care costs were stable or slightly lower in these patients on ART. Other studies have also shown a decrease in opportunistic illness and improved survival. However, the use of

new technology in future, such as resistance testing, as well as factors such as ART-related complications and longer survival, will also modify the costs in future. A wait-and-see-attitude exists at present. Whether the costs during the end of life (in the era of HAART) are merely increasing as dying is prolonged or whether these costs will become part of a chronic disease management scenario remains to be seen. Krentz (2003) found that the total health care average payments for inpatients with a CD4 cell count < 200 cells/μL were more than twice as high as the costs for early presenters. The HIV-related hospital care costs were 15 times higher for late presenters in the same study. However the non HIV-related hospitalization costs were 2x higher in the early presenters, where costs were incurred by HIV testing. The findings in a study by Rosenblum (1994) suggests that the convergence of HIV and tuberculosis has had an increasing effect on the cost (inpatient days) and morbidity/mortality. Costs in the last three months of life increased at least threefold, according to an Australian study by Beck (2001).

In a study by Wenberg (2004) the outcomes of care during the last six months of life in patients with chronic disease were studied in a population of 77 US best practice accredited hospitals. The conclusion was that greater frequency in the use of hospital, ICU and physician visits was associated with worse outcomes, higher costs and mortality. Patients' stated preferences to avoid deaths in hospitals were unfulfilled, whereas the local bed supply correlated to deaths in hospitals. Hospice enrolment did not lead to less ICU and physician visits, but was associated with fewer hospital deaths and deaths in ICU. Providing end of life care should be determined by the needs and wants of patients and not the capacity of the acute care system. In the setting of HIV/AIDS the development of World Health Organization's Quality of Life Instrument by WHOQOLHIV Group (2003), could help stratify and clarify patient's needs at the end of life. Rabow (2004) stated that physicians should perhaps listen more carefully in order to understand the perceptions of patients and their families regarding decisions about life-sustaining treatment, dying at home and the meaning of death.

From the literature it is apparent that little is understood in the South African context on the cause of death profile for HIV-infected adults in the era of ART, and on the extent to which this could impact on palliative care approaches for HIV, including the location of death. There is also a paucity of baseline data on the end-of-life costs (to the health care system) associated with HIV-deaths in this context.

The AfA program, by virtue of being having accumulated many years of experience, and having reasonably good information systems, provides an excellent opportunity to describe these parameters as a first step towards re-evaluating palliative care approaches for HIV in the ART era.

Chapter 3

3. Aims, Objectives and Methodology

3.1 Aims and Objectives

The study aims to describe the cost implications from the perspective of the health system for patients dying with HIV/ AIDS while they have access to antiretroviral therapy (ART) in the last six months of their lives and to characterize the places and causes of death.

3.2 Objectives

The following are the objectives of this study:

- to describe the study population
- to describe the clinical indicators at registration with AfA
- to define why and where patients with end stage AIDS on ART die
- to define the costs during the last 6 months for those dying with AIDS and
- to define the level of care that patients receive during the terminal phase, whether
  - in hospitals (ICU, high care or general wards)
  - in step-down care centers (hospice or accredited step-down care centre)
  - at home
- to describe the differences between gender in terms of the place and cause of death

3.3 Methodology

3.3.1 Study Design

This is a retrospective cross-sectional study.

3.3.2 Population

The Standard option (020) comprises about 80% of the Bonitas membership base (210 000 principle members) and is the second most expensive of the five options. These members are scattered around the country and work for over 3 500 different companies. Bonitas was founded in 1982 to cater for black civil servants. Black membership, on average, is still around 90% with the other race groups making up the balance of 10%. Membership varies. During 2003, for instance, principle members were 250 000.

Until 2002 Bonitas 020 membership contributions were income-based with the following annual limits.

1998 – R150 000

1999 – R250 000

2000 – R250 000

2001 – R500 000

2002 – R500 000

2003 – R700 000

These limits definitely affected the cost data when compared to schemes with unlimited total benefits.

Bonitas was one of the first schemes contracted to AfA. In 1998 it had an HIV disease program limit of R25 000 per beneficiary per year. During those early stages they had a three-year ruling, permitting only those patients who belonged to the scheme for more than 3 years or longer to register for the HIV benefit with AfA. This ruling was revoked by the beginning of 1999. The ART benefit was also limited, and is reflected in the data from 1998-2002 when most patients could only afford duel therapy. The first ART prices to drop by May 2001 were those of d4T (Zerit), ddI (Videx) and NVP (Nevirapine) and therefore most patients were started on or changed to this combination of drugs from mid-2001 onwards.

Data was gathered from the Medscheme and AfA data bases and therefore only include patients who died during the time period from 1998 – 2003. The year 1998 was chosen as this was when ART became available to most patients who qualified for medical intervention according to the AfA clinical guidelines.

Common characteristics:

- Life- threatening Illness: HIV/AIDS
- Belongs to the cohort of Bonitas Medical Aid Option 020
- Registered with HIV disease management program administered by AfA
- Time period within which death occurred: 1998 – 2003
- Age at death >18

3.3.3 Sampling

The range of outcomes is varied and difficult to anticipate, complicating the calculation of the sample size. Using one outcome, namely deaths related to AIDS-defining events pre- and post-ART (the initial study hypothesis), data from three published studies were used to estimate sample size.

Bonnet (2002): 85% vs. 48% (3)

Mocroft (2002): 93% vs. 73% (2)

Sansone (2000): 20,9% vs. 8,5% (1)

With alpha=0.05 and power=0.90, the required sample size to demonstrate the above differences ranges from 38 individuals per group to 186.

It was therefore decided to aim for a sample-size of 250 individuals. Sampling would be done by taking consecutive dying patients, working backwards from the end of 2003 until the sample size was reached. After piloting (see below) the formal analytical component of comparing two groups was abandoned in favour of a descriptive study of all deaths, and as such all eligible patients were included in the study, without sampling.

Cost data was extracted from the database in full and therefore sampling was not necessary. All the costs were available in excel format for editing and incorporation into the study.

3.4 Measurements

3.4.1 Outcomes measured

- First and last viral load and CD4 counts recorded
- Time period on ART since first CD4
- Description of treatment regimes utilized
- Cause of death
- Direct costs measured, according to Tolley and Gylmark:

  Drugs

  Outpatient/ inpatient clinical care

  Inpatient hospital care

  Community based care could not be measured as there was no funding structure available for this measurement

- Total costs in the last 6 months until death
- Hospitalization at the end of life in terms of:

  - level of care : either as 1. ICU/High care 2. General ward 3. Hospice or step-down unit and 4. Home

  - diagnosis: primary and secondary

  - number of inpatient days: in last 6 months, total inpatient days since registration and number of days during the last hospitalization prior to death

- Gender, race and age

3.5 Pilot Study

All instruments were piloted prior to formal data collection. The initial study was planned to compare two groups, with the following research question: "What are the implications regarding the financial cost, place of death and the cause of death in the last six months of life for patients dying with HIV/AIDS after significant benefit from ART compared to those not receiving ART?" The initial analysis of the pilot data indicated that the group who died after significant benefit from ART was very small in comparison to the total deaths. Early death within the first three months on ART, followed by poor compliance were the important reasons why patients did not have significant benefit from ART, as reflected by serial CD4 and viral load estimates. Sample size in the initial group would not have been met and it was therefore decided to revert to a descriptive study of the deaths recorded of patients during the period 1998 – 2003 and registered with the AfA disease management company. These deaths therefore include patients who 1. did not meet the criteria for starting on ART, 2. those dying shortly after registration and not on ART due to other complications, 3. those patients dying shortly after the introduction of ART and 4. those patients who were on ART for longer periods. A total of 783 deaths occurred during this time period.

3.6 Ethical Considerations

The data which was gathered for this research belongs to Medscheme. On signing the medical aid application form, patients give consent to Medscheme to retrieve their information from hospital and medical practitioners' records. All records are confidential documents and were treated as such in this study. As a part-time employee at Medscheme holdings, I had access to the password protecting the electronic data. On accepting the position, I had to sign a confidentiality clause and am therefore held responsible to respect it.

This study used unidentifiable data. Because it was not practical or in the deceased patient's best interest to obtain expressed consent, Section 4.2.2(b) of the Guidelines for Good Practice with regards to disclosing information without consent, was met.The data presented will not contain any personal reflection to names, medical aid numbers or other descriptions, which could identify individual patients. The data is therefore anonymous and will not cause any harm to the memory of the late patient or his/her family.

