EVALUATION OF MORTALITY AMONG HIV PATIENTS ON HAART IN LUSAKA, ZAMBIA-AN OBSERVATIONAL STUDY

BY
AGGREY MWEEMBA
BSc.HB, MBChB

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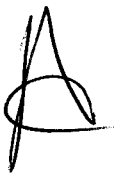
DECLARATION

I , AGGREY MWEEMBA, hereby declare that this dissertation is the product of my own work and, in submitting it for my Masters of Medicine (Internal Medicine), further attest that it has not been submitted in part or in whole for a degree, diploma or certificate to this or another university.



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CERTIFICATE OF APPROVAL

This dissertation, entitled, "Evaluation of Mortality among HIV Patients on Antiretroviral Therapy in Lusaka, Zambia-An Observational Study" by AGGREY MWEEMBA is approved in partial fulfilment for the award of degree of Masters in Medicine (Internal Medicine) of the University of Zambia in the year 2006.

	Name	Signature	Date
Supervisor:	DR MWABA PETER	[redacted]	9/7/2007
HOD:	[illegible]	[illegible]	09-07-2007
Student:	AGGREY MWEEMBA	[illegible]	06.07.07

EXAMINERS

Examiner 1:	DR MWABA PETER	[redacted]	9/7/2007
Examiner 2:	.....	.....	.....
Examiner 3:	DR IMAM ITAG	.....	9/7/2007

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ABSTRACT

Objectives: To evaluate mortality and determine the causes of death in HIV patients initiating HAART in Lusaka District clinics

Design: An Observational Study

Methods: Mortality was assessed in first patients enrolled between May, 2004 and May, 2005 in the Lusaka District Management clinics. Medical charts and interviews with medical staff, who were attending to the patients before they died, were done to ascertain the probable cause of death. For the predictors of death analysis, we estimated Kaplan-Meier probability of survival for those who remained alive on antiretroviral therapy compared to those who died while on ART. To investigate the relationship between those who remained alive on ART and those who died while on ART, we used univariate and multivariate Cox's proportional hazard models, confidence interval (CI) and log-rank tests.

Results: We evaluated 13,672 individuals who were seen in the eight clinics. Of these 8,497 were females (62%) and the median age was 34 years. Patients with CD4 < 50 cells/mm^3 and those with CD4 between 51 and 200 cells/mm^3 accounted for the majority of patients in all the groups except for "surviving" patients who had "not initiated HAART". A preponderance of patients that died had a BMI < 18.5 kg/m^2 and 20kg/m^2 for males and females respectively (P-value < 0.0001). Probable causes of death were identified for 294 (44%) of the 670 deaths. In the majority of patients, cause of death could not be determined. Dying at a health centre did not improve the probability of determining the cause of death. For instance, 59 percent of patients that died at a health facility had no diagnosis at the time of death compared to 51 percent for patients that died at home. The cause of death in most cases was attributed to Opportunistic infections. Mortality rate was found to be high in the initial stages of HAART. Ninety seven percent (391) of deaths occurred in the first six months (180 days) of ART initiation (p-value <0.0001). The mortality rate was 21 deaths per 100 person-years (95% CI) in the first month of ART. The rate declined five-fold (4 deaths per 100 person-years; 95% CI) after one to six months of ART. The mortality rate continued to decline such that after 6 months the rate was 0.43 per 100 person years (95% CI).The overall mortality among patients who were on ART was 4.9 deaths per 100 person-years. Kaplan-Meier survival curves for all patients enrolled into the programme showed that WHO stage 3 & 4, baseline CD4<50 cells/mm^3, BMI <1 8.5 kg/mm^3, hemoglobin < 6.0g/dl were associated with a substantially lower survival probability compared with other patients. Overall WHO stage 3 & 4 diseases and CD4 < 50 cells/mm^3 accounted for 86.4 percent (579) and 41.5 percent (278) respectively. In contrast, patients with WHO stage 1 & 2, CD4 ≥201 cell/mm^3, Hemoglobin ≥ 6g/dl and BMI ≥ 18.5 kg/m^2 had a lower risk of death.

Conclusion: Mortality was high in the early phase of initiation of HAART due to severe immunosuppression and late presentation of patients. Benefits of HAART were noted by declining mortality rates over a period of time. The lack of diagnostics and the critical shortage of staff were reflected by failure to identify cause of death in the majority of patients.

Recommendations: There is need to increase staffing levels and equip laboratories in the clinics to improve diagnosis and management of opportunistic infections in HIV patients. Robust follow of HIV patients initiating HAART with severe disease, low BMI, Anaemia and Low CD4 is required to in order to reduce associated mortality.

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LIST OF ABBREVIATIONS

3TC	*Lamivudine*
ADL	Activities of daily living
AFB	Acid Fast Bacilli
AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Therapy
ART-CC	ART Cohort Collaboration
ART-LINC	ART in Lower Income Countries
AZT	*Zidovudine*
BMI	Body Mass Index
CASCADE	Concerted Action on Seroconversion to AIDS and Death in Europe
CD4	Cluster of Differentiation type 4
CD8	Cluster of Differentiation type 8
CIDRZ	Centre for Infectious Disease Research in Zambia
D4T	*Stavudine*
GRZ	Government of the Republic of Zambia
HAART	Highly Active Antiretroviral Therapy
HIV-1	Human Immune deficiency virus type 1
KS	*Kaposi's Sarcoma*
LDHMT	Lusaka District Health Management Team
NGO	Non-Governmental Organisation
OIs	Opportunistic Infections
PCP	*Pneumocystis Jiroveci* Pneumonia
PEPFAR	US President's Emergency Plan For AIDS Relief Fund
RNA	Ribonucleic Acid
TB	Tuberculosis
UAB	University of Alabama at Birmingham
WHO	World Health Organisation
NVP	*Nevirapine*
EFZ	*Efavirenz*

CHAPTER 1: INTRODUCTION

The major determinants of HIV-1 disease progression and death before the era of highly Active Antiretroviral therapy (HAART) were age at seroconversion and duration of infection in developed countries.[2] The younger age group had a better probability of survival than older group (median survival of 12.5 years for people aged 15-24 years compared to 7.9 years for those aged 45-54 years.[2] Introduction and general uptake of HAART has resulted in decreased risk of Acquired Immune Deficiency Syndrome (AIDS) and death in people infected with Human Immune-deficiency Virus type-1 (HIV-1).[2, 20] Early survival improvements after the introduction of HAART in 1996 has continued to increase in developed countries and HAART is itself probable to be responsible for at least part and most likely much of this improvement.[2]

Even though survival times continued to increase in developed countries between 1997 and 2001, they were not equal to the early reductions in risk of death and disease progression seen after the introduction of HAART.[2] AIDS has been transformed from a rapidly and equally fatal disease into a more prolonged illness with exacerbations and remissions, and a growing cumulative disease burden.[31] HIV-1 infected patients have continued to die from both HIV and non-HIV related causes.[29] New drugs or drug classes on the market and the development of resistance, which leads to treatment failure and other changes in clinical management of HIV, make the longer term effect of HAART difficult to foresee in this setting.[2] The non- HIV causes of death have become more and more significant because of increased survival of HIV-1 infected patients in developed countries.[2] Consequently, the concern in developed countries is whether there is levelling off in the reduction in mortality rates or even whether mortality will begin to go up again.[2]

There is limited data on the effectiveness of HAART in developing countries[30] despite the fact that 60 percent of the world's 42 million with HIV infection or AIDS live in Sub-Saharan Africa and that the region has the highest number of deaths due to HIV and AIDS.[37] In 2005, of the 3.1 million people that died of HIV/AIDS worldwide, 2.4 million deaths were in Sub-Saharan Africa, making it the principal cause of death in this

region.[8, 37] This is a massive burden of suffering and disease, mostly affecting the young adults who are the most productive members of society.[1] Therefore, there is need to study the causes and predictors of mortality in sub-Saharan Africa for future planning and interventions.

While the concerns in developed countries are the long term effects of HAART like development of resistance, metabolic effects [2] and long term survival on HAART,[8] low access to treatment and early mortality due to advanced disease are the major concerns in Sub-Saharan Africa.[9, 15] '*Whereas mortality has significantly reduced in developed countries, thanks to the use of HAART, access to treatment is still low in Africa owing mainly to low access to treatment (only 11 percent of patients in urgent need were receiving it as of June, 2005)*'[7] reports Etard et al. This is somewhat because in those countries worst affected by the pandemic, the likely benefits of a successful ART programme were widely argued before.[6] Some esteemed health experts opposed the introduction of HAART in severely affected countries citing the limitations and dangers of ART including the negative impact HAART would have on preventive measures.[1] On the other hand, many had argued strongly for ART to be a key part of an integrated reaction to the epidemic in resource-limited countries even where general access to treatment for those who could benefit from it was not possible.[6]

Luckily, the prejudice to global inequalities in HIV care continues to be addressed.[39] There are a number of initiatives that have been developed to address the inequalities in treatment accessibility.[15] With the launching of initiatives by international organisations like World Health Organisation (WHO) to treat 3 million by the year 2005, the Global Fund to fight AIDS, TB and Malaria and the US President's Emergency Plan for AIDS Relief fund (PEPFAR) and with falling prices of antiretroviral drugs, more patients infected with HIV-1 will have access to treatment.[35]

Even with an increase in funding towards HIV treatment in Africa, there is less information on how best to deliver treatment services.[15] Human resource and inadequate health- care infrastructure remain to be major barriers to the scaling up of treatment in Sub-Saharan Africa.[9] This has been compounded by the large number of patients requiring treatment (about four million patients aged between 15 to 49years needed

treatment in sub-Saharan Africa by the end of 2004[15] and high rates of co-infections like Malaria and TB.

Zambia, like the rest of Sub-Saharan Africa, has not been spared by the HIV and AIDS pandemic. Of the estimated 11 million people living in Zambia, more than 1 million people are infected with HIV.[38] Zambia only has 0.17 percent of the world's population, yet carries 3.0 percent of the global burden of disease. HIV prevalence in Zambia varies widely by sub-population and area; with urban areas more affected at 23% versus rural areas with a prevalence of 11 percent.[10, 44] This is significant because nearly half of all Zambians live in urban areas.

In 2000, HIV/AIDS accounted for a 32 percent increase in the number of deaths in Zambia. This has been projected to continue to increase to 83 percent by 2015.[10] Approximately 6.2 million Zambians would have died as a result of the epidemic by 2050; the single largest health burden and cause of death in Zambian history.[10]

The Zambian government had targeted 100,000 people to start antiretroviral therapy (ART) by the end of December 2005 but only 67,000 patients were on treatment as of October 2006.[22] The number of HIV patients that require treatment has also increased to around 290,000.[22] This high burden of disease has further stretched the economy enormously and has put more pressure on the health services and workers who have to attend to more patients. ART was introduced into the Lusaka Health District Clinics by the Government of the Republic of Zambia (GRZ) through the Lusaka District Health Management Team (LDHMT) under the Ministry of Health in collaboration with the Centre for Infections Disease Research in Zambia (CIDRZ) a Non-governmental Organisation (NGO) supported by the University of Alabama at Birmingham (UAB) starting in April, 2004. The overarching goal of the Lusaka District Care and treatment program is to provide long-term care to patients living with HIV/AIDS. In addition, this program is helping in strengthening the existing Zambian government health infrastructure and increasing human capacity in HIV care and treatment. Prior to April 2004 ART was hardly available to the larger population in Zambia as a result of limited economical and logistical resources. Only private hospitals or clinics and the University Teaching Hospital in Lusaka were providing ART to HIV patients prior to April 2004.

A number of studies have looked at mortality in HIV patients after the introduction of ART in resource limited settings. The most recent studies in South Africa and Malawi published by lawn et al and Ferradini et al respectively demonstrated that deaths were attributable to advanced disease.[9,15] Patients in these cohorts generally started ART with severe immunosuppression which led to Opportunistic infections(OIs).[9,15] Poor adherence and treatment interruptions also appear to have contributed to the increased likelihood of death.[6] Similar trends were observed in Uganda and Senegal based ART programmes as well.[14,39]

Though the trends of mortality are similar across Africa, there were considerable differences between regions [35] thus the need for evaluation of mortality among HIV-1 infected patients by local ART programmes through research.