Ethics approval to continue with the research project was obtained from the ethical committee at UCT on May14, 2004; REC REF: 165/2004.

3.7 Data Management and Processing

Data was extracted from two different data bases (AfA and Medscheme data base) according to the measurement instrument as described above. This was received in a spreadsheet defining each incident per candidate from the date of registration with AfA until the date of death. A systematic search of each individual file was conducted from each data base and information was expanded accordingly. Data bases were compared for authenticity and only the reliable and most sufficient data was incorporated in the study material. Limitations existed where incomplete data was documented in terms of clarification of the diagnoses to the highest level, whether or not a diagnosis of TB was present and with laboratory results. The reason for these limitations was that the forwarding of this information was practitioner or patient dependant. In many cases only the first and last viral load and CD4 were available, and not the full testing history.

The diagnosis used was either:

- Those made by physicians and reflected in either of the two databases. Examples are single component diagnosis such as PCP, TBM, ARF, PTB, Pneumonia etc.
- Presented as a differential diagnosis and refined to the highest level. These include terms such as meningitis confirmed as cryptococcal meningitis, acidosis confirmed as lactic acidosis once specific results became available. Some of these results were available only after death and therefore a retrospective diagnosis was entertained. Occasionally such results were never documented and a diagnosis entertained on the apparent clinical picture combining the information from both sources. The diagnosis of lactic acidosis was made in three of these cases, where a clinical history of weight loss, abdominal pain and anorexia preceded an admission with acidosis in patients with undetectable viral loads on either d4T or ddI or both.
- A combination of various problem statements within a single admission. The predominant example is end stage AIDS, which is a term used to describe two or more AIDS defining conditions occurring at the same time, such as; esophageal candidiasis, excessive weight loss, chronic diarrhea, anemia, sepsis and dehydration. Within this context it was impossible to determine the leading cause of death amongst a variety of disease processes.

- A reflection of the diagnosis during the last and previous admissions, requiring a higher category, such as recurrent pneumonia, chronic gastro-enteritis and chronic renal failure, instead of the singular term.

A total of 783 deaths occurred according to the data gathered from 1998 – 2003, but due to incomplete data only 757 of these cases were described in detail within the study population.

Chapter 4

4. Results

4.1 Descriptive

4.1.1 Demographics

The baseline characteristics of patients registering to the AfA program and studied in this cohort are described below.

Out of a total of 783 patients who died between 1998 - 2003, 378 were female (48%) and 405 male (52%).

4.1.2 Age and Gender

The age distribution within the cohort, is graphically presented below with a median age of 39,1 at death. The median age at death for women was 37,2. The median age at death for men was 40,7.

The difference in age between gender was not found to be statistically significant with p= 0.35 within the analysis with sigma-restricted parameterization.

More men than women died. Women died at a younger age than men. The graph below shows the ages at death in relation to gender.

Comparison of Age at Death between Gender

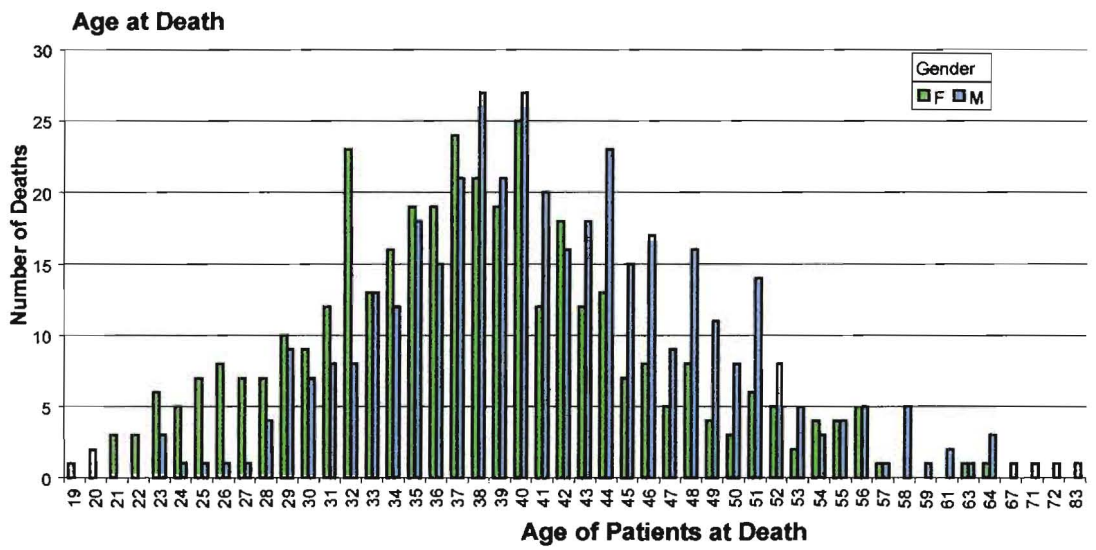


Figure 1: Graphical Description of Age and Gender within the Cohort

4.2 Clinical Indicators at the registration with AfA

The table below describes the initial and median CD4 results on registration with AfA, the median age of death and the median viral load in log value.

Gender	First Median	First Median IQR	Nonparametric compare son	Median Age at Death in years	Analysis of Variance between Age and Gender	Median of the first Viral Load in log value	Median of the first Viral Load
Female 360	62 cells/µL	20 – 138 cells/µL	Mann-Whitney U Test	37.19	Sigma-restricted parameterizati on	5.33	269 300 copies /ml
Male 383	66 cells/µL	21 – 154 cells/µL		40.7		5.37	232 644 copies/ml
Total 743	63 cells/µL	20-147 cells/µL	p=0.79 Non significant	39.1	P=0.35 Non significant	5.40	251 955 copies /ml

Table 1: Table depicting the Gender in relation to the first CD4 and first Viral load

4.2.1 First CD4

The distribution of the cohort of patients according to their first CD4 counts and viral loads are reflected below. Of note is the high percentage of patients registering with the program with a CD4 < 50 cells/µL (45%) and viral load in excess of log 5.4. Another 36.5% (271 out of 743) of the patients with a CD4 between 50 and 200 cells/µL, were registered with the disease management program. In total 605 out of 743 (81%) patients who died and for whom CD4 data was available had a CD4 of less than 200 cells/µL at registration.

A graphical description of the initial CD4 and Viral load is shown below.

Graph showing the First CD4 and First Viral Load

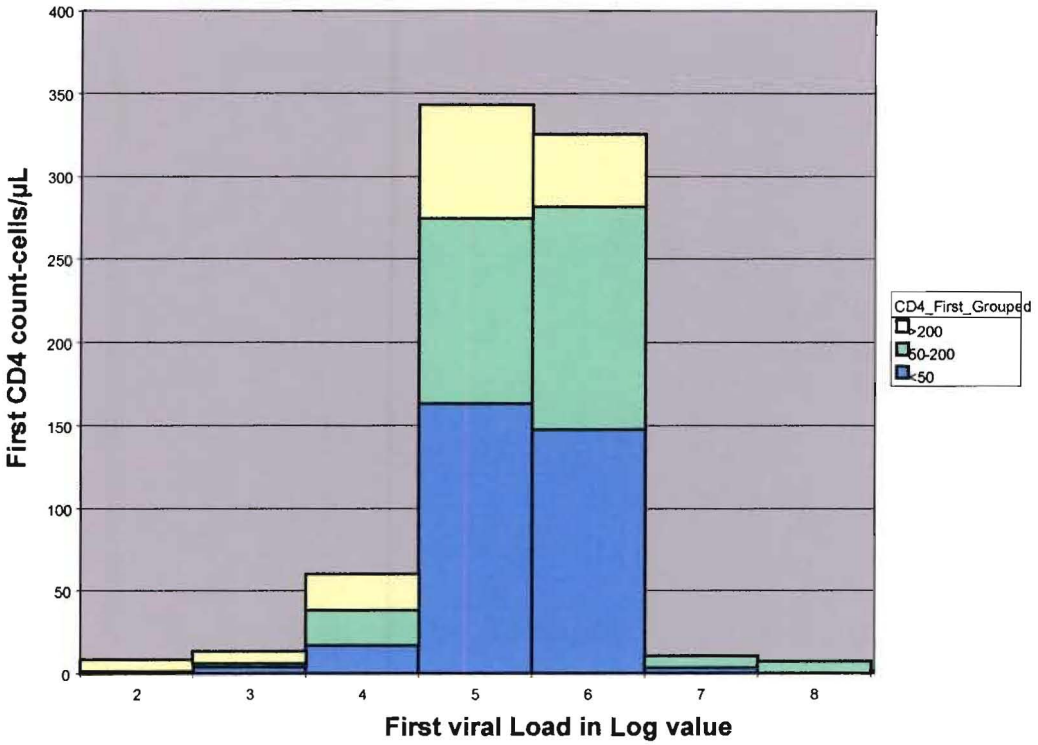


Figure 2: CD4 in terms of the Viral load in Log value

4.2.2 First Viral load

Of the 729 patients within the cohort in which an initial viral load was documented, the median measured viral load was 252 000, and the interquartile range (IQR) 96 800 - 585 500.