Clinical observations among HIV-1 infected patients in Lusaka indicate that advanced disease is the commonest cause of mortality in adult patients presenting to clinics under the Lusaka District Management Team. The possible explanations for advanced disease at first presentation may not differ so much with similar settings in Africa. The interaction of HIV-1 virus with tropical infections like malaria and TB accelerates the progression to AIDS disease.[13] Wasting, a sign of malnutrition, is quite prevalent in Zambia and in the presence of HIV-1 infection may increase disease progression and death. Stigma is still a big problem among the Zambian population and may affect health seeking behaviours among HIV patients.

This study was undertaken to determine factors contributing to mortality among HIV-infected patients enrolled in HIV and treatment care in the eight clinics under LDHMT over the course of the first year of the program. The standard practice for classifying cause-of-death statistics is to identify the underlying cause of death, as this should be targeted for public health intervention.

However, in a country such as Zambia like most of Africa, it is hard to determine with reasonable specificity and sensitivity the cause of death because the medical charts are often incomplete; laboratory monitoring of toxic effects is not routinely practiced or available. Patient's medical charts may also be incomplete because the patient may have come for one or two initial visits and then months later they are reported as being deceased.

There are also diagnostic limitations in Zambia as most diseases are diagnosed syndromically and patients are treated empirically. The diagnostic tests that are usually available in the Lusaka District include full blood count, acid fast bacilli (AAFB), chest x-ray, and peripheral blood smear for Malaria. As a result of this dearth of information, the cause of death is often unknown and there may be a misclassification to the immediate cause of death rather than the underlying cause which often takes place.

As a baseline for future comparisons of the mortality experience of ART patients, we describe the distribution of cause of death that represents the early experience in the scale up of antiretroviral programs in Zambia. The distribution by cause of death as well as the amount of information available is an important part of monitoring and evaluation of this historical public health initiative.

CHAPTER 2: LITERATURE REVIEW

The introduction of highly active antiretroviral therapy has with no reservation improved the outcome of patients with HIV infection in both low-income and resource rich countries.[7, 14, 15, 30, 35] Several studies have shown that a number of factors predict survival among HIV-1 infected individuals. Some of these factors include; advanced immune suppression, [8, 15, 35] CD4 cell count, [8, 14, 35] body mass index (BMI), [24] karnosfky score, [12] age[2] and gender.[3] Factors like level of adherence[42], haemoglobin[7] and HAART regimen [24] may also influence the outcome of HIV disease in these patients.

The mortality rates are higher among HIV-1 infected patients initiating antiretroviral therapy in low-income countries than high-income countries.[35] In general, the mortality rates tend to be highest in the first few months of initiation ART in both low-income countries and high-income countries.[35] Nevertheless, the biological and immunological responses to HAART in HIV-1 patients from low-income countries are comparable with resource-rich countries.[35]

The causes of mortality are poorly documented in low-income countries due to poor record keeping,[35] lack of laboratory equipment and inadequate human resource; making it difficult to diagnose diseases.[9] Most patients die at home making it impractical to deduce the cause of death.[7] The commonest causes of death are due to advanced disease and OIs.[35]

A number of factors could limit the effectiveness of HAART and contribute to mortality in low-income countries. These factors include:

A. high prevalence of OIs [9, 35]
B. late presentation of patients for medical attention [9, 14]
C. interruptions in drug supply at he programme level [14, 35, 39]
D. patients' financial constraints [35]
E. scarce human resource [14]
F. poor and inadequate health care infrastructure [14, 39]
G. complexities of antiretroviral drug administration and its effects [14, 39]

The following section focuses on available literature on the following subjects/topics that relate to mortality in HIV-1 infected individuals:

2.1 factors predicting mortality in HIV patients

2.2 The mortality rates among HIV-1 infected patients
2.3 The causes of mortality in HIV-1 infected patients

Comparisons with data from rich- resource countries were made where appropriate.

2.1 Factors Predicting Mortality in HIV Patients

Several factors have been cited as predictors of mortality in HIV patients. These factors are discussed below.

2.11 Advanced Immunosuppression

Studies in low-income countries and high- income countries show that mortality among HIV-1 infected individuals is associated primarily with severe immune suppression at enrolment.[15, 35] Data from several Sub-Saharan African countries demonstrate that advanced HIV disease is an independent predictor of mortality in HIV infected individuals.[6, 7, 9, 15, 35]

In South Africa, for example, Lawn et al reported no deaths among patients with stage 1 or 2 disease who received ART; in contrast to those with stage 3 or 4 disease who had a higher risk of death.[15] Patients who died in this study were more likely to have WHO stage 4 disease than those who survived.[14] Stage 4 disease and CD4 count less than 50 cell/mm^3 were associated with lower survival probability compared with other patients.[9, 15] Early mortality was higher in stage 4 disease than other patients [15, 35]; for instance 66% of the patients that died within three months of being on HAART had stage 4 disease in the South African community study.[15] *'Once patients developed stage 4 disease, the mortality was so high that the inevitable delays in accessing care, diagnosis, referral to an ART programme, preparation for treatment and actually initiating ART result in an unacceptable mortality rate, of the order 7 percent per month'*, reports Lawn et al.[15] In a South African observational study, Laurent et al reported that all the patients that died in this study had AIDS from the time they started treatment.[14]

Mortality was highest among HIV-1 patients in the first six to 12 months in almost all the studies reporting from sub-Saharan Africa[6, 9, 15] which was partly explained by advanced clinical stage at initial presentation.[15, 35] Most patients in low-income countries

presented with OIs like Tuberculosis (TB), Bacterial infections and fungal infections which led to increased mortality in the early stages of treatment.[35]

Most of these infections are either missed by clinicians due to lack of diagnostic facilities or patients remain without treatment or prophylaxis due to lack of drugs. The result is ineffective treatment of OIs in Sub-Saharan Africa.[35]

Advanced HIV disease has also been associated with Immune-Reconstitution Inflammatory Syndrome (IRIS) especially TB.[14, 35] Inflammatory reactions tend to occur in a third of co-infected patients receiving both HAART and TB treatment, and may contribute to mortality.[35]

So, strategies to help HIV-1 infected patients have early access to HAART, improve the diagnosis and treatment of OIs, and better identify and treat IRIS are needed in low-income countries like Zambia.

2.12 CD4+Cell Count

CD4 count is another strong predictor of early mortality in HIV-1 infected individuals.[15, 17, 35] Low CD4 counts have been associated with increased mortality both in low-income[17, 35]and high-income countries[25] and ART reduces mortality and morbidity for patients with severe CD4 cell depletion (CD4 <100 cells/mm^3.[17,25] However, some patients on HAART have slow and inadequate immune function and recovery; thus remain at more risk of AIDS-associated events and death than those with more rapid recovery of the immune system.[24]

There is no agreement on the benefits of earlier initiation of therapy as reflected by current treatment guidelines allowing for the delay of ART until a lower CD4+ cell threshold–usually 350 cells/mm^3 or 200 cells/mm^3 for some patients.[25] Some of researchers have reported that CD4+ cell percentage may be an independent predictor of death in a subgroup of AIDS-free HIV-infected patients with absolute CD4 cell counts of between 200 to 350 cells/mm^3.[21]

Though existing literature demonstrates immunological (CD4+ cell count) response to ART in HIV-1 patients with higher CD4+ cell counts, it is uncertain what the long term improvements are like in terms of mortality and morbidity.[25] The likely benefits of HAART in such patients will most probable be weighed against the long term effects of

treatment including; emergency of drug resistant strains, with resultant depletion of effective remaining drugs, development of metabolic abnormalities, cost and access.[25]
Patella, F. J. et al in a prospective observational study in the United States demonstrated that among HIV–1 infected individuals with CD4+ cell counts of 201 to 350 cells/mm^3, initiating HAART was associated with reduced mortality compared with delaying such therapy (mortality rate ratio 0.27; P< 0001).[25] Survival benefits were also noted in patients with CD4+ cell counts between 351 to 500 cells/mm^3 who initiated treatment than those who deferred treatment. Mortality rates were lowest among patients with high CD4 counts (500-750 cells/mm^3) whether on treatment or not. In other words, there were no survival benefits between those who started treatment and those who delayed in the subgroup of patients with CD4+ cell counts 500 cells/mm^3 and above. In this subgroup, the cause of death was not AIDS. Several other studies have observed that for HIV–1 infected individuals with CD4+ cell counts 201 to 350 cells/mm^3, initiation of ART was associated with marked reductions in observed mortality compared with delaying treatment.[25] However, the potential benefits of starting ART or delaying above CD4 +350cells still needs a longer follow-up period to clearly demonstrate any benefits.
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A comparison between low-income and high-income countries demonstrated that patients in low-income settings had lower CD4 cell counts at initiation of HAART but gain in number of CD4+ cell counts after six months were comparable.[35] This somewhat explains the high rate of mortality established among HIV patients in the first months of ART.[35] The risk of death (pre-treatment and on treatment) is independently associated with baseline CD4 + cell count in Sub-Saharan Africa.[15]
Lawn, D.S. et al in a prospective community based ART cohort in Cape Town, South Africa, demonstrated increasing risk of death with decreasing CD4 count. Among the 44 deaths that occurred within the first 3 months among this cohort, 50 percent had blood CD4+ cell count < 50 cells/mm^3. Within 3 months of the programme, WHO stage 4 disease and /or blood CD4+ cell count < 50 cells/mm^3 accounted for 80 percent of all deaths. Patients with CD4+ count > 151 cells/mm^3 had a low risk of death. Even after adjusting for treatment effects, multivariate analysis still showed association between

mortality rate and CD4 + cell counts. Mortality rate ratio comparing those with CD4 counts < 50 and > 50 cells/mm^3 was 3.34 (95% CI).[15]

Starting HAART when CD4 cell count fell below 50 cells/mm^3 was strongly associated with an increased risk of death in African patients, according to findings from Malawi, Kenya, South Africa and Uganda.[9, 15, 17, 39] The researchers in these studies observed that a CD4 < 50 cells/mm^3 was associated with high mortality rates in the early phase of HAART.[9, 15, 17, 39] Whereas CD4+ cell counts of between 51 and 200 cells/mm^3 were associated with reduced mortality rates in some Sub-Saharan Studies,[14] it was not true in both the Senegalese and Kenyan studies.[7, 17]

The lack of consensus on the benefits of early initiation of treatment may continue for sometime. Lawn et al suggested that initiation of ART among patients with CD4+ cell counts between 150 and 200 cells/mm^3 should be an accepted goal for initiating treatment based on mortality outcomes in South Africa. The Author argues that in the absence of resources, this might avoid greater extension of patient numbers requiring treatment that would result from recommendations to treat HIV-1 infected patients with CD4 cell counts < 350 cells/mm^3 as is practised in the developed countries.[15] On the other hand, due to conflicting results from other studies, this suggestion if implemented, may leave out several patients who would benefit from initiating HAART at a higher CD4+ cell count.

There are a number of reasons for early and high mortality rates among HIV-1 infected individuals. Infections, psychosocial problems[11] and malnutrition[4] all seem to affect CD4+ cell counts in HIV patients.

A relationship has been documented between depression and disease progression (drop in CD4+ cell count) and mortality among men who have sex with men and bisexual men.[4] Ickovies et al found an increased mortality (twice as high) among women with chronic depressive symptoms than women with limited or no symptoms at all. Women with CD4+ counts < 200 cells/mm^3, mortality was 54% in those with chronic depressive symptoms compared to 21% in those with limited or no symptoms.[4]

Psychosocial problems like depression may play a role in HIV-1 mortality in low-income countries like Zambia. This may be attributed to high levels of poverty and

unemployment among HIV patients. Stigma to HIV patients, which is still prevalent in Zambia may contribute too.

Evidence from historical accounts, recent epidemiological observations and clinical findings has strengthened the idea that malnutrition weakens response and change vulnerability to infections and other diseases.[4] OIs are more widespread among patients with cancer and AIDS who are malnourished.[4]

Infections like TB, Parasitic infections, viral infections and fungal infections reduce the host CD4+ cell count independently of the HIV infection. Consequently, HIV infection, tropical infections, malnutrition and probably psychosocial co-morbidities create a vicious cycle and each of them independently depresses CD4+ cell production. This results in early high mortality rates due to overwhelming OIs and IRIS in HIV patients especially in poor countries where laboratory facilities and treatment of OIs are lacking.[9, 30]

2.13 Body Mass Index and Weight

In developed countries, in spite of the benefits of HAART in HIV-1 infected patients, not all patients have an optimal response to therapy.[24] There is proof that several patients die with very good viral suppression and immunological response.[24] Pre-HAART studies show that malnutrition was associated with reduced survival [24] and weight loss remained an independent predictor of mortality in HIV-infected individuals. [16]

Some cohort studies of patients show that wasting still remains an important predictor of death even in patients using HAART.[24] However; only one study seems to have specifically looked at the impact upon survival of malnutrition at the time of initiation of HAART.[23] A retrospective cohort study in Singapore showed that BMI and weight were both significantly associated with death.[24] Malnutrition, using BMI as an indicator (BMI $< 17 kg/m^2$), was among the three significant predictors of death, the others being HAART regimen and advanced disease.[24] For patients who initiated ART with moderate to severe malnutrition, the hazard ratio for death was double overall.[24] Initiating HAART with moderate to severe malnutrition, hazard ratio was 6-fold higher than those with normal nutritional status.[24] The study confirmed the observations made

in the pre-HAART era that showed a significant relationship between survival and malnutrition in HIV-1 infected patients.

In poor countries, the burden of inter current infections differs substantially, and hence, it is debateable whether BMI is a helpful simple clinical indicator of survival.[9] Even then, recent data still suggest that BMI at the time of HIV diagnosis and initiation of antiretroviral therapy still remains an important predictor of mortality in resource poor settings.[30, 38]

Poverty and malnutrition are some of the challenges involved in providing antiretroviral therapy in developing countries.[30] Poverty affects all aspects of care in these countries; including the capacity to buy food, right to use to clean water and housing.[30] The evidence that malnutrition is a very essential co-factor in AIDS progression in low-income countries is on the rise.[30]

Severe, P. et al reports from Haiti that a body weight in the in the lowest quartile for sex was an independent predictor of death with a hazard ratio of 3.3 (P-value<0.001) compared to 2.1 (P-value <0.001) and 1.6 (P-value 0.04) for AIDS-defining illness and CD4+cell count < 50 cells/mm^3 respectively.[30] Other studies in Malawi and the Gambia showed similar results; with a BMI < 18.5 kg/m^2 being associated with early mortality.[9, 38]. The Gambian study recorded a strong and independent predictive value of BMI within 3 months of HIV diagnosis.[38] The magnitude of the predictive effect, and the sensitivity and specificity was similar to those of CD4+ cell counts; the risk of a BMI < 18kg/m^2 was comparable to CD4+ cell count < 200 cells/mm^3.[37] Different from other studies reporting from Africa in the past 12 months of ART, baseline weight did not predict the risk of death according to findings from Kenya.[17, 23, 32]

Malnutrition may weaken immune response to ART thus prolonging the duration during which patients are in danger of OIs and an increased risk of death.[24] Malnutrition may thus represent a potentially reversible cause of mortality in patients initiating HAART [24] especially in resource poor countries. Adjuvant treatments like nutritional supplements in patients with low BMI may hasten the recovery of immune system and facilitate additional benefits in survival in patients with advanced disease starting HAART.[24] However, preliminary reports from Zambia indicate no significant rise in CD4+ cell counts between HIV-1 infected patients receiving food supplements and non-food

supplements after 12 months.[18] Whether BMI could be used to inform interventions like the decision to initiate HAART, and whether BMI monitoring would also be useful to assess the success of such treatment remain to be seen from other prospective studies.

2.14 Gender

The differences in survival in some demographic groups like men and women, blacks and whites, led to the assumption that HIV disease progressed faster in some groups than others.[3] Several studies which have investigated the existence of gender related differences in the natural history and prognosis of HIV infection have yielded contradictory results.[28] Although different biological response to HIV might have influence on survival,[3] several authors report disparity in the use of health care resources which may explain the differences found in some studies.[28] Women and Blacks in the United States were least expected to receive correct treatment for HIV infection.[3]

Socioeconomic status may affect survival in HIV-1 infected patients even when no discrepancies in access to medical care exist.[28] Studies in Canada and Brazil have reported poor survival among HIV infected patients with low incomes in spite of seemingly equal access to medical care.[3, 28]

In a Brazilian study, Lopez, S. et al found that survival after the diagnosis of AIDS was shorter among women than men with no differences in access to treatment. Women had a lower CD8+cell count, the prognostic value of which has not yet been well defined, at the time of diagnosis compared to men. There are conflicting reports of both rapid progression to AIDS and longer survival being associated with high levels.[3] The authors in this study thought the reduced CD8+cell count among women was probably associated with loss of T-cell homeostasis.[3]

Viral load after HIV seroconversion has been documented as an independent predictor of the risk to progress to AIDS in men.[33] Some few cross-sectional and longitudinal studies have reported lower plasma HIV-1 RNA levels in women than men after controlling for CD4+cell count. The viral loads remain lower for years in women than men.[33]

In view of this, one would expect women to progress less to AIDS than men but several studies have found that the risk to of AIDS does not differ significantly between men

and women.[33] The reasons for no difference remain obscured despite high viral load in men.[33]

In Africa, most studies except one, have reported no independent association between sex and mortality in HIV infected persons. A South African study showed that the mortality rate was not independently associated with sex in HIV-1 infected persons.[15] Similar findings in Senegal and Uganda have been reported.[7, 39] The most recent study in Malawi reports that the male sex was associated with early mortality and since no other cohort study had previously reported such a finding in Sub-Saharan Africa, early mortality in this case was ascribed to some unidentified confounding factors.[9]

The antiretroviral therapy in Lower Income Countries (ART-LINC) Collaboration, a network of treatment programmes in Africa, Asia and South America in a similar collaboration of cohort studies in High-income countries from North America and Europe, the ART Cohort Collaboration (ART-CC) reported that there was little evidence for differences in progression rates between men and women.[35] Therefore, available data seems to suggest that sex does not play a major role in determining mortality rates in HIV-1 infected individuals.

It is not clear if biological responses have a negative or positive influence on female gender. However, it's evident that disparities in access to medical services and social status have a negative influence on female survival rates. These imbalances are particularly important in Sub-Saharan Africa where a large proportion of HIV infected women live.[28] Even if some data show that more women than men access treatment in some studies,[7, 8, 15, 30, 35] women tend to be affected more than men by these social injustices. The provision of free medical services and education to women may partially help reduce the imbalances.

2.15 Karnofsky Performance Scale

The importance of functional status in predicting mortality has been shown in patients with AIDS,[12] other diseases and populations.[31] While there is significant literature validating CD4+cell count as a strong predictor of survival and disease progression among those with early and moderately advanced disease, limited data exists relating those with severe immune suppression.[31] Relying on conventional markers of HIV

disease progression especially in the HAART era, may be less useful in predicting mortality in HIV-1 infected patients with severely advanced disease.[31] Previous studies show that CD4+ cell counts may be less predictive of inpatient care with AIDS than assessment of functional status as indicated by activities of daily living (ADL).[12, 31] Shen, J.M. et al showed that functionality, as assessed through the karnofsky score or ADL impairments, may be a stronger indicator of prognosis in chronically ill population on the verge of death.[31]

The value of functional status has been evaluated and shown in other diseases.[31] For instance, functional status has been shown to be an important predictor of hospital outcomes in older patients, Pneumonia patients, and Congestive Heart Failure patients.[31] Studies have shown that there is increased cardiovascular mortality in individuals aged 65 years and above who had difficulty with several instrumental ADL. [31]Karnofsky score has also been used to predict outcomes in cancer and acute myocardial infarction.[31]

We are not aware of any study in Sub-Saharan Africa that has reported on the importance of functional status in HIV–1 infected individuals. The Senegalese study reports on karnofsky score as having increased non -significantly during an 18-month follow-up study.[14] The study does not mention the significance of baseline functional status in this cohort.

Clinical observations in Lusaka, Zambia, indicate that a significant number of HIV-1 infected patients have low karnofsky score at first presentation. Hence, assessing the functional status of HIV-1 infected patients may be essential for advising patients about long term care requirements, home-care needs, and evaluating the care-giver's needs [31]Knowledge of functional status of HIV-1 patients may help guide care, planning and be a potentially imperative predictor of mortality risk.[31] Therefore, there is need for studies in Sub-Saharan Africa to evaluate the impact of baseline functional status on survival among HIV-1 patients initiating HAART.

2.16 Age as a predictor of mortality

The importance of age and exposure category as determinants of disease progression and mortality seem to have changed since the introduction of HAART.[2] this perhaps is a surprise because immune recovery is likely to be more difficult in older people.[2]

Studies on HIV-1 in the elderly have shown reduced survival compared with that of the younger patients in the pre-HAART era.[2, 5, 27, 34, 40] and that age was predictive of a decreased AIDS- free interval.[40] In older patients, clinical presentation of HIV/AIDS disease is different.[28] Available literature support the clinical impression that HIV disease progressed faster in elderly patients from the initial asymptomatic stage to full blown AIDS.[7] The number of AIDS cases diagnosed in the same month as death occurred increased with age.[27, 40]

The high rate of mortality among the elderly has been attributed to late diagnosis; resulting from a low index of suspicion of HIV-1 infection by both patients and their doctors and as well as non-specific signs heralding the onset of disease in older patients.[27,40] Increased mortality has also been explained by a wide range of both infection and malignancies among the elderly people which are worsened by AIDS.[34] The actual damage by the virus itself, co-morbid conditions of HIV, problems in adherence to treatment and in delivery of service[34] as well as non–HIV related co-morbid conditions such as diabetes, cardiovascular disease, stroke and neoplasm predict reduced survival among older people.[40]

Other studies have reported that decreased survival among the elderly may be attributed to the natural decline in the immune system, reduced use of HAART, and increased drug side effects and toxicities in the elderly.[40] Poor short term and long term response rates to HAART by older people have been noted by some researchers.[2] However, other studies suggest greater use and adherence to HAART in older HIV-1 infected patients [2]

Before 1997, age had a strong effect on survival with those older than 45 years at high risk of AIDS and death.[2] The CASCADE collaboration study noted that this effect was smaller by 1999 to 2001.[2] The study observed that before 1997 the Hazard ratio of progression was 1.27 and 1.03 in 1999 to 2001. The group ascribed the change to the introduction of HAART in 1996.[2]

Having an AIDS diagnosis may well be preserving an overall age effect on mortality in the elderly than the young.[2] This is for the reason that an AIDS diagnosis would more severely damage immune function in the elderly than the young.[2] Even though reduction in survival with increasing age at seroconversion have been shown to be independent of natural aging before HAART, natural aging might have a greater role after the introduction of HAART, concludes the researchers in this study.[2]

Most studies in sub-Saharan Africa report no major association between mortality and age in HIV infected individuals[7, 15, 39] However, in ART-LINC, older age was associated with increased mortality in both low-income and high-income countries.[35] In ART-LINC, the hazard ratio of progression to death for patients 50 years and above was 1.53 compared to 1.0 for the 16 to 29 years in HAART programmes in low-income countries.[35]

In Zambia, HIV is more prevalent among the economically productive and reproductive group (15 to 49years)[36] and as a result, most preventive and treatment interventions are focused on this group. Accordingly, it is no surprise that no study has investigated the impact of age on survival in this setting.