4.3 Description of the Program

The figure below, graphically describes the date of registration per patient with the AfA program. From the graph it can be seen that the registrations gradually increased, reaching a maximum by mid 2001. The initial low registration numbers from 1998-1999 correlate with the initial funding rules, whereby a patient had to belong to Bonitas for more than three years before the HIV disease management program could be accessed.

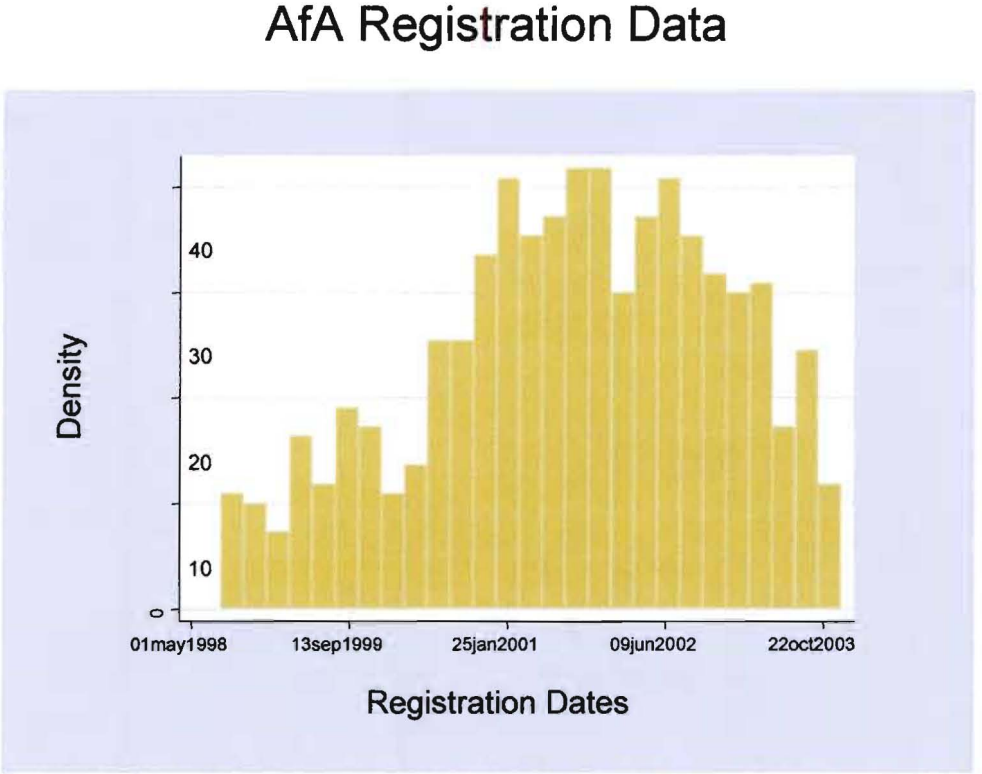


Figure 3: Graphical Description of the Number of Patients registering with AfA per annum

In comparison to the figure above, the figure below shows the distribution of deaths in the study population during the period 1998 – 2003. From the graph it is evident, that there is a constant rise in the number of deaths reaching a peak between 2001- 2002. This corresponds with the registration data, where the number of registrations also increased during the period 2001-2002.

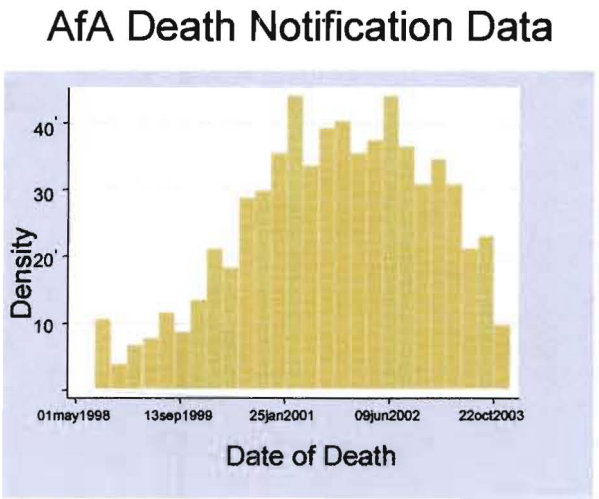


Figure 4: A Graphical Description of the Time of Death within the Cohort

4.3.1 Type of Antiretroviral Therapy

Out of the 758 individuals that were studied, 74 patients had not started on any antiretroviral combination by the time of their death, whilst 181 received dual therapy and 503 triple therapy. The gold standard of triple therapy was not affordable in the earlier years of 1998/1999 as the drugs were very expensive at the time and most patients could not afford the co-payment required to acquire triple therapy within the benefit structure for ART. From 2001 onwards triple therapy became affordable to most patients within the benefit structure at the time. The first affordable triple therapy regime consisted of d4T, ddI and NVP (nevirapine).

Count of ART Combinations		
ART Combinations	**Total**	**Percentage**
0	74	9,76%
2	181	23,88%
3	503	66,36%
Grand Total	**758**	

Table 2: ART Combinations

4.3.2 Duration on Program since Registration

The median number of months patients received ART prior to death was 2,84, with the IQR ranging from 0,82 – 13,07 months. Women died almost one month later than men. This finding was not found to be statistically significant.

Duration on Program				
Gender	**Number of cases**	**Median number of months since registration**	**Nonparametric comparison of Time to Death and Gender**	**IQR**
Male	347	2,60	Mann-Whitney U Test	0,76 – 12,
Female	336	3,63		0,86 - 15,6
Total	**683**	**2,84**	**p=0.13 non significant**	**0,82- 13,12**

Table 3: Time till Death in terms of Gender

The median period to starting ART once registered with AfA was 0,033 months. The IQR was 0-0,30 months. The median time to death since registering with AfA was 3,76 months with an IQR of 1,04 - 16,47 months.

PROGRAM	Median	IQR
Time until death since registration in months.	3,76	1,04 - 16,47
Time until death since starting ART in months.	2,84	0,82 - 13,7
Total number of days in hospital since registration	26,5	10 - 36
Total number of days admitted in last six months	13,5	6 - 24
Total number of days admitted during the last admission	6	3 - 11

Table 4: Description of the Data in terms of Registration, ART, Death and Hospitalization

4.3.3 Hospitalization

A total of 758 cases were studied, for which data regarding hospitalization existed.

The median number of days during which patients in this study were hospitalized (the entire period from 1998 till 2003 taken into account) was 26,5. The interquartile range (IQR) was 10 - 36 days. The full range varied from 0 – 114 days.

During the last admission prior to or as part of the terminal event, the median number of inpatient days was 6, with the IQR ranging from 3 - 11 days.

During the last six months prior to death, limited to those with at least six months of follow-up prior to death, the median number of inpatient days within this group, was 13,5 days with an IQR of 6 - 24 days.

4.3.4 Time until Death

The median time until death was 3,76 months since registration with the disease management company AfA. A total of 684 valid cases were studied. It is apparent that 74 patients were not registered officially with AfA by the time of their death and, therefore, no measurement of time until death was done. These patients were typically those who were diagnosed as HIV positive in hospital and remained critical until death, unable to sign the registration forms. The IQR was 1,04 – 16,47 months.

4.3.5 Last Viral load and CD4 count

Of the 729 valid cases for which a last viral load was available, the median last viral load was 203 000, with the IQR at 62 600 - 500 000. The log value of 1,69, relates to a value of < 50 viral copies per ml and is the lowest level measured, indicating an undetectable viral load.

The last CD4 was measured in 744 cases with a median of 56. The IQR was 19 - 133.

Gender	CD4 Last Median	Nonparametric comparison of gender and last CD4	CD4 Last IQR	Median of the last Viral load	Median Viral load Last in log value
Female	56,5 cells/µL	Mann-Whitney U Test	17.5-131.5 cells/µL	211 915 copies/ml	5.43
Male	54,0 cells/µL		19-134 cells/µL	186 500 copies/ml	5.37
Total	56 cells/µL	p=0.9 non-significant	19-133 cells/µL	202 500 copies/ml	5.31

Table 5: CD4 and Viral load last in terms of Gender

The majority of patients did not have a subsequent CD4 or viral load value recorded as they died before the next blood test was due. If a second test was done it did not demonstrate any benefit. The data was insufficient to determine if these results were the same or not.