2.17 Other prognostic factors predicting mortality.

Other factors which have been cited as important predictors of survival in HIV-1 infected individuals initiating HAART include;

2.17A. level of adherence to HAART[19, 42]
2.17B. baseline Haemoglobin[7, 17]
2.17C. HAART regimen[24]

2.17A. Level of Adherence to HAART

The optimal time to initiate HAART is vague and as such specialist recommendations on when to instigate treatment generally varies.[42] Some studies have suggested a high possibility of disease progression only in patients who initiated HAART when CD4+ cell count was below 200 cells/mm^3.[42] While other studies have observed that it may be dangerous to delay HAART after the CD4+ cell count falls below 350 cells/mm^3.[42] The related increase in mortality at different CD4+ cell counts among HIV-1 infected

patients maybe explained by incomplete adherence to ART in some of the previous studies which did not adjust for patient adherence.[42]

Available data have shown the relationship between survival and adherence to treatment.[42] A prospective observational study in Canada showed that among an unselected population-based cohort of ART-naïve patients initiating HAART, starting HAART at CD4+ cell count of 200 cells/mm^3 or more had no significant impact on survival.[42] The mortality rates were uniformly low among HIV-infected patients with baseline CD4+ cell counts of at least 200 cells/mm^3 who were adherent to treatment.[42] There was significant increase in mortality rates among the non-adherent patients for all CD4 cell strata; including patients who initiated HAART at CD4+ cell counts of 350 cells/mm^3 or more.[42] This data supports the argument that HAART maybe safely initiated at around 200 cells/mm^3 but not below this level.[42]

The best time for ART initiation is crucial for disease progression or diminished effectiveness of HAART.[42] Therefore, there is need for more evidence on adherence and its impact on survival at different CD4+ cell strata in low-income countries like Zambia.

A number of studies previously investigated how adherence to HAART impacted on plasma HIV-RNA suppression and rebound rates.[42] Higher and more sustained virological suppression rates during HAART were associated with higher levels of adherence.[42] This data suggest that the dangerous effects of non-adherence cannot be prevented by early initiation of HAART[42] and that non-adherence may be the strongest determinant of patient survival at a CD4+ cell count of about 200 cells/mm3.[42]

Studies in low-income countries report high levels of adherence to treatment in patients on HAART, [7, 9, 15] at least in the first year of treatment. In spite of earlier concerns that African patients, many of whom live in poverty and lack formal education, would be less adherent to ART, which could lead to development and spread of drug resistance, one study reported to the contrary. This study revealed that African patients maybe more adherent to ART than their counterparts in North America.[19] A collective analysis of African and North American studies indicate positive levels of adherence can be achieved in Sub-Saharan African settings.[19] The analysis indicated a pooled estimate of 55% of the population achieving adequate adherence in North America while 77% of the population achieved adequate adherence in sub-Saharan Africa.[19]

Treatment efficacy relies on sustained adherence and consequently constitutes a serious challenge to those receiving ART.[19] Different dosing schedules, food restrictions and adverse effects complicate HAART regimens and compromise adherence.[19] Maximal viral suppression and prevention of resistance, disease progression and death, require persistently very high levels of adherence.[19] Therefore, maintaining these relatively high levels of adherence should be the aim in Sub-Saharan Africa. Strategies that may help improve level of adherence to ART, like nutritional supplements as reported in a pilot project in Zambia,[18] may go a long way in preventing deaths among HIV-1 infected especially in low-income countries. However, more sound and appropriate evidence on adherence in low-income countries is needed through research to help formulate policies that take into account local settings.

2.17B. Baseline Haemoglobin

Anaemia is yet another factor that has been documented to be an independent predictor of death among HIV-1 infected patients.[7, 17] A few studies in Sub-Saharan Africa show that anaemia is a strong predictor of death independent of CD4+ cell count in HIV-1 infected patients.[7, 17] In both Uganda and Senegal, scientists found that anaemia and haemoglobin of less than 10g/dl were associated with a worse survival.[7, 17] These findings maybe crucial in settings like Lusaka and the rest of Zambia where prevalence of anaemia is high among HIV-1 infected and non-HIV patient as observed from clinical practise.

2.17C. HAART regimen

HAART regimen has been mentioned, at least by some researchers, to predict mortality among HIV-1 infected individuals.[24] Though the comparison of two most frequently recommended first line regimen found that the combination of two nucleosides and Efavirenz may be more durable over two years than combining two nucleosides with ritonavir-boosted lopinavir.[26] Data from Africa indicate little evidence for differences in progression rates between patients starting HAART with different first line recommended regimens.[9,35] In ART-LINC, there was little evidence for an association

between mortality during the first year and use of generic drugs,[35] which could be an important result to most developing countries most of whom use generic drugs.

2.2 Mortality rates in HIV infected individuals

Most studies report higher mortality rates in the first months after starting HAART than in the later months.[6, 7, 9, 14, 35, 39,] In ART-LINC and ART-CC, 78 percent and 62 percent of deaths in low-income countries and high-income countries occurred in the first six months respectively.[35] Mortality rates fell significantly within the first few months of treatment (Table 2.1) and approached mortality rates seen in developed countries within four to six months of treatment.[35] The risk of dying reduced from 3.31-fold (HR 4.31; 95% CI) during the first months of HAART to 0.42-2-fold (HR 1.42-2; 95% CI) during the second half of the first year.[35]

Table.2.10. Mortality rates per 100 years-persons in low-income and high- income countries

Duration on HAART (months)	Low income countries mortality rates	High income countries mortality rates
1	147	-
2	106	-
3-4	51	-
5-6	51	24
7-12	27	16

The Antiretroviral Therapy in Lower Income Countries (ART-LINC) Collaboration and ART Cohort Collaboration (ART-CC) groups. 2006. Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. Lancet ,367,817-824.

In a South African study, 65% of deaths happened in the first 90 days from enrolment.[15] Pre-treatment mortality was 35.6 per 100 person-years (95% CI) in this study. Mortality rate was still high at one month of treatment (17.5/100 person-years, 95% CI) but 2.03-fold (95%CI) lower than the pre-treatment rate. The death rates continued to decline and were about 13.2 and 14.2-fold lower than the pre-treatment rate at six to nine and 12 months of treatment respectively.[15]

CHAPTER 3: JUSTIFICATION FOR THE STUDY AND OBJECTIVES

3.1 Justification for Study

The introduction of ART in sub-Saharan Africa has the potential to prolong the lives of HIV-1 infected individuals.[14] Previously the provision of ART to regions with limited resources such as Sub-Saharan Africa was thought to be impractical and economically infeasible.[1, 6] Although expense and effective delivery remain formidable barriers, public health policy makers have re-examined the possibilities of using ART in resource limited environments as prices for drugs have fallen over the past five years.[15, 35]

The Lusaka District Health Management Team recently introduced ART to the public in a primary-care setting. The overarching goal of the Lusaka District HIV Care and treatment Program is to provide long-term care. In addition, this program will help strengthen existing Zambian government health care infrastructure and increase human capacity in HIV care and treatment.

Though mortality in patients on antiretroviral therapy in sub-Saharan Africa has been reported for the first year in a number studies[7] with underlined similar reports in terms of virological and immunological responses, there has been significant differences in rates and causes of mortality between countries.[35] In some instances these differences would be partly be explained by different set up of ART programmes. Programmes with free access to ART tend to have lower rates of mortality than those that attach some cost to treatment.[35] Mortality rates may also be influenced by follow up programmes put in place by ART programmes i.e. whether follow-up is passive or active.[35] Therefore evaluation of mortality among HIV patients on treatment should be undertaken by individual ART programmes taking into account the local conditions.

Clinical observations in Lusaka district indicate that patients with advanced HIV disease and low CD4 counts have early mortality after initiation of HAART. This mortality could be attributed to so many factors like late presentation, delay in initiation of treatment by health workers and co-infections like TB and Malaria.

With a large number of patients of about 290,000 patients requiring urgent treatment, [22] there is great need to investigate the determinants and causes of mortality in these

patients. By so doing, the data generated from the programme would help identify approaches to optimize outcomes.

3.2 Objectives and Study Design

3.21 Primary Objectives

- The primary objective of the study was to determine possible causes of death in HIV patients initiating HAART during the period May 2004 to May 2005.

3.22 Secondary Objectives

The secondary objectives of the study were;

- To assess existing co-morbidities at the time of death.
- To identify possible predictors of death in HIV patients
- To determine mortality rates among HIV patients during the first year of HAART
- To evaluate the general management of OIs and ART drug toxicities,

disease was chosen as the most likely to initiate the cascade leading to death. Some data were broadly grouped in the analysis owing to lack of precision in the data as a result of limited specificity in the charts.

If at the end of the chart review, the two physicians did not agree on the probable factors leading to the cause of death and there was sufficient data in the chart, the following procedures was followed:

1. Clinic staff (identified from the chart) who were directly involved with the patient's care around the time of death were interviewed by both physicians
2. If the two physicians still disagreed on the cause of death, and there was sufficient data from the medical interview and/or chart review, then a consensus was forced by requesting independent opinion of one or two other physicians.

Only those patients, who truly had insufficient data in the charts to arrive at the cause of death after a thorough chart review, interview with medical staff and/or chart review by independent physician(s), were placed in the unknown cause of death category.

4.21 Sample Size Determination

By the end of April 2005, the projected total enrolment at the eight Lusaka District Health clinics was 6444 HIV-1 infected patients; with 3479 patients expected to be on ART. Our sample size was 3479. Using reports from other studies in Sub-Saharan Africa, we assumed that patients with CD4+ cell count above 50 cell/mm^3 at enrolment had 20 percent increase in survival compared to patients with lower CD4 counts. Based on the number of HIV-1 infected patients enrolled, number put on ART, and the observed death rate among patients on ART, we estimated the ability to detect differences in death rate by several predictors of death. The table below presents a range of expected death rates, smallest risk ratios detectable, and number of patients needed to detect such differences. As seen in the table, our expected study population of 3479 on ART provided a statistical power in order to detect a risk ratio of 1.5 with 78 percent power (see highlighted row in Table 4.1).[6,39]

Table 4.10 Calculations done in Epi Info (at $\alpha = 0.05$, $\beta = 0.20$) based on CD4 count stratified above or below 50cells/mm^3 (one of several predictors of death studied):

Expected death rate	Smallest risk ratio detectable with sample size	Number of patients on ART with CD4 count less than 50cell/mm^3	Number of patients on ART with CD4 count above 50mm^3	Total number of patients on ART needed
3.3%	1.4	3,575	3,575	7,150
4.3%	1.4	2,711	2,711	5,422
5.3%	1.4	2,172	2,172	4,344
3.3%	1.5	2,399	2,399	4,792-2
4.3%	1.5	1,818	1,818	3,636
5.3%	1.5	1,456	1,456	2,912
3.3%	1.6	1,742	1,742	3,484
4.3%	1.6	1,320	1,320	2,640
5.3%	1.6	1,057	1,057	2,114

4.22 Data collection:

We entered data from the clinical charts, including discontinuation forms and medical staff interviewer's forms for deceased HIV-1 patients whether or not were on HAART, into the CIDRZ computer access database. We trained four qualified data entry technicians for a day to help with data entry under strict supervision by the two physicians. Each of the two physicians would then go through all charts entered for that day to check the entries made by each data-entry technician and counter-check the entries (verifications) made by the other physician. Data collection took seven months, November 2004 to May 2005.

4.30 Data analysis

Data on deceased HIV patients from computer-access database (initially entered by the research team) and the already existing data on surviving HIV patients on the CIDRZ excel database (routinely entered by the staff from the individual clinics) were exported to SAS software and analysis was done using SAS statistical software.

We based all causes of death on data available in the clinical records and interviews with medical staff treating patients. We grouped causes of death into functional classifications by organ systems and analyzed the causes of death. As part of the descriptive analysis, we also evaluated the general management of OIs and reported ART toxicities.

We developed an independent analysis of important predictors of death based on data available in the clinical records. We analyzed the following variables to find out predictors of death.