4.4 Outcomes

4.4.1 Cause of Death

A pragmatic classification of cause of death was developed based on available data. It is evident from the data that most patients died due to:

a. AIDS - defining conditions (ADE; WHO stage 4), of which the most frequent diagnoses were:

1. End stage AIDS = 91
2. Cryptococcal Meningitis = 38
3. Recurrent Pneumonia = 38
4. PCP (Pneumocystis Carinii Pneumonia) = 21
5. TBM (Mycobacterium Tuberculosis Meningitis) = 15
6. Extrapulmonary TB excluding TBM = 13

Additional diagnoses such as Kaposi Sarcoma = 10, Non Hodgkins Lymphoma = 8 and MAC and cancer of the cervix= 2 cases each were found in addition to the commoner causes of death listed above.

b. These were followed by HIV Related causes (HRE; WHO Stage 3), of which the most common diagnosis in order of prevalence was:

1. Pneumonia = 118 cases,
2. Pulmonary TB = 21
3. Chronic Renal Failure = 21
4. G/E and dehydration = 17
5. Meningitis = 16

c. Other causes of death included diagnosis such as hepatitis related causes = 10, acute renal failure = 6, chronic cardiac failure = 5, post procedure deaths = 5, PET = 3 and CVA and breast cancer = 2 each.

Death related to ART (24) was caused by:

1. Lactic Acidosis = 17
2. Pancytopenia/Anemia = 2
3. Pancreatitis = 2
4. One death each related to: Liver failure due to nevirapine, Steven Johnson syndrome due to nevirapine and one unknown cause of death

In 151 of cases studied (20%) the cause of death remains unknown. 123(16.2%) of these deaths occurred at home and the remainder died soon after admission to hospital.

Either these patients died before a diagnosis could be confirmed or the data about their deaths was inadequate to confirm the cause. It can be postulated that, within this group, the majority of patients with a CD4 of less than 200 died due to AIDS-defining or HIV-related causes. It is understandable that the cause of death remains unknown in the group of patients who died at home. In this group it was difficult to determine the relationship to TB and in the majority of cases the incidence of TB was recorded as uncertain.

More men (390) than women (367) died in total, but the distribution of the cause of death was similar. The statistical analysis, using a Chi-square test comparing the cause of death in relation to gender was not significant with p=0.44.

Diagnosis	Gender		Chi-square test	Grand Total
	Female	Male		
ADE	145 (39.5%)	135 (34.6%)		280(37%)
HRE	110 (30%)	123 (31.5%)		233(31%)
Other	31 (8.4%)	38 (9.7%)		69(9%)
ART Related	14 (3.8%)	10 (2.6%)		24(3%)
Uncertain	67 (18%)	84 (21.5%)		151(20%)
Total	**367 (100%)**	**390 (100%)**	**p=0.44**	**757**

Table 6: Cause of Death

From the table above it is evident that in the group where a diagnosis was confirmed (606 of the cases) 46,2% of patients died due to ADE, 38% due to HIV related causes and 4% due to ART related causes.

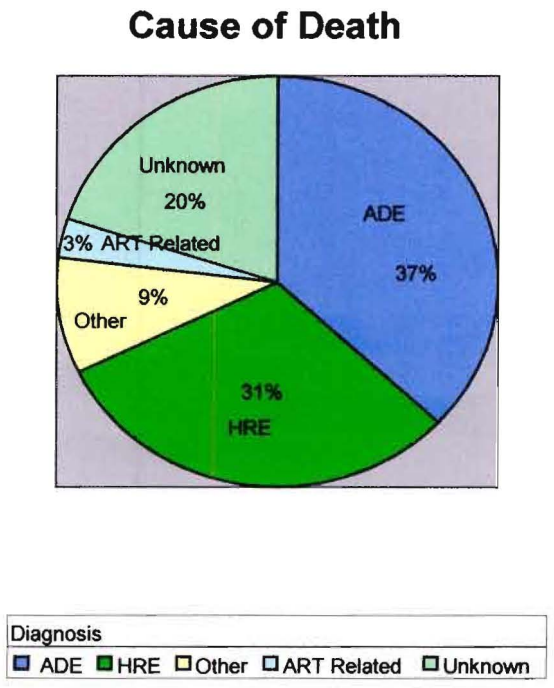


Figure 5: Cause of Death

The diagnoses are displayed graphically below, showing the difference between men and women.

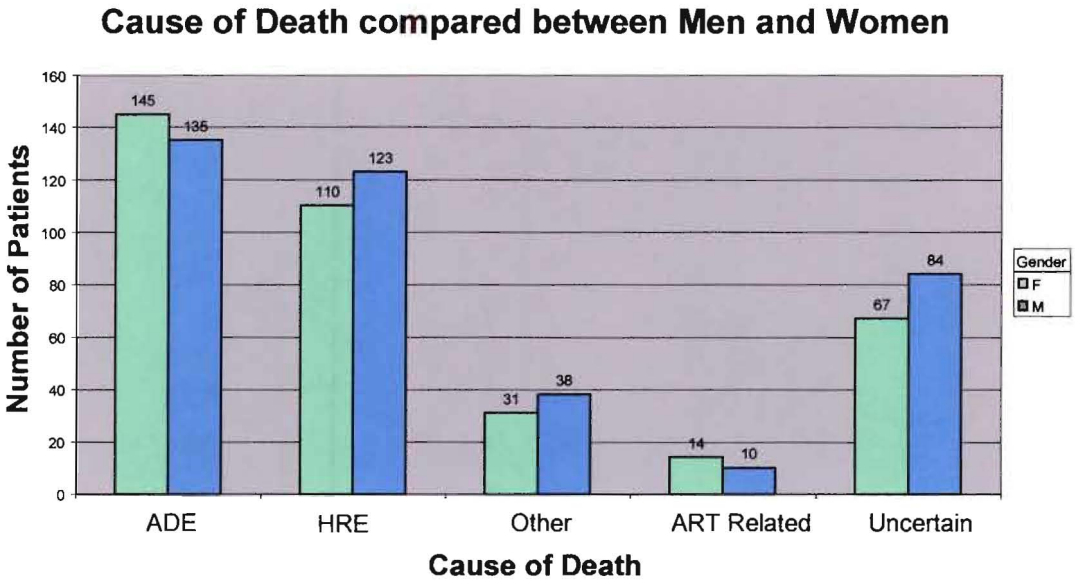


Figure 6: A comparison of the Cause of Death between Men and Women

ART Related Causes of Death

The table below shows the distribution according to the level of care and cause of death in all the patients where the cause of death was found to be associated with ART. The three men who died at home with lactic acidosis were diagnosed by their doctors in hindsight and the information found on the AfA clinical data sheet. Clearly the predominant number of patients (9) with a diagnosis of lactic acidosis died in ICU. Nine women compared to eight men died of lactic acidosis. One pregnant lady died due to liver failure on nevirapine. Her CD4 count was 300. One male patient died due to a Steven Johnson's Syndrome on nevirapine at home. The two patients who died due to pancreatitis were both on efavirenz, D4T and DDI. The male patient who died due to a nosebleed was on lamivudine/zidovudine and had a documented pancytopenia. Another female patient died with anemia on lamivudine/zidovudine. Only two patients received TB therapy at the time of death; a patient who died with lactic acidosis in the ward and another who died on the day of admission with an undetectable viral load on ritonavir/indinavir and efavirenz. The sudden death with no previous diagnosis classified her as an ART related death. Arguably other causes of death may also be entertained. None of these patients died in a Hospice or a Step-down unit.

Cause of Death in all Patients classified as an ART-Related Diagnosis	Place of Death and Gender									
	ICU/H/C		ICU/H/C Total	Ward		Ward Total	Home		Home Total	Grand Total
Single Diagnosis	F	M		F	M		F	M		
?COD				1		1				1 (0.13%)
Anemia				1		1				1 (0.13%)
Lactic acidosis	5	4	9	4	1	5		3	3	17 (2.25%)
Liver failure	1		1							1 (0.13%)
Pancreatitis	1	1	2							2 (0.26%)
Pancytopenia with acute Hemorrhage					1	1				1 (0.13%)
Steven Johnson							1		1	1 (0.13%)
Grand Total	**7**	**5**	**12**	**6**	**2**	**8**	**1**	**3**	**4**	**24 (3.2%)**

Table 7: Description of all Patients with an ART-related Cause of Death

4.4.2 Place of Death

The diagnosis coded as AIDS defining=1, HIV related=2, Other causes=3, ART-related=4 and unknown=9 is displayed graphically below, in relation to the place of death.