- ***Age*** *(≤49 versus >49 yrs old)*
- ***Current antiretroviral therapy prescribed*** *(Stavudine, Lamivudine, Nevirapine versus Zidovudine, Lamivudine, Nevirapine)*
- ***Enrolment functional status****(to compare mortality associated with each level of functionality i.e.75-100%, 50-74%,<50%, bedridden)*

- ***Enrolment CD4+ count*** *(The stratification of CD4+ count of 50 cell/mm^3 was motivated by the potential to compare to other studies that have used these categories. We compared the following levels of CD4 count;<50cell/mm^3versus 50-200 cells/mm^3 versus >200 cels/mm^3).*
- ***Enrolment renal function tests*** *(We compared creatinine clearance ≤ 50mls/min versus >50mls/min)*
- ***Enrolment full blood count*** *(The stratification of Haemoglobin < 6g/dl was motivated to find out patients with severe anemia and the need for blood transfusion. We compared mortality between those patients with Haemoglobin ≤ 6g/dl versus >6g/dl)*
- ***Enrolment WHO clinical Stage*** (We *compared mortality between patients with WHO 1 & 2 versus WHO 3 & 4)*
- ***Enrolment Body Mass Index*** *(we compared BMI ≤ 18.5kg/m^2 versus >18.5kg/m^2)*

In all sub-analyses, we controlled for age and gender, with the exception of analysis stratified by gender and or age. To analyze the outcome measures-functional classifications of causes of death by organ systems, co-morbidities at time of death, and other variables predicting death, we used chi-square and student t-tests.

For the predictors of death analysis, we estimated Kaplan-Meier probability of survival for those who remained alive on antiretroviral therapy compared to those who died while on ART. To investigate the relationship between those who remained alive on ART and those who died while on ART, we used univariate and multivariate Cox's proportional hazard models, confidence interval (CI) and log-rank tests.

4.40 Ethical considerations

This study was reviewed and approved by the University of Zambia Research Ethics Committee (REC) as well as the Institutional Review Board of the University of Alabama at Birmingham.

At that time, Lusaka District HIV Care and Treatment Program transported all deceased patient's files to a centralized location. We kept the charts under double lock and key at

this facility. The research team conducted chart reviews from this location in a private room. We only allowed approved study personnel to view the charts. Each deceased patient's chart had name and a confidential code number called the patient tracking identification number (PTID), which was for clinical care. We only used the PTID number during this study; the patient's name was not necessary for the purposes of this study.

CHAPTER 5: RESULTS

Table 5.1A Baseline characteristics of patients

	Died On ART	Surviving Patients on ART	P-Value	Died Not on ART	Surviving Not on ART	P-Value
Total patients , n	494	8495		176	4507	
Median age in yrs (range)	36.0 (16.0 - 68.0)	34.0 (16.0 - 66.0)	< .0001	35.0 (22.0 - 68.0)	31.0 (16.0 -71.0)	< .0001
Female n (%)	256 (51.8)	5155 (60.7)	< .0001	83 (47.7)	3003 (66.6)	< .0001
CD4 count (cells/mm^3) • Median (range)	64.0 (1.0 - 805.0)	118.0 (4.0 - 833.0)	< .0001	54.0 (1.0 - 433.0)	293.0 (4.0 - 1200.0)	< .0001
• <50 n (%) • 50–200 n (%) • >200 n (%)	213 (43.4) 219 (44.6) 59 (12.0)	1870 (22.8) 4383 (53.5) 1941 (23.7)	< .0001	65 (45.8) 55 (38.7) 22 (15.5)	410 (9.8) 916 (22.0) 2841 (62.8)	< .0001
Creatinine(micromol/l) Median for females (range)	75.5 (31.0-416.0)	69.0 (39.0 -201.0)	0.002	86.4 (22.0 –239.0)	65.0 (32.0 -143.0)	< .0001
Median for males (range)	96.0 (44.0 -1114)	81.5 47.0 -363.0)		113.0 (67.0 -275.0)	77.0 (35.0 – 155.0)	0.0006
BMI (kg/m^2) • Median (range)	18.0 (11.0 - 34.0)	19.9 (12.0 - 32.0)	< .0001	16.9 (14.0 - 26.0)	21.0 (16.0 - 35.0)	< .0001
For females: < 20 n(%) For males:<18.5 n(%)	172 (74.8) 118 (54.1)	2093 (47.2) 972 (35.5)	< .0001 < .0001	53 (77.9) 44 (62.9)	712 (32.9) 258 (26.1)	< .0001 < .0001

Abbreviations: BMI, Body Mass Index; WHO, World Health Organization; g/dl, grams per deciliters.
Symbols: n, number of patients; %, percentage of outcome

Table 5.1A Continued

Haemoglobin in g/dl Median for females (range)	9.0 (4.0 - 14.0)	10.3 (5.0 - 15.0)	< .0001	9.0 (5.0 - 14.0)	11.3 (5.6 - 14.7)	< .0001
Median for males (range)	10.0 (4.0 - 17.0)	11.0 (5.0 - 16.9)	<.0001	10.0 (5.0 -15.0)	12.2 (5.8 -16.6)	< .0001
Females ≤12 n (%) Males ≤13 n (%) • ≤6 n (%)	213 (84.9) 196 (84.5) 10 (2.1)	3797 (80.0) 2379 (78.0) 102 (1.3)	0.0580 0.0200 0.1592	49 (80.3) 58 (86.6) 10 (7.8)	1276 (63.8) 605 (60.6) 50 (1.7)	0.0080 < .0001 < .0001
WHO staging • 1 n (%) • 2 n (%) • 3 n (%) • 4 n (%)	11 (2.3) 41 (8.4) 298 (61.3) 136 (28.0)	856 (10.2) 1562 (18.7) 5046 (60.4) 887(10.6)	< .0001	6 (3.8) 9 (5.6) 98 (61.2) 47 (29.4)	1400 (31.8) 1318 (29.9) 1494 (33.9) 193 (4.4)	< .0001

Abbreviations: BMI, Body Mass Index; WHO, World Health Organization; g/dl, grams per deciliters.
Symbols: n, number of patients; %, percentage of outcome

Table 5.1A Continued

Haemoglobin in g/dl Median for females (range)	9.0 (4.0 - 14.0)	10.3 (5.0 - 15.0)	< .0001	9.0 (5.0 - 14.0)	11.3 (5.6 - 14.7)	< .0001
Median for males (range)	10.0 (4.0 - 17.0)	11.0 (5.0 - 16.9)	<.0001	10.0 (5.0 -15.0)	12.2 (5.8 -16.6)	< .0001
Females ≤12 n (%)	213 (84.9)	3797 (80.0)	0.0580	49 (80.3)	1276 (63.8)	0.0080
Males ≤13 n (%)	196 (84.5)	2379 (78.0)	0.0200	58 (86.6)	605 (60.6)	< .0001
• ≤6 n (%)	10 (2.1)	102 (1.3)	0.1592	10 (7.8)	50 (1.7)	< .0001
WHO staging						
• 1 n (%)	11 (2.3)	856 (10.2)	< .0001	6 (3.8)	1400 (31.8)	< .0001
• 2 n (%)	41 (8.4)	1562 (18.7)		9 (5.6)	1318 (29.9)	
• 3 n (%)	298 (61.3)	5046 (60.4)		98 (61.2)	1494 (33.9)	
• 4 n (%)	136 (28.0)	887(10.6)		47 (29.4)	193 (4.4)	

Abbreviations: BMI, Body Mass Index; WHO, World Health Organization; g/dl, grams per deciliters.
Symbols: n, number of patients; %, percentage of outcome

Table 5.1B HAART Regimen and duration of Treatment

	Patients died on ART	surviving patients on ART	P- Value
Initial HAART regimen D4T/3TC/NVP D4T/3TC/EFV AZT/3TC/NVP AZT/3TC/EFZ	 261 (53.7) 13 (2.7) 197 (40.5) 15 (3.1)	 3345 (39.6) 217 (2.6) 4579 (54.2) 307 (3.6)	< .0001
Duration on ART in days • Median (range)	32 (1 – 1460)	118 (1 – 720)	< .0001
• < 30 n(%) • 30–180 n(%) • > 180 n(%)	190 (47.3) 201 (50.0) 11 (2.7)	913 (10.8) 4995 (58.9) 2578 (30.4)	< .0001

Abbreviations: AZT, *Zidovudine*; D4T, *Stavudine;* 3TC, *Lamivudine;* EFZ, *Efavirenz;* NVP, *Nevirapine*
Symbols: n, number of patients; %, percentage of outcome.

Table 5.2A Place of death and the likelihood of having a diagnosis at the time of death

Place of death	Cause of death known	Cause of death unknown	p-value
Health f* n (%)	201 (71.0)	289 (77.4)	0.0598
Home n (%)	82 (28.9)	84 (22.5)	

Abbreviations/symbols: n, number of patients; % , percentage of outcome; f*, facility

Table 5.2B showing the probable cause of death among HIV In Lusaka District clinics

PROBABLE CAUSE OF DEATH	Number, n (Percentage, %)
RESPIRATORY SYSTEM	
TB	51 (7.66)
Non- TB pneumonia	32 (4.80)
PCP	10 (1.50)
Non- specific Pulmonary process	08 (1.20)
GASTROINTESTINAL SYSTEM	
Gastroenteritis and Dehydration	71 (10.66)
Drug Induced Hepatitis	08 (1.20)
CENTRAL NERVOUS SYSTEM	
Non-Specific Neurological infections	20 (3.00)
Cryptococcal meningitis	07 (1.05)
OTHERS	
Unknown	373(56)
Anaemia	27(4.05)
Malaria	18 (2.70)
Kaposi's Sarcoma	14 (2.10)
AIDS related	09 (1.53)
Congestive Heart Failure	08 (1.20)
Septicemia	05(0.75)
Kidney failure	02(0.30)
Carcinoma of the cervix	01(0.15)
DIC	01(0.15)
Suicide	01(0.15)

Abbreviations:*PCP,Pneumocystis Jiroveci Pneumonia* ; *DIC,Disseminated Intravascular Coagulation;* TB,Tuberculosis.
Symbols: n, number of patients; %, percentage of outcome

Fig.5.1A.
Kaplain-Meier Curves showing more than six-month survival of patients initiating HAART by baseline CD4 count. The log-Rank test was used to examine statistical difference among the groups ($P < 0.001$).

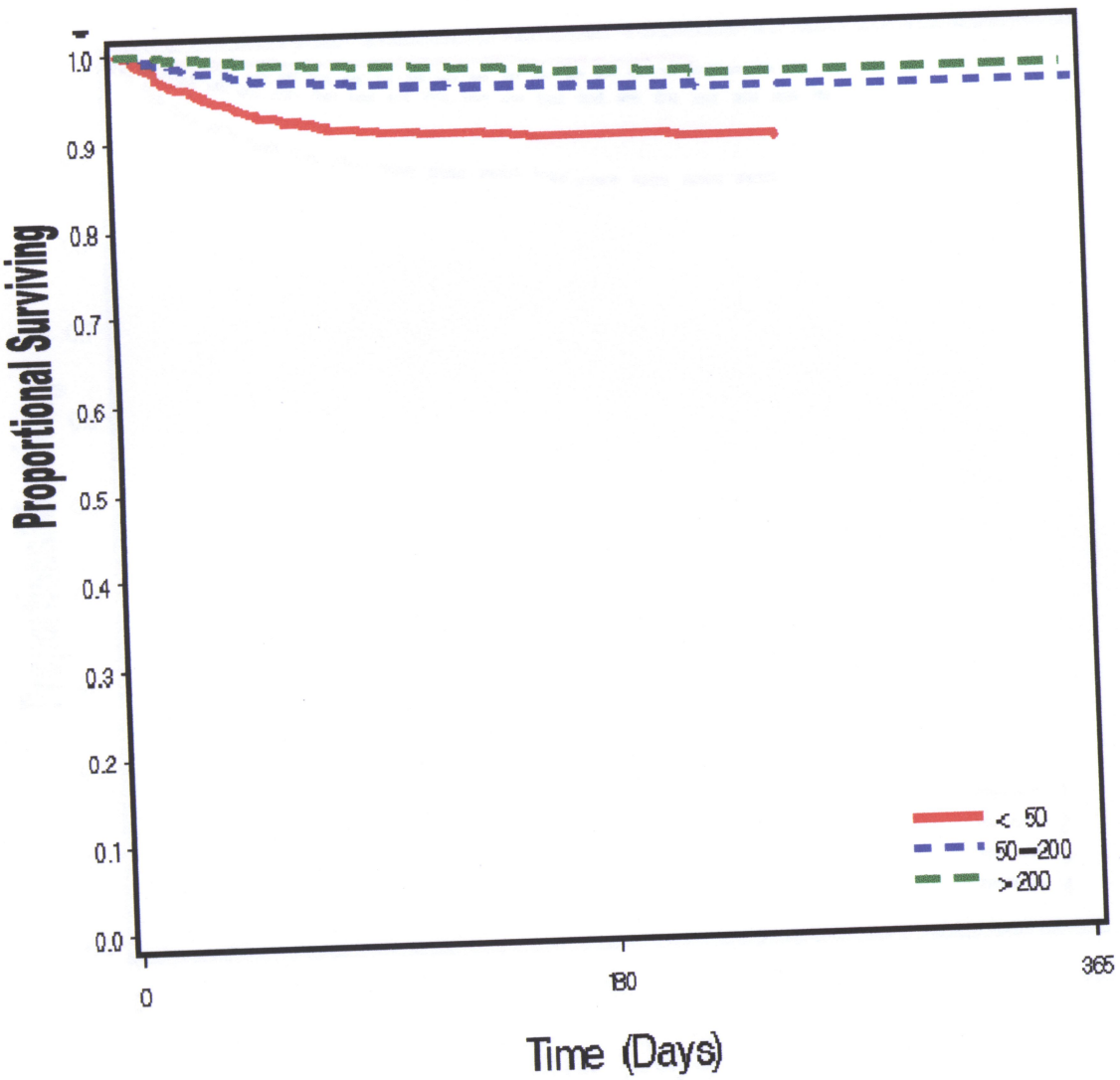

Fig.5.1B

Kaplan-Meier Curves showing more than six -month Survival of patients initiating HAART by baseline WHO staging. The log-Rank test was used to examine statistical difference among the groups ($P < 0.001$).

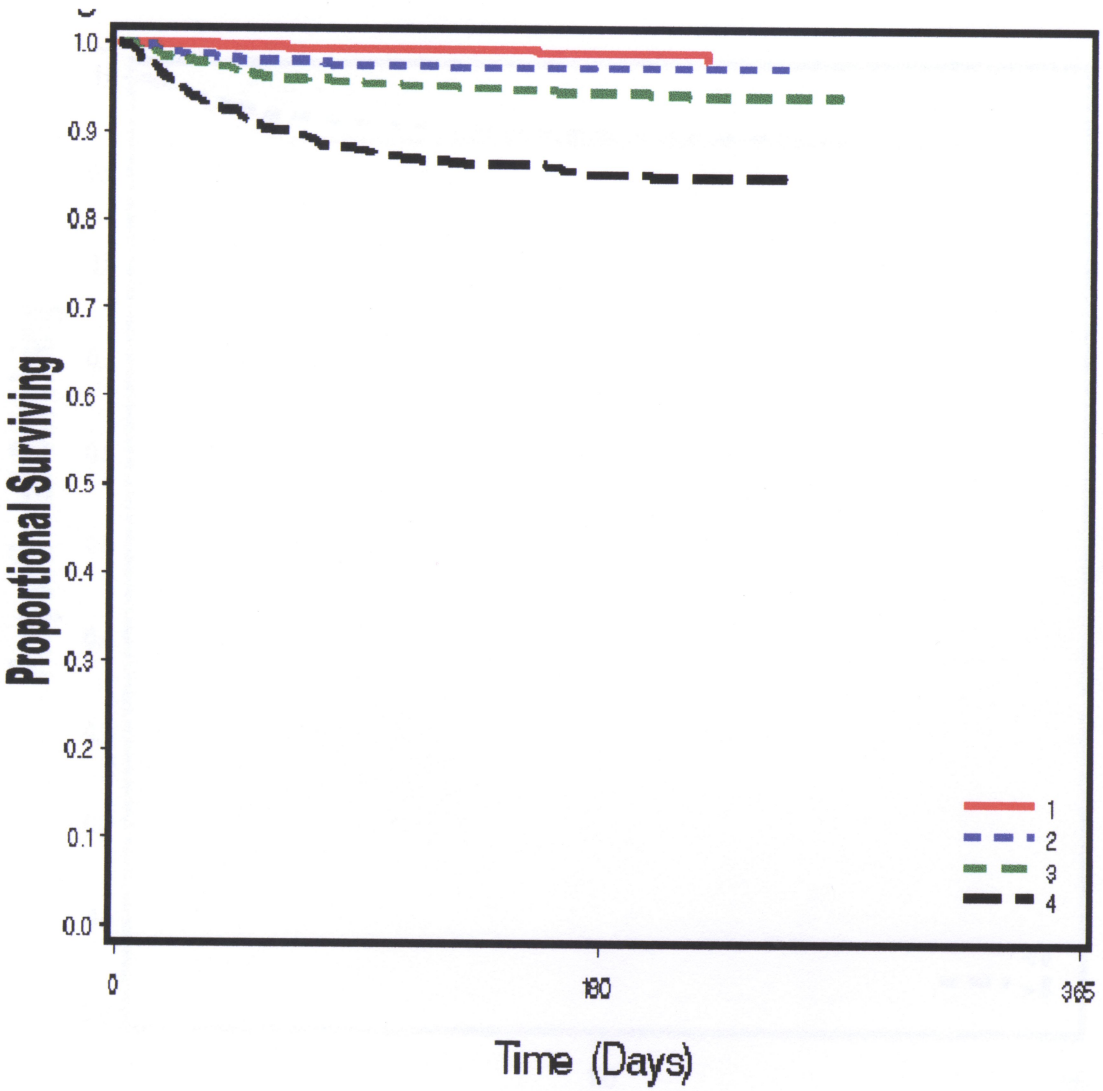

Fig.5.1C.
Kaplan-Meier Curve showing more than six- month Survival of patients initiating HAART by baseline Haemoglobin. The log-Rank test was used to examine statistical difference among the groups ($P < 0.001$).

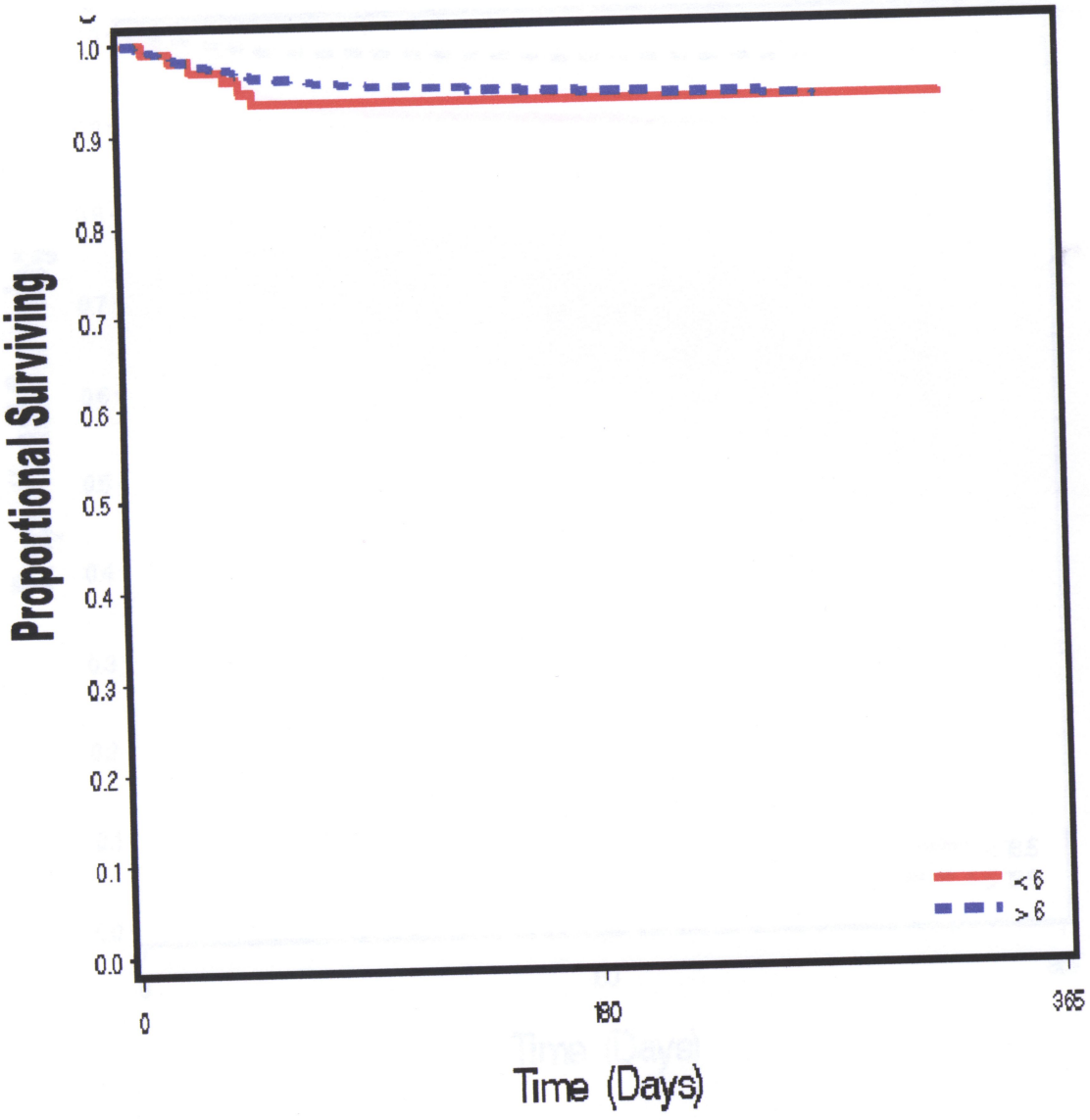

Table 5.30. Predictors of death among patients initiating HAART in Lusaka District Clinics

Predictor of mortality	HR (95% CI)	Adjusted HR analysis (95% CI)
BMI ≥ 18.5kg/m^2 BMI < 18.5kg/m^2	1.000 3.074 (2.496-3.786)	1.000 2.572 (1.673-3.959)
WHO 3 & 4 WHO 1 & 2	1.000 0.305 (0.221-0.420)	1.000 0.193 (0.084-0.445)
CD4 > 200cell/mm^3 CD4 50-200cell/m^3 CD4 < 50 cell/mm^3	1.000 2.617 (2.149-2.149)	1.000 - -
Age >49 Age ≤ 49 years	1.000 0.919 (0.637-1.326)	1.000 0.637 (0.317-1.280)
Male Female	1.000 0.682 (0.561-0.829)	1.000 0.858 (0.558-1.317)
AZT regimen D4T regimen	1.000 1.813 (1.488-2.210)	1.000 1.668 (1.087-2.560)

Abbreviations: BMI, Body Mass Index; WHO, World Health Organization; AZT, *Zidovudine*; D4T, *Stavudine;* HR, Hazard Ratio; CI, Confidence Interval.
Symbols: n, number of patients; %, percentage of outcome

5.2 Results

Patients' characteristics

We evaluated 13,672 individuals who were seen in the eight clinics in Lusaka from May 2004 to May 2005. Of these 8,497 were females (62%) and the median age was 34 years. Baseline CD4+ cell count was available for 12,996 (95%) of the individuals. The median blood CD4+ cell counts for the different groups of patients are shown in Table 5. 1A. Patients with CD4 < 50 cells/mm^3 and those with CD4 between 51 and 200 cells/mm^3 formed the majority of patients (Table 1A) in all the groups except for "surviving" patients who had "not initiated HAART". A preponderance of patients that died had a BMI < 18.5 kg/m^2 and 20kg/m^2 for males and females respectively (P-value < 0.0001) (Table 5. 1A). Anemia was very common among this cohort affecting all the categories of patients (Table 5.1A). Of the total number of patients, 13,402 (98%) were categorized into the four WHO stages (Table 5.1A); data was missing for 270 (2%) patients. WHO stage 3 accounted for the majority of patients (Table 5.1A). Sixty-six percent (8,989) initiated HAART during the study period and most of them were on a *Nevarapine* containing regimen. *Zidovudine, Stavudine* and *Lamivudine* were the most prescribed nucleoside reverse transcriptase inhibitors (Table 5.1B).