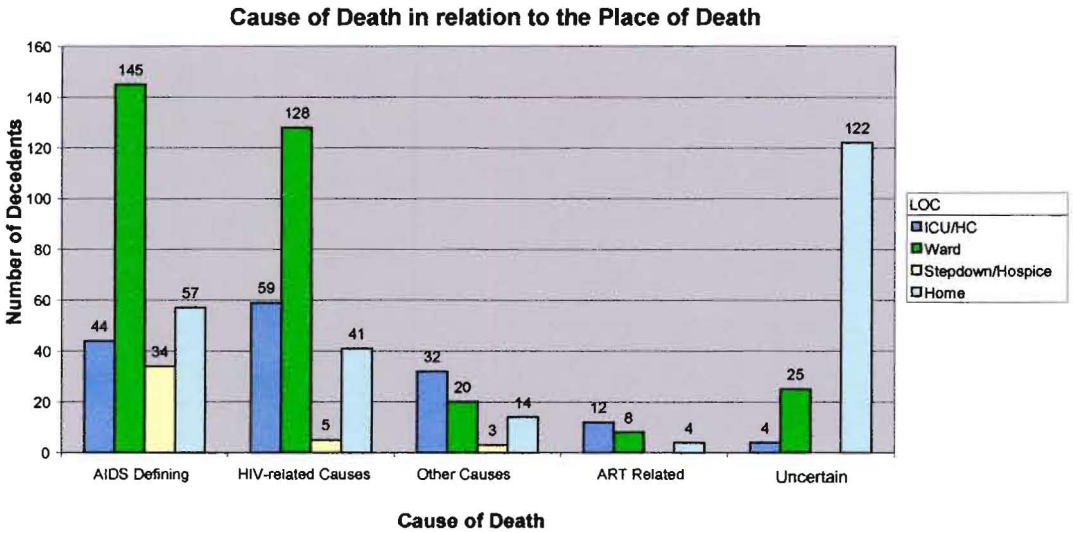


Figure 7: The Cause of Death in relation to the Place of Death

From the graph it can be seen that most patients (326=43%) died in a general ward, of which 145 had an AIDS-defining event (ADE), followed by 128 with a HIV-related illness (HRE) at the end of life. In 20 patients the death related to other causes. ICU deaths accounted for 151 (19.9%) of all deaths in this cohort of 757 documented individuals. 59 of these deaths were HRE and 44 due to ADE. Within the group of patients dying at home, in 122 out of 238 (51.3%) no diagnosis could be established, followed by 57(29.4%) with an ADE, 41(17.2%) with a HRE and 4(1.7%) due to ART-related causes.

The graph below describes the place of the terminal event. Of the 757 cases studied, 330 (43.6%) of the patients died either at home or in an unspecified hospice. In addition 428 (56.6%) of the patients died in a hospital or step-down unit.

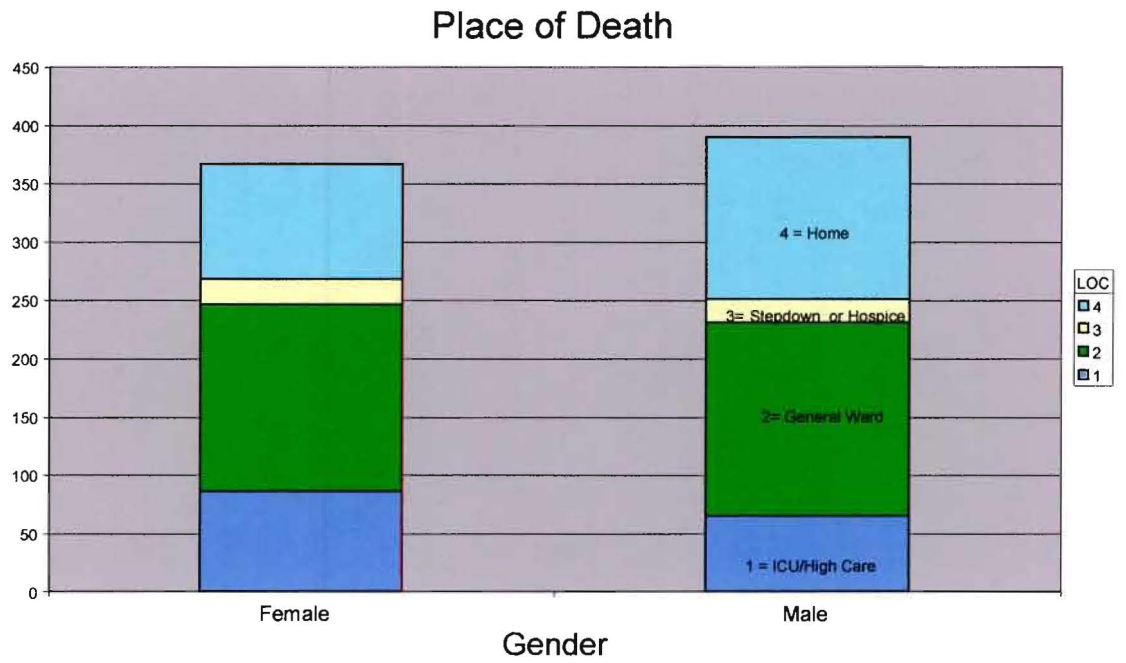


Figure 8: Place of Death in terms of Gender

The table below compares the cause of death and level of care at the time of death between men and women. A fairly similar amount of women (160) to men (165) died in a general hospital ward. The same applies to death in a step-down unit or hospice with two more women (22) than men (20) dying there. The statistical analysis comparing gender to place of death was found to be significant with a Pearson Chi-square test, p= 0.03. A M-L Chi-square test yielded the same result. The predominant difference is the higher incidence of men dying at home = 58% against only 42% of women dying at home.

Place and Cause of Death		**Gender**		**Pearson Chi-square Test**	**Grand Total**
LOC	**Diagnosis**	**F**	**M**		
ICU/H/C	ADE	29	15		44
	HRE	33	26		59
	Other	14	18		32
	ART Related	7	5		12
	Uncertain	3	1		4
1 Total		86 (22.8%)	65 (16.7%)		151 (19.9%)
General Ward	ADE	72	73		145
	HRE	62	66		128
	Other	7	13		20
	ART Related	6	2		8
	Uncertain	13	12		25
2 Total		160 (43.6%)	166 (42.6%)	p=0.03	326(43.1%)
Hospice/Step-down	ADE	18	16		34
	HRE	1	4		5
	Other	3			3
3 Total		22 (6%)	20 (5.1%)		42(5.5%)
Home	ADE	26	31		57
	HRE	14	27		41
	Other	7	7		14
	ART Related	1	3		4
	Uncertain	51	71		122
4 Total		99(27%)	139 (35.6%)		238(31.4%)
Grand Total		**367(48.5%)**	**390(51.5%)**		**757**

Table 8: Place and Cause of Death in relation to each other

4.4.3 Costs at the end of Life

The graph below describes the different costs from 24 months prior to death. Costs have been grouped together for easier comparison.

1. Hospital costs, which consistently remain the biggest cost driver, includes all costs related to an admission, drugs, procedures and accommodation, but does not include medical consultations or radiology costs. Hospital costs generally start escalating from 6 months prior to death and dramatically increases during the last 3 months of life.
2. The second biggest cost driver in the last 6 months of life falls under "path/rad". This amount includes all pathology and radiology costs, whether as an inpatient or as an outpatient. As with hospital costs there is a two-fold increase in these costs during the last three months of life.
3. The third biggest cost driver falls under 'practitioners' and includes all consultations with specialists and general practitioners, whether as an in- or as an outpatient cost. These costs also generally doubled from the fourth to the third month prior to death.
4. ARV costs remain fairly stable during the last year of life and decrease slightly in the last month prior to death.
5. Costs falling under 'other medication' reflect outpatient medication only, as all drugs given during hospitalization with the exception of ART are included in this amount. General over–the-counter-medicine (OTC) which was not claimed from the medical aid is not included in this data.
6. Included in the heading 'average of others', are additional costs relating to physiotherapy, optometrists and other related medical and paramedical services.

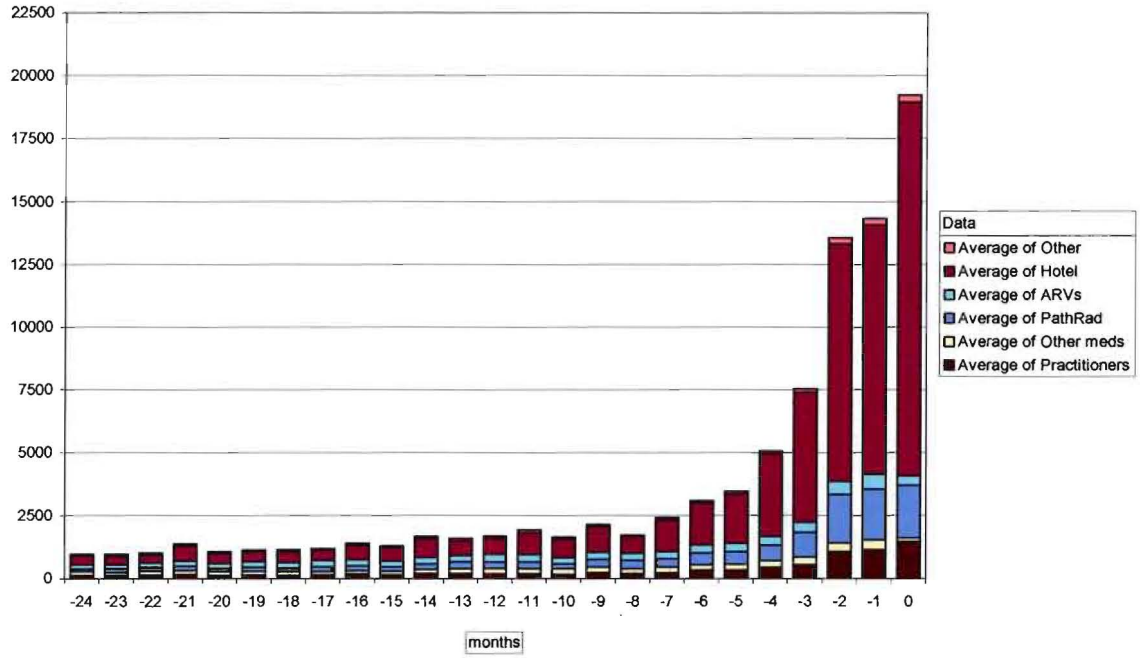


Figure 9: Costs from 24 months prior until Death

The table gives a numerical average value from 24 months prior to death, until the last month of life. The average total was drawn from the data after 24 months on treatment. Only patients who were registered with the HIV program>=6 months were included in the data (n=336).

Months	Average of Practitioners	Average of other medications	Average of Pathology/ Radiology	Average of ART	Average of Hospital	Average of Other
-24	R122.76	R143.45	R114.45	R169.30	R346.81	R68.40
-23	119.53	128.47	141.16	153.51	327.94	90.49
-22	131.52	152.54	154.79	179.56	318.04	84.10
-21	163.04	153.00	175.15	195.86	604.19	79.05
-20	127.51	140.74	144.56	195.21	387.57	74.39
-19	130.75	156.42	162.33	226.02	362.81	84.84
-18	127.47	142.95	155.28	201.38	438.98	86.40
-17	143.32	130.43	199.44	254.12	408.89	48.14
-16	176.13	144.87	198.78	236.25	554.53	96.84
-15	153.56	135.91	183.09	219.43	545.11	66.22
-14	199.19	163.04	220.08	257.35	754.32	73.12
-13	191.24	193.84	287.47	251.84	574.31	95.19
-12	181.33	220.07	260.83	301.21	639.90	91.13
-11	181.49	217.46	261.06	285.34	856.45	131.09
-10	170.52	218.39	195.09	242.07	735.28	80.43
-9	246.69	211.24	317.07	264.64	1009.88	85.76
-8	199.56	189.66	327.56	289.79	659.88	53.69
-7	232.77	225.32	325.18	281.28	1259.81	87.73
-6	346.44	196.49	477.23	320.84	1663.32	91.08
-5	347.92	225.16	498.85	328.19	1956.17	114.84
-4	443.93	259.58	626.39	344.05	3279.23	111.82
-3	548.12	306.49	982.80	389.48	5178.78	149.83
-2	1063.51	357.72	1906.39	528.84	9462.11	246.36
-1	1149.98	393.20	2018.70	580.36	9938.36	256.82
0	1459.48	152.99	2094.08	370.07	14874.17	272.94
Average of Total	**R318.35**	**R195.92**	**R466.13**	**R278.08**	**R2129.95**	**R105.67**

Table 9: Numerical values of Costs from 24 months prior until Death

It is evident from the data that hospital-related costs are by far the biggest at almost 7x the costs of the second biggest cost driver namely pathology and radiology. It is also evident that the major cost escalation started around 6 to 7 months prior to death.

4.5 Clinical associations with Outcomes

4.5.1 CD4 > 200 cells/μL

The subgroup of patients with a CD4 >200 cells/μL at the end of life was studied in terms of the relatedness to TB and cause of death. Only 80 patients who died had a last CD4 > 200 cells/μL, measured within the last 8 months prior to death. Amongst this group 18 patients had confirmed TB prior to death, whereas the diagnosis was uncertain in 20 patients who died out of the 80. In 18 patients TB was not confirmed. By eliminating the 18 unknown causes of death, 14.5% of these deaths were caused by lactic acidosis, 14.5% were TB related and 19.4% due to pneumonia (including PCP).

The most common diagnosis in the order of prevalence was:

1. Unknown cause of death: 18
2. Lactic Acidosis: 9
3. TB related cause of death: 9
4. Pneumonia/recurrent pneumonia: 7
5. PCP: 5

4.5.2 Relatedness to TB:

A positive relationship was made with TB if a patient was receiving TB therapy at the time of death. TB could not be proven in all patients with sputum or other tissue diagnostic tests. It was evident from the notes that experienced clinicians used their clinical skills by reviewing patient history, examination and X-ray reports to predict possible TB.

TB-related	Gender	Total
Uncertain of TB		225 (29.8%)
	Female	93
	Male	132
No TB		330 (43.7%)
	Female	175
	Male	155
Yes TB		200(26.5%)
	Female	98
	Male	102
Grand Total		**755**

Table 10: TB-relatedness in terms of Gender

In studying the above chart, 26.5% of the patients were treated for TB, 43.7% of patients did not receive anti-TB therapy and in 29.8% of patients it could not be established whether TB therapy was utilized at the time of death as no inpatient note was

available, either because they died at home or because the information was not available. TB is a notifiable condition and therefore treated at TB clinics within the DOTS program. Patients who could/did not volunteer this information to their providers, therefore would not be included in the database. If an uncertain incidence of TB is eliminated from the data, 38 % (200/530) of patients who died were also diagnosed with TB at the end of life. The cross tabulation results between gender and TB-relatedness, as performed with the Chi-square test ($p=0.0316$) found a significant difference between men and women, especially where the diagnosis of TB was found to be uncertain in 41% of women against 59% of men. In a large proportion of the patients who died at home (124), it was uncertain if TB therapy was used at the time of death.

Tuberculosis as the single final diagnosis occurred in only a small number of cases, but an association with concomitant TB as a secondary diagnosis was therefore found in 38% of cases where a definitive distinction with or without TB could be established.

4.5.3 Viral load < 5 000

Only 53 patients were found to have a viral load < 5 000 copies/ml measured within 8 months from the time of death. Within this small group the:

- Median time to death = 9.68 months
- Median CD4 1st = 111
- Median CD4 last = 133
- Total inpatient days = 20

It is evident from the table below that the largest number of deaths in this group was due to:

1. Lactic Acidosis = 14
2. ?COD = 8
3. Pneumonia = 7
4. TB related complications = 4.

Final Diagnosis (Dx)	Gender		Grand Total
	Female	Male	
?COD	4	4	8
CRF	1		1
Cryptococcal Meningitis	1		1
Died post procedure		1	1
End AIDS	1		1
Hepatitis	1		1
Hepatobiliary Disorder	2		2
Herpes Encephalopathy		1	1
Lactic Acidosis	9	5	14
Liver Failure	1		1
Meningitis		1	1
Metastatic Cervix Cancer	1		1
NHL	1	1	2
Obstructive Hydrocephalus due to Cysticercosis		1	1
P TB	1		1
PCP		1	1
PET	1		1
Pneumonia	3	4	7
Sepsis	2	1	3
TB Disseminated	1	1	2
TBM Pneumonia		1	1
Transverse Myelitis	1		1
Grand Total	**31**	**22**	**53**

Table 11: Cause of Death in Cases with a Viral load < 5 000

Chapter 5

5. *Discussion*

5.1 General

The 783 patients studied, represents a significant sample from which to develop an understanding of the place, cause and cost related to dying with HIV/AIDS. The inability to do the initial study as it was planned, by selecting and comparing two groups in terms of a benefit from ART or no ART, is a significant finding by itself. The pilot study was abandoned as the group of patients who died and received benefit from ART was too small, not meeting sampling criteria. It is therefore evident, that very few patients, who benefit from ART (through being on treatment for long enough to benefit substantially both immulogically and virologically), died within the study period of five years.