Unfortunately, only deceased individuals had their creatinine clearance calculated using the Cockcroft-Gualt Formula. Of the 670 deceased individuals, 309 (46%) had baseline creatinine clearance calculated. A higher proportional of deceased patients who were "not on HAART" had a creatinine clearance of < 50 ml/minute than deceased patients who were "on HAART". Among those who were "on HAART", twenty percent (51) had a creatinine clearance < 50 mls/minute compared to forty-one percent (23) among those who were "not on HAART'. This finding was non-significant due to small number of patients (53) with baseline creatinine clearance among the deceased individuals who were "not on HAART".

Mortality Rates in HIV patients

Mortality rate was found to be high in the initial stages of HAART. For instance 47 percent (190) and 97 percent (391) occurred in the first one month (30 days) and six months(180 days) of ART initiation respectively (p-value <0.0001). The mortality rate

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was 21 deaths per 100 person-years (95% CI) in the first month of ART. The rate declined five-fold (4 deaths per 100 person-years; 95% CI) after 1-6 months of ART. The mortality rate continued to decline and after 6 months, it was 49- fold lower than the first month (0.43 per 100 person years; 95% CI).

The overall mortality among patients who were on ART was 4.9 deaths per 100 person-years (95% CI).

Probable Causes of Mortality

Probable causes of death were identified for 294 (44%) of the 670 deaths; no data was available for four patients. In the majority of patients, cause of death could not be determined (Table 5.2A). More than two thirds of deaths occurred at a health facility (Table 5.2A). Dying at a health centre did not improve the probability of determining cause of death. For instance, 59 percent of patients that died at a health facility had no diagnosis at the time of death compared to 51 percent for patients that died at home; although there was no statistical significance (P-value = 0.0060).

Where we managed to determine probable cause of death, OIs and malignancies were the common attributable cause of death. Chronic gastroenteritis, TB, Central Nervous System infections, Pneumonias including *Pneumocystis Jiroveci Pneumonia* (PCP), Anaemia, and *Kaposi's Sarcoma (KS)* accounted for over 66 percentof deaths among the known probable causes of mortality(Table 5.2B).

Of the eight patients (1.2%) that died of suspected drug-induced hepatitis, we attributed seven deaths to *Nevirapine* and one to anti-tuberculous medications. One patient died of severe skin reaction, which we thought to have been complicated by Septicemia. Regrettably, we did not determine the role of IRIS though the bulk of patients that died had very low CD4+ cell counts when initiating HAART.

Predictors of mortality in HIV patients

Our hypothesis was that early mortality among HIV patients was associated with severe immune suppression. We therefore examined the association between survival probability and baseline CD4, WHO stage and other factors associated with low

immunity like BMI and Haemoglobin. Among patients that received HAART, ten percent of deaths occurred in patients with stage 1 & 2 disease; in contrast, patients with stage 3 & 4 had an incrementally greater risk of death (90% of deaths) (Table 5.1A). Increasing risk of death was also associated with low baseline CD4 cell counts (Fig.5. 1A). The median blood CD4+ cell count of those who died was lower than that of those who survived (64 versus 118 cell/mm^3; $P < 0.0001$ and 54 versus 293 cells/mm^3; $P < 0.0001$ for patients who were "on HAART" and those "not on HAART" respectively). Patients who died were more likely to have a lower BMI adjusted for sex than those who did not (median BMI 18 kg/m^2 versus 20 kg/m^2; $P < 0.0001$ and 17 kg/m^2 versus 21 kg/m^2 for patients "on HAART" and "not on HAART" respectively).

Low levels of Haemoglobin were also associated with mortality. The median Haemoglobin among the deceased patients was lower than that of surviving patients (9.0 versus 10.3g/dl; $P<0.0001$ and 9.0 versus 11.3g/dl; $P<0.0001$ for patients "on HAART" and not "on HAART" respectively).

Kaplan-Meier survival curves for all patients enrolled into the programme showed that WHO stage 3 & 4, baseline CD4 < 50 cells/mm^3, BMI< 18.5 kg/mm^3, Haemoglobin < 6.0g/dl were associated with a substantially lower survival probability compared with other patients (Fig.5.1A, B, C, D). Overall WHO stage 3 & 4 diseases and CD4 < 50 cells/mm^3 accounted for 86.4 percent (579) and 41.5 percent (278) respectively. In contrast, patients with CD4 ≥ 201 cell/mm^3, Haemoglobin ≥ 6g/dl and BMI ≥ 18.5 kg/m^2 had a lower risk of death (Fig.5.1A, C, D).

Multivariate analysis showed that mortality was not independently associated with age and sex but was associated with CD4+ cell count, WHO stage, BMI and a *Stavudine* based regimen (Table 5.3). After adjusting for other independent variables (Table 5.3), individuals with WHO stage 1 & 2 disease were 80 percent less likely to die than those with WHO stage 3 & 4 (adj. HR 0.19; 95% CI, 0.084-0.445). A lower BMI was associated with a 2.5 fold higher mortality compared to a normal BMI (adj. HR 2.57; 95% CI, 1.673-3.959). Individuals on a regimen containing *Stavudine* had a seventy percent higher mortality compared to individuals on *Zidovudine* regime (adj.HR 1.662-2; 95% CI,1.087-2.560).

A note should be made that due to the power of our sample size most of the associations were found to be statistically significant.

CHAPTER 6: DISCUSSION

6.1 Discussion

This study, which defined mortality rates, probable causes and predictors of mortality among HIV-1 patients accessing a public sector ART program in eight clinics in Lusaka, Zambia, was first of its kind. Our data highlights the significant mortality that occurs in the initial six months of initiating ART and is comparable to previous studies reported from sub-Saharan Africa.[7, 9, 14, 15, 35] We were also able to determine the mortality risk associated with differing levels of baseline CD4, BMI and WHO Staging providing an evaluation of enrolment criteria. Regrettably, it is also important to note that we were unable to identify probable cause of death in the majority of patients. This dearth of information provides an insight to the problems of scarce human resource, diagnostics and management of OIs in ARV programs in resource-limited settings.

Like most studies reported from sub-Saharan Africa and high-income countries, [6, 7, 9, 15, 35] mortality rates were extremely high on initiating HAART and a significant reduction was apparent within the first few months of treatment.

In our study, 97 percent of deaths occurred in the first six months; representing a higher proportion of early death than what was reported in ART-LINC and other sub-Saharan African studies. In ART-LINC and ART-CC, 78 percent and 62 percent of deaths in low-income countries and high-income countries occurred in the first 6 months respectively.[35] In a Senegalese study, 50 percent of deaths occurred in the initial 12 months.[7]

However, our mortality rate of four deaths per 100 person-years after six months of HAART is better than that observed in ART-LINC and ART-CC (51 and 24 deaths per 100 person years for low-income and high-income countries at 6 months of HAART). For instance, the mortality in a South African study was 2.5 deaths per 100 person-years at one year[15] compared to 0.43 deaths per 100 person–years at six to 12 months in our study. The large number of patients in our study compared to other studies would explain the difference in mortality rates between our study and other studies. We also did not take into account the lost-to-follow patients as a result we may have underestimated the actual number of patients that died in our study (We couldn't even document the number of patients lost-to-follow).

The extremely high mortality in the first six months from initiating HAART is partly explained by patients presenting with severely advanced HIV disease at enrolment. This is supported by the finding that mortality was strongly associated with CD4 cell count and WHO stage. Anaemia and low BMI, which are common findings in severely immunosuppressed patients, were also associated with higher mortality.

Certainly, WHO stage 3 & 4 accounted for 89.3 percent of deaths and CD4 < 50 cells/mm^3 accounted for 43.4 percent of deaths. We found that mortality among those with CD4 between 51 and 200 cells/mm^3 was also noteworthy accounting for 44.6 percent of all deaths. Patients with CD4 < 50 cells/mm^{3}and those with CD4 between 51 and 200 cells/mm^3 together, accounted for 88 percent of deaths.

Therefore, the idea by some scientists that the clinical criterion for initiating HAART should be when patients first develop symptomatic disease[15] (stage 3) was also true for our study. Initiating HAART among patients with CD4 cell counts ≤ 200 cells/mm^3 would be acceptable range in our setting. Lawn et al reports from South Africa that mortality was low among patients with CD4 >151 cells/mm^3; suggesting that initiating of HAART with CD4 cell counts of between 150 and 200 cells/mm^3 would be an acceptable range.[15] We did not specifically consider patients with CD4 cell counts between 151 and 200 cells/mm^3 in our study and hence difficult to comment on this recommendation; although there is still lack of consensus on the best time to initiate treatment based on CD4+ cell counts. We also did not specifically evaluate the risk of mortality in patients with CD4 count between 201 and 350 cells/mm^3; except that CD4 ≥ 201 cells/mm^3 accounted for 12.0 percent and 15.5 percent of deaths in patients "on HAART" and "those not on HAART" respectively. Therefore, patients with CD4 ≥ 201cells/mm^3 appear to have a risk of death too; even if this risk is less than that in patients with lower CD4 counts. The WHO 2006 guidelines recommends initiation of HAART in Stage 3 patients with CD4 count < 350 cells/mm^3 and WHO stage 2 patients with CD4 counts approaching 200 cells/mm^3.[41] The recommendations were based on the risk observed in patients with CD4 counts between 201 and 350 cells/mm^3 from different studies.[41] Basing our opinion on our findings, these recommendations should be followed until such a time we generate enough data suggesting otherwise.

BMI < 18.5kg/m^2 was independently associated with mortality in our study (Fig.1D). Similar findings have also been reported from studies in Malawi and the Gambia.[9, 38] The Gambian study recorded a strong and independent predictive value of BMI within three months of HIV diagnosis.[38] The magnitude of the predictive effect, and the sensitivity and specificity was similar to those of CD4+ cell counts; the risk of a BMI <18 kg/m^2 was comparable to CD4+count < 200 cells/mm.[3, 38] However, a study from Kenya found that baseline weight did not predict the risk of death in the first year on HAART.[17, 23, 32]

Wasting syndrome and weight loss > 10 percent are common conditions associated with HIV Stage 3 & 4 disease among HIV patients. In developed countries, in spite of the benefits of HAART in HIV-1 infected patients, not all patients have an optimal response to therapy.[24] There is proof that several patients die with very good viral suppression and immunological response.[24]

Low BMI has been associated with malnutrition and poor immune response which results in OIs; partly explaining the related mortality in these patients. Most HIV patients have improved appetites after initiating HAART which might complicate into *re-feeding syndrome* (*a condition associated with hypophosphataemia and hyperglycemia in wasted patients as a result of increased utilisation of phosphates in the formation of ATP from a high carbohydrate diet)* especially when large quantities of carbohydrates are taken. Therefore, *re-feeding syndrome* is a possible cause of mortality in patients with very low BMI who initiate HAART in our setting; considering that the Zambian diet is mainly composed of carbohydrates *(nshima)*. More research is required to specifically find out the reasons for increased mortality in patients with low BMI.

A few studies in Sub-Saharan Africa demostrated that anaemia was a strong predictor of death independent of CD4+ cell count in HIV-1 infected patients.[7, 17] In both Uganda and Senegal, scientists found that anaemia and haemoglobin of less than 10g/dl were associated with a worse survival.[7, 17] In our study a haemoglobin of less than 6g/dl was associated with mortality in the early phase of initiating HAART but the effect waned off the longer the patient remained on treatment (Fig.1C). The median Haemoglobin for deceased patients was lower than those for surviving patients (Table 5.1A). The number of patients with Haemoglobin ≤ 6g/dl was very small in all categories of patients and as

a result there no statistical difference between patients that died while "on HAART' and those "not on HAART" (Table 5.1A).

Zidovudine is known to cause bone-marrow depression in HIV patients but as to what type of HIV patients are susceptible to *Zidovudine*-induced anaemia and to what extent, is not known in our setting. The role of Erythropoietin in the treatment of *Zidovudine* induced anaemia and the interaction of *Zidovudine* with other drugs like *cotrimxazole* (routinely prescribed in HIV patients with severe disease) is yet to be clearly defined in Sub-Saharan Africa. With so many other causes of anaemia in this part of the world, research is needed to find out the common causes of anaemia in HIV patients and their interaction with HIV virus. Until these research questions are answered, anaemia will remain a major cause of mortality in this setting.