Women died at a younger age than their male counterparts, but also presented at registration with slightly lower CD4 counts. This is in accordance with the data published by Bonnet (2002) and Van Der Loeff (2002). The gender distribution and age at death is consistent with the epidemic, but conclusions cannot be drawn regarding the death rates. A study by Nachega (2005) reported a crude mortality rate of 3.5% amongst a similar group of patients registered with the same disease management company, AfA.

The low CD4 counts at registration is not surprising within the social and political context of denial, disgrace and discrimination towards those diagnosed with HIV/AIDS in SA. Patients do not actively seek VCT whilst still fairly healthy, but present late with advanced disease for medical intervention. It is well documented that a significant percentage of these patients subsequently die soon after starting ART. It was not possible to establish immune reconstitution inflammatory syndrome (IRIS) as a possible cause of death from the available data. It is possible that IRIS could have played a role in these deaths as described by Bekker (2002), within the context of :

- low CD4 counts at starting ART
- high incidence of AIDS defining events (ADE)
- high incidence of concomitant TB
- high incidence where the diagnosis of TB remained uncertain.

Similar results were found in a study by Coetzee (2004), where 71% of deaths occurred before 3 months duration on ART. The median CD4 count at baseline in the above

mentioned study group was 43 cells/μL. In our study, it is therefore not surprising that the median time till death since starting ART was 2.84 months with a median CD4 count of 63 cells/μL at registration to the program. The very ill patients died soon after being diagnosed, not gaining much immunological benefit from ART. The natural history of HIV in the absence of therapy for patients with similar CD4 counts would be that the majority would die within a year. In our study only 10% of patients died before ART was commenced. It is not surprising therefore that some of these patients would have been extremely ill at the time of starting ART, and may have proceeded to die before gaining benefit from the intervention.

Not much significance can be drawn to the initial and last viral load. In more than 50% of cases these two results will be the same, as 50% of patients died within four months of registering with AfA. In addition Nachega (2005) found that <80% adherence and a baseline CD4T-cell count < 50 cells/μL was associated with poor survival. In this study only 80/755 (10.6%) of patients died with a CD4 count > 200 cells/μL. Within this group the causes of death were unknown in 18, related to lactic acidosis in 9 and TB complications in 8. It is possible that more of the 18 unknown causes of death could be related to lactic acidosis, which remained undiagnosed at the time of death.

In keeping with a maturing epidemic more patients register with the program and die as time progresses. This is evident on studying graphs 3 and 4 and substantiated by a median time period till death of less than 4 months since registration to the program. It is however significant that 90% of patients were started on ART prior to death. As patients died within 4 months of registering with the program, it was difficult to quantify inpatient days for a full 6 months. There is therefore a problem with selection bias. The median number of six inpatient days during the last admission, is in keeping with the assumption that patients are admitted repeatedly as the median number of inpatient days increased to 13.5 at six months since registration and to 26.5 days since registration for those patients with six months or more of follow-up.

5.2 Cause of Death

A diagnosis could be determined in 80% of cases reviewed. Not surprisingly ADE was the predominant cause of death, with end stage AIDS (a specific syndrome used to classify a multitude of symptom complexes and ADE occurring in a single patient at a specific stage) being the most common finding. These results are in keeping with the low initial CD4 counts and progression to death within four months of registering with AfA and 3 months since starting ART. Within these results it is evident that in the SA context patients die of AIDS-defining conditions more than from any other cause, followed closely

by HIV related events. This finding is in contrast with the European and American studies reviewed, as the COD related to ADE and sepsis decreased significantly in all of them. Woods (2005 AIDS Conference) stated that young people (median age = 39 in this study) are still dying due to ADE in 6% of all patients, HRE in 2% and due to ART complications in 0.28% of all patients diagnosed with HIV/AIDS. This estimate includes all patients within the HIV/AIDS program, whether they died or survived.

TB is not mentioned as a contributory to death in any of the overseas studies, whereas in this SA study in up to 38% of cases, TB was found to be a contributing factor at the end of life (out of a group of 530 cases where a correlation to TB was confirmed as positive or negative). This could be an overestimate as the status may be more likely to be definitively recorded in patients diagnosed with TB than those without symptoms. TB was found to be uncertain in 41% of women against 59% of men. Although statistically not significant, more men (52%) than women (48%) died in this study, however a statistically larger percentage of women died due to AIDS-defining conditions (39.5%) comparing to 34.6% of men. This finding is in accordance with the results of Bonnet (2002), and it becomes more significant in view of the survival data presented by Nachega (2005), where 61% of patients studied were female. It can be argued that the large proportion of patients dying at home (predominantly men in 58% of cases) also die from AIDS defining illnesses especially end stage AIDS, as most of these patients disappear from follow-up, and do not access medical care at the end of life.

Only 53/755 (7%) of patients who died in this cohort had a viral load result of < 5 000 copies/ml within 8 months from the time of death. The majority of these patients died due to ART related incidents of which lactic acidosis was the confirmed cause of death in 14 of these cases. Within the larger group, 17 patients (2.25% of all deaths and 4% of all deaths with a confirmed diagnosis) died with a confirmed diagnosis of lactic acidosis. It may be possible that confirmation of all the CD4 and viral load results remained outstanding at the time of death and was therefore not reported in the initial group with viral load < 5000. All these patients received d4T or ddI or both at the time of death. It is therefore important that providers should suspect the diagnosis of lactic acidosis and aggressively investigate this possibility, should their patient happen to be on these drugs. In this study, the majority of patients were diagnosed retrospectively with lactic acidosis. The incidence of lactic acidosis or symptomatic hyperlactataemia of 1.7-25.2 cases per 1 000 person-years on ART with a mortality rate of 30-60% is presented in a review article by Calza (2005). Another literature review published as part of the 2004 guidelines for the use of ART in children, presents an incidence of lactic acidosis in adults of 0.2 – 2.5%, Adverse drug effects (2004).

A large proportion of patients therefore fail to achieve a prolonged and lasting benefit from ART. It is clear from this study that the fast progression to death is firstly due to the low initial CD4 counts and secondly the high proportion of WHO stage 4-diagnosis at the time of registration as defined in the Athena study as risk factors for AIDS/death. It would therefore be important from survival and cost considerations to recruit patients for VCT (voluntary counseling and testing) at an earlier stage of the disease process and prepare them for a lifelong commitment to ART. Early enrollment provides a valuable educational opportunity and enables ART to be commenced at the optimal time.

5.3 Place of Death

Within this study no evidence of active choice in terms of a place of death either at home or in a hospital could be found from the patient records. The majority of patients who died at home did not seek active care and interestingly are predominantly male. This is evident from: 1.The large percentage of patients dying at home without a diagnosis. 2. Very low Hospice and step-down admissions. The majority of step-down admissions were related to patients who had reached the hospital benefit limit and suffered with end stage illnesses. It was therefore a forced transition to step-down care, rather than a voluntary choice by the patient. Very few patients died in Step-down and Hospice units, usually only after a long inpatient stay and it is therefore clear from the data that the transition to pure palliative management in this patient population is not clearly defined. It may also be possible that the complexity of end of life care is such that step-down care is not a cost-effective option within per diem and fee for service rates as prescribed by hospital contracts with the medical aid and administrator. In general most patients died of pneumonia, which is a potentially curable disease process within which pure palliative care will not be the initial goal.

ICU deaths accounted for 19.9% of all the deaths within this cohort. More women (86) than men (65) died in the intensive care unit of which in 44/151 ICU deaths, (29% of ICU deaths) the diagnosis relates to an ADE. It can be argued that this level of care is inappropriate in a setting of end stage illness, where a combination of palliative care and sound medical practice should go hand in hand. It is therefore evident that even in this group, patients encountered biomedicine at the end of life. This finding is not uncommon and documented by Bonnet (2002), in their study in France, where the median CD4 was 162 cells/μL and 14% of deaths occurred in the ICU. It seems that within the context of HIV/AIDS it remains difficult to predict death, to entertain choice as a component in treatment decisions and especially for these young individuals and their families to consider their own mortality and physical decline in a rational manner. An inability amongst

medical staff to differentiate between organic brain syndromes and the delirium of dying at the end of life, leads to additional curative interventions such as ventilation and aggressive medical treatment being pursued, instead of recognizing the natural progression to death. It seems that the emphasis in medicine is prevention of death at all cost and thereby denying a good death within a recognizable terminal process. In view of these difficulties which are in keeping with a study by Drought (2002), it would be preferential to combine effective palliative intervention as a significant part of active inpatient care, instead of seeing it as an end of life option once the patient is either discharged or transferred to a step-down unit.

Most patients die in the general ward (42.9%) with an equal distribution in gender. It can be agued that dealing with an AIDS-defining diagnosis at the end of life becomes very difficult, especially since most patients die from end stage AIDS, cryptococcal meningitis and recurrent pneumonia and therefore qualify for admission to a hospital at the end of life, in terms of the seriousness of the disease complex and the multiple symptoms which become unmanageable at home. These very ill patients will access hospitalization in accordance with the three reasons described by Uys (2003) in her study of end stage AIDS deaths where ART was not available:

- the care became too difficult for the caregiver
- the family believed that they had not done enough if they did not take the patient to hospital or
- there were certain symptoms that the family could not control such as difficulty in breathing, intense pain and multiple fistulas and wounds

More research about palliative care for patients with WHO stage 3 and 4 disease processes combined with potentially curative infective conditions, such as pneumonia, is needed. Active rehabilitation (as would happen in the event of other serious and incapacitating illnesses such as spinal cord injury and CVA) towards becoming ART candidates in terms of fitness, ability to walk, either aided or independently and cognitive improvement could be introduced either at home or in a step-down/hospice facility and needs urgent attention. The association between TB in this study is in accordance with the study by Rosenblum (1994), indicating a higher incidence of morbidity/mortality and higher costs with a positive diagnosis of TB. In addition, there are autopsy studies showing high rates of undiagnosed TB in HIV patients who die. It is clear on studying individual patient records, that making a conclusive diagnosis of TB in late stage HIV remains very difficult.

5.4 Costs

It is clear from this study that the largest proportion of costs relating to the treatment of terminal AIDS entails the hospitalization costs. Radiology and pathology costs are the second biggest cost driver and are indicators of the extent of further investigations within the last 3-6 months of life. There is a dramatic increase in costs within the last 6 months of life. These costs could have been much higher if hospital/total benefits were unlimited. These limits definitely affected the cost data in comparison to schemes with unlimited total benefits. The ART benefit was also limited, and is reflected in the data from 1998-2002 where most patients could only afford dual therapy. It is significant that the escalation in costs in the last month of life in relation to the average hospital costs increased seven fold. This is more than the three fold increase in costs found amongst AIDS patients treated in Australia during the last three months of life as described by Beck (2001). As average costs in the last-year-of-life were 3.2 times average costs in the second-year-of life as found in cancer and chronic related illnesses, the seven fold average increase in the last six months of life in HIV/AIDS deaths is significantly higher.

These increased costs probably relate to the increased use of biomedicine at the end of life in terms of increased ICU/High Care interventions as well as ongoing and increased radiology and laboratory tests at this time period. It must however be remembered that this is a retrospective description of events and therefore it is probably much easier to view an intervention as possibly futile with hindsight.

ART drug-related costs remain fairly stable throughout and decrease during the last month of life, indicating that patients stop filling their scripts and taking therapy with increasingly worsening general health.

5.5 Palliative Care Needs

It is clear from this study that patients often encounter biomedicine at the end of life in the private medical aid driven practices. There is a concern that palliative care needs are not met in allowing the patient a good death within this setting. Creative ways of providing good palliative care in addition to appropriate medical intervention must be sought, to facilitate the dichotomy of wanting a good death and every medical intervention possible. The large proportion of patients dying at home with end-stage AIDS desperately need palliative care intervention to allow patient autonomy in supporting the ideal of a good death, within the setting of advanced multi-faceted disease profiles. It would be important from survival and cost consideration to recruit patients for VCT (voluntary counseling and

testing) at an earlier stage of the disease and prepare them for a lifelong commitment to ART.

Research, planning, implementing and monitoring of palliative care interventions needs urgent enhancement in the day to day management of patients and their families: 1. When accessing ART 2. When dying with end-stage AIDS and 3. When presenting with ADE at HIV diagnosis to ensure that good quality of life and care principles are met in allowing a good death or positive health. The development of proper rehabilitation programs and facilities in late diagnosed AIDS is an urgent and crucial requirement to improve outcomes, wellbeing and to reduce costs.

Utilizing hospitalization cost-effectively is a high priority within the setting of terminal HIV/AIDS. Palliative care is needed as a crucial part of ART and within a step-down approach where further active management is futile. Both can be provided within a well-managed and supervised home-based service with respite admissions to Hospice or step-down units when needed for the sake of both patient and carer.

Chapter 6

6. Conclusions and Recommendations

6.1 Conclusions

a. Patients present very late in the disease process and this leads to most patients who die after starting ART, to die within the first four months since registration. IRIS may be a contributing disease process within this setting.

b. The causes of death in the SA setting is predominantly due to ADE in late presenters and noncompliant individuals who die without significant benefit from ART and ART related causes in patients who have responded immunologically and virologically prior to death.

c. Death occurs predominantly in the hospital general ward and ICU, whilst those patients who seem to opt out of care die at home.

d. Hospital costs account for the largest increase in costs within the last six months of life. These costs are more than seven times higher than baseline average costs.

6.2 Recommendations

a. *The high proportion of patients dying with AIDS-defining events while they are receiving ART is an indication of late presentation, possible IRIS and of poor compliance. These patients need to be identified earlier in the disease process and need active rehabilitation and urgent preparation to start ART.*

It is clear from the data that a large proportion of patients fail to achieve a prolonged and lasting benefit from ART. This is caused, firstly, due to the very low initial CD4 counts at registration and shortly before death and secondly could be due to poor compliance leading to a failure to respond to therapy. These very sick individuals present too late within the disease process and therefore fail to achieve a lasting benefit from ART. Strategies are urgently needed that would empower patients on the one hand to register for VCT earlier and, on the other hand, to ensure that providers provide holistic care when counseling patients pre- and post-HIV diagnoses. The poor benefits allowed for primary care or outpatient visits could contribute to poor compliance or prevent the identification of early signs of complications or opportunistic infections in the first few months on ART. Funders should revise the benefits provided to these primary care practitioners in order to allow patients to see their providers regularly within the first months following diagnosis and starting of ART. This is crucial in securing a longstanding benefit from ART.

b. Clinical guidelines are needed for effective end-of-life-care

Utilizing hospitalization cost-effectively is a high priority within the setting of terminal HIV/AIDS. Good palliative care can be provided within a well-managed and supervised home-based service with respite admissions to Hospice or step-down units when needed for the sake of both patient and carer. Palliative care should not be seen as an option to be taken instead of ART, but as an important part there-of. A lot of work is needed in order to provide this holistic approach in the SA setting. Networking between private medicine and palliative care associations is drastically needed. This will also mean that the provision, networking and training of palliative care physicians become a priority.

The use of biomedicine in futile cases should be debated and prevented in providing justice to all members of the fund. Escalating private health care costs will position new members outside the financial realm of becoming members to a fund if this trend continues. Training is needed for physicians to provide holistic care when faced with the dichotomy of a potentially curable condition versus futile further intervention. Family discussions can provide valuable guidance and insight into these processes.

The development of proper rehabilitation programs and facilities in late diagnosed AIDS is an urgent and crucial requirement to improve outcomes and wellbeing and reduce unnecessary costs.

c. Accurate diagnosis and treatment of ART related side-effects should be a priority when caring for patients accessing ART.

A high index of suspicion is needed to identify and treat potentially lethal ART related side-effects and complications such as lactic acidosis, hepatitis and anemia. This should include patient education to help patients to self-refer when necessary.

d. Cost effective and accurate diagnosis and management of ADE, IRIS and TB early within the disease process is crucial to reduce cost, in-effective care and mortality at the end of life.

Guidelines to identify disseminated and sputum negative tuberculosis is a high priority, given the association between tuberculosis and death in patients with HIV.

Chapter 7

7. References

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