Surprisingly, a *Stavudine*-based regimen was independently associated with mortality (Table 5.3). Patients on a Stavudine-regimen were more likely to die than those on *Zidovudine*-based regimen. In Malawi and ART-LINC, the type of initial HAART regimen was not associated with mortality.[9, 35] In any case, we expected early mortality to be high in HIV patients on *Zidovudine*-based regimen due to increased risk of anaemia (an independent predictor of mortality on its own). In the long term, *Stavudine*-related mortality is expected due to metabolic derangements[41] In view of the fact that no other studies have documented these findings, we concluded that the association of early mortality with *Stavudine* could have been due to unrecognised confounding factors.

Interestingly, though not statistically significant, was the higher percentage of deaths with creatinine clearance ≤ 50 ml/minute among deceased patients who were "not on HAART" (41%) than among those were "on HAART" (20%). This finding may possibly suggest HIV-associated nephropathy with improvement once patients initiate HAART. This finding was not statistically significant because of a very small number of patients that had baseline creatinine documented at enrolment. It is also important to note that a number of patients with low BMI had normal serum creatinine (not shown in the results) but low creatinine clearance (renal dysfunction). This was a very important finding because renal dysfunction could easily be missed in such patients without calculating creatinine clearance. Equally important is the fact that the majority of patients initiating HAART in our setting are usually wasted. Hence, with the

introduction of *Tenofovir* in Zambia for first line treatment of HIV disease, all clinicians should learn to calculate creatinine clearance before initiating HAART especially in wasted patients.

The impact of HAART explains the marked decline in mortality rate from 21 deaths per 100 person-years in the first month of ART to 0.43 per 100 person-years after 6 months of ART. There was a 49-fold reduction in mortality rate from the first month of ART to after six months of ART. Significant declines in mortality rates after the initiating HAART have been reported in several other African studies.[6, 7, 9, 15, 39]

Whereas there is proven initial benefit to HAART, patients with advanced HIV disease, low BMI and anaemic entail particular attention especially in the first six months of HAART. ART programs will need to initiate interventions and protocols that will ensure such patients are adequately investigated for OIs before and after initiating HAART. Interventions should also include tight follow-up programs in the first months of HAART for early detection of IRIS.

Unlike other reports, we could not identify probable cause of mortality in more than 56 percent of deaths. Noteworthy is the fact that dying at a health centre did not improve the probability of having a probable cause of death unlike in other studies in Africa.[7, 9] For instance, 59 percent of patients that died at a health facility had no probable cause of death compared to 51 percent for patients that died at home; although there was no statistical significance (P-value = 0.0060). This finding in our study implies that whether one died at home or health facility, it did not make a difference to the likelihood of knowing the probable cause of death. It reflects on the burden of HIV disease to the health sector where few health workers have to attend to a large number of patients thereby compromising quality. It also reflects on the lack of diagnostic facilities in most clinics where patients are treated empirically for most OIs.

Surprisingly, despite inadequate information from the medical charts, mortality rates among patients on HAART were better than most sub-Saharan studies as earlier stated. Whether these conflicting results reflects on clinicians making a diagnosis and intervention without fully documenting their clinical findings, remain unanswered at least in this study.

In similar settings like ours, medical records have been used to identify possible cause of mortality with better results. In South Africa and Senegal, for instance, the likely causes of death were identified for 89.7 perecnt and 86 percent respectively[15,7] The most likely causes of death were mainly extracted from medical records and a small proportional from verbal autopsy and post mortems.[1,7] Information from medical records were used to assign a likely cause of death in about 75 percent and verbal autopsy was used to assign only in 21 percent of the deceased patients in a Senegalese study.[7] So, medical records could still be used to assign the likely cause of death in the absence of verbal autopsy and post-mortems. Even if medical records and verbal autopsy do not allow the assignment of an exact cause of death, they do help to classify deaths in broad categories given the available information,[7] which could be useful for interventions. Our study failed to allocate probable cause of death in about 52 percent of deaths and as such, post-mortems would be the way forward.

Similar to other reports, the causes of death were mostly attributed to OIs and malignancies. Chronic Gastroenteritis, *TB,* Central Nervous system infections, pneumonias including *PCP*, anaemia, and *KS* were the common conditions causing death in this cohort. The extent to which IRIS contributed to mortality was not determined but the bulk of patients had initiated HAART with low CD4 cell counts. Of note is a number of patients with hypotension most likely secondary to severe dehydration or *addisons* 'disease (not shown in results) that died at home few hours or days after they were discharged from a health facility; again emphasizing the shortages of staff in most clinics and the pressure to decongest wards in the clinics.

Like other reports from Sub-Saharan Africa, HAART was a rare cause of mortality in our study. Of the eight patients (1.2%) that died of suspected drug-induced hepatitis, we attributed seven deaths to *Nevirapine* and one to anti-TB medications. Screening for hepatitis B is not routinely done in Zambia even when the national prevalence is estimated to be high (10-20%). The likelihood of background hepatitis B and IRIS in some of these patients is a possibility.

It is apparent that OIs are the leading cause of mortality among HIV-1 infected patients in Sub-Saharan Africa and early initiation of HAART, diagnosis and management of OIs

are some of the sure ways that mortality can be reduced. Clinicians should be aware of IRIS among patients with severe immune depression initiating HAART.

6.2 Limitations

Though we believe the results of this study will provide reliable, valid information, a number of limitations were encountered:

1. In order to determine with reasonable specificity and sensitivity the cause of death among patients taking HAART, the data must be complete and accessible. The medical charts were incompletely filled in by medical staff, making it difficult to ascertain the exact cause of death. Some of the reasons for incomplete documentation were as follows:

- During interviews, medical or nursing staff were unable to recall all the medical details regarding the deaths of specific patients; especially where mortality happened at home or the patient had not been to the clinic for several weeks before death. .
- The Lusaka District HIV Care and Treatment clinics have had nursing shortages since their inception in May 2004. This made documentation and recall of patient information difficult and more unreliable.

2. Laboratory monitoring of toxic effects was not routinely practiced and therefore information was missing in a number of charts. This made it hard to evaluate for toxicities associated with HAART.
3. There are diagnostic limitations in Zambia as most diseases are diagnosed syndromically and patients are treated empirically. The diagnostic tests that were usually available in the Lusaka District included; full blood count, acid fast bacilli (AFB), chest x-ray, peripheral blood smear, and cerebral spinal fluid analysis. We captured this data when available but in most cases, it was missing.
4. Other clinical and laboratory parameters that would have influenced mortality in HIV patients were not routinely entered in the main CIDRZ database for surviving HIV patients by the staff at the various clinics. We learnt about this only after we had completed data entry for the diseased patients. We could not therefore determine the extent to which these factors predict mortality in HIV

patients in this set up. These factors include; karnofsky functional status, level of adherence to treatment, and creatinine clearance.

5. We did not account for the lost-to follow-up patients as a result our mortality rates were lower than in other studies.
6. Failure to identify the probable cause of death in the majority of patients in this study was a major concern. We would have liked to carry out verbal autopsies but due to limited time in which we were to carry out the study, it was not possible.

6.3: Conclusion

This study has highlighted the critical issues that concern management of HIV patients in the eight clinics in Lusaka. It has defined the predictors of mortality among HIV patients which include; baseline CD4 cell count, WHO HIV stage, BMI, haemoglobin and probably HAART regimen. Sex and age were not predictors of mortality.

The study has also shown the benefits of HAART in a resource-poor setting indicated by reduction in mortality rates from 21 per 100 person-years in the first month of treatment to 0.43 per 100 persons-years after six months of treatment. The early mortality rate was attributed to advanced disease as most patients had severe immune suppression with co-existing OIs at initiation of HAART.

The study failed to attribute possible causes of death in the majority of deceased patients. This was as a result of lack of adequate information from the medical charts and staff shortages in most clinics. Dying at home did not have any impact on the possibility of knowing the likely cause of death; highlighting the scarcity of human resource and diagnostics.

OIs and malignancies were the common causes of mortality reflecting again that most patients tend to come late for medical attention.

We could not determine or conclude on several other factors that have been documented as predictors of mortality in other studies due to a number of reasons. These factors

include; adherence level, baseline creatinine clearance and kanofsky score. We hope future studies will look at these factors.

As we endeavour to improve management of HIV patients, we must equally focus our efforts into research so as to come up with better strategies and interventions best suited for our settings.

CHAPTER 7: RECOMMENDATIONS

The following recommendations were made as a result of both our positive findings and limitations of the study. We would like to make the recommendations to the following institutions; government ministries, Funding Agencies, NGOs, Professional bodies and Individuals.

1. Patients initiating HAART with low CD4, WHO stage 3 & 4 disease, low BMI and anemia are at high risk of dying early. We recommend close follow-up of these patients in the early phase of treatment. Ministry of health in conjunction with professional bodies should formulate specific follow-up protocols (different from the routine) that will assist attending medical staff identify those at increased risk.
2. There is great need to improve staffing levels in the clinics to cope with the current high numbers of HIV patients attending these clinics. Government has to find ways of recruiting and retaining health workers in order to improve health delivery to HIV patients.
3. Excellent laboratory support is a key to good health delivery. Most patients die of OIs which in most cases go undiagnosed due to lack of laboratory support. We strongly recommend that government and funding agencies should invest into this area. This will help diagnose OIs in those patients with severe disease and/or those who develop IRIS.
4. More health infrastructure is required to contain the increasing number of patients initiating HAART.
5. Professional bodies like the Zambia Medical Association and Zambia Nurses Association should take up the challenge of updating members on new guidelines in the management of HIV. For instance it is very important that patients with severe HIV disease especially those with low BMI should have their creatinine clearance calculated and urinalysis done. This will ensure that those with renal dysfunction are identified early with prompt intervention.

6. Our study failed to answer some critical questions. These questions include the mortality associated with;

   - IRIS
   - Re-feeding syndrome
   - Zidovudine associated anaemia and role of Erythropoetin
   - Poor renal creatinine clearance and HIVAN
   - Karnofsky functional status
   - Chronic hepatitis B infection

We recommend that individual scientists or organisations dealing in matters that relate to HIV and AIDS should take up the challenge to investigate mortality associated with the above conditions.

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APPENDICES

Appendix A: Addendum to Discontinuation Form

Patient ID number _____
Interviewer name_____

1.Has she/he been told in the past month that they have (check all the apply):

	Yes	No	Don't Know	Remarks
Malaria				
TB				
High blood pressure				
Anemia				
Lung disease				
Liver disease				
Pneumonia				
Meningitis				

2. Please ask the following opened ended questions:

-What happened before she/he died including circumstances around her/his death (for example, if she/he saw a health care provider, switched medications, etc.)?
-What do you think the cause of death may have been?

_____

_____

_____

_____

_____

_____

3. At time of death did patient have any of the following (tick the correct box and note duration):

	Yes	No	How long?	Remarks
Cough				Productive or non-productive or hemoptysis (please circle one)
Shortness of breath				
Chest Pain				
Anemia				
Diarrhea				
Vomiting				
Rash				Describe rash:
Weight loss				
Fever				
Night Sweats				
Headache				
Confusion				
Fits/convulsions (seizures)				
Yellow eyes or yellow skin or uncontrollable itching (jaundice)				

Appendix B: Medical Staff Interviewer's Form

Patient ID number _____
Interviewer name_____
Medical Staff name_____

1. What happened before she/he died including circumstances around her/his death (for example what medications did patient receive, etc.) and what do you think the cause of death may have been?

_____

_____

_____

_____

_____

_____

_____

2. At time of death did patient have any of the following (tick the correct box and note duration):

	Yes	No	How long?	Remarks
Cough				Productive or non-productive or hemoptysis (please circle one)
Shortness of breath				
Chest Pain				
Anemia				
Diarrhea/dehydration				
Vomiting				
Rash				Describe rash:

Fever				
Night Sweats				
Headache				
Confusion				
Seizures				
Jaundice				
TB				
Heart disease				
High blood pressure				
Liver disease				
Pneumonia				
Meningitis